Transition Metal-Catalyzed Carbocyclizations in Organic Synthesis

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Received June 30, 1995 (Revised Manuscript Received September 13, 1995)

Contents

I. Introduction

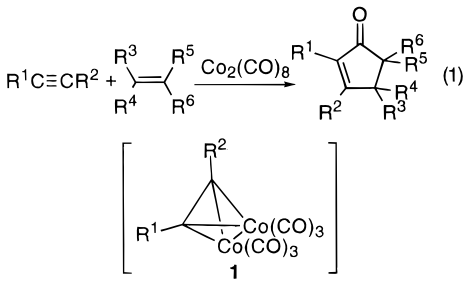
Carbocyclizations of alkenes and alkynes are extremely important and useful reactions for the syntheses of a variety of carbocyclic and heterocyclic compounds. The term "carbocyclization" has been used to describe a annulation process involving carbon−carbon bond formation via carbometalation, which distinguishes itself from radical cyclization as well as thermal and photochemical cycloadditions. "Carbometalation" is one of the several important basic processes that organometallic species undergo wherein C*−M species delivers C* and M across C=C bond or C≡C bond forming C*−C−C−M or C*−C=C−M products. Carbocyclizations are usually promoted by transition metals or their complexes, i.e., not by typical elements.

Carbocyclizations have been reviewed as a part of transition metal−mediated cycloadditions or carbometalations. Excellent reviews by Negishi (Zr),[1] Schore,[2] Trost (Pd),[3] and Tamao (Ni)[4] compiled rather specific aspects of the advances in carbocyclizations up to 1992. The objective of this review is to update the recent advances on this topic by organizing the text *on the basis of metal species*, i.e., *not on the basis of reaction types*, with clear emphasis on truly *catalytic* reactions. Relevant papers that have appeared by the end of 1994 are compiled.[5,6]

II. Cobalt-Mediated Carbocyclizations

1. The Pauson–Khand Reaction

The Pauson−Khand reaction was discovered in 1973[7] by Pauson and Khand during their study on the reaction of various (alkyne)hexacarbonyldicobalt complexes with norbornadiene. Since then, this reaction has attracted considerable interest among synthetic and organometallic chemists as evidenced by the number of publications in the last two decades.[2,8,9] The reaction combines an alkyne, an alkene, and a carbon monoxide into a cyclopentanone ring in the presence of *stoichiometric* amounts of dicobalt octacarbonyl (eq 1). The mechanism of the reaction is not fully established yet. However, it has been shown that the reaction proceeds through the alkyne complex **1**. Krafft and co-workers have also



isolated other intermediates using substrates with sulfur or oxygen atoms.[10]

Although the Pauson−Khand reaction results in moderate yields[8,11] and has limitations for the type of the alkene and alkyne that can be used,[12,13] the reaction usually gives good regio- and stereoselectivity[14] and has found many applications.[14]

Extensive investigation on the Pauson−Khand reaction has revealed that the addition of silica gel,[15] tertiary amine oxides,[16,17] phosphine oxides,[18] and DMSO[19] accelerate the reaction, improve the selectivity, and achieve higher yields under milder conditions. The role of these additives on the mechanism of the reaction is not completely understood, but it seems that silica gel acts as an electron-donor surface, facilitating the carbonyl ligand exchange in

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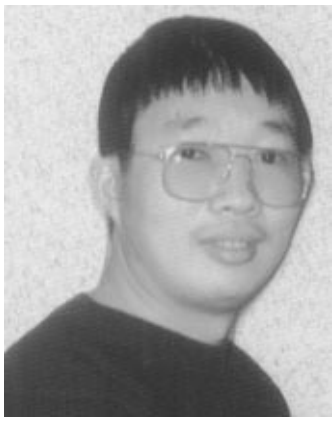
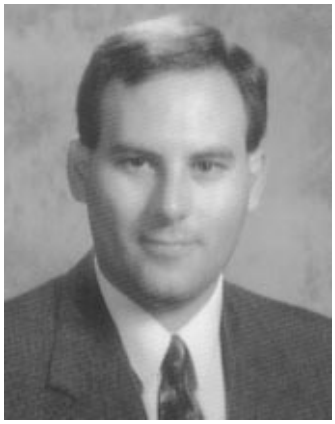
0009-2665/96/0796-0635$25.00/0

Iwao Ojima was born in Yokohama, Japan, in 1945. He received his B.S. (1968), M.S. (1970), and Ph.D. (1973) degrees from the University of Tokyo, Japan. He joined the Sagami Institute of Chemical Research and held a position as Senior Research Fellow and the Group Leader of Organometallic and Catalysis Research until 1983. He joined the faculty at the Department of Chemistry, State University of New York at Stony Brook first as Associate Professor (in 1983; he was then promoted to Professor (1984), Leading Professor (1991), and Distinguished Professor (1995). He has a wide range of research interest in synthetic organic, organometallic, and medicinal chemistry. Homogeneous catalysis of Rh and Rh–Co complexes, its development as new synthetic processes, and applications to organic syntheses and catalytic asymmetric synthesis have been the major interests in this area. He has published more than 220 papers and reviews in leading journals and more than 140 patents and patent applications. He is a recipient of the Arthur C. Cope Scholar Award from the American Chemical Society (1994). He is a John Simon Guggenheim Memorial Foundation Fellow (1995–1996). He has served as advisory committee members for National Institutes of Health, National Science Foundation and the U. S. Department of Energy. He is an Editorial Advisory Board member for *The Journal of Organic Chemistry*.

Maria Tzamarioudaki was born in Hania, Greece, in 1967. She received her B.S. degree in chemistry in 1990 from the Aristotle University of Thessaloniki, Greece. After a short period of research training in Roussel-Uclaf, Romainville, France, in organic syntheses, she started her graduate study at the Department of Chemistry, State University of New York at Stony Brook in 1991. She has been engaged in the development of new catalytic methods for organic syntheses as her Ph.D. research under the guidance of Professor Iwao Ojima. She has coauthored three original papers, one book chapter, and one review article.



Zhaoyang Li was born in 1962 in Fujian, China. He his received B.S. degree in 1983 and a M.S. Degree in chemistry in 1987, both from Nankai University, China. In the summer of 1987 he joined the faculty of Chemistry Department of Tianjin University as an Assistant Professor. He performed his graduate study at the Department of Chemistry, University of South Carolina (1990–1994) on the synthesis, characterization, and catalytic study of platinum–ruthenium cluster complexes and obtained his Ph.D. degree in 1994 under the direction of Professor Richard D. Adams. In 1994 he received the Outstanding Student Award from International Precious Metals Institute. He has been working with Professor Iwao Ojima as a postdoctoral associate on the organometallic Chemistry and homogeneous catalysis of Rh and Rh–Co clusters at the Department of Chemistry at Stony Brook since 1994. He has coauthored eight original papers and one review.



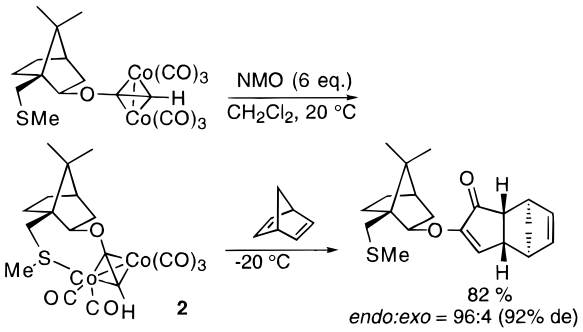
Robert J. Donovan was born in Long Island, NY, in 1966. He received a B.S. in chemistry from the State University of New York at Stony Brook in 1988. He performed his graduate study at the Department of Chemistry, State University of New York (1988–1993) on the synthesis and reactivity of Rh and Rh–Co complexes and their catalysis with hydrosilanes and obtained Ph.D. degree in 1993 under the direction of Professor Iwao Ojima. In the meantime, he also worked with Dr. Myron Strongin at the Department of Physics, Brookhaven National Laboratory as a research associate (1988–1990) on a surface science project. From 1993 to 1994, he worked with Professor Ojima as a postdoctoral associate to further his Ph.D. research project. In 1994, he joined faculty at the Department of Chemistry, Long Island University, Brooklyn Campus, as an Assistant Professor. He is also holding an Adjunct Assistant Professorship at the Rockefeller University from 1995. His current research interests include the development of new catalytic processes and organometallic reagents for organic syntheses as well as mechanistic studies of these catalytic processes. He has coauthored 11 original papers and one review article.

a key intermediate, while amine oxides and phosphine oxides act as oxidants, oxidizing the carbonyl ligand to carbon dioxide which subsequently dissociates, creating a vacant coordination site on the metal.

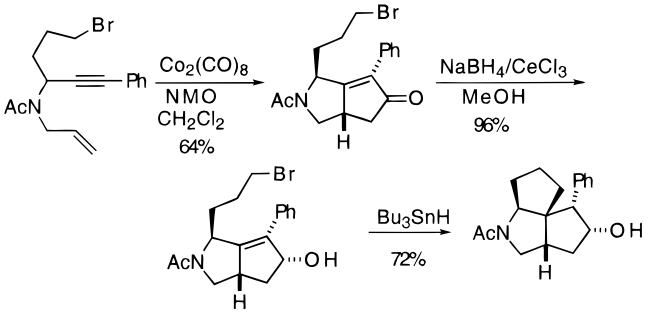
High stereoselectivity was achieved in an asymmetric intermolecular Pauson−Khand reaction of the (alkyne)$Co_2(CO)_6$ complex **2** bearing 10-(methylthio)-isoborneol as the chiral auxiliary by using *N*-morpholine oxide to promote the dissociation of a carbonyl ligand (Scheme 1).[20] Attempts to control the stereochemistry of the products in intermolecular Pauson−Khand reactions using the chiral phosphine ligand "glyphos" have been reported[21,22] which give products with moderate to excellent enantiomeric purity.

Electron-deficient alkynes are, in general, poor substrates for the Pauson−Khand reaction. However, these alkynes have been successfully incorpo-

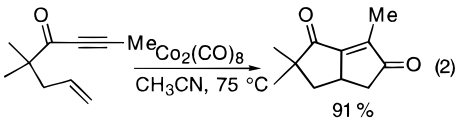
Scheme 1

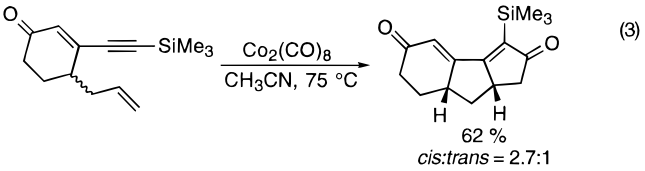


Scheme 2



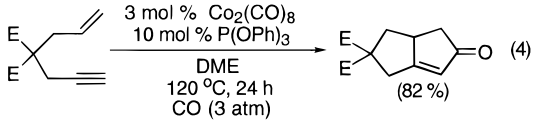
rated either by adding *N*-morpholine oxide to the reaction system[23] or by using alkynes conjugated to metal carbenes.[24] It has also been shown [25] that the intramolecular Pauson−Khand reaction of electron-deficient alkynes proceeds smoothly to give the corresponding bicyclic enediones in high yield when acetonitrile is used as the solvent (eqs 2 and 3).



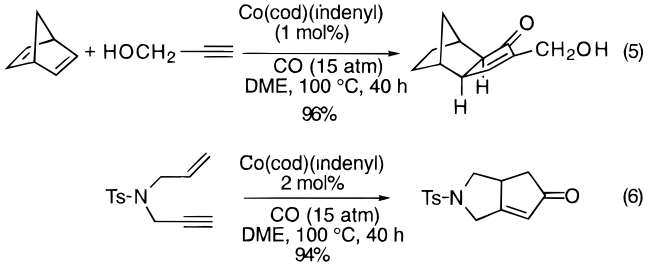


The Pauson−Khand reaction has been used in the syntheses of angularly fused triquinanes.[14,26] A combination of Pauson−Khand reaction and radical cyclization is shown in Scheme 2.[27]

Catalytic Pauson−Khand Reaction. Attempts were made to promote the Pauson−Khand reaction catalytically with limited success:[28−31] Pauson and Khand[7] developed a reaction system with turnover numbers in the order of 10−20 by using isooctane as the solvent, but this process suffered from the formation of byproducts and low yields. Rautenstrauch et al.[32] reported a relatively high turnover number of 220, but the scope of the reaction was limited to the use of ethylene as the alkene. In 1994, however, Jeong et al.[33] realized the first effective catalytic Pauson−Khand reaction by using triphenyl phosphite as the additive and DME as the solvent (eq 4). Yields were moderate under ambient pressure of CO, but substantially improved by carrying the reaction under 3 atm of CO.

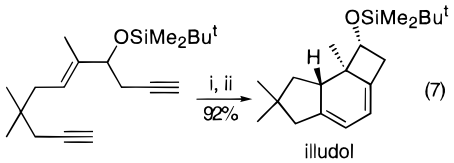


The same research group has further reported[34] efficient catalytic intermolecular and intramolecular Pauson−Khand reactions using a Co(I) complex with an indenyl ligand as the catalyst and DME as the solvent under 15 atm of CO (eqs 5 and 6). Stereoselectivity as well as product yield of this process is excellent, and the turnover numbers reach as high as 500.



2. Cobalt-Catalyzed Carbocyclizations

The cobalt-*mediated* [2 + 2 + 2] cycloaddition reaction has been the subject of extensive investigation.[35,36] The major advantage of this process (stoichiometric to Co) is its ability to construct fused-polycyclic compounds with or without heteroatoms in one step from simple starting materials. Alkyne, alkene, nitriles and isocyanate as well as carbon monoxide can take part in this process to give products with four-, five- or six-membered rings. These reactions proceed with good chemo-, regio-, and stereoselectivities and found many applications in organic synthesis.[35,37−41] For example, in the total synthesis of illudol, the [2 + 2 + 2] cyclization step produced three stereocenters with complete stereocontrol as shown in eq 7.[40]

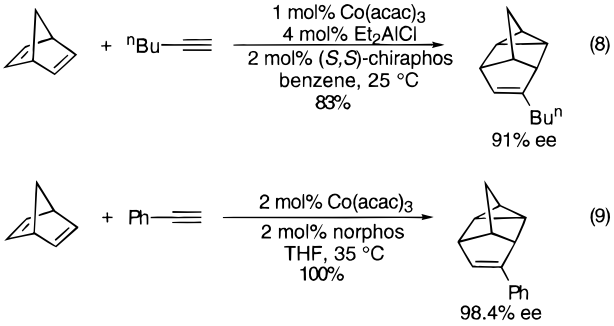


i) $CpCo(CO)_2$ (1.1 equiv.), toluene, 110 °C, hv, 6 h;
ii) $CuCl_2.2\,H_2O$, DME, 23 °C, 3 h

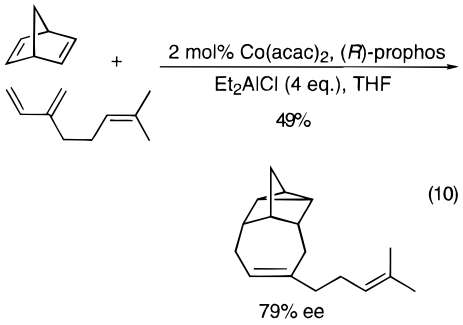
A Co(I) complex, $CpCo(CO)_2$, appears to be the catalyst of choice for this type of reactions. Combinations of Co(II) or Co(III) complexes with aluminum reagents in the presence of phosphines have also been used for the homo-Diels−Alder reactions of norbornadienes with alkenes or alkynes.[42,43]

Enantioselective homo-Diels−Alder reaction is catalyzed by cobalt complexes with chiral diphosphines

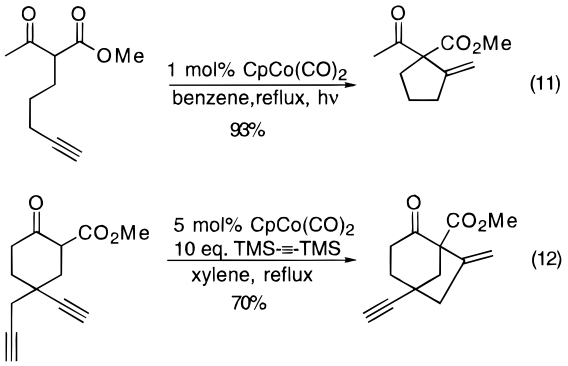
(eqs 8 and 9).[44,45] Exceptionally high enantiomeric excess (98.4% ee) was achieved in the reaction of norbornadiene with phenylacetylene catalyzed by (+)- or (−)-norphos−Co complex (eq 9).[45]



In a similar manner, good asymmetric induction was achieved in Co(II)-catalyzed [4 + 2 + 2] cycloadditions (eq 10).[46]

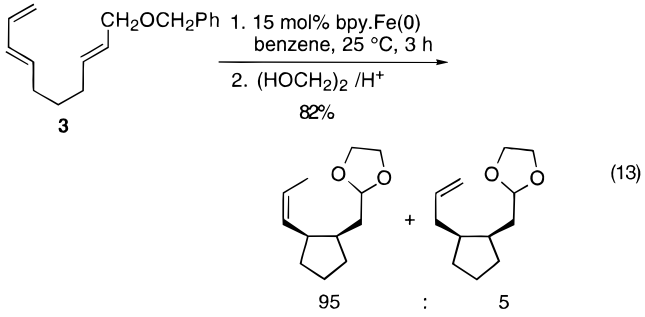


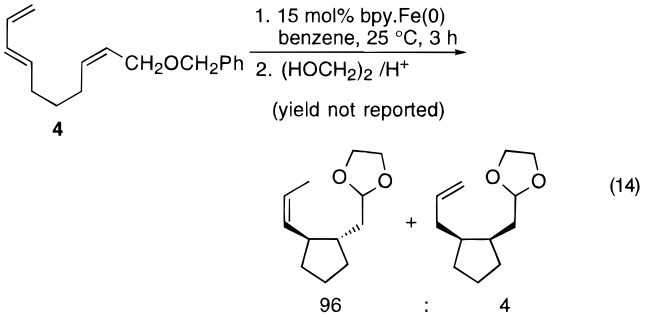
The intramolecular ene reactions of β-keto esters bearing ϵ-terminal alkyne moieties proceed with excellent selectivity in high yield (eqs 11 and 12).[47]

