Top Organomet Chem (2007) 22: 149–189
DOI 10.1007/3418_039

Published online: 22 July 2006

Palladium-Catalyzed Oxidation Reactions: Comparison of Benzoquinone and Molecular Oxygen as Stoichiometric Oxidants

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Abstract Palladium-catalyzed oxidation reactions are among the most diverse methods available for the selective oxidation of organic molecules, and benzoquinone is one of the most widely used terminal oxidants for these reactions. Over the past decade, however, numerous reactions have been reported that utilize molecular oxygen as the sole oxidant. This chapter outlines the fundamental reactivity of benzoquinone and molecular oxygen with palladium(0) and their catalyst reoxidation mechanisms. The chemical similarities

between benzoquinone and dioxygen are reinforced by catalytic reactions that undergo successful catalytic turnover with either or both of these oxidants. The results highlight substantial opportunities for the development of new aerobic oxidation reactions.

Keywords Palladium · Oxidation · Dioxygen · Benzoquinone · Catalysis

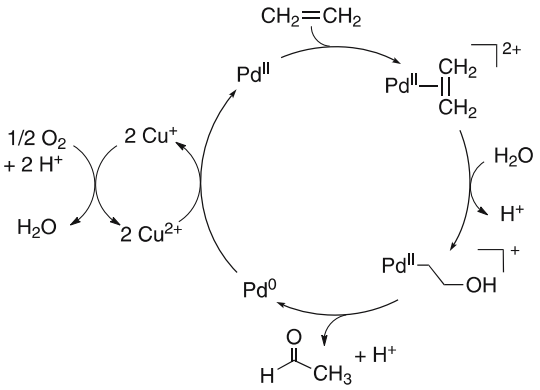
Abbreviations

Ar-Bian	1,2-Bis[(2,6-diisopropylphenyl)imino]acenaphthene
bc	Bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline)
Bn	Benzyl
bpy	2,2′-Bipyridine
BQ	Benzoquinone
BOC	*t*-Butoxycarbonyl
bpym	Bipyrimidine
Cbz	Benzyloxycarbonyl
*chex*DAB	*N*,*N*′-Dicyclohexylethylenediimine
COD	1,5-Cyclooctadiene
dafe	4,5-Diazofluorene
dafo	4,5-Diazafluorenone
dba	Dibenzylideneacetone
dh-phen	5,6-Dihydro-1,10-phenanthroline
DIPEA	Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
dmphen	2,9-Dimethyl-1,10-phenanthroline
DMSO	Dimethyl sulfoxide
EWG	Electron-withdrawing group
HOAc	Acetic acid
HQ	Hydroquinone
IMes	1,3-Dimesitylimidazolin-2-ylidene
ITmt	1,3-Bis(2,6,2″,6″-tetramethyl-[1,1′;3′,1″]terphenyl-5′-yl)-2,3-dihydro-1*H*-imidazol-2-ylidene
MeO-BIPHEP	(*R*)-(6,6′-Dimethoxybiphenyl-2,2′-diyl)bis(3,5-di-*tert*-butylphenyl-phosphine)
MOM	Methoxymethyl
(*M*,*S*,*S*)-ip-SPRIX	(*M**,3a*S**,3a′*S**)-3,3′,3a,3a′,4,4′,5,5′-octahydro-3,3,3′,3′-tetramethyl-6,6′-spirobi[6*H*-cyclopent[*c*]isoxazole]
NHC	*N*-Heterocyclic carbene
NMM	*N*-Methylmorpholine
NQ	Naphthoquinone
Ns	Benzenesulfonyl
ns	*trans*-β-Nitrostyrene
NSN	Bis(2-pyridylmethyl)sulfide
OAc	Acetate
P2Bn	1,2-Bis[(di-*tert*-butylphosphino)methyl]benzene
PAd-Ph	2,4,6-Trioxa-8-phosphatricyclo[3.3.1.13,7]decane, 1,3,5,7-tetramethyl-8-phenyl
PAd-*o*Tol	2,4,6-Trioxa-8-phosphatricyclo[3.3.1.13,7]decane, 1,3,5,7-tetramethyl-8-(2-methylphenyl)

Pc	Phthalocyanine
PG	Protecting group
salophen	[α,α′-(*o*-phenylenedinitrilo)di-*o*-cresolato]$^{2-}$
phen	1,10-Phenanthroline
Q	Quinone
SNS	2,6-Bis(methylthiomethyl)pyridine
sp	(–)-Sparteine
(*S*,*S*)-ip-boxax	Oxazole, (1*R*)-2,2′-[1,1′-binaphthalene]-2,2′-diylbis[4,5-dihydro-4-(1-methylethyl)-, (4*S*,4′S)]
TBDMS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetate
TFAH	Trifluoroacetic acid
TIPS	Triisopropylsilyl
tmeda	*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl, *p*-toluenesulfonyl
TPP	*meso*-Tetraphenylporphyrinato
2-pymeim	2-Pyridinylmethylene-4-methoxyaniline

1 Introduction

The Wacker process (Eq. 1) was developed nearly 50 years ago [1–3] and represents one of the most successful examples of homogeneous catalysis in industry [4–9]. This palladium-catalyzed method for the oxidation of ethylene to acetaldehyde in aqueous solution employs a copper cocatalyst to facilitate aerobic oxidation of Pd^0 (Scheme 1). Despite the success of this process, certain features of the reaction have limited the development of related aerobic oxidation reactions. Many organic molecules are only sparingly sol-



Scheme 1 Catalytic mechanism for the Wacker process

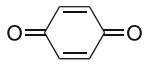
uble in water, the industrial reaction medium, and the copper cocatalysts often are less effective in organic solvents. In the absence of efficient catalyst reoxidation, Pd^0 generally decomposes into inactive metallic palladium. Such factors contribute to the fact that the majority of Pd-catalyzed reactions developed in subsequent decades consist of nonoxidative methods, such as cross-coupling reactions [10].

$$CH_2{=}CH_2 + 1/2\ O_2 \xrightarrow[H_2O]{[Pd]/[Cu]} CH_3CHO \qquad (1)$$

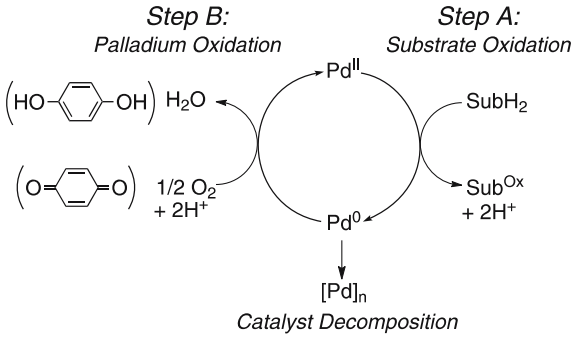
Oxidation reactions remain among the most important reactions in organic chemistry because they intrinsically *increase* functionality within the organic substrate. Palladium(II) is widely recognized as a versatile and selective oxidant, but its high cost limits its utility as a stoichiometric reagent. This limitation has been addressed by the identification of cooxidants and/or cocatalysts that permit the use of palladium in catalytic quantities. The $CuCl_2/O_2$ combination employed in the Wacker process (Scheme 1) is perhaps the best-known cooxidant mixture; however, a number of other reagents have also been used, including benzoquinone, polyoxometallates, stoichiometric Cu^{II} salts, and organic and inorganic peroxides [11]. Benzoquinone (BQ) is perhaps the most widely used stoichiometric oxidants for small-scale Pd-catalyzed oxidation reactions.

Molecular oxygen is perhaps the most attractive terminal oxidant. Over the past decade, numerous Pd-catalyzed oxidation reactions have been identified that undergo direct dioxygen-coupled turnover, namely, in the absence of redox-active cocatalysts or cooxidants. These reactions, which have been the subject of a number of recent reviews [12–18], are thought to proceed via a two-stage "oxidase" mechanism in which the Pd^{II} catalyst oxidizes the organic substrate (Scheme 2, step A) and the reduced catalyst is oxidized by molecular oxygen (Scheme 2, step B) [13]. This class of aerobic oxidation reactions is quite attractive because it permits a wide range of oxidation reactions to be achieved with molecular oxygen as the stoichiometric oxidant. The substrate does not react directly with molecular oxygen (or an activated oxygen intermediate). Therefore, the reactions are not limited to oxygenation of the organic substrate. As the Wacker process reveals, however, oxygen-atom transfer reactions are still possible by using water as the oxygen-atom source.

The catalytic mechanism for BQ-coupled Pd-catalyzed oxidation reactions is formally identical to that of the aerobic oxidation reactions (Scheme 2). Benzoquinone replaces O_2 as the oxidant for Pd^0 and hydroquinone is formed as a by-product. This similarity suggests that it might be possible to convert



benzoquinone (BQ)



Scheme 2 Simplified catalytic cycle for palladium-catalyzed aerobic oxidation ("oxidase") reactions

BQ-coupled oxidation reactions into direct dioxygen-coupled oxidation reactions. In many studies of Pd-catalyzed oxidation reactions, however, BQ and dioxygen were not compared directly. Historically, the reaction between molecular oxygen and Pd^0 was commonly thought to be disfavored kinetically, for example, by the spin-forbidden nature of the reaction (see Fig. 1; dioxygen is a ground-state electronic triplet, Pd^0 is a closed-shell singlet). For cases in which both BQ and O_2 have been tested, neither oxidant has proven to be universally better in catalytic reactions. These observations suggest the catalytic cycle presented in Scheme 2 is overly simplified. Nevertheless, recent research results reveal that the reactivity of dioxygen and benzoquinone in Pd-catalyzed oxidation reactions may be more closely related than previously appreciated.

In this chapter, we analyze the chemistry of dioxygen and benzoquinone in the context of palladium-catalyzed oxidation reactions. After a brief histor-

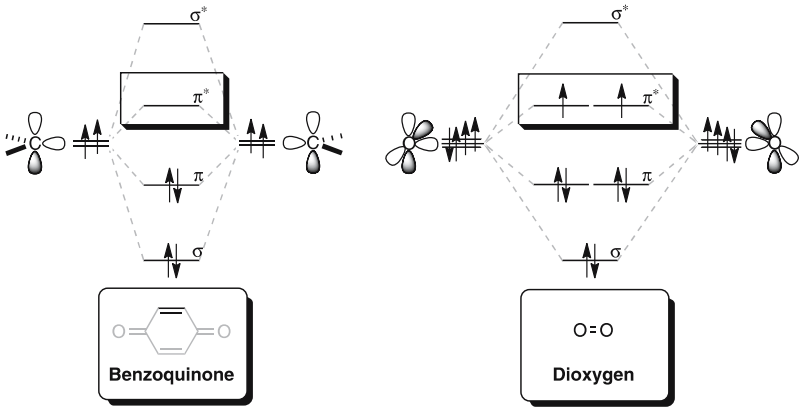
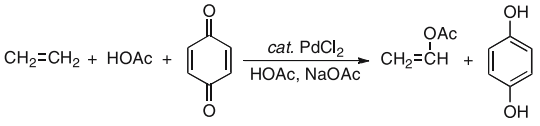


Fig. 1 Qualitative molecular orbital diagrams for the alkene fragment of benzoquinone and dioxygen highlighting the key differences in their respective frontier orbitals

ical overview of palladium oxidation catalysis, we evaluate the fundamental reactivity of dioxygen and benzoquinone with well-defined Pd^0 complexes and the mechanisms by which these reagents oxidize Pd^0 to Pd^{II}. Subsequently, we survey selected classes of Pd-catalyzed oxidation reactions for which both benzoquinone and dioxygen have been used as oxidants. The similarities observed between benzoquinone and dioxygen in both fundamental and catalytic studies suggests that numerous opportunities exist for further development of aerobic oxidation reactions.

