The Behavior of 1,*n*-Enynes in the Presence of Transition Metals

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1. Introduction

Since synthetic strategies to highly functionalized polycyclic compounds have become directed increasingly toward both efficiency and stereoselectivity, transition-metal-mediated cyclizations have grown at an exponential rate. Transition-metal catalysis is used to perform, in a selective manner, carbon−carbon bond-forming reactions that would be much more difficult, even impossible, with conventional organic reagents alone. In addition, in some favorable cases, the metal catalysts allow the formation of several bonds in a single step.

Typical examples are the cycloaddition reactions of unactivated olefins, dienes, and acetylenes which require extreme conditions or special methods to allow the formation of the cycloadducts in good yields. Indeed, transition-metal-induced cycloisomerizations of 1,*n*-enynes or 1,*n*-dienes and 1,*n*-diynes have emerged as extremely attractive and unique tools for the synthesis of various type of cyclic compounds in a very easy one-pot process. Thus, the rate accelerations provided by catalysis expand the scope of reactions such as the Alder ene reactions[1] that normally required harsh conditions.[2−5] On the other hand, these cyclizations which generate 1,3- or 1,4-dienes provide clean chemical processes without any wasteful byproducts. Cyclization of 1,*n*-enynes have been achieved with a wide range of transition-metal complexes either in a catalytic or in a stoichiometric

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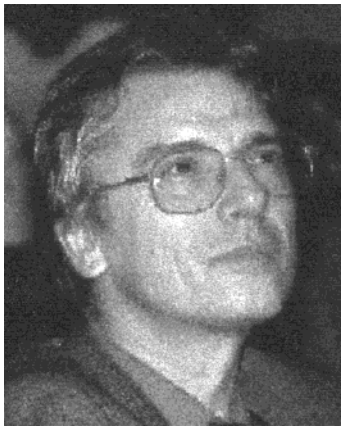
Corinne Aubert is a native of Les Ardennes, North of France. After having studied chemistry at the University of Champagne-Ardennes, Reims, she attended the Ecole Nationale Supérieure de Chimie de Strasbourg. She received her Ph.D. degree in 1985 at the University of Paris-Sud, Orsay, under the direction of Dr. J.-F. Biellmann and Dr. J.-P. Bégué. She was appointed by the CNRS in 1985 as Chargée de Recherches in the laboratory of Dr. J.-P. Bégué and worked on fluorine chemistry. After doing postdoctoral research with Professor K. P. C. Vollhardt at the University of California, Berkeley, from September 1987 to 1989, she joined the group of Professor Max Malacria at the University Pierre & Marie Curie (Paris VI). In 2001, she was appointed Directeur de Recherches. Her research interests concern the new developments of transition-metal-mediated reactions, the efficient approaches of basic skeletons of polycyclic natural compounds, and asymmetric synthesis.

Olivier Buisine was born in Paris in 1972. He joined Max Malacria's group at the Université Pierre & Marie Curie in 1994, where he worked on the Co(I)-mediated cycloisomerizations and its application in asymmetric synthesis. He received his Ph.D. degree in 1999, and then he moved to Istvan E. Marko's group at the Université Catholique de Louvain in Louvain-la-Neuve (Belgium). He worked on platinum–carbene-catalyzed hydrosilylations in order to form silicon oils. Currently, he is Reasearch Scientist in the Research Center of Lyon of Rhodia's company based in St-Fons (France). His research interests are asymmetric synthesis and organometallic catalysis.



Max Malacria was born in Marseille in 1949. He received his Ph.D. degree in 1974 at the University of Aix-Marseille III under the supervision of Professor Marcel Bertrand. From September 1974 to August 1981, he served as an Assistant and Maître Assistant at the University of Lyon I and worked under the supervision of Professor Jacques Goré. From September 1981 to December 1982, he worked as a postdoctoral fellow with Professor K. Peter C. Vollhardt at the University of California, Berkeley. In 1983, he returned at the University of Lyon I as a Maître de Conférences. In 1988, he was appointed Full Professor at the University Pierre & Marie Curie (Paris VI). In 1991, he was elected as a member of the "Institut Universitaire" de France. His current research interests include the development of new selective and efficient approaches to complex polycyclic molecules, transition-metal-catalyzed reactions, radical cyclizations, and asymmetric synthesis of natural compounds of biological interests. In 1997, he received the award of the Organic Division of the French Chemical Society, in 2000 the prize Grammaticakis Neumann from the French Academy of Sciences, and in 2001 the "Médaille d'Argent" from the CNRS. Since September 2001, he has been Editor of the *European Journal of Organic Chemistry*.

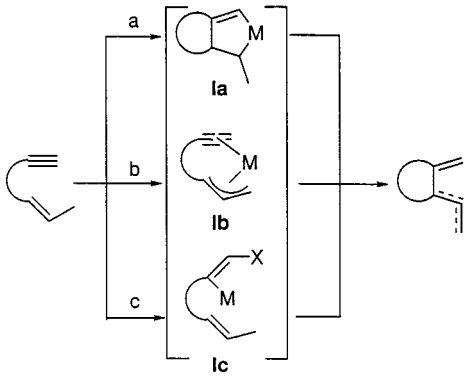
manner and represent a versatile approach to a variety of products by a simple manipulation of the catalyst. Excellent reviews which have compiled differents aspects of the advances in these cyclizations have been published.[6−11]

Considering the mechanistic rationales of the transition-metal-catalyzed cycloisomerization of enynes, different pathways can be considered depending on the reaction conditions and on the choice of the precatalyst. Generally, the complexation of the metal to an alkene or alkyne allows the activation of either both moieties or only one of them. Depending on the unsaturation which will react first, three main mechanisms can be proposed (Scheme 1).

The simultaneous complexation of both unsaturations (path a) led preferentially to the metallacycle **Ia**. Almost all the transition-metal complexes could react to generate such intermediates; however, their reactivity can be quite different. The presence of a functional group in the allylic position allows the formation of a π-allyl complex **Ib** (path b) which could further react with the triple bond. Finally, hydrometalation of the alkyne led to the corresponding vinylmetal **Ic** (path c) which is reactive enough to allow the carbometalation of the olefin.

A discussion of established transition-metal-mediated cycloisomerizations of 1,*n*-enynes is presented in this review by organizing the text on the basis of the intermediate **Ia**−**c** involved in the cyclization and

Scheme 1

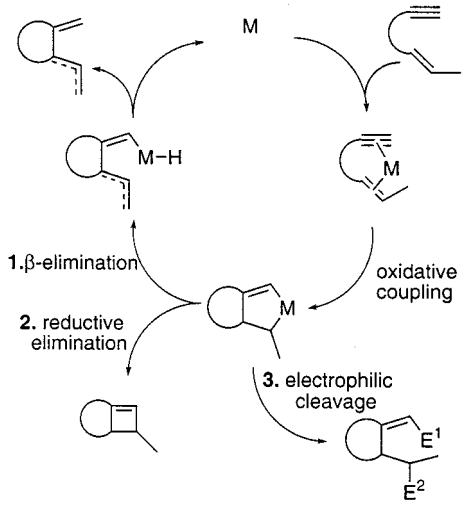


then further subdivided according to their reactivity. In each case, an illustration of representative reactions will be given; however, this article does not aim at the complete collection of all individual reactions.

2. The Metallacyclopentene Pathway

The formation of metallacyclopentenes is very general and occurs with a large variety of transition metals and unsaturated partners. The main steps of the catalytic cycle are described in Scheme 2.

Scheme 2



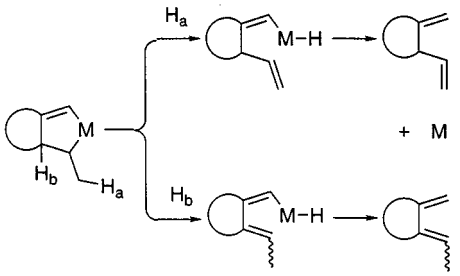
After complexation of the enyne with the metallic moiety, which has to be coordinatively unsaturated, the oxidative coupling leads to the metallacyclopentene. The latter can undergo three kinds of transformations. The first one and the most usual is the β-hydride elimination, which is the major and fastest process. It furnishes after reductive elimination either one or a mixture of 1,3- and 1,4-dienes. The second—a reductive elimination of the metallacyclopentene—occurs with the metals that are not able to give a β-elimination and leads to bicyclic systems or rearranged compounds. Finally, if an electrophile is present in the reaction mixture, the electrophilic cleavage of the carbon−metal bonds allows the functionalization of the substrate.

2.1. Metallacyclopentene/β-Elimination

The β-elimination is usually followed by the reductive elimination of the metal which leads to the cycloadduct and regenerates the active metal species. Depending on the regioselectivity of the elimination (Ha or Hb), two dienes—1,3- and/or 1,4-diene—can be obtained (Scheme 3).

The β-elimination required a vacant coordination site on the metal and a cis relationship between the carbon−metal and carbon−hydrogen bonds which have to be aligned to optimize the orbital overlap. While the C−Ha bond energy is higher than C−Hb, the alignment for the insertion into the C−Ha bond is good. On the contrary, the geometry for the β-hydrogen elimination of C−Hb bond is not ideal (the dihedral angle is different from 0°) but is compensated by a lower bond strength due to its

Scheme 3

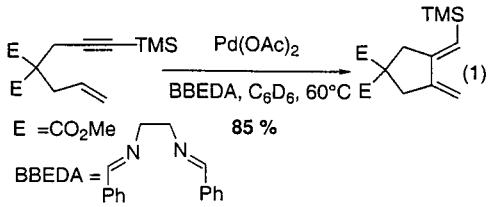


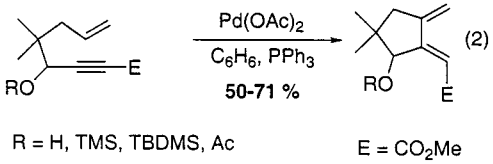
allylic nature. Four metals are more affected by such a transformation: palladium, ruthenium, cobalt, and rhodium. However, it has been reported recently that iridium[12] and an early transition metal (titanium)[13] are able to catalyze the cycloisomerizations of enynes or dienynes. For the past 15 years, the contribution of B. M. Trost's group in this field has been very important and a plethora of articles compiling the factors governing the palladium-mediated cycloisomerizations of 1,*n*-enynes[14,15] and the applications in the field of natural product synthesis have been published.[16,17]

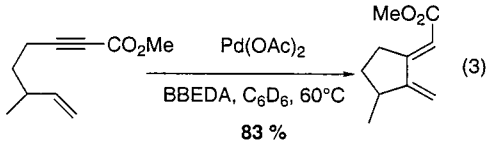
2.1.1. Metallacyclopentene/β-Elimination: Palladium Catalysts

Assuming a pallada(+4)cyclopentene intermediate,[15] Trost showed that the cyclization of 1,6-enynes led exclusively to 1,3-dienes when there is no allylic substituent bearing hydrogen. The existence of such a Pd(IV) intermediate which was questionable in early studies has been now accepted, and few palladium(IV) species have been isolated and characterized.[18−21]

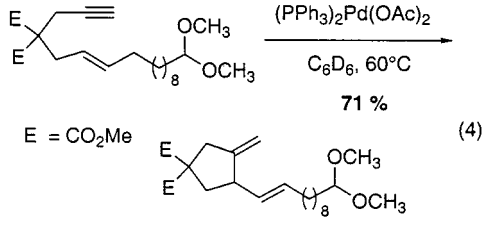
The effects of substituents on the tether between both unsaturations were briefly examined: the presence of geminal electron-withdrawing groups (eq 1) or alkyl substituents (eq 2) on the tether facilitates the cyclization by enhancing the rate of the reactions, but they are not required (eq 3).[22,23]







Steric factors influence the regioselectivity of the cyclization. Indeed, whereas an allylic methylene group furnishes the Alder ene type product—a 1,4-diene (eq 4)—branching at the allylic position completely changed the regioselectivity and gives the 1,3 diene (eq 5).[1,22]



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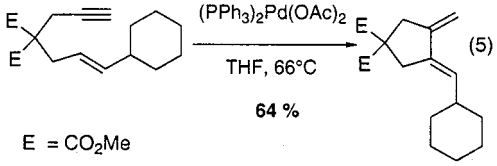
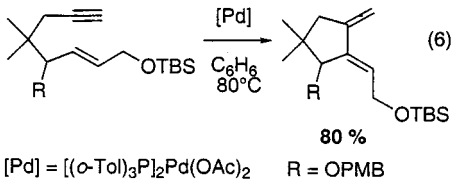
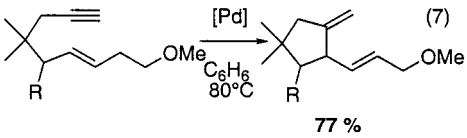


(5)

Trost found that the presence of an oxygen substitution also has a profound effect on the regioselectivity of the cyclization. Thus, an oxygenated group at the allylic position furnishes the corresponding 1,3-diene (eq 6), whereas oxygen substitution at the homoallylic position gives exclusively the 1,4-diene (eq 7).