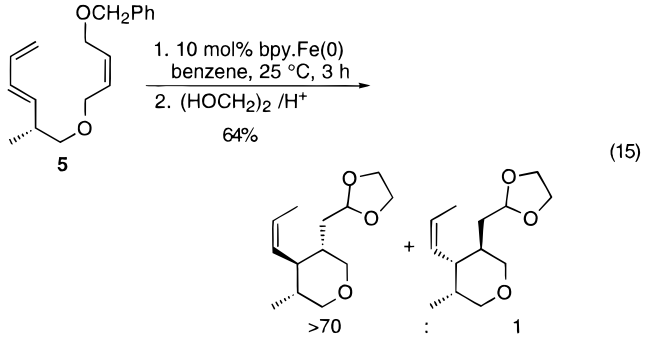


III. Iron-Catalyzed Carbocyclizations

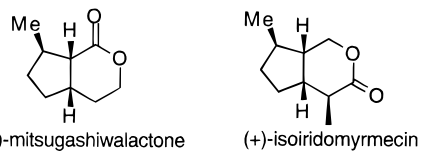
The iron-catalyzed [4 + 4] ene cyclization of trienes which is followed by allylic hydrogen transfer has been extensively studied.[48−50] For example, the reactions of (2*E*,7*E*)-decatriene ether **3** and (2*Z*,7*E*)-decatriene ether **4** proceed with high stereospecificity to yield the corresponding *cis*- and *trans*-disubstituted cyclopentanes, respectively, in high yields (eqs 13 and 14).[48] In these reactions, the formation of a small amount of regioisomers and/or [4 + 2] ene products was observed. When 2-substituted triene esters are used, *trans*-disubstituted cyclopentanes were formed regardless of the stereochemistry at the C-2.[49] In addition, the reaction showed excellent stereocontrol when substituted triene ethers such as **5** were used in order to generate three contiguous chiral centers (eq 15).[48,51]



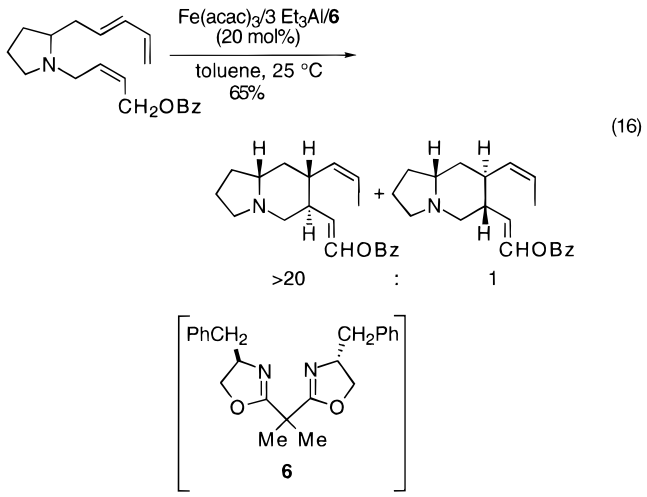




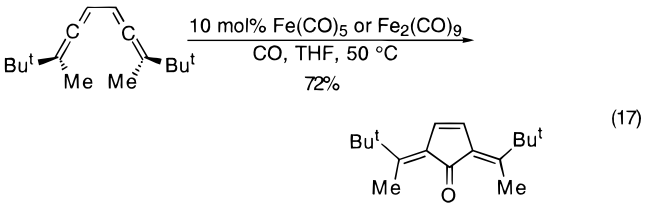
This method was successfully applied for the synthesis of (−)-mitsugashiwalactone and (+)-isoiridomyrmecin.[52]



Asymmetric induction in this ene reaction was attempted by using a combination of $Fe(acac)_3$ and Et_3Al as the catalyst and a chiral bisoxazoline ligand **6**.[53] No asymmetric induction took place, but high 1,3-stereoinduction was observed (eq 16).

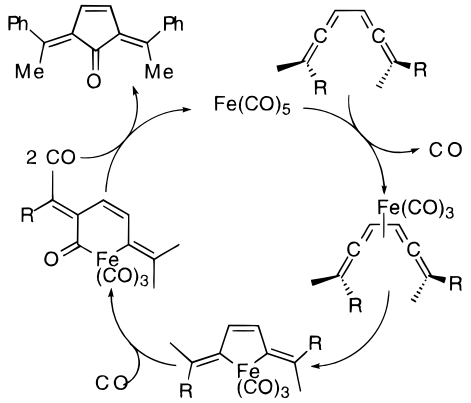


The first iron(0)-catalyzed [4 + 1] cycloaddition reaction was reported in 1992,[54] in which conjugated diallenes were converted to cyclopentenones in the presence of carbon monoxide (eq 17). The stereose-



lectivity of the reaction indicates an initial "π-facial coordination" of the diallene substrate to the metal, followed by the formation of a metallacyclopentene intermediate and subsequent CO insertion (Scheme 3).

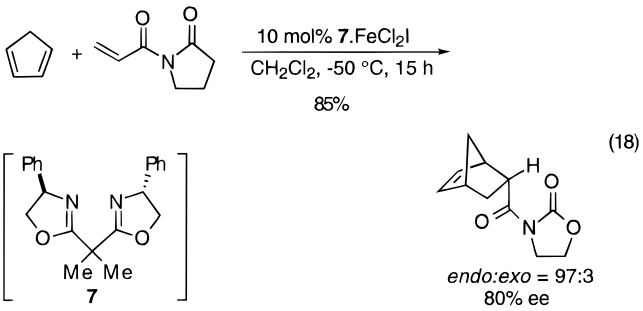
Scheme 3



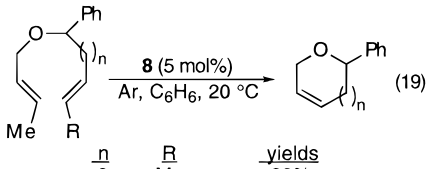
It has been shown that Diels–Alder reactions can be promoted by Fe(II) complexes.[55] Recently, a reasonably high asymmetric induction was observed in a Diels–Alder reaction of cyclopentadiene with an acrylamide catalyzed by a chiral bisoxazoline–Fe complex (eq 18).[56]

IV. Molybdenum-Catalyzed Reactions

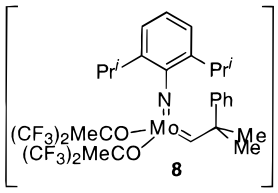
Molybdenum is not a very common metal in homogeneous catalysis and its applications in synthesis are rather limited. However, recently molybdenum–alkylidene complexes have been used as catalysts in ring-closing olefin metathesis reactions.

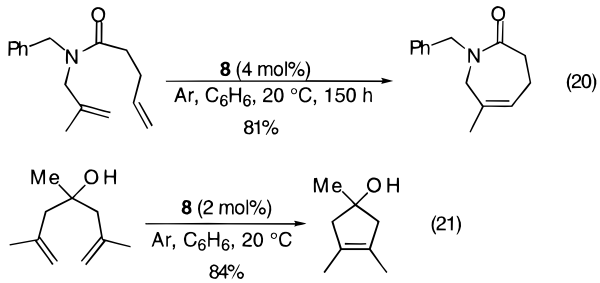


Grubbs and co-workers have investigated the scope and limitation of this reaction and were able to prepare five-, six- and seven-membered ring unsaturated oxygen heterocycles,[57,58] nitrogen-heterocycles,[59] and carbocycles[60] from acyclic dienes (eqs 19–21).

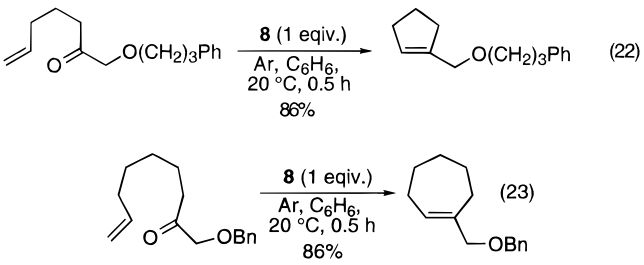


n	R	yields
0	Me	92%
1	H	92%
2	Et	75%

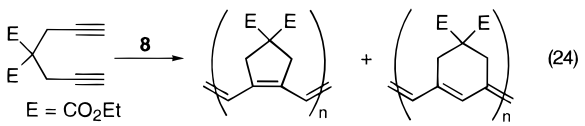




Ring-closing metathesis of enones (olefin metathesis–carbonyl olefination) has also been performed (eqs 22 and 23),[60] which requires a stoichiometric amount of the complex **8**. Many functional groups are tolerated in these reactions.



Molybdenum–alkylidine complexes have also been employed in the cyclopolymerization of diethyl dipropargylmalonate to afford polymers with randomly distributed unsaturated five- and six-membered rings (eq 24).[61]



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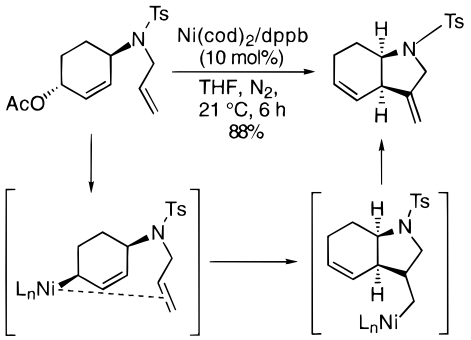
V. Nickel-Catalyzed Carbocyclizations

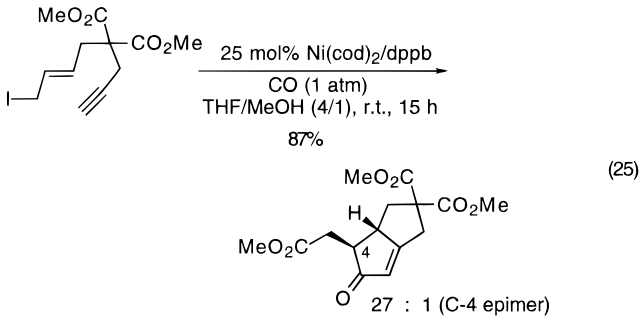
Although several nickel-promoted carbocyclizations have been reported, most of them use stoichiometric amounts of nickel complexes[4,62−66] and only a few are truly catalytic. Nickel-promoted oligomerization and co-oligomerization reactions giving cyclic or polycyclic systems have attracted considerable interest.[67−70]

Dienes and enynes bearing an allylic acetate or a halide moiety undergo nickel-catalyzed ene reactions to afford monocyclization or bicyclization products.[71] The reaction is suggested to proceed via olefin insertion into an initially formed allylnickel complex, followed by β-hydride elimination (Scheme 4).[71] The

Scheme 4



cyclization step proved to be highly cis selective.[72,73] When the reaction was carried out under carbon monoxide atmosphere, CO insertion became faster than β-hydride elimination and a second cyclization took place (eq 25). Introduction of substituents can exercise good stereocontrol in this reaction (eq 26).[73]



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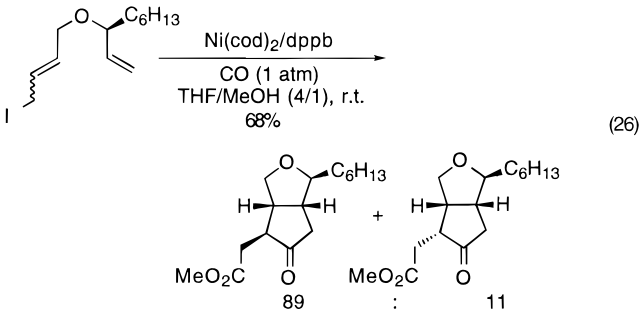
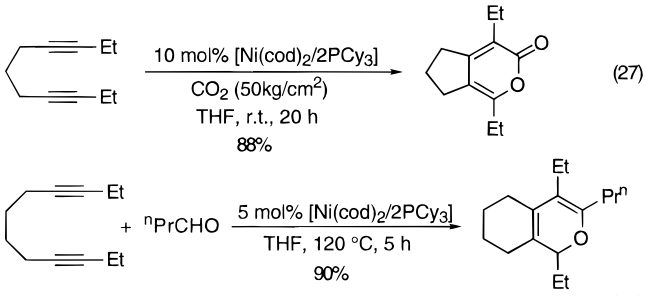


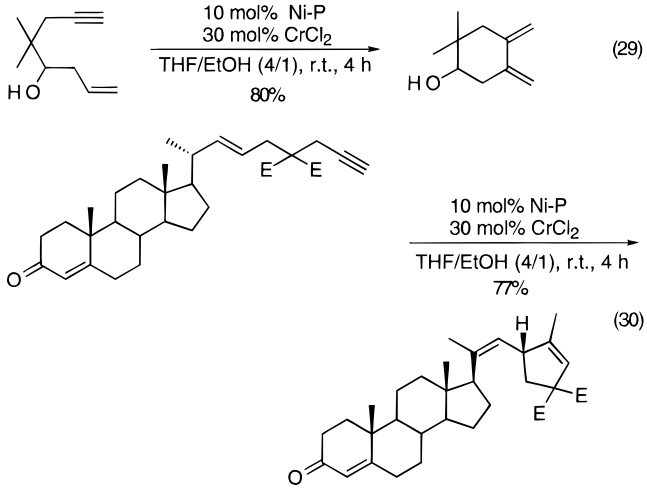
(26)

Cycloaddition of substituted diynes with carbon dioxide[74−76] or aldehydes[77] takes place in the presence of nickel(0)−phosphine catalysts to afford the corresponding bicyclic α-pyrones (eqs 27 and 28).



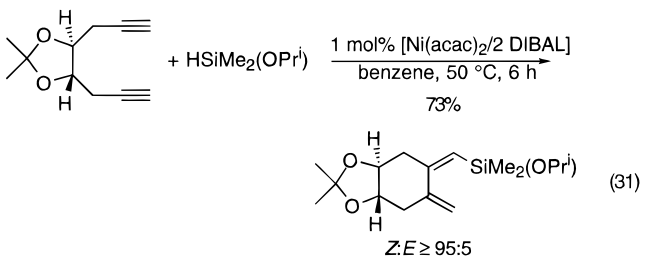
(27) (28)

A polymer-supported Ni(II)/$CrCl_2$ system promotes the intramolecular cyclization of enynes to 1,2-bis(methylene)cyclopentanes or cyclohexanes in high yields (eqs 29 and 30).[78]



(29) (30)

Carbocyclization of 1,7-diynes via hydrosilylation is catalyzed by a Ni(II)/DIBAL system to give the corresponding vicinal *exo*-bis(methylene)cyclohexanes (eqs 31 and 32).[79] The reaction is applicable to the syntheses of heterocycles (eq 33). When a diyne is unsymmetrical, however, a mixture of regioisomers is formed in some cases.



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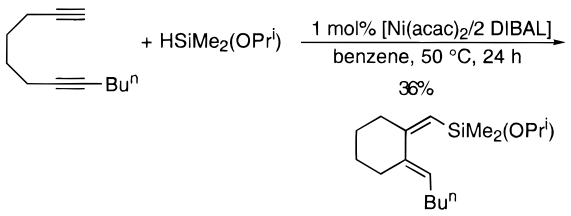

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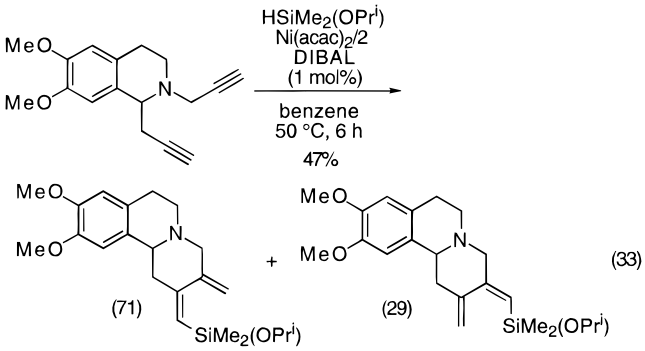
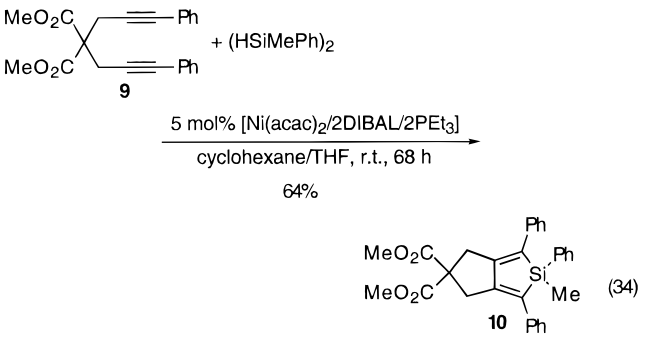


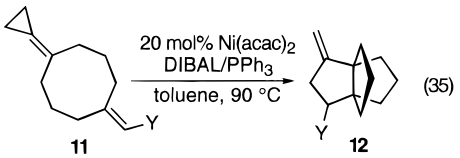
(33)

Nickel-catalyzed carbocyclization of diyne **9** using a 1,2-dihydrodisilane gives a bicyclic silacyclopentadiene **10** (eq 34).[4]



(34)

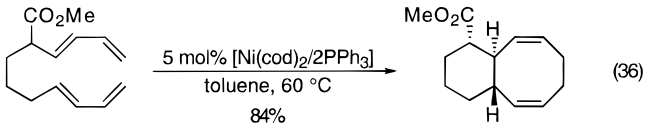
[3.3.3]Propellanes such as **12** are synthesized via a nickel-catalyzed transannular cycloaddition of 5-cyclopropylidene-1-(*exo*-methylene)cyclooctanes such as **11** (eq 35).[80] It is postulated that the reaction proceeds via a π-trimethylenemethane−Ni complex like **13**.



