Chapter 9
Organometallic C–H Oxidation with O_2 Mediated by Soluble Group 10 Metal Complexes

Andrei N. Vedernikov

Abstract Selective catalytic C–H functionalization of organic compounds with O_2 as the terminal oxidant is an important and challenging practical goal justified from both economic and environmental perspective. Recent advances in organometallic palladium-catalyzed aerobic C–H functionalization chemistry are reviewed with an emphasis on the mechanism of the reaction basic steps. These steps include activation of alkenes, arenes, and alkanes at a palladium(II) center to form organopalladium intermediates with new Pd–C bonds, C–X bond-forming reactions at palladium(II) or palladium(IV) center, O_2 activation by palladium(II) hydrocarbyls, palladium(II) hydrides, and palladium(0) complexes. Some limitations of the current palladium-based systems and directions toward their possible future development are discussed. Considering organometallic aerobic C–H functionalization catalysis by other group 10 metals, a brief review is provided of a few existing platinum-based systems. Although no such catalytic systems based on nickel complexes have been reported yet, some relevant stoichiometric reactions at a nickel center have already been discovered which promises possible future development of organometallic aerobic C–H functionalization catalysis by this metal.

Keywords Selective aerobic C–H functionalization · Dioxygen activation · Mechanism · Organometallic catalysis · Palladium complexes · Platinum complexes · Nickel complexes

9.1 Introduction

Selective oxidative functionalization of hydrocarbons with O_2 as the terminal oxidant is an attractive goal. From an economic standpoint, atmospheric oxygen is one of the least expensive and abundant oxidizing agents. From an environmental perspective, the development of selective aerobic oxidation processes could minimize or even

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eliminate chemical waste. Organotransition metal catalysis is a viable approach to achieve these goals. In this Chapter, catalytic transformations of hydrocarbon C–H bonds will be considered that involve the use of O_2 as terminal oxidant and soluble organometallic group 10 metal complexes as catalysts or catalytic intermediates. As it will be shown in this Chapter, the involvement of organometallic species may allow for diverse transformations of their metal–carbon bonds [1] leading toward various value-added hydrocarbon functionalization products. Along with an overview of representative examples of major reaction types, a discussion of the mechanisms of the reactions will be provided.

Among the transition metals, and the group 10 metals, in particular, palladium has played a prominent role in the development of selective organic oxidation reactions with O_2 ("aerobic oxidation reactions"). A classic example of such processes is the oxidation of ethylene with O_2 to acetaldehyde in the presence of aqueous $[Pd^{II}Cl_4]^{2-}$ and $Cu^{II}Cl_2$ cocatalysts (the Wacker process) developed in the 1950s (Eq. 9.1) [2–4]:

$$2CH_2{=}CH_2 + O_2 \rightarrow 2CH_3CH{=}O \tag{9.1}$$

The Wacker process is an organometallic oxidation involving reactive alkylpalladium(II) species as key intermediates. The $[Pd^{II}Cl_4]^{2-}$complex is responsible for ethylene oxidation to acetaldehyde with palladium(0) as another reaction product, which is a known stoichiometric reaction. In turn, the role of the copper cocatalyst is twofold. In its oxidized form, $Cu^{II}Cl_2$, it can convert palladium(0) back to palladium(II) producing copper(I) species as another product. In its reduced form, $[Cu^{I}Cl_2]^{-}$, it activates O_2 with concomitant conversion of copper(I) species back to copper(II). Reaction (9.1) has been used on an industrial scale since the 1960s.

The use of soluble platinum complexes in aerobic oxidation of organic substrates has been known since the 1980s. An early example of such transformations utilizing O_2 as the oxidant is the Shilov reaction, conversion of methane to CH_3X products (X=OH, Cl) catalyzed by aqueous $[Pt^{II}Cl_4]^{2-}$ and a heteropolyacid redox cocatalyst (Eqs. 9.2, 9.3) [5]:

$$2CH_4 + O_2 \rightarrow 2CH_3OH \tag{9.2}$$

$$2CH_4 + O_2 + 2HCl \rightarrow 2CH_3Cl + 2H_2O \tag{9.3}$$

The original version of the reaction reported about 10 years earlier [6] utilized expensive H_2PtCl_6 as the oxidant. It was then discovered that H_2PtCl_6 could be used in a catalytic fashion with O_2 as the terminal oxidant when a heteropolyacid redox cocatalyst is employed [5]. The Shilov reaction, similar to Wacker process, is also an organometallic oxidation process which involves methylplatinum(II) intermediates resulting from methane activation by platinum(II), as well as their methylplatinum(IV) derivatives resulting from oxidation of the former [7, 8]. The Shilov reaction's main limitations are low catalyst turnover numbers (TON) resulting from gradual conversion of platinum(II) catalyst to inactive platinum(IV) and platinum(0)

species, as well as poor ($\leq$50%) selectivity in CH_3X-type products due to "overoxidation" of methane leading to formaldehyde, formic acid, and CO_2. Aerobic C–H functionalization reactions mediated by soluble platinum complexes have gained, so far, no practical applications although they remain in the focus of academic research [9, 10].

Finally, organometallic functionalization reactions of organic substrates mediated by nickel complexes are under development [11, 12] and the use of O_2 as the terminal oxidant in such reaction has not yet been reported.

This quick introduction suggests that the most part of this chapter will be dedicated to organopalladium catalysis with much less attention paid to reactions of the other two group 10 metals.

9.2 Homogeneous Organometallic Palladium-Catalyzed Aerobic C–H Functionalization

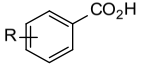
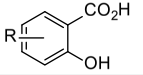
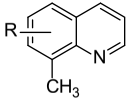
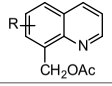
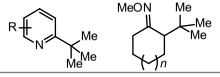
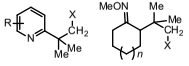
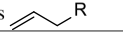
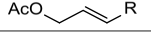
Various types of organometallic palladium-catalyzed C–H oxidation (Eq. 9.4) and aerobic oxidative coupling of C–H (R–H) and X–H fragments (Eq. 9.5) leading to products with new C–X (R–X) bonds have been reported:

$$2R{-}H + O_2 \rightarrow 2ROH \tag{9.4}$$

$$2R{-}H + 2X{-}H + O_2 \rightarrow 2R{-}X + 2H_2O \tag{9.5}$$

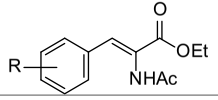
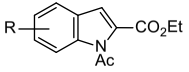
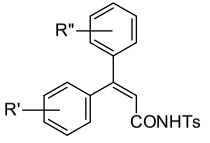
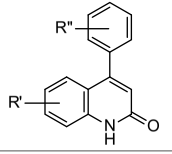
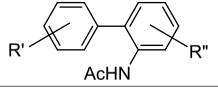
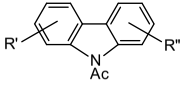
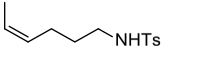
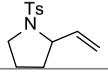
In an ideal case of a 100% selective transformation, reactions of the first type would produce no chemical waste. In the second case, ideally, the only by-product would be water. An extensive recent review covering aerobic functionalization of olefinic substrates is available [13]. Some representative examples of reactions of both types, (Eq. 9.4) and (Eq. 9.5), are listed in Table 9.1 and structures of the specific ligands **1**–**11** used in these reactions are given in Fig. 9.1. A literature analysis shows that oxidative aerobic transformations of olefinic substrates and arenes are explored better than those of alkanes. While compiling representative organometallic palladium-catalyzed aerobic C–H functionalization reactions, preference was given to more challenging processes involving arene, olefin, or alkane C–H activation (all entries except 9–12). The assignment of the type of a C–H bond involved in oxidative functionalization is purely formal for some reactions involving olefins serving either as hydrocarbon substrates (entries 9–12) or as coupling partners (entries 20–26). In these specific examples, the relevant organopalladium intermediates result from the addition of palladium(II) species across an olefin C=C bond (olefin insertion into Pd^{II}-ligand bond) and not from the olefin C–H bond activation. As an alternative to the olefin insertion, activation of olefins at a Pd^{II} center may involve direct allylic C–H bond cleavage leading to allylpalladium(II) intermediates (entry 5).

Table 9.1 Some representative examples of C–H oxidation and oxidative aerobic coupling of C–H bonds of organic substrates and X–H bonds of their coupling partners mediated by Pd complexes. The structures of specific ligands **1–11** used in these reactions are given in Fig. 9.1

	C–H bond type/substrate	X–H bond type/coupling partner	Resulting bond/coupling product	Catalyst, loading in mol%	References
Arene hydroxylation					
1	$C(sp^2)$–H/benzoic acids 		$C(sp^2)$–O/2-hydroxybenzoic acids 	$Pd(OAc)_2$, 10	[14]
Arene and alkane acetoxylation and chlorination					
2	$C(sp^2)$–H/benzene	O–H/AcOH	$C(sp^2)$–O/phenylacetate	$Pd(OAc)_2$, 0.1/HNO_3 (conc.), 30	[15]
3	$C(sp^3)$–H/8-methylquinolines 	O–H/AcOH	$C(sp^3)$–O/8-(acetoxymethyl) quinolines 	$Pd(OAc)_2$, 5/4-hydroxy-2,6-pyridinedicarboxylic acid **1**, 5	[16, 17]
4	$C(sp^3)$–H/2-alkylpyridines, oxime ethers 	O–H/AcOH or HCl	$C(sp^3)$–O or $C(sp^3)$–Cl/acetates or chlorides 	$Pd(OAc)_2$, 5/$NaNO_3$, 100	[18]
5	$C(sp^3)$–H (allylic)/ olefins 	O–H/AcOH	$C(sp^3)$–O/allylacetates 	$Pd(OAc)_2$, 5/4,5-diazafluoren-9-one **2**, 5	[19]

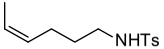
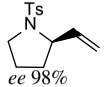
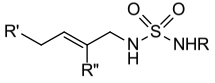
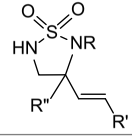
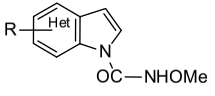
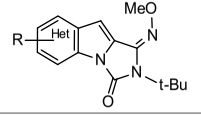
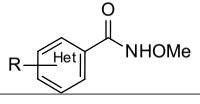
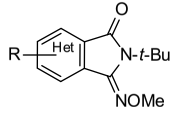
(continued)

Table 9.1 (continued)

