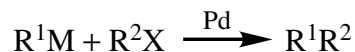


PART III

Palladium-Catalyzed Reactions Involving Reductive Elimination



III.1 Background for Part III

EI-ICHI NEGISHI

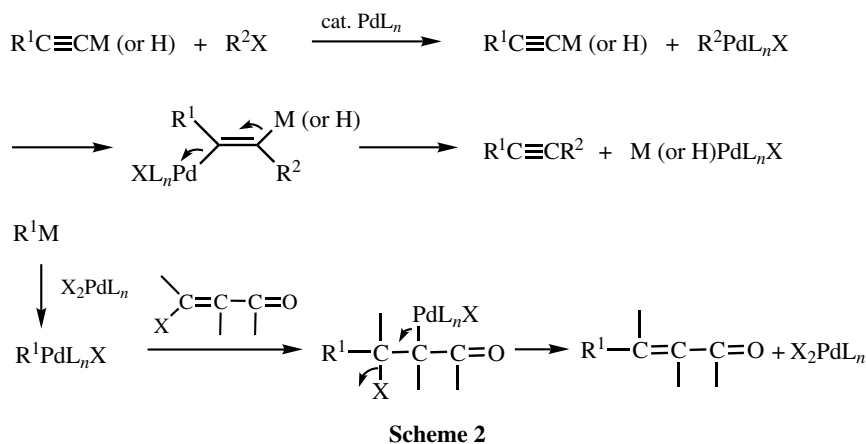
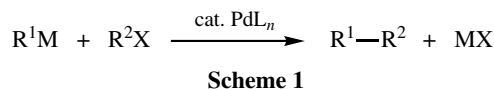
A. DEFINITION OF Pd-CATALYZED CROSS-COUPLING

As discussed in **Sect. I.2**, *reductive elimination* is one of only a few to several basic patterns permitting the formation of various types of single bonds in organic compounds including C—C, C—H, C—X, where X is N, O, or a related heteroatom, and even bonds between two heteroatoms. Reductive elimination is thought to be an important microstep in Pd-catalyzed cross-coupling. In this Part, these Pd-catalyzed cross-coupling reactions leading to the formation of C—C (**Sect. III.2**), C—H (**Sect. III.3.1**), C—N and C—O (**Sects. III.3.2 and III.3.3**), as well as C—M (**Sect. III.3.4**) bonds are discussed. It should be noted, however, that reductive elimination occurs in many other types of Pd-catalyzed reactions as well, and it is discussed throughout this Handbook. Thus, for example, the Heck reaction (**Part IV**) must involve regeneration of Pd(0) complexes via reductive elimination of H(X)Pd(II) complexes, and a similar reduction of Pd(II) species must occur in the Tsuji–Trost reaction (**Part V**). Reductive elimination is also a critical step in the generation of organic acyl derivatives from acylpalladium intermediates with concomitant two-electron reduction of Pd(II) complexes (**Part VI**), while it is well accepted that reductive elimination to form the C—H bond is the product-forming step in various Pd-catalyzed hydrogenations (**Part VII**). So, the scope of reductive elimination of Pd(II) complexes is far wider than that in Pd-catalyzed cross-coupling. With this understanding, however, our attention in this Part will be focused on Pd-catalyzed cross-coupling leading to the formation of C—C, C—H, C—N, C—O, and C—M bonds within the context of cross-coupling.

Cross-coupling between organometals (R^1M) and organic electrophiles (R^2X) is undoubtedly one of the most straightforward methods for the formation of carbon–carbon bonds (**Scheme 1**). As discussed in **Sect. I.1**, the use of Grignard reagents and organolithiums without involving any transition metal catalysts was first introduced many decades ago. Both stoichiometric and catalytic use of $\text{Cu}^{[1],[2]}$ revolutionized the art of cross-coupling mainly during the 1960s and 1970s. Most notably, organic electrophiles containing $\text{C}_{\text{sp}^2}\text{—X}$ and $\text{C}_{\text{sp}}\text{—X}$ bonds became usable and useful in cross-coupling. Over the past three decades Ni- and Pd-catalyzed cross-coupling, the latter in particular, has substantially improved and expanded the cross-coupling methodology. The historical evolution of Pd-catalyzed cross-coupling is discussed in **Sect. I.1**, and many reviews are available on this topic.^{[3]–[17]} The narrow definition of cross-coupling presented above may be

expanded so as to include H, N, O, and other heteroatom groups, as well as metals and metal-containing groups in R^1 or R^2 in **Scheme 1**.