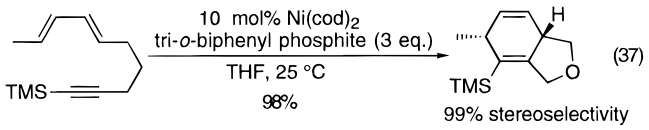
(35)

Y	DIBAL/PPh$_3$	yield
H	1/2	74%
CO_2Et	1/0.5	91%

Nickel(0) has been reported to promote intramolecular [4 + 4] cycloadditions of tetraenes to produce bicyclic products bearing an eight-membered ring (eq 36).[81,82] Intramolecular Diels−Alder reactions can also be promoted by nickel(0) catalysts (eq 37).[83]



(36)



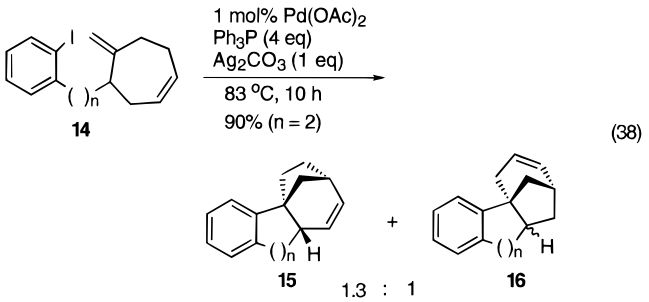
(37)

VI. Palladium-Catalyzed Carbocyclizations

1. The Heck Reaction

Palladium-catalyzed Heck reaction has been attracting much interest.[84] For example, the Heck olefination was employed to synthesize a highly functionalized C-aryl baccatin precursor as an approach to the total synthesis of paclitaxel.[85] Palladium-catalyzed tandem cyclization of 6-bromo 1,6-enynes was used for the synthesis of dihydroindenes and benzodihydropyrrole skeletons.[86a] Intramolecular cyclization of 6-bromo 1,6-enynes was also applied to the synthesis of the A ring of antitumor antibiotic neocarzionstatin chromophore.[86b] Hetero- and carboannulations of vinylic cyclopropanes and cyclobutanes were successfully performed to give benzodihydrofurans, benzodihydropyrrole, and dihydroindenes in good to high yields.[87]

An intramolecular Heck cyclization generates a σ-alkylpalladium(II) intermediate which can be efficiently captured by neighboring olefinic bonds to give double cyclization products having a spiro or fused skeleton.[88] The power of this method is exemplified in the cyclization of **14**, which gives the corresponding polycyclic compounds **15** and **16** (eq 38). A tetracyclic skeleton **18** can be constructed in one step from enynylalkenyl bromide **17** (eq 39).[89]



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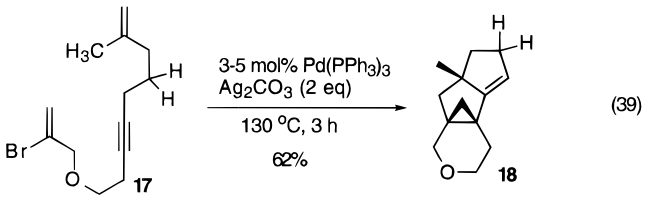
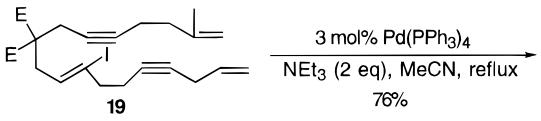


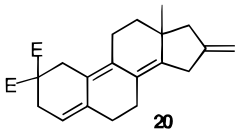
(39)

The Pd-catalyzed cascade carbometalation of alkynes and alkenes provides an efficient method for the construction of cyclic and polycyclic structures, e.g., the reactions of bromo dienynes give bicyclic or tricyclic compounds in good yields.[90] A "zipper-mode" one-step tetracyclization of properly spaced alkatrienediyne **19** that includes sequential cyclocarbopalladation was achieved (eq 40).[91]



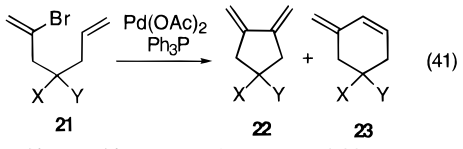
19

E = COOEt (40)



20

The reaction of 2-bromo 1,6-dienes catalyzed by a palladium phosphine complex resulted in the formation of a mixture of **22** and **23**; the regioselectivity of the reaction appears to depend on the structure of the substrate **21** and catalyst used (eq 41).[92]

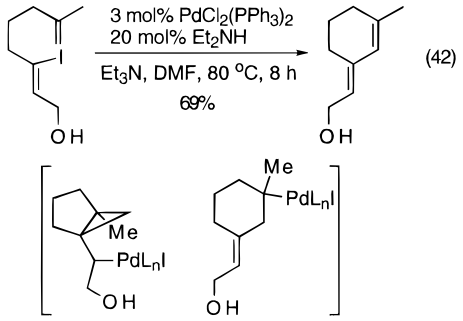


(41)

21 **22** **23**

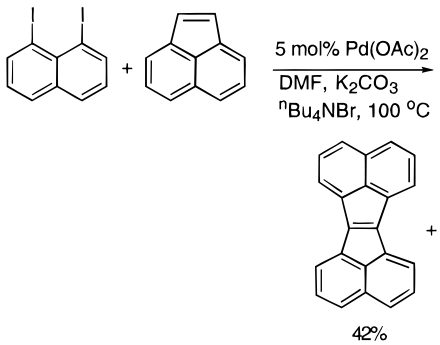
X	Y	catalyst	yield	22:23
CO_2Et	CO_2Et	$Pd(PPh_3)_4$	74%	1:10
COMe	COMe	$Pd(OAc)_2/PPh_3$	74%	2.8:1

An apparent *endo*-mode cyclopalladation with inversion of configuration in the *E*/*Z* geometry of the alkene moiety has recently been reported (eq 42).[93] This apparent *endo*-mode reaction is found to proceed via *exo*-mode cyclization−cyclopropanation rearrangement (eq 42).



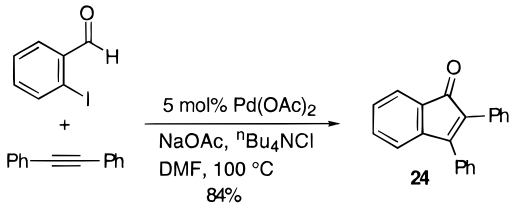
(42)

In the presence of $Pd(OAc)_2$, 1,8-diiodonaphthalene couples with alkenes and alkynes to afford various acenaphthene and acenaphthylene derivatives. Reported yields are, however, only modest with some exceptions (eq 43).[94]



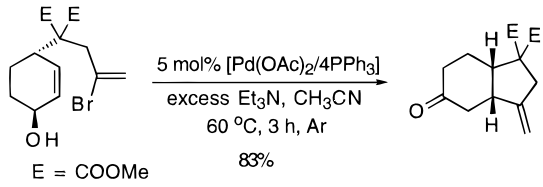
(43)

The coupling of *o*-iodobenzaldehyde and diphenylacetylene was reported to give 2,3-diphenyl-1-indenone (**24**) in high yield (eq 44); the syntheses of indenones and related oxygen and nitrogen heterocycles through this type of carboannulation and heteroannulation have been extensively studied.[95−99]

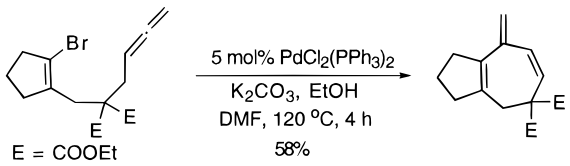


24 (44)

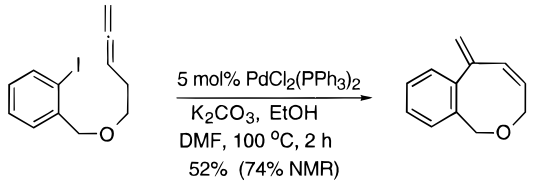
Intramolecular Heck reaction of substrates having an allylic alcohol moiety together with a vinyl or aryl bromide (or iodide) in a molecule gives the corresponding cyclized products in good yields (eq 45).[100] Reactions of aryl and alkenyl halides bearing allene moiety give seven- and eight-membered *exo*-methylenecycloalkenes in good yields (eqs 46 and 47).[101]



E = COOMe (45)



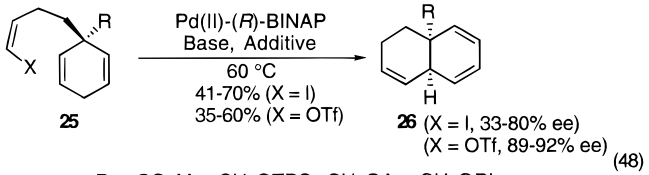
E = COOEt (46)



(47)

Asymmetric Heck reaction has recently been developed as a powerful method for enantioselective synthesis of quaternary carbons and construction of bicyclic and polycyclic frameworks of biologically active natural products.[102−115] The first successful examples of the asymmetric Heck reaction were reported in 1989 for the synthesis of chiral nonracemic *cis*-decalin derivatives **26** (up to 46% ee using $Pd(OAc)_2$, (*R*)-BINAP, and Ag_2CO_3) (eq 48)[102] and spiro-tricyclic hydrindenone **28** (up to 45% ee) (eq 49).[103] In the latter case, enol triflate **27** was used as the substrate instead of conventional alkenyl halides. The optimization of the process in eq 48 was carried out by examining the effects of the chiral catalyst preparation and silver salts used, and the enantioselectivity has been improved to 80% ee (R = $CH_2OTBDMS$) by using Cl_2Pd[(*R*)-BINAP] as the catalyst, $CaCO_3$, and Ag_3PO_4 (eq 48).[104,114] When the corresponding triflate **25** (X = OTf) was used, **26** with 89−95% ee was obtained under optimum conditions (eq 48).[116,117] The *cis*-decalin derivative **26** (R = CO_2Me) was used as a key intermediate for the synthesis of (+)-vernolepin (*vide infra*, section VI. 6).[117]

Asymmetric Heck reaction has also been successfully applied to the syntheses of enantioenriched

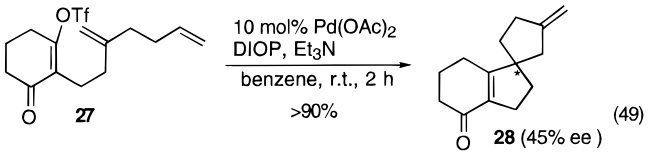


(48)

R = CO_2Me, CH_2OTBS, CH_2OAc, CH_2OPiv

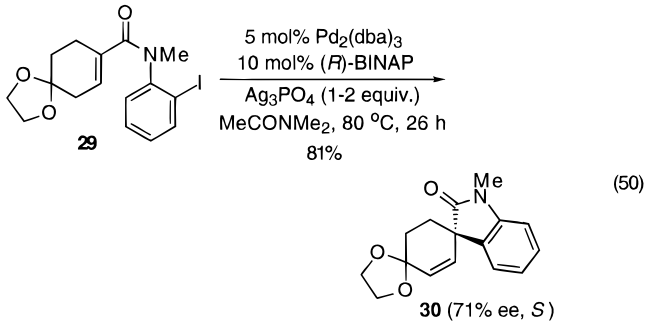
X = I: 5-10 mol% $Pd(OAc)_2$-(*R*)-BINAP or Cl_2Pd[(*R*)-BINAP], Ag^+, ($CaCO_3$), NMP

X = OTf: 5 mol% $Pd(OAc)_2$, 10 mol% (*R*)-BINAP, K_2CO_3 (2 equiv.), toluene

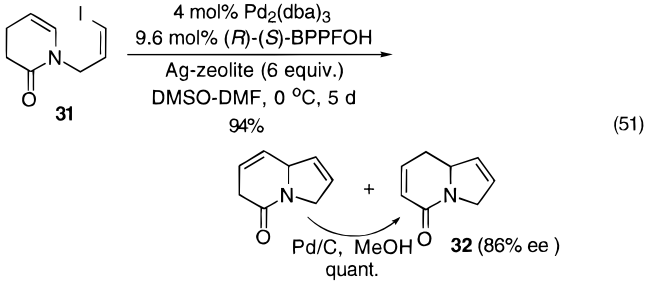


(49)

spirooxindoles,[106] key intermediates to (−)-physostigmine,[108] (−)-eptazocine,[112] halenaquinol,[115] and indolizidine alkaloids.[113,114] Syntheses of a spirooxindole **30**[106] and an indolizidine skeleton **32**[113,114] are typically shown in eqs 50 and 51, respectively.



(50)

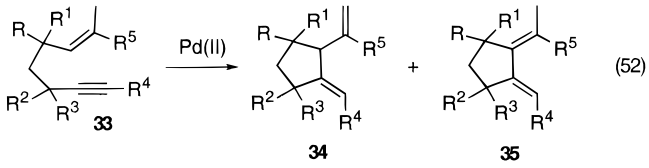


(51)

2. [2 + 2] and [2 + 2 + 2] Cycloadditions

2.1. Palladium-Catalyzed Cyclization of Enynes and Dienes

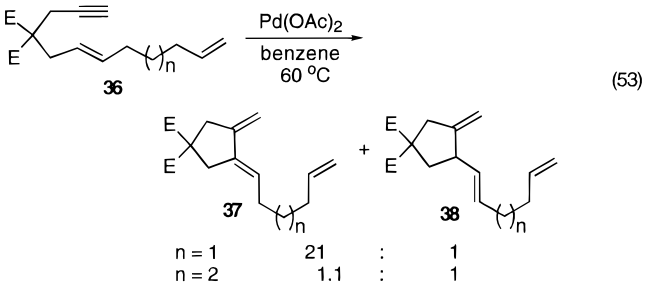
Palladium(II)-catalyzed cycloisomerization of 1,6-enynes has been extensively studied (eq 52).[118] This



(52)

catalytic version of the Alder ene reaction can bring down the reaction temperature from >250 °C necessary for thermal reactions to 25−65 °C. The reaction of **33** gives a mixture of 1,4-diene **34** and 1,3-diene **35** in general, but **34** is formed exclusively in some cases depending on the substitution pattern and the catalyst used. It has been shown that the simpler the substitution pattern on the carbon atoms α to the unsaturated moiety, the higher the proportion of 1,3-diene **35** is. The diastereoselectivity of the reaction also depends on substitution pattern, i.e., excellent diastereoselectivity (>99:1) is observed in the cases for the substrates bearing an internal acetylene moiety, while those with terminal acetylene moiety give low to moderate diastereoselectivity.

Halogen- and sulfur-containing substituents in the alkyne moiety are not tolerated for this reaction.[119] The study has revealed that a remote ethylenic (or acetylenic) bond with a proper length attached to the allylmalonate moiety of **36** directs the reaction toward the selective formation of 1,3-diene **37** (eq 49).[119]

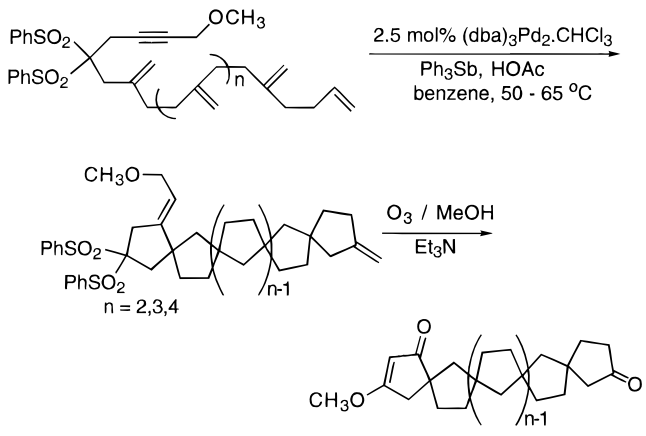


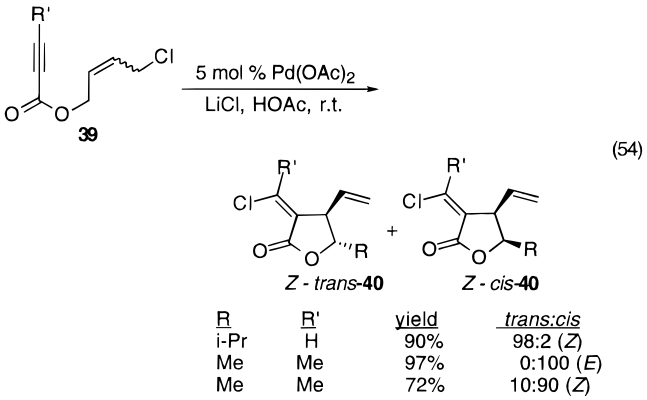
(53)

A Pd-catalyzed zipper reaction has been developed as an application of the cycloisomerization of 1,6-enynes.[120,121] Starting from appropriately spaced polyenynes, triquinanes, propellanes, spiranes, and polyspiranes up to seven spirocycles can be synthesized in high yields in one step. The proposed mechanism involves three stages: (i) initiation, (ii) propagation, and (iii) termination (Scheme 5) wherein the initiation step includes the complexation of a catalyst to the acetylenic bond, and thus an acetylenic moiety in the substrate is a requisite to this zipper reaction.

Controlling factors for the stereochemistry of Pd-catalyzed 1,6-enyne cyclization have been studied in detail.[122] 1′-Alkyl-4′-chloro-2′-alkenyl 2-propynoates (**39**) undergo carbocyclization to form *trans*- and *cis*-3-*exo*-methylene-4-vinyl-5-alkylbutyrolactones (**40**) in the presence of LiCl and a palladium catalyst, Pd(OAc)$_2$, in 50−98% yields (eq 54). The *trans*/*cis* selectivity depends largely on the bulkiness of R′. When R′ is hydrogen, the *trans* isomer is the major product. When R′ is an alkyl or silyl group, the *cis*

Scheme 5

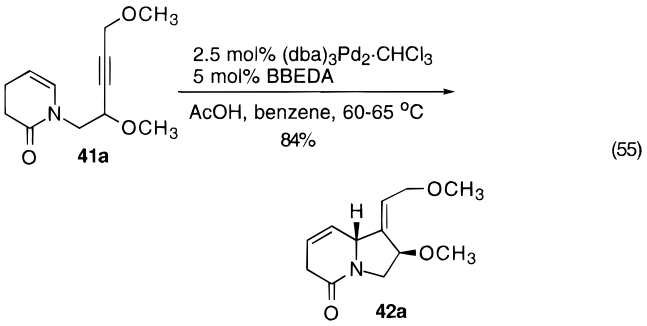




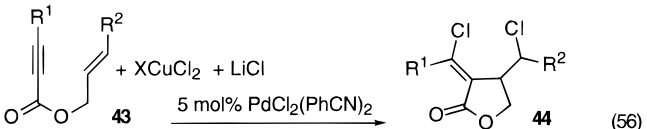
R	R'	yield	trans:cis
i-Pr	H	90%	98:2 (*Z*)
Me	Me	97%	0:100 (*E*)
Me	Me	72%	10:90 (*Z*)

isomer is formed almost exclusively and the stereochemisry (*Z*/*E*) of the *exo*-double bond is dependent on the amount of LiCl.

Palladium-catalyzed cycloisomerization of alkynyl *N*-acyl enamines (**41**) provides an efficient route to indolizidine skeletons.[123] The cationic cyclization of **41** using formic acid gives quinolizidines via iminium ion species. In sharp contrast with this, the reaction of **41**, in the presence of a Pd catalyst such as $Pd_2(dba)_3$ and $Pd(OAc)_2$, triphenylphosphine or *N*,*N*′-bis(benzylidene)ethylene-diamine (BBEDA) as a ligand, and acetic acid, affords indolizidines in good to excellent yields. The reaction of **41a** gives **42a** as single stereo- and regioisomer (eq 55). It has been shown that BBEDA is a better ligand than triphenylphosphine and $Pd(OAc)_2$ exerts an excellent control on the stereochemistry of the newly forming exocyclic double bond, giving only one stereoisomer.