	C–H bond type/substrate	X–H bond type/coupling partner	Resulting bond/coupling product	Catalyst, loading in mol%	References
Arene and alkene amidation/amination					
6	$C(sp^2)$–H/2-(N-acetylamino)cinnamate esters 	(Ac)N–H/(intramolecular)	$C(sp^2)$–N(Ac)/N-acetylindoles 	$Pd(OAc)_2$, 10/DMSO (solvent)	[20]
7	$C(sp^2)$–H/3,3-diarylacrylamides 	N–H/(intramolecular)	$C(sp^2)$–N/4-aryl-2-quinolinones 	$PdCl_2$, 10/$Cu(OAc)_2$, 50	[21]
8	$C(sp^2)$–H/N-(biphenyl-2-yl)acetamides 	(Ac)N–H/(intramolecular)	$C(sp^2)$–N(Ac)/N-acetylcarbazoles 	$Pd(OAc)_2$, 5/$Cu(OAc)_2$, 100	[22]
9	C–H/olefins 	(R)(R′)N–H/e.g., phthalimide	$C(sp^2)$–N(R)(R′)/N-vinylphthalimides 	$Pd(OAc)_2$, 10/PhCN (solvent)	[23, 24]
10	C–H/N-(hex-4-enyl)tosylamide 	(Ts)N–H (intramolecular)	$C(sp^3)$–N(Ts)/racemic 2-vinylpyrrolidine 	$Pd(OAc)_2$, 5/4,5-diazafluoren-9-one **2**, 5	[25]

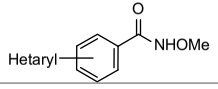
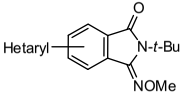
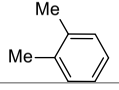
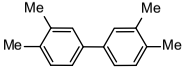
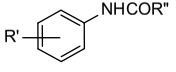
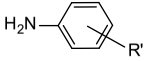
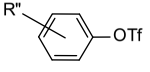
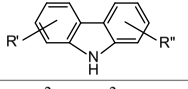
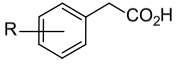
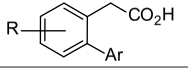
(continued)

Table 9.1 (continued)

	C–H bond type/substrate	X–H bond type/coupling partner	Resulting bond/coupling product	Catalyst, loading in mol%	References
11	C–H/N-hex-4-enyltosylamide 	(Ts)N–H (intramolecular)	$C(sp^3)$–N(Ts)/(*R*)-2-vinylpyrrolidine  *ee* 98%	$Pd(O_2CCF_3)_2$, 5/(*R*)-pyrox **3**, 7.5	[26]
12	C–H/N-allylsulfonediamide 	(SO_2)N–H (intramolecular)	$C(sp^3)$–N/N,N'-alkylidenesulfonediamide 	$Pd(O_2CCF_3)_2$, 5/DMSO, 10	[27]
(Hetero)arene imidoylation					
13	$C(sp^2)$–H/N-methoxy pyrrolohetarenecarboxamides 	- /*t*-BuNC	$C(sp^2)$–$C(sp^2)$/hetarene-fused imidazopyrroles 	$Pd_2(dba)_3$, 5	[28]
14	$C(sp^2)$–H/N-methoxyhetarenecarboxamides 	- /*t*-BuNC	$C(sp^2)$–$C(sp^2)$/pyrrolohetarenes 	$Pd_2(dba)_3$, 2.5	[29]

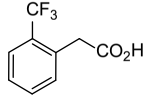
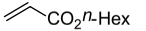
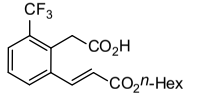
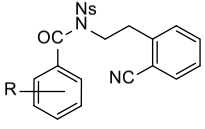
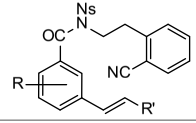
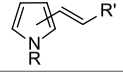
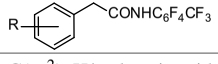
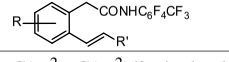
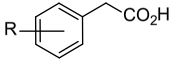
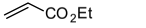
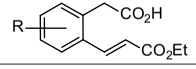
(continued)

Table 9.1 (continued)

	C–H bond type/substrate	X–H bond type/coupling partner	Resulting bond/coupling product	Catalyst, loading in mol%	References
15	$C(sp^2)$–H/N-methoxy-hetarylbenzamides 	- /*t*-BuNC	$C(sp^2)$–$C(sp^2)$/hetarylisoindolines 	$Pd_2(dba)_3$, 5	[30]
Arene homocoupling					
16	$C(sp^2)$–H/*o*-xylene 	$C(sp^2)$–H/*o*-xylene	$C(sp^2)$–$C(sp^2)$/ 	$Pd(OAc)_2$, 0.1/$Cu(OTf)_2$, 0.1/2-fluoropyridine **4**, 0.2	[31, 32]
Arene arylation					
17	$C(sp^2)$–H/N-acylanilines 	$C(sp^2)$–H/arenes 	$C(sp^2)$–$C(sp^2)$/N-acyl-2-aminobiphenyls 	$Pd(OAc)_2$, 5–10/DMSO, 10–20/TFA, 500–1000	[33]
18	$C(sp^2)$–H/anilines 	$C(sp^2)$–H/aryltriflates 	$C(sp^2)$–$C(sp^2)$/carbazoles 	$Pd(OAc)_2$, 10/phosphine **5**, 15	[34]
19	$C(sp^2)$–H/arylacetic acids 	$C(sp^2)$–B/aryltrifluoroborates $[ArBF_3]^-$	$C(sp^2)$–$C(sp^2)$/(2-arylphenyl)acetic acids 	$Pd(OAc)_2$, 5/N-acetylisoleucine **6**, 10/benzoquinone, 5	[35]

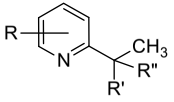
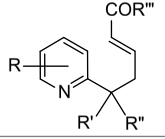
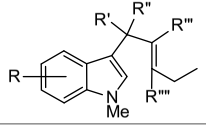
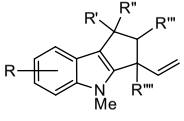
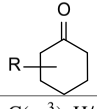
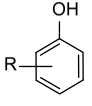
(continued)

Table 9.1 (continued)

	C–H bond type/substrate	X–H bond type/coupling partner	Resulting bond/coupling product	Catalyst, loading in mol%	References
Arene and alkane alkenylation					
20	$C(sp^2)$–H/arylacetic acids  acids	C–H/*n*-hexylacrylate 	$C(sp^2)$–$C(sp^2)$/2-vinylarylacetates 	$Pd(OAc)_2$, 5/N-acetylisoleucine **6**, 10	[36]
21	$C(sp^2)$–H/N-sulfonylbenzamides 	C–H/olefin 	$C(sp^2)$–$C(sp^2)$/N-sulfonyl-3-vinylbenzamides 	$Pd(OAc)_2$, 10/N-acetylglycine **7**, 60–100	[37]
22	$C(sp^2)$–H/N-protected pyrroles 	C–H/olefin 	$C(sp^2)$–$C(sp^2)$/2- or 3-vinylpyrroles 	$Pd(OAc)_2$, 10/DMSO (solvent)	[38]
23	$C(sp^2)$–H/N-(perfluoro-*p*-tolyl)arylacetamides 	C–H/alkene	$C(sp^2)$–$C(sp^2)$/N-(perfluoro-*p*-tolyl)-2-vinylarylacetamides 	$Pd(OAc)_2$, 5/quinoline **8**, 10/$Cu(OAc)_2$, 20	[39]
24	$C(sp^2)$–H/arylacetic acids 	C–H/ethylacrylate 	$C(sp^2)$–$C(sp^2)$/2-vinylarylacetic acids 	$Pd(OAc)_2$, 5/N-acetylisoleucine **6**, 10	[40]

(continued)

Table 9.1 (continued)

	C–H bond type/substrate	X–H bond type/coupling partner	Resulting bond/coupling product	Catalyst, loading in mol%	References
25	$C(sp^3)$–H/2-alkylpyridines 	C–H/ 	$C(sp^3)$–$C(sp^2)$/2-homoallylpyridines 	$Pd(MeCN)_4(BF_4)_2$, 10/NaOAc, 10/$H_4[PMo_{11}VO_{40}]$, 3	[41]
Alkylation					
26	$C(sp^2)$–H/3-alkenylindoles 	C–H/olefin (intramolecular)	$C(sp^2)$–$C(sp^3)$/cyclopenta[b]indoles 	$Pd(OAc)_2$, 10/ethylnicotinate **9**, 40	[42]
Dehydrogenation					
27	$C(sp^3)$–H/cyclohexene	$C(sp^3)$–H (intramolecular)	$C(sp^2)$=$C(sp^2)$/benzene	$Pd(O_2CCF_3)_2$, 5	[43]
28	$C(sp^3)$–H/cyclohexanones 	$C(sp^3)$–H (intramolecular)	$C(sp^2)$=$C(sp^2)$/phenols 	$Pd(O_2CCF_3)_2$, 5/2-dimethylaminopyridine **10**, 10/TsOH, 20	[44]
29	$C(sp^3)$–H/cyclohexenes 	$C(sp^3)$–H (intramolecular)	$C(sp^2)$=$C(sp^2)$/arenes 	$Pd(O_2CCF_3)_2$, 5/anthraquinone **11**, 20	[45]

