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Gold and Platinum Catalysis of Enyne Cycloisomerization

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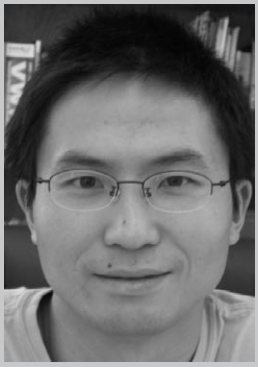
Abstract: This account provides a comprehensive overview of the development of gold and platinum catalysis of the enyne cycloisomerization. The use of these soft, alkynophilic metals enables mild, chemoselective and efficient transformations of a variety of readily available acyclic enynes to a wide range of synthetically useful carbocyclic and heterocyclic products. The review is organized according to diverse structural types of enynes that undergo skeletal cycloisomerizations. The account begins with an overview of transformations of primarily 1,6-enynes to 1-alkenylcyclopentenes, bicyclo[4.1.0]heptenes, methylenecycloalkenes, bicyclo[4.3.0]nonadienes and bicyclo[3.2.0]heptenes. This section is followed by the discussion of cycloisomerizations of 1,5-enynes, which enable a rapid access to a range of other cyclic products, including bicyclo[3.1.0]hexenes, cyclohexadienes, heterobicycloalkenes, methylenecyclopentenes, naphthalenes and methyleneindenes. In addition, the [3,3] rearrangement of 1,5-enynes provides efficient access to the corresponding allenes. The account concludes with an overview of the most recent studies on gold- and platinum-catalyzed cycloisomerizations of 1,4- and 1,3-enynes. Due to the rapidly increasing interest in this area during the past three to five years, we believe that this review provides a timely and comprehensive discussion of the development gold- and platinum-catalyzed cycloisomerization starting from the initial pioneering investigations to the latest advances in the field. A significant emphasis is placed on the mechanistic discussion of the observed manifolds of skeletal reorganizations.

Keywords: alkenes; alkynes; C–C bond formation; cyclization; gold; platinum

1 Introduction

The transition metal-catalyzed enyne cycloisomerization is among the most important strategies for the synthesis of functionalized cyclic structures.[1] The significance of this process stems from the rapid increase in structural complexity starting with relatively simple acyclic subunits containing ene and yne fragments. Among a range of transition metal complexes capable of catalyzing enyne cycloisomerizations, gold and platinum complexes are particularly powerful as they are capable of delivering a diverse array of cyclic products that are produced under mild conditions, with excellent chemoselectivity and high synthetic efficiency. While the pioneering work in this area goes back to the 1990s, there has been an explosive increase of interest in Au and Pt catalysis during the last three to five years. This review provides a comprehensive discussion of the development of Au- and Pt-catalyzed enyne cycloisomerizations.[2]



Liming Zhang received his B.S. degree in chemistry at Nanchang University in 1993. After his Master's in organometallic chemistry at Nankai Univeristy, P. R. China, in 1996, he moved to the University of Alabama and obtained a Master's degree in organic chemistry with Michael P. Cava in 1998. He received his Ph.D. with Masato Koreeda from the medicinal chemistry program at the University of Michigan in 2003 and carried out a postdoctoral study with Sergey A. Kozmin at the University of Chicago. In July of 2005, he joined the Department of Chemistry, the University of Nevada, Reno as an Assistant Professor. His research interests include late transition metal-catalyzed reactions, natural product synthesis and medicinal chemistry.

Jianwei Sun was born in P. R. China in 1979. In 2001, he received his B.S. in Chemistry from Nanjing University. In the next three years he worked with Professor Yuefei Hu as a graduate student and received his Master's degree in 2004 from Nanjing University. In the same year, he moved to the University of Chicago and began his Ph.D. studies in organic chemistry with Professor Sergey A. Kozmin. His research interests include the development of new gold-, silver- and platinum-catalyzed transformations, as well as the applications of these methods in the area of complex molecule synthesis.

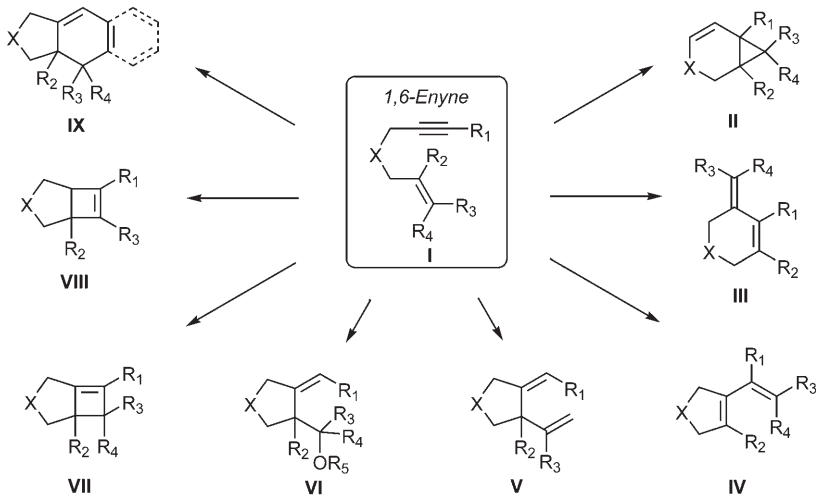
Sergey A. Kozmin received his Undergraduate Diploma at the Moscow State University in 1993. He obtained his Ph.D. in 1998 at the University of Chicago with Viresh H. Rawal, and completed postdoctoral studies at the University of Pennsylvania with Amos B. Smith, III in 2000. He started his independent academic career at the University of Chicago as an Assistant Professor; in 2006 he was promoted to the rank of Associate Professor. Kozmin has been recognized as the Alfred P. Sloan Fellow, the American Cancer Society Research Scholar, the Amgen Young Investigator, GlaxoSmithKline Chemistry Research Scholar, the Camille Dreyfus Teacher-Scholar and a recipient of the NSF CAREER award. His research program combines several complementary efforts, including (a) development of new catalytic reactions of conceptual and practical utility; (b) synthesis of complex natural products of notable biological significance; and (c) generation of highly diverse chemical libraries, featuring the complexity of natural metabolites.

2 Cycloisomerizations of 1,6-, 1,7- and 1,8-Enynes

Scheme 1 summarizes a range of observed reaction topologies for cycloisomerizations of 1,6-enynes (**I**). The diversity of cyclic structural motifs that can be efficiently accessed from a common enyne precursor is remarkable. The process can furnish the six-membered carbocyclic or heterocyclic products **II** and **III**. Alternatively, the cycloisomerization provides an efficient access to five-membered dienes or alkenes **IV**, **V** and **VI**. Highly strained bicyclo[3.2.0]alkenes **VII** and **VIII** can also be obtained as a result of this transformation. Incorporation of arene and alkene groups (R_1) at the terminal alkyne position provides access to bicyclic and tricyclic products **IX** as a result of a formal [4+2] cycloaddition. The substitution pattern of the starting enyne, as well as the nature of the catalyst, influences significantly the outcome of the cycloisomerization process.

2.1 Formation of 1-Alkenyl-1-cyclopentenes

During the period of 1985 to 1994, Trost and co-workers described a series of skeletal cycloisomerizations of 1,6-enynes employing a range of Pd complexes.[3]



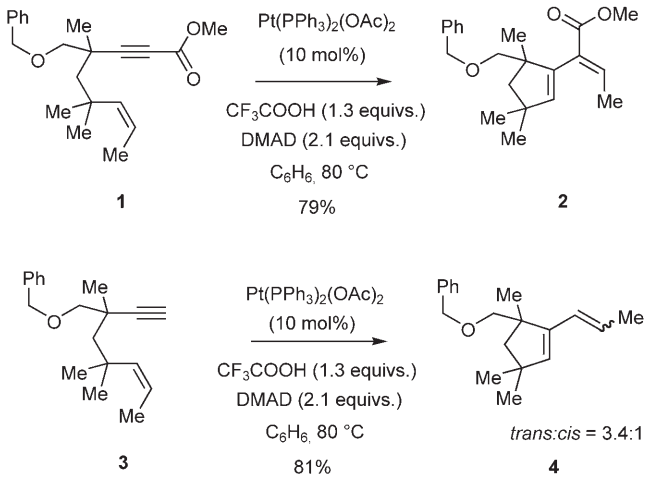
Scheme 1. Observed reaction topologies in cycloisomerizations of 1,6-enynes.

In the course of these studies, the authors reported that, in the presence of TFA and dimethyl acetylenedicarboxylate (DMAD), $(Ph_3P)_2Pt(OAc)_2$ catalyzed the cycloisomerization of enyne **1** to the corresponding diene **2**, which was isolated in 79% yield (Scheme 2).[4] Enyne **3** containing a terminal alkyne similarly afforded diene **4**, albeit as a 3.4:1 mixture of *trans/cis* alkene isomers. While the palladium-based catalysis was proposed to proceed *via* a formation of metallocyclopentene, followed by a β-hydride elimination, no mechanistic rational for the Pt-catalyzed process was proposed at the time.

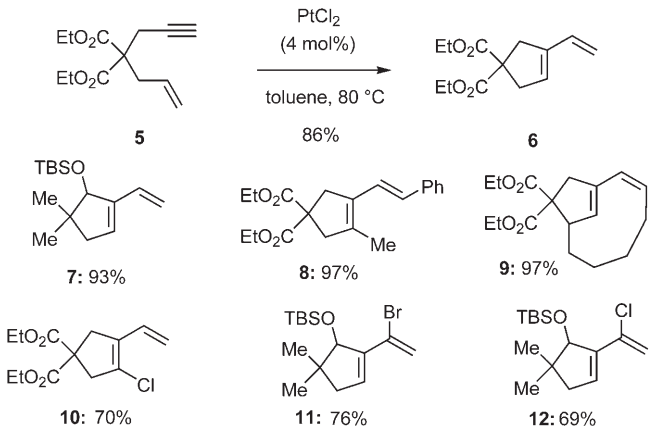
In 1994, Murai and co-workers reported their discovery of $[RuCl_2(CO)_3]_2$-catalyzed skeletal cycloisomerizations of 1,6-enynes to vinylcyclopentenes, which were proposed to proceed *via* the intermediacy of a polarized (η^2-alkyne)ruthenium alkyne complex.[5] Two years later, the same group reported that $PtCl_2$ efficiently catalyzed cycloisomerizations of 1,6- and 1,7-enynes to 1-vinylcycloalkenes (Scheme 3).[6]

In a typical experiment described in this report, treatment of enyne **5** with 4 mol% of $PtCl_2$ in toluene at 80 °C under a nitrogen atmosphere afforded the cyclorearranged product **6** in 86% yield. A representative scope of this process is depicted in Scheme 3. The reaction was broadly tolerant of mono-, di- and trisubstituted alkenes, as well as terminal, internal and electron-deficient alkynes. The authors noted that $PtCl_4$ catalyzed the reactions with comparable efficiency. However, a range of other Pt complexes, including $PtCl_2(COD)$ and $PtCl_2(PPh_3)_2$, were found to be ineffective, indicating that both the presence of the halide ions and the absence of other coordinating ligands was required for productive catalytic turnover.

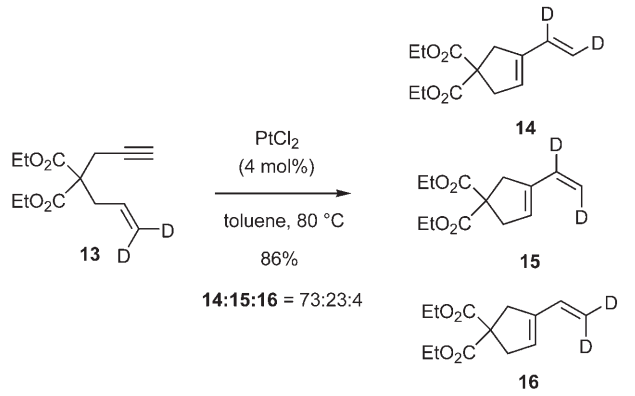
Cycloisomerization of double deuterium-labeled enyne **13** resulted in formation of three products **14**, **15**, and **16** in a 73:23:4 ratio (Scheme 4). While no catalytic mechanism was proposed, Murai and co-



Scheme 2. $(PPh_3)PtCl_2$-catalyzed cycloisomerizations of 1,6-enynes.



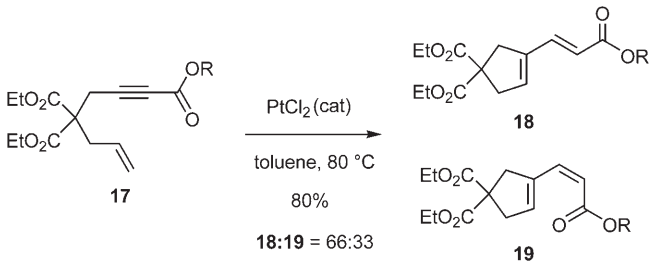
Scheme 3. $PtCl_2$-catalyzed cycloisomerization of 1,6-enynes **5**.



Scheme 4. Cycloisomerization of deuterium-labeled enyne **13**.

workers speculated that two catalytic cycles were operating competitively in this reaction.

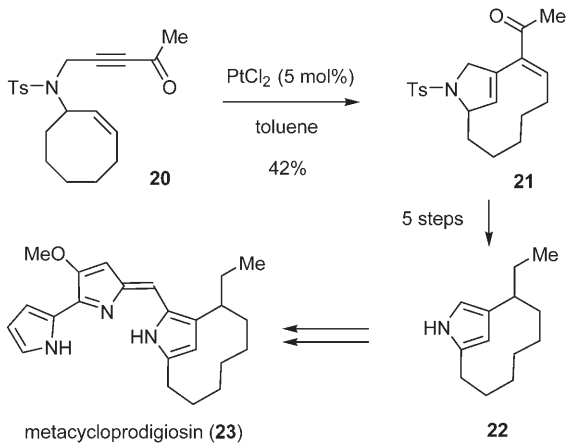
Another interesting and unusual result was obtained upon treatment of ester **17** with a catalytic amount of $PtCl_2$, which afforded a mixture of products **18** and **19**, having the ester group exclusively at the terminal position of the diene (Scheme 5).[6] This



Scheme 5. Cycloisomerization of enynoate **17**.

anomalous result of the skeletal reorganization corresponded to the formal insertion of the methylene group of the alkene between the two carbons of the alkynes. While no mechanistic rational was provided by Murai and co-workers at the time, the outcome of these experiments has been rationalized (see Scheme 14).

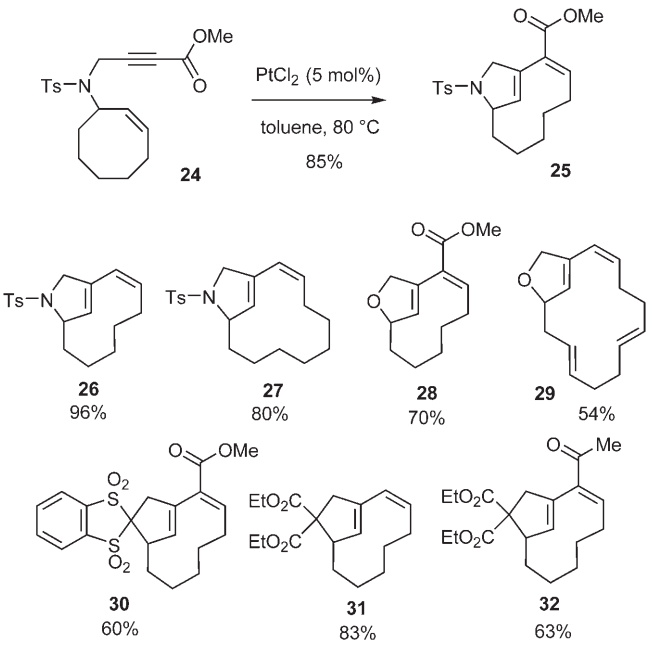
In 1998, Fürstner and co-workers were the first to recognize the utility of Pt-catalyzed enyne cycloisomerization for the assembly of the bicyclic ring systems of streptorubin B and metacycloprodigiosin, the two representative members of the prodiginine family of antibiotics.[7] Indeed, the authors found that a range of platinum salts readily promoted the cycloisomerization of sulfonamide **20** to give the ring-expanded diene **21** in 45–95% yields depending on the nature of the carbonyl group (Scheme 6). It is noteworthy that this ring expansion could also be promoted equally effectively by a range of other Lewis and



Scheme 6. Synthesis of metacycloprodigiosin intermediate **22**.

