Review

Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective

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Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective

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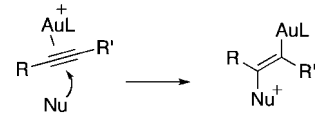
1. Introduction

Gold salts and complexes have emerged in the past few years as the most powerful catalysts for electrophilic activation of alkynes toward a variety of nucleophiles under homogeneous conditions. In a simplified form, nucleophilic attack on the $[AuL]^+$-activated alkyne proceeds via π complexes **1** to give *trans*-alkenyl gold complexes of type **2** as intermediates (Scheme 1).[1–6] This type of coordination is also a common theme in gold-catalyzed cycloisomerizations of enynes, in which the alkene function acts as the nucleophile.

Scheme 1



In the reaction of enynes with complexes of other transition metals, an Alder-ene cycloisomerization can take place by simultaneous coordination of the alkyne and the alkene to the metal followed by an oxidative cyclometalation.[3,5] In contrast, this process does not occur for gold(I)[7–9] since oxidative addition processes are not facile for this metal. [6] In addition, the $[AuL]^+$ fragment, which is isolobal to H^+ and HgL^{2+},[10] adopts a linear coordination and binds to either the alkene or the alkyne. Thus, cycloisomerizations of enynes catalyzed by gold proceed by an initial coordination of the metal to the alkyne, and as illustrated in Scheme 2, the resulting complex **3** reacts with the alkene by either the 5-exo-dig or 6-endo-dig pathway to form the *exo*- or *endo*-cyclopropyl gold carbene **4** or **5**, respectively, as has been established with other electrophilic transition-metal complexes or halides MX_n as catalysts.[11–18]

The proposed involvement of cyclopropyl metal carbenes of type **4** in the electrophilic activation of enynes by transition metals was first substantiated in reactions catalyzed by Pd(II), in which the initially formed cyclopropyl palladium carbenes undergo [4 + 2] cycloaddition with the double bond of the conjugate enyne.[19] Strong evidence for the existence of cyclopropyl metal carbenes as intermediates was also obtained in the reaction of enynes bearing additional double bonds at the alkenyl chain with Ru(II)[12c] and Pt(II)[20] catalysts. In these reactions, the cyclopropyl metal carbenes are trapped intramolecularly by the terminal alkene to give tetracycles containing two cyclopropanes.[21]

Gold(I) complexes usually surpass the reactivity shown by Pt(II) and other electrophilic metal salts and complexes for the activation of enynes. They are highly reactive yet uniquely selective Lewis acids that have a high affinity for π bonds. This high π-acidity is linked to relativistic effects, which reach a maximum in the periodic table with gold.[6,22,23] However, on occasion, the stronger Lewis acidity of gold complexes can be detrimental in terms of selectivity and because of their low tolerance to certain functional groups. In these instances, the less-strongly Lewis acidic Pt(II) complexes could be the catalysts of choice.[24–26]

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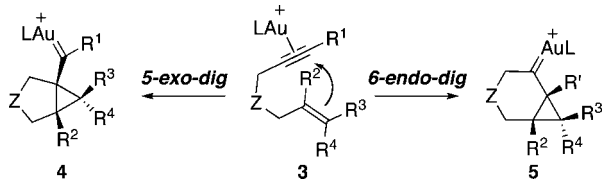
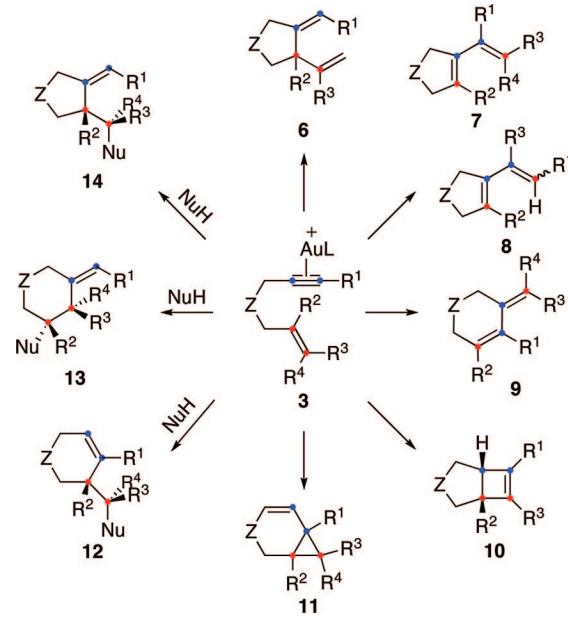
Antonio M. Echavarren was born in Bilbao, Basque Country, Spain, in 1955. He obtained his Ph.D. at the Universidad Autónoma de Madrid in 1982 with Professor Francisco Fariña. After a postdoctoral appointment at Boston College with Professor T. Ross Kelly, he joined the UAM as an Assistant Professor (1984−1986). Following a two-year period as a NATO Fellow in the group of Professor John K. Stille at Colorado State University, he joined the Institute of Organic Chemistry of the CSIC (Spanish Research Council) in Madrid. In 1992, he moved to the UAM as a Professor of Organic Chemistry. He has also been a Professor of Research of the CSIC since 2004. In March 2004, he was appointed as a group leader at the newly created Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain. His research interests include the development of new catalytic methods based on the organometallic chemistry of late transition metals as well as the synthesis of natural and nonnatural products. He received the 2004 Janssen−Cilag Award in Organic Chemistry from the Spanish Royal Society of Chemistry (RSEQ) and the 2006 Liebig Lectureship of the Organic Division of the German Chemical Society.

Although detailed mechanistic studies have only been done in a few cases, all of the results reported with enynes as substrates can be explained in terms of selective activation of the alkyne function by gold. However, complexes of gold(I) with the alkene function of the enyne are most

Scheme 2



Scheme 3



probably formed in solution in equilibrium with the alkyne−gold complexes. Indeed, well-characterized complexes of gold(I) with simple alkenes are known.[27−31] On the other hand, although simple alkyne−Au(I) complexes are stable only at low temperatures,[32] a few complexes of this type have been characterized.[33−36]

Products **6** of apparent Alder-ene cycloisomerization have occasionally been found in gold-catalyzed reactions of 1,6-enynes (Scheme 3), although these products are formed by other mechanisms. In the absence of nucleophiles, enynes usually evolve via cyclopropylcarbenes by skeletal rearrangement to form dienes **7** (single cleavage) and/or **8** (double cleavage). This transformation of enynes is one of the most intriguing rearrangements in organic chemistry. Products **9** of endocyclic skeletal rearrangement, cyclobutenes **10**, and products **11** of intramolecular cyclopropanation have also been obtained. In the presence of nucleophiles, adducts **12**−**14** have been obtained in stereospecific processes. More-complex transformations starting from more-functionalized enynes are also possible.

Formation of C−C bonds can be catalyzed by gold(I) or gold(III) complexes. Although donor ligands such as phosphines and N-heterocyclic carbenes (NHCs) stabilize the gold(I) oxidation state, disproportionation to gold(0) and gold(III) may occur in some cases. Conversely, gold(III) may be reduced to gold(I) by easily oxidizable substrates.[37]

1.1. Scope and Organization of the Review

Homogeneous catalysis by gold is a relatively young area of research that has grown very rapidly in the last 3−4 years. Since excellent comprehensive reviews of gold chemistry have already been published recently,[2,5] this review will cover gold-catalyzed cycloisomerization reactions of 1,*n*-enynes in detail, with a focus on their mechanisms. Cyclizations with concomitant addition of nucleophiles to 1,*n*-enynes are also covered, as these reactions shed light on the general mechanism of cyclizations of enynes. These reactions are domino-type transformations in which two bonds (C−C/C−X or two C−C) are consecutively formed. Reactions of dienes, allenenes, and allenynes, for which mechanistic studies are still scarce, are not covered. However, reactions

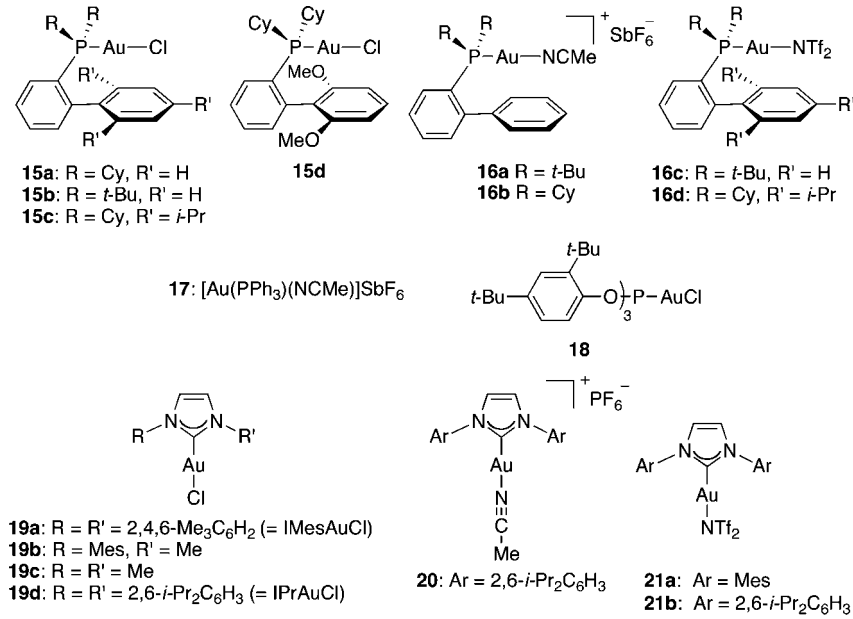


Figure 1. Gold complexes that serve as catalysts or precatalysts for enyne cycloisomerizations.

of arenes and heteroarenes with alkynes that are mechanistically related to those of enynes are included. The review is organized by general reaction types, and according to Occam's razor, the mechanisms will be presented in the most concise manner.

Many of the intermediates in gold-catalyzed reactions of enynes are more conveniently drawn as gold carbenes, since back-bonding in Au(I) has been shown to be significant.[5,6,38] However, it is important to recall that no intermediate has been spectroscopically characterized in this area[39] and that according to density functional theory (DFT) calculations, intermediates involved in cyclizations of enynes are highly delocalized structures (see section 2.2).

The discussion starts with 1,6-enynes, since these substrates have been historically the most important in developing new reactions and understanding the mechanistic aspects of this chemistry.

1.2. Gold Complexes

Simple AuCl or $AuCl_3$ are sufficiently alkynophilic to catalyze many reactions of the more reactive enynes. However, for many gold-catalyzed transformations, the most convenient catalysts are cationic complexes generated by chloride abstraction from [AuCl(PPh$_3$)] or similar phosphine complexes, using 1 equiv of a silver salt with a noncoordinating anion to generate the corresponding cationic species [Au(S)(PPh$_3$)]X (S = solvent or substrate molecule) in situ.[7,8,40] Similar cationic complexes can be obtained in situ by cleavage of the Au−Me bond in [AuMe(PPh$_3$)] using a protic acid.[7,8,41,42] The gold−oxo complex $[(Ph_3PAu)_3O]BF_4$[43] has also been introduced as a catalyst in certain reactions of enynes.[44] Figure 1 shows a number of other gold complexes that act as catalysts or precatalysts. The gold(I) complexes **15a−d** bearing bulky, biphenyl-based phosphine ligands, which have been shown to be excellent ligands for Pd-catalyzed reactions,[45] yield very active catalysts when mixed with Ag(I) salts.[46] More convenient are the cationic complexes **16a**, **16b**, and **17**,[8] which are stable crystalline solids that can be handled under ordinary conditions yet are very reactive as catalysts in a variety of transformations.[47–49] The structures of **15a−d**, **16a**, **16b**, and **17** have been confirmed by X-ray crystallography.[50,51] The related complexes **16c** and **16d** containing weakly coordinated bis(trifluoromethanesulfonyl)amide [NTf_2 (Tf = CF_3SO_2)] have also been prepared.[52] Cationic complexes or those with NTf_2 ligands lead to cleaner reactions in the absence of Ag(I) salts. Gold(I) complex **18** bearing tris(2,6-di-*tert*-butylphenyl)phosphite as a bulky ligand leads to a highly electrophilic cationic Au(I) catalyst in situ upon chloride abstraction with $AgSbF_6$.[53,54] Gold complexes such as **19a−d** that contain strongly donating NHC ligands are also good precatalysts.[46,55–57] Cationic complexes bearing NHC ligands (such as **20**, which shows moderate stability at room temperature)[58] and those with NTf_2 ligands (**21a** and **21b**) have also been reported.[59,60]

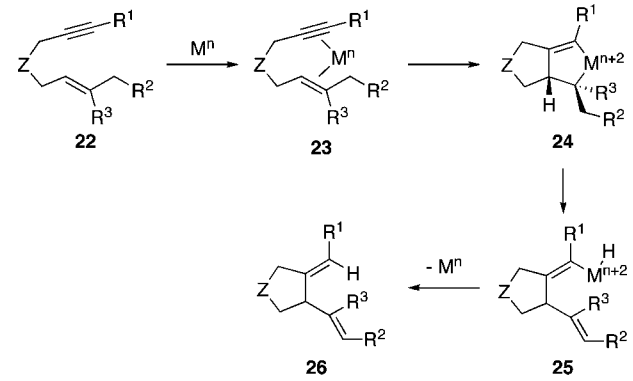
2. Cycloisomerizations of 1,*n*-Enynes

2.1. Cycloisomerization of 1,*n*-Enynes without Skeletal Rearrangement

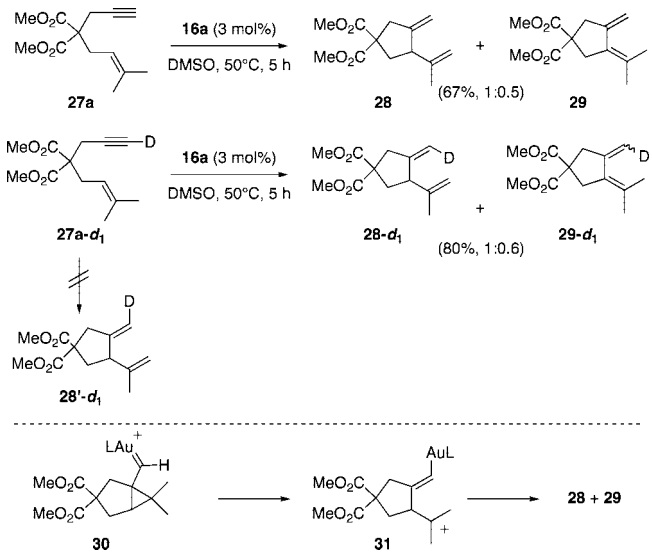
The Alder-ene cycloisomerization of enynes, one of the fundamental transformations in enyne chemistry,[1,5,17a,b] requires coordination of the metal to both the alkyne and the alkene. Thus, as has been shown for the $PtCl_2$-catalyzed reaction of enyne **22**, this reaction takes place by coordination of the transition metal to both unsaturated ligands to form **23**, which then undergoes an oxidative cyclometalation to form metallacycle **24** (Scheme 4). Metallacycle **24** evolves by β-hydrogen elimination from one of the alkyl chains to form **25**, which finally undergoes reductive elimination to give the cycloisomerized product **26** and regenerate catalytically active M^n. The β-hydrogen elimination in the Pt(II)-catalyzed process occurs from the allylic position in the chain with the trans configuration in the starting enyne, which presumably adopts an equatorial disposition in the intermediate platinacycle. On the other hand, the Ru(II)-catalyzed cycloisomerization of enynes takes place via related ruthenacycles that can suffer elimination from either *trans*- or *cis*-allylic positions.[17b]

Importantly, the cation $[Au(PR_3)]^+$, which is isolobal to H^+,[10] cannot coordinate to the alkene and the alkyne

