Chem. Rev. **1996,** 96, 365–393

Cyclic Carbopalladation. A Versatile Synthetic Methodology for the Construction of Cyclic Organic Compounds

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Received July 17, 1995 (Revised Manuscript Received September 30, 1995)

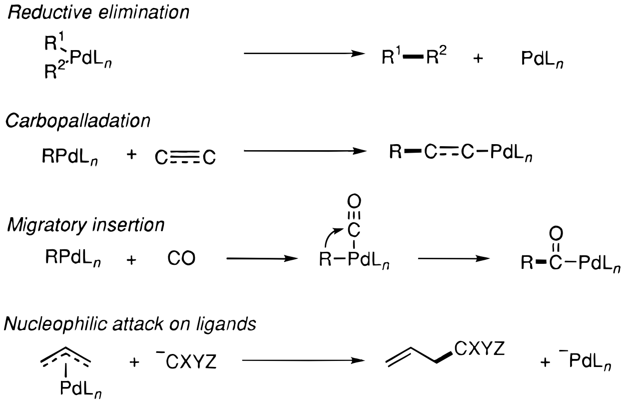
Contents

I. Introduction

A. Use of Palladium in Carbon–Carbon Bond Formation

Until about 1970, palladium had been used mainly to reduce and oxidize organic compounds, Pd-catalyzed hydrogenation and Wacker oxidation being representative examples.[1] Over the last few decades, however, palladium has emerged as one of the most versatile and useful metals in organic synthesis, especially for the formation of carbon–carbon bonds.[2] The ready accessibility of two stable oxidation states, *i.e.*, 0 and +2, and the readily reversible interconversion between the two oxidation states as well as the ready availability of Pd-containing species having simultaneously one or more empty and filled nonbonding orbitals are a few of the important factors that are responsible for the versatility and usefulness of Pd complexes as catalysts. Specifically, palladium readily participates in reductive elimination, carbometalation, migratory insertion, and nucleophilic substitution shown in Scheme 1 leading to carbon–carbon bond formation. Reductive elimination is thought to be a critical step in the Pd-catalyzed cross coupling[3] developed since the mid-1970s, while carbopalladation undoubtedly is the key step in the Heck reaction.[4] The Tsuji–Trost reaction[5] is an example of carbon–carbon bond-forming processes involving nucleophilic attack on organic ligands of palladium complexes. Migratory insertion accounts for the great majority of carbonylative carbon–carbon bond formation.[1,2]

Scheme 1



B. Carbopalladation

This review discusses a new and versatile cyclization methodology based on cyclic carbopalladation. Carbopalladation may be defined as those processes that involve addition of the C–Pd bond to C=C or C≡C bonds of alkenes, alkynes, allenes, conjugated dienes, and other carbon–carbon multiple bonds including even arenes. The typical courses of carbopalladation with alkenes, alkynes, conjugated dienes,

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Christophe Copéret performed his undergraduate studies in France in the area of chemistry and chemical engineering at the Lyon Institute of Technology (Institut Universitaire de Technologie de Lyon) and the Lyon School of Industrial Chemistry (Ecole Supérieure de Chimie Industrielle de Lyon, ESCIL) and moved to Purdue University in 1991 to undertake graduate studies under the supervision of Professor Negishi. He received his degree of “Ingénieur” from ESCIL in 1992 and is currently working on his Ph.D. dissertation, which is mainly focused on the transition metal-catalyzed formation of new carbon–carbon bonds, specifically via carbopalladation of alkenes and alkynes under carbonylative conditions.

Shengming Ma obtained his B.S. degree at Hangzhou University (China) in 1986. He then moved to Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences as a graduate student, and obtained a Ph.D. degree there in 1990 under the supervision of Professor X. Lu. After working at the same institute as a Research Associate followed by an appointment as a Research Associate Professor, he joined Professor L. M. Vananzi's group at ETH (Switzerland) as a postdoctoral research fellow. One year later, he joined Professor E. Negishi's group at Purdue University. His research interests are development of new methodologies with an emphasis on organometallic chemistry, especially asymmetric catalysis, and their application to the highly selective synthesis of biologically active molecules including natural products.

Show-Yee Liou was born in Taiwan in 1965. He obtained his baccalaureate degree from Tunghai University in 1987. After spending two years serving in the military and working for two years as a Teaching Assistant at Tunghai University, he came to the United States to pursue the further degrees. He received an M.S. degree from the University of Alabama in Huntsville in 1993, and then he joined Professor Negishi's group at Purdue as a Ph.D. degree student. He likes sports, arts, and especially synthetic organic chemistry.

and allenes reported in the literature (*vide infra*) are indicated in Scheme 2.

One of the earliest studies of carbopalladation was on some Pd-catalyzed cyclooligomerization reactions of alkynes.[6] These reactions as such are of very limited synthetic applicability which are not readily adaptable to the selective synthesis of natural products and other unsymmetrical molecules. In 1968 Heck[7] reported the reaction of organomercuries and related organometals with alkenes in the presence of the stoichiometric amount of Pd(II) complexes leading to substitution of a vinylic or allylic hydrogen with a carbon group. The use of organic halides containing aryl and alkenyl groups in place of organomercuries led to the development of a catalytic process.[8] The catalytic version of the Heck reaction may be defined as a Pd-catalyzed reaction of organic halides with alkenes leading to substitution of a vinylic or allylic hydrogen with a carbon group which is thought to proceed via carbopalladation−dehydropalladation (Scheme 3).

A few notable features of carbopalladation are as follows. First, in reflection of the predominantly electrophilic nature of d^8 organopalladium(II) derivatives the reaction is generally accelerated by electron-donating substituents on alkenes and retarded by electron-withdrawing substituents. Another critically important feature is the strict *syn* stereochemistry of carbopalladation in essentially all known cases. Although the reversibility of carbopalladation has not been observed in most cases, decarbopalladation, when observed, also appears to be a strictly *syn* process, as in the conversion of cyclopropylcarbinylpalladium derivatives into homoallylpalladium

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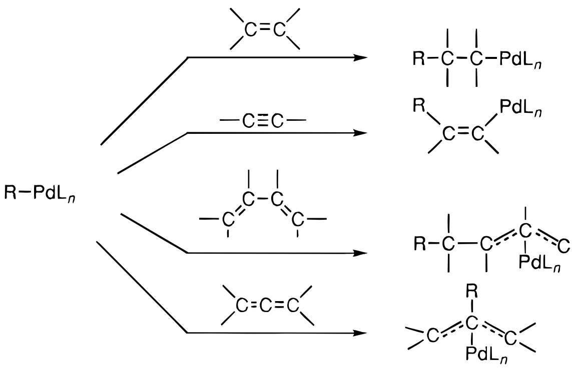
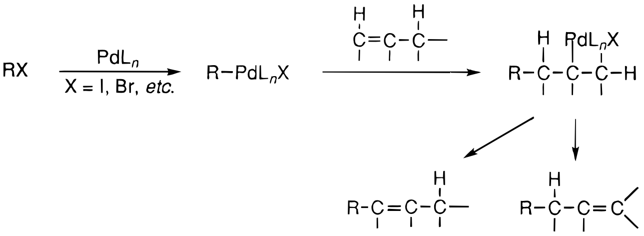
Scheme 2



Scheme 3



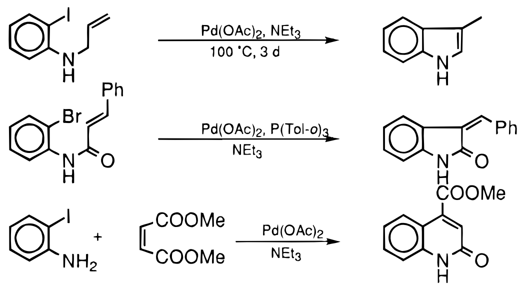
derivatives[9] (*vide infra*). It is therefore reasonable to view *syn*-selective carbopalladation and decarbopalladation as concerted addition and elimination processes in which synergistic interactions between the π and π^* frontier orbitals of alkenes or alkynes and an empty orbital of Pd and a C−Pd bonding orbital are critical. Essentially the same interpretation using the H−Pd bond in place of the C−Pd bond may be applied to the strict *syn* addition and elimination processes observed in hydropalladation and dehydropalladation. As amply demonstrated throughout this review, this strict *syn* requirement for these critical processes leads to a number of striking and useful consequences. On the other hand, the regiochemistry of carbopalladation is much less clean and variable.[4] In general, the so-called linear substitution products involving placement of Pd at an internal position of terminal alkenes and alkynes predominate to the extents of 80−100% except with enamines and enol derivatives.[4] With the use of bidentate phosphines, however, reversal of regiochemistry leading to the formation of so-called branched 1,1-disubstituted alkenes has been observed except with α,β-unsaturated carbonyl and related derivatives.[4e] Cationic palladium intermediates have been proposed for the latter cases. It does not appear to be clear if the strict *syn* stereochemistry is also observed in these cases.

II. Cyclic Heck Reaction

A. Cyclic Carbopalladation Involving Aryl- and Alkenylpalladiums

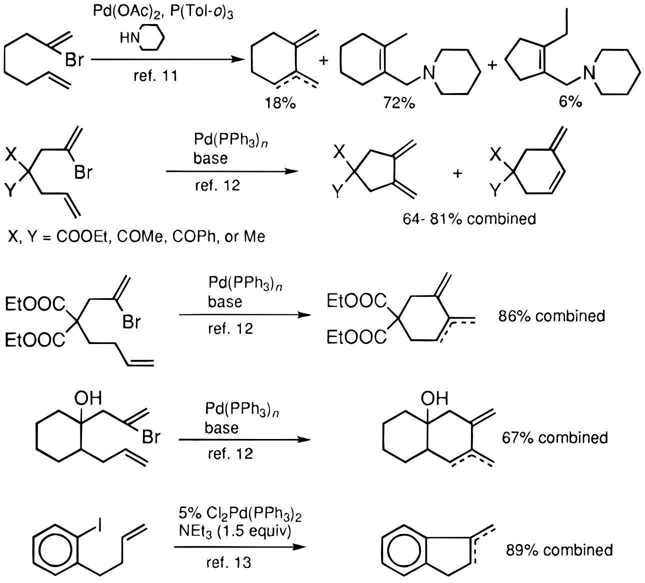
The development of the cyclic version of the Heck reaction began in the late 1970s. All of the early examples reported before 1983 involved the formation of heterocycles,[10] as exemplified by those shown in Scheme 4. The lack of examples of their applications to the synthesis of complex natural products during the first 10 or dozen years may, in part, be due to the relatively low product yields reported in those early studies.

Scheme 4



The development of the procedures for the synthesis of carbocycles via cyclic Heck reaction was further delayed by several years and was very sluggish until the late 1980s. Several examples reported by Heck,[11] Grigg,[12] and ourselves[13] shown in Scheme 5 appear

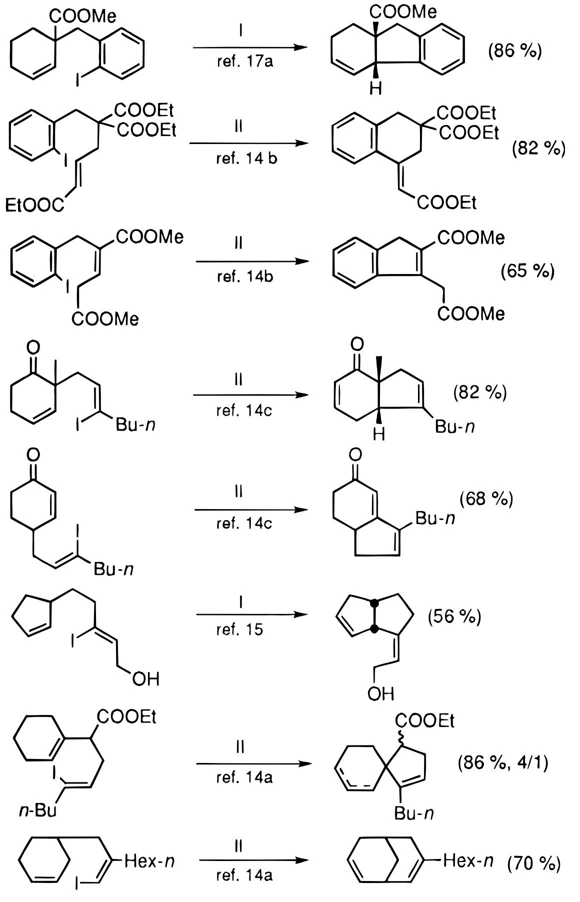
Scheme 5



to be the only ones reported as of a decade ago. However, intensive studies made since the late 1980s have firmly established that the cyclic Heck reaction represents a novel and versatile methodology for the construction of both carbocycles and heterocycles. Besides those by the authors,[14] studies by Larock,[15] Grigg,[16] and Overman[17] led to subsequent extensive applications of the cyclic Heck reaction. Some more recent developmental works by Fuchs[18a,b] and others are also noteworthy.

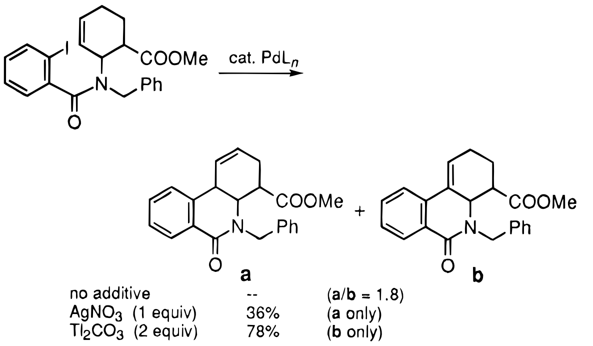
The following generalizations based on the currently available results delineate the scope and limitations as well as some salient features of the cyclic Heck reaction. The reaction is widely applicable to the synthesis of common (five- through seven-membered) rings. There has been no clear-cut indication that the formation of common rings can be readily reversed. Some early representative examples shown in Scheme 6 indicate that the reaction is readily adaptable to the formation of fused, spirofused, and bridged bicyclic and polycyclic ring systems. Facile formation of a quaternary carbon center required in the formation of spirofused ring systems is particularly noteworthy.

Scheme 6



I = Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$. II = Pd(PPh$_3$)$_4$, NEt$_3$.

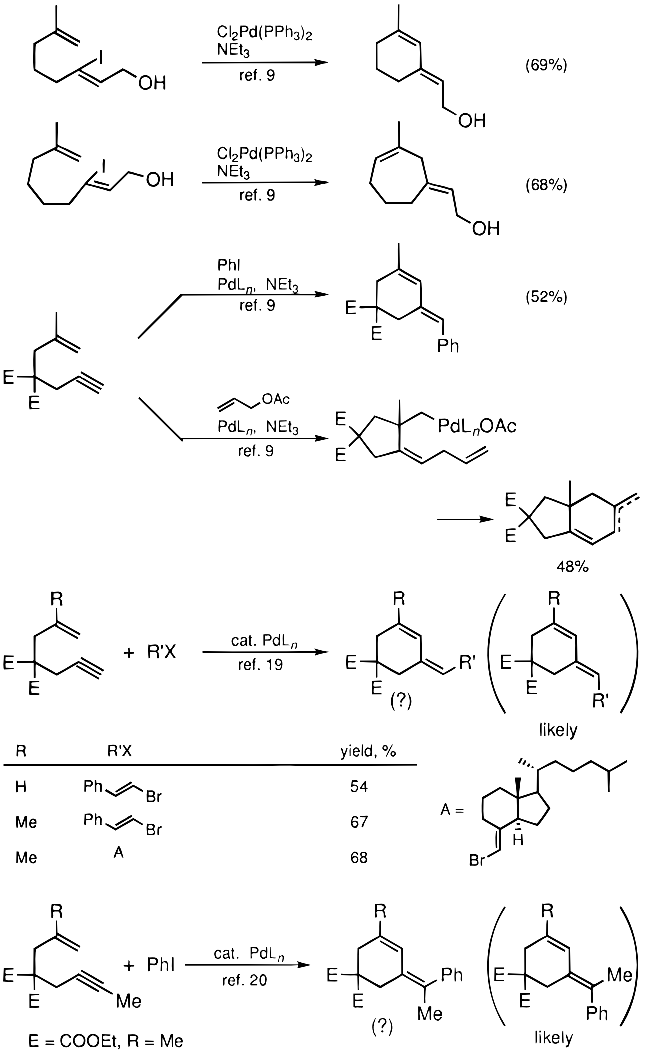
One distinct shortcoming of the cyclic Heck reaction is that the reaction often yields a mixture of alkene regioisomers. In cases where some regiocontrolling functional groups are present, however, regiocontrolled alkene formation has been observed. Alternatively, the use of Ag or Tl salts can often lead to the regiospecific formation of alkenes[16c] (eq 1).



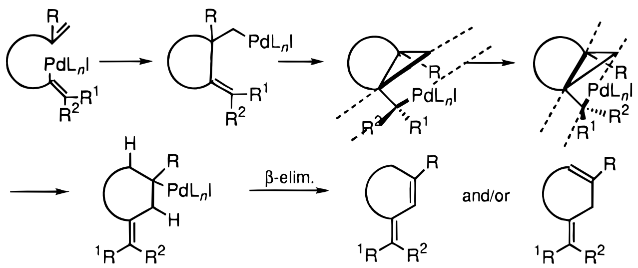
(1)

Another regiochemical issue of significance is the mode of cyclization. The exo mode of cyclization has been dominant in the cases of common rings, as amply demonstrated in Scheme 6. However, some six- and seven-membered rings have been obtained via "apparent" endo-mode cyclization[9,19,20] (Scheme 7). This seemingly capricious behavior prompted the authors to investigate the mechanistic details of the "apparent" endo-mode cyclization which led to the conclusion that it actually involves the more usual exo-mode cyclization, which is followed by cyclopropanation, cyclopropylcarbinyl-to-homoallyl rearrange-

Scheme 7

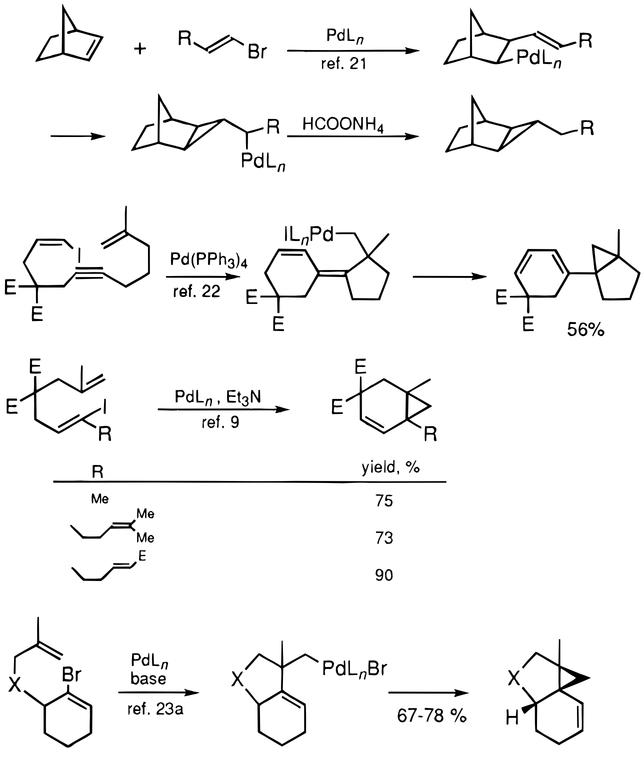


Scheme 8



ment, and β-dehydropalladation[9] (Scheme 8). One key to this finding was the recognition of the stereoisomerization of the exocyclic alkene moiety. In this connection, some stereochemical assignments reported in the literature[19,20] may have to be revised. It is striking that the cyclopropylcarbinyl-to-homoallyl rearrangement can be kinetically more favorable than β-dehydropalladation. Unlike the formation of common rings, that of cyclopropanes via cyclic carbopalladation is readily reversible. The cyclopropylcarbinyl system has two equivalent carbon−carbon bonds that can be cleaved. If the one that is formed via cyclic carbopalladation is cleaved, the reaction is merely reversed. On the other hand, cleavage of the other carbon−carbon bond gives rise to a new homoallylpalladium species which can then undergo β-elimination to give the "apparent" endo-mode cyclization product. This, however, requires that the cyclopropylcarbinylpalladium intermediates be conformationally nonrigid. If, on the other hand, they are conformationally rigid, they can be trapped as cyclopropane derivatives as shown in Scheme 9.[21−23] Much of the driving force in such cases must be provided by the elimination of HX (X = I, Br, etc.) as salts. These results also strongly indicate that both

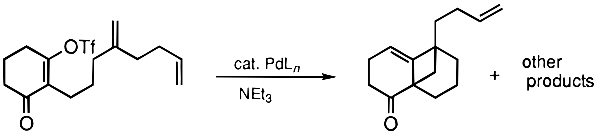
Scheme 9



X = NSO$_2$Ph, C(COOMe)$_2$.

