

## I.2 Fundamental Properties of Palladium and Patterns of the Reactions of Palladium and Its Complexes

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### A. FUNDAMENTAL PROPERTIES OF Pd

Palladium (Pd) is the 46th atom in the periodic table with an average atomic weight of 106.4, and it consists of six isotopes. As mentioned earlier, it was named after the asteroid Pallas.<sup>[1]</sup> This name (i.e., *Pallas* in Latin or *Palladium* in Greek) was in turn derived from that of the mythological goddess of wisdom or learning, and palladium also means any object considered essential to the safety of a community, according to English dictionaries. Some of the notable properties of Pd are summarized in **Table 1**. Attempts are made below to probe the origins of the versatility, selectivity, and overall synthetic usefulness of Pd in organic synthesis in terms of some of its fundamental properties shown in **Table 1**.

First, as the 46th atom in the periodic table, Pd is a second row transition metal of moderately large atomic size, which is, of course, larger than Ni but smaller than Pt. This size factor appears to significantly contribute to a number of its chemical properties, such as moderate stability of its compounds and their controlled but wide-ranging reactivity leading to both versatility and certain kinds of selectivity features associated with it.

Second, Pd strongly favors the 0 and +2 oxidation states. Although other oxidation states, such as +1, +3, and +4, may prove to be significant in the future, they are currently rather rare (**Sect. II.4**). The facts presented above may, at least in part, stem from the size factor discussed previously. Thus, larger Pt tends to form Pd(IV)  $d^6$  octahedral complexes more readily than Pd, while smaller Ni is more prone to produce Ni(I) species via one-electron processes than Pd. This might possibly make Ni an even more versatile metal than Pd. In a sense, it is perhaps true. However, reactivity and instability are like the two faces of a coin, and they come together. Thus, the low tendency of Pd to undergo one-electron or radical processes appears to be responsible for making many organopalladium reactions selective possibly through avoidance and minimization of unwanted side reactions. There are also a number of indications that, in Ni-catalyzed reactions, the products are generally more prone to product-consuming side reactions than the corresponding Pd-catalyzed reactions. In those reactions that are catalyzed by both Pd and Ni, the Pd-catalyzed reactions tend to be cleaner and more chemo- and

TABLE 1. Some Fundamental Properties of Pd

Property	Value and/or Description			
Atomic number	46			
Atomic weight	106.4			
Isotopes and relative abundance <sup>a</sup>	<sup>102</sup> Pd	0.8%	<sup>104</sup> Pd	9.3%
	<sup>105</sup> Pd	22.6%	<sup>106</sup> Pd	27.1%
	<sup>108</sup> Pd	26.7%	<sup>110</sup> Pd	13.5%
Magnetic property	<sup>105</sup> Pd has $I = \frac{5}{3}$ , but it is of very low sensitivity.			
Electronic configuration	1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>6</sup> 3s <sup>2</sup> 3p <sup>6</sup> 4s <sup>2</sup> 4p <sup>6</sup> 4d <sup>10</sup> = [Kr]4d <sup>10</sup>			
Common oxidation states and coordination numbers	Oxidation State	Electronic Configuration		Geometry
	0	d <sup>10</sup>		Tetrahedral
	+2	d <sup>8</sup>		Square planar
	+4 (rare)	d <sup>6</sup>		Octahedral
Electronegativity <sup>b</sup>	2.2 (Pauling), 1.57 (Sanderson)			
Occurrence in the lithosphere <sup>c</sup>	0.015 ppm			
	Some data for comparison:			
	C (180 ppm), Ni (99 ppm), Pt (0.01 ppm), Ru and Rh (0.001 ppm each)			

<sup>a</sup>*Handbook of Chemistry and Physics*, 42nd ed., C. D. Hodgman, R. C. Weast, and S. M. Selby, Eds., The Chemical Rubber Publishing Co., Cleveland, **1960**, p. 470.

<sup>b</sup>(i) L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, NY, **1960**, p. 93.

(ii) R. T. Sanderson, *Inorganic Chemistry*, Van Nostrand-Reinhold, New York, **1967**, p. 72.

<sup>c</sup>W. S. Fyfe, *Geochemistry*, Oxford University Press, **1974**.

stereoselective than the corresponding Ni-catalyzed reactions. On the other hand, organoplatinum derivatives appear to be often too stable to be synthetically useful. The crude generalization made above with the Ni triad appears to be applicable also to some other triads, such as the Ti triad.

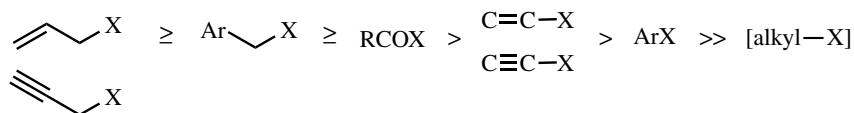
Third, as the second member of the group 10 Ni triad, Pd is a representative late transition metal, which tends to form  $d^{10}$  and  $d^8$  complexes of relatively low oxidation states (i.e., 0 or +2). Both high d-electron counts and low oxidation states as well as the moderately large size among those atoms that are commonly encountered in organic synthesis render Pd rather "soft." Coupled with the ready formation of coordinatively unsaturated species of 16 or even less electrons providing one or more empty coordination sites, Pd can indeed provide simultaneously at least one each of empty and filled nonbonding orbitals. Valence-shell empty orbitals provide Lewis acidic or electrophilic sites, one of which would serve as the LUMO (i.e., lowest unoccupied molecular orbital), while filled nonbonding orbitals provide Lewis basic or nucleophilic sites, one of which would act as the HOMO (i.e., highest occupied molecular orbital). It can therefore be easily understood why Pd can readily participate in a variety of concerted reactions of relatively low activation energies. Indeed, the great majority of the Pd-catalyzed reactions appear to be concerted processes where orbital symmetry and alignment are critically important. Some of the selectivity features, especially stereoselectivity, observed with them may readily be attributable to this nature.

One significant consequence of the high propensity for concerted processes is the high general affinity of Pd for nonpolar  $\pi$ -compounds, such as alkynes, alkenes, and even arenes. It can also readily form  $\sigma$  bonds with nonbonding electron donors ( $n$ -electron donors or  $n$ -donors, hereafter), such as amines, imines, nitriles, phosphines, phosphites, and various other N, P, S, and even O containing donors. Carbon monoxide and isoelectronic isonitriles are representative examples of C-centered  $n$ -electron donors. Some of these  $\pi$ - and  $n$ -electron donors rank among the most reactive functional groups toward Pd, and their presence in appropriate locations in the reactants is often critically important in observing various reactions of other functional groups, such as halides and carbonyl derivatives, as well.