Brønsted acids, including BF_3, HBF_4, $SnCl_4$, and $ZnCl_2$. Conversion of dienone **21** to *m*-pyrrolophane **22** was accomplished in 5 steps. Since pyrrole **22** was previously converted to metacycloprodigiosin (**23**), construction of this intermediate represented a formal synthesis of the natural product. A similar sequence was utilized for the assembly of the advanced precursor *en route* to streptorubin B (not shown).

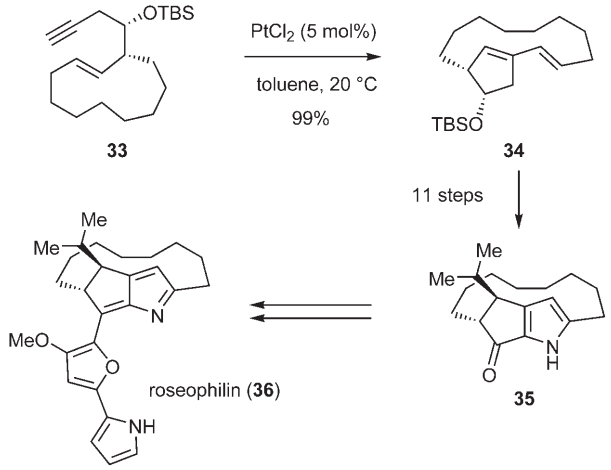
Fürstner and co-workers further explored the scope of this ring-expansion process.[8,9] The results are summarized in Scheme 7. In addition to the formation of 10-membered dienes **25, 26**, **28**, **31** and **32**, the cycloisomerization was suitable for production of bicyclic products containing 12-membered dienes and 14-membered tetraenes (**27** and **29**). A particular advant-



Scheme 7. Cycloisomerizations of cyclic enynes.

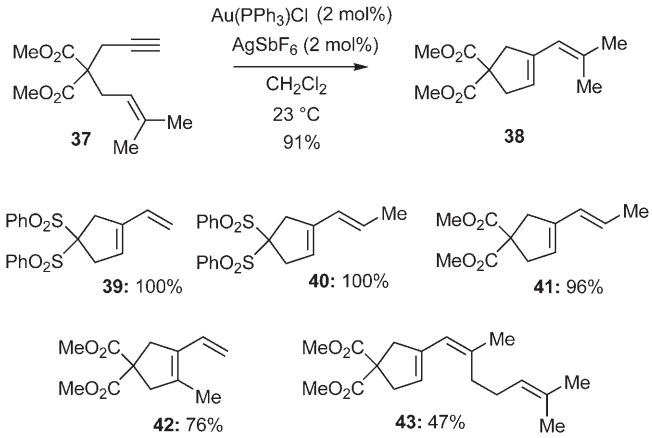
age of this process is the ability to rapidly access molecular complexity starting with enynes that can be assembled in a few steps starting from readily available building blocks.

The utility of the Pt-catalzyed enyne cycloisomerization for the construction of roseophilin, yet another member of prodiginine family of alkaloids, was independently recognized by Trost and Doherty, who reported in 2000 their approach to this intricate natural product.[10] The critical step in the synthesis entailed the conversion of enyne **33** to bicyclic diene **34**. While Pd catalysis was found to be ineffective, the authors reported that the use of the Pt-based catalytic system developed by Murai enabled this transformation, which proceeded in essentially quantitative yield. Diene **34** was converted to tricyclic pyrrole intermediate **35** in an 11-step sequence. Since **35** was previously converted to roseophilin (**36**), this represented a formal synthesis of this alkaloid (Scheme 8).



Scheme 8. Synthesis of roseophilin intermediate **35**.

In 2004, Echavarren and co-workers published a seminal study which demonstrated that Au-based catalysts were very effective for accomplishing a series of 1,6-enyne cycloisomerizations (Scheme 9).[11a] One of the reaction pathways reported by the authors was similar to that observed for Pt-based catalysts discussed above. The catalyst was generated by treatment of $Au(PPh_3)Cl$ with $AgSbF_6$, which resulted in precipitation of AgCl and formation of highly reactive cationic $Au(PPh_3)^+$. In the presence of 2 mol% of this complex, enyne **37** was converted to diene **38** in 91% yield. Notably, the reaction proceeded at room temperature, indicating a significantly more reactive nature of the Au-based catalyst compared to the Pt counterpart. This process was successfully employed for conversion of a range of 1,6-enynes to the corresponding dienes shown in Scheme 9. Subsequently,

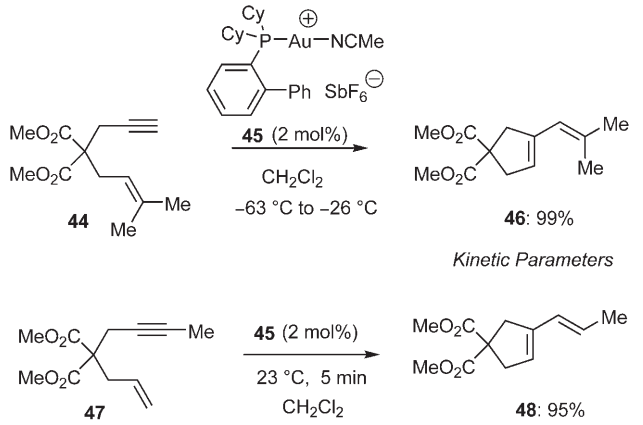


Scheme 9. Au-catalyzed cycloisomerizations of 1,6-enynes.

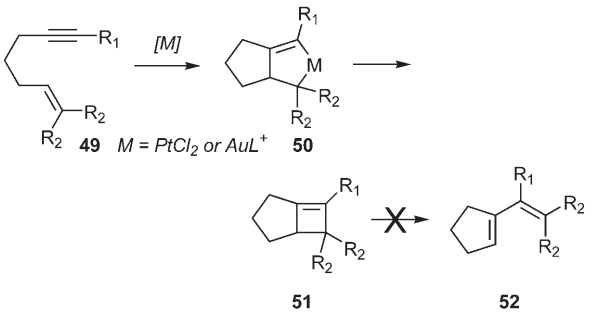
$Au(PPh_3)NTf_2$ was also found to be effective in catalyzing the same transformation.[12]

Further studies by Echavarren and co-workers revealed that, depending on the structure of the enyne, two alternative cycloisomerization pathways could be observed.[13] This finding was in agreement with the earlier results obtained by Murai for the Pt-catalyzed cycloisomerizations. Treatment of enyne **44**, containing a trisubstituted alkene and a terminal alkyne, with cationic gold complex **45** afforded diene **46**. On the other hand, subjection of enyne **47**, armed with a terminal alkene and an internal alkyne, to the same catalyst afforded diene **48**, which corresponded to the formal insertion of the methylene carbon of the alkene between the two carbons of the alkyne (Scheme 10). It is noteworthy that the replacement of PPh_3 with bulkier phosphine ligands resulted in enhancement of catalytic activity of the resulting gold complexes.

While the mechanism shown in Scheme 11 could explain the formation of the observed alkenylcyclopentene **52**, this reaction pathway seems to be highly

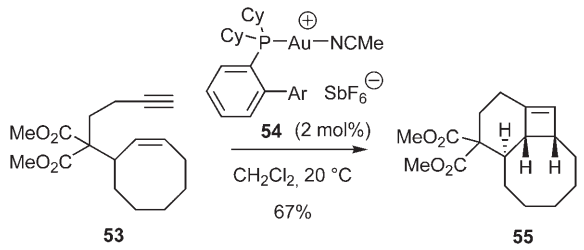


Scheme 10. Cycloisomerizations of enynes **44** and **47** using cationic gold complex **45**.



Scheme 11. A plausible, albeit unlikely, mechanism for the 1,5-enyne cycloisomerization to alkenylcyclopentenes.

unlikely based on several lines of evidence. First, this mechanism does not explain the observed deuterium scrambling in Murai's labeling experiment shown in Scheme 4. Second, the activation parameters for the cycloisomerization of enyne **44** (Scheme 10), which were determined by Echavarren and co-workers, are $\Delta G^{\ddagger}_{298} = 21.7\ \text{kcal mol}^{-1}$, $\Delta H^{\ddagger}_{298} = 3.7\ \text{kcal mol}^{-1}$ and $\Delta S^{\ddagger} = -60.6\ \text{cal K}^{-1}\text{mol}^{-1}$.[13] This entropy of activation suggests that an associative ligand substitution maybe the rate-determining step. Furthermore, the low activation energy of the process is inconsistent with the expected activation energy for the ring-opening of bicycle **51** (Scheme 11), for which an activation energy of *ca.* 30 kcal mol^{-1} is expected. Finally, Echavarren and co-workers demonstrated that cyclobutene **55** (Scheme 12), which was efficiently prepared from enyne **53** using Au catalyst **54**, was thermally stable at 120–150 °C.[13]



Scheme 12. Assembly of tricyclic cyclobutene **55**.

The bonding in late transition metal complexes with alkynes and olefins is described by a combination of the interaction of the occupied ligand π-orbtal to the metal vacant "*dsp*", and donation of metal "*d*" electrons to olefin or acetylene empty π*. $PtCl_2$ and $AuCl_3$ are isoelectronic and form mostly square planar complexes with alkynes, but Au(I) complexes are predominantly linear. The coordination of alkynes to Pt/Au metal centers is the initial step during cycloisomerization and the exceptional activation of the C-C triple bond by these metal complexes/salts are the key for the subsequent reactivity manifestations. Although in theory alkynes can serve as 4e donors and supply both π electron pairs for coordination, this phenomenon mainly involves early transition metals such as Mo and W.[14] The efficient activation of alkynes by Pt(II) and Au(I/III) toward nucleophilic attacks can be rationalized by a simplified molecular orbital treatment of metal alkyne complexes according to Maitlis's model.[15] Due to the relativistic effects,[16] Au is the most electronegative metal on Pauling's scale with a value of 2.54, and Pt has a value of 2.28.[17] Consequently, the energies of the valence shell *dsp* orbitals of Pt(II) and Au(I)/Au(III) are lower than alkyne π-bonding orbitals (Figure 1), and

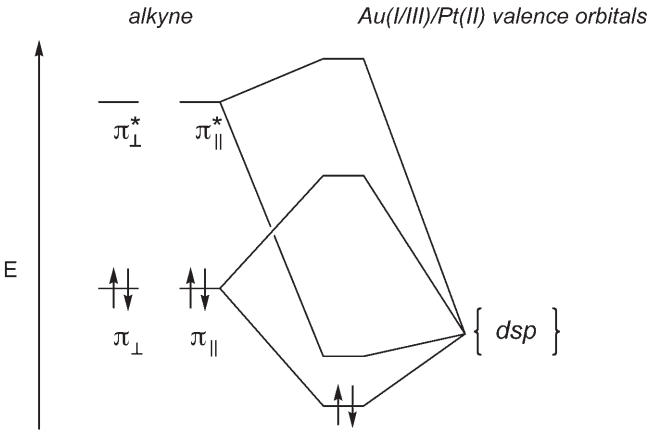
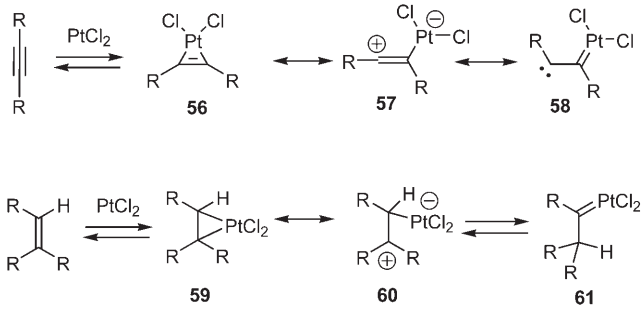


Figure 1. Bonding in Au(I/III)/Pt(II) alkyne complexes.

the bonding molecular orbitals formed from alkyne π and metal orbitals will have mostly metal characters and conversely, the corresponding antibonding orbital will be predominantly of alkyne character. As a result, the pair of π electrons is effectively transferred to the metal center. Moreover, the orbital interaction between π* and metal valence orbitals should be weak due to the large energy gap, and so is the π-back-donating from the metal to the alkyne.[18] Consequently, the coordinated C-C triple bond becomes electron-deficient and susceptible to nucleophilic attacks.

Zwitterionic complexes **57** and **60** represent resonance structures of **56** and **59**, respectively. Another important resonance structure of the Pt alkyne complex is the carbene **58**, which is implicated in cyclopropanation reactions that will be discussed below. Examination of Pt complex **60** reveals that the [1,2] hydride shift would produce the corresponding Pt carbene **61**. Applying the principle of microscopic reversibility, a frequently observed conversion of alkenes from Pt carbene **61**, can be seen as a [1,2] hydride shift, followed by elimination of $PtCl_2$ from intermediate **60**. Similar behavior can be expected upon



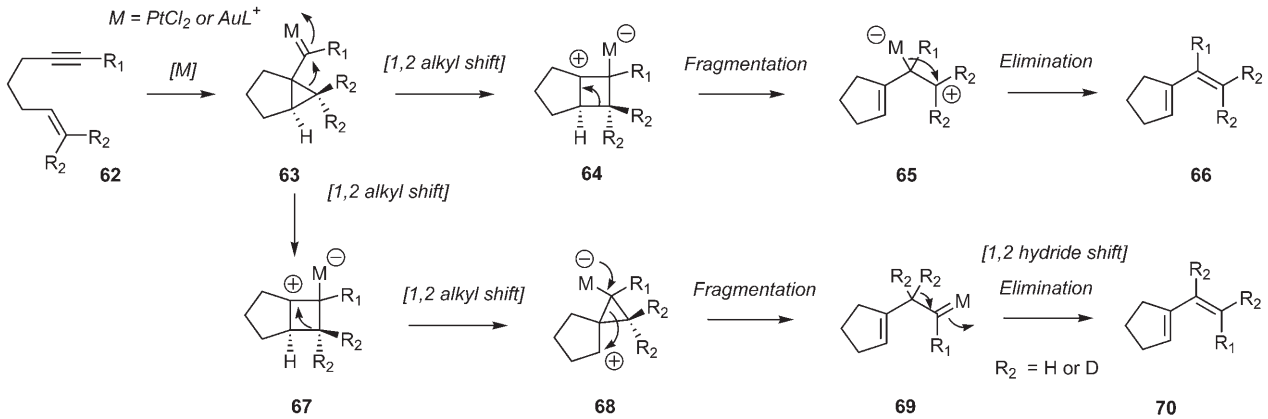
Scheme 13. Complexation of $PtCl_2$ with alkynes and alkenes.

complexation of Au complexes with alkynes and alkenes.

