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**CRITICAL REVIEW**

# Strained small rings in gold-catalyzed rapid chemical transformations

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Gold-catalyzed reactions, which have been widely explored over the past several years, are powerful tools in organic synthesis to access complex molecular frameworks, and some corresponding excellent reviews have been reported. However, little attention has been paid to summarize the reactions of strained small-ring-containing molecules catalyzed by gold. This *critical review* mainly puts its emphasis on the recent progress in the field of gold-catalyzed transformations of cyclopropyl-, cyclopropenyl-, epoxy- and aziridinyl-containing molecules. The rapid construction of interesting building blocks in organic synthesis from strained small rings catalyzed by gold has been summarized in this review (106 references).

## 1. Introduction

Gold salts and complexes have emerged in the past few years as the most powerful catalysts for electrophilic activation of carbon–carbon multiple bonds toward a variety of nucleophiles.[1] Generally, this type of reaction relies on interaction between gold catalysts and π-bonds of alkenes, alkynes, and allenes. In this regard, the development of new methods that explore the scope of other functional groups in gold-catalyzed reactions has gained momentum.

The introduction of strained small ring structures as molecular building blocks has drawn increasing attention. Due to their inherent ring strains, interesting preparations and applications specific to these cyclic compounds have been developed.[2] As the first example of gold-catalyzed rearrangement of strained small rings was reported by Meyer and de Meijere in 1976,[3] the number of gold-catalyzed reactions concerning this aspect increased rapidly. In this mini review, we have summarized the development of various novel types of gold-catalyzed reactions such as strained small ring opening reactions, ring expansion reactions as well as ring rearrangement cascades. Both strained small homocycles (cyclopropane, cyclopropene *etc.*) and heterocycles (oxirane and