Ring-Closing Reactions

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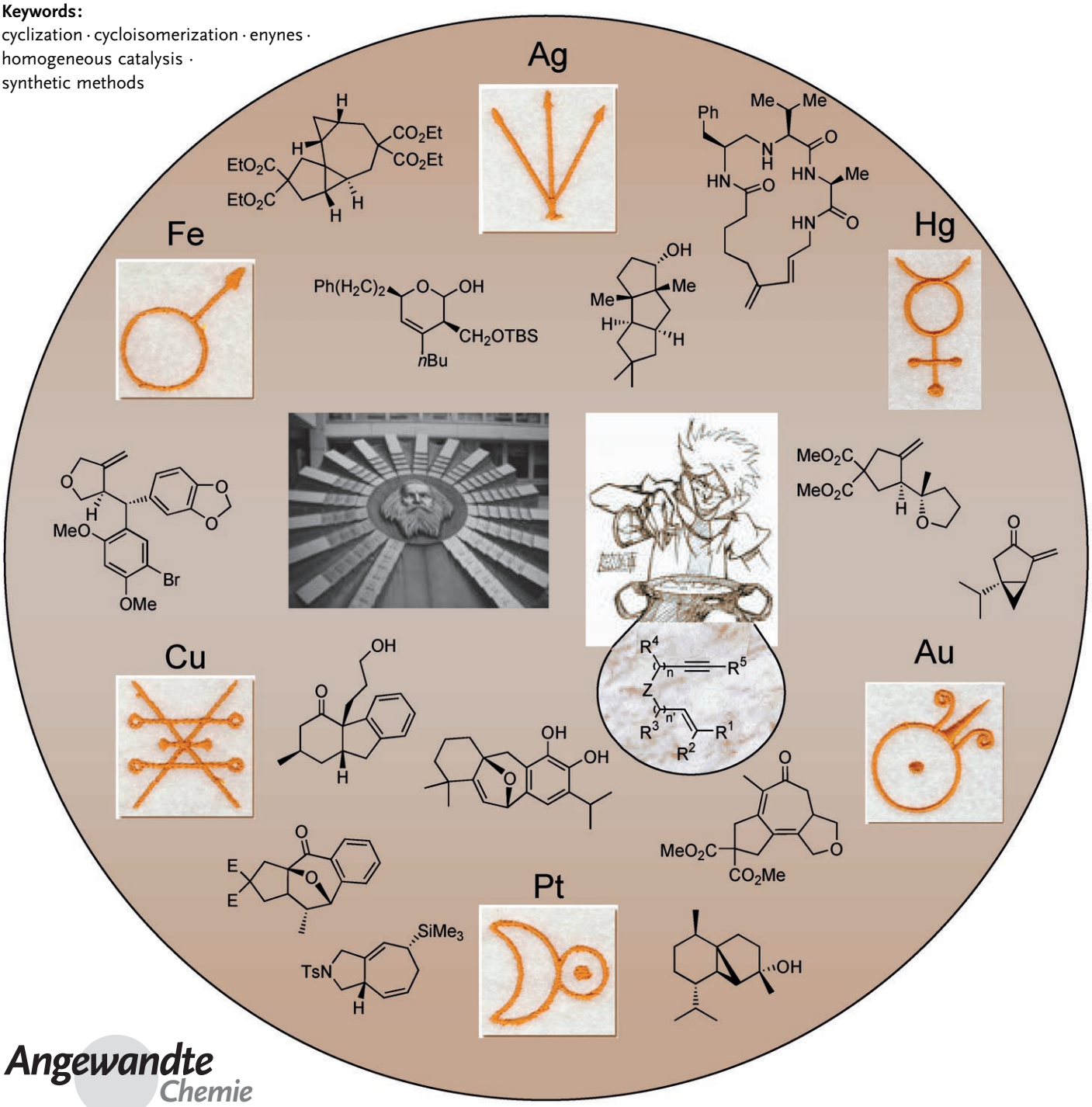
Cycloisomerization of 1,*n*-Enynes: Challenging Metal-Catalyzed Rearrangements and Mechanistic Insights

Véronique Michelet, Patrick Y. Toullec, and Jean-Pierre Genêt*

Keywords:
cyclization · cycloisomerization · enynes · homogeneous catalysis · synthetic methods



Metal-catalyzed cycloisomerization reactions of 1,n-enynes have appeared as conceptually and chemically highly attractive processes as they contribute to the highly demanded search for atom economy and allow the discovery of new reactions. Since the pioneering studies with palladium by the research group of Barry Trost in the mid-1980s, several other metals have been identified as excellent catalysts for the rearrangement of enyne skeletons. Moreover, the behavior of 1,n-enynes may be influenced by other functional groups such as alcohols, aldehydes, ethers, alkenes, or alkynes, thus enhancing the molecular complexity of the synthesized products. Apart from the intrinsic rearrangements of 1,n-enynes, several tandem reactions incorporating intramolecular trapping agents or intermolecular partners have been discovered. This Review aims to highlight the main contributions in this field of catalysis and to propose and comment on the mechanistic insights of the recent discoveries.

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1. Introduction

Metal-catalyzed reactions are of major importance for challenging organic transformations. The development of new catalytic systems has been one of the most important research fields in modern organic chemistry. One reason for this is the large contribution of catalysis to the concepts of atom economy and green chemistry in the 21st century.[1] Anastas and Warner presented 12 principles that contribute to green chemistry, and catalysis was placed as a main directive for modern chemistry.[2] The use of transition metals and main-group organometallic compounds expanded the manifold of tools available to address this challenge. Among the extraordinary variety of transformations, 1,*n*-enyne rearrangements are growing in importance as—depending on the functional groups and the experimental conditions—several transformations are possible which lead to cyclic derivatives. Such metal-catalyzed processes are inherently atom economical and result in a significant increase in structural complexity. In general, they are operationally simple, safe, and convenient to perform even on a large scale. Thus, they meet many of the stringent criteria imposed upon contemporary organic synthesis. Moreover, the development of tandem reactions and rearrangements to construct organic polyfunctional frameworks through the formation of carbon–hydrogen, carbon–carbon, or carbon–heteroatom bonds constitutes a prime issue for organic chemists.[3]

This Review does not aim to cover all the possible rearrangements, as some reviews published in recent years have focused on general and specific reorganization reactions.[4,5] The latest discoveries will be placed within a historical context, but the main thrust is to highlight the new possibilities that metal-catalyzed cycloisomerization reactions currently offer to the synthetic chemist. Thus, this Review will attempt to emphasize historical and major contributions to the field and will focus on studies within the last ten years. This survey will also describe the specific properties of metals, starting from palladium, and will include some mechanistic insights in specific cases. Highly valuable and challenging asymmetric approaches will be highlighted in each section. Related reactions, such as metathesis and the Pauson–Khand reaction, will not be considered.

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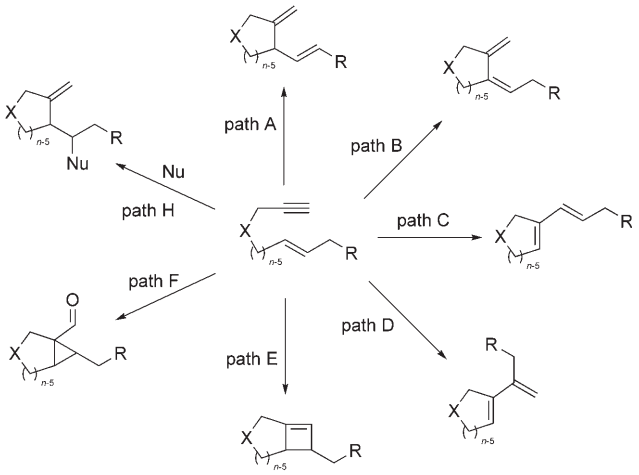
2. Pd-Catalyzed Cycloisomerizations

From a historical perspective, palladium has played a pivotal role in the discovery and development of metal-catalyzed cycloisomerization reactions of 1,*n*-enynes. Several reviews and accounts have outlined earlier achievements in the field and stressed the numerous catalyst systems tested and the variety of transformations that can be attained with a high level of selectivity.[4,5] This section will highlight the most significant early contributions as well as the most recent advances, with a particular emphasis on enantioselective processes.

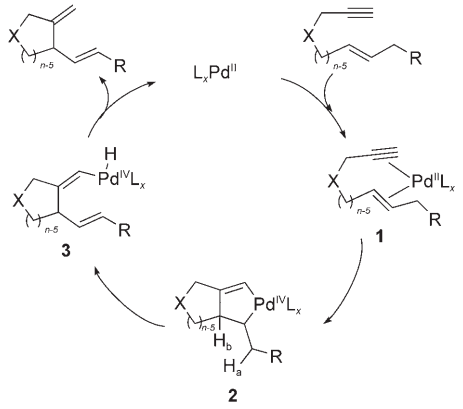
2.1. Enyne Rearrangements

Since the initial discovery of the palladium-catalyzed Alder–ene reaction by the research group of Trost in 1984,[6] extensive studies on a variety of catalysts and substrates have led to a large array of cycloisomerizations or tandem addition/cycloisomerization transformations (Scheme 1).



Scheme 1. Pd-catalyzed cycloisomerizations and related reactions.

The Alder–ene reaction[7] itself (path A) has been proposed to occur through two different mechanisms, depending on the reaction conditions and the palladium precatalyst used.[1b,2] Palladium(II) precatalysts are believed to react with an enyne via the formation of a Pd^{IV}–metallacyclopentene intermediate **2** (Scheme 2). β-Hydride elimination to give the vinylpalladium complex **3**, and a subsequent reductive elimination regenerate the catalytically active species. Palladium(0) species in combination with a carboxylic acid also catalyze the reaction.[8] The postulated mechanism relies on the initial oxidative addition of acetic acid to the Pd center to form an H-Pd-OAc species (Scheme 3). The subsequent selective hydrometalation of the triple bond gives vinylpalladium intermediate **5**. An intramolecular carbopalladation of the double bond and a subsequent β-hydride elimination of the alkyl palladium intermediate **6** completes the catalytic cycle.



Scheme 2. Postulated Pd^{II}/Pd^{IV} catalytic cycle.

From these two catalytic cycles, it appears that the β-hydride elimination is a crucial step in determining the fate of the diene formed. Whereas elimination of H_a leads to a 1,4-diene (path A, Scheme 1), in complete analogy with the thermal Alder–ene reaction, elimination of H_b leads to the formation of a 1,3-diene (path B, Scheme 1). The regiochemical outcome of the transformation was found to be determined primarily by the stereoelectronic nature of the substrate.[9] Bulky olefinic substituents favored the formation of 1,3-dienes [Eq. (1)].[10] Ether functions are able to influence the regioselectivity of the diene synthesis through their position of attachment in the molecule. The cyclization of allylic ether **9** (TBDMS: *tert*-butyldimethylsilyl, PMB: *para*-methoxybenzyl) selectively led to 1,3-diene **10** by path B[11]

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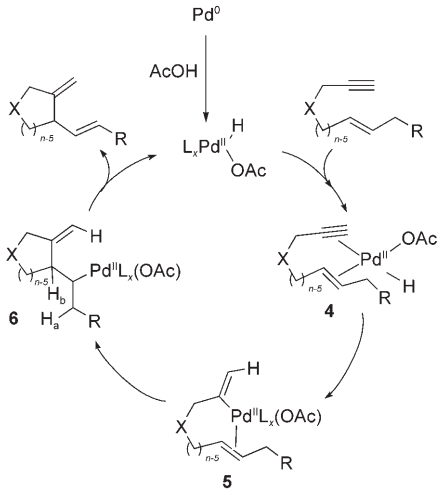
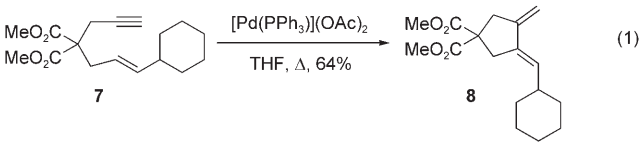
Patrick Toullec studied chemistry at the Université de Rennes, and completed his PhD at the Ecole Polytechnique (Palaiseau) under the guidance of F. Mathey in 2002. After postdoctoral studies with A. Togni at the ETH Zürich and with B. Feringa at the University of Groningen, he joined the research group of J.-P. Genêt and V. Michelet in 2005 at the Ecole Nationale Supérieure de Chimie de Paris (France). His research interests include the development of new transition-metal-catalyzed organic syntheses, particularly of asymmetric variants.



Scheme 3. Postulated Pd^0/Pd^{II} catalytic cycle.



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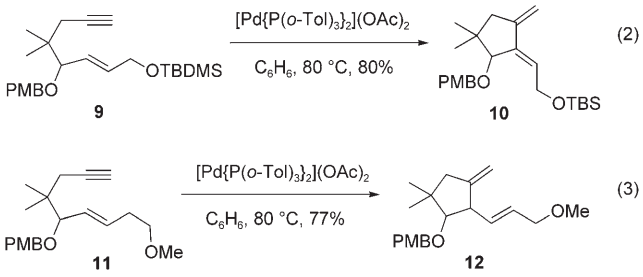
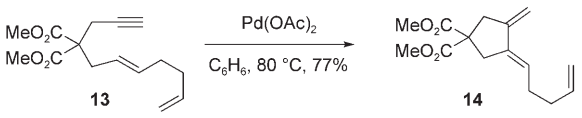
[Eq. (2)], whereas homoallylic ether **11** gave exclusively 1,4-product **12** by following path A [Eq. (3)].[10] The exact nature



(2)

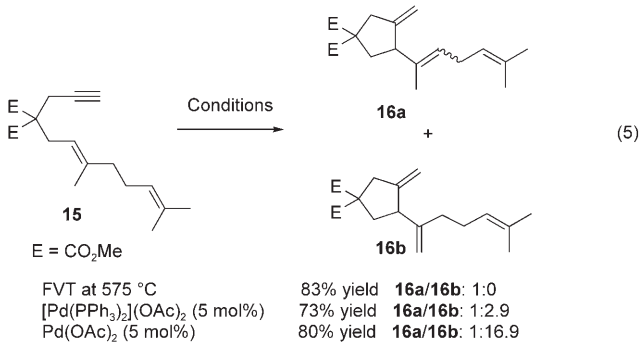
(3)

of the interactions governing the selectivity have not been established unambiguously, but the authors favor electronic factors rather than additional coordination of the oxygen atom to the palladium center.[2a] The presence of a remote double bond, as in substrate **13**, also furnished the 1,3-diene product **14** [Eq. (4)].[10]



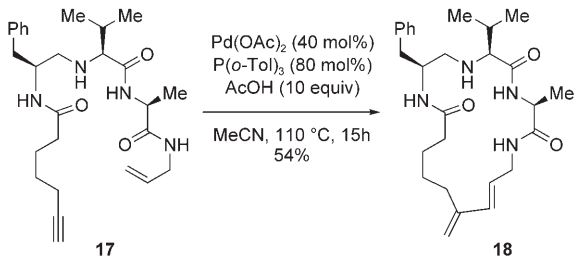
(4)

In the case of the Alder–ene reaction, the nature of the catalyst system employed also strongly influenced the regioselectivity of the 1,4-diene formed [Eq. (5), FVT = flash vacuum thermolysis].[12] Whereas only product **16a** was formed under thermal conditions, the related palladium-catalyzed reaction (in C_6D_6 at 66 °C for 1 h) gave **16b** as a major product. The ratio **16a**/**16b** is itself dependant on the nature of the ligands coordinated to the palladium center. As an example, $[Pd(PPh_3)_2](OAc)_2$ and $Pd(OAc)_2$ lead to regioisomeric ratios of 1:2.9 and 1:16.9, respectively.



(5)

Whereas most studies have focused on the synthesis of five-membered rings starting from 1,6-enynes, the formation of six-membered rings has also been reported[13] from 1,7-enynes. The synthesis of larger ring systems has been much less investigated, Trost et al.[10] reported the formation of a 12-membered carbocycle in only 9% yield. More recently, the research group of Iqbal[14] also applied the methodology to the synthesis of macrocyclic peptidomimetics **18** from enyne **17** [Eq. (6)]. Rings containing up to 19 atoms have been



(6)

obtained in synthetically useful yields (33–54%). Remarkably, in these cases the regiochemistry of the reaction leads to the formation of a conjugated diene possessing exocyclic and endocyclic C–C double bonds, which is in accordance with the

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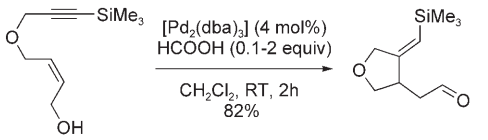
related intermolecular palladium-catalyzed coupling reaction[15] of an alkene with an alkyne.

Kressierer and Müller[16] have investigated the possibility of exploiting palladium-catalyzed cycloisomerizations to achieve the in situ generation of reactive aldehydes [Eq. (7),

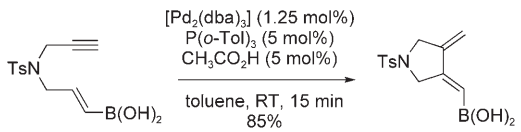


(7)

19 20

dba: *trans,trans*-dibenzylideneacetone]. Subsequent transformations of the aldehyde function by a variety of known organic reactions, such as Wittig olefination, Knoevenagel condensation, and reductive amination, allowed the preparation of multicomponent libraries of small organic molecules.

Very recently, Carboni and co-workers[17] described the cycloisomerization of boronated 1,6-enynes such as **21** in the presence of a system consisting of a Pd^0 source, tris(*ortho*-tolyl)phosphane, and acetic acid [Eq. (8)]. Boronic acid



(8)

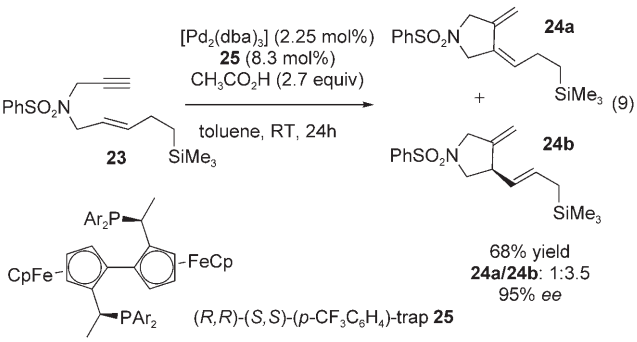
21 22

substituted 1,3-dienes such as **22** were obtained in moderate to good yields. Such relatively unstable intermediates serve as reactive substrates for tandem [4+2] cycloaddition and [4+2] cycloaddition/allylboration sequences.

The issue of the heterogeneization of the palladium catalyst has also been addressed. Nakai and Uozumi et al.[18] developed a family of amphiphilic polymer-bound triarylphosphane/palladium entities on a resin support. The catalyst activity was demonstrated to remain constant after two recycling experiments.

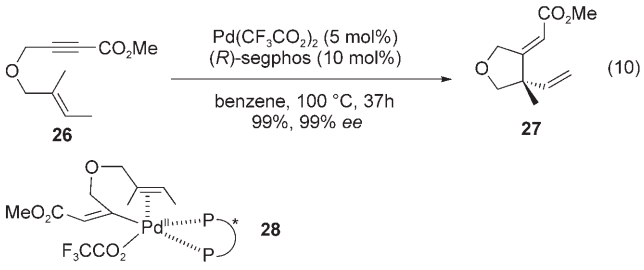
The major impetus of the Alder–ene reaction in synthetic chemistry during the last few years came from the development of an enantioselective variant of the process.[19] Despite earlier attempts that investigated the use of chiral carboxylic acids as co-catalysts[8a] ((*S*)-binaphthoic acid gave *ee* values up to 33%) or synergetic effects arising from a combination of a chiral bidentate phosphorus ligand and an intramolecular carboxylic acid[20] (up to 50% *ee* for one example), the first highly enantioselective version of this transformation was reported in 1996 by the research group of Ito.[21] A Pd^0/carboxylic acid combination together with a *trans*-coordinating trap derivative **25** as a ligand led to an enantioselectivity of up to 95% [Eq. (9)]. Nevertheless, the catalytic activity, chemoselectivity, and substrate scope remained limited.

The research group of Mikami[22] reported in 2001 that a chiral tetrahydrofuran derivative **27** was obtained by the cycloisomerization of allylpropargyl ether **26** in the presence



(9)

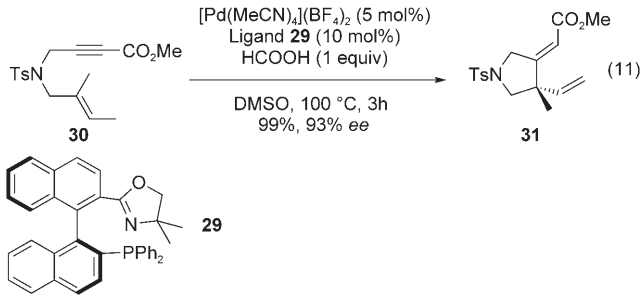
of a catalyst system consisting of $Pd(CF_3CO_2)_2$ and C_2-symmetric bidentate phosphorus ligands such as (*R*)-segphos [Eq. (10)]. An almost quantitative yield and an enantioselec-



(10)

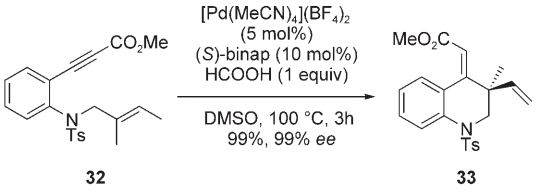
tivity of 99% were reached under optimized conditions. In sharp contrast with the system described by Ito and coworkers, *cis*-coordinating chiral ligands were extremely efficient in controlling the enantiopurity of the products. On the basis of deuterium labeling experiments as well as solvent effects, and in accordance with the Pd^0/Pd^{II} mechanism depicted in Scheme 3, the authors favored the formation of a five-coordinate neutral Pd^{II} complex **28** as the enantiodetermining step. The same research group later presented a new catalytic system that exhibited higher activity:[23] The use of the palladium precursor $[Pd(MeCN)_4](BF_4)_2$ and the chiral P,N ligand **29** in a 1:2 ratio allowed full conversion of the nitrogen-tethered enyne **30** into the chiral pyrrolidine **31** in DMSO at 100 °C in only 3 h in the presence of one equivalent of formic acid [Eq. (11), Ts: tosyl].

Hatano and Mikami extended their study to the asymmetric cycloisomerization of 1,7-enynes.[24] In the presence of



(11)

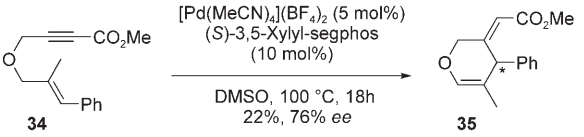
a combination of the palladium dicationic precursor $[Pd(MeCN)_4](BF_4)_2$ and (*S*)-binap, enyne **32** has been converted in 99% yield into a single enantiomer of quinoline heterocycle **33** bearing a quaternary center [Eq. (12)]. Nevertheless,



(12)

the substrate scope described was rather limited. Whereas the cycloisomerization of terminal acetylenes led to the same selectivity, aryl- and silyl-protected acetylenes failed to provide any products. Furthermore, the presence of the benzene ring in substrate **32** is an essential condition for obtaining a six-membered-ring product.

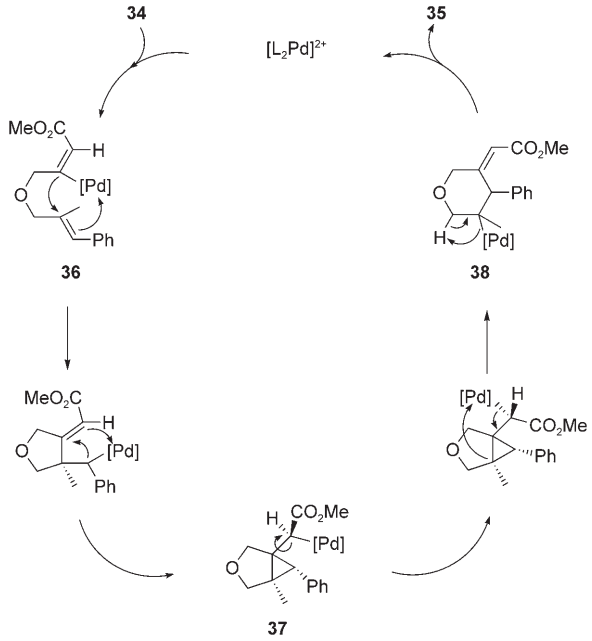
The formation of six-membered-ring products from the cyclization of 1,6-enynes has also been reported.[25] For example, Hatano and Mikami described the synthesis of dihydropyran **35** from allylpropargyl ether **34** in the presence of a dicationic palladium/biphosphane system in DMSO as the solvent for 18 h at 100 °C [Eq. (13)]. A very modest 22%



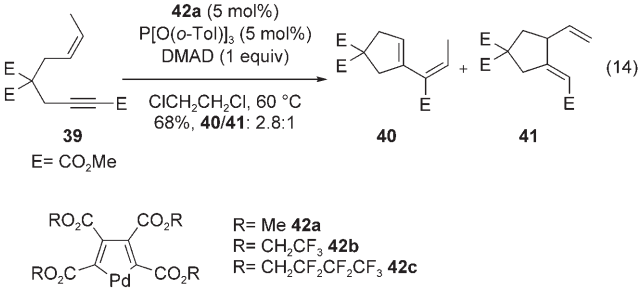
(13)

yield and a good enantioselectivity (76% *ee*) were obtained with a segphos derivative. The regioselectivity of the *exo* C–C double bond has been rationalized by the authors through a mechanism that involves initial formation of a hydridopalladium species (Scheme 4): *syn*-hydropalladation of the C–C triple bond then forms the vinylpalladium intermediate **36**. Two consecutive insertions into the C–C double bonds lead to the formation of the cyclopropylalkylpalladium intermediate **37**. Rotation around the C–C bond at the β-position to the palladium atom and a ring opening release the organometallic dihydropyrane species **38**. Product **35** is finally obtained through β-hydride elimination.

The next type of palladium-catalyzed transformations, represented in Scheme 1 by path C and D, has often been refered to as "metathesis". However, the metathesis mechanism only explains the formation of products resulting from path C. As palladium-catalyzed transformations often lead to dienes as a mixture by both pathways, those reactions should best be described as "skeletal rearrangements".[26] In 1988, Trost and Tanoury[27] reported the formation of the 1,3-diene **40** (path C) along with the Alder–ene product **41** (path A) in the presence of the palladacyclopentadiene **42a**, tris(*o*-tolyl)phosphite, and one equivalent of dimethyl acetylenedicarboxylate (DMAD) [Eq. (14)]. Substrates bearing electron-



Scheme 4. Pd-catalyzed enantioselective formation of dihydropyrans according to Equation (13).



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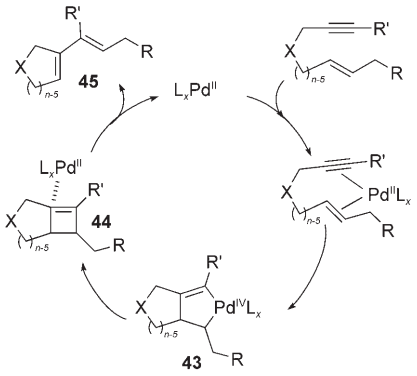
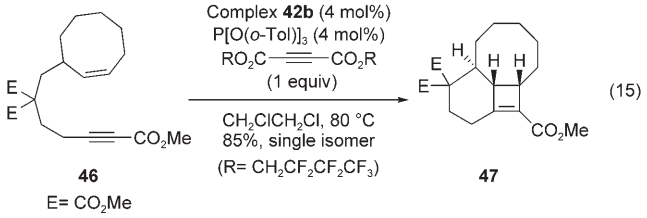
withdrawing substituents on the acetylene moiety are more reactive than ones bearing a halide, while thioether groups failed to produce any rearrangements.

The initial postulated mechanism relies on the formation of a palladium(IV) bicycle **43** followed by a reductive elimination leading to cyclobutene **44** (Scheme 5). A thermal, conrotatory opening of this intermediate would release the



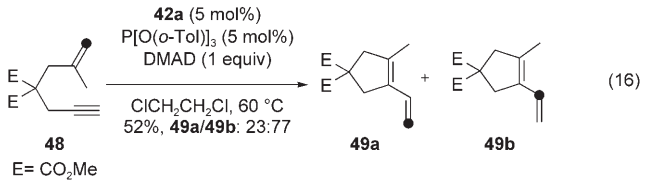
Scheme 5. Initial mechanism proposed by Trost et al. for the Pd-catalyzed skeletal rearrangement of enynes to 1,3-dienes.

1,3-diene **45**. Support for this mechanism came from the isolation of cyclobutenes or isomerized cyclobutenes formed from the cyclization of 1,6-,[28] 1,7-,[29] and 1,8-enyne [Scheme 1, path E, and Eq. (15)]. Substrate **46** was readily converted into the tricyclic compound **47** in the presence of complex **42b**.



(15)

However, ^{2}H- and ^{13}C-labeling experiments[20] have shown that two different kinds of rearranged dienes are obtained. Treatment of labeled enyne **48** in the presence of **42a** led to a mixture of 1,3-dienes **49a** and **49b**, which were designated as "single cleavage" and "double cleavage" products, respectively [Eq. (16)]. The generation of **49b** as a major product

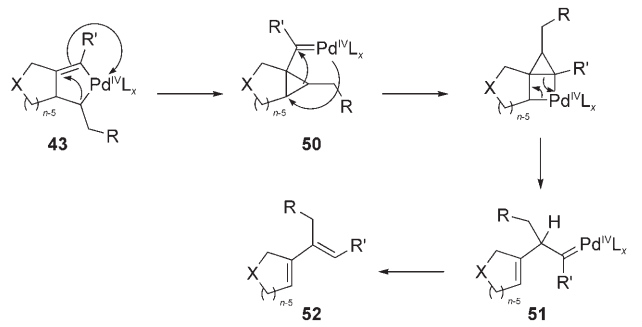


(16)

(Scheme 1, path D) is indicative of two competitive mechanisms for the rearrangement transformation.