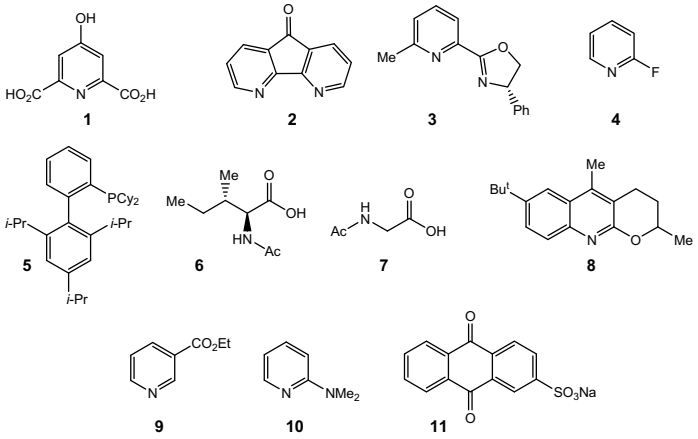


Fig. 9.1 Ligands **1**–**11** used in reactions in Table 9.1

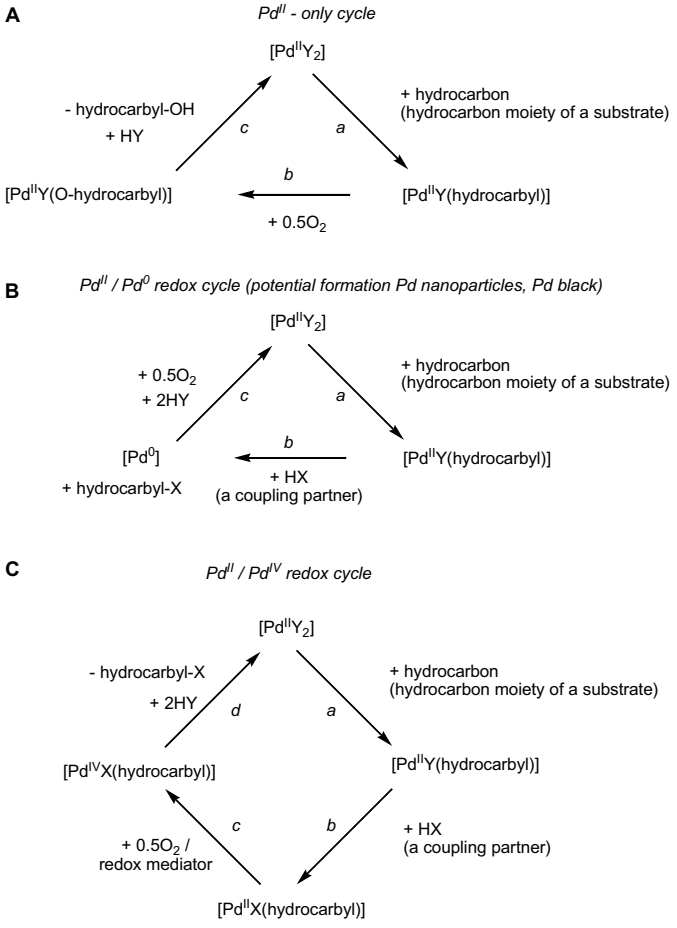
The reactions in Table 9.1 are organized according to the type of the functional group introduced and new C–X bond formed, the type of the substrate C–H bonds involved, and the type of the X–H coupling partner, when applicable. Reactions leading to functionalization of substrate C(sp^2)–H bonds include hydroxylation (entry 1), acetoxylation (entry 2), amidation/amination (entries 6–9), imidoylation (entries 13–15), homocoupling (entry 16), arylation (entries 17–19), alkenylation (entries 20–24), and alkylation (entry 26). Transformations of substrate C(sp^3)–H bond include acetoxylation (entries 3–5), chlorination (entry 4), amidation/amination (entries 10–12), alkenylation (entry 25), and oxidative dehydrogenation of cyclohexane derivatives (entries 27–29). Besides X–H type coupling partners, boronic acid derivatives were also used in some cases (entry 19). Notably, the use of chiral supporting ligands may lead to a highly enantioselective product formation with the product enantiomeric excess up to 98% (entry 11).

The key to understanding and overcoming challenges associated with the development of aerobic C–H functionalization reactions and, in particular, most difficult aerobic functionalization of alkanes, lies in the understanding of their mechanisms. Notably, in the past two decades, the rapid development of Pd-catalyzed aerobic oxidative C–H functionalization has become possible thanks to close attention paid to mechanisms of palladium-mediated C–H bond activation [46] and O_2 activation reactions [47]. Accordingly, in the subsequent discussion, some key mechanistic details of these reactions will be considered.

9.2.1 General Mechanisms of Palladium-Mediated Aerobic C–H Functionalization

Three plausible catalytic cycles showing major steps of palladium-catalyzed aerobic C–H functionalization are given in Scheme 9.1. In the "non-redox" Pd^{II}—only catalytic cycle **A**, the metal oxidation state remains the same during three major steps, the substrate activation step *a*, the O_2 activation step *b*, and the product-releasing step *c* leading to the substrate functionalization product (hydrocarbyl-OH).

In mechanism **B**, a Pd^{II}/Pd^0 redox couple is involved. The +2 metal oxidation state is not changed at the substrate activation step *a*. The step *b* leading to substrate functionalization product (hydrocarbyl-X) involves elimination of C–X bond from a



Scheme 9.1 Plausible simplified catalytic cycles for palladium-mediated aerobic C–H bond functionalization

palladium(II) center with concomitant reduction of Pd^{II} to Pd^0, and the O_2 activation step *c* leads to reoxidation of Pd^0 to Pd^{II}.

Finally, the mechanism **C** is also palladium redox-based and involves Pd^{II}/Pd^{IV} redox couple. The Pd^{II} center does not change its oxidation state during the substrate activation step *a* and subsequent reaction with a coupling partner HX, step *b*. Two other steps, *c* and *d*, involve oxidation of Pd^{II} hydrocarbyls to their Pd^{IV} derivatives and C–X elimination of the product (hydrocarbyl-X) from the palladium(IV) center with concomitant reduction of Pd^{IV} to Pd^{II}, respectively.

9.2.1.1 Substrate Activation Step

All the basic mechanisms **A–C** in Scheme 9.1 imply that substrate activation leading to hydrocarbylpalladium(II) species (step *a*) occurs without change of the metal oxidation state +2.

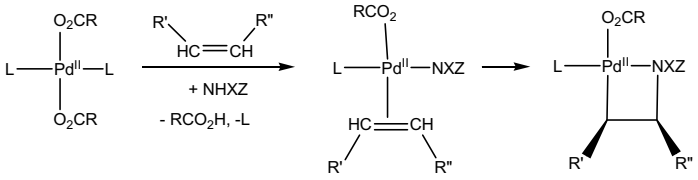
Even in the cases where palladium(0) complexes are used as pre-catalysts (examples in entries 13–15 in Table 9.1), the authors argue that the actual catalytically active species are palladium(II) complexes. The latter result from oxidation of palladium(0) species with O_2 involving N–H acidic substrates, O-methyl hydroxamic acids, which serve as a source of anionic amido ligands for the resulting Pd^{II} center (see step *b*, mechanism **B**) [29], see, e.g. Eq. 9.6:

$$2\left[Pd^0\right] + O_2 + 4H{-}N(OMe)(COR) \rightarrow 2\left[Pd^{II}(N(OMe)COR)_2\right] + 2H_2O \quad (9.6)$$

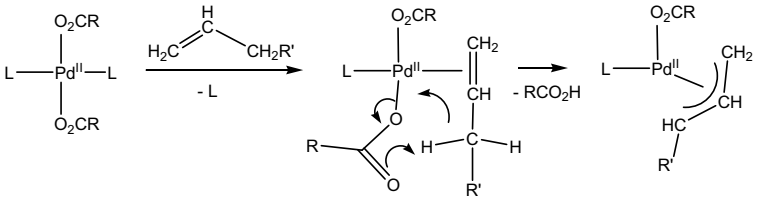
Similar may be the role in Pd^0 recycling of protected aminoacids **6** and **7** (Fig. 9.1) used as ligands in some aerobic C–H functionalization reactions (examples in entries 19–21, 24, Table 9.1).

Importantly, all the mechanisms of substrate activation by palladium(II) complexes discussed below require prior substrate coordination to the metal. Hence, the slow rates of ligand substitution in catalytically active metal species and strong coordination to palladium(II) center of a supporting ligand or substrate may decrease dramatically the overall catalyst turnover frequency. As a result, the judicious choice of supporting ligand for a catalyst may be very important, which is, in particular, a reason for the success of catalytic systems utilizing weakly coordinating 2-fluoropyridine **4** [31, 32] or bidentate 4,5-diazafluoren-9-one **2** [25] ligands (Fig. 9.1).

Holding these considerations in mind, it is very remarkable that the $Pd_2^0(dba)_3$-based catalytic system in examples in entries 13–15, Table 9.1 is very tolerant of heterocyclic donor groups present in substrates. These donor groups can strongly bind to palladium(II) center and severely inhibit catalysis of C–H functionalization by palladium(II) complexes. A possible explanation to this tolerance is that the palladium(II) center which is generated in reaction (9.6) above is coordinated to basic amido ligands and as such can be involved in substrate C–H bond activation/deprotonation (vide infra), experiencing minimal inhibiting effect of coordinating heterocyclic donor groups of the substrates [29].



Scheme 9.2 Formation of alkylpalladium(II) intermediates as a result of *cis*-aminopalladation of olefinic substrates



Scheme 9.3 Formation of allylpalladium(II) intermediates as a result of deprotonation of allylic C–H bonds of olefinic substrates involving coordinated carboxylate ligand

Olefin Insertion into Pd^{II}-Ligand Bond

Following substrate coordination to a palladium(II) center, its activation by the metal leading to hydrocarbylpalladium(II) species may proceed either as the substrate C–H bond cleavage or, for unsaturated substrates, as an addition (insertion) reaction. For olefinic substrates, even with available relatively acidic allylic C–H bonds, step *a* may not involve the substrate C–H activation, as it is the case in oxidative amination of olefins in the examples in entries 9–12, Table 9.1. Instead, based on available mechanistic tests, authors of these catalytic systems propose that formation of alkylpalladium(II) intermediates in step *a* occurs as *cis*-aminopalladation of the olefinic C=C bonds (Scheme 9.2), and not as allylic C–H bond cleavage [27].

Deprotonation of Pd^{II}–Coordinated C–H Bonds

Allylic C–H Deprotonation of Olefins

In turn, in the absence of strong nucleophilic ligands such as amides in examples given in entries 9–12, Table 9.1, olefinic substrates with available allylic C–H bonds can undergo allylic C–H deprotonation by the action of a metal-coordinated carboxylate (Scheme 9.3) [19] or a similar basic ligand [29], or even a free carboxylate serving as a base, as it was found computationally [48]. Some representative reactions involving activation of olefinic substrates via allylic C–H bond cleavage are given in entries 5, 27–29, Table 9.1.