2
Historical Perspective on the Use of Benzoquinone and Dioxygen in Palladium-Catalyzed Oxidation Reactions

In 1960, Moiseev and coworkers reported that benzoquinone (BQ) serves as an effective stoichiometric oxidant in the Pd-catalyzed acetoxylation of ethylene (Eq. 2) [19, 20]. This result coincided with the independent development of the Wacker process (Eq. 1, Scheme 1) [1]. Subsequently, BQ was found to be effective in a wide range of Pd-catalyzed oxidation reactions. For example, BQ was used to achieve Wacker-type oxidation of terminal alkenes to methyl ketones in aqueous DMF (Eq. 3 [21]), dehydrogenation of cyclohexanone (Eq. 4 [22]), and alcohol oxidation (Eq. 5 [23]). In the final example, 1,4-naphthoquinone (NQ) was used as the stoichiometric oxidant.



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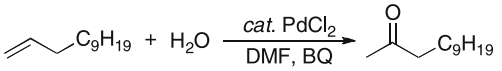

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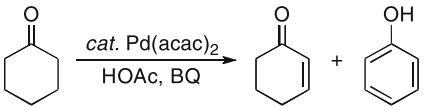

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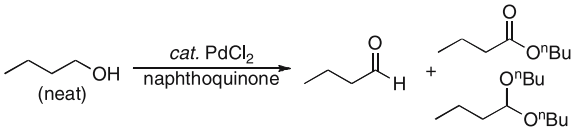
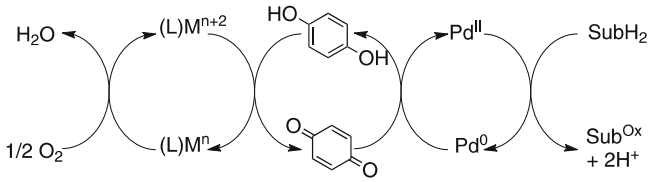


(5)

Despite the utility of BQ as an oxidant, the formation of hydroquinone as a stoichiometric by-product represents an unattractive feature of these

reactions. Bäckvall and coworkers recognized that BQ could be used in catalytic quantities by employing a cocatalyst capable of mediating the in situ oxidation of hydroquinone by a more attractive terminal oxidant [24]. Initial progress in the development of these "multicomponent" or "embedded" catalytic systems featured the use of manganese dioxide [25–27], hydrogen peroxide, or organic peroxides [28, 29] as stoichiometric oxidants.

Subsequently, Bäckvall and coworkers developed "triple-catalysis" systems to enable the use of dioxygen as the stoichiometric oxidant (Scheme 3) [30–32]. Macrocyclic metal complexes (Chart 1) serve as cocatalysts to mediate the dioxygen-coupled oxidation of hydroquinone. Polyoxometallates have also been used as cocatalysts [33]. The researchers propose that the cocatalyst/BQ systems are effective because certain thermodynamically favored redox reactions between reagents in solution (including the reaction of Pd^0 with O_2) possess high kinetic barriers, and the cocatalytic mixture exhibits highly selective kinetic control for the redox couples shown in Scheme 3 [27].



Scheme 3 "Triple-catalysis" strategy for aerobic palladium-catalyzed oxidation reactions

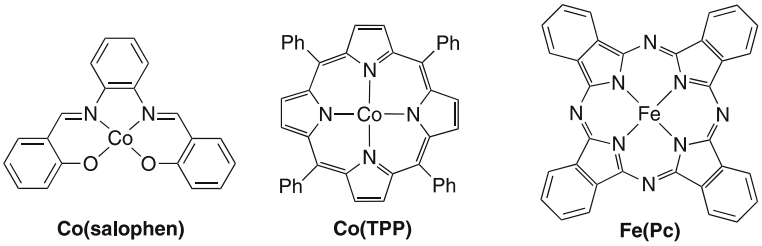
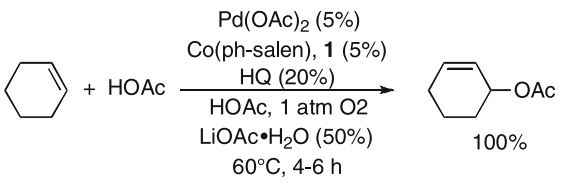


Chart 1 Transition metal cocatalysts used in multicomponent aerobic palladium-catalyzed oxidation reactions

These multicomponent catalyst systems have been employed in a variety of aerobic oxidation reactions [27]. For example, use of the Co(salophen) cocatalyst, **1**, enables selective allylic acetoxylation of cyclic alkenes (Eq. 6). Cyclohexadiene undergoes diacetoxylation under mild conditions with Co(TPP), **2** (Eq. 7), and terminal alkenes are oxidized to the corresponding methyl ketones with Fe(Pc), **3**, as the cocatalyst (Eq. 8).



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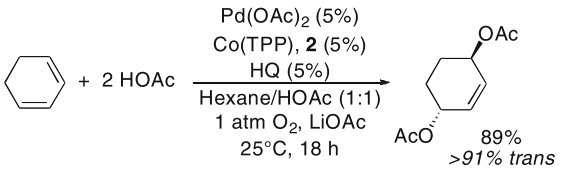

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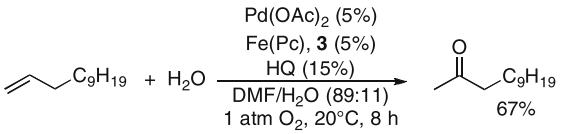
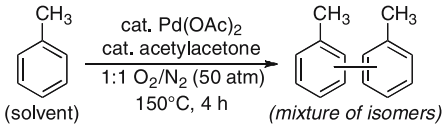


(8)

Although the methods illustrated above describe important steps toward the use of molecular oxygen in selective oxidation reactions, the need for co-catalysts increases the reaction's complexity and decreases the overall atom economy of the reaction [34, 35]. It would be even more attractive if dioxygen could be used as the sole oxidant for Pd^0. Indeed, early examples of direct dioxygen-coupled catalysis had been reported (Eqs. 9–11) [36–39], but prospects for this class of Pd-catalyzed oxidation reactions did not become widely appreciated until recently [12–18].



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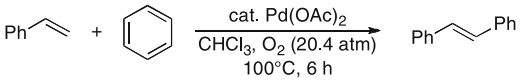

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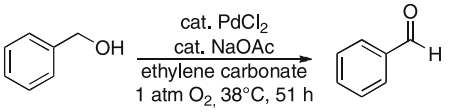


(11)

The recognition that certain organic ligands can promote direct dioxygen-coupled turnover (Scheme 2) prompted a resurgence of interest in Pd-catalyzed oxidation reactions [12–18]. For example, numerous new catalysts have been developed for aerobic alcohol oxidation (Chart 2) [40–56], which

have been the subject of extensive experimental and computational investigation [57–78]. The results of these studies reveal that reactions between Pd^0 and dioxygen are not necessarily slow. In nearly every reaction studied thus far, the rate-limiting step during catalytic turnover is associated with Pd^{II}-mediated oxidation of the substrate (Scheme 2, step A), *not* aerobic oxidation of the catalyst (Scheme 2, step B). Despite these promising recent results, many Pd-catalyzed oxidation reactions still do not undergo effective catalytic turnover with O_2 as the sole oxidant. Ongoing efforts are directed toward understanding the origin of this limitation and developing improved catalytic reactions.

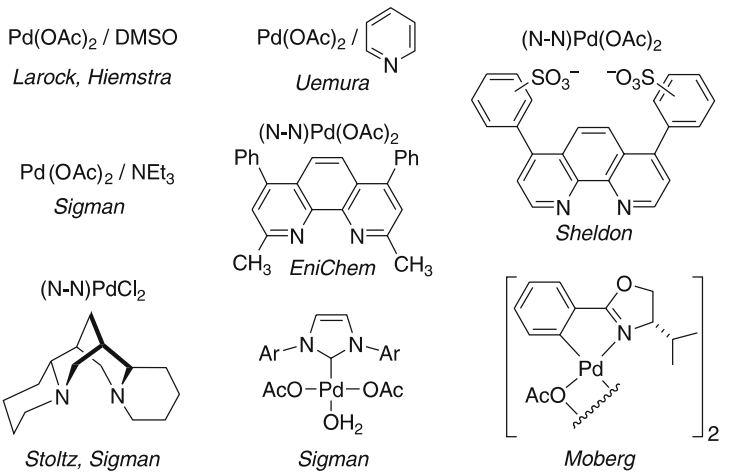


Chart 2 Catalytic systems developed for direct dioxygen-coupled palladium-catalyzed alcohol oxidation

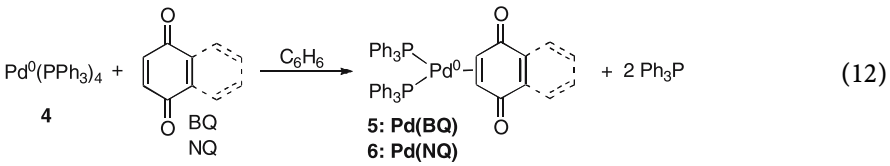
3
Fundamental Studies of Palladium(0) Oxidation by Benzoquinone and Dioxygen

3.1
Palladium(0) Oxidation by Benzoquinone

3.1.1
Palladium–Quinone Complexes

Benzoquinone is widely recognized as a useful oxidant in organic and inorganic chemistry [79, 80]. It often reacts with transition metals by coordination of the electron-deficient alkene fragment to the metal center, forming

an η^2–π complex [81, 82]. The first examples of palladium–quinone complexes were reported by Hagihara and coworkers in 1967 [83]. In benzene, $Pd(PPh_3)_4$, **4**, reacts with BQ or NQ to form the corresponding bis-phosphine palladium–quinone complexes, **5** and **6** (Eq. 12). An X-ray crystal structure of the platinum analog, $(PPh_3)_2Pt(BQ)$, was determined in 1977 [84]. The analogous structure of $(PPh_3)_2Pd(BQ)$, **5**, was reported only recently [85].



(12)

A number of palladium–quinone complexes have been prepared. Several of these have been characterized by X-ray crystallography [86–91], including other examples of complexes bearing monodentate phosphine ligands [92–94]. Related complexes with bidentate, *cis*-chelating ligands (Chart 3) tend to be more stable. The earliest use of chelating ligands was reported by Ishii, Ibers, and coworkers in 1974 with the preparation of bidentate, nitrogen-ligated Pd(Q) complexes using phen, bpy, and tmeda [95]. Numerous additional examples of stable BQ and NQ complexes of Pd are known [96–98].