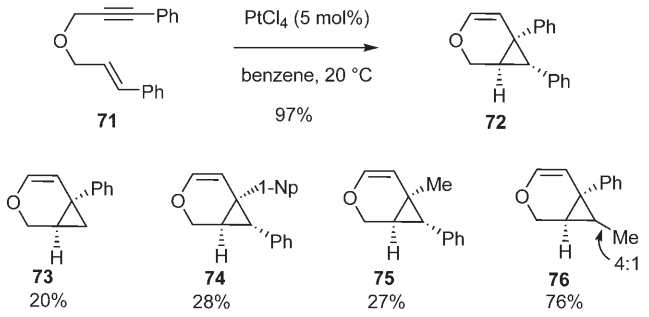
A mechanistic analysis of Pt or Au-catalyzed cycloisomerization of 1,6-enyne **62** to alkenyl cyclopentenes **66** or **70** is presented in Scheme 14. The process begins by chemoselective metal complexation to the alkyne, followed by cyclopropanation of the proximate alkene to produce cyclopropyl metal carbene **63**. This initial step can be explained by invoking the resonance contribution of carbene **58** (Scheme 13), which results in direct alkyne cyclopropanation. Alternatively, the cyclopropanation can be envisioned to occur step-wise *via* initial reaction of alkene with alkenyl cation **57** (Scheme 13), followed by nucleophilic interception of the resulting carbocation by alkenyl platinum. DFT calculations, which were carried out by Echavarren and co-workers,[11] suggested that in the case of Au(I) catalysis cyclopropanation proceeds directly *via* a single transition state located on the potential energy surface. In the absence of external nucleophile, highly electron deficient carbene **63** can undergo [1,2] alkyl shift to give zwitterion **64**. Depending on the nature of the R_2 alkene substitution, complex **64** can undergo either a fragmentation to give cyclopentene **65** or another [1,2] shift to produce spirocycle **68**. Subsequent fragmentation of **68** affords carbene **69**. Elimination of the metal fragment from **65** and **69** gives the two alternative diene products **66** and **70**, respectively. The mechanism in Scheme 14 is presented to proceed in a step-wise manner, primarily in order to provide the reader with a detailed mechanistic analysis of bond-breaking and bond-forming steps. DFT calculations indicated, however, that conversions of carbene **63** to complexes **65** and **69** were direct processes.[13] In the absence of the information on the kinetic isotope effects in these reactions, it is difficult to make an unambiguous mechanistic rational. The two pathways depicted in Scheme 14 explain the formation of two observed products. Indeed, in the case of trisubstituted alkene **62** (R_2=Me, Scheme 14), the carbocation **65** will be stablizied by the two adjacent methyl groups. This effect is expected to favor the formation of the product of type **66**. In the case of monosubstituted alkenes (R_2=H), formation of primary carbocation **65** will be disfavored thus derailing the reaction to proceed *via* an alternative formation of carbene **69**, followed by [1,2] hydride shift and elimination to give diene **70**. This mechanism explains the results of the deuterium labeling experiment conducted by Murai (Scheme 4).

2.2 Formation of Bicyclo[4.1.0]heptenes

In 1995, Blum and co-workers reported that treatment of enyne **71** with 5 mol% of $PtCl_4$ resulted in the formation of oxabicyclo[4.1.0]heptene **72** in 97% yield (Scheme 15).[19] The product was obtained as a single diastereomer. The structure and relative stereochemistry were confirmed by X-ray crystallography of the naphthyl-substituted cycloisomerization product **74**. The relative stereochemistry corresponded to a stereospecific cyclopropanation of *E*-alkene. Indeed, subjection of a 4:1 mixture of *E*:*Z*-alkene isomers to the same reaction protocol afforded the corresponding 4:1 mixture of cyclopropanes **76**. No mechanistic rationale for this process was provided at the time.

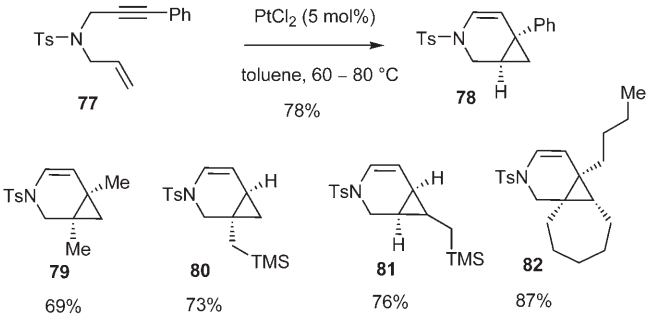


Scheme 14. Proposed mechanisms for cycloisomerizations of 1,6-enynes to dienes **66** and **70**.



Scheme 15. Pt-catalyzed cycloisomerization of 1,6-enynes to oxabicyclo[4.1.0]heptenes.

Aiming at increasing the efficiency of this process, Fürstner and co-workers examined a series of enyne-containing sulfonamides. They found that treatment of these substrates with a catalytic amount of $PtCl_2$ at elevated temperature (60–80 °C in toluene) resulted in the assembly of the corresponding azabicyclo-[4.1.0]heptenes (Scheme 16).[8,9] Mono-, di-, and tri-substituted alkenes efficiently participated in this process.

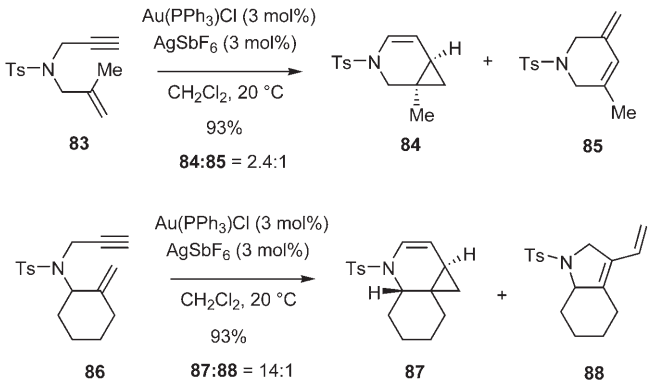


Scheme 16. Pt-catalyzed cycloisomerization of 1,6-enynes to azabicyclo[4.1.0]heptenes.

In 2004, Echavarren and co-workers described two examples of the gold-catalyzed assembly of azabicyclo[4.1.0]heptenes **83** and **86** (Scheme 17).[11a] While the corresponding dienes **85** and **88** were obtained as by-products, the mild reaction conditions (20 °C in CH_2Cl_2) and excellent efficiency of these reactions are highly noteworthy. The same group also reported an interesting example of Pt-catalyzed formation of tricyclic oxabicyclo[4.1.0]heptenes.[11b]

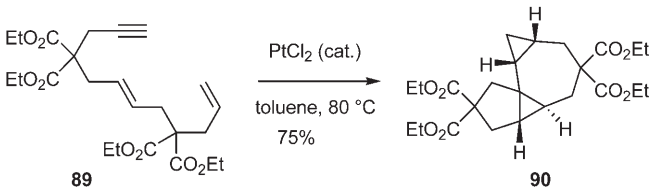
In 2005, Marco-Contelles and co-workers reported the $PtCl_2$-catalyzed assembly of highly functionalized bicyclo[4.1.0]heptene enol esters from 1,5-enynes containing the propargylic carboxylate moiety. This group subsequently reported a series of theoretical studies of the reaction mechanism.[20]

In 1998, Murai and co-workers reported the first example of the tandem cyclopropanation of dienyne **89**.[21] Subjection of **89** to a catalytic amount of $PtCl_2$



Scheme 17. Au-catalyzed cycloisomerization of 1,6-enynes to azabicyclo[4.1.0]heptenes.

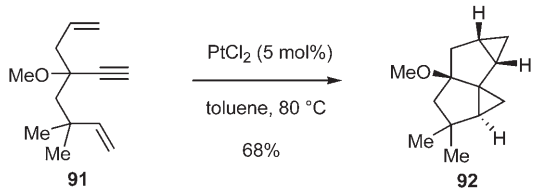
at 80 °C afforded tetracycle **90** in 75% yield (Scheme 18). Remarkably, the formation of four C–C bonds occurred with complete diastereoselectivity.



Scheme 18. Pt-catalyzed tandem bis-cyclopropanation of dienyne **89**.

The authors found that this interesting transformation could also be catalyzed by a series of other metal complexes, including $[RuCl_2(CO)_3]_2$, $[Rh(OOCCF_3)_2]_2$, $[IrCl(CO)_3]_n$, and $ReCl(CO)_5$. This example illustrates the power of cycloisomerization processes to provide a rapid access to molecular complexity starting from readily accessible acyclic building blocks.

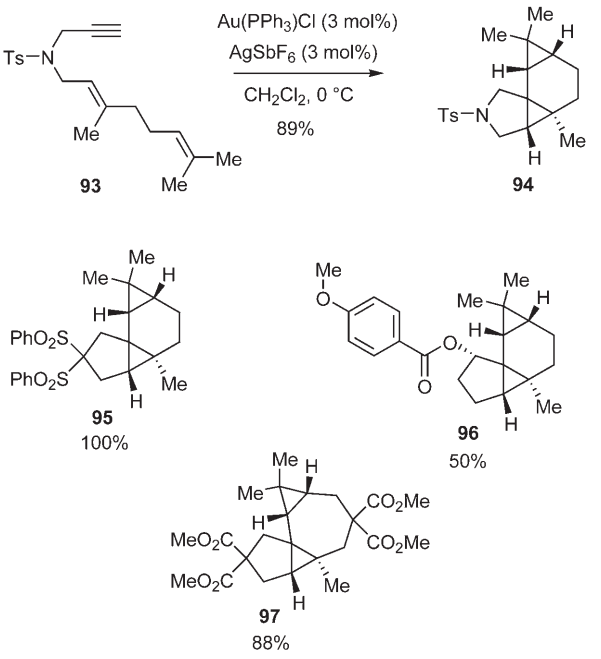
Malacria and co-workers described another example of the Pt-catalyzed tandem cyclopropanation of dienyne **91**.[22] Interestingly, since the two alkenes were attached at the 3-postion of the terminal alkyne, this process afforded a different polycyclic product, tetracyclo[4.4.0.$0^{1,3}$.$0^{8,10}$]decane **92** (Scheme 19). The



Scheme 19. Pt-catalyzed tandem bis-cyclopropanation of dienyne **91**.

structure and stereochemistry of the product analogous to **92** were established by X-ray crystallography.

Echavarren and co-workers reported that cationic gold(I) complexes also promoted tandem intramolecular bis-cyclopropanations. Once again, compared to the use of $PtCl_2$, the Au-catalyzed transformations proceeded under milder conditions and with excellent efficiency. Representative scope of this study is summarized in Scheme 20. Treatment of dienyne **93** with 3 mol% of $Au(PPh)_3^+$ afforded tetracycle **94** in 89% yield as a single diastereomer. Polycyclic products **95–97** were obtained from the corresponding dienynes with comparably high efficiency and diastereoselectivity.

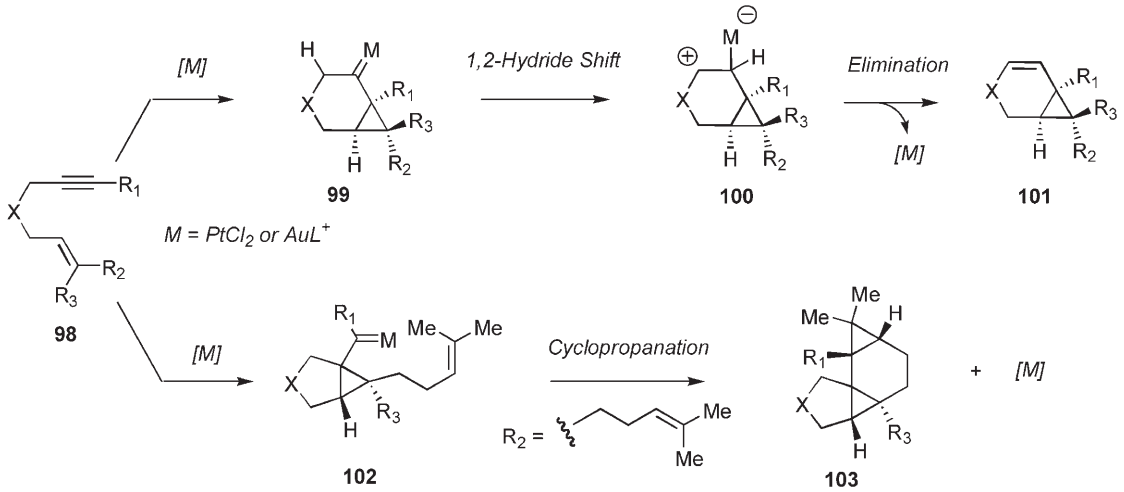


Scheme 20. Au-catalyzed tandem bis-cyclopropanation of dienynes.

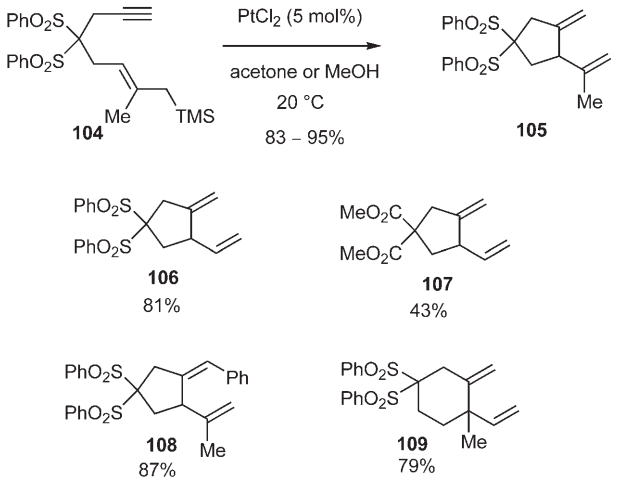
A detailed mechanistic analysis of the cyclopropanation reactions is presented in Scheme 21. The first steps entail a metal-based alkyne activation, which is followed by intramolecular cyclopropanation. Two alternative metal carbenes **99** and **102** can be produced, which correspond to the cyclopropanation at either one of the two carbons of the alkyne. Carbene **99** is expected to undergo facile [1,2] hydride shift, followed by elimination of the metal fragment to produce [4.1.0]bicycloheptene. Importantly, the presence of a heteroatom in the tether (X = O or NR) is expected to favor this process due to the stabilization of an intermediate cation **100** by the heteroatom lone pair. Carbene **102**, on the other hand is poised for a second intramolecular cyclopropanation to give tetracycle **103** and regeneration of the metal catalyst, which enters the next catalytic cycle.

2.3 Formation of Alkyl- and Alkenylmethylenecyclopentanes and Cyclohexanes

In 2000, Echavarren and co-workers reported that a range of transition metal complexes catalyzed the cyclizations of enynes, containing allylsilanes or allylstannanes.[24] In a typical experiment, allylsilane **104** was treated at ambient temperature with 5 mol% of $PtCl_2$ in either acetone or methanol to give diene **105** in 83% yield. Cyclizations of disubstituted alkynes afforded exclusively the corresponding *Z*-alkenes (i.e., **108**, Scheme 22). In addition to 1,6-enynes, the authors reported two examples of successful transformations of 1,7-enynes to give the expected six-membered cyclization products (i.e., **109**, Scheme 22).

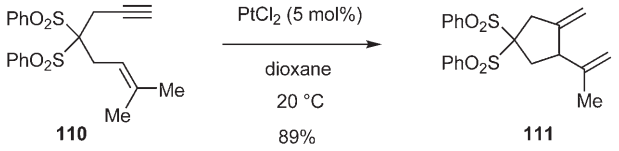


Scheme 21. Proposed mechanism of Pt- and Au-catalyzed intramolecular cyclopropanations of 1,6-enynes.



Scheme 22. Pt-catalyzed cyclizations of allylsilanes with alkynes.

