

# Palladium-Catalyzed Cyclization via Carbopalladation and Acylpalladation

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**Abstract** Over the past two decades, cyclic carbopalladation and related cyclic acylpalladation of alkenes, allenes, alkynes, and related  $\pi$  complexes including the cyclic Heck reaction have been developed into new and attractive synthetic methods. This chapter mainly discusses catalytic cyclization reactions via cyclic carbopalladation and cyclic acylpalladation, which may not be classified under the cyclic Heck reaction.

**Keywords** Acylpalladation · Cascade Carbopalladation · Cyclic Acylpalladation · Cyclic Carbopalladation

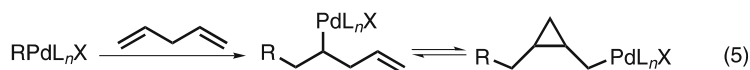
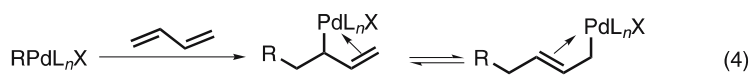
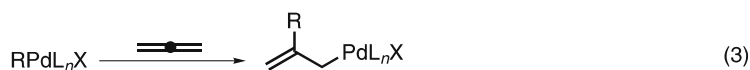
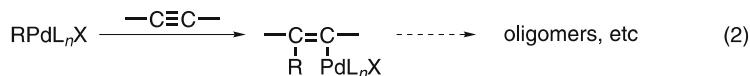
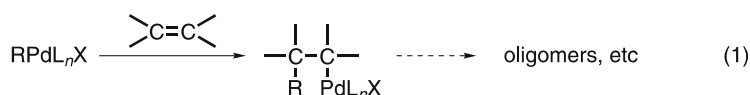
## 1 Introduction and General Discussion

Alkenes and alkynes represent some of the most reactive classes of functional groups toward Pd. They are generally more reactive than various

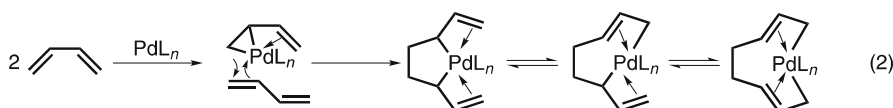
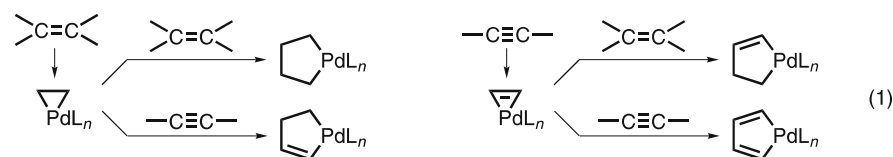
carbonyl functionalities including ketones, esters, amides and even aldehydes [1]. Their presence also makes otherwise relatively unreactive functional groups, such as halogens, in their vicinity much more reactive. Thus, alkenyl, alkynyl, allyl, propargyl, as well as aryl and benzyl halides and related electrophiles are generally more reactive than the corresponding ordinary alkyl halides toward Pd.

Those interactions mentioned above lead to  $\pi$ -complexation and oxidative addition, representing two of the several most widely employed routes to organopalladium derivatives along with transmetalation with Pd, hydropalladation, and heteropalladation defined as addition of Pd–X bonds to  $\pi$ -bonds, where X is any element other than C or H [2].

Organopalladium derivatives obtained by any of the methods indicated above can undergo *carbometallation* which may be defined as a process of addition, generally *syn*-addition, of a C–Pd bond to alkenes and alkynes (Schemes 1 and 2). The regiochemistry of carbometallation can be affected by mutually competing factors and is therefore often somewhat unpredictable.



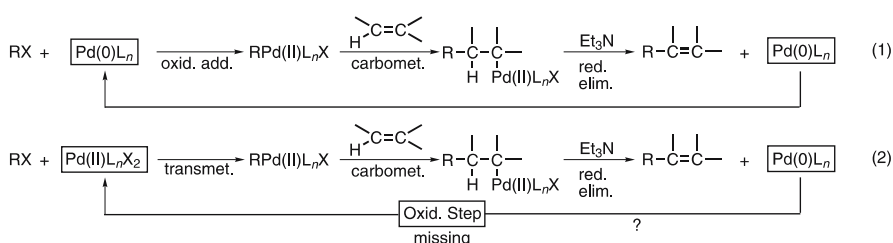
**Scheme 1**



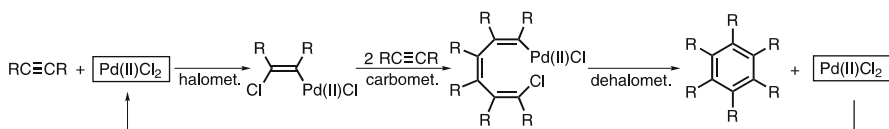
**Scheme 2**

Carbopalladation itself is a process that is only stoichiometric in Pd (Schemes 1 and 2). It must therefore be combined with some processes for regeneration of Pd to devise catalytic cycles. In the Heck reaction [3–5], which undoubtedly is currently the most widely used synthetic reaction involving carbopalladation, the critical carbopalladation process is followed by  $\beta$ -dehydropalladation for regeneration of Pd(0)L<sub>n</sub> as a catalyst (Eq. 1 in Scheme 3). It is instructive to note that the original version of the reaction [6] was only stoichiometric, because the required organopalladium intermediate, RPd(II)L<sub>n</sub>X, was generated by non-redox transmetallation (Eq. 2 in Scheme 3). So, a Pd(0)-to-Pd(II) oxidative process was missing for completion of a catalytic cycle. These two reactions vividly indicate the significance of correctly choosing and linking appropriate microsteps to come up with synthetically useful catalytic cycles.

Another prototypical catalytic process proceeding via carbopalladation is the Maitlis alkyne cyclotrimerization to give benzene derivatives [7, 8], the discovery of which predates that of the Heck reaction. Although its mechanistic details are somewhat unclear, the process most likely involves one halopalladation, two carbopalladations, and one dechloropalladation (Scheme 4). As attractive as this reaction might appear, it is important to note that the reaction generally lacks control over regiochemistry and alkyne “pair”-selectivity in cases where two or three different unsymmetrically substituted alkynes are to be incorporated into benzene derivatives. Consequently, its synthetic application is practically limited to the synthesis of symmetric benzene derivatives perhaps of materials chemical interest. This indeed is a very serious and important consideration in the development of methods for the synthesis of organic compounds of biological and medicinal interest, which is the main topic of this chapter.



Scheme 3



Scheme 4

Currently, there seems to be a widespread tendency to call many reactions proceeding via carbopalladation the Heck reaction. However, this practice is clearly incorrect, since the scope of carbopalladation is significantly wider than that of the Heck reaction. The alkyne carbopalladation reaction shown in Scheme 4, which is not accompanied by  $\beta$ -dehydropalladation may not be viewed as an example of the Heck reaction. In fact, this chapter focuses its attention on various carbopalladation reactions that may not be considered as examples of the Heck reaction. Although some of such processes are combined with the Heck reaction in many cases.

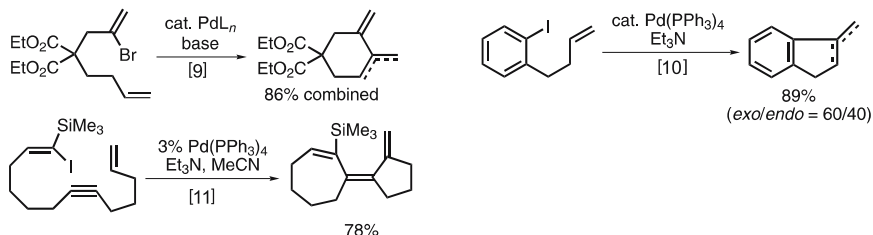
Since both starting organometals and products in carbopalladation are organopalladium derivatives (Schemes 1 and 2), the process of carbopalladation can, in principle, repeat itself as exemplified in the reaction shown in Scheme 4. Thus, unless intercepted by some C–Pd bond cleaving process, this “living” process will stay alive, and no catalytic process will result. In both Heck and Maitlis reactions, the carbopalladation steps are spontaneously followed by  $\beta$ -dehydropalladation and dechloropalladation, respectively. In cases where no such process occurs spontaneously, some processes must be deliberately devised usually through addition of appropriate reagents. In addition to dehydropalladation and dechloropalladation shown in Schemes 3 and 4 as well as in Eqs. 1 and 2 in Scheme 5, several other reactions used for this purpose are exemplified with prototypical cases of catalytic cyclic carbopalladation shown in Scheme 5 [9–19].

**Patterns of cyclic carbopalladation.** As discussed above, the fundamentally stoichiometric and “living” nature of carbopalladation imposes various difficulties to be overcome. Carbopalladation can, in principle, be either a single-stage process or double- or multiple-stage processes. Double- and multiple-stage carbopalladation reactions have often been called either “domino” or “cascade” carbopalladation reactions. In some cases, two-stage carbopalladation reactions have also been called “tandem” carbopalladation reactions. None of these three words is a chemical term, and choice between them is a matter of taste. In this chapter, the term “cascade” will be used for both double- and multiple-stage carbopalladation processes.

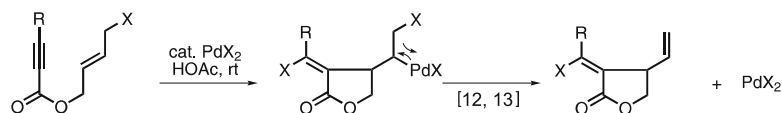
As discussed in conjunction with the intermolecular cascade carbopalladation reaction shown in Scheme 4, it has been very difficult to satisfactorily control both “queuing” or “pair”-selectivity and regioselectivity of intermolecular cascade carbopalladation processes. Consequently, essentially all of the cascade carbopalladation reactions discussed here are at least partially intramolecular. The currently known cyclic cascade carbopalladation processes can be classified into a few to several types shown in Scheme 6.

At this point, it is appropriate to point out that not all cyclization reactions of organopalladation with  $\pi$ -bonds involve *syn*-addition of the C–Pd bonds to carbon–carbon  $\pi$ -bonds. Some processes have been shown to involve *anti*-addition, as exemplified in Scheme 7. This reaction is believed to proceed via  $\pi$ -complexation, nucleophilic attack from the side opposite to Pd,

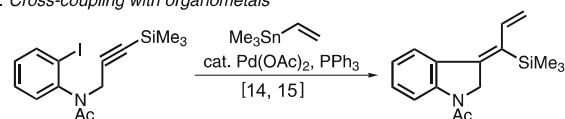
## 1. Dehydropalladation, i.e., Heck reaction



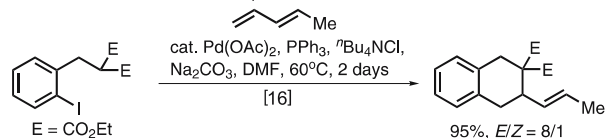
## 2. Deheteropalladation



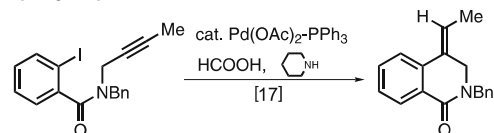
## 3. Cross-coupling with organometals



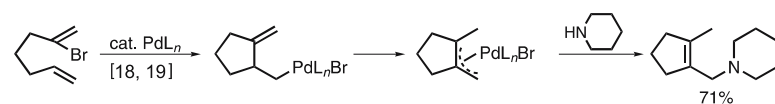
## 4. Substitution with other C nucleophiles



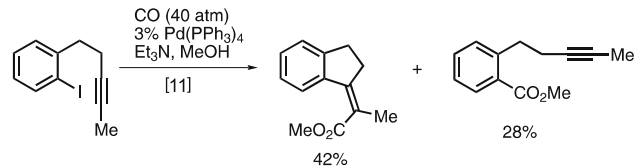
## 5. Hydrogenolysis



## 6. Substitution with N, O, and other heteroatom nucleophiles



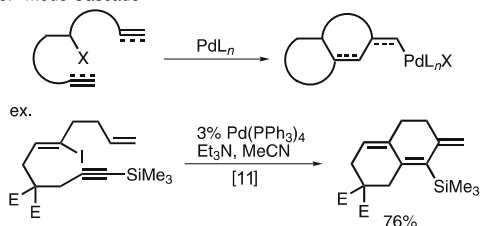
## 7. Termination via carbonylation



## Scheme 5

and reductive elimination [22]. No additional discussion of this type of cyclization reactions will be presented in this chapter. The readers are referred to a recent review of this subject [23].

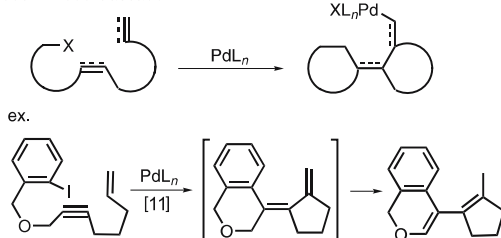
## "Zipper"-Mode Cascade



## Applicability

Alkyne	Alkene
readily applicable	applicable but prone to $\beta$ -elimination and other side reactions

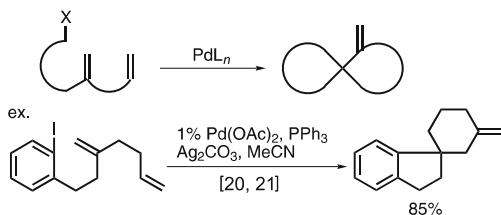
## "Dumbbell"-Mode Cascade



readily applicable

applicable but prone to  $\beta$ -elimination and other side reactions

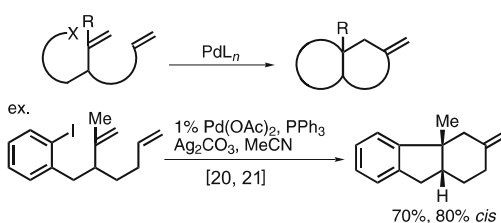
## Spiro-Mode Cascade



not applicable

readily applicable

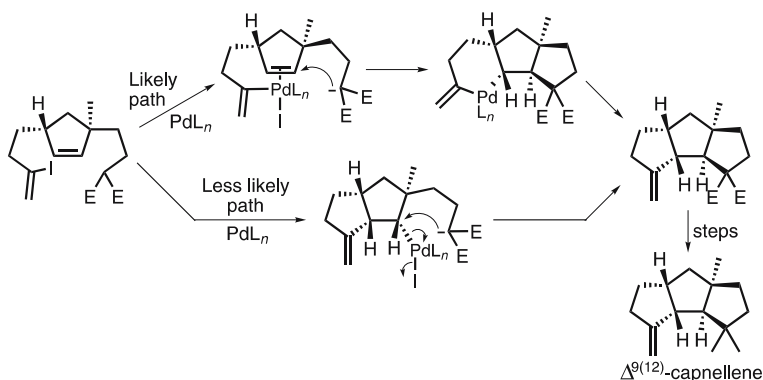
## Linear-Fused-Mode Cascade

unknown and it would require *anti*-carbopalladation

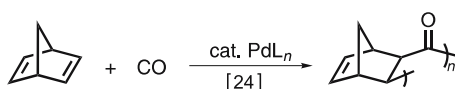
readily applicable

## Scheme 6

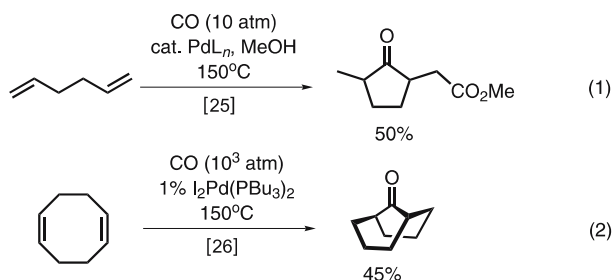
**Cyclic acylpalladation.** Another major subtopic of carbopalladation is acylpalladation. In the mid-1960s, two seemingly independent papers were published by J. Tsuji [24] and P.R. Hughes [25, 26]. The former reported a perfectly alternating copolymerization of norbornadiene with CO (Scheme 8), while the latter described two related Pd-catalyzed carbonylation cyclizations shown in Scheme 9.