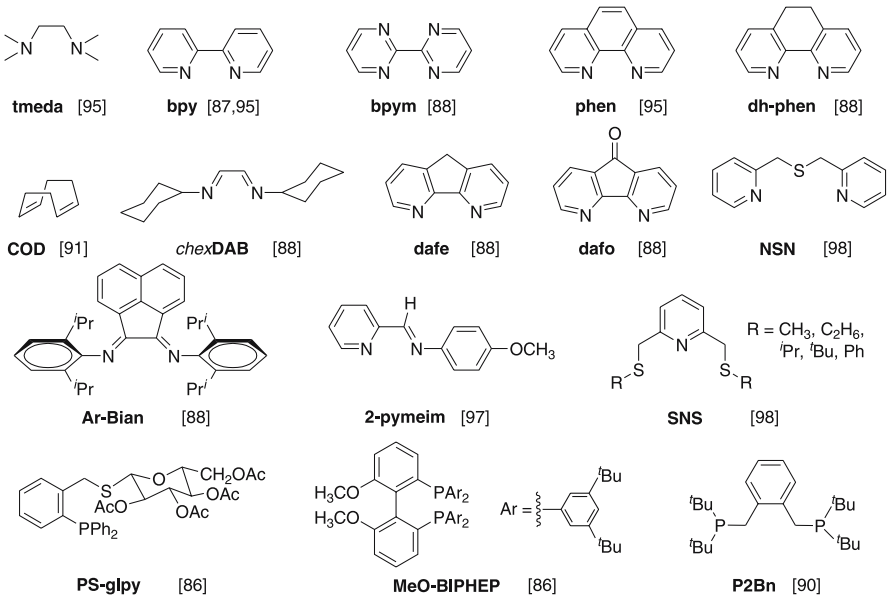


Chart 3 Examples of chelating ligands that form quinone complexes of Pd [references in brackets]

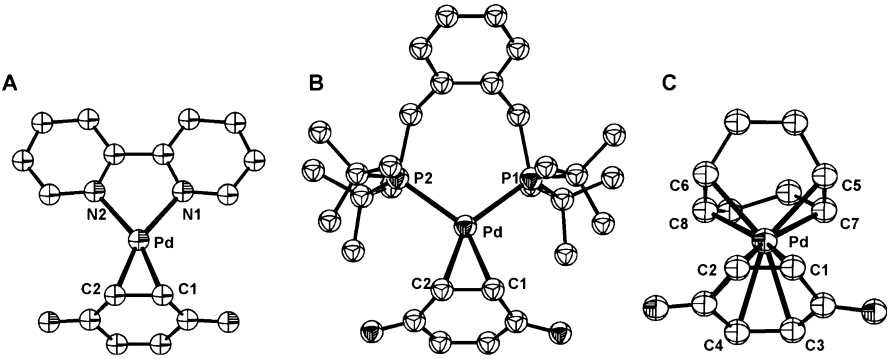
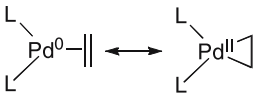


Fig. 2 ORTEP of (bpy)Pd(η^2-BQ) (**9**) (P2Bn)Pd(η^2-BQ) (**10**), and (COD)Pd(BQ) (**11**). Hydrogen atoms have been omitted for clarity

Based on X-ray crystallographic data, the coordination geometry of Pd–quinone complexes can be described as trigonal or square planar, depending on the preferred resonance structure, Pd^0–alkene versus Pd^{II}–metallacyclopropane (Eq. 13). X-ray crystal structures of (bpy)Pd(BQ), **9** [87], and (P2Bn)Pd(BQ), **10** [90] (Fig. 2) reveal that the C = C bond in these complexes is elongated significantly (1.423(6) and 1.425(10) Å for **9** and **10**, respectively) with respect to free BQ (1.33 Å) [99]. This observation is consistent with substantial Pd → alkene back-bonding and a palladium oxidation state that lies between 0 and + 2 (Eq. 13). The crystal structure of (COD)Pd(BQ), **11** [91], reveals a tetrahedral coordination environment in which both alkene fragments of BQ are coordinated to Pd. The cyclooctadiene ligand competes with BQ for π-back-bonding electron density, and, therefore, the C = C bond lengths are considerably shorter (1.373(14) Å) than those in **9** and **10**.



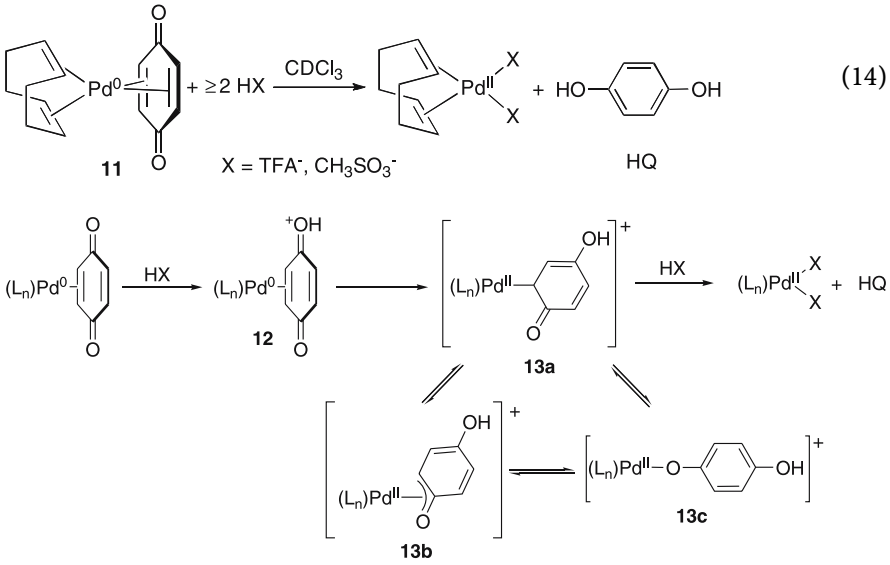
(13)

7 **8**

3.1.2 Mechanism of Palladium(0) Oxidation by Benzoquinone

The oxidation of Pd^0 by BQ to form Pd^{II} and hydroquinone requires two proton equivalents (Scheme 2). In order to probe the BQ-mediated oxidation of Pd^0, Bäckvall and coworkers investigated the reaction of (COD)Pd(BQ), **11**, with different Brønsted acids, including AcOH, CF_3CO_2H (TFAH), and CH_3SO_3H (Eq. 14) [100]. These acidic reagents possess different pK_a values, and only the strongest acid, CH_3SO_3H, is capable of reacting with **11** in

2 : 1 stoichiometry to yield hydroquinone. The reactions with AcOH and TFAH require excess acid (10 equiv) to achieve quantitative formation of hydroquinone and Pd^{II}. Addition of only two equivalents of acetic acid to BQ complex **11** yields the protonated BQ adduct **12** (Scheme 4). Although no direct evidence was obtained for oxallyl intermediates of the type **13a–c** (Scheme 4), these species represent probable intermediates in the conversion of **12** to $Pd^{II}X_2$ and hydroquinone (Scheme 4).



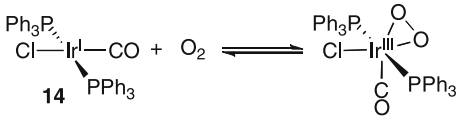
(14)

Scheme 4 Mechanism of benzoquinone/acid-promoted oxidation of palladium(0)

3.2 Palladium(0) Oxidation by Dioxygen

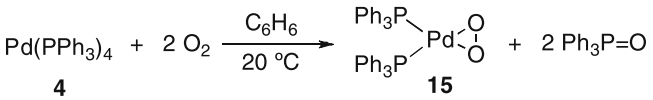
3.2.1 Palladium–Dioxygen Complexes

The reaction of dioxygen with transition metal complexes has stimulated the curiosity of scientists for decades. Seminal studies by Vaska in the 1960s revealed that dioxygen coordinates reversibly to the the Ir^{I} center in $(Ph_3P)_2Ir(CO)Cl$, **14** (Eq. 15) [101–104]. Following this report, numerous groups reported dioxygen adducts of other late transition metals [105].



(15)

In 1966, Hagihara and coworkers reported that dioxygen oxidizes the phosphine ligands of $Pd(PPh_3)_4$, **4**, and they proposed the existence of a palladium–dioxygen intermediate [106]. The following year, the groups of Hiembach and Wilkinson independently reported isolation of $(Ph_3P)_2Pd(O_2)$, **15**, as the product of this Pd^0 oxygenation reaction (Eq. 16) [107, 108], although an X-ray crystal structure of **15** was determined only recently (see below) [109]. Chart 4 illustrates additional ligands for which peroxopalladium(II) complexes have been isolated and structurally characterized [110–115].



4 **15** (16)

X-ray crystal structures of three representative η^2-peroxopalladium(II) complexes are shown in Fig. 3. Each of these complexes exhibits pseudo-square-planar geometry in which the dioxygen moiety is coplanar with the two donor ligands. The O – O bond lengths in each of the structurally characterized $Pd(\eta^2\text{-}O_2)$ complexes (Table 1) are elongated relative to dioxygen and superoxide (O_2^-) and approach the value for hydrogen peroxide (Table 2). In addition, the O – O vibrational frequencies (Table 1) confirm the highly reduced nature of the O_2 fragment. The O – O bond lengths and vibrational frequencies of transition metal–dioxygen complexes have been shown to correlate with the extent of dioxygen reduction [116]. These characterization data justify the description of these complexes as peroxopalladium(II) species.

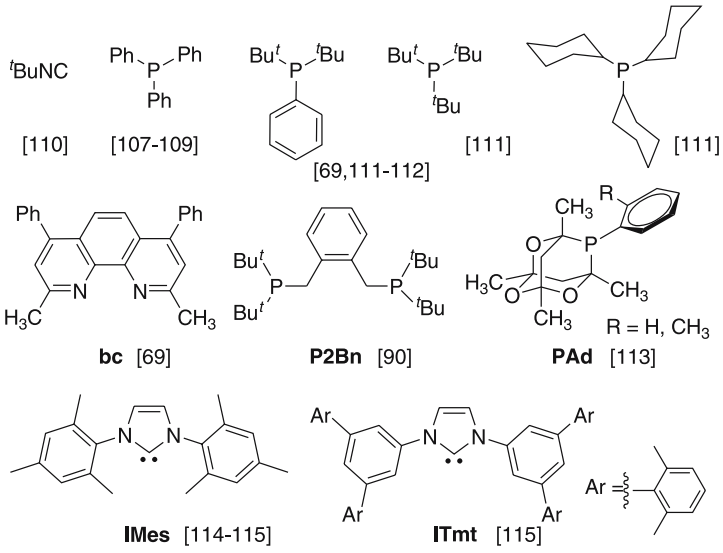


Chart 4 Ligands that form $(L_n)Pd(\eta^2 - O_2)$ complexes [references in brackets]

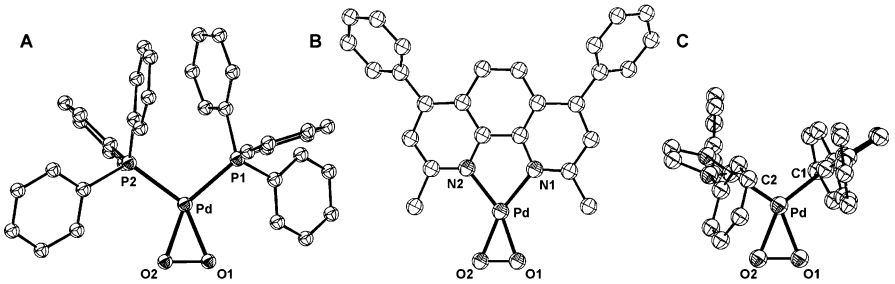


Fig. 3 ORTEP of $(Ph_3P)_2Pd(\eta^2\text{-}O_2)$, **15**, (bc)$Pd(\eta^2\text{-}O_2)$, **16**, and $(IMes)^2Pd(\eta^2\text{-}O_2)$, **17**. Hydrogen atoms have been omitted for clarity

Table 1 Available structural and infrared spectroscopic data for $(L_n)Pd^{II}(\eta^2\text{-}O_2)$ complexes

Complex (ligand[a])	O – O (Å)	$\nu_{O\text{-}O}$ (cm^{-1})	Refs.
18 (^{t}Bu$_2$PhP)	1.37(2)	915	[112]
	1.412(4)		[69]
19 (PAd-*o*Tol)	1.412(2)	–	[113]
20 (PAd-Ph)	1.413(3)	–	[113]
16 (bc)	1.415(15)	891	[69]
15 (PPh_3)	1.422(3)	885	[109]
21 (P2Bn)	1.443(3)	–	[90]
17 (IMes)	1.443(2)	868	[114]
22 (ITmt)	1.479(11)	–	[115]

[a] For abbreviations, see Chart 3

Table 2 Structural and infrared spectroscopic data for dioxygen species [117]

	Bond length (Å)	$\nu_{O\text{-}O}$ (cm^{-1})
O_2	1.21	1580
O_2^-	1.33	1097
O_2^{2-}	1.49	802

Early studies of these complexes focused primarily on the investigation of their oxygen-atom-transfer reactivity. Relatively little success was achieved, however. The peroxo fragments in these complexes exhibit nucleophilic character, and, therefore, they are generally ineffective oxidants for reactions with synthetically interesting electron-rich substrates such as alkenes and sulfides. Most of the known reactivity involves electrophilic substrates that, in many cases, insert into the Pd – O bond of peroxopalladium(II) species (Fig. 4) [105, 118].