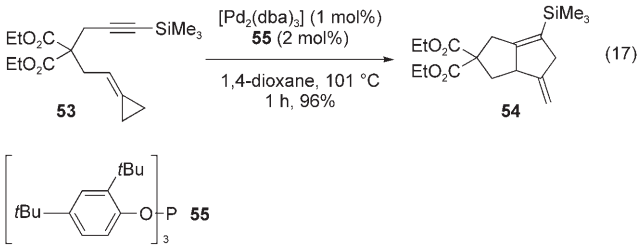
To take those facts into account, the authors have invoked a second mechanism, which relies on the generation of a (cyclopropylcarbene)palladium intermediate **50** (Scheme 6). Successive [2+2] and retro-[2+2] rearrangements lead to the formation of carbene **51**. A 1,2-hydride shift and elimination complete the catalytic cycle to form a diene of type **52**, which corresponds to path D. The hypothesis supporting the existence of intermediate **50** has been backed up through the trapping of analogues by conjugated dienes.[30]

Finally, Mascareñas and co-workers[31] have described the synthesis of a bicycle based on the specific reactivity of



Scheme 6. Alternative mechanism for the palladium-catalyzed skeletal rearrangement of enynes to 1,3-dienes.

alkynylidenecyclopropanes. The addition of enyne **53** to a combination of a Pd^0 source and a bulky phosphite such as **55** led to the formation of 1,4-diene **54** [Eq. (17)]. Superior reactivities have been obtained with phosphorus ligands bearing electron-withdrawing groups.



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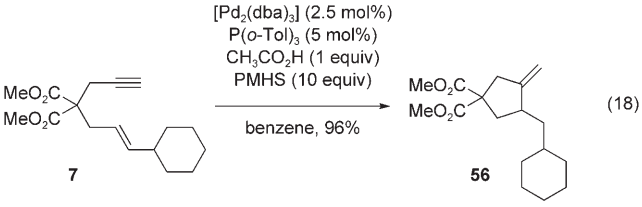
2.2. Enyne Tandem Reactions

The success of palladium-catalyzed cycloisomerizations in the synthesis of a large variety of carbo- and heterocycles with a high level of selectivity under mild conditions has prompted the development of tandem reactions, with the goal to further extend the level of functionalization of the products and provide a very attractive way to reach complex target molecules by using highly atom-economical transformations. The following five sections will deal with 1) reductive cyclizations, 2) polycyclization sequences, 3) tandem cyclization/nucleophilic addition processes, 4) oxidative cycloisomerizations, and 5) tandem cycloisomerization/metalation processes.

2.2.1. Palladium-Catalyzed Reductive Cyclizations

In the course of earlier investigations on the cycloisomerization of enynes, Trost and Rise[32] reported the reaction of enyne **7** with a system consisting of $[Pd_2(dba)_3]$, P(*o*-Tol)$_3$, and acetic acid in the presence of 10 equivalents of polymethylhydrosiloxane (PMHS) at room temperature in benzene. Product **56** was obtained in 96% yield as a single isomer [Eq. (18)]. This catalyst system is perfectly compatible with

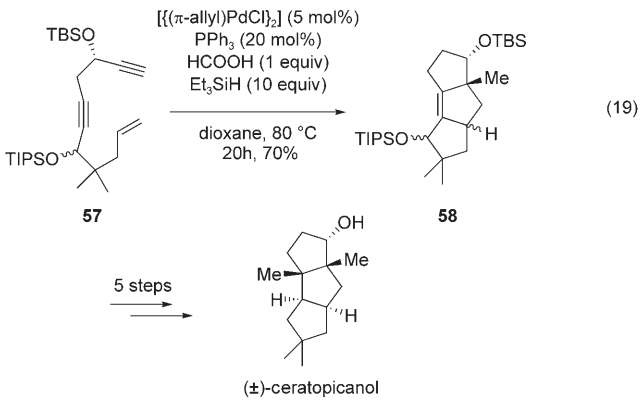


(18)

the presence of extra double bonds. The competitive simple reduction of the triple bond is not observed under optimized conditions. On the basis of cross-labeling experiments, an alkyl palladium complex of type **6** (Scheme 3) was invoked as the key intermediate, which is susceptible to undergo reduction in the presence of Si-H groups as hydrogen donors. Similar strategies have been developed for alkylative cyclization sequences of enynes.[33] In the presence of

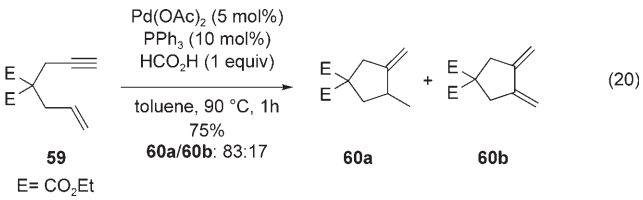
alkenyltin reagents, a cross-coupling step related to the Stille reaction leads to allyl-substituted carbo- and heterocycles.

This reductive cyclization has recently been applied to the total synthesis of (±)-ceratopicanol.[34] The tricyclic core of the molecule has been obtained through a methodology in which Et_3SiH is employed as a reducing agent [Eq. (19), TIPS: triisopropylsilyl]. Under optimized conditions, endiyne **57** is transformed into intermediate **58** in 70% yield as a mixture of two diastereoisomers.



(19)

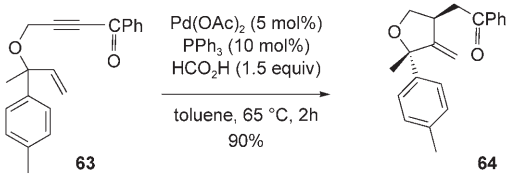
To circumvent the necessary use of a large excess of reducing agents in this methodology,[32,33] Oh and Jung[35] described an alternative system based on the use of a stoichiometric amount of formic acid. Treatment of enyne **59** with $Pd(OAc)_2$ and PPh_3 led to the synthesis of cyclized products **60a** and **60b** in an overall yield of 75% and an isomer ratio of 83:17 [Eq. (20)]. Formic acid has a dual role



(20)

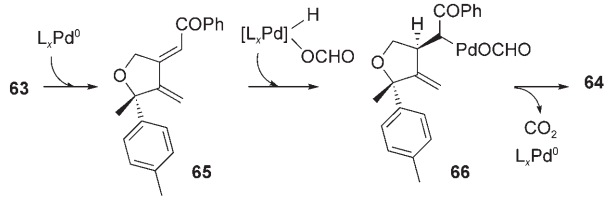
which results in the incorporation of both hydrogen atoms in the cyclized reduced product **60a**: 1) in accordance with the Pd^0/Pd^{II} mechanism depicted in Scheme 3, formic acid oxidatively adds to a Pd^0 complex (formed in situ from the Pd^{II} salt with PPh_3) to form the active species $H{-}L_xPd{-}OCHO$, which effects enyne cyclization via intermediates **4** and **5** (Scheme 3) to give palladium complex **61** (Scheme 7). 2) Cleavage of the formate ion from intermediate **61** gives a Pd-hydride species **62** that undergoes reductive elimination to give alkene **60a**. This pathway favorably competes with the β-hydride elimination from **61** to give 1,3-diene **60b** by following path B in Scheme 1. The selectivity of this transformation is highly dependent on the temperature and the solvent.

Oh et al. have also described orthogonal reactivity of enynes by using the Pd/formic acid system.[36] Enyne **63** with the activated triple bond was reductively cyclized to the corresponding γ,δ-unsaturated enone **64** in 90% yield [Eq. (21)]. The reversal of selectivity was rationalized by a



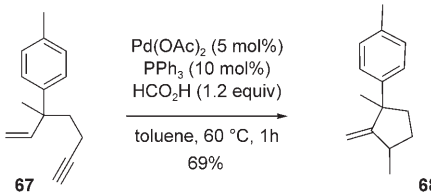
(21)

mechanism involving two separate steps (Scheme 8). In a first step, $H{-}L_xPd{-}OCHO$ catalyzes the transformation of **63** to the conjugated diene **65** (path B, Scheme 1). Subsequently, selective hydropalladation of the C–C double bond conjugated to the carbonyl compound furnishes the alkyl palladium intermediate **66**. Cleavage of the formate ion and reductive elimination complete the catalytic cycle and release the Pd^0 precatalyst. Remarkably, the reduction step is highly diastereoselective and implies a counterintuitive addition of the hydridopalladium complex on to the more hindered face of alkene **65**.



Scheme 8. Mechanism for the Pd-catalyzed reductive cyclization of electron-deficient 1,6-enynes according to Equation (21).

The complementarity between the Pd/R_3SiH system and the Pd/HCO_2H system was later highlighted during studies directed towards the total synthesis of laurene (**69**).[37] Enyne



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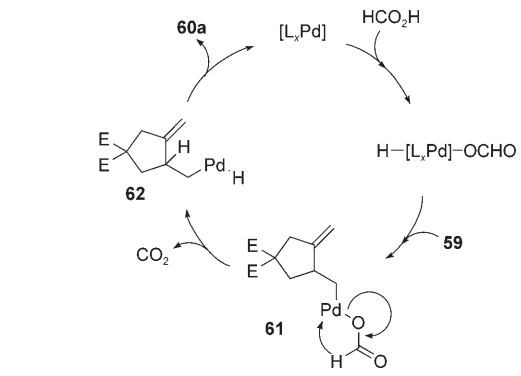
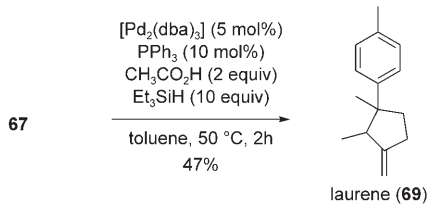


Scheme 7. Mechanism of the Pd-catalyzed reductive cyclization of 1,6-enynes according to Equation (20).

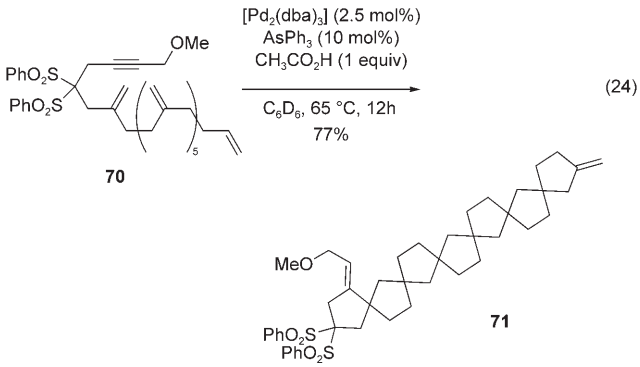
67 was transformed to carbocycle **68** or **69** in moderate to good yields, depending on the conditions used [Eqs. (22) and (23)].



(23)

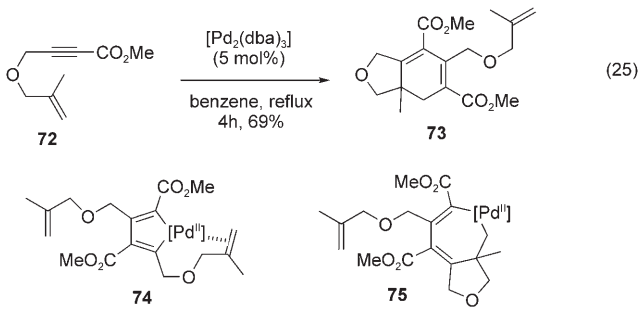
2.2.2. Palladium-Catalyzed Polycyclization Sequences and Cyclodimerizations

The possibility of trapping the alkyl palladium species **6** (Scheme 3) by intramolecular insertion into an electrophilic part of the molecule, such as a double bond, has been studied by the research group of Trost.[38] A variety of highly strained polycyclic structures have been obtained through this extension of the original Alder–ene reaction. The most spectacular example was probably the synthesis of the polyspirane **71** in one step and in 77% yield starting from polyenyne **70** [Eq. (24)].



(24)

Yamamoto et al.[39] reported the cyclodimerization of 1,6-enynes possessing electron-withdrawing substituents on the triple bond. In the presence of a Pd^0 precursor, such as $[Pd_2(dba)_3]$, substrate **72** was converted into cyclohexadiene **73** in 69% yield in benzene at reflux [Eq. (25)]. On the basis of the regioselectivity of the reaction, a mechanism relying on the oxidative dimerization of the triple bonds to form a palladacyclopentadiene intermediate of type **74** has been

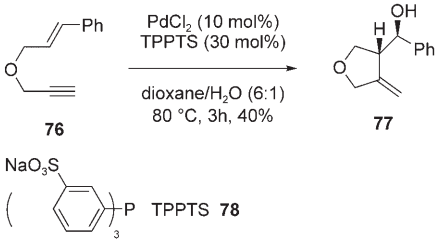


(25)

proposed. Alkene insertion leading to palladacycloheptadiene **75** and subsequent reductive elimination complete the catalytic cycle.

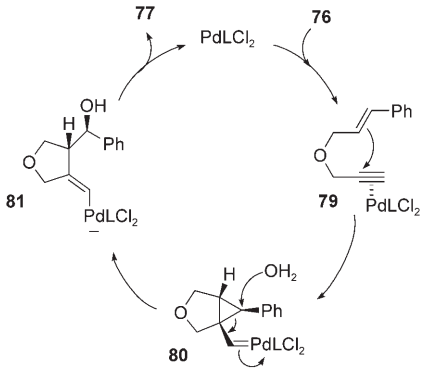
2.2.3. Palladium-Catalyzed Tandem Cycloisomerization and Nucleophilic Addition Reactions

In the course of studies directed towards the application of aqueous organic conditions to the cycloisomerization of 1,6-enynes, Genêt and co-workers discovered the first carbohydroxypalladation[40] (Scheme 1, path H) of allyl propargyl ethers **76**. This process allowed the synthesis of tetrahydrofuran **77** in moderate to good yields and diastereospecificity [Eq. (26)]. Other oxygen nucleophiles such as MeOH were also introduced diastereoselectively.



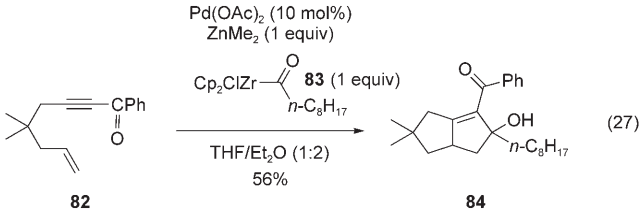
(26)

From deuterium labeling experiments, and in accord with more recent mechanistic investigations on Pt- and Au-related transformations (see Sections 5 and 6), the reaction is believed to proceed via the formation of a cyclopropylcarbene complex **80** (Scheme 9).[41] Nucleophilic opening of this intermediate by water leads to the rearranged vinylpalladium **81**. Proto-demetalation completed the catalytic cycle.



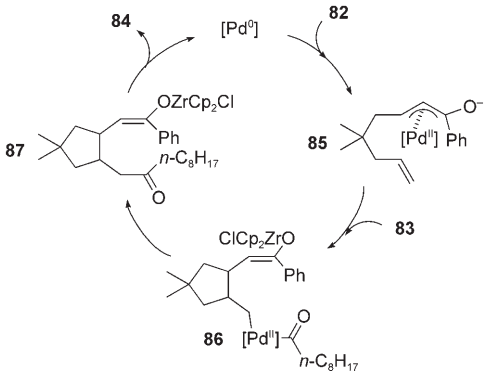
Scheme 9. Mechanism for the Pd-catalyzed hydroxycyclization of 1,6-enynes according to Equation (26).

Organometallic reagents have also been used as nucleophilic partners in cycloisomerization reactions. Hanzawa, Taguchi, and co-workers reported the formation of the bicyclic alcohol **84** from the reaction of the activated enyne **82** with acylzirconocene complex **83** in the presence of $Pd(OAc)_2$ as a catalyst and $ZnMe_2$ as an additive [Eq. (27), Cp: C_5H_5].[42] The reaction is proposed to proceed through the



(27)

oxidative addition of an in situ formed Pd^0 complex to the ynone function of **82** to give the π-allyl intermediate **85** (Scheme 10). Cyclization and transmetalation of the acyl

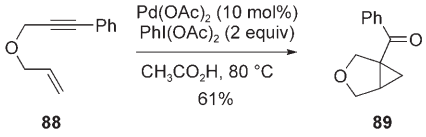


Scheme 10. Mechanism for the Pd-catalyzed tandem reaction (27) consisting of acyl addition cycloisomerization and aldolization of enynes.

fragment generates complex **86**, which undergoes reductive elimination to give enolate **87**. A subsequent intramolecular aldol reaction furnishes the bicyclic β-hydroxyketone **84**.

2.2.4. *Palladium-Catalyzed Oxidative Cycloisomerizations*

In two very recent publications, the research groups of Tse[43] and Sanford[44] independantly reported the first examples of oxidative cyclization of 1,6-enynes, which allowed the formation of cyclopropylketones of type **89** [Eq. (28), Scheme 1 path F]. In a typical experiment, enyne **88** is treated with the oxidating agent (diacetoxyiodo)benzene in the presence of $Pd(OAc)_2$ in acetic acid at 80 °C to give **89** in modest yields. The reaction scope of the transformation is large, as a wide range of alkyl and aryl substituents as well as ynone and ynamide functionnalities are tolerated. Both research groups postulate a mechanism involving Pd^{IV} intermediates (Scheme 11). In a first step, acetoxypalladation of the triple bond proceeds in a *trans* fashion to give the vinylpalladium intermediate **93**. Subsequent alkene insertion



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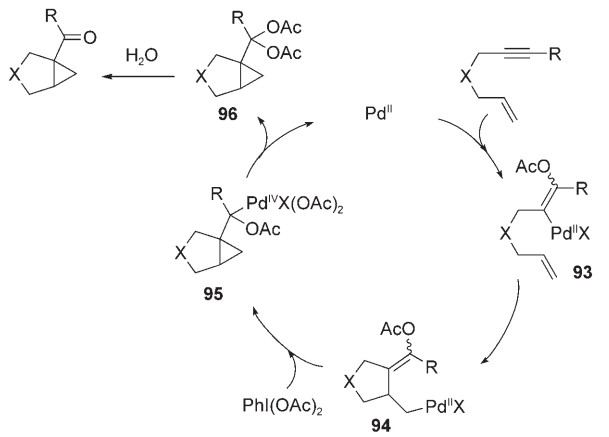
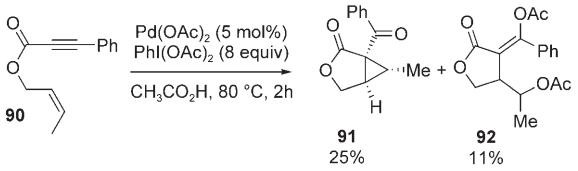


Scheme 11. Mechanism for the Pd-catalyzed oxidative cycloisomerization of 1,6-enynes according to Equation (28).

provides the alkyl palladium species **94**. Oxidation of the palladium center and cyclopropanation by insertion into the enol ester function produce the alkyl Pd^{IV} intermediate **95**. Reductive elimination releases the active Pd^{II} species and **96**, which gives the cyclopropylketone upon hydrolysis. The existence of **94** is backed up by the isolation of a diacylated lactone of type **92** as a by-product upon oxidative cyclization of enyne **90** [Eq. (29)].

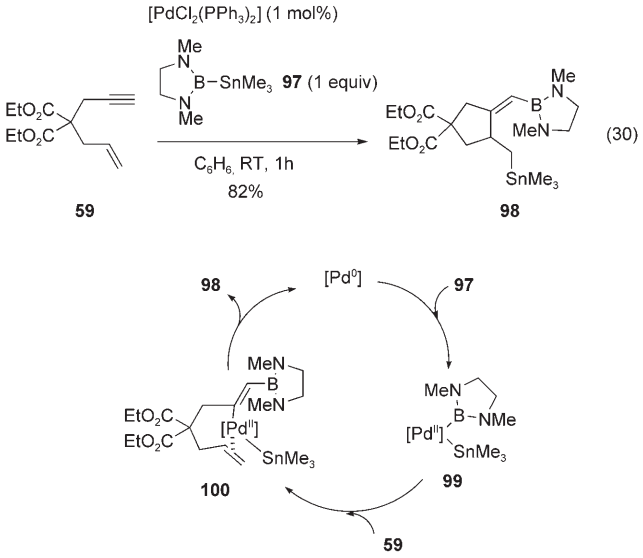


(29)

2.2.5. *Palladium-Catalyzed Tandem Cycloisomerization and Metalation Reactions*

In view of their versatility as partners in cross-coupling reactions and the multitude of accessible synthetic transformations, attention has been devoted to methodologies that allow the synthesis of complex organometallic reagents. The addition of metal–hydrogen or metal–metal reagents to carbon–carbon multiple bonds represents a well-established approach towards this end.[45] Only a few examples of the application of this concept to the field of cycloisomerization of 1,*n*-enynes have so far been described.

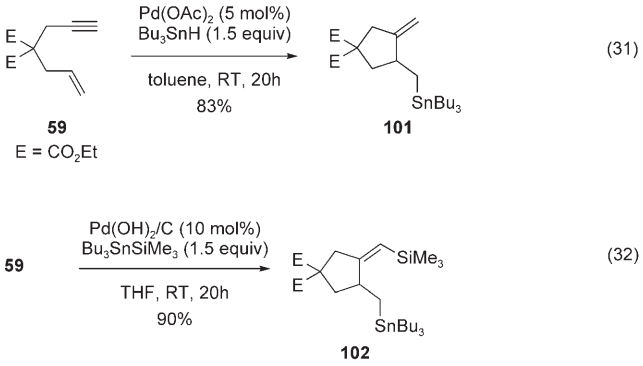
The research group of Tanaka[46] reported a single palladium-catalyzed borylstannylation of a 1,6-enyne. Exposure of enyne **59** to borylstannane **97** in the presence of $[PdCl_2(PPh_3)_2]$ effected the smooth conversion into the bismetalated product **98** [Eq. (30)]. On the basis of the structure of **98**, the authors proposed a catalytic cycle based on the oxidative addition of the B–Sn bond to a Pd^0 species generated in situ to form a boryl(stannyl)palladium complex **99** (Scheme 12). Insertion of the alkyne unit into the more reactive Pd–B bond gives the vinylpalladium complex **100**. Subsequent insertion of the alkene unit and reductive



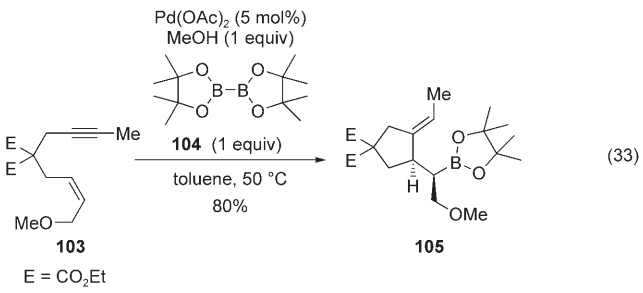
Scheme 12. Mechanism for the Pd-catalyzed borylstannylation of 1,6-enynes according to Equation (30).

elimination leads to **98** and regenerates the catalytically active species.

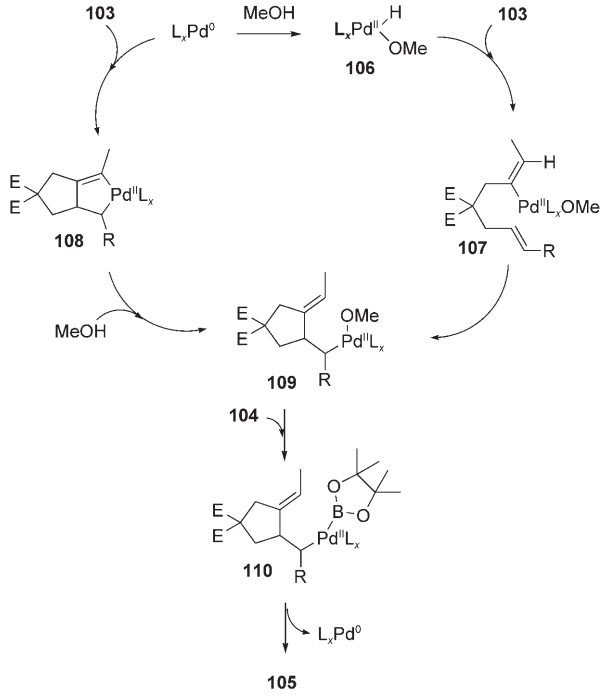
Similar reactivities have been observed by the research groups of Lautens[47] and Mori[48] in studies dealing with the cyclizative hydrostannation and silylstannation of enynes [Eq. (31) and (32)]. Enyne **59** could be easily transformed into stannane **101** or its silylated derivative **102** in yields of 83 and 90%, respectively.



Very recently, Cárdenas and co-workers presented a palladium-catalyzed borylative cyclization of 1,6-enynes [Eq. (33)].[49] Treatment of carbon-bridged enynes with bis-(pinacolato)diboron **104** in the presence of a catalytic amount of $Pd(OAc)_2$ and MeOH as an additive resulted in the smooth convertion into the carbocyclic alkyl boronate **105** in moderate to excellent yields (47–95%). In line with the observations made on the hydroxycyclization reaction [Eq. (25), Scheme 9),[40,41] the process is stereospecific.



The authors propose a mechanism that relies on the formation of intermediate **109**, either through initial generation of Pd-H compound **106**, hydropalladation of the alkyne to give intermediate **107**, and insertion into the alkene, or through oxidative cyclometalation to give **108** and subsequent protolysis (Scheme 13). Alkoxide-promoted transmetalation of **104** to the palladium center and reductive elimination liberates **105** and regenerates the active Pd^0 complex.



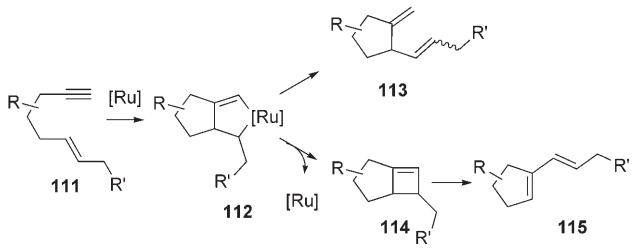
Scheme 13. Mechanism for the Pd-catalyzed borylative cycloisomerization of enynes according to Equation (33); R = CH_2OMe.

3. Ru-Catalyzed Cycloisomerization Reactions

Ruthenium-based systems are not only highly useful for the well-documented alkene metathesis reactions. Indeed, Ru-catalyzed cycloisomerizations of 1,*n*-enynes have proven highly selective and have led to broad applications.[50]

3.1. Enyne Rearrangements

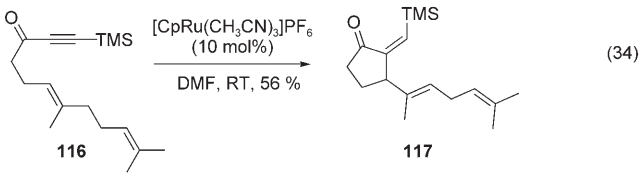
These reactions have been widely studied and are generally initiated by metallacyclopentene or vinylidene intermediates. The major developments involving enynes are based on ruthenacyclopentene intermediate **112** (Scheme 14), which is generated in the presence of a Ru^{II}



Scheme 14. Key intermediates in the Ru-catalyzed cycloisomerization of 1,6-enynes.

catalyst. Further β-elimination and reductive elimination affords the 1,4-diene **113**. Another route may be a reductive elimination that leads to the cyclobutene **114**. Conrotatory cycloreversion of the latter compound gives rise to the cyclopentene adduct **115**. These two processes are completely in accord with some previous Pd-catalyzed reactions (Schemes 2, 3, and 5).

For example the geranyl-substituted enyne was cleanly converted into a 1,4-diene in the presence of a catalytic amount of $[CpRu(CH_3CN)_3]PF_6$ [Eq. (34), TMS: trimethylsilyl].[51] Other 1,6- and 1,7-enynes bearing carbon, oxygen, or nitrogen bridges underwent similar cyclization reactions [Eqs. (35) and (36)]. This methodology has been successfully applied to the total synthesis of (+)-allocyathin B_2.[52]



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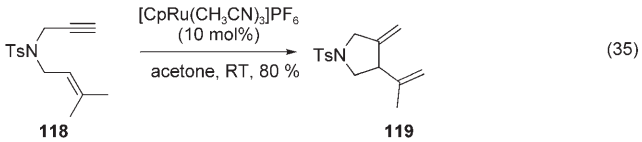

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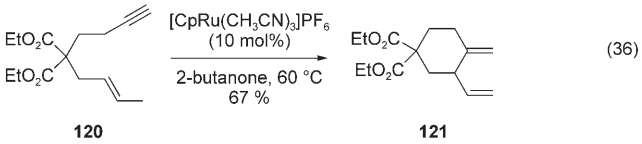
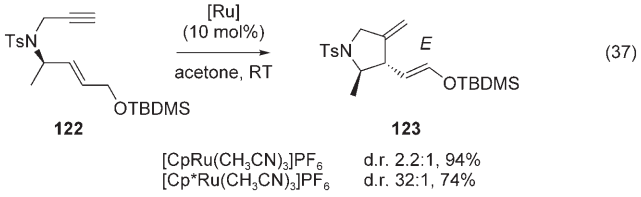


(36)

The use of such ruthenium catalysts may be seen as a complementary method to palladium catalysis for the selective preparation of 1,4-dienes. These cationic catalytic systems are compatible with a wide range of functional groups. The presence of an allylic silyloxy moiety was indeed tolerated in the presence of ruthenium catalysts.[53] The cycloisomerization of enyne **122** was carried out in the presence of either $[CpRu(CH_3CN)_3]PF_6$ or $[Cp^*Ru(CH_3CN)_3]PF_6$ (Cp*: C_5Me_5) In both cases, the *N*-tosylpyrrolidine **123** was obtained in good yield and high diastereomeric ratio [Eq. (37)]. The relocated double bond was found to have an *E* configuration. It is remarkable that, depending on the catalyst, *E* or *Z* isomers are obtained as the major products [Eq. (38)).