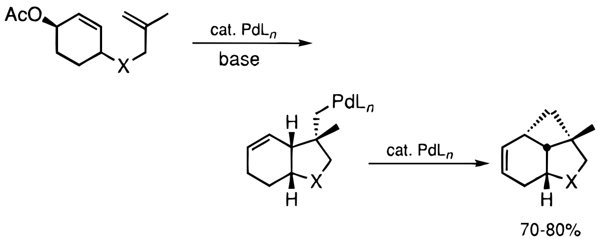
carbopalladation and hydropalladation as well as their microscopic reversals are all strictly *syn* processes. Mechanistic details aside, it now is very clear that plans for the synthesis of cyclic compounds by cyclic carbopalladation of alkenes must take into consideration this fast and reversible cyclopropanation, whether it is to be avoided or promoted.

In sharp contrast with cyclopropanation, cyclobutanation appears to be very slow, and it generally does not compete with other more favorable processes, although what appears to be the first reported example of cyclobutanation[24] represents an exception to this generalization (eq 2). A more likely scenario



(2)

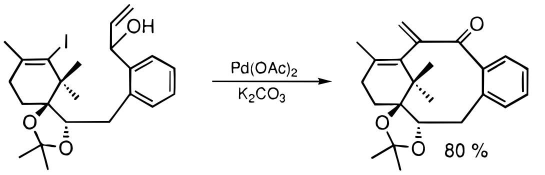
is that, in the absence of other competing processes, cyclobutanation proceeds, albeit slowly, to give cyclobutane derivatives as in the example shown in eq 3.[23b]



(3)

X = C(COOMe)$_2$ or NSO$_2$Ph

The formation of medium (eight- through twelve-membered) rings in high yields via cyclic Heck reaction has been very rare. The formation of a nine-membered ring in 80% yield shown in eq 4[25] represents a significant exception. Undoubtedly, this reaction must be greatly facilitated by the high rigidity of the cyclization precursors. In general, however, medium rings are not readily prepared by the cyclic Heck reaction.

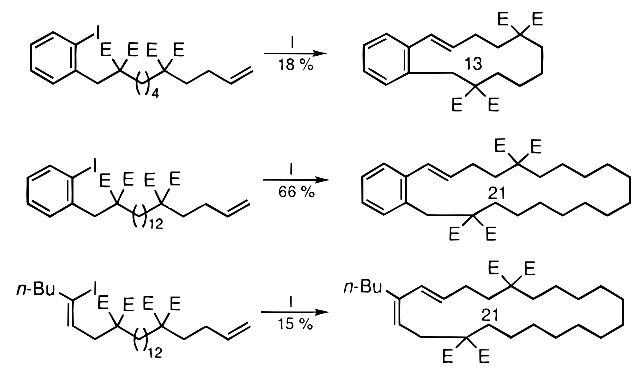


(4)

The formation of large (thirteen-membered and larger) rings via cyclic Heck reaction can take place under dilute solution conditions to give detectable amounts of products[26] (Scheme 10). It should be noted that the endo-mode cyclization and formation of the *E* isomer are the predominant course of reaction. The observed regiochemistry is in accord with that of intermolecular Heck reaction (*vide supra*), which is expected in the absence of strong stereoelectronic effects.

Although different, the Pd-catalyzed cycloisomerization of enynes mainly developed by Trost[27] appears to share two critical elementary steps, *i.e.*, carbopalladation and dehydropalladation, with the Heck reaction. The requisite alkenylpalladium derivatives

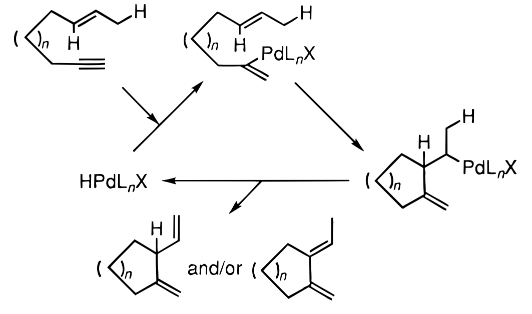
Scheme 10



E = COOEt

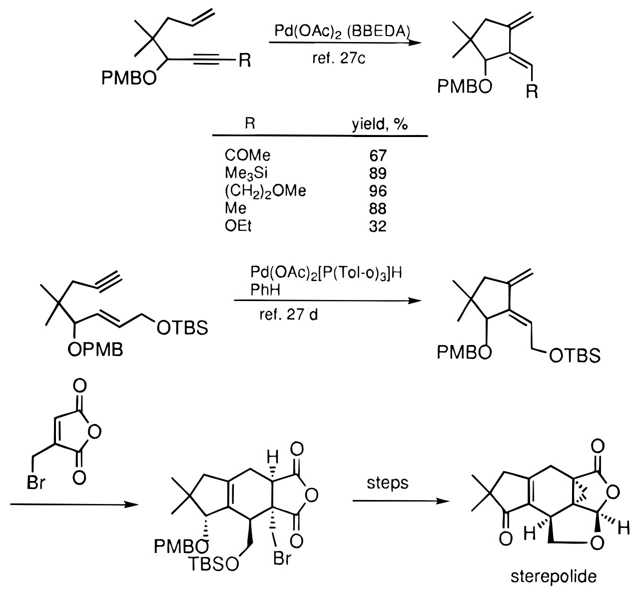
I = 5 % $Cl_2Pd(PPh_3)_2$, K_2CO_3 (5 equiv) and n-Bu_4NCl (1 equiv), DMF.

Scheme 11



are presumably generated *in situ* via hydropalladation of alkynes (Scheme 11). From a practical viewpoint the reaction offers an advantage in that it does not require halides leading to the formation of hydrogen halides which must be removed as salts. It should not be overlooked, however, that the use of halides often leads to higher specificity and versatility and that the formation of halide salts often provides a significant driving force. Thus, for example, the current scope of cycloisomerization reaction appears to be limited to the formation of five- and six-membered rings. Some notable examples are shown in Scheme 12.

Scheme 12

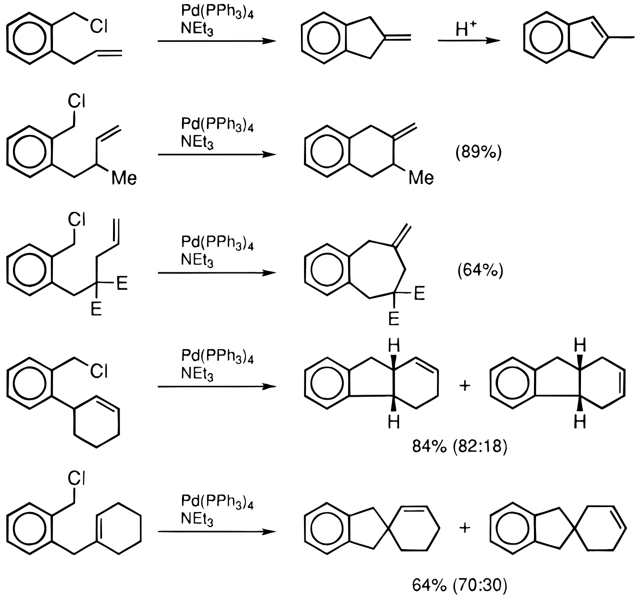


R	yield, %
COMe	67
Me_3Si	89
$(CH_2)_2OMe$	96
Me	88
OEt	32

B. Cyclic Carbometalation Involving Benzyl-, Allyl-, and Acylpalladiums

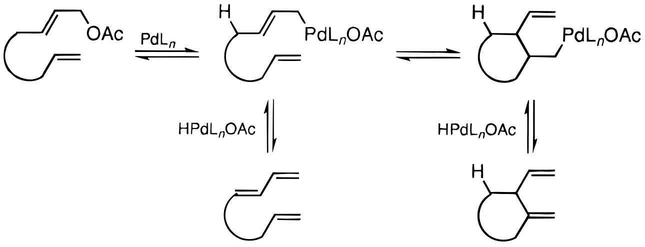
The Pd-catalyzed cyclization of ω-alkenylbenzyl chlorides and other halides proceeds well in a manner similar to that of related aryl and alkenyl derivatives[28] (Scheme 13). In some cases, deconjugated exomethylene derivatives are formed in a completely regiospecific manner. The high regiospecificity appears to be due to the use of Cl, rather than I or Br, as a leaving group. Hydrogen chloride, which is a considerably weaker acid than HI or HBr, should be less effective in inducing acid-catalyzed alkene isomerization in the presence of NEt_3. Although underdeveloped, this reaction appears to hold considerable promise as a synthetic tool.

Scheme 13

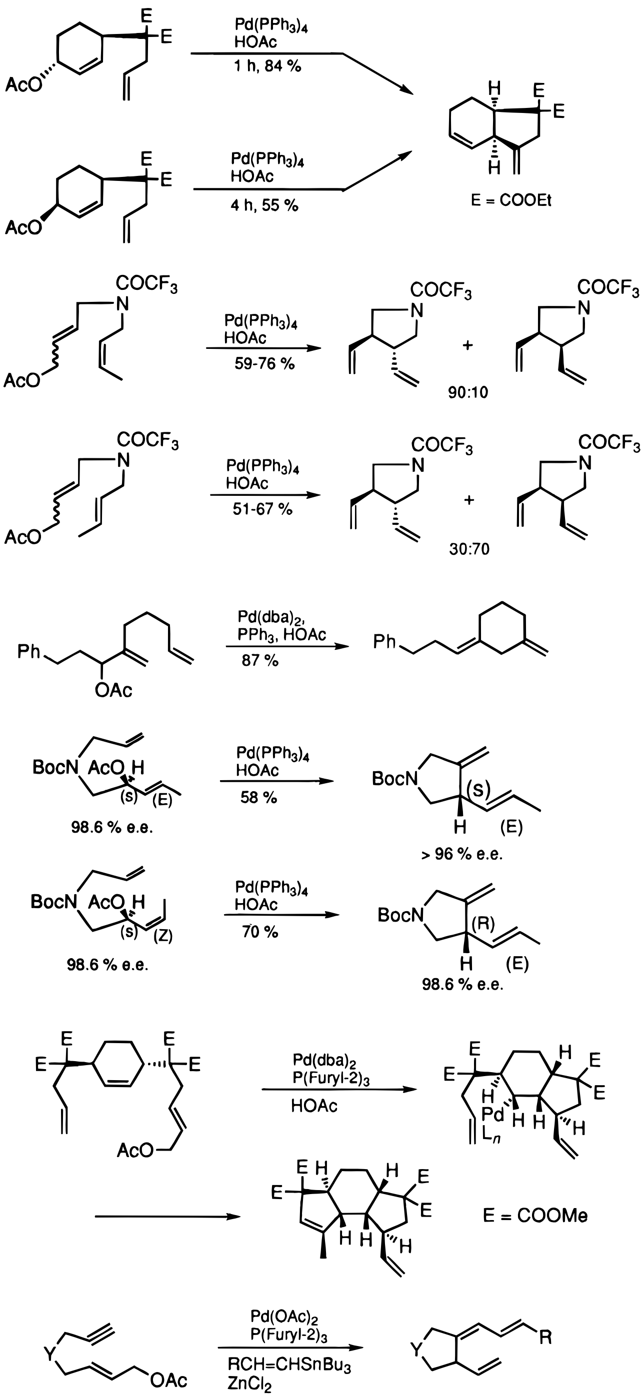


The related reactions of ω-alkenylallyl derivatives are much more complex, and they appear to be distinct from the other classes of cyclic Heck reaction. Earlier attempts by the authors to induce cyclic allylpalladation were met with difficulties arising from predominant dehydropalladation. A general solution to this problem was provided by Oppolzer[29] using mainly HOAc as a solvent. Evidently, HOAc serves as a source of hydride, which prevents decomposition of $HPdL_nOAc$. Under such conditions, the formation of the unwanted trienes is prevented or readily reversed, thereby promoting the formation of cyclic dienes (Scheme 14). Some representative examples of the cyclic allylpalladation reactions are shown in Scheme 15.

Scheme 14



Scheme 15

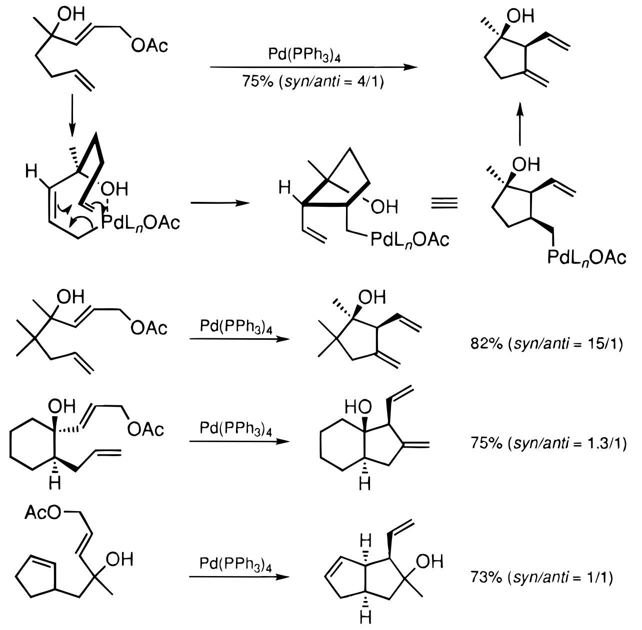


Y	R	yield %
C(SO$_2$Ph)$_2$	H	76
	COOEt	74
C(SO$_2$Ph)$_2$	CH$_2$OTHP	61
C(SO$_2$Ph)$_2$	H	72
C(COOMe)$_2$	H	83
NTs		

Interestingly, the use of δ-hydroxy-substituted allyl acetates lacking δ-hydrogens yielded favorable results summarized in Scheme 16.[30] Favorable diastereoselection observed in some cases is explained by invoking chelation by the δ-hydroxyl group.

Although mechanistic details of cyclic allylpalladation are still not very clear, the reaction appears to require the availability of a six-centered arrangement between the allylpalladium moiety and the ω-alkenyl group. If so, the reaction is mechanistically distinct from those of aryl, alkenyl, and even benzyl halides.

Scheme 16



Yet another class of cyclic carbopalladation involves addition of acyl–palladium bonds to alkenes and alkynes[13,14c,31] (Scheme 17). This reaction also displays many features that are not shared by the usual Heck reactions. So, it will not be further discussed in this review.

C. Applications to Natural Products Synthesis

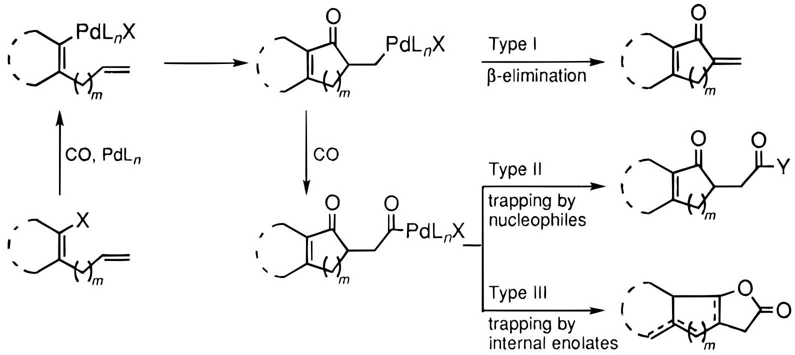
The development of the cyclic Heck reaction producing heterocycles and carbocycles led to a surge of its application to the synthesis of natural products and related complex molecules since around 1990. Notable examples of application of the single-stage cyclic Heck reaction include the syntheses of tazettine (Overman[32]), dehydrotubifoline (Rawal[33]), camptothecin (Comins[34]), lycoricidine (Ogawa,[35] Hudlicky[36]), morphine (Overman[37]), crinan (Grigg[38]), FR 900482 (Danishefsky[39]), duocarmycin SA (Natsume[40]), and CC-1065 (Tietze[41]) (Scheme 18). Further explosive and widespread use of this cyclization methodology in the synthesis of natural products may be anticipated.

D. Enantioselective Cyclic Heck Reaction

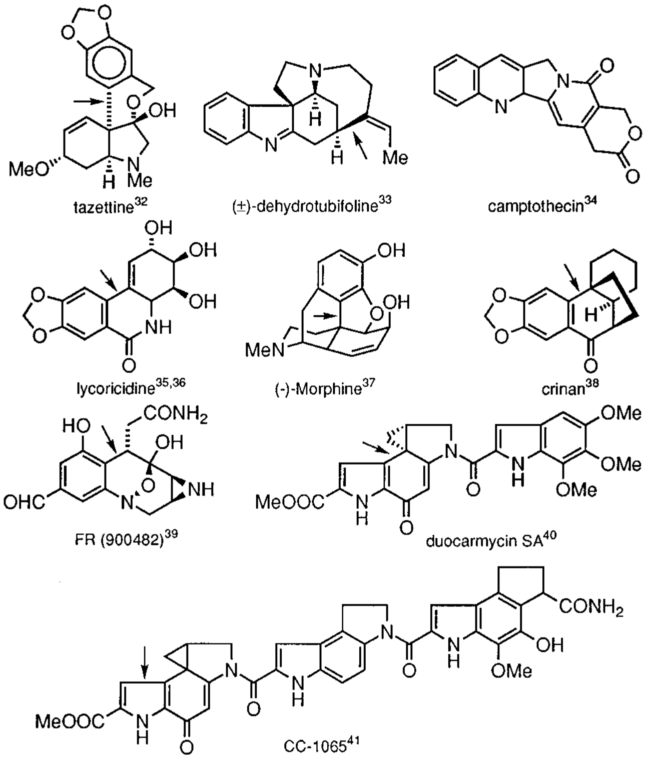
One significant consequence of the strict *syn* relationship observed in both carbopalladation and dehydropalladation is the generation of a chiral center in cases where cyclic alkenes are used. Such cases are therefore subject to asymmetric induction, representing one of the final refinement features of the Heck reaction (Scheme 19).

Intensive studies by Overman[24,42] and Shibasaki[43] have led to the realization of ≥80–90% ee in some favorable cases using mostly Pd(BINAP) complexes as catalysts. The use of either organic triflates or a combination of iodides and silver salts, *e.g.*, Ag$_2$CO$_3$ and Ag$_3$PO$_4$, appears to be desirable (Scheme 20[42] and Scheme 21[43d,43e]).

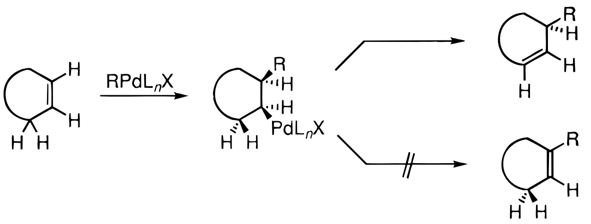
Scheme 17



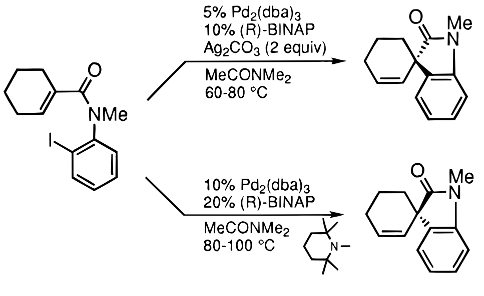
Scheme 18



Scheme 19



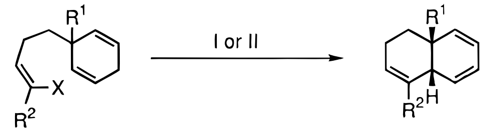
Scheme 20



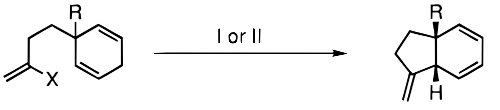
74 %
(S) 79-81 % e.e.

45 %
(R) 89-95 % e.e.

Scheme 21



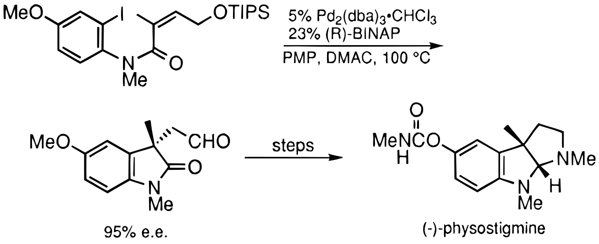
X	R^1	R^2	I or II	yield, %	e.e. %
OTf	COOMe	H	I	54	91
OTf	CH$_2$OCOBu-*t*	H	I	60	91
I	CH$_2$OTBDMS	CH$_2$OAc	II	67	87



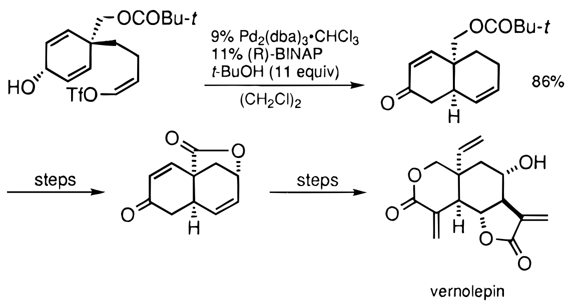
X	R	I or II	yield, %	e.e. %
I	CH$_2$OTBDMS	I	63	73
OTf	COOMe	II	73	83

I: 5% Pd(OAc)$_2$, 10% (R)-BINAP, K$_2$CO$_3$ (2 equiv), benzene or toluene, 60 °C
II: 10% Cl$_2$Pd(BINAP-R), Ag$_2$PO$_4$ (2 equiv), CaCO$_3$ (2.2 equiv), benzene or toluene, *N*-methylpyrrolidone, 60 °C

Some of the procedures developed above have been applied to enantioselective syntheses of (−)-physostigmine[44] (eq 5) and a key intermediate for the synthesis of vernolepin[43f] (eq 6).