Scheme 4



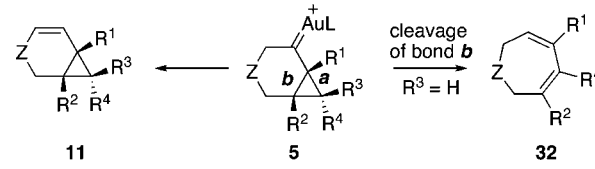
Scheme 5



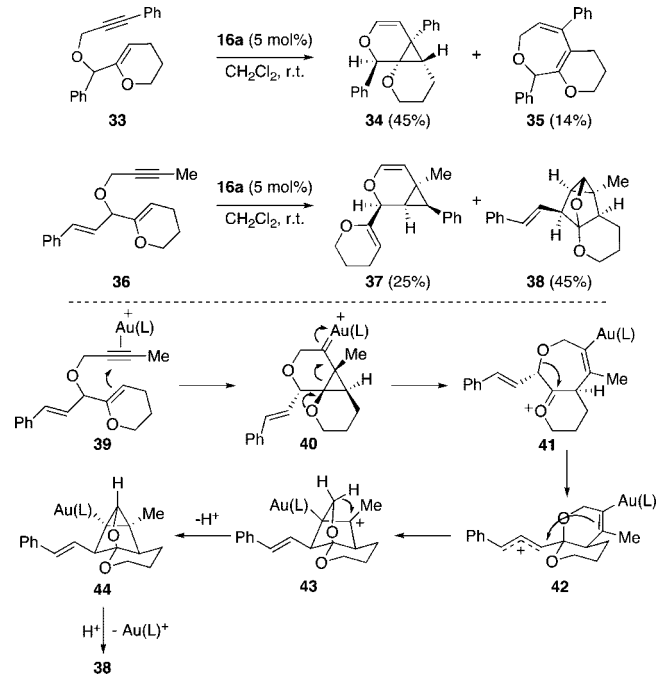
simultaneously; consequently, the Alder-ene cycloisomerization does not compete, and the cyclizations proceed exclusively through complexes of type **3** (Scheme 2). However, when the reaction of enyne **27a** was performed in DMSO at 50 °C with catalyst **16a**, a mixture of dienes **28** and **29** was obtained (Scheme 5).[8] Although diene **28** is the product of formal Alder-ene-type cycloisomerization of **27a**, it was shown that reaction of **27a-*d*$_1$** with **16a** (3 mol %) in DMSO at 50 °C afforded dienes **28-*d*$_1$** and **29-*d*$_1$** having a deuteration pattern that excluded the participation of Alder-ene-type cycloisomerization in this transformation, which would have led to formation of **28′-*d*$_1$**.[17b] Formation of **28** and **29** can be explained by ring opening of intermediate **30** to carbocation **31** followed by proton loss. Alternatively, the coordinating solvent may act as a nucleophile in this case. Enynes related to **27**, with two methyl substituents at the terminal alkene carbon, also suffer proton loss to form dienes such as **28** when a catalyst generated from [AuCl(PPh$_3$)] (5 mol %) and AgOTf (7 mol %) is used.[61] Products of type **28** have been obtained previously in intramolecular reactions of allylstannanes and allylsilanes with alkynes.[62]

In the absence of nucleophiles, 1,6-enynes may give rise to bicyclo[4.1.0]hept-4-ene derivatives **11** (see Scheme 3), which are the products of a cyclopropanation of the alkene by the alkyne. These products are formed by endo cyclization via intermediates **5** by proton loss and protodemetalation (Scheme 6).[13a,b,17f,63,64] This type of reaction is particularly facile for enynes tethered with an ether (as in **33**) or sulfonamide function. Addition of heteronucleophiles at the terminal alkene carbon by cleavage of the bond labeled **a** in intermediate **5** has been observed using $PtCl_2$ or $AuCl_3$ as the catalyst, leading to adducts of type **12** (Scheme 3).[17c] Cleavage of bond **b** in intermediate **5** to form derivatives **32** has also been observed in a few cases using electrophilic Au(I) or Pt(II) catalysts (Scheme 6).[40] Thus, enyne **33** reacts with gold catalyst **16a** to give the intramolecular cyclopropanation product **34** along with 3,4,7,9-tetrahydro-2*H*-pyrano[2,3-*c*]oxepine **35**, a product of type **32** (Scheme 7). In the case of substrate **36**, the intramolecular cyclopropanation occurs on the cinnamyl chain to form **37**. In addition, a more complex product **38** was obtained as the major compound.[40] Formation of rearranged **38** also proceeds via seven-membered ring intermediates. Accordingly, 6-endo-dig cyclization of **39** should give the gold(I) carbene **40**, whose opening could form oxonium cation **41**. In this case, instead of the loss of a proton, a ring contraction from **41** could lead to carbocation **42**, which would react with the alkenyl gold to give **43**. The cyclopropane ring could be formed as shown in Scheme 7 to give **44**, and a final protodemetalation would then afford **38**.

Scheme 6

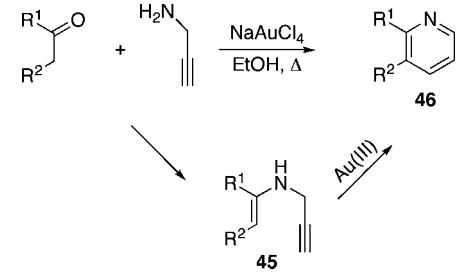


Scheme 7

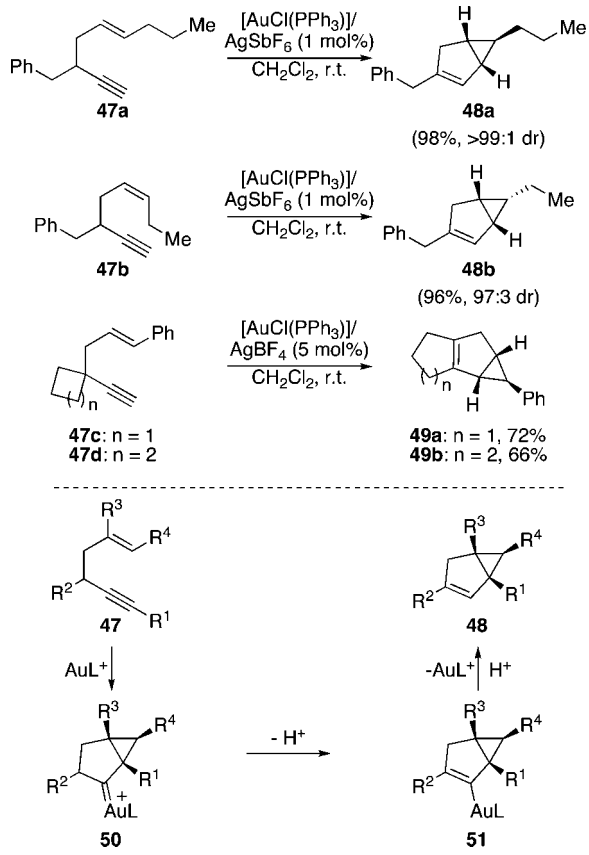


The first examples of cyclization of 1,5-enynes with gold were actually reported in the context of a new synthesis of pyridines (Scheme 8).[65] Thus, cyclization of propargyl enanimes **45** catalyzed by $NaAuCl_4 \cdot 2H_2O$ gives substituted pyridines **46** in a general way via a transformation that involves a dehydrogenation. The enamines are formed in situ by condensation of propargylamine and the corresponding ketone. Other catalysts, including AuCl, Cu(I), Cu(II), Pt(IV), Ag(I) salts, and $FeCl_3$ could also be used, although the corresponding yields were usually lower. This pyridine

Scheme 8



Scheme 9

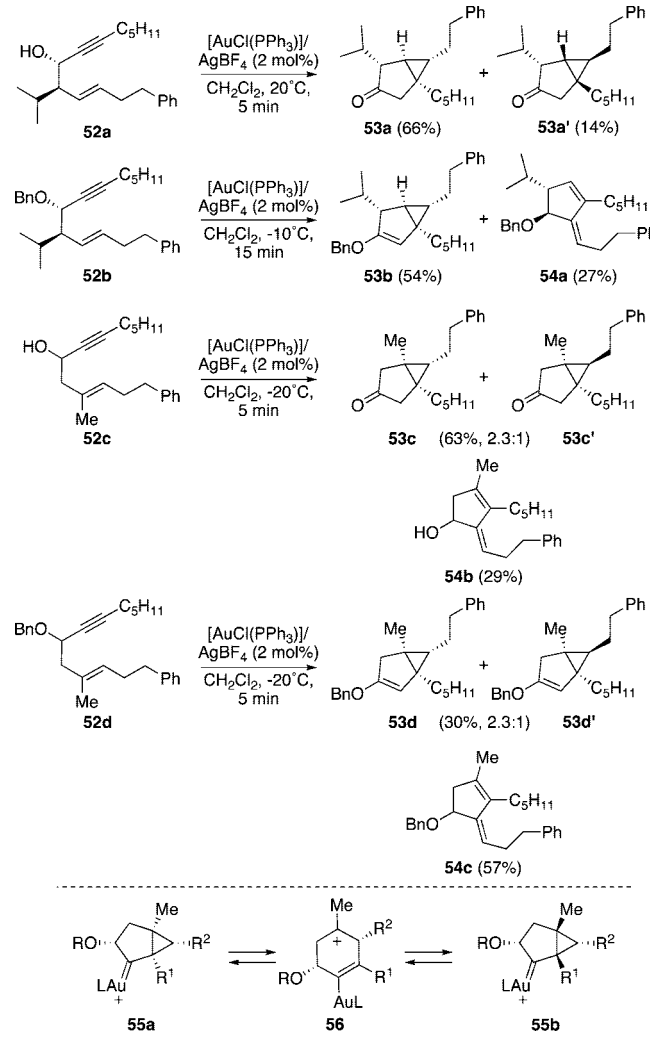


synthesis could proceed through a cyclopropyl metal carbene or a six-membered-ring cation (see Scheme 10).

Three groups found independently in 2004 that the gold- or platinum-catalyzed cyclization of 1,5-enynes gives bicyclo[3.1.0]hexanes.[20b,66,67] Thus, for example, simple enynes **47** afford derivatives **48** under mild conditions (Scheme 9).[67] The reaction is stereospecific: substrate **47a** exclusively affords bicyclo[3.1.0]hexane **48a**, whereas **47b**, with a cis-configured alkene, yields **48b** (97:3 diastereoselectivity). Interestingly, substrates **47c** and **47d** react with concomitant ring expansion to form the tricyclic derivatives **49a** and **49b**, respectively. Reaction of 1,5-enynes **47** probably proceeds by formation of cyclopropyl gold carbenes **50**, which evolve by proton loss to form alkenyl gold complexes **51** followed by protonolysis to form bicyclo[3.1.0] hexanes **48**. In the case of **47c** and **47d**, formation of **49a** and **49b** can be explained by ring expansion of an intermediate of type **50** (instead of proton loss) followed by elimination of AuL^+.

In a similar vein, enynes **52** gave bicyclo[3.1.0]hexanes **53** (Scheme 10).[52,68,69] However, in this case, products of skeletal rearrangement such as **54a**−**c** were also obtained

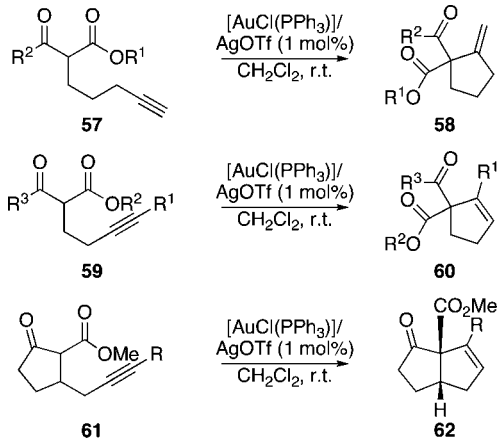
Scheme 10



(see section 2.5) Although the presence of an additional stereogenic center in **52a** leads to mixtures of diastereomers **53a** and **53a′**, formation of **53c′** and **53d′** as minor products in the cycloisomerizations of substrates **52c** and **52d**, respectively, is noteworthy since these products correspond to those expected from the Z isomers of the starting enynes. This lack of stereospecificity was explained in terms of an equilibrium between two rapidly interconverting six-membered-ring cations.[68] This result can also rationalized in terms of the opening of the initially formed cyclopropyl gold carbene **55a** to give six-membered-ring tertiary cation **56**, which can cyclize to form diastereomeric cyclopropyl gold carbene **55b**, the precursor of **53c′** and **53d′**. The fact that R^2 (as well as OR) in **55b** is in the more congested concave face of the bicyclo[3.1.0]hexane ring system can explain the stereoselectivity of these reactions, which favor **53c** and **53d** over **53c′** and **53d′**. Intermediate six-membered-ring cations of type **56** can be intercepted by an *O*-Boc group in reactions of Boc-protected hex-1-en-5-yn-3-ols, leading to cyclohex-4-ene-1,2-diol derivatives.[70] Intermediates related to **56** have also been proposed in the gold-catalyzed cyclization of *cis*-1-ethynyl-2-vinylcyclopropanes.[71]

In these reactions, 1,5-enynes react exclusively by endocyclic pathways. For a Pt(II)-catalyzed reaction, this was rationalized to be a result of the formation of a bicyclo[3.1.0]hexane system in the endo cyclization, which is more favorable than the strained bicyclo[2.1.0]pentane system that would be

Scheme 11



formed in the exo cyclization.[17c] Endo cyclization was also observed in the gold(I)-catalyzed cyclization of 1-alkynyl-2-alkenylbenzenes to form naphthalenes.[72,73] In this case, however, exo cyclization was also observed as a minor pathway from substrates bearing terminally substituted alkynes.[73] The exo derivatives became the major products when substrates with terminal alkynes or iodoalkynes were used. When a catalyst generated from [AuCl(PPh_3)] and AgOTf is used, 3-hydroxy-1,5-enynes also react by an endocyclic process; this has been applied in the synthesis of tetrahydronaphthalenes.[74] A totally different outcome was observed in the cyclization of 1,6-enynes with Grubbs catalysts, which leads to vinyl cyclobutenes.[75]

The addition of β-ketoesters to alkynes (Conia-ene cyclization) is also catalyzed by gold(I).[76,77] Thus, substrates **57** react in an exo fashion to give derivatives **58**, whereas **59** and **61** react by endocyclic pathways to give **60** and **62**, respectively (Scheme 11). These transformations can be viewed as intramolecular reactions of enols with alkynes that proceed exo- or endocyclically depending on the length of the tether. The reaction can be also performed efficiently using a gold catalyst with a triethynylphosphine ligand bearing bulky silyl end caps[78] or a catalyst generated in situ from a cyclic thiourea−AuCl complex and AgOTf.[79] An enantioselective version of this reaction was developed using chiral palladium complexes.[80–82] Silylketene amides or carbamates react similarly with alkynes to form cyclopentanes or dehydro-δ-lactams.[83]

The analogous gold-catalyzed reaction of silyl enol ethers with alkynes was applied in the synthesis of the alkaloids (+)-licopladine A (**65**)[84] and (+)-fawcettimine (**68**) (Scheme 12).[85] In these syntheses, a similar gold-catalyzed 5-endo-dig cyclization of a TBS enol ether with a iodoalkyne was used to efficiently convert the enantiomerically pure intermediates **63** and **66** into the key bicyclic compounds **64** and **67**, respectively. Reactions of simpler substrates bearing a 1,6- or 1,7-relation between the silyl enol ether and the alkyne take place in an exo fashion to form five- or six-membered rings.[86] The cyclization of aldehydes with alkynes that takes place in the presence of secondary amines proceeds similarly via enamines formed in situ.[87]

Tethering the alkene and the alkyne through an oxygen in substrates **69** leads to different reactions (Scheme 13).[44] Propargyl vinyl ethers **69** undergo Claisen rearrangement with Au(I) catalysts to give allenes **70**, which were isolated as the corresponding alcohols **71**. A similar gold-catalyzed transformation of propargyl allyl ethers, which proceeds by the initial isomerization to the propargyl vinyl ethers, has also been observed.[40,88] When the reaction of substrates **69** was performed in the presence of water or alcohols, dihydropyrans **72** were obtained in good yields.[89] These results can be interpreted in terms of ring expansion of the initial cyclopropyl gold carbene **73** to form the oxonium cation **74**, which can undergo C−O fragmentation to afford the allene **70**. Alternatively, trapping of the oxonium cation **74** with heteronucleophiles forms **72**.

A related transformation of enol ethers **75** leads to allenes **76**, which cyclize to afford furans **77** (Scheme 14).[90] A variation of this procedure, in which the first rearrangement is performed with a Ag(I) catalyst, has been developed for the synthesis of pyrroles.[91] In this procedure, the intermediate 1,3-dicarbonyl compounds **76** were then condensed with primary amines, and this step was followed by a final Au(I)-catalyzed cyclization.

In the above transformations, either 1,5- or 1,6-enynes were cycloisomerized using gold catalysts. Although less studied, 1,7-enynes also react uneventfully with gold catalysts in skeletal rearrangements (see section 2.4) and hydroxy- and alkoxycyclizations (see section 4.2). However, no example of the cyclization of a simple 1,8-enyne with a gold catalyst has been reported to date (see however, section 3.1). Recently, a remarkable cyclization of the 1,9-enyne **78** to form the 10-member ring **79** has been disclosed (Scheme 15).[92] This reaction presumably occurs via intermediates **80** and **81**. Although a single example of this reaction was reported and a large amount of gold(I) is required, this result nevertheless shows that formation of large rings from 1,*n*-enynes ($n \geq 7$) using gold catalysts is possible.