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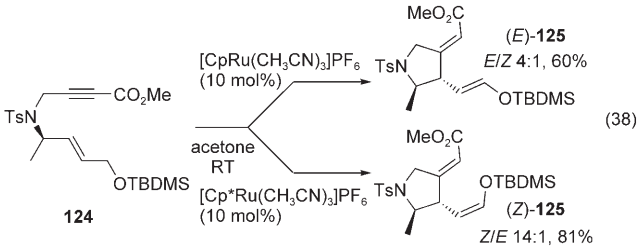
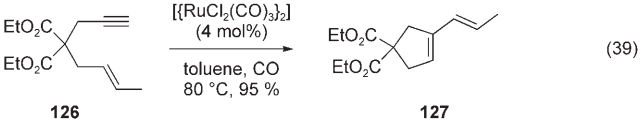


(38)

The formal metathesis of enynes involving cyclobutenyl intermediates is also extremely well described.[54] Katz and Sivavec discovered the reaction by using tungsten, but then tested it with several transition metals.[55] Its application in total synthesis is quite recent and well-exemplified in a recent review by Nicolaou et al.[56] Various catalysts including the dimer $[\{RuCl_2(CO)_3\}_2]$,[57] the Grubbs catalyst,[58] and 16-electron cationic complex $[RuCl(\eta^6\text{-}p\text{-cymene})(PCy_3)]CF_3SO_3$[59] (Cy: cyclohexyl)were found to be highly active for such transformations, and led to structurally interesting carbo- or heterocycles such as **127**, **129**, and **131** [Eq. (39)–(41)]. The ruthenium–arene species used by Dixneuf and co-workers showed a remarkable turnover frequency (TOF) of 47.5 h^{-1} [Eq. (41)].



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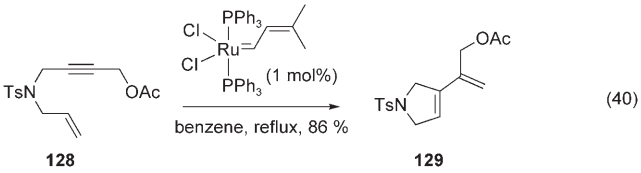

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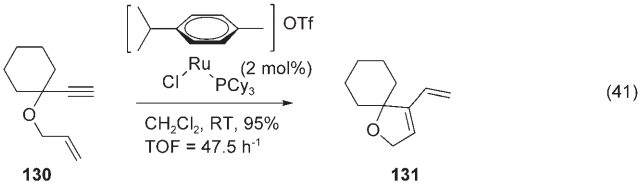
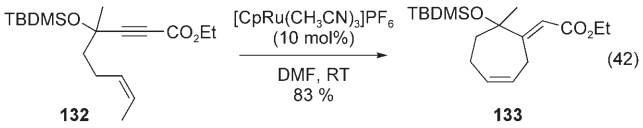


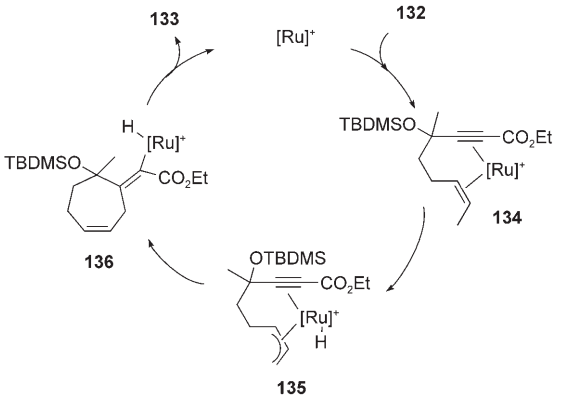
(41)

Other mechanistic pathways have been advocated for the ruthenium-catalyzed cycloisomerization of enynes, including the possible intervention of a π-allylruthenium intermediate generated by an allylic C–H activation. A proposal for the formation of **133** from **132** [Eq. (42)] is shown in



(42)

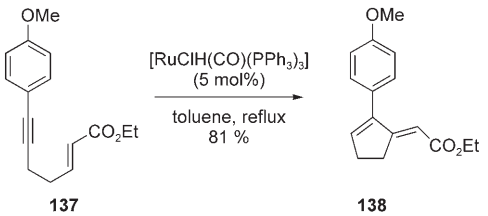
Scheme 15:[60] the cationic Ru catalyst $[CpRu(CH_3CN)_3]PF_6$ may activate the allylic position of **132** to give the π-allyl intermediate **135**. A 7-*exo-dig* carboruthenation of the alkyne



Scheme 15. Proposed mechanism for the Ru-catalyzed 7-*exo-dig* cyclization according to Equation (42).

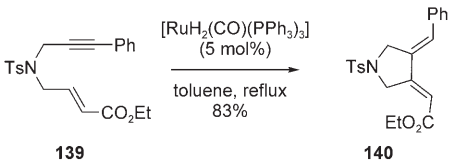
affords the hydridoruthenium species **136**, which upon equilibration and β-elimination produces the cycloheptene derivative **133**. Deuterium labeling experiments supported this mechanism.

Reactions may also be initiated by hydrometalation to give functionalized 1,3-dienes,[61] as hydroruthenation of the triple bond is followed by a 5-*exo-trig* cyclization and then a β elimination. For example, α,β-unsaturated ester **137** underwent a clean cyclization in the presence of the $[RuClH(CO)(PPh_3)_3]$ catalyst to give a single regioisomer **138** [Eq. (43)]



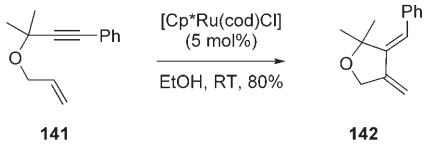
(43)

and the dihydride $[RuH_2(CO)(PPh_3)_3]$ promoted the same reaction of **139** to give **140** [Eq. (44)].[62] This strategy was applied to the synthesis of highly valuable carbapenam



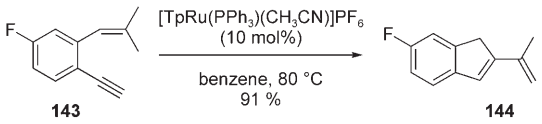
(44)

skeletons. The combination of [CpRu(cod)Cl] (cod: cyclo-1,5-diene) and an alcohol such as ethanol can also generate a ruthenium hydride, and therefore lead, for example, to the conversion of **142** into 1,3-diene **142** [Eq. (45)].[63]



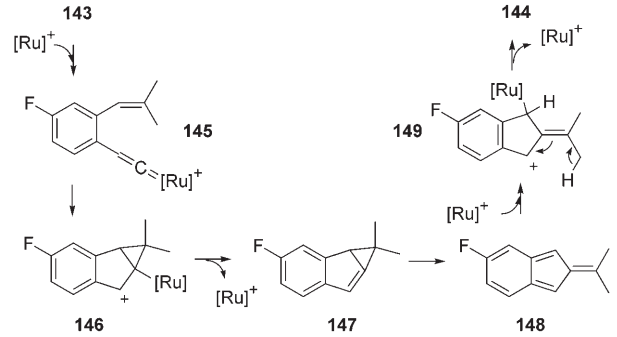
(45)

An atypical enyne cycloisomerization reaction was recently observed in the case of (*o*-ethynylphenyl)alkene **143**.[64] The synthesis of 2-alkenyl-1*H*-indene **144** was promoted by 10 mol% of the cationic catalyst $[TpRu(PPh_3)(CH_3CN)]PF_6$ [Eq. (46), Tp = hydridotris(pyrazolyl)borate].



(46)

The skeletal rearrangement implies a complete cleavage of the double bond, and insertion of the terminal alkynyl carbon atom. The reaction mechanism was elucidated by ^2H and ^{13}C labeling experiments. The authors proposed an activation of the triple bond, which led to the cationic ruthenaallene **145**; this species then undergoes a 5-*endo-dig* cyclization to give a transient tertiary carbocation, which evolves into the cyclopropylbenzyl cation **146** (Scheme 16). This intermediate is

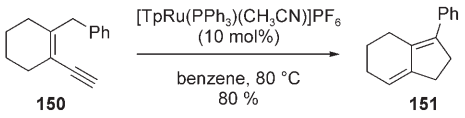


Scheme 16. Proposed mechanism for the Ru-catalyzed 5-*endo-dig* cyclization reaction according to Equation (46).

transformed into a fulvene species **148** according to the "methylenecyclopropane-trimethylenemethane" rearrangement. Further transformation of fulvene **148** to the observed

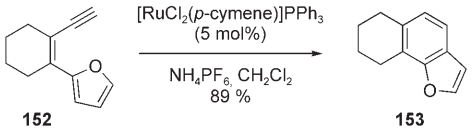
indene can be achieved with the regenerated cationic catalyst through the formation of the benzyl cation **149**. The formation of the nonclassical carbocation **146** likely occurs because of orbital overlap.

The formation of vinylidene intermediates has also been advocated in other cycloisomerizations, in which addition of a C–C bond to a triple bond is always necessary. The cyclization of *cis*-enynes **150** in the presence of $[TpRu(PPh_3)(CH_3CN)]PF_6$ led to the preparation of diene **151** in good yield [Eq. (47)].[65] The formation of the cyclopentene ring

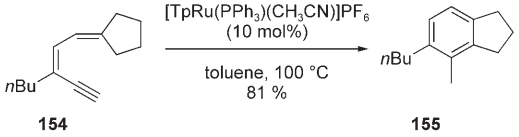


(47)

probably implies a 1,5-sigmatropic hydrogen shift of vinylideneruthenium intermediates. Such intermediates are also involved in the synthesis of functionalized aromatic rings. Enynes bearing a furanyl group, such as **152**,[66] or an alkyl group, such as **154**,[67] can be converted efficiently into aromatic derivatives **153** and **155** in the presence of an in situ generated cationic Ru^{II} species or in the presence of $[TpRu(PPh_3)(CH_3CN)]PF_6$ [Eqs. (48) and (49), respectively].

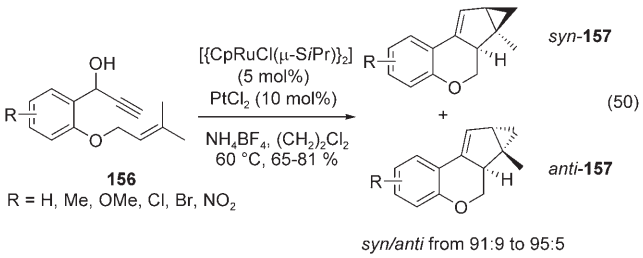


(48)



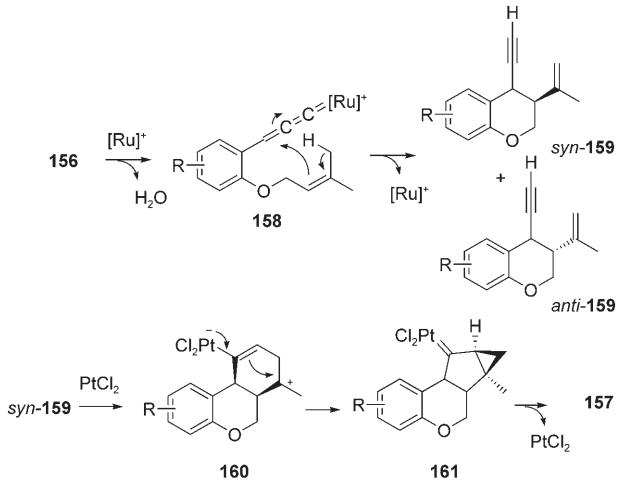
(49)

The combination of the activity of a ruthenium and platinum catalyst [Eq. (50), Scheme 17] was used by the research group of Uemura and Nishibayashi for the prepa-



(50)

ration of fused polycyclic compounds **157** by intramolecular cyclization of propargylic alcohols bearing an alkene moiety at a suitable position.[68] The two catalysts promoted a sequence of catalytic cycles in the same medium and gave polycyclic compounds **157**, with the *syn* isomer being the major product. The catalytic activity was demonstrated by performing each step sequentially. In the presence of the cationic ruthenium catalyst, the first step was the classical formation of the vinylidene carbene **158** with elimination of water (Scheme 17). Cyclization then afforded the cyclic ethers

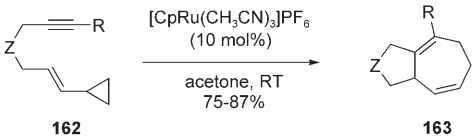


Scheme 17. Proposed mechanism for the combined Pt- and Ru-catalyzed cycloisomerization reaction according to Equation (50).

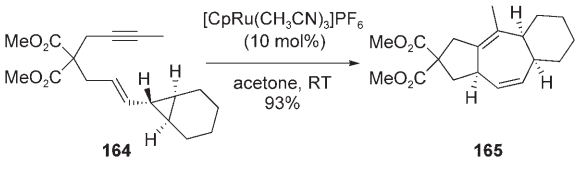
159 as a diastereomeric mixture. The authors showed that only *syn*-**159** can be transformed to tetracyclic **157** derivatives, while *anti*-**159** was always recovered intact. Some deuterium incorporation also supported the proposed mechanism. The cyclization to give **157** was explained through vinylplatinate **160**, which evolved towards the carbenic species **161**.

3.2. Tandem Reactions with Enynes

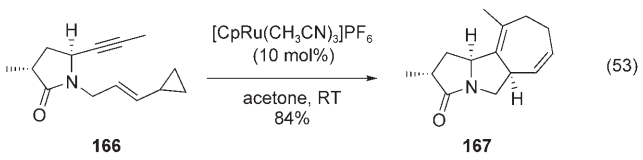
Besides the tandem ring-closing metathesis,[69] which has been well developed, the construction of other polycyclic derivatives was based on Ru-catalyzed tandem reactions. Motivated by the stimulating work by Wender et al. on rhodium catalysts (see Section 3), Trost et al. studied the Ru-catalyzed [5+2] cycloaddition of various enynes.[70] The ruthenium catalyst $[CpRu(CH_3CN)_3]PF_6$ proved to be highly efficient at room temperature and highly tolerant to functional groups and substitution on the triple and double bonds as well as on the cyclopropane ring [Eq. (51)–(53)]. The



(51)



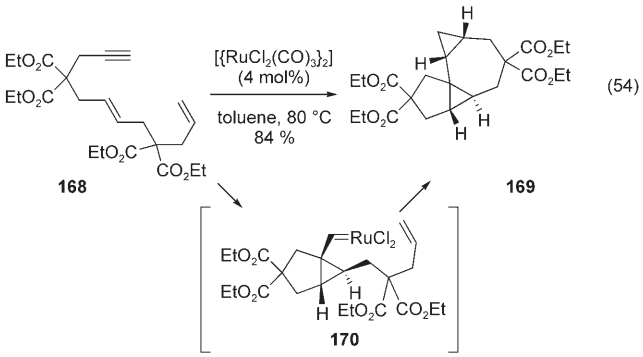
(52)



(53)

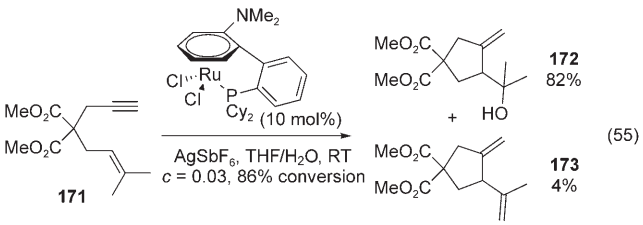
ability to increase the molecular diversity of the reaction was demonstrated through the formation of tricyclic derivatives **165** and **167** in excellent yields and selectivity by cyclization of enynes **164** and **166**.[70c]

The cycloisomerization of enynes with further unsaturated groups can lead to novel polycyclic ring systems. The research group of Murai pioneered this field by using ruthenium as the catalyst.[71] Dodeca-1,6-dien-11-yne **168** could be cleanly converted into a single isomer of the polycyclic derivative **169** through formation of four carbon–carbon bonds in the presence of 4 mol% $[\{RuCl_2(CO)_3\}_2]$ [Eq. (54)], and the reaction could be generalized to several



(54)

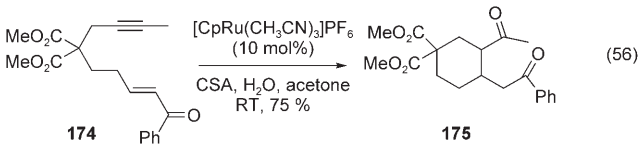
dienynes. The formation of a bicyclic carbene **170** as an intermediate was advocated, and at that time indeed constituted a new beginning for metal-catalyzed cycloisomerization of 1,6-enynes. This intermediate is a key species in several Pt- and Au-catalyzed reactions. The trapping of the carbene with water [Eq. (55)] was recently described—according to



(55)

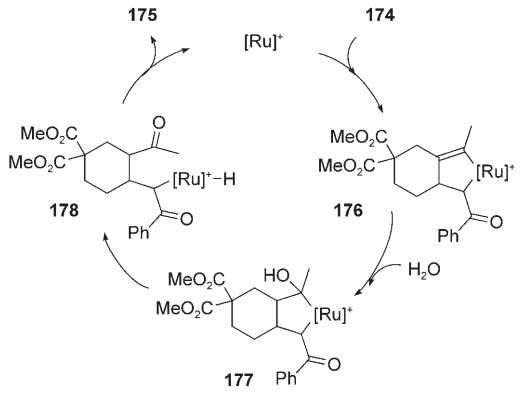
the same methodology developed with palladium [Eq. (26)]. The use of undried THF led to the hydroxylated alkene **172**.[72] The cationic ruthenium species formed by the addition of silver salts to the chiral arene–ruthenium catalyst[73] allowed the enyne cycloisomerization reaction, similar to the use of $[CpRu(CH_3CN)_3]PF_6$ [see Eq. (35)] but affords the alcohol **172**, and not diene **173**, as the major product.

The addition of water to a ruthenacycle can also occur, such as in the addition of $[CpRu(CH_3CN)_3]PF_6$ to the enyne **174** bearing a ketone moiety.[74] The formation of 1,5-diketone **175** was observed in aqueous acetone when camphorsulfonic acid (CSA) was used as a co-catalyst [Eq. (56)]. The proposed



(56)

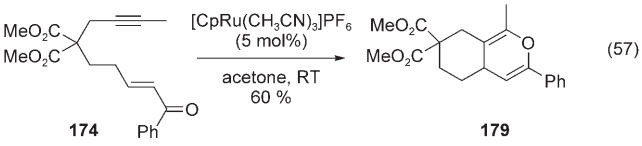
mechanism may involve the addition of water to the ruthenacycle **176** (→**177**) followed by a hydride elimination (→**178**) and a reductive elimination step (Scheme 18). This hydration



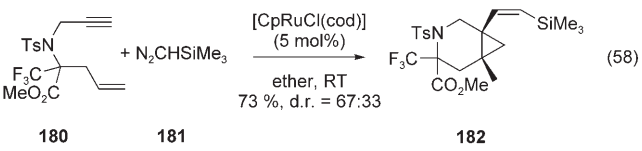
Scheme 18. Proposed mechanism for the Ru-catalyzed synthesis of 1,5-diketones according to Equation (56).

still needs to be completely established, as the authors also envisioned that the 1,5-diketone **175** could arise by the simple hydration of a transient pyran. It is indeed noteworthy that the use of dry acetone changed the course of the reaction: A [4+2] cycloaddition of **174** occurred to afford functionalized pyran **179** [Eq. (57)].

An alkylideneruthenium complex may also be generated by the reaction of [CpRuCl(cod)] with the diazo compound $N_2CHSiMe_3$ **181**.[75] The reactivity of this complex was found to be specific: no ring-closing metathesis reaction but a tandem alkenylation/cyclopropanation was observed, for example, in the transformation of **180** to **182** [Eq. (58)]. The



(57)



(58)

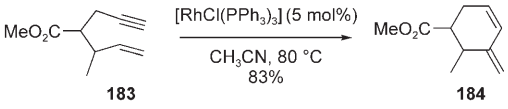
authors showed that the Cp(Cl)Ru moiety in ruthenacyclobutane favored reductive elimination over the expected alkene metathesis. The vinylbicyclo[4.1.0]heptanes are isolated in excellent yields. It is noteworthy that bicyclo[3.1.0]hexanes can be formed according to the same methodology. Moreover, the catalytic formation of alkenylbicycloderivatives is also possible in the presence of N_2CHCO_2Et or N_2CHPh instead of **181**.[76]

4. Rh-Catalyzed Cycloisomerizations

Several reports have been published on Rh- and Ir-catalyzed cycloisomerization of enynes. The main applications have been achieved in the presence of rhodium catalysts including the enantioselective synthesis of chiral cyclic dienes.

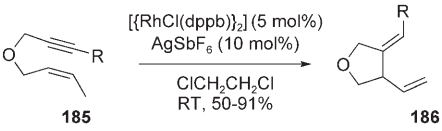
4.1. Enyne Rearrangements

One of the first reports concerning the Rh-catalyzed enyne cyclizations concerned the use of the Wilkinson catalyst for a 6-*exo*-*trig* process [Eq. (59)].[77] The cyclization of enyne



(59)

183 led to the formation of 2-methylenecyclohexene **184** in good yield. Substituents on either the triple or double bonds inhibited the reaction. The research group of Zhang described a rhodium-catalyzed Alder–ene-type reaction [Eq. (60)]. The

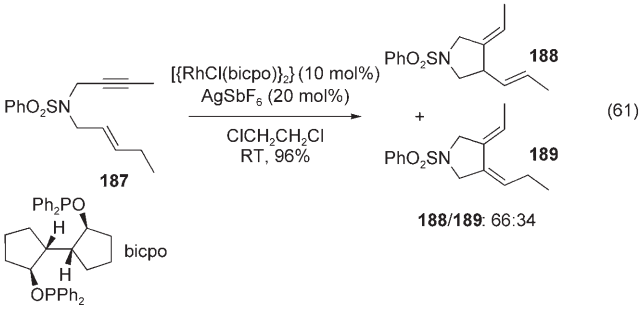


(60)

R = Ph, *p*-Me-C_6H_4, *p*-Cl-C_6H_4, *p*-CF_3-C_6H_4, CH_2Ph, CO_2Me, Me

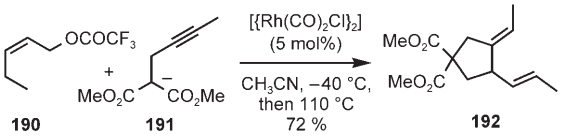
use of [{Rh(dppb)Cl}$_2$] (dppb: 1,4-bis-(diphenylphosphanyl)-butane) in combination with a silver salt in dichloroethane promoted the cycloisomerization of several ether-linked 1,6-enynes **185** [Eq. (60)].[78] As this system was limited by the range of substrate that could be used, the authors screened other phosphorus ligands and found that the ligand bicpo was efficient for nitrogen-bridged enynes [Eq. (61)]. One limitation is that only enynes **185** bearing a (*Z*)-allylic side chain cleanly cyclize to give a unique diene **186**. When the allylic side chain had an *E* configuration (such as in **187**), a mixture of 1,3- and 1,4-dienes **188** and **189** was observed [Eq. (61)].

[{Rh(CO)Cl}$_2$] can promote domino reactions involving an allylic substitution and carbocyclization. The allylic substitution of the malonate anion **191** with various allyl trifluoroacetates was followed by the cycloisomerization of

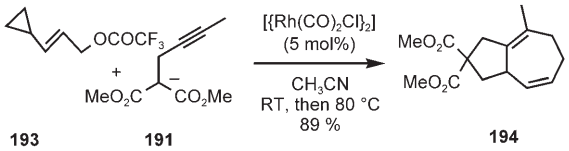


(61)

the resulting enyne. Depending on the alkenyl substituent, a classic carbocyclization or a [5+2] cycloaddition was observed and afforded dienes **192** and **194**, respectively [Eqs. (62) and (63)].[79]

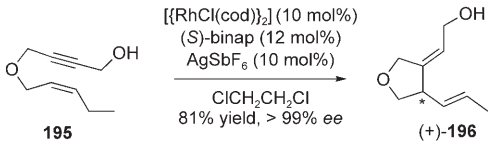


(62)

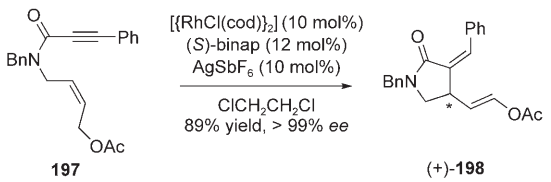


(63)

The asymmetric version of the cycloisomerization reaction of 1,6-enynes was reported by Zhang and co-workers shortly after the racemic version.[80] The binap ligand, which did not seem to be a good candidate in the first report from Cao and Zhang[80a] appeared as the best, and the catalyst system consisting of [{Rh(cod)Cl}$_2$], binap, and $AgSbF_6$ was highly efficient either for the synthesis of chiral tetrahydrofurans or functionalized lactams [Eqs. (64) and (65), respectively]. It is noteworthy that the allylic acetate **197** reacted



(64)

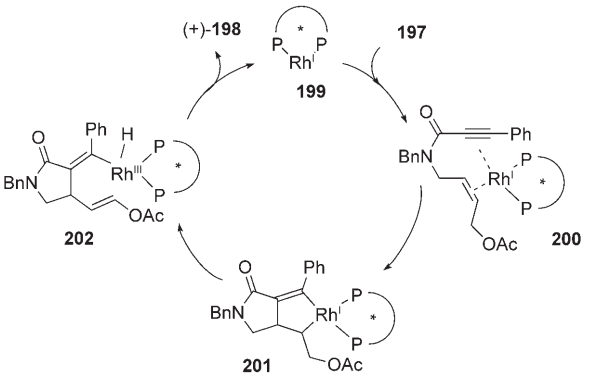


(65)

very cleanly and that no oxidative addition, which is usually observed in the case of palladium or nickel catalysts, was observed [Eq. (65)]. Some alternative systems have been

described recently, but did not give higher enantioselectivity nor could they solve the problem of the reactivity of substrates with (*E*)-allylic side chains.[81]

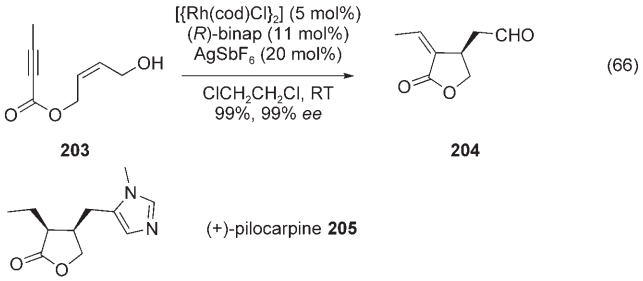
A catalytic cycle has been proposed by the authors (Scheme 19). After coordination of the enyne **197** to the chiral



Scheme 19. Proposed mechanism for the Rh-catalyzed Alder–ene reaction according to Equation (65).

Rh catalyst **199**, an oxidative cyclization could take place to give the metallacyclopentene **201**. Subsequent β-hydride elimination would allow the formation of the Rh-H species **202**, which upon reductive elimination would regenerate **199** and give the desired cyclized product (+)-**198**. The regioselective formation of the 1,4-diene may be explained by considering the favored *cis* relationship between the C–Rh and C–H bonds for the β-hydride elimination.

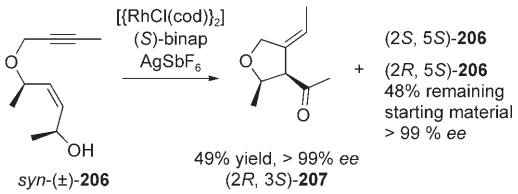
A concise application of the Rh-catalyzed asymmetric cycloisomerization developed by Zhang and co-workers was the formal synthesis of (+)-pilocarpine (**205**), one of the most important imidazole alkaloids, which is used in the treatment of narrow- or wide-angle glaucoma.[82] The allylic alcohol **203** was subjected to the optimized system, and the cyclization afforded the enantiomerically pure aldehyde **204** [Eq. (66)].



(66)

This aldehyde could be transformed in two steps to (+)-pilocarpine, as shown in the total synthesis by Büchi and co-workers.[83] The research group of Nicolaou also took advantage of this reaction in their recent total synthesis of (−)-platensimycin.[84]

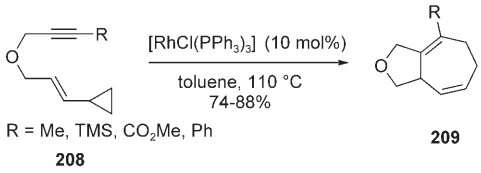
The Rh-catalyzed cycloisomerization reactions were also expanded to a kinetic resolution process in the case of ether-linked substrates [Eq. (67)].[85] When the racemic *syn* substrate **206** was subjected to the previously described conditions, the corresponding cyclized product (2*R*,3*S*)-**207** was obtained in 49% yield and with over 99% *ee*, while a mixture of (2*R*,5*S*)-**206** (>99% *ee*) and (2*S*,5*S*)-**206** (>99% *ee*) remained unchanged.