Fourth, Pd is relatively electronegative, its Pauling and Sanderson electronegativity values being 2.2 and 1.57, respectively. Consequently, C—Pd bonds are relatively nonpolar, and they display rather low reactivity toward those polar groups that are very reactive toward Grignard reagents and organolithiums including various carbonyl compounds, such as ketones, esters, amides, and even aldehydes, as well as nitro compounds, and single-bonded polar electrophiles, such as alkyl halides and epoxides lacking proximal  $\pi$ - or  $n$ -donors. Acyl halides represent one notable exception, and their high reactivity toward Pd must stem from the simultaneous presence of a carbonyl and a carbon–halogen bond sharing one common C atom. As mentioned earlier, nitriles, representative triply bonded polar carbon electrophiles, do react readily as  $n$ -electron donors, but organopalladium derivatives do not readily add to the C $\equiv$ N triple bond.

Even though there is hardly any generally applicable reactivity scale in chemistry, **Scheme 1** might give a useful, if somewhat vague and limited, guideline, which must be used judiciously.

*Functional groups reactive toward Pd*



- Notes:**
1. Alkyl halides lacking proximal  $\pi$ - or  $n$ -donor groups are relatively inert but included for comparison.
  2. The X groups and approximate reactivity order are: I > OTf > Br > Cl > OZ > NZ<sub>2</sub>, CZ<sub>3</sub>, etc., where Z is any atom or group attached to O, N, and C.

*Functional groups relatively unreactive toward Pd*



- Notes:**
1. Acyl halides are very reactive, but included for comparison.
  2. Other relatively inert groups, such as NO<sub>2</sub> and C $\equiv$ N, may not be readily placed on the scale.

**Scheme 1**

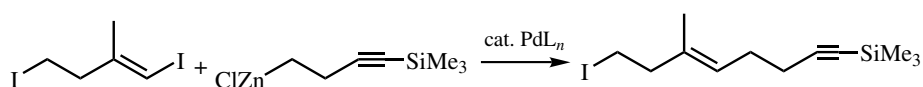
Despite some ambiguities and complications, it is clear that the reactivity trend observed with Pd and its compounds is largely opposite to that observed with the Grignard reagents and other “hard” and polar organometals. Thus, organopalladium chemistry has nicely complemented the traditional organometallic chemistry mostly involving Mg and Li. This is also one of the main reasons why organopalladium reactions are very loosely termed “very chemoselective,” which usually means that those electrophilic functional groups that are reactive toward polar organometals are tolerated. It should, however, be clearly noted that “chemoselectivity,” unlike stereoselectivity, is a rather vague and subjective term that heavily depends on one’s viewpoint, reaction conditions, presence or absence of other functional groups, and so on.

Fifth, although the relative inertness of carbonyl compounds excluding acyl halides was emphasized above, most everything in chemistry is relative, and organopalladium chemistry is no exception. Thus, in the absence of faster reaction paths, Pd and its complexes may react with aldehydes via C—H activation to give acylpalladium derivatives and subsequent decarbonylation (**Sect. VI.5.1**), while ketones may be reduced to alcohols and even to hydrocarbons, as discussed in **Sect. VII.2.3.1**, although the presence of proximal  $\pi$ - or  $n$ -donors may be critical in such reactions.

Another important group of compounds that are relatively unreactive under mild conditions but can react with Pd and its complexes under more forcing or favorable conditions are H donors including aldehydes mentioned above and  $H_2$  widely used in Pd-catalyzed hydrogenation (**Sect. VII.2**). In fact, Pd and its complexes can react, under a variety of different conditions, with almost any H-containing compounds, and this versatility may, in most cases, be attributable to the ability of Pd to provide simultaneously one or more empty and filled nonbonding orbitals. Those reactions that involve Pd(0) complexes may be interpreted in terms of concerted oxidative addition. In these reactions, the so-called acidity of the H compounds may play some roles, but it may not be the dominant factor. Thus, H donors that are reactive toward Pd include (i)  $H_2$ , (ii) hydrogen halides, (e.g., HCl) and other mineral acids, (iii) carboxylic acids, alcohols, and other OH-containing compounds, (iv) amines, and (v) a wide variety of C—H compounds including aldehydes mentioned above and formic acid derivatives, alkynes, alkenes, arenes, and other proximally activated C—H compounds, such as carbonyl compounds containing  $\alpha$  hydrogens, cyclopentadiene, and even unactivated alkanes, such as  $CH_4$ . Metal hydrides, be they electrophilic, neutral, or nucleophilic, also are generally reactive toward Pd complexes. The conventional wisdom regarding the relationship between the reactivity of H compounds and their acidity expressed in  $pK_a$  must be significantly modified. While this author never suggests that one stop being analytical, logical, and rational, liberation of one’s thinking from some old dogmas is always critically needed in science. For example, it would be absurd to use strong acids as H sources for generating metal hydrides containing “hard” and highly electropositive metals, such as Li and Mg, but it is perfectly acceptable for generation of palladium hydrides. While the definitions of and distinction between proton and hydride or, for that matter, neutral hydrogen are unmistakably clear, one must not forget that hydrogen is hydrogen regardless of whether it is viewed as proton, neutral hydrogen, or hydride in any given H-containing compounds. Perhaps, one only needs to recall that anionotropic 1,2-hydride shift may be initiated by protonation of alkenes.

It is clear from the foregoing discussion that the reactivity of Pd and its complexes can be modified over a very wide range, as needed. Of course, this statement may apply to almost any class of reagents and compounds, but it does appear that Pd and some

other transition metals, especially late transition metals, possess a remarkable ability to elevate or lower their reactivity toward a given substrate according to given reaction conditions, which leads to many different consequences ranging from a facile reaction to no reaction. Although not very clear, one can speculate that this may once again stem from their size and the availability of many interaction sites that may be filled or emptied, as needed. In any case, it is reasonable to state that Pd is very versatile and yet its reactions can be very selective. These two features are not mutually exclusive. For example, alkyl halides, even iodides, may be totally inert to Pd, as in a highly chemoselective transformation shown in **Scheme 2**<sup>[2]</sup> (**Sect. III.2.11.2**). And yet, in the absence of faster and more favorable reactions, alkyl halides, such as neopentyl iodide, can undergo Pd-catalyzed reactions.



**Scheme 2**

It is indeed advisable not to consider any compounds to be inert to Pd and its complexes. Tertiary amines, such as Et<sub>3</sub>N, are often used mainly to neutralize some acids generated as by-products. However, amines can react with Pd complexes to undergo oxidation, as discussed in **Sect. VIII.3.2**. So, unless the desired reaction is much faster than this oxidation reaction, there can be some undesirable consequences. Many solvents, such as HOAc, are also reactive with Pd complexes. In some cases, such reactions have been shown to be essential to observing favorable results<sup>[3]</sup> (**Sect. IV.4**). Even a small amount of adventitious impurities, such as H<sub>2</sub>O, can significantly alter the courses of organopalladium reactions,<sup>[4]</sup> as discussed in **Sect. VI.4.3**, even though many other organopalladium reactions can be satisfactorily carried out in water, where the molar ratio of water to substrate may exceed 100.