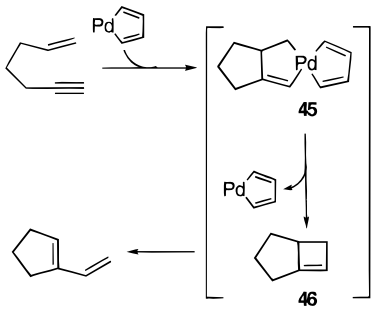


α-(Chloromethylene)-γ-butyrolactones (**44**) are synthesized through Pd-catalyzed intramolecular cyclization of acyclic allylic 2-alkynoates (**43**) (eq 56).[124]

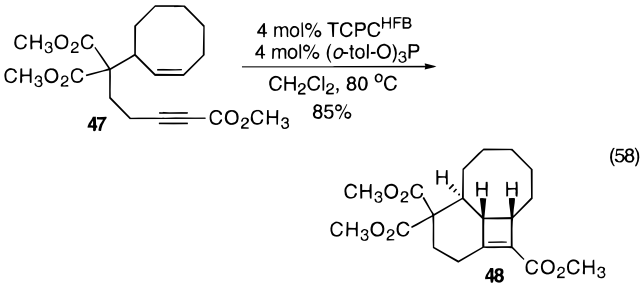


R¹	R²	X	
H	Ph	5	56% (E/Z = 91/9)
CH_3	H	6	85% (E/Z = 5/95)
n-Bu	Ph	6	69% (E/Z = 9.5/90.5)

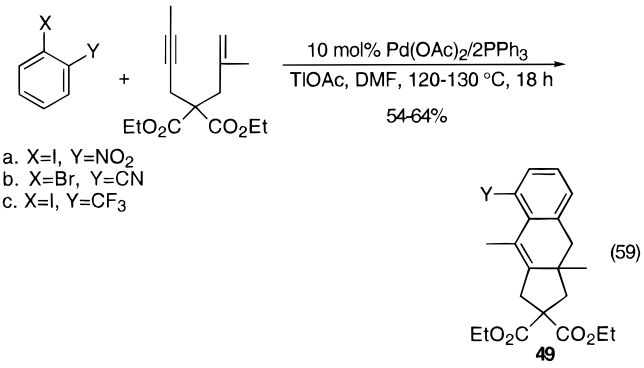
Palladium-catalyzed metathesis of 1,6-enynes was postulated to include a palladometalabicyclo[3.3.0]-octene **45** and a highly strained fused cyclobutene **46** that is equivalent of *trans*-cycloheptene (eq 57).[125,126] The fused cyclobutene **46** is the formal [2 + 2] cycloaddition product of a 1,6-enyne.



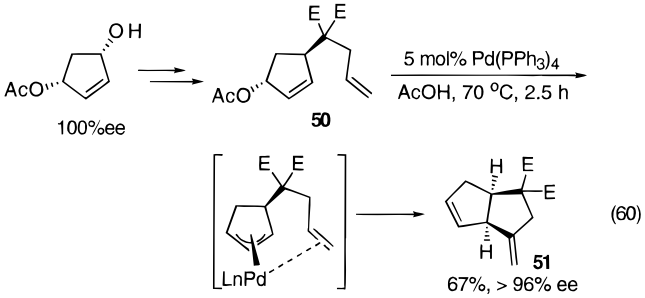
Although bicyclo[3.2.0]heptene (**46**) is too unstable to isolate, the corresponding bicyclo[4.2.0]octene may be isolable since *trans*-cyclooctene is known to be stable at ambient temperature.[127] In fact, two 8−6−4 and 6−6−4 fused tricyclic cyclobutenes have been isolated, which are generated through Pd-catalyzed [2 + 2] cycloaddition of 1,7-enynes using tetrakis(heptafluorobutoxycarbonyl)palladacyclopentadiene ($TCPC^{HFB}$). The structure of the 8−6−4 fused tricyclic cyclobutenes **48** was determined by X-ray crystallography, which unambiguously showed the existence of cyclobutene structure and also revealed an unexpected *trans*-8,6 ring fusion (eq 58).[128]



The reaction of 1,6-enynes with aryl or heteroaryl halides promoted by a Pd(0) catalyst system, generated *in situ* from $Pd(OAc)_2$, PPh_3, and TlOAc, gives the corresponding fused tricyclic products such as **49** in good yield through a [2 + 2 + 2] cycloaddition process (eq 59).[129] This cascade process includes the regiospecific carbopalladation of a 1,6-enyne with an aryl- or heteroaryl-Pd(II) species in the initiation step.

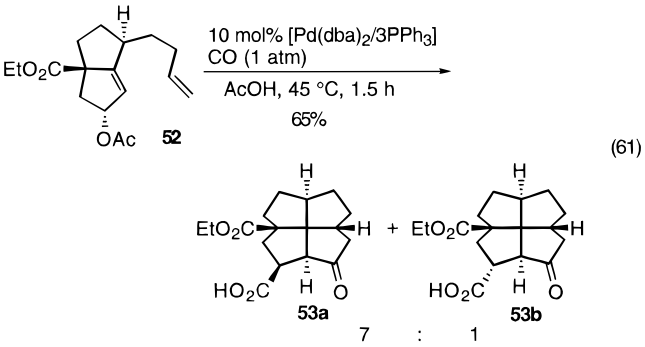


Palladium-catalyzed intramolecular metallo-ene reactions provide efficient routes to a variety of carbocyclic and heterocyclic compounds with high regio- and stereocontrol as exemplified in eq 60.[71−73]



(60)

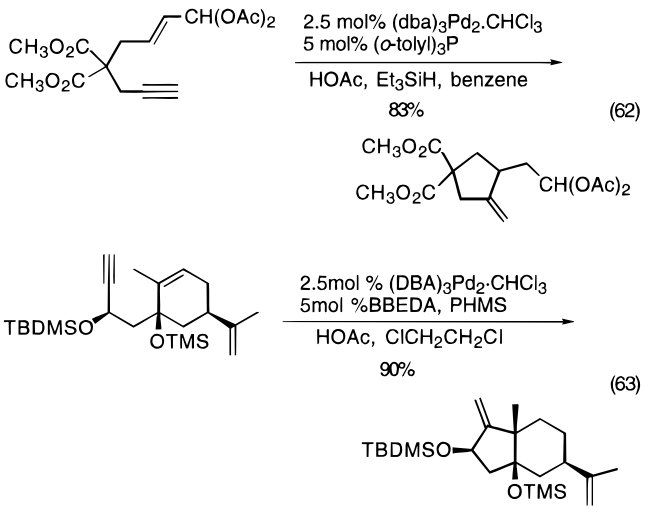
The "palladium-ene" reaction of 1,6-diene **52** followed by carbonylative cyclization, i.e., carbonylative double annulation, gives the corresponding [5.5.5.5]-fenestranes **53a** and **53b** (eq 61).[130] This process is applicable to 1,6-diynes as well.



(61)

2.2. Palladium-Catalyzed Reductive Cyclization of Enynes

Reductive cyclization of 1,6-enynes catalyzed by palladium in the presence of triarylphosphine, acetic acid, and triethylhydrosilane or polymethylhydrosiloxane (PMHS) gives the corresponding cyclopentanes bearing an *exo*-methylene moiety in high yields (eqs 62 and 63).[131] This cyclization is applicable to 1,7-enynes, yielding *exo*-methylenecyclohexanes.



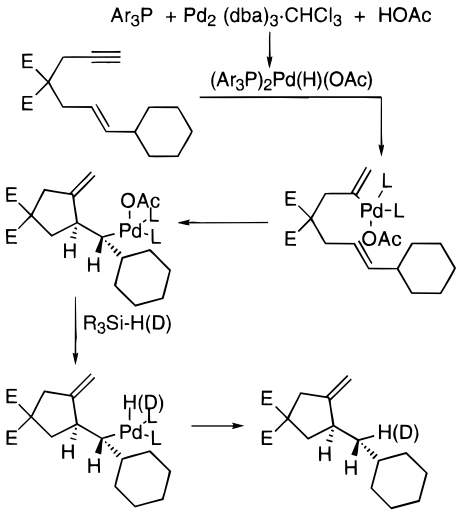
(62)

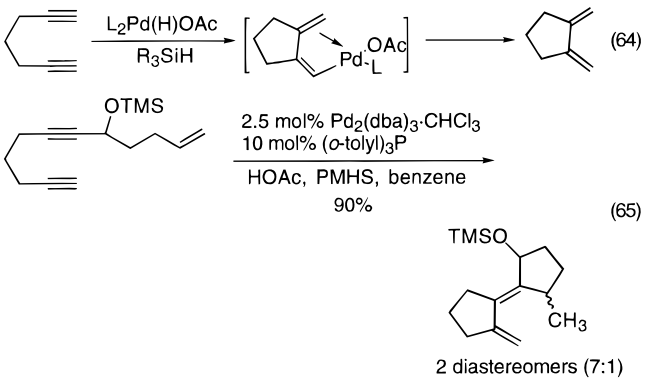
(63)

The active catalyst species of this process has been identified as $L_2Pd(H)(OAc)$ on the basis of deuterium-labeling experiments. The proposed mechanism is shown in Scheme 6.[131]

In a similar manner, palladium-catalyzed reductive cyclization of 1,6-diynes gives 1,2-bis(*exo*-alkylidene)-cyclopentanes in good to high yields (eqs 64 and 65).[132] This process is compatible with acid-sensitive functionalities such as silylacetylenes, silyl ethers, acetals, and propargyl and allyl ethers, in addition to many other functional groups like esters, ketones, enones, alcohols, sulfones, olefins, and dienes.

Scheme 6



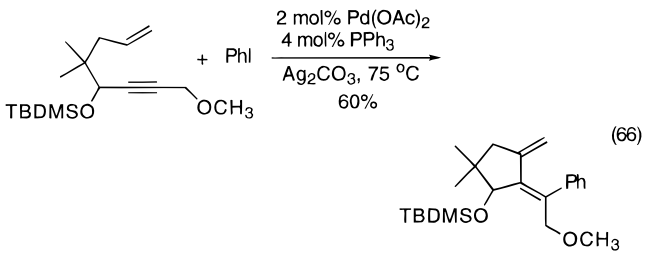


(64)

(65)

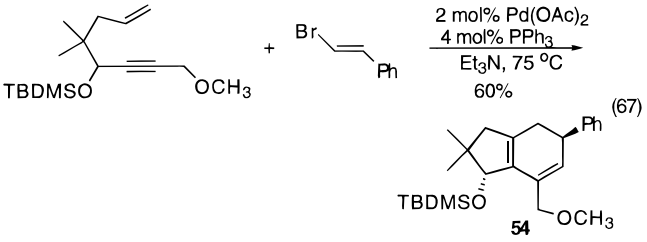
2.3. Palladium-Catalyzed Alkylative Cyclization of 1,6- and 1,7- Enynes

An arylpalladium iodide or bromide, generated from the oxidative addition of an aryl bromide or iodide with a palladium catalyst, can initiate carbocyclization of a 1,6- or 1,7-enyne to give the corresponding 1,2-dialkylidenecycloalkane with excellent chemo-, regio- and stereoselectivity as exemplified in eq 66.[133] This alkylative cyclization process

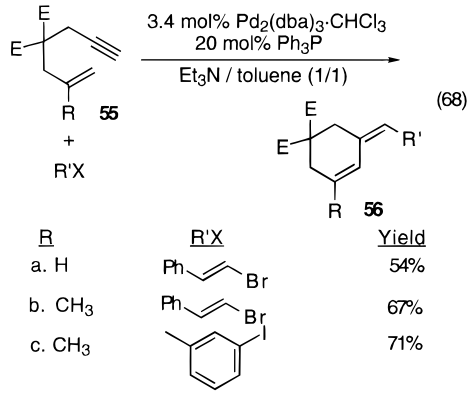


(66)

proceeds thorough exclusive addition of Ar−Pd−X species to the acetylene moiety of the 1,6- and 1,7-enynes. When an alkenyl bromide is used, the second cyclization takes place to give a bicyclic product such as **54** (eq 67).[133]

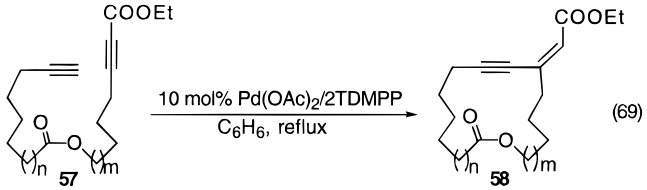


Carbocyclization of 1,6-enynes proceeds via 5-*exo-trig* mode in general due to ring constraints. It has been shown, however, that 6-*endo-trig* mode cyclization forming alkylidenecyclohexenes (**56**) can take place when 1,6-enynes bearing terminal acetylene moiety (**55**) and a palladium catalyst generated from $Pd_2(dba)_3{\cdot}CHCl_3$, triphenylphosphine, and triethylamine are employed for the reaction (eq 68).[134] This reaction was successfully applied to the synthesis of a vitamin D analog.[134]



2.4. Cycloisomerization of α,ω-Diynes

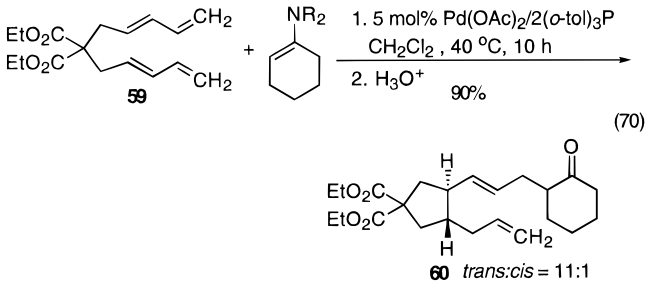
Palladium-catalyzed cycloisomerization of α,ω-diynes, which includes the addition of an (alkynyl)-$Pd(L_2)X$ species to the other acetylenic bond, has been successfully applied to the syntheses of macrocycles.[135] For example, macrocyclic lactones (**58**) up to 26-membered ring can be obtained in good yields in the reactions of α,ω-diynes **57** using a palladium catalyst with tris(2,6-dimethoxylphenyl)phosphine (TDMPP) (eq 69).



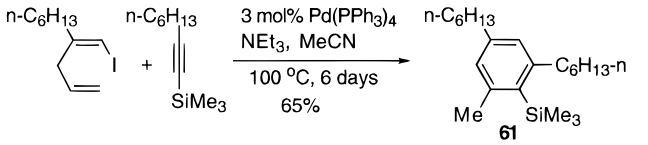
3. Other Type [2 + 2] and [2 + 2 + 2] Cycloadditions

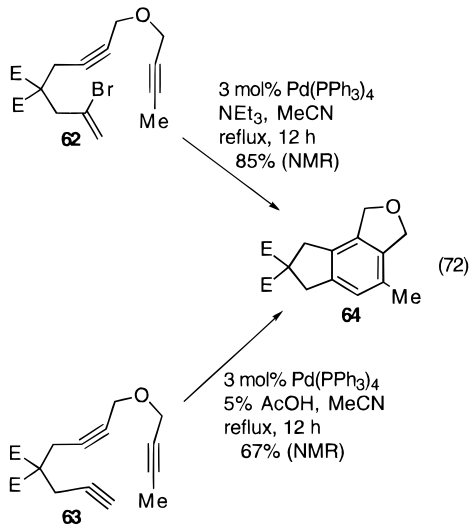
Palladium-catalyzed carbocyclization of a tetraene **59** in the presence of an enamine gives **60** through [2 + 2] cyclization followed by allylation of the enamine (eq 70).[136,137]

Intermolecular [2 + 2 + 2] cyclotrimerization of alkynes to yield benzene derivatives usually does not give a good control of "pair" selectivity nor regioselectivity. Highly regiocontrolled syntheses of polysubstituted benzenes such as **61** and **64** have been



developed through inter−intra cascade carbometalation (eq 71) and cyclic cascade carbometalation (eq 72).[90,138]

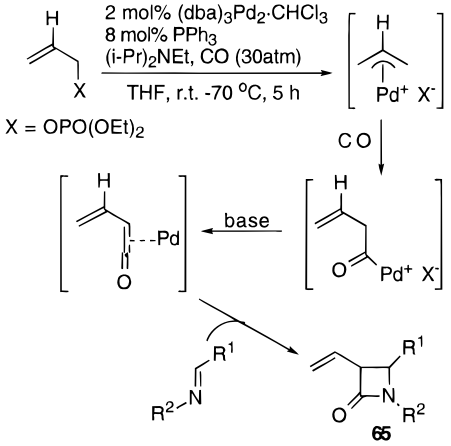




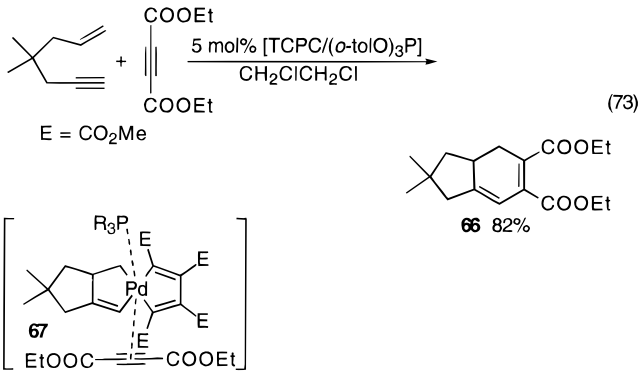
Palladium-catalyzed carbonylative [2 + 2] cycloaddition of allyl phosphates to imines gives either *cis*- or *trans*-3-vinyl-*β*-lactams (**65**) in moderate to high yields.[139] The stereoselectivity is dependent on the nature of imines, i.e., imines conjugated to a carbonyl functionality give *cis*-*β*-lactams selectively, whereas unconjugated imines afford *trans*-*β*-lactams exclusively. The reaction is deemed to proceed via the enolate of a 3-butenoyl−Pd species which is a vinylketene equivalent (Scheme 7).[139]

Palladium-catalyzed cyclizations of 1,6-enynes are suggested to proceed via palladacyclopentene intermediates (*vide supra*). Such an intermediate can be indeed trapped by an acetylenedicarboxylate when tetra(carbomethoxy)palladacyclopentadiene (TCPC)−triarylphosphine (1 equiv) is used as the catalyst.[140] This [2 + 2 + 2] cycloaddition process gives bicyclo[4.3.0]nonadienes **66** in high yields (eq 73). Mechanistic study of this trapping reaction strongly suggests the existence of the palladacycle **67** as a key intermediate. No crossover was observed between

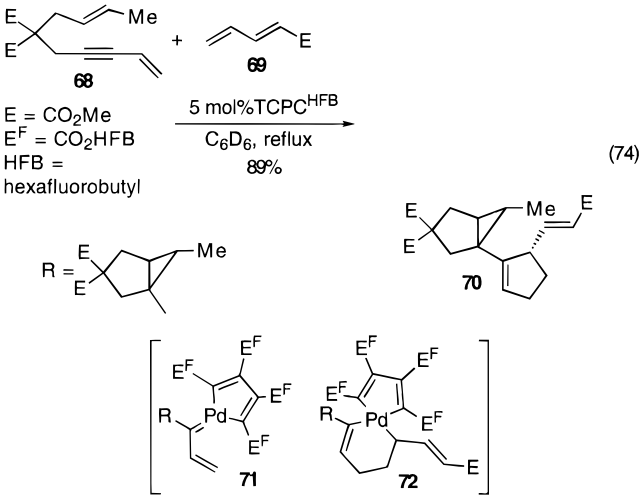
Scheme 7



TCPC and acetylenedicarboxylate as exemplified in eq 73.