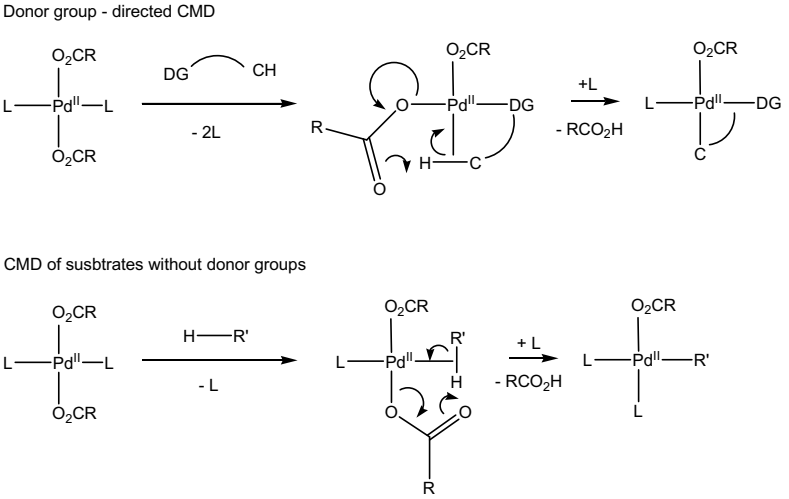
Directed C–H Activation. Concerted Metallation–Deprotonation Mechanism

Considering non-olefinic substrates in Table 9.1, their quick inspection shows that many of them have metal-coordinating heteroatoms, e.g., carboxylate oxygens, examples in entries 1, 19–20, 24, a quinoline nitrogen, entry 3, an oxime or pyridine nitrogen in entries 4, 25, an anionic amide nitrogen resulting from N–H bond deprotonation in entries 6–8, 13–15, 17, 23, in a close proximity to C–H bonds involved in subsequent oxidative functionalization reaction. It was shown that functionalized hydrocarbon substrates containing suitable donor groups undergo C–H bond activation only after prior coordination of the donor group to the metal [49]. As a result, only those C–H bonds of the substrate that are accessible for the donor group-coordinated metal can be involved in subsequent transformations. Hence, the position of the donor groups relative to the substrate's various C–H bonds determines the regioselectivity of the C–H activation step *a*. Formation of five-membered palladacyclic intermediates is usually kinetically favored over six-membered metallacycles. Notably, metallacyclic intermediates with both smaller and larger rings can form. As a result, for arene derivatives with donor groups (DG) attached to one of the arene carbon atoms, such as CO_2^-, $CH_2CO_2^-$, $CONR_2$, NHCOR, CH_2NR_2, 2-pyridyl, 2-oxazolyl, 2-imidazolyl, N=NAr, CH_2SR, or CH_2OH selective metallation and subsequent functionalization is most facile for the arene C–H bonds that are positioned *ortho*- to the donor group [49, 50] (examples in entries 1, 6–8, 13–15, 17–20, 23–24, Table 9.1). Similar rules apply for alkane C–H bond functionalization when dealing with functionalized alkane substrates bearing directing groups [49, 51] (examples in entries 3, 4, 25, Table 9.1). Importantly, by changing the length and configuration of a tether between an arene carbon to which the tether is attached and the donor group, one can achieve a rare selective *meta*-C–H bond functionalization of the arene, as it is the case in an example in entry 21 in Table 9.1 [37].

The considerations above also imply that for substrates having several types of chemically nonequivalent C–H bonds, selective functionalization of some of them may be a daunting problem in palladium catalysis. At the same time, this is one of the points of growth and development of this area [37, 47], where joint experimental and computational modeling efforts are especially promising [52].

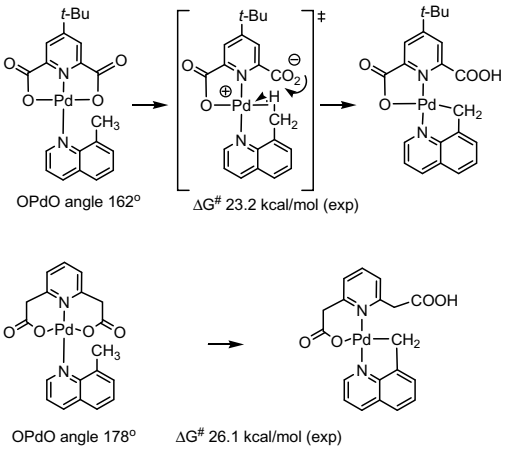
The mechanism of C–H activation most common for substrates with donor groups and substrates not having directing groups such as non-functionalized arenes or alkanes (entries 2, 16, Table 9.1) is the concerted metallation–deprotonation (Scheme 9.4) [46], which was also studied computationally [53, 54]. In either case, before the deprotonation step can occur, a substrate C–H bond has to be coordinated to the metal center. Such coordination can enhance dramatically the C–H bond acidity and facilitate subsequent C–H deprotonation. Expectedly, C–H bonds of nonactivated alkane fragments are the least acidic and, as such, are most difficult to activate and functionalize.

A substrate C–H bond coordination to the metal is greatly facilitated when the substrate has a donor group that can coordinate to the metal, thanks to the absence of the entropic penalty for the C–H bond coordination step (Scheme 9.4, top). Since hydrocarbon C–H bonds are very poor electron donors, the latter effect is of immense



Scheme 9.4 Formation of palladium(II) hydrocarbyls as a result of a concerted metallation-deprotonation (CMD)

Scheme 9.5 C–H bond activation by palladium(II) pyridine-2,6-dicarboxylate complexes [16]



importance for metal-mediated C–H activation and functionalization. Interestingly, coordination of a substrate C–H bond to the metal center can be facilitated when a palladium(II) carboxylate is a strained chelate, such as palladium(II) pyridine-2,6-dicarboxylate (Scheme 9.5, top) [16, 17]. Dissociation of a carboxylate arm from the metal relives the chelate ring strain and is, therefore, facilitated, which accelerates coordination of the substrate C–H bond to be functionalized. Non-strained analogs with larger chelate size are less reactive (Scheme 9.5, bottom).

9.2.1.2 C–X Bond Formation Step

This step is the most critical for achieving a desirable type of C–H bond functionalization. Since the key reaction intermediates produced at the step *a* are organopalladium(II) species, knowledge of their reactivity [1] is very important when designing new catalytic reactions. This step can be viewed as functionalization of transient organopalladium species.

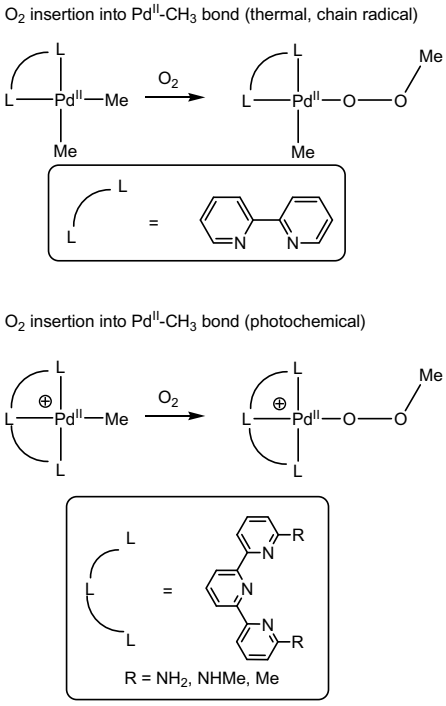
In any of the mechanisms **A–C** (Scheme 9.1), the C–X bond formation may result already at the step *a* when the substrate is an olefin involved in an insertion reaction (see, e.g., Scheme 9.2).

If step *a* involves a substrate C–H bond cleavage which results in a hydrocarbylpalladium(II) intermediate, then the C–X bond formation occurs typically at the step *b* (mechanisms **A**, **B**) or *d* (mechanism **C**).

O_2 Insertion into Pd^{II}–C Bond

According to mechanism **A** in Scheme 9.1, the Pd^{II}–C bond functionalization (step *b*) may be as "simple" as O_2 insertion into Pd^{II}–C bond which does not involve the metal redox change, (see an example in entry 1 in Table 9.1 as well as a discussion in the next section, "O_2 activation step"). The expected O_2 insertion product is a hydrocarbylperoxo complex. A few such well-defined stoichiometric reactions are known. They involve methylpalladium(II) complexes [55–59]. One of the first reported O_2 insertion reactions (Scheme 9.6, top) involves a dimethylpalladium(II) species and is a radical chain process [55], similar to a reported later analogous O_2 insertion involving a neutral monomethylpalladium(II) compound [56]. Another reaction in Scheme 9.6 is photochemical and involves cationic monomethylpalladium(II) species (Scheme 9.6, bottom) [57–59]. All of these reactions occur in aprotic media and the resulting methylperoxo palladium(II) species are formed in high yields.

Protonolysis of the products of O_2 insertion into Pd^{II}–CH_3 bond in Scheme 9.6 can lead to free methylhydroperoxide, an unstable and explosive chemical. Hence, the practical value of such products may be low. In this regard, an in situ conversion of hydrocarbylperoxo metal species into palladium(II) alkoxo complexes or free alcohols would be more desirable. In fact, both MeO_2H and MeOH form in a photocatalytic reaction of O_2 with a water-soluble anionic methyl palladium complex $[(dpms)Pd^{II}Me(OH)]^-$, besides ethane which is a major reaction product (Scheme 9.7, top) [60]. Importantly, the formation of MeO_2H can be fully suppressed by a slight modification of the reaction conditions with a concomitant increase of the MeOH yield up to 50% with the rest of the balance being ethane. It was shown that various hydroperoxides RO_2H (R=H, Me, *t*-Bu) react cleanly and rapidly with the methylpalladium(II) reagent, $[(dpms)Pd^{II}Me(OH)]^-$, to form the corresponding ROH in high yields. A proposed reaction sequence shown in Scheme 9.7 (center and bottom) involves formation of a hypothesized highly electrophilic methylpalladium(IV) species responsible for the production of various Me–X products detected in the



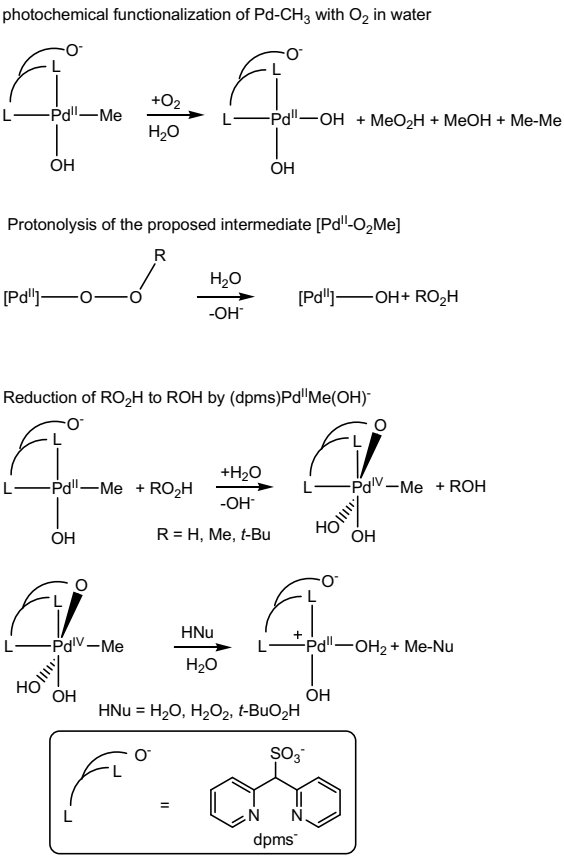
Scheme 9.6 Some reported examples of direct thermal [55] or photochemical [57–59] O_2 insertion into Pd^{II}–CH_3 bond of methylpalladium(II) species

mixtures with various nucleophiles and resulting from their attack at the CH_3–Pd^{IV} fragment of the proposed methylpalladium(IV) transient.