Sixth, Pd is rare and expensive. Therefore, all efforts must be made to use Pd as a catalyst or a catalyst component. In the majority of Pd-catalyzed reactions, some interconversions between Pd(0) and Pd(II) species must occur. Two crucial requirements in this respect are (i) that such Pd(0)–Pd(II) interconversions be kinetically facile and (ii) that they occur in either direction under one set of reaction conditions. As a late d-block transition metal that can readily provide at least one empty valence-shell orbital, Pd very well fulfills both of these two requirements. To further illustrate this point, consider S, for example. Many S compounds are known to be readily oxidized or reduced. However, concurrent oxidation and reduction of S compounds may not be readily observed in one pot under a single set of reaction conditions.

Some other important features associated with catalysts in redox reactions are that two and only two oxidation states separated by two elections be readily available and that the catalyst must not undergo other serious side reactions, especially those that would destroy the catalysts. So, the well-known fact presented earlier that Pd very strongly favors the 0 and +2 oxidation states appears to be serving as a very favorable factor rather than a limitation.

Finally, Pd appears to be relatively nontoxic, although there may never be completely nontoxic substances. Despite its relative lack of toxicity, all efforts should be made to avoid product contamination with Pd, and some potential toxicity that might be associated

**TABLE 2. Relationships between Some Fundamental Properties of Pd and Chemical Consequences**

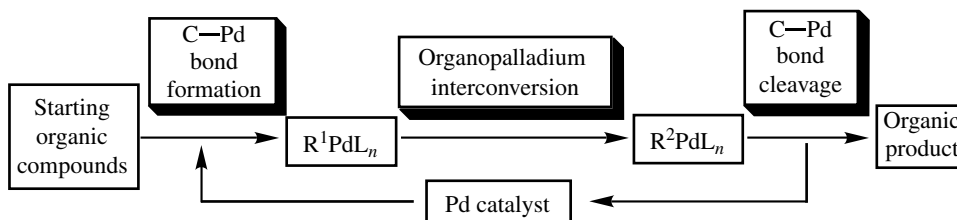
Fundamental Properties of Pd	Consequences
<ul style="list-style-type: none"> <li>• Moderately <i>large size</i></li> </ul>	<ul style="list-style-type: none"> <li>• <i>Moderate stability</i> of organopalladiums (Ni &lt; Pd &lt; Pt)</li> </ul>
<ul style="list-style-type: none"> <li>• Strong preference for the 0 and +2 oxidation states separated by a relatively narrow energy gap</li> </ul>	<ul style="list-style-type: none"> <li>• Relatively <i>rare one-electron or radical processes</i> (e.g., relative to Ni)</li> <li>• <i>Ready and reversible two-electron oxidation and reduction</i> (<math>\Rightarrow</math> catalysis)</li> </ul>
<ul style="list-style-type: none"> <li>• Late transition metal favoring <math>d^{10}</math> Pd(0) and <math>d^8</math> Pd(II) configurations <math>\Rightarrow</math> (i) <i>soft</i>, (ii) ready availability of Pd complexes containing <i>both empty and filled non-bonding orbitals</i> (LUMO and HOMO)</li> </ul>	<ul style="list-style-type: none"> <li>• High propensity for <i>concerted processes</i></li> <li>• High affinity toward <i>soft <math>\pi</math>- and <math>n</math>-donors</i></li> <li>• <i>Selective and yet very resourceful reactivity</i> permitting reactions with almost any type of compounds</li> </ul>
<ul style="list-style-type: none"> <li>• Relatively <i>electronegative</i></li> </ul>	<ul style="list-style-type: none"> <li>• Relatively <i>unreactive</i> toward <i>polar functional groups</i></li> <li>• High <i>chemoselectivity</i></li> <li>• Largely <i>complementary</i> with the chemistry of <i>Grignard reagents</i> and <i>organolithiums</i></li> </ul>

with Pd-containing derivatives either introduced as reagents or generated in their reactions must always be anticipated and carefully examined, as needed.

The foregoing discussions may be summarized as shown in **Table 2**.

## B. GENERAL PATTERNS OF THE REACTIONS OF Pd AND Pd COMPLEXES

Synthesis of any organic compounds via organopalladium complexes must involve generation of C—Pd bonds and their cleavage. Additionally, interconversion of organopalladium intermediates occurs between the generation and cleavage of C—Pd bonds in most cases. Furthermore, if such reactions are to be catalytic in Pd, active Pd catalysts must be regenerated via cleavage of C—Pd bonds under these reaction conditions. So, most of the Pd-catalyzed organic synthetic reaction may be represented schematically by **Scheme 3**. In a relatively small number of cases, the organopalladium interconversion process may be omitted.

**Scheme 3**

Although a large number of reactions for each of the three crucial processes—that is, formation and cleavage of C—Pd bonds as well as organopalladium interconversion—are known, the great majority, probably more than 80–90%, of the currently known processes may be classified into approximately 20 general patterns summarized in **Table 3**. It is important to note that these are reaction patterns rather than mechanisms. They merely indicate starting material–product relationships without implying detailed mechanisms. In fact, detailed well-established mechanisms are not known in many cases. And yet, it is these reaction patterns that are most useful and hence important in the use of organopalladium chemistry for organic synthesis. The following discussion is intended to provide reasonable understanding of many of the known organopalladium reactions and some predictive power for the discovery and development of many additional organopalladium reactions in the future. It should also be mentioned here that, in **Table 3**, some rare processes and examples are deliberately omitted for the sake of simplicity and clarity. For example, Pd(IV) as well as Pd(I) and Pd(III) species are omitted from consideration, even though the significance of various processes involving Pd(IV) species is expected to increase in the future. For oxidative addition, only the mononuclear 1,1-oxidative addition process is shown, but this may be well justified, as the others are still of negligible importance from the organic synthetic viewpoint. For each pattern, exceptions to and deviations from the summary may be found. However, the main goal of this table is not complete accuracy but an aid to the development of some useful framework for rational thinking with predictive power. Due allowance must be made for some exceptions and deviations, and such cases must be handled accordingly.