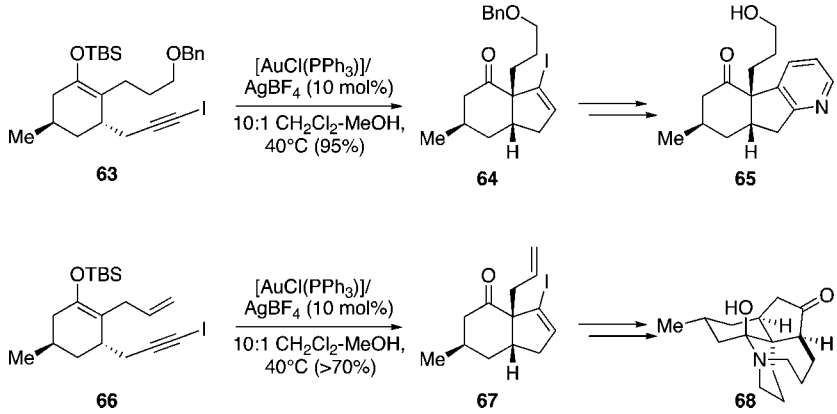
2.2. Single- and Double-Cleavage Skeletal Rearrangement of 1,6-Enynes

In non-nucleophilic solvents, 1,6-enynes react with gold(I) catalysts under mild conditions to give products of skeletal rearrangement (Scheme 16).[3c,7,8] In this way, enyne **27a** reacts with [AuCl(PPh_3)] and $AgSbF_6$ in CH_2Cl_2 to form diene **82a**, in contrast to what occurred when the reaction was carried out in DMSO, which led to a mixture of **28** and **29** (Scheme 5). Formation of **82a** from **27a** can be accomplished even at −40 to −60 °C using catalyst **16a** or **16b**.[93] Similarly, enynes **27b−e** gave dienes **82b−e** in a stereospecific rearrangement in which the configuration of the starting alkene is retained in the final product. Similar transformations have been carried out with other gold(I) catalysts.[52,60,94]

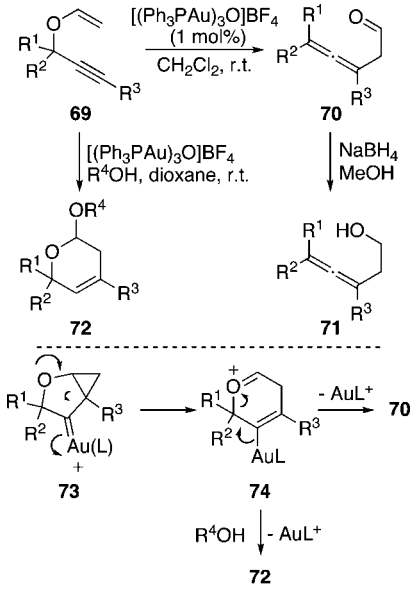
The transformations of **27a−e** into **82a−e** are examples of single-cleavage rearrangements in which only the alkene is cleaved. On the other hand, enyne **27f**, with a methyl substituent at the alkyne, exclusively affords diene **82b** by a double-cleavage rearrangement[11–14] in which both the alkene and the alkyne suffer cleavage.[93]

Formation of single-cleavage products **82a−e** via metal-catalyzed reactions of enynes had been proposed to take place by conrotatory ring opening of intermediate cyclobutenes (see section 2.4). However, experimental and theoretical calculations do not support that proposal.[93] Thus, in a detailed study of the rearrangement of enyne **27a** to give diene **82a**, which proceeds smoothly at low temperatures with **16a** or **16b** as the catalyst, the activation parameters were determined. This reaction was found to have a small enthalpy of activation ($\Delta H^{\ddagger} = 6.2$ or 3.7 kcal mol^{-1} for **16a** or **16b**, respectively) and a negative entropy of activation ($\Delta S^{\ddagger} = -50.3$ or −60.6

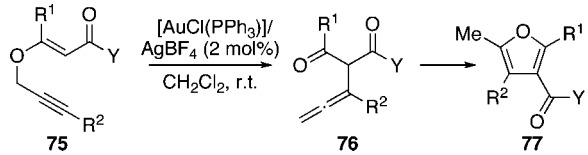
Scheme 12



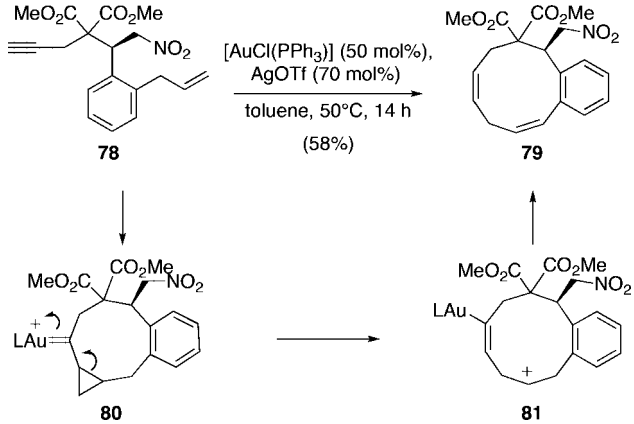
Scheme 13



Scheme 14

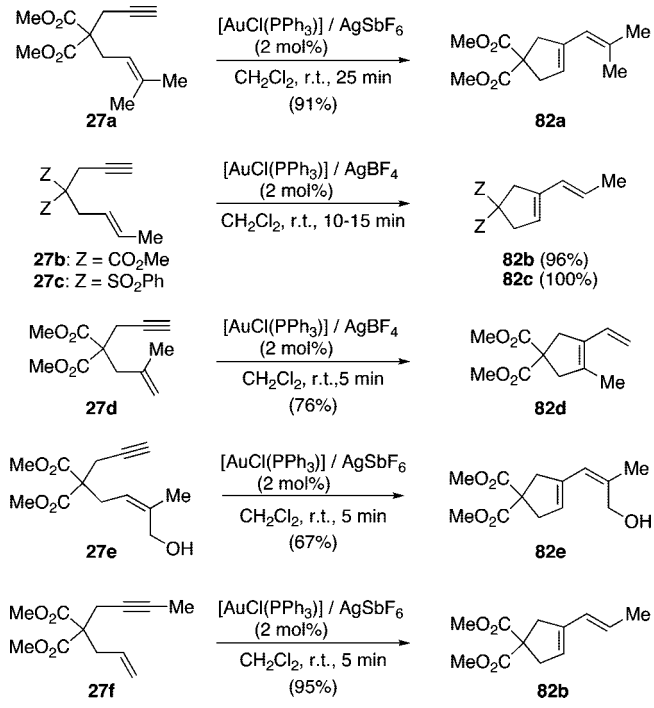


Scheme 15



cal mol^{-1} K^{-1} for **16a** or **16b**, respectively). These results establish a very low activation energy for the hypothetical conrotatory opening of a cyclobutene, which should be a

Scheme 16



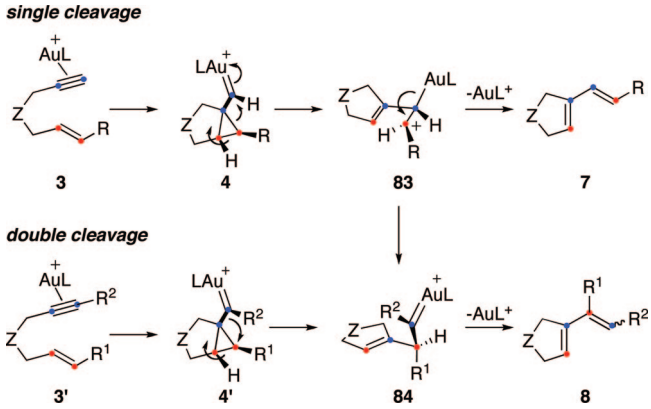
fast process at temperatures as low as −63 °C. This is not consistent with theoretical data for ring opening of cyclobutenes related to bicyclo[3.2.0]hept-5-ene.

Overall, the mechanism for the skeletal rearrangement is consistent with evolution of the initial *anti*-cyclopropyl gold carbenes **4** (formed in the 5-exo-dig cyclization) to give carbocations **83**, which then undergo metal elimination to give dienes **7** (single cleavage) (Scheme 17). For the double-cleavage rearrangement, intermediates **4′** can suffer a dio-tropic rearrangement[95,96] to give new carbenes **84**, which lose an α-hydrogen and then protodemetalate to form dienes **8** (double cleavage). Intermediates **84** can also be formed by a carbocationic 1,2-shift of the cyclic alkenyl group in **83**.[93]

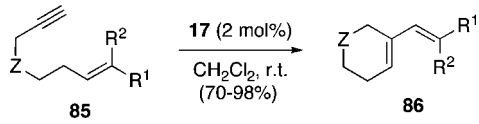
Evidence for the involvement of the cyclopropyl gold carbenes **4** and **84** has been obtained from intra- and intermolecular cyclopropanations (see section 2.7). Further evidence for the involvement of these species was provided by the formation of the corresponding aldehydes when the cyclizations were performed with Au(I) catalysts in the presence of Ph_2SO as a mild oxidant.[97]

Although the intermediates **4** are conventionally drawn as cyclopropyl gold carbenes, DFT calculations have shown that

Scheme 17



Scheme 18



they have highly distorted structures with a rather short C−C bond connecting the carbene and the cyclopropane, consistent with substantial double-bond character.[93,98] The structures of **4a** and **4b** are actually consistent with a delocalized cyclopropylmethyl/cyclobutyl/homoallyl carbocation[99] stabilized by gold (Figure 2).

2.3. Skeletal Rearrangement of 1,7-Enynes

Only a few examples involving skeletal rearrangement of 1,7-enynes using non-gold catalysts have been reported; in these cases, $[RuCl(CO)_2]_2$,[12a] $PtCl_2$,[12b,f] $PtCl_4$,[11a] $[IrCl(CO)_3]_n$,[12d] $GaCl_3$,[12e,100,101] and $InCl_3$[12g] were used as catalysts. With the exception of rearrangements catalyzed by $GaCl_3$, which proceeded with 10−20 mol % catalyst at 23−40 °C, higher temperatures were required for all of these catalysts. Gold(I) complexes are again the best catalysts to effect this skeletal rearrangement.[78,102] Thus, a variety of enynes **85** variously substituted at the alkene react at room temperature with the cationic catalyst **17** to provide dienes **86** in good yields (Scheme 18).[102]

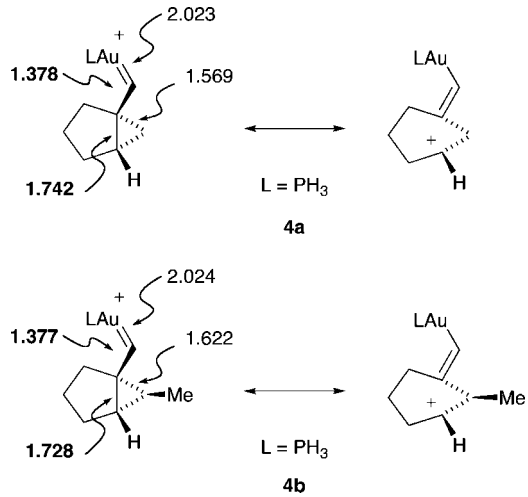
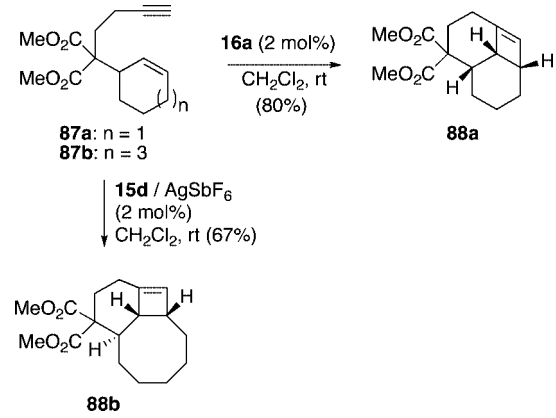
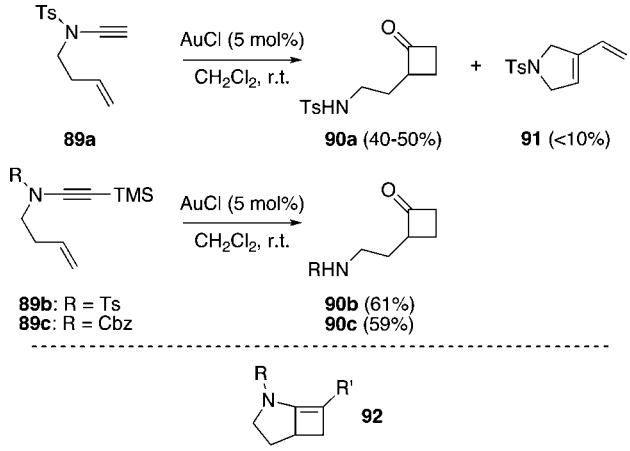


Figure 2. Calculated bond distances (Å) for **4a** and **4b** obtained from DFT calculations at the B3LYP/[6-31G(d) (C, H, P); LANL2DZ (Au)] level.[93,98]

Scheme 19



Scheme 20



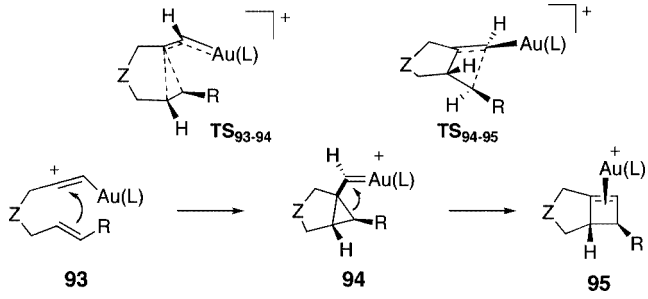
2.4. Formation of Cyclobutenes from 1,6- and 1,7-Enynes

Cyclobutenes resulting from a formal [2 + 2] cycloaddition have been obtained in certain reactions of 1,7-enynes catalyzed by electrophilic transition metals.[11,12e,13a,103] These bicyclo[4.2.0]oct-6-enes are quite stable compounds. Thus, for example, the gold-catalyzed reactions of 1,7-enynes **87a** and **87b** stereoselectively provide the tricyclic compounds **88a** and **88b**, respectively (Scheme 19), which do not undergo ring opening at 120−150 °C to form 1,3-dienes. Furthermore, heating **88a** in MeCN at 120 °C with 5 mol % $PtCl_2$ only gave the product of double-bond migration into the six-membered ring.[93]

Other type of cyclobutenes have also been obtained from 1,6- or 1,7-enynes (see section 4.3).[11b,104] However, there is not a single example of a stable bicyclo[3.2.0]hept-5-ene obtained by a metal-catalyzed reaction from a 1,6-enyne.[105–107] A 3-oxabicyclo[3.2.0]hept-5-ene was proposed to be an intermediate in a Pt(IV)-catalyzed cyclization, but it could not be isolated.[63] Interestingly, following earlier work done with $PtCl_2$ as catalyst,[108] it was found that the gold-catalyzed reaction of 1,6-ene-ynamines **89** affords cyclobutanones **90** (Scheme 20)[109] in a process that probably takes place through the unstable bicyclic enamines **92**. Interestingly, in the reaction of **89a**, the skeletal-rearrangement diene **91** was obtained as a minor product, whereas in the reaction of the same substrate catalyzed by $PtCl_2$, **91** was obtained in 98% yield.[108]

No direct pathway for the formation of cyclobutenes from *anti*-cyclopropyl gold carbenes such as **4** (Scheme 17) was

Scheme 21



found to occur by a low-energy process.[93] Similar results were obtained for the analogous platinum carbenes.[9] DFT calculations carried out on a different system found a relatively high barrier (25.4 kcal mol^{-1}) for the formation of a cyclobutene from an *anti*-cyclopropyl platinum carbene (an endothermic process for which $\Delta H = 11.5$ kcal mol^{-1}).[110,111] In contrast, a syn attack of the alkene in **93** can form *syn*-cyclopropyl gold carbene **94** via $\mathbf{TS_{93-94}}$ ($E_a = 9.4$ kcal mol^{-1}); **94** then undergoes smooth ring expansion to form cyclobutene **95** via $\mathbf{TS_{94-95}}$ ($E_a = 7.8$ kcal mol^{-1}) (Scheme 21). The anti-to-syn isomerization from **4** to **94** requires a higher activation energy (~25 kcal mol^{-1}).[9,93]

2.5. Endocyclic Skeletal Rearrangement of 1,6-Enynes

Endocyclizations to give products of type **9** (Scheme 3) were first observed using gold(I) catalysts.[7,8] Thus, enynes **27g−k** gave six-membered ring derivatives **96a−e** as the major or exclusive products of the rearrangement (Scheme 22). As shown in the reactions of **27h** and **27k**, this endocyclic rearrangement is stereospecific. Only a few additional examples of this type of rearrangement from simple 1,6-enynes have been reported; these have used $InCl_3$[12f,g] or Ru(II)[112] as the catalyst. Endocyclic rearrangements have also been observed in the reaction of *cis*-4,6-dien-1-yl-3-ol derivatives with gold or platinum catalysts.[113] Products of type **96** are obtained in cyclizations of 1,6-enynes catalyzed by Rh(I), although labeling experiments have shown that the mechanism proceeds through vinylidene intermediates in this case.[114]

Labeling experiments have yielded results that are consistent with an intramolecular process in which the terminal carbon of the alkene is attached to C-2 of the alkyne (Scheme 23).[98] Thus, **27g-*d*$_1$** and **27l-*d*$_1$** provided a mixture of monodeuterated derivatives **96a-*d*$_1$** and **96f-*d*$_1$**. Interestingly, whereas gold catalysts provide single-cleavage-rearrangement dienes **82i-*d*$_1$** and **82j-*d*$_1$** as the major products, the platinum-catalyzed reaction of **27g-*d*$_1$** gives the double-cleavage-rearrangement product **82i-*d*$_1$′**. DFT calculations support a mechanism in which cyclopropyl gold(I) carbene **4** rearranges with ring opening to give cation **97** in a moderately endothermic process that has an activation energy of only 9.6 kcal mol^{-1}. Metal loss from **97** gives product **9**. Interestingly, the mechanism of this endocyclic rearrangement is just a variation of the single-cleavage rearrangement of **4** to give **7** via intermediate **83** (see also Scheme 17).