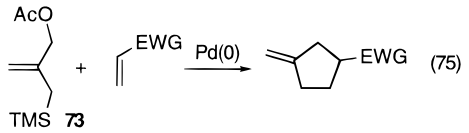


Reactions of ynedienes **68** and 1,3-dienes **69** afford bicyclo[3.1.0]cyclohexan-1-yl-5-ethenyl-1-cyclopentene **70** in good to high yields (eq 74).[141] This reaction appears to include 1-pallada-1,3-diene species **71** and its cycloadduct with methyl 2,4-pentanedienoate **72** as key intermediates.[141]

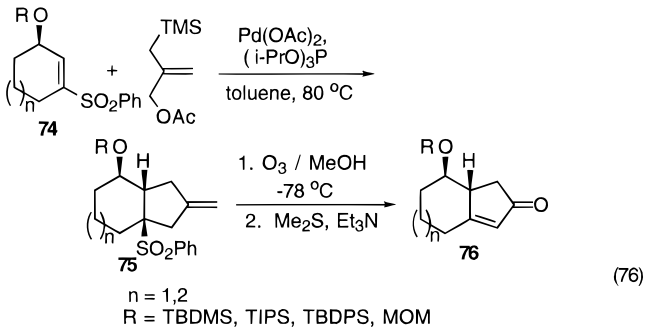


4. [3 + 2] and [4 + 3] Cycloadditions

Palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane (TMM), generated *in situ* from 2-[(trimethylsilyl)methyl]allyl acetate (**73**) to electron-deficient olefins, provides attractive routes to functionalized cyclopentanes (eq 75).[3,142−145] This process is likely to involve TMM−PdL_2 species.



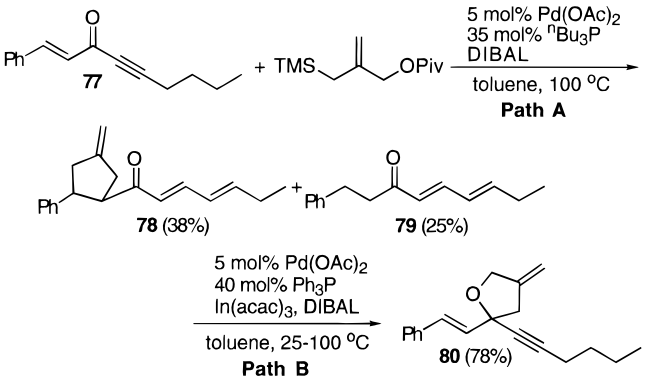
However, the application of this "methylenecyclopentannulation" to cyclic enones does not necessarily give satisfactory results. In order to overcome this problem, the use of 3-(protected hydroxy)-1-sulfonyl-1-cycloalkenes **74** has been introduced.[146] The reaction gives bicyclic *exo*-methylenecyclopentanes **75** in moderate to good yields wherein the major products are formed through the addition of TMM to **74** from the face opposite to the protected hydroxy group (eq 76). The adducts **75** can readily be converted to the corresponding bicyclic cyclopentenones (**76**) in excellent yields (eq 76).[146]



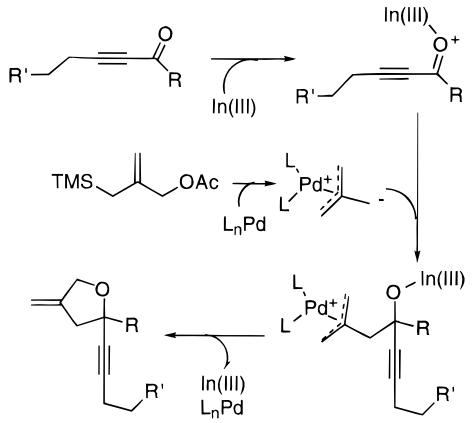
The Pd-catalyzed cycloaddition of TMM to vinylalkynylketone **77** under the standard conditions gives a mixture of *exo*-methylenecyclopentane **78** (38%) and trienone **79** (25%) (path A, Scheme 8).[147] In sharp contrast with this, the addition of indium acetylacetonate to the reaction system dramatically changes the reaction course, producing *exo*-methylenetetrahydrofuran **80** in 78% yield through selective TMM addition to the carbonyl double bond (path B, Scheme 8), i.e., In(III) salt acts as an efficient "chemoselectivity switch".[147] The presence of acetylenic bond conjugated to ketone functionality is the requisite for the path B to occur. Thus, the ketone moiety of enones and simple ketones is inactive for this reaction even when In(III) salt is used as the cocatalyst.[147]

The observed "indium effect" can be accommodated by assuming that In(III) coordinates to the oxygen

Scheme 8

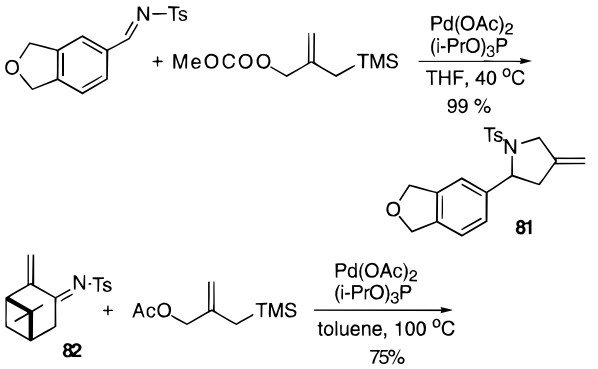


Scheme 9



of ynones to activate the carbonyl group and improve the reactivity of the oxygen terminus toward a π-allyl−Pd intermediate (Scheme 9).[147]

The Pd-catalyzed [3 + 2] cycloaddition of TMM is applicable to imines, giving *exo*-methylenepyrrolidines (**81**) in excellent yields (eq 77).[148] An α,β-unsaturated imine **82** has been shown to react with TMM-Pd species in [4 + 3] manner, affording fused-ring azepine **83** (eq 78).[148]



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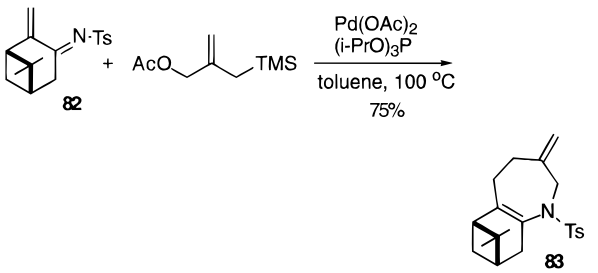
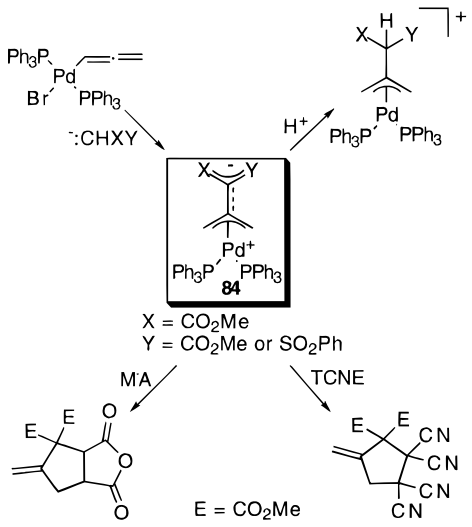


(78)

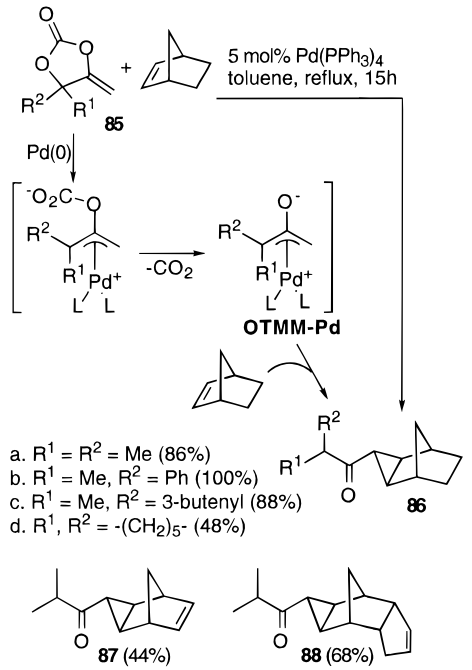
Zwitterionic TMM−Pd complexes are believed to be the key transient species in palladium-catalyzed cycloadditions as described above. Indeed, the single-crystal X-ray structure of a stable zwitterionic TMM−Pd complex **84** (X = Y = COOMe) has been obtained, which has an asymmetric η^3 mode structure that makes a sharp contrast to the well-studied η^4-TMM complexes.[149] Moreover, **84** undergoes facile cycloaddition to electron-deficient olefins such as maleic anhydride and TCNE to form the corresponding *exo*-methylenecyclopentanes, providing stoichiometric evidence for the Pd-mediated [3 + 2] cycloaddition process. The preparation and some reactions of **84** are illustrated in Scheme 10.

Transition-metal complexes of *hetero*trimethylenemethanes have been proved to be useful in organic synthesis.[150,151] For example, (*oxa*trimethylenemethane)palladium species (OTMM-Pd) were generated from 4-methylene-1,3-dioxalan-2-ones (**85**) and $Pd(PPh_3)_4$, which were subsequently trapped by norbornene, norbornadiene, and dicyclopentadiene to

Scheme 10



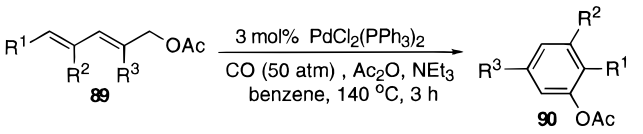
Scheme 11



afford the corresponding tricyclic cyclopropanes (**86**−**88**) in good to excellent yields (Scheme 11).[151] Cycloadditions of OTMM-Pd to aryl isocyanates, *N*,*N*-diphenylcarbodiimide, and diphenylketene forming five-membered heterocycles have also been reported.[151]

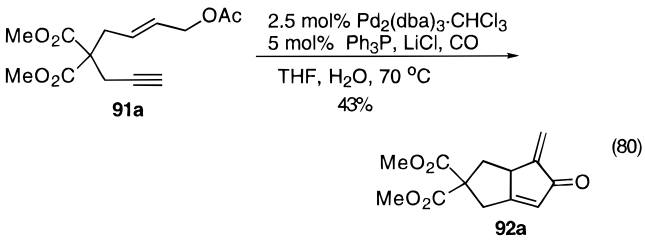
5. Palladium-Catalyzed Cyclocarbonylations

Palladium-catalyzed cyclocarbonylation of 3-arylallyl acetate has been shown to serve as an efficient synthetic route to fused aromatic compounds such as naphthalene, phenanthrene, benzofuran, benzothiophene, and indole derivatives.[152−157] Recently, the Pd-catalyzed cyclocarbonylation has been successfully applied to the syntheses of phenol derivatives.[158] The cyclocarbonylations of substituted and unsubstituted 2,4-pentadienyl acetates (**89**) catalyzed by $PdCl_2(PPh_3)_3$ in the presence of triethylamine and acetic anhydride at 140 °C gives the corresponding *O*-acetylphenols (**90**) in moderate to high yields (eq 79).



(79)

α-Methylenecyclopentenones (**92** or **94**) can be obtained in moderate to good yields from 8-acetoxyoct-6-en-1-ynes (**91**) or 6-benzoxyoct-7-en-1-ynes (**93**) through palladium-catalyzed intramolecular alkyne−carbon monoxide−alkene insertion cascade (eqs 80 and 81).[159]



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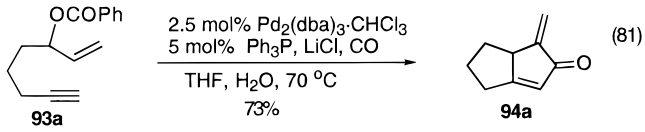
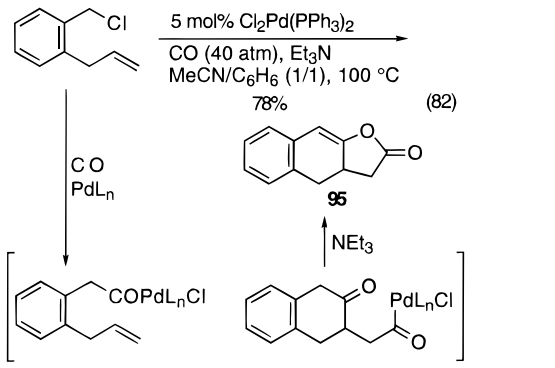


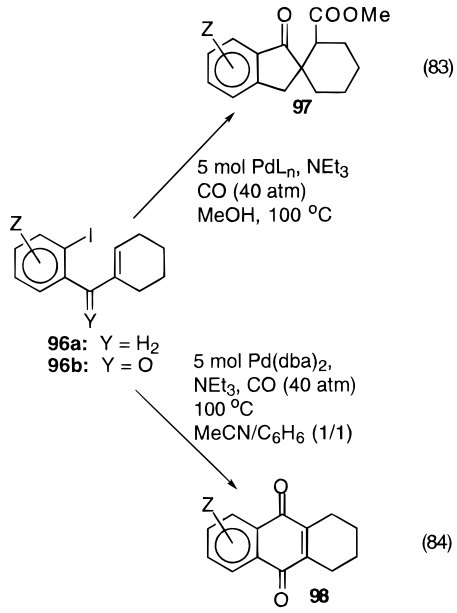
(81)

Palladium-catalyzed cyclocarbonylation of *o*-allylbenzyl chloride in the presence of triethylamine provides an efficient route to benzoannulated enol lactone **95** in high yield (eq 82), which is the key intermediate for the synthesis of antiulcer agent U-68,215.[160]



(82)

The cyclocarbonylation (or cyclic acylpalladation) of *o*-iodoaryl alkenyl ketones (**96a**) catalyzed by palladium complexes with phosphine ligands proceeds exclusively in an *exo* mode to give spirocarbocycles **97** (eq 83).[161] However, when a palladium catalyst that does not contain any phosphine ligand, e.g., $Pd(dba)_2$, is employed for the cyclocarbonylation of **96b**, the reaction gives tricyclic quinones **98** in excellent yields (eq 84).[162]



(83)

(84)

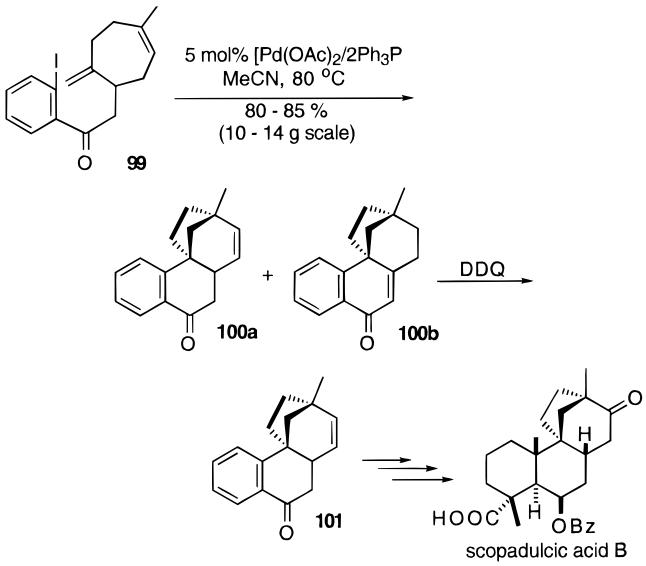
6. Applications of Palladium-Catalyzed Carbocyclization Reactions

The Pd-catalyzed Heck reaction of **99**, giving **100**, has been used as a key step in the first total synthesis of scopadulcic acid B, an active component of a Paraguayan folk medicine (Scheme 12).[163]

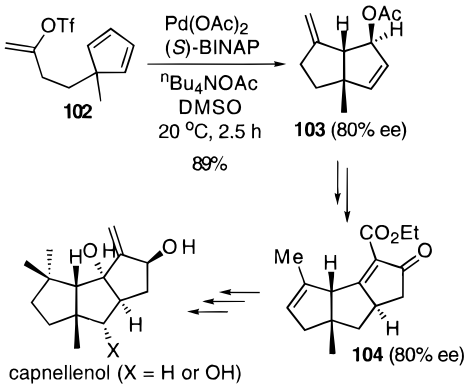
Asymmetric Heck reaction of **102** followed by an anion capture process has been applied to the synthesis of an advanced key intermediate **104** for capnellennols (Scheme 13).[105,109]

The first asymmetric synthesis of (+)-vernolepin has been achieved using *cis*-decalin derivative **26** (R = CO_2Me, 86% ee), obtained through the asymmetric Heck reaction of **25** (*vide supra*), as a key intermediate (Scheme 14).[117] On the basis of this asymmetric synthesis, the absolute stereochemistry of this natural product was determined.[117] This asymmetric Heck reaction approach has been also applied to the corresponding functionalized cyclohexa-2,5-dien-4-ol and cyclohexa-2,5-dien-4-one, giving bicyclo[4.4.0]-decadienone (86% ee)[110] and trienone (86% ee)[111]

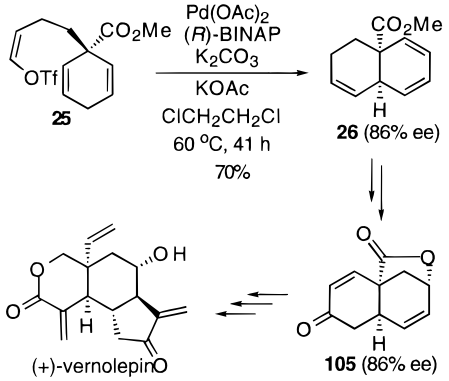
Scheme 12



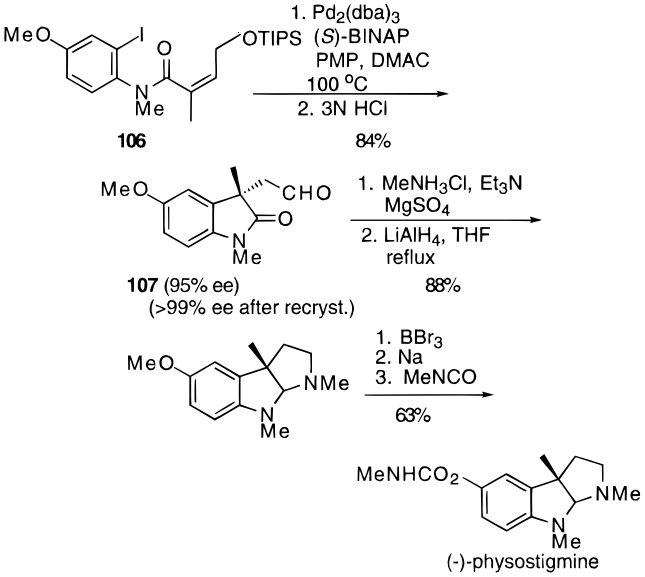
Scheme 13



Scheme 14



Scheme 15

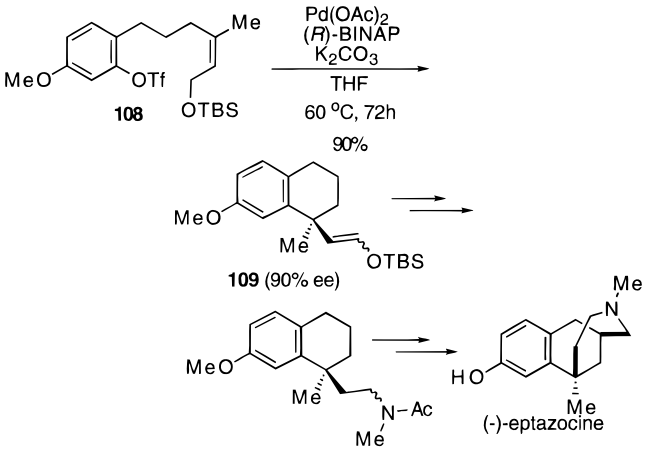


which are the derivatives of **26**.[115] In a similar manner, *cis*-hydrindans (up to 86% ee) were synthesized.[107]