(67)

4.2. Enyne Tandem Reactions

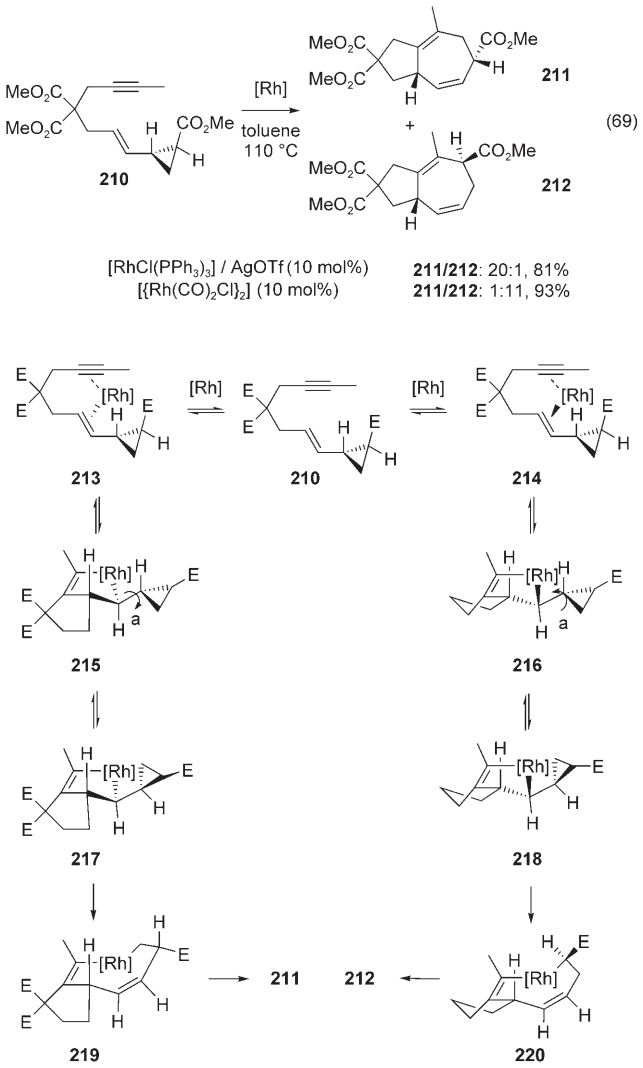
Most research on Rh-catalyzed tandem reactions concerns the Pauson–Khand reaction, which has been widely reviewed and will not be discussed here.[86] Other tandem reactions are based on the trapping of the metallacyclopentene intermediate of type **201** (Scheme 19). Intramolecular cycloadditions are part of a wide area of research based on the original and inventive work from the research groups of Wender and Ojima.[87] The formal intramolecular [5+2] cycloaddition was firstly reported in 1995, with the Wilkinson catalyst used with or without silver salts [Eq. (68)].[88] The use



(68)

of [{Rh(CO)$_2$Cl}$_2$] and [(C$_{10}$H$_8$)Rh(cod)]BF$_4$ opened up new perspectives in this area, as these catalysts were generally more reactive and more selective than the Wilkinson catalyst.[89] Substituents on the cyclopropyl ring and the choice of catalyst also had an interesting influence on the outcome of the reaction.[90] The *syn* or *anti* configuration of the cyclopropyl substituents directly determined the diastereomeric nature of the cycloadducts. Moreover, as the two systems [RhCl(PPh$_3$)$_3$]/AgOTf (TfO: trifluoromethanesulfonate) and [{Rh(CO)$_2$Cl}$_2$] possess different steric and electronic properties, a substituted enyne such as **210** can be cyclized and transformed to different major isomers [Eq. (69)].

Mechanistic analysis of the reaction of substituted cyclopropanes revealed that **211** and **212** are formed from a unique enyne–metal system (Scheme 20). Coordination of a metal to either of the two sides of the double bond of **210** leads to intermediates **213** or **214**, which evolve into **215** and **216**, respectively, on oxidative addition. These diastereomeric intermediates are in equilibrium with **217** and **218**, respectively, which have a *syn* alignment of the protons along bond a. These conformations allow the formation of the *cis* olefin and the ring expansion of the cycloproane rings.

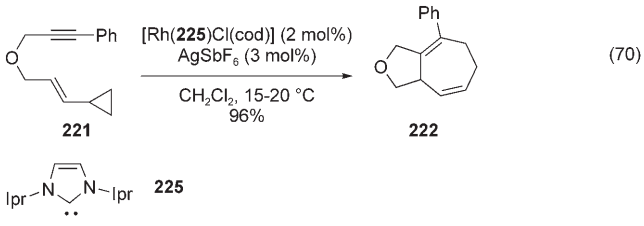


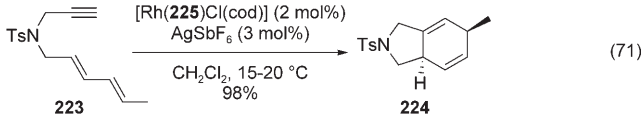
Scheme 20. Proposed mechanism for the Rh-catalyzed formal [5+2] cycloaddition according to Equation (69); E: CO_2Et.

Since a different cyclopropane bond is aligned in complexes **217** and **218** different products are obtained, namely, **219** and **220**, respectively. Further reductive elimination could explain the formation of both dienes **211** and **212**. The authors proposed that the high selectivity is a consequence of the reversibility of the initial steps and the influence of the substituent on the last steps.

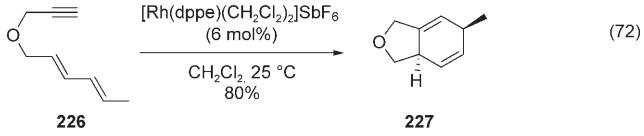
The formal intramolecular [5+2] and [4+2] cycloadditions were also possible with other catalysts such as $[\{Rh(CO)_2Cl\}_2]$, $[\{Rh(nbd)Cl\}_2]$ (nbd: norbornadiene), or a rhodium complex with an N-heterocyclic carbene (**225**, Ipr: 2,6-diisopropylbenzene) ligand.[91] The carbene catalyst was extremely active, with the reaction occurring under mild conditions in less than ten minutes [Eqs. (70) and (71)]. The cyclization of dienyne **223** afforded the diene **224** completely selectively in 98% yield. When the compound contains a cyclopropane ring instead of the second double bond (for example, **221**), a seven-membered ring is formed.[91]

A very reactive catalyst $[Rh(dppe)(CH_2Cl_2)_2]SbF_6$ may be generated from $[Rh(dppe)(nbd)]SbF_6$ (dppe = 1,2-(diphenyl-

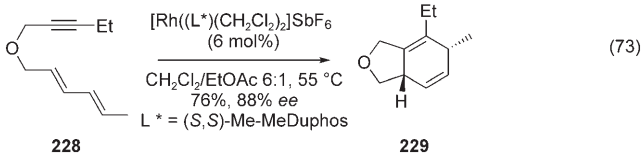




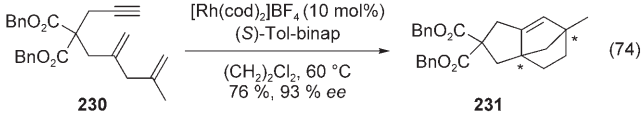
phosphanyl)ethane) in dichloromethane under hydrogen [Eq. (72)]. An asymmetric version of the [4+2] cycloisomerization[91d] was described by Gilbertson et al., based on their



previous work with **226** [Eq. (72)]. Several enynes were cyclized under mild conditions, and the use of a chiral ligand such as (*S*,*S*)-Me-MeDuphos instead of the dppe ligand afforded diene **229** in 88% *ee* [Eq. (73)].

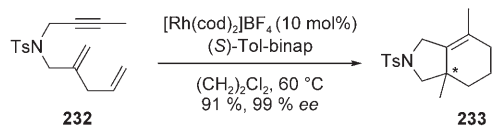


The position and substitution of the double bonds are particularly crucial for the reaction outcome, as other interesting rearrangements occur with 1,1-disubstituted alkenes. An enantioselective [2+2+2] cycloaddition was indeed recently reported by Shibata and Tahara.[92] Tricyclic compounds, including a bicyclo[2.2.1]heptene skeleton with two quaternary carbon stereocenters, were obtained enantiomerically by using a chiral Rh catalyst [Eq. (74)]. Of the binap



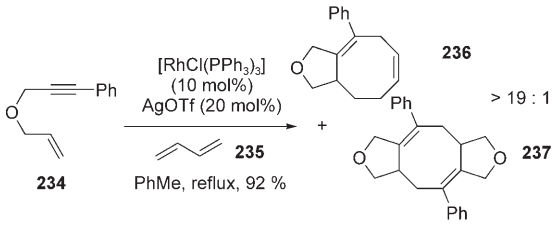
derivatives, tolbinap was found to be the best chiral ligand. The enantiomeric excess depends on the type of bridge between the ene and yne units, and was generally around 90%. In the case of dieneynes that do not have a substituent

at the 2-position of the diene, the enantioselectivity exceeded 90% for C, N [Eq. (75)], and O bridges.

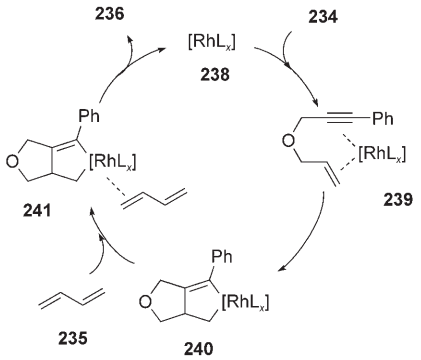


(75)

Some reports have also shown that the trapping of metallacyclopentene intermediates may occur intermolecularly by adding a diene or an alkyne to the enyne substrate. The reaction of enyne **234** and 1,3-butadiene (**235**) in the presence of the Wilkinson catalyst and a silver salt led to a fused five- and eight-membered ring product **236** as well as **237** [Eq. (76)].[93] The proposed mechanism (Scheme 21)



(76)

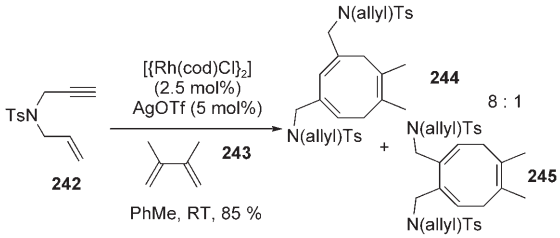


Scheme 21. Proposed mechanism for the Rh-catalyzed formal [4+2+2] cycloaddition according to Equation (76).

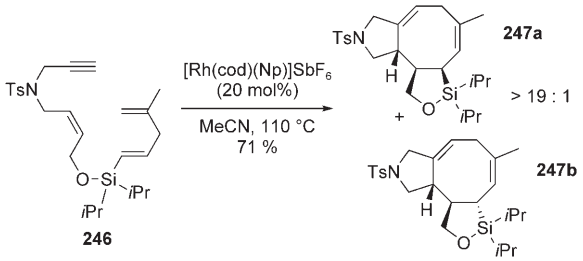
starts classically with a complexation of the enyne to the catalyst followed by an oxidative addition to give the metallacycloprentene **240**.

Other dienes such as 2,3-dimethyl-1,3-butadiene (**243**) or cyclohexa-1,3-diene could also be used for an intermolecular [4+2+2] cycloaddition in the presence of the [{Rh(cod)Cl}$_2$]/AgOTf system [Eq. (77)].[94] An intramolecular version of this reaction was recently reported, in which trieneyne **246** with a Si–O unit was cyclized to the two isomeric tricycles **247a** and **247b** [Eq. (78), Np: naphthalene].[95]

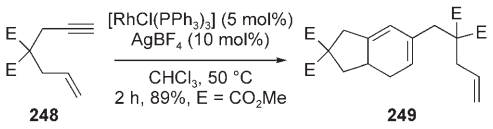
The difference in reactivity between both enyne and 1,4-diene allowed the possibility to increase the diversity and to suppress the competitive dimerization/cyclization of the enyne [Eq. (79)].[96] Gilbertson and DeBoeuf used the intra-



(77)



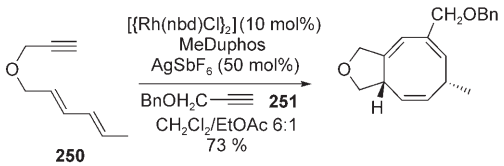
(78)



(79)

and intermolecular versions for an original [4+2+2] cyclization between dienyne **250** and the alkyne **251** [Eq. (80)].[97]

A novel formal [2+2+2+1] cycloaddition of an enediyne and carbon monoxide was recently reported by Ojima and coworkers [Eq. (81)].[98] This tandem reaction gave rise to 5-7-5



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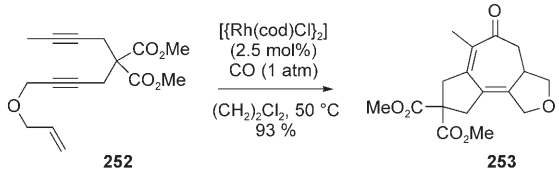
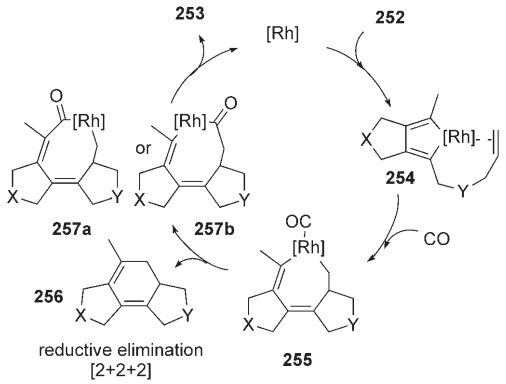


(81)

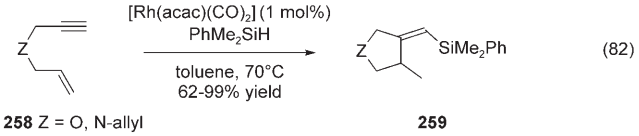
ring systems in good yields and excellent selectivity. The proposed mechanism (Scheme 22) includes a selective coordination of the diyne moiety of the starting enediyne followed by the formation of the classic metallacycle **254**. An insertion of the double bond into the Rh–C bond to form the fused tricyclic rhodacycle intermediate **255** was then advocated. The coordination of carbon monoxide in **255** followed by the migratory insertion of CO into the Rh–C bond to form 5–8–5 rhodacycle may lead to two potential intermediates **257a** and **257b**. These can then evolve through a reductive elimination to form a [2+2+2+1] cycloadduct and regenerate the active Rh catalyst. It is noteworthy that reductive elimination of the



Scheme 22. Proposed mechanism for the carbonylative cycloisomerization of enediynes according to Equation (81); X: $C(CO_2Me)_2$, Y: O

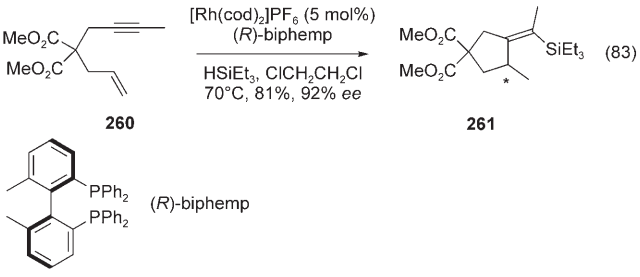
5-7-5 rhodacycle **255** would give the [2+2+2] cycloadduct **256**, which was not observed for $X = C(CO_2Me)_2$, Y = O, and only seen in trace amounts for $X = Y = C(CO_2Me)_2$.

Other tandem reactions are based on the addition of an Rh–Si or Rh–C intermediate to the triple bond and then trapping of the resulting vinylrhodium complex by the alkene unit. These reactions have opened up original routes to cyclic vinylsilanes or functionalized dienes. Ojima et al. described the silylcarbocyclization of nitrogen- and oxygen-bridged 1,6-enynes in the presence of $[Rh(acac)(CO)_2]$ (acac: acetylacetonate) and a substituted silane [Eq. (82)].[99] They studied this



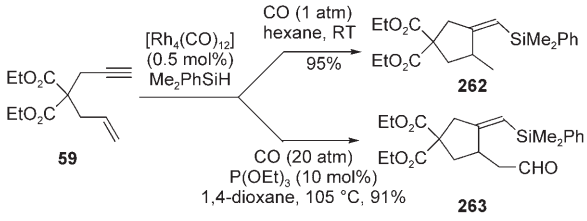
(82)

silicon-initiated carbocyclization reaction extensively, and have spurred substantial interest in this field. The reaction conditions were compatible with the use of ionic liquids as solvents.[100] Denmark and Liu recently combined the silylcarbocyclization with silicon-based cross-coupling reactions to prepare arylidene-substituted cyclopentene derivatives.[101] The enantioselective synthesis of chiral vinylsilanes was recently optimized in the presence of a cationic rhodium catalyst and (*R*)-biphemp as the chiral ligand [Eq. (83)].[102]



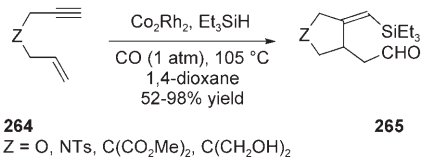
(83)

The presence of both hydrosilane and carbon monoxide promoted a carbonylative silylcarbocyclization of 1,6-enynes.[103] While the reaction of 1,6-enyne **59** with a hydrosilane catalyzed by $[Rh_4(CO)_{12}]$ under CO or N_2 (1 atm) gave 2-methyl-1-(silylmethylidene)-2-cyclopentane **262** in excellent yield [Eq. (84)], the same reaction in the presence of a phosphite ligand such as $P(OEt)_3$ under 20 atm of CO



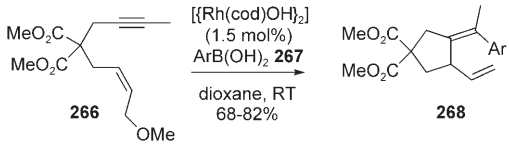
(84)

afforded the corresponding 2-oxoethyl derivative **263**. The mechanism of this carbonylative silylcarbocyclization process presumably shares some key intermediate complexes as the Rh-catalyzed silylcarbocyclization reaction, and is based on a classic hydrosilylation and silylformylation of alkynes. Immobilized rhodium/cobalt nanoparticles were highly selective and active towards the formation of silylated aldehydes in good to excellent yields, irrespective of how the alkene and alkyne parts of the enyne **264** were joined [Eq. (85)].



(85)

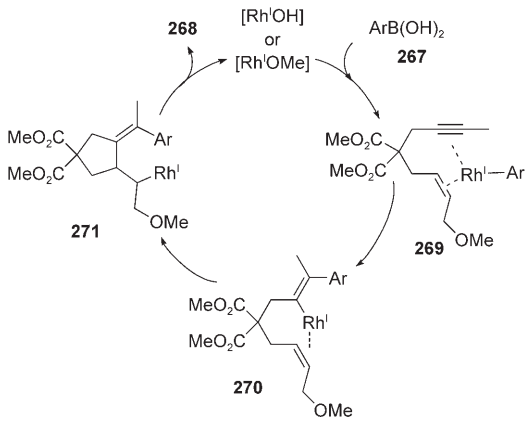
Based on the original Rh-catalyzed addition of boronic acids to alkynes,[104] the tandem addition of aryl boronic acids to enynes were investigated. Enyne **266** afforded the functionalized dienes **268** in excellent yield [Eq. (86)].[105,106] The



(86)

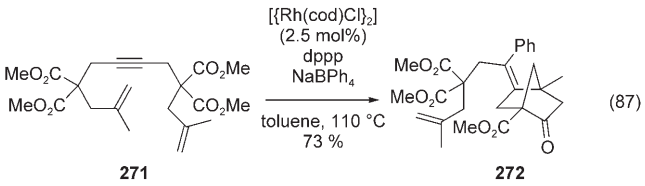
key to this success is the high efficiency of the $[\{Rh(cod)OH\}_2]$ catalyst and the Rh-OMe species for the transmetalation step (Scheme 23). The presence of the methoxy group was indeed crucial and the authors proposed an elimination of an active Rh-OMe species. The main difference with the cycloisomerization presented previously is that the rhodium has an oxidative state of (I) in all the reactions. The authors also examined the asymmetric version of this novel tandem reaction and obtained an excellent enantiomeric excess (97%) for the synthesis of **268** (Ar = Ph) by using (*R*)-binap.

The same research group envisioned a novel cyclization based on the elimination of $[Rh^I(OMe)L_x]$, which would possibly occur on an ester functionality to form a ketone.[107] Various ester-substituted dienynes were therefore subjected to the $[\{RhCl(cod)\}_2]$/dppp (dppp: 1,3-bis(diphenylphospha-



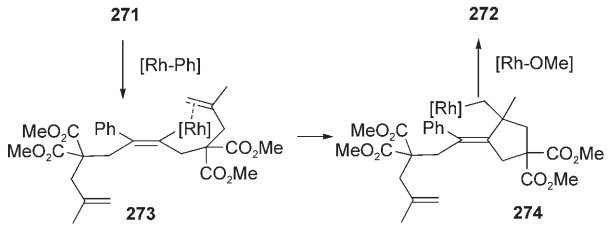
Scheme 23. Rh-catalyzed tandem reaction of boronic acid addition and cyclization according to Equation (86).

nyl)propane) system, and afforded the corresponding bicyclo-[2.2.1]heptan-2-ones [Eq. (87)]. From the alkenylrhodium



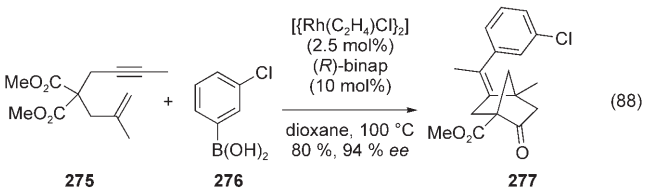
(87)

intermediate **273**, intramolecular carborhodation to a pendant olefin in a 5-*exo* process occurred preferentially to a 1,4-rhodium shift, to give intermediate **274** (Scheme 24). This



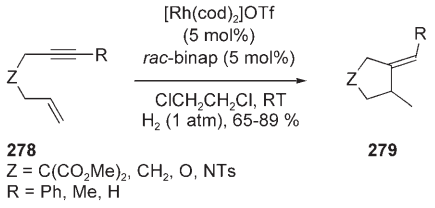
Scheme 24. Rh-catalyzed tandem reaction of $NaBPh_4$ addition and cyclization according to Equation (87).

alkylrhodium species may then react with one methoxycarbonyl group, thereby giving the ketone and regenerating the catalyst. The asymmetric version in which boronic acids were used instead of sodium tetraphenylborate also occurred efficiently, and gave optically enriched bicyclic heptanones **277** [Eq. (88)].



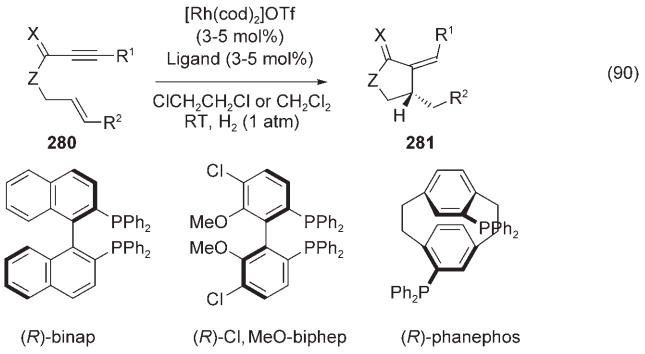
(88)

Krische and co-workers found that the use of a hydrogen atmosphere resulted in hydrogenolysis of the rhodium–carbon bond and allowed the synthesis of the functionalized alkene [Eq. (89)].[108] The authors proposed two possible



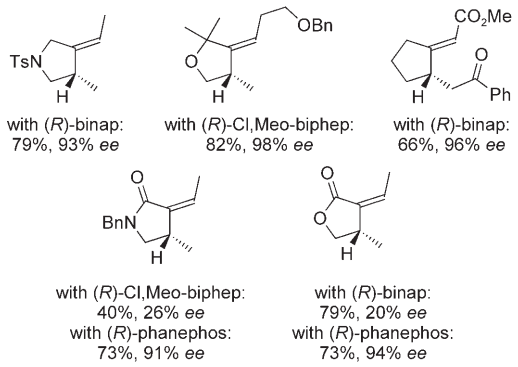
(89)

pathways, one based on the cyclometalation and the other on hydrometalation of the triple bond. There is no unambiguous discrimination between the two possible mechanisms, but as the reaction is completely regioselective, the authors preferred the metallacyclopentene pathway. The enantioselective version was also successful in the presence of (*R*)-binapP, (*R*)-Cl,MeObiphep, and (*R*)-phanephos [Eq. (90)]. The atropiso-



(90)

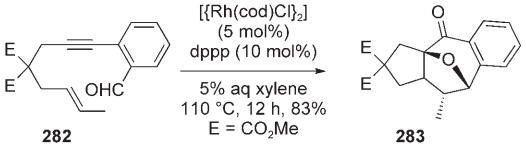
meric ligands gave similar results for 1,6-enynes bearing nitrogen, oxygen, or carbon bridges, with enantiomeric excess values over 90% (Scheme 25). In contrast, the ligand (*R*)-phanephos afforded complex mixtures of conventional hydrogenated products. In the case of propargylic esters and amides, low yields and/or *ee* values were obtained with (*R*)-binap and (*R*)-Cl,MeObiphep, while the use of (*R*)-phane-



Scheme 25. Products, yields, and enantiomeric excess of some asymmetric tandem reaction according to Equation (90).

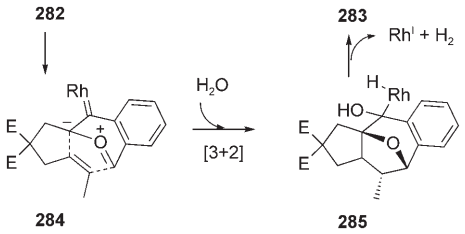
phos afforded the expected cyclic derivatives in high yield and high enantioselectivity (Scheme 25).

o-(1,6-Ynenyl)benzaldehydes underwent a novel mode of cycloaddition in the presence of [{Rh(cod)Cl}$_2$] and dppp as the ligand.[109] The formation of a polycyclic skeleton—presumably by a [3+2] cycloaddition—was observed in good to excellent yield in the case of carbon- [Eq. (91)] and



(91)

nitrogen-bridged enynes. The authors postulated the generation of a rhodium-carbenoid-carbonyl ylide **284**, which upon addition of water, would undergo a [3+2] cycloaddition to give the intermediate **285** (Scheme 26). Dehydrogenation may then occur to give the cyclic ketone **283**.

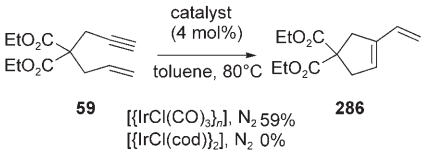


Scheme 26. Proposed mechanism for the [3+2] cycloaddition reaction according to Equation (91).

5. Ir-Catalyzed Cycloisomerizations

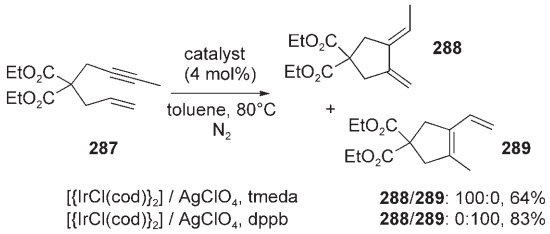
5.1. Enyne Rearrangements

There are fewer reports in the literature of the use of iridium. Murai and co-workers showed that the skeletal rearrangement highly depends on the reaction conditions and on the enyne derivative.[110] Simple unsubstituted enyne **59** could be rearranged in the same manner as in the presence of Ru or Pt catalysts, but the Ir^I catalyst required a CO ligand to show catalytic activity [Eq. (92)]. However, no reaction



(92)

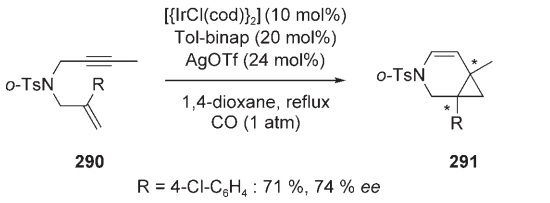
occurred under the previous reaction conditions when the triple bond was substituted with a methyl group. The authors, therefore, optimized a new system consisting of an Ir^I catalyst, a silver salt, and an additional ligand [Eq. (93)]. The influence of the ligand was particularly interesting: the presence of



(93)

tetramethylethylenediamine (tmeda) led to the formation of **288** as the main product while the use of 1,4-bis(diphenylphosphanyl)butane (dppb) gave 1-vinylcyclopentene derivative **289** as a single product. The formation of **288** may be explained by the isomerization of a double bond in the initial product, as was proposed by Trost et al. for the palladium catalyzed reaction.[10] The efficiency of the catalyst system was highly substrate-dependant, with mixtures sometimes observed in the case of allyl propargyl ethers. The authors solved this problem by adding some acetic acid to [IrCl(cod)$_2$], which presumably generates an H-Ir species[111] and leads to the dienes of type **288** in good yields.