2.6. Skeletal Rearrangement of 1,5-Enynes

The formation of rearrangement products **54a−c** from 1,5-enynes (Scheme 10)[68] can be rationalized as shown in Scheme 24. Thus, upon complexation of Au(I) to the alkyne in **98**, an endocyclization occurs to form cyclopropyl gold carbene **55**, which may suffer a skeletal rearrangement via **99** to give **54**. This is an example of a single-cleavage rearrangement occurring in 1,5-enynes.

Siloxy 1,5-enynes such as **100a−c** react with AuCl as the catalyst to give cyclohexadienes **101a**, **102a**, and **102b** (Scheme 25).[115] The analogous reaction of 1,5-enynes in which the OTIPS group has been replaced by an alkyl or aryl group is better performed with less-electrophilic $PtCl_2$.[115b] This mechanistically intriguing transformation probably involves a double-cleavage rearrangement of 1,5-enynes. Thus, complex **103** (X = OTIPS) could form gold carbene **104**, which then undergoes ring expansion in a diatropic rearrangement to give **105** by a process reminiscent of that found for **4′** in the double-cleavage rearrangement of 1,6-enynes (Scheme 17). Proton loss and demetalation then affords 1,4-cyclohexadiene **101** or **102**. Similar transformations have been found with other 1,5-enynes.[68]

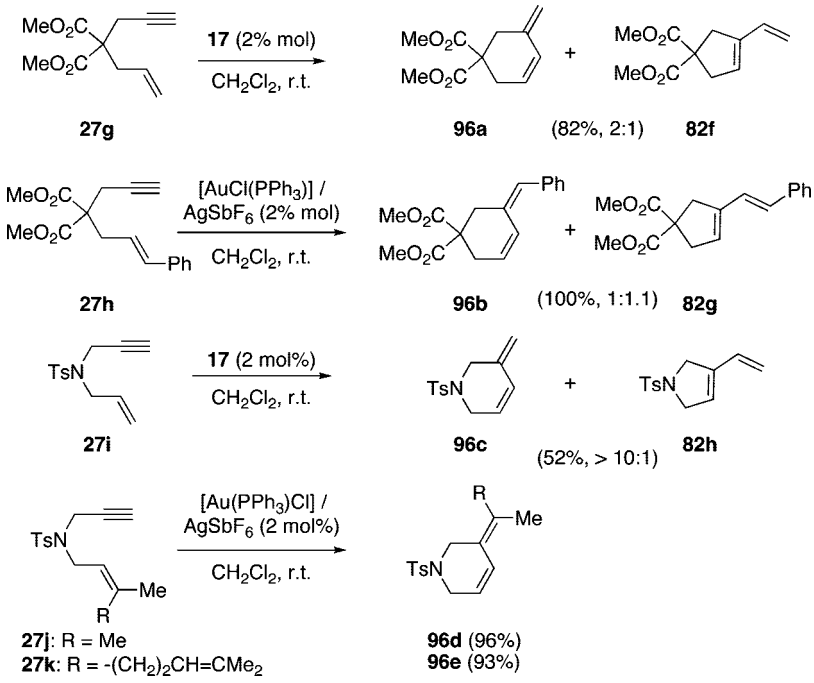
2.7. Cyclopropanation by Intermediate Gold Carbenes

Through the use of Au(I) catalysts, dienynes **106a−c** undergo totally stereoselective cyclizations to yield tetracyclic compounds **107a−c** via intermediates **108** (Scheme 26)[7,47] under milder conditions than those required with other metal catalysts.[12c,20,21] According to calculations,[47] cyclopropanation of the terminal alkene by gold carbene **108** takes place in one step to form a cyclopropane metalated at the corner. This biscyclopropanation also takes place with Ag(I), albeit less efficiently.[116] Intramolecular cyclopropanations of gold carbenes formed in other reactions have also been observed.[117] Products of intramolecular cyclopropanation have also been obtained via reactions of dienynes catalyzed by [Cp*RuCl(cod)], although a different mechanism has been proposed.[118]

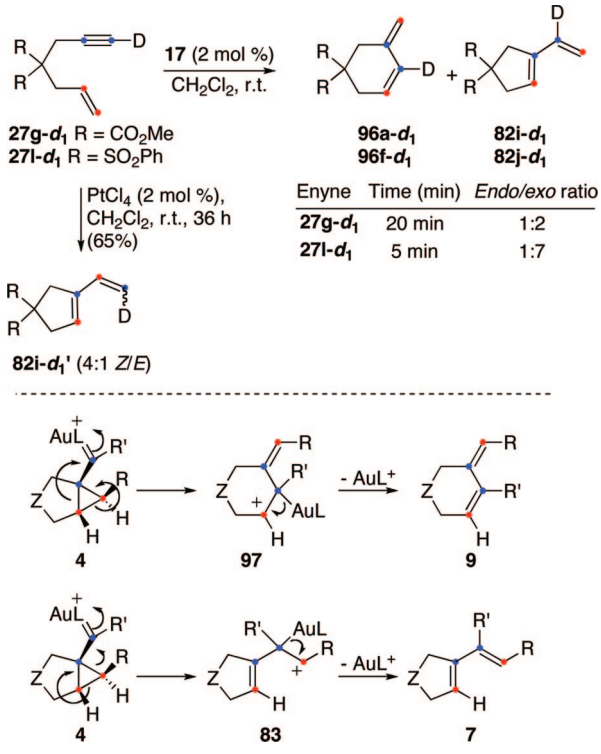
A remarkable transformation of this type that highlights the increase in molecular complexity that can be achieved using gold catalysis under mild conditions was disclosed through the use of dienynes such as **109a−c** as substrates (Scheme 27).[119] In this reaction, the initially formed cyclopropyl gold carbenes **111** react intramolecularly with the double bond of the cyclohexene to form the pentacyclic derivatives **110a−c**. Similarly, the intermolecular reaction between 1,6-enynes and alkenes proceeds with catalysts formed in situ from complexes **18** or **19a** (Scheme 28).[53] Interestingly, whereas enyne **27h** reacts with norbornene to give **112** via an intermediate of type **4** (see Scheme 17), **27g** and **27d** react with styrene and norbornene to give **113** and **114**, respectively, via rearranged gold carbenes of type **84**. Gold carbene intermediates formed by 1,2-acyl migration (see section 3.1) also undergo cyclopropanation reactions with olefins.[71,120] In this case, use of DTBM-SEGPHOS as the chiral ligand for gold(I) yielded 60−85% ee in the intermolecular reaction.

Additional evidence for the involvement of metal carbenes in these reactions was obtained in the reaction of dimeric substrates **115** with the cationic Au(I) catalyst **16a** to give **116/116′** (Scheme 29).[53] This reaction can be explained by isomerization of the initially formed cyclopropyl gold carbene **117** to give **118** via a [1,3]-metallotropic shift, followed by intramolecular trapping of the gold carbene by the alkene. This type of [1,3]-metallotropic shift has been observed previously for carbene complexes of Rh;[121] Cr, Mo, and W;[122] and Ru.[123–125] Additional examples of [1,3]-

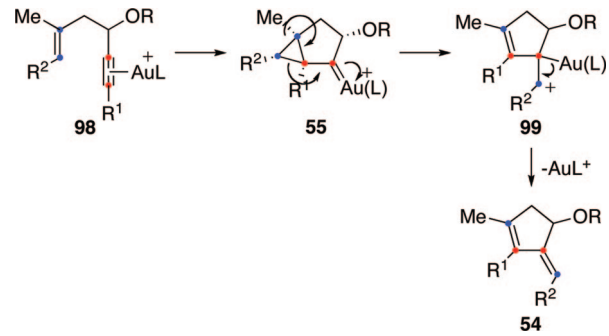
Scheme 22



Scheme 23



Scheme 24



metallotropic shifts in gold chemistry have also been observed.[126–129]

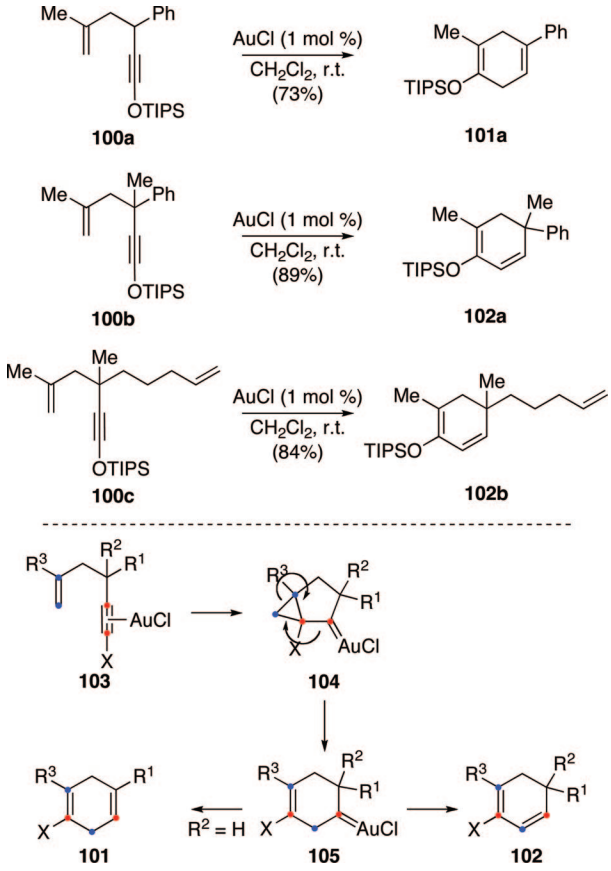
3. Cycloisomerizations of Enynes Bearing Propargylic Carboxylates or Ethers

3.1. Cycloisomerizations of Enynes via Propargylic 1,2- and 1,3-Acyl Migration

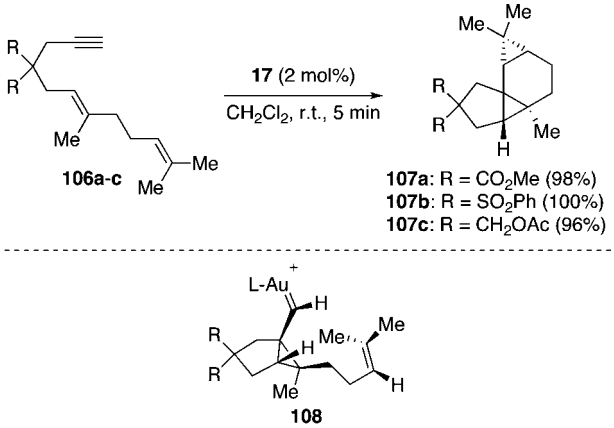
Propargylic esters coordinate to gold, forming complexes **119** that can undergo 1,2- or 1,3-acyl migrations to give α-acyloxy-α,β-unsaturated carbenes **120** or allene-gold complexes **121**, respectively (Scheme 30).[130–132] According to DFT calculations, formation of **120** and **121** is not concerted but proceeds in two steps through five- and six-membered-ring intermediates, respectively.[131,132] Similar pathways have been described for other metal catalysts.[20a,b,133–135] Evidence for the involvement of gold carbenes **120** has been obtained in intermolecular cyclopropanation reactions with alkenes,[53,120,135,136] trapping with carbon nucleophiles[137] and sulfides,[138] and oxidation with Ph_2SO to form α,β-unsaturated carbonyl compounds.[97]

In principle, for the gold-catalyzed cyclization of enynes bearing α-acyloxy substituents at the propargylic position, two mechanistically distinct possibilities that depend on the order of attack by the acyloxy group and the alkene on the alkyne in complexes of type **122** probably exist (Scheme 31). If the alkene were to react first, the cyclopropyl metal carbene **123** would be formed, which could then suffer intramolecular attack by the acyl on the carbene followed by elimination (formal 1,2-migration of the acyl) to give **124** after metal loss. Alternatively, the carboxylate group might first undergo the 1,2-migration to form carbene **125**, which would then form **124** by intramolecular cyclopropanation. The overall process is known as the Ohloff−Rautenstrauch rearrangement (or, more simply, the Rautenstrauch rearrangement), following its original discovery in the context

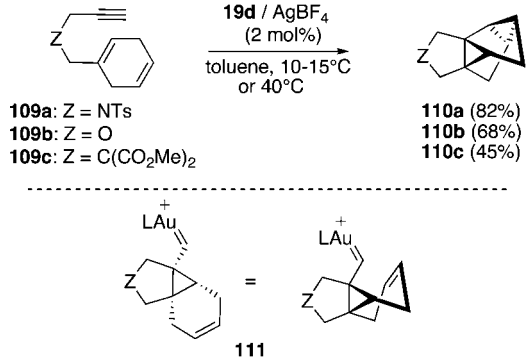
Scheme 25



Scheme 26

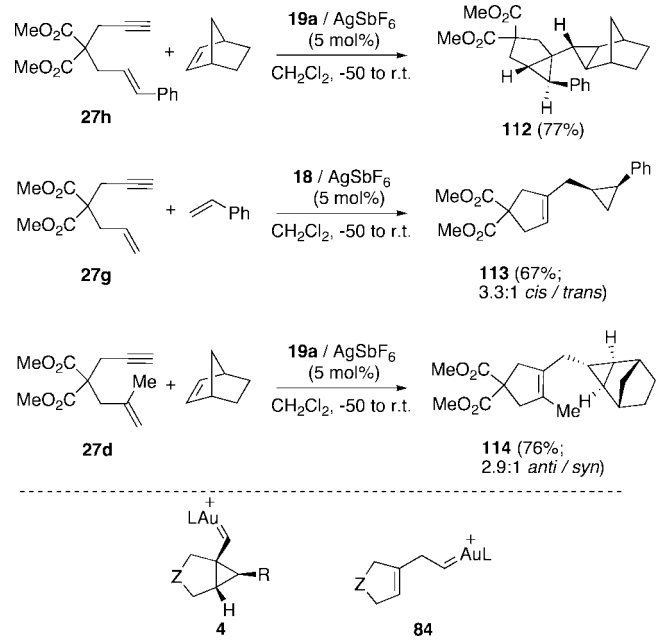


Scheme 27

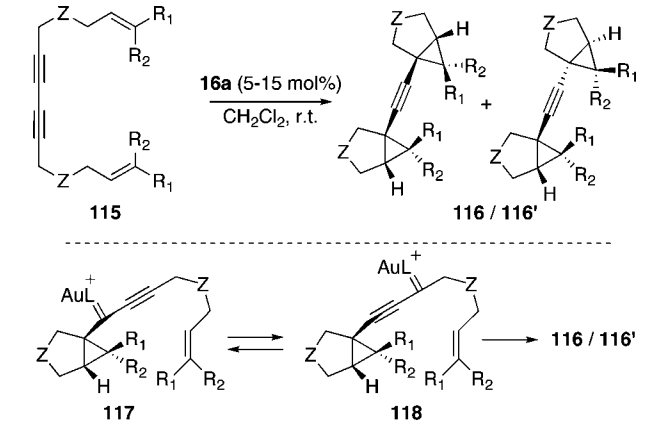


of zinc- or palladium-catalyzed cyclizations of similar systems.[139,140]

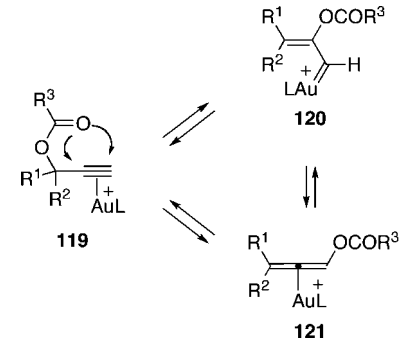
Scheme 28



Scheme 29



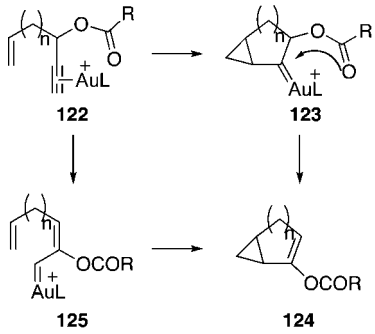
Scheme 30



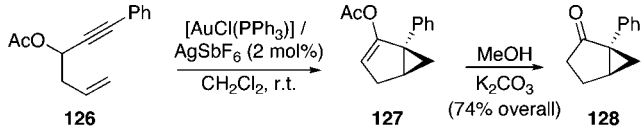
The gold-[66] and platinum-catalyzed[20b] Rautenstrauch rearrangements were discovered independently by two groups. Thus, for example, the gold-catalyzed cyclization of propargylic acetate **126** gives **127**, the product of cyclization and 1,2-acetate migration, which can be methanolyzed to yield ketone **128** (Scheme 32).[66]

The first Rautenstrauch mechanistic pathway mentioned above (**122** to **123**, Scheme 31) is probably followed when $n = 2$, as shown in a key Pt(II)-catalyzed cyclization for the synthesis of (-)-α-cubebene and (-)-cubebol.[141] This was established on the basis of the observation that the config-