Some additional comments pertaining to **Table 3** are also in order. Although  $\pi$ -complexation and oxidative complexation as well as  $\pi$ -decomplexation and reductive decomplexation are listed separately, distinction within each pair is essentially a semantic matter. It is desirable to list them separately, since some numbers, such as  $\Delta$ FOS (change in formal oxidation state) and  $\Delta$ Coord. No. (change in coordination number) are different. It may also be argued that, unless the formation of Pd(IV) species is considered to be likely, the reaction of  $\pi$ -compounds ( $X=Y$ ) with Pd(II) complexes may not be viewed as oxidative complexation. In general, however, either of the two options may be chosen, as deemed appropriate. As indicated in the footnote *f* of **Table 3**, various addition processes of Pd species involving alkenes and alkynes may involve the formation of  $\pi$ -complexes as discrete species, while others may not. For this reason, the terms used in this Handbook for addition processes, such as hydropalladations, include both  $\pi$ -complexation and addition. Patterns **11** through **19** are formally the reversals of the corresponding patterns **1** through **9**. It should be remembered that they merely are patterns without mechanistic implications. So, each corresponding pair (e.g., **1** and **11**) may or may not be the microscopic reversal of each other. Nucleophilic or electrophilic attack on ligands cannot readily be represented by one generic equation. In organopalladium chemistry, electrophilic attack still appears to be relatively insignificant, and most of the known processes involve nucleophilic attack. Two representative examples of nucleophilic attack on ligands are shown in **Scheme 4**. Finally, there are some other miscellaneous processes that may not be readily represented by any of those listed in **Table 3**, which should be supplemented, as needed.

As such, all of the processes shown in **Table 3** are stoichiometric in Pd. As stated earlier, they must be combined and sequenced appropriately to come up with Pd-catalyzed reactions. One critical requirement is that all of the Pd complexes in the catalytic cycle must be regenerated in the same forms and structures. In the redox process-containing

TABLE 3. Fundamental and General Patterns of Chemical Processes of Pd and Pd Complexes<sup>a</sup>

General Pattern	FOS <sup>b</sup> of Starting Compound	Δ FOS <sup>b</sup>	Δ Coord. No. <sup>c</sup>	Formation of C—Pd Bond	Cleavage of C—Pd Bond	Interconversion of RPdL <sub>n</sub>
<i>Mostly C—Pd Bond Formation</i>						
1. σ-Complexation	Pd(0) or Pd(II)	0	+1	Applicable	—	Possible
$\text{X} \cdot + \text{PdL}_n \rightarrow \text{X} \text{---} \text{PdL}_n$						
2. π-Complexation	Pd(0) or Pd(II)	0	+1 (or + 2) <sup>d</sup>	Applicable	—	Possible
$\begin{array}{c} \text{X} \\    \\ \text{Y} \end{array} + \text{PdL}_n \rightarrow \begin{array}{c} \text{X} \\    \\ \text{Y} \end{array} \text{---} \text{PdL}_n$						
3. Oxidative Complexation	Pd(0) <sup>e</sup>	+2	+2	Applicable	—	Possible
$\begin{array}{c} \text{X} \\    \\ \text{Y} \end{array} + \text{PdL}_n \rightarrow \begin{array}{c} \text{X} \\   \\ \text{Y} \end{array} \text{---} \text{PdL}_n$						
4. Oxidative Addition	Pd(0) <sup>e</sup>	+2	+2	Applicable	—	Possible
$\text{X} \text{---} \text{Y} + \text{PdL}_n \rightarrow \text{XYPdL}_n$						
5. Hydropalladation <sup>f</sup>	Pd(II)	0	0	+	—	Possible <sup>g</sup>
$\text{>C=C<} + \text{HPdL}_n \rightarrow \text{H} \text{---} \begin{array}{c}   \\ \text{C} \\   \end{array} \text{---} \begin{array}{c}   \\ \text{C} \\   \end{array} \text{---} \text{PdL}_n$						



<b>6. Metallopalladation<sup>f</sup></b> $\text{>C=C<} + \text{MPdL}_n \rightarrow \text{M}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\text{PdL}_n$	Pd(II)	0	0	+	—	Possible <sup>g</sup>
<b>7. Heteropalladation<sup>f,h</sup></b> $\text{>C=C<} + \text{XPdL}_n \rightarrow \text{X}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\text{PdL}_n$	Pd(II)	0	0	+	—	Possible <sup>g</sup>
<b>8. Migratory Deinsertion</b> $\text{X}-\text{Y}-\text{PdL}_n \rightarrow \text{Y}-\underset{\text{X}}{\text{PdL}_n}$	Pd(II)	0	+	Applicable	—	Applicable

*Both Formation and Cleavage of C—Pd Bonds*

<b>9. Carbopalladation<sup>f</sup></b> $\text{>C=C<} + \text{RPdL}_n \rightarrow \text{R}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\text{PdL}_n$	Pd(II)	0	0	+	+	+
<b>10. Transmetallation</b> $\text{X}^1\text{PdL}_n{}^1 + \text{X}^2\text{PdL}_n{}^2 \rightleftharpoons \text{X}^2\text{PdL}_n{}^1 + \text{X}^1\text{PdL}_n{}^2$	Pd(II) or Pd(0) <sup>i</sup>	0 or + 2 <sup>i</sup>	0 or + 2 <sup>i</sup>	Applicable	Applicable	Applicable

*Mostly C—Pd Bond Cleavage*

<b>11. σ-Decomplexation</b> $\text{X}-\text{PdL}_n \rightarrow \text{X} \cdot + \text{PdL}_n$	Pd(II) or Pd(0)	0	—1	—	Applicable	Possible
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(Continued)

TABLE 3. (Continued)

General Pattern	FOS <sup>b</sup> of Starting Compound	$\Delta$ FOS <sup>b</sup>	$\Delta$ Coord. No. <sup>c</sup>	Formation of C—Pd Bond	Cleavage of C—Pd Bond	Interconversion of RPdL <sub>n</sub>
<b>12. <math>\pi</math>-Decomplexation</b> $\begin{array}{c} \text{X} \\    \\ \text{Y} \end{array} \text{—PdL}_n \rightarrow \begin{array}{c} \text{X} \\    \\ \text{Y} \end{array} + \text{PdL}_n$	Pd(II) or Pd(0)	0	$-1(\text{or } -2)^d$	—	Applicable	Possible
<b>13. Reductive Decomplexation</b> $\begin{array}{c}   \\ \text{Y} \end{array} \text{—PdL}_n \rightarrow \begin{array}{c} \text{X} \\    \\ \text{Y} \end{array} + \text{PdL}_n$	Pd(II) <sup>j</sup>	−2	−2	—	Applicable	Possible
<b>14. Reductive Elimination</b> $\text{XYPdL}_n \rightarrow \text{X—Y} + \text{PdL}_n$	Pd(II) <sup>j</sup>	−2	−2	—	Applicable	Possible
<b>15. Dehydropalladation</b> $\text{H—}\begin{array}{c}   \\ \text{C} \\   \end{array}\text{—}\begin{array}{c}   \\ \text{C} \\   \end{array}\text{—PdL}_n \rightarrow \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \begin{array}{c} \diagdown \\ \text{C} \\ \diagup \end{array} + \text{HPdL}_n$	Pd(II)	0	0	—	+	Possible
<b>16. Demetallopalladation</b> $\text{M—}\begin{array}{c}   \\ \text{C} \\   \end{array}\text{—}\begin{array}{c}   \\ \text{C} \\   \end{array}\text{—PdL}_n \rightarrow \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \begin{array}{c} \diagdown \\ \text{C} \\ \diagup \end{array} + \text{MPdL}_n$	Pd(II)	0	0	—	+	Possible
<b>17. Deheteropalladation</b> $\text{X—}\begin{array}{c}   \\ \text{C} \\   \end{array}\text{—}\begin{array}{c}   \\ \text{C} \\   \end{array}\text{—PdL}_n \rightarrow \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \begin{array}{c} \diagdown \\ \text{C} \\ \diagup \end{array} + \text{XPdL}_n$	Pd(II)	0	0	—	+	Possible