Similar results were obtained with other iridium catalyst systems, both in ionic liquids[112a] and in the presence of other ligands.[112b] The problem of the enantioselectivity of the Ir-catalyzed cycloisomerizations has been studied by the research group of Shibata.[113] After optimization of the reaction conditions, they proposed the use of a catalyst consisting of [{IrCl(cod)}$_2$], AgOTf, and Tol-binap. The importance of CO (1 atm) was once again observed; presumably CO acts as an excellent π-acceptor ligand in the catalyst. The enynes are limited to nitrogen-bridged ones, such as **290** [Eq. (94)], and the enantioselectivity is dependant on the

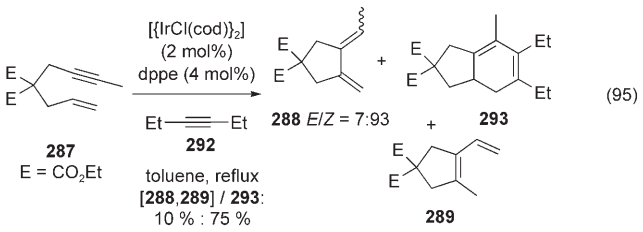


(94)

substrate. The presence of a chloro-substituted aryl group on the double bond afforded the product **291** with 74% *ee*, whereas substitution by a napthyl group gave rise to a large decrease in the *ee* value.

5.2. Enyne Tandem Reactions

To the best of our knowledge, a unique tandem cycloaddition was described in the presence of an iridium catalyst.[112b] The cycloisomerization of **287** in the presence of 3-hexyne (**292**) led to the formation of the cycloadduct **293** [Eq. (95)]. The classic cycloisomerization of **287** [Eq. (93)] could not be suppressed, and a mixture of dienes **288** and **289** were also obtained. The addition of phosphane ligands modified the ratio of the products, and 1,2-bis(diphenylphosphanyl)ethane was found to give the best results.



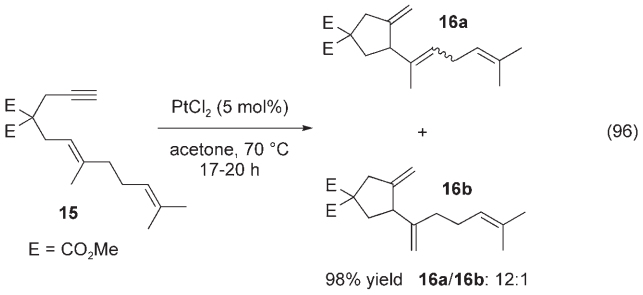
(95)

6. Pt-Catalyzed Cycloisomerizations

The field of platinum- and gold-catalyzed cycloisomerizations has recently been reviewed.[114] As a consequence, this section and the following will highlight the main features of the reactivity of these metals and put the stress on most recent advances.

6.1. Enyne Rearrangements

In contrast to the numerous palladium-catalyzed Alder–ene methodologies described in Section 1, only a few reports of platinum-based systems have been reported. Echavarren and co-workers[115] have reported the cycloisomerization of enynes, such as **15**, to give a mixture of 1,4-dienes **16a** and **16b** by using $PtCl_2$ as a catalyst [Eq. (96)]. In complete analogy

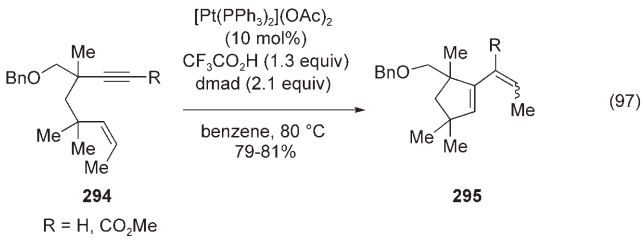


(96)

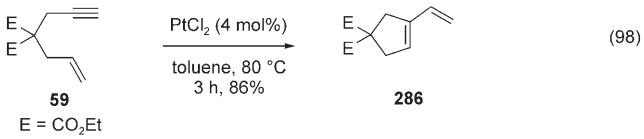
with the reported results for the palladium-catalyzed reaction, a good regioselectivity in the β-hydride elimination in the absence of ligand favors the formation of **16a**. However, it must be noted that the reaction is limited to trisubstituted alkenes.

However, platinum-based systems are extremely versatile catalysts for skeletal rearrangements. In the course of their extensive studies dealing with the palladium-catalyzed cycloisomerization of 1,*n*-enynes (see Section 1), Trost and Chang[116] reported the first platinum-catalyzed skeletal rearrangement of an enyne (**294**) to a 1,3-diene (**295**) in the presence of a catalyst system consisting of $[Pt(PPh_3)_2](OAc)_2$, dimethyl acetylene dicarboxylate (dmad), and CF_3CO_2H [Eq. (97)].

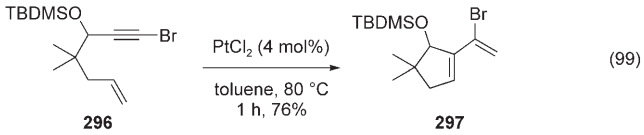
Murai and co-workers reported in 1996 that $PtCl_2$ can promote skeletal rearrangement.[117] A rather wide variety of enynes was found to undergo cyclorearrangement in toluene at 80 °C over 1–20 h [Eq. (98)–(100)]. The presence of aryl- and halide-substituted triple bonds, such as in **296**, does not hamper the reaction and furnishes 2-halogenated-1,3-dienes



(97)



(98)



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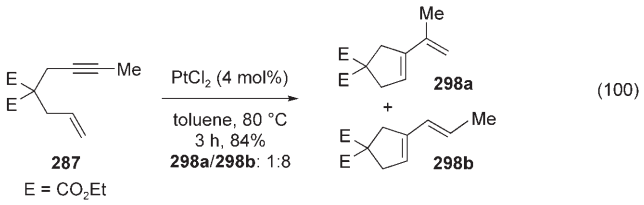
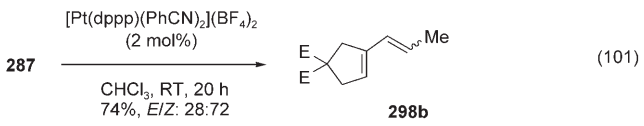


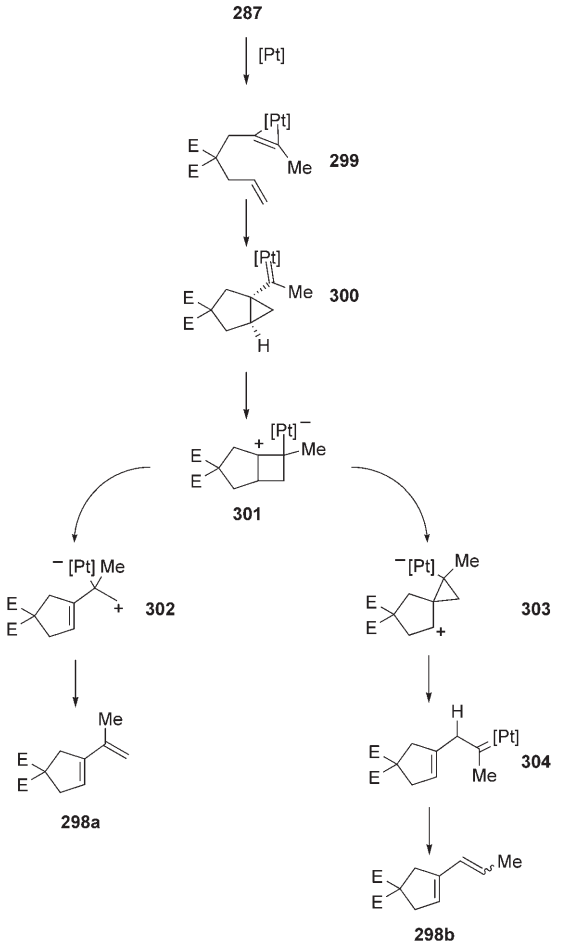
(100)

such as **297** [Eq. (99)]. Oi, Inoue, and co-workers.[118] later introduced dicationic platinum complexes as highly efficient catalysts which allowed the reaction to proceed at room temperature in $CHCl_3$ [Eq. (101)].



(101)

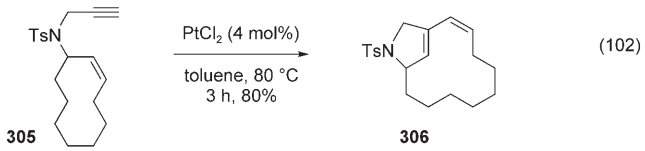
The authors postulated two competing mechanisms (analogous to (paths C and D in the palladium-catalyzed reactions; see Scheme 1) since cycloisomerization of enyne **287** led to a mixture of the isomers **298a** and **298b**. The regiochemical outcome of this transformation has been confirmed by ^2H- and ^{13}C-labeling experiments. Thorough investigations were conducted to understand the mechanistic rationale of these transformations. The isolation of a set of minor by-products, as well as DFT calculations, led the research groups of Fürstner[121,123] and Echavarren,[119] respectively, to present a comprehensive mechanistic picture that accounts for the observed regioselectivity (Scheme 27). Initial coordination of the platinum center occurs at the C–C triple bond to give an η^2 complex **299**.[120] Nucleophilic attack by the alkene group results in the formation of the cyclopropylcarbene intermediate **300**. This species rearranges by a 1,2-alkyl shift to form the zwitterionic cyclobutane **301**. This highly reactive intermediate reacts either by fragmentation to give alkene **302** followed



Scheme 27. Proposed mechanism for the Pt-catalyzed skeletal rearrangement of 1,6-enynes according to Equation (100); E: CO_2Et.

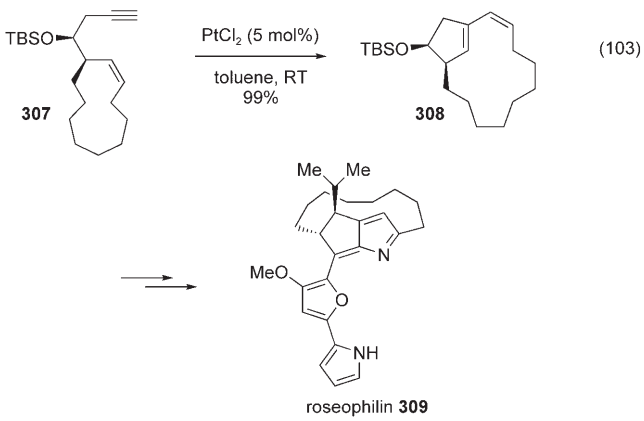
by elimination to give product **298a**, or it reacts by a second 1,2-alkyl shift to produce cyclopropane **303**. Subsequent fragmentation to intermediate **304**, a 1,2-hydride shift, and elimination result in the formation of product **298b**.

Skeletal rearrangement has most notably found applications in macrocyclic synthesis. Fürstner et al.[121–123] optimized the reaction conditions, which allowed the synthesis of the 12-membered ring **306** in 80% yield by using $PtCl_2$ as a catalyst [Eq. (102)]. The reaction is rather versatile as the cyclization



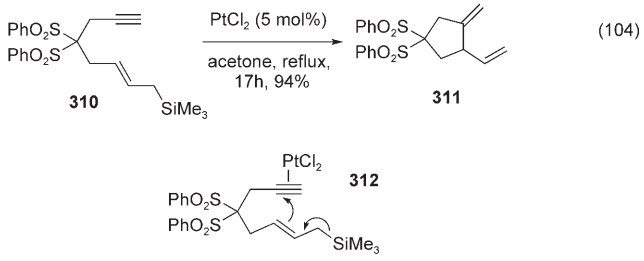
(102)

of carbon-, oxygen-, and nitrogen-bridged substrates lead to the corresponding bicyclic compounds in high yields. This strategy has been applied to the construction of the bicyclic unit of prodiginine antibiotics such as streptorubin B, metacycloprodigiosin,[121] and roseophilin (**309**)[124] [Eq. (103)].



(103)

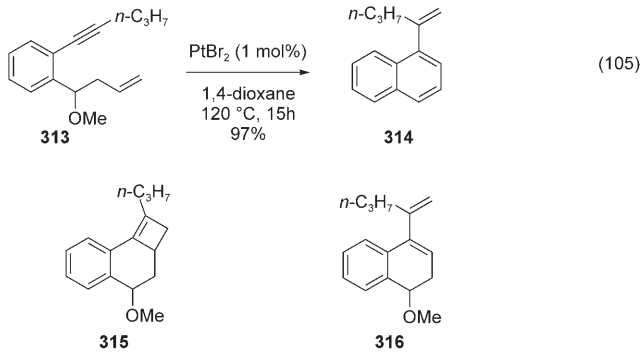
Echavarren and co-workers have also investigated the possibility of using allylsilanes and allylstannanes as alkene partners in the cycloisomerization of 1,6- and 1,7-enynes.[125] In acetone under reflux, silylated enyne **310** is transformed in the presence of $PtCl_2$ to 1,4-diene **311** in 94% yield [Eq. (104)]. The reaction proceeds with *anti* selectivity, thus



(104)

favoring a mechanism based on the nucleophilic attack of the allylsilyl fragment on an η^2-coordinated triple bond (intermediate **312**).

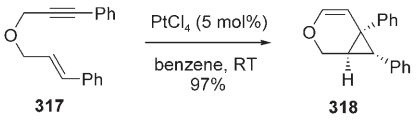
The research group of Yamamoto[126] investigated the skeletal rearrangement of 1,7-enynes which contain a benzene ring between the alkene and alkyne units. Substrate **313**, which possesses a leaving group at the 4-position, is converted into vinylnaphthalene **314** in the presence of $PtBr_2$ at 120°C for 15 h [Eq. (105)]. A mechanism has been proposed that involves the initial formation of a cyclobutene intermediate by a [2+2] cycloaddition which thermally rearranges to give a



(105)

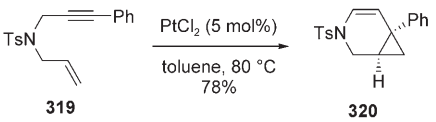
1,3-diene. Indeed, intermediates **315** and **316** have been isolated and characterized by using milder reaction conditions.

In 1995, Blum et al.[127] reported the synthesis of cyclopropane-annulated dihydropyrans, such as **318**, which result from the reaction of allyl propargyl ethers, such as **317**, in the presence of $PtCl_4$ [Eq. (106)]. As part of a study aimed at



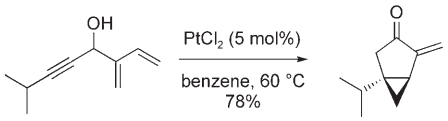
317 318 (106)

expanding the scope of this process, Fürstner et al.[122] reported a modification of the original catalytic system so that nitrogen-bridged compounds could be converted in the presence of $PtCl_2$ [Eq. (107)]. Echavarren and co-workers[128]



319 320 (107)

investigated the specific case of enol ethers as alkene partners in this cycloisomerization reaction. The research groups of Fürstner[129] and Malacria[130] elegantly extended this methodology to 3-hydroxylated 1,5-enynes. For example, Fürstner and co-workers applied the procedure to the total synthesis of sabinone (**322**) starting from dienyne **321** [Eq. (108)]. The

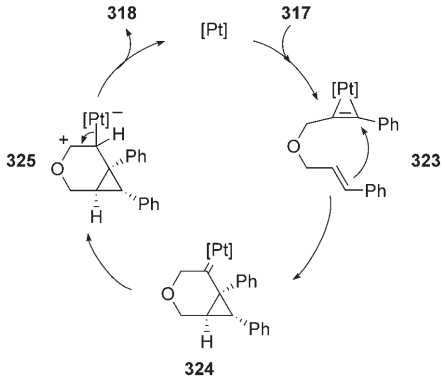


321 322 (108)

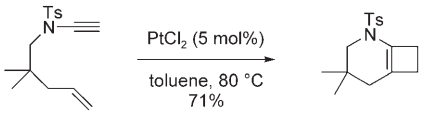
cycloisomerization step proceeds nicely in benzene at 60 °C to give **322** in 78 % yield.

The mechanism of this transformation has been studied by Soriano et al.[131] by using computational methods. From these they proposed a mechanism for the skeletal rearrangement (Scheme 28): the initial step is the formation of a metallacyclopropene intermediate **323**. Nucleophilic attack of the alkene group in a 6-*endo* fashion results in the formation of the cyclopropylcarbene **324** stereospecifically. A 1,2-hydride shift to give zwitterion **325** and elimination complete the catalytic cycle.

The synthesis of cyclobutenes by a formal [2+2] cycloaddition in the presence of Pt catalysts has been investigated in detail. Fensterbank, Malacria, and co-workers[132] described the cycloisomerization of enynes with a tosylynamide bridge to form bicyclic enamines in the presence of $PtCl_2$ [Eq. (109)]. The yields were moderate to excellent. Fürstner et al.[133] later presented a study outlining the influence of substituents on the selectivity of the reaction. As the transformation of

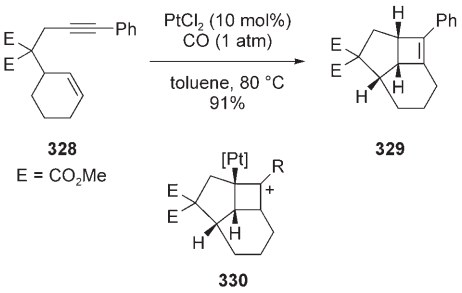


Scheme 28. Proposed mechanism for the Pt-catalyzed formation of bicyclo[4.1.0]heptenes according to Equation (106).



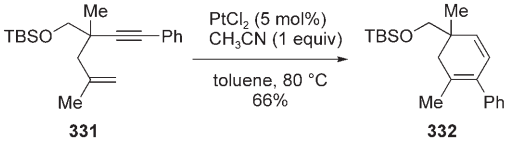
326 327 (109)

enynes such as **328** was assumed to proceed through the intermediacy of the cationic cyclobutane **330**, the incorporation of stabilizing aryl groups at the terminal position of the triple bond should favor the invoked pathway. Furthermore, the authors identified a strong accelerating effect when the reaction was carried out under an atmosphere of CO—analogous to what had already been observed in the case of iridium catalysts (see Eq. (94)]. This behavior is explained by the increase of electrophilicity resulting from the coordination of a π-acceptor ligand at the platinum center. Under the optimized conditions, enyne **328** was converted into tricyclic product **329** in 91 % yield [Eq. (110)].



328 E = CO_2Me 329 330 (110)

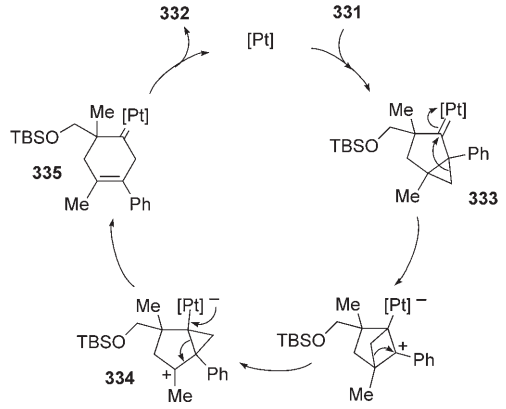
In 2006, Kozmin and co-workers[134] introduced a general method for the synthesis of 1,3-cyclohexadienes from from 1,5-enynes. Substrate **331** reacted at 80 °C in the presence of $PtCl_2$ and 1 equivalent of acetonitrile in toluene to give diene **332** as a single isomer [Eq. (111)]. The presence of a



331 332 (111)

quaternary center at the 4-position is a prerequisite for this transformation to occur. Terminal and substituted triple bonds react equally well, whereas terminal or trisubstuted double bonds hinder the reaction.

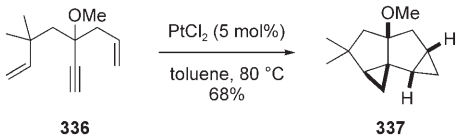
In accordance with the mechanism proposed in Scheme 28 for the synthesis of bicyclo[4.1.0]heptenes, the rationale for this transformation is postulated to result from the initial coordination of the electrophilic platinum center to the triple bond and the subsequent nucleophilic attack of the alkene unit to generate the cyclopropylcarbene **333** (Scheme 29). Two consecutive 1,2-alkyl shifts produce zwitterionic complex **334**. Opening of the cyclopropyl ring and elimination release the catalytically active species and product **332**.



Scheme 29. Proposed mechanism for the Pt-catalyzed cycloisomerization of 1,5-enynes to 1,3-cyclohexadienes according to Equation (111).

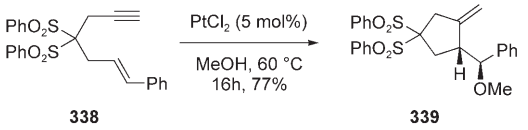
6.2. Enyne Tandem Reactions

In line with mechanistic considerations developed in Section 6.1, platinum-catalyzed tandem cycloisomerizations are dominated by the trapping of the various platinumcarbene complexes generated upon nucleophilic attack of the alkene unit on the π-coordinated triple bond. As already mentioned for the ruthenium-catalyzed cycloisomerization of 1,6-enynes [Eq. (54)], an early example illustrating this principle is the diastereoselective biscyclopropanation sequence that occurs with enynes possessing an additionnal pendant double bond. The original paper of Murai and co-workers[71] already highlighted the catalytic activity of $PtCl_2$ in this transformation. Another application of this methodology has been presented in 2002 by Fensterbank, Malacria, Marco-Contelles, and co-workers[135] [Eq. (112)]. Treatment of dienyne **336** with $PtCl_2$ in toluene at 80 °C for 2.5 h afforded polycyclic **337** in 68% yield, with the reaction being diastereospecific.[136]



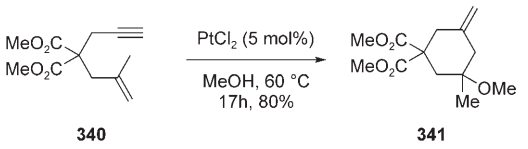
(112)

The trapping of highly reactive cyclopropylcarbene intermediates can also be achieved through the nucleophilic addition of external nucleophiles. Echavarren and co-workers[137] reported highly versatile platinum-catalyzed hydroxy-, alkoxy-, and acyloxycyclization of 1,6-enynes. A large variety of carbon- and oxygen-bridged enynes possessing disubstituted or trisubstituted double bonds have been efficiently cyclized to the corresponding alcohols, ethers, and esters. In a typical experiment, enyne **338** was treated with $PtCl_2$ in methanol under reflux to give carbocyclic ether **339** in 77% yield [Eq. (113)]. Geminal disubstituted alkenes such as **340**



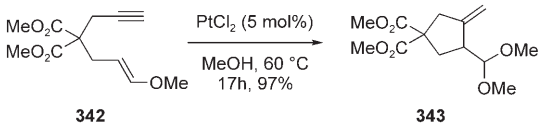
(113)

exhibit a different reactivity: in this case, the six-membered carbocycle **341** resulting from a 6-*endo* mode of addition of the alkene unit to the C–C triple bond was obtained in 80% yield [Eq. (114)]. The transformation is completely stereo-



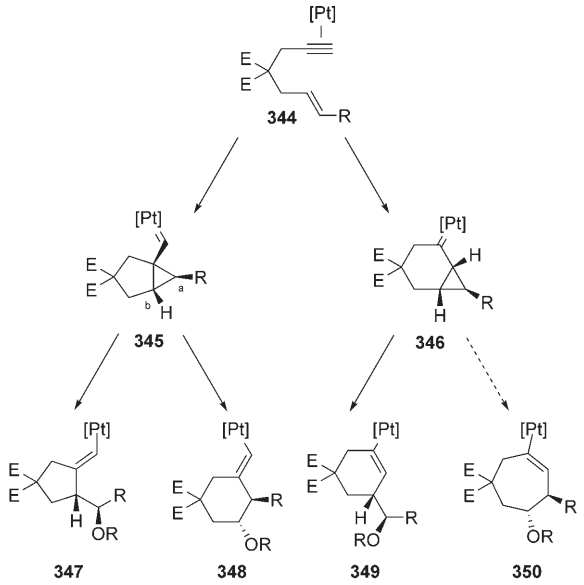
(114)

specific. The same research group[138] extended the reaction to enynes possessing an enol ether function (for example, **342**), which allowed the synthesis of acetals of type **343** [Eq. (115)].



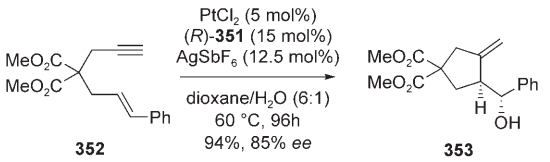
(115)

On the basis of deuterium labeling experiments[41,138] and DFT calculations,[115,138] the authors invoked the initial formation of an electrophilic π-alkyne–platinum complex **344**. Nucleophilic attack of the alkene moiety can occur by 5-*exo-dig* or 6-*endo-dig* pathways to give cyclopropylcarbenes **345** and **346**, respectively (Scheme 30). The opening of the cyclopropane ring and rearrangement of the platinum complex **345** upon *anti* addition of the oxygen nucleophile can take place at either carbon atom a or b to lead selectively to the vinylmetal intermediates **347** or **348**. Proto-demetalation completes the catalytic cycle. This mechanism explains the diastereospecificity of the transformation and accounts for the possibility to obtain five- and six-membered ring products derived from **347** and **348**, respectively. Whereas an intermediate analogous to **346** has already been invoked in related transformations (Scheme 28), only a trace amount of the product resulting from proto-demetalation of **349** has so far been reported with platinum catalysts.

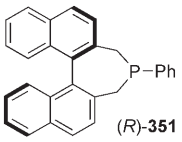


Scheme 30. Mechanistic rationale for the Pt-catalyzed alkoxycyclization of 1,6-enynes according to Equations (113)–(115).

In an enantioselective version of this transformation,[139] a dicationic platinum complex prepared from $PtCl_2$, (*R*)-binepine ((*R*)-**351**), and $AgSbF_6$ catalyzed the reaction of enyne **352** to alcohol **353** in dioxane/H_2O; the product was obtained in 94% yield and 85% *ee* [Eq. (116)]. The choice of

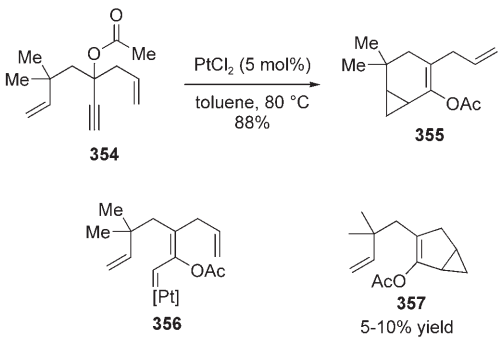


(116)



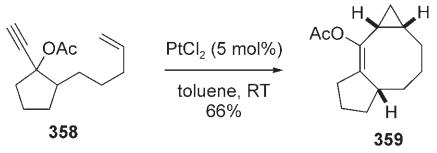
the ligand was crucial for achieving a good level of enantioselectivity: bidentate ligands led to disappointing results (up to 41% *ee*). The scope of the reaction was limited to carbon- and nitrogen-bridged substrates and to water or methanol as the nucleophile. The mechanism of the reaction was not discussed by the authors, but is postulated to occur in a similar manner as in Scheme 30.

Carbonyl groups have also been identified as potential nucleophiles towards activated alkynes in tandem reactions.[140] In the course of their studies on tandem dienyne cycloisomerizations [Eq. (112)],[135] the research group of Malacria observed a change in reactivity on introduction of an ester-protected alcohol at the propargylic position. Indeed, when substrate **354** was treated with $PtCl_2$, enol ester **355** was obtained in 88% yield [Eq. (117)]. The authors have rationalized this behavior through the involvement of a 1,2-shift of the acyl function to furnish carbene **356**. The isolation of



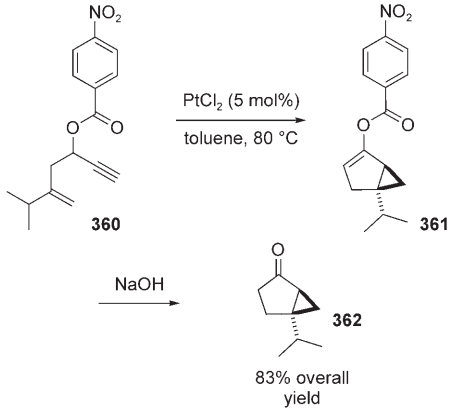
(117)

bicyclic product **357** as a minor isomer supports the mechanism. Remarkably, the reaction can be applied successfully to the synthesis of macrocyclic structures: the 1,8-enyne **358** was converted into tricyclic enol ester **359** as a single diastereoisomer in 66% yield [Eq. (118)].



(118)

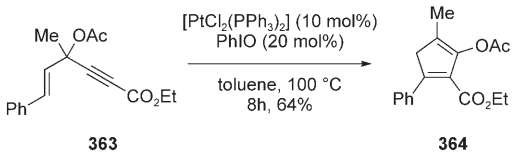
Subsequent to the study of the intermolecular version of this transformation by Miki, Ohe, and Uemura,[141] the research groups of Fürstner[129] and Malacria[130,142] independently reported on the cycloisomerization of 4-acyloxy-1-en-5-ynes to afford bicyclo[3.1.0]hexenes in good to excellent yields. The reaction tolerates a wide range of substituents on the double and triple bonds and can also be applied successfully to carbonated propargylic nucleophiles. An example of the application of this reaction is the two-step total synthesis of the terpenoid building block Sabina ketone **362** by Malacria and co-workers [Eq. (119)].[130]



(119)

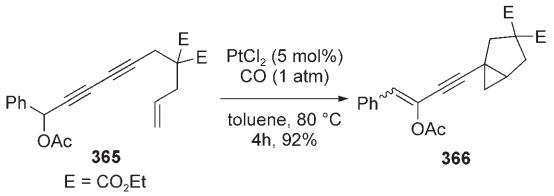
By extension of this concept to 1,4-enynes, Sarpong and co-workers[143] proposed a new pentannulation protocol based on a similar strategy. A catalyst system consisting of a combination of $[PtCl_2(PPh_3)_2]$ and PhIO allowed the con-

version of substrate **363** into carbocycle **364** in 64% yield [Eq. (120)]. Although the catalytically active species has not been assigned unambiguously, the authors postulate a Pt^{IV}



363 **364** (120)

intermediate resulting from the oxidation of the Pt^{II} precursor in the presence of PhIO. Lee and co-workers[144] tested the potential use of conjugated 6,8-diyn-1-enes in this reaction. Substrate **365** reacted in the presence of $PtCl_2$ at 80°C in toluene under an atmosphere of CO to give 1,3-enyne **366** in 92% yield [Eq. (121)].