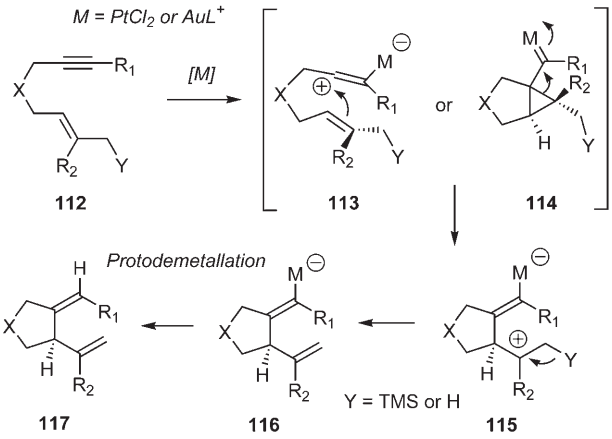
In addition to allylsilanes and allylstannanes, Echavarren and co-workers later reported that enynes containing trisubstituted alkenes also underwent similar cyclizations.[25] Subjection of enyne **110** to 5 mol% of $PtCl_2$ in dioxane at 70°C afforded diene **111** in 89% yield (Scheme 23). Several additional successful examples were also described. The use of $RuCl_3$ enabled cyclizations of disubstituted alkenes, while the $PtCl_2$-catalyzed reactions were limited to the trisubstituted alkenes.



Scheme 23. Pt-catalyzed cyclizations of 1,6-enynes.

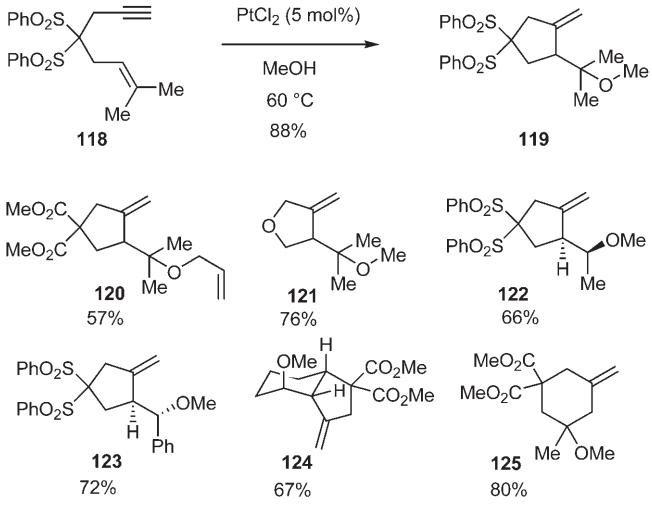
The mechanism of metal-catalyzed carbocyclizations of 1,6-enynes is shown in Scheme 24. The reaction can be viewed to proceed *via* a concerted process involving alkyne activation and addition of the alkene to generate carbocationic intermediate **115**. Alternatively, the cyclization may proceed *via* a stepwise mode involving initial generation of highly electrophilic cyclopropyl carbene **114**, which undergoes ring opening by the proximate alkene to generate the same intermediate **115**. Elimination of either silyl cation (Y = TMS) or a proton (Y = H) affords alkenyl metal complex **116**. Subsequent protodemetallation takes place to give the observed diene **117**, regenerating the active catalyst.

The above mechanism suggests that the carbocation **115** can be intercepted in the presence of an external nucleophile, which would enable generation of addi-



Scheme 24. Mechanism of Pt-catalyzed cyclizations of 1,6-enynes.

tional complexity in the reaction product. Indeed, following their initial report on cyclizations of allylsilanes and stannanes, Echavarren and co-workers described a series of alkoxy- and hydroxycarbocyclization reactions of 1,6-enynes using a catalytic amount of $PtCl_2$ (Scheme 25).[26] A range of disubstituted and

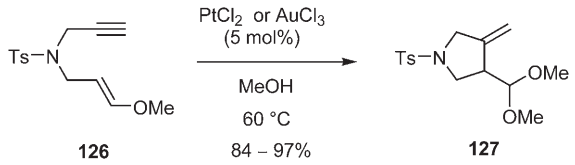


Scheme 25. Pt-catalyzed alkoxycarbocyclizations of 1,6-enynes.

trisubstituted alkenes successfully participated in this process. In the case of disubstituted alkenes, the reaction was stereospecific to the starting alkene geometry producing single diastereomers of the cyclized products, which resulted from *anti*-addition of alkyne and alcohol to the alkene moiety. In two cases, the formation of six-membered cyclization products was reported (**124** and **125**, Scheme 25).

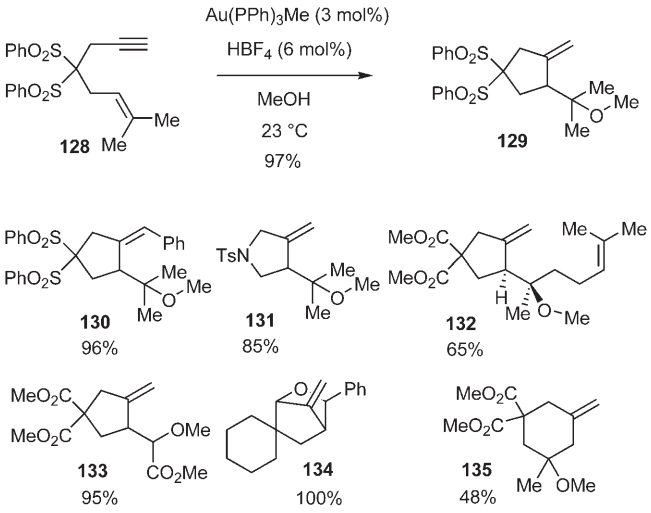
Subsequently to the initial report of Pt-catalyzed alkoxycarbocyclizations, the scope of this process was further expanded to include a range of enol ethers.[27]

For example, treatment of enyne **126**, containing a methyl enol ether, with $PtCl_2$ or with $AuCl_3$ in MeOH at 60 °C afforded dimethyl acetal **127** with excellent efficiency (Scheme 26). A series of other enol ethers successfully participated in this reaction as well.



Scheme 26. Pt-catalyzed alkoxycarbocyclizations of enol ethers with alkynes.

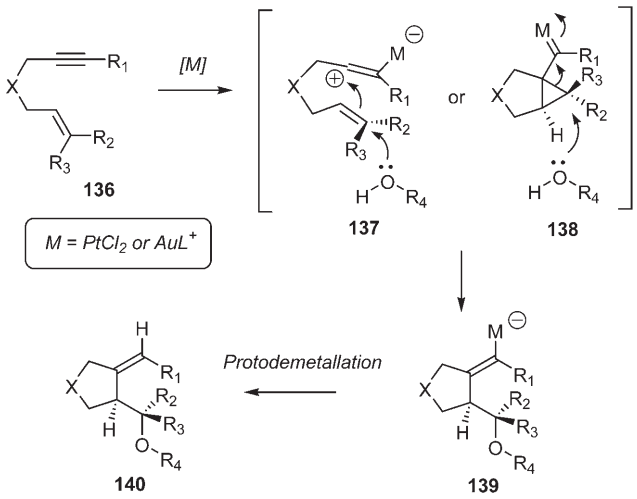
In 2004, as a part of their comprehensive study of gold-based catalysis of enyne cycloisomerizations, Echavarren and co-workers reported that cationic gold complexes were exceedingly effective in promoting alkoxycarbocyclizations of a wide range of 1,6-enynes.[11,28] A representative scope of this process, as well as the typical reaction conditions, is shown in Scheme 27.



Scheme 27. Au-catalyzed alkoxycarbocyclizations of 1,6-enynes.

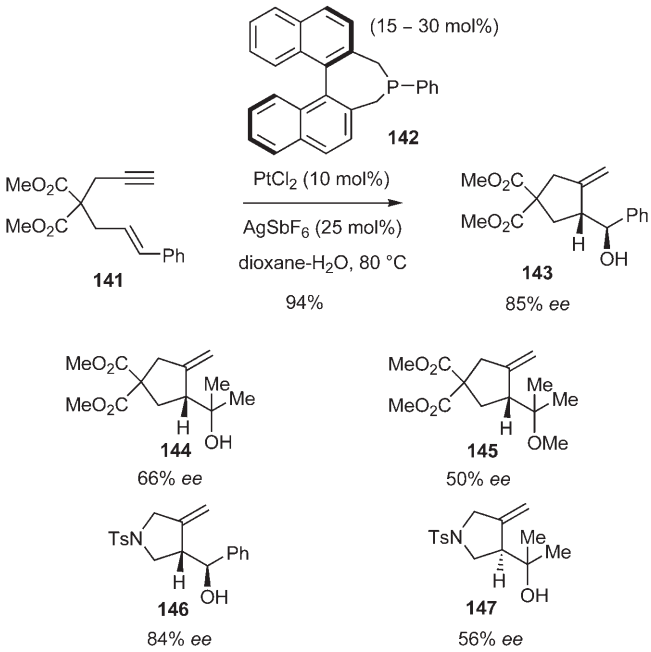
The mechanism of alkoxycarbocyclizations can be depicted to proceed in a highly concerted manner involving simultaneous attack of the activated alkyne by the alkene with a concomitant addition of the alcohol nucleophile. Alternatively, the process may involve a stepwise formation and opening of cyclopropane intermediate **138**. The final step involves protodemetallation of an alkenyl metal complex **139** (Scheme 28).

In 2004, Genet and co-workers reported the results of their studies on the ability of chiral phosphines to



Scheme 28. Mechanism of Au- and Pt-catalyzed alkoxycarbocyclizations of 1,6-enynes.

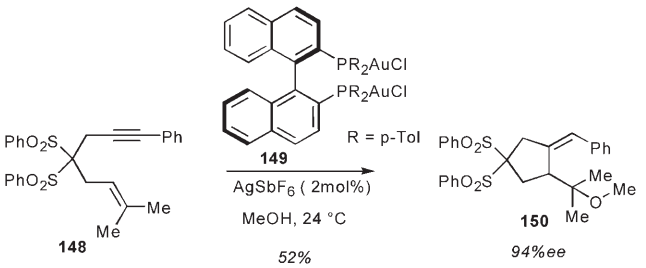
induce asymmetry in the Pt-catalyzed alkoxycarbocyclizations (Scheme 29).[29] The authors utilized Pt-based complexes obtained from a range of chiral phosphines. Interestingly, monodentate Ph-BINEPINE (**142**) produced the best results (up to 85 % *ee*), which are summarized in Scheme 29.



Scheme 29. Enantioselective Pt-catalyzed alkoxycarbocyclizations of 1,6-enynes.

In 2005, Echavarren and co-workers reported the results of their studies aimed at the development of catalytic enantioselective alkoxycarbocyclizations.[30] While the cyclization products were produced gener-

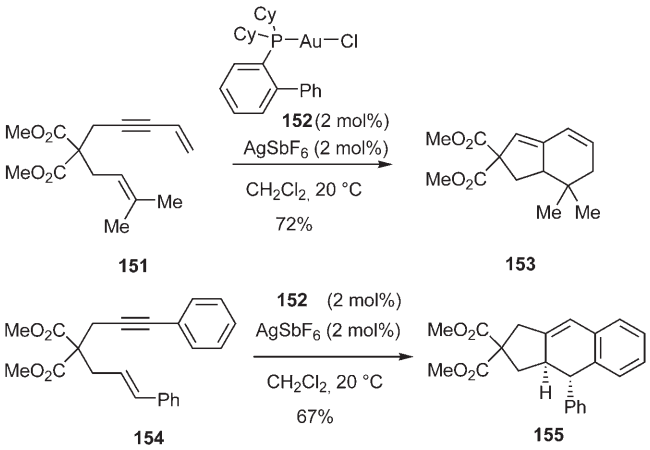
ally with only moderate enantioselectivity, one of the examples is highly noteworthy. Treatment of enyne **148** with a gold complex **149** produced by complexation of 2 equivalents of AuCl to BINAP afforded the expected cyclization product **150** in 94% *ee* (Scheme 30). This example demonstrated the ability to effectively differentiate enantiotopic faces of prochiral alkene by a distant phosphine ligand.



Scheme 30. Enantioselective Au-catalyzed alkoxycarbocyclizations of 1,6-enynes.

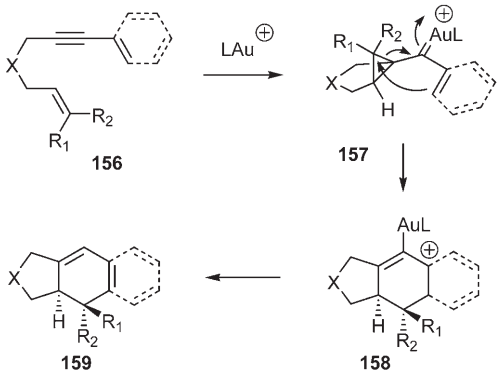
2.4 Intramolecular [4+2] Cycloadditions of Alkenes with Enynes and Arylalkynes

In 2005, Echavarren and co-workers described the synthesis of a series of new gold(I) complexes armed with bulky, biphenyl-based phosphines, i.e., **152** (Scheme 31).[31] The authors found that these complexes, upon activation with $AgSbF_6$, displayed enhanced catalytic activity and were able to promote a novel process, which corresponded to a formal intramolecular [4+2] cycloaddition of alkenes with enynes or aryl alkynes. Two representative examples are shown in Scheme 31. Treatment of dienyne **151** with 2 mol% of complex **152** and 2 mol% of $AgSbF_6$ resulted in efficient assembly of bicyclic diene **153**. Subjection of enyne **154** to the same conditions afforded tricyclic product **155** as a single diastereomer, corresponding to the *syn* addition of arylalkyne to the olefin.



Scheme 31. Au-catalyzed intramolecular [4+2] cycloadditions.

The initial stage of the intramolecular [4+2] cycloadditions is similar to other catalytic processes discussed above. It entails alkyne activation by Au(I), followed by intramolecular olefin cyclopropanation. The cyclopropane is poised for intramolecular ring-opening by the proximate alkene or arene in the process, which is analogous to the cationic Nazarov cyclization. The cyclization is followed by the loss of a proton, which in turn initiates the protodemetallation step concluding the catalytic cycle (Scheme 32).

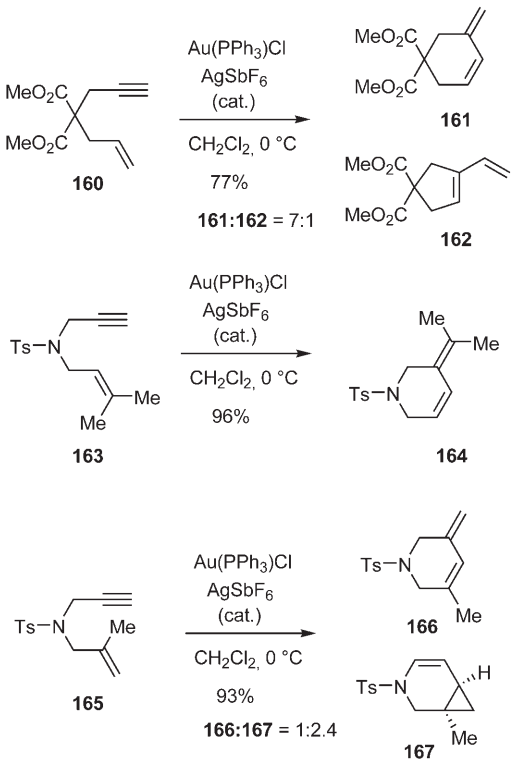


Scheme 32. Mechanism of Au-catalyzed intramolecular [4+2] cycloadditions.

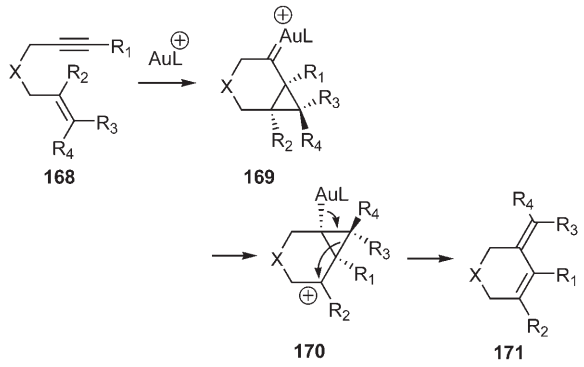
2.5 Conversion of 1,6-Enynes to Methylenecyclohexenes

Echavarren and co-workers observed that treatment of enyne **160** with the cationic $(PPh_3)Au(I)$ catalyst resulted in the formation of two diene-containing products **161** and **162** (Scheme 33).[11,28] The minor product **162** corresponded to the expected cycloisomerization process, which was discussed above. The major product, however, was determined to be methylenecyclohexene **161**, corresponding to a new reaction manifold. Treatment of enyne **163**, containing a trisubstituted alkene, resulted in the exclusive formation of **164**. In the case of disubstituted alkene **165**, a 1:2.4 mixture of diene **166** and cyclopropane **167** was obtained. These results indicated that the substitution of the 1,6-enyne greatly influenced the outcome of the cycloisomerization.