**18. Migratory Insertion**

Pd(II)

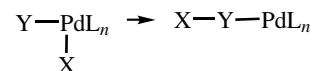
0

-1

-

Applicable

Applicable

*Both Formation and Cleavage of C—Pd Bonds***19. Decarbopalladation**

Pd(II)

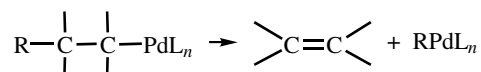
0

0

+

+

+

*Other Processes***20. Nucleophilic or Electrophilic**

Pd(II) or Pd(0)

-2 or 0

-2 or -1

-

Possible

Possible

*Attack on Ligands (see text)*

<sup>a</sup> X, Y = Atoms and groups containing H, C, heteroatoms, and metals. L<sub>n</sub> = Ligands. + or - Signs mean that the indicated process either occurs or does not occur, respectively. Term “applicable” means that the indicated process occurs if X and/or Y are C groups, while term “possible” means that the indicated process can occur with varying degrees of probabilities in cases where L<sub>n</sub> contains C groups.

<sup>b</sup> Backdonation is not considered in determining FOS. Δ FOS = Change in FOS.

<sup>c</sup> Δ Coord. No. = Change in coordination number.

<sup>d</sup> In Some cases, η<sup>2</sup>-ligands may be considered to occupy two coordination sites.

<sup>e</sup> In some cases, Pd(II) complexes may undergo this process to form Pd(IV) complexes.

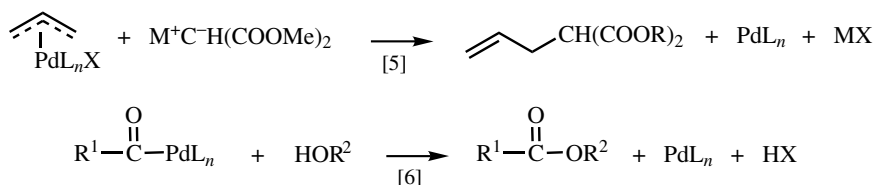
<sup>f</sup> The process involves both π-complexation and addition.

<sup>g</sup> Possible but relatively rare.

<sup>h</sup> Heteropalladation = Addition of heteroatom—Pd bonds to π-bonds.

<sup>i</sup> Some transmetallation processes, such as Pd(0) + 2 CuCl<sub>2</sub> → Pd(II)Cl<sub>2</sub> + 2 CuCl, are redox processes.

<sup>j</sup> This process involving Pd(IV) species is possible.



Scheme 4

catalytic cycles, oxidation must be precisely counterbalanced by reduction. In cases where this requirement cannot be met with the reagents present in the desired reactions, some external oxidizing or reducing agents must be introduced. It should also be noted that some Pd-catalyzed reactions, especially those using Pd(II) catalysts, may not involve redox processes.

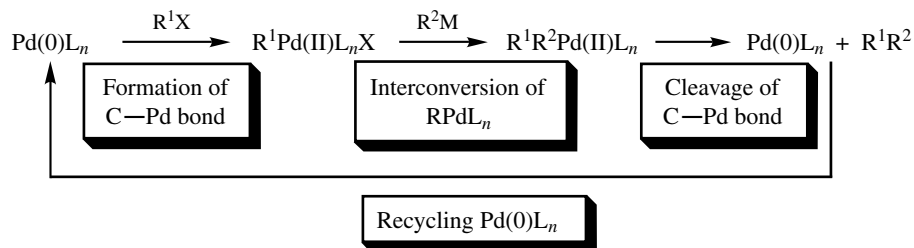
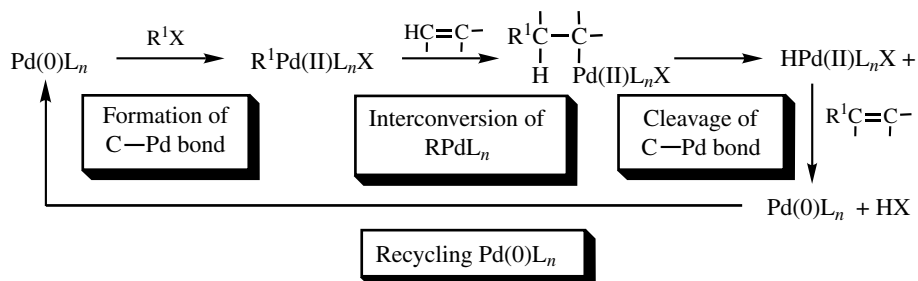
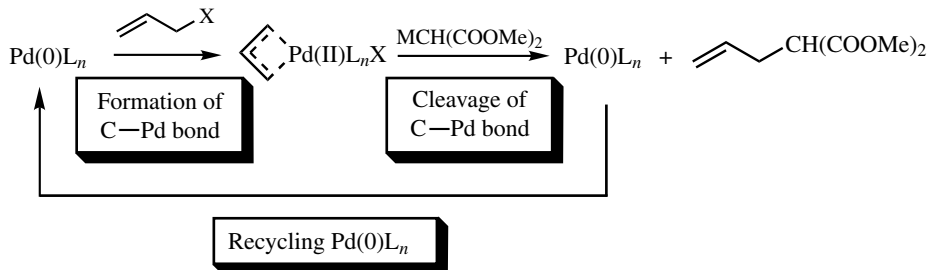
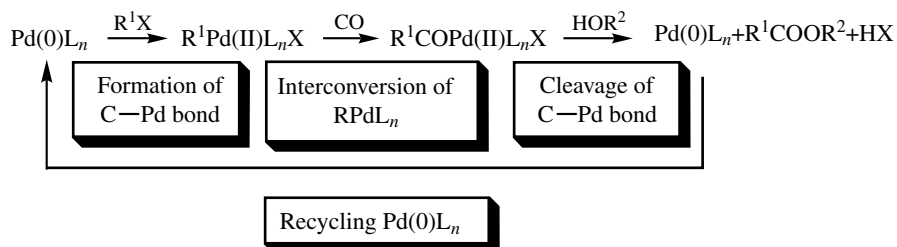
In **Table 3**, patterns **1** through **10** as well as **19** represent the processes for the formation of C—Pd bonds, and one of them may be chosen to come up with a desired catalytic cycle represented by **Scheme 3**. These processes are discussed in detail in **Sect. II.3**. Similarly, patterns **9** through **20** provide a menu for C—Pd bond cleavage processes that can be used in **Scheme 3**. Interconversion of organopalladium intermediates can be accomplished by essentially all of the processes listed in **Table 3**. However, (i) carbometallation and (ii) decarbometallation, (iii) migratory insertion and (iv) migratory deinsertion, as well as (v) transmetallation represent several most frequently encountered interconversion processes. Further discussions of these processes are presented throughout this Handbook.