(6)



(7)

It has been suggested that the coordination of the oxygen atom with the metal is not the regiochemical determining factor and that the source of the oxygen effect appears to be electronic. Therefore, by a simply interchanging the alkyne and alkene functions, either type of diene may be obtained (Scheme 4).[14]

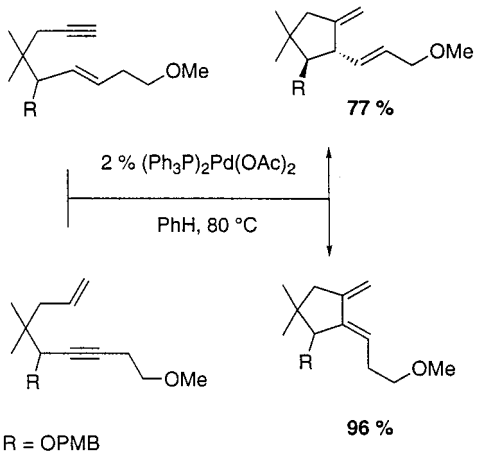
The 1,4-diene is obtained as a unique diastereomer and results from the palladacyclopentene in which the C−R and the "a" bonds are in an anti relationship since the palladadacyclopentene having nearly eclipsed C−R and "a" bonds destabilized the transition state leading to the cis product (Scheme 5).[22]

While the coordination of an oxygen substituent with the metal is apparently without effect on the regioselectivity, a remote double bond can control the regioselectivity of the cyclization.[24] By comparing the behavior of the dienyne **1** and the enyne **2**, the critical role played by the remote double bond was established (Scheme 6). A very good selectivity for the formation of the 1,3-diene **3** is observed in the presence of the remote olefin, whereas an excellent selectivity for the formation of the 1,4-diene **4** occurred in its absence. An intermediate such as **5** accommodates these observations. Due to the remote binding, the geometry for insertion into either the C−Ha or the C−Hb bond is not ideal; however, the lower C−Hb bond strength compensates for the geometrical drawback.[14,22]

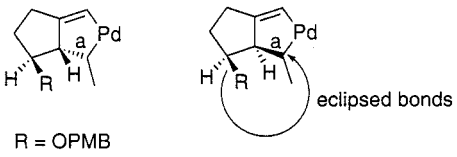
If the remote olefin is one more carbon away as in the dienyne **6**, the resulting 1,3-diene is ideally set up for an intramolecular Diels−Alder reaction. Thus, refluxing in toluene provides directly the tricyclic compound **7** in 72% yield (eq 8).

The creation of a six-membered ring is also feasible but is more limited and the reaction proved more sensitive to the reaction conditions (eq 9). The difficulty for forming cyclohexanes was ascribed to the poorer ability of 1,7-enynes to function as bidentate ligands. This problem was partially circumvented by introducing on the alkene moiety a substituent able

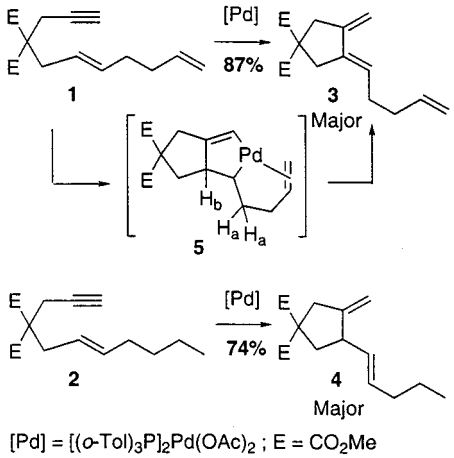
Scheme 4

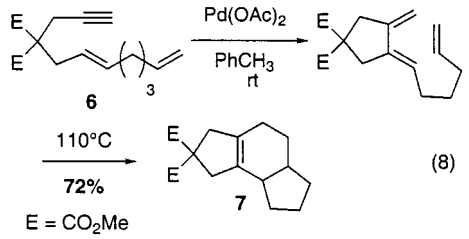


Scheme 5

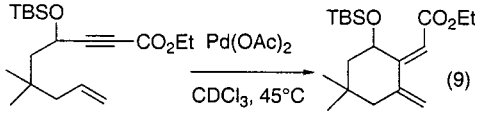


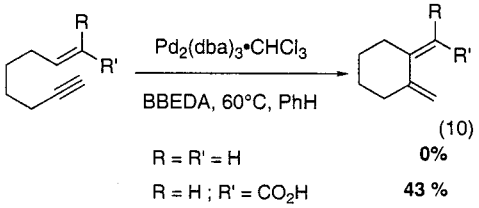
Scheme 6





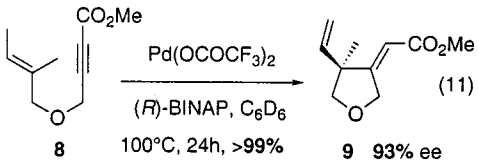
to coordinate the metal, such as a free carboxylic acid (eq 10).[25]





Later in this review we will describe that the Pd(0)−acetic acid catalyst and also the Ni−Cr system proceed somewhat better for the construction of six-membered rings.

Very recently, Mikami reported a highly enantioselective version of the cyclization of a 1,6-enyne which allows the construction of an enantioenriched quaternary chiral center.[26] Indeed, by using 5 mol % of $Pd(OCOCF_3)_2$ and 10 mol % of (*R*)-BINAP (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) in thoroughly degassed benzene at 100 °C, the cyclization of the enyne **8** provided quantitatively the cycloadduct **9** and with ee up to 93% (eq 11).

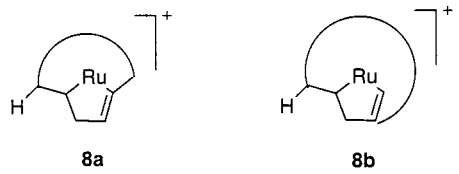


2.1.2. Metallacyclopentene/β-Elimination: Ruthenium Catalysts

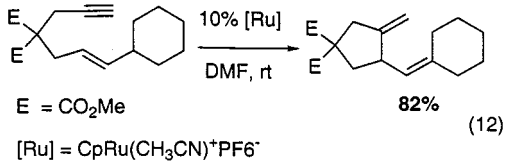
This reaction was essentially developed with unactivated alkynes and alkenes in the intermolecular version.[27] In some initial attempts to develop the intramolecular version, it was observed that CpRu(cod)Cl was able to catalyze only the cycloisomerization of 1,6-enynes having monosubstituted olefins. This requirement for the alkene substituent to be attached to ruthenium, to allow the β-elimination, demands that the postulated ruthenacyclopentene has a 1,3-bridging **8a** or **8b** (Scheme 7)—a type of bridging that cannot be accommodated by short tethers.

Very recently, Trost discovered that the use of the cationic ruthenium catalyst $CpRu(CH_3CN)_3^+PF_6^-$

Scheme 7



tolerates the participation of 1,2-di- and trisubstituted alkenes and allows the cyclizations of 1,6- and 1,7-enynes to five- and six-membered ring cycles in good yields.[28] In a number of examples, the ruthenium reaction is complementary to the Pd-catalyzed cyclization, selectively forming the 1,4-diene (eq 12) in place of the 1,3-diene (see eq 5).

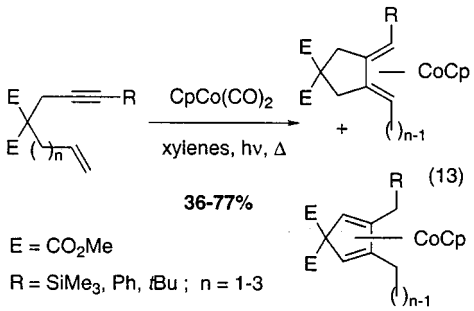


In that case, the mechanism of the cyclization is not elucidated but the authors favored a mechanism involving a ruthenacyclopentene; however, the possibility remained that the reaction proceeded via a ruthenium π-allyl generated by C−H activation (see section 3.2.2).[29]

2.1.3. Metallacyclopentene/β-Elimination: Cobalt Catalysts

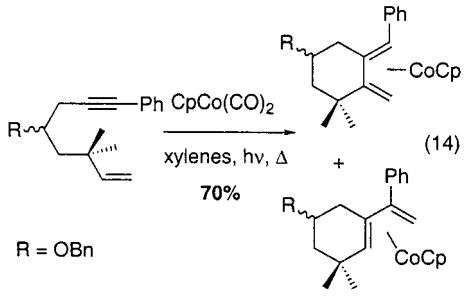
Among the number of distinct cyclizations that cobalt facilitates,[10] it has been disclosed that cobalt(I) complexes are able to catalyze a formal Alder ene reaction of unactivated allenynes in which the allene is the ene partner and the alkyne the enophile, affording six-membered carbocycles in a totally regioselective manner.[30]

Recently, it has been shown also that $CpCo(CO)_2$ induced the cyclization of 1,*n*-enynes (eq 13).[31,32]

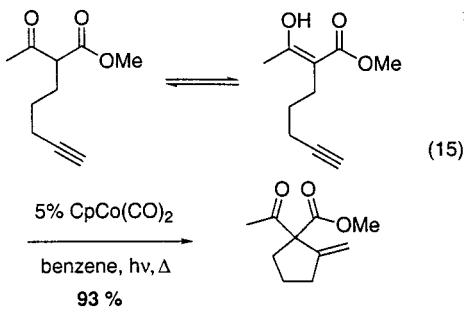


Whatever the length of the tether between both unsaturations, five-membered ring carbocycles were only obtained. The formation of these latter carbocycles involves the isomerization of the terminal double bond of the starting enyne through probably the oxidative formation of a cobalt η^3-allyl hydride via a C−H activation process. By changing the nature of the substituent of the triple bond, our laboratory reported that the isomerization of the double bond and therefore the regioselective formation of the exo- and endo-complexed cyclopentadienes is controlled by steric factors. When the allylic position of the enyne is disubstituted, six-membered ring systems are

obtained in high yields as well (eq 14), thus providing an interesting alternative to the palladium-mediated cyclizations of 1,7-enynes which require a functionalized directing group. This cobalt(I) catalysis of the Alder ene reaction presumably involves two different but complementary reactivities of the cobalt complex: the formation of π-allyl cobalt hydrides and a cobaltacyclopentene as the intermediate of the cyclization.

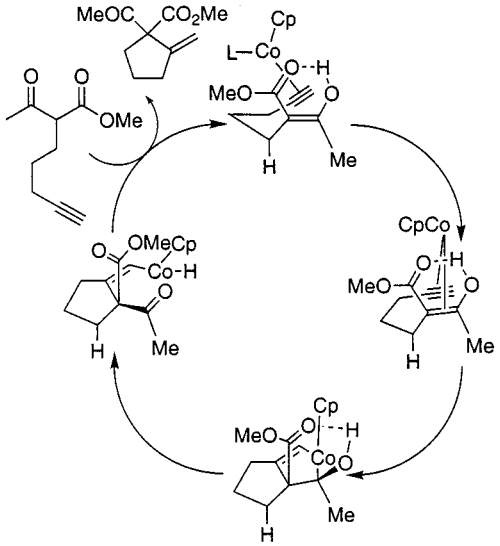


Cobalt(I) complexes such as $CpCo(CO)_2$ are also able to mediate another ene reaction: the Conia ene-type reaction of ω-acetylenic β-ketoesters leading to functionalized methylenecyclopentanes (eq 15).[33]

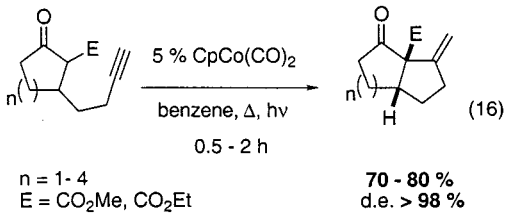


The mechanism (Scheme 8) involves the oxidative coupling between the alkyne (enophile) and the double bond of the enol form (ene) of the β-ketoester moiety to furnish the corresponding cobaltacyclopentene. The β-elimination of the enolic hydrogen followed by the reductive elimination provides the cycloadduct.