Reductive Elimination of C–X Bond from a Pd^{II} or a Pd^{IV} Center

According to mechanisms **B** and **C** (Scheme 9.1), C–X bond formation occurs as a result of reductive elimination from Pd^{II}(X) hydrocarbyls (mechanism **B**, step *b*) or Pd^{IV}(X) hydrocarbyls (mechanism **C**, step *d*) species. The ligands X necessary for such reductive coupling are introduced into palladium(II) coordination sphere prior to the C–X bond elimination (mechanism **B**) and, typically, but not always, prior to the Pd^{II} to Pd^{IV} oxidation step *c* (mechanism **C**) as a result of a ligand exchange, olefin insertion into palladium(II)-ligand bond (examples in entries 20–26) or, rarely, C–H bond activation at the electrophilic Pd^{IV} center [61].

Mechanism **C** involving a Pd^{II}/Pd^{IV} redox couple is rare in aerobic C–H functionalization chemistry. In particular, the authors of the catalytic system in entry 2 [15], Table 9.1, proposed involvement of a Pd^{II}/Pd^{IV} redox couple with a C(sp^2)–O reductive elimination from a Pd^{IV} hydrocarbyl resulting from the oxidation of its Pd^{II} precursor with HNO_3. Similarly, possible involvement of the Pd^{II}/Pd^{IV} redox couple was discussed for reactions in entries 3 [16] and 4 [18] leading to C(sp^3)–X (X=O, Cl) reductive elimination from Pd^{IV} species which, in fact, occurs as an S_N2 process. In the latter system, the oxidant responsible for the generation of Pd^{IV} hydrocarbyls



Scheme 9.7 Photochemical dioxygen activation by a water-soluble methylpalladium(II) complex and conversion of RO_2H to ROH [60]

is HNO_3, similar to the reaction in entry 2. In turn, for the catalytic system in entry 3, the Pd^{IV} hydrocarbyls were speculated to be produced aerobically from their Pd^{II} precursors [16]. It was shown computationally that the formation of Pd^{IV} transients is thermodynamically viable thanks to the ability of the tripod ligand **1** (Fig. 9.1) to adapt a facial coordination mode. At the same time, a mechanism involving an O_2 insertion into Pd^{II}–C bond also could not be excluded [17]. Notably, there are precedents of reactions between O_2 and dimethylpalladium(II) complexes supported by facially chelating ligands that lead to palladium(IV) derivatives [62, 63].

The involvement of Pd^{II}/Pd^0 redox catalysis (mechanism **B**) is most commonly proposed in various aerobic C–H functionalization reactions. The relevant examples in Table 9.1 are the reactions leading to $C(sp^3)$–O bond formation, such as in the catalytic system in entry 5, $C(sp^2)$–N bond formation, such as in arene and alkene amination reactions in entries 6–12, and C–C bond formation, such as in the arene imidoylation reactions (entries 13–15), arene homocoupling (entry 16), arene arylation (entries 17–19), arene and alkane alkenylation (entries 20–25) and alkylation (entry 26).

Finally, a special case of the product forming step associated with the mechanism **B** which does not require the presence of an actual coupling partner is dehydrogenation of various cyclohexane derivatives in reactions in entries 27–29. In this case, the new C=C bonds result from β-hydrogen atom elimination of palladium(II) hydrocarbyl intermediates.

O_2 Activation Step

Another step which is critical for any catalytic aerobic C–H functionalization process is O_2 activation. Direct O_2 insertion into Pd^{II}–C bond is one of the possibilities which has been already characterized in section "O_2 Insertion into Pd^{II}–C Bond".

O_2 Activation by Redox Cocatalysts

O_2 activation carried out by a redox cocatalyst is very common in aerobic Pd-catalyzed C–H functionalization, especially in its older versions. Some redox cocatalysts that were proven efficient are copper(II) complexes, heteropolyacids, and lower nitrogen oxides NO_x ($x = 1, 1.5, 2$). These cocatalysts in their reduced form, e.g., copper(I) or NO, react rapidly with O_2 to form species capable of oxidizing palladium center from lower to higher oxidation states, Pd^0 to Pd^{II} (mechanism **B**, Scheme 9.1) or, in some cases, converting Pd^{II} hydrocarbyls to Pd^{IV} hydrocarbyls (mechanism **C**). Some of the catalytic systems in Table 9.1 utilize these cocatalysts, CuX_2 (entries 7, 8, 23), NO_x (entries 2, 4), and a heteropolyacid $H_4[PMo_{11}VO_{40}]$ (entry 25). While copper(II) cocatalysts are traditionally assumed to support recycling of Pd^0 to Pd^{II} species (mechanism **B**), the systems utilizing NO_x as redox mediators (entries 2, 4) are proposed to support reactions involving a Pd^{II}/Pd^{IV} redox couple (mechanism **C**, Scheme 9.1).

The presence of a redox-active cocatalyst in a catalytic system, such as those mentioned above, does not exclude the option that O_2 activation will actually be carried out by palladium species. In particular, the authors of the reaction in entry 16 have observed only negligible effect of $Cu(OTf)_2$ additive on Pd^0 reoxidation. They have concluded that the major role of $Cu(OTf)_2$ cocatalyst in the palladium-catalyzed oxidative homocoupling of *o*-xylene is not O_2 activation but rather that of a Lewis acid enhancing reactivity of $Pd(OAc)_2$ [31].

O_2 Activation by Pd^0 Species

The catalytic systems where O_2 activation is carried out by Pd^0 species are becoming increasingly important practically and are interesting mechanistically. These reactions convert Pd^0 complexes to Pd^{II} peroxo species (Eq. 9.7), e.g., $Pd(PPh_3)_4$ is oxidized to $Pd(\kappa^2\text{-}O_2)(PPh_3)_2$ [64]. Notably, triphenylphosphine liberated in the latter reaction can reduce palladium peroxide and form corresponding phosphine oxide. This fact suggests that the practical value of phosphine ligands in aerobic palladium catalysis may be limited.

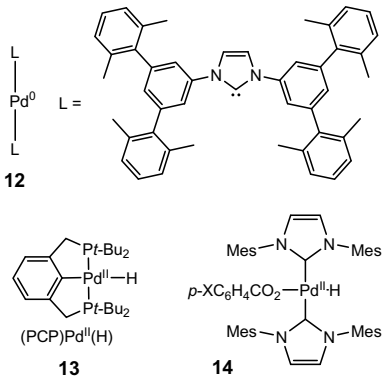


Fig. 9.2 Some palladium complexes characterized in O_2 activation

O_2 activation by Pd^0 species can be most efficient when suitable ligands are present. For instance, a PdL_2 complex **12** with very bulky N-heterocyclic carbene (NHC) ligands L=N,N'-bis(2,2",6,6"-tetramethyl-*m*-terphen-5'-yl)imidazole-2-ylidene) (Fig. 9.2) reacts with O_2 at room temperature even in a solid state [65].

$$L_nPd^0 + O_2 \rightarrow \text{cis-}L_2Pd^{II}(O_2) + (n-2)L \tag{9.7}$$

The resulting palladium(II) peroxo complexes are relatively basic and can react stepwise with acids to form first palladium(II) hydroperoxo complexes (Eq. 9.8) and, eventually, H_2O_2 (Eq. 9.9):

$$\text{cis-}L_2Pd^{II}(O_2) + HX \rightarrow Pd^{II}X(OOH)L_2 \tag{9.8}$$

$$Pd^{II}X(OOH)L_2 + HX \rightarrow Pd^{II}X_2L_2 + H_2O_2 \tag{9.9}$$

In turn, H_2O_2 released in the last reaction may act as an oxidant with respect to Pd^0 and/or reactive hydrocarbyl Pd^{II} species (e.g., Scheme 9.7, bottom) [60] or decompose into O_2 and H_2O.

In the absence of suitable ligands, the rate of the oxidation reaction in Eq. 9.7 may be too slow and/or the stability of Pd^0 complexes may be too low, so that a catalyst deactivation leading to the formation of catalytically inactive Pd black may become highly competitive with the reaction (9.7). Such catalyst deactivation is the major reason why many palladium-based catalytic systems involving Pd^{II}/Pd^0 couple (mechanism **B**, Scheme 9.1) require high catalyst loading, 10–20% and even higher (see Table 9.1 for examples). Notably, at some intermediate stages leading to the formation of palladium black, palladium(I) species [25, 66] and, ultimately, soluble palladium clusters/nanoparticles may be produced which often are also catalytically active in aerobic oxidation reactions [67, 68].

Interestingly, until recently, the utilization of organic ligands in aerobic functionalization catalysis by palladium compounds was not practiced, although some polar solvents such as DMSO that can coordinate to palladium(II) center were used successfully in a number of aerobic palladium-catalyzed C–H functionalization reactions (examples in entries 6, 22, Table 9.1). This situation is, in part, a reflection of a formerly poor understanding of the underlying aerobic chemistry of Pd^0 species [47]. One of the important reasons for this lag is related to the fact that rates of aerobic C–H functionalization by soluble palladium complexes are often zero order in $[O_2]$, and their turnover-limiting step is the substrate C–H activation, so making the characterization of the O_2 activation step difficult in such systems.

O_2 Activation by Pd^{II} Hydrides Versus Pd^0 Species

Catalytically competent palladium(0) species are expected to result from C–X reductive elimination of Pd^{II}(hydrocarbyl)X complexes in mechanism **B**, Scheme 9.1. Alternatively, palladium(0) species may be produced as a result of H–Y elimination of palladium(II) hydrides (Eq. 9.10) which, in turn, are formed as a result of β-hydrogen atom elimination of suitable palladium(II) alkyl, alkoxo, or similar species.

$$L_nPd^{II}(H)Y \rightarrow L_nPd^0 + HY \tag{9.10}$$

Importantly, palladium(II) hydrides are also able to react with O_2. The reaction proceeds via O_2 hydrogen atom abstraction/radical recombination pathway leading to O_2 insertion into Pd–H bond and formation of palladium(II) hydroperoxides [69] (Eq. 9.11), so allowing to return Pd^{II} back to the catalytic cycle.

$$L_nPd^{II}(H)Y + O_2 \rightarrow L_nPd^{II}(OOH)Y \tag{9.11}$$

The reaction between O_2 and a (PCP)Pd^{II}(H) complex **13** (Fig. 9.2) was characterized kinetically to reveal a first-order dependence of its rate on pO_2 and a large deuterium kinetic isotope effect, $k_{PdH}/k_{PdD} = 5.8$, all consistent with an H-atom abstraction mechanism. The mechanism was also analyzed computationally [70].