Scheme 7



Scheme 8

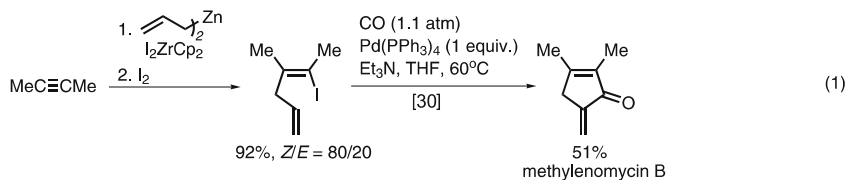


Scheme 9

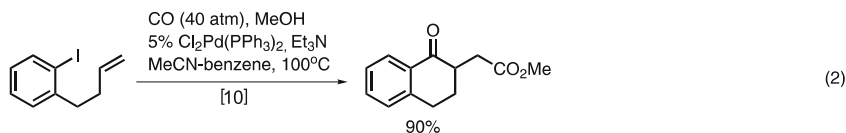
Although the Pd-catalyzed alkene-CO copolymerization reaction must involve a series of acylpalladation reactions, it is outside the scope of this chapter. And, the readers are referred to recent reviews and pertinent references cited therein [27–29]. As such, the cyclic carbonylation reactions of dienes were of limited synthetic utility because of difficulties in controlling regiochemistry and other aspects of importance in fine chemicals synthesis. Whatever the reasons might have been, little had been reported further until the 1980s.

Development of cyclic acylpalladation of halodienes and haloarylalkenes during the 1983–1985 period [10, 30] (Scheme 10) proved to be a breakthrough triggering many subsequent investigations both by the authors' group and by others including W. Oppolzer, R. Grigg, and K. Yamamoto. The two discrete cyclic acylpalladation reactions shown in Eqs. 1 and 2 of Scheme 10 have been conveniently termed Type I and Type II cyclic acyl-

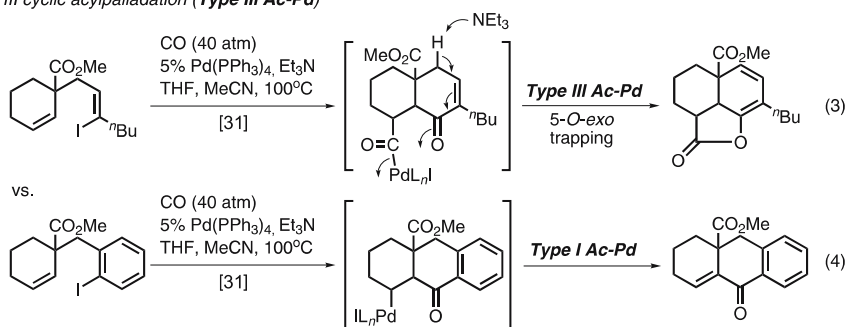
## Type I cyclic acylpalladation (Type I Ac-Pd)



## Type II cyclic acylpalladation (Type II Ac-Pd)



## Type III cyclic acylpalladation (Type III Ac-Pd)

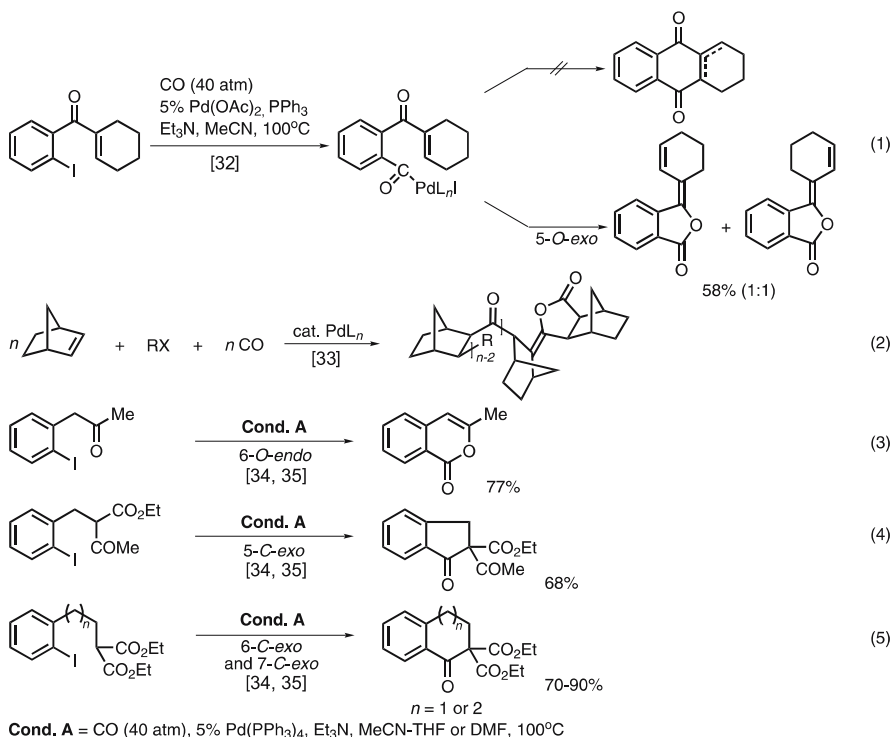


## Scheme 10

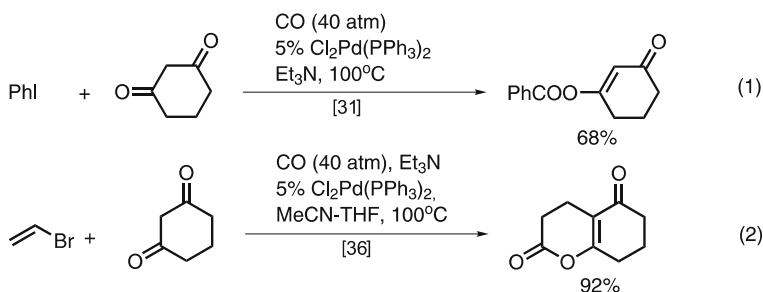
palladation reactions and abbreviated as Type I Ac-Pd and Type II Ac-Pd, respectively. In addition to these processes, yet another process involving trapping of acylpalladium intermediates by enolates generated in situ by cyclic acylpalladation was discovered in 1990 [31] and termed Type III cyclic acylpalladation abbreviated as Type III Ac-Pd (Eq. 3 in Scheme 10).

Although no cyclic acylpalladation was involved, trapping of acylpalladation derivatives by enolates had already been discovered in 1986 [32]. Thus, an attempted cyclic acylpalladation of an iodoketone intermediate was aborted by trapping of the acylpalladium intermediate by an enolate generated under the reaction conditions (Eq. 1 in Scheme 11). A few years later, a similar trapping of acylpalladium species by enolates was shown to serve as a process of termination of the alkene-CO copolymerization [33] (Eq. 2 in Scheme 11). Later systematic investigations [34–36] have established that trapping of acylpalladium derivatives with enolates can occur both intramolecularly [34, 35] (Scheme 11) and intermolecularly [31, 36, 37] (Scheme 12) and that intramolecular trapping can be achieved either with *O*-enolates or with *C*-enolates depending on the tether length [34, 35] (Eqs. 3–5 in Scheme 11).





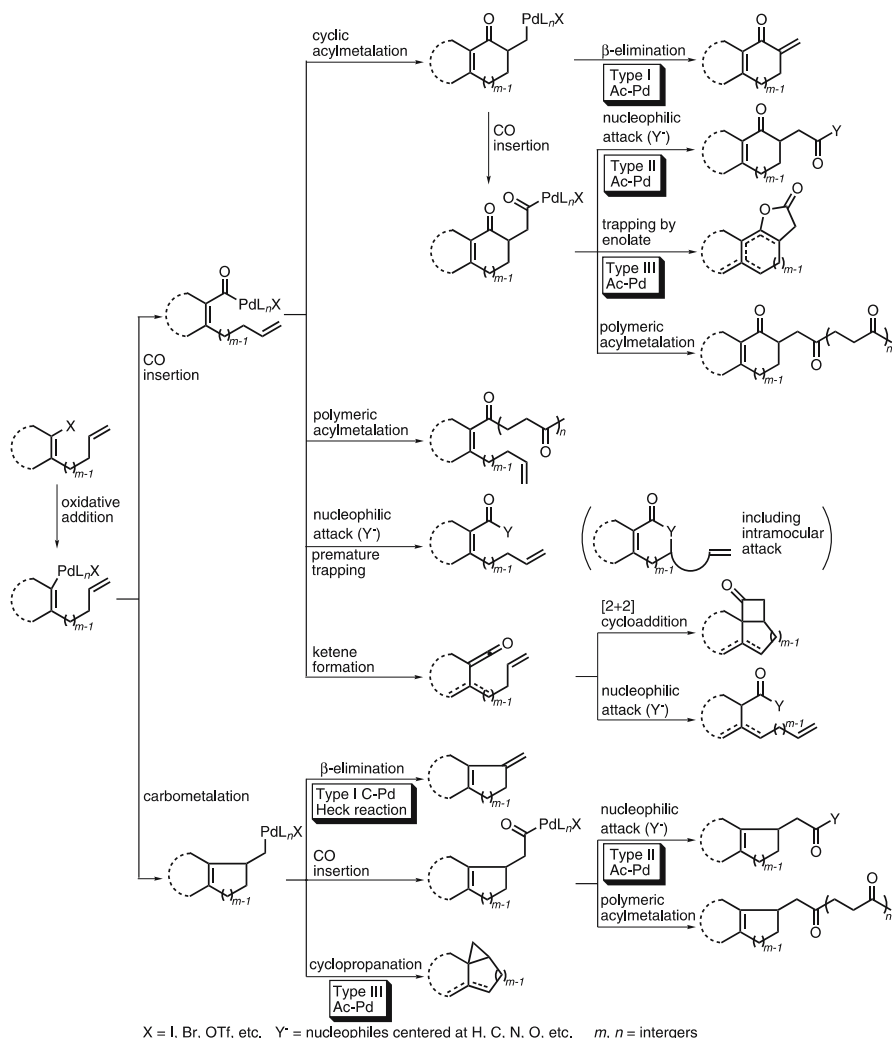
Scheme 11



Scheme 12

The currently available data indicate that seven or eight discrete processes including Type I–III Ac-Pd reactions can take place under carbonylative conditions. In many cases, non-carbonylative cyclic carbopalladation has been observed even in the presence of CO. A summary of all of these observed processes is presented in Scheme 13 as a “guide map”.

It is clearly not practical to discuss in detail all of the reactions to be covered in this chapter. Fortunately, most of the reactions reported before

**Scheme 13**

2000 have been discussed in detail in reviews and book chapters, as summarized below. In this chapter, only some noteworthy highlights from earlier investigations and important recent results will be presented in the following sections.

In addition to a couple of reviews focused on results obtained in the authors' group [38, 39], a comprehensive book on organopalladium chemistry for organic synthesis [40] contains two dozens or so chapters on cyclic carbopalladation and cyclic acylpalladation. Thus, its Part IV (p1123–1659) on carbopalladation contains reviews of cyclic carbopalladation on the synthe-

sis of carbocycles [41], heterocycles [42], asymmetric cyclization [43], non-Heck-type cyclic carbopalladation of alkenes [44], cyclic carbopalladation of alkynes terminated by trapping with nucleophilic reagents [45], by trapping with electrophiles [46], cyclic cascade carbopalladation terminated with alkenes [47], with nucleophiles [48], by carbonylative reaction [49], cyclic allylpalladation [50], alkynylpalladation [51], arene analogs of the cyclic Heck reaction [52], cyclic carbopalladation of allenes [53], conjugated dienes [54], conjugated enynes and diynes [55], Pd-catalyzed cyclic alkylzincation [56], and synthesis of natural products via cyclic carbopalladation [57]. And, Part VI contains reviews on cyclic acylpalladation [58], its arene analogs [59], and synthesis of natural products via cyclic acylpalladation [60]. Additionally, those chapters pertaining to polymerization by acylpalladation [29], trapping to acylpalladium derivatives with enolates [37], intermolecular acylpalladation [61], and formation and reactions of ketones generated via acylpalladium derivatives [62] discuss topics related to this chapter.

## 2

### Palladium-Catalyzed Cyclization via Carbopalladation

Although the catalytic version of the Heck reaction, as defined by Eq. 1 of Scheme 3, was discovered as early as the 1971–1972 period by Mizoroki [4] and Heck [5], it was not until the mid-1980s that examples of its cyclic version shown at the top of Scheme 5 [9, 10] were reported. In fact, no example of the cyclic Heck reaction appears to be described in a comprehensive survey of the Heck reaction published in 1982 [3].

In the Heck reaction, acyclic or cyclic, the organopalladium intermediates generated via carbopalladation are short-lived owing to the ensuing  $\beta$ -dehydropalladation. In cases where such organopalladium intermediates generated as above should prove to be “living” or long-lived, their further transformations to give organic products must be induced by some processes other than  $\beta$ -dehydropalladation, leading to various Pd-catalyzed organic synthetic reactions that cannot be represented by Eq. 1 of Scheme 3. Despite its inherent limitations as a method of synthesis of fine chemicals, the Maitlis alkyne cyclooligomerization [7, 8] (Scheme 4) is a prototypical example of “non-Heck” cyclic carbopalladation reactions. Another seminal example is the process shown as the item 6 of Scheme 5 reported by Heck himself [18, 19]. In this case, the initially formed Heck alkene substitution product must isomerize to a stable and “living”  $\pi$ -allylpalladium species that must be decomposed by an external reagent, namely piperidine in this example. As the cyclic Heck reactions as defined above are extensively discussed elsewhere in one or more chapters in this compilation, they are not further discussed in this chapter, even though those cascade reactions that involve the use of the Heck reaction as a cascade-terminating device, e.g., those shown

Scheme 6, represent important exceptions. After all, the main attention in these cases is focused on the “living” and cascading process providing a previously unrecognized synthetic tool for constructing carbon skeletons.

## 2.1

### Cyclization via Single Carbopalladation

All examples shown in Scheme 5 except one shown as part of the item 1 involve just one carbopalladation step. They can be classified according to the  $\pi$ -compound types. As detailed below, allenes, i.e., 1,2-dienes, conjugated dienes, i.e., 1,3-dienes, and higher dienes display reaction characteristics that are different from monoenes. In this connection, it is instructive to note that  $\beta$ -dehydropalladation, critically important for the production of organic products by the Heck reaction, requires a *syn*-coplanar arrangement of the H – C – C – Pd moiety. Thus, any factors inhibiting this *syn*-coplanar arrangement can, in principle, lead to “non-Heck” carbopalladation processes. Such factors include (a) simple absence of a  $\beta$ -hydrogen, (b) conformational constraint due to cyclic structures, (c) configurational constraint due to *trans* geometry, (d) opportunity for the formation of  $\pi$ -allylpalladium and cyclopropylcarbinyllpalladium derivatives and so on. Another useful notion of general and fundamental significance is that various organopalladium processes including hydropalladation, halopalladation, and even carbopalladation producing cyclopropylcarbinyllpalladiums can be readily reversible. A myriad of seemingly mysterious processes may be readily understood with a good grasp of these fundamental properties and characteristics of organopalladium derivatives.