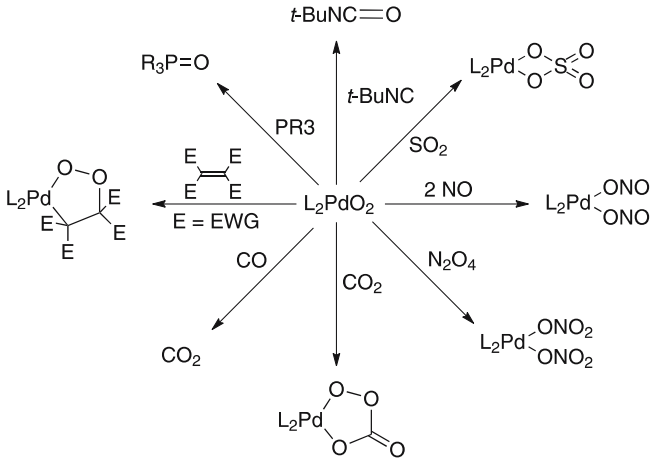
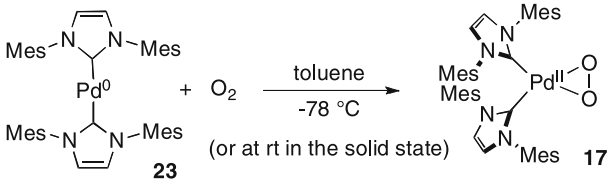


Fig. 4 Known reactions of $(L_n)Pd(\eta^2\text{-}O_2)$ complexes

3.2.2 Mechanism of Palladium(0) Oxidation by Dioxygen

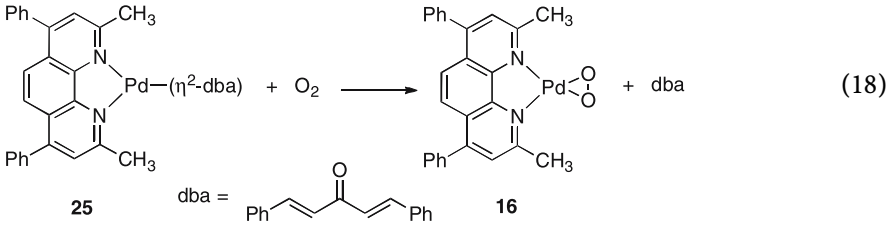
Interest in peroxopalladium(II) complexes has returned in recent years. Research efforts have shifted away from the oxygen-atom-transfer reactivity of these complexes toward their role in "oxidase"-like reactions depicted in Scheme 2. The success of recent Pd-catalyzed aerobic oxidation reactions is linked to the identification of oxidatively robust ancillary ligands that stabilize Pd^0 to prevent catalyst decomposition and promote efficient oxygenation of Pd^0.

Several studies in recent years have provided fundamental insights into the reactions between molecular oxygen and Pd^0 complexes bearing catalytically relevant ligands. *N*-Heterocyclic carbenes (NHCs) represent a promising ligand class for Pd-catalyzed oxidation reactions [52, 54, 71, 73, 119, 120] (see the chapter by T. Strassner, in this volume). The NHC–Pd^0 complex $(IMes)_2Pd^0$, **23**, reacts with molecular oxygen (Eq. 17) very rapidly in solution (within the solution mixing time at – 78 °C) as well as in the solid state [114]. A similar solid-state reaction with dioxygen was subsequently reported for the related Pd^0 complex, $(ITmt)_2Pd^0$, **24** (Chart 4) [115]. These observations suggest that direct addition of O_2 to a Pd^0 center can be extremely facile.



(17)

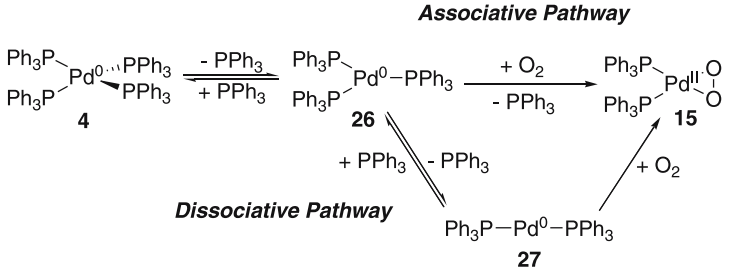
One of the first fundamental studies of Pd^0 oxygenation focused on the reactivity of (bc)Pd(dba) (bc = bathocuproine, dba = dibenzylideneacetone), **25** [69], a model Pd^0 complex based on catalysts reported earlier by coworkers at Enichem (Eq. 18) [121]. Mechanistic studies reveal that dioxygen reacts via associative displacement of the η^2-bound alkene ligand. The reaction exhibits a simple bimolecular rate law (rate = k[(bc)Pd(dba)]·pO_2) and a large negative entropy of activation ($\Delta S^{\ddagger}$ =– 43 e.u.). In contrast to the fast rate observed for the oxygenation of the *N*-heterocyclic carbene complexes noted above, this reaction requires 30–40 min to reach completion at room temperature ([Pd] = 220 mM, $pO_2 = 1$ atm). The electron-deficient dba ligand reduces electron density at the Pd^0 center and causes it to be less reactive with molecular oxygen.



(18)

A study of $Pd(PPh_3)_4$, **4**, reported recently by Roth and coworkers, reveals yet another mechanistic pathway for Pd^0 oxygenation [122]. Complete dissociation of one PPh_3 ligand from Pd^0 occurs in solution to produce a three-coordinate palladium(0) species, **26**. Kinetic studies reveal that **26** reacts with dioxygen via parallel associative and dissociative pathways (Scheme 5). The latter dissociative pathway results in the formation of the two-coordinate complex **27**, which undergoes very rapid reaction with dioxygen in a manner directly analogous to that of the well-defined two-coordinate NHC complexes **23** and **24**.

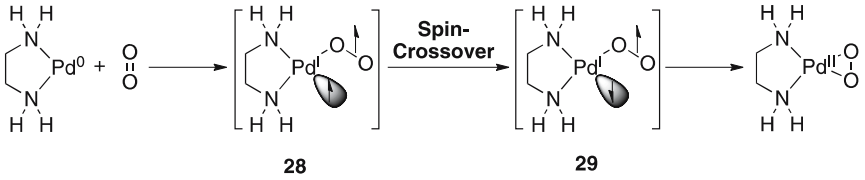
In order to probe electronic structural issues in the Pd^0 oxygenation reaction, Landis, Stahl, and coworkers performed a computational study on



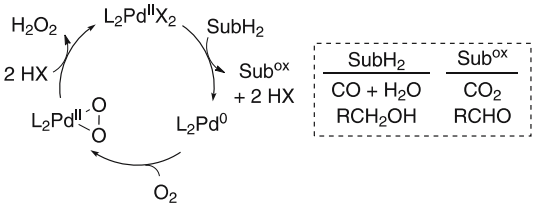
Scheme 5 Mechanism of oxygenation of $Pd(PPh_3)_4$ proceeds by competitive associative and dissociative pathways

the reaction of dioxygen with a singlet Pd^0 fragment bearing the chelating nitrogen ligand, ethylene diamine [123]. The results of this study indicate that triplet dioxygen initially approaches the palladium center with an end-on trajectory. Charge transfer from Pd^0 to O_2 results in formation of a triplet biradical η^1-superoxopalladium(I) species, **28** (Scheme 6) [124]. Coordination of dioxygen to the Pd center reduces the electronic exchange interaction between the unpaired spins, and the energy difference between the triplet and singlet energy surfaces (~ 3 kcal/mol) is significantly smaller than that of free dioxygen (23 kcal/mol). At short Pd – O distances, these surfaces converge (~ 2.2 Å) and triplet–singlet spin crossover occurs to enable formation of the second Pd – O bond. Estimation of the spin-crossover rate based on Pd spin–orbit coupling ($\sim 10^{12}$ s^{-1}) reveals that intersystem crossing will have little influence on the rate of the overall reaction. Once the molecule progresses to the singlet surface, it collapses to the stable η^2-peroxo structure.

Addition of Brønsted acids, HX, to $L_2Pd(O_2)$ complexes forms hydrogen peroxide and L_2PdX_2. This process, which completes the stepwise sequence for dioxygen-promoted oxidation of Pd^0 to Pd^{II} [125], was first observed by Kamiya and coworkers, who investigated the reaction of acetic acid with $(Ph_3P)_2Pd(O_2)$, **15** [126]. Analogous reactivity has been exploited to achieve the Pd-catalyzed synthesis of hydrogen peroxide from dioxygen in the presence of a sacrificial reductant (i.e., CO, RCH_2OH; Scheme 7) [121, 127–132]. Biphasic reaction conditions must be used to achieve significant buildup of H_2O_2 because, under normal reaction conditions, H_2O_2 undergoes rapid disproportionation into dioxygen and water (Eq. 19) [59]. The mechanism of



Scheme 6 Mechanistic insight into the reaction of $(en)Pd^0$ with triplet O_2 based on density functional theory (DFT)

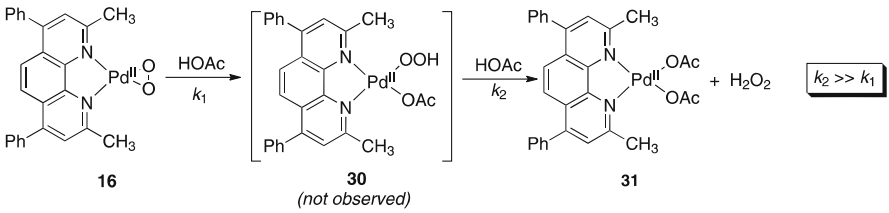


Scheme 7 Catalytic cycle for the synthesis of hydrogen peroxide from dioxygen

this "catalase"-like activity is not presently known; however, this reaction has important practical consequences because it permits all four oxidizing equivalents in dioxygen to be used in substrate oxidation.

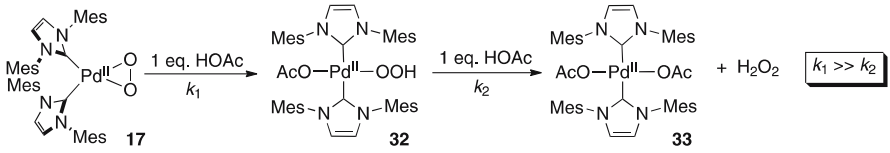
$$H_2O_2 \xrightarrow{[Pd]} 1/2\ O_2 + H_2O \qquad (19)$$

In order to gain a better understanding of the overall Pd^0 oxidation sequence, Stahl and coworkers recently investigated the protonolysis of two different peroxo Pd^{II} complexes. In the first study, acetic acid was added to (bc)$Pd(O_2)$, **16** (Scheme 8) [69]. The presumed intermediate hydroperoxo Pd^{II} complex, **30**, does not build up in this reaction. If only one equivalent of acetic acid is added, 0.5 equivalents of the diacetate complex, **31**, is formed together with 0.5 equivalents of unreacted **16**. This result implies that the second protonation step proceeds much more rapidly than the first.



Scheme 8 Protonolysis of (bc)$Pd(O_2)$, **16**, with acetic acid

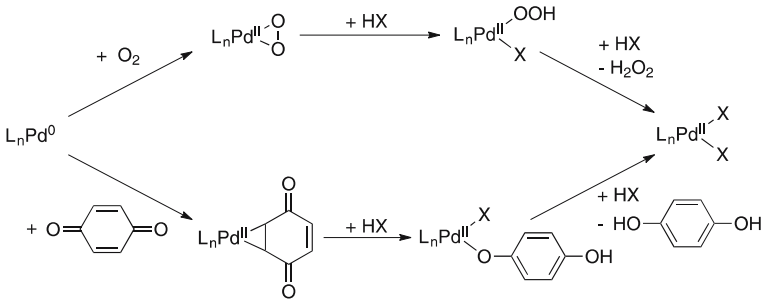
In a second study, the protonolysis of $(IMes)_2Pd(O_2)$, **17**, was investigated [114]. Addition of one equivalent of acetic acid generates the hydroperoxo-Pd^{II} complex, **32**, which has undergone *cis–trans* isomerization in the protonolysis step (Scheme 9). The ability to isolate and characterize this complex reveals that protonolysis of the second Pd – O bond is much slower than the first. Addition of a second equivalent of acetic acid forms the diacetate complex, **33**, but only after 3 days at room temperature. The systematic studies summarized in Eqs. 17 and 18 and Schemes 8 and 9 reveal the strong influence of ancillary ligands on fundamental rate constants associated with aerobic oxidation of Pd^0 to Pd^{II}. Similar effects undoubtedly will impact the success of Pd-catalyzed aerobic oxidation reactions.