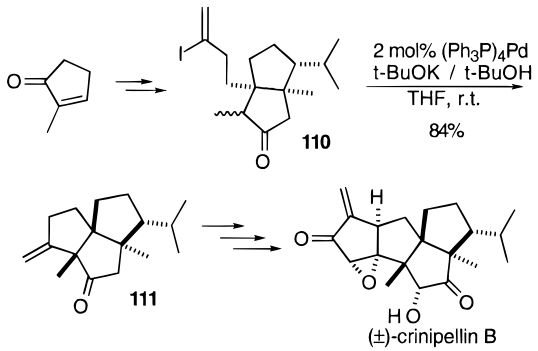
(−)-Physostigmine, a powerful inhibitor of acetylcoline-esterase, was synthesized using the asymmetric Heck reaction of **106** giving **107** (95% ee) as the key step (Scheme 15).[108]

(−)-Eptazocine, an analgesic, was also synthesized by using an efficient asymmetric Heck reaction of **108** that gives a key intermediate **109** (90% ee) (Scheme 16).[112] By means of the same strategy, a key tricyclic intermediate for halenaquinol, an antibiotic, was synthesized.[115]

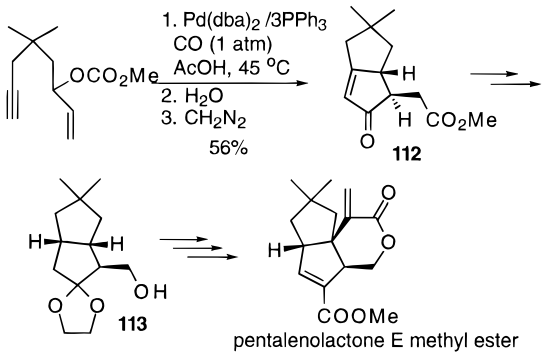
Scheme 16



Scheme 17



Scheme 18

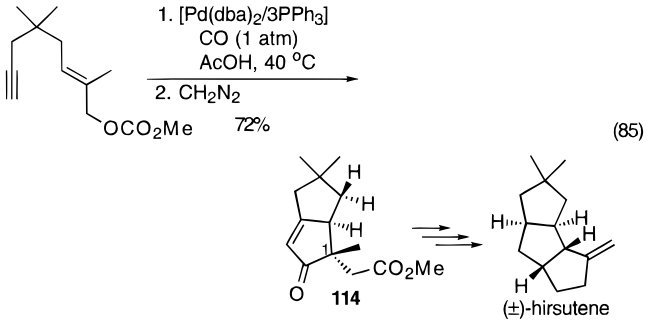


Palladium-catalyzed carbocyclization of **110** has been employed to synthesize a triquinane intermediate **111** in the total synthesis of a tetraquinane diterpenoid (±)-crinipellin B that possesses antibiotic activity (Scheme 17).[164]

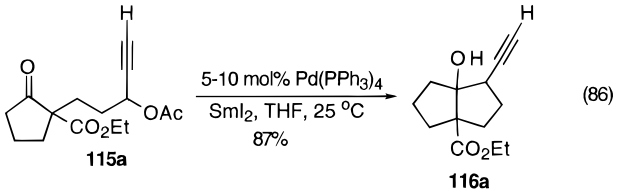
The "palladium-ene cyclization" has been applied to the syntheses of cyclopentanoids such as a key intermediate **113** via bicyclo[3.3.0]octenone **112** for the synthesis of (±)-pentalenolactone E methyl ester (Scheme 18)[165] and a key intermediate **113** (obtained as a 85/15 mixture of C-1 epimers) for the synthesis of hirsutene (eq 85).[166]

7. Miscellaneous

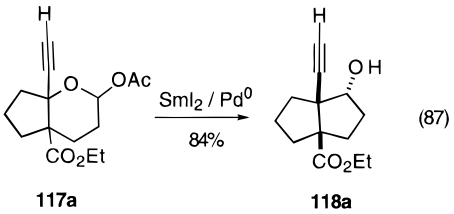
The SmI_2-promoted carbocyclization of 1-(4-oxoalkyl)-2-alkynyl esters **115** catalyzed by $Pd(PPh_3)_4$ gives the corresponding homopropargylcycloalkanols **116** in good to excellent yields (eq 86).[167] The reaction appears to proceed via an allenyl-Pd species followed



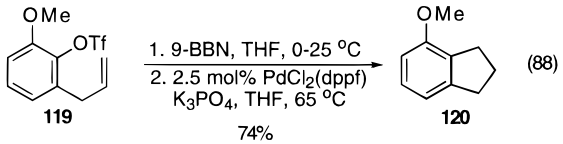
by transmetalation to an allenyl-Sm species that undergoes cyclization with the carbonyl moiety of **115**.

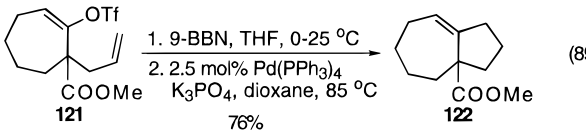


Aldehydes are not suitable substrates for this reductive carbocyclization. However, γ-alkynyllactol esters **117**, serving as masked aldehydes or ketones, undergo ring contraction to form cyclic homopropargyl alcohols **118** as the single diastereomer in high yields (eq 87).[167] This process is also assumed to involve essentially the same allenyl-Pd and allenyl-Sm species as those in the reactions of **115**.[167]

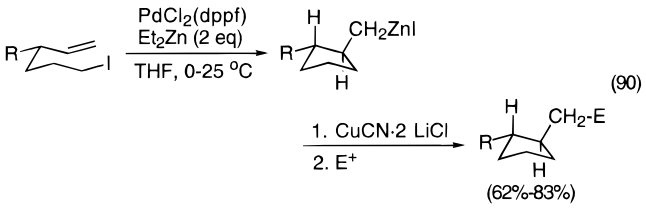


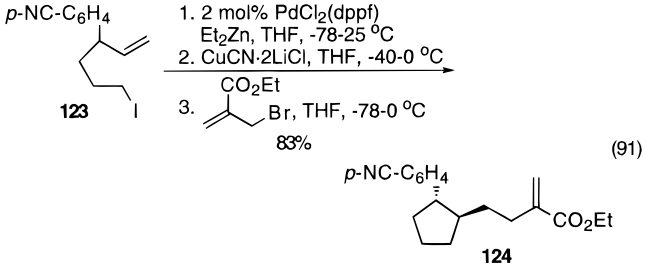
Palladium-catalyzed cross-coupling reaction of organoboron compounds with organic triflates, i.e., "Suzuki coupling",[168] has been applied to the carbocyclization of an aryl triflate **119** and a vinyl triflate **121** bearing alkenyl tethers through hydroboration of the alkenyl tethers followed by the Pd-catalyzed intramolecular cross-coupling, giving **120** and **122** in good yields (eqs 88 and 89).[169]





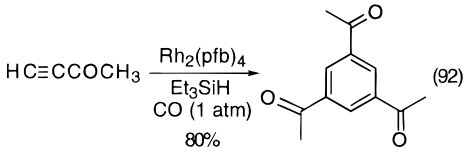
Palladium-catalyzed carbozincation of alkenes can be carried out in an intramolecular fashion. Since organozinc species have exceptional functional group compatibility, this intramolecular carbometalation process provides convenient routes to polyfunctionalized cyclopentanes (eq 90).[170] For example, the Pd-catalyzed carbozincation of alkenyl iodide **123** followed by transmetalation to copper and cross-coupling with bromomethacrylate gives **124** in 83% yield (eq 91).[170]



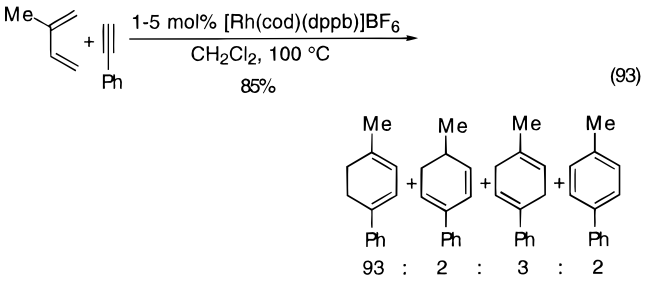


VII. Rhodium-Catalyzed Carbocyclizations

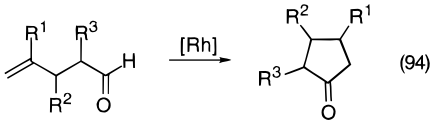
Trimerization and polymerization of alkynes catalyzed by transition metal complexes are well-known reactions but usually their selectivities are poor, producing mixtures of products. However, 1,3,5-trisubstituted benzene can be obtained as the sole product in good yield when 3-butyn-2-one is used as the substrate in the presence of $Rh_2(pfb)_4$ (pfb = perfluorobutyrate) and Et_3SiH under CO atmosphere (eq 92).[171]



A cationic rhodium complex-catalyzed codimerization of 1,3-dienes and alkynes gives the corresponding cyclohexadienes in good yields and high regioselectivity as exemplified in eq 93.[172]

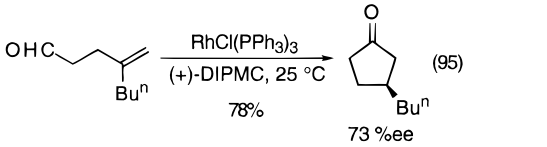


The Rh-catalyzed intramolecular hydroacylation of 4-pentenals to yield cyclopentanones (eq 94) is a synthetically useful process, which was first reported by Sakai et al. in 1972.[173]



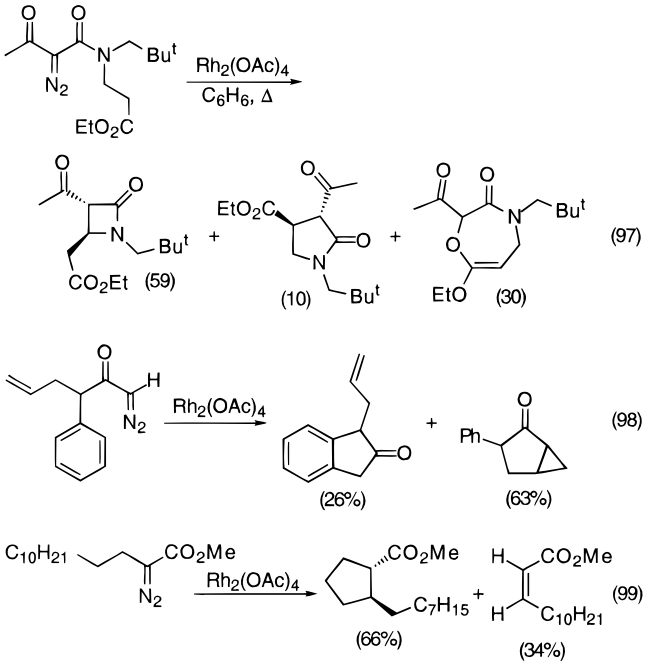
The effects of various Rh(I) catalyst species[174] and reaction variables[175] on this process has been extensively investigated and much attention has been drawn to its possible mechanisms,[175−178] stereoselectivity,[176] and applications to the syntheses of natural products.[179−183] This process initially suffered from low yields and small turnover of catalyst species except for using ethylene as the additive,[175] but later high turnovers were achieved by heating or by using dirhodium complexes as the catalysts.[184−186]

Kinetic resolution of racemic 2-methyl-2-phenyl-4-pentenal catalyzed by (*S*,*S*)-Chiraphos−Rh complex gave enantioenriched 2-methyl-2-phenylcyclopentanone with up to 69% ee.[187,188] Initial attempts to achieve asymmetric induction in this process using substituted 4-pentenals and chiral diphosphine ligands such as (−)-BPPM, (+)-DIOP, and (+)-*trans*-1,2-bis-[(diphenylphosphino)methyl]cyclohexane (DIPMC) gave the corresponding cyclopentanones with up to 73% ee (eq 95).[189,190] More recently, extremely high enantioselectivity (>99% ee) was achieved in the reactions of 4-substituted 4-pentenals catalyzed by cationic Rh−(*S*)-BINAP complex (eq 96).[191]



The chemistry of rhodium carbenes has attracted much interest in the last two decades, and the existence of such species is strongly suggested on the basis of circumstantial evidence, e.g., product analyses of the rhodium-catalyzed reactions of diazoalkanes.[192−196] Rhodium carbenes afford carbocyclization products through intramolecular C−H insertion, addition to alkynes, and alkenes (cyclopropanation). The cyclopropanation reactions promoted by transition metals including rhodium have been extensively studied, which can be treated as an independent subject for reviews. Accordingly, the cyclopropanation processes will not be discussed in this review. For recent advances on this subject, see excellent reviews by Doyle,[192] Maas,[194] and Adams et al.[195]

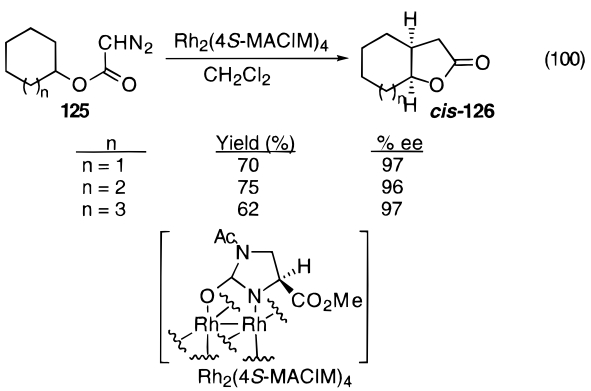
Rh−carbene insertion reactions into carbon−hydrogen bonds find many applications in organic syntheses.[192,196−205] However, these reactions sometimes suffer from low yields and/or low product selectivity because of the occurrence of other competing carbene reactions such as different C−H insertions (eq 97),[203] cyclopropanation (eq 98),[206] and β-hydride elimination (eq 99). It has been shown that the five-membered ring formation is favored, in general, over four- or six-membered ring formation in the Rh-catalyzed C−H insertion reactions giving *carbocycles*.[207−209]



The catalyst precursors used in these reactions are Rh(II) complexes, e.g., $Rh_2(OAc)_4$, $Rh_2(pfb)_4$, $Rh_2(acam)_4$ (acam = acetamide), and other dirhodium tetracarboxylates.[210−212] Among these Rh(II) complexes, $Rh_2(OAc)_4$ is by far the most frequently used catalyst. Electronic and steric effects of various carboxylate as well as amide ligands on the regioselectivity of the reactions has been studied in detail.[211,212]

Stereoelectronic effects of substituents and substitution patterns on the regioselectivity of the reactions have been extensively studied.[213−218]

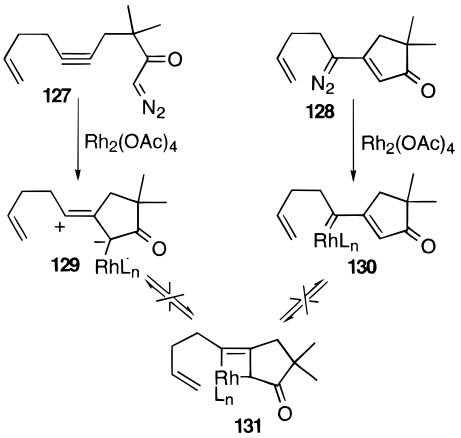
Asymmetric carbocyclizations based on intramolecular C-H insertion of chiral rhodium carbenes have been explored for the syntheses of enantio-enriched lactones,[171,204] chromanones,[219] lactams,[220] and cyclopentanones.[221] These processes proceed with moderate to excellent enantioselectivity. Excellent diastereo- as well as enantioselectivity has been achieved in the reactions of diazoacetates **125** using $Rh_2(4S\text{-MACIM})_4$ (MACIM = methyl 1-acetyl-2-oxoimidazolidine-4*S*-carboxylate) as the chiral catalyst, which give bicyclic lactones *cis*-**126** with 98% de and 96−97% ee (eq 100).[171]



n	Yield (%)	% ee
n = 1	70	97
n = 2	75	96
n = 3	62	97

Addition of rhodium carbenes to alkynes has found many applications since this process can be coupled with subsequent transformations involving other Rh-

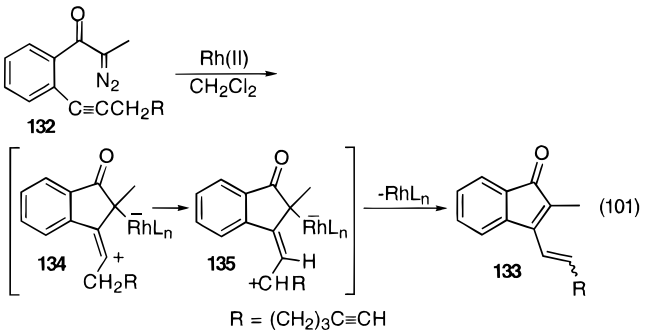
Scheme 19



carbene species to give products with complex structure in one step.[222−228]

For possible mechanisms and key intermediates of these processes, an interesting observation was made that strongly suggested the formation of zwitterionic allylic rhodium species **129** rather than that of Rh-carbene species **130** when the diazo ketone **127** was treated with $Rh_2(OAc)_4$ in benzene (Scheme 19).[229] The reaction of **127** catalyzed by $Rh_2(OAc)_4$ gives five products whereas the reaction of **128** affords only two products, which are common to those arising from **127**. The two common products are *E* and *Z* isomers at the newly formed olefin moiety, but the *E*/*Z* ratio is markedly different in these reactions. Consequently, it is evident that these two reactions do not generate a common intermediate **131** which is the crucial intermediate for generation of Rh-carbene species **130** from **129**.