Even without mechanistic information, one can begin to rationalize and, perhaps more importantly, predict various catalytic organopalladium reactions in consultation with **Table 3** and **Scheme 3**. For example, the following four reactions shown in **Scheme 5** are representative of the four most important types of Pd-catalyzed C—C bond formation processes discussed in detail in **Parts III–VI**. It is useful to note that only four patterns in **Table 3**, that is, (i) *carbopalladation*, (ii) *reductive elimination*, (iii) *migratory insertion*, and (iv) *nucleophilic* (or *electrophilic*) *attack on ligands*, can achieve C—C bond formation. This summary can also be appropriately modified for the formation of other types of bonds, such as C—H, C—M, C—X, and X—X bonds, where M is a metal and X is a heteroatom.

Although the catalytic cycles shown in **Scheme 5** do contain some mechanistic implications, they remain as rationalizations and, in some cases, predictions of Pd-catalyzed reactions rather than mechanisms until further scrutinized and experimentally supported. Even so, they are of considerable value from the viewpoints of rational interpretations and predictions. So, readers are well advised to become thoroughly familiar with the basic knowledge presented in this section and skillful in using such knowledge.

### C. SOME USEFUL PRINCIPLES AND GENERALIZATIONS PERTAINING TO Pd-CATALYZED REACTIONS

All Pd-catalyzed organic synthetic reactions discussed in this Handbook consist of a series of stoichiometric processes. However, good understanding of individual stoichiometric

*Pd-catalyzed cross-coupling (Part III)**Heck reaction (Part IV)**Tsuji–Trost reaction (Part V)**Carbonylative esterification of organic halides (Part VI)*

Scheme 5

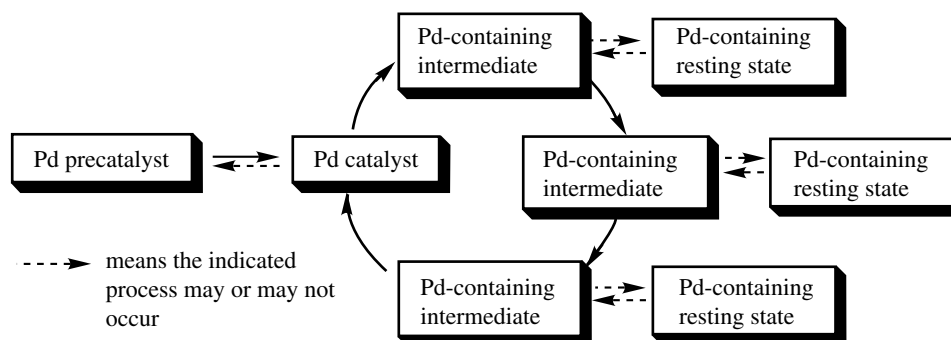
processes alone is insufficient for understanding the overall catalytic processes. The following principles and generalizations are presented to fill this gap.

### C.i. “Zero Sum” Principle with Respect to the Oxidation State of Pd

It has already been repeatedly mentioned that any Pd catalysts and Pd-containing intermediates in a catalytic cycle itself must be regenerated in the reaction vessel under one set of reaction conditions without any additional external manipulations. This requires that the sum of  $\Delta FOS$  (i.e., *change in formal oxidation state*) for the entire catalytic cycle be zero. This is but one of many “zero sum” principles governing various aspects of chemical processes. Although no additional discussion of this principle per se will be presented, it is nonetheless useful to become familiar with various different kinds of reagents and reactions that can reduce Pd(II) species to Pd(0) species or undergo reverse oxidations for devising catalytic cycles satisfying this “zero sum” principle. Although not discussed here, similar considerations should be made in cases where  $\text{Pd(II)} \rightleftharpoons \text{Pd(IV)}$  redox processes are involved.

It has often been loosely stated that a wide variety of reactions involving the reactants, ligands, and/or solvents present in a given reaction mixture would reduce Pd(II) species and that deliberate reduction of Pd(II) species by externally added reducing agents is unnecessary in most cases. In fact, this statement is true. If so, what actually reduces Pd(II) species and how? Inspection of **Table 3** indicates that only reductive elimination, reductive decomplexation, and some processes involving nucleophilic attack on ligands can reduce Pd(II) species.

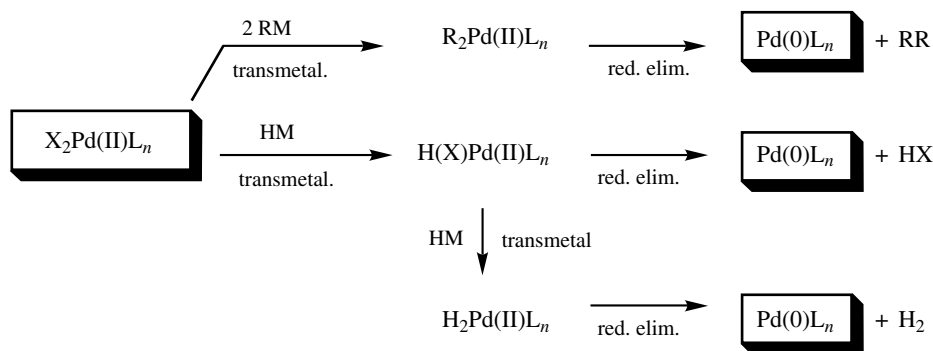
A systematic discussion of reduction of Pd(II) species with organic compounds is presented in **Sect. VII.1.** from the viewpoint of oxidation of organic compounds. After all, two-electron reduction of Pd must be precisely offset by two-electron oxidation. Below, several widely observable process of two-electron reduction of Pd are presented primarily to provide a reasonable notion of how Pd(II) species added as precatalysts might be transformed into catalysts that appear in catalytic cycles themselves. Any externally added Pd compounds that must be converted to Pd catalysts are usually called “precatalysts,” while any other Pd compounds that lie outside catalytic cycles but are interconvertible with Pd-containing intermediates are normally termed “resting states” or “resting forms.” Their schematic relationships are shown in **Scheme 6**.