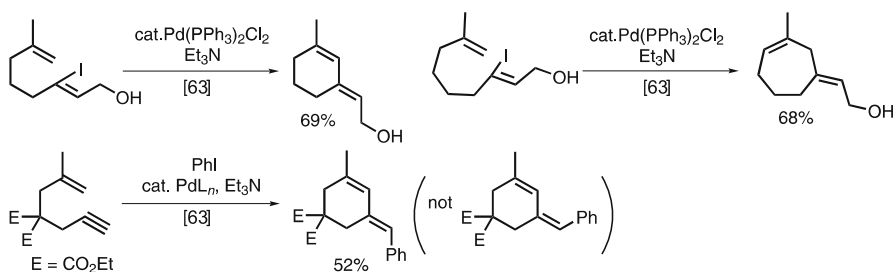
#### 2.1.1

##### Cyclic Heck Reactions, Noteworthy Variations

Although this chapter focuses its attention on cyclic carbopalladation reactions other than the cyclic Heck reaction, it might be useful to discuss here the following variants of the cyclic Heck reaction. For the vast topic of the cyclic Heck reaction including those variants discussed below, the reader are referred to the following chapters of the Handbook of Organopalladium Chemistry for Organic Synthesis [40].

- Synthesis of Carbocycles (Chap. IV. 2.2.1) [41]
- Synthesis of Heterocycles (Chap. IV. 2.2.2) [42]
- Asymmetric Heck Reaction (Chap. IV. 2.3) [43]
- Arene Analogs of the Heck Reaction (Chap. IV. 6.1) [52]
- Synthesis of Natural Products via Carbopalladation (Chap. IV. 8) [57]

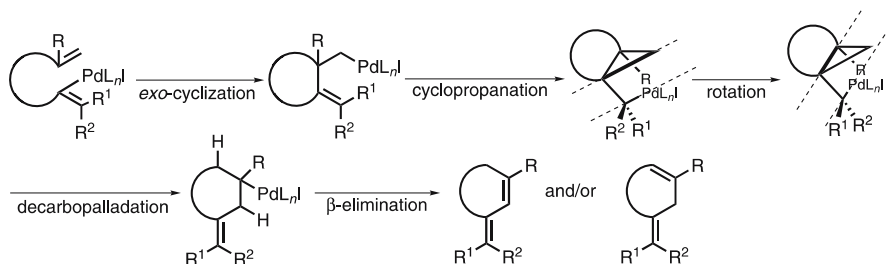
(i) **Apparent *endo*-mode cyclic Heck reaction.** The reactions shown in Scheme 14 might appear to be ordinary examples of the cyclic Heck reaction.

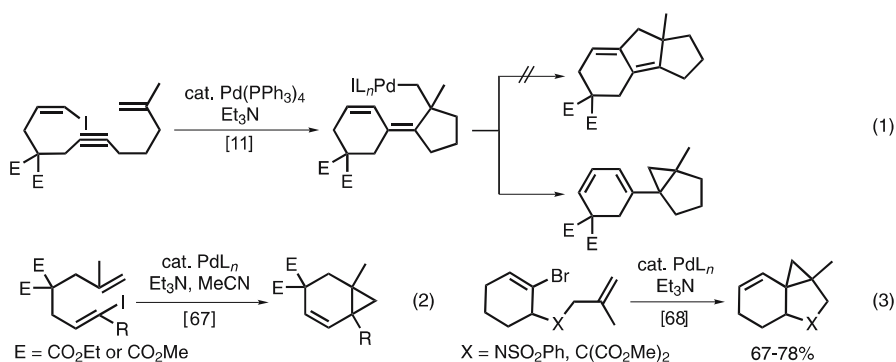
**Scheme 14**

However, both the *endo*-mode cyclization and the mysterious geometry of the *exo*-cyclic C = C bond, which go counter to simple-minded expectations, led to clarification of a circuitous mechanistic route shown in Scheme 15 [63]. This mechanism has provided plausible explanations for a number of other cases [64, 65], as can be seen later in this chapter.

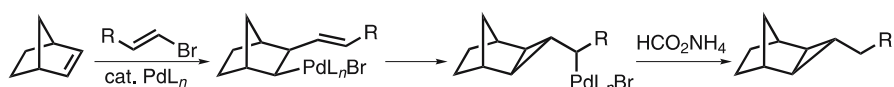
(ii) **Cyclic Heck reaction accompanied by cyclopropanation and cyclobutanation.** It is readily anticipated that, in cases where the cyclopropylcarbinyl-palladium species shown in Scheme 15 can undergo  $\beta$ -dehydropalladation rather than decarbopalladation to undergo ring expansion, cyclopropyl-alkenes can be obtained as the products. The example shown in Eq. 1 of Scheme 16 [11] appears to be the first such example observed in cyclic carbopalladation reactions, although formation of cyclopropanes via homoallylpalladium derivatives was reported earlier for the reaction shown in Scheme 17 [66]. A number of the synthesis of cyclopropane derivatives [67–70] as well as reverse conversion of cyclopropanes into alkenes via cyclopropylcarbinyl-to-homoallyl rearrangement [44] and homologous cyclobutanation [71] (Scheme 18) have also been reported over the past 15 or so years.

(iii) **Asymmetric cyclic Heck reactions.** In most cases, the Heck reaction proceeds, as shown in Eq. 1 of Scheme 3 with no generation of new asymmetric carbon atoms. In cases where  $\beta$ -dehydropalladation is forced to take place with an allylic H atom in the reacting alkenes; however, a new asym-

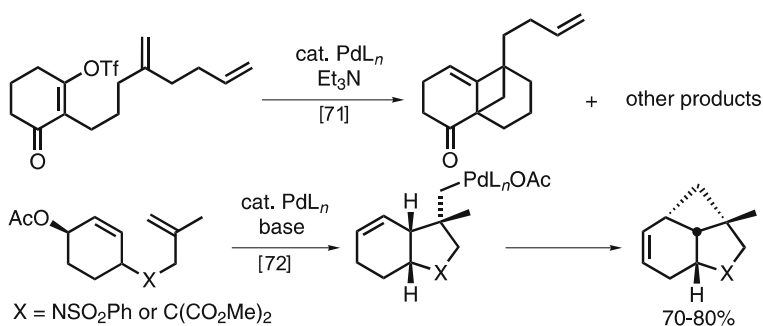
**Scheme 15**



Scheme 16



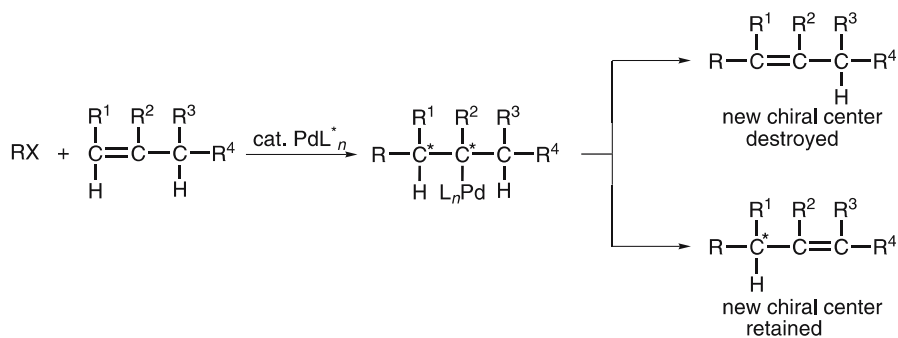
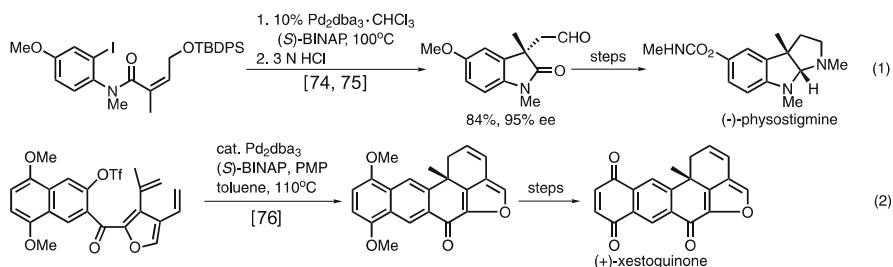
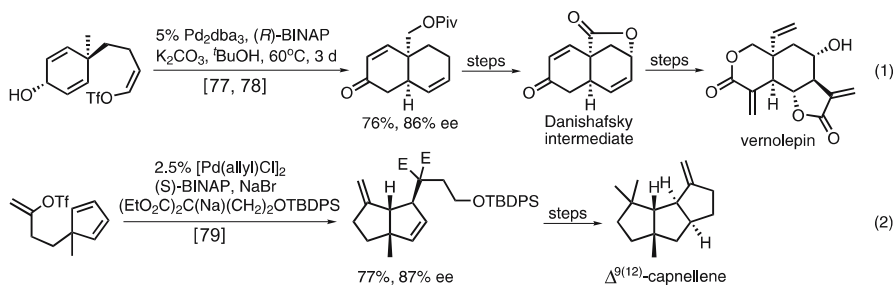
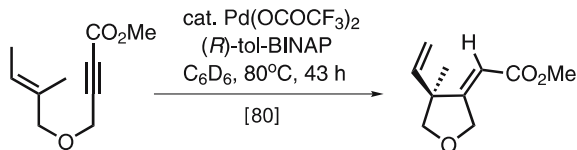
Scheme 17



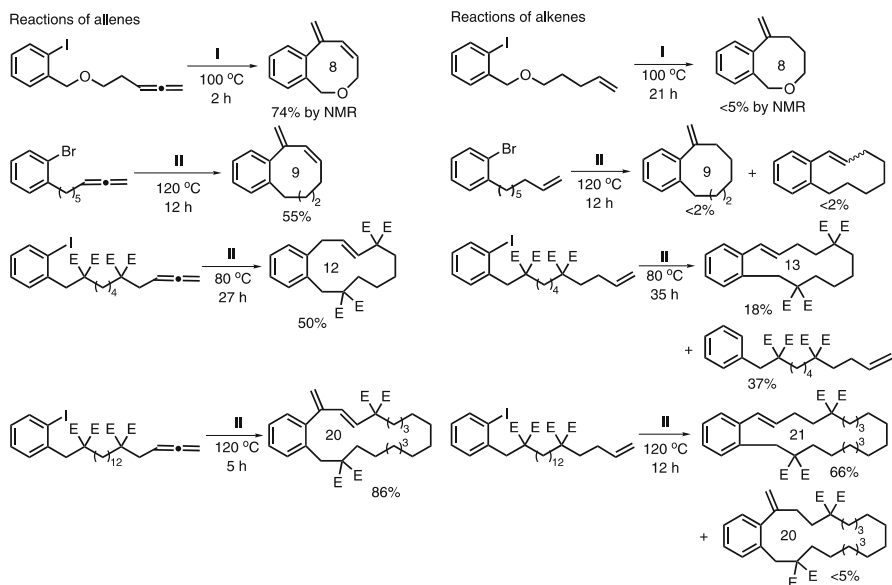
Scheme 18

metric carbon center generated via carbopalladation is retained. Under the influence of either external or internal chiral sources, asymmetric Heck reactions can then be observed (Scheme 19). Alternatively, desymmetrization of prochiral dienes may also be exploited to achieve asymmetric synthesis even in cases where an alkenyl carbon-bound H atom participates in  $\beta$ -dehydropalladation.

Seminal contributions to the development of asymmetric cyclic Heck reaction were made in 1989 by Overman [72] and Shibasaki [73]. These and other groups have since developed the reaction as a useful tool for asymmetric synthesis of complex natural products as indicated by representative examples shown in Schemes 20 [74–76] and 21 [77–79]. For further details, the readers are referred to recent reviews [43, 57].

**Scheme 19****Scheme 20****Scheme 21****Scheme 22**

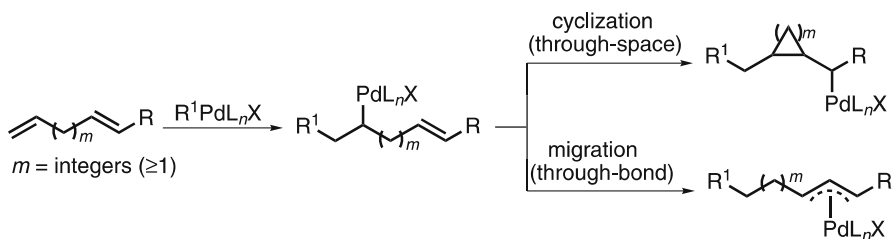
Although mechanistic details are not very clear, a recently reported Pd-catalyzed asymmetric ene reaction may proceed via hydropalladation-initiated asymmetric Heck reaction [80] (Scheme 22).

**Scheme 23**

(iv) **Cyclic carbopalladation of allenes.** Although the cyclic carbopalladation–dehydropalladation tandem reaction of allenes shown in Scheme 23 [81, 82] is no more than another variation of the cyclic Heck reaction, it has proved to be one of as yet a very limited number of cyclization reactions that can be satisfactorily applicable to the synthesis of common (5- through 7-membered), medium (8- through 12- or 13-membered), and large (> 12- or 13-membered) rings. Comparably structured allenes and alkenes display striking differences in the ease of cyclization reflected by the product yields. The differences must at least in part be due to the more rigid allene moiety relative to the isolated C = C bond. Another noteworthy aspect of the reaction is that the initially formed organopalladium product before dehydropalladation is an allylpalladium derivative, which is significantly more stable and longer-living than organopalladium derivatives generated in more usual Heck reactions. The allylpalladium derivatives can be further transformed under the same reaction conditions into various “non-Heck” products [81, 82], as discussed later in detail.

(v) **Formation of allylpalladium derivatives and conjugated dienes in other cyclic carbopalladation reactions.** In any carbopalladation reactions of alkenylpalladium derivatives with alkenes, the initial carbopalladation products are homoallylpalladium derivatives. Their cyclopropanation was discussed in Sect. (i) and (ii) (Schemes 15 and 16). Although very significant in the cyclic carbopalladation chemistry, it, nevertheless, is not the most commonly observable process for homoallylpalladium derivatives. In cases



**Scheme 24**

where they contain a hydrogen atom that is both allylic to C = C bond and  $\beta$  to Pd, a facile regioisomerization via dehydropalladation–rehydropalladation to generate more stable allylpalladium derivatives can take place. The dichotomy observable with homoallylpalladium derivatives is, in fact, a generally observable phenomenon, as summarized in Scheme 24, except with the shorter and shortest allylpalladium derivatives which do not process the cyclization option. Of course, the cyclization path represents the very subject of this chapter. On the other hand, much less attention has been paid to the through-bond palladotropy to generate  $\pi$ -allylpalladium derivatives.

One significant consequence of the formation of allylpalladium derivatives is that it represents an “escape” from the Heck reaction manifold permitting a wide variety of “non-Heck” processes via carbopalladation, which is the focal point of the rest of this chapter.