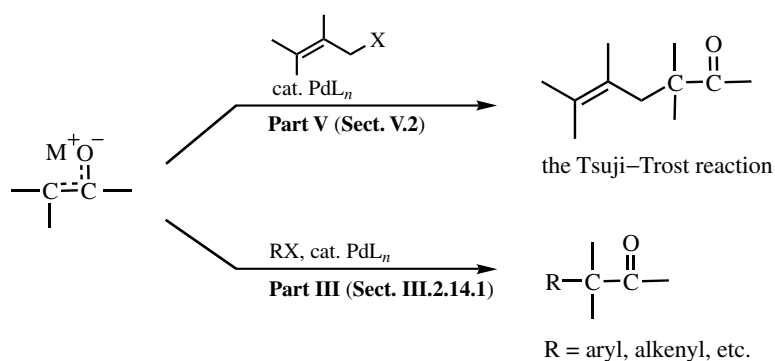
The relationships between the cross-coupling reaction shown in **Scheme 1** and some other related reactions should briefly be discussed here. Whether or not one should consider those Pd-catalyzed reactions in which M is H in **Scheme 1**, such as the Heck reaction with alkenes and the Sonogashira reaction with alkynes, as cross-coupling reactions is largely a matter of semantics or a personal preference. For mainly historical and practical as well as somewhat vague mechanistic and other chemical reasons, the Heck alkene hydrogen substitution reaction is discussed mostly in **Part IV** as a representative carbopalladation reaction. On the other hand, the Sonogashira and related Heck-type alkyne hydrogen substitution reactions are discussed in this section in part because ammonium or copper acetylides are considered to serve as R^1M in these reactions. In contrast, no such species derived from alkenes are considered for the Heck alkene substitution. It should, however, be noted that, even if discrete acetylide anions are involved as actual reactive species in the alkyne substitution, they may still undergo the Heck-type non-redox addition–elimination process suggested as early as 1978^[3] (**Scheme 2**). Furthermore, it is not unreasonable to consider some of the more genuine cross-coupling reactions, such as the reaction of preformed alkynylmetals with organic halides (**Sect. III.2.8.2**) and the conjugate substitution reaction (**Sect. III.2.15**) shown in **Scheme 2**, as non-redox carbometallation–elimination reactions. Irrespective of their mechanistic details, however, these are genuine examples of Pd-catalyzed cross-coupling reactions discussed in this Part.



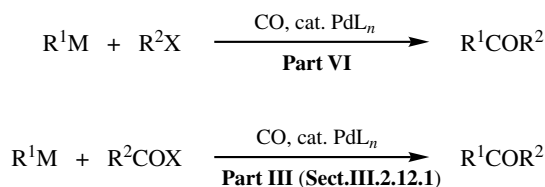
The Tsuji–Trost allylation of enolates can be viewed as a variant of Pd-catalyzed cross-coupling involving allylic electrophiles (**Sects. III.2.9 and III.2.10**). In recognition of the widely accepted mechanism involving a nucleophilic attack by enolates at the π -allyl ligand of an allylpalladium derivative on the side opposite to Pd, however, it is discussed separately in **Part V** together with the Wacker and related reactions, which are

also thought to involve nucleophilic attack on π -ligands of Pd π -complexes. However, the same mechanistic interpretation cannot be applied to most of the other Pd-catalyzed α -substitution of enolates and related compounds including α -arylation and α -alkenylation. These reactions are therefore viewed as Pd-catalyzed cross-coupling reactions and discussed in **Sect. III.2.14.1 (Scheme 3)**.

Various Pd-catalyzed carbonylation reactions have often been referred to as carbonylative cross-coupling reactions (**Scheme 4**). However, these reactions involving the formation of two C—C bonds with incorporation of CO clearly display a pattern of chemical transformation that is different from **Scheme 1**. So, these reactions are discussed in **Parts VI and VIII**. On the other hand, Pd-catalyzed acylation with acyl halides and related derivatives are examples of the reaction represented by **Scheme 1**, where R^2 is acyl, and they are therefore discussed in this Part (**Sect. III.2.12.1**), even if CO may be used to prevent decarbonylation.