A possible mechanistic explanation of the conversion of 1,6-enynes to methylenecyclohexenes is presented in Scheme 34. Initial cyclopropanation gives the highly electrophilic carbene **169**. Subsequent rearrangement of **169** affords the cationic intermediate **170**. This process could occur as a series of two con-



Scheme 33. Au-catalyzed formation of methylenecyclohexenes.

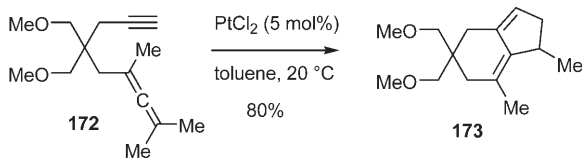


Scheme 34. Mechanism of Au-catalyzed formation of methylenecyclohexenes.

secutive [1,2] alkyl shifts or as single [1,3] alkyl shift,[11] which is much less precedented. Fragmentation of the C–C bond of the cyclopropane with concomitant elimination of the cationic [AuL] fragment produces the observed methylenecyclohexene **171**.

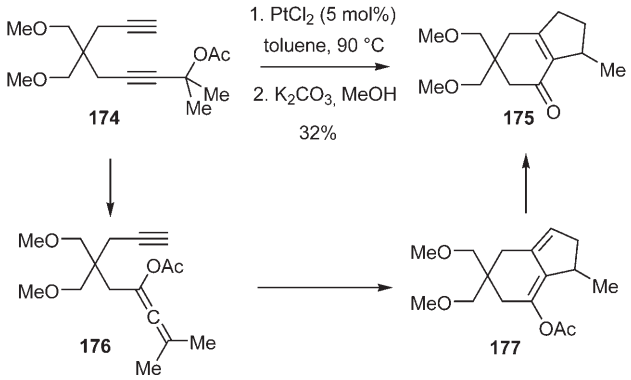
2.6 Conversion of Allenynes to Bicyclo[4.3.0]nonadienes

In 2004, Malacria and co-workers reported that the replacement of an alkene moiety in 1,6-enynes with an allene dramatically changes the outcome of the cycloisomerization process.[32a] Indeed, treatment of allenyne **172** with 5 mol% of $PtCl_2$ in toluene at 20 °C afforded a bicyclic diene **173** in 80% isolated yield (Scheme 35).



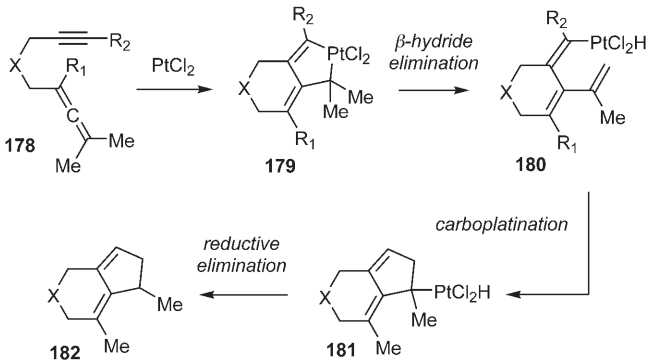
Scheme 35. Pt-catalyzed cycloisomerization of allenyne **172**.

Another interesting version of this double cyclization is shown in Scheme 36. This reaction entails the initial generation of acyloxyallene *via* an *in situ* isomerization of propargyl acetate **174**. Subsequent $PtCl_2$-catalyzed cycloisomerization converts allene **176** to bicyclic enol acetate **177**, which produces the enone upon basic hydrolysis. While the efficiency of the overall process is moderate, this result is significant taking into account the number of individual transformations that occur *en route* to **175**.

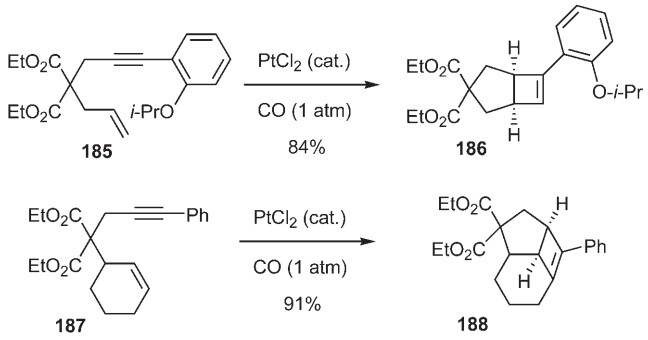


Scheme 36. Pt-catalyzed cycloisomerization of diyne **174**.

Malacria and co-workers proposed that allenyne cycloisomerization proceeds *via* a series of steps depicted in Scheme 37. The initial step is suggested to entail the formation of platinacyclopentene **179** which, upon β-hydride elimination, is converted to platinum hydride **180**. Intramolecular carboplatination is expected to produce alkyl platinum complex **181**. Final reductive elimination affords the observed bicyclic diene **182** and regenerates the $PtCl_2$ catalyst. This proposed



Scheme 37. Mechanism of Pt-catalyzed cycloisomerization of allenynes.

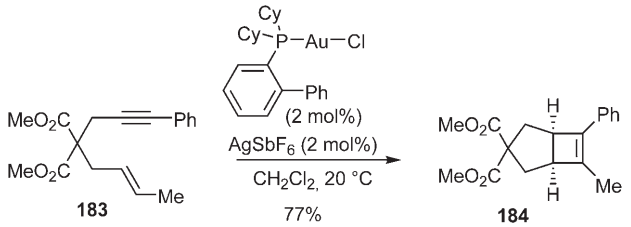


Scheme 39. Pt-catalyzed cycloisomerization of enynes to cyclobutenes.

mechanism was consistent with the results of the deuterium labeling experiment.

2.7 Formation of Bicyclo[3.2.0]heptenes

In the course of their studies on Au-catalyzed [4+2] cycloadditions, Echavarren and co-workers found that treatment of enyne **183** with a phosphine gold complex in the presence of $AgSbF_6$ afforded cyclobutene

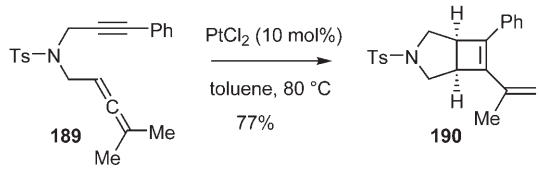


Scheme 38. Au-catalyzed cycloisomerization of enyne **183** to cyclobutene **184**.

184 (Scheme 38).[31] The change in the outcome of the reaction was attributed to the lack of stabilization of the developing positive charge by the methyl group of the alkene. Indeed, an enyne containing a terminal alkene produced the corresponding cyclobutene in 57% yield. It is noteworthy that related cyclobutenes have been obtained previously by Trost and co-workers using Pd-based catalysis. Another interesting example of Pt-catalyzed formation of cyclobutenes was described by Malacria in 2004.[32b]

Fürstner and co-workers independently described the formation of cyclobutenes *via* Pt-catalyzed cycloisomerizations of 1,6-enynes.[33] Similar to Echavarren's observation, these bicyclic products were obtained from enynes containing terminal alkenes and 1,2-dialkyl-substituted alkenes. Two representative examples are depicted in Scheme 39. The authors reported that the presence of CO had a significant effect on increasing the reaction rates of production of cyclobutenes while decreasing the rate of competing formation of alkenylcyclopentenes.

Murakami and co-workers reported that treatment of allenyne **189** with 10 mol% of $PtCl_2$ in toluene at 80 °C resulted in formation of cyclobutene **190** (Scheme 40).[34] This result is quite unusual in light of

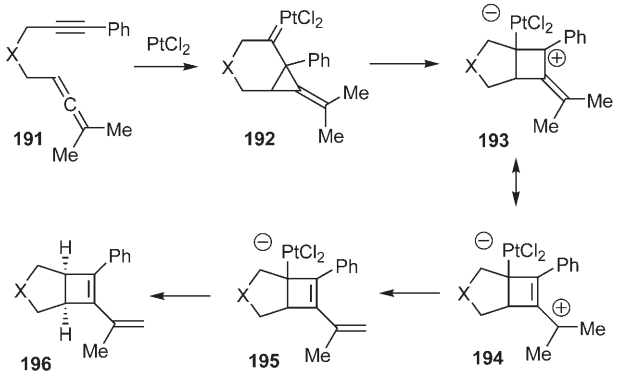


Scheme 40. Pt-catalyzed cycloisomerization of allenyne to cyclobutene.

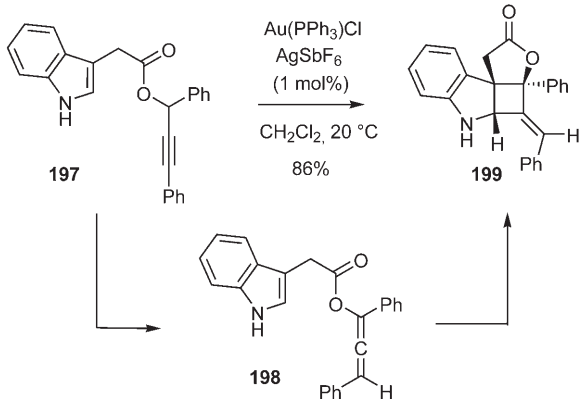
Malacria's earlier report on the formation of bicyclo[4.3.0]nonadienes from structurally similar enynes. In addition to the use of a sulfonamide tether, the allenynes utilized in Murakami's study contained exclusively bis-substituted alkynes while those employed by Malacria and co-workers were terminal alkynes. Indeed, the Murakami group noted that the use of an allenyne containing a terminal alkyne or an all-carbon tether produced complex mixtures of products.

Scheme 41 shows the proposed mechanism of cyclobutene formation in the case of Pt-catalyzed cycloisomerization of allenynes.[34] The process begins, as in many other reactions described above, with intramolecular cyclopropanation to give platinum carbene **192**. Subsequent [1,2] alkyl shift produces a zwitterionic intermediate, which is depicted in two resonance forms **193** and **194**. Elimination of a proton, followed by protodemetallation of the alkyl platinum complex **195** affords cyclobutene **196**.

Recently, one of us described another example of the formation of highly strained, four-membered products in Au-catalyzed reactions involving enynes.[35] The ene component in this case is the part



Scheme 41. Mechanism of Pt-catalyzed cycloisomerization of allenyne **191**.



Scheme 42. Au-catalyzed tandem [3,3]-rearrangement-[2+2] cycloaddition.

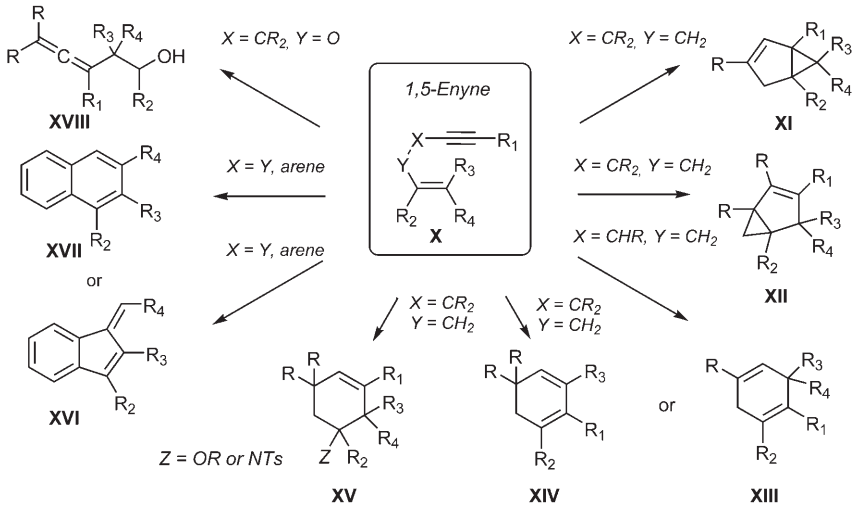
of the indole π-system, formally corresponding to an example of a 1,7-enyne. Indeed, subjection of propargyl ester **197** to 1 mol% of cationic gold catalyst formed from $Au(PPh_3)Cl$ and $AgSbF_6$ afforded tetracycle **199** in 86% yield as a single diastereomer (Scheme 42). The tetracyclic structure was verified by X-ray crystallography. The reaction occurs by initial Au-catalyzed isomerization of propargyl ester **197** *via* a [3,3] sigmatropic rearrangement. The resulting carboxyallene **198** is subsequently activated by highly reactive cationic Au phosphine complex towards a stepwise [2+2] cycloaddition with the proximate indole moiety to give cyclobutane **199**.

3 Cycloisomerizations of 1,5-Enynes

Au- and Pt-catalyzed skeletal reorganizations of 1,5-enynes (**X**) can also deliver a range of synthetically useful products (Scheme 43). Some of the products resemble those that were obtained in isomerizations of the homologous 1,6-enynes, i.e., bicyclo[3.1.0]hexenes **XI** and **XII**. However, the majority of other processes produce different cyclic structures. Several types of six-membered dienes and alkenes (**XIII**, **XIV**, and **XV**) can be obtained as a result of cycloisomerization of 1,5-enyne **X**. Incorporation of the arene moiety in the tether enables access to naphthalenes (**XVII**) and indenes (**XVI**). Furthermore, a formal [3,3] rearrangement process provides an efficient access to the corresponding allenes **XVIII.**

3.1 Formation of Bicyclo[3.1.0]alkenes

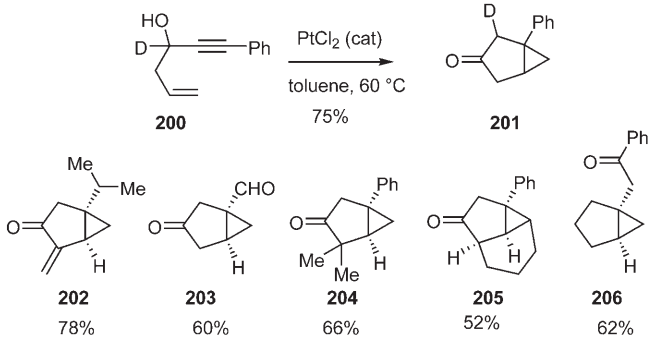
In 2004, Fürstner and Malacria published back-to-back their independent studies of Pt-catalyzed 1,5-enyne cycloisomerizations to bicyclo-[3.1.0]hexenes.[36,37] These reports were soon followed by a communication from the Toste laboratory, describing a series of independently observed cycloiso-



Scheme 43. Observed reaction topologies in cycloisomerizations of 1,5-enynes.

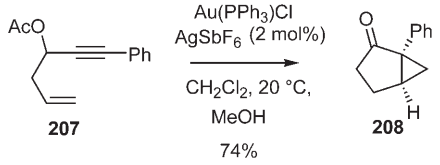
merizations of 1,5-enynes, which were catalyzed by cationic gold-phosphine complexes.[38]

Fürstner and co-workers reported that subjection of enyne **200** to a catalytic amount of $PtCl_2$ in toluene at 60 °C afforded bicyclic ketone **201** in 75% yield (Scheme 44).[36] The deuterium label in the product



Scheme 44. Pt-catalyzed cycloisomerization of 1,5-enynes.