More extensive studies of reactions between various palladium(II) hydride complexes and O_2 (Eq. 9.11) have led to a conclusion that an alternative reaction sequence (9.10)–(9.7)–(9.8), that is HY reductive elimination—oxidation, leading to palladium(II) hydroperoxo complexes can be faster than the direct route (9.11) [71], although, in general, both pathways may be very competitive kinetically [72, 73]. In some cases, just a minor variation in the electronic properties of the anionic ligand Y, e.g., a *p*-substituted benzoate in *bis*-NHC palladium(II) hydride complexes *trans*-$L_2Pd^{II}(H)(O_2CC_6H_4$-*p*-X) **14** (Fig. 9.2), can lead to a change in the reaction mechanism from the direct O_2 insertion (Eq. 9.11), with a large deuterium kinetic isotope effect, $k_{PdH}/k_{PdD} = 3.1$ for X = OMe [73], to a stepwise transformation (9.10)–(9.7)–(9.8), with a very small $k_{PdH}/k_{PdD} = 1.3$ for X = H [71]. Interestingly, benzoquinone additives which are often present as a cocatalyst in palladium-

catalyzed aerobic C–H functionalization reactions (see, e.g., an example in entry 19 in Table 9.1) were found to accelerate the reaction sequence (9.10)–(9.7)–(9.8) [74].

Notably, the HY reductive elimination—oxidation reaction sequence (9.10)–(9.7)–(9.8) and, in particular, its first step (9.10), is strongly favored in palladium(II) complexes bearing labile monodentate L-type ligands since three-coordinate $LPd^{II}(H)Y$ species resulting from a ligand L dissociation eliminate H–Y at faster rates (Eq. 9.10, $n = 1$ vs. $n = 2$). The use of bidentate ligands appears to also favor the HY reductive elimination—oxidation reaction sequence, as compared to the direct pathway (Eq. 9.11), when one of the ligand's donor atoms is basic enough to deprotonate the Pd^{II}–H bond. That is usually the case for N-donor ligands. The deprotonation can occur upon this donor atom dissociation from the metal. As a result, the authors of [47] conclude that the O_2 activation in most aerobic catalytic systems used till date is carried out, most typically, by Pd^0 species and not by palladium(II) hydrides.

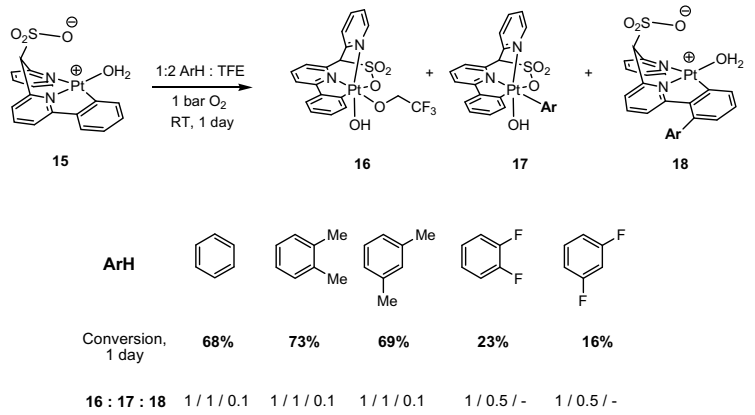
9.3 Homogeneous Organometallic Platinum—Catalyzed Aerobic CH Oxidation

As it was mentioned in the introduction, the first-ever developed platinum-based catalytic system for aerobic C–H functionalization allowed to carry out an overall very challenging transformation, the conversion of gaseous methane to CH_3X products (Eqs. 9.2, 9.3), albeit with low $[PtCl_4]^{2-}$ catalyst turnover ($\leq$6) and poor selectivity in CH_3X products ($\leq$50%) [5]. The reaction mechanism [7, 8] is similar to mechanism C shown in Scheme 9.1 for aerobic palladium catalysis. Notably, the heteropolyacid used in these experiments as a redox mediator was also shown by the authors to oxidize methanol, so contributing to the overall low reaction selectivity in CH_3X products. Subsequent attempts to develop more efficient variants of the reaction were made. In 2001, some modifications to the aerobic system were undertaken by introducing aqueous $CuCl_2$ as a redox mediator instead of a heteropolyacid and using water-soluble alkanesulfonic acids as substrates which are much easier to handle than gaseous methane. Water was used as the reaction medium [75]. These changes allowed to achieve the catalyst turnover numbers up to 43–52 after 4 h of reaction at 160 °C for ethanesulfonic acid as a substrate (Eq. 9.12):

$$2C_2H_5SO_3Na + O_2 \rightarrow 2HOCH_2CH_2SO_3Na \qquad (9.12)$$

The reaction was ~50–76% selective with respect to the methyl group oxidation product, 2-hydroxyethanesulfonic acid shown in Eq. 9.12, with the rest of the balance being mostly the corresponding aldehyde and carboxylic acid.

A more recent reinvestigation of the Shilov reaction was undertaken in 2010 [9]. The authors used microfluidics technique and screened a number of redox mediators for the reaction of CH_4 with O_2 in water at 180 °C. They observed up to 49 catalyst



Scheme 9.8 Aerobic stoichiometric C–H functionalization of arenes mediated by platinum(II) complex **15** [10]

turnovers after 6 h with the selectivity in CH_3OH ~50% using either $Fe_2(SO_4)_3$ or a heteropolyacid as a redox mediator. Formic acid accounted for the rest of the balance.

Although the catalyst turnover numbers in both cases are much better than in the original Shilov publication [5] and, in fact, in many palladium-based systems listed in Table 9.1, the resulting oxidation products, 2-hydroxyethanesulfonic acid and methanol, may, most likely, be readily available at a lower cost using traditional methods of their preparation. Further reaction developments are in order.

Notably, learning from recent progress in aerobic catalytic C–H functionalization by palladium complexes, a possible direction for future research in catalytic platinum chemistry may target a better understanding of the underlying C–H activation, aerobic oxidation, and C–X reductive elimination chemistry of platinum species involved and rational design of ligands for these transformations [76]. As an example of such efforts, platinum(II) complex **15** supported by a newly designed sulfonated pincer ligand in Scheme 9.8 supports facile aerobic stoichiometric C–H functionalization of a series of arenes leading to derived arylplatinum(IV) complexes **17** [10]. The reaction is more efficient for electron-rich arenes. The minor products of the arenes functionalization are oxidatively C–C coupled complexes **18**. The fraction of the undesirable product **16** forming along with **18** can be significantly reduced in the presence of *p*-hydroquinone.

9.4 Development of Homogeneous Organometallic Nickel-Catalyzed Aerobic CH Oxidation

Nickel-based catalytic systems for organometallic aerobic C–H functionalization are still at an early stage of development. In fact, no such systems have been reported so far. At the same time, some basic step of a plausible catalytic cycle incorpo-

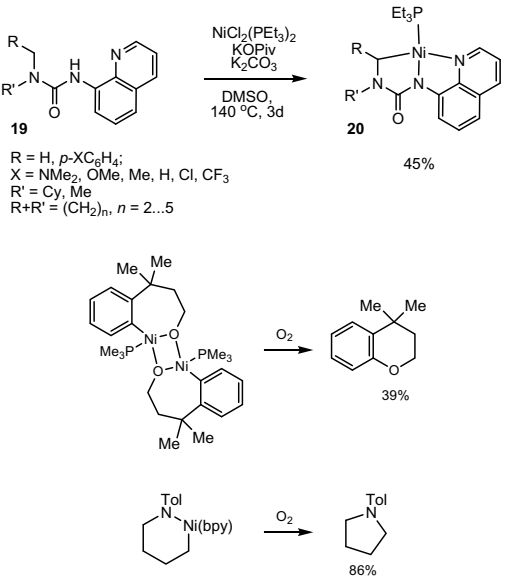
rating nickel complexes can be envisioned. A recent publication [77] discloses a possible approach toward donor group/auxiliary **19**-directed C(sp^3)–H activation at a nickel(II) center to produce metallacyclic nickel(II) alkyls **20** (Scheme 9.9). The behavior of the reported system resembles that of similar palladium(II) systems, although at somewhat higher temperatures for the nickel-based one. The kinetics of the reaction in Scheme 9.9 has been characterized in detail, including a large deuterium kinetic isotope effect, $k_H/k_D \sim 7$, and the reaction was proposed to operate a concerted metallation—deprotonation mechanism also common in palladium chemistry.

Notably, although not shown to involve organonickel intermediates, hydrogen atom transfer (HAT) chemistry involving C–H bonds of a series of alkylarenes such as 9,10-dihydroanthracene, toluene, and ethylbenzene has also been demonstrated in their reactions with a few isolated nickel(III) complexes [78].

In turn, stoichiometric aerobic Ni–C bond functionalization reactions have been known for a long time. Examples of aerobic oxidative C(sp^2)–O [79] and C(sp^3)–N [80] coupling reactions are given in Scheme 9.9, bottom.

Finally, there is a substantial body of recent work detailing the intimate chemistry of dioxygen activation at a nickel(I) center supported by various chelating ligands which can lead to nickel(II) superoxo or peroxo complexes and even nickel(III) peroxo species [81].

Overall, the fact that the key steps of a potential catalytic cycle of aerobic C–H functionalization by nickel are established, may be viewed as a promise of possible future development of the related catalytic chemistry.



Scheme 9.9 Auxiliary-directed C(sp^3)–H activation at a nickel(II) center (top) [77] and aerobic oxidative functionalization of Ni^{II}-C(sp^3) bonds (bottom) [78, 79]

9.5 Conclusions

Aerobic organometallic C–H functionalization catalysis by palladium complexes has shown a significant development over the past two decades. The major driving force behind this success was an increased attention to and an improved understanding of the reaction mechanisms and the role that the ligand environment at the metal plays in such reactions. Numerous challenges remain on the way toward making hydrocarbon C–H bonds a "functional group" that can be readily and selectively transformed to another "classic" functional group by using the right catalytic system. Understanding the mechanism of C–H activation and the factors that control its selectivity in substrates with chemically non-equivalent C–H bonds can drive the progress in this area. A collaboration of experimentalists and computational chemists in such a challenging area of research may become fruitful. While organometallic palladium aerobic oxidation catalysis has already been an established and has a solid reputation among synthetic chemists, analogous platinum-based systems for aerobic C–H functionalization are scarce. Slower reaction rates of reactions involving platinum species, as compared to analogous palladium chemistry, maybe a reason behind such poor performance in aerobic platinum catalysis. But as in the case of the recent development in aerobic palladium catalysis, greater attention to reaction mechanisms and ligand design might help improve the situation. Finally, organometallic nickel aerobic oxidation catalysis is not established yet but there are some promising reports that suggest possible future development of this field. Overall, selective catalytic aerobic C–H functionalization reactions are poised to grow in their importance in the coming years and the group 10 metals can continue contributing to this development.