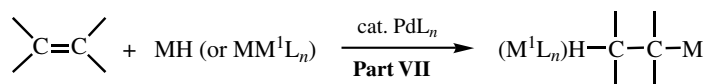
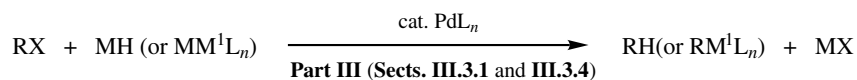
Scheme 3



Scheme 4

Finally, most Pd-catalyzed hydrogenation reactions are discussed in **Part VII**. However, Pd-catalyzed hydrogenolysis of organic halides and related electrophiles can be viewed as Pd-catalyzed cross-coupling of organic electrophiles with hydrides. The corresponding reactions of metal-centered nucleophiles have also been developed. Although these reactions are closely related to hydrogenation and related reduction reactions discussed in **Part VII**, those that are discussed in **Part VII** generally involve addition of metal–hydrogen and metal–metal bonds to alkenes and alkynes, displaying different patterns of chemical transformation. These two discrete patterns are shown in **Scheme 5**.

As discussed above, distinctions among many closely related reactions and processes are often vague and somewhat arbitrary. Some are based on chemical and mechanistic



Scheme 5

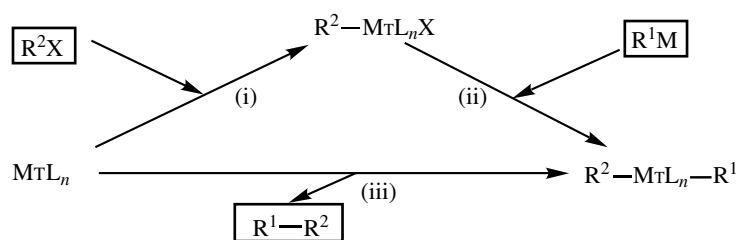
reasonings, but many other factors including historical and semantic ones have also been taken into consideration. After all, inasmuch as many Pd-catalyzed reactions involve more than one microstep and are hence multidimensional, some compromises are necessary in any unidimensional arrangement of Pd-catalyzed reactions.

B. OVERVIEW OF Pd-CATALYZED CARBON-CARBON CROSS-COUPLING

B.i. General

Cross-coupling as defined above is, in general, thermodynamically favorable. In **Scheme 1**, M and X are typically the most electropositive and most electronegative elements and/or groups, respectively, and the formation of MX as the by-product generally makes the overall process thermodynamically favorable. The discoveries and developments of various cross-coupling reactions have been guided and aided by a simplistic mechanistic hypothesis that the reaction shown in **Scheme 1** catalyzed by either Ni or Pd complexes can proceed via (i) oxidative addition, (ii) transmetalation, and (iii) reductive elimination (**Scheme 6**). As discussed in **Sect. III.2.19**, the three-step mechanism shown in **Scheme 6** is, in most cases, a gross oversimplification. In some cases, the reaction may even involve totally different paths as indicated in **Schemes 2** and **3**. Despite all these, it is still a useful working hypothesis so long as one is aware that many additional processes involving (i) interconversions between intermediates in the catalytic cycle and the resting states and (ii) other additional interactions, such as complexation including solvation and dissociation, may occur, thereby substantially complicating the overall mechanistic schemes. Furthermore, some of the microsteps may not occur discretely. It is likely, for example, that reductive elimination and oxidative addition may be more tightly coupled than indicated in **Scheme 6** so as to make the overall kinetics more favorable. With these in mind, however, the mechanism shown in **Scheme 6** will be used as a convenient tool for the discussion of various aspects of Pd-catalyzed cross-coupling. It is also important to fully realize that each microstep, that is, oxidative addition, transmetalation, or reductive elimination, need not be thermodynamically favorable but that each must be kinetically favorable. As in any catalytic processes, the only two crucial requirements are that the overall thermodynamics independent of catalysis be favorable and that each catalytic microstep be kinetically readily accessible.