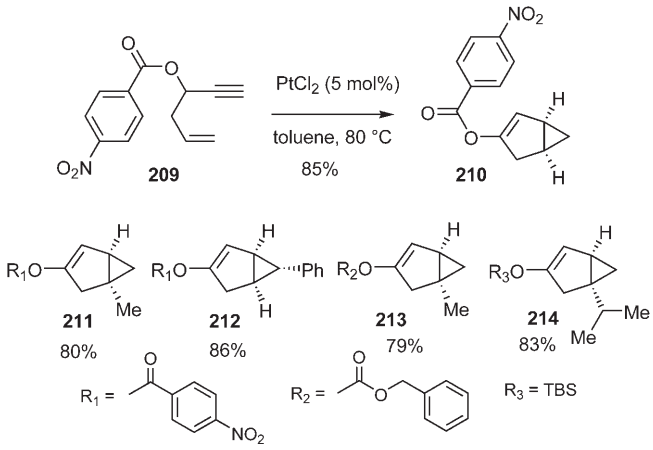
appeared exclusively at the C(2) position of **201**. Representative examples of the scope of the cycloisomerization are depicted in Scheme 44. In addition to $PtCl_2$ catalysis, the authors reported that the combination of $Au(PPh_3)Cl$ and $AgSbF_6$ was effective in conversion of acetate **207** to bicyclic ketone **208** (Scheme 45).



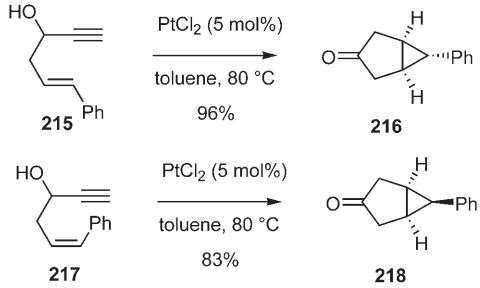
Scheme 45. Au-catalyzed cycloisomerization of 1,5-enyne **207**.

The studies of Malacria and co-workers are summarized in Scheme 46 and Scheme 47.[37] This work demonstrated that enynes containing terminal alkynes successfully participated in the cycloisomerization process. In addition, the authors established that the formation of bicyclo[3.1.0]hexenes was stereospecific. Subjection of enyne **215** containing an *E*-alkene afforded ketone **216**, while a similar reaction using *Z*-alkene **217** furnished the diastereomeric product **218.** In 2004, the same group also reported a transannular version of this reaction, which assembled a series of tricyclic compounds from cyclic 1,5-enynes.[39]

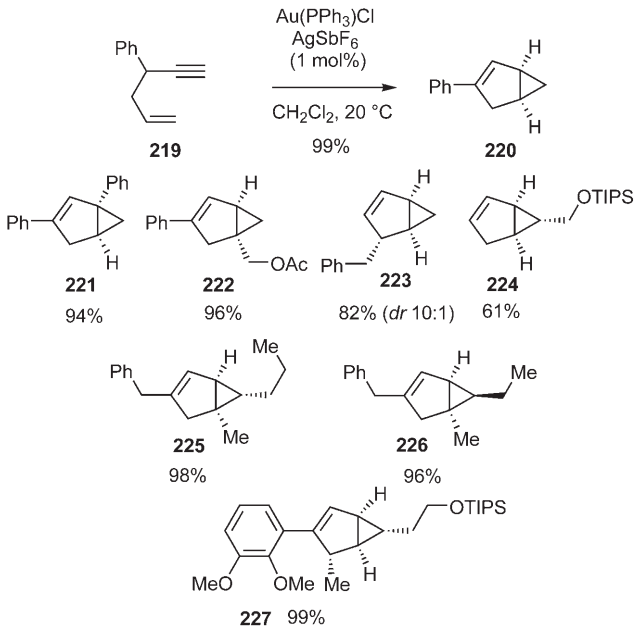
Scheme 48 summarizes the studies of Toste and co-workers.[38] Unlike the two previous reports, which utilized exclusively C(3)-acyloxy- and hydroxy-substituted enynes, Toste and co-workers found that gold catalysis of the 1,5-enyne cycloisomerization enabled efficient conversions of enynes bearing aryl and alkyl



Scheme 46. Pt-catalyzed cycloisomerizations of 1,5-enynes.



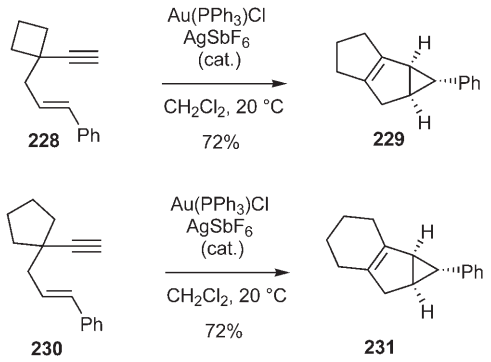
Scheme 47. Stereospecificity of Pt-catalyzed cycloisomerizations of 1,5-enynes.



Scheme 48. Au-catalyzed cycloisomerizations of 1,5-enynes.

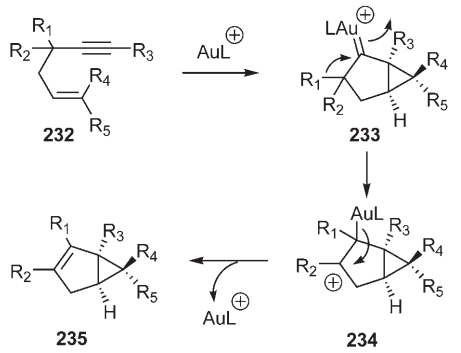
groups at the C(3) position. In a typical experiment, subjection of enyne **219** to 1 mol% of cationic gold-

phosphine complex at ambient temperature afforded bicyclo[3.1.0]hexene **220** in quantitative yield. Toste and co-workers also demonstrated a series of interesting ring expansion reactions that occurred during cycloisomerizations of enynes **228** and **230** (Scheme 49).



Scheme 49. Ring-expansion during Au-catalyzed cycloisomerizations of 1,5-enynes.

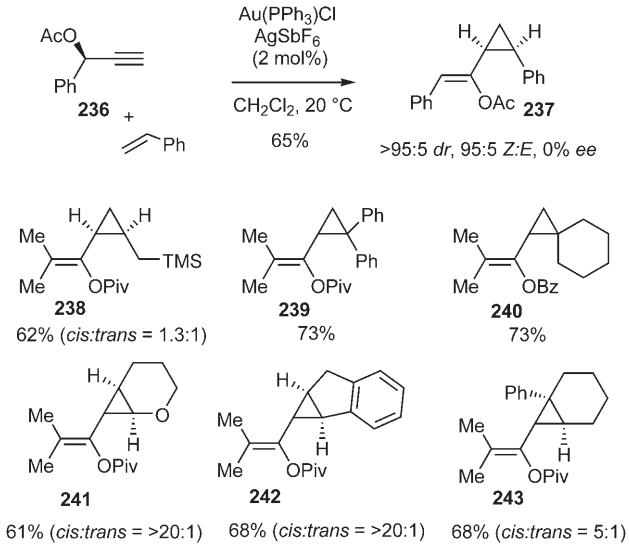
The proposed mechanism of 1,5-enyne isomerizations to the corresponding bicyclo[3.1.0]hexenes is depicted in Scheme 50. The process begins with the intramolecular cyclopropanation to give cyclopropyl metal carbene **233**, which undergoes a [1,2] shift of a hydride or an alkyl group to give **234**. Elimination of a cationic metal fragment results in the formation of the observed bicyclic alkene **235** and regeneration of the active metal catalyst.



Scheme 50. Mechanism of cycloisomerizations of 1,5-enynes to bicyclo[3.1.0]hexenes.

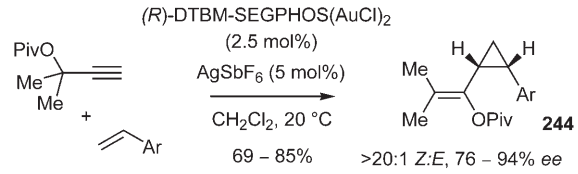
In 2004, Nishibayashi and co-workers also reported a sequential reaction transforming 1,5-enyne, which was generated *in situ* from a propargyl alcohol, to a bicyclo[3.1.0]hexene skeleton by tandem Ru and Pt catalysis.[40]

Based on the ability of phosphine-gold(I) complexes to catalyze the intramolecular cycloisomerization of enynes, Toste and co-workers examined the possibility of conducting the corresponding intermolecular reaction of propargylic esters with alkenes.[41] Indeed, they demonstrated that such condensations readily occurred using 5 mol% of $Au(PPh_3)Cl$ and 5 mol% of $AgSbF_6$ to give the corresponding cyclopropanes (Scheme 51). In the case of enantiomerically enriched propargylic acetate **236**, the reaction proceeded to give cyclopropane **237** with high diastereoselectivity, but no enantiomeric excess. This result is consistent with the initial formation of the achiral gold carbene from acetate **236**, followed by alkene cyclopropanation.



Scheme 51. Au-catalyzed intermolecular cyclopropanation.

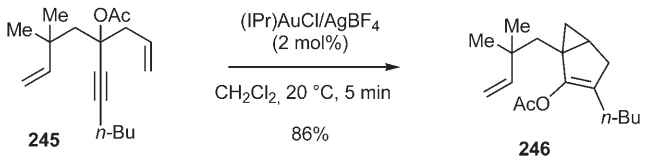
Toste and co-workers also demonstrated that the use of a chiral phosphine ligand, such as DTBM-SEGPHOS, resulted in the formation of cyclopropanes in enantiomerically enriched form (Scheme 52).[41] These results provide further support of the involvement of gold-carbenes as reactive intermediates, and demonstrate the ability to efficiently induce asymmetry in gold-catalyzed reactions, which remains a highly challenging task.



Scheme 52. Enantioselective Au-catalyzed intermolecular cyclopropanation.

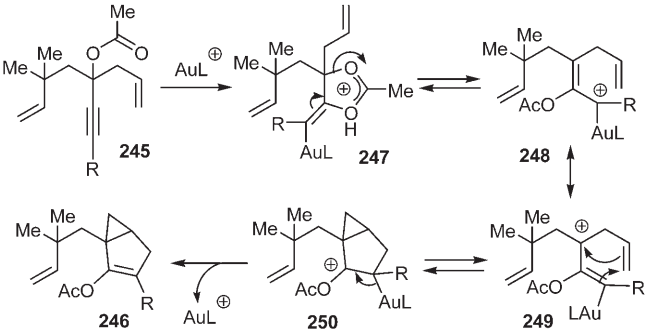
Recently, Nolan and co-workers reported the use of the N-heterocyclic carbene (IPr) ligand to enable an Au(I)-catalyzed cycloisomerization of 1,5-enyne **245**,

which resulted in the formation of a new bicyclo-[3.1.0]hexene skeleton **246** (Scheme 53).[42]



Scheme 53. Au-catalyzed cycloisomerization of enyne **245**.

One of the proposed mechanisms by the Nolan's group is shown in Scheme 54. The reaction begins with a known acetoxy group shift promoted by the cationic gold complex to give intermediate **248**, which undergoes two intramolecular C–C bond forming steps to give the observed product **246** with concomitant regeneration of the gold catalyst.



Scheme 54. Mechanism of cycloisomerization of enyne **245**.

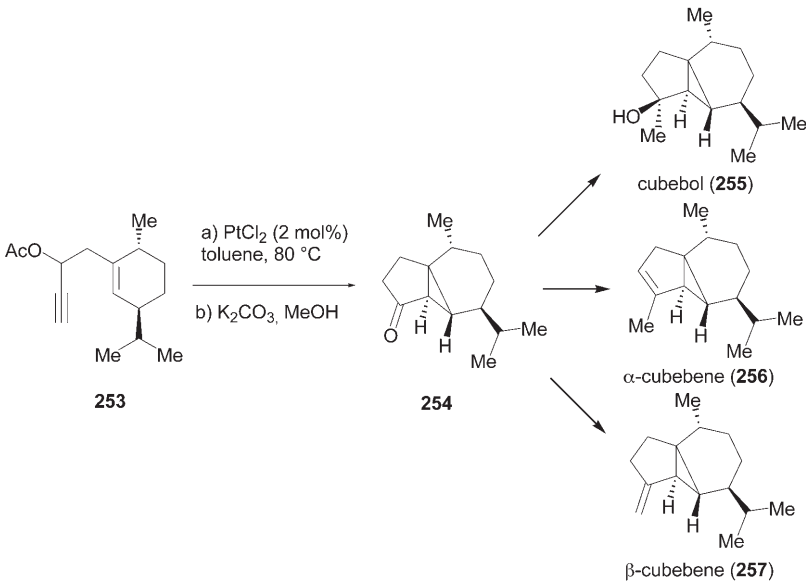
In 2006, Fürstner and Hannen reported the application of $PtCl_2$-catalyzed cycloisomerization of 1,5-enyne **253** to efficient syntheses of (−)-cubebol **255**, (−)-**α**-cubebene **256**, and (−)-β-cubebene **257** (Scheme 55), which were efficiently accessed from a common intermediate **254**.[43] Interestingly, an essentially identical approach to (−)-cubebol was communicated independently by Fehr and Galindo.[44]

3.2 Isomerization of 1,5-Enynes to Cyclohexadienes

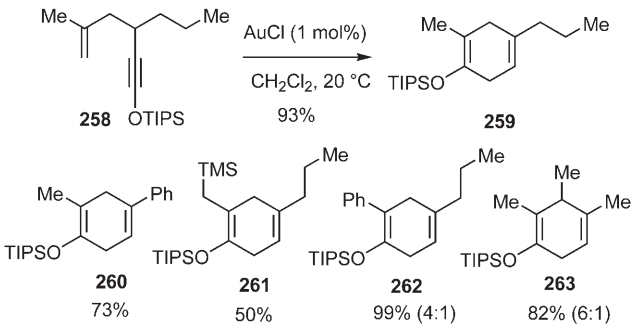
In 2004, we demonstrated that subjection of 1-siloxy-5,1-enyne **258** to 1 mol% of AuCl resulted in the highly efficient formation of a new product, which was subsequently identified as siloxycyclohexadiene **259**.[45] Interestingly, during this process, the siloxy group formally migrated from the C(1) to the C(6) position. This observation was quite general and a range of 1,4-cyclohexadienes could be obtained by this reaction (Scheme 56). While addition of the phosphine inhibited the reaction, $Au(PPh_3)Cl$ in combination with a silver salt was found to be equally effective.

Introduction of the quaternary center at the C(3) position of the enyne resulted in exclusive formation of 1,3-cyclohexadienes (Scheme 57). Both alkyl and aryl substitution at the C(3) position were well tolerated. Importantly, protodesilylation of siloxycyclohexadienes efficiently afforded the corresponding 1,3- or 1,2-cyclohexenone (not shown), highlighting the general synthetic utility of this catalytic process.

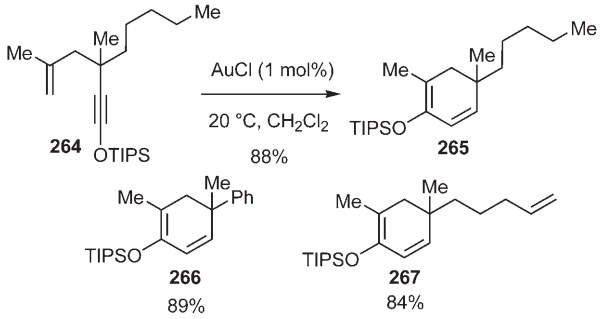
Experiments depicted in Scheme 58 provided important insights into the mechanism of the cycloisomerization. Cycloisomerization of enyne **268** contain-



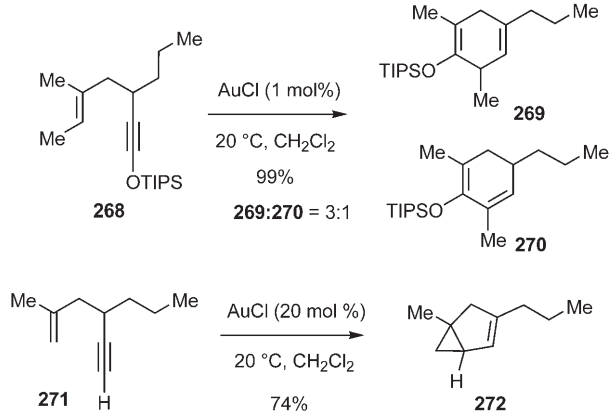
Scheme 55. Syntheses of (−)-cubebol, (−)-α-cubebene, and (−)-β-cubebene.