Scheme 8



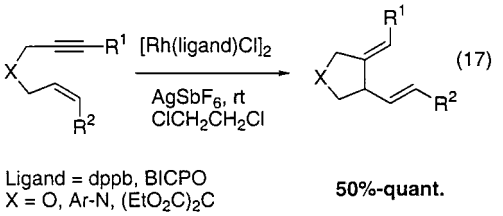
The observed regio-, chemo-, and stereoselectivities support the process of an enol−yne cycloisomerization which controls the relative stereochemistry of two contiguous stereogenic centers.[34,35] The relative stereochemistry of 1,3- and 1,4-stereogenic centers can be controlled as well with moderate to high levels of diastereoselectivity.[36,37] In the same way, this cycloisomerization provides a rapid and totally diastereoselective access to 5,5-, 5,6-, 5,7-, and 5,8-ring systems from simple starting materials (eq 16) and also to bicyclo[3.2.1]octane derivatives.[35,38]



This cobalt(I)-mediated ene-type reactions has found nice applications in the field of cascade chemistry. Thus, it is the cornerstone of the cyclization cascade that opened novel and efficient routes to the basic skeletons of tetracyclic diterpenes in the phyllocladane[39] and kaurane[36] families. The combining of this cyclization with a Pauson−Khand reaction has allowed us to propose an entry into angular triquinane.[37]

2.1.4. Metallacyclopentene/β-Elimination: Rhodium and Iridium Catalysts

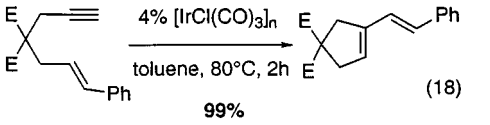
Very recently, a new highly effective and selective rhodium-catalyzed 1,6-enyne cycloisomerization has been discovered (eq 17).[40]



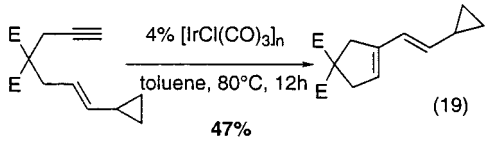
The key for this reaction is the generation of a highly coordinatively unsaturated metallic moiety to bind the enyne so that the formation of the metallacyclopentene can proceed smoothly. $[Rh(dppb)Cl]_2$ and $[Rh(BICPO)Cl]_2$ (dppb = 1,2-bis(diphenylphosphino)butane; BICPO = (2*R*,2′*R*)-bis(diphenylphosphinite)-(1*R*,1′*R*)-dicyclopentane) were selected as clean catalyst precursors; the cationic Rh catalysts were prepared in situ from the reaction of the dimer with $AgSbF_6$ in the presence of the enyne substrate. The features of this cyclization are as follows: 1,4-dienes are formed selectively in this cyclization and an easy variation of the diphosphine ligand allows the rhodium catalyst to be fine-tuned with respect to the steric and electronic requirements of the substrates. Finally, the cycloisomerization of an enyne with an allylic ester tether gives a α-methylene-γ-butyrolactone.

The first enantioselective version of the cycloisomerization has been reported as well.[41] High enantioselectivities have been observed, for example, ee up to 95% was achieved with Rh/Me-DuPhos catalyst (DuPhos = 1,2-bis(phospholano)benzene); however, this asymmetric C−C bond-forming reaction is highly substrate dependent.

This year, Murai disclosed that the iridium complex $[IrCl(CO)_3]_n$ catalyzes the cycloisomerization of 1,6-enynes providing the corresponding 1,3-dienes in good yields (eqs 18 and 19).[12] The reaction patterns depend on the structure of the substrates; in particular, the substitution of an alkyl or aryl group at the olefinic part accelerated the reaction and increased the yield. When the alkene is a vinylcyclopropane, no [5+2] cycloaddition occurs (see section 2.3.5.i) and the 1,3-diene is obtained with the cyclopropane ring being intact.

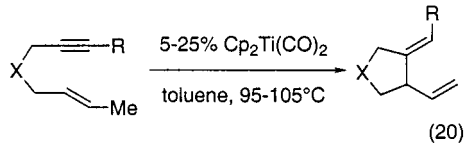


E = CO_2Et



2.1.5. Metallacyclopentene/β-Elimination: Titanium Catalysts

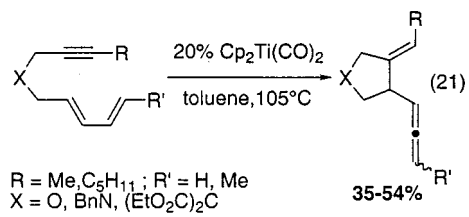
In the course of their studies on the titanocene-catalyzed Pauson−Khand-type reaction, the Buchwald group reported that $Cp_2Ti(CO)_2$ can serve as a catalyst for the cycloisomerization of enynes (eq 20).[13] *β*-Hydride elimination exclusive of Ha (see Scheme 3) occurs and gives the 1,4-diene.



R = Me, Ph, *n*-Pr
X = O, BnN, $(EtO_2C)_2C$ **79-97%**

The scope of this process was examined with respect to structural variations on the enyne. While the *trans*-olefins are cycloisomerized, *cis*-olefins either do not react or are partially converted to cyclopentenones.

The authors also described also the first example of the titanium-based catalyst for the cycloisomerization of dienynes leading to 1,4,5-trienes (eq 21).



R = Me,C_5H_{11} ; R' = H, Me
X = O, BnN, $(EtO_2C)_2C$ **35-54%**

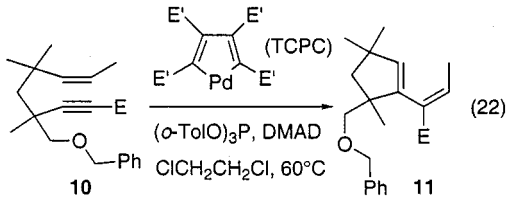
2.2. Metallacyclopentene/Reductive Elimination

When the rate of the *β*-elimination slows down for geometrical, steric, and/or electronic reasons, the reductive elimination of the metallacyclopentene can occur and becomes competitive. Usually this reductive elimination affords a formal product of [2+2] cyclization—a bicyclic cyclobutene—that is occasionally isolable and in which electrocyclic ring opening leads to a 1,3-diene. Formally, the overall process is a metathesis of the enyne. Obviously, when no *β*-hydrogens are available (*gem*-disubstituted alkene), the reductive elimination process is exclusive.

As far as we are aware, only three metals are known to mediate such eliminations from metallacyclopentenes in intramolecular version: palladium, platinum, and ruthenium.

2.2.1. Metallacyclopentene/Reductive Elimination: Palladium Catalysts

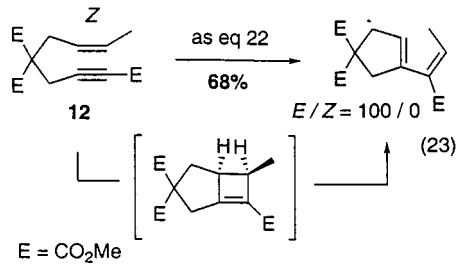
Exposure of the 1,6-enyne **10** to the palladium complex 2,3,4,5-tetrakis(methoxycarbonyl)palladacyclopentadiene (TCPC; E′ = CO_2CH_3) in the presence of tri-*o*-tolyl phosphite and dimethylacetylenedicarboxylate (DMAD) effects smooth conversion to the 1,3-diene **11** (eq 22).[42]



10 **11**

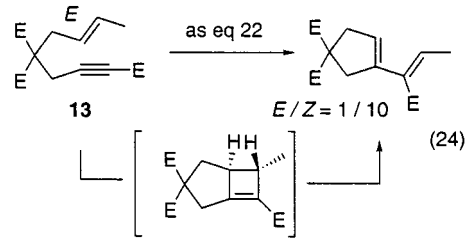
E = E' = CO_2Me **85%**

The hypothesis that the reductive elimination of the intermediate palladacyclopentene led to the corresponding cyclobutene that further rearranges by a conrotatory thermal opening has been proved by different experiments such as the cyclizations of enynes **12** and **13** (eqs 23 and 24).[43,44] Indeed, *Z* isomer **12** produced the *E* product, while *E* isomer **13** gave the *Z* product.



12

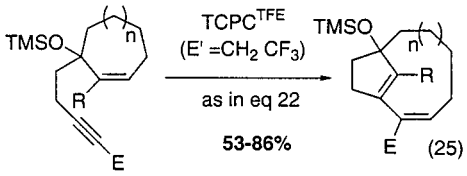
E = CO_2Me



13

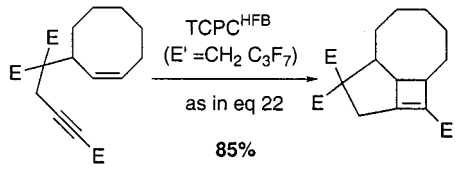
Stereoelectronic features of the substrate influenced the competition between metathesis and cycloisomerization. Thus, the presence of an electron-withdrawing group on the alkyne promotes the metathesis. Disubstitution at the allylic position also favors the metathesis, whereas geminal substitution at the propargylic position completely retards this process.[45] In general, severe steric congestion enhances the effectiveness of the reaction.

When the double bond is endocyclic, the metathesis allows a ring expansion to bridged bicycles having bridgehead olefins (eq 25).[45]



E = CO_2Me R = H, Me ; n = 1, 2, 6

In addition, in some cases, the electrocyclic opening of the cyclobutene is not possible, and therefore, it could be isolated as the unique cycloadduct (eq 26).[46]

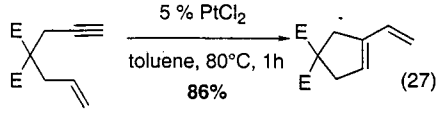


E = CO_2Me (26)

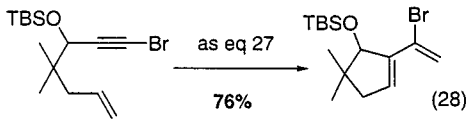
2.2.2. Metallacyclopentene/Reductive Elimination: Platinum Catalysts

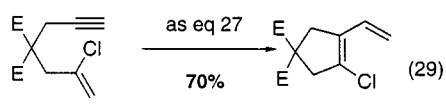
In connection with the palladium-mediated metathesis, Trost has shown that the platinum complex $(Ph_3P)_2Pt(OAc)_2$ is also able to catalyze this reaction, even without a terminal substituent on the alkyne.[42]

Pionnering work of Murai has shown that platinum(II) chloride ($PtCl_2$) is a versatile catalyst for the enyne metathesis. The cyclization occurs in very mild conditions, is comptatible with a lot of functional groups including vinylic and acetylenic halides, and no additional ligands are necessary (eqs 27−29).[47] The reaction of 1,7-enyne to a six-membered ring is also feasible but proceeds slowly (4 days), and the 1,3-diene is isolated in moderate yield (40%).

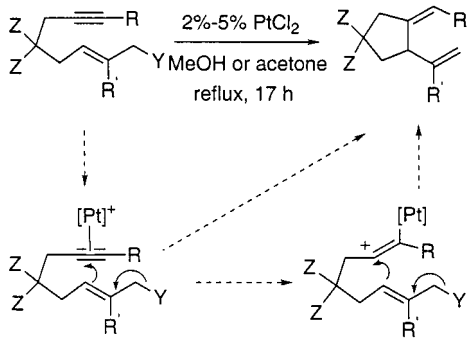


E = CO_2Et





Scheme 9

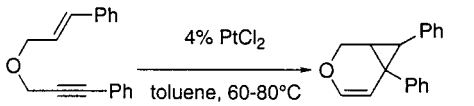


However, anomalous carbon−carbon bond formation was observed and indicates that different mechanistic pathways are operating for such a cyclization.

In pursuit of this result, Murai described the formation of novel polycyclic compounds starting from dienynes, suggesting the intervention of a carbenoid intermediate.[48] Further studies directed by different groups suggest that this cyclization proceeds probably through a cationic mechanism triggered by the coordination of Pt(II) onto the alkyne group of the substrate. Thus, Echavarren reported that 1,6-enynes can be converted into 1,4-dienes, if the alkene group is part of an allylsilane (stannane) entity via an anti nucleophilic attack onto the (η^2-alkyne)metal complex (Scheme 9).[49]

Simple enynes can react analogously, and the transient carbocation can be trapped by an external nucleophile ROH.[50]

After having been reported in early studies,[51,52] Fürstner described novel rearrangements of enynes mediated by $PtCl_2$ via also cationic pathways (eq 30).[53]



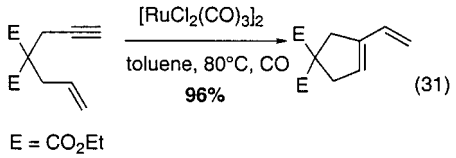
Very recently, Oi and Inoue also observed a cationic platinum complex mediated skeletal reorganization of enynes.[54]

However, up to now debate about the mechanism of these platinum-mediated cycloisomerizations continues, and unambiguous interpretation of these results must await further studies.