The historical evolution in the discoveries and developments of Pd-catalyzed cross-coupling are presented in **Sect. I.1** and will not be repeated here. In this section, several parameters in **Scheme 1**, that is, M, R¹, R², X, catalysts, added reagents, solvents, and so on, are discussed in a general manner.



(i) oxidative addition, (ii) transmetalation, (iii) reductive elimination
 Mt = Pd or Ni. M = metal counteraction.
 $R^1, R^2 = \text{C groups}$. X = I, Br, Cl, OTf, etc.

Scheme 6

B.ii. Metal Counteractions (M)

Some of the earliest investigations of Pd-catalyzed or Pd-promoted cross-coupling were performed with alkali metals, for example, Na^[18] and Li,^[19] and Mg.^[20] While Mg is still widely used, alkali metals are generally inferior to many other metals for various reasons. In short, organometals containing them are generally of low chemoselectivity. Moreover, their intrinsically high reactivity evidently interferes with Pd catalysis in many cases. Today, they are indeed rarely used, even though organolithiums are widely used as precursors to other organometals.

The discoveries that alkenylalanes^{[21],[22]} and alkenylzirconium derivatives^{[23],[24]} readily participate in Pd- or Ni-catalyzed cross-coupling are significant milestones for at least two reasons. First, they clearly indicated that Pd- or Ni-catalyzed cross-coupling might be observed with a wide variety of metal counteractions other than Mg and Li. Equally significant is that, for the first time, stereo- and regiodefined alkenylmetals generated *in situ* by hydrometallation of alkynes are used in Pd- or Ni-catalyzed cross-coupling.

Prompted by these discoveries and developments, the first systematic screening of metal counteractions was conducted by using the Pd-catalyzed reaction of readily and widely available alkynylmetals with *o*-tolyl iodide. The latter was to probe the regioselectivity and the effects of steric hindrance. The results of the systematic survey summarized in **Table 1** have indicated the following. The Pd-catalyzed alkynyl-aryl coupling is indeed quite general with respect to the metal counteractions (M). Metals covering a wide range of electronegativity can participate in the reaction. Under the mild conditions at room temperature, Zn exhibits the highest reactivity. Although the results observed with Mg in the initial screening were not highly satisfactory, later studies^{[25],[26]} have shown that alkynylmagnesiums not only are very reactive but also can yield highly satisfactory results in many cases. Significantly, this survey also identified two unexpected metals—B and Sn. The alkynylmetals containing them were relatively slow-reacting, but the product yields observed with them were comparable to those observed with Zn. The alkynylboron reaction appears to be the first reported example of the Pd-catalyzed cross-coupling reaction with B, and the alkynyltin reaction is one of the earliest examples. It is striking to note that Zn, B, and Sn are indeed the three most widely used metal counteractions. These three and Mg as well as three other metals that can be used in conjunction with their hydrometallation and/or carbometallation (i.e., Al, Zr, and Cu) are seven counteractions to be seriously considered in a given case of Pd-catalyzed cross-coupling. In addition to

TABLE 1. Reaction of 1-Heptynylmetals with *o*-Tolyl Iodide in the presence of Cl₂Pd(PPh₃)₂ and 2 DIBAH

M	Temperature(°C)	Time (h)	Product Yield (%)	Starting Material (%)
Li	25	1	Trace	88
Li	25	24	3	80
Na ^[18]	Reflux	24	58	41
MgBr	25	1	29	55
MgBr	25	24	49	33
ZnCl	25	1	91	8
ZnCl	25	3	88	2
HgCl	25	1	Trace	92
HgCl	Reflux	6	Trace	88
BBu ₃ Li	25	3	10	76
BBu ₃ Li	Reflux	1	92	5
Al(Bu- <i>i</i>) ₂	25	3	49	46
AlBu ₃ Li	25	3	4	80
AlBu ₃ Li	Reflux	1	38	10
SiMe ₃	Reflux	1	Trace	94
SnBu ₃	25	1	75	14
SnBu ₃	25	6	83	6
ZrCp ₂ Cl	25	1	0	91
ZrCp ₂ Cl	Reflux	3	0	80

Li and Na mentioned above, Cd,^[27] Hg,^[28] Si,^[29] and Mn^[30] have also been used (**Sect. III.2.4**), and others will undoubtedly be reported in the future. Some of the metals mentioned above, for example, Si and Mn, might become widely used. However, their scope, limitations, and merits must be further delineated before any of these other metals become widely used in preference to some of the seven metals mentioned above.