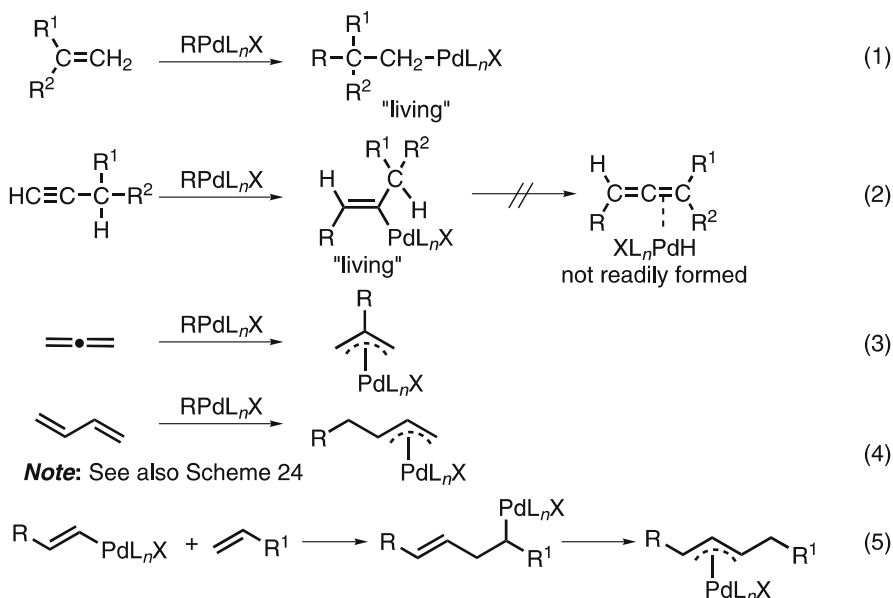
### 2.1.2

#### Cyclic Carbopalladation Terminated by Processes Other than $\beta$ -Dehydropalladation

(i) **Generation and classification of thermally stable and “living” organopalladium derivatives.** Organopalladium derivatives generated via carbopalladation can be classified into several categories according to their thermal and chemical stabilities.

(a) *Allylpalladium derivatives.* The initial products of carbopalladation of alkenes are alkylpalladium derivatives (Eq. 1 in Scheme 1). If they contain a  $\text{Csp}^3\text{–H}$  bond that is  $\beta$  to Pd and can be *syn*-coplanar with the adjacent  $\text{Csp}^3\text{–Pd}$  bond, they can readily undergo  $\beta$ -dehydropalladation. Otherwise, they can be stable. Although the regiochemistry of carbopalladation of alkenes is capricious and somewhat unpredictable, carbopalladation of 1,1-disubstituted alkenes generally produce “neopentyl-type” alkylpalladium derivatives that are generally stable and “living” (Eq. 1 in Scheme 25). Any other factors preventing the *syn*-coplanar arrangement of the  $\text{H–C–C–Pd}$  moiety can also stabilize alkylpalladium derivatives, though it is not practical to discuss all available factors at this point.

(b) *Alkenyl-, aryl-, and alkynylpalladium derivatives.* These organopalladium derivatives are generally relatively stable and long-lived. Thus, alkenyl-



### Scheme 25

palladium derivatives generated via carbopalladation of alkynes or, for that matter via any route, may generally be considered to be stable and “living” even in cases where there is a  $\text{Csp}^2$ -bound  $\beta$ -H atom (Eq. 2 in Scheme 25). Evidently,  $\beta$ -dehydropalladation of alkenylpalladium derivatives to give alkynes and  $\text{HPdL}_n$  must be energetically unfavorable.

(c) *Allyl-, Propargyl-, and benzylpalladium derivatives.*  $\pi$ -Allylpalladium derivatives (Scheme 24 and Eqs. 3–5 in Scheme 25) are chemically reactive but thermally stable. Thus, they are fundamentally capable of undergoing all types of reactions listed in Scheme 5.

(d) *Acylpalladium derivatives and palladium enolates or  $\alpha$ -palladocarbonyl derivatives.* These compounds are chemically reactive and labile. They can readily be decomposed by treatment with either acids or bases, whereas other types of organopalladium compounds are much more resistant to them. For example, water and alcohols do not decompose the categories (a) and (b) organopalladium compounds. The high chemical lability of acylpalladium derivatives makes carbonylative trapping of organopalladium derivatives a useful synthetic tool, as detailed later.

(ii) **Conversion of organopalladium derivatives via cross-coupling.** Conversion of “living” organopalladium derivatives generated via cyclic carbopalladation can be achieved by their reactions with added organometals present in the reaction mixtures [14, 15, 83] (Entry 3 in Scheme 5). In these seminal studies, however, little or no mention was made to the competition between the desired cross-coupling after cyclic carbopalladation and that be-

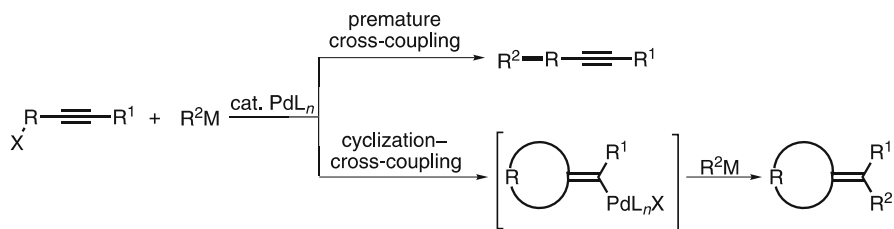
fore cyclization (Scheme 26). Nor was any trend among different metal counterions discussed. A systematic investigation summarized in Scheme 27 clearly indicated the following. Firstly, highly reactive organozincs tend to favor cross-coupling before cyclization. Secondly, organometals containing metals of moderate electronegativity, such as Zr, Al as well as Sn and B, may lead to the cyclic carbopalladation–cross-coupling tandem proceeding in high yields.

The superior ability of alkynyltins to defer Pd-catalyzed alkylation until after completion of the competing cyclic carbopalladation has been exploited in the synthesis of neocarzinostatin model compounds [85–87] (Scheme 28).

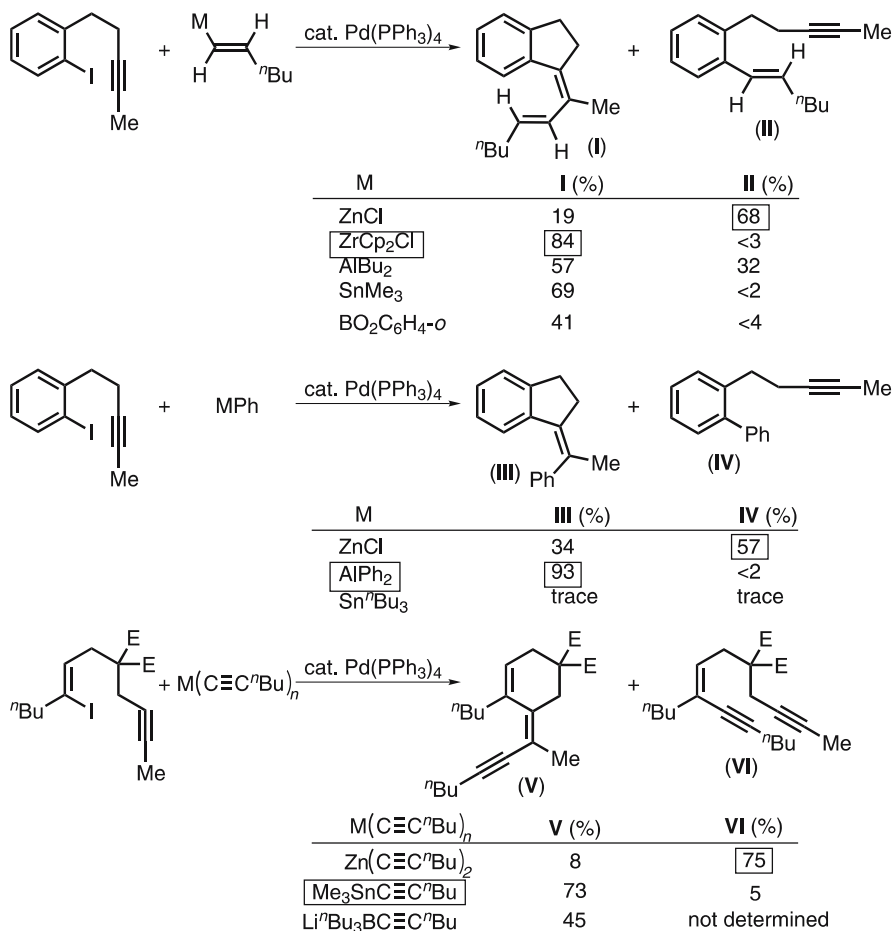
The cyclic carbopalladation–cross-coupling tandem reaction has been extensively developed over the past several years. Despite earlier favorable findings with Al and Zr [84], these metals are still scarcely used. On the other hand, organometals containing Sn and B have been widely used, and favorable results have been obtained for the formation of five-membered carbocycles and heterocycles containing N and O from halodienes [88] (Eqs. 1 and 2 in Scheme 29), haloynes [89–92] (Eqs. 3–5 in Scheme 29), haloarylalkynes [94, 95] (Eqs. 6 and 7 in Scheme 29), and allenene derivatives [93, 96] (Eqs. 8 and 9 in Scheme 29).

(iii) **Hydrogenolysis of organopalladium derivatives.** Hydrogenolysis of organopalladium derivatives can be achieved with various hydride sources. As exemplified in Scheme 5 (Entry 5), formic acid and its derivatives have been commonly used as hydride sources [95, 97]. In a recent comparative study, however,  $\text{Et}_3\text{SiH}$  was shown to be generally superior to  $\text{HCO}_2\text{NH}_4$  as a hydride source in the reactions shown in Scheme 30 [98].

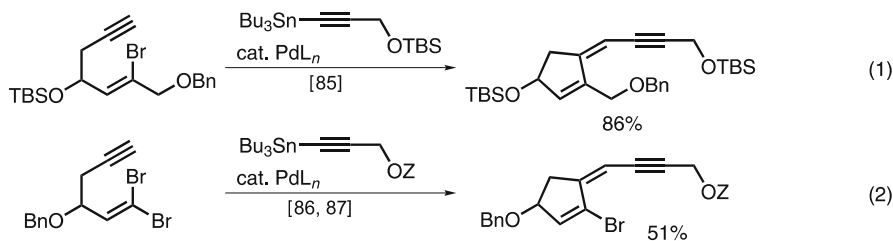
(iv) **Trapping of  $\pi$ -allylpalladium and other organopalladium derivatives with “soft” carbon nucleophiles.**  $\pi$ -Allylpalladium derivatives generated by the reactions shown in Schemes 24 and 25 can be subjected to various reactions that  $\pi$ -allylpalladium derivatives can undergo. The Tsuji–Trost reaction [99–105] is a representative carbon–carbon bond-forming reaction of  $\pi$ -allylpalladium derivatives, and it has indeed been used for converting cyclic carbopalladation products to organic products, as exemplified by the results shown in Scheme 31. The potential scope of the tandem process consisting of cyclic carbopalladation to give  $\pi$ -allylpalladium derivatives and



**Scheme 26**

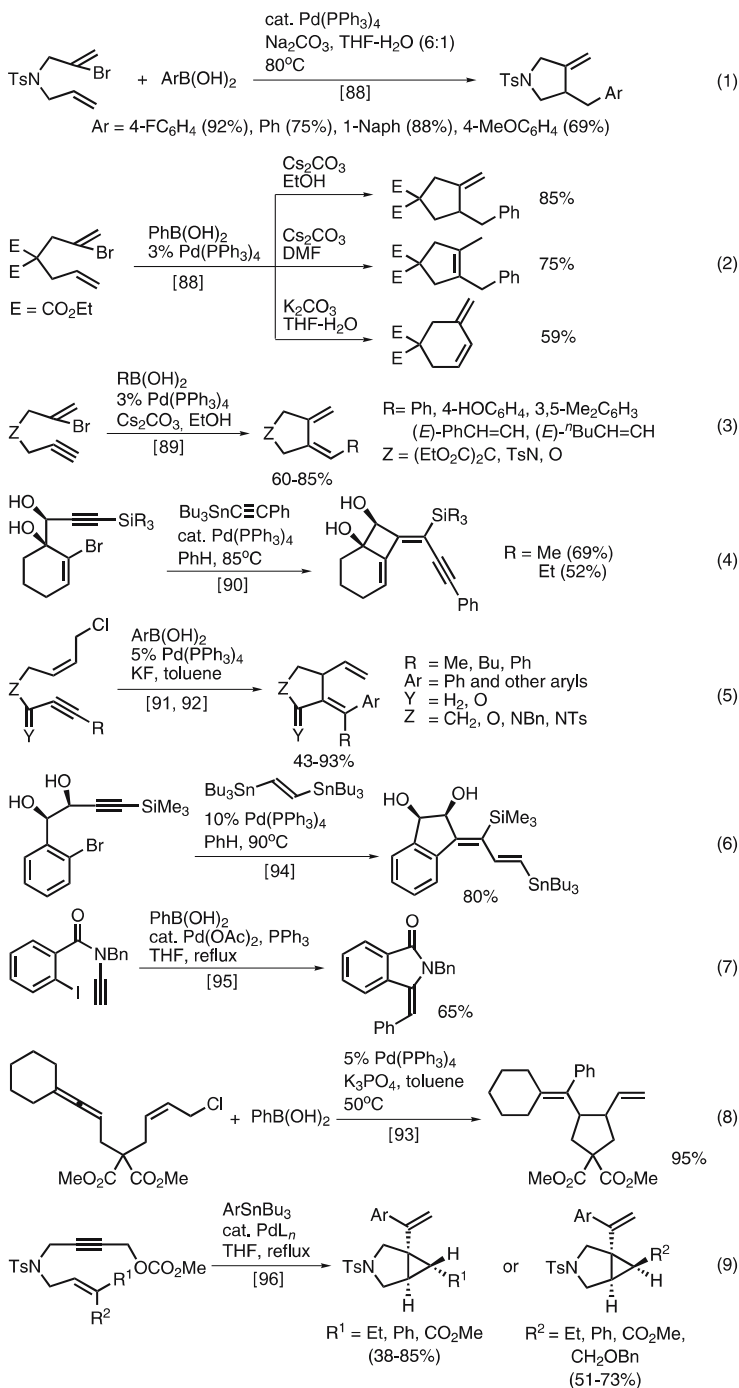


Scheme 27

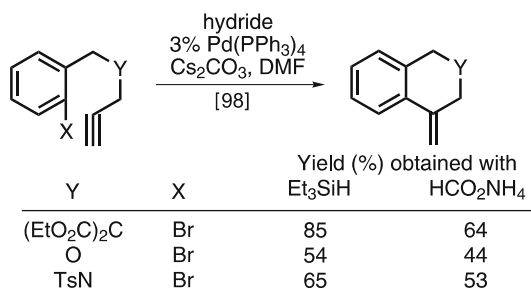


Scheme 28

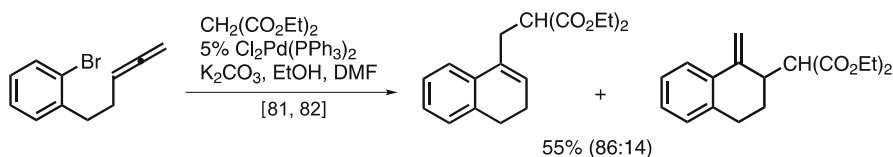
their trapping with “soft” carbon nucleophiles should be considerable, and it appears to deserve further systematic investigations.