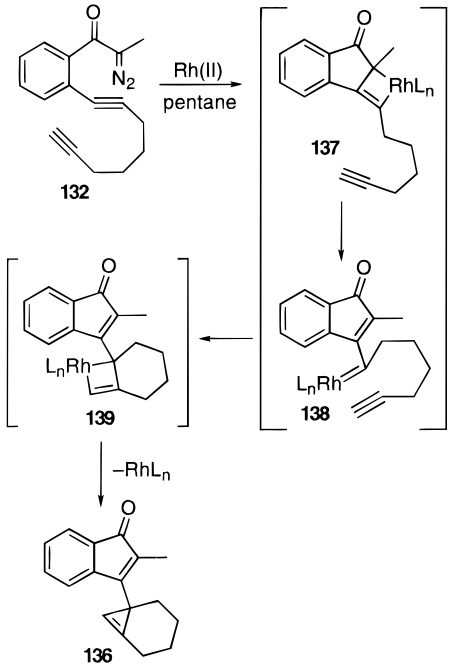
Later, it was found that the course of the Rh−carbene reactions was highly dependent on the nature of the solvent used, viz., the zwitterionic species is selectively formed in dichloromethane while Rh-carbene species is exclusively generated in pentane.[230] The reaction of diazo ketone **132** catalyzed by $Rh_2(OAc)_4$ in dichloromethane gives alkene **133** as an *E*/*Z* mixture and virtually no cycloaddition product **136** is formed, which strongly indicates the intermediacy of zwitterionic species **134** and **135** (eq 101).[230] In sharp contrast to this, when the same



(101)

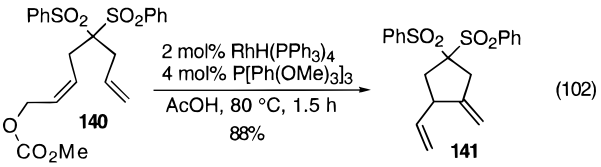
reaction is carried out in pentane, cyclopropene **136** is the exclusive product, which is consistent with the Rh−carbene pathway involving intermediates **137**−**139** (Scheme 20).[230] It should be noted that the reaction course, i.e., product selectivity, is also influenced by the subtle difference in the nature of

Scheme 20



catalyst (precursor) used. Thus, the reaction of **132** catalyzed by $Rh_2(oct)_4$ (oct = octanoate) in dichloromethane gives a 3:2 mixture of **133** and **136**.[230] Accordingly, further investigation appears to be necessary to generalize marked solvent effects on the course of these reactions.

It is well known that "metallo-ene" cyclizations are promoted by palladium and nickel catalysts (*vide supra*), but recently Rh(I) complexes have also been shown to promote the same type of reactions efficiently.[231] Typically, the reaction of 1,6-octadienyl-8-carbonate **140** or its 4-aza counterpart **142** is carried out using $RhH(PPh_3)_4$−tris(2,4,6-trimethoxyphenyl)phosphine system as the catalyst in acetic acid at 80 °C for 1−1.5 h to give the corresponding 1-*exo*-methylene-2-vinylcyclopentane **141** or pyrrolidine **143** in high yield (eqs 102 and 103). Formation of six-membered rings is also possible, but it requires more catalyst and longer reaction times affording the products in lower yields.



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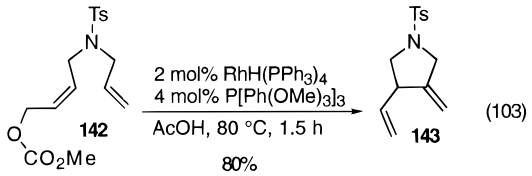
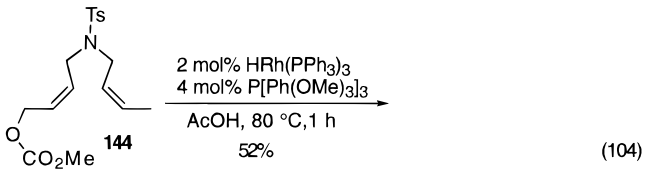


(103)

The reaction of 5-aza-2,7-nonadienyl-9-carbonate **144** gives 3,4-divinylpyrrolidine **145** with moderate *cis*-selectivity (eq 104) while 1-(*trans*-4-acetoxycyclohexenyl)allylmalonate **146** affords *cis*-fused bicyclo[4.3.0]nonene **147** exclusively (eq 105).



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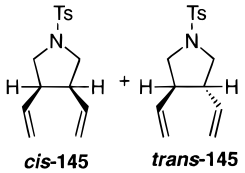
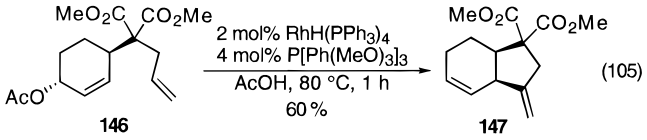
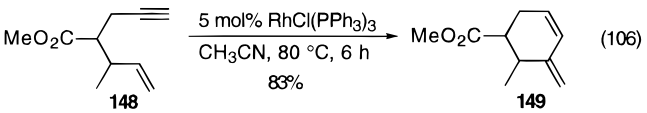




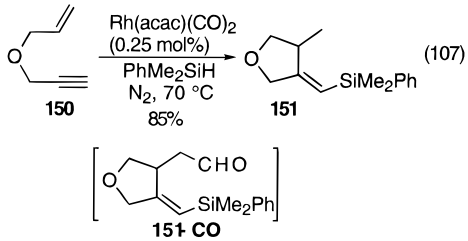
(105)

Cyclization of 1,6-enynes **148** catalyzed by RhCl(PPh$_3$)$_3$ gives 1-*exo*-methylene-2-cyclohexenes **149** regioselectively via 6-*exo-trig* mode in good yields (eq 106).[232] Substitution on the alkene moiety suppresses the cyclization significantly and that of the terminal triple bond shuts down the reaction.



(106)

Reactions of 1,6-enynes **150** and **151** with hydrosilanes catalyzed by Rh or Rh−Co complexes such as Rh(acac)(CO)$_2$, Rh$_4$(CO)$_{12}$, Rh$_2$Co$_2$(CO)$_{12}$, Rh(CNBu^t)$_4$-Co(CO)$_4$ proceed via 5-*exo-trig* mode to give the corresponding silylcarbocyclization (SiCaC, type 1) products **151** and **153**, respectively in high yields (eqs 107 and 108).[233] The reaction of **150** under CO



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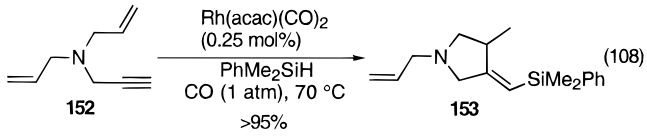
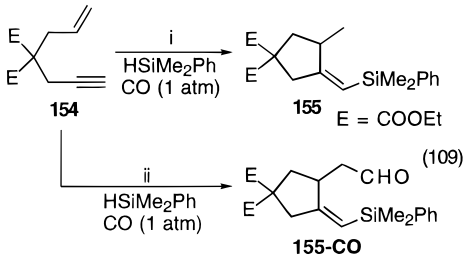


(108)

atmosphere also gives **151** accompanied by a small amount of CO−SiCaC product **151**−**CO** (9%). For the reaction of 1,6-enyne **154**, either SiCaC product **155** (90% yield) or CO−SiCaC product **155**−**CO** (90% yield) can be obtained selectively just by changing reaction conditions (eq 109).[234]

Allyldipropargylamine (**156**), a 1,6,6′-enediyne, when reacted with a hydrosilane under CO atmosphere in the presence of a Rh or Rh−Co catalyst, undergoes another type of silylcarbocyclization (SiCaC, type 2) involving only 1,6-diyne moiety to give *exo*-methylene-4-piperidinone **157** in high yield (eq 110).[233] The SiCaC (type 1) reaction also takes place with 5-hexyn-

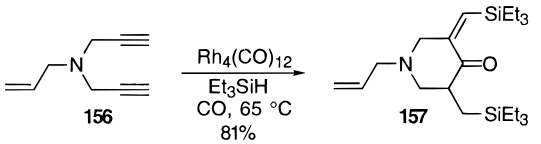


(109)

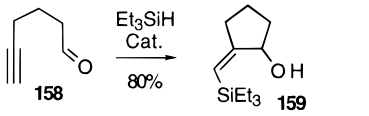
i) Rh(acac)(CO)$_2$,80 °C, 0.5 M **154** in hexane: **155**/**155-CO** = 10/1, 99%.

ii) Rh(acac)(CO)$_2$/P(OPh)$_3$,50 °C, 0.2 M **154** in toluene; **155**/**155-CO** = 1/19, 90%.

1-al (**158**) to give *exo*-(silylmethylene)cyclopentanol (**159**) in high yield (eq 111).[235]



(110)

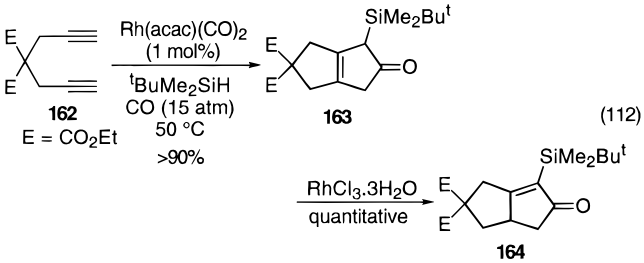


(111)

Cat. = Rh$_2$Co$_2$(CO)$_{12}$ or Rh(acac)(CO)$_2$

The mechanisms of these SiCaC reactions are proposed to include (*β*-silylethenyl)metal species (**160**) (metal = Rh$_n$ or Rh−Co) as a key intermediate, which is trapped by an alkene or an aldehyde moiety in the SiCaC (type 1 reaction or by an alkyne moiety after carbon monoxide insertion, generating (*β*-silylacryloyl)metal species (**161**) (metal = Rh$_n$ or Rh−Co) in the SiCaC, (type 2 reaction (Scheme 21).[233,235]

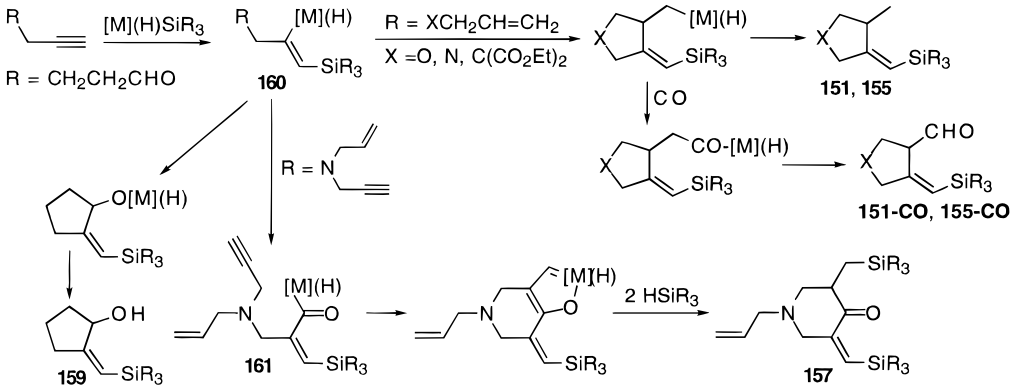
The reaction of a 4,4-*gem*-disubstituted 1,6-diyne, diethyl propargylmalonate (**162**), with *t*-BuMe$_2$SiH under 15−50 atm of CO proceeds with another SiCaC mode (SiCaC, type 3, or silylcarbobicyclization), giving 2-silylbicyclo[3.3.0]oct-1,5-en-3-one (**163**) in excellent yield, which is readily isomerized to **164** (eq 112). In contrast to SiCaC (type 2), the trapping of the intermediate **160** by the alkyne moiety is faster than CO insertion in this case.[236]



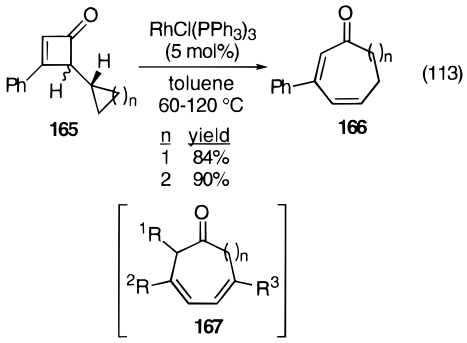
(112)

A Rh(I)-catalyzed intramolecular carbocyclic ring-enlargement reaction of 4-cycloalkyl-2-cyclobutenone **165** gives cyclohepta- or cycloocta-2,4-dienones **166** in high yield through fusion of three- and four-membered rings or two four-membered rings (eq 113).[237] Depending on the substitution pattern of the cyclobutenone moiety, cycloalka-3,5-dienone **167** aris-

Scheme 21

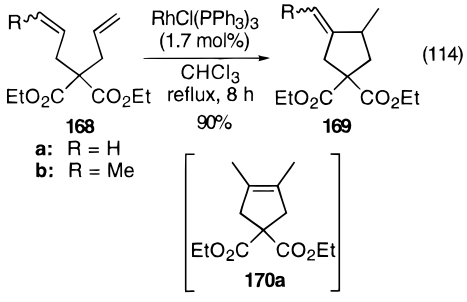


ing from thermal isomerization is accompanied when the reaction is run at higher temperatures (90−120 °C).



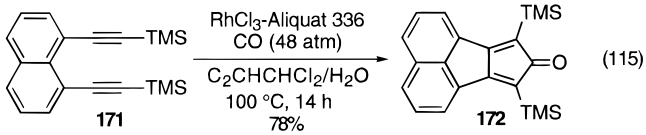
(113)

A Rh(I)-catalyzed carbocyclization of 1,6-diene **168a** (R = H) gives 1-methyl-2-(*exo*-methylene)-cyclopentanes **169a** in high yields (eq 111).[238] When the reaction is carried out in the presence of dry HCl in ethanol, isomerization takes place to afford 1,2-dimethylcyclopentene **170a** in 85% yield (eq 114). This reaction has, however, rather limited scope since the attempted carbocyclization of 1,7- and 1,8-dienes has not been successful, and the reaction suffers from producing a mixture of double-bond isomers when R is not hydrogen, e.g., when R is methyl, a mixture of five isomers are formed.[238]



(114)

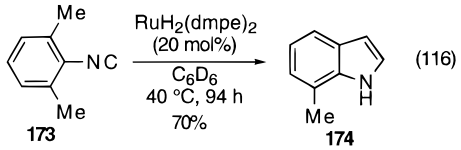
A phase-transfer rhodium catalyst, $RhCl_3$−Aliquat 336, i.e., $[(C_8H_{17})_3NMe]^+[RhCl_4(H_2O)_2]^-$, has been shown to promote a number of transformations of aromatic diynes.[239] Unfortunately, the selectivities of these reactions are rather poor and in most cases mixtures of polycyclic products are obtained. However, the reaction of 1,8-bis(trimethylsilyl)ethynyl]-naphthalene (**171**) catalyzed by the $RhCl_3$−Aliquat 336 under CO pressure (48 atm) gives 8H-cyclopent-[*a*]acenaphthylen-8-one **172** as the sole product in good yield (eq 115).[240]



(115)

VIII. Ruthenium-Catalyzed Carbocyclizations

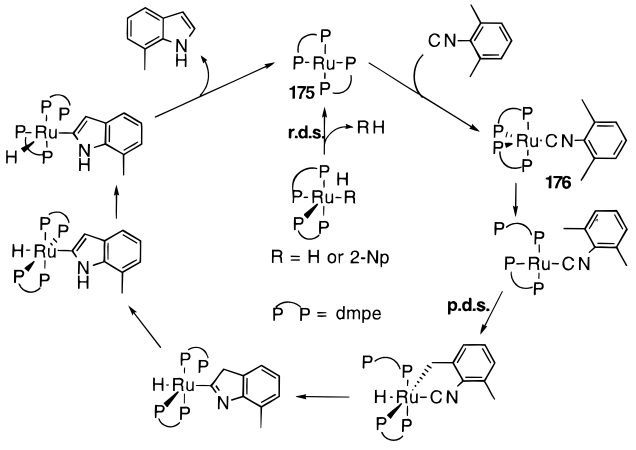
A unique catalytic route to indole **174** from 2,6-xylyl isocyanide (**173**) through intramolecular C−H insertion catalyzed by RuH[2-naphthyl](dmpe)$_2$ or RuH_2(dmpe)$_2$ (dmpe = bis(dimethylphosphino)-ethane) was discovered and its scope and mechanism studied (eq 116).[241,242]



(116)

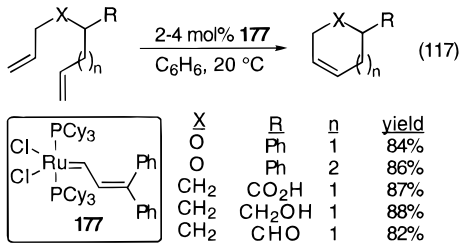
A proposed mechanism is shown in Scheme 22. The kinetic and isotope labeling experiments indicate that the rate determining step (rds) is the formation of the coordinatively unsaturated "Ru(dmpe)$_2$" species (**175**) and the irreversible formation of isocyanide−Ru complex **176** takes place prior to the intramolecular C−H insertion to the methyl group at C-2 (or C-6), which is the product-determining step (pds). This catalytic indole synthesis is applicable only to 2,6-dialkylphenyl isocyanides, i.e., the reactions of

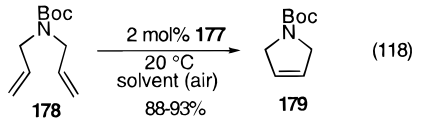
Scheme 22

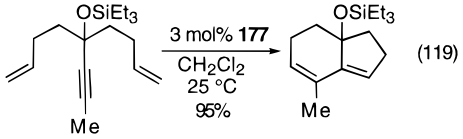


less hindered 2-alkylphenyl isocyanides suffer from decomposition of the isocyanides at 140 °C or become non-catalytic at 60 °C.