B.iii. Carbon Groups (R¹ and R²)

Since both R¹ and R² are to be incorporated into the product (R¹—R²), these are not changeable parameters in a given synthesis. It should, however, be noted that cross-coupling between R¹ and R² can be achieved either by the reaction of R¹M with R²X or by that of R¹X with R²M. Inasmuch as these two reactions are to converge at R¹R²MtL_n in **Scheme 6**, one might think that two reactions are synthetically equivalent, but that is far from being true. Both may work comparably in many cases. In many other cases, however, only one may work well, while the other may not work well or at all, as amply

demonstrated later in this chapter. In order to readily distinguish the two modes of cross-coupling, an adjective consisting of the names of the R^1 group in R^1M and R^2 group in R^2X is generated by linking R^1 and R^2 in this order with a dash. Thus, the reaction of alkynylmetals with aryl iodide in **Table 1** is referred to as the alkynyl–aryl coupling reaction, while the reaction of arylmetals with alkynyl halides is referred to as the aryl–alkynyl coupling reaction.

In this Handbook, the organometals (R^1M) and organic electrophiles (R^2X) are classified into roughly ten categories each. This, in turn, generates roughly 100 different classes of cross-coupling reactions, most of which are shown in **Table 2**. The currently available data clearly indicate that each and every one of these 100 or so classes of cross-coupling displays its own unique characteristics and limitations, demanding separate and individualized attention. For practical reasons, however, they are divided into about ten groups, as indicated in **Table 2**. At the risk of ignoring many exceptions, the current overall status of each group of cross-coupling reactions is labeled as (a) generally favorable and less demanding (indicated by bold frame), (b) favorable but demanding and delicate (indicated by regular solid-line frame), and (c) generally unfavorable (indicated by broken-line frame).

B.iv. Leaving Groups (X)

Some of the most reactive leaving groups and their approximate reactivity order are $I > OTf > Br \gg Cl$. With aryl and alkenyl as well as alkynyl groups as R^2 , good leaving groups, such as I, OTf, and Br, are generally required. Clearly, the development of satisfactory procedures permitting the widespread use of aryl and alkenyl chlorides is highly desirable. With acyl and benzyl as R^2 , Cl is generally sufficiently reactive and widely used. Allyl and propargyl derivatives are some of the most reactive electrophiles. Allyl and propargyl iodides and bromides are generally unnecessary and rarely used. Moreover, these compounds are generally unstable and difficult to handle. In addition to chloro derivatives, those containing a wide range of oxy groups including carbonates, carboxylates, aryl ethers, phosphates, and even silyl ethers as well as other heteroatom groups containing S, N, and so on have been successfully used (**Sects. III.2.9 and V.2**). At the other end of the spectrum lie alkyl electrophiles other than allyl, propargyl, and benzyl derivatives. The difficulties associated with alkyl electrophiles are at least twofold. First, the absence of an α,β - or β,γ -unsaturated group renders their oxidative addition an inherently difficult and slow process. Second, even if alkylpalladium derivatives are formed, those containing β -H atoms are prone to undergo β -dehydropalladation in competition with the desired cross-coupling. Promotion of oxidative addition through the use of highly nucleophilic ligands, for example, dippp,^[31] might provide a solution to the problem associated with oxidative addition. However, it is expected to retard reductive elimination. Clearly, this is an interesting and largely pending problem to be solved.

B.v. Pd Catalysts

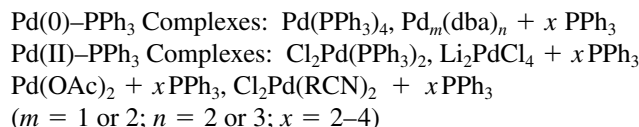
Both Pd(II) and Pd(0) complexes have been used as Pd catalysts or precatalysts. Some of the Pd(II) complexes [e.g., $Cl_2Pd(PPh_3)_2$] have been convenient and preferred precatalysts because of their longer shelf lives as compared with some of the commonly used Pd(0) complexes [e.g., $Pd(PPh_3)_4$]. However, the initial generation of Pd(0) complexes from Pd(II) complexes may require nonproductive consumption of the organometallic reagents