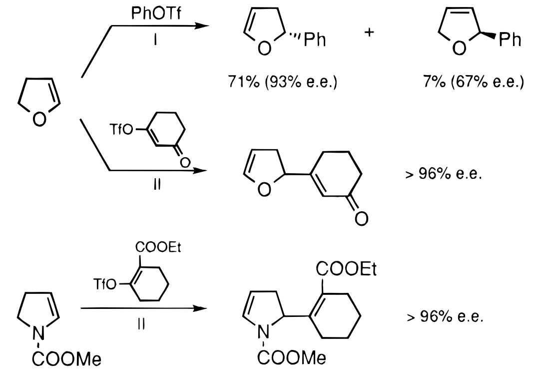
(5)



(6)

In related intermolecular reactions of 2,3-dihydrofuran and related enamines with organic triflates catalyzed by Pd(OAc)$_2$ and (*R*)-BINAP, some remarkably high % ee figures (≥93% ee) have been observed.[45] Interestingly, it has been demonstrated that the observed high % ee figures are in part due to kinetic resolution stemming from differential rates of Pd migration in the two diastereomeric carbopalladation intermediates. In accord with this interpretation the absolute configurations of the stereo-

Scheme 22



I : Pd[(R)-BINAP]$_2$, *i*-Pr$_2$NEt, benzene. II : Pd[(R)-BINAP]$_2$, proton sponge, benzene.

genic centers in the major stereoisomers of two regioisomeric products in the phenylation of 2,3-dihydrofuran are opposite (Scheme 22).

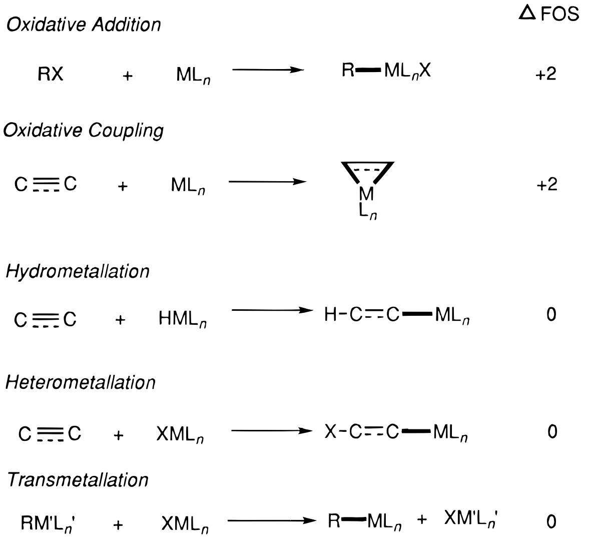
III. Cyclic Cascades Involving Carbopalladation

A. General Principle

In any transition metal-catalyzed organic synthesis via organometals there are three distinct stages. The first is the formation of organometals (C–M bond formation), which is followed by organometallic interconversion. In the final stage, the transition metal catalysts must be regenerated by some processes involving C–M bond cleavage (Scheme 23). In the widely accepted mechanism for the catalytic version of the Heck reaction,[8] organopalladiums are generated via oxidative addition of organic halides with Pd(0) complexes. Carbopalladation involving addition of organopalladiums to alkenes converts one organopalladium intermediate to another. The second organopalladium species then undergoes dehydropalladation via C–Pd bond cleavage, which completes the organic synthetic component of the reaction. However, completion of the catalytic cycles requires reductive elimination of HPdL$_n$X to regenerate the initial, active Pd(0) catalyst and HX, which is to be neutralized. In general, any oxidative (or reductive) processes must be counterbalanced by suitable reductive (or oxidative) processes for completion of catalytic cycles.

A number of other related catalytic processes that involve carbopalladation and satisfy the fundamental principle discussed above may be devised and have, in fact, been devised in recent years. Organotransition metal complexes are commonly prepared via (i) oxidative addition, (ii) oxidative coupling, (iii) hydrometalation, (iv) halometalation and other heterometalations, *i.e.*, addition of X–M bonds to π-bonds where X is halogen or a heteroatom group containing N, O, S, etc., and (v) transmetalation. These processes along with the change in formal oxidative states of the metal (ΔFOS) are shown in Scheme 24.

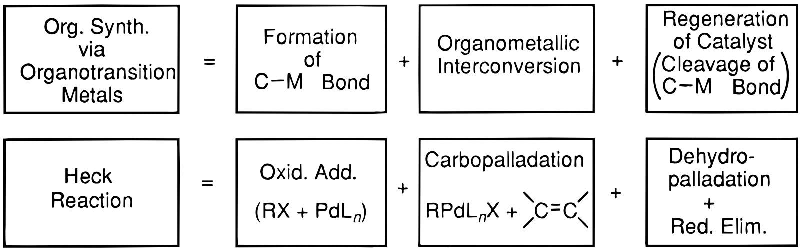
Scheme 24



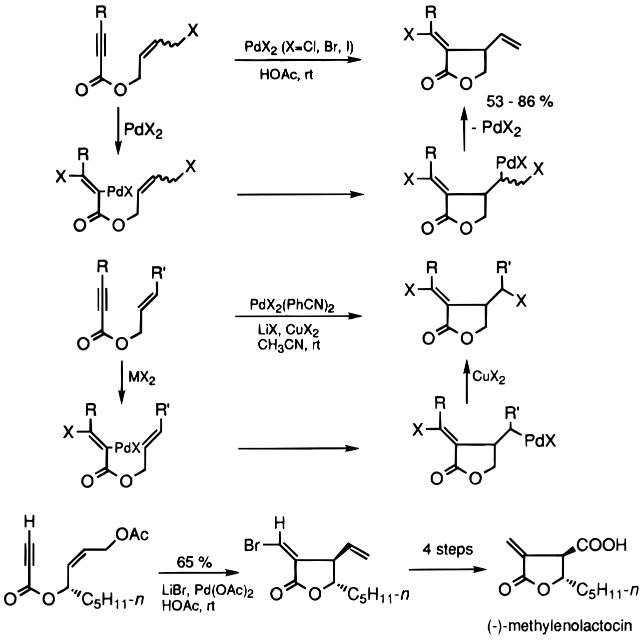
Catalytic processes similar to the Heck reaction can be devised by substituting the oxidative addition step with other processes shown in Scheme 24. Thus, for example, hydropalladation of alkynes has been employed to generate alkenyl palladium intermediates which then undergo carbopalladation and dehydropalladation as in the Heck reaction to induce the Pd-catalyzed enyne cycloisomerization discussed earlier.[27] In the catalytic cycle of this reaction, no redox process appears to be involved. In the cyclization of 4′-halo-2′-alkenyl 2-alkynoates and 2′-alkenyl 2-alkynoates catalyzed by palladium(II) halides,[46] halopalladation of the alkyne moiety generates alkenylpalladiums for subsequent carbopalladation. In these reactions, however, dehalopalladation[46b,c,f–h] and oxidative cleavage by CuX$_2$,[46d,j–m] respectively, must replace the dehydropalladation step in the Heck reaction to generate palladium halides as catalysts (Scheme 25). These reactions can proceed in a stereospecific manner, permitting asymmetric synthesis of natural products, such as (–)-methylenolactocin.[46e]

When organopalladium derivatives are generated via oxidative coupling, the three-membered organopalladium derivatives are expected to follow a similar but different course of reaction. The following conversion of enynes into vinylcyclopentene derivatives[47] can be explained in terms of oxidative coupling–carbopalladation–reductive elimination–electrocyclic

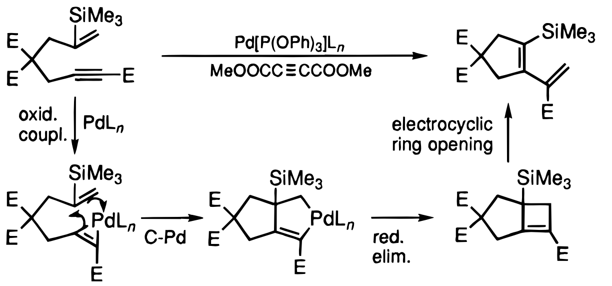
Scheme 23



Scheme 25



Scheme 26

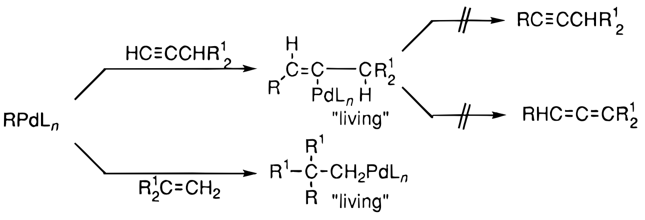


ring openings, as shown in Scheme 26. These variations (Schemes 11, 25, and 26) do share carbopalladation as a crucial step with the Heck reaction, but they clearly fall outside the definition of the Heck reaction presented earlier.

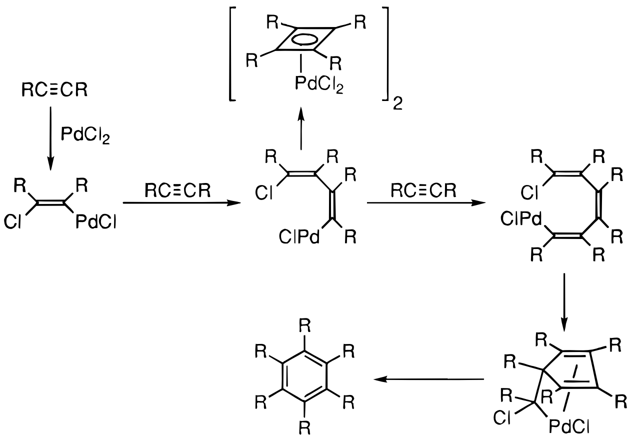
In the original stoichiometric version of the Heck reaction,[7] organopalladiums were generated via transmetalation between organomercuries and Pd(II) complexes. After carbopalladation and dehydropalladation, $HPdL_nX$ thus generated is not *in situ* converted to the original Pd(II) catalyst. If this missing link is provided in a suitable form, this reaction, too, would become catalytic.

Many other variations can also be generated as one considers carbopalladation of other π-compounds, such as alkynes, conjugated dienes, and allenes as well as 1,1-disubstituted alkenes and even arenes (Scheme 2). With alkynes and 1,1-disubstituted alkenes the carbopalladation products are, in general, thermally stable ("living"), because they do not readily undergo dehydropalladation (Scheme 27). In the case of alkynes the strict *syn* stereochemistry of the carbopalladation prevents generation of alkenylic β-hydrogens that are *cis* to Pd. Even allylic β-hydrogens that can be *syn*-coplanar with Pd do not readily participate in dehydropalladation, presumably because formation of allenes is energetically unfavorable. In the case of 1,1-disubstituted alkenes, dehydropalladation is not feasible in cases where carbon−carbon bond formation generates β-quaternary carbon centers. Consequently, the alkyne and 1,1-disubstituted alkene versions of the Heck reaction do not occur in these cases. The "living" nature of carbopalladation offers many exciting synthetic opportunities because additional carbon−carbon bond formation and other chemical transformations ("propagation") are feasible so long as organopalladium derivatives stay alive. At the same time, however, it also offers a challenging problem of when and how to terminate organopalladium interconversion steps. To this end, suitable means of termination for regeneration of Pd catalysts via cleavage of C−Pd bonds must be found. It should be clearly recognized in their connection that any termination devise involving cleavage of C−Pd bonds may, in principle, terminate any organopalladium intermediates that are to be generated. Therefore, they are in direct conflict with "living" organopalladium interconversion steps mentioned above. Consequently, the timing of termination becomes as important as the action of termination itself. In an earlier study of the Pd-catalyzed intermolecular alkyne oligomerization reaction,[6] the propagation via intermolecular cascade carbopalladation of alkynes is terminated by faster cyclization processes after dimerization and trimerization, strongly suggesting that poly(acetylenes) may not be readily obtained via intermolecular cascade carbopalladation of alkynes (Scheme 28). It should also be noted that this reaction as such is applicable only to the synthesis of a very limited range of rather symmetrical benzene derivatives and cyclobutadiene−palladium complexes.

Scheme 27

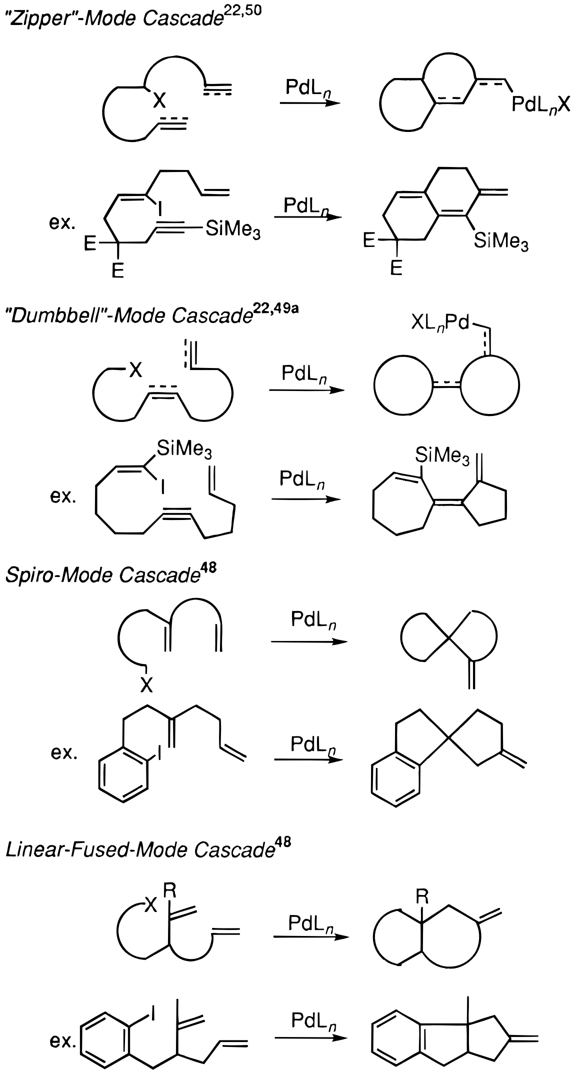


Scheme 28



Since intramolecular cyclic processes can be either strongly favored by entropic factors or strongly disfavored by enthalpic factors (mainly ring strains), these processes may be exploited to develop procedures that are suited for the synthesis of unsymmetrical and complex molecules. Such carbopalla-

Scheme 29



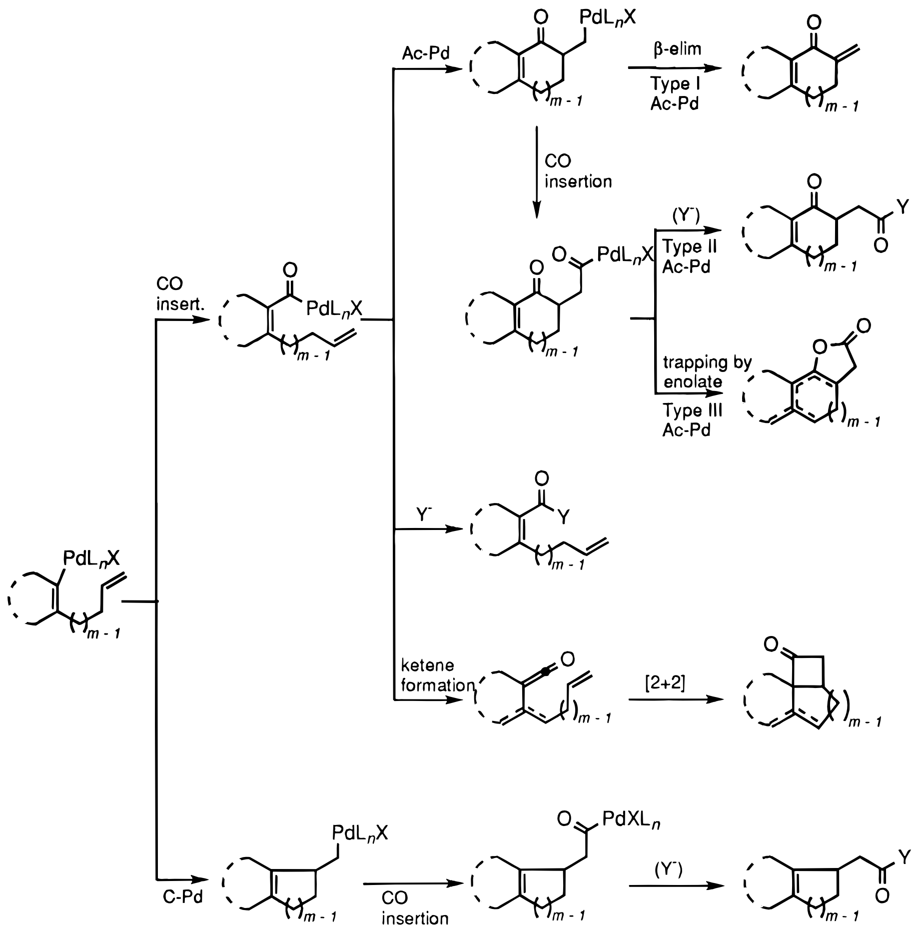
	applicability	
	alkyne	alkene
"Zipper"-Mode Cascade	readily applicable	potentially applicable but prone to β-elimination and other side reactions
"Dumbbell"-Mode Cascade	readily applicable	potentially applicable but prone to β-elimination and other side reactions
Spiro-Mode Cascade	not applicable	readily applicable
Linear-Fused-Mode Cascade	requires anti-carbo-palladation	readily applicable

dation cascades may be either fully or partially intramolecular. If one considers two-stage cascades or tandem processes, for example, there are three possible combinations, *i.e.*, intra–intra, intra–inter, and inter–intra. Of various conceivable modes of cascades alkynes can readily participate in the "zipper"-mode as well as "dumbbell"-mode and circular cascades, while 1,1-disubstituted alkenes are suited for the spiro-mode and linear-fused-mode cascades (Scheme 29). Somewhat surprisingly, these intramolecular cascade cyclic carbopalladation had not been recognized or reported until Overman,[48] Trost,[49a] and ourselves[22] disclosed some prototypical examples in 1988 (Scheme 28). This aspect of carbopalladation has since been extensively investigated, and it has provided a number of attractive and potentially useful synthetic methods. Although not shown in Scheme 29, partially intramolecular processes, such as intra–inter and inter–intra cascades, further expand the synthetic scope of cascade cyclic carbopalladation.

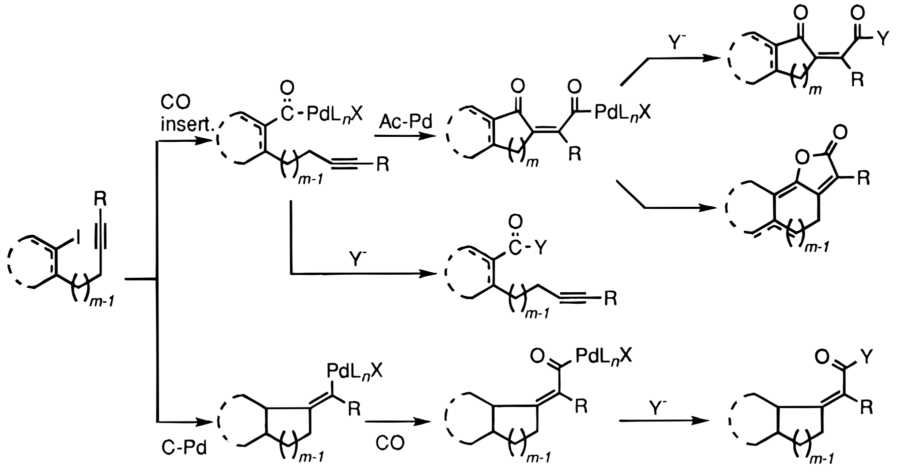
Some other interesting variants of propagation processes have also been found and developed. One is the "tail-biting" cyclopropanation process[9,21,22] shown earlier in Scheme 9 which tends to short-circuit the desired cascade processes. In cases where the cascading carbopalladation process involves addition of alkenylpalladiums to 1,1-disubstituted alkenes to produce homoallylpalladiums, it can be complicated by cyclopropanation leading to a few unexpected consequences, as discussed earlier and also later in this section. The presence of CO in the cascading carbopalladation process has some profound effects. Although a full-scale discussion of the Pd-catalyzed carbonylative cyclization processes is the subject of separate reviews,[50,51] systematic studies[31,52] conducted since 1983 have revealed at least five carbonylative cyclization processes in addition to the straightforward CO insertion–nucleophilic trapping process (Scheme 30). Recent studies[31g,53,54] have also disclosed similar processes (Scheme 31) as well as some intriguing and discrete processes (Scheme 32) in the Pd-catalyzed carbonylative reaction of alkynes. As is clear from these schemes, formation of acylpalladiums via CO insertion and acylpalladation, *i.e.*, addition of the acyl–palladium bond to alkenes and alkynes, are both organometallic interconversion processes which must be followed by appropriate termination steps for recycling Pd catalysts as in the cases of noncarbonylative processes.