2.2.3. Metallacyclopentene/Reductive Elimination: Ruthenium Catalysts

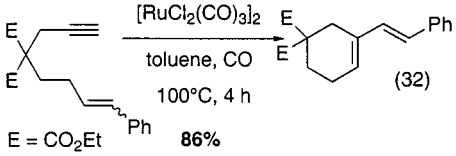
The ruthenium carbene complexes are very well-known and useful catalysts for the olefin metathesis.[55] Their use represents a mechanistic alternative to the metallacyclopentene/reductive elimination we are presenting in this part; thus, we will not discuss it. Nevertheless, 1,6-, 1,7-, and 1,8-enynes are converted in the presence of Grubb's catalyst or ruthenium carbene complexes to the corresponding 1-vinylcycloalkenes in good yields.[56−58]

On the other hand, exposure of 1,6-enynes to a catalytic amount of the dimeric complex $[RuCl_2(CO)_3]_2$ provides an efficient method for the preparation of 1-vinylcycloalkenes as well.[59] As for the platinum catalysts, the reaction occurs in mild conditions, can be applied to enynes having a terminal acetylene moiety, and furnished the cycloadducts in very high yields (79−97%) (eq 31).



(31)

This catalytic reaction is also appplicable to 1,7-enynes, giving the 1-vinylcyclohexenes in 86% yield (eq 32).



(32)

Even if the reaction mechanism is not totally elucidated, the authors suggested that the formation of a ruthenacyclopentene complex in the first step is possible.

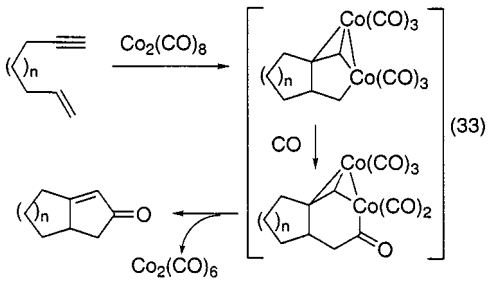
2.3. Metallacyclopentene/Electrophilic Cleavage of the Carbon-Metal bonds

In addition to the β- and reductive eliminations, a metallacycle can react with one or two electrophiles if they are present in the reaction mixture. Indeed, a metallacyclopentene exhibits two different carbon−metal bonds: Csp^2−metal/Csp^3−metal, which can react selectively with an electrophile. The metallacyclopentenes from the group 8, 9, and 10 metals are usually involved in β- and reductive elimination processes, as already described. Therefore, the electrophilic cleavage of the C−M bonds can only occur if the cleavage process is faster than the reductions, which is more probable in intramolecular reactions or in rearrangements of the metallacycle. The metallacycles derived from the group 4 metals (Ti, Zr) possess no vacant site of coordination and are inert toward the β-elimination. Consequently, they are able to react selectively with one or two electrophiles inter- and intramolecularly.

In this review, we will highlight the carbonylation, the hydrolysis and halogenolysis, the transmetalation and addition of carbonyl compounds as intermolecular reactions, and the rearrangements as intramolecular ones.

2.3.1. Metallacyclopentene/Electrophilic Cleavage of the C–M Bonds: Carbonylation

The carbonylation reactions are very important in synthesis and for industrial applications as well. Perhaps the best known and most widely used in laboratories is the cobalt-mediated Pauson−Khand reaction which combines an alkyne, an alkene, and a carbon monoxide ligand into cyclopentenones (eq 33).



(33)

The formation of the metallacyclopentene is identical to that previously described; however, the metalated species are a dimer, and the cobalt atom that is out of the cycle remains complexed to the double bond of the metallacyclopentene. The insertion of carbon monoxide takes place into the Csp^3−cobalt bond, and the reductive elimination gives the cyclopentenone.

This reaction, formally a [2+2+1] cycloaddition, was discovered in 1973[60] and since then has attracted considerable interest as evidenced by the number of publications. Excellent reviews have been published and compiled on all the aspects of this reaction in terms of scope and limitations, mechanism, regio- and stereoselectivities, examples in inter- and intramolecular versions, and several synthetic applications.[61−66]

While cobalt remains the metal of choice for the Pauson−Khand reaction, other transition metals have been shown to be quite effective in inducing this [2+2+1] cyclization. Those metals are nickel, iron, molybdenum, ruthenium, rhodium, titanium, and zirconium. The use of alternative metals has been really effective in the development of a catalytic version of this cycloaddition. Very recently, Brummond reviewed all the advances in such [2+2+1] reactions and, particularly, presented the significant interests in employing metals other than dicobaltoctacarbonyl.[67]

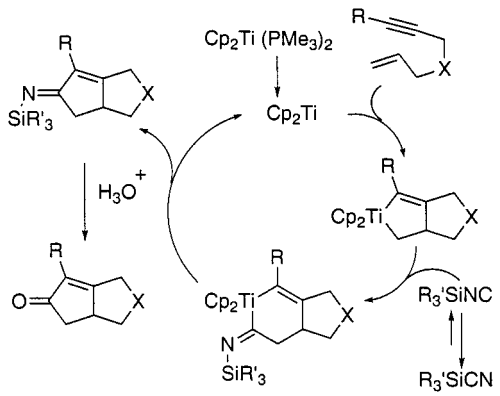
For this reason, we will not develop further the presentation of this possible transformation of a metallacyclopentene.

However, in some cases isocyanide can replace advantageously the carbon monoxide. For instance, Buchwald has reported the titanium-catalyzed Pauson−Khand reaction that utilizes a titanocene catalyst ($Cp_2Ti(PMe_3)_2$) to promote the cyclization between an enyne and an isocyanide.[68−70] The resulting bicyclic iminocyclopentene is hydrolyzed directly to generate the cyclopentenone (Scheme 10).

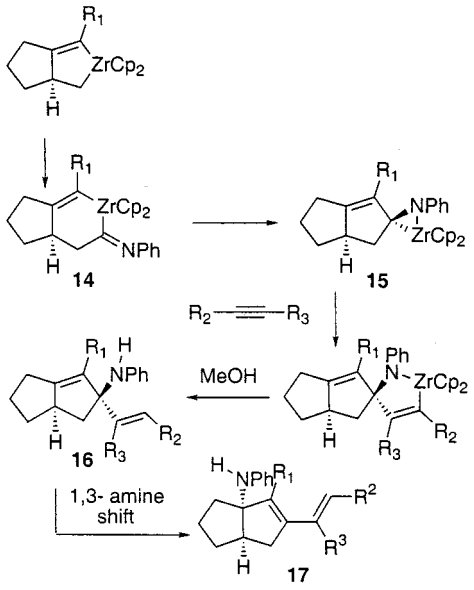
In addition, under pressure of CO, cyclopentenones can be obtained in good yields in the presence of a catalytic amount of the titanocene $Cp_2Ti(CO)_2$.[69] By using an enantiomerically pure analogue, Buchwald was able to perform a highly enantioselective catalytic Pauson−Khand reaction (ee up to 96%).[71]

On the contrary, Whitby has shown that insertion of phenylisocyanide into bicyclic zirconacyclopentenes affords iminoacyl complexes **14** which rearrange to give α,β-unsaturated zirconocene η^2-imine complexes **15**.[72] These latter can insert alkenes or alkynes to

Scheme 10



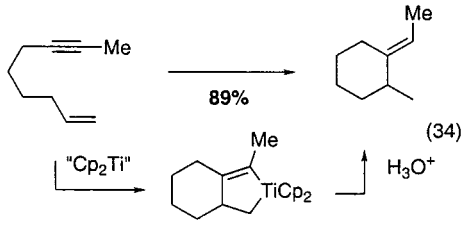
Scheme 11



furnish cyclopentenylamines **16** on protic workup that undergo an unusual but facile *anti*-1,3-amine shift to give the bridgehead product **17** (Scheme 11).

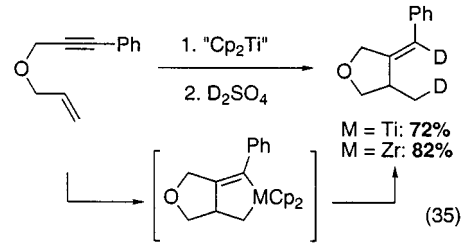
2.3.2. Metallacyclopentene/Electrophilic Cleavage of the C–M Bonds: Hydrolysis, Halogenolysis

The metallacyclopentenes, usually derived from titanium and zirconium, can be hydrolyzed to release the corresponding alkylidenecycloalkanes (eq 34).

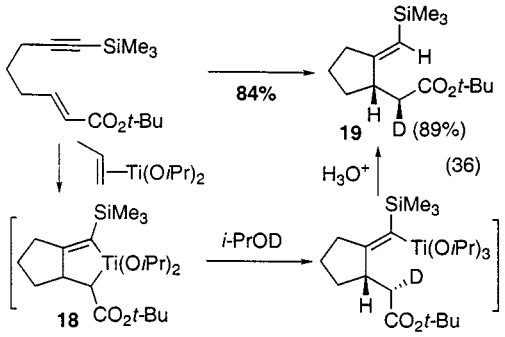


RajanBabu reported that the alkylidene moiety is introduced with a total control of the stereoselectivity in favor of the *E* isomer. This provides an excellent starting place for the elaboration of carbocyclic targets with chiral side chains.[73] The halogenolysis (iodo- or bromolysis) is also interesting because it generates simultaneously a vinylic and an alkyl halide. Both halides can be further involved in coupling reactions (Stille, Suzuki couplings) or alkylation reactions.

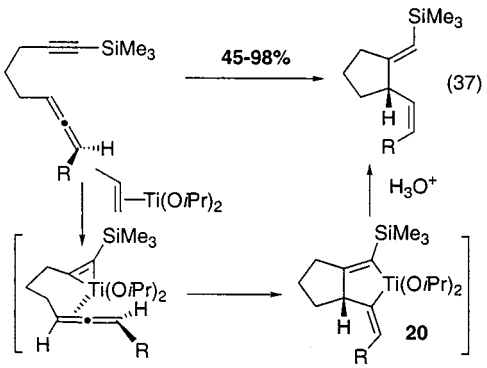
Hosomi utilized the hydrolysis of titana- and zirconacyclopentenes obtained from the titanocene- and zirconocene-mediated cyclizations of allyl propargyl ethers for the stereoselective synthesis of 3-methylenetetrahydrofurans (eq 35). It has been also shown that depending on the metal, the cyclizations proceed with inverse stereoselectivity.[74]



In the case of the titanacyclopentenes, Sato established that the Csp^3–Ti bond is first hydrolyzed. Indeed, treatment of the titanacycle **18** with *i*-PrOD (1.1 equiv) and then with acid afforded the methylenecyclopentane **19** bearing one deuterium atom in α of the ester (eq 36). Thus, the alcoholysis of the first carbon–titane bond is totally diastereoselective.[75,76]



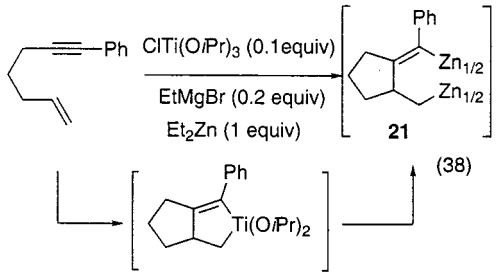
When the alkene moiety is replaced by an allene, the formation of the titanabicycle **20** results from an approach of the titanium atom on the less hindered face of the allene (i.e., anti to the substituent R) which accounts for the stereochemistry of the cyclization. The hydrolysis of **20** affords the 1,4-diene bearing a bis-allylic stereogenic center (eq 37). When the allene is chiral, the cyclization occurs with a nearly complete chirality transfer.[77]



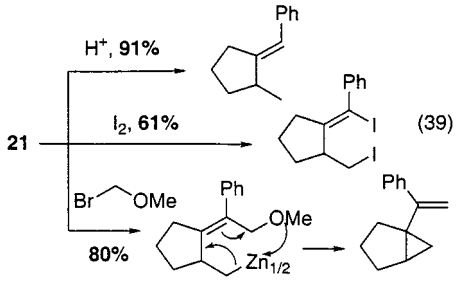
2.3.3. Metallacyclopentene/Electrophilic Cleavage of the C–M Bonds: Transmetalation

Some organometallic compounds can be considered as electrophiles regarding the metallacycles, particularly titana- and zirconacycles. This transmetalation reaction produces new organometallic species that could react with other electrophiles such as iodine, proton, or alkyl bromides. This transmetalation reaction presents two major interests: one is the possibility to carry out the reaction with a catalytic amount of metal (Ti, Zr), and the second is the modification of the reactivity of the newly formed carbon−metal bonds compared to the initial carbon−metal bonds in the metallacycle.

Indeed, Negishi was able to transmetalate a titanacyclopentene with diethylzinc (eq 38). The active catalyst is generated in situ from the reduction of the titanium(IV) complex by the Grignard reagent. Only 1 equiv of Et_2Zn is necessary and allows the use of 0.1 equiv of titanium catalyst. Although the exact structures of the organozinc products remain unclear beyond those represented by **21**, the need for a Grignard reagent strongly suggests Ti(II) derivatives as the active species such as in the stoichiometric versions.