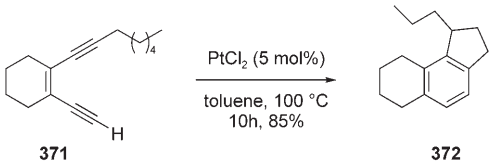


365 **366** (121)

E = CO_2Et

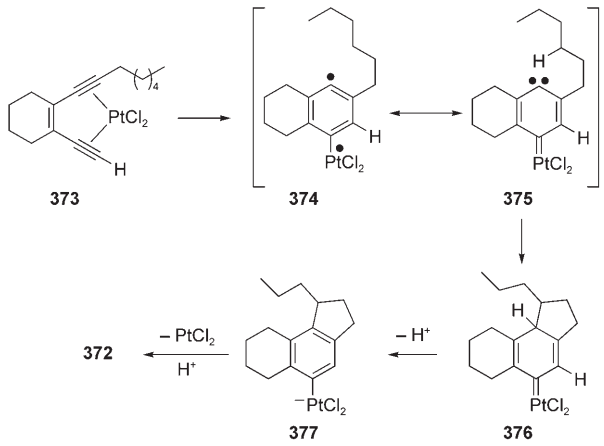
A theoretical analysis of the mechanism of the reaction has been carried out by Marco-Contelles and co-workers.[145] Whereas the initial proposal implied the formation of an intermediate similar to **356** [Eq. (117)], this analysis led to the proposal of a nucleophilic addition of the alkene unit to a π-alkyne complex **367** to furnish cyclopropylcarbene intermediate **368**. A subsequent 1,2-acyl migration via zwitterionic intermediate **369** yields the expected cyclic enol ester **370** (Scheme 31).

Platinum complexes such as $PtCl_2$ have also been shown recently to catalyze the cyclizative aromatization of enediynes.[146] Substrate **371** cyclized in toluene at 100°C in the presence of $PtCl_2$ to afford the tricyclic benzene derivative **372** in 85% yield [Eq. (122)]. The observed structure corresponds to the cyclization of the enediyne fragment and the concomitant C–H insertion of the pendant alkyl chain.



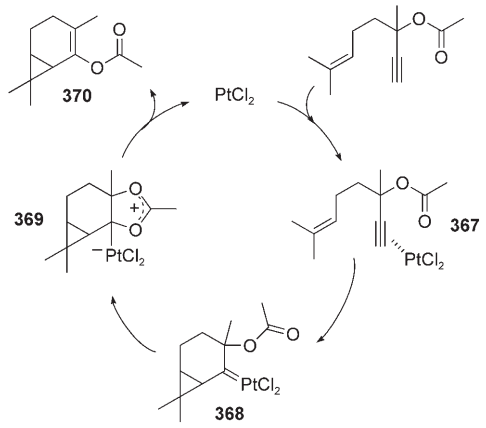
371 **372** (122)

On the basis of deuterium labeling experiments, the authors have postulated a mechanism (Scheme 32) based on the initial π coordination of the Pt center to the two triple



Scheme 32. Mechanism for the Pt-catalyzed tandem aromatization/C–H insertion of enediynes according to Equation (122).

bonds (intermediate **373**), which results in the formation of an aromatic diradical intermediate **374**. The carbenoid isomer **375** reacts with the pendant alkyl chain to form the tricyclic platinum complex **376**. Rearomatization and proto-demetalation complete the catalytic cycle.



Scheme 31. Proposed mechanism for the Pt-catalyzed cycloisomerization of enyne acetates according to Equation (117).

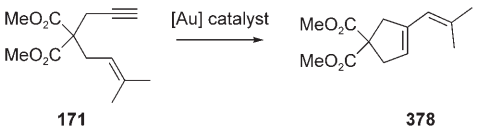
7. Au-Catalyzed Cycloisomerizations

Gold-catalyzed enyne rearrangements are part of a wide program directed towards the discovery of novel and original reactions.[147] Gold was considered as catalytically inactive for a long time! The research groups of Bond, Haruta, Hutchings, Ito, and Hayashi have carried out pioneering studies on gold, and have opened up new perspectives for all synthetic chemists.[148]

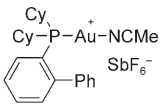
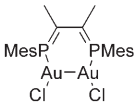
7.1. Enyne Rearrangements

The cycloisomerization reactions of classic enynes such as **171** led—depending on the substrate—to dienes by an *exo* or *endo* process. This finding was in agreement with previous work with platinum, and the bonus of using gold was the

mildness of the conditions.[149] Different catalyst systems have been described for the transformation of **171**, with diene **378** being isolated in all cases in high yield [Eq. (123)].

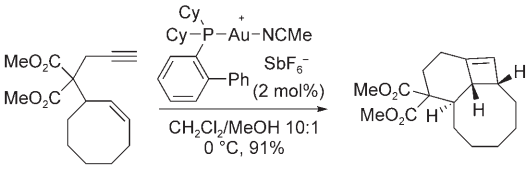


171 **378** (123)

Conditions	Yield
$[AuCl(PPh_3)]$ (2 mol%), $AgSbF_6$ (2 mol%), CH_2Cl_2, 23 °C	91%
$[Au(PPh_3)(NTf_2)]$ (0.01 mol%), CH_2Cl_2, RT	97%
 (2 mol%), CH_2Cl_2, –63 °C → –26 °C	99%
 (2.5 mol%), CH_2Cl_2, RT	100%

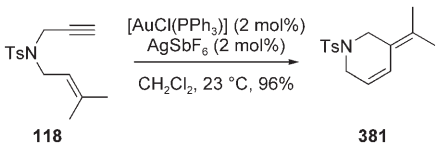
Mes = 2,4,6-$tBu_3C_6H_2$

The use of $[Au(PPh_3)(NTf_2)]$was particularly interesting as this catalyst was found to be highly stable and efficient for many other enyne rearrangements.[150] The replacement of PPh_3 by a bulkier and more electron-rich phosphane increased the activity of the gold catalyst. A digold(I) complex was also recently prepared and showed a good activity for the cycloisomerization of enyne **171**.[151] While the mechanism was initially proposed to be similar to the ruthenium-catalyzed process (see Scheme 14), more recent studies tend to prove that a conrotatory ring opening of the cyclobutene intermediates may not be the only pathway to explain the formation of **378**.[152] The cyclopropylcarbene equivalent to **300** (Scheme 27) may evolve from a single or a double cleavage, and lead to the corresponding dienes.[119] The isolation and stability of cyclobutene **380** were also consistent with the proposed mechanism [Eq. (124)].



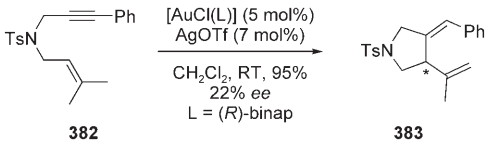
379 **380** (124)

Nitrogen-bridged substrate **118** underwent a 6-*endo* cyclization process to afford diene **381** in high yield [Eq. (125)]. An asymmetric induction was recently observed



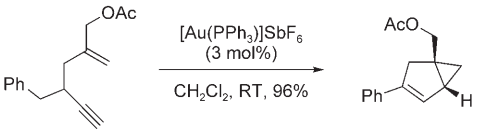
118 **381** (125)

in the presence of the (*R*)-binap ligand: **383** was isolated in 95% yield with a modest enantiomeric excess of 22% [Eq. (126)].[153]



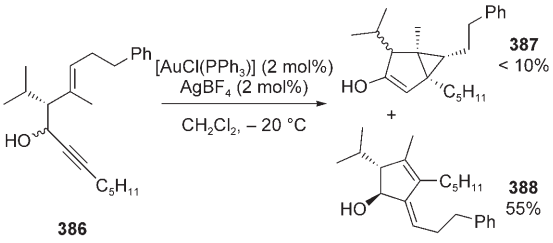
382 **383** (126)

1,5-Enynes are special substrates, which upon addition of a transition metal are sufficiently reactive to promote facile access to bicyclo[3.1.0]hexenes.[154] The rearrangements were performed in the presence of (triphenylphosphane)gold(I) hexafluoroantimonate and proceeded smoothly irrespective of the substitutents on the double bond of the 1,5-enyne. The terminal alkyne **384** also underwent reaction and afforded functionalized cyclopropane **385** in 96% yield [Eq. (127)].



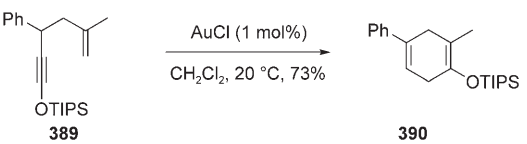
384 **385** (127)

It is noteworthy that the cycloisomerization reactions are generally highly substrate-dependent. Thus, other 1,5-enynes may undergo different rearrangements and give mixtures of cyclopropanes and alkylidenecyclopentenes [Eq. (128)].[155,150] In the case of alcohol **386**, the diene **388**



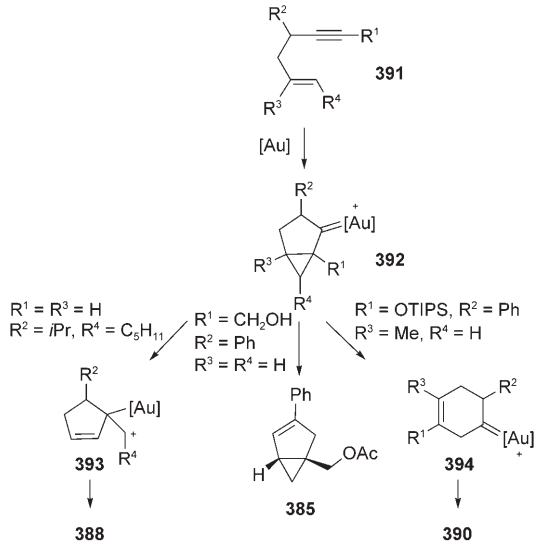
386 (128)

was obtained as the major product and the yield was improved to 80% when the alcohol was protected as a benzyl ether. Another new 1,5-enyne rearrangement was reported by Kozmin and co-workers in connection with their work with platinum [see Eq. (111)]. Silyloxy enynes such as **389** could be converted into cyclohexadiene in the presence of gold(I) catalyst [Eq. (129)].[156] The authors proposed the use of AuCl as an efficient catalyst, as the addition of phosphane



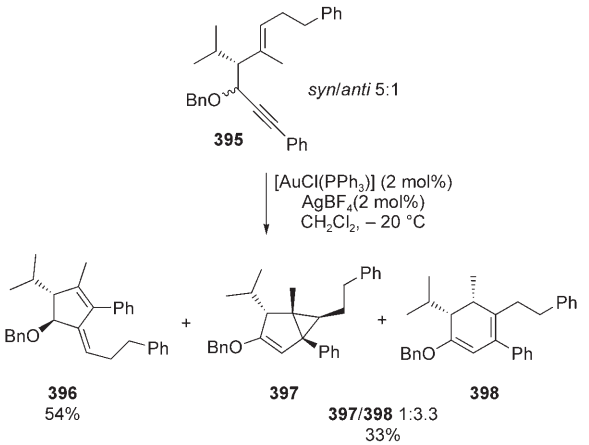
389 **390** (129)

inhibited the activity. The efficiency could be recovered by using the $[AuCl(PPh_3)]/AgBF_4$ system. The formation of the three possible rearranged products **385**, **388**, and **390** could be explained on the basis of the involvement of a carbene of type **392** (Scheme 33), generated by an *endo* process. An α-hydride



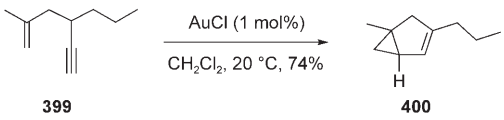
Scheme 33. Proposed intermediates for the Au-catalyzed 1,5-enyne cycloisomerization according to Equations (127)–(129).

elimination followed by a proto-demetalation step rationalized the formation of **385**. Alternatively, the carbene may evolve towards cationic species **393** or carbene **394** (ring-expansion pathway). The cationic intermediate **393** would give rise to the cyclopentene derivative **388**, whereas the rearrangement of carbene **394** would afford cyclohexadiene **390**. In the case of the enyne **395**, the formation of the possible three products was observed, which led to a mixture of cyclopropane, cyclohexadiene, and cyclopentene derivatives **397**, **398**, and **396**, respectively [Eq. (130)].[151]



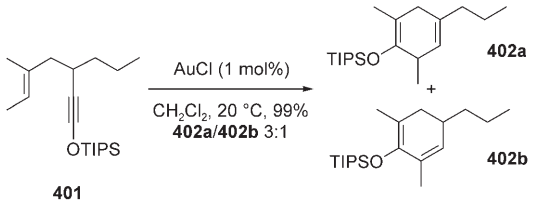
(130)

The selective formation of cyclohexadiene was therefore a specificity of silyloxy-substituted alkynes.[156] The cyclization of enyne **399** afforded the cyclopropyl derivative **400** by using a standard protocol used with platinum catalysts [Eq. (131)]. The substitution pattern of the enyne was also crucial:



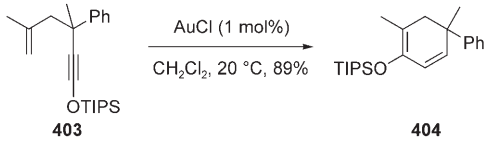
(131)

Kozmin and co-workers observed the formation of conjugated and nonconjugated cyclohexadienes **402** [Eq. (132)]. The selective access to conjugated cyclohexadiene **404** was



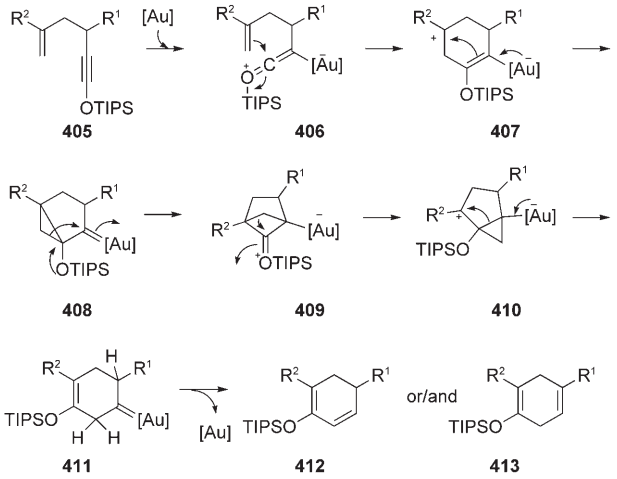
(132)

possible by the cyclization of alkyne **403** bearing two substituents at the propargylic position [Eq. (133)].



(133)

The authors rationalized the synthesis of cyclohexadienes through the following mechanism (Scheme 34): The activation of the silyloxyalkyne moiety by the gold catalyst would

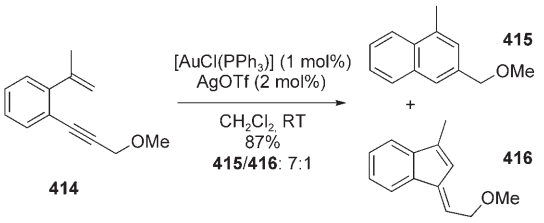


Scheme 34. Proposed intermediates for the cycloisomerization of silyloxy-substituted 1,5-enynes according to Equation (132).

give the cyclopropylcarbene **408**, presumably via stabilized intermediates **406** and **407**. At this stage, instead of the previously observed hydride migration and elimination path-

way, the carbene intermediate **408** would undergo an unusual 1,2-alkyl shift to give the oxonium ion **409**. Another 1,2-alkyl shift followed by a fragmentation of the zwitterionic intermediate **410** could lead to the six-membered-ring carbene **411**. Then, depending on the nature of the R^1 and R^2 substituents on the enyne, the gold–carbene complex can participate in two alternative elimination pathways to afford isomeric 1,3- and 1,4-cyclohexadienes **412** and **413**, respectively.

The research group of Shibata showed that an Au^I catalyst allowed a clean cyclization reaction of 1,5-enynes leading to substituted naphthalenes [Eq. (134)].[157] Depending on the



(134)

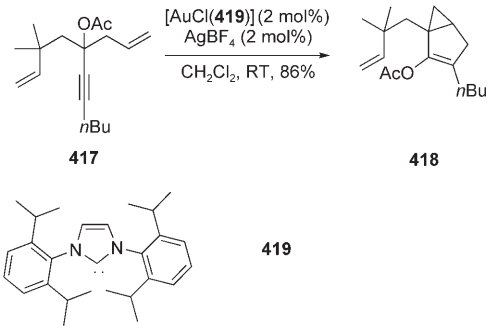
substitution pattern of the triple bond, a 5-*exo*-*dig*-type cyclization can also proceeded and be competitive to the 6-*endo*-type cycloisomerization. The benzannulation of enyne **414** gave an 87% yield of a 7:1 mixture of the naphthalene **415** and the corresponding indene **416**. Similar results were obtained by Grisé and Barriault in the preparation of tetrahydronaphthalenes.[158]

Further studies were devoted to the trapping of intermediates or the chemoselective intervention of inter- or intramolecular nucleophiles.

7.2. Enyne Tandem Reactions

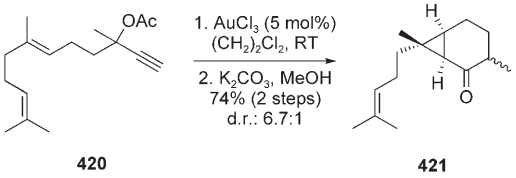
The dependence of the rearrangement of propargylic acetates on substituents at the double bond was studied by numerous research groups.[140] Following the work from Ohloff and co-workers and Rautenstrauch with zinc and palladium, respectively,[159] several enyne cycloisomerizations were identified as key reactions to create molecular diversity on carbocyclic structures. The research groups of Nolan and Malacria studied the influence of N-heterocyclic carbenes as ligands in the cycloisomerization of 1,5-enynes, a reaction that was introduced in the section on platinum [see Eq. (117)].[160] The use of gold complexed to carbenic ligand **419** generally led to a mixture of products, in which an unexpected bicyclo[3.1.0]hexene was detected. The bicyclohexene **418** was obtained as a single isomer in 86% yield when acetate **417** was subjected to the standard conditions [Eq. (135)]. The authors proposed a formal 1,4-acyl migration to explain the formation of bicyclic derivative **418**.

The Ohloff–Rautenstrauch-type rearrangement was achieved in the presence of either platinum (see previous section) or gold, and led to the formation of cyclopropyl-substituted hexenes and particular natural products, such as (−)-α-cubebene and (−)-cubebol. An alternative strategy in which



(135)

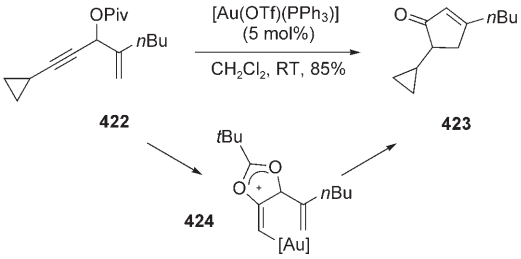
a copper catalyst is used will be presented in the next section. The synthesis of sesquicarene **421** was realized in the presence of gold trichloride in dichloroethane [Eq. (136)].[161] By using



(136)

the same methodology, 2-carene and episesquicarene were readily prepared from the requisite propargylic acetates.

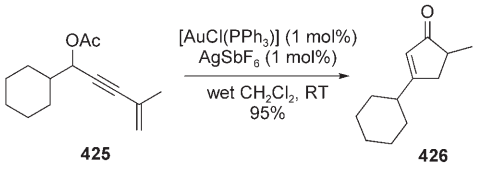
In the case of 1,4-enynes, Toste and co-workers showed that a gold(I) catalyst promoted the synthesis of cyclopentenones in good to excellent yields.[162] Switching from acetates to pivaloates increased the chemical yield of the desired cyclopentenones. Thus, the cyclization of enyne **422** afforded the cyclopentenone **423** in 85% yield [Eq. (137)]. The



(137)

mechanism was recently studied by DFT calculations, and presumably involves a 1,2-acyl migration that leads to the vinylgold species **424**, which may undergo an electrocyclization reaction.[163] Enantiomerically enriched cyclopentenones were also prepared from enantioenriched propargylic alcohols.[162]

A related tandem reaction leading to functionalized cyclopentenones was recently described in which a 3,3-rearrangement followed by a Nazarov-type reaction was envisaged.[164] Propargylic ester **425** was cleanly cyclized to the substituted enone **426** in 95% yield [Eq. (138)]. The research group of Malacria and Fensterbank developed an expedient method for the synthesis of polycyclic derivatives from simple 5-acetate-1,3-enynes with a carbon–carbon double bond in a side chain [Eq. (139)].[165] They anticipated a classic 3,3-



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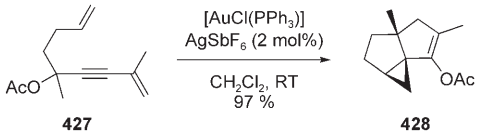
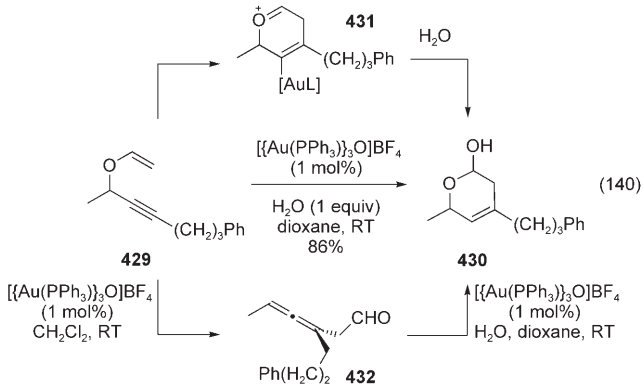


(139)

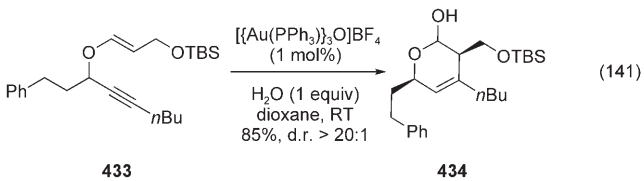
rearrangement in the presence of the $[AuCl(PPh_3)]/AgSbF_6$ catalyst system, which was then followed by a metalla-Nazarov reaction and an electrophilic cyclopropanation. The tandem process was extremely efficient for substituted 1,3-enynes and gave the corresponding tricyclic derivative **428** in 97% yield.

The reactivity of allyl vinyl ethers was also investigated by Toste and co-workers.[166] Based on their findings of a Claisen-type rearrangement for the synthesis of functionalized allenes,[166b] they described a cascade sequence to prepare pyrans via the transient oxonium intermediate **431**. The use of 1 mol% $[\{Au(PPh_3)\}_3O]BF_4$ efficiently converted the enyne **429** into the pyran **430** [Eq. (140)]. It was also shown that



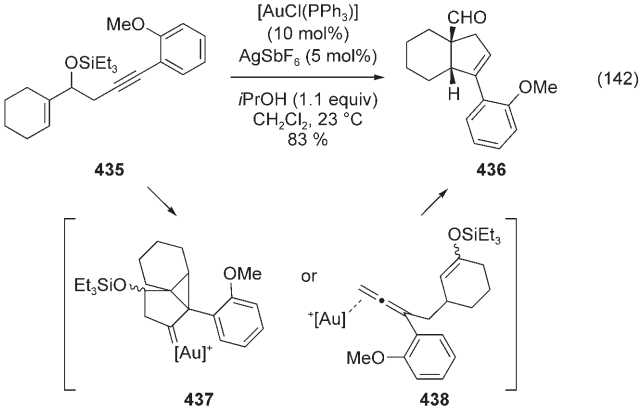
(140)

subjecting the allene **432** to the Au^I catalyst in wet dioxane rather than in dichloromethane afforded the desired 2-hydroxy-3,6-dihydropyran **430**. The scope of the Claisen/heterocyclization cascade was broad and completely diastereoselective; for example, (*E*)-disubstituted enol ether **433** was rearranged to 3,6-*syn*-substituted pyran **434** in 85% yield and with an excellent diastereomeric ratio [Eq. (141)].



(141)

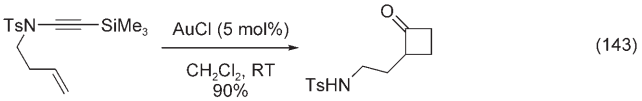
A tandem cyclization/pinacol rearrangement was also shown to be promoted by an Au^I catalyst.[167] Indeed, 3-silyloxy-1,5-enyne **435** underwent a clean cyclization followed by a pinacol rearrangement in the presence of 2-propanol at room temperature in CH_2Cl_2 to afford cyclopentene derivatives **436** in good to excellent yields [Eq. (142)]. The proposed



(142)

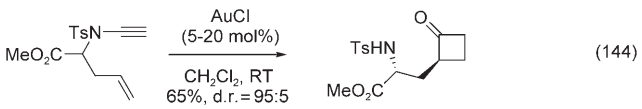
mechanism may involve either the cyclopropylcarbene **437** or the allenic intermediate **438**.

The research group of Cossy recently developed a gold-catalyzed cycloisomerization of eneynamides to give cyclobutanones.[168] The reactivity of eneynamides had previously been studied by Malacria and co-workers [Eq. (109)][132] and showed a similar reactivity in the presence of platinum, albeit at a higher temperature. Although Cossy and co-workers carried out the reaction [Eq. (143)] under anhydrous con-



(143)

ditions, subsequent exposure to atmospheric moisture during the workup seemed to be sufficient to promote the hydrolysis of the presumed cyclobutene intermediate to give the cyclobutanone in 90% yield. The cyclization in the presence of substituents at the α-position to the nitrogen bridge occurred with complete diastereoselectivity and led to the cyclobutanone in 65% yield [Eq. (144)]. The authors proved that

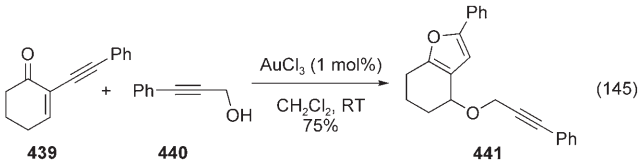


(144)

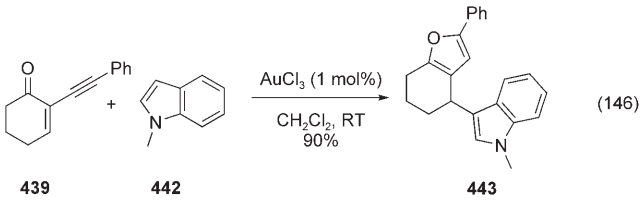
similar results were obtained with 1,6-eneynamides with a substituent in the β-position.

Larock and co-workers described an interesting tandem reaction starting from 2-(1-alkynyl)-2-alken-1-ones to give substituted furans through the simultaneous formation of C–O and C–Nu bonds.[169] Silver, copper, and mercury salts were

also found to be active, but were less efficient than $AuCl_3$. The nucleophilic derivatives could be either oxygen or carbon nucleophiles. The addition of the substituted propargylic alcohol **440** or *N*-methylindole (**442**) afforded the corresponding furans **441** and **443** in 75% and 90% yield, respectively [Eqs. (145) and (146)]. The authors proposed two conceivable

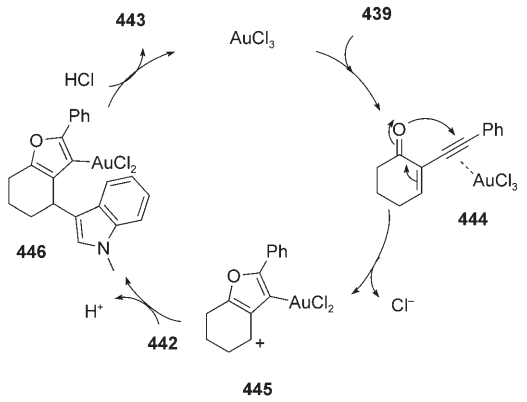


(145)



(146)

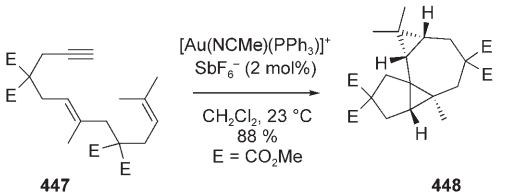
mechanisms for this gold-catalyzed cyclization, in which the 1,4-addition of the nucleophile could arise prior or after the cyclization. The latter hypothesis was preferred, as no traces of the 1,4 adduct were detected when 2-cyclohexenone and methyl vinyl ketone were separately subjected to the standard conditions in methanol. The mechanism would therefore involve an activation of the triple bond to give **444** (Scheme 35). The formation of the furan-based cationic



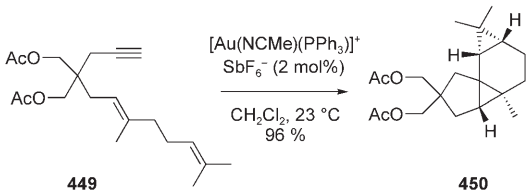
Scheme 35. Proposed intermediates for the sequencial cyclization/nucleophilic addition of 2-(1-alkynyl)-2-alken-1-ones according to Equation (146).

species **445** would then be followed by the addition of the indole nucleophile. A proto-demetalation step brought about by the presence of the generated HCl would then regenerate the catalyst.