Termination of cascading organopalladium interconversion reactions can be achieved by either inter-

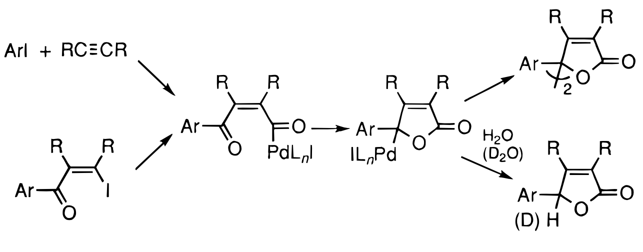
Scheme 30



Scheme 31

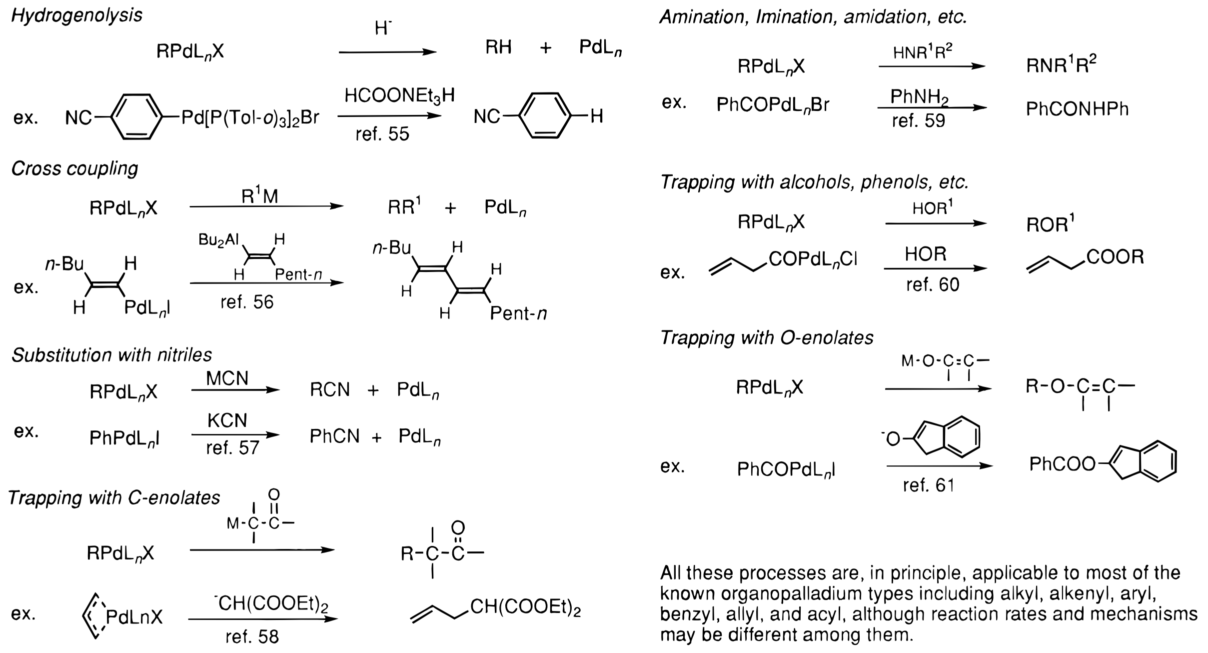


Scheme 32



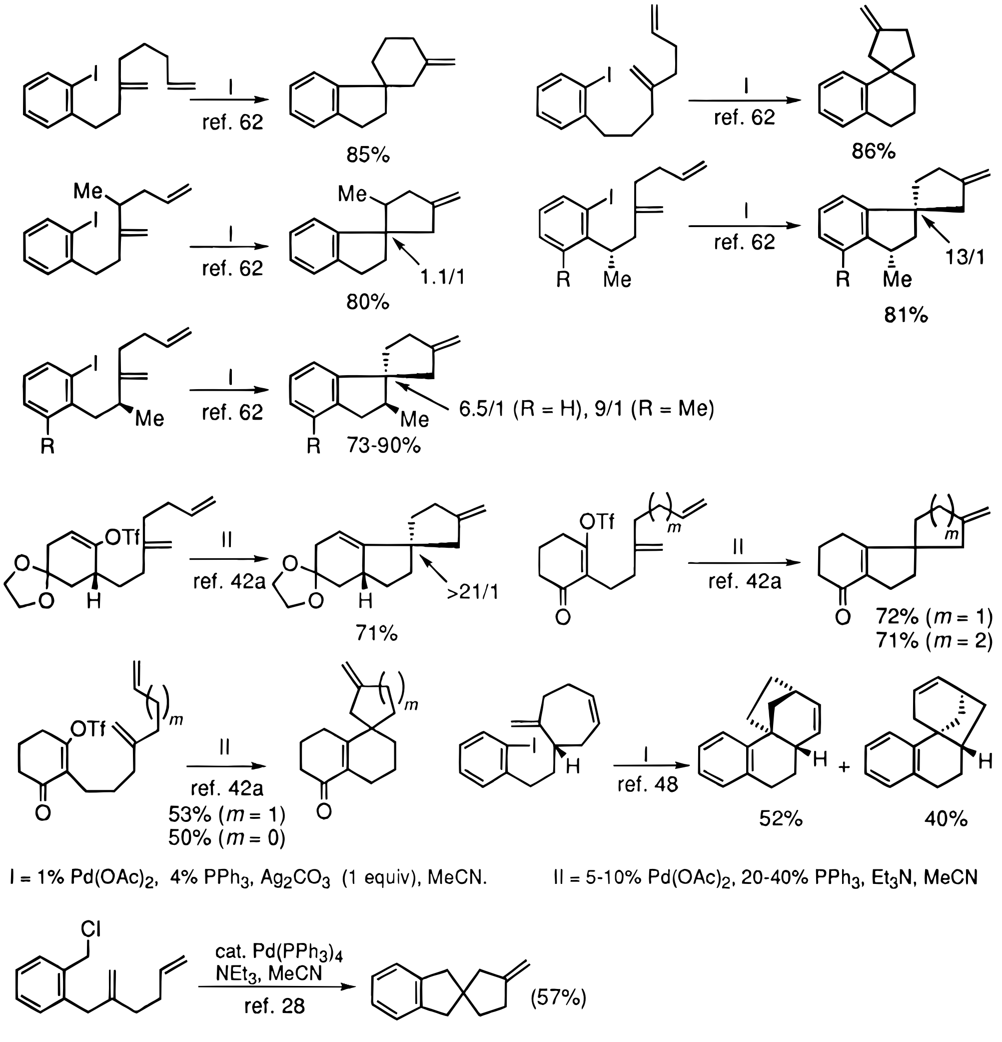
nally generated agents or external trapping agents, and the critical requirement for termination is cleavage of the C−Pd bond. As might be expected, the microscopic reversal of any of the C−Pd bond-forming processes shown in Scheme 24 can, in principle, serve for cleaving C−Pd bonds. Indeed, dehydropalladation, which is the microscopic reversal of hydropalladation, serves as the catalyst-regenerating step in the Heck reaction, and dehalopalladation serves in a similar function in Scheme 25. In these cases, no external terminating or trapping agents are required. In cases where cascading organopalladium interconversion processes are not terminated internally, some external terminating agents must be employed, and a wide variety of C−Pd bond-cleaving agents have been developed over the last few decades.[1,2] They are mostly nucleophilic in nature, reflecting the generally

Scheme 33



All these processes are, in principle, applicable to most of the known organopalladium types including alkyl, alkenyl, aryl, benzyl, allyl, and acyl, although reaction rates and mechanisms may be different among them.

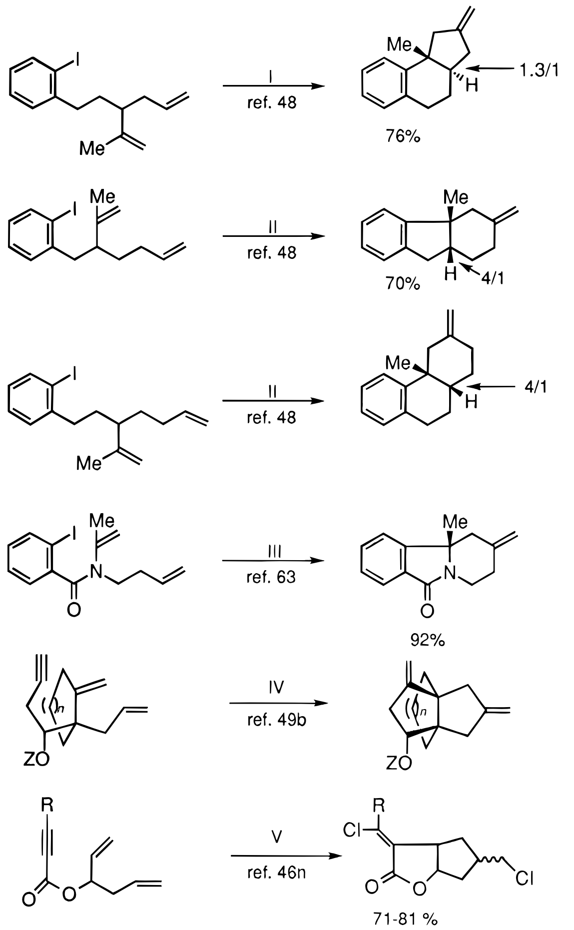
Scheme 34



I = 1% Pd(OAc)$_2$, 4% PPh$_3$, Ag$_2$CO$_3$ (1 equiv), MeCN. II = 5-10% Pd(OAc)$_2$, 20-40% PPh$_3$, Et$_3$N, MeCN

electrophilic nature of organopalladium(II) derivatives. Widely known reagents are H, C, N, and O centered, and some representative processes with prototypical examples are shown in Scheme 33.[55−61]

Scheme 35[a]



[a] I = 5% $Pd(OAc)_2$, 20% PPh_3, Ag_2CO_3, CH_3CN. II = 5% $Pd(OAc)_2$, 20% PPh_3, Ag_2CO_3, THF. III = 10% $Pd(OAc)_2$, 20% PPh_3, K_2CO_3, Et_4NCl, MeCN. IV = $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, HOAc. V = $PdCl_2$, $CuCl_2$, LiCl.

B. Cyclization via Carbopalladation–Termination Tandem Processes

1. Termination by the Heck Reaction

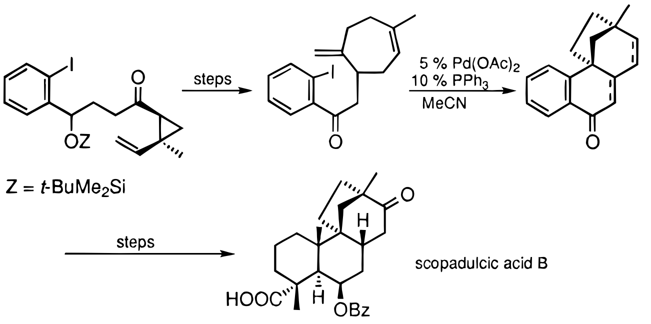
"Living" carbopalladation reactions can be terminated by combining them with the Heck reaction. The examples shown in Scheme 29 indeed represent the "intra–intra" carbopalladation tandem processes, *i.e.*, intramolecular two-step carbopalladation cascades in which the second step is the Heck reaction serving as the propagation–termination step. Some additional examples of the spiro-mode and linear-fused-mode processes are shown in Schemes 34 and 35, respectively. The diastereoselectivity of the reaction can exceed 80% in some cases.[62,63]

An application of the spiro-mode "intra–intra" carbopalladation tandem process is seen in an ingenious scheme for the construction of the skeleton of scopadulcic acid B[64] (Scheme 36).

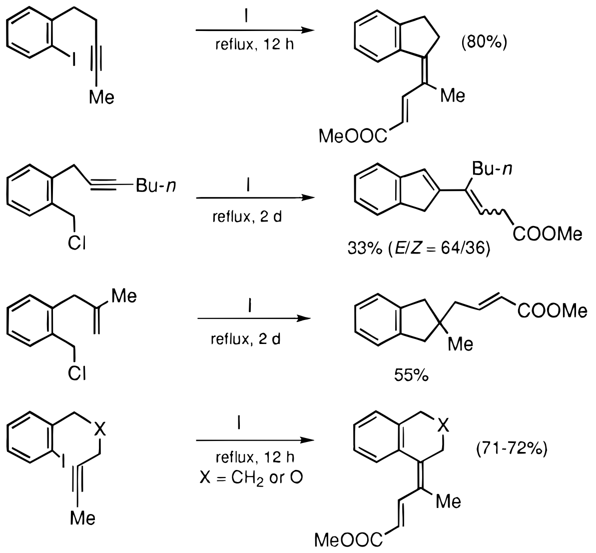
In addition to these "intra–intra" tandem processes, some "intra–inter" and "inter–intra" carbopalladation tandem cyclization processes have also been devised. Some prototypical examples of such "intra–inter" and "inter–intra" processes[22,28] reported in 1989 are shown in Schemes 37 and 38, respectively.

An efficient synthesis of vitamin D's shown in Scheme 39[27e] represents an example of the "inter–intra" tandem process.

Scheme 36

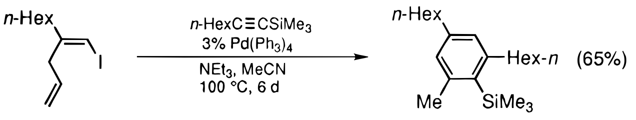


Scheme 37

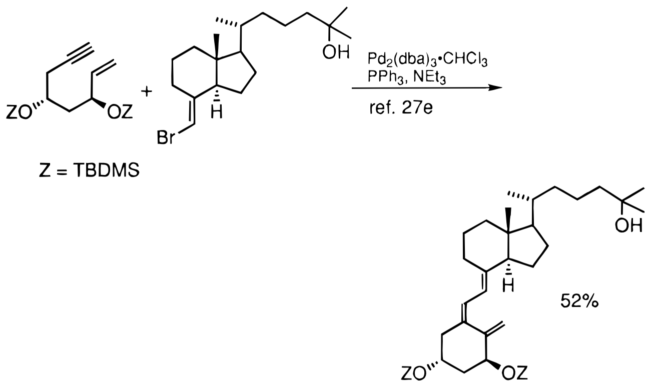


I = $CH_2{=}CHCOOMe$, 3% $Pd(PPh_3)_4$, NEt_3 (2-3 equiv)

Scheme 38



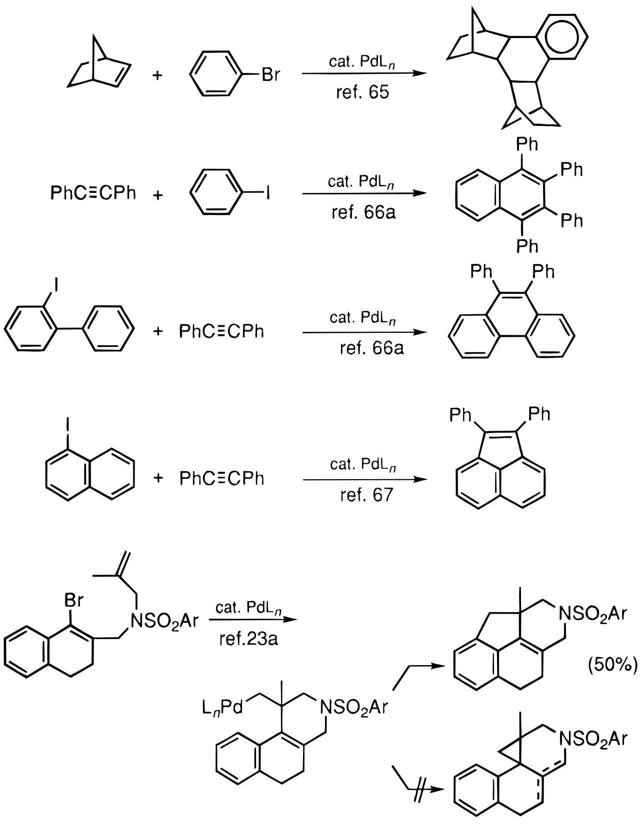
Scheme 39



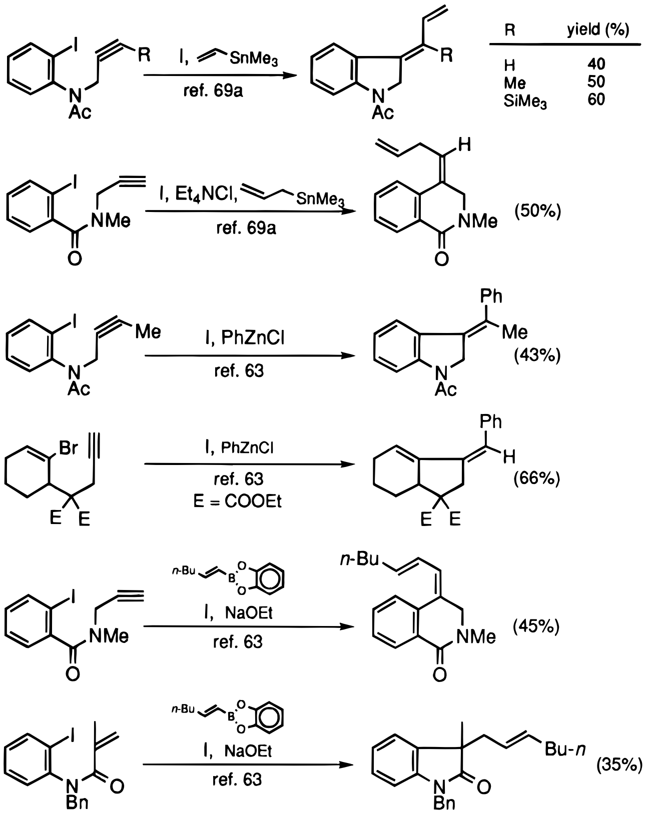
2. Termination via Arene Substitution

A potentially general variation of the Heck reaction involves carbopalladation of arenes leading to aromatic substitution. A combination of a "living" carbopalladation reaction and this arene substitution provides another carbopalladation–termination tandem cyclization process. Some of the early examples[65,66] shown in Scheme 40 involve dimerization of π-compounds, which are not readily conducive to the synthesis of unsymmetrical molecules. More recent applications, however, show the feasibility of using it in such syntheses[23,66c,67] (Scheme 40).

Scheme 40



Scheme 41



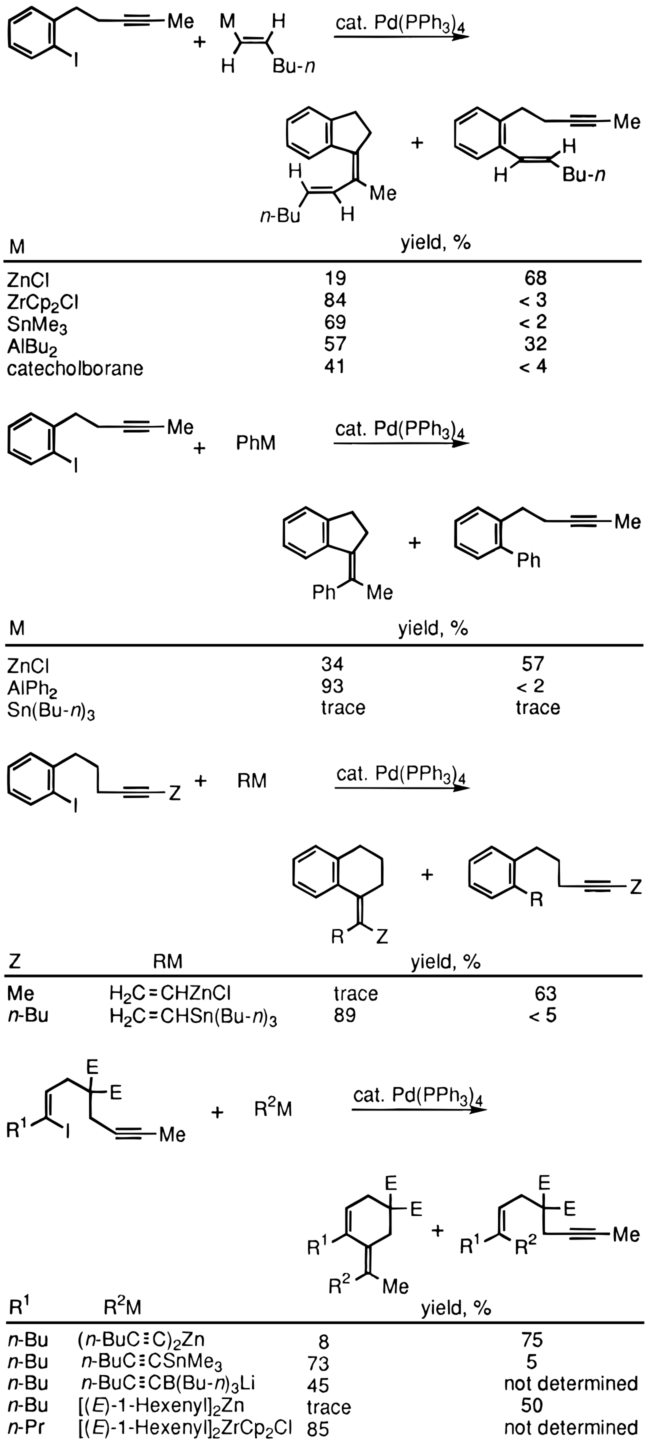
R	yield (%)
H	40
Me	50
SiMe$_3$	60

I = Pd(OAc)$_2$, PPh$_3$

3. Termination with Organometals and Other Carbon Nucleophiles

Organopalladium derivatives generated via “living” carbopalladation can be trapped via cross coupling.[3] Earlier attempts by the authors with organozincs were mostly disappointing. More promising but generally modest and often puzzling results have since been reported[63,69,70] (Scheme 41). As in any other carbopalladation–termination sequences, the termination step must be sufficiently slow relative to the carbopalladation step to avoid premature termination. A systematic study[68] summarized in Scheme 42 shows that very reactive organozinc

Scheme 42



M	yield, %	
ZnCl	19	68
ZrCp$_2$Cl	84	< 3
SnMe$_3$	69	< 2
AlBu$_2$	57	32
catecholborane	41	< 4

M	yield, %	
ZnCl	34	57
AlPh$_2$	93	< 2
Sn(Bu-n)$_3$	trace	trace

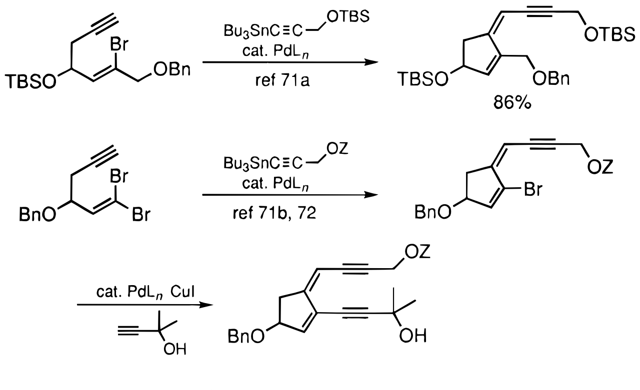
Z	RM	yield, %	
Me	$H_2C{=}CHZnCl$	trace	63
n-Bu	$H_2C{=}CHSn(Bu\text{-}n)_3$	89	< 5

R^1	R^{2}M	yield, %	
n-Bu	(n-BuC≡C)$_2$Zn	8	75
n-Bu	n-BuC≡CSnMe$_3$	73	5
n-Bu	n-BuC≡CB(Bu-n)$_3$Li	45	not determined
n-Bu	[(E)-1-Hexenyl]$_2$Zn	trace	50
n-Pr	[(E)-1-Hexenyl]$_2$ZrCp$_2$Cl	85	not determined

compounds are generally unsatisfactory and that highly satisfactory results may be obtainable with organometals containing Sn and Zr for alkenylation, Sn for alkynylation, and Al for arylation.