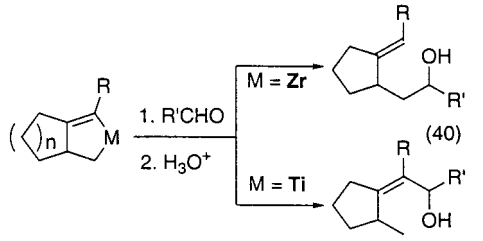
The reactivity of the organozinc compound **21** with an electrophile is opposite to the one of the titanacyclopentene. Indeed, it is the Csp^2−Zn bond that is the most reactive bond, as shown in the reaction with bromomethoxymethane (eq 39).[78]



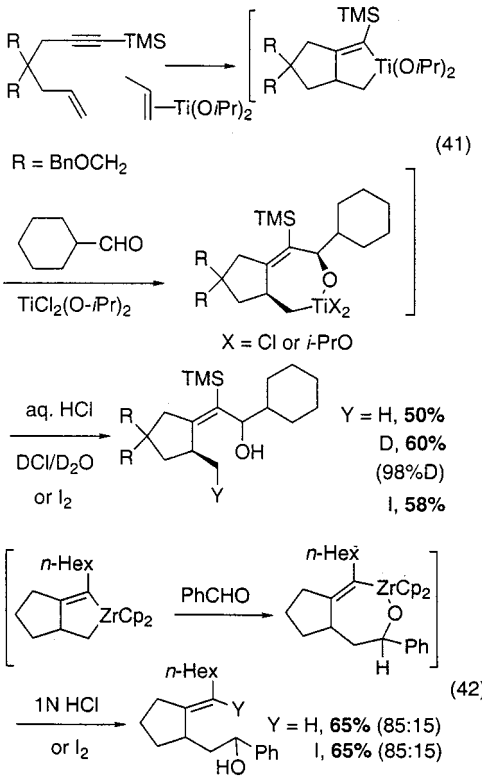
The zirconacyclopentenes also can be transmetalated with different organometallic complexes. However, the yields are moderate and the best one was obtained using triethylaluminum. The corresponding aluminabicycle can be converted to the corresponding cyclopentenones and alkenylcyclopropanes by treatment with carbon dioxide and $BrCH_2OCH_3$, respectively.[79]

2.3.4. Metallacyclopentene/Electrophilic Cleavage of the C–M Bonds: Addition of Carbonyl Compounds

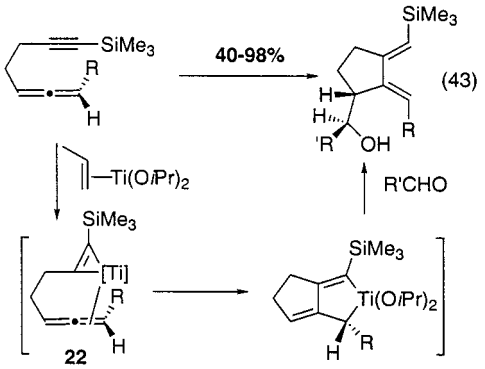
The reactions of the metallacycles with carbon electrophiles such as carbonyl and related compounds provide a straightforward method for the side-chain extension after the cyclization. These reactions have been documented for metallabicycles derived from zirconium and titanium. The reactivity of the metallacycles toward aldehydes or ketones depends mainly on the metal (eq 40).



For instance, the titanacyclopentenes react with aldehydes at their Csp^2−Ti bond (eq 41),[80,81] while zirconacyclopentenes afford the adducts at their Csp^3−Zr bond (eq 42).[82]



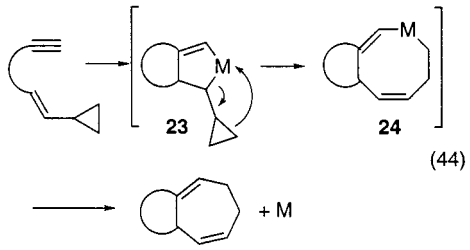
Sato studied the reactivity of numerous titanacycles, even azatitanacyclopentenes, toward aldehydes and also carbon dioxide.[76,77,81,83−85] In this field, the cyclization of 1,2-dien-6-ynes is interesting because it involves the terminal double bond of the allene and allows the formation of a new type of titanacyclopentene **22**. Upon reaction with aldehydes, **22** afforded the corresponding alcohols with very high regio-, stereo-, and diastereoselectivities (eq 43).



2.3.5. Metallacyclopentene/Electrophilic Cleavage of the C–M Bonds: Rearrangements

When the metallacyclopentene is substituted by a functional group, rearrangement or intramolecular nucleophilic additions can occur. In this part, we will present the case of the cyclization of cyclopropylenynes and the case of the rearrangement of titanacyclopentenes.

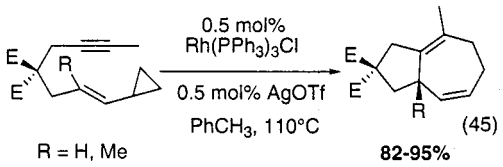
2.3.5.i. Cyclizations of Cyclopropylenynes. If the alkene is a vinylcyclopropane, the intermediate metallacyclopentene **23** can rearrange easily in metallacyclooctadiene **24**. The reductive elimination produces the corresponding cycloheptadiene (eq 44).



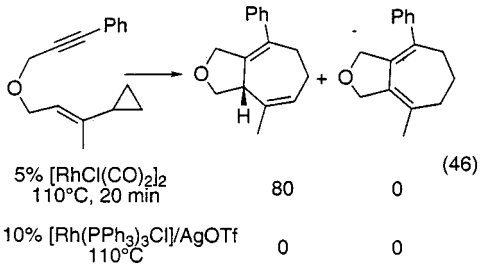
Such a transformation provides conceptually a new method for the synthesis of seven-membered rings based on a [5+2] cycloaddition. After having discovered that rhodium is able to mediate such a reaction,[86] Wender's group explored this rhodium-mediated intramolecular [5+2] cyclization between vinylcyclopropanes and π-systems (alkenes, alkynes, allenes) in terms of scope and limitations, regio-, chemo-, and stereoselectivity,[87,88] chirality transfer,[89] and applications in the total synthesis of natural products of structural and medicinal interest.[90] In the intermolecular version, this [5+2] reaction works as well.[91]

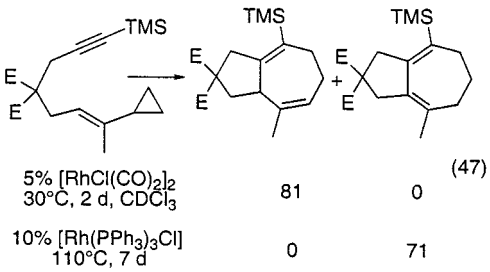
Indeed, the yne−vinylcyclopropanes in the presence of 10 mol % $[RhCl(PPh_3)_3]$ in toluene at 110 °C lead to the cycloadducts in very high yields. When the polarity of the solvent increases, the reaction proceeds more rapidly even at lower temperature, presumably due to facilitated ligand dissociation. The use of silver triflate, which irreversibly forms a cationic rhodium(I) species, is a particularly effective additive (eq 45).

This reaction is very general for a variety of alkynes including terminal, internal, electron-rich, electron-poor, conjugated, and sterically encumbered systems. Investigations centered on the choice of the



catalyst have shown a higher reactivity of $[Rh(CO)_2Cl]_2$ relative to Wilkinson's catalyst (eq 46).[92] In addition to the facility and efficiency of the reaction with this new catalyst, the reaction proceeds without isomerization of the cycloadduct (eq 47).



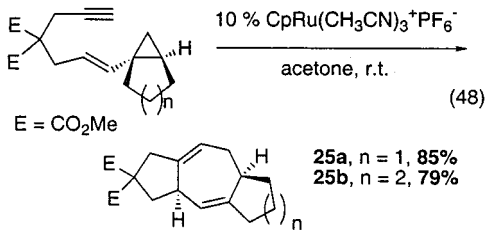


The effects of cyclopropane substitution on selectivities have been studied. 1,1-Disubstituted cyclopropanes react efficiently in all cases; for 1,2-disubstituted systems, while two regioisomers are possible, only one isomer is observed and is derived from cleavage of the less substituted bond.[93,94] Thus, by a judicious choice of cyclopropyl substituents and/or catalyst modifications, excellent control of the regiochemical outcome of the cyclization can be achieved.

Zhang reported recently the use of a new rhodium catalyst system $[Rh(bisphosphine)Cl]_2/AgSbF_6$ at room temperature, affording the cycloadducts in high yields.[95]

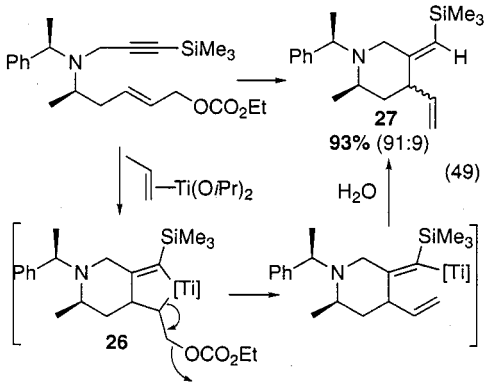
Trost also found that the cationic ruthenium catalyst $CpRu(CH_3CN)_3PF_6$ is efficient for this [5+2] cyclization,[96] which occurs with 10% of catalyst in acetone at room temperature. Excellent chemoselectivity was observed, and the influence of substituents on which the cyclopropyl bond cleaves has been studied.[97] The prospects for construction of complex ring systems is very high as demonstrated by the obtention of the tricyclic product **25a, b** with complete regio- and diastereoselectivity (eq 48).

2.3.5.ii. Rearrangement of Titanacyclopentenes. When a leaving group is on the β position of the metal, its elimination provides a diene or polyene. The classical leaving groups—acetate, carbonate, and ether—can be involved in such a process. For instance, the diene **27** results from the elimination of the allylic carbonate on the titanabicycle **26** (eq 49).[98]



(48)

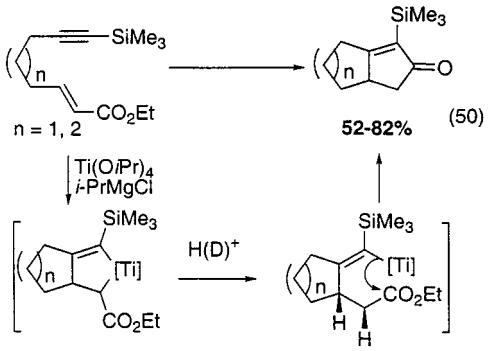
The order of the reactions is inverted related to the palladium cyclizations in which the formation of the π-allylic complex occurs before the cyclization.



(49)

Sato reported two different behaviors in the cyclization of enyoates.[75]

As already described in the cyclization of enynes having a *tert*-butyl ester at the vinylic position (see eq 36), the hydrolysis of the titanabicycle gives the substituted methylenecyclopentane. Under the same conditions, treatment of the corresponding ethyl ester affords the cyclopentenone (eq 50).

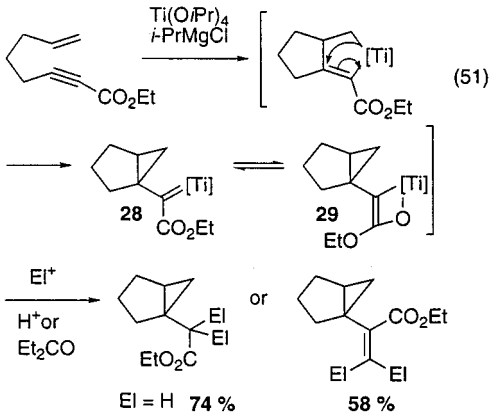


(50)

Indeed, after the selective protonation of the titanacycle, an intramolecular attack of the alkenyltitanium moiety to the ester group furnishes the cyclopentenone. Such a process can only occur in the presence of a limited amount of proton source. By switching the position of the ester at the acetylenic terminus, the reaction takes place in a quite different way (eq 51).

The Csp^3−Ti bond of the titanacycle, which is more reactive, attacks the proximate terminus of the electron-deficient C−C bond to give the titanium carbene **28** and/or the bis-titanated species, which upon addition of the electrophile affords the bicyclic products.

This 3 *exo-trig* cyclization has been also observed with a palladacyclopentene.[43,99]



(51)

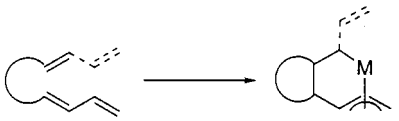
3. The π-Allylmetal Pathway

The second mechanistic possibility for the cyclization of the 1,*n*-enynes is the pathway via a π-allylmetal. The π-allylic transition-metal complexes have known great development in organometallic chemistry for the alkylation reactions as well as for the cyclizations.[100] The cyclizations of enynes involving a π-allylic complex are quite rare. Thus, in this part of the review, we turn our attention to the cyclizations of polyenes that are related and present large synthetic interests.