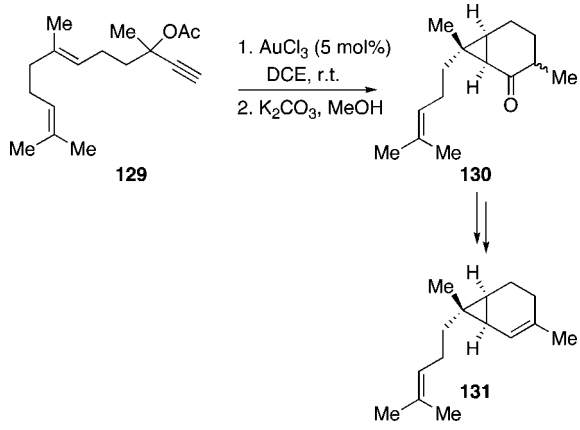
Scheme 31



Scheme 32



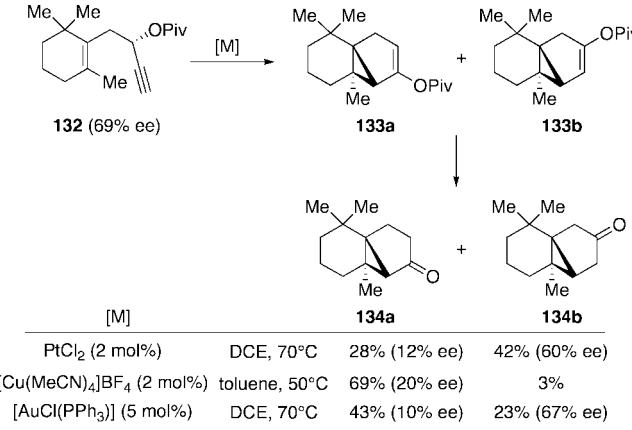
Scheme 33



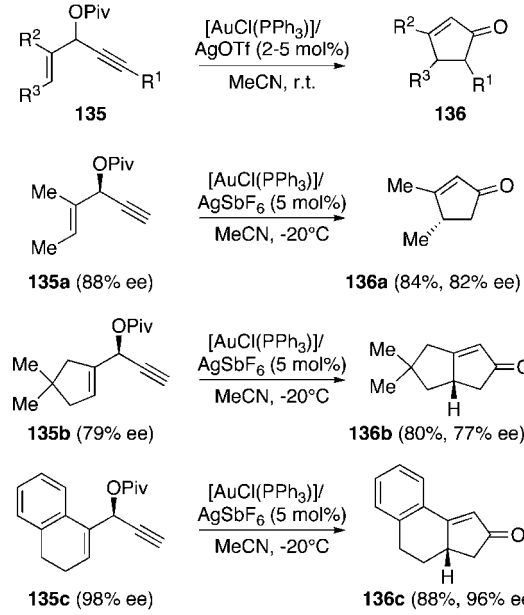
uration at the stereogenic center carrying the acetate translates into the configuration of the final products, thereby excluding planarization of the intermediate. (-)-Cubebol was also synthesized using a similar cyclization catalyzed by Pt(II), Au(I), or Cu(I).[142] A cyclization of this type catalyzed by $AuCl_3$ was used for the synthesis of 2-sesquicarene (**131**) and related compounds (Scheme 33).[141,143] The key step in the synthesis of **131** was the stereoselective cyclization of propargyl acetate **129** to give a bicyclic enol acetate that was methanolized to give ketone **130**.

It is interesting to compare the effect of different metals on the cyclization of substrate **132**, a 1,5-enyne, carried out with Cu(I), Pt(II), and Au(I) (Scheme 34).[143] The product of pivalate migration (**133a**) was selectively formed in the Cu(I)- and Au(I)-catalyzed reactions, whereas the reaction catalyzed by $PtCl_2$ provided as the major product **133b**, in which the pivalate has not migrated. Interestingly, in contrast with the expected retention of the enantiomeric excess observed for **133b**, as demonstrated in the corresponding ketone **134b** (of unknown absolute configuration), substantial loss of the enantiomeric excess was observed for **133a**, which could suggest that acyl migration (**122** to **125**, $n = 1$, Scheme 31) predominates in this case. However, a theoretical study of these cyclization reactions catalyzed by $PtCl_2$ supports a mechanism taking place through intermediates **123**.[144,145] The small enantiomeric excesses obtained for **133a** were explained as a result of competitive cyclopropanation of the

Scheme 34



Scheme 35



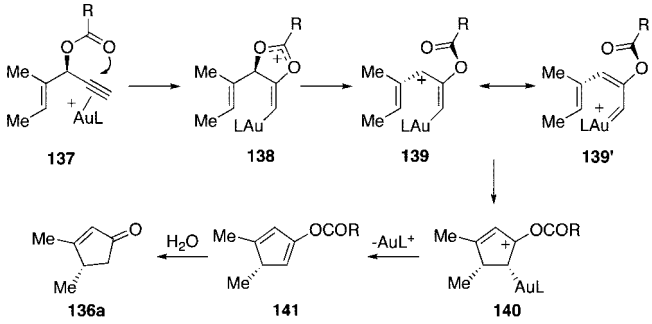
two diastereotopic faces of the alkene proceeding via transition states having similar energies.

1,4-Enynes **135** substituted with a carboxylate group at the propargylic position undergo the Rautenstrauch rearrangement in a general way to afford cyclopentenones **136** (Scheme 35).[146] The reaction proceeds with remarkable transfer of chirality, allowing the efficient enantioselective synthesis of cyclopentenones **136a−c** from the corresponding enantiomerically enriched propargylic pivalates **135a−c**.

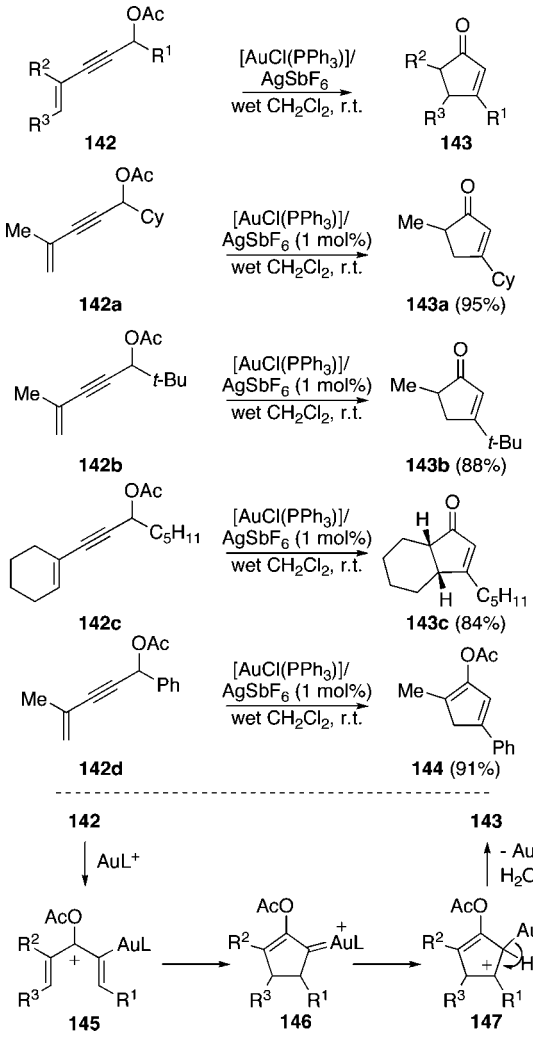
This reaction was proposed to proceed by 1,2-acyl migration via intermediates **137** and **138** to give pentadienyl cation **139** (Scheme 36). This intermediate can also be considered to be a conjugated gold carbene **139′**, a species of type **125** ($n = 0$, Scheme 31). Cation **139** then undergoes electrocyclization to form **140**, which suffers metal loss to give cyclopentadiene **141**. The final cyclopentenones are obtained by hydrolysis of the enol acetates. The enantioselectivity can be explained by a remarkable center-to-helix chirality transfer, which was supported by DFT calculations.[147] These results indicate that the cyclization rate is greater than the rates of helix interconversion and carboxylate rotation.[147]

A synthesis of cyclopentenones somewhat related to that shown in Scheme 36 was found to start from conjugated 1,3-enynes **142** (Scheme 37).[148] Cyclopentenones **143** are

Scheme 36



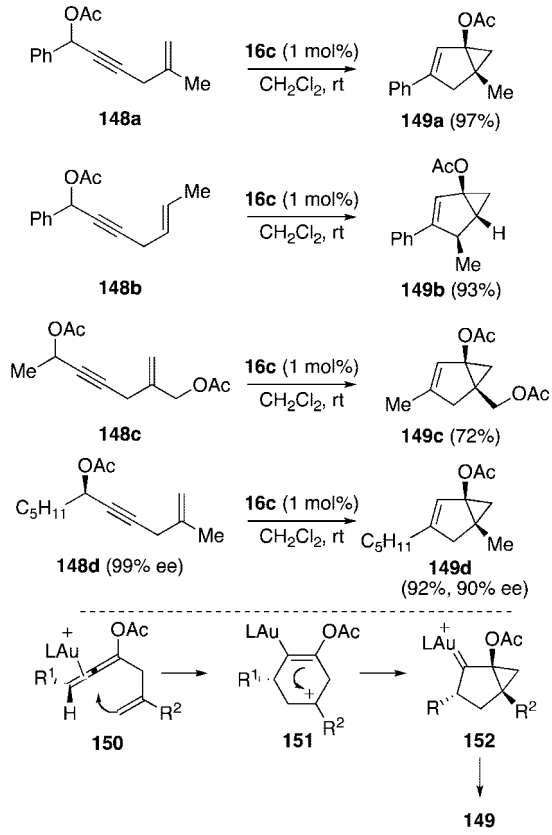
Scheme 37



obtained by the hydrolysis of enol acetates such as **144**. This transformation involves a 1,3-migration of the acetate to form pentadienyl cation **145**, which undergoes a Nazarov-type cyclization to form gold carbene **146**. 1,2-Hydrogen migration to form **147** followed by metal loss and hydrolysis then leads to cyclopentenones **143**. DFT calculations support this mechanism and provide interesting insight into the mechanism of the final stages of the process (**146** to **143**).[131] Interestingly, this theoretical study showed that although the 1,2-hydrogen migration to form **147** is possible, a more facile proton loss assisted by H_2O, followed by a protodemetalation, is preferred in the presence of water.

Propargylic acetates **148** react differently in a process that also takes place via 1,3-acyl migration (Scheme 38).[149] Thus,

Scheme 38

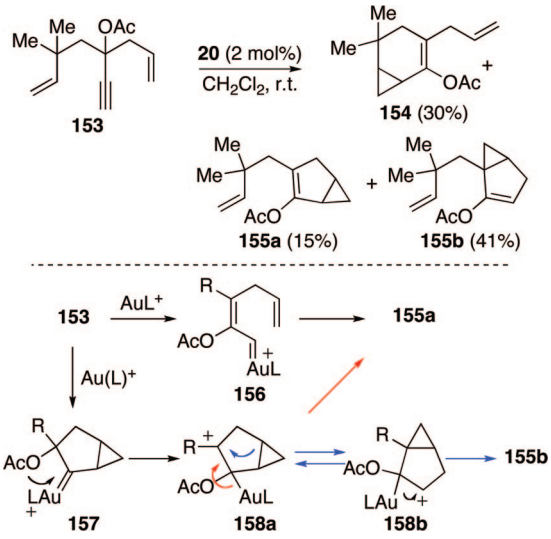


reaction of substrates such as **148a**−**d** gives bicyclo[3.1.0]hexenes **149a**−**d**, which can be transformed into cyclohexenones by treatment with K_2CO_3 in MeOH. As shown in the transformation of **148d** into **149d**, the reaction takes place with nearly complete transfer of the stereochemical information. The reaction was proposed to take place via the allene−gold complex **150**, which reacts with the alkene to produce cyclohexyl carbocation **151**, leading to formation of cyclopropyl gold carbene **152**. Finally, proton loss and demetalation forms **149**.

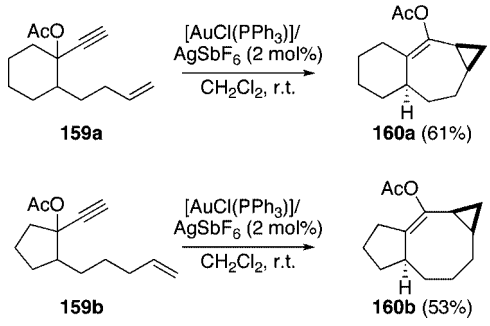
An interesting cyclization of propargylic acetate **153** has been shown to afford a mixture of the three compounds **154**, **155a**, and **155b** when the Au(I) complex **20** bearing an NHC ligand is used (Scheme 39).[150] Product **154** is the one expected from a 1,6-enyne (see section 2.1 and Scheme 6). On the other hand, formation of products **155a** and **155b** by cyclization of the 1,5-enyne suggests that the two alternative mechanisms outlined in Scheme 31 might take place in this case. Thus, a 1,2-acetate migration in the gold complex of **153** would give carbene **156**, which could react with the terminal alkene to give **155a**. Alternatively, reaction of the alkene with the alkyne could give **157**, which after 1,2-acetate migration would give **158a**. This carbocation could be in equilibrium with **158b** (blue arrows in Scheme 39), from which metal loss would give cyclopropane **155b**. Elimination of Au(I) from **158a** (red arrows in Scheme 39) could also afford **155a**.

Cyclization of substrates such as **159a** and **159b** gives bicyclic derivatives **160a** and **160b**, respectively, with high stereoselectivity by an endocyclic pathway (Scheme 40).[151] In the cyclization of this type of substrate, better yields were usually obtained with $PtCl_2$ or $AuCl_3$ as the catalyst. Remarkably, the cyclization of **159b** is an example of a cyclization of a 1,8-enyne, although it could be interpreted

Scheme 39



Scheme 40



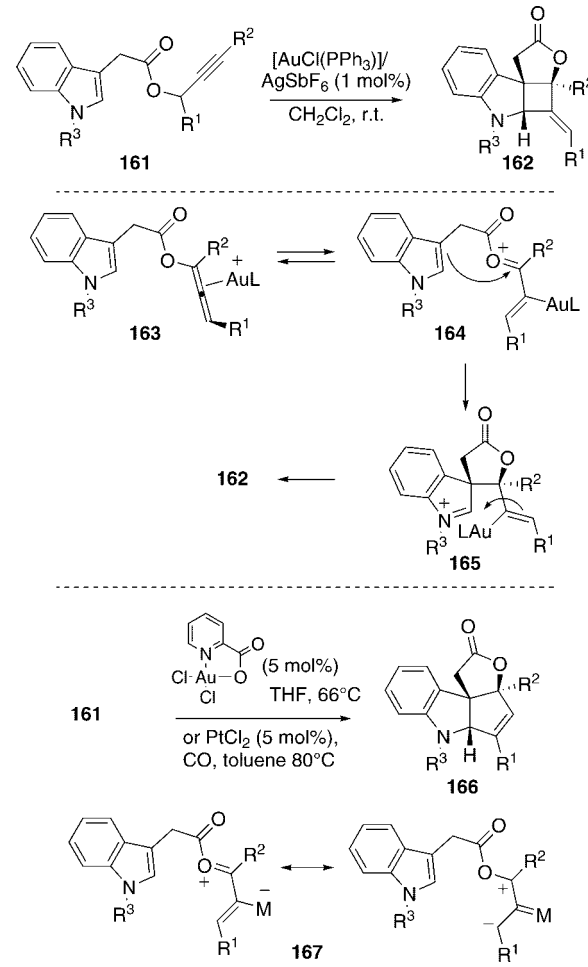
mechanistically as an intramolecular cyclopropanation of the terminal alkene by the gold carbene formed in a 1,2-acyl migration.

3.2. Cycloisomerizations of Related Substrates Proceeding via 1,2- or 1,3-Acyl Migration

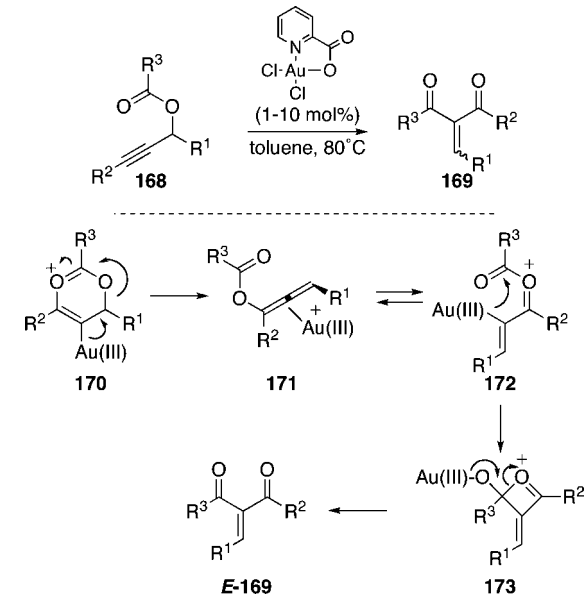
An interesting transformation involving the indole nucleus was found to start from propargylic carboxylates **161**, which yield tetracyclic compounds **162** with Au(I) (Scheme 41).[152] This reaction proceeds by formation of allene−gold complex **163** in equilibrium with **164**, which reacts intramolecularly with the indole to form **165** and then **162**. An allene of type **163** was isolated when the reaction was performed with $AuCl_3$ as the catalyst. [152] Interestingly, when the reaction of substrates **161** is performed with dichloro(pyridine-2-carboxylato)gold(III) or Pt(II) as catalysts, products **166** are obtained instead.[153] This new reactivity can be explained by formal [3 + 2] cycloaddition of the 1,3-dipoles in **167** with the indole nucleus.