Scheme 29



Scheme 30

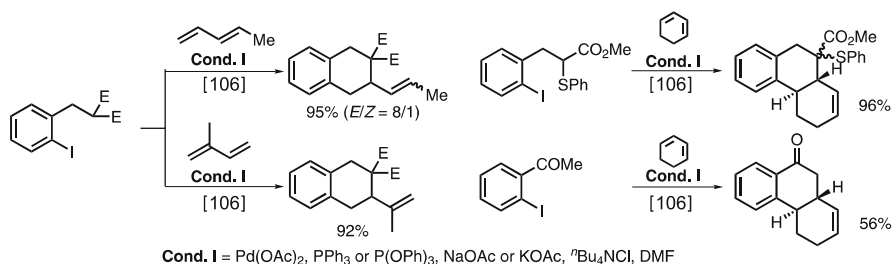


Scheme 31

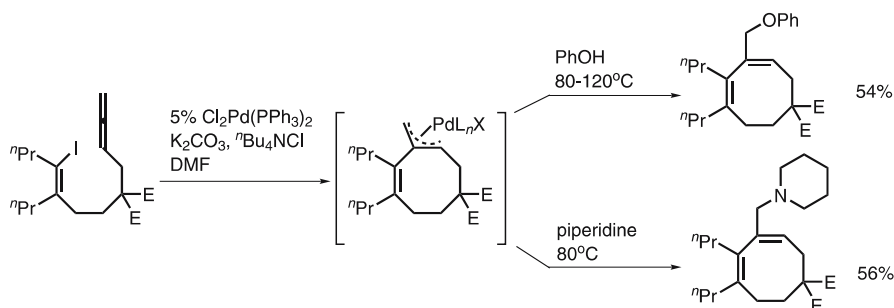
Although no cyclic carbopalladation is involved, the synthetic potential of the tandem process shown in Scheme 32 [106] consisting of conjugated diene carbopalladation and trapping of the resulted  $\pi$ -allylpalladium derivatives with enolates appears to be very high.

(v) **Trapping of  $\pi$ -allylpalladium and other organopalladium derivatives with N, O, and other heteroatom nucleophiles.** The prototypical example of trapping of the product of cyclic carbopalladation with piperidine [18, 19] (Entry 6 in Scheme 5) must involve a nucleophilic attack of a  $\pi$ -allylpalladium derivatives by piperidine. This and many other related reactions can also be exploited to further expand the scope of cyclic carbopalladation, as indicated by the results shown in Scheme 33 [81, 82].

Very interesting and potentially useful tandem processes shown in Scheme 34 [107–109] involve the conjugated diene cyclodimerization shown in Eq. 2 in Scheme 2 followed by trapping of the resultant  $\pi$ -allylpalladium derivatives with an amine or alcohol. In this chapter, the vast and important

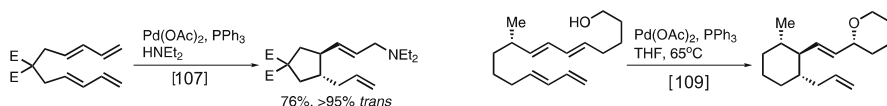


Scheme 32

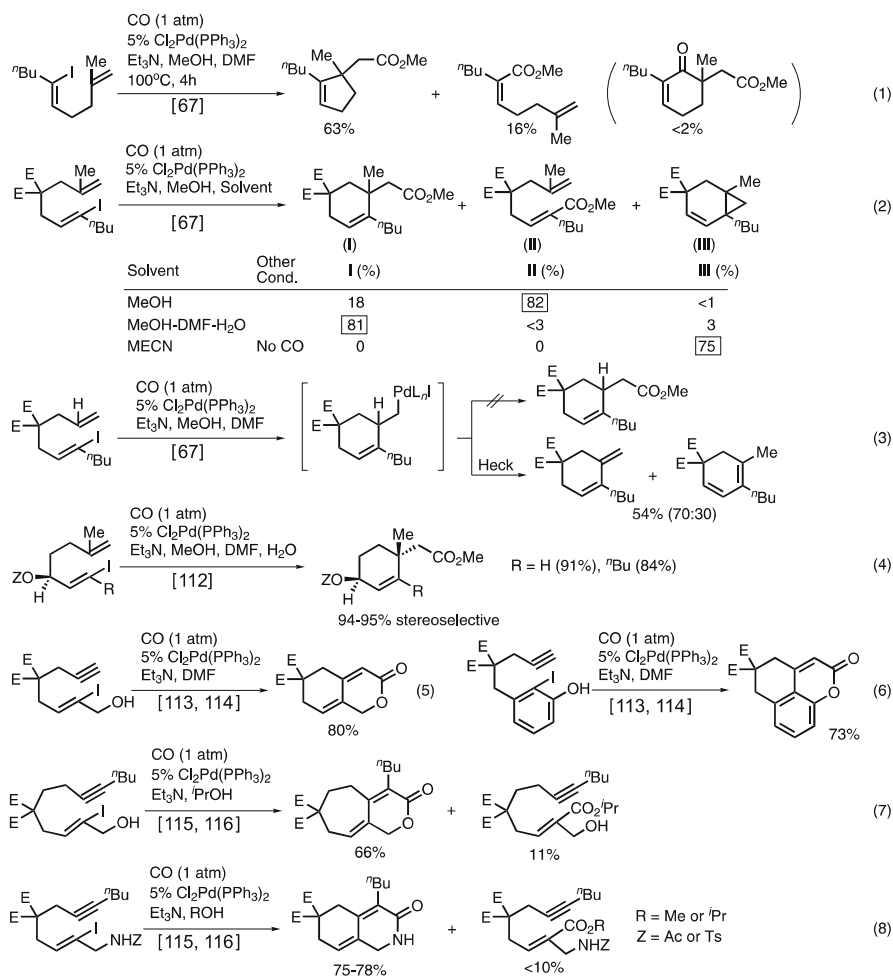
**Scheme 33**

topics of Pd-catalyzed cyclodimerization is not discussed further. The readers are referred to a recent review [54].

(vi) **Trapping of cyclic carbopalladation products via carbonylation with CO.** One of the novel and synthetically attractive methods of trapping cyclic carbopalladation products is based on unexpected and initially disappointing results observed by the authors' group (Entry 7 in Scheme 5) in an attempt to achieve cyclic acylpalladation with incorporation of CO into the desired cyclic ketone [11]. This reaction was soon recognized as a useful means of trapping the products of cyclic carbopalladation without incorporation of CO into the ring moieties [11, 49] (Scheme 35). The available data permit the following tentative generalization as a useful guide to be further scrutinized (Table 1) [67, 110, 111]. In short, common five- and six-membered rings can be prepared by cyclic carbopalladation even in the presence of CO. Although there is one example of the synthesis of a seven-membered ring, the scope of the synthesis of medium and large rings would be limited due to slower cyclization rates vis-à-vis premature esterification.

**Scheme 34****Table 1** Effect of ring size on the competition between cyclic carbopalladation and cyclic acylpalladation in the presence of CO

Ring size	Substrate	Cyclic carbopalladation	Cyclic acylpalladation
4 vs. 5	Alkenes and alkynes	not observed	<b> favored </b>
5 vs. 6	Alkenes	<b> can be competitive </b>	<b> can be dominant </b>
	Alkynes	<b> favored </b>	not observed
6 vs. 7	Alkenes and alkynes	<b> favored </b>	not observed

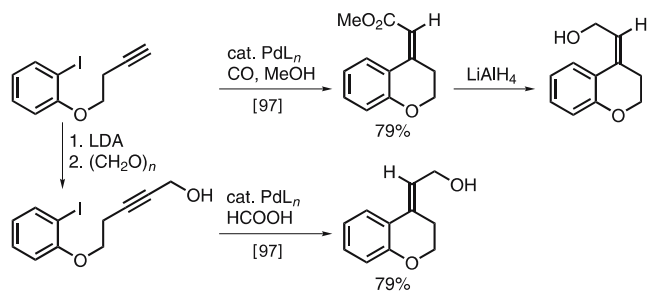


### Scheme 35

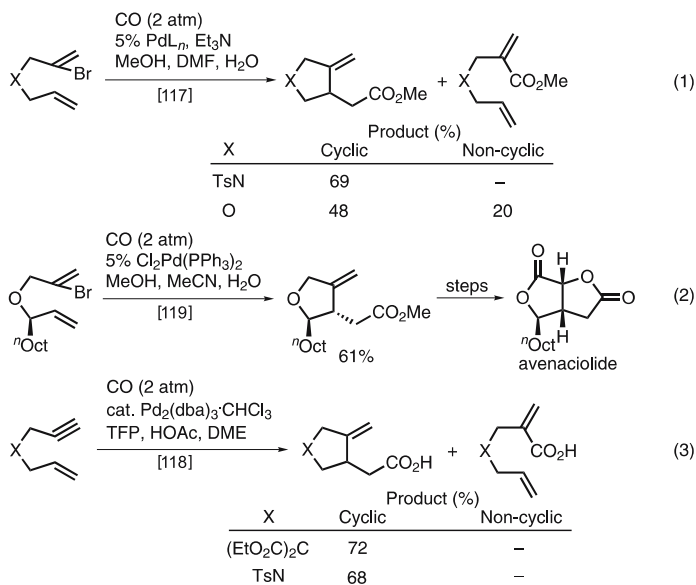
Some notable examples of the use of carbonylative termination of cyclic carbopalladation are shown in Schemes 36–39.

Despite an earlier failure to achieve cyclic carbopalladation–carbonylative termination in competition with the cyclic Heck reaction [67] (Eq. 3 in Scheme 35), a series of investigations by Aggarwal [117–119] has provided useful solutions to this problem. In cases where the substrates contain a heteroatom group, such as O or NTs, the cyclic Heck reaction can be suppressed [117] (Eq. 1 in Scheme 37). This reaction has been applied to an asymmetric synthesis of avenaciolide [119] (Eq. 2 in Scheme 37). A more general solution to avoiding the cyclic Heck reaction is not to use a base, e.g., Et<sub>3</sub>N, and promote rehydropalladation to reserve β-elimination through the

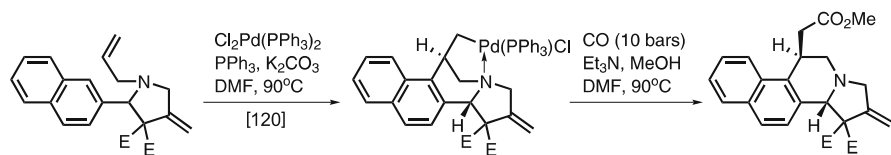




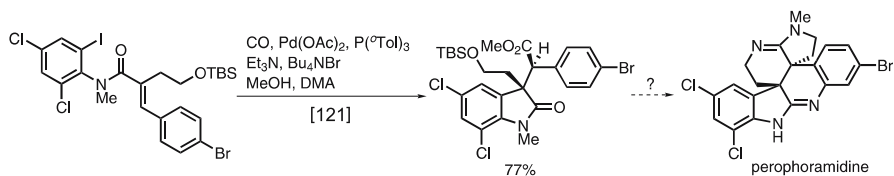
Scheme 36



Scheme 37



Scheme 38



Scheme 39

use of HOAc [118] (Eq. 3 in Scheme 37). Though only stoichiometric, a proximal heteroatom effect to promote carbonylative esterification by suppressing  $\beta$ -dehydropalladation was also reported recently [120] (Scheme 38).

A spectacular example of application of the cyclic carbopalladation–carbonylative esterification tandem process is the synthesis of a possible intermediate for the synthesis of perophoramidine [121] (Scheme 39).

## 2.2

### Cyclization via Double and Multiple Carbopalladation Reactions

In Sect. 2.1 various sequential or “tandem” combinations of cyclic carbopalladation and trapping of the “living” carbopalladation products are discussed with the goal of devising Pd-catalyzed synthesis of cyclic organic compounds. The great majority of examples presented above involve just one carbopalladation or acylpalladation process. Since carbopalladation itself is intrinsically repeatable, oligomerization and polymerization via carbopalladation can be exploited for the synthesis of mono-, oligo-, and even polycyclic compounds via cascading carbopalladation processes. Competitive formation of acyclic and partially cyclic polymers and any kind of premature termination, such as  $\beta$ -dehydropalladation must, of course, be avoided, even though any cyclic carbopalladation cascades must eventually be terminated in a preprogrammed manner to produce the desired cyclic compounds. As indicated in Scheme 25, carbopalladation of alkynes is intrinsically “living” and is therefore well-suited for developing cascade cyclization processes exemplified by the Maitlis Pd-catalyzed alkyne cyclotrimerization to give benzene derivatives (Scheme 4). In this chapter, however, strong emphasis is placed on those processes that are designed to produce unsymmetrically structured cyclic compounds and/or those lacking homodimeric and homooligomeric fragments.

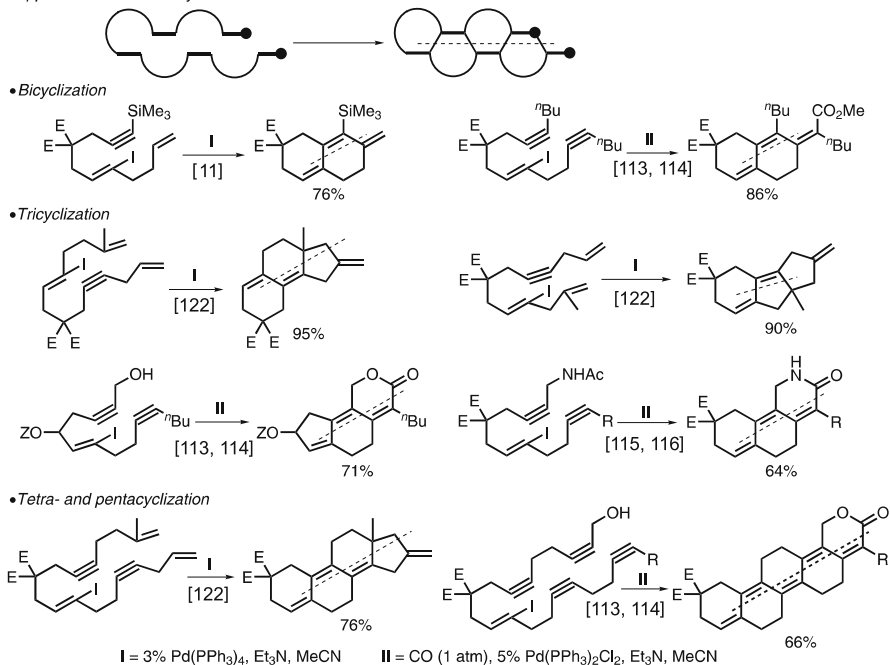
As indicated in Scheme 6, alkynes are well-suited for the “zipper”-mode and “dumbbell”-mode cascades, the latter of which can be extended to “circular” cascades. Although some other modes of cyclizations are conceivable, the two mentioned above appear to be the two representative ones involving *syn*-carbopalladation.

#### 2.2.1

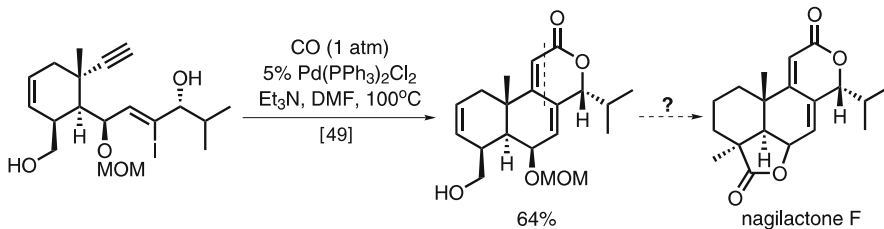
##### “Zipper”-Mode Cascade Cyclization via Carbopalladation

The propagation steps of the “zipper”-mode cascade cyclization are by definition all-intramolecular processes. Some prototypical examples of the “zipper”-mode cascade cyclic carbopalladation producing two to five fused rings in one step are summarized in Scheme 40 [11, 113–116, 122]. One of the major attractive features of this synthetic methodology is the ease of retrosynthetic analysis, which involves finding a linear line of dissection indicated in bro-

## "Zipper"-mode cascade cyclization



Scheme 40



Scheme 41

ken lines in Scheme 38. One very promising application of the "zipper"-mode cascade cyclization is the preparation of a potential key intermediate for the synthesis of nagilactone F [49] (Scheme 41).