Gold catalysts are also suitable and efficient for some previously described Ru- and Pt-catalyzed polycyclization reactions [see Eqs. (54) and (112)]. The cycloisomerization reaction of dienyne **447** in the presence of [AuNCMe-(PPh_3)]SbF_6 afforded the polycyclic derivative **448** in high yield [Eq. (147)].[170] Excellent selectivities were observed, irrespective of the bridge in the enyne [Eq. (148)]. DFT calculations proved that similar intermediates are most



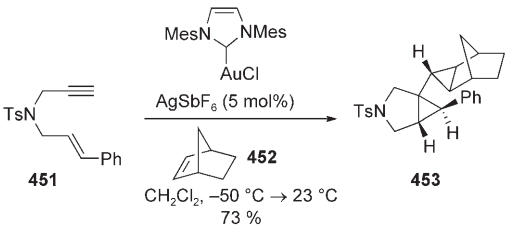
(147)



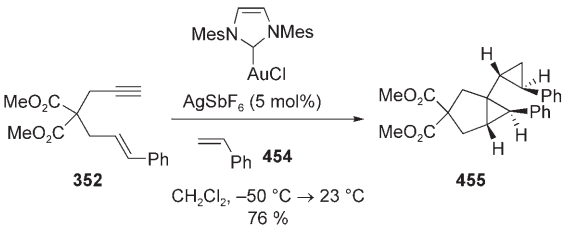
(148)

probably involved in Ru- and Au-catalyzed tandem cyclopropanation reactions.

Intermolecular cyclopropanations were recently described in the presence of a complex formed between gold chloride and an N-heterocyclic carbene [Eq. (149)–(151)].[171]



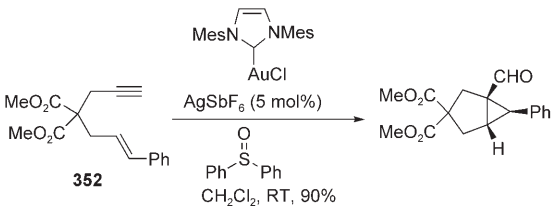
(149)



(150)

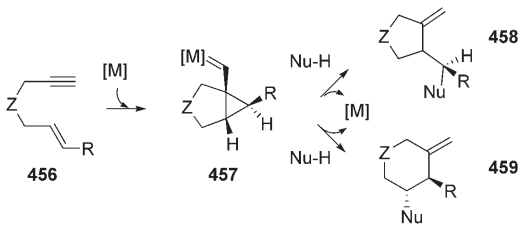
The reaction of 1,6-enyne **451** with norbornene (**452**) afforded **453** as a single isomer in 73% yield. The configuration of isomer **453** was in accord with the previous report on the intramolecular process.[170] The scope of the reaction was broad in regard to the enyne and the alkene moieties. The addition of styrene **454** to **352** led to the biscyclopropane **455** in good yield. Toste and co-workers reported recently a major contribution in the field, namely, the trapping of a carbenoic intermediate by diphenylsulfoxide to give aldehydes [Eq. (151)].[172]

One common feature generally postulated in the reactivity of 1,6-enynes in the presence of electrophilic transition-metal complexes is the transient cyclopropylcarbene **457**



(151)

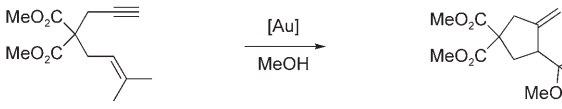
(Scheme 36). The carbene may be trapped by another alkene [Eq. (147)–(150)] or by a sulfoxide [Eq. (151)], but the intermediate may also react differently in the presence of



Scheme 36. Proposed intermediates for the cycloisomerization of 1,6-enynes in the presence of external nucelophiles.

oxygen, nitrogen, or carbon nucleophiles. Indeed, as previously reported in the presence of palladium and platinum catalysts [see Eqs. (26) and (113)–(116)], the addition of an oxygen nucleophile, such as water or an alcohol, was found to add highly efficiently in the presence of gold.

One main challenge was the possibility of accessing a large variety of alcohols and ethers under extremely mild conditions. Several catalyst systems function at room temperature and these are based either on gold(I)[173,149,150] or gold(III)[174,115] precursors [Eq. (152)]. Echavarren and co-

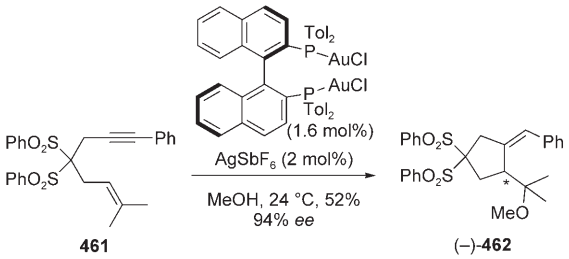


(152)

conditions	yield
[Au(PPh$_3$)Me] (1 mol%), TFA (2 mol%), RT	82%
[Au(PPh$_3$)(NTf$_2$)] (0.1-1 mol%), RT	77-94%
AuCl$_3$ (5 mol%), reflux	98%
AuCl$_3$ (10 mol%)/PPh$_3$ (10 mol%)/AgSbF$_6$ (30 mol%), RT	85%

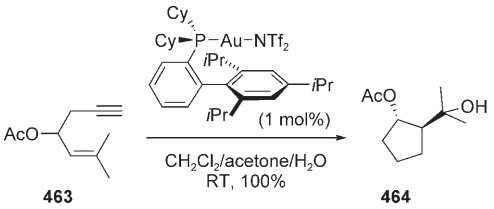
workers proposed the addition of a catalytic amount of trifluoroacetic acid (TFA) to [Au(PPh$_3$)Me] to generate the complex [Au(PPh$_3$)(MeOH)]$^+$.[173,149] The catalytic activity of [Au(PPh$_3$)NTf$_2$] was once again extremely high, as only 0.1 mol% was needed to afford a 77% yield.[150] Gold trichloride has been described as a good promoter, although a high temperature was needed.[115] The combination of AuCl$_3$, triphenylphosphane, and the silver salt AgSbF$_6$ allowed for milder and general conditions to afford a large variety of alcohols and ethers.[174]

A promising enantiomeric excess was obtained in the presence of the (*R*)-Tol-binap–gold chloride complex, but the scope was limited to carbon-bridged derivative **461**, which bears two sulfone moieties and a substituted triple bond [Eq. (153)].[175] The methoxycyclization product (−)-**462** was isolated in 52% yield and 94% *ee*.



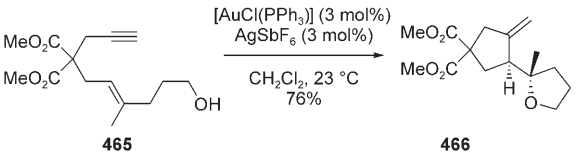
(153)

The hydroxy- and alkoxycyclization reactions are not limited to 1,6-enynes, as shown by a recent report from Gagosz and co-workers who proposed a similar reactivity for 1,5-enynes [Eq. (154)].[176] The treatment of acetate **463** with a



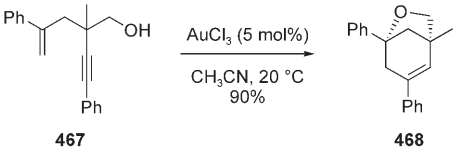
(154)

gold catalyst with a modified biphenylphosphane ligand furnished the alcohol **464** in excellent yield. The scope of the reaction was broad and several nucleophiles such as allylic alcohol, 2-propanol, acetic acid, and 4-methoxyphenol could be cleanly and diastereoselectively introduced. Intramolecular hydroxycyclization reactions originally gave rise to an easy access to heterocyclic compounds **466** and **468** [Eqs. (155) and



(155)

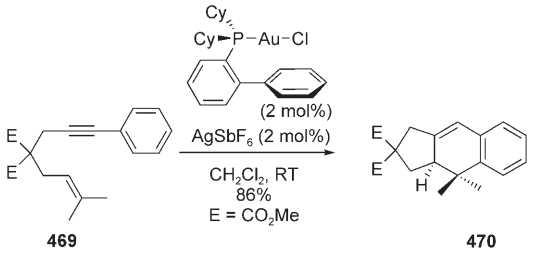
(156)].[177,173] Remarkably, the conditions developed by Kozmin and co-workers were compatible with nitrogen as the nucleophile. The authors also found that the combination



(156)

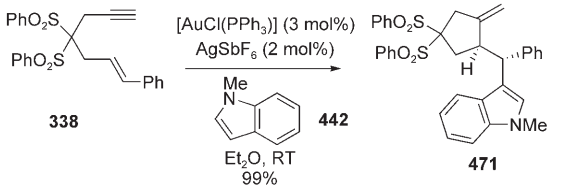
of [AuCl(PPh$_3$)] and AgClO$_4$ proved to be equally as effective.

Recently, the formation of C–C bonds—both intra- and intermolecularly—was also disclosed. The cyclization of aryl alkyne **469** promoted a selective [4+2] cycloaddition to give 2,3,9,9a-tetrahydro-1*H*-cyclopenta[b]naphthalene **470** in 86% yield [Eq. (157)].[178] Various catalysts were efficient

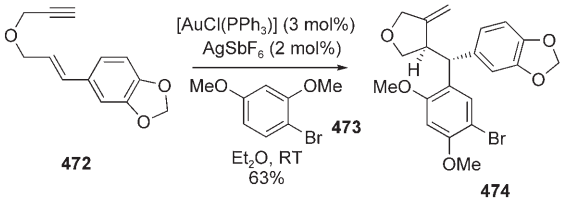


(157)

for this transformation, with a (biarylphosphane)gold chloride being the most reactive. The biaryl was either a biphenyl or a methoxybiphenyl group. The research group of Michelet and Genêt showed that the tandem Friedel–Crafts-type alkylation/cyclization was possible in the presence of [AuCl(PPh$_3$)]/AgSBF$_6$ in diethyl ether at room temperature [Eqs. (158) and (159)].[179] The scope of the reaction is



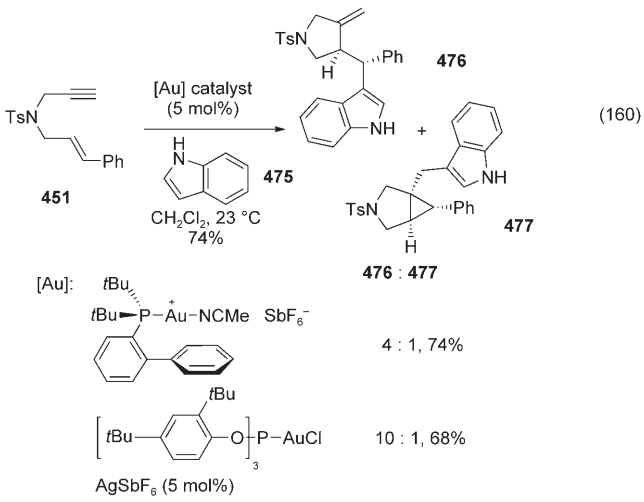
(158)



(159)

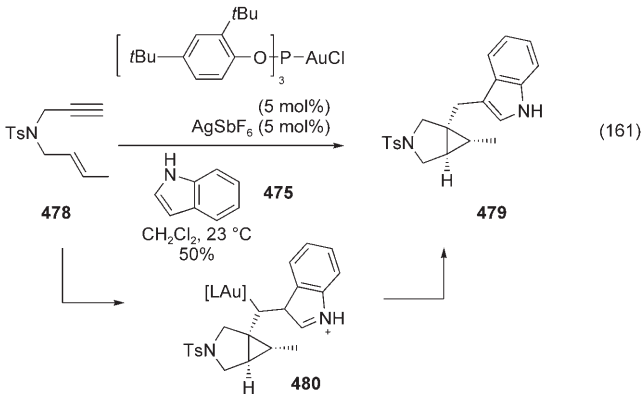
broad, with all the 1,6-enynes (carbon, oxygen, and nitrogen bridged) reacting cleanly to afford the corresponding functionalized arenes in good to excellent yield. Various electron-rich aromatic compounds, substituted indoles, and pyrroles could participate in the reaction. The functionalized compounds **471** and **474** were, for example, isolated in 99% and 63% yield, respectively.

The research group of Echavarren observed independently a similar reactivity of 1,6-enynes.[180] It is interesting to note that the reactivity of the presumed gold carbene intermediate **457** [see Scheme 36 and Eqs. (149) and (150)] was evident, as shown by the formation of cyclopropane **477** as a minor product. The phosphite-based gold complex showed the best selectivity [Eq. (160)], and the aryl-substituted derivatives were isolated as the major or exclusive compounds for a broad range of enynes and nucleophiles. The cyclopropyl derivative **479** was obtained in 50% yield from



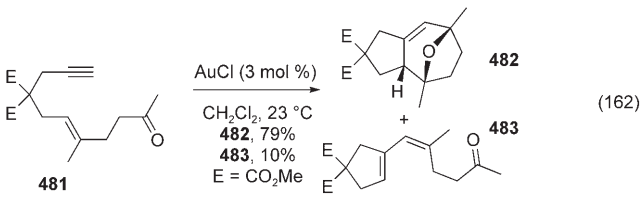
(160)

the methyl-substituted alkene **478**. The formation of **479** may be explained by a direct C–H-type activation of the indole ring to give the alkyl gold intermediate **480**, which upon rearomatization and proto-demetalation afforded the corresponding cyclopropane **479** [Eq. (161)].



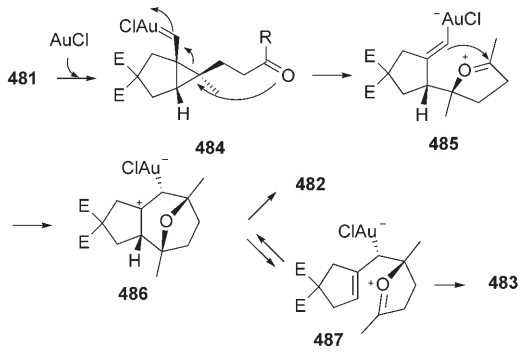
(161)

Polycyclic heterocycles bearing an oxygen bridge were obtained by a tandem cyclization/Prins reaction.[181] The cyclization of **481** afforded the corresponding tricyclic derivative **482**, along with a small amount of the ketone **483** [Eq. (162)]. The cycloisomerization of enyne **481** may lead to



(162)

carbene **484**, which evolves towards the oxonium ion **485** through a nucleophilic addition of the carbonyl group (Scheme 37). A Prins-type reaction would then give the intermediate **486**, which may give the desired tricyclic compound **482** or the ketone **483**, via the intermediate species **487**.

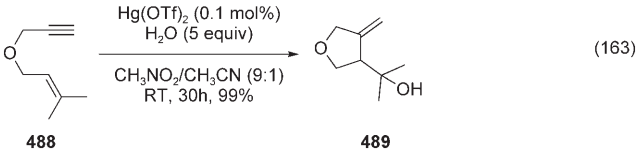


Scheme 37. Proposed intermediates for the tandem cyclization/Prins reaction according to Equation (162).

8. Hg-Catalyzed Cycloisomerizations

Whereas the use of stoichiometric quantities of mercury[182] has been known for a long time to effect enyne cycloisomerization, very few reports of mercury-catalyzed carbocyclizations have appeared in the literature.

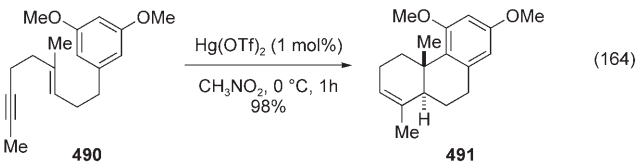
By exploiting the alkynophilic nature of $Hg(OTf)_2$, Nishizawa et al.[183] developed a highly active protocol for the hydroxycyclization of 1,6-enynes possessing oxygen or carbon bridges. Enyne **488** was converted into alcohol **489** in almost quantitative yield at room temperature in the presence of $Hg(OTf)_2$ in quantities as low as 0.1 mol% [Eq. (163)]. In



(163)

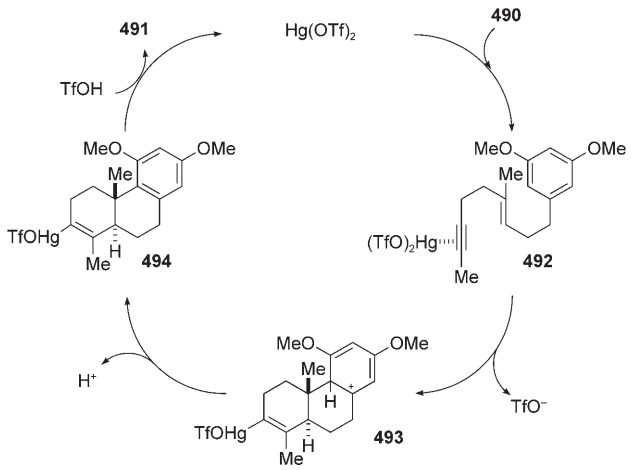
agreement with observations made with gold catalysts, competitive hydration of the alkyne moiety occurs with less reactive substrates such as nitrogen-bridged molecules or 1,7- and 1,8-enynes.

The same research group also applied this system to a intramolecular tandem cycloisomerization/Friedel–Crafts-type reaction.[184] Treatment of enyne **490** with 1 mol% $Hg(OTf)_2$ at 0°C furnished polycycle **491** in 98% yield as a single diastereomer [Eq. (164)]. The authors postulate an



(164)

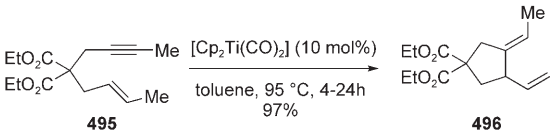
initial π coordination of the triple bond to the Hg center (intermediate **492**) followed by a stepwise cyclization leading to carbocationic intermediate **493** (Scheme 38). Proto-demetalation results in the formation of vinylmercuric intermediate **494**, which reacts with in situ generated TfOH to give product **491**.



Scheme 38. Mechanism of the Hg-catalyzed tandem hydroarylation/cycloisomerization of 1,5-enynes according to Equation (164).

9. Ti-Catalyzed Cycloisomerizations

In 1999, Buchwald and co-workers[185] reported the first titanium-catalyzed cycloisomerization of 1,6-enynes. In a typical experiment, enyne **495** was treated at 95°C in toluene with 10 mol% of $[Cp_2Ti(CO)_2]$ to give diene **496** in 97% yield [Eq. (165)]. The proposed mechanism relies on the initial loss



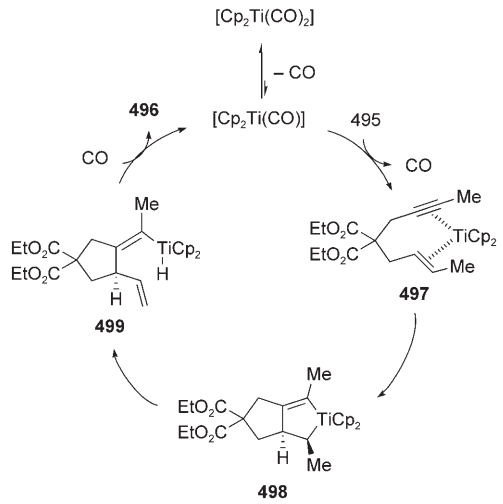
(165)

of one molecule of CO to give the coordinatively unsaturated complex $[Cp_2Ti(CO)]$ (Scheme 39). The reaction between this complex and the substrate leads to the formation of metallacyclopentene **498**. Subsequent β-hydride elimination and reductive elimination via Ti-hydride intermediate **499** regenerate the titanium(II) complex and liberate diene **496**.

Strikingly, the reaction is specific for *E*-substituted alkenes. *Z* alkenes exhibit either no reactivity or low conversion into cyclopentenones arising from CO insertion into intermediates analogous to **498**. Orbital geometries disfavoring the β-hydride elimination have been invoked to explain this reaction pattern.

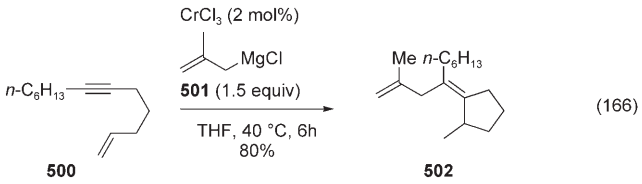
10. Cr-Catalyzed Cycloisomerizations

In 2002, Nishikawa, Shinobuko, and Oshima[186] described a tandem carbometalation/cycloisomerization of 1,6-enynes that relied on the combination of $CrCl_3$ acting as a catalyst



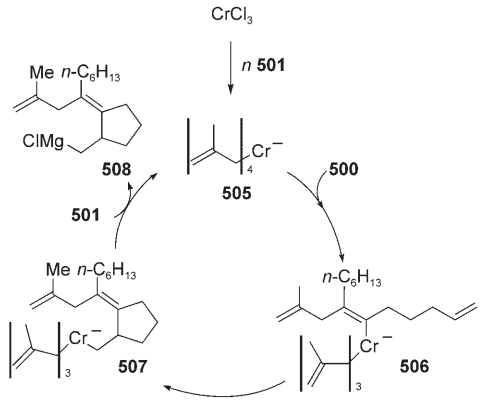
Scheme 39. Mechanism for the Ti-catalyzed cycloisomerization of 1,6-enynes according to Equation (165).

and a Grignard reagent acting as a nucleophile. In a typical experiment, enyne **500** was treated with methallylmagnesium chloride (**501**) in the presence of 2 mol% $CrCl_3$ at 40 °C in THF to give the alkylidenecyclopentane **502** in 80% yield [Eq. (166)].



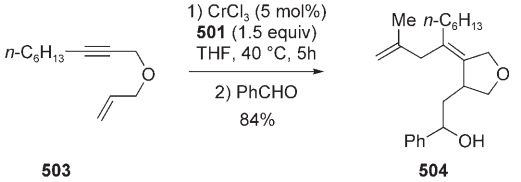
(166)

In accordance with experiments conducted using stoichiometric quantities of chromate reagents, the authors postulated a mechanism based on the initial nucleophilic allylation of the C–C triple bond of the substrate by an in situ generated chromate complex **505** to form the vinylchromate intermediate **506** (Scheme 40). Insertion into the C–C double bond allows the formation of the five-membered ring **507**. Exchange of the organometallic fragments by metathesis



Scheme 40. Mechanism of the Cr-catalyzed tandem carbometalation/cycloisomerization of 1,6-enynes according to Equation (166).

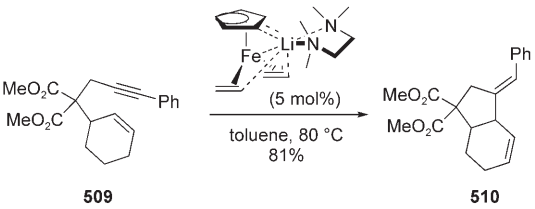
furnishes the alkylmagnesium complex **508** and regenerates the catalytically active chromate species **505**. The trapping of intermediate **508** with different electrophiles to allow further functionalization has also been studied, as shown by the example in Equation (167).



(167)

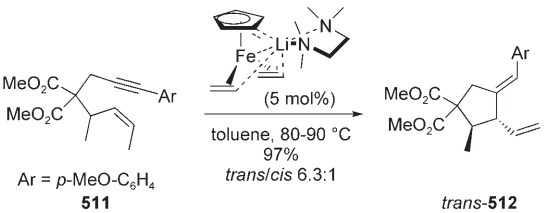
11. Fe-Catalyzed Cycloisomerizations

The use of iron in catalysis is highly challenging. Based on the results of some iron-catalyzed cross-coupling reactions, Fürstner et al. were the first research group to propose a catalytic version of the cycloisomerization of enynes.[187–189] The low-valent iron complex $[Li(tmeda)][CpFe(C_2H_4)_2]$, readily prepared and isolated from inexpensive ferrocene, was found to be extraordinarily active for enyne rearrangements. The weakly ligated ethylene ligands can be readily substituted by an enyne moiety—in a similar way as for previously presented Pd-catalyzed reactions—and lead to an oxidative addition to give a cycloferrate complex. Enynes bearing cyclic alkene moieties such as **509** underwent clean cycloisomerization at 80 °C in toluene in the presence of 5 mol% of the catalyst [Eq. (168)]. Other enynes such as



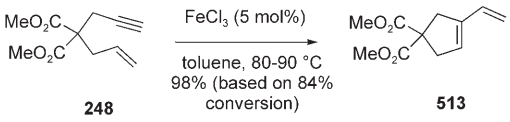
(168)

$C(CH_2OSiiPr_3)_2$ as well as oxygen- and nitrogen-bridged ones were also cyclized in good yields. Likewise, different substituents on the triple bond were well-accommodated, including electron-withdrawing substituents as well as cyclopropyl and silyl groups. Acyclic enynes proved to be trickier; substitution in the allylic position was required in these cases for a productive cyclization. The rearrangement of enyne **511** was nevertheless highly efficient and led to *trans*-**512** as the major product [Eq. (169)]. The role of this substitution pattern has not yet been explained.



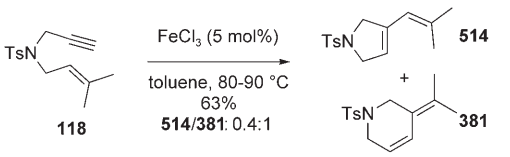
(169)

Iron trichloride was recently found to promote skeletal rearrangements of enynes.[173] The reaction of **248** was carried out in toluene at 80–90 °C and afforded the *exo*-adduct **513** as the major product [Eq. (170)]. This reaction outcome was



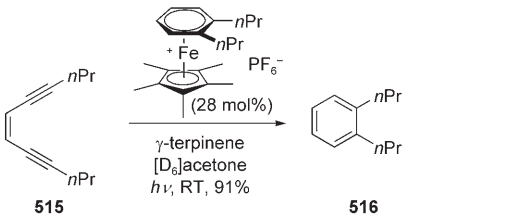
(170)

generally the case for carbon-bridged enynes. The authors observed that the reaction scope was limited compared to the analogous gold-catalyzed reaction. The *endo*-skeleton rearrangement could be observed in the case of nitrogen-bridged enyne **118** [Eq. (171)].



(171)

Similar to previous studies carried out in the presence of ruthenium and platinum for enediynes and dienynes [see Eqs. (48), (49), and (122)], the controlled cyclotrimerization of enediynes was reported with iron.[190] The authors showed that the air-stable complex $[(\eta^5\text{-}C_5Me_5)Fe(\eta^6\text{-}(1,2\text{-}(n\text{Pr})_2\text{-}C_6H_4)]PF_6$ could promote the cycloisomerization of (*Z*)-dodeca-6-en-4,8-diyne (**515**) to give the aromatic derivative **516** [Eq. (172)]. The catalytic reaction was followed by NMR



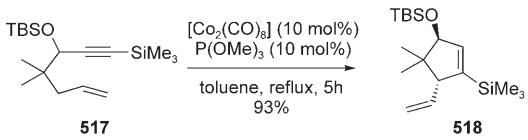
(172)

spectroscopy and was limited by the slow arene dissociation step.

12. Co-Catalyzed Cycloisomerizations

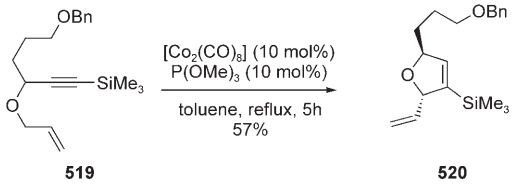
The transformations of enynes in the presence of cobalt complexes are directly linked to studies carried out on the Pauson–Khand reaction[191] and [2+2+2] cyclotrimerizations.[192] Over the years, a variety of carbocycles resulting from the cyclization of enynes have been observed as side products in the Pauson–Khand reaction carried out in the presence of stoichiometric quantities of cobalt compounds.[193,194]

In 2003, Ajamian and Gleason[195] reported the first catalytic cycloisomerization of 1,6-enynes in the presence of a combination of $[Co_2(CO)_8]$ and $P(OMe)_3$: Enyne **517** was converted into compound **518** within 5 h in the presence of the catalyst system in refluxing toluene [Eq. (173)]. The reaction



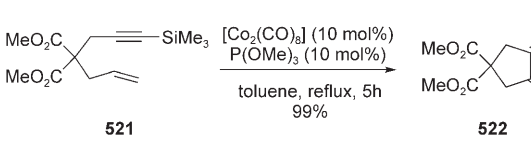
(173)

is amenable to oxygen-bridged substrates. The cyclization of allyl propargyl ether **519** gives dihydrofuran **520** in 57% yield [Eq. (174)].



(174)

Although the mechanism is not known, the reaction proceeds formally through an allylic C–H activation/insertion pathway and leads to the formation of vinylcyclopentenes with excellent yields and diastereoselectivities. Remarkably, the substitution of the alkyne by a trimethylsilyl substituent is a prerequisite for the cycloisomerization. The nature of the bridge also seems to have a profound influence on the course of the reaction: malonate derivative **521** produces 1,3-diene **522** in quantitative yield under the catalytic conditions [Eq. (175)].