**Note:** There may be more or less steps in a catalytic cycle.

**Scheme 6**

1. Organometals, enolates, and metal hydrides used throughout this Handbook, especially in cross-coupling and related reactions (**Part III**) and the Tsuji–Trost reaction (**Part V**), can, in general, readily reduce Pd(II) complexes via transmetalation–reductive elimination, as shown in **Scheme 7**.

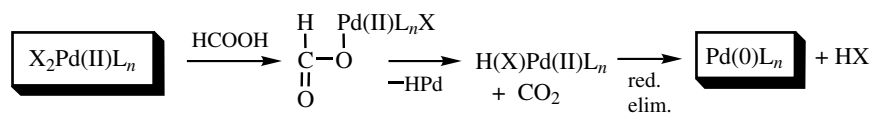


Scheme 7

2. Alkenes, alkynes, and  $\pi$ -compounds including even arenes can reduce Pd(II) species to Pd(0) species. Recall that reduction of  $PdCl_2$  with ethylene and water is a crucial part of the Wacker oxidation of ethylene<sup>[7]</sup> (**Scheme 2** of **Sect. I.1**). Many other related processes of this type are discussed in **Sect. V.3**.

3. Various  $n$ -electron donors, such as phosphines, amines, and ethers, used as reagents, ligands, and solvents can reduce Pd(II) species typically via  $\sigma$ -complexation–dehydropalladation–reductive elimination. A few such reactions of phosphines and amines are discussed in **Sect. II.2.3**, and many additional examples are discussed in **Part VIII**.

4. Various H donors in addition to those already discussed above can reduce Pd(II) species via formation and reductive elimination of  $H(X)Pd(II)L_n$ . One typical example<sup>[8]</sup> is shown in **Scheme 8**, and various other reactions of this class are discussed throughout this Handbook.



Scheme 8

5. Although  $\sigma$ -organyl substituents, such as  $\sigma$ -alkenyl and  $\sigma$ -aryl, on Pd are relatively resistant to nucleophilic attack, many others, such as allyl, propargyl, acyl, and related CO-containing substituents, are readily attacked by various nucleophiles. So, a combination of any compounds that can generate  $\sigma$ -bonded (or  $\sigma, \pi$ -bonded) organopalladium species and suitable nucleophiles can be used to reduce Pd. A few such examples have already been presented in **Scheme 5** in **Sect. I.2**, and many additional examples may be found throughout this Handbook, especially in **Sect. V.2** and **Parts VI** and **VIII**.

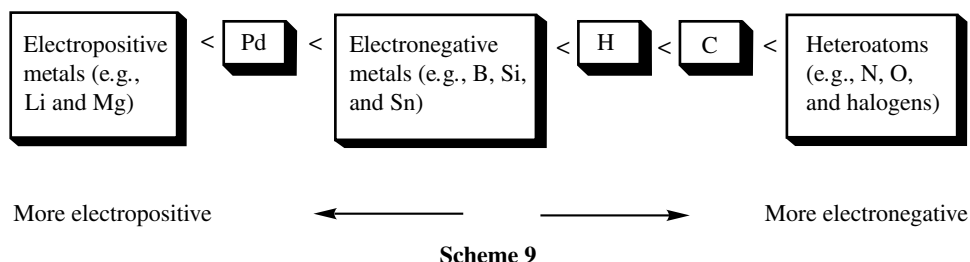
In summary, the discussions presented in the items 1–5 above amply support the widely accepted notion that Pd(II) species added as precatalysts can be reduced to Pd(0) catalysts by various compounds present in the reaction mixtures without resorting to externally added reducing agents.

Although the majority of Pd-catalyzed reactions are initiated by Pd(0) catalysts, which then undergo a series of  $\text{Pd(0)} \rightleftharpoons \text{Pd(II)}$  redox processes, there are many other Pd-catalyzed reactions that are initiated by Pd(II) complexes. Some such reactions are nonredox processes that do not involve Pd(0) species, as exemplified by a Pd(II)-catalyzed hydrogen transfer hydroalumination<sup>[9]</sup> discussed in detail in **Sect. VII.4.1**; most of the Pd(II)-initiated reactions do involve reduction of Pd(II) species to Pd(0) species, as in the Wacker oxidation (**Scheme 2** in **Sect. I.1** and **Sect. V.3.1**). In many of these reactions, the Pd(0) species thus generated must be externally oxidized to regenerate the original Pd(II) catalysts. In addition to  $\text{O}_2$  and  $\text{CuCl}_2$  used in the Wacker oxidation, quinones (e.g., DDQ), peroxides (e.g., *t*-BuOOH) halogens, and halo-derivatives including organic halides have been used, as discussed in various sections, in particular **Sect. V.3**.

### C.ii. Some Rules Concerning Formal Oxidation State and Electron Counting

As the term itself implies, “formal oxidation state” is a formalism with which the oxidation state of an atom or species in question is expressed in a round number and often somewhat arbitrarily. Thus, for example, the formal oxidation state (FOS) of Pd in a  $\pi$ -complex obtained by  $\pi$ -complexation of an alkene with Pd(0) species is considered to be 0, whereas the same Pd atom in the same complex may be assigned an FOS of +2, if the process of formation is regarded as oxidative complexation and if the product is viewed as a palladacyclop propane, as indicated in **Table 3**. This sort of seeming ambiguity is not a concern, at least in the great majority of cases, as long as this formalism is dealt with in an internally consistent and logically sound manner. After all, most of the practical and synthetic matters in chemistry are dealt with in terms of formalism.

The FOS of any atom or group may be determined by merely considering the bond polarity of all bonds to the atom or group in consideration. In this Handbook the following somewhat arbitrary relative order of electronegativity is assumed (**Scheme 9**). As mentioned above, the arbitrariness has no serious consequences, although reasonable assignments of relative electronegativity values are desirable.