Simple propargylic esters **168** also undergo a 1,3-acyl migration catalyzed by Au(III), leading finally to 1,3-dicarbonyl compounds **169** as mixtures of E and Z isomers (Scheme 42).[154] The reaction presumably proceeds by initial formation of complex **170**, followed by ring opening to give **171**.[155] The allene−gold complex **171** then generates **172**, which undergoes intramolecular acylation via cyclic intermediate **173** to form ***E*-169**. The 1,3-dicarbonyl compounds ***E*-169** would equilibrate readily with their Z isomers. Interestingly, propargylic esters **168** react with $[Cu(MeCN)_4]BF_4$ as the catalyst to form ***E*-169** products, whereas Z isomers were preferentially formed with $PtCl_2$.[156]

Scheme 41

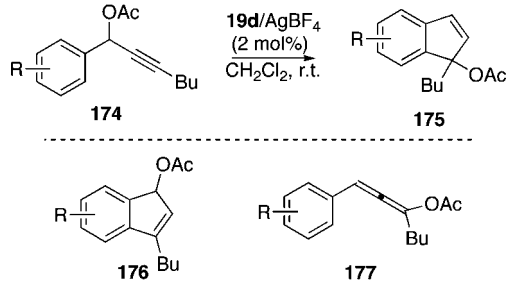


Scheme 42

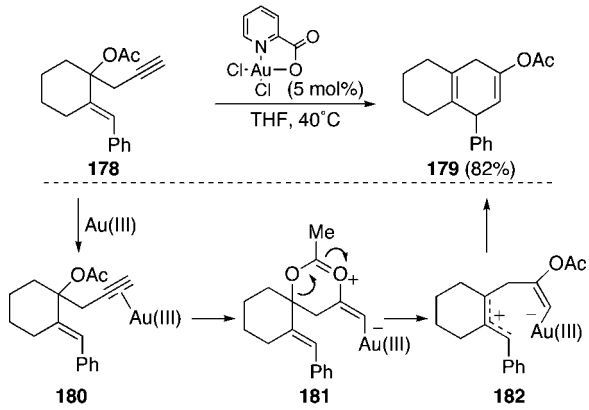


Other 1,3-acyl migrations of propargylic carboxylates catalyzed by gold give intermediate allenes that can afford heterocyclic compounds by intramolecular attack of the appropriate nucleophiles.[157] The intermediate allenes formed by 1,3-acyl migrations can also react intramolecularly with alkynes to form naphthalenes, although this reaction proceeds more efficiently with Ag(I) catalysts.[158]

Scheme 43



Scheme 44



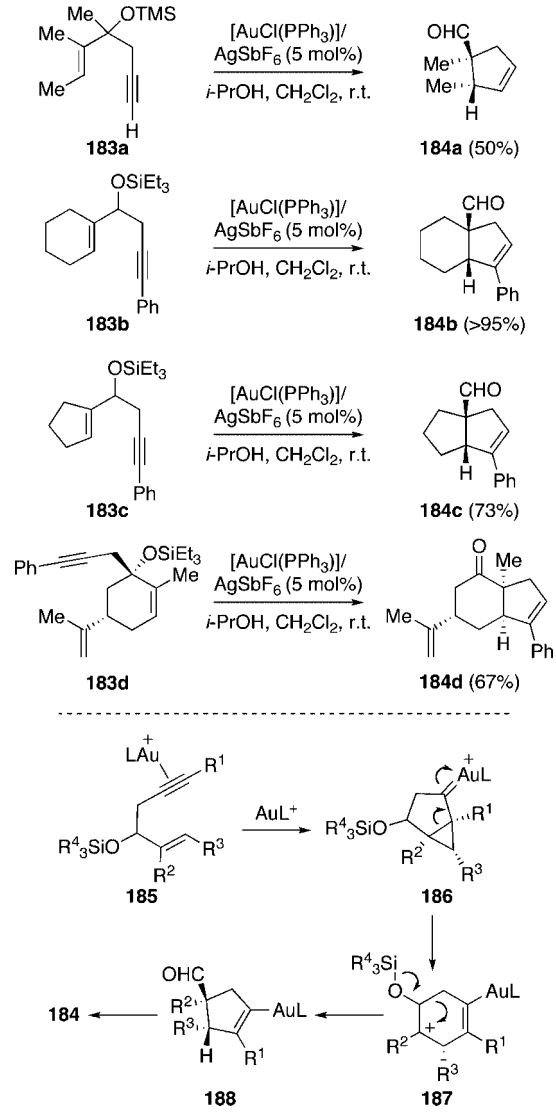
Acyl migration in substrates **174** was also applied to the synthesis of indenes **175** (Scheme 43).[159] Isomeric indenes **176** were also obtained as minor products. Formation of **175** was actually shown to proceed via allenes **177**, which could be independently prepared by Ag(I)-catalyzed 1,3-acetate migration from **174**. Related cyclizations to form indenes had been previously reported using Ru(II)[160] or Pt(II)[134] catalysts, although in these reactions, the acetate undergoes a metal-catalyzed 1,2-migration. Propargylic sulfides and dithioacetals undergo transformations similar to those of propargylic carboxylates with Au(I) or Au(III) catalysts, yielding indene derivatives.[161]

A different type of 1,3-acyl migration occurs in homopropargyl acetates **178** (Scheme 44).[162] In this case, coordination of the alkyne with Au(III) to form **180** followed by migration of the acetate via **181** probably gives the zwitterionic species **182**, which then collapses to form **179**. A somewhat related transformation of an alkenyl gold moiety with a benzylic carbocation is involved in the gold(I)-catalyzed intramolecular reaction of benzylic ethers with alkynes.[163]

3.3. Cycloisomerizations of Hydroxy- and Alkoxy-Substituted Enynes

An interesting method based on the cyclization of 3-silyloxy-1,5-enynes **183** under mild conditions with gold(I) catalysts in a process that involves a pinacol rearrangement has been developed for the synthesis of carbonyl compounds (Scheme 45).[164] Carbonyl compounds such as **184a**−**d** are probably formed by 5-endo-dig cyclization of **185** to form **186**. These intermediates may open to form six-membered-ring carbocations **187**, which would undergo a pinacol rearrangement to form intermediates of type **188**. As shown in other cases, a final protodemetalation would then give **184**. A concerted transformation of **186** to **188** could also be conceived. When the reaction is carried out in the presence of 1 equiv of *N*-iodosuccinimide, the corresponding iodoalk-

Scheme 45



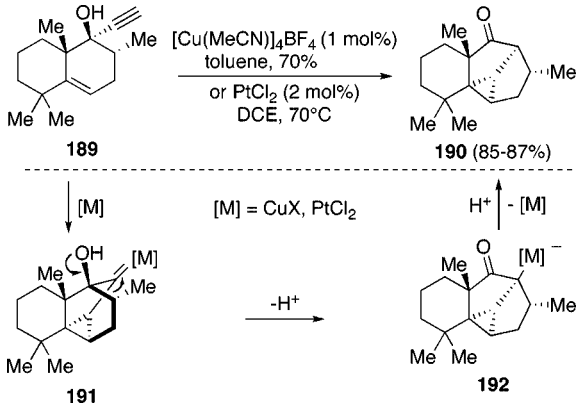
enes can be obtained in moderate yields by a final iododemetalation. This process corresponds to an overall iodocyclization catalyzed by Au(I).[164] Pinacol rearrangements have also been observed in reactions of *cis*-4,6-dien-1-yn-ols catalyzed by Au(III).[113b]

An interesting transformation that also involves a pinacol rearrangement merits attention from a mechanistic point of view, although gold(I) catalysts were not used in that case (Scheme 46).[165] The reaction proceeds satisfactorily with platinum(II) and copper(I) catalysts to give ketones **190** from propargylic alcohols **189** and probably proceeds via cyclopropyl metal carbenes **191** that undergo pinacol-type rearrangement to give **192**, which afford **190** after protodemetalation.

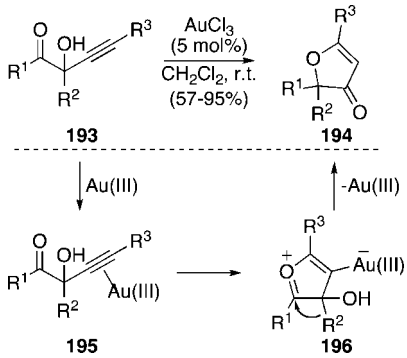
Another interesting transformation that yields 3(2*H*)-furanones **194** occurs upon treatment of hydroxyketones **193** with $AuCl_3$ at 23−38 °C in CH_2Cl_2 or $PtCl_2$ at 80 °C in toluene (Scheme 47).[166] The reaction proceeds through intermediates **195** and **196**, where the 1,2-migration of R^2 takes place. When R^1 and R^2 are part of a ring, this rearrangement leads to a ring contraction. A related process takes place in the gold(I)-catalyzed reaction of alkynylcyclopropanes to give furans.[167]

The Meyer−Schuster rearrangement (isomerization of propargylic alcohols to α,β-unsaturated carbonyl compounds)

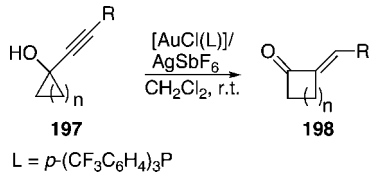
Scheme 46



Scheme 47



Scheme 48



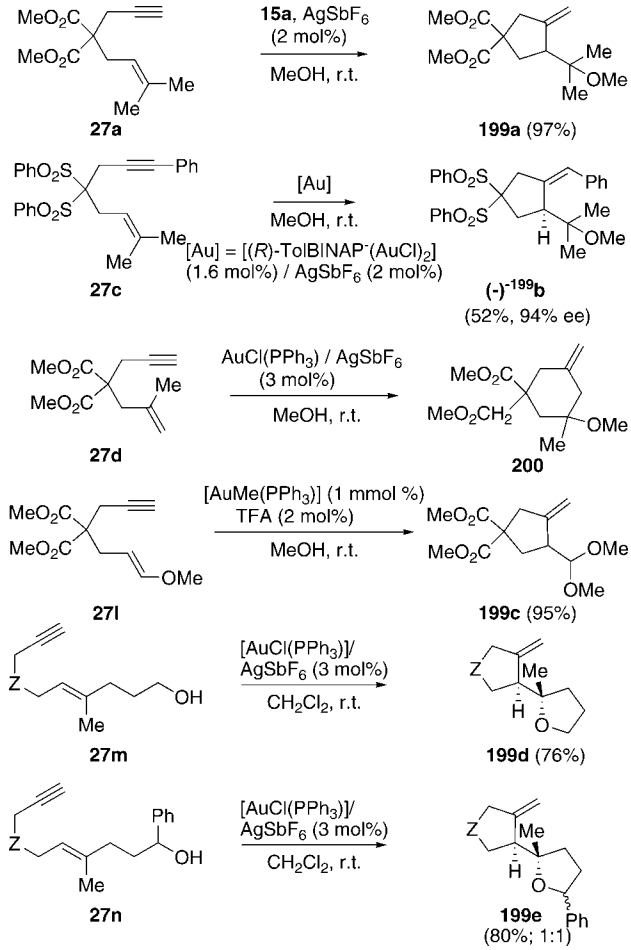
can be efficiently promoted by use of $AuCl_3$ as the catalyst in the presence of EtOH.[168,169] Related transformations take place starting from propargylic carboxylates using Au(I) catalysts.[170,171] On the other hand, cyclopropanols and cyclobutanols **197** undergo ring expansion by initial formation of an η^1-alkenyl gold cation to give cyclobutanones and cyclopentanones **198** (Scheme 48).[172,173]

4. Addition of Nucleophiles to 1,n-Enynes

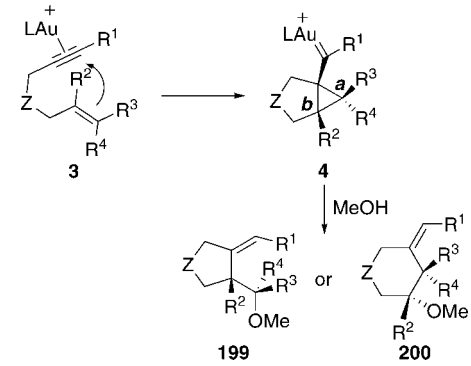
4.1. Hydroxy- and Alkoxycyclizations of 1,6-Enynes

As has been shown previously for reactions catalyzed by Pt(II) or Pd(II),[16,174–176] 1,6-enynes also react stereospecifically with alcohols or water in the presence of Au(I) catalysts. Reaction with gold proceeds more efficiently and under milder conditions than that with other metal catalysts (Scheme 49).[7,8] This reaction can be performed inter- or intramolecularly. In the later case, enynes bearing hydroxy groups react with Au(I) to give cyclic ethers: for example, **27m** and **27n** react with Au(I) to give **199d** and **199e**, respectively. Methoxycyclization of substrate **27c** with a chiral gold catalyst gave **(-)-199b** with good enantioselectivity, although the reaction was rather slow (reaction time = 7 days).[177] Terminally unsubstituted enynes led to lower enantioselectivities (30−49% ee) with the same catalyst.

Scheme 49



Scheme 50

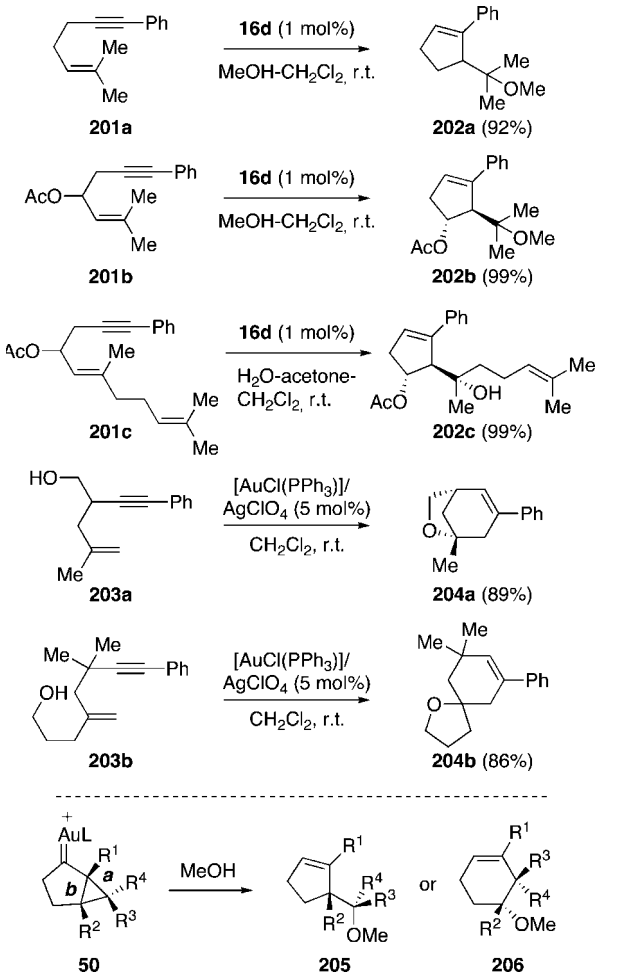


Although similar results were obtained from a catalyst generated in situ from [AuMe(PPh_3)] and a protic acid or [AuCl(PPh_3)] and $AgSbF_6$, the catalysts of choice for the hydroxy- and alkoxycyclizations of 1,6-enynes are those bearing bulky biphenyl phosphines (e.g., **15a**−**d**) or preformed cationic gold complexes such as **16a**−**d**.[9,52] Similar results can be obtained with NHC−Au(I)[60] or Au(III) complexes as catalysts.[17c,178] The hydroxy- and alkoxycyclizations of 1,7-enynes takes place similarly.[102]

Formation of products of both exo- and endo-trig cyclization (**199a**−**e** and **200**, respectively) shows that intermediates **4** can react with MeOH and other ROH nucleophiles at carbon **a** (to give **199**) or **b** (to give **200**) (Scheme 50), which is similar to the reactivity found for Pt(II).[16,179]

1,5-Enynes such as **201a**−**c** also react in a similar manner with MeOH or H_2O in the presence of Au(I) to give adducts

Scheme 51



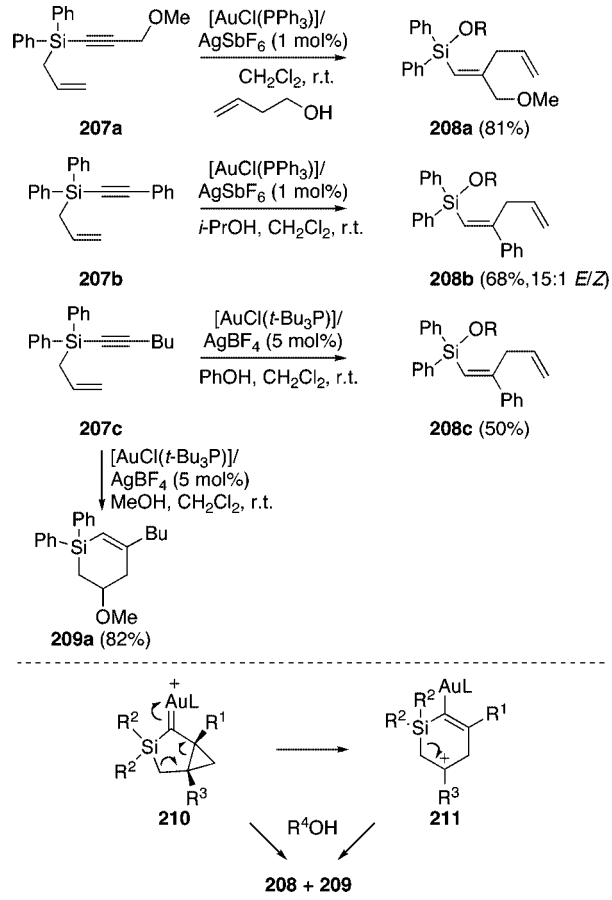
202a−c (Scheme 51).[180] Whereas substrates **201a−c** react with the heteronucleophiles to form **205** via exo-trig pathways involving cleavage of bond **a** of intermediates **50**, the endo-trig pathway (cleavage of bond **b**) to give **206** is also possible. Thus, the intramolecular hydroxycyclizations of 1,5-enynes **203a** and **203b** give six-membered-ring derivatives **204a** and **204b**, respectively.[181]

Allyl propargyl ethers **69** (oxygen-tethered 1,5-enynes) also react intermolecularly with alcohols or water to give six-membered-ring acetals or hemiacetals **72** (Scheme 13).[89] Allyl silyl alkynes **207** react somewhat similarly with Au(I) catalysts in the presence of alcohols to give alkenylsilanes **208** and/or products **209** (Scheme 52).[182,183] Both types of product **208** and **209** are the result of endocyclic cleavage of the initial cyclopropyl gold carbene **210** by attack of the nucleophile at the silicon atom or the cyclopropane carbon. Alternatively, ring expansion of **210** to **211** followed by ring opening would form **208**.