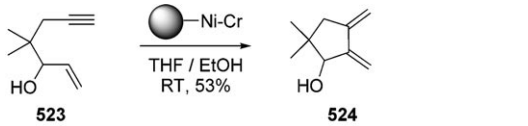


(175)

13. Ni-Catalyzed Cycloisomerizations

13.1. Enyne Rearrangements

Enyne cycloisomerization may also be effected by nickel-based catalysts. A single report has described the formation of 1,3-dienes by using a Ni-Cr polymer.[196] Systems based on the Ni-Cr/PPh_3 catalyst system had a narrow reaction scope, whereas a polymer prepared from $[NiCl_2(PPh_3)_2]$ and a phosphanylated 2% cross-linked polystyrene (10 mol%) in association with $CrCl_2$ (30 mol%) was highly active for several types of enynes such as **523** [Eq. (176)]. Mechanisti-



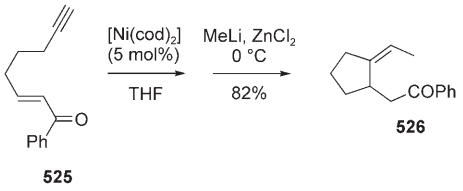
(176)

cally, the reaction most likely proceeds along a pathway similar to that reported for the Pd-catalyzed reactions, but, to our knowledge, no further evidence has so far been reported.

A recent report described the use of $[Ni(cod)_2]/PPh_3/ZnCl_2$ as the catalyst for the cycloisomerization of 1,6-enynes.[197] The selectivity was in complete accord with the study performed by Trost and co-workers and led to 1,3-dienes as major products.

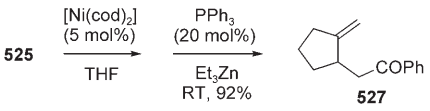
13.2. Enyne Tandem Reactions

Since the pioneering work by the research group of Ikeda and Sato,[198] intramolecular tandem reactions have proven to be possible in the presence of nickel.[199] α,β-Unsaturated enynes and an organozinc or aluminum derivative were found to participate, in general, in the coupling process.[200] Electron-deficient double bonds in combination with a terminal triple bond, as in **525**, generally underwent efficient cyclization upon exposure to $[Ni(cod)_2]$ and an organozinc compound (generated from MeLi and $ZnCl_2$) to give alkylidenecycloalkanes [Eq. (177)]. A significant ligand effect was observed



525 526 (177)

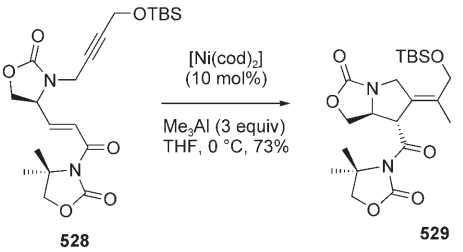
when the reaction was carried out in the presence of triphenylphosphane ligand: instead of the introduction of the organozinc substituent, an efficient reductive cyclization with the incorporation of a hydrogen atom occurred [Eq. (178)]. In some cases such as the enyne **528**,[200f] the precursor of (+)-a-allokainic acid, the use of trimethylalumi-



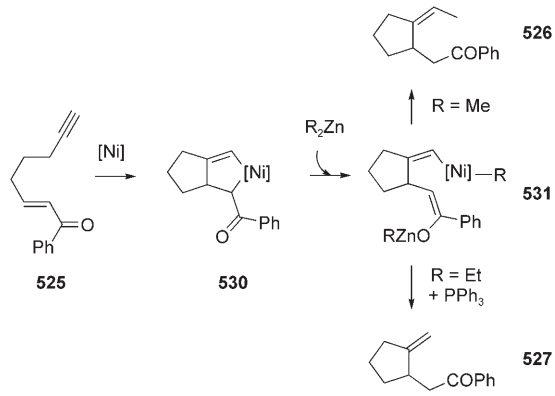
527 (178)

num gave higher yields and diastereoselctivity [Eq. (179)]. The presence of a reducing agent such as Et_3B can also provide access to the cyclic alcohols.[201]

The proposed mechanism (Scheme 41) involves the formation of a metallacycle **530**, the existence of which was



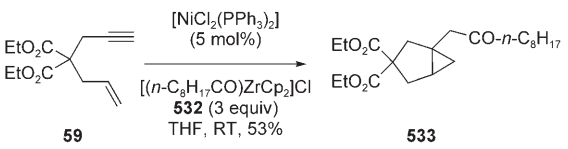
528 529 (179)



Scheme 41. Ni-catalyzed synthesis of functionalized alkylidene cycloalkanes according to Equations (177) and (178).

demonstrated recently by an X-ray structure of a tmeda–Ni complex.[202] A transmetalation step with various organometallic species would produce intermediate **531**, which would undergo a reductive elimination to form the desired product. In the presence of triphenylphosphane, a β-hydride elimination would afford alkene **527**.

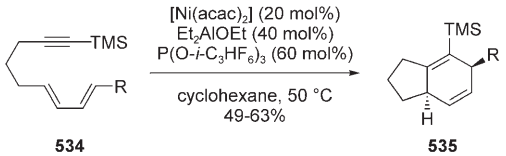
The use of *n*-nonanoylzirconocene chloride **532** as the transmetalating agent gave rise to a clean acylation combined with a cyclization reaction [Eq. (180)].[203] The mechanism of



59 533 (180)

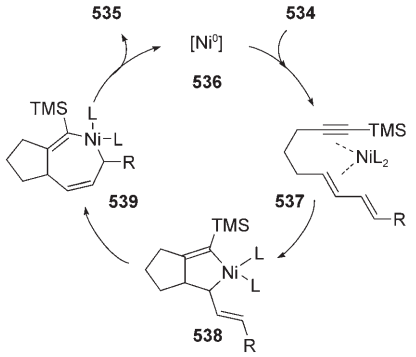
this tandem reaction has not yet been studied, but would presumably involve a metallacyclopentene (similar to **530**, Scheme 41). The authors proposed a regioselective transfer of the acyl group followed by a reductive elimination step. The formation of the cyclopropane would finally arise from an intramolecular Michael-type addition of an organometallic species.

The presence of multiple unsaturated bonds also influenced the Ni-catalyzed cyclization process. Formal [4+2] and [2+2+2] cycloadditions have been described using Ni^0 catalysts.[200e,204] The [4+2] cyclization of dienynes **534** led stereoselectively to the bicyclic dienes **535** in 49–63% yields, irrespective of the terminal substituent on the diene moiety [Eq. (181)]. Mechanistically, the Ni^0 catalyst initially coordinates to the triple bond and the internal double bond to give the intermediate **537** (Scheme 42). The classic, completely stereoselective cyclometalation then occurs to form the first



534 535 (181)

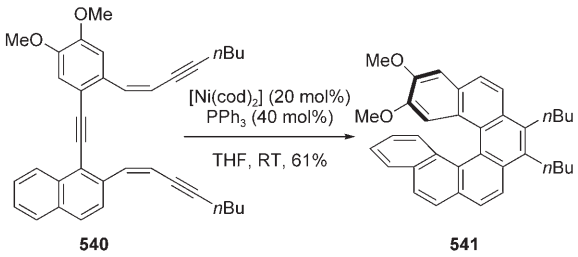
R = CO_2Et, Ph, *p*-CO_2Et-C_6H_4, *p*-Cl-C_6H_4



Scheme 42. Ni-catalyzed tandem cycloisomerization of dienynes according to Equation (181).

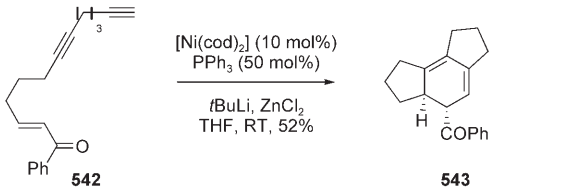
carbon–carbon bond which is followed by insertion in the other alkenyl bond to afford the nickelacycloheptadiene **539**. Reductive elimination then provides the desired diene **535**.

The cycloisomerization of *cis*,*cis*-dienetriyne **540** was also studied and gave an easy entry to [6]helicene **541** [Eq. (182)].



(182)

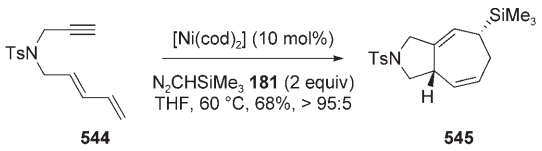
In the case of diyne derivative **542**, a formal [2+2+2] occurred—especially in the presence of a hindered organozinc derivative—and afforded a tricyclic diene **543** in 52% yield [Eq. (183)].



(183)

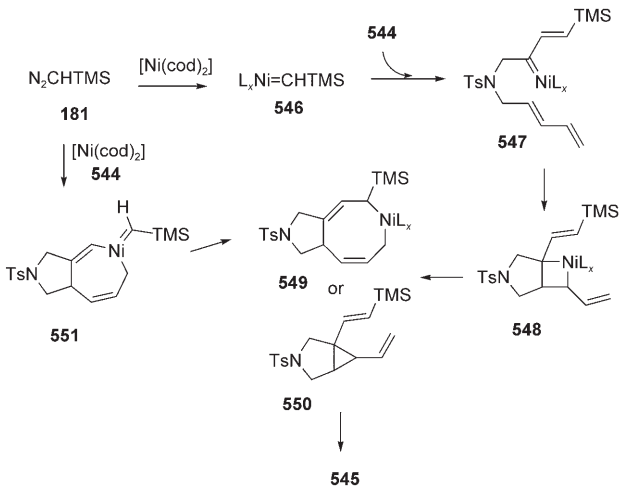
A novel Ni-catalyzed [4+2+1] cycloaddition was described in 2004 which involved a dienyne and trimethylsilyldiazomethane (**181**).[205] For example, the cycloaddition of **544** occurred very cleanly and led to the functionalized seven-membered-ring derivative **545** [Eq. (184)]. It is noteworthy that substitution on either the diene terminus or at an internal position of the diene could be tolerated as could substitution within the tether chain.

The mechanism is still unclear, but may be similar to the Ru-catalyzed cycloisomerization reactions[50,75] and analogous to some stoichiometric molybdenum–carbene mediated dienyne cyclizations. The proposed mechanism involved a nickel



(184)

carbene intermediate **547**, which would evolve towards the metallacyclobutane **548** through a metathesis cascade (Scheme 43). Rearrrangement of **548** to **549** would then



Scheme 43. Proposed mechanism for the formal Ni-catalyzed [4+2+1] reaction of dienynes according to Equation (184).

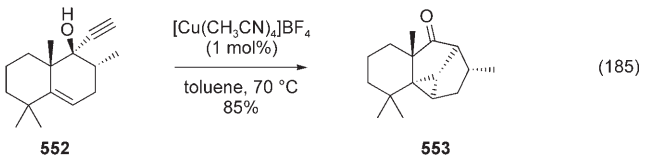
allow direct production of seven-membered ring **545** by reductive elimination. Alternatively, reductive elimination of **548** could produce cyclopropyl **550**, which upon a Cope rearrangement would lead to **545**. In a similar way as previously observed and proposed for enyne cycloisomeriations, an oxidative addition could lead to intermediate **551**, which upon carbene insertion would afford the same intermediate **549**.

14. Cu-Catalyzed Cycloisomerizations

Cycloisomerization reactions in the presence of copper salts are quite rare, even though copper(I) salts are known to have a good affinity for alkynes and promote nucleophilic additions.[206]

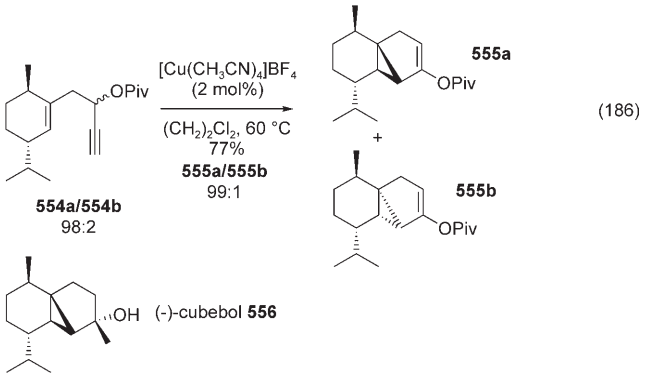
14.1. Enyne Rearrangements

Fehr et al. recently studied highly valuable rearrangements based on cupper catalysis. The Cu^{I}-catalyzed cycloisomerization of tertiary 5-en-1-yn-3-ols (such as **552**) and an sccompanying 1,2-alkyl shift affords tri- and tetracyclic compounds of high molecular complexity (such as **553**) stereoselectively [Eq. (185)].[207] These results are in agreement with a mechanism in which the cyclopropanation precedes the rearrangement. The same research group also



552 553 (185)

described an efficient synthesis of a potential flavor compound (−)-cubebol (**556**) by a stereoselective cycloisomerization.[208] Several platinum and gold catalysts were efficient, but the use of the inexpensive $[Cu(CH_3CN)_4]BF_4$ was particularly original. The cyclization of pivaloyl derivatives **554a** and **554b**, prepared from (*R*,*R*)-tetrahydrocarvone, afforded the cyclopropyl tricycles **555a** and **555b** in 77% yield [Eq. (186)]. The authors showed that the configuration

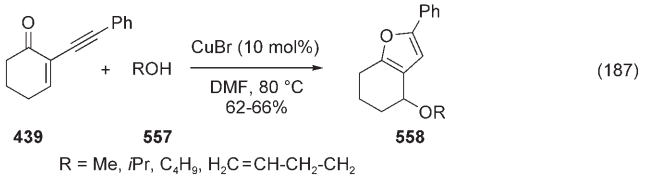


(186)

of the propargylic carbon atom was essential for the facial selectivity.

14.2. Enyne Tandem Reactions

An efficient Cu-catalyzed tandem reaction was reported in 2005 for the synthesis of furans from 2-(1-alkynyl)-2-alken-1-ones such as **439** [Eq. (187)].[209] This reaction had previ-

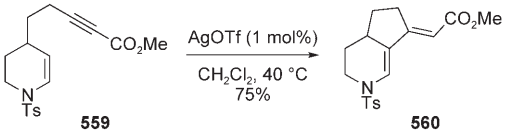


439 557 558 (187)

ously been reported by Larock and co-workers, who used a gold catalyst.[169] The authors proposed here the use of inexpensive copper bromide in DMF at 80 °C. The addition of various alcohols **557**, such as methanol, butanol, 2-propanol, and but-3-enol, gave rise to further cyclization and led to functionalized furans. The use of DMF was essential for the reaction: the cyclization failed in other organic solvents such as benzene, toluene, dichloromethane, tetrahydrofuran, and 1,4-dioxane. Two mechanistic pathways were proposed, which depended on whether the formation of the furan ring occurred before or after the addition of the alcohol. The first mechanism is similar to the one proposed by Larock and co-workers [see Scheme 35 as well as Eqs. (145) and(146)], while the second involves the 1,6-addition of the alcohol prior to the formation of the furan ring.

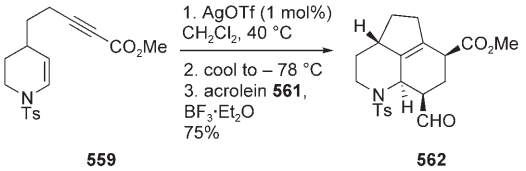
15. Ag-Catalyzed Cycloisomerizations

The use of silver salts as halide scavengers for metal chloride precursors are extremely common in cycloisomerization reactions. To the best of our knowledge, a very limited number of reports have been published on Ag-catalyzed enyne cyclizations. The use of silver triflate converted enyne **559** efficiently into bicyclic derivative **560** in 75% yield [Eq. (188)].[210] The type of substitution on the triple bond was



559 560 (188)

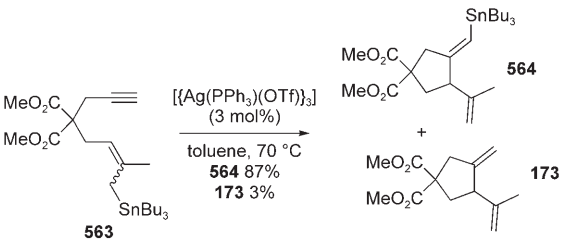
critical: no reaction occurred for methyl- or phenyl-substituted alkynes, while the presence of an electron-withdrawing group such as a ketone, ester (**559**), amide, or nitrile was necessary and sufficient for the activity of the enyne towards AgOTf. As the robust *p*-toluenesulfonyl protecting group can sometimes be difficult to remove, the authors also prepared the Boc-protected enecarbamate, which was cleanly cyclized in good yield. A sequential cycloisomerization/Diels–Alder reaction in the presence of acrolein (**561**) under mild conditions led to tricyclic derivative **562** [Eq. (189)]. The



559 562 (189)

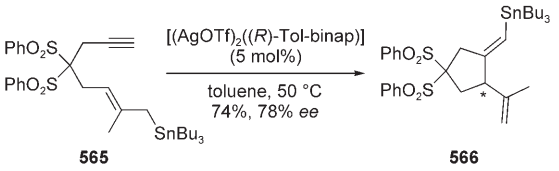
authors compared the silver activity with platinum dichloride salts.

Porcel and Echavarren recently described a highly valuable Ag-catalyzed intramolecular carbostannylation.[211] When the allylstannane **563** was subjected to silver salts at 70 °C in toluene, the stannane **564** was isolated along with a small amount of diene **173** [Eq. (190)]. The silver source was



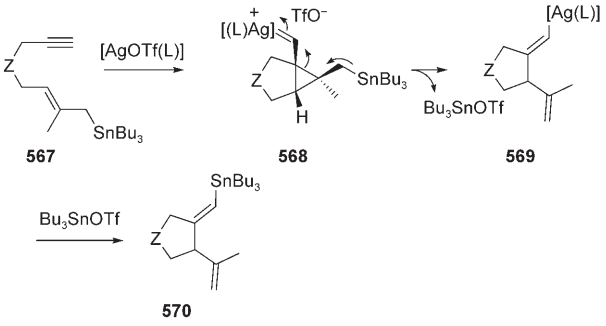
563 (190)

optimized and consistent results were obtained with the preformed [{Ag(PPh_3)(OTf)}$_3$] complex.[212] The reaction could be extended efficiently to the synthesis of six- and seven-membered-ring compounds by using 1,7- and 1,8-enines. The enantioselectivity of this reaction was a major success: a 78% enantiomeric excess was achieved in the presence of [$(AgOTf)_2$((*R*)-Tol-binap)] as the catalyst [Eq. (191)].



(191)

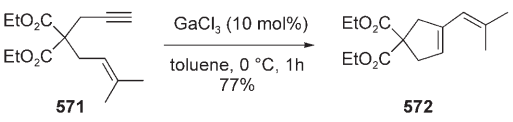
Mechanistically, the authors proposed the formation of the silver carbene **568**, which may evolve to the alkenylsilver(I) complex **569**. This latter species can react with the tin electrophile generated in situ to give stannane **570**, with total control over the stereoselectivity (Scheme 44).



Scheme 44. Proposed mechanism for the Ag-catalyzed carbostannylation of 1,6-enynes according to Equation (190).

16. Ga-Catalyzed Cycloisomerizations

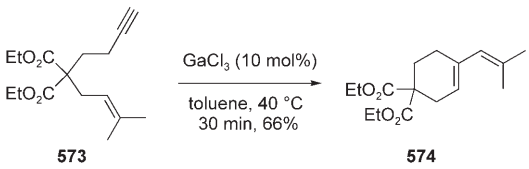
The first report dealing with applications of Ga catalysts in enyne cycloisomerization appeared in 2002 when Chatani et al.[213] presented their study on the use of $GaCl_3$ for the skeletal rearrangement of 1,6-enynes. Treatment of enyne **571** with 10 mol% $GaCl_3$ in toluene at 0 °C afforded 1,3-diene **572** in 77% yield by skeletal rearrangement and the cleavage of one bond [Eq. (192)]. The reaction was also successful for the



(192)

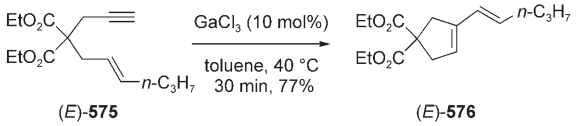
rearrangement of 1,7-enyne **573**, and gave easy access to 1,3-diene **574** [Eq. (193)].

In contrast with the use of Ru and Pt catalysts [see for example Eqs. (100) and (101)], the reaction with the Ga catalyst is completely stereospecific: enyne (*E*)-**575** leads to

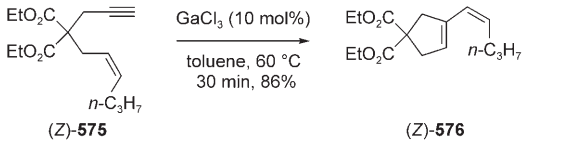


(193)

product (*E*)-**576**, while enyne (*Z*)-**575** afforded the *Z* product [Eqs. (194) and (195)].

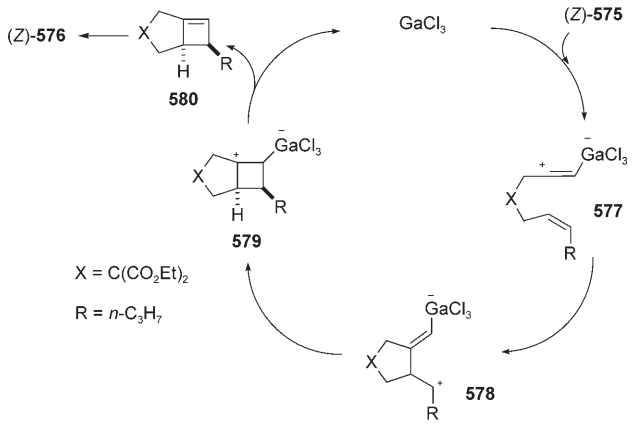


(194)



(195)

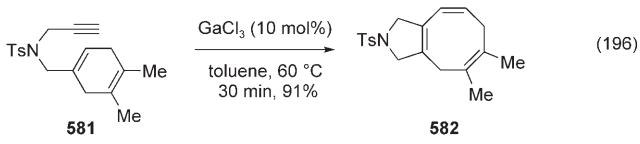
To explain the selectivity observed, the authors propose a mechanistic rationale based on the intermediacy of cyclobutenes (Scheme 45). An initial electrophilic addition of



Scheme 45. Mechanism for the Ga-catalyzed skeletal reorganization of 1,6-enynes according to Equation (195).

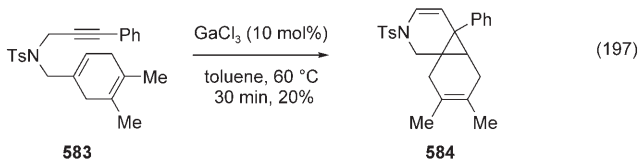
$GaCl_3$ to the triple bond of substrate (*Z*)-**575** leads to the formation of vinylgallate **577**. Nucleophilic attack of the alkene function and subsequent ring closing of intermediate **578** delivers cyclobutane **579**. Elimination of $GaCl_3$ then gives cyclobutene **580**. Conrotatory opening of this strained four-membered ring releases 1-vinylcyclopentene (*Z*)-**576** with retention of the double-bond configuration.

This new transformation was successfully applied to the synthesis of a series of polycyclic compounds. Chung and coworkers[214] described the formation of bicyclo[6.3.0] compounds by cycloisomerization of dienynes such as **581** [Eq. (196)]. This reaction was nevertheless limited to terminal



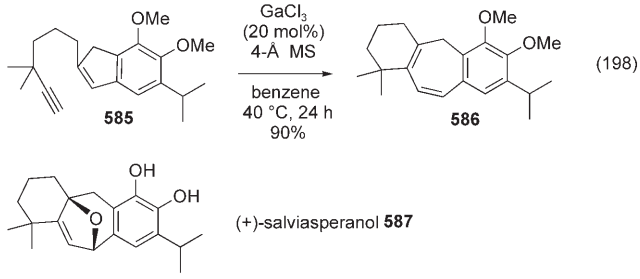
(196)

alkynes. Cycloisomerization of enynes possessing a disubstitued triple bond afforded polycycles containing a cyclopropane ring in low yields [Eq. (197)].



(197)

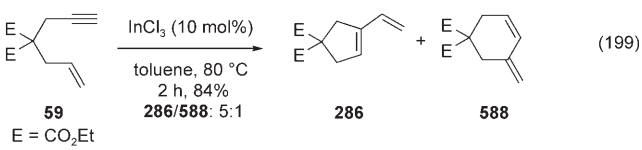
Simmons and Sarpong[215] also utilized this methodology as part of a total synthesis of (±)-salviasperanol (**587**) [Eq. (198)]. Treatment of alkynyl indene **585** with 20 mol% $GaCl_3$ in benzene at 40 °C gives cycloheptatriene **586** in 90% yield.



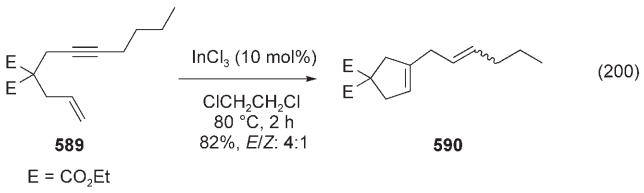
(198)

17. In-Catalyzed Cycloisomerizations

Recently, Miyanohana and Chatani presented the first example of indium salts in cycloisomerization transformations.[216] They were able to show that $InCl_3$ effects the skeletal rearrangement of a variety of 1,6- and 1,7-enynes. For example, enyne **59** was converted into vinylcyclopentene **286** in 84% yield along with 1,3-diene **588** [Eq. (199)]. The presence of isomer **588** is indicative of a competition between a skeletal rearrangement and an *endo*-type cycloisomerization. Only skeletal rearrangement is observed in the case of 1,7-enynes. Alkyl-substituted enynes react by a different pathway. Substrate **589** is readily converted into allylcyclopentene **590** at 80 °C in dichloroethane in the presence of 10 mol% $InCl_3$ [Eq. (200)].

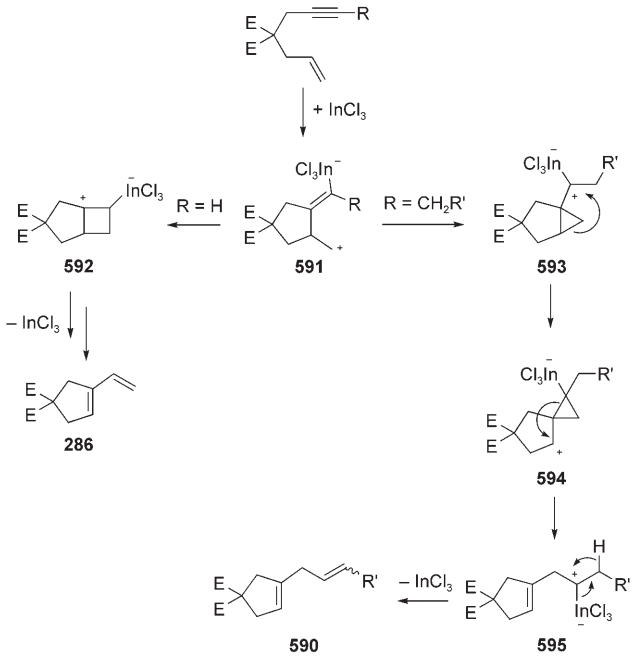


(199)



(200)

In close analagy with the already discussed skeletal rearrangement mechanisms in the presence of Pt and Ga (Schemes 27 and 45), and based on extensive labeling experiments, the authors postulate the mechanism depicted in Scheme 46 to explain the dichotomy between terminal and internal triple bonds. Zwitterionic intermediate **591** which results from a sequence of transformations—analoguous to intermediate **578** in Scheme 42—can either follow the same path to form vinylcyclopentene **286** ("single cleavage pathway") or react through two consecutive 1,2-alkyl shifts and subsequent β-hydride elimination to give **590** ("modified double cleavage pathway").



Scheme 46. Mechanism for the In-catalyzed skeletal reorganization of 1,6-enynes according to Equations (199) and (200).

18. Conclusion

An important step in enyne rearrangements has been made since the seminal work of B. M. Trost et al. in palladium chemistry. Various 1,*n*-enynes have been cyclized in the

presence of several metals through different reaction pathways to give functionalized carbo- or heterocycles. Many research groups have studied the influence of functional groups in the rearrangement pathways. Ruthenium, rhodium, iridium, and nickel catalysts have shown interesting activities and generally complementary selectivity to palladium chemistry. There is no doubt that platinum and gold catalysts are particularly attractive for the discovery of novel rearrangements. Other metals such as mercury, cobalt, chromium, and titanium are more specific catalysts for some substrates or reactions. Of particular note is the extraordinary activity of silver, copper, and iron catalysts, which open new perspectives in catalysis.

For all the metals, the presence of nucleophilic or electrophilic moieties on the 1,*n*-enyne completely controls the outcome of the cycloisomerization reactions and has enables a huge advance in the skeletal diversity of the synthesized molecules. For each novel rearrangement or tandem reaction, a mechanism has been proposed and sometimes demonstrated through labeling experiments. Some interesting arguments have been given recently thanks to progress in DFT calculations.

The use of transition-metal-catalyzed 1,*n*-enyne reactions has created a large diversity in the obtained cyclic structures. Most of the polycyclic derivatives may be key intermediates in the total synthesis of natural or biologically active products.[217] However, few reports have appeared on asymmetric catalysis. Indeed, although substantial efforts have been made to develop new efficient reactions, it is still essential to develop strategic asymmetric protocols that are general and applicable to various structural types.

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