Scheme 9 Model study of the sequential protonation of $(IMe)_2Pd(O_2)$, **17**

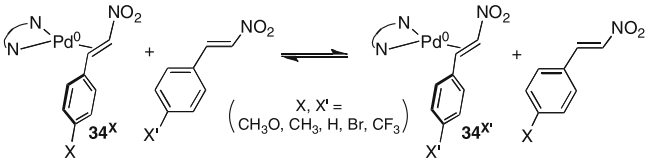
3.3 Relationship Between Reactions of Dioxygen and Alkenes (Including Benzoquinone) with Palladium(0)

The results outlined above highlight numerous similarities between dioxygen- and BQ-mediated oxidation of palladium(0). The key steps in the respective pathways appear virtually identical (Scheme 10). Recent studies of the reactivity of dioxygen and electron-deficient alkenes with Pd^0–alkene complexes reinforce these similarities.



Scheme 10 Mechanistic similarity between the oxidation of Pd^0 by dioxygen and benzoquinone

The oxygenation of (bc)Pd(dba), **25**, to form (bc)Pd(O_2), **16** (Sect. 3.2.2, Eq. 18), was found to proceed by an associative-substitution mechanism that closely resembles alkene exchange reactions at Pd^0 [133–135]. In order to compare these reactions directly, Stahl and coworkers investigated both oxygenation and alkene exchange reactions with a uniform class of Pd^0 complexes, (bc)$Pd^0(ns^X)$, $\mathbf{34}^X$ (ns^X = *para*-substituted *trans*-β-nitrostyrene; X = CH_3O, CH_3, H, Br, CF_3, NO_2) (Eqs. 20 and 21) [70, 136]. Mechanistic data confirm that both reactions proceed via associative pathways (e.g., both reactions exhibit a bimolecular rate law and have large negative entropies of activation).



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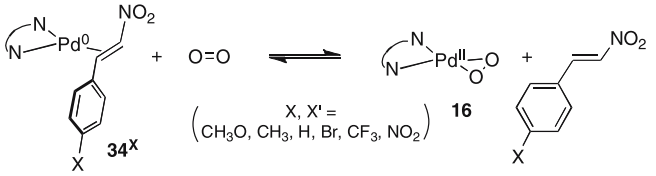


(21)

Hammett studies probing the correlation between the reaction rate and *para* substituents of the nitrostyrene ligand (or substrate) provided key insights into the similarity between these reactions. In the oxygenation reaction (Eq. 21), more-electron-rich nitrostyrene ligands promote faster reaction with O_2 [137]. This result is expected because the Pd^0 center is formally oxidized to Pd^{II} in the reaction, and more-electron-rich metal centers should undergo more facile oxidation. In alkene exchange reactions, the Pd center does not change oxidation state; however, a similar electronic trend is observed. The maximum substitution rate occurs in the reaction between an electron-deficient alkene and a Pd^0 complex bearing an electron-rich nitrostyrene ligand. These results indicate that *both* oxygenation and alkene exchange follow "oxidative" trajectories, in which the Pd^0 center is formally oxidized in the transition state [70, 136]. Density functional theory calculations support this conclusion and reveal the orbital picture shown in Fig. 5 [136]. Both reactions involve charge transfer from the electron-rich Pd^0 center to the π^* orbital of the incoming ligand. A similar analysis should apply to the reaction of Pd^0 with BQ, which is also an electron-deficient alkene.

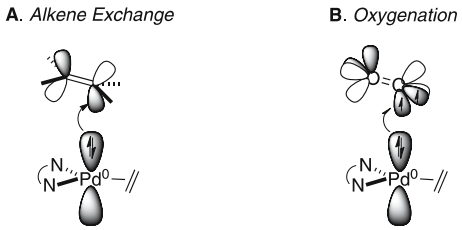
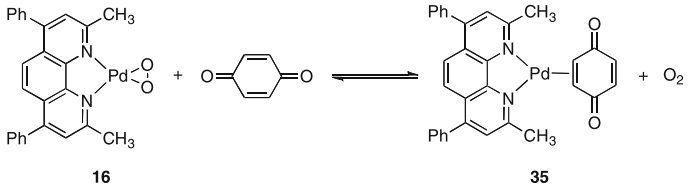


Fig. 5 Illustration of the "oxidative" trajectory for alkene exchange and oxygenation of Pd^0–alkene complexes

Further studies revealed that electron-deficient alkenes are capable of displacing O_2 from a peroxopalladium(II) complex. The reaction of nitrostyrene derivatives with (bc)Pd(O_2) results in quantitative displacement of dioxygen and formation of the (bc)Pd(ns^X) complex (i.e., the reverse reaction in Eq. 21) [138]. Moreover, preliminary results reveal that dioxygen and BQ undergo reversible exchange at a bathocuproine-coordinated Pd center (Eq. 22) (Popp BV, Stahl SS, unpublished results). This observation is the most direct experimental result to date that establishes the similar reactivity of dioxygen and BQ with palladium.



16 35 (22)

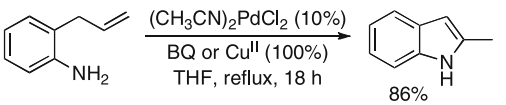
4
Palladium-Catalyzed Oxidation Reactions with Benzoquinone and Dioxygen as Stoichiometric Oxidants

The previous sections illustrate the close relationship between the fundamental reactions of molecular oxygen and BQ with well-defined palladium complexes. The insights from these studies complement those obtained from catalytic reactions. The following sections highlight catalytic reactions for which both dioxygen and BQ have been employed as stoichiometric oxidants, and the results suggest these oxidants may be more similar than previously appreciated. Rather than provide a comprehensive review of Pd-catalyzed oxidation reactions, selected examples are presented that highlight the use of both dioxygen and BQ. Reaction classes include oxidative hetero- and carbocyclization reactions of alkenes, intermolecular oxidative functionalization of alkenes (C – N and C – C bond formation), dehydrosilylation of silyl enol ethers (Saegusa oxidation), and allylic C – H acetoxylation.

4.1
Oxidative Hetero- and Carbocyclization Reactions of Alkenes Bearing Tethered Nucleophiles

4.1.1
Heterocyclization Reactions

Palladium-catalyzed, Wacker-type oxidative cyclization of alkenes represents an attractive strategy for the synthesis of heterocycles [139]. Early examples of these reactions typically employed stoichiometric Pd and, later, cocatalytic palladium/copper [140–142]. In the late 1970s, Hegedus and coworkers demonstrated that Pd-catalyzed methods could be used to prepare nitrogen heterocyles from unprotected 2-allylanilines and tosyl-protected amino olefins with BQ as the terminal oxidant (Eqs. 23–24) [143, 144]. Concurrently, Hosokawa and Murahashi reported that the cyclization of allylphenol substrates can be accomplished by using a palladium catalyst with dioxygen as the sole stoichiometric reoxidant (Eq. 25) [145].



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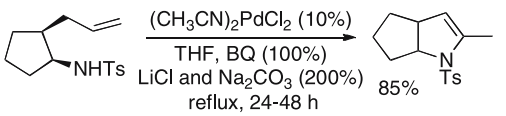

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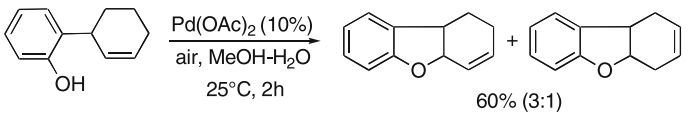
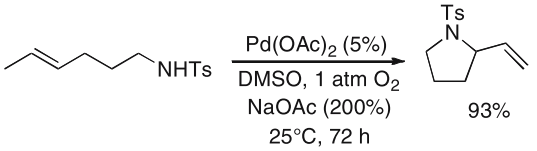


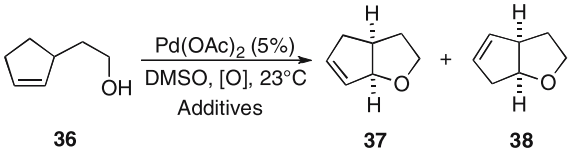
(25)

In the 1990s, the groups of Hiemstra and Larock independently discovered that $Pd(OAc)_2$ in DMSO serves as an effective catalyst for direct dioxygen-coupled catalytic turnover, and this catalyst system was applied widely to oxidative heterocyclization reactions. Examples include the addition of carboxylic acid, phenol, alcohol, formamide, and sulfonamide nucleophiles to pendant olefins (Eq. 26) [146–149].



(26)

In a subsequent study of oxygen heterocyclization, Andersson et al. investigated various catalyst reoxidation conditions with the $Pd(OAc)_2$/DMSO catalyst system (Eq. 27, Table 3) [150]. Several conditions result in high substrate conversion to the product, including the use of BQ, BQ with methanesulfonic acid, and molecular oxygen, with and without copper(II) salts as a cooxidant. Only the aerobic methods enable formation of the product **37** with high regioselectivity. The presence of a copper cocatalyst enhances the rate but is not necessary for catalysis.



36 **37** **38**

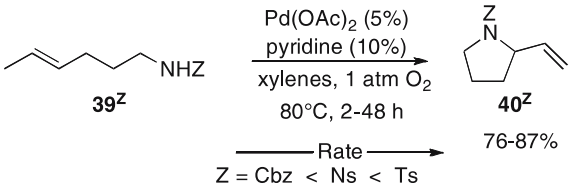
(27)

Table 3 Terminal oxidant and additive screen for Eq. 27

Entry	[O]	Additives	Time (h)	Conversion (%)	**37 : 38**
1	BQ	None	24	> 95	76 : 24
2	BQ	10 mol % $MeSO_3H$	0.5	> 95	66 : 34
3	O_2	10 mol % $Cu(OAc)_2$	5	> 95	> 95 : 5
4	O_2	2 equiv. $Cu(OAc)_2$	2	> 95	> 95 : 5
5	O_2	None	7	> 95	> 95 : 5

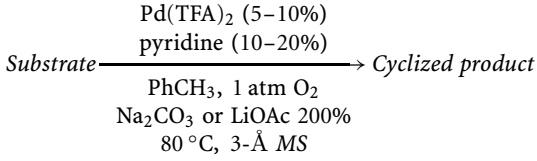
The $Pd(OAc)_2$/pyridine catalyst system, initially developed for aerobic alcohol oxidation [41, 42], was shown by Stahl and coworkers to be highly

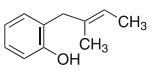
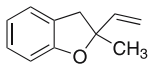
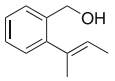
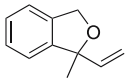
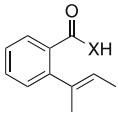
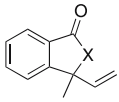
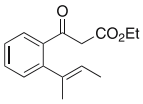
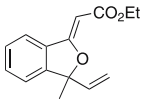
effective for the oxidative synthesis of nitrogen heterocycles. Molecular oxygen is the sole oxidant for the Pd catalyst in this reaction (Eq. 28) [151]. The nitrogen nucleophile must possess an electron-withdrawing group, and the identity of this group has a significant effect on the reaction time. The tosyl-protected substrate (**39^{Ts}**) proceeds to completion in 2 h, whereas the Cbz substrate requires 48 h under comparable conditions. Stoltz and coworkers subsequently employed $Pd(O_2CR)_2$/pyridine-based catalysts for additional heterocyclization reactions [152, 153]. Several oxygen and nitrogen functional groups undergo cyclization onto tethered alkenes in good to excellent yields (Table 4). Trifluoroacetate is more effective than acetate as an anionic ligand in these reactions.