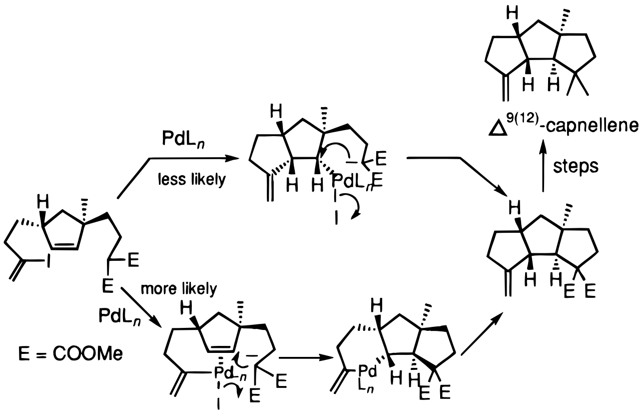
Some persuasive examples of this tandem sequence have been provided by the synthesis of neocarzinostatin model compounds[71,72] (Scheme 43).

Scheme 43



Termination of cyclic carbopalladation processes with other carbon nucleophiles, such as malonate derivatives, is also known but rather rare. The bicyclization reaction leading to the synthesis of $\Delta^{9(12)}$-capnellene shown in Scheme 44[73] might be explained in terms of carbopalladation producing an alkylpalladium derivative that lacks β-hydrogens capable of being *syn*-coplanar with Pd followed by attack by a malonate anion on the C−Pd bond with inversion of stereochemistry. However, it appears more plausible to explain the results in terms of π-complexation, nucleophilic attack on the π-ligand on the backside, and reductive elimination of a palladacyclohexane derivative.

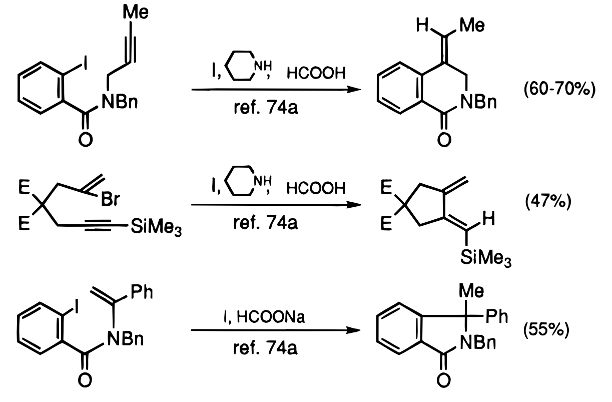
Scheme 44



4. Termination via Hydrogenolysis

Removal of Pd from organopalladium derivatives via hydrogenolysis has been most extensively achieved with formic acid and its salts.[55] It is very likely that organopalladium halides and related derivatives react with a formate to give an organo(formyloxy)palladium species which then loses CO_2 to generate organo(hydrido)palladium derivatives. Its reductive elimination completes hydrogenolysis with regeneration of Pd(0) catalysts. This reaction is applicable to the hydrogenolysis of a wide variety of organopalladiums including alkyl, alkenyl, aryl, allyl, and benzyl derivatives. Some representative examples of the carbopalladation−hydrogenolysis tandem cyclization processes are shown in Scheme 45.[74] The reported product yields have been generally modest, and some improvements are desirable for this tandem process to be truly useful for organic synthesis.

Scheme 45

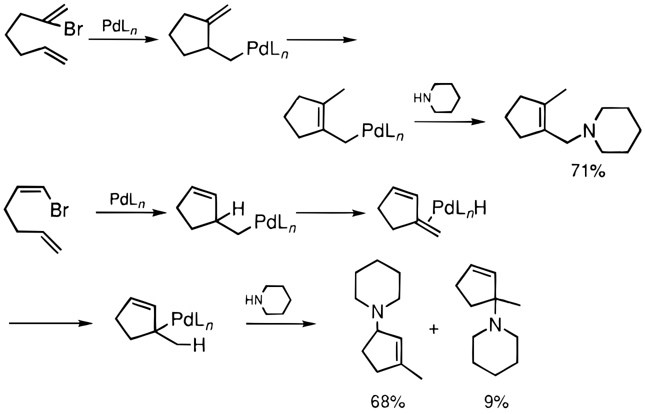


E = COOEt I = Pd(OAc)$_2$-PPh$_3$

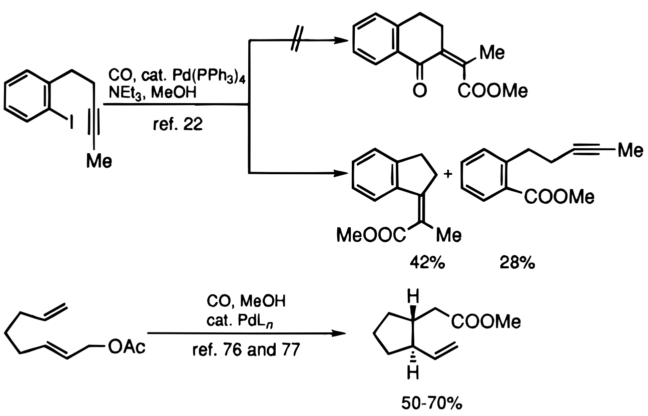
5. Termination with N, O, and Other Heteroatom Nucleophiles

Organopalladiums containing alkyl, alkenyl, and aryl groups are relatively inert toward ordinary N nucleophiles, such as amines and amides, and O nucleophiles, such as water, alcohols, and carbonyl compounds, although recent investigations have made Pd-catalyzed amination of aryl and alkenyl halides a useful synthetic method.[75] This is in sharp contrast with the generally high reactivity toward a wide variety of heteroatom nucleophiles exhibited by acyl, allyl, and some other related organopalladium derivatives discussed later. It is worth mentioning here that the formation of allylamines via cyclic carbopalladation of dienyl halides[11] (Scheme 46) must involve isomerization of the initially formed homoallylpalladiums into allylpalladiums which are then aminated in accord with the general discussion presented above. The double-bond isomerization appears to proceed via dehydropalladation−rehydropalladation. Cyclopropanation of homoallylpalladiums must be occurring, but it must be readily reversed and largely nonproductive.

Scheme 46



Scheme 47

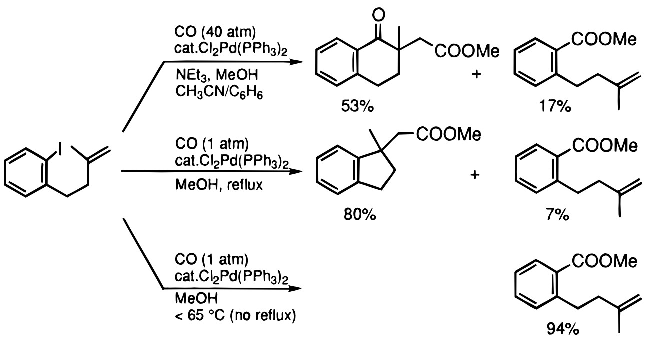


C. Cyclization via Carbopalladation–Carbonylation–Termination Processes

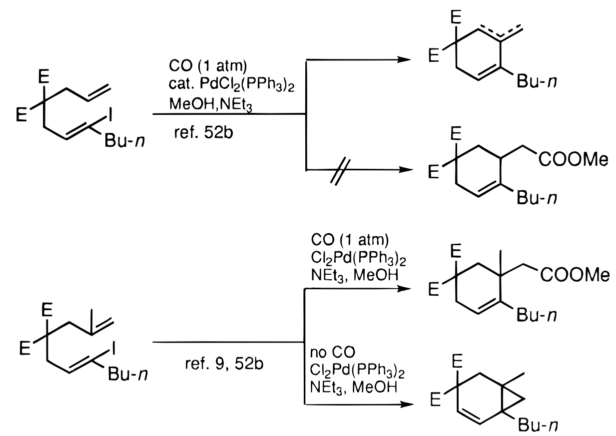
As discussed in section III.A, organopalladiums can be readily interconverted to acylpalladiums via reversible CO insertion. Although readily decarbonylated, acylpalladiums are otherwise relatively stable, *i.e.*, “living”, by themselves. In the presence of a variety of external and internal reagents, however, acylpalladiums are readily converted to organic compounds[2] and Pd complexes that can be recycled as catalysts. Practically all types of terminating agents discussed above including β-hydrogen-providing alkenes, as well as H, C, N, O, and other heteroatom nucleophiles readily react with acylpalladiums. Thus, the CO insertion−termination tandem processes can, in principle, provide yet another series of processes to be combined with the cyclic carbopalladation processes. On the other hand, systematic investigations by the authors during the 1983−1986 period[13,31a,b] disclosed three types of cyclic acylpalladation processes and a ketene cyclization reaction (Scheme 30). A few years later, some of these cyclic acylpalladation processes were incorporated in the palladium-ene reaction-based methodology by Oppolzer.[77] These processes involved cyclization reactions incorporating a molecule of CO in a ring via cyclic interaction of acylpalladiums with π-compounds in competition with noncarbonylative cyclic carbopalladation. Consequently, they would not serve as processes for terminating cyclic carbopalladation. In 1989 the authors unexpectedly found the following transformation which would amount to a cyclic carbopalladation−termination tandem[22] (Scheme 47). Independently, Yamamoto[76] and Oppolzer[77] reported examples of the palladium-ene cyclization−esterification via CO insertion tandem (Scheme 47).

A recent study by the authors[52] indicates that partition among various competitive processes in these reactions is dependent on a number of factors including ring size, nature of the π-bond and the C−Pd bond, CO pressure, solvents, temperature, Pd catalysts, and added reagents. Thus, for example, either carbonylative or noncarbonylative cyclization can be observed with the same substrate and reagents using either 40 or 1 atm of CO, respectively.[52] A minor difference in the reaction temperature can also radically change the reaction course[52] (Scheme 48). Even in cases where cyclic carbopalladation is achieved without incorporation of CO there can be at least three different courses of reactions that can compete among them, *i.e.*, the Heck reaction via dehydropalladation and cyclopropanation in addition to the desired carbonylative termination. The currently available data indicate that, in cases where dehydropalladation leading to the Heck product can readily occur, carbonylative termination may not be readily achieved, where cyclopropanation of “living” alkylpalladium intermediates can be readily suppressed in favor of carbonylative termination[52] (Scheme 49). A few examples of the synthesis of heterocycles[78] and the use of triflates[79] are shown in Scheme 50.

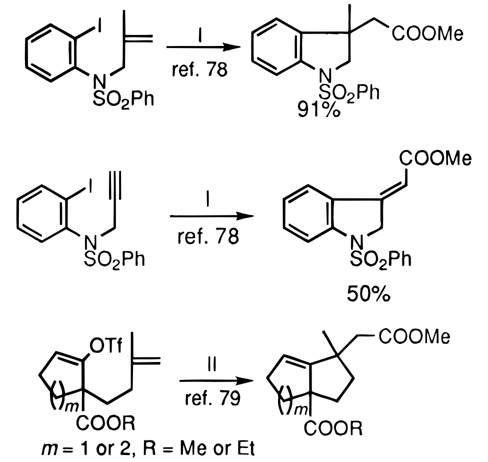
Scheme 48



Scheme 49



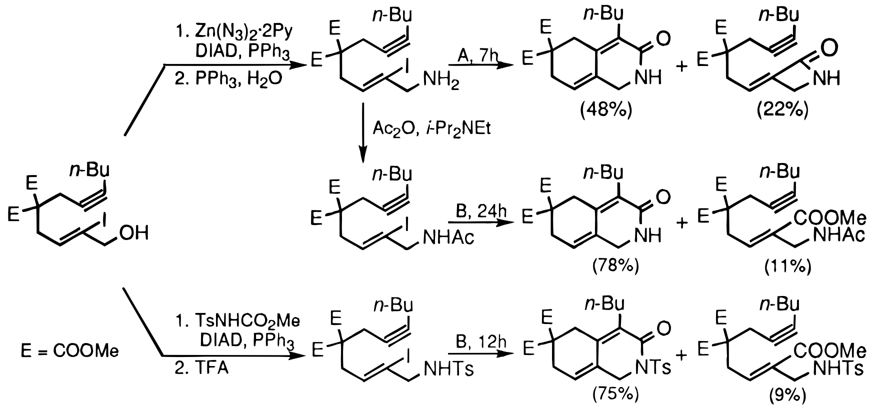
Scheme 50



I = CO (1 atm), $Cl_2Pd(PPh_3)_2$, TlOAc, MeOH

II = CO (1 atm), $Pd(OAc)_2$, PPh_3, NEt_3, MeOH, reflux

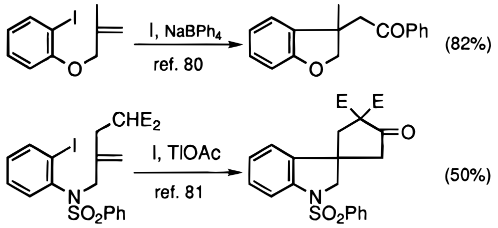
Scheme 51



A = 5 %$PdCl_2(PPh_3)_2$, Et_3N (4 equiv) in *i*-PrOH. B = Same as A except in MeOH.

Various other types of nucleophiles including N nucleophiles, such as amines and amides (Scheme 51)[54] and C nucleophiles, such as organometals[80] and C-enolates[81] (Scheme 52), have also been used as terminating agents in place of methanol and other O nucleophiles. The latter example in Scheme 52 makes use of trapping of acylpalladiums with C enolates reported several years ago.[82]

Scheme 52



E = COOEt I = CO (1 atm), $Pd(OAc)_2$, PPh_3.

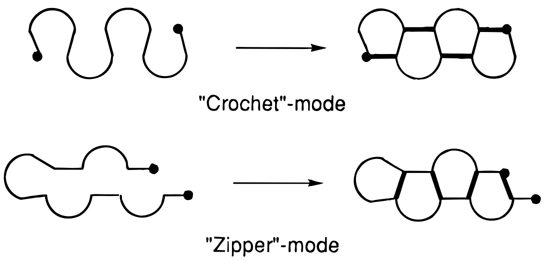
D. Cyclization via Multiple Carbopalladation–Termination Cascade Processes

All examples shown in section III.B involve formation of one or two carbon–carbon bonds except in the first two examples of Scheme 40 where homodimerization of an alkene or alkyne takes place. As in these and earlier examples of alkyne cyclooligomerization,[6] "living" carbopalladation reactions can, in principle, be linked together to devise cascading carbopalladation processes. Some such processes involving the formation of three or more carbon–carbon bonds that are readily adaptable to the synthesis of complex and unsymmetrical natural products and other organic molecules are discussed in this section.

1. "Zipper"-Mode Cascade

The prototypical example of the "zipper"-mode cascade was devised several years ago[22] as shown in Scheme 29, which prompted the authors to develop a general synthetic methodology based on the notion shown in Scheme 53. The "zipper"-mode cascade contrasts itself with a previously developed "crochet" mode of ring construction found in the biogenetic formation of steroids and related biomimetic polyene cyclization reactions.[83] It promises to provide a novel and potentially efficient approach to the synthesis of polyfused systems based on a very straightforward retrosynthetic analyses.

Scheme 53

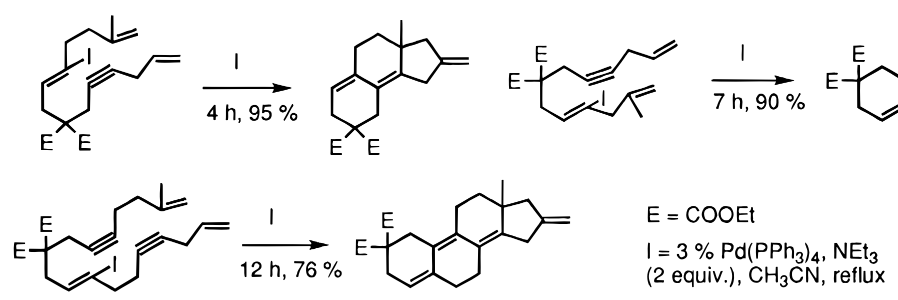


The feasibility of developing the "zipper"-mode cascade cyclization was clearly demonstrated by the examples shown in Scheme 54.[84] It should be noted that these exceptionally selective and clean transformations take advantage of the facts that cyclic processes producing five-and six-membered rings are generally faster by a few to several orders of magnitude than potentially competitive intermolecular and cyclic processes producing four-membered as well as medium and large rings.

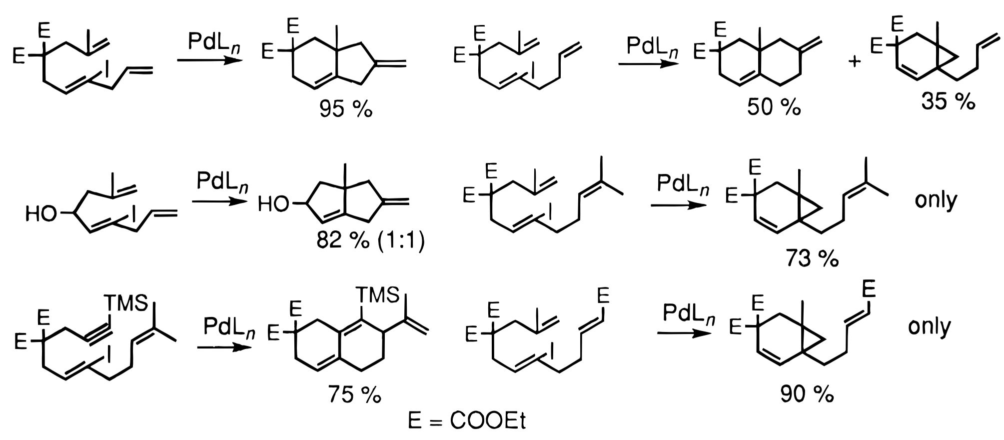
Alkenes that are capable of providing *β*-*syn* hydrogens can serve as cascade-terminating functional groups through their participation in the Heck reaction. Cyclopropanation discussed in section II.A is another cascade-terminating process. Intricate and competitive relationships between common ring formation and cyclopropanation are seen in Scheme 55.[9] Here again, a number of factors including ring size and nature of π-bonds appear to influence the balance between the two competing processes. Since cyclopropanation has been shown to be readily reversible,[9] blockage of dehydropalladation or other trappings of cyclopropylcarbinylpalladiums must be sufficient to prevent the formation of cyclopropanated products, although this point has yet to be established. Unlike homoallylpalladiums, dienylpalladiums formed via carbopalladation of alkynes do not appear to readily undergo cyclopropenation, as indicated by the reaction of a dienyne derivative in Scheme 55.