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References

1. Hartwig JF (2010) The organotransition metal chemistry: from bonding to catalysis. University Science Books, Sausalito
2. Smidt J, Hafner W, Jira R et al (1959) Catalytic reactions of olefins on compounds of the platinum group. Angew Chem 71(5):176–182. https://doi.org/10.1002/ange.19590710503
3. Moiseev II, Vargaftik MN, Syrkin YK (1960) Mechanism of the reaction of palladium salts with olefins in hydroxyl-containing solvents. Dokl Akad Nauk SSSR 133:377–380
4. Smidt J, Hafner W, Jira R et al (1962) The oxidation of olefins with palladium chloride catalysts. Angew Chem Int Ed 1(2):80–88. https://doi.org/10.1002/anie.196200801
5. Geletii YV, Shilov AE (1983) Catalytic oxidation of alkanes by molecular oxygen - oxidation of methane in the presence of platinum salts and heteropoly acids. Kinet Catal 24:413–416
6. Goldshleger NF, Shteinman AA, Shilov AE et al (1972) Reactions of alkanes in solutions of chloride complexes of platinum. Russ J Phys Chem 46:785–786
7. Shilov AE, Shulpin GB (1997) Activation of C–H bonds by metal complexes. Chem Rev 97:2879–2932. https://doi.org/10.1021/cr9411886

8. Shteinman A (2017) Activation and selective oxy-functionalization of alkanes with metal complexes: Shilov reaction and some new aspects. J Mol Catal A Chem 426:305–315. https://doi.org/10.1016/j.molcata.2016.08.020
9. Lin MR, Shen CY, Garcia-Zayas EA et al (2001) Catalytic Shilov chemistry: platinum chloride-catalyzed oxidation of terminal methyl groups by dioxygen. J Am Chem Soc 123(5):1000–1001. https://doi.org/10.1021/ja001926+
10. Watts D, Zavalij PY, Vedernikov AN (2018) Consecutive C–H and O_2 activation at a Pt(II) center to produce Pt(IV) aryls. Organometallics 37(22):4177–4180. https://doi.org/10.1021/acs.organomet.8b00662
11. Chong E, Kampf JW, Ariafard A, Canty AJ et al (2017) Oxidatively induced C–H activation at high valent nickel. J Am Chem Soc 139(17):6058–6061. https://doi.org/10.1021/jacs.7b02387
12. Camasso NM, Sanford MS (2015) Design, synthesis, and carbon-heteroatom coupling reactions of organometallic nickel(IV) complexes. Science 347(6227):1218–1220. https://doi.org/10.1126/science.aaa4526
13. McDonald RI, Liu G, Stahl SS (2011) Palladium-catalyzed alkene functionalization via nucleopalladation: stereochemical pathways and enantioselective catalytic applications. Chem Rev 111(4):2981–3019. https://doi.org/10.1021/cr100371y
14. Zhang Y-H, Yu J-Q (2009) Pd(II)-catalyzed hydroxylation of arenes with 1 atm of O_2 or air. J Am Chem Soc 131(41):14654–14655. https://doi.org/10.1021/ja907198n
15. Zultanski SL, Stahl SS (2015) Palladium-catalyzed aerobic acetoxylation of benzene using NOx-based redox mediators. J Organomet Chem 793:263–268. https://doi.org/10.1016/j.jorganchem.2015.03.003
16. Zhang J, Khaskin E, Anderson NP et al (2008) Catalytic aerobic oxidation of substituted 8-methylquinolines in pd^{ii} – 2,6-pyridinedicarboxylic acids systems. Chem Commun 31:3625–3627. https://doi.org/10.1039/B803156H
17. Wang D, Zavalij PY, Vedernikov AN (2013) Aerobic C–H acetoxylation of 8-methylquinoline in PdII – pyridinecarboxylic acids systems: some structure – reactivity relationships. Organometallics 32(17):4882–4891. https://doi.org/10.1021/om400618n
18. Stowers KJ, Kubota A, Sanford MS (2012) Nitrate as a redox co-catalyst for the aerobic Pd-catalyzed oxidation of unactivated sp^3-C–H bonds. Chem Sci 3(11):3192–3195. https://doi.org/10.1039/c2sc20800h
19. Campbell AN, White PB, Guzei IA et al (2010) Allylic C−H acetoxylation with a 4,5-diazafluorenone-ligated palladium catalyst: a ligand-based strategy to achieve aerobic catalytic turnover. J Am Chem Soc 132(43):15116–15119. https://doi.org/10.1021/ja105829t
20. Clagg K, Hou H, Weinstein AB et al (2016) Synthesis of indole-2-carboxylate derivatives via palladium-catalyzed aerobic amination of aryl C–H bonds. Org Lett 18(15):3586–3589. https://doi.org/10.1021/acs.orglett.6b01592
21. Inamoto K, Saito T, Hiroya K et al (2010) Palladium-catalyzed intramolecular amidation of C(sp^2)-H bonds: synthesis of 4-aryl-2-quinolinones. J Org Chem 75(11):3900–3903. https://doi.org/10.1021/jo100557s
22. Tsang WCP, Zheng N, Buchwald SL (2005) Combined C–H functionalization/C–N bond formation route to carbazoles. J Am Chem Soc 127(42):14560–14561. https://doi.org/10.1021/ja055353i
23. Rogers MM, Kotov V, Chatwichien J et al (2007) Palladium-catalyzed oxidative amination of alkenes: improved catalyst reoxidation enables the use of alkene as the limiting reagent. Org Lett 9(21):4331–4334. https://doi.org/10.1021/ol701903r
24. Brice JL, Harang JE, Timokhin VI et al (2005) Aerobic oxidative amination of unactivated alkenes catalyzed by palladium. J Am Chem Soc 127(9):2868–2869. https://doi.org/10.1021/ja0433020
25. White PB, Jaworski JN, Zhu GH et al (2016) Diazafluorenone-promoted oxidation catalysis: insights into the role of bidentate ligands in Pd-catalyzed aerobic aza-wacker reactions. ACS Catal 6(5):3340–3348. https://doi.org/10.1021/acscatal.6b00953
26. McDonald RI, White PB, Weinstein AB et al (2011) Enantioselective Pd(II)-catalyzed aerobic oxidative amidation of alkenes and insights into the role of electronic asymmetry in pyridine-oxazoline ligands. Org Lett 13(11):2830–2833. https://doi.org/10.1021/ol200784y

27. McDonald RI, Stahl SS (2010) Modular synthesis of 1,2-diamine derivatives by palladium-catalyzed aerobic oxidative cyclization of allylic sulfamides. Angew Chem Int Ed 49(32):5529–5532. https://doi.org/10.1002/anie.200906342
28. Kong W-J, Chen X, Wang M et al (2018) Rapid syntheses of heteroaryl-substituted imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazole via aerobic C2-H functionalizations. Org Lett 20(1):284–287. https://doi.org/10.1021/acs.orglett.7b03596
29. Liu Y-J, Xu H, Kong W-J et al (2014) Overcoming the limitations of directed C–H functionalizations of heterocycles. Nature 515(7527):389–393. https://doi.org/10.1038/nature13885
30. Tereniak SJ, Stahl SS (2017) Mechanistic basis for efficient, site-selective, aerobic catalytic turnover in Pd-catalyzed C–H imidoylation of heterocycle-containing molecules. J Am Chem Soc 139(41):14533–14541. https://doi.org/10.1021/jacs.7b07359
31. Wang D, Stahl SS (2017) Pd-Catalyzed aerobic oxidative biaryl coupling: non-redox cocatalysis by $Cu(OTf)_2$ and discovery of $Fe(OTf)_3$ as a highly effective cocatalyst. J Am Chem Soc 139(16):5704–5707. https://doi.org/10.1021/jacs.7b01970
32. Izawa Y, Stahl SS (2010) Aerobic oxidative coupling of o-xylene: discovery of 2-fluoropyridine as a ligand to support selective Pd-catalyzed C–H functionalization. Adv Synth Catal 352(18):3223–3229. https://doi.org/10.1002/adsc.201000771
33. Brasche G, Garcia-Fortanet J, Buchwald SL (2008) Twofold C–H functionalization: palladium-catalyzed ortho arylation of anilides. Org Lett 10(11):2207–2210. https://doi.org/10.1021/ol800619c
34. Watanabe T, Ueda S, Inuki S et al (2007) One-pot synthesis of carbazoles by palladium-catalyzed N-arylation and oxidative coupling. Chem Commun 43:4516–4518. https://doi.org/10.1039/B707899D
35. Engle KM, Thuy-Boun PS, Dang M et al (2011) Ligand-accelerated cross-coupling of $C(sp^2)$-H bonds with arylboron reagents. J Am Chem Soc 133(45):18183–18193. https://doi.org/10.1021/ja203978r
36. Baxter RD, Sale D, Engle KM et al (2012) Mechanistic rationalization of unusual kinetics in Pd-catalyzed C–H olefination. J Am Chem Soc 134(10):4600–4606. https://doi.org/10.1021/ja207634t
37. Li S, Cai L, Ji H et al (2016) Pd(II)-catalyzed *meta*-C–H functionalizations of benzoic acid derivatives. Nat Commun 7:10443. https://doi.org/10.1038/ncomms10443
38. Beck EM, Grimster NP, Hatley R et al (2006) Mild aerobic oxidative palladium (II) catalyzed C–H bond functionalization: regioselective and switchable C–H alkenylation and annulation of pyrroles. J Am Chem Soc 128(8):2528–2529. https://doi.org/10.1021/ja058141u
39. Lu M-Z, Chen X-R, Xu H et al (2018) Ligand-enabled ortho-C–H olefination of phenylacetic amides with unactivated alkenes. Chem Sci 9(5):1311–1316. https://doi.org/10.1039/C7SC04827K
40. Engle KM, Wang D-H, Yu J-Q (2010) Ligand-accelerated C–H activation reactions: evidence for a switch of mechanism. J Am Chem Soc 132(40):14137–14151. https://doi.org/10.1021/ja105044s
41. Stowers KJ, Fortner KC, Sanford MS (2011) Aerobic Pd-catalyzed sp^3 C–H olefination: a route to both N-heterocyclic scaffolds and alkenes. J Am Chem Soc 133(17):6541–6544. https://doi.org/10.1021/ja2015586
42. Ferreira EM, Stoltz BM (2003) Catalytic C–H bond functionalization with palladium(II): aerobic oxidative annulations of indoles. J Am Chem Soc 125(32):9578–9579. https://doi.org/10.1021/ja035054y
43. Bercaw JE, Hazari N, Labinger JA (2008) oxidative aromatization of olefins with dioxygen catalyzed by palladium trifluoroacetate. J Org Chem 73(21):8654–8657. https://doi.org/10.1021/jo8016296
44. Izawa Y, Pun D, Stahl SS (2011) Palladium-catalyzed aerobic dehydrogenation of substituted cyclohexanones to phenols. Science 333(6039):209–213. https://doi.org/10.1126/science.1204183
45. Iosub AV, Stahl SS (2015) Palladium-catalyzed aerobic oxidative dehydrogenation of cyclohexenes to substituted arene derivatives. J Am Chem Soc 137(10):3454–3457. https://doi.org/10.1021/ja512770u