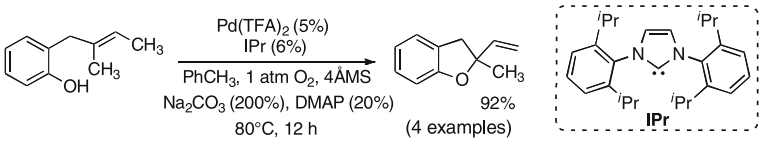
(28)

Table 4 Substrate scope for direct dioxygen-coupled heterocyclization using the Pd/pyridine catalyst system



Entry	Substrate	Product		Time	Yield (%)
1				20 min	95
2				3 h	87
3			X = O	8 h	90
4			X = NTs	8 h	88
5			X = NOBn	4 h	82
6				48 h	63

N-Heterocyclic carbenes (NHCs) are also useful ancillary ligands for direct dioxygen-coupled Pd-catalyzed oxidation reactions [119]. Sigman described $(NHC)Pd(O_2CR)_2$ catalysts for aerobic alcohol oxidation [54, 71], and, more recently, related catalysts have been used by the groups of Muñiz and Stahl in the oxidative heterocyclization of alkenyl phenols and tosylamides, respectively (Eqs. 29 and 30) [154, 155]. These results highlight the potential of NHC ligands to facilitate the direct reaction between dioxygen and Pd^0 under catalytic conditions (Eq. 17).



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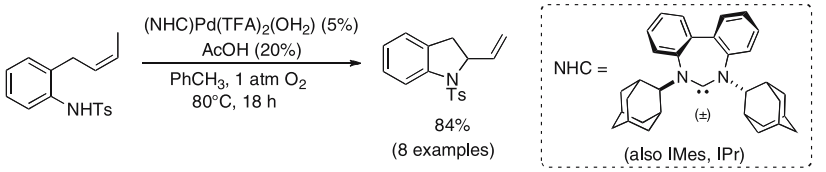
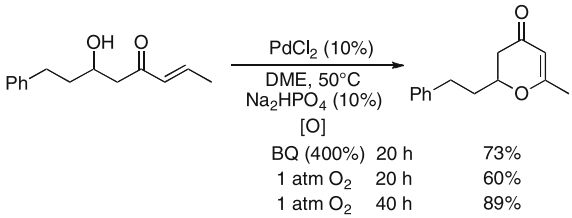


(30)

Gouverneur and coworkers showed that α,β-unsaturated esters can be cyclized in good to excellent yields (Eq. 31) [156]. Optimization of the reaction conditions revealed that four equivalents of BQ were necessary to achieve good yields (73%). Aerobic conditions, without a copper cocatalyst, proved to be superior, resulting in 89% yield over extended reaction times. No cyclization product was observed with the Pd/pyridine catalyst system described above.

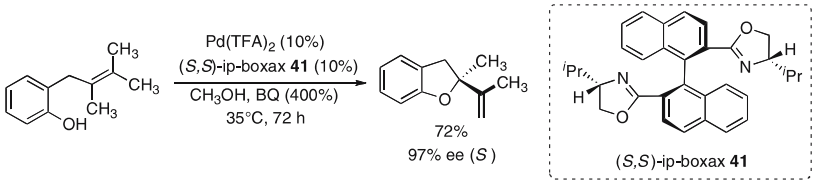


(31)

In addition to the development of new catalysts and reaction conditions for aerobic oxidative heterocyclization, considerable effort has been directed toward asymmetric transformations. Hosokawa and Murahashi reported the first example of asymmetric Pd-catalyzed oxidative heterocyclization reactions of this type [157, 158]. They employed catalytic $[(+)\text{-}(\eta^3\text{-pinene})Pd^{II}(OAc)]_2$ together with cocatalytic $Cu(OAc)_2$ for the cyclization of 2-allylphenol substrates; however, the selectivity was relatively poor ($\leq$ 26% ee).

Highly enantioselective transformations have been achieved recently with the use of chiral chelating nitrogen ligands for Pd^{II}. Both BQ and molecular oxygen have been used as oxidants in these reactions. Uozumi and Hayashi

reported one of the most successful examples, which features C_2-symmetric bis(oxazoline) ligands based on a 1,1′-binaphthyl framework (e.g., (*S*,*S*)-ip-boxax, **41**) (Eq. 32) [159–161]. The use of weakly coordinating anionic ligands, such as trifluoroacetate (TFA) and BF_4^-, benefits both catalytic activity and enantioselectivity. Sasai and coworkers achieved an enantioselective tandem cyclization of alkenyl alcohols by utilizing a similar catalyst system with a spirocyclic bis(isoxazoline) ligand, (*M*,*S*,*S*)-ip-SPRIX **42** (Eq. 33) [162]. Both of these reactions are optimal with methanol as the solvent or cosolvent, and they employ four equivalents of BQ as the oxidant. The yields can be enhanced if the reactions containing BQ are performed under an oxygen atmosphere [161]; however, the use of dioxygen alone was not described.



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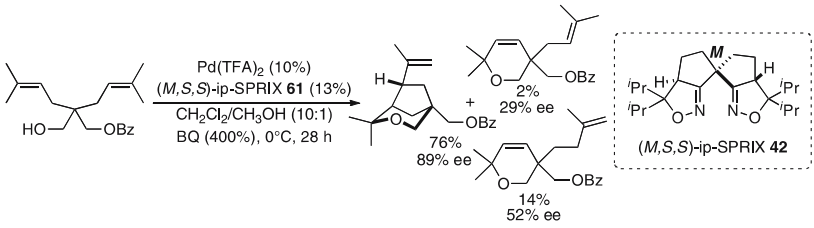
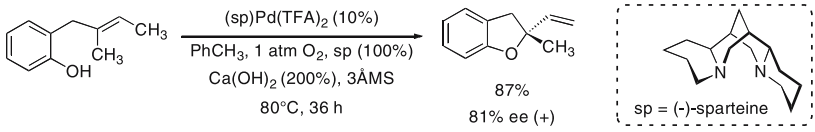


(33)

Analogous reactions have been achieved recently with molecular oxygen as the sole stoichiometric oxidant by employing (–)-sparteine (sp) as the chiral ligand [153, 163]. Stoltz and coworkers demonstrated asymmetric oxidative cyclization of a 2-allylphenol substrate (Eq. 34). A stoichiometric quantity of the sp ligand was necessary, perhaps because it also serves as a base in the reaction. Enantioselective oxidative tandem cyclization of 2-allyl anilides was achieved by Yang and coworkers (Eq. 35). The reactions proceed exclusively to the five-membered exocyclization products.



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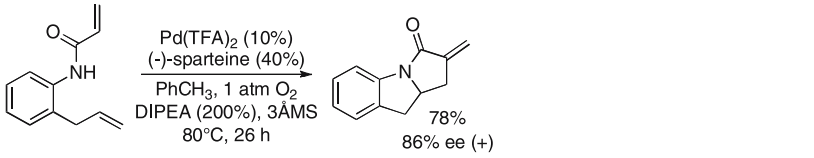
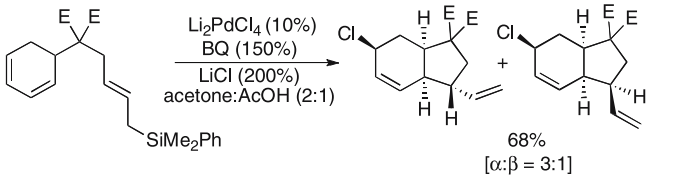


(35)

4.1.2
Carbocyclization Reactions

The intramolecular addition of carbon nucleophiles to alkenes has received comparatively little attention relative to heterocyclization reactions. The first examples of Pd-catalyzed oxidative carbocyclization reactions were described by Bäckvall and coworkers [164–166]. Conjugated dienes with appended allyl silane and stabilized carbanion nucleophiles undergo 1,4-carbochlorination (Eq. 36) and carboacetoxylation (Eq. 37), respectively. The former reaction employs BQ as the stoichiometric oxidant, whereas the latter uses O_2. The authors do not describe efforts to use molecular oxygen in the reaction with allyl silanes; however, BQ was cited as being unsuccessful in the reaction with stabilized carbanions. Benzoquinone is known to activate π-allyl-Pd^{II} intermediates toward nucleophilic attack (see below, Sect. 4.4). In the absence of BQ, β-hydride elimination occurs to form diene **43** in competition with attack of acetate on the intermediate π-allyl-Pd^{II} species to form the 1,4-addition product **44**.



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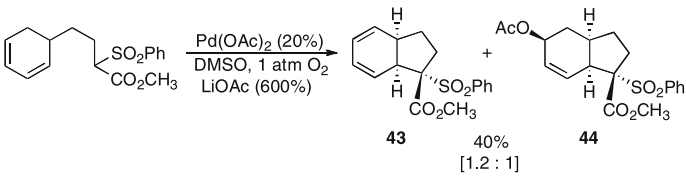
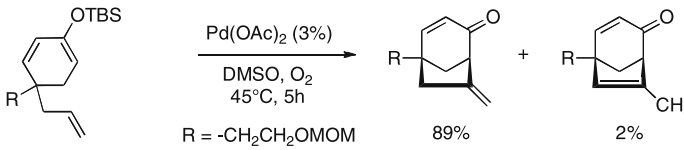


(37)

Toyota, Ihara, and coworkers demonstrated that silyl enol ethers undergo Pd^{II}-promoted intramolecular nucleophilic attack on alkenes [18]. Although early examples required stoichiometric Pd^{II} [167], they have also shown that $Pd(OAc)_2$ in DMSO is an effective catalyst in the presence of an aerobic atmosphere (Eq. 38) [168–170]. The reaction is proposed to proceed through an oxo-π-allyl intermediate that can undergo competitive alkene insertion or β-hydride elimination (Scheme 11). The latter reaction is the basis for the synthetically useful conversion of silyl enol ethers to α,β-unsaturated carbonyl compounds (see below). Efforts to use BQ as an oxidant were not described.



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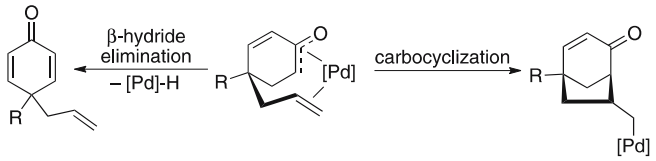
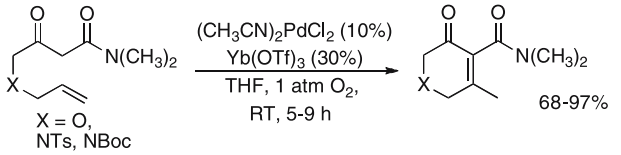


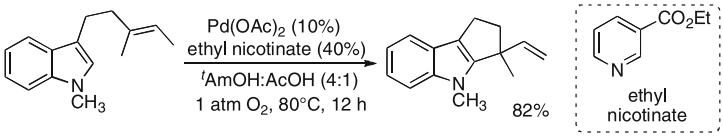
Scheme 11 Alternative fates of the oxo-π-allylpalladium(II) intermediate in the oxidative carbocyclization of silyl enol ether substrates

Widenhoefer has developed methods for Pd-catalyzed addition of 1,3-dicarbonyl nucleophiles to alkenes [171–173]. Most of these reactions employ stoichiometric copper as the oxidant; however, Yang and coworkers recently reported a modified procedure that employs cocatalytic lanthanide Lewis acids to achieve direct dioxygen-coupled turnover (Eq. 39) [174]. The Lewis acid is thought to activate the carbon nucleophile, β-keto amide, toward attack on the tethered alkene.