Although no detailed discussion of electron counting is intended, it is important to be thoroughly familiar with at least one version of electron counting. In one extreme version



all bonds to an atom in question are homolytically cleaved. It is the simplest of all conceivable versions, but it does not readily provide crucial information about FOS. For this reason, a hybrid method blending heterolysis of heteroatomic bonds ( $X-Y$ ) according to the electronegativity scale shown in **Scheme 9** and homolysis of homoatomic bonds ( $X-X$ ) is recommended. This is widely used, and a detailed discussion may be found in various textbooks of organometallic chemistry, such as the one by Collman et al.<sup>[10]</sup> To illustrate the process of analysis including the determination of FOS and electron count, the following two representative examples are presented (**Scheme 10**). Note how analysis of ligands leads to the FOS of Pd, then to the  $d^n$  configuration, and eventually to the total number of valence-shell electrons. Furthermore, one-half of the  $d^n$  configuration gives the number of lone pairs of electrons, and the total number of valence-shell electrons readily gives the number of empty orbitals.

### C.iii. Thermodynamic Principles Pertaining to Pd-Catalyzed Reactions

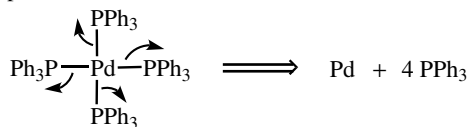
Two crucial requirements for any catalytic reactions are (i) that the overall catalytic processes be thermodynamically favorable (i.e.,  $\Delta\Delta G < 0$ ) and (ii) that all steps in a given catalytic cycle be kinetically accessible (i.e., of reasonably low activation energies). Moreover, so long as these two requirements are met, one or more of the microsteps in a catalytic cycle can be thermodynamically unfavorable. This is an obvious principle that nonetheless is frequently misunderstood. For example, the stoichiometric oxidative addition reaction of allyl acetate with Pd(0) complexes does not normally give the desired allylpalladium derivative in significant yields, and it may well be thermodynamically unfavorable. And yet, the Tsuji–Trost reaction of allyl acetate with malonates is normally facile. It is very important not to rule out any potentially feasible catalytic processes simply because some microsteps are or appear to be thermodynamically unfavorable.

Since many of the Pd-catalyzed reactions involve reversible processes of relatively low activation energies, they are often subject to the Curtin–Hammett principle.<sup>[11]</sup> In cases where rapidly equilibrating stereoisomeric and/or regioisomeric mixtures are involved, less stable isomers often react more rapidly in part by virtue of their instability, leading to the predominant formation of the corresponding stereo- and/or regioisomeric products. Quite often, readily detectable and characterizable organopalladium species represent resting states rather than intermediates in the catalytic cycle itself.

### C.iv. Relationship between Intrinsic Reactivity and that in Catalytic Reactions: Catalyst Poisoning

Yet another important notion in dealing with catalytic reactions is that high intrinsic reactivity of a reagent does not necessarily lead to a high catalytic reaction rate. In fact, excessively reactive reagents often retard or even totally block catalytic processes (i.e., catalyst poisoning). For example, highly reactive organolithium compounds tend to be ineffective or even incapable of participating in Pd-catalyzed cross-coupling.<sup>[12]</sup> And yet, there have been indications that organolithiums are stoichiometrically very reactive in Pd-promoted reactions.<sup>[12]</sup> One possible mode of Pd catalyst poisoning may involve interaction of a highly nucleophilic reagent with an empty coordination site of Pd, which effectively prevents some desired processes requiring one or more empty coordination sites. Formation of coordinatively saturated 18-electron species may not be required for catalyst poisoning. In an attempted catalytic reaction between an alkynyllithium and

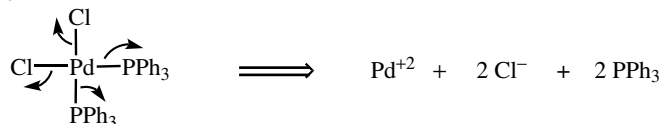
## Example 1



**Note:** Cleavage of neutral ligands does not generate charges. Recall that the  $\text{Pd}-\text{PPh}_3$  may be represented as  $^-\text{Ph}-^+\text{PPh}_3$  and that its heterolysis as shown above will nullify the charges. For the sake of simplicity, all these details are omitted.

Atom or Group	FOS	Number of Electrons Contributed
$4 \times \text{PPh}_3$	$0 (4 \times 0)$	$8 (4 \times 2)$
Pd	$\boxed{0} (\text{d}^{10})$	10
Total Number of Electrons		$\boxed{18}$

## Example 2



Atom or Group	FOS	Number of Electrons Contributed
$2 \times \text{Cl}^-$	$-2 (-1 \times 2)$	$4 (2 \times 2)$
$2 \times \text{PPh}_3$	$0 (0 \times 2)$	$4 (2 \times 2)$
Pd	$\boxed{+2} (\text{d}^8)$	8
Total Number of Electrons		$\boxed{16}$

$$\boxed{\text{Number of Lone Pairs of Electrons}} = \frac{1}{2} \text{d}''$$

$$\boxed{\text{Number of Empty Orbitals}} = \frac{18 - \text{Valence Shell Electrons}}{2}$$

Scheme 10

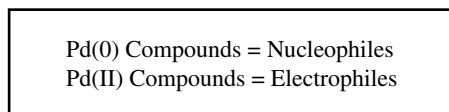
aryl iodide in the presence of  $\text{Pd}(\text{PPh}_3)_4$ , displacement of all  $\text{PPh}_3$  to produce a species tentatively identified as  $\text{Li}_2\text{Pd}(\text{C}\equiv\text{CR})_4$ , a 16-electron species as a monomer, was formed.<sup>[13]</sup>

In general, it is useful to note that, in a series of reagents, ligands, or solvents of various reactivities, especially nucleophilicities and polarities, the maximum reactivity or efficiency in a catalytic sense may be found away from the two extreme points of any scale.

### C.v. Substituent Effects in Pd-Catalyzed Reactions

The electronic effects exerted by substituents in reagents, ligands, and solvents on the Pd-catalyzed reactions are rather complex and often difficult to predict. This is in part due to the fact that more than one microstep are involved in these reactions. Thus, substituent effects in one step may be opposite to or at least different from those in another. In oxidation, for example, some electrons must be removed from the substrates. So, electron-rich substrates may be expected to be more readily oxidized than related but more electron deficient substrates. The opposite may be true for reduction. This is, in fact, a widely applicable and useful generalization, but it may not apply very well to some Pd-catalyzed multi-step reactions, such as catalytic hydrogenation (**Sect. VII.2**). It is important to note that the generalization presented above should be applicable to individual microsteps. In oxidative addition involving organic halides, for example, Pd is oxidized by two electrons, while organic halides are reduced by two electrons. So, electron-withdrawing substituents in organic halides may be expected to accelerate the oxidative addition reaction. The same reasoning also predicts that electron-donating substituents in the ligands on Pd would accelerate oxidative addition. Both of these predictions are generally true and useful.

Although somewhat different, the generalization summarized in **Scheme 11** provides a useful notion, provided that the redox processes involve only Pd(0) and Pd(II) species. This is, however, a "soft" generalization rather than a "hard" principle.



**Scheme 11**

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