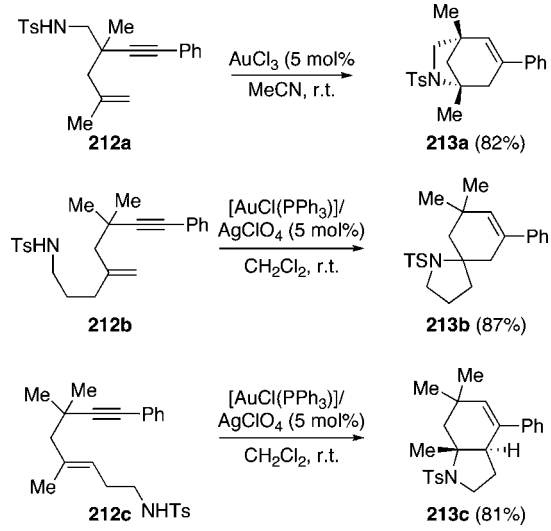
4.2. Amination of Enynes

The intramolecular amination of 1,5-enynes **212a−c** proceeds similarly to the intramolecular hydroxycyclizations of related substrates to give products **213a−c** (Scheme 53).[181] The intermolecular reaction of 1,6-enynes with a series of carbamates RO_2CNH_2 or anilines $ArNH_2$ substituted at the para or ortho positions with strong electron-withdrawing groups has also been reported.[184] This reaction is mechanistically similar to the gold-catalyzed hydroxy- and alkoxycyclizations of 1,6-enynes (Schemes 49 and 50).

Scheme 52



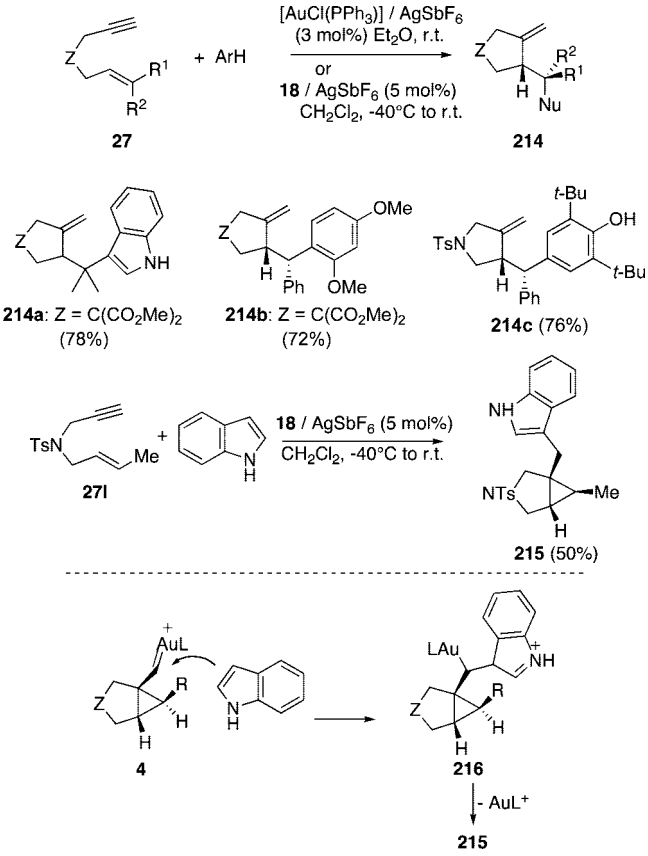
Scheme 53



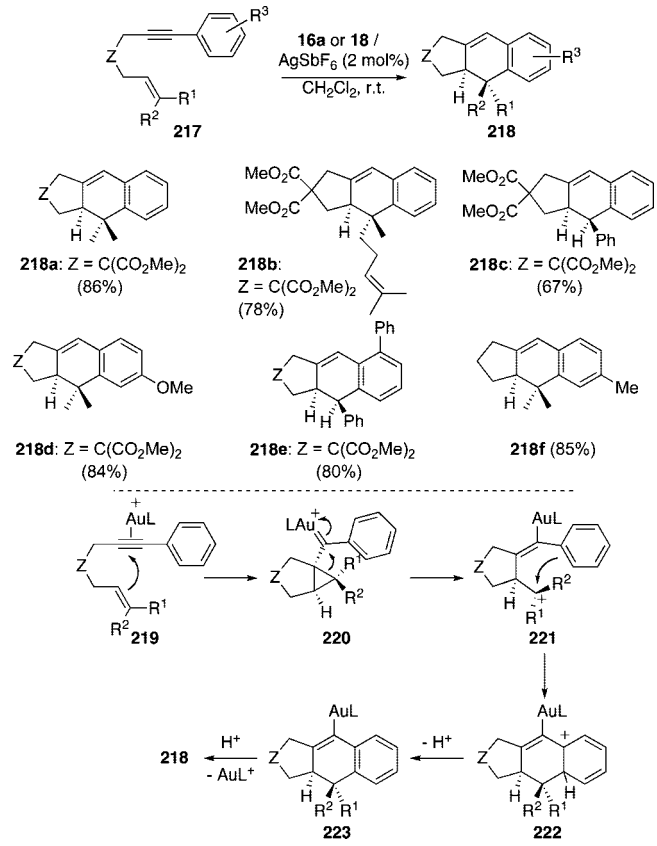
4.3. Inter- and Intramolecular Additions of Carbon Nucleophiles to 1,6-Enynes

Electron-rich aromatic and heteroaromatic compounds add to 1,6-enynes **27** in the presence of Au(I) catalysts (Scheme 54).[185,186] This reaction stereospecifically leads to adducts such as **214a−c** via nucleophilic addition to intermediates of type **4** by a process that is mechanistically related to that of the hydroxy- and alkoxycyclizations of 1,6-enynes. Interestingly, in a few cases, addition of the nucleophile takes place in a different fashion to give adducts of type **215**.[186] Formation of products in which the cyclopropane is retained

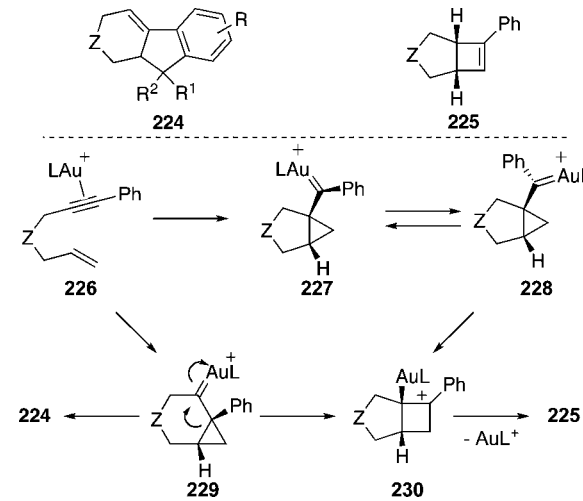
Scheme 54



Scheme 55



Scheme 56



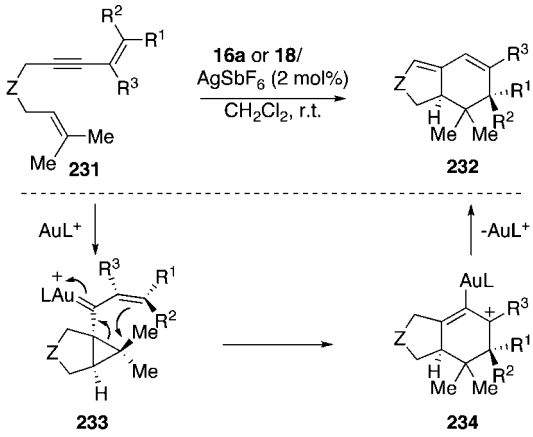
can be explained by attack of the carbon nucleophile at the metal carbene carbon to form intermediates such as **216**. Attack at the gold carbene carbon has also been observed in gold-catalyzed reactions of propargyl acetates with indole.[137]

Enynes **217** substituted at the alkyne with an aryl group react with a variety of gold catalysts to provide products such as **218a**−**f** that result from a formal intramolecular [4 + 2] cycloaddition occurring at an unusually low temperature (Scheme 55).[46,54] This reaction tolerates both electron-releasing and electron-withdrawing substituents at several positions on the arene. According to the experimental results and DFT calculations, the mechanism of the [4 + 2] cycloaddition of arylenynes proceeds by opening of **220** to form **221**, which reacts by a Friedel−Crafts-type reaction to form **222**, which in turn aromatizes to form alkenyl gold intermediate **223**. A final protodemetalation then forms product **218**. The total stereospecificity observed indicates that carbocation **221** does not undergo rotation to exchange R^1 and R^2 groups prior to cyclization. The rate-determining step is the attack by the alkene on the Au(I)-coordinated alkyne (**219** to **220**) rather than the electrophilic aromatic substitution, which explains the relative insensitivity of the reaction to the presence of electron-withdrawing substituents on the arene. Somewhat related cyclizations of allenes with alkynes[187,188] and diynes[189,190] have been described.

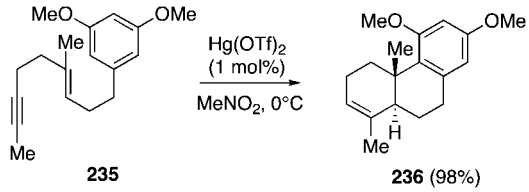
Products of type **224** and cyclobutenes **225** are also formed in a few cases in the cyclizations of arylenynes, which is mechanistically intriguing (Scheme 56).[46,54] Cyclobutenes **225** are obtained in a more general way through the use of Pt(II) catalysts.[24,191] Formation of cycloadducts **224** shows that in competition with 5-exo-dig cyclization via **227**, 6-endo-dig cyclization via **229** can also take place. Interestingly, formation of products of type **224** was the major pathway in the Pt(II)-catalyzed cycloaddition of arylalkynes with enesulfonamides or enamines.[192] Cyclobutenes **225** can also arise from intermediates **229** via benzylic carbocations **230**. Alternatively, a rotation of *anti*-cyclopropyl gold carbene **227** can provide *syn*-cyclopropyl gold carbene **228**, which can undergo ring expansion to form **230**. In contrast to the case of the corresponding cyclopropyl gold(I) carbene formed from (*E*)-oct-6-en-1-yne, for which the anti-to-syn rotation was found to require 24.7 kcal mol^{-1},[93] the phenyl-substituted system requires only 8.6 kcal mol^{-1} for the anti-to-syn isomerization.

Dienynes **231** also cyclize through a similar mechanism to give hydrindanes **232** as the major products (Scheme 57).[46,54] This reaction presumably proceeds through intermediates such as **233**, which undergoes ring expansion in a

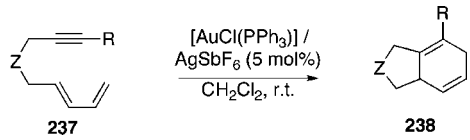
Scheme 57



Scheme 58



Scheme 59



process that is reminiscent of the Nazarov cyclization to form allyl cation **234**; subsequently, loss of a proton followed by protodemetalation gives hydrindanes **232**.

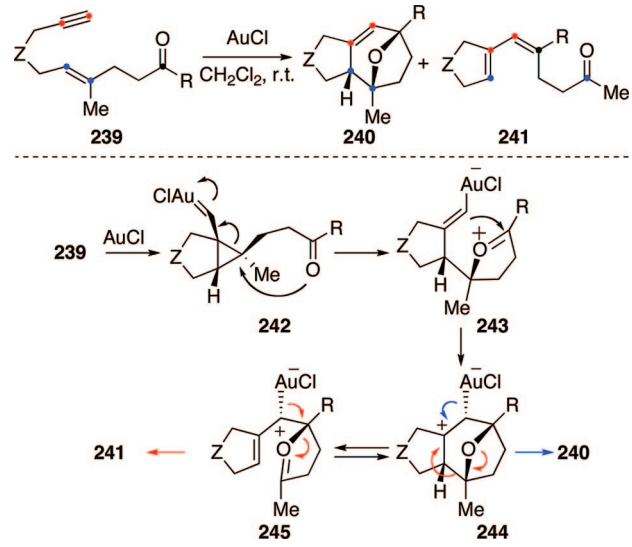
Although it is not a gold-catalyzed process, the cyclization of 1,5-enyne **235** is worth including here; it leads to **236** in excellent yield by an endo cyclization (Scheme 58) in a transformation that is probably mechanistically related to those of Schemes 54 and 56.[193]

1,3-Dien-8-ynes **237** undergo formal intramolecular Diels−Alder reactions catalyzed by Au(I) to give adducts **238** (Scheme 59).[194] This reaction was proposed to take place by evolution of the intermediate vinylcyclopropyl gold carbenes via a metalla-Cope rearrangement or by formation of a six-membered-ring cation. Indeed, vinylcyclopropyl gold carbenes could be trapped intramolecularly by a hydroxy group in the diene chain or by a phenyl group in the alkyne in a [4 + 2] cycloaddition process, as in Scheme 55. The Diels−Alder reaction of substrates **237** (R = H) could be also efficiently catalyzed by Cu(I) by a different mechanism involving a copper acetylide.[194]

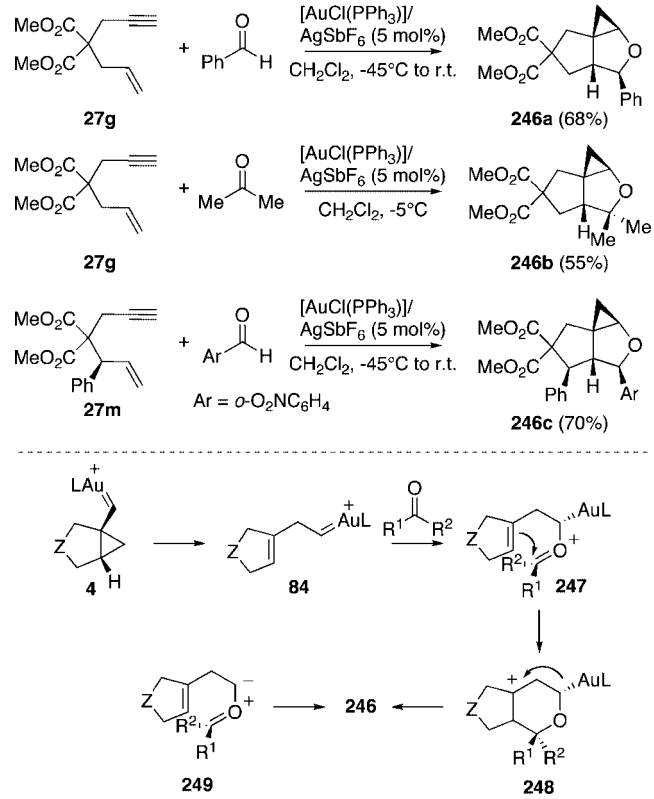
4.4. Other Inter- and Intramolecular Nucleophilic Additions to 1,6-Enynes

Cyclizations of enynes **239** bearing carbonyl groups with Au(I) catalysts provide tricyclic compounds **240** along with ketones **241** as minor products (Scheme 60).[48] The best yields of **240** were obtained using AuCl as the catalyst. In these cyclizations, the carbonyl group acts as an internal nucleophile, as shown in the reaction of **242** to form oxonium cation **243**, which undergoes an intramolecular Prins reaction to give **244**. Elimination of the metal fragment forms tricyclic

Scheme 60



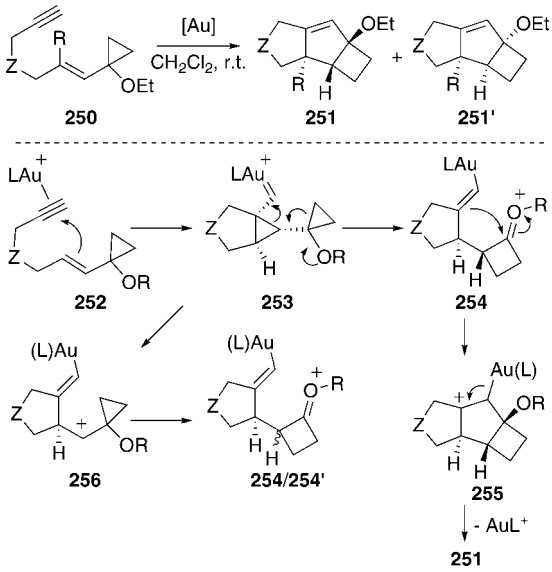
Scheme 61



compounds **240**. Formation of rearranged ketones can be explained by the alternative elimination of the metal with fragmentation of the seven-membered ring via **245**.