TABLE 2. Classification and Current Status of Pd-Catalyzed Cross-Coupling Reactions^a

$\begin{array}{c} R^2X \\ \hline R^1M \end{array}$	ArX	=X	\equiv X	=X	Ar-X	\equiv X	Alkyl X	RCOX
ArM	III.2.5 III.2.7	III.2.6 III.2.7	III.2.8(b)		III.2.9(a)			
=M	III.2.6 III.2.7	III.2.6						
\equiv M	III.2.8(a)							
=M								
Ar-M		III.2.9(b)			III.2.10		III.2.11.3	III.2.12.1
\equiv M								
Alkyl M			III.2.11.1 and III.2.11.2					
$\text{N}\equiv\text{C-M}$		III.2.13.1(a)			III.2.13.1(b)			
—C=OM		III.2.14.1		V.2	III.2.14.1	V.2		

^aThe numbers in the frames indicate the pertinent sections. Bold-line frame: generally favorable and not highly demanding; broken-line frame: generally unfavorable; solid-line frame: others.

(R¹M). This problem has been circumvented by using an added reducing agent [e.g., DIBAH].^[21] In some cases, phosphine-free Pd complexes have been satisfactorily used.^[32] In most cases, however, Pd–phosphine complexes are used, and triphenylphosphine is by far the least expensive and generally satisfactory phosphine ligand. In less demanding cases of Pd-catalyzed cross-coupling, it is advisable to consider first Pd–PPh₃ complexes. The following Pd(0)–PPh₃ and Pd(II)–PPh₃ complexes are some of the most commonly used.



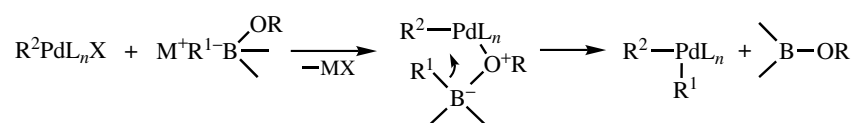
In more demanding cases where Pd–PPh₃ complexes are unsatisfactory, the use of more effective, if more expensive, phosphines and other ligands may be profitably considered. In principle, there can be a large number of phosphines and other ligands available for consideration (**Sect. II.2**). At present, several phosphines including tris(2-furyl)phosphine (TFP)^[33] and some bidentate phosphines, for example, dppp and dppf,^[34] have been shown to be superior to PPh₃ in many demanding cases, as detailed later. This aspect of Pd-catalyzed cross-coupling will be significantly advanced in the near future, and many additional ligands in many different forms including chiral, water-soluble, and polymer-bound ligands will be developed. Along with the catalytic reactivity, many other practically important aspects associated with ligands and catalysts, such as catalyst recovery, attrition rate, and especially toxicity, will become increasingly important. The use of Ph₃As, for example, has been effective in the reactions of organotin^[35] and organoborons.^[36] However, its toxicity has been a serious concern, and it should be carefully examined and evaluated. This concern, of course, applies to any other ligands and reagents used in organic synthesis as well.

B.vi. Added Reagents and Cocatalysts

The Pd-catalyzed reaction of sterically demanding alkenylalanes and alkenylzirconium derivatives was significantly accelerated by the addition of ZnCl₂ or ZnBr₂.^[37] This probably was the first reported example of cocatalysis by an added reagent in Pd- or Ni-catalyzed cross-coupling. Since then, many additional examples of rate acceleration by added reagents have been reported. A noteworthy example is the finding that relatively unreactive triorganylboranes can be significantly activated with appropriate bases, which not only boost the nucleophilicity of organoboron compounds but also are thought to facilitate the transfer of a carbon group from B to Pd through coordination^[13] (**Scheme 7**). In principle, this concept should be applicable to the Pd-catalyzed reaction of other organometals as well. In general, promotion of Pd-catalyzed cross-coupling with added reagents will be further investigated and advanced.