Scheme 56. Au-catalyzed cycloisomerization of siloxyenynes to 1,4-cyclohexadienes.



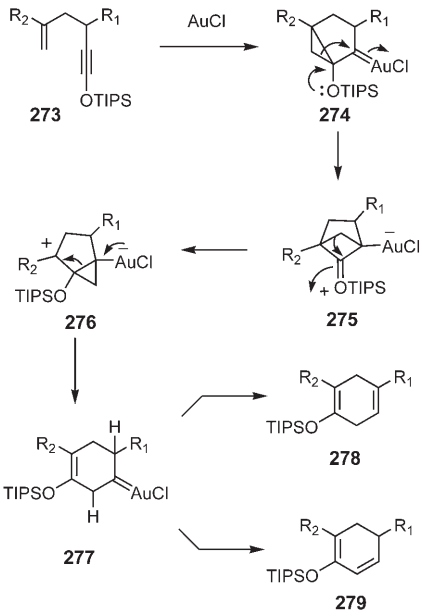
Scheme 57. Au-catalyzed cycloisomerization of siloxyenynes to 1,3-cyclohexadienes.



Scheme 58. Au-catalyzed cycloisomerizations of enynes **268** and **271**.

ing a trisubstituted alkene resulted in the formation a 3:1 mixture of cyclohexadienes **269** and **270**. Importantly, not only the migration of the siloxy group was observed; the C(6) methyl substituent migrated to the C(1) positon. Treatment of enyne **271** with AuCl (20 mol%) resulted in the formation of bicyclo-[3.1.0]hexene **272**, indicating that the presence of the C(1)-siloxy group was crucial to the formation of cyclohexadienes.

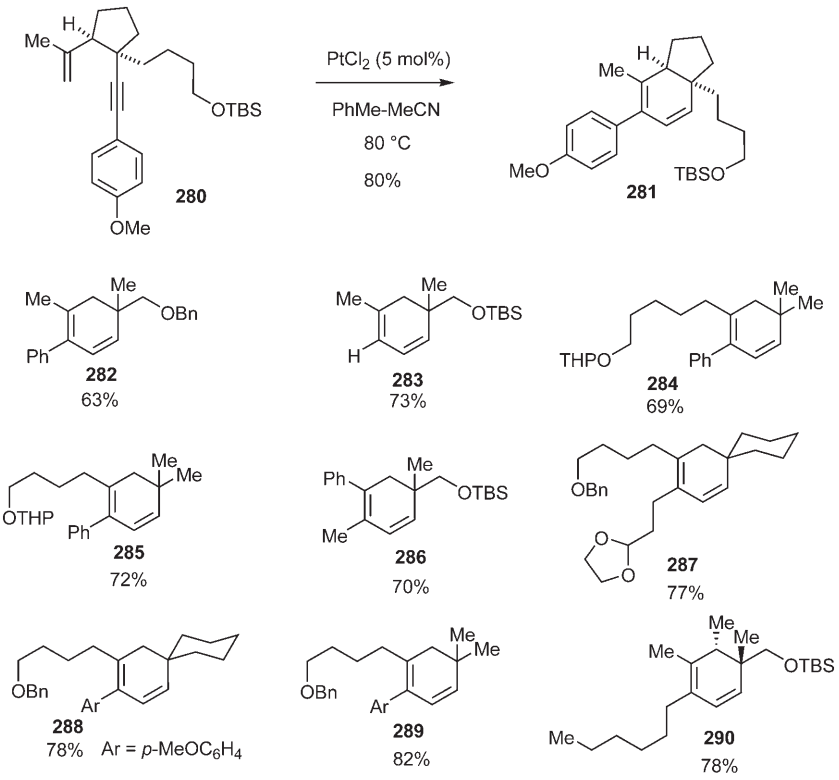
We proposed that the cycloisomerization of 1-siloxy-5,1-enynes proceeds *via* a series of steps depicted in Scheme 59.[45] The process begins with a gold-



Scheme 59. Mechanism of Au-catalyzed cycloisomerizations of siloxyenynes.

alkyne complexation, which results in the cyclopropanation of the pendant alkene to give gold carbene **274**. While hydride migration and elimination represented the dominant pathway in the previously observed enyne cycloisomerizations, the presence of the C(1) siloxy group changes the mechanistic scenario. Indeed, a subsequent [1,2] alkyl shift results in formation of oxocarbenium ion **275**. Another [1,2] alkyl shift delivers an intermediate **276**, which undergoes facile fragmentation to give gold carbene **277**. Depending on the availability of the hydride at the α-position, final elimination occurs to give either the 1,4-cyclohexadiene **278** or 1,3-cyclohexadiene **279**.

Recently, we were able to further expand the scope of the enyne cycloisomerization to form a wide range of 1,3-cyclohexadienes starting with enynes containing terminal, internal and arene-conjugated alkynes.[46] Indeed, we found that incorporation of the quaternary center at the C(3) position of the enyne prevented the competing formation of bicyclo[3.1.0]hexene, favoring exclusively the cycloisomerization of 1,5-enynes to 1,3-cyclohexadienes. The best results were obtained using $PtCl_2$ (5 mol%) and toluene-acetonitrile reaction medium. A representative scope of the reaction is provided in Scheme 60.

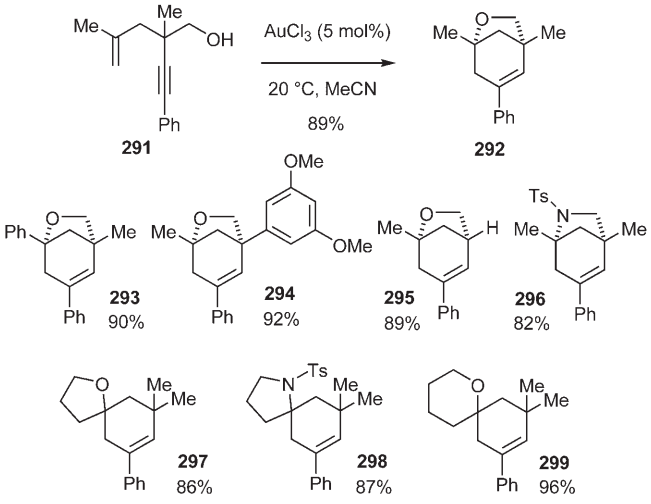


Scheme 60. Mechanism of Pt-catalyzed cycloisomerizations of 1,5-enynes.

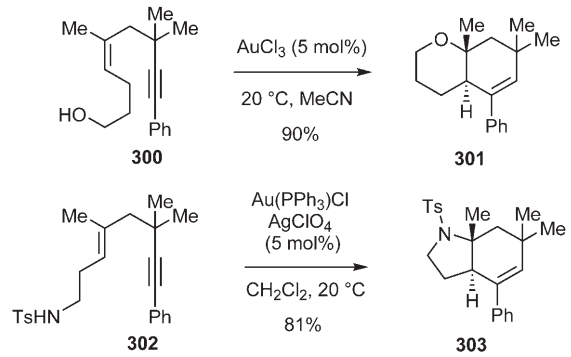
3.3 Formation of Oxa- and Azabicycloalkenes

During our studies on Au- and Pt-catalyzed cycloisomerizations of 1,5-enynes, we found that treatment of enyne **291** with either Au(I)- or Au(III)-based catalyst resulted in the facile formation of 6-oxabicyclo-[3.2.1]octane **292** (Scheme 61).[47] Importantly, subjection of enyne **291** to 50 mol% of HCl affords exclusively the tetrahydrofuran (not shown), which demonstrates unambiguously that Au-based alkyne activation is uniquely responsible for the observed tandem cyclization. We found that a range of enynes successfully participated in this reaction, providing rapid access to a series of bridged bicyclic alkenes as well as spirocyclic alkenes shown in Scheme 61.

We also examined the formation of fused heterobicyclic alkenes.[47] Treatment of alcohol **300** with 5 mol% of $AuCl_3$ afforded oxabicycloalkene **301** in 90% yield as a single diastereomer. Similarly, subjection of sulfonamide **302** to the cyclization conditions furnished azabicycloalkene **303** in 81% yield, also as a single diastereomer (Scheme 62). The sterospecificity of the tandem cyclization reactions is highly note-



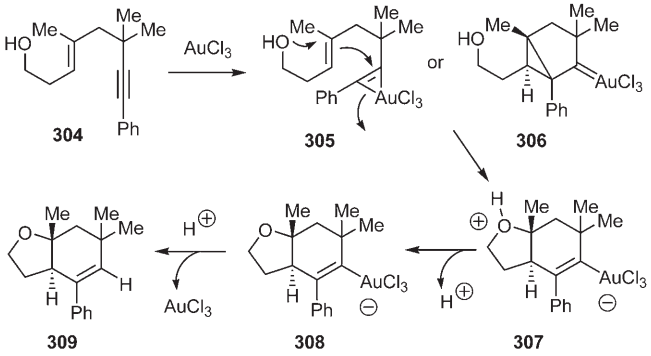
Scheme 61. Au-catalyzed assembly of heterobicyclic systems.



Scheme 62. Au-catalyzed assembly of fused heterobicyclic systems.

worthy and is fully consistent with earlier observations of stereospecific cyclopropanations.

The mechanism of Au-catalyzed double cyclizations is depicted in Scheme 63.[47] The reaction can be viewed as a concerted process involving the nucleophilic attack of the alkene at the gold-alkyne complex **305** with a concomitant interception of the developing carbocation by the oxygen or nitrogen nucleophile. Alternatively, the mechanism may involve the ring-opening of cyclopropyl gold carbene **306**. Release of the proton, followed by final protodemetallation delivers the observed bicyclic product **309**. Based on the number of observations cited in the original report, we had suggested that the reaction is likely to follow a concerted pathway *via* an intermediacy of **305**.



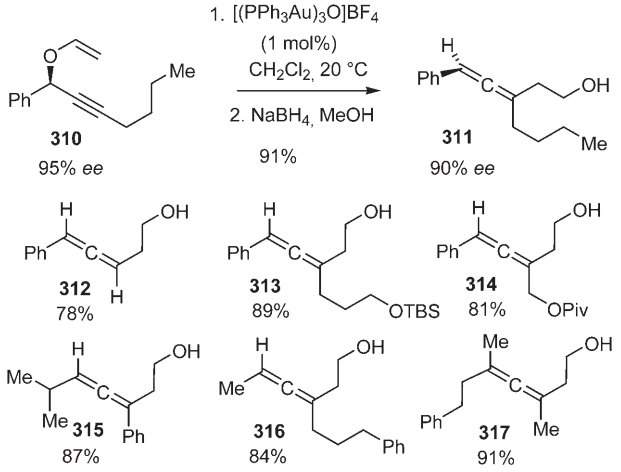
Scheme 63. Mechanism of Au-catalyzed double cyclization.

3.4 Formation of Allenes *via* a [3,3] Rearrangement

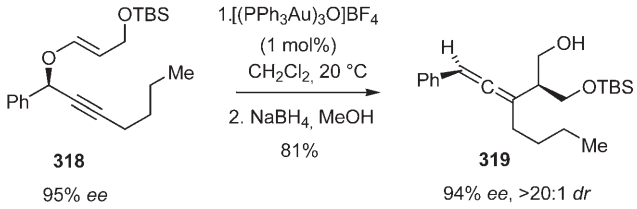
In 2004, Toste and Sherry reported that phosphine-gold(I) complexes efficiently catalyzed the propargyl-Claisen rearrangement.[48] In a typical experiment, subjection of enantiomerically enriched vinyl ether **310** to $[(AuPPh_3)_3O]BF_4$ at ambient temperature in CH_2Cl_2, followed by reduction afforded allene **311** in 91% yield and 90% *ee*. The efficient chirality transfer during this process is particularly noteworthy as it provides access to chiral allenes. The process was amenable to the construction of a range of allenes depicted in Scheme 64.

In addition to the efficient chirality transfer, excellent diastereoselectivity was observed upon rearrangement of ether **318** containing a disubstituted alkene to give allene **319** in 81% yield, 94% *ee* and >20:1 *dr* (Scheme 65).

The proposed mechanism of the rearrangement begins with the gold-based alkyne activation towards the nucleophilic attack by the proximate alkene to give cyclic intermediate **322**. Fragmentation of the C–O bond with a concomitant elimination of the cationic



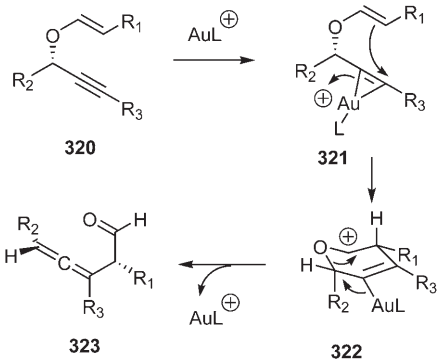
Scheme 64. Au-catalyzed propargyl-Claisen rearrangement.



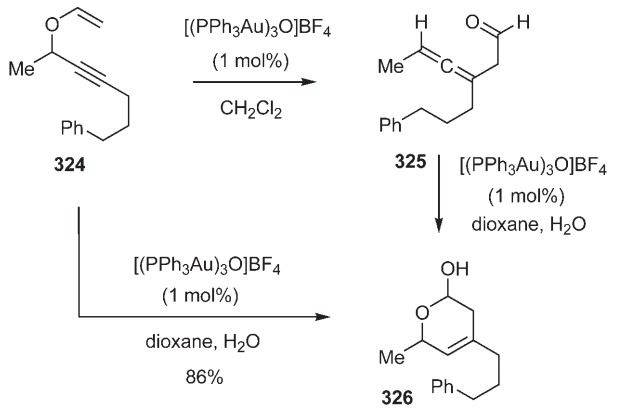
Scheme 65. Au-catalyzed propargyl-Claisen rearrangement of ether **318**.

phosphine gold complex affords the observed allene **323** (Scheme 66).

Recently, Toste and co-workers reported the assembly of dihydropyrans using a tandem Claisen rearrangement/heterocyclization sequence shown in Scheme 67.[49] Subjection of propargyl vinyl ether **324** to $[(PPh_3PAu)_3O]BF_4$ afforded aldehyde **325** by the same mechanism as shown in Scheme 66. Subjection of **325** to the same catalyst, but in wet dioxane, resulted in the formation of dihydropyran **326**. This two-step process was then combined into a single opera-



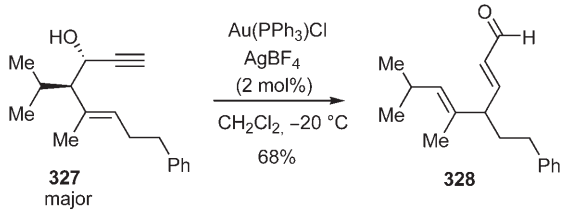
Scheme 66. Mechanism of Au-catalyzed propargyl-Claisen rearrangement.



Scheme 67. Au-catalyzed Claisen rearrangement/heterocyclization cascade.

tion using wet dioxane as a solvent to give dihydropyran **326** in 86% yield.