Carbonyl compounds can also act as nucleophiles in intermolecular processes involving 1,6-enynes.[195] Thus, the gold(I)-catalyzed reaction between enynes **27g** and **27m** with aldehydes or acetone stereoselectively gives tricyclic compounds **246a−c** (Scheme 61). The transformation is mechanistically intriguing, as it proceeds by rearrangement of the initially formed cyclopropyl gold carbene **4** to give **84** (the intermediate in the double-cleavage mechanism), which is then trapped by the carbonyl compound to form **247**. This transformation is similar to that observed in the trapping of the same rearranged gold carbene **84** by styrene to form cyclopropanes **110** (Scheme 25).[53] It was suggested that a

Scheme 62



six-membered-ring cation **248** could then be formed via attack by the alkene on the oxonium cation, which would be followed by trapping of the cation by the alkyl gold moiety. Formation of 1,3-dipole **249** from **247** followed by an intramolecular 1,3-dipolar cycloaddition was also considered as an alternative.

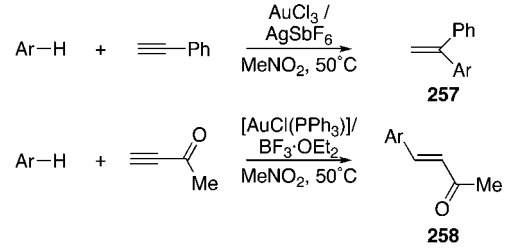
A Prins cyclization is also involved in the reaction of cyclopropylenynes **250** with AuCl or cationic Au(I) complexes to give tricyclic derivatives **251/251′** with an octahydrocyclobuta[*a*]pentalene skeleton (Scheme 62).[48] Formation of stereosiomers **251′** was unexpected and suggests that two different pathways are competing in this process. Accordingly, complex **252** forms cyclopropyl metal carbene **253**, which undergoes ring expansion to form **254**. The alkenyl gold moiety of **254** could undergo a Prins reaction with the oxonium cation to form carbocation **255**, which upon demetalation forms tricycles **251**. The concerted pathway (**253** to **254**) is favored when AuCl is the catalyst, whereas cationic Au(I) complexes apparently favor a nonconcerted reaction via cyclopropyl-stabilized cation **256**, which undergoes a nonstereospecific ring expansion to give mixtures of **254/254′**, leading to **251/251′**. Cyclobutanones were also formed as minor side products in this reaction.[48]

5. Mechanistically Related Reactions of Arenes and Heteroarenes with Alkynes

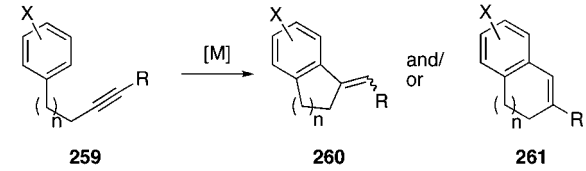
5.1. Cyclizations of Arylalkynes by Friedel−Crafts-Type Processes

In general, two pathways are followed in the reactions of alkynes with arenes catalyzed by transition metals. Reaction of $[M(CO)_6]$ (M = Cr, Mo, W) and certain Ru(II) complexes with terminal alkynes or alkynes substituted with migrating groups (SiR_3, SR, I) may proceed via vinylidene metal complexes. On the other hand, electrophilic metal salts or complexes favor coordination to the alkyne, triggering an electrophilic substitution reaction with the arene. Gold complexes generally promote reactions according to this second pathway.[196] The direct metalation (auration) of electron-rich arenes and heteroarenes is a well-known reaction,[197–199] but the resulting Ar−AuL complexes are

Scheme 63



Scheme 64



apparently not involved in subsequent C−C bond-formation reactions with alkynes.

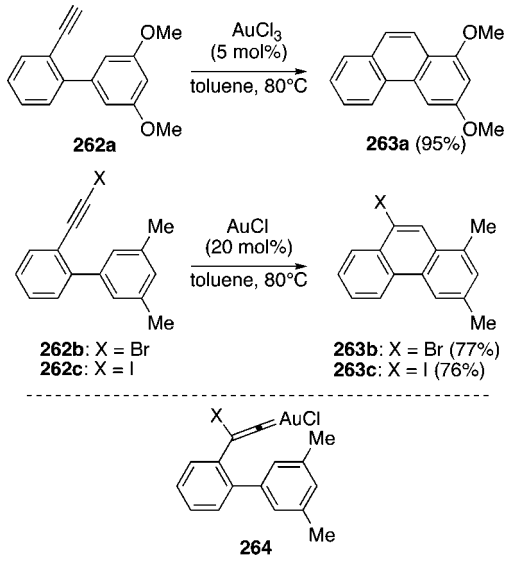
Gold-catalyzed intermolecular hydroarylation of alkynes (or alkenylation of arenes) leads to 1,1-disubstituted alkenes **257** (Scheme 63).[200–202] 1,2-Disubstituted derivatives **258** are obtained from alkynes with electron-withdrawing groups.[203]

Experimental and computational work on the Pt(II)-catalyzed exo or endo cyclization of aryl alkynes **259** to give products of type **260** or **261**, respectively (Scheme 64) indicates that two pathways with very similar activation energies compete: a Friedel−Crafts alkenylation and a reaction proceeding through metal cyclopropyl carbenes.[204] According to theoretical work, the endo cyclization of 3- or 4-but-3-ynylphenols catalyzed by Pt(II) is strongly favored, in agreement with the experimental results obtained for this type of system with Ru(II),[205] Pt(II),[204,205] Pt(IV),[206] Ga(III),[207] and Hg(II)[208] as catalysts. Cyclizations of systems with $n = 2, 3$ also proceed selectively by endocyclic pathways to furnish products of type **261**.[204,205] Endocyclic reactions of pyrroles with alkynes have also been reported.[72]

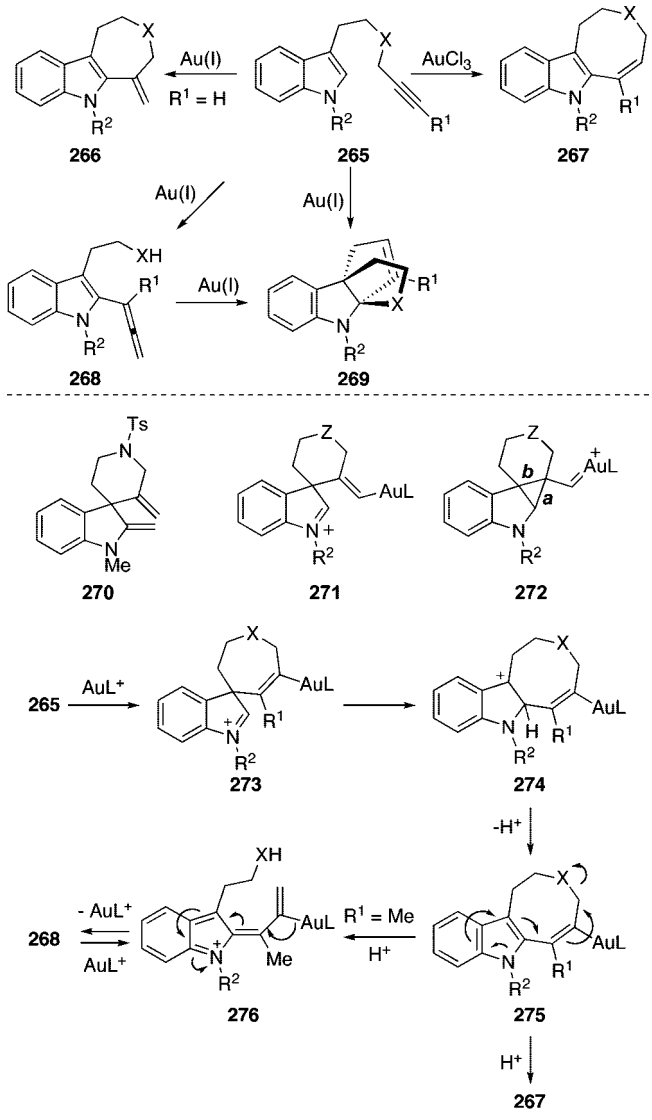
Cyclization of ortho-alkynylated biphenyl derivatives **262** with Au(III) and other metal catalysts also proceeds preferentially by the endo pathway, leading to phenanthrenes **263** (Scheme 65).[209] Interestingly, haloalkynes **262b** and **262c** react with AuCl to give phenanthrenes **263b** and **263c**, respectively, in which the halide has suffered a 1,2-shift. In contrast, the reaction of substrates **262b** and **262c** with the stoichiometric amount of $InCl_3$ gives the corresponding phenanthrenes with halide retention. Formation of **263b** and **263c** suggests that in these cases, the cyclization proceeds via gold vinylidene species **264**. A similar iodine migration and electrocyclization was reported in cyclizations promoted by the $W(CO)_5$ fragment.[210] DFT calculations support the involvement of a vinylidene of type **263** (X = I) as an intermediate in the AuCl-catalyzed cyclization that reacts through a small barrier (0.76 kcal mol^{-1}) in an electrocyclization process.[211] Gold vinylidene species were also suggested as intermediates in some gold-catalyzed cyclizations of 1-alkynyl-2-alkenylbenzenes to form naphthalenes[72] as well as in the reaction of 2-(prop-2-ynyl)pyridines with $AuBr_3$ to form indolizines.[212] In this reaction, Au(I) formed by reduction of $AuBr_3$ was proposed to be the active catalyst.

The reaction of substituted indoles **265** with alkynes catalyzed by Au(I) or Au(III) leads to seven- (**266**) or eight-membered (**267**) rings, respectively (Scheme 66).[213] Deriva-

Scheme 65

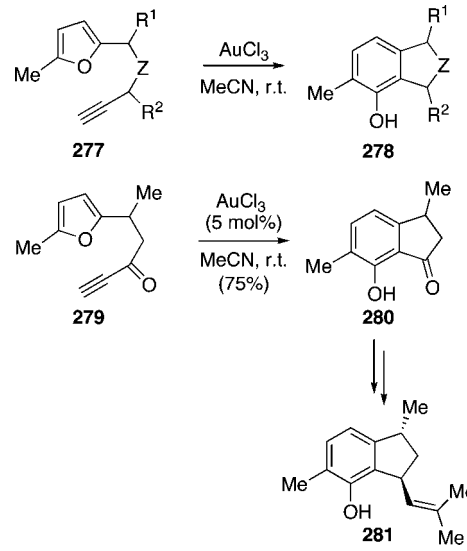


Scheme 66



tives **267** are formed in an 8-endo-dig process, a type of cyclization that has not been observed in other hydroarylations of alkynes or cyclizations of enynes. Allenes **268** and tetracyclic compounds **269** could also be obtained. A domino transformation of **265** into **269** could be done in one step by using Au(I) as the catalyst. The isolation of spiro derivative **270** in one of the cyclization reactions suggests that cyclizations of indoles catalyzed by gold(I) can take place by initial formation of a C−C bond at C-3 followed by a 1,2-migration to give the final indoles. Thus, the 7-exo-dig cyclizations shown in Scheme 66 presumably proceed via spiro derivatives of type **271**, which could be formed directly by a Friedel−Crafts-type reaction or indirectly by opening of cyclopropyl carbenes **272** at C−C bond **a**. Eight-membered ring compounds **267** may also arise by a 1,2-shift of the initially formed seven-membered-ring iminium cation **273** to form **274**. Proton loss from **274** would give **275**, from which eight-membered-ring compounds **267** would be formed. An alternative elimination from **275** would yield allenes **268** via cationic intermediate **276**. The gold(I)-catalyzed intermolecular reaction of indoles with alkynes also takes place.[213b] This reaction can also be carried out with $GaCl_3$[214] and Pt(II)[215] as catalysts.

Scheme 67

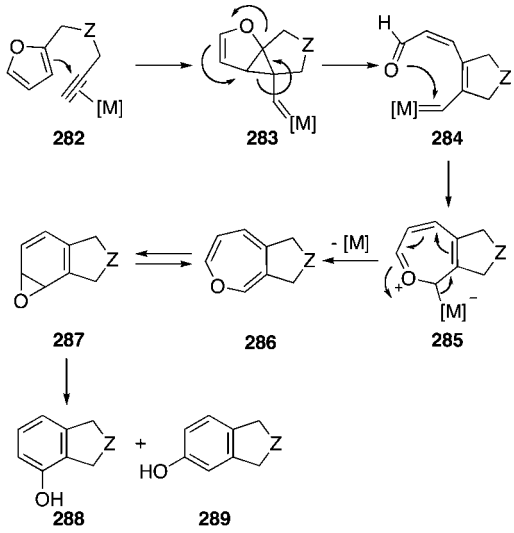


5.2. Reactions of Furans with Alkynes

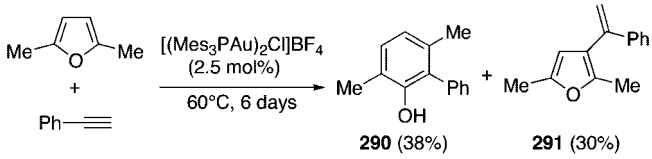
In contrast to the usual Friedel−Crafts-like cyclizations of arenes with alkynes, alkynyl furans **277** afford phenols **278** in good-to-excellent yields when $AuCl_3$ is used as the catalyst (Scheme 67).[216] Au(I),[217] heterogeneous gold,[218] and Pt(II)[219] can also be used as catalysts. Phenols bearing bulky groups at the ortho position can also be prepared by this method.[220] In addition, gold-catalyzed Michael addition of furans to ethynyl vinyl ketones gives substrates[221−223] that can undergo in situ cyclization leading to hydroxyindanones in a domino process.[222] A synthesis of sesquiterpene jungianol (**281**) together with its cis isomer illustrates the application of this phenol synthesis starting from **279** to form key intermediate **280**.[216d]

According to experimental and theoretical studies on gold- and platinum-catalyzed reactions,[216b,e,f,219,224] the phenol synthesis proceeds via nucleophilic attack by the furan on the (η^2-alkyne)−metal complex **282** to form carbene **283**, which is similar to the intermediates formed in reactions of enynes with Au(I) or other metal complexes (Scheme 68). Cleavage of C−C and C−O bonds of the tricyclic intermediate yields a new carbene **284**, which cyclizes to form **285**. Elimination of the metal forms oxepine **286**, which is in

Scheme 68



Scheme 69



equilibrium with the arene oxide **287**; ring opening of **287** leads to the formation of phenols **288**, the major compounds of this phenol synthesis, and their regioisomers **289**. Oxepines **286** and arene oxides **287** have been observed in the reaction catalyzed by Au(III) complexes.[216f,225]

Although it proceeds in the absence of solvent with moderate yield, the formation of phenol **290** in the intermolecular reaction of 2,5-dimethylfuran with phenylacetylene is remarkable (Scheme 69).[226] This reaction required the use of the Schmidbaur−Bayler salt $[(Mes_3PAu)_2Cl]BF_4$ [227] as the Au(I) catalyst and also provided furan **291**, the product of a Friedel−Crafts-type process.

6. Conclusions

Gold complexes, in particular, cationic complexes bearing bulky phosphines, phosphites, or NHC ligands, usually surpass the most active platinum complexes reported to date for the activation of enynes. As has already been pointed out,[3,9] the similarities between reactions of enynes catalyzed by gold or other electrophilic transition metals and the carbocationic rearrangements of the cyclopropylmethyl−cyclobutyl manifold are striking.[5,10] However, stabilization of gold confers special reactivity to these cationic species. Although the basic pathways in the cycloisomerization of enynes are now better understood mechanistically, many unresolved questions still remain in this area. Thus, for example, the factors that control the choice of single versus double cleavage of enynes are still not clear. Ligand control of closely related pathways is still very limited. In addition, the area of chiral gold catalysis in the context of alkyne chemistry is relatively underdeveloped. Gold-catalyzed reactions are particularly suited for the development of tandem processes for the ready formation of complex architectures. Application of gold-catalyzed cycloisomerization of enynes to the formation of medium or large rings and the discovery of general methods for intermolecular reactions of alkynes with alkenes are still-unmet challenges.

7. Acknowledgments

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