B.vii. Solvents

A wide range of solvents have been used in Pd-catalyzed cross-coupling. They include (i) relatively nonpolar hydrocarbons (e.g., benzene and toluene), (ii) ethereal solvents (e.g., THF, dioxane, and DME), (iii) polar double and triple bond-containing solvents



Scheme 7

(e.g., MeCN and acetone), (iv) other polar aprotic solvents (e.g., DMF, DMSO, HMPA, and NMP), and (v) polar protic solvents (e.g., alcohols and water). In early investigations, THF was probably the most commonly used solvent, and it is still widely used in many less demanding cases. In more demanding cases, however, DMF and other polar aprotic solvents have proved to be superior to THF. One of the potential advantages associated with more electronegative metals, for example, B, Si, and Sn, is that they are, in most cases, compatible with many polar protic solvents, allowing even aqueous conditions for Pd-catalyzed cross-coupling (Sect. X.1). The range of solvents available for Pd-catalyzed cross-coupling is considerably more limited than those of ligands and added reagents. At the same time, their systematic investigations within the context of Pd-catalyzed cross-coupling have also been rather limited. So, further systematic investigations along this line are expected to bring about some significant advances in Pd-catalyzed cross-coupling.

B.viii. Side Reactions

As simple as the cross-coupling reaction is, it can still be associated with a number of side reactions. Cross-homo scrambling processes of various origins that lead to the formation of one or both of the two possible homo-coupled products have been widely observed. Another commonly encountered side reaction is the reduction of organic electrophiles (R^2X) to the corresponding hydrocarbons (R^2H). The most common path leading to this side reaction appears to be the conversion of the oxidative addition intermediates (R^2PdL_nX) into R^2PdL_nH , which can then undergo reductive elimination to give R^2H . On the other hand, protonolysis of R^2PdL_nX is rather rare. β -Dehydropalladation is a widely observable route to R^2PdL_nH , but various other routes are also conceivable. β -Dehydropalladation of alkylpalladium derivatives leads to the formation of alkenes. Various side reactions that have been observed in Pd-catalyzed cross-coupling, including those mentioned above, are listed in Table 3. These reactions are diverse in nature, and their concise discussion cannot be presented in a generalized manner. So, they will be discussed in pertinent sections. It is, however, useful to consult with this table for some clues to identifying the origin of side products.

B.ix. Special Topics on Pd-Catalyzed Carbon–Carbon Cross-Coupling

Essentially all types of organic compounds can be synthesized via Pd-catalyzed cross-coupling. The syntheses of the following classes of compounds are particularly noteworthy. So, special discussion of their syntheses are presented in the sections indicated in parentheses.

- Heteroaromatics (Sect. III.2.7)
- Chiral compounds and their asymmetric synthesis (Sect. III.2.16)

TABLE 3. Side Reactions in Pd-Catalyzed Cross-Coupling

Entry	Side Reaction
1.	Formation of R^1-R^1
2.	Formation of R^2-R^2
3.	Reduction of R^2X to give R^2H
4.	β -Elimination of alkylpalladium derivatives to give alkenes
5.	Stereoisomerization of alkenyl and other compounds
6.	Regioisomerization of allyl, propargyl, and other derivatives
7.	Reactions of functional substituents (chemoselectivity problems)
8.	Other undesirable reactions of the starting compounds and organic products (e.g., alkyne cyclotrimerization to give benzenes)
9.	Other undesirable reactions of organopalladium intermediates
10.	Undesirable reactions of ligands, solvents, added reagents, and adventitious chemicals (e.g., water and O_2)

- Conjugated oligomers of biological significance (**Sect. III.2.17.1**)
- Conjugated oligomers and polymers of materials chemical interest (**Sect. III.2.17.2**)
- Natural products (**Sect. III.2.18**)

Finally, any cross-coupling procedures should, in principle, be applicable to the synthesis of homodimers. In addition, other Pd-catalyzed protocols specifically aimed at the synthesis of homodimers have also been developed. Most of them involve Pd-catalyzed dimerization of organometals or organic electrophiles, rather than the reaction of an organometal with an organic electrophile. Some of these homocoupling procedures can be applied to the synthesis of cyclic cross-dimers. These reactions are discussed in **Sect. III.2.20**.

C. Pd-CATALYZED CARBON-HYDROGEN, CARBON-HETEROATOM, AND CARBON-METAL BOND FORMATION

With due modifications, the discussions presented in **Sect. B** are applicable to the other types of the Pd-catalyzed cross-coupling reactions discussed in **Sect. III.3**.

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