The use of external agents for terminating multiple carbopalladation cascades offers a formidable synthetic challenge, since termination may compete with the cascading carbopalladation before and after each carbopalladation step. Clearly, such termination

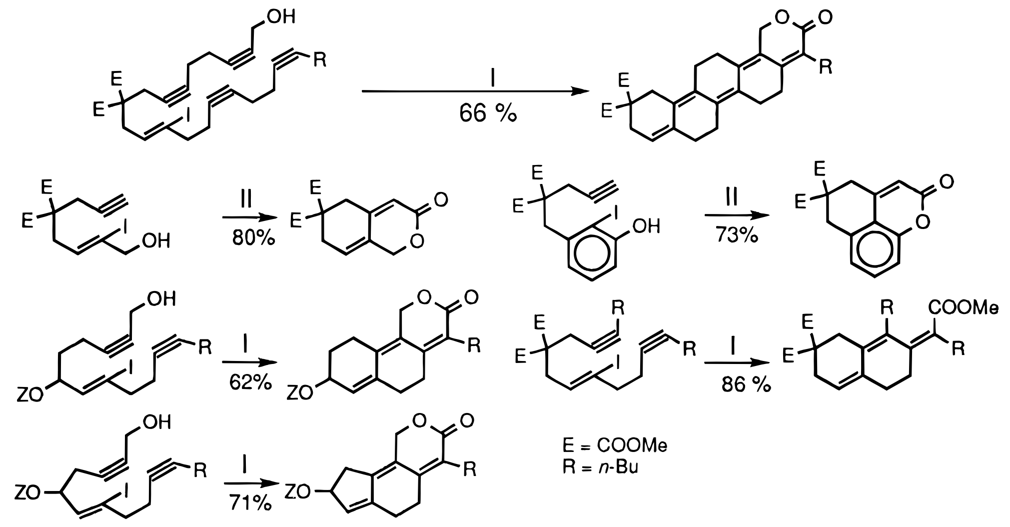
Scheme 54



Scheme 55



Scheme 56



I = CO (1 atm), 5 % $Cl_2Pd(PPh_3)_2$, NEt_3 (2 equiv.) MeOH.
II = CO (1 atm), 5 % $Cl_2Pd(PPh_3)_2$, NEt_3 (2 equiv.), DMF.

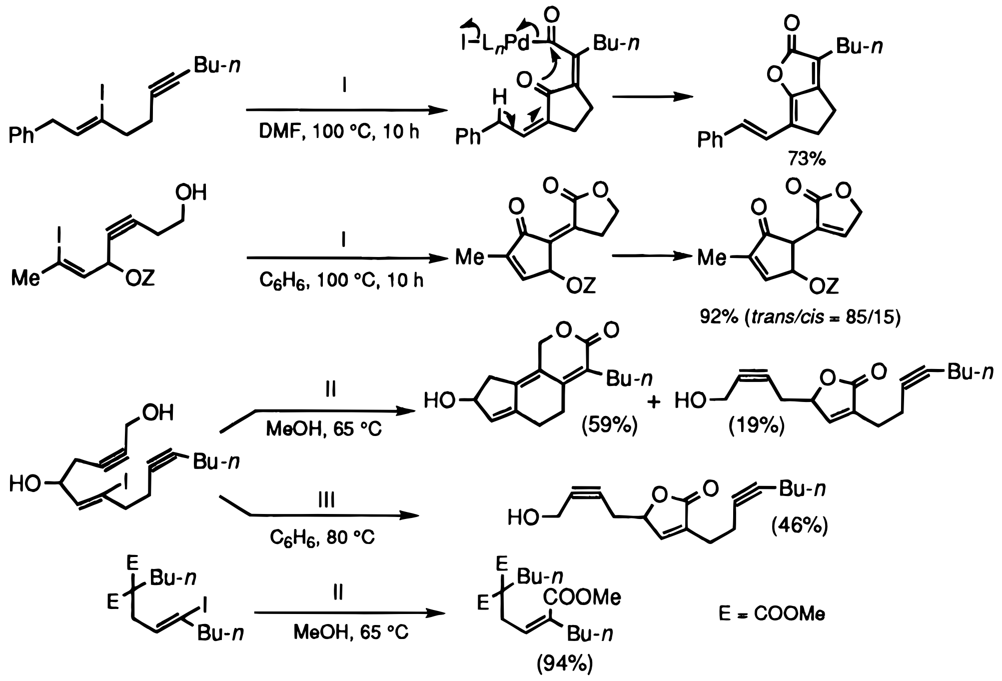
reactions must be sufficiently slow to allow intramolecular carbopalladation cascades to complete without termination. At the same time, however, it must be fast enough to prevent unwanted intermolecular carbopalladation. Carbonylative termination introduced in 1989[22] is generally well suited for this purpose (Scheme 56)[53] and also readily modifiable by changing reaction parameters, such as CO pressure, solvents, and reaction temperature. Some possible side reactions that can, in principle, take place are seen in the reactions of modified substrates shown in Scheme 57.[53]

As discussed earlier, carbonylative amidation also serves as a termination device in the carbopalladation cascade process[54] (Scheme 58).

2. "Dumbbell"-Mode and Circular Cascades

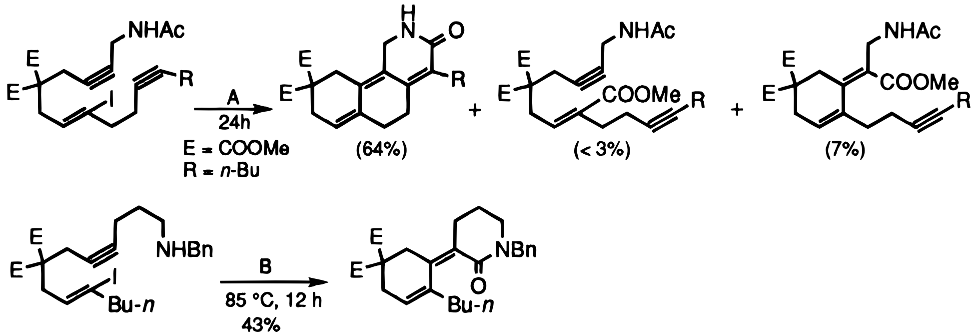
The "dumbbell"-mode carbopalladation cascade shown in Scheme 29 can, in principle, be extended for the preparation of linear structures in which three or more rings are linked together. In reality, however, it is very likely that some intramolecular processes take over the linear processes to produce circular structures (Scheme 59). Completion of the circular cascade process may or may not involve organopalladium species. In the latter case, some pericyclic reactions, such as Diels–Alder reaction, Cope rearrangement, ene reaction, and 6π and 4π electrocyclic reactions, may serve as the final cyclization step. Arenes, cyclohexadienes, and fulvenes

Scheme 57



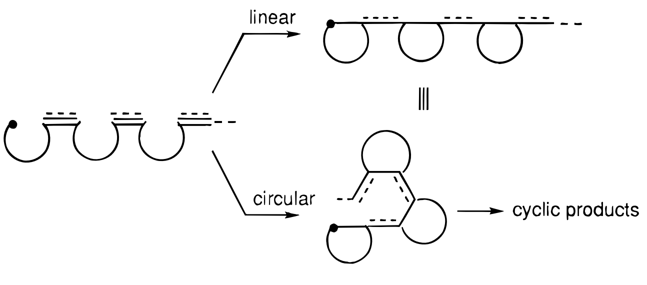
I = CO (40 atm), 5% $Cl_2Pd(PPh_3)_2$, NEt_3 (2 equiv). II = CO (1 atm), 5% $Cl_2Pd(PPh_3)_2$, NEt_3 (4 equiv).
III = CO (20 atm),5% $Cl_2Pd(PPh_3)_2$, NEt_3 (4 equiv), MeOH (4 equiv).

Scheme 58

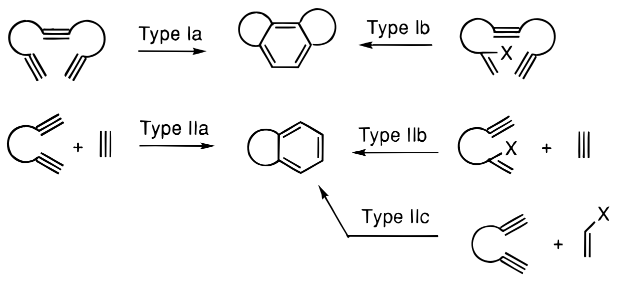


A = CO (1 atm), $Cl_2Pd(PPh_3)_2$, Et_3N (4 equiv.) in MeOH. B = Same as A except in *i*-PrOH.

Scheme 59



Scheme 60

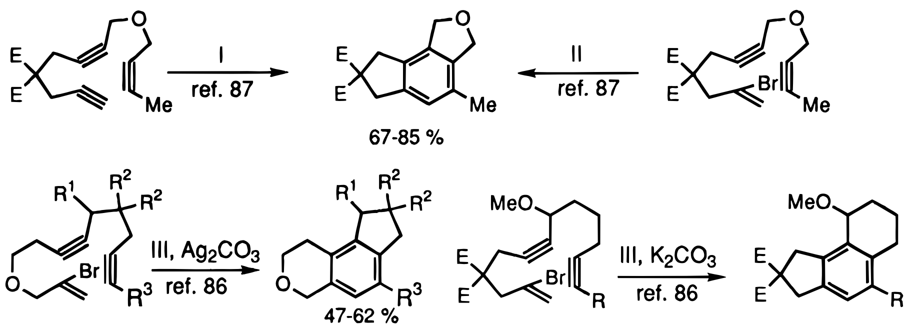


have been the predominant cyclization products of the circular cascade cyclization processes.

The feasibility of synthesizing benzene derivatives with two or more substituents in some predetermined positions via circular carbopalladation cascade or tandem processes was demonstrated by the reaction shown in Scheme 38.[22] This reaction involves the formation of only two carbon–carbon bonds. Various approaches involving formal [2 + 2 + 2] cyclization processes[85] shown in Scheme 60 based on carbopalladation have been explored by several research groups.

As might be expected, all intramolecular processes (type Ia and Ib processes) can readily proceed in good yields[86,87] (Scheme 61). In either case, the initial step must be the formation of diyne-containing alkenylpalladium derivatives via either oxidative addition or hydropalladation. These intermediates are then converted to bicyclic alkenylpalladiums via "dumbbell"-mode bicyclization involving exo-carbopalladation. The fate of these bicyclic intermediates is less clear. Two likely paths are (i) six-electron electrocyclic reaction followed by dehydropalladation and (ii)

Scheme 61



a : R^1, R^2 = H, R^3 = Me

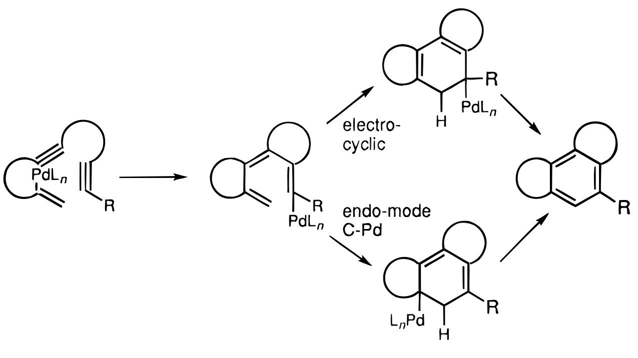
b : R^1= OBn, R^2 = Me, R^3 = COOMe

a : R = COOMe (61%). ***b*** : R = H (42%)

c : R = $C(OH)Et_2$ (67%). ***d***: R = $COCH_3$ (75%)

I = 3 % $Pd(PPh_3)_4$, 5 % HOAc, MeCN, reflux. II = 3 % $Pd(PPh_3)_4$, Et_3N (2 equiv), MeCN, reflux.
III = 3 % $Pd(OAc)_2$, PPh_3, MeCN. E= COOEt

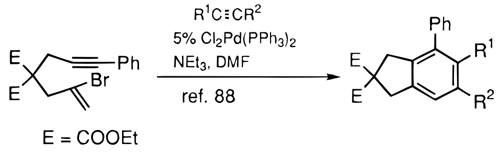
Scheme 62



endo-mode carbopalladation followed by dehydropalladation (Scheme 62).

Selective synthesis of benzene derivatives via partially intramolecular cyclic carbopalladation is substantially more complicated than the totally intramolecular processes. Of the three types of processes shown in Scheme 60, *i.e.*, types IIa, IIb, and IIc, type IIa process does not appear to be well suited for selective synthesis of substituted benzenes. Many attempts by the authors uniformly led to unattractive mixtures of compounds. The previously developed Co-based methodology[85] is clearly much more favorable. Even so, it should be noted that the reported yields range from very low to very high figures and that favorable results often require a large excess of a specially structured alkyne, such as $Me_3SiC{\equiv}CSiMe_3$, used in many cases as a solvent. In a "pair"-selective reaction of a diyne and a monoyne to produce a benzene derivative, a Pd catalyst must interact alternatingly with the two substrates. This requirement is easily met, if the two substrates are appropriately linked with a tether as in the type Ia processes. Some other mechanism-based devises are also conceivable, and the Co-catalyzed process may fall into such cases. In general, however, perfect or near perfect alternation between two similar compounds, *i.e.*, a diyne and a monoyne would be a highly unlikely event. This difficulty would be solved, if one of the two alkynes is replaced with an alkenyl halide, as in the types IIb and IIc processes. In these cases, the point of initiation in each catalytic cycle is specified at the alkenyl halide. In the type IIb process, a rapid intramolecular carbopalladation should follow the initial oxidative addition step. The only key requirements for the desired alternation would be that the rate of intermolecular carbopalladation of the monoyne be substantially greater than that of the haloenyne leading to homooligomers but that the termination step be faster than homooligomerization of the monoyne. The desired type IIb process should be favorable within the window defined above. On this basis, the authors compared the relative reactivity of various alkynes under competitive conditions and found the following general order:[88] $HC{\equiv}CR(alkyl) > HC{\equiv}CPh > RC{\equiv}CR > Me_3SiC{\equiv}CR > Me_3SiC{\equiv}CPh$. Diphenylacetylene is less reactive than 4-octyne, but its reactivity relative to silylated alkynes was not determined. Some experimental results shown in Scheme 63[88] seem to support the discussion presented above. The results also indicate that, even in cases where a monoyne of low reactivity is used, favorable results may be obtained by the use of an excess of the monoyne. The reaction is generally highly regioselective (>90%), and the regiochemistry is as discussed earlier in section I.B.

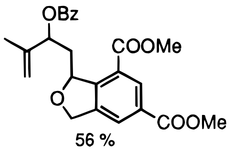
Scheme 63

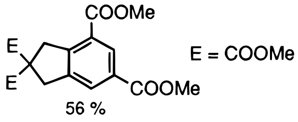


E = COOEt

R^1	R^2	yield, % using n equiv of $R^1C{\equiv}CR^2$ n = 5	n = 1	regioselectivity, %
H	*n*-Hex	67	76	> 93
H	Ph	73	55	> 92
n-Hex	$SiMe_3$	63	67	> 98
Ph	$SiMe_3$	62	45	> 98
n-Pr	*n*-Pr	83	67	-
Ph	Ph	62	21	-

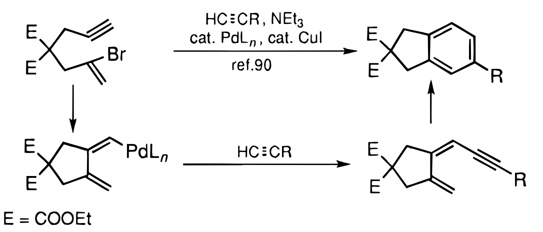
A few other benzene derivatives prepared by this reaction are shown below.[89]





In an independent study,[90] bromoenynes and monoynes containing the terminal ethynyl groups were converted to benzene derivatives using both Pd and Cu catalysts. A mechanism involving cross

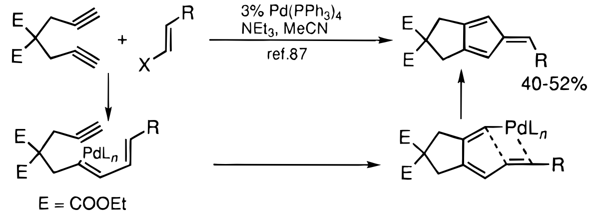
Scheme 64



coupling to produce dienynes as intermediates was proposed (Scheme 64). This mechanism cannot operate in the cases where one or both of the alkynes are internal. Even with terminal monoynes the cascade carbopalladation mechanism shown in Scheme 62 appears to be more plausible at least under the conditions used by us,[88] since the use of $DC\equiv CHex$-*n* produced the desired product retaining D (75−85%) in the position expected from Scheme 62.

One might think that the type IIc process should be even more favorable as a route to benzene derivatives, since no major difficulties pertaining to "pair" selectivity exist. After oxidative addition of an alkenyl halide, the intermolecular (and hence generally slow) carbopalladation step which generally proceeds regioselectively should be followed by a faster cyclic carbopalladation step. Unexpectedly, however, a few experiments along this line led to the formation of bicyclic fulvenes in moderate yields[87] (Scheme 65).

Scheme 65

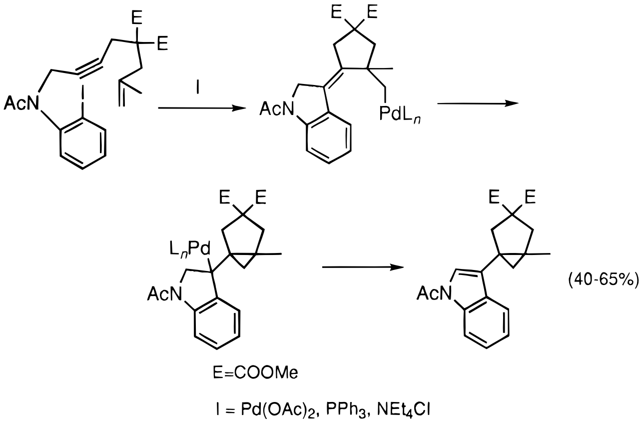


A related intermolecular reaction is also known[91] but much less favorable, as might be anticipated from the discussion presented earlier. The crucial difference between type IIb and type IIc reactions appears to be that, in the former, the conformational rigidity of the trienylpalladium intermediates does not readily allow the coplanar four-centered arrangement of the C−Pd bond and the exomethylene group for 5-exo carbopalladation, whereas this restriction is absent in the latter.

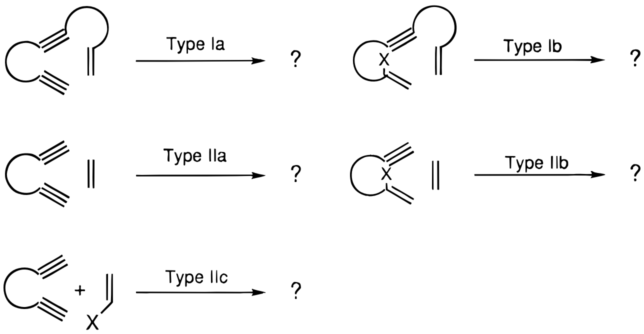
Replacement of one alkynyl group with an alkenyl group in the reactions shown in Scheme 60 introduces some additional complications. In fact, the first documented attempt at developing totally intramolecular circular carbopalladation cascades[22] that do not involve homooligomerization yielded an unexpected product containing a cyclopropane ring (Scheme 9). Closely related to this reaction is the transformation shown in Scheme 66.[92] As discussed earlier, cyclopropanation can also lead to "apparent" endo-mode carbopalladation[9] (Scheme 8).

Analogous to the transformations shown in Scheme 60, the corresponding cases may be defined as type I and type II processes according to the substrate types specified in Scheme 67.

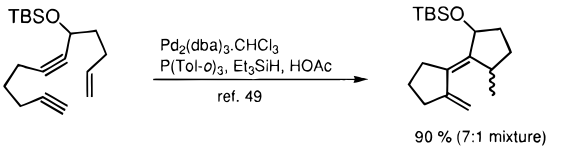
Scheme 66



Scheme 67



a. Cyclization of Enediynes (Type Ia) and Halodienynes (Type Ib). Cyclization of enediynes was originally performed using Et_3SiH (up to 10-fold) and HOAc as hydrogen sources in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and P(Tol-*o*)$_3$.[49] Under these conditions, a dumbbell-mode bicyclization reaction shown in eq 7 was observed.