Two modes of cyclizations can be considered: (i) the cyclization of the two unsaturated partners generates the π-allylic complex, or (ii) if a functional group is present at the allylic position, the π-allyl complex is generated before the cyclization with the alkyne.

3.1. The π-Allylmetal Pathway: Generation of the π-Allyl Complex after the Cyclization

The cyclization of the two unsaturated partners generates the π-allylic complex (eq 52).

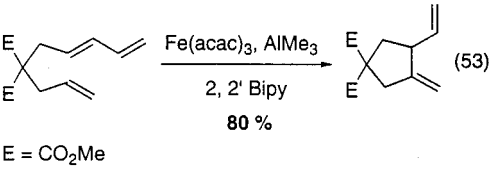


(52)

As far as we are aware, two metals allow such an intramolecular cyclization. The ω-enedienes react easily with iron complexes, while the bis-dienes are more reactive with palladium complexes.

3.1.1. Carbocyclization of Polyenes: Iron Catalysts

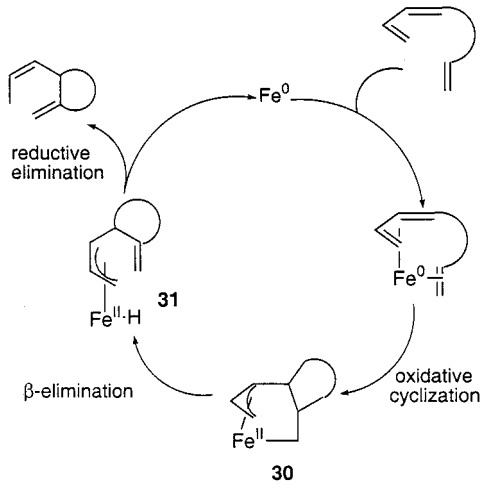
Takacs reported the cyclization of ω-enedienes in the presence of iron(0) complex that is generated in situ from the reduction of iron(III) 2,4-pentanedionate [Fe(acac)$_3$] with triethylaluminum in the presence of a ligand such as 2,2′-bipyridine or bisoxazoline. The cycloadducts—a 1,4-diene—are obtained in very good yields (eq 53).[101−103]



(53)

After complexation of the two π-systems, the oxidative cyclization furnishes the iron(II) complex **30**.

Scheme 12

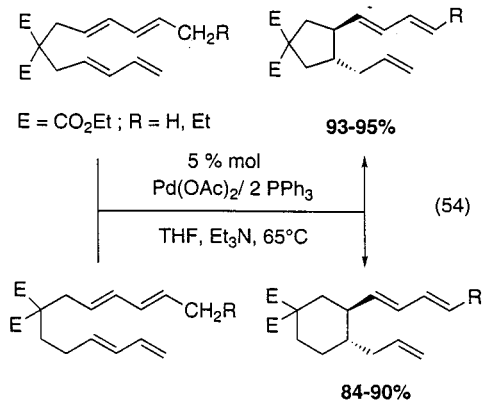


After β-hydride elimination, the reductive elimination affords the cycloadduct. (Scheme 12).

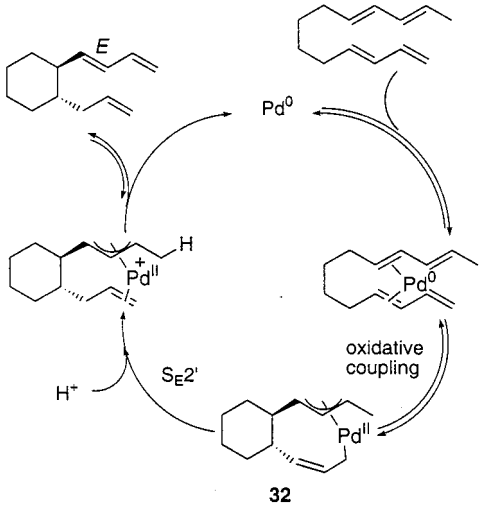
The effects of the allylic substituent, the alkene geometry, and the diene substitution and the influence of resident stereogenic centers incorporated in the tether chain connecting the 1,3-diene and the alkene subunits were totally investigated.[103] Thus, due to the anti configuration of the π-allyl iron complex **31**, the propenyl side chain is always formed predominantly with the *Z*-geometry (>95%). The sense and the degree of the diastereoselection is dependent upon the (2*E*/2*Z*)-alkene geometry. (2*E*,7*E*)-Decatrienes give *cis*-disubstituted cyclopentanes as a single diastereomer, while the (2*Z*,7*E*)-decatrienes give rise to the *trans*-disubstituted cyclopentanes, however with a variable diastereoselectivity. Decatrienes possessing a nonchelating substituent adjacent to either the diene or the alkene moieties cyclize with a high 1,2-stereoinduction in such a manner that the resident center and the newly formed stereocenter have a trans relative sterochemistry. This cyclization was used successfully in the stereoselective preparation of *N*-acylpiperidines[101] and in the enantioselective syntheses of iridoid monoterpenes[104] and some alkaloids.[105]

3.1.2. Carbocyclization of Polyenes: Palladium Catalysts

The palladium complexes are the catalysts of choice for the cycloisomerization of the bisdienes and allow the formation of either five- or six-membered enedienes in high yields (eq 54).[106]



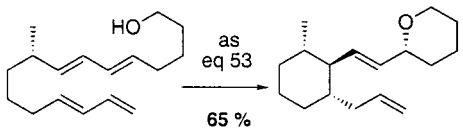
Scheme 13



Takacs reported his observations on substrate requirements, on the stereoselectivity of the cyclization, and on the influence of the catalyst precursor.[107] By using deuterium labeling, he proposed a model to rationalize these different aspects (Scheme 13).

Three key features stand out from this proposed mechanism. (1) After the complexation of the two dienic systems, the C−C bond is forming during the oxidative coupling leading to the palladacycle **32**. (2) The proton that is delivered to the propenyl (bottom) side chain is not delivered intramolecularly. (3) The alkene that ends up nearer the newly formed C−C bond is formed exclusively with the *E*-geometry.

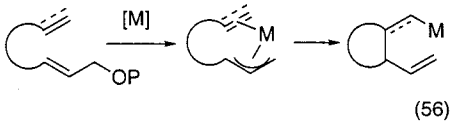
If a hydroxyl group is judiciously tethered to the starting bisdiene, a tandem cycloisomerization and intramolecular trapping occurs (eq 55). The high diastereoselectivity is remarkable as the relative stereochemistry of three stereogenic centers is controlled.[108]



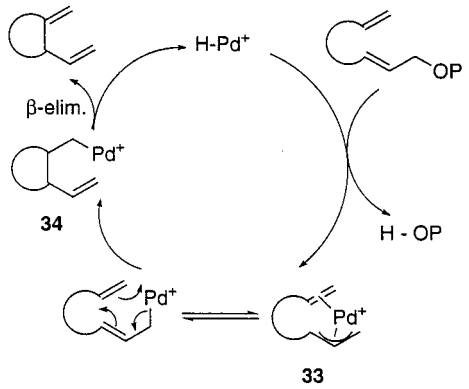
3.2. The π-Allyl Metal Pathway: Cyclization of a Preformed π-Allyl Complex

3.2.1. Palladium Catalysts

If a functional group (acetate, carbonate) is present at the allylic position, the π-allylmetal complex is generated and may carbometalate a second unsaturation (alkene, alkyne) (eq 56). Depending on the nature of this second unsaturation (enophile), a β-hydride elimination can occur and furnish a 1,4-diene. In this case, palladium-based catalysts have proven to be very efficient.

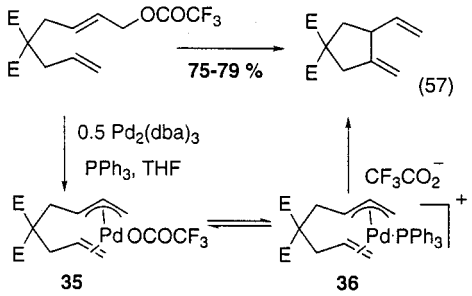


Scheme 14



The palladium-catalyzed intramolecular carbocyclization of allylic acetates with alkenes is a powerful method for the formation of five- and six-membered rings. After the formation of the π-allyl palladium complex **33**, a carbometalation of the second double bond occurs and creates the new C−C bond. The behavior of the resulting alkylpalladium complex **34** depends on the possiblity of a β-elimination. If the β-elimination is possible, it generates a metalated hydride and furnishes the cycloadduct (Scheme 14). This cyclization could be viewed as a pallada−ene reaction in which the palladium replaced the hydrogen atom of the ene partner.[109,110]

However, Echavarren studied the carbometalation step of the olefin and showed that the reaction proceeds through a cationic complex of type **36** (eq 57).[111]

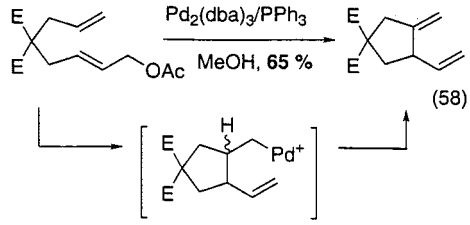


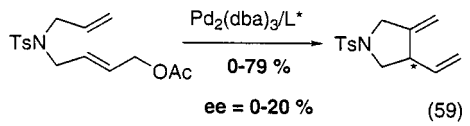
Thus, after the formation of the π-allyl complex **35** from the corresponding allyl trifluoroacetate, an exchange of ligand with triphenylphosphine led to **36**. The formation of the latter is the key to successful cyclization, because the complex **35** failed to cyclize.

If the enophile is an alkene, the β-hydride elimination is possible and a 1,4-diene is obtained in good yield (eq 58). An asymmetric version of such a cyclization has been developed; however, the yields and the enantiomeric excesses are moderate (eq 59).[112]

If the alkylpalladium intermediate is unable to undergo a β-elimination, i.e., if the enophile is a conjugated diene, an allene, or an alkyne, some other transformations such an alkylation, cyclization, etc., can occur.

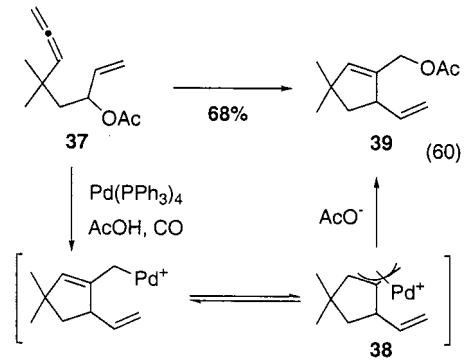
Thus, the cyclization of the enallene **37** provides the cyclopentane derivative **39**. The initially formed π-allylpalladium complex undergoes exclusively an



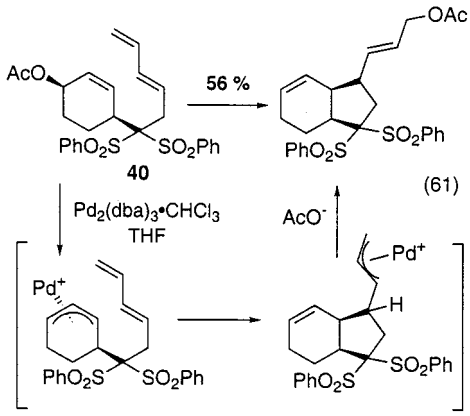


L* = *(S, S)*-DIOP, *(R)*-BINAP, *(R)*-MOPI

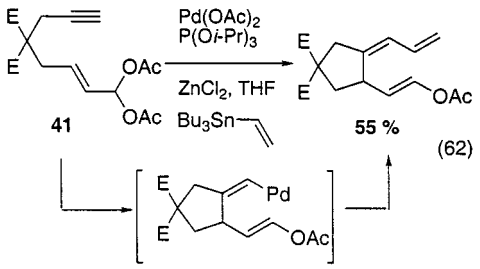
alkene insertion at the distal site on the allenic unit, resulting in a new π-allyl complex intermediate **38** which proceeds back to the corresponding allylic acetate (eq 60). It has been also shown that complex **38** is able to react further with other alkene moieties to provide polycyclic compounds.[113]



This tandem cyclization is the same when a conjugated diene is the enophile. Thus, the π-allylpalladium complex generated from **40** carbometalates the appendant diene to generate a second π-allyl that recombines with the acetate (eq 61).[114]

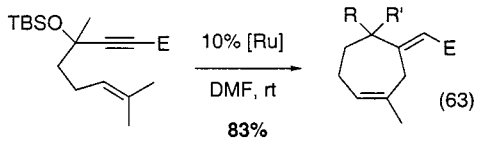


Finally, the cyclization of the 1,6-enyne of type **41** led to the corresponding vinylpalladium that is inert toward the nucleophilic attack of the leaving group but which can be intercepted by vinyltributyltin in a transmetalation step (eq 62).[115]



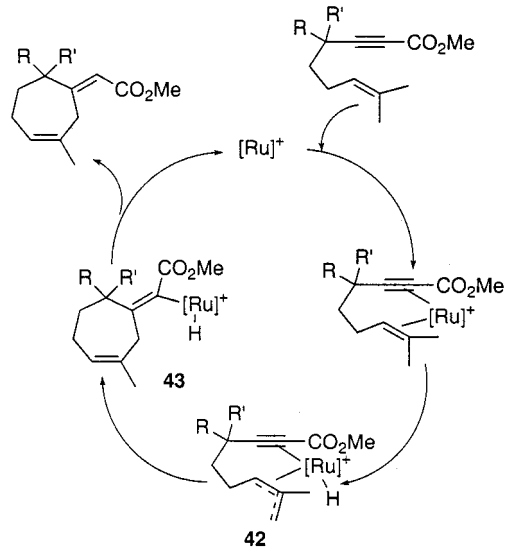
3.2.2. Ruthenium Catalysts

Trost observed the formation of seven-membered rings from the cyclization of alkenes and alkynoates (eq 63).[29]



It has been postulated that these cycloheptenes must form via a π-allylruthenium intermediate (Scheme 15). The cyclization is initiated by activation

Scheme 15

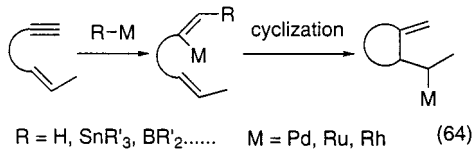


of the allylic C−H bond to form the π-allylruthenium **42**. A 7-*exo*-dig carboruthenation of the alkynoate produces (hydrido)−ruthenium enolate **43**. Equilibration followed by a β-elimination gives the corresponding cycloheptenes and regenerates the cationic ruthenium.