(39)

Oxidative carbocyclization reactions can also be achieved by an oxidative Heck strategy in which an alkene inserts into an intermediate Pd–aryl bond formed by direct palladation of an arene. Stoltz and coworkers recently demonstrated such reactions with electron-rich arenes that possess tethered alkenes. Successful substrates include indoles and oxygen-substituted arenes (Eqs. 40 and 41) [175, 176]. The catalyst is a variant of the $Pd(OAc)_2$/pyridine system in which pyridine is replaced by the electron-deficient analog ethyl nicotinate. Molecular oxygen was the only oxidant used for the indole reactions; however, both BQ and dioxygen were successful in the reactions with oxygenated arenes (Eq. 41). Subsequent optimization of the latter reactions permitted yields as high as 80% by using BQ as the oxidant with cocatalytic NaOAc.



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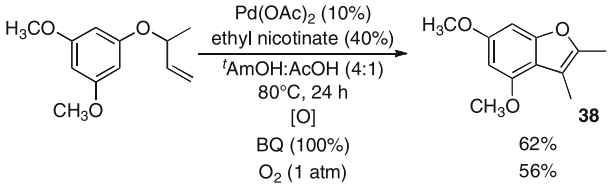


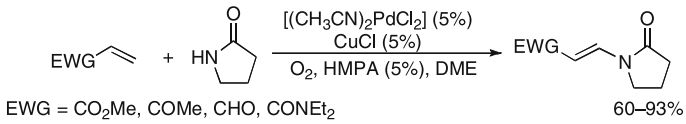
(41)

4.2
Intermolecular Oxidative Functionalization of Alkenes

4.2.1
Carbon–Nitrogen Bond Formation

Palladium-catalyzed addition of oxygen nucleophiles to alkenes dates back to the Wacker process and acetoxylation of ethylene (Sects. 1 and 2). In contrast, catalytic methods for intermolecular oxidative amination of alkenes (i.e., "aza-Wacker" reactions) have been identified only recently. Both O_2 and BQ have been used as oxidants in these reactions.

Hosokawa, Murahashi, and coworkers demonstrated the ability of Pd^{II} to catalyze the oxidative conjugate addition of amide and carbamate nucleophiles to electron-deficient alkenes (Eq. 42) [177]. Approximately 10 years later, Stahl and coworkers discovered that Pd-catalyzed oxidative amination of styrene proceeds with either Markovnikov or anti-Markovnikov regioselectivity. The preferred isomer is dictated by the presence or absence of a Brønsted base (e.g., triethylamine or acetate), respectively (Scheme 12) [178, 179]. Both of these reaction classes employ O_2 as the stoichiometric oxidant, but optimal conditions include a copper cocatalyst. More recently, Stahl and coworkers found that the oxidative amination of unactivated alkyl olefins proceeds most effectively in the absence of a copper cocatalyst (Eq. 43) [180]. In the presence of 5 mol % $CuCl_2$, significant alkene amination is observed, but the product consists of a complicated isomeric mixture arising from migration of the double bond into thermodynamically more stable internal positions.



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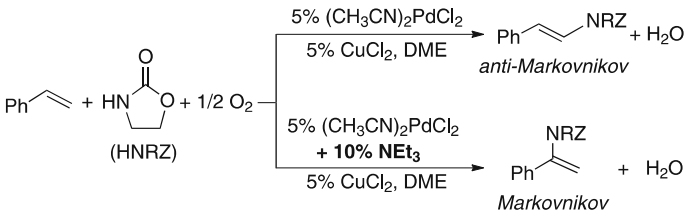
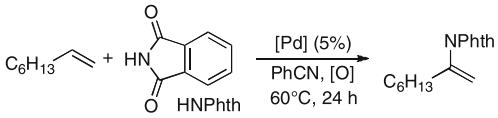


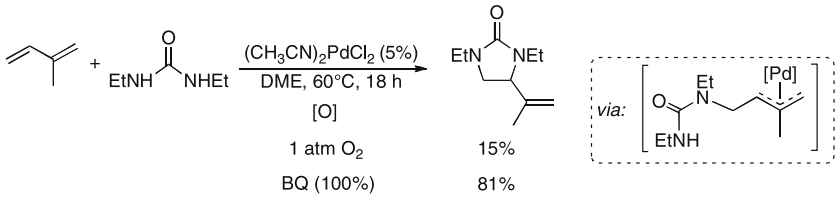
Scheme 12 Regioselective Pd-catalyzed oxidative amination of styrene



(43)

[Pd]	[O]	Yield (%)
$PdCl_2$	O_2 (1 atm)	17
	BQ (200%)	10
$Pd(OAc)_2$	**O_2 (1 atm)**	**81**
	BQ (200%)	10
$Pd(TFA)_2$	O_2 (1 atm)	4

Catalyst conditions very similar to those employed in Eq. 42 and Scheme 12 were used recently by Lloyd-Jones, Booker-Milburn, and coworkers to achieve Pd-catalyzed diamination of conjugated dienes with urea nucleophiles (Eq. 44) [181]. Both dioxygen and BQ were evaluated as oxidants, and BQ proved to be significantly more effective (Eq. 44). The beneficial effect of BQ probably arises from its ability to promote nucleophilic attack on the intermediate π-allyl palladium complex (see below, Sect. 4.4). This hypothesis is supported by the observation that the oxidative amination of styrene with urea, which does not undergo the second nucleophilic attack, proceeds equally effectively with both O_2 and BQ as the oxidant (Eq. 45).



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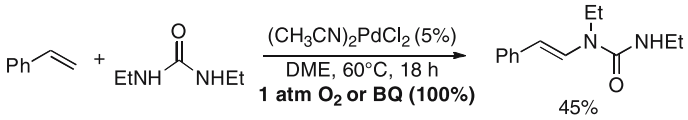
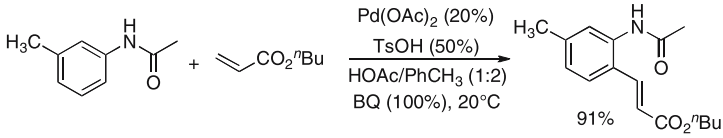


(45)

4.2.2 Carbon–Carbon Bond Formation

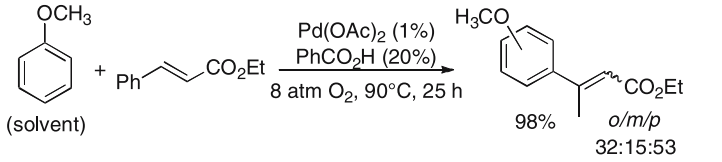
Palladium(0)-catalyzed cross-coupling of aryl halides and alkenes (i.e., the Heck reaction) is widely used in organic chemistry. "Oxidative Heck" reactions can be achieved by forming the Pd^{II}-aryl intermediate via direct palladation of an arene C – H bond. Intramolecular reactions of this type were described in Sect. 4.1.2, but considerable effort has also been directed toward the development of intermolecular reactions. Early examples by Fujiwara and others used organic peroxides and related oxidants to promote catalytic turnover [182–184]. This section will highlight several recent examples that use BQ or dioxygen as the stoichiometric oxidant.

Palladium(II) effects orthometalation of acetanilides to form the corresponding palladacycles [185]. De Vries, van Leeuwen, and coworkers exploited this reactivity to achieve regioselective oxidative coupling of acetanilides and *n*-butyl acrylate that proceeds efficiently with BQ as the stoichiometric oxidant (Eq. 46) [186]. The use of TsOH as an additive and acetic acid as a cosolvent significantly improves the results. Inferior results are observed with hydrogen peroxide or copper(II) acetate as the stoichiometric oxidant, but efforts to use molecular oxygen were not described.



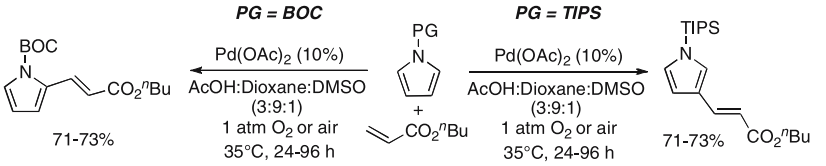
(46)

Jacobs and coworkers subsequently reported an aerobic method to achieve arene–alkene coupling in the absence of directing groups [187]. $Pd(OAc)_2$, dissolved in neat aromatic solvents (e.g., benzene, toluene, anisole), undergoes electrophilic activation of an aromatic C – H bond. Reaction of the aryl-Pd^{II} intermediate with electron-deficient alkenes yields Heck-type products. Various redox-active cocatalysts were investigated to promote dioxygen-coupled turnover, including $Mn(OAc)_3$, $Mn(acac)_2$, and $Co(OAc)_2$; however, the most effective condition simply features benzoic acid as a cocatalyst, allowing subsequent alkene insertion to yield Heck-type products. The use of 0.1 mol % $Pd(OAc)_2$ and 20 mol % benzoic acid results in 762 turnovers and a turnover frequency of 73 h^{-1} for the reaction in Eq. 47. The reactions proceed in high yield (typically > 90%) with respect to the alkene as the limiting reagent; however, all three regioisomers are generated.



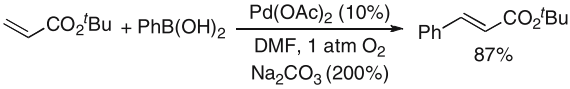
(47)

A regioselective example of aerobic oxidative coupling has been achieved by Gaunt and coworkers in the reaction of pyrroles with electron-deficient alkenes [188]. Selective functionalization of the C-2 or C-3 position of pyrroles is controlled by the identity of the nitrogen-protecting group. Groups with minimal steric bulk (e.g., BOC, Ts, Bn) lead to selective alkenylation at the C-2 position, whereas the sterically bulky group, TIPS, results in selective functionalization of the C-3 position (Eq. 48). The reactions proceed with air, pure O_2, or *t*BuOOBz as the oxidant.



(48)

Regioselective oxidative Heck coupling can also be accomplished by forming aryl-Pd^{II} species via transmetalation from arylboronic acids. This method was first developed by Jung and coworkers (Eq. 49) [189]. The aerobic reaction conditions are compatible with a range of electron-deficient alkenes and aryl boron sources. Subsequently, Larhed and coworkers employed a catalyst system featuring a bidentate nitrogen ligand (dmphen) and *N*-methyl morpholine (NMM), which exhibits higher turnover numbers (1% Pd^{II} catalyst) and generally improved yields (Eq. 50) [190–192].



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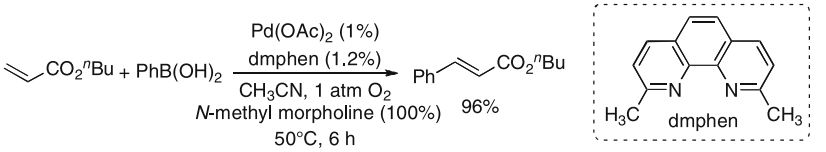
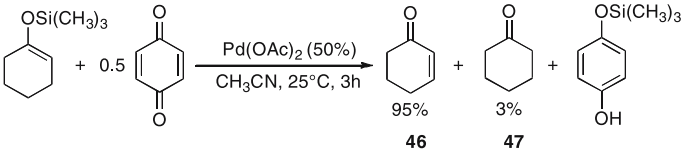


(50)

4.3
Dehydrosilylation of Silyl Enol Ethers

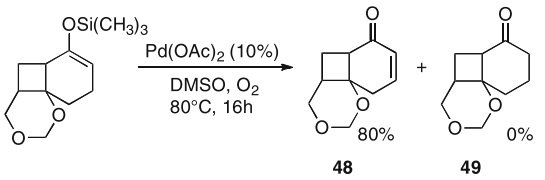
In 1978, Saegusa and coworkers discovered that silyl enol ethers can be converted into α,β-unsaturated ketones and aldehydes by Pd^{II} [193]. In the presence of 0.5 equivalents of BQ, substoichiometric $Pd(OAc)_2$ (0.5 equiv) effects nearly quantitative conversion of the substrate into product in acetonitrile (Eq. 51). Attempts to lower the catalyst loading further results in longer reaction times as well as increased yields of saturated carbonyl by-product, **47**.