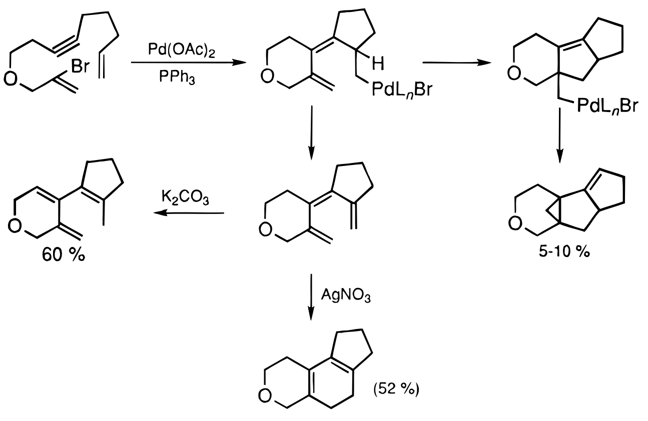


(7)

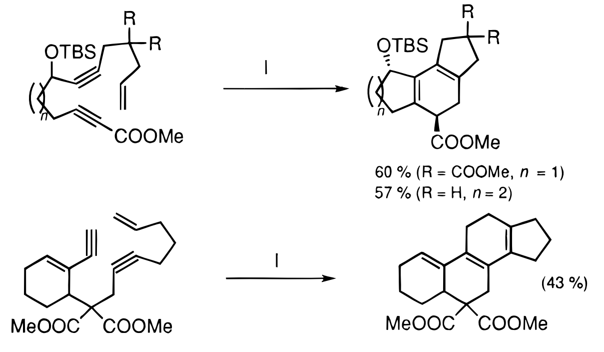
Under nonreducing conditions at least four different processes have been observed. In cases where alkylpalladium intermediates formed via two successive carbopalladation processes contain a *β-cis* hydrogen, dehydropalladation to give conjugated trienes is usually the predominant path.[93,94] The trienes thus formed can undergo cyclization to produce cyclohexadienes.[93,94] Under certain conditions, however, the initially formed trienes undergo double double-bond migration to give a cross-conjugated triene.[93a] This does not appear to be a serious side reaction in the reaction of enediynes. In the reaction of halodienynes the use of silver salt, *e.g.*, $AgNO_3$, effectively blocks this double-bond migration. Several additional cyclohexadienes have been prepared under these conditions.[93] The initial dumbbell-mode bicyclization products can also undergo exo-mode carbopalladation to give a "living" alkylpalladium species that can undergo cyclopropanation and dehydropalladation (Scheme 68).[93] Additional examples of the synthesis of cyclohexadienes by type Ia reaction are shown in Scheme 69.[94]

When the terminal vinyl group of enediynes is replaced with a geminally disubstituted alkenyl

Scheme 68



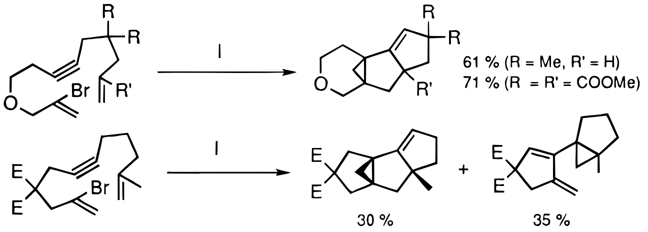
Scheme 69



I = $Pd_2(dba)_3 \cdot CHCl_3$, PPh_3, HOAc

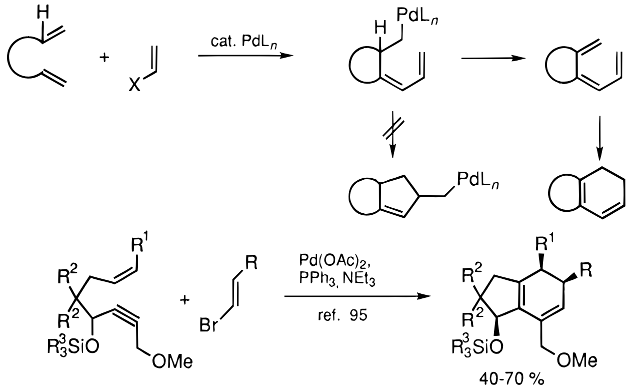
group, the dumbbell-mode bicyclization process produces "living" alkylpalladiums that may undergo cyclopropanation as in Schemes 9 and 66. A more recent study indicates that delicate competition exists between 3-exo and 5-exo processes (Scheme 70).[93a] It is noteworthy that the 5-exo cyclopentanation can be favored over dehydropalladation.

Scheme 70



E = COOEt, I = $Pd(OAc)_2$, PPh_3, Ag_2CO_3

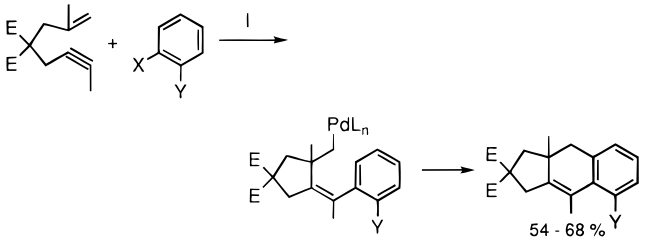
Scheme 71



R = *n*-Pent, Ph, 2-Furyl R^1 = $SiMe_3$, COOR. R^2 = H, Me. R^3_3Si = TMS or TBS.

b. Cyclization via Type II Processes. There does not appear to be any reported examples of type IIa and IIb processes. As with the reactions of diynes with monoynes discussed earlier, selective cocyclodimerization of diynes with monoenes would be a very difficult process to observe. Although more realistic, the type IIb process requires that the monoene to be used should be more reactive than the alkyne moiety. In sharp contrast with these unlikely processes, the type IIc process can be favorable and has been developed since 1992.[9,95] Here again, at least three different types of reactions have been observed depending on the substrate structure and reaction parameters as shown in Schemes 7 and 71. In each case, however, the reaction must produce a common alkylpalladium intermediate containing a conjugated diene moiety. If a β-*cis* hydrogen is available, dehydropalladation to produce conjugated hexatrienes appears to be the predominant path. If conjugated hexatrienes are sufficiently stable, they may be obtained as the final products. This reaction has been successfully applied to an efficient synthesis of vitamin Ds[27e] (Scheme 39). In cases where hexatrienes are less stable, their cyclization to give cyclohexadienes has been observed[95] (Scheme 71). If the initial cyclic carbopalladation product lacks a β-*cis* hydrogen, "apparent" endo-mode carbopalladation[9] may be observed (Scheme 7). Interesting and potentially useful variants of type II reaction involve the use of allyl acetate[9] (Scheme 7) and aryl halides[20] (Scheme 72) in place of alkenyl halides. In these cases, "living" alkylpalladium intermediates give six-membered rings rather than undergoing "apparent" endo-mode cyclization.

Scheme 72



E = COOEt, X = I or Br. Y = NO_2, CN, CF_3. I = $Pd(OAc)_2$, PPh_3, TlOAc, DMF

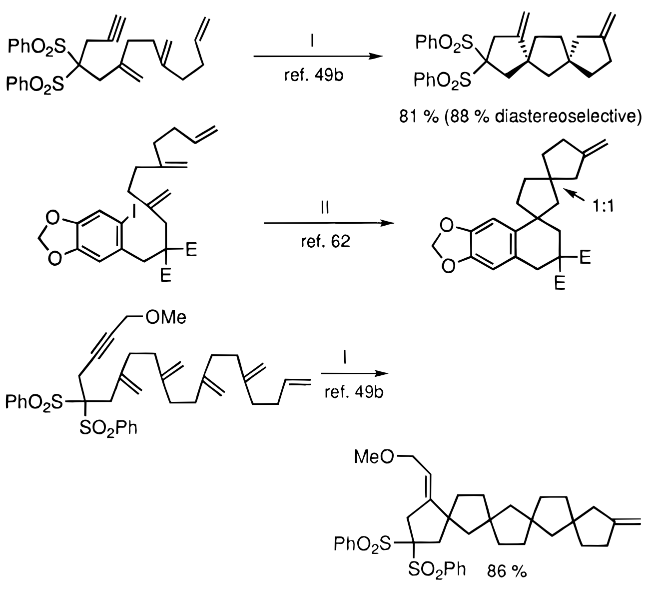
3. Cascade Carbopalladation Involving 1,1-Disubstituted Alkenes

Although the spiro-mode bicyclization process via tandem carbopalladation has been extensively developed and applied to the synthesis of some complex natural products (section III.B.1), its cascades involving the formation of three or more carbon−carbon bonds are still very rare. A few reactions shown in Scheme 73 appear to be the only known examples.[49b,62] There does not appear to be any example of the linear-fused mode carbopalladation cascades involving the formation of three or more carbon−carbon bonds.

IV. Cyclic Carbopalladation of Allenes and Conjugated Dienes

Carbopalladation of allenes[96,97] and conjugated dienes[98] produces allylpalladiums (Scheme 2), while

Scheme 73



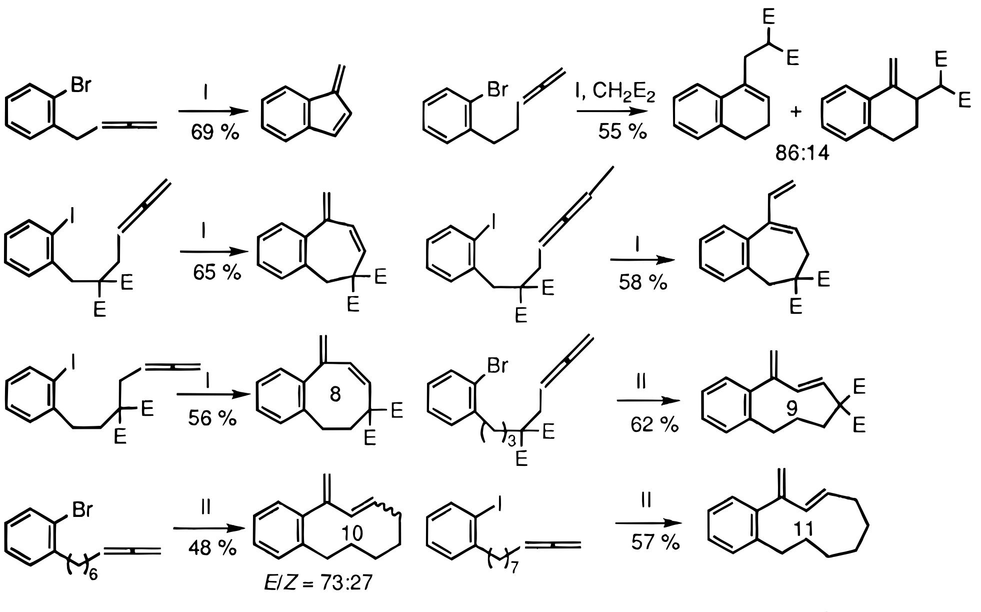
I = $Pd_2(dba)_3 \cdot CHCl_3$, PPh_3 or $SbPh_3$, HOAc. II = $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN.

that of arenes[65,66] presumably gives cyclohexadienylpalladium derivatives as a transient species. These allyl- and cyclopentadienylpalladiums can undergo dehydropalladation to provide conjugated dienes and arenes, respectively. Such reactions involving the carbopalladation−dehydropalladation sequence may therefore be viewed as variants of the Heck reaction. It should be noted, however, that allylpalladiums, in general, are considerably more stable than their simple alkyl analogues. Consequently, they either can participate in further organometallic interconversion processes involving carbopalladation and/or CO insertion or can be trapped by various nucleophiles and other reagents discussed earlier. In short, they share the “living” characteristics with alkenylpalladiums and alkylpalladiums lacking *β-cis* hydrogens.

A. Cyclic Carbopalladation of Allenes

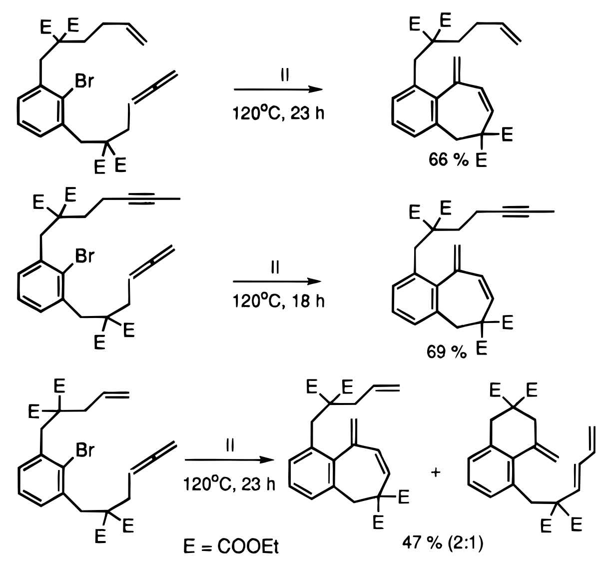
The intermolecular carbopalladation reaction of allenes has been extensively studied by Cazes and Goré[96,97a,b] as well as by Larock[98] since 1984. Once allylpalladiums are generated, the subsequent steps are the same as those observed with organopalladiums derived from allylic electrophiles via oxidative addition.[5] Some of these works reported cyclic processes involving carbopalladation of allenes,[97,98] but those dealing with cyclic carbopalladation of allenes and their unique features have been developed only within the past couple of years.[26,99] Some representative examples are shown in Scheme 74,[26] and the following features are noteworthy. First, the cyclic carbopalladation reaction of allenes is applicable to the synthesis of cyclic compounds of almost any ring size with the probable exception of three- and four-membered rings. It is particularly noteworthy that the reaction represents a relatively small number of cyclization reactions capable of producing medium (eight- through twelve-membered) rings in respectable yields. The enhanced reactivity of allenes due to their high strain energies and the structural rigidity of allenes must be largely responsible for the favorable results. The relative reactivities of allenes, alkenes, and alkynes are indicated in the results shown in Scheme 75.[26] It should be recalled that the Heck reaction involving alkenes is not generally applicable to the synthesis of medium rings (section II.A). Some additional results of comparison between allenes and alkenes are shown in Scheme 76.[26] Second, in accord with the results observed in the intermolecular carbopalladation of allenes, the carbon−carbon bond formation takes place exclusively and uniformly at the central carbon of allenes. On the other hand, the regiochemistry of cyclic carbopalladation of alkenes is a function of various factors, of which ring size is the most significant. Third, as expected, allylpalladium intermediates can be either

Scheme 74



I = 5 % $PdCl_2(PPh_3)_2$, K_2CO_3 (5 equiv), EtOH (10 equiv), DMF. E = COOEt
II = 5 % $PdCl_2(PPh_3)_2$, K_2CO_3 (5 equiv), n-Bu_4NCl (1 equiv), DMF.

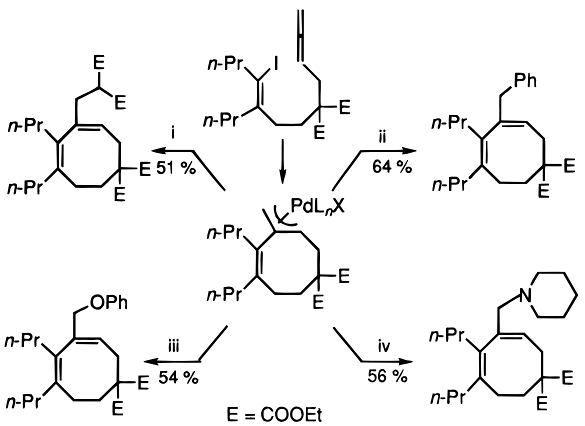
Scheme 75



II = 5 % $PdCl_2(PPh_3)_2$, K_2CO_3 (5 equiv), n-Bu_4NCl (1 equiv), DMF.

converted to conjugated dienes via dehydropalladation or trapped by various nucleophilic reagents (Scheme 77).[26]

Scheme 77

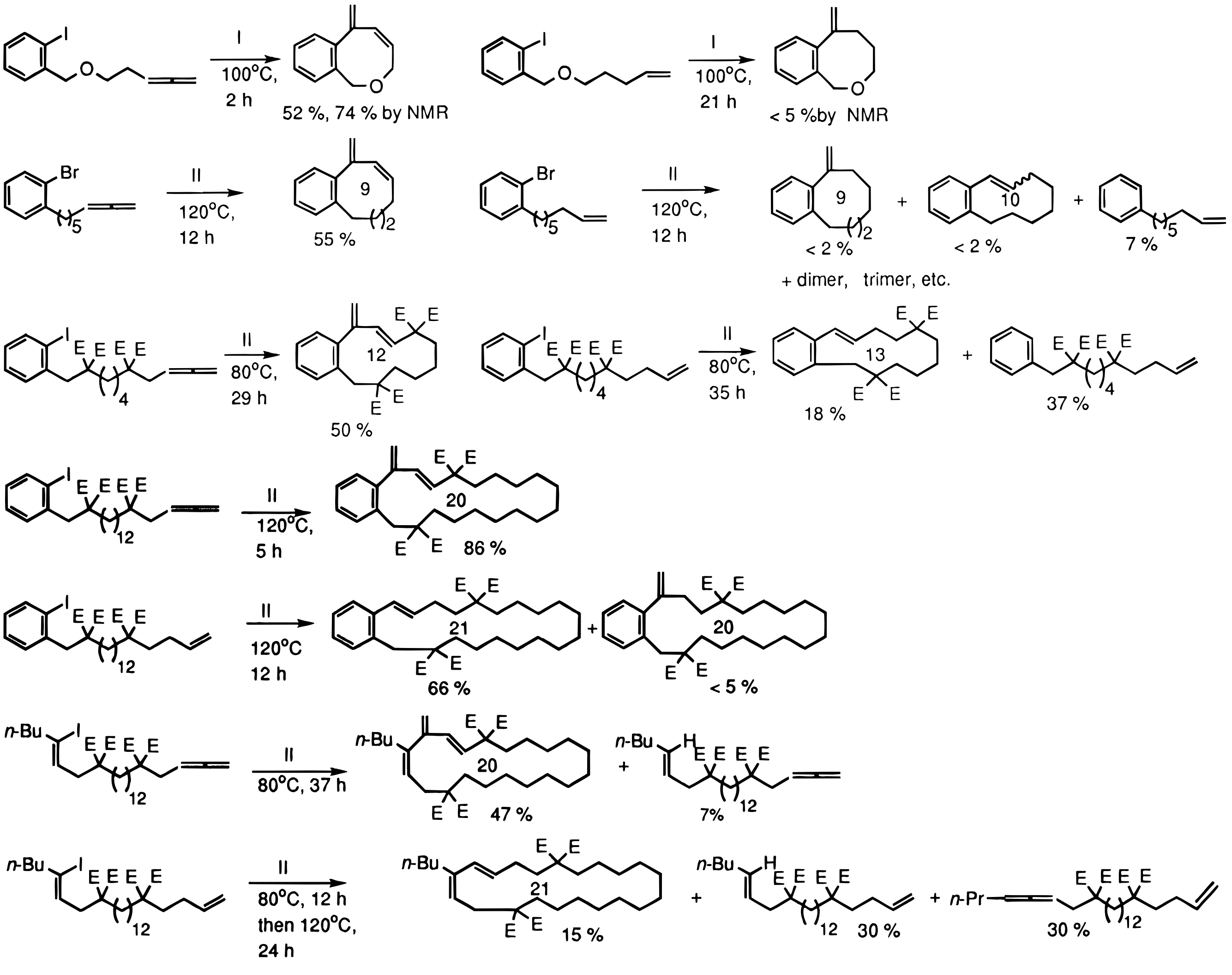


i: I, CH_2E_2 (3 equiv), 0.05 M, 120°C, 23 h
ii: II, PhSn(n-Bu)$_3$ (2.2 equiv), 0.014 M, 120°C, 11 h
iii: II, PhOH (5 equiv), 0.013 M, 80°C, 24 h, 120°C, 7 h
iv: II, piperidine (2 equiv), 0.014 M, 80°C, 9 h

I = 5 % $PdCl_2(PPh_3)_2$, K_2CO_3 (5 equiv), EtOH (10 equiv), DMF.
II = 5 % $PdCl_2(PPh_3)_2$, K_2CO_3 (5 equiv), n-Bu_4NCl (1equiv), DMF.

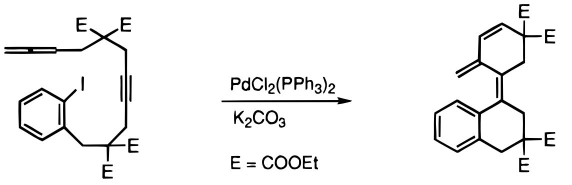
Very recently, some examples of cyclic carbopalladation cascades have been devised as exemplified by the results shown in Scheme 78.[100]

Scheme 76



I = 5 % $Cl_2Pd(PPh_3)_2$, K_2CO_3 (5 equiv) and EtOH (10 equiv), DMF. E = COOEt
II = 5 % $Cl_2Pd(PPh_3)_2$, K_2CO_3 (5 equiv) and n-Bu_4NCl (1 equiv), DMF

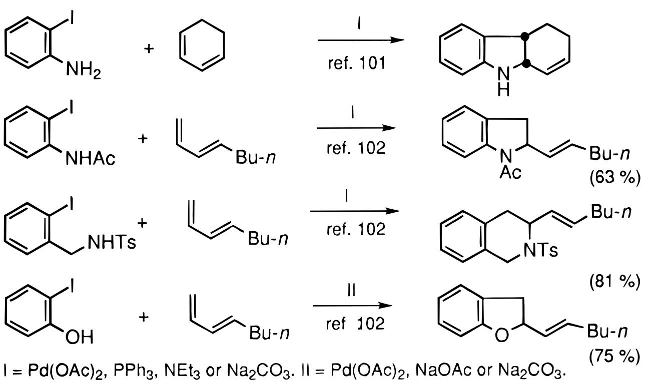
Scheme 78



B. Cyclic Carbopalladation of Conjugated Dienes

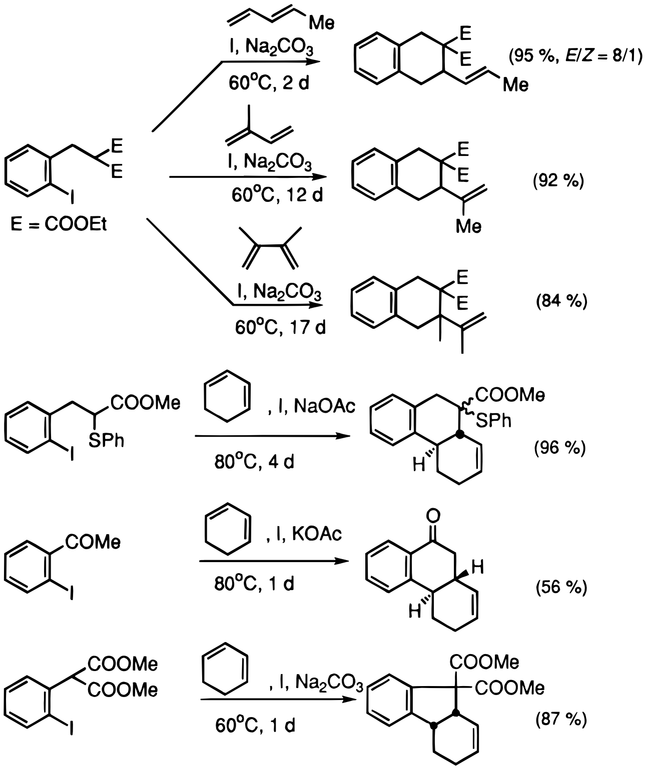
Carbopalladation of conjugated dienes produces allylpalladiums via carbon–carbon bond formation at one of the two terminal carbon atoms (Scheme 2). As in the case of carbopalladation of allenes, the resultant allylpalladiums can then undergo various reactions, such as dehydropalladation and substitution with nucleophiles. Tandem processes consisting of intermolecular carbopalladation of dienes followed by trapping with a nucleophile have been recently developed to provide efficient routes to both heterocycles[101,102] (Scheme 79) and carbocycles[103] (Scheme 80).