In 2005, Gagosz demonstrated another example of a [3,3] rearrangement involving enyne **327**, which corresponds to an acetylenic oxy-Cope rearrangement.[50] Treatment of alcohol **327** (5:1 mixture of *syn* and *anti* diastereomers) with 2 mol% of $Au(PPh_3)Cl$ and 2 mol% of $AgBF_4$ at −20 °C afforded aldehyde **328** in 68% yield without any detectable isomerization of the trisubstituted alkene (Scheme 68). The rearrangement was proposed to proceed *via* the intermediacy of a similar six-membered cyclic intermediate, followed by fragmentation of the C–C bond.

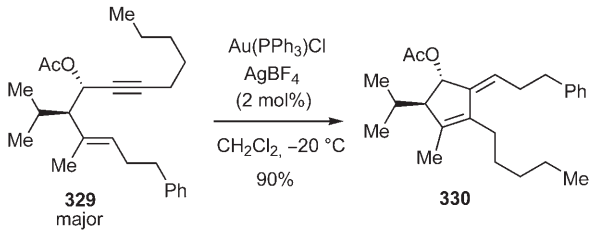


Scheme 68. Au-catalyzed acetylenic oxy-Cope rearrangement.

3.5 Formation of Methylenecyclopentenes

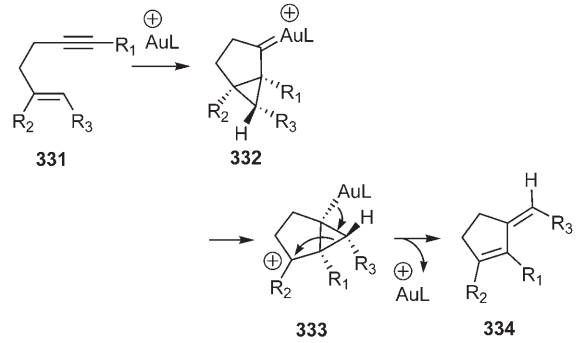
As a part of the same account,[50] which described the acetylenic oxy-Cope rearrangement, Gagosz reported that subjection of propargyl ester **329** to a cationic phosphine-gold(I) complex resulted in the highly efficient formation of a new product, which was identified as a diene **330** (Scheme 69). The course of this cycloisomerization reaction is similar to that observed previously by Echavarren in the case of 1,6-enynes. However, this outcome was not precedented for cycloisomerization of 1,5-enynes.

The postulated reaction mechanism may involve the initial intramolecular cyclopropanation to give



Scheme 69. Au-catalyzed cycloisomerization of 1,5-enyne **329**.

gold carbene **332**, which undergoes two consecutive [1,2] alkyl shifts to afford carbocation **333** (Scheme 70). Fragmentation of the cyclopropane C–C



Scheme 70. Mechanism of Au-catalyzed cycloisomerization of 1,5-enyne **331**.

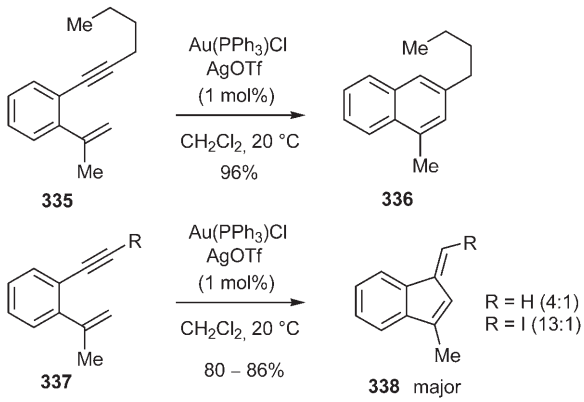
bond with the concomitant loss of cationic phosphine gold(I) complex completes the catalytic cycle.

3.6 Formation of Naphthalenes and Methyleneindenes

In 2006, Shibata and co-workers reported efficient cycloisomerization of 1,5-enynes conjugated to an aromatic ring (Scheme 71).[51] Depending on the nature of the alkyne, the cyclization followed either *6-endo* or *5-exo* manifolds. The alkyl-substituted alkyne **335** afforded naphthalene **336**, while the terminal or halogen-substituted alkynes **337** favored the formation of indenes **338**

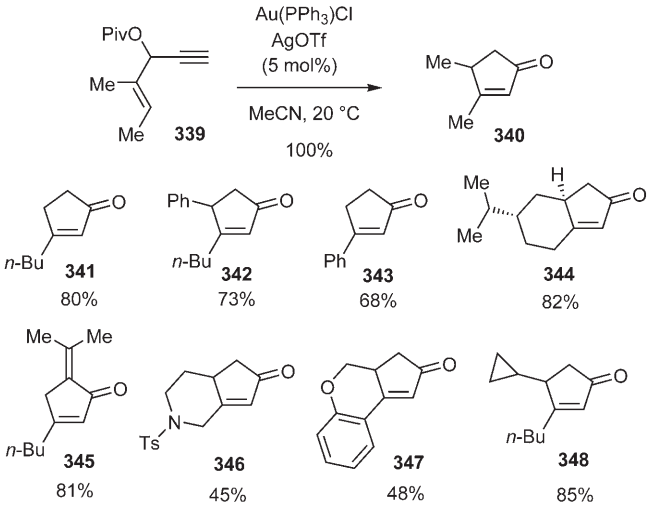
4 Cycloisomerizations of 1,4-Enynes

Reported in 1984,[52] the Rautenstrauch rearrangement provided an access to cyclopentenes starting with acyclic 1-ethynyl-2-propenyl acetates. The original reaction was catalyzed by Pd(II) complexes and was postulated to proceed *via* the intermediacy of Pd carbenes. In 2005, Toste and co-workers reported that



Scheme 71. Au-catalyzed cycloisomerization of enynes **335** and **337**.

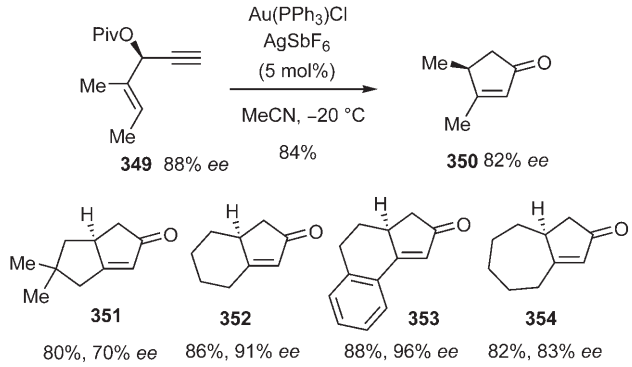
cationic phosphine-gold(I) complexes are effective catalysts for this process, which also enabled the construction of enantiomerically enriched cyclopentenes.[53] The study of the initial scope of the process is depicted in Scheme 72. The reaction exhibited a broad substrate scope, including terminal and internal alkynes, as well as di- and trisubstituted alkenes, which enabled construction of bicyclic and tricyclic enones.



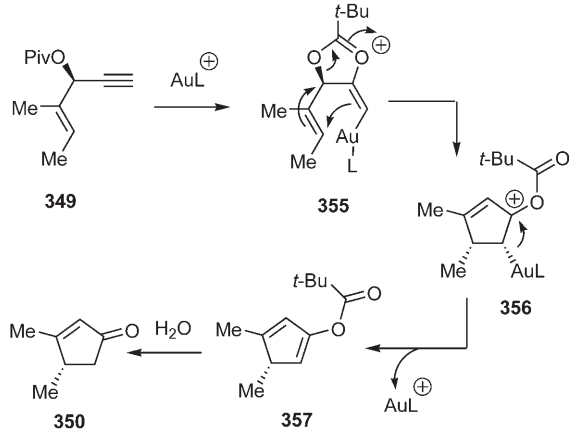
Scheme 72. Au-catalyzed Rautenstrauch rearrangement.

The authors demonstrated that the Au-catalyzed Rautenstrauch rearrangement enabled an efficient chirality transfer from the propargylic position of the enyne **349** to the C(4) position of the cyclopentenone **350**. Several additional examples of this enantioselective process are depicted in Scheme 73.

The proposed mechanism, which is responsible for the observed stereochemical course of the process, is depicted in Scheme 74. The process begins with a



Scheme 73. Au-catalyzed enantioselective Rautenstrauch rearrangement.

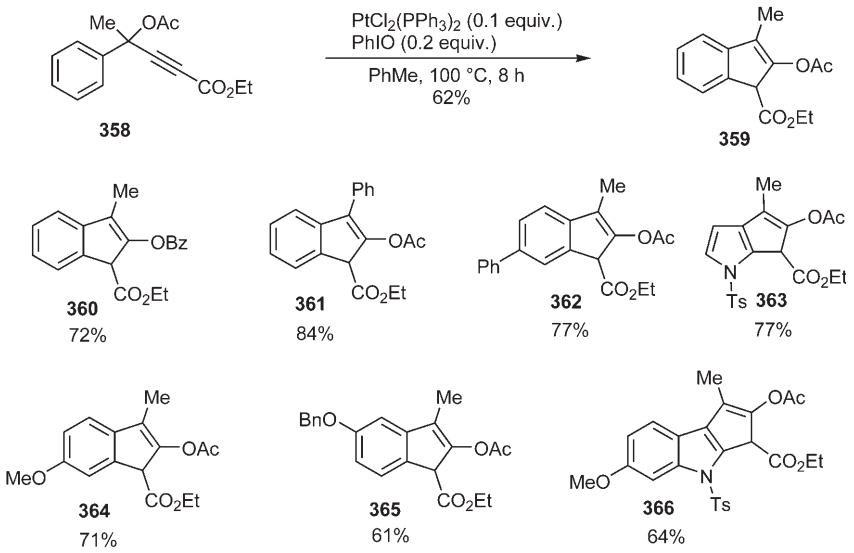


Scheme 74. Mechanism of Au-catalyzed Rautenstrauch rearrangement.

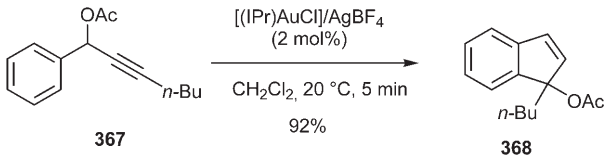
gold-promoted intramolecular addition of ester onto the alkyne to give alkenyl gold complex **355**. Subsequent cyclization produces intermediate **356**, which upon the loss of cationic gold phosphine fragment gives cyclopentadienol acetate **357**. Aqueous hydrolysis of **357** affords cyclopentenone **350.** The stereoselectivity of the reaction has been attributed to the orthogonal disposition of the leaving group relative to the plane of the olefin in the transition state for cyclization of **355**. This mechanistic proposal was followed by a more detailed theoretical study.[54]

In 2005, Sarpong and co-workers reported an efficient Pt-catalyzed pentannulation of propargylic esters with quarternary propargylic position (Scheme 75).[55] Interestingly, iodosobenzene was employed as an additive in this reaction. The authors proposed participation of Pt(IV) species as the active catalytic species.

Recently, Nolan and co-workers reported another interesting example of an Au-catalyzed cycloisomerization of a propargyl acetate containing an adjacent aryl fragment (Scheme 76).[56] While a 1,2-migration of the acetate was observed in the previously de-



Scheme 75. Pt-catalyzed cycloisomerization of arene-containing propargyl acetates.



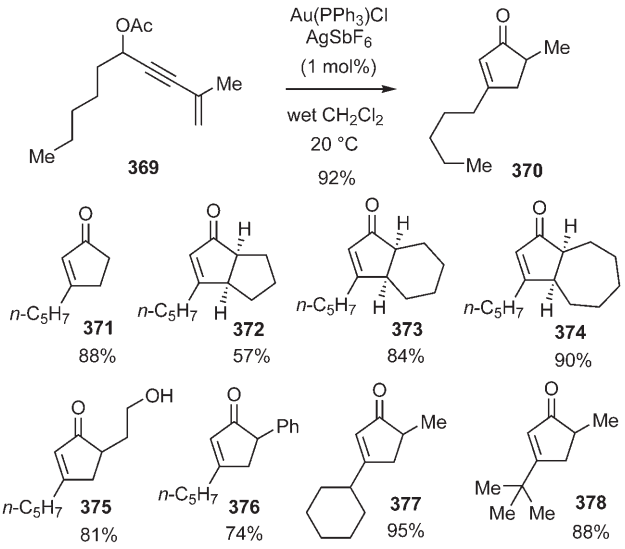
Scheme 76. Au-catalyzed cycloisomerization of propargyl acetate **367**.

scribed study, the current reaction entailed a formal 1,3-migration of the acetate moiety to give indene **368.**

5 Cycloisomerizations of 1,3-Enynes

In 2006, Zhang and Wang reported the efficient construction of cyclopentenones by an Au(I)-catalyzed cycloisomerization of 1,3-enynes, which was proposed to involve a cascade of sigmatropic [3,3] rearrangement and Nazarov cyclization reactions. Subjection of propargyl acetate **369** to 1 mol% of $Au(PPh_3)Cl$ and 1 mol% of $AgSbF_6$ in wet CH_2Cl_2 at 20 °C efficiently afforded cyclopentenone **370** (Scheme 77). This process enabled an efficient accces to a range of 3,5-disubstituted and 3,4,5-trisubstituted cyclopentenones, as well as several bicyclic enones.

This remarkable transformation can be rationalized by the series of individual mechanistic steps depicted in Scheme 78. The reaction begins with the gold-promoted attack of the ester carbonyl onto the alkyne fragment to give cationic intermediate **381**. Subsequent [3,3] sigmatropic rearrangement affords cationic intermediate **382**, which is poised to undergo the Nazarov cyclization. The resulting cation **383** can be

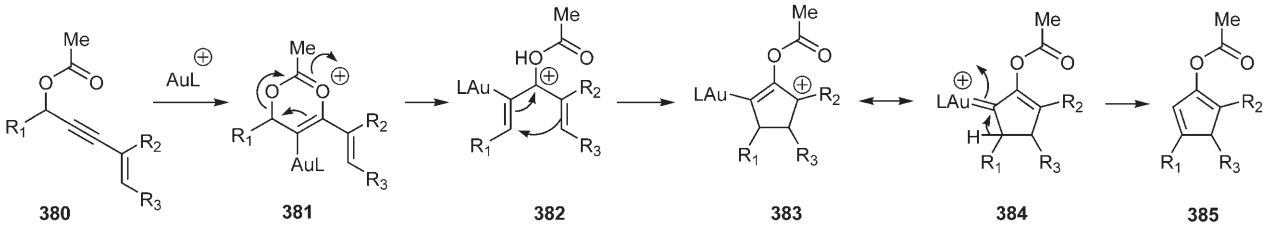


Scheme 77. Au-catalyzed synthesis of cyclopentenones from 1,3-enynes.

depicted in the resonance form **384**, which explains the subsequent [1,2] hydride shift, followed by elimination of the cationic gold complex to give cyclopentadienol acetate **385**. Aqueous hydrolysis of **385** produces the observed cyclopentenone.

6 Conclusions and Future Outlook

We have presented a comprehensive overview of the development of the gold and platinum catalysis of enyne cycloisomerization. Use of soft, alkynophilic metals enables mild, chemoselective and efficient transformations of readily available acyclic enynes to



Scheme 78. Mechanism of Au-catalyzed synthesis of cyclopentenones from 1,3-enynes.

a wide range of synthetically useful carbocyclic and heterocyclic products. While the vast majority of new catalytic processes has been uncovered during the past three years, we anticipate that many additional reactions will be invented in the next decade. The development of new transformations should be facilitated by the mechanistic foundation provided by the previous studies. The asymmetric Au and Pt catalysis of enyne cycloisomerization is currently in its infancy. We anticipate that this important area will continue to develop in the future. Furthermore, the rapid increase in molecular complexity enabled by enyne cycloisomerizations will result in many subsequent applications of these catalytic processes in the area of complex molecule synthesis of natural and unnatural products.

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