(51)

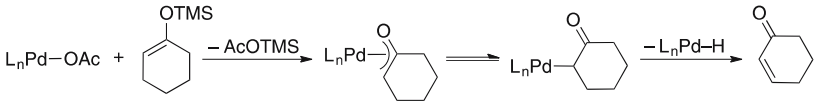
By using $Pd(OAc)_2$ in DMSO, Kraus, Larock, and coworkers developed a dioxygen-coupled catalytic procedure for this class of reactions (Eq. 52) [194]. Additives (e.g., exogenous base) were not beneficial in this reaction. Attempts to conduct the reaction in a solvent mixture of DMSO and H_2O (9 : 1) leads

to an equal ratio of the desired α,β-unsaturated ketone **48** and the saturated ketone by-product **49**. A number of other silyl enol ethers were shown to undergo catalytic dehydrosilylation under these reaction conditions.

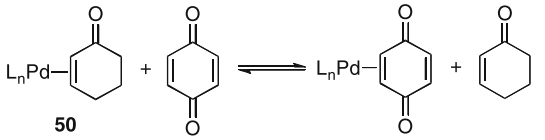


(52)

The Saegusa oxidation is believed to proceed through the mechanism shown in Scheme 13. An oxo-π-allyl intermediate can undergo β-hydride elimination to form a Pd^{II} hydride and the α,β-unsaturated product. Loss of H^+ from the Pd^{II} hydride will form Pd^0 that can be reoxidized by BQ or O_2. The difficulty in achieving efficient reoxidation of the Pd^0 catalyst might arise from strong coordination of the α,β-unsaturated product to the reduced metal center. Indeed, Mulzer et al. have isolated and crystallographically characterized a tetraolefin Pd^0 complex obtained from a Saegusa oxidation reaction [195]. Equilibrium reactions between the Pd^0–alkene complex **50** and BQ (Eq. 53) or dioxygen are reminiscent of the fundamental oxygenation reactions described above in Sect. 3.3.



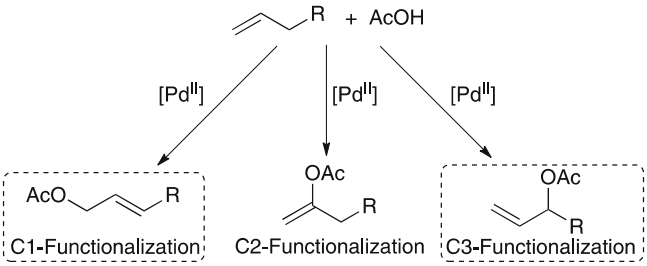
Scheme 13 Mechanism for the Saegusa oxidation reaction



(53)

4.4
Acetoxylation of Allylic C–H Bonds

The formation of vinyl acetate via the oxidative coupling of ethylene and acetic acid was among the earliest Pd-catalyzed reactions developed (Sect. 2) [19, 20]. Subsequent study of this reaction with higher olefins revealed that, in addition to C-2 acetoxylation, allylic acetoxylation occurs to generate products with the acetoxy group at the C-1 and C-3 positions (Scheme 14). The synthetic utility of these products underlies the substantial historical interest in these reactions, and both BQ and dioxygen have been used as oxidants.



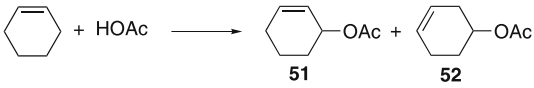
Scheme 14 Possible outcomes for the palladium-catalyzed oxidative acetoxylation of alkenes

Historically, cyclohexene has been a benchmark substrate for Pd-catalyzed allylic acetoxylation reactions. 2-Cyclohexenyl-1-acetate, **51**, is the desired product; however, in many cases, the homoallylic acetoxylation product **52** is also observed. Early efforts employed $Cu^{II}Cl_2$ and BQ to promote catalytic turnover (Table 5, entries 1 and 2) [196]. Unfortunately, these early methods proved to be rather unselective, including the formation of chlorinated products [197]. In 1984, two groups reported methods that achieved higher selectivity. McMurray employed a more electrophilic Pd^{II} catalyst, $Pd(O_2CCF_3)_2$, together with *o*-methoxyacetophenone and stoichiometric BQ at room temperature (Table 5, entry 3) [198]. Heumann and Åkermark used $Pd(OAc)_2$ and cocatalytic BQ with MnO_2 as the stoichiometric oxidant (Table 5, entries 4 and 5) [199, 200]. In both cases, selective allylic acetoxylation to form **51** occurs in good yield. The allylic acetoxylation of other cyclic and acyclic alkenes was described in these studies based on similar protocols. In subsequent years, Åkermark and Bäckvall developed multicomponent catalytic systems that use cocatalytic BQ with more environmentally benign terminal oxidants, including O_2 and H_2O_2, to carry out selective alkene acetoxylation (Table 5, entries 6–9) [27, 28, 201].

The proposed mechanism for allylic acetoxylation of cyclohexene is illustrated in Scheme 15. Pd^{II}-mediated activation of the allylic C – H bond generates a π-allyl Pd^{II} intermediate. Coordination of BQ to the Pd^{II} center promotes nucleophilic attack by acetate on the coordinated allyl ligand, which yields cyclohexenyl acetate and a Pd^0–BQ complex. The latter species reacts with two equivalents of acetic acid to complete the cycle, forming $Pd(OAc)_2$ and hydroquinone. The HQ product can be recycled to BQ if a suitable cocatalyst and/or stoichiometric oxidant are present in the reaction. This mechanism reveals that BQ is more than a reoxidant for the Pd catalyst. Mechanistic studies reveal that BQ is required to promote nucleophilic attack on the π-allyl fragment [25, 204–206].

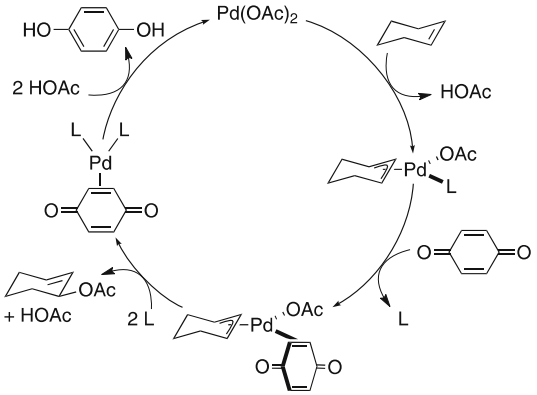
Two important extensions of this chemistry have been reported in recent years. White and coworkers demonstrated that terminal alkenes undergo regioselective acetoxylation at the C-1 or C-3 position, depending on the re-

Table 5 Methods for the selective generation of functionalized cyclohexene

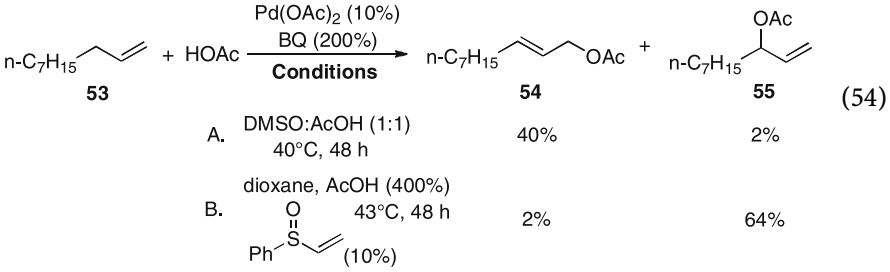


Entry	Catalyst	Cocatalyst	[O]	Additive	Temp. (°C)	Time (h)	**51** (%)	**52** (%)	Refs.
1	$PdCl_2$	None	$CuCl_2$ (unspecified loading)	NaOAc	20	NA	73	27	[196]
2	$PdCl_2$	None	BQ (unspecified loading)	NaOAc	20	NA	76	24	[196]
3	$Pd(TFA)_2$ (5%)	None	BQ (100%)	 40%	20	24	80	–	[198]
4	$Pd(OAc)_2$ (0.5%)	BQ (10%)	MnO_2 (110–200%)	None	60	50	77	–	[200]
5	$Pd(OAc)_2$ (5%)	BQ (20%)	MnO_2 (110–200%)	None	20	75	82	–	[200]
6	$Pd(OAc)_2$ (5%)	BQ (10%)	H_2O_2 (150%)	None	50	2	77	–	[28]
7	$Pd(OAc)_2$ (5%)	$Cu(OAc)_2$ (5%) HQ (10%)	1 atm O_2	None	50	22	> 85	–	[201]
8	$Pd(OAc)_2$ (5%)	Fe(Pc), **3** (5%) HQ (20%)	1 atm O_2	$LiOAc{\cdot}H_2O$ (50%)	60	4–6	90	–	[27]
9	$Pd(OAc)_2$ (5%)	Co(salophen), **1** (5%) HQ (20%)	1 atm O_2	$LiOAc{\cdot}H_2O$ (50%)	60	4–6	100	–	[27]

action conditions (Eq. 54). Very little formation of Wacker/Moiseev-like vinyl acetate by-product (i.e., C-2 acetoxylation) is observed. Preliminary mechanistic studies of the reaction under conditions B (Eq. 54) [207, 208] reveal that the vinyl sulfoxide promotes allylic C – H activitation of the terminal alkene by Pd^{II} to form a π-allyl species. As noted in the earlier studies, benzoquinone is required to promote nucleophilic attack by acetate on the π-allyl fragment.

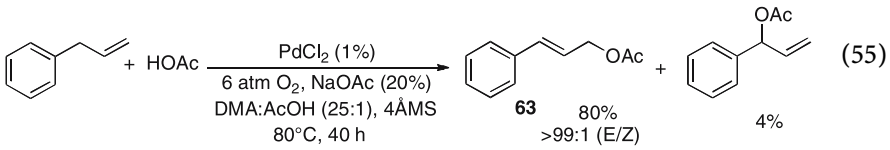


Scheme 15 Proposed mechanism for the allylic acetoxylation of cyclohexene



(54)

The mechanistic role of BQ in the allylic acetoxylation of alkenes suggests that it may not be possible to achieve direct dioxygen-coupled turnover. Recently, however, Kaneda and coworkers reported BQ-free conditions for aerobic allylic acetoxylation that feature a solvent mixture of acetic acid and *N*,*N*-dimethylacetamide (DMA) and O_2 as the sole oxidant for the Pd catalyst (Eq. 55) [209]. The reactions are highly selective for C-1 acetoxylation (C-1 : C-3 = 7–45 : 1). High pressures of O_2 (6 atm) are required to achieve these results.



(55)

The results of Kaneda are mechanistically interesting because they reveal that BQ is not required for functionalization of the intermediate π-allyl Pd^{II} species (Scheme 15). In Sect. 3, we outlined the fundamental similarities between BQ and dioxygen in their reactions with Pd^0. The allylic acetoxylation results described above suggest that similarities also exist between the reactions of BQ and O_2 with Pd^{II}. Because little is known about the coordination

properties of BQ and O_2 to Pd^{II}, further study will be necessary to elucidate this relationship.

5 Conclusion

Palladium-catalyzed oxidation reactions are attractive methods for the selective oxidation of organic molecules, and their utility could be further enhanced by the development of more effective ways to use molecular oxygen (or air) to promote catalyst oxidation. The results outlined in this chapter reveal significant similarities between the reaction of dioxygen and BQ, both in fundamental reactions with palladium and in catalysis. These observations imply that BQ-based Pd-catalyzed oxidation reactions represent an important starting point for the development of new aerobic oxidation reactions. The results further suggest that complex, multicomponent, coupled catalyst systems for the in situ oxidation of hydroquinone may not be required to achieve efficient dioxygen-coupled catalytic turnover. Rather, dioxygen alone can be an effective oxidant in Pd-catalyzed reactions. Despite this optimistic outlook, dioxygen and BQ do not perform identically in catalytic reactions, and further studies will be necessary to elucidate the mechanistic origin of these differences. Such studies will play an important role in the ongoing development of Pd-catalyzed aerobic oxidation reactions.

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