Scheme 79



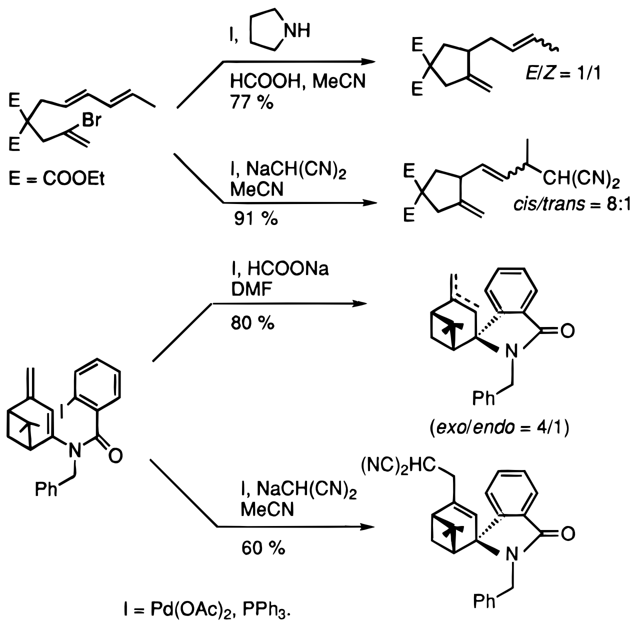
I = Pd(OAc)$_2$, PPh$_3$, NEt$_3$ or Na$_2$CO$_3$. II = Pd(OAc)$_2$, NaOAc or Na$_2$CO$_3$.

Scheme 80



I = Pd(OAc)$_2$, PPh$_3$ or P(OPh)$_3$, *n*-Bu$_4$NCl, DMF.

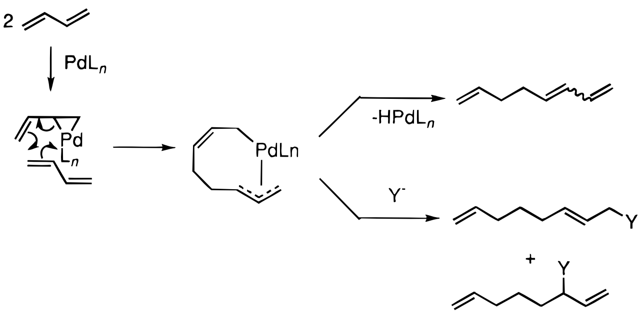
Scheme 81



Tandem cyclization processes consisting of intramolecular carbopalladation of conjugated dienes followed by trapping with hydride donors[74b] as well as C and N nucleophiles,[104] such as malonates and amines, have also been recently reported (Scheme 81). There does not appear to be any reported example of cyclic carbopalladation cascades, in which two or more carbopalladation reactions, including that of conjugated dienes, take place in succession.

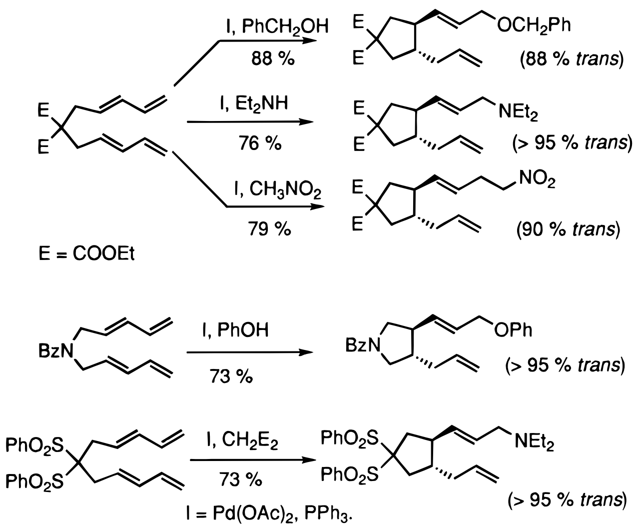
Oxidative coupling of Pd(0) complexes with conjugated dienes generates organopalladiums that can be viewed as allylpalladium derivatives.[4,5] Such species may be expected to undergo the palladium-ene reaction (section II.B) to produce bis(allyl)palladium derivatives that can be spectroscopically and crystallographically characterized.[105] Dehydropalladation of bis(allyl)palladium derivatives gives the corresponding trienes, and their trapping with nucleophiles produces allylic substitution products[106–108] (Scheme 82). Similar trimerization and oligomerization reactions have also been observed. These so-called telomerization reactions of conjugated dienes have proved to be useful for the synthesis of not only acyclic but also a wide variety of cyclic compounds.[108]

Scheme 82

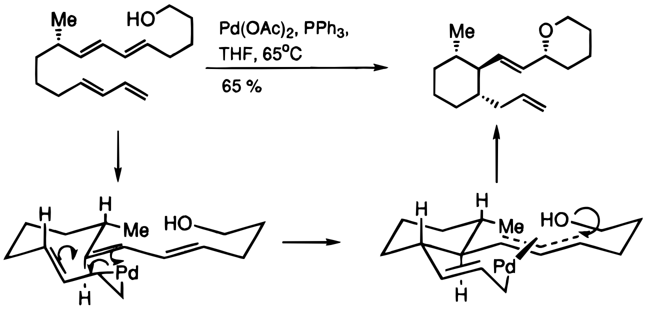


The intramolecular version of these reactions have been recently investigated mainly by Takacs.[109] Some representative results are shown in Scheme 83. It is noteworthy that this reaction is often >90–95% stereoselective producing predominantly the *trans*-

Scheme 83



Scheme 84



1,2-substituted five-membered rings. The stereochemistry of the internal alkene moiety is presumably *E*.

In a more recent study,[110] further stereochemical details of the reaction were examined. Some notable results are summarized in Scheme 84. In the first example, the relative stereochemistry of the Me and alkenyl substituents is readily explained in terms of a pseudo-chair transition state placing all substitutents in the equatorial position, and the relative stereochemistry of the O-bearing C center is that which corresponds to net *anti* 1,4-addition to conjugated dienes.

V. Conclusions

Carbopalladation of alkenes, alkynes, allenes, conjugated dienes, and other related π-compounds provides a general, versatile, stereoselective, and chemoselective methodology for carbon−carbon bond formation. In particular, the Heck reaction involving alkenes has been extensively developed and widely used in organic synthesis. Its cyclic version provides attractive routes to common and large rings, and it has recently been applied to the synthesis of natural products and other complex organic compounds. Undoubtedly, many additional applications must be forthcoming. In this connection, further development of both diastereoselective and enantioselective procedures appears to be highly desirable.

Since the late 1980s the cyclic carbometalation reaction of alkynes and 1,1-disubstituted alkenes has been extensively investigated by various groups, especially those led by Grigg, Negishi, Overman, and Trost. Several noteworthy features distinct from those of the Heck reaction have been found and exploited. Cyclic carbopalladation of these π-compounds produces organopalladiums that are thermally stable, *i.e.*, "living", due to the absence of hydrogens that can be β-*cis* to Pd. The "living" nature of these reactions can be exploited in developing tandem and cascade processes involving one or more carbopalladation steps. At the same time, however, the very "living" characteristics of these reactions requires that they must be combined with some suitable termination steps. Various termination processes including the Heck reaction itself and trapping with nucleophilic reagents, such as hydrides, C- and O-enolates, organometals, amines, alcohols, and phenols, have been devised. The use of CO in these reactions further broadens the synthetic scope of the cyclic carbopalladation methodology. Migratory insertion of CO not only provides an additional means of expanding the scope of organopalladium interconversion processes but also significantly increases the number of options for devising termination steps. In contrast with the simple cyclic Heck reaction which permits, in general, formation of only one carbon−carbon bond, its alkyne and 1,1-disubstituted alkene counterparts are intrinsically much more complex, and much additional developmental work is needed before its widespread use in the synthesis of complex organic compounds. Even so, a limited number of noteworthy applications including enantioselective transformations have already been reported. Even less well investigated are the cyclic carbopalladation reactions of allenes and conjugated dienes. These reactions share some common features with both the Heck reaction and the "living" carbopalladation reactions. Investigation of these reactions with the goal of developing versatile and attractive cyclization methodology is still in its infancy. Even so, the cyclic carbopalladation reaction of allenes, for example, has already proved to be one of the limited number of cyclization reactions readily applicable to the synthesis of common, medium, and large rings in respectable yields.

As has already been demonstrated in a limited number of cases, the "living" carbopalladation processes will permit their combinations leading to a plethora of synthetic possibilities to be explored, and many research efforts along this line will undoubtedly be forthcoming. It appears safe to predict at this time that the carbopalladation-based cyclization methodology as a whole will prove to be one of the most general, versatile, and selective. Above all, its many unique characteristics will permit the development of a methodology that is complementary with the existing classical ones.

VI. Acknowledgments

We are deeply indebted to our co-workers whose names appear in our papers cited herein, especially Drs. J. M. Tour, Y. Zhang, B. O'Connor, G. Wu, F. Lamaty, Z. Owczarczyk, and T. Sugihara. Our work in this area has been mainly supported by NIH (GM 36792). A loan of Pd compounds from Johnson-Matthey is also acknowledged.

VII. References

(1) For a review, see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, 1987.

(2) For some recent reviews, see: (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985. (b) Hegedus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994.

(3) For reviews, see: (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.

(4) For reviews, see: (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4. (d) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (e) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(5) (a) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144. (b) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (c) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (d) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(6) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93.

(7) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

(8) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. See also: Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(9) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. See also: Terakado, M.; Miyazawa, M.; Yamamoto, K. *Synlett* **1994**, 134.

(10) (a) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1977**, 1037; **1979**, 1133; **1982**, *23*, 3894. (b) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952. (c) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281. (d) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (e) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938. (f) Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035. (g) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927.

(11) (a) Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792. (b) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894.

(12) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073.

(13) Negishi, E.; Tour, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 8289.

(14) (a) Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (b) O'Connor, B.; Zhang, Y.; Negishi, E.; Luo, F. T.; Cheng, J. W. *Tetrahedron Lett.* **1988**, *29*, 3903. (c) Zhang, Y.; O'Connor, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5588. (d) Negishi, E.; Nguyen, T.; O'Connor, B.; Evans, J. M.; Silveira, A., Jr. *Heterocycles* **1989**, *28*, 55.

(15) Larock, R. C.; Song, B. E.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.

(16) (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003. (c) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687. (d) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thornton-Pett, M.; Worakun, T. *Tetrahedron* **1991**, *47*, 9703.

(17) (a) Abelman, M. R.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133. (b) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859.

(18) (a) Jin, Z.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 5205. (b) Lee, S. W.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 5209.

(19) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19.

(20) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157.

(21) (a) Catellani, M.; Chiusoli, G. P.; Ciroldini, W.; Salerno, G. *J. Organomet. Chem.* **1980**, *199*, C21. (b) For a review, see: Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1983**, *250*, 509.

(22) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. See also 196th American Chemical Society Meeting, Los Angeles, CA, September 25−30, 1988; ORGN 264.

(23) (a) Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855. (b) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1992**, *33*, 7965.

(24) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

(25) (a) Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253. (b) Young, W. B.; Masters, J. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5228.

(26) Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345.

(27) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) For a review, see: Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (c) Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1502. (d) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586. (e) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836. (f) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924.

(28) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507.

(29) (a) Oppolzer, W. *Pure Appl. Chem.* **1988**, 60, 39. (b) Oppolzer, W. *Angew. Chem., Ind. Ed. Engl.* **1989**, *28*, 38. (c) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. (d) Oppolzer, W.; Gaudin, J. M. *Helv. Chim. Acta* **1987**, *70*, 1477. (e) Oppolzer, W.; Gaudin, J. M.; Birkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705. (f) Oppolzer, W.; Swenson, R. E.; Gaudin, J. M. *Tetrahedron Lett.* **1988**, *29*, 5529. (g) Oppolzer, W.; Swenson, R. E.; Pachinger, W. *Helv. Chim. Acta* **1989**, *72*, 14. (h) Oppolzer, W.; Birkinshaw, T. N.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 6995. (i) Oppolzer, W.; DeVita, R. J. *J. Org. Chem.* **1991**, *56*, 6256. (j) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266.

(30) Negishi, E.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 291.

(31) (a) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. (b) Negishi, E.; Tour, J. M. *Tetrahedron Lett.* **1986**, *27*, 4869. (c) Negishi, E.; Sawada, H.; Tour, J. M.; Wei, Y. *J. Org. Chem.* **1988**, *53*, 913. (d) Negishi, E.; Wu, G.; Tour, J. M. *Tetrahedron Lett.* **1988**, *29*, 6745. (e) Wu, G.; Shimoyama, I.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 6506. (f) Negishi, E.; Copéret, C.; Sugihara, T.; Shimoyama, I.; Zhang, Y.; Wu, G.; Tour, J. M. *Tetrahedron* **1994**, *50*, 425. (g) Copéret, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422.

(32) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.

(33) (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695. (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030.

(34) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

(35) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525.

(36) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694.

(37) (a) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (b) Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453.

(38) Grigg, R.; Santhakumar, V.; Sridharan, V.; Thronton-Pett, M.; Bridge, A. W. *Tetrahedron* **1993**, *49*, 5177.

(39) (a) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094. (b) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722.

(40) Muratake, H.; Abe, I.; Natsume, M. *Tetrahedron Lett.* **1994**, *35*, 2573.

(41) Tietze, L. F.; Grote, T. *J. Org. Chem.* **1994**, *59*, 192.

(42) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.

(43) (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953. (c) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093. (d) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (e) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593. (f) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4219. (g) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965. (h) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477. (i) Kagechika, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **1993**, *49*, 1773.

(44) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

(45) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267. (c) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485. (d) Ozawa, F.; Kubo, A.; Hayashi, *Chem. Lett.* **1992**, 2177. (e) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505. (f) For a review, see: Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421.

(46) (a) Lu, X.; Ma, S.; Ji, J.; Zhu, G.; Jiang, H. *Pure Appl. Chem.* **1994**, *66*, 1501. (b) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 733. (c) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (d) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (e) Lu, X.; Zhu, G. *Synlett* **1993**, 68. (f) Ma, S.; Zhu, G.; Lu, X. *J. Org. Chem.* **1993**, *58*, 3692. (g) Ma, S.; Lu, X. *J. Organomet. Chem.* **1993**, *447*, 305. (h) Zhu, G.; Ma, S.; Lu, X. *J. Chem. Res.* **1993**, 366. (i) Ji, J.; Lu, X. *Tetrahedron* **1994**, *50*, 9067. (j) Zhu, G.; Ma, S.; Lu, X.; Huang, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 271. (k) Zhu, G.; Lu, X. *Tetrahedron: Asymmetry* **1995**, *6*, 345. (l) Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087. (m) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160. (n) Ji, J.; Lu, X. *Synlett* **1993**, 745.

(47) Trost, B. M.; Tanoury, G. *J. Am. Chem. Soc.* **1988**, *110*, 1636.

(48) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.

(49) (a) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701.

(50) Negishi, E. *Pure Appl. Chem.* **1992**, *74*, 323.

(51) Negishi, E.; Copéret, C.; Ma, S.; Mita, T.; Amanfu, J. Manuscript in preparation.

(52) (a) Negishi, E.; Copéret, C.; Ma, S.; Mita, T.; Sugihara, T.; Tour, J. M. Submitted for publication. (b) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. Submitted for publication.
(53) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923.
(54) Copéret, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.* **1995**, *36*, 1771.
(55) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491.
(56) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
(57) (a) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471. (b) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298.
(58) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
(59) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
(60) Tsuji, J.; Kiji, J.; Morikawa, M. *Tetrahedron Lett.* **1963**, 1811.
(61) Shimoyama, I.; Zhang, Y.; Wu, G.; Negishi, E. *Tetrahedron Lett.* **1990**, *31*, 2841.
(62) Overman, L. E. *Pure Appl. Chem.* **1992**, *64*, 1813.
(63) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135.
(64) (a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. (b) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.
(65) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1982**, *239*, C35.
(66) (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Reiser, O.; Weber, M.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1037. (c) Albrecht, K.; Reiser, O.; Weber, M.; Knieriem, B.; de Meijere, A. *Tetrahedron* **1994**, *50*, 383.
(67) Grigg, R.; Kennewell, P.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 153.
(68) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (Note: The structure numbers **2** and **3** in Scheme I should be reversed.)
(69) (a) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 5565. (b) Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 6573.
(70) Wang, R.-T.; Chou, F. L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846.
(71) (a) Nuss, J. M.; Levine, B. H.; Rennels, R. A.; Heravi, M. M. *Tetrahedron Lett.* **1991**, *32*, 5243. (b) Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991.
(72) Torii, S.; Okumoto, H.; Tadokoro, T.; Nishimura, A.; Rashid, A. *Tetrahedron Lett.* **1993**, *34*, 2139.
(73) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403.
(74) (a) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325. (b) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4329.
(75) (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (c) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.
(76) Yamamoto, K.; Terakado, M.; Murai, K.; Miyazawa, M.; Tsuji, J.; Takahashi, K.; Mikami, K. *Chem. Lett.* **1989**, 955.
(77) Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883.
(78) Grigg, R.; Kennewell, P.; Teasdale, A. J. *Tetrahedron Lett.* **1992**, *33*, 7789.
(79) Brown, A.; Grigg, R.; Ravishankar, T.; Thornton-Pett, M. *Tetrahedron Lett.* **1994**, *35*, 2753.
(80) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429.
(81) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 7471.
(82) Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018.
(83) For reviews, see: (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.
(84) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590.
(85) For an extensive review of the Co-catalyzed [2 + 2 + 2] cyclization methodology, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.
(86) Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777.
(87) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253.
(88) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471.
(89) Parsons, P. J.; Stefinovic, M.; Willis, P.; Meyer, F. *Synlett* **1992**, 864.
(90) Torii, S.; Okumoto, H.; Nishimura, A. *Tetrahedron Lett.* **1991**, 4167.
(91) (a) Lee, G. C. M.; Tobias, B.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Am. Chem. Soc.* **1990**, *112*, 9330. (b) Silverberg, L. J.; Wu, G.; Rheingold, A. L.; Heck, R. F. *J. Organomet. Chem.* **1991**, *409*, 411.
(92) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343.
(93) (a) Meyer, F. E.; Parsons, P. J.; de Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487. (b) Meyer, F. E.; Brandenburg, J.; Parson, P. J.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1992**, 390. (c) Meyer, F. E.; Henniges, H.; de Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039.
(94) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791.
(95) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923.
(96) (a) Ahmar, M.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1984**, *25*, 4505. (b) For a review, see: Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867.
(97) (a) Ahmar, M.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1985**, *26*, 3795; *Tetrahedron* **1987**, *43*, 3453. (b) Besson, L.; Bazin, J.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1994**, *35*, 2881.
(98) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.
(99) Ma, S.; Negishi, E. *J. Org. Chem.* **1994**, *59*, 4730.
(100) Ma, S.; Negishi, E. Unpublished results.
(101) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807.
(102) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3450.
(103) Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882.
(104) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 1139.
(105) Jolly, P. W.; Mynott, R.; Raspel, B.; Schick, K. P. *Organometallics* **1986**, *5*, 473.
(106) Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793.
(107) Takahashi, I.; Shibano, T.; Hagihara, N. *Tetrahedron Lett.* **1967**, 2451.
(108) Tsuji, J. *Pure Appl. Chem.* **1981**, *53*, 2371.
(109) (a) Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989**, *54*, 5193. (b) Takacs, J. M.; Zhu, J. *Tetrahedron Lett.* **1990**, *31*, 1117. (c) Takacs, J. M.; Zhu, J.; Chandramouli, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 773.
(110) Takacs, J. M.; Chandramouli, S. V. *J. Org. Chem.* **1993**, *58*, 7315.

CR950020X