## 2.2.2

## "Dumbbell"-Mode and Related Circular Cascade Cyclization Processes via Carbopalladation

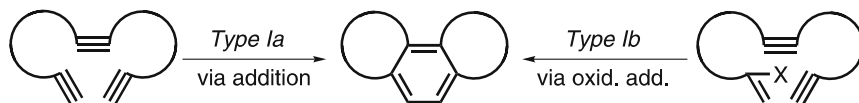
Synthesis of benzene, cyclohexadiene, along with other related six-membered rings via circular trimerization of three C  $\equiv$  C and/or C = C bonds has long attracted attention of the synthetic chemists. In most cases, it is thermo-

dynamically very favorable. From the viewpoint of fine chemicals synthesis where symmetrical and/or repeating substitution patterns are to be avoided in the great majority of cases,  $\pi$ -bond-pairing selectivity ("pair"-selectivity or copuloselectivity) and regioselectivity are two factors of paramount importance. Therefore, only those processes that may be judged to be useful for "pair"-selective and regioselective synthesis of cyclic compounds will be discussed below. For example, although very attractive and useful for the synthesis of a limited number of benzene derivatives of perhaps materials chemical interest, the Maitlis cyclotrimerization of alkynes (Scheme 4) fails to offer a "pair"-relative and regioselective route to benzene derivatives. It may well be that even today there is no *catalytic and all-intermolecular* cyclotrimerization of three different alkynes with excellent control of regiochemistry, even though a stoichiometric Zr-mediated "one-pot" synthesis of benzene derivatives with five different substituents and one H from three different unsymmetrically substituted alkynes has recently been reported [123].

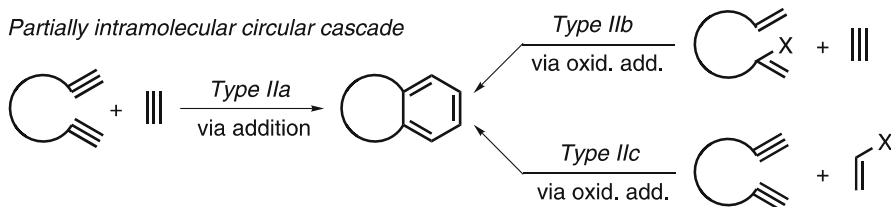
(i) **Benzene and fulvene derivatives.** Aside from the all-intermolecular cascade carbometallation process discussed above, various all-intramolecular (Type I) and partially intramolecular (Type II) circular cascade processes are conceivable (Scheme 42). All-intramolecular (Type I) processes in most cases would proceed via "dumbbell"-mode cascade cyclization, which can be very satisfactory as shown in Scheme 43 [124, 125].

Selective synthesis of benzene derivatives via partially intramolecular cyclic carbopalladation is considerably more complex than the corresponding all-intramolecular processes. As it is generally difficult to specify the cascade-initiation point in the Type IIa cyclization process, it would generally be the least selective path. A priori, the most favorable might be the intra-inter cascade cyclization process (Type IIb), since both the point of initiation and the queuing order between the two alkynes is sharply differentiated by the fact that one is intramolecular, while the other is intermolecular. Still, in-

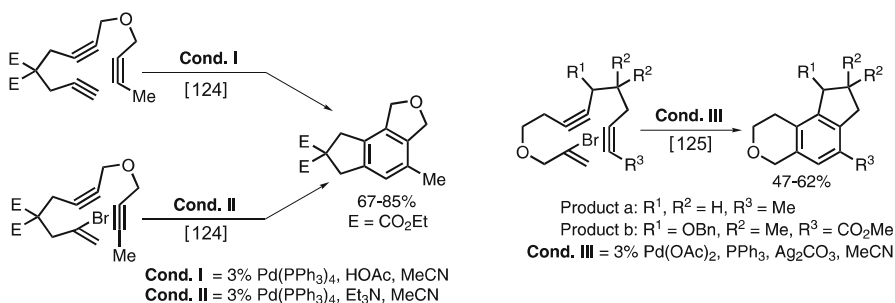
*All-intramolecular circular cascade via "dumbbell"-mode cyclization*



*Partially intramolecular circular cascade*

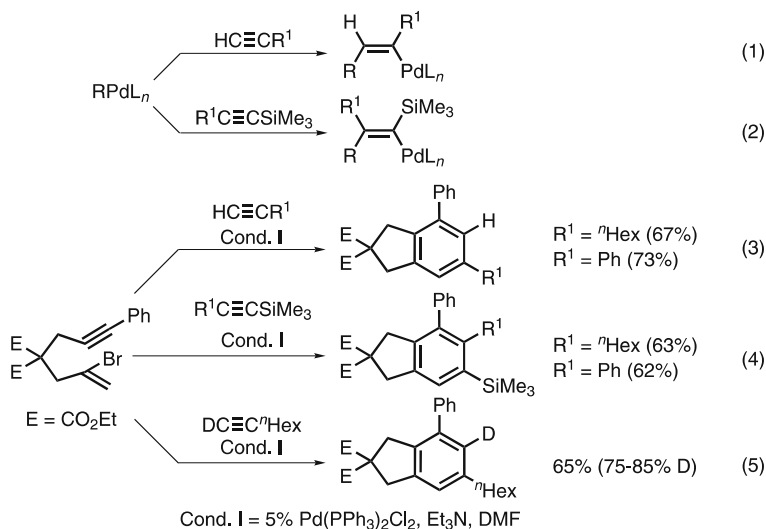


**Scheme 42**



### Scheme 43

incorporation of unsymmetrically substituted monoynes is a challenging task. The following regioselectivity patterns observed in alkyne carbopalladation (Eqs. 1 and 2 in Scheme 44) can be exploited in achieving highly regioselective (> 92–98%) incorporation of monoynes (Scheme 44) [126]. In many other cases, however, formation of regioisomeric mixtures would result. In a related study with terminal alkynes [127], a mechanistic path involving the formation of conjugated dienes and their electrocyclic transformation to give benzene derivatives was proposed. This mechanism is applicable only to those cases where terminal alkynes are used. Furthermore, one reaction with  $DC \equiv C^{\eta}\text{Hex}$  run under the conditions indicated in Scheme 44 produced the desired product retaining D to the extent of 75–85% in the position expected from the mechanism involving a sequential intra–inter cascade carbopalladation [126] (Eq. 5 in Scheme 44).

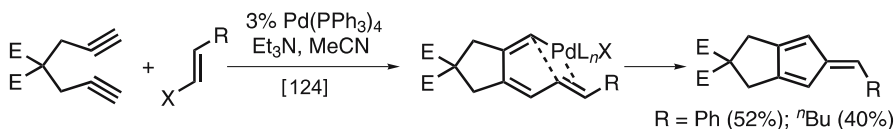


### Scheme 44

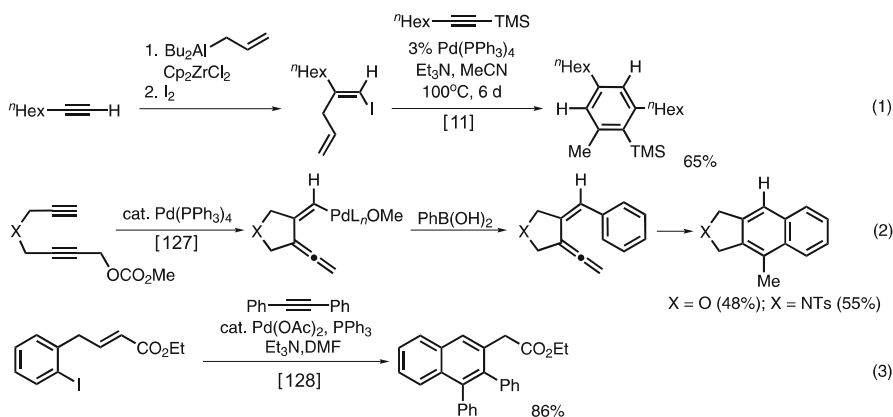
There are at least two issues to be addressed regarding the Type IIc circular cascade process shown in Scheme 42. One is the regioselectivity in the initial intermolecular carbopalladation. Since it is not very difficult to differentiate the two terminal positions of  $\alpha,\omega$ -diynes, this is not a serious problem in most cases. A more serious problem is the exclusive formation of fulvene derivatives observed in a couple of cases [124] (Scheme 45). It is not very clear what the scope of the fulvene formation is and whether the course of the reaction could be altered to give benzene derivatives.

Many other related but alternative routes to benzene derivatives are conceivable. One inter-intra cascade carbopalladation route which is potentially highly selective is shown in Eq. 1 of Scheme 46 [11]. Another proceeds via cyclic allenylpalladation of alkynes followed by cross-coupling with  $\text{PhB(OH)}_2$  [127] (Eq. 2 of Scheme 46). Yet another related process is the synthesis of naphthalene derivatives shown in Eq. 3 of Scheme 46 [128]. If the regioselectivity problem could be overcome, it would provide an attractive route to naphthalenes.

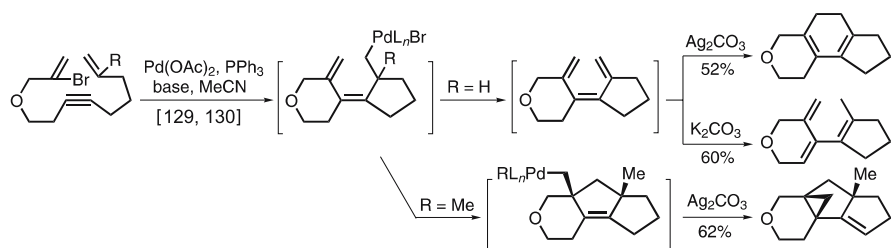
(ii) **Cyclohexadienes.** Substitution of one of the alkynes in the circular cascade reactions shown in Scheme 42 is expected to produce cyclohexadienes. However, even all-intramolecular cyclization reactions of halodienynes have been shown to be very capricious and both substrate and reagent dependent, as demonstrated in Scheme 47 [129, 130].



**Scheme 45**



**Scheme 46**



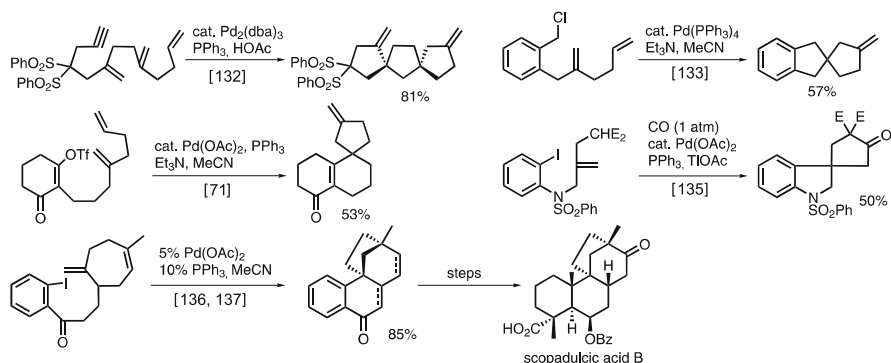
Scheme 47

Since this topic is discussed in detail elsewhere in this monograph, no further discussion is intended here.

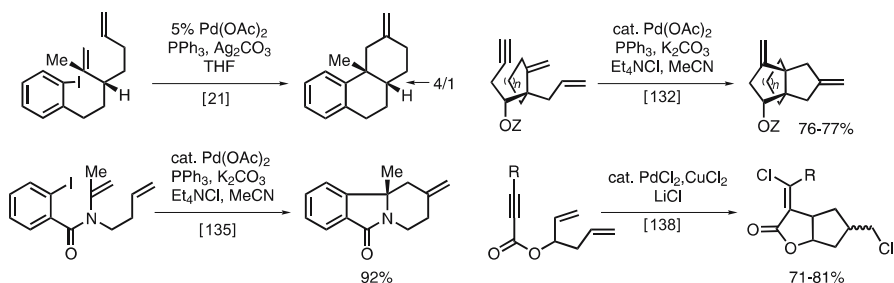
### 2.2.3

#### Spiro-Mode and Linear-Fused-Mode Cascade Cyclization Processes via Carbopalladation

Both spiro-mode and linear-fused-mode cascade cyclization processes via carbopalladation were introduced in 1988 [20, 21, 131]. In addition to the



Scheme 48



Scheme 49

seminal examples shown in Scheme 6, some representative examples [20, 21, 133–137] of the spiro-mode cascade cyclization via carbopalladation including its application to the synthesis of scopadulcic acid B [136, 137] are presented in Scheme 48.

Representative examples of the linear-fused-mode cascade cyclization shown in Scheme 49 also suggest that its potential synthetic utility is considerable.

### 3

#### Palladium-Catalyzed Cyclization via Acylpalladation

As described in Sect. 1, a couple of versions of the cyclic acylpalladation reactions of  $\omega$ -alkenyl halides and related electrophiles were discovered by the authors' group during the 1983–1985 period [10, 30]. Subsequent extensive and systematic investigations have led to Scheme 13 showing several competitive carbonylative processes including three types of cyclic acylpalladation processes (Type I–III Ac-Pd Processes) along with carbonylative polymerization, premature and noncyclic carbonylative reactions, and ketene generation and their cycloaddition reactions. Furthermore, it has also been found that, even in the presence of CO, non-carbonylative cyclic carbopalladation can be competitive or even dominant [11]. This finding has, in turn, led to the development of non-carbonylative cyclization reactions terminated by carbonylative trapping [113–116]. In short, formation of acylpalladation species is known to be highly reversible, and competition among carbonylative and non-carbonylative processes is governed by a number of reaction parameters. One generalization of considerable predictive value is that summarized in Table 1 (Sect. 2.1.2). As is well-known, formation of five- and six-membered rings is considerably more favorable than that of either four- or seven-membered rings somewhat irrespective of their structural details. Thus, carbonylative formation of five-membered rings is strongly favored over that of non-carbonylative four-membered rings from the same starting compounds [113, 114, 116]. On the other hand, non-carbonylative six-membered ring formation is strongly favored over carbonylative seven-membered ring formation. A more subtle, tentative, and yet seemingly reliable generalization also indicated in Table 1 is that non-carbonylative five-membered ring formation from alkynes is strongly favored over the potentially competitive carbonylative six-membered ring formation. Consequently, six-membered  $\alpha,\beta$ -unsaturated ketones have not been readily accessible via carbonylative cyclic acylpalladation of alkynes, although the corresponding cyclic acylpalladation of similarly structured alkenes can be very favorable, as exemplified in Eq. 2 of Scheme 10 [10]. Today, it seems reasonable to state that the initially highly capricious cyclic acylpalladation processes in the presence of CO may be advantageously exploited to complement and supplement the non-



carbonylative cyclic carbopalladation processes discussed in Sect. 2 through judicious planning. Taken together, the non-carbonylative carbopalladation discussed above and acylpalladation processes discussed in this section provide a very promising methodology for the synthesis of a wide range of carbocycles and heterocycles, even through the scope of acylpalladation is predicted to be essentially limited to the synthesis of five- and six-membered rings, as discussed above.