The reaction requires the quaternary center at the propargylic position and also the acetylenic ester. Enynes having *cis*-1,2-disubstituted or *cis*-trisubstituted alkenes participate extremely well; in contrast, *trans*-1,2-disubstituted alkenes normally give a complex mixture.

4. The Vinylmetal Pathway

The third mechanism for the cycloisomerization of 1,*n*-enynes is the pathway which involves a vinylmetal intermediate (eq 64).



Indeed, the addition of a R−M moiety to the triple bond led to the corresponding vinylmetal, which is activated enough to react with the alkene. The β-hydride elimination or if some additional unsaturations are present in the molecule, coupling reactions or cyclizations cascade provide functionalized ene adducts. The R group can be a hydrogen, tin, or boron atom or even a halogen. Palladium and ruthenium are the most used metals for such transformations.

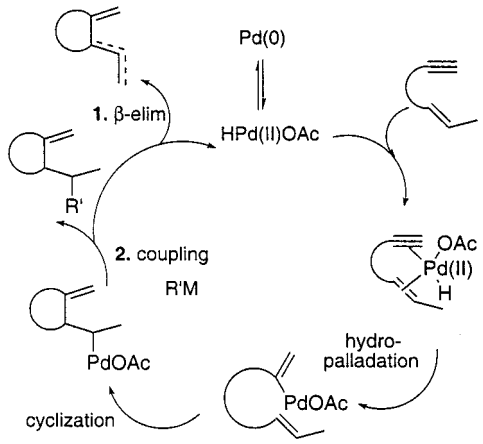
The vinylmetals are also efficiently prepared by oxidative addition of a metal onto a Csp^2−halogen bond. However, we will not present in this review the Heck reaction and its wide application in synthesis which has been extensively reviewed.[116] We are just summarizing the cycloisomerization of 1,*n*-enynes involving in the first step a hydro-, stanno,- or borylmetalation.

4.1. Vinylmetal Pathway/Hydrometalation

4.1.1. Vinylmetal Pathway/Hydrometalation: Palladium Catalysts

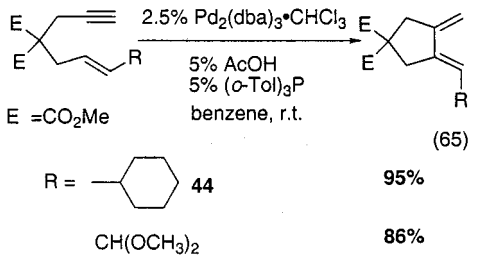
The mechanism and the factors governing the regio-, chemo-, and stereoselectivity have been fully determined by the Trost group.[15] In the presence of a carboxylic acid, a Pd(0) precatalyst generates a Pd(II) hydride that is the active species during the cyclization (Scheme 16).

Scheme 16

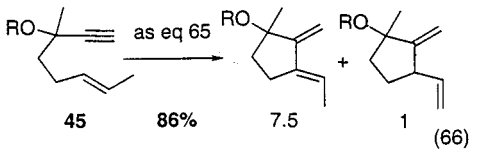


After the complexation of the latter to both unsaturated moieties, a hydrometalation of the alkyne provides the vinylmetal that is able to carbometalate the alkene. The resulting alkylpalladium can react following two ways: a β-elimination furnishes the 1,3- or 1,4-diene and regenerates the palladium(II) hydride or coupling reactions or further cyclizations lead to functionalized cycloadducts. It has to be noted that in this pathway the oxidation state of the metal remains unchanged during the whole process of the cyclization.

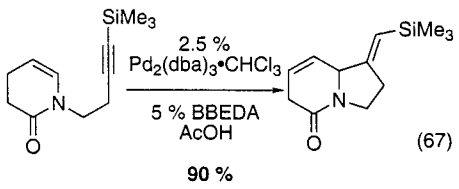
4.1.1.i. β-Elimination. The sequence cyclization/β-elimination is quite general and usually gives the cycloadducts in high yields[117] (eq 65) sometimes in better yields than using the catalytic system based on Pd(0)−Pd(IV). For example, the enyne **44** led to the 1,3-diene in 95% yield instead of 64% (see eq 5).

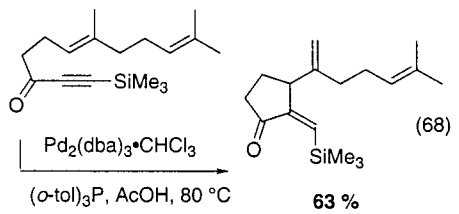


The effects of substituents on regioselectivity are identical for the metallacyclopentene pathway. Both steric and electronic effects direct the regioselectivity of the β-elimination to form either 1,3- or 1,4-diene cycloadducts. The nature of the substituents at the allylic site is important but also the substitution pattern of the tether linking the alkyne and the olefin. Thus, the enyne **45** gave mainly the 1,3-diene rather than the 1,4-diene in ligandless conditions (eq 66).



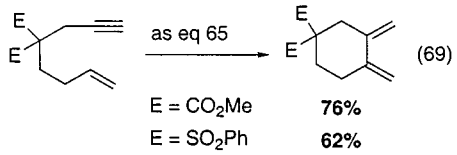
The chemoselectivity is particularly remarkable; free alcohols, silyl ethers, esters, amines, and acetals are compatible. This reaction tolerates substrates in which the ene or the enophile partners are polarized by appendant electron-donating or -withdrawing groups (eqs 67 and 68).[118,119]

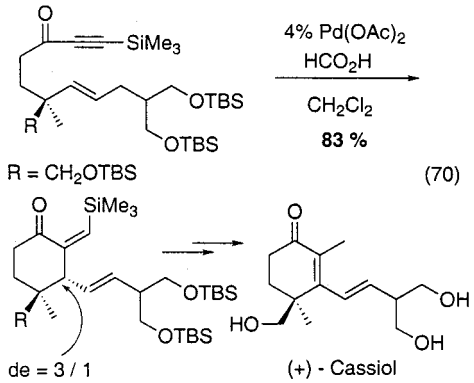




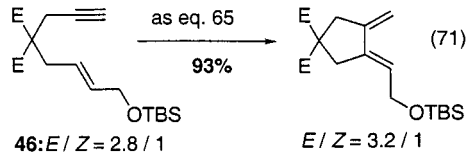
Six-membered rings can also be formed through this pathway, and their formation is easier than with the catalytic system Pd(II)−Pd(IV) (eq 69).

The feasibility of their formation has been nicely demonstrated in an enantioselective approach to the potent antiulcerogenic cassiol (eq 70).[17]



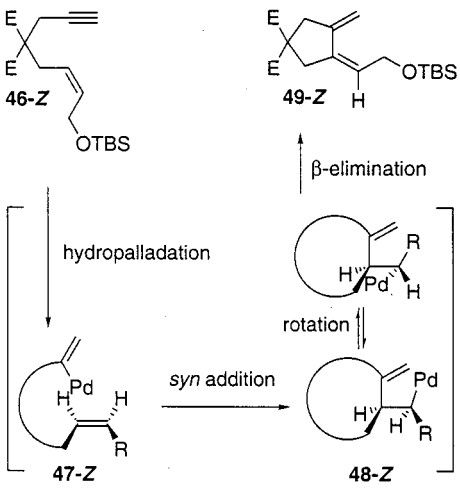


Concerning the mechanism of this cyclization, deuterium labeling strongly supports the hydropalladation step. In addition, it has been proposed that the dependence of alkene geometry of the cycloadduct on that of the starting enyne supports the involvement of a carbopalladation and a β-hydrogen elimination step (eq 71).



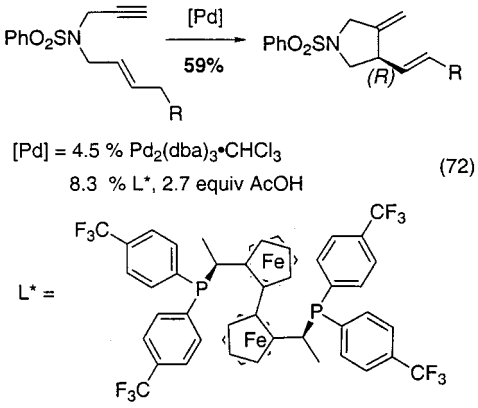
Indeed, the vinylpalladium intermediate **47-*Z*** from **46-*Z*** produces **48-*Z*** via a syn addition. A rotation would occur to allow the *syn*-β-elimination which furnishes **49-*Z*** (Scheme 17). The geometrical isomer provides complementary results.

Scheme 17

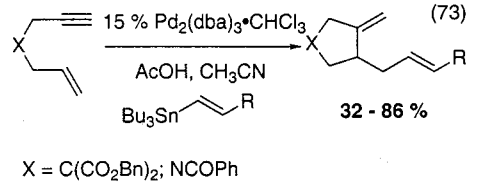


Asymmetric induction for enynes that generate a 1,4-diene was explored by Trost who used optically active acid *S*(−)-binaphthoic acid as a chiral catalytic inducing agent. However, the induction was modest (ee = 33%).[117] By using chiral diphosphines, Trost was able to reach induction up to 71%,[120] and finally,

Ito obtained a 1,4-diene with very high enantiomeric excesses (95%) (eq 72).[121]

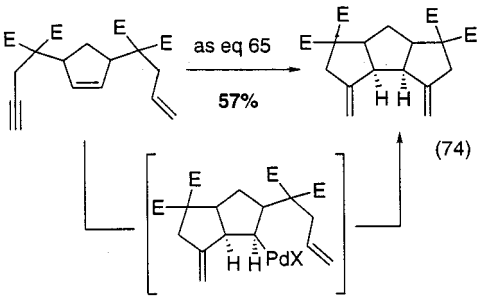


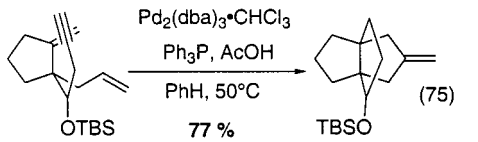
4.1.1.ii. Coupling Reactions and Polycyclizations. If some additives are present in the reaction, the β-elimination can be totally or partially inhibited and the σ-alkylpalladium complex, generated from the carbometalation, can be intercepted for further transformations. In particular, it can undergo in situ Stille-type cross-coupling with vinyltin reagents to give cyclized products bearing allyl appendages (eq 73). However, to prevent the formation of the β-elimination products, the reaction has to be carried out in the absence of ligands.[122]



Up to now, few examples of such a sequence of reactions have been described. Oh also reported the palladium-catalyzed cycloreductions of 1,6-enynes in the presence of formic acid or triethylsilane via an alkylpalladium intermediate and its application in synthesis.[123,124]

Iterative trapping of the alkylpalladium species with tethered olefins can be also possible and allows tandem cycloisomerizations. Thus, depending upon

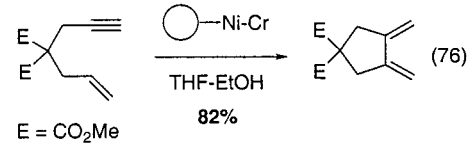


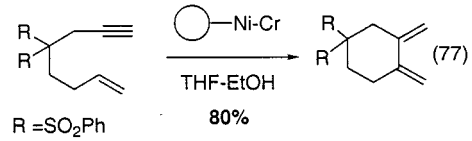


the juxtaposition of the unsaturations, Trost achieved highly atom economical syntheses of triquinanes, propellanes, and polyspiranes (eqs 74 and 75).[125]

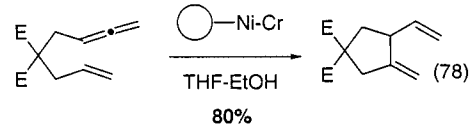
4.1.2. Vinylmetal Pathway/Hydrometalation: Nickel–Chromium Catalysts

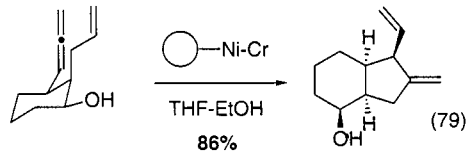
Cycloisomerization of 1,*n*-enynes can be promoted by nickel−chromium-based catalyst systems.[126] For an adequate catalytic activity, the Ni−Cr system is attached to a polymer (phosphinylated 2% cross-linked polystyrene). Although the definition of the catalyst remains unclear, mechanistically the cyclization seems to proceed via the same pathway as that described for the Pd(0)−Pd(II) system. The benefit to using this Ni−Cr system is the equal facility for the formation of five- and six-membered rings (eqs 76 and 77). High chemoselectivity is observed; in particular, esters, ketones, sulfones, and free hydroxyl groups are all tolerated.