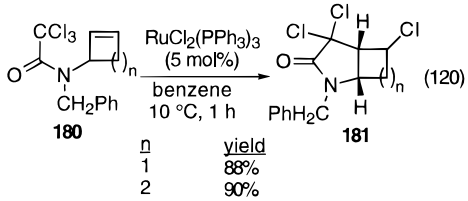
A Ru-catalyzed "ring-closing metathesis" reaction of dienes using a Ru−carbene complex **177** has opened a new and efficient route to unsaturated carbocyclic and heterocyclic compounds.[243] This reaction is applicable to the syntheses of carbocycles and heterocycles with different ring sizes and is tolerant of a variety of functional groups, which makes this process versatile and useful as synthetic method (eq 117).[243] This catalytic reaction is surprisingly insensitive to oxygen, moisture, and adventitious impurities included in reagent-grade solvents. Thus, the reaction of diallylamine **178** in undistilled reagent-grade benzene, dichloromethane, THF or *tert*-butyl alcohol gives dihydropyrrole **179** in excellent yield (eq 118).[243] Unique bicyclization of dienynes has also been achieved using **177** as the catalyst (eq 119).[244]



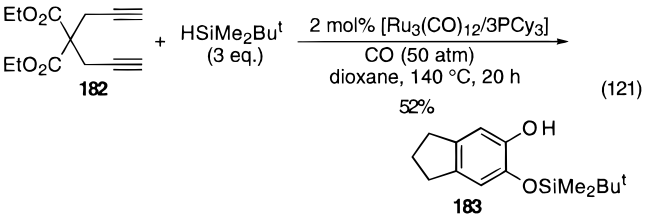


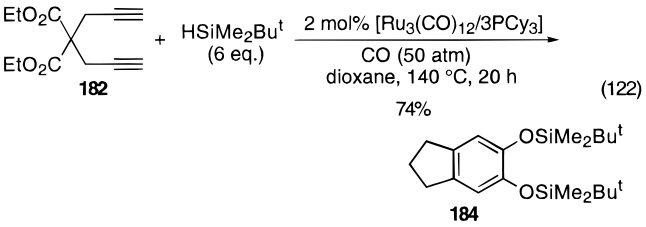


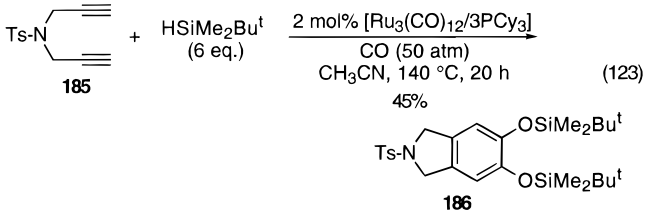
Carbocyclization of cycloalkenyl-*N*-benzyltrichloroacetamides (**180**) through activation of C−Cl bond by a Ru(II) catalyst gives the corresponding bicyclic γ-lactams **181** in excellent yields (eq 120).[245]



A very unique carbonylative Ru-catalyzed carbocyclization of 1,6-diynes (e.g., **182** and **185**) in the presence of a hydrosilane is discovered that gives bicyclic *o*-catechol derivatives (e.g., **183**, **184**, and **186**) by incorporating two carbon monoxide molecules as the 1,2-dioxyethenyl moiety (eqs 121−123).[246] This reaction is tolerant of functional groups such as ester, ketone, ether, and amide. The di-silylated product **184** is formed through dehydrogenative silylation of the initially formed mono-silyl product **183** under the reaction conditions (eq 122).

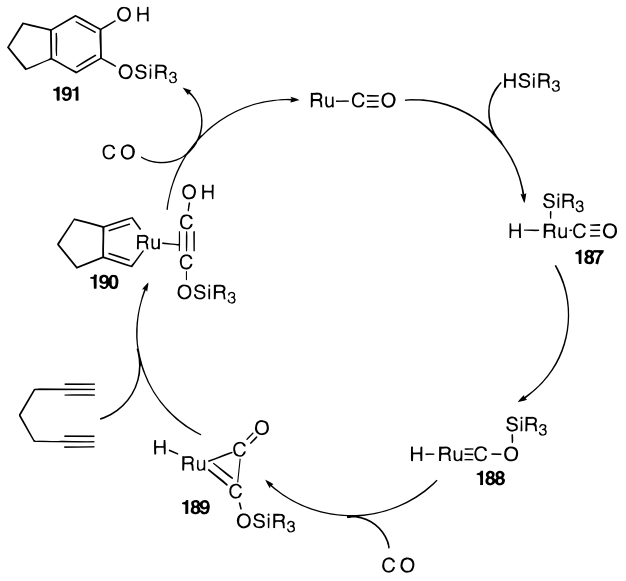




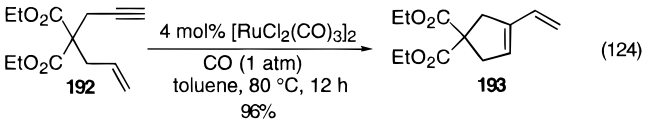


The proposed catalytic cycle for this unique process includes (i) oxidative addition of a hydrosilane to [Ru-CO] species to form silyl(hydrido)Ru complex **187**, (ii) silyl migration to generate siloxycarbyne-Ru species **188**, (iii) carbyne reaction with CO to form metallacyclopropenone **189**, (iv) hydride shift to generate oxyacetylene−Ru complex **190**, and (v) carbocyclization to form *o*-catechol **191** and regenerate active [Ru-CO] species (Scheme 23).[246] Transformation of a metal−carbyne complex (e.g., **188**) to the corresponding bicyclic *o*-catechol (e.g., **191**) is precedented in the stoichiometric reactions of W−carbyne and Cr−carbyne complexes with 1,6-diynes.[247] Thus, the proposed catalytic cycle appears to be quite reasonable.

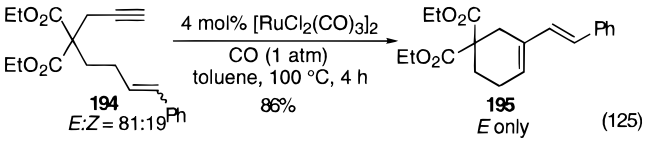
Scheme 23



Novel carbocyclizations of 1,6-enynes (e.g., **192**) and 1,7-enynes (e.g., **194**) via a "skeletal reorganization" process are effected by ruthenium catalysts, e.g., $[RuCl_2(CO)_3]_2$, $[RuBr_2(CO)_3]_2$, $[Ru(p\text{-cymene})]_2$, and $RuCl_3 \cdot xH_2O$, to give 1-vinylcycloalkenes (e.g., **193** and **195**) in excellent yields (eqs 124 and 125).[248] Cata-



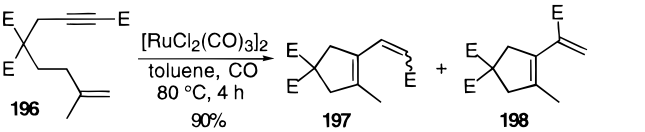
(124)



(125)

lytic activity of various ruthenium complexes was examined, and it has been shown that both halide and carbon monoxide are essential for ruthenium catalysts to be active. Accordingly, all reactions are run under CO atmosphere. However, phosphine−Ru complexes, e.g., $RuCl_2(CO)_2(PPh_3)_2$ and $CpRuCl(PPh_3)_2$, are inactive even under CO atmosphere. This Ru-catalyzed process is substantially different from the Pd-catalyzed process discussed in **VI.2.1.** (*vide supra*). For instance, the reaction of **194** giving **194** provides the first example of the transformation of a 1,7-enyne to vinylcyclohexene (eq 125).

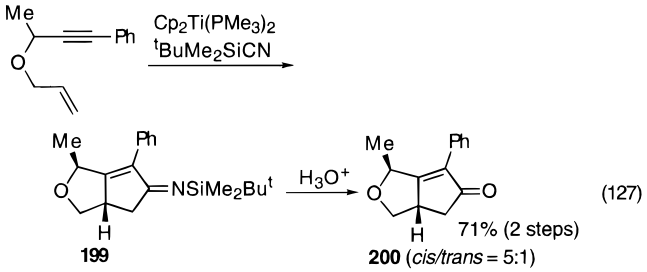
Although the mechanism of this unique reaction must wait further investigation, this unique process appears to include bicyclic cyclobutene or its Ru complex as the key intermediate. However, the fact that the reaction of **196** gives **197** as the major product (eq 126), which is not formed in the corresponding Pd-catalyzed reaction,[125,126] implies that a rather sophisticated "skeletal reorganization" or metathesis process is involved.



(126)

IX. Titanium-Catalyzed Carbocyclization

Only a limited amount of attention has been paid on the use of titanium complexes as the catalysts for carbocyclizations. The first successful Ti-catalyzed carbocyclization of 1,6- and 1,7-enynes was realized by using $Cp_2Ti(PMe_3)_2$ (10 mol %) in the presence of *tert*-butyldimethylsilyl cyanide.[249] The reactions give bicyclo[*n*.3.0]alkenones (e.g., **200** and **202**) in good yields via the corresponding silylimines (e.g., **199** and **201**) followed by acidic hydrolysis (eqs 127 and 128).[249] Bicyclo[*n*.3.0]alkenones, thus obtained, serve as useful intermediates for the syntheses of a variety of cyclopentane natural products.



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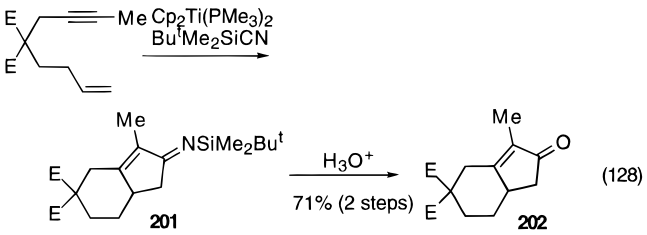


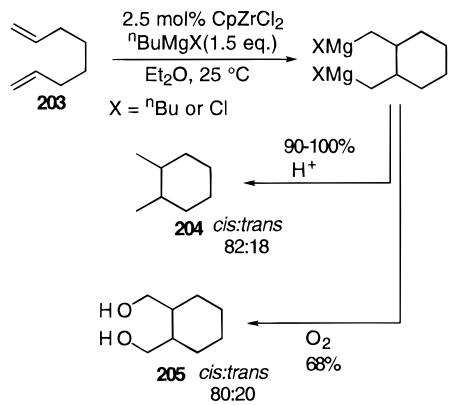
(128)

X. Zirconium-Catalyzed Reactions

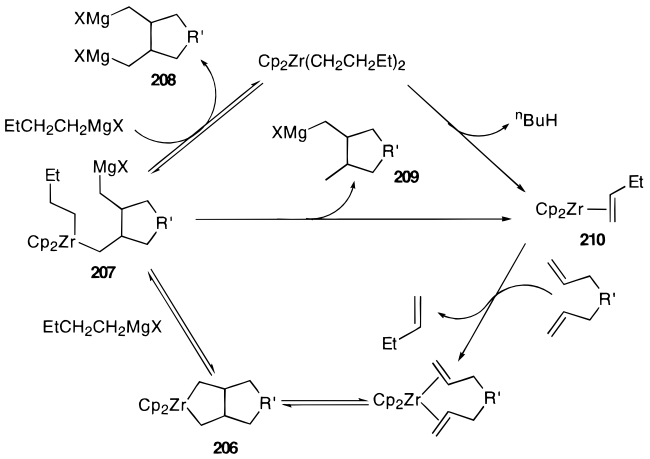
Zirconium-mediated cyclizations and bicyclizations have attracted significant interest because of their importance in organic syntheses.[1,250−254] The mechanism of zirconium-promoted reactions has been extensively studied, and the reactions are proven to involve metallacycle intermediates, which can sometimes be isolated.[255] Zirconium-promoted carbocyclizations usually proceed in excellent yields with high regio- and stereoselectivities.[1,256] However, the vast majority of the zirconium-mediated reactions require stoichiometric amounts of the metal. Recently, zirconium-catalyzed carbocyclizations have been developed in combination with Grignard or dialkylmagnesium reagents as significant extensions of the carbomagnesiation processes discovered by Dzhemilev et al.[257,258]

Zirconocene-catalyzed cyclomagnesiations of 1,6- and 1,7-dienes have been extensively studied with regard to their mechanism, scope, and limitations.[259−261] The carbocyclization of 1,7-octadiene (**203**) to cyclohexane derivatives **204** and **205** via Zr-catalyzed cyclomagnesiation is shown in Scheme 24 as a typical example.[261] The diastereoselectivity of these processes is highly dependent on the reaction temperature and the concentration of dialkylmagnesium, i.e., low concentrations of dialkylmagnesium

Scheme 24



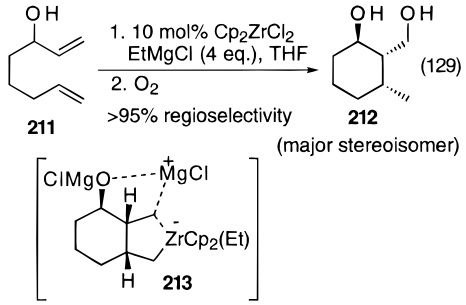
Scheme 25



and high temperatures favor the formation of *trans* products.[261]

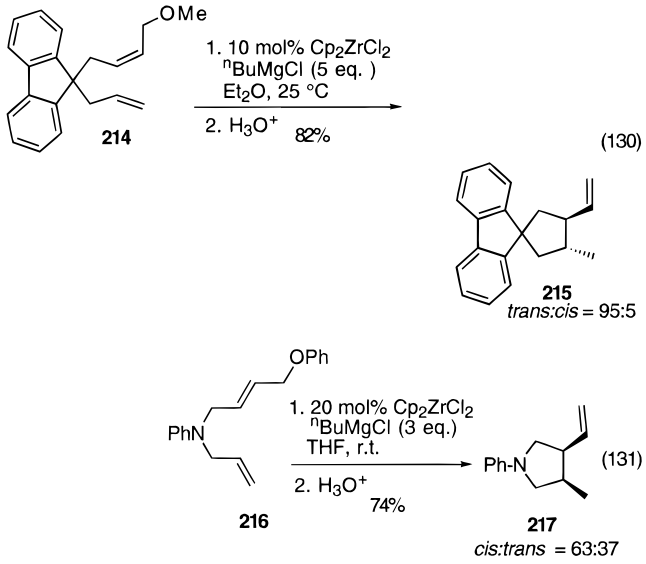
According to the proposed mechanism depicted in Scheme 25, the reaction proceeds via zirconacycle **206**, that undergoes transmetalation with a Grignard or dialkylmagnesium reagent to form bis-magnesiation product **208** or mono-magnesiation product **209** via mixed-metal species **207**, and the active catalyst species **210** is regenerated. The formation of **208** is favored in ether while **209** is the favorable product in THF on the basis of deuterium-labeling experiments.[261]

Cyclomagnesiation of 3-hydroxy-1,7-octadiene (**211**) under the conditions that favor the formation of mono-magnesiation product, followed by oxidation gives 2-(hydroxymethyl)-3-methyl-1-cyclohexanol (**212**) with >95% regioselectivity (eq 129).[262] The result clearly indicates a strong directing effect of the hydroxyl group on "site specific" magnesiation through a chelated transition state such as **213**.[262]



Carbocyclization of 1,6-dienes bearing an allylic ether linkage at the terminus (e.g., **214** and **216**) is catalyzed by zirconocene dichloride in the presence of *n*-BuMgCl to give the corresponding 1-ethenyl-2-methylcycloalkanes (e.g., **215**) or heterocycles (e.g., **217**) (eqs 130 and 131).[263,264]

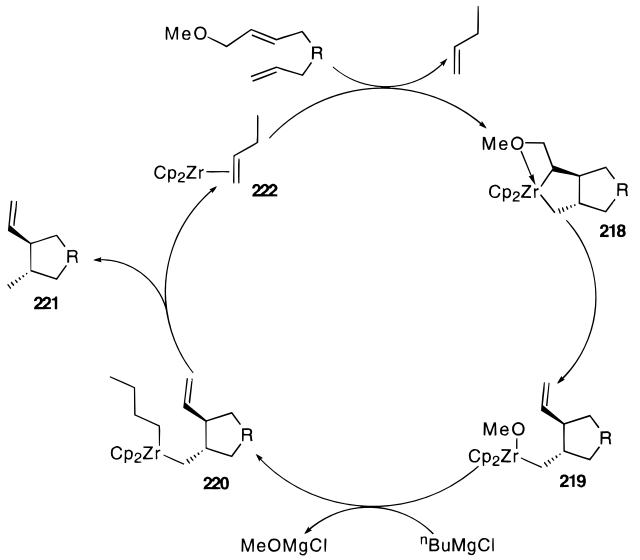
The proposed mechanism[263,264] for this process (Scheme 26) includes (i) formation of zirconacyclopentane **218**, (ii) β-alkoxy elimination[265−268] to generate an alkoxyzirconium species **219**, (iii) transmetalation of the alkoxy group from Zr to Mg with *n*-BuMgCl to form dialkylzirconium species **220**, and

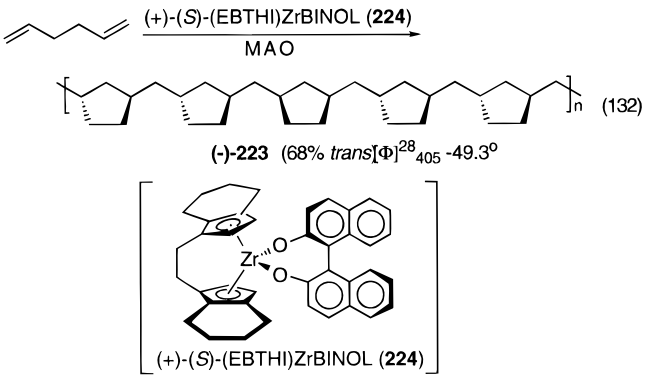


(iv) β-hydride elimination to give the carbocyclization product **221** and regenerate the active catalyst species **222**.

Cyclopolymerization of 1,5-hexadiene catalyzed by Cp_2ZrX_2 or $Cp^*_2ZrX_2$ (X = Cl or Me; Cp* = pentamethylcyclopentadienyl) and methyl aluminoxane (MAO) gives poly(methylene-1,3-cyclopentane) (**223**).[269] The diastereoselectivity, i.e, *trans*/*cis* selectivity of cyclopentane moieties in the polymer, is dependent on the bulkiness of the catalyst used. The use of Cp_2ZrMe_2 at −78 °C gives 91% *trans* polymer, whereas the $Cp^*_2ZrCl_2$-catalyzed reaction at −25 °C yields 14% *trans* polymer.[269] Enantioselective cyclopolymerization of 1,5-hexadiene has been achieved using chiral zirconocene catalyst, (−)-(*R*)-ethylenebis(tetrahydroindenyl)zirconium (*R*)-binaphtholate (**224**), and MAO as the cocatalyst to afford a unique chiral polymer bearing chirality in the main chain (eq 132).[270] This Zr-catalyzed asymmetric cyclopolymerization serves as a powerful method for the synthesis of chiral polymers that are currently impossible to create by any other method.

Scheme 26





XI. Concluding Remarks

This review compiled recent advances in carbocyclizations in organic synthesis catalyzed by transition metals and their complexes including Co, Fe, Mo, Ni, Pd, Rh, Ru, Ti, and Zr. As it is clearly shown, carbocyclizations catalyzed by Pd complexes constitute the largest part of the accomplishments to date. However, the use of metal species other than Pd has been steadily increasing and new types of reactions and processes have been emerging. Stereocontrol in carbocyclization is apparently an extremely important aspect, and asymmetric carbocyclizations catalyzed by chiral metal complexes started showing great promise as exemplified by asymmetric Heck reactions (Pd) and asymmetric cyclopolymerizations (Zr). Catalytic asymmetric carbocyclizations will surely become powerful tools for organic syntheses in the next decade.

XII. Acknowledgments

The authors thank National Science Foundation and National Institutes of Health (NIGMS), and Mitsubishi Chemical Corporation for their generous support of their research in this area.

XIII. References

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