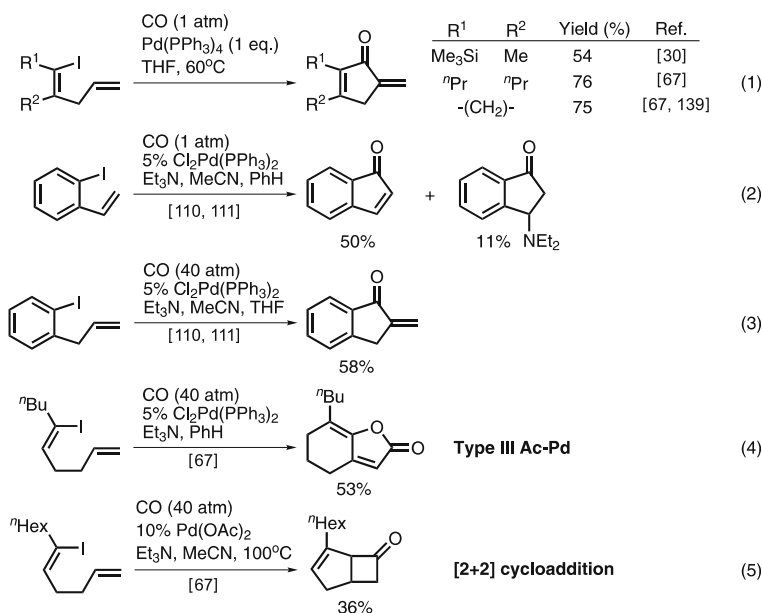
### 3.1

#### Cyclization via Single Acylpalladation

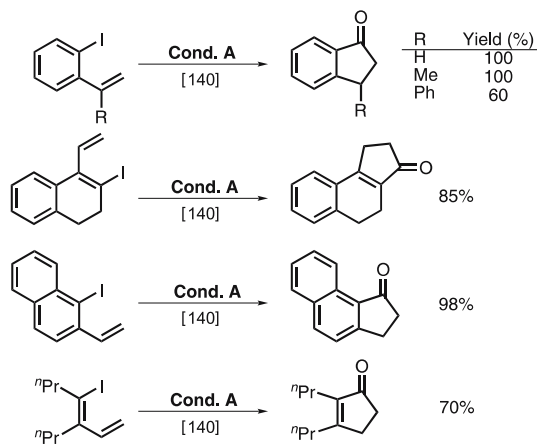
(i) **Type I cyclic acylpalladation (Type I Ac-Pd).** Several of the earliest examples of the Type I Ac-Pd reactions are shown in Eq. 1 of Scheme 10 and Eq. 1 of Scheme 50 [30, 67, 139]. These reactions were run with the stoichiometric amounts of Pd catalysts, and a few attempts to observe catalytic processes were not successful. However, later studies using *o*-iodostyrene and *o*-iodoallylbenzene [110, 111] have indicated that these substrates undergo the Type I Ac-Pd reaction under catalytic conditions. It does appear that even those reactions shown in Eq. 1 of Scheme 50 could be carried out under catalytic conditions. In general, the Type I Ac-Pd reactions of  $\omega$ -vinylated substrates represent some of the most capricious and least favorable cases. In addition to the difficulties described above, the Type III Ac-Pd process involving the trapping of acylpalladation derivatives with internal enolates (Eq. 4) [67] and ketene-alkene bicyclization (Eq. 5) [67] can also be dominant processes. Clearly, further investigations are desirable. In this context, a recent investigation of this reaction has led to the discovery of a variant of Type I Ac-Pd reaction most probably via hydrolysis of palladium enolates. A related hydrolysis of palladium enolates had previously been reported [141].

The Type I Ac-Pd reactions of internal alkene-containing organic halides are generally more favorable and predictable (Scheme 52) [67, 110, 111]. In cases where the alkenyl group is stereodefined, the Type I Ac-Pd reaction is not stereospecific but stereoselective, favoring the *E* isomer.

A number of variations of the Type I Ac-Pd reactions are conceivable. The reaction shown in Scheme 53 involves *endo*-mode cyclization producing naphthoquinones [32]. It should be reminded that conversion of *o*-iodostyrenes into indenones (Scheme 50) and indanones (Scheme 51) also involves *endo*-mode cyclic acylpalladation. In general, cyclic carbopalladation including acylpalladation can proceed both in *exo*-mode and in *endo*-mode. In some cases, the regiochemistry of cyclic carbopalladation is mechanistically defined in a rigid manner, as shown in Scheme 15. In other cases, the regiochemistry of cyclic carbopalladation appears to be more loosely defined, as suggested by the formation of either of the two possible regioisomers, i.e., *exo* or *endo*. Formation of *E* and *Z* stereoisomeric mixtures also



Scheme 50

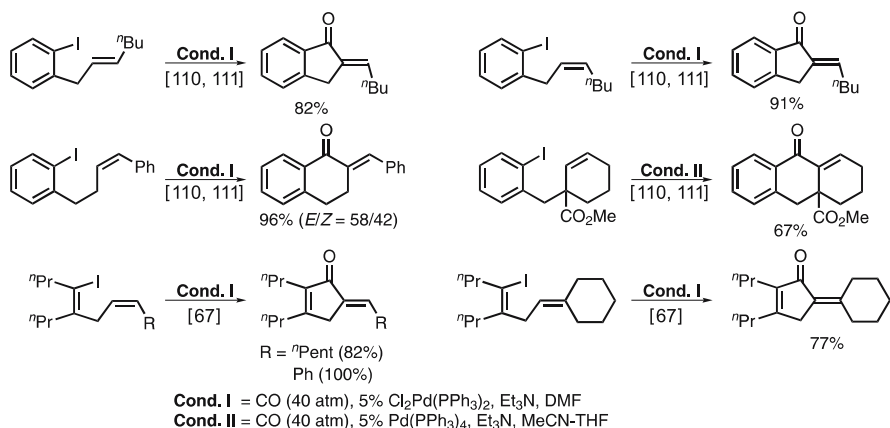


Cond. A = CO (1 atm), 10% Pd(OAc)<sub>2</sub>, pyridine, <sup>n</sup>Bu<sub>4</sub>NCl, DMF, CO (1 atm), 100°C

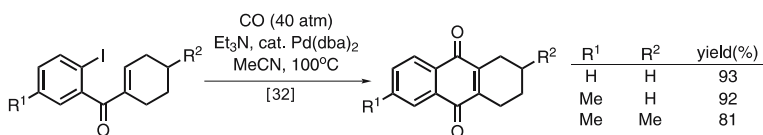
Scheme 51

suggest that these conjugated enone-producing reactions are mechanistically loose or flexible.

(ii) **Type II cyclic acylpalladation (Type II Ac-Pd).** In the Type I cyclic acylpalladation process, the termination step involves  $\beta$ -dehydropalladation. In this sense, the Type I Ac-Pd process resembles the cyclic Heck reaction. The Type II Ac-Pd process reported in 1985 [10] provided some of the earliest ex-

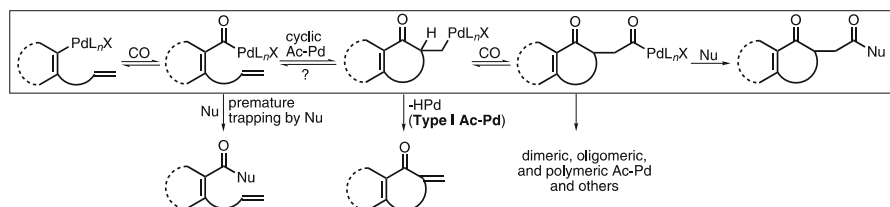


Scheme 52



Scheme 53

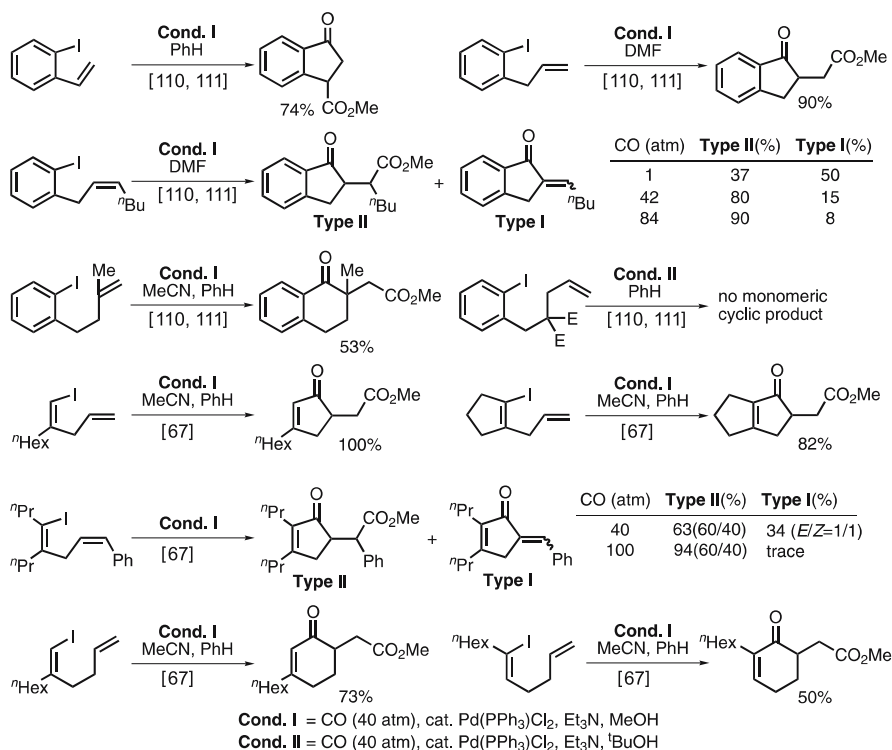
amples of the trapping of cyclic organopalladium intermediates with external nucleophiles, i.e., MeOH, along with the amine synthesis shown in Entry 6 of Scheme 5 [18, 19]. It is important to note that trapping of acylpalladium species with any nucleophiles can take place either before or after cyclization (Scheme 54). Thus, the desired trapping process must be slower than the desired cyclic acylpalladation to avoid premature trapping of acylpalladium species before cyclization. At the same time, it must be faster than any other cyclization product-depleting side reactions including dimeric, oligomeric, and polymeric acylpalladation. Since these product-depleting acylpalladation processes are intermolecular, they are expected to be slower by a few to several orders of magnitude than favorable processes of cyclic acylpalladation, which is practically limited to five- and six-membered ketone formation.



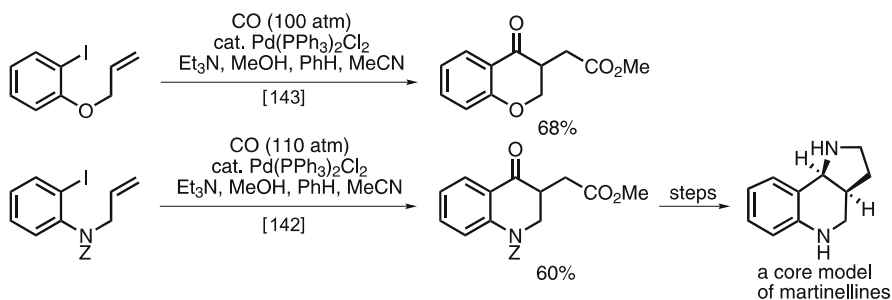
Scheme 54

Despite the seemingly narrow window given to the Type II Ac-Pd process, it has proved to be a very useful synthetic reaction as indicated by the results shown in Scheme 55. In fact, one of the major side reactions is the Type I Ac-Pd process that can be dominant in cases where the reacting alkene is di- or trisubstituted. In cases where the reacting alkene is a terminal vinyl group; however, the Type II Ac-Pd process is generally much more predictable, dependable, and satisfactory. Moreover, a variety of alcohols and many other nucleophiles may be considered for successful trapping of the cyclic acylpalladium derivatives. Although still very limited, the Type II Ac-Pd process has also been applied to the synthesis of heterocycles including some medically interesting compounds, such as a core model of martinellines [142, 143] (Scheme 56).

The scope of the Type II Ac-Pd process has been significantly expanded by the development of those employing  $\omega$ -alkenyl allyl halides and related electrophiles. Initially formed  $\beta,\gamma$ -unsaturated ketones must isomerize to give the  $\alpha,\beta$ -unsaturated ketones thus obtained are the same as those obtainable from the corresponding alkenyl halides, the two



Scheme 55

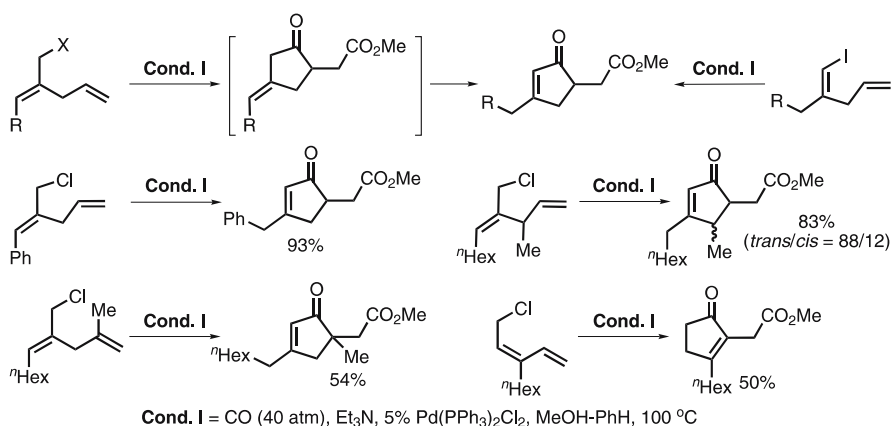


Scheme 56

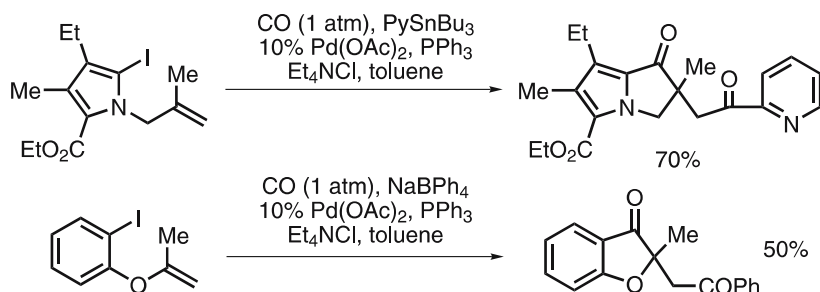
processes offer two synthetic options for the same class of compounds [144] (Scheme 57).

Nucleophilic trapping agents used in the Type II Ac-Pd process are not limited to MeOH and other alcohols. A wide range of heteroatom and carbon nucleophiles may be used as in the cases of the Type II cyclic carbopalladation processes terminated by various nucleophilic reagents (Sect. 2.1.2). A couple of reactions shown in Scheme 58 [145] provide additional examples of heterocycles synthesis via Type II Ac-Pd process terminated by cross-coupling.