This Ni−Cr catalyst system is also able to effect the cycloisomerization of enallenes to provide 1,4-diene as the exclusive regioisomeric cycloadduct (eqs 78 and 79).[127,128] The same mechanism as Pd(0)−Pd(II), involving hydrometalation of the allene, then carbometalation of the alkene, and finally β-hydride elimination could be probably effective.



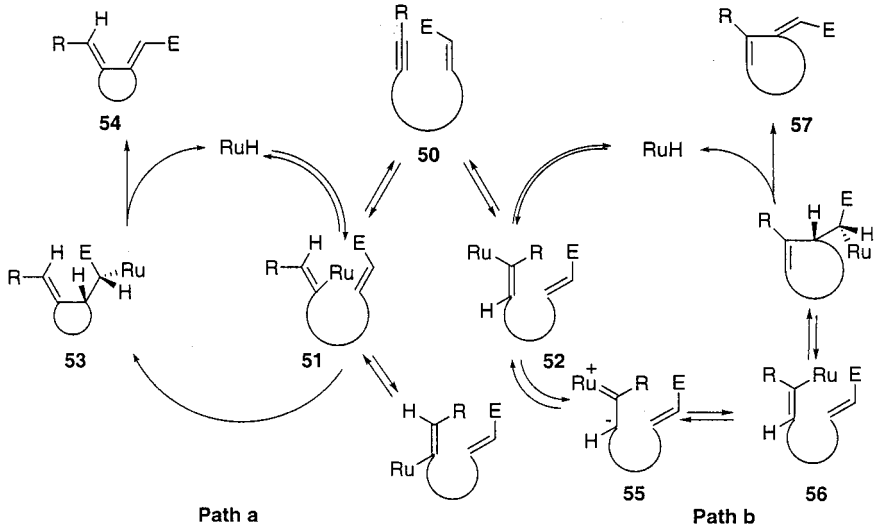


4.1.3. Vinylmetal Pathway/Hydrometalation: Ruthenium Catalysts

Ruthenium hydride catalysts can also initiate a variety of cycloisomerizations of 1,5- and 1,6-enynes and also dienes.[129] For example, ruthenium hydride catalyzes the hydrometalation of 1,5- or 1,6-enynes to initially generate the vinylruthenium complex **51** or **52** which is in a state of equilibrium with the starting enyne **50** (Scheme 18).

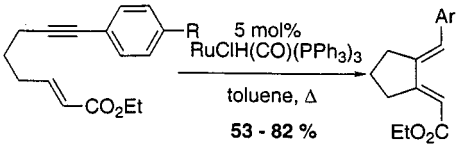
In the reaction with 1,6-enyne and RuClH(CO)-$(PPh_3)_3$, intramolecular olefin insertion into the Ru−C bond occurs to give the alkylruthenium complex **53**.

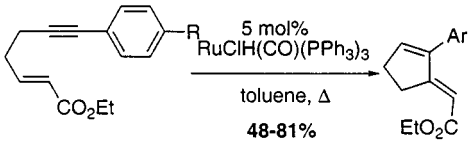
Scheme 18



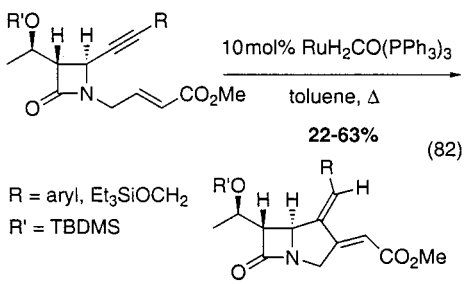
Then a *syn*-β-elimination releases the cycloadduct **54** and regenerates the ruthenium hydride catalyst. On the other hand, in the reaction of 1,5-enynes, **52** which is a cis addition product isomerizes to the vinylruthenium **56** via a dipolar intermediate **55**. Then, successive carbometalation of the alkene and *syn*-β-elimination take place providing the cycloadduct **57** exclusively.

In both reactions of 1,5- and 1,6-enynes, five-membered ring formation preceded all other ring formation. Typical examples of these processes are shown in eqs 80 and 81.

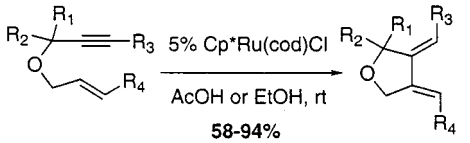




Mori also proposed a synthesis of carbapenam skeletons by using this ruthenium-catalyzed cyclization (eq 82).[130]



The precatalyst $RuCl(cod)C_5Me_5$ in the presence of acetic acid or ethanol generates the ruthenium hydride by decoordination of the cod ligand and allows the selective one-step cycloisomerization of allyl propargyl ethers into 3,4-dialkylidenetetrahydrofurans in quite good yields (eq 83).[131]



The authors invoked the same mechanism as the previous examples: hydrometalation of the triple bond to generate the corresponding vinylruthenium, carbametalation of the alkene, and then β-elimination.

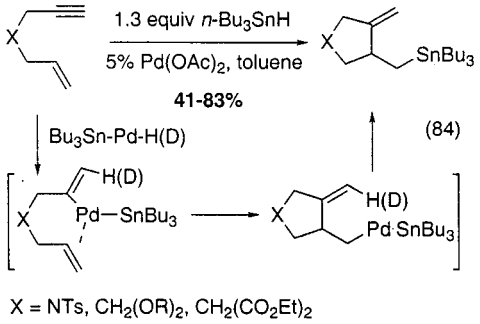
4.2. Vinylmetal Pathway/Stanno- and Borometalation: Palladium Catalysts

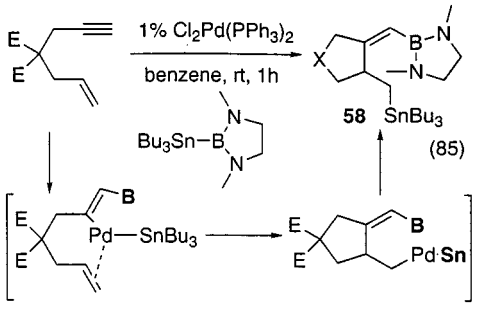
Even if the mechanism of the reactions is not fully elucidated, palladium-catalyzed stannylative, borostannylative, or bismetalative cyclizations of enynes involve the formation of a vinylmetal intermediate.

Lautens reported the formation of homoallyl stannanes via the treatment of 1,6-enynes with tributyltin hydride in the presence of a catalytic amount of $Pd(OAc)_2$.[132] The catalytic species is generated by reduction of Pd(II) to Pd(0) by Bu_3SnH, which then oxidatively inserts into the Sn−H bond of another hydride. The reaction is believed to proceed via a hydropalladation of the acetylenic moiety to generate the vinylpalladium. Then the carbopalladation of the alkene via a 5-*exo*-trig process followed by a reductive elimination give the cyclized compound and regenerate the Pd(0) (eq 84).

The borostannylation of an enyne was also described in high yield (eq 85).[133]

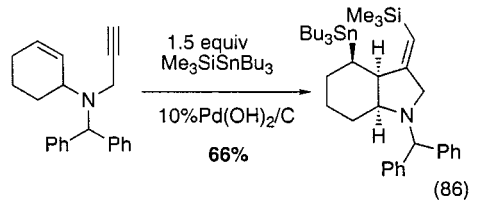
The mechanism of this cyclization has not been investigated in detail, but the insertion of the alkyne is preferential into the Pd−B bond instead of the Pd−Sn bond. Then the addition of the vinylpalladium to





the alkene followed by the reductive elimination furnished the cycloadduct **58**. However, the authors did not exclude a palladacycle intermediate.

Finally, recently it has been shown that various enynes are able to react with $Me_3SiSnBu_3$ in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ or $Pd(OH)_2$ on charcoal to afford cyclized products bearing a vinylsilane moiety and a homoallyltin moiety in good yields.[134] Bicyclic heterocycles are produced stereospecifically from the corresponding enynes (eq 86).

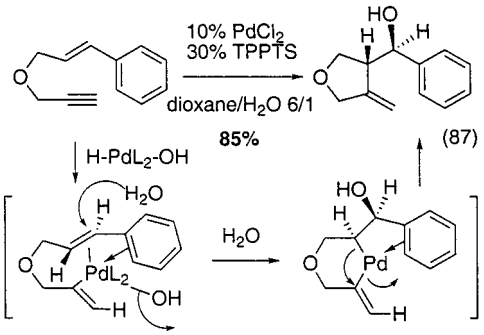


The mechanism suggested is totally similar to that proposed for the borylstannylation.

5. Miscellaneous

5.1. Palladium-Based Catalysts

Recently, Genet reported the first cycloisomerization of 1,6-enynes in organoaqueous medium to give functionalized furans by using Pd(trisulfonated phosphine)[$Pd(TPPTS)_3$].[135,136] The water-soluble palladium catalyst is preformed from $PdCl_2$ and TPPTS in water, and the cyclization is then conducted at 80 °C in a homogeneous mixture of acetonitrile and water (eq 87). Various propargyl ethers bearing aromatic or heteroaromatic and ethylenic substituents on the alkene are able to provide the hydroxyfurans in good yields and with good diastereoselectivities. However, carbocycles are obtained in moderate yields, and when the double bond of the enyne is substituted by an aliphatic chain, the expected cycloadduct is not obtained.



The mechanism of the carbohydroxypalladation is not yet established, but it appears that it is different in the last step from the catalytic cycle established for the cycloisomerizations in anhydrous medium. The authors envision first the formation of a hydroxypalladate species which adds to the acetylenic moiety. Then, the stereoselective introduction of the hydroxy group could be a "Wacker"-type process which undergoes a nucleophilic attack of water α to the aromatic ring and anti to the palladium. Finally, reductive elimination gives the cycloadduct and regenerates the catalyst.

This cyclization has been illustrated in the synthesis of a key intermediate of podophyllotoxin.

5.2. Group VI Carbene-Based Catalysts

Several groups investigated the reactivity of 1,6- and 1,7-enynes with group VI Fischer carbene complexes, and a number of distinct reaction pathways have been proposed. Representative examples of these reactions with the appropriate literature are presented in the paper published by Mori, and a synthesis of pyrrolidine and piperidine derivatives from a chromium carbene and enynes having nitrogen in the tether was reported as well.[137]

6. Conclusion

The use of transition-metal catalysts to promote the cyclization of 1,*n*-enynes is exponentially growing. The metal catalysts either induce impossible reactions to occur or accelerate the rate of known reactions. As it clearly appeared in this review, cyclizations catalyzed by palladium complexes constitute the largest part of the accomplishments to date. However, the use of metal species other than Pd has really increased, and new types of reactions and processes have emerged.

Indeed, the cyclizations of 1,*n*-enynes have been achieved either in a catalytic or stoichiometric manner and represent a versatile and powerful approach to a large variety of products by simple manipulation of the catalyst and by proper choice of the substrate. These cyclizations which mostly generate 1,3- or 1,4-dienes enhance the ability to construct polycyclic compounds in a highly atom economical approach by combining with Diels−Alder or coupling reactions or polycyclizations. Thus, numerous applications in the field of natural product synthesis have been reported.

Stereocontrol in these reactions appears as an important feature, and the understanding of the steric, electronic, and conformational effects allows

the alteration and fine-tuning of the regio-, chemo-, and stereoselectivity of the processes. Enantioselective transformations have been achieved and have started showing great interest. Of course, further advances can be expected as more active catalysts are discovered and new ligands are designed.

7. Acknowledgment

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