46. Gorelsky SI, Lapointe D, Fagnou KJ (2012) Analysis of the palladium-catalyzed (aromatic) C−H bond metalation − deprotonation mechanism spanning the entire spectrum of arenes. J Org Chem 77(1):658–668. https://doi.org/10.1021/jo202342q
47. Wang D, Weinstein AB, White PB et al (2018) Ligand-promoted palladium-catalyzed aerobic oxidation reactions. Chem Rev 118(5):2636–2679. https://doi.org/10.1021/acs.chemrev.7b00334
48. Engelin C, Jensen T, Rodriguez- Rodriguez S et al (2013) Mechanistic investigation of palladium-catalyzed allylic C–H activation. ACS Catal 3(3):294–302. https://doi.org/10.1021/cs3007878
49. Ryabov AD (1990) Mechanisms of intramolecular activation of C−H bonds in transition-metal complexes. Chem Rev 90(2):403–424. https://doi.org/10.1021/cr00100a004
50. Engle KM, Mei T-S, Wasa M et al (2012) Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. Acc Chem Res 45(6):788–802. https://doi.org/10.1021/ar200185g
51. He J, Wasa M, Chan KSL et al (2017) Palladium-catalyzed transformations of alkyl C−H bonds. Chem Rev 117(13):8754–8786. https://doi.org/10.1021/acs.chemrev.6b00622
52. Yang Y-F, Houk KN, Hong X et al (2017) Experimental-computational synergy for selective Pd(II)-catalyzed C–H activation of aryl and alkyl groups. Acc Chem Res 50(11):2853–2860. https://doi.org/10.1021/acs.accounts.7b00440
53. Davies DL, Donald SMA, Macgregor SA (2005) Computational study of the mechanism of cyclometalation by palladium acetate. J Am Chem Soc 127(4):13754–13755. https://doi.org/10.1021/ja052047w
54. García-Cuadrado D, Braga AAC, Maseras F et al (2006) Proton abstraction mechanism for the palladium-catalyzed intramolecular arylation. J Am Chem Soc 128(4):1066–1067. https://doi.org/10.1021/ja056165v
55. Boisvert L, Denney MC, Hanson SK et al (2009) Insertion of molecular oxygen into a palladium(II) methyl bond: a radical chain mechanism involving palladium(III) intermediates. J Am Chem Soc 131(43):15802–15814. https://doi.org/10.1021/ja9061932
56. Zeitler HE, Kaminsky WA, Goldberg KI (2018) Insertion of molecular oxygen into the metal − methyl bonds of platinum(II) and palladium(II) 1,3-bis(2-pyridylimino)isoindolate complexes. Organometallics 37(21):3644–3648. https://doi.org/10.1021/acs.organomet.8b00573
57. Taylor RA, Law DJ, Sunley GJ et al (2009) Towards photocatalytic alkane oxidation: the insertion of dioxygen into a platinum(II) − methyl bond. Angew Chem Int Ed 48(32):5900–5903. https://doi.org/10.1002/anie.200806187
58. Petersen AR, Taylor RA, Vicente-Hernández I et al (2014) Oxygen insertion into metal carbon bonds: formation of methylperoxo Pd(II) and Pt(II) Complexes via photogenerated dinuclear intermediates. J Am Chem Soc 136(40):14089–14099. https://doi.org/10.1021/ja5055143
59. Fernández-Alvarez VM, Ho SKY, Britovsek GJP et al (2018) A DFT-based mechanistic proposal for the light-driven insertion of dioxygen into Pt(II) − C bonds. Chem Sci 9(22):5039–5046. https://doi.org/10.1039/c8sc01161c
60. Sberegaeva AV, Zavalij PY, Vedernikov AN (2016) Oxidation of a monomethylpalladium(II) complex with O_2 in water: tuning reaction selectivity to form ethane, methanol or methylhydroperoxide. J Am Chem Soc 138(4):1446–1455. https://doi.org/10.1021/jacs.5b12832
61. Maleskis A, Sanford MS (2011) Facial tridentate ligands for stabilizing palladium(IV) complexes. Organometallics 30(24):6617–6627. https://doi.org/10.1021/om200779j
62. Khusnutdinova JR, Qu F, Zhang Y et al (2012) Formation of the palladium(IV) complex [(Me3tacn)PdIVMe3] + through aerobic oxidation of (Me3tacn)PdIIMe2 (Me3tacn = N, N′, N″- Trimethyl-1,4,7-triazacyclononane). Organometallics 31(13):4627–4630. https://doi.org/10.1021/om300426r
63. Tang F, Zhang Y, Rath NP et al (2012) Detection of Pd(III) and Pd(IV) intermediates during the aerobic oxidative C–C bond formation from a Pd(II) dimethyl complex. Organometallics 31(18):6690–6696. https://doi.org/10.1021/om300752w
64. Wilke G, Schott H, Heimbach P (1967) Oxygen complexes of zerovalent nickel, palladium, and platinum. Angew Chem Int Ed 6(1):92–93. https://doi.org/10.1002/anie.196700921

65. Yamashita M, Goto K, Kawashima T (2005) Fixation of both O_2 and CO_2 from air by a crystalline palladium complex bearing heterocyclic carbene ligands. J Am Chem Soc 127(20):7294–7295. https://doi.org/10.1021/ja051054h
66. Jaworski JN, McCann SD, Guzei IA et al (2017) Detection of palladium(I) in aerobic oxidation catalysis. Angew Chem Int Ed 56(13):3605–3610. https://doi.org/10.1002/anie.201700345
67. Vargaftik MN, Zagorodnikov VP, Stolarov IP et al (1989) Giant palladium clusters as catalysts of oxidative reactions of olefins and alcohols. J Mol Catal 53(3):315–348. https://doi.org/10.1016/0304-5102(89)80066-5
68. Pun D, Diao T, Stahl SS (2013) Aerobic dehydrogenation of cyclohexanone to phenol catalyzed by $Pd(TFA)_2$/2-dimethylaminopyridine: evidence for the role of Pd nanoparticles. J Am Chem Soc 135(22):8213–8221. https://doi.org/10.1021/ja403165u
69. Denney MC, Smythe NA, Cetto KL et al (2006) Insertion of molecular oxygen into a palladium(II) hydride bond. J Am Chem Soc 128(8):2508–2509. https://doi.org/10.1021/ja0562292
70. Keith JM, Muller RP, Kemp RA et al (2006) Mechanism of direct molecular oxygen insertion in a palladium(II) − hydride bond. Inorg Chem 45(24):9631–9633. https://doi.org/10.1021/ic061392z
71. Konnick MM, Stahl SS (2008) Reaction of molecular oxygen with a Pd^{II}-hydride to produce a Pd^{II}-hydroperoxide: experimental evidence for an HX-reductive-elimination pathway. J Am Chem Soc 130(17):5753–5762. https://doi.org/10.1021/ja7112504
72. Popp BV, Stahl SS (2007) Insertion of molecular oxygen into a palladium-hydride bond: computational evidence for two nearly isoenergetic pathways. J Am Chem Soc 129(14):4410–4422. https://doi.org/10.1021/ja069037v
73. Konnick MM, Decharin N, Popp BV et al (2011) O_2 insertion into a palladium(II)-hydride bond: Observation of mechanistic crossover between HX-reductive-elimination and hydrogen-atom-abstraction pathways. Chem Sci 2(2):326–330. https://doi.org/10.1039/C0SC00392A
74. Decharin N, Stahl SS (2011) Benzoquinone-promoted reaction of O_2 with a Pd^{II}-hydride. J Am Chem Soc 133(15):5732–5735. https://doi.org/10.1021/ja200957n
75. Kreutz JE, Shukhaev A, Du W et al (2010) Evolution of catalysts directed by genetic algorithms in a plug-based microfluidic device tested with oxidation of methane by oxygen. J Am Chem Soc 132(9):3128–3132. https://doi.org/10.1021/ja909853x
76. Vedernikov AN (2012) Direct functionalization of M-C (M=PtII, PdII) bonds using environmentally benign oxidants, O_2 and H_2O_2. Acc Chem Res 45(6):803–813. https://doi.org/10.1021/ar200191k
77. Beattie DD, Grunwald AC, Perse T et al (2018) Understanding Ni(II)-mediated $C(sp^3)$ − H activation: tertiary ureas as model substrates. J Am Chem Soc 140(39):12602–12610. https://doi.org/10.1021/jacs.8b07708
78. Pirovano P, Farquhar ER, Swart M et al (2016) Tuning the reactivity of terminal nickel(III) − oxygen adducts for C−H bond activation. J Am Chem Soc 138(43):14362–14370. https://doi.org/10.1021/jacs.6b08406
79. Han R, Hillhouse GL (1997) Carbon–oxygen reductive-elimination from nickel(II) oxametallacycles and factors that control formation of ether, aldehyde, alcohol, or ester products. J Am Chem Soc 119(34):8135–8136. https://doi.org/10.1021/ja9714999
80. Koo K, Hillhouse GL (1995) Carbon-nitrogen bond formation by reductive elimination from nickel(II) amido alkyl complexes. Organometallics 14(9):4421–4423. https://doi.org/10.1021/om00009a054
81. Kieber-Emmons MT, Riordan CG (2007) Dioxygen activation at monovalent nickel. Acc Chem Res 40(7):618–625. https://doi.org/10.1021/ar700043n