(iii) **Type III cyclic acylpalladation (Type III Ac-Pd) and Generation-Cycloaddition of Ketenes.** Trapping of acylpalladium derivatives with internal enolates was reported as early as 1986 [32], as described in Sect. 1 (Schemes 11 and 12). It was later accidentally discovered that the Type I Ac-Pd process could be diverted to produce  $\gamma$ -alkylidenebutyrolactones via trapping of the second acylpalladium derivatives generated after the cyclic acylpalladation with the enolate ions generated by deprotonation of the initially formed acylpalladium derivatives. Since it is an intramolecular process,



Scheme 57

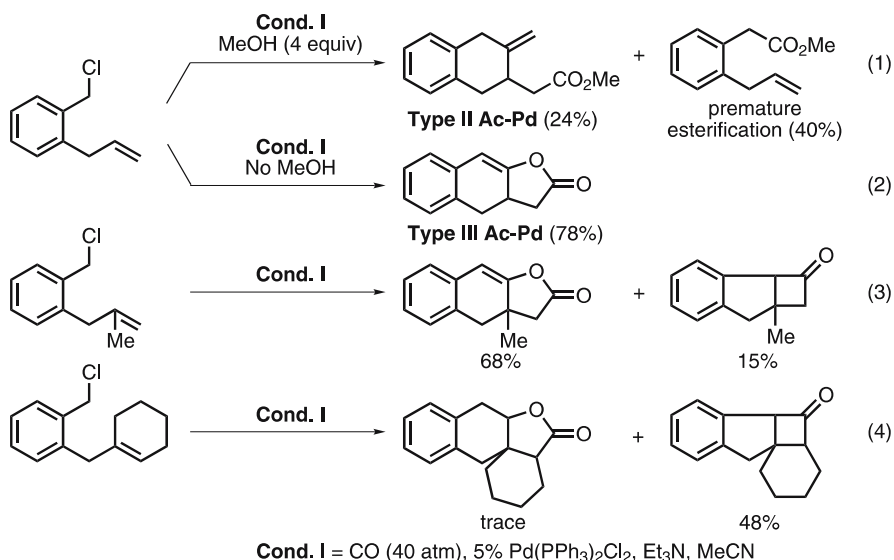


Scheme 58

it could be very favorable, as exemplified by Eq. 3 in Scheme 10 [31] and Eq. 4 in Scheme 50 [67]. Even some of the Type II Ac-Pd processes may proceed in some cases via Type III Ac-Pd processes. Yet another process that does not involve cyclic acylpalladation is the formation and [2 + 2]cycloaddition of ketenes generated via  $\beta$ -dehydropalladation of acylpalladium species. Since this ketene cycloaddition reaction has often occurred in competition with the Type III Ac-Pd process, these two reactions are discussed together in this section. A series of Pd-catalyzed carbonylation reactions of *o*-chloromethylallyl benzenes have provided the following interesting set of results [146] (Scheme 59). As expected, the Type II Ac-Pd process was the only cyclic acylpalladation process observed with the parent *o*-chloromethyl allylbenzene in the presence of MeOH (4 equiv.), but the predominant process was premature esterification (Eq. 1). In the absence of MeOH or any other added trapping agent, the Type III Ac-Pd cyclization product was obtained in high yield (Eq. 2). No Type I Ac-Pd product or other products was formed in a significant yield. The presence of a substituted allyl group in the starting compounds tends to competitively give [2 + 2] ketene cycloaddition products and Type III Ac-Pd cyclization products. With  $\beta,\gamma$ -disubstituted allyl groups present in the starting compounds, the [2 + 2] ketene cycloaddition can be the dominant path (Scheme 59).

All of the examples of trapping of acylpalladium species with enolates discussed above as part of the Type III Ac-Pd process involve trapping with *O*-enolates. As discussed earlier, however, acylpalladium derivatives can also be trapped with *C*-enolates (Eqs. 4 and 5 in Scheme 11), and this trapping with *C*-enolates has since been exploited for terminating acyclic carbopalladation process [135] (Scheme 48). However, this process does not appear to have been used for terminating cyclic acylpalladation processes.

(iv) **Cyclic acylpalladation of alkynes.** All cyclic acylpalladation reactions discussed above in this section are those of alkenes. Many earlier attempts to observe cyclic acylpalladation reactions of alkynes failed. These failures have, in turn, led to a tentative conclusion that, for some unknown reasons, acylpalladation of alkynes must be an intrinsically unfavorable process. This



Scheme 59

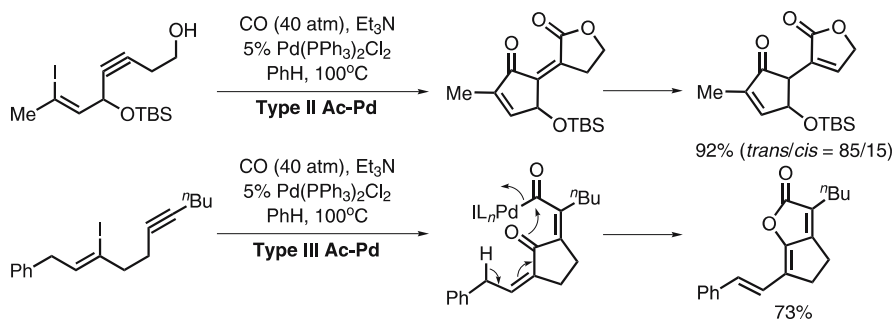
conclusion has since been proven to be incorrect. The current notion, which hopefully is correct, is that there is nothing intrinsically unfavorable about acylpalladation of alkynes, but that the ready reversibility of CO insertion and the availability of kinetically more favorable non-carbonylative cyclic carbopalladation processes must be competitively overshadowing acylpalladation of alkynes. This notion has been strongly supported by the results shown in Scheme 60 [113, 114]. In these cases, the cyclic acylpalladation of alkynes to give five-membered ketones can favorably compete with the non-carbonylative cyclic carbopalladation to produce four-membered rings. These reactions appear to represent the first two examples of cyclic alkyne acylpalladation reactions.

A closely analogous Pd-catalyzed carbonylative bicyclization of 2-(propargyl)allyl phosphates reported recently [147] can readily be explained in terms of a Type III Ac-Pd mechanism shown in Scheme 61, even though the authors of this paper additionally proposed an alternate ketene-alkyne bicyclization mechanism also shown in Scheme 61.

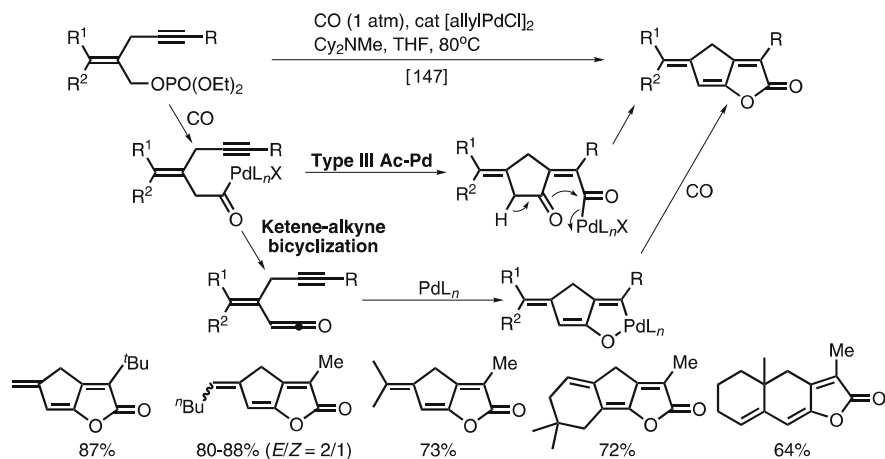
### 3.2

#### Double or Multiple Carbopalladative Cyclization Reactions Involving One or More Cyclic Acylpalladation Processes

(i) **Allylpalladation–Acylpalladation Cascades.** Applications of the Types I and II cyclic acylpalladation processes to trapping the products of cyclic allylpalladation by W. Oppolzer [148, 149] and K. Yamamoto [150] led



Scheme 60

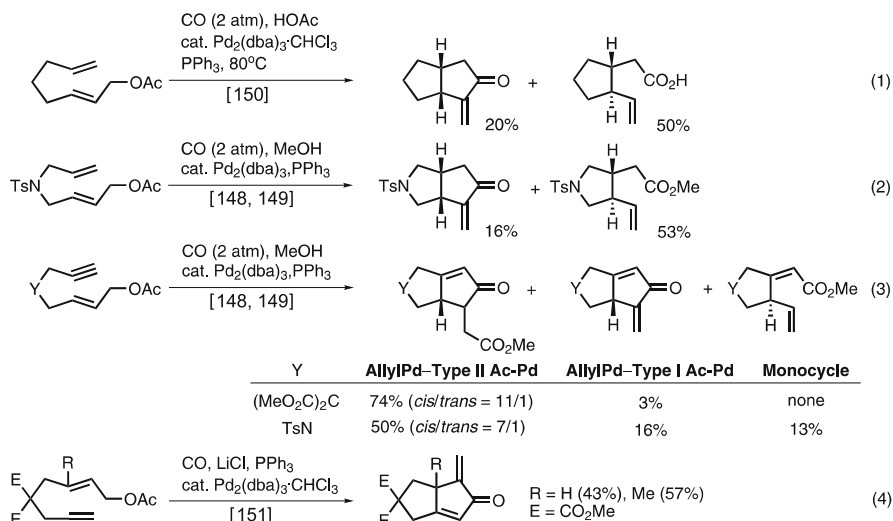


Scheme 61

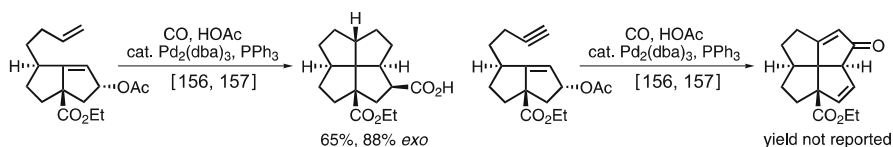
to the development of the cyclic allylpalladation–acylpalladation cascades (Scheme 61).  $\omega$ -Vinyl-substituted allyl acetates mainly underwent a tandem process consisting of monocyclization via allylpalladation followed by carbonylative esterification, since the cyclic allylpalladation produced predominantly *trans*-disubstituted five-membered rings (Eqs. 1 and 2). On the other hand,  $\omega$ -ethynylallyl acetates gave bicyclic products obtained via allylpalladation–acylpalladation–carbonylative esterification cascade in good yields (Eq. 3) [148, 149]. A later study by Heathcock described a related allylpalladation–Type I Ac-Pd bicyclization process (Eq. 4) [151].

These allylpalladation–acylpalladation cascade bicyclization reactions have been applied mainly by Oppolzer to the synthesis of various natural products including ( $\pm$ )-pentalenolactone E methyl ester [152], 3-isorauniticine [153], ( $\pm$ )-coriolin [154], and ( $\pm$ )-hirsutene [155]. Their application to the syntheses of [5.5.5.5]fenestrane derivatives by Keese [156, 157] (Scheme 63) is also noteworthy.





Scheme 62



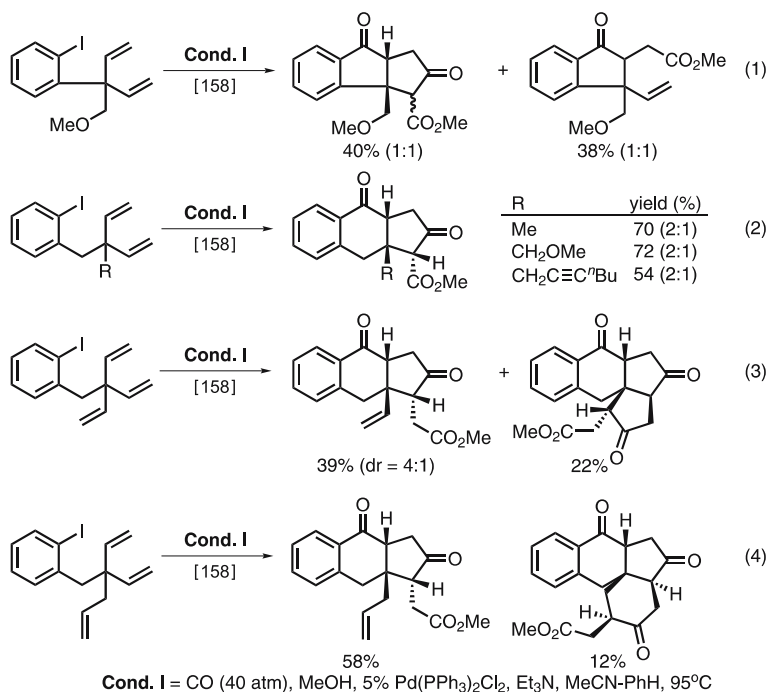
Scheme 63

(ii) **Cyclic acylpalladation cascades.** Two groups led by E. Negishi [158] and K. Yamamoto [159] reported prototypical examples of double and triple cyclic acylpalladation cascades (Schemes 64 and 65). In the reaction shown in Scheme 65, a double cyclic acylpalladation cascade was set up by a double cyclic allylpalladation cascade to achieve tetracyclization of an acyclic starting compound. As attractive as these reactions are, further development is clearly desirable.

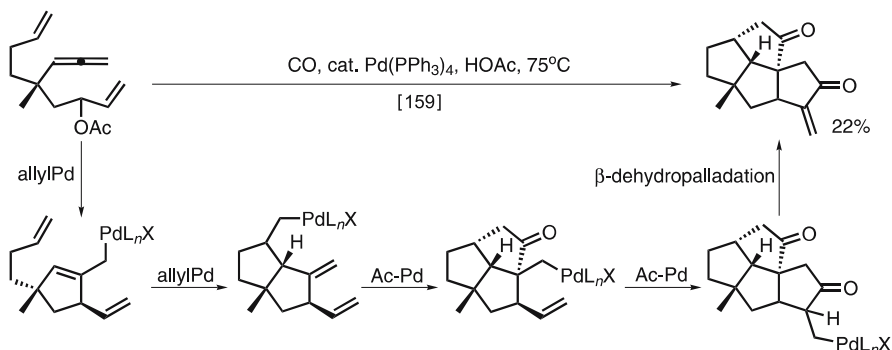
## 4

### Conclusion

A couple of prototypical examples of the cyclic version of the Heck reaction, defined as a process consisting of alkene carbopalladation followed by  $\beta$ -elimination, were reported during the 1984–1985 period [9, 10]. Almost concurrently, seminal examples of both the “non-Heck” cyclic carbopalladation reactions [10, 30] were reported during the 1983–1985 period. Thus, with due respect paid to earlier discoveries of alkyne cyclooligomerization via cascade carbopalladation [7, 8] as well as copolymerization [24] and cocyclization [25,



Scheme 64



Scheme 65

26] of CO with alkenes and dienes, respectively, via a acylpalladation, which intrinsically lack control over “pair”-selectivity, regioselectivity, and/or degree of polymerization, it may be stated that the carbopalladation-based cyclization methodology of both Heck and “non-Heck” types, was founded during the 1983–1985 period. Those involving single cyclic carbopalladation are discussed in Sect. 2.1. Collectively, these cyclic acylpalladation reactions

have provided a novel cyclization methodology of wide synthetic applicability and have indeed been widely used.

Another epoch-making advance was made during the 1988–1989 period. In dealing with “living” carbopalladation of alkynes and 1,1-disubstituted ethylenes that are incapable of undergoing facile  $\beta$ -dehydropalladation and hence the Heck reaction, a few research groups realized that the “living” nature of these carbopalladation reactions could be exploited to develop cascade carbopalladation processes (Sect. 2.2). These cascade reactions and those involving acylpalladation cascades discussed in Sect. 3.2 have collectively provided new and attractive opportunities for the synthesis of oligocyclic compounds to be further developed and exploited by the synthetic chemists.

A systematic investigation of cyclic acylpalladation of haloenes, haloynes, and related electrophiles conducted since 1983 [30] has led to the development of three types of cyclic acylpalladation processes (Types I–III Ac-Pd) and Pd-catalyzed carbonylation-induced ketene [2 + 2] cycloaddition (Sect. 3.1). Collectively, these cyclic acylpalladation and related reactions have provided a number of new and attractive routes to cyclic compounds. Significantly, they nicely complement and supplement the non-carbonylative cyclic carbopalladation reactions. Thus, they have become integral and indispensable parts of the carbopalladation-based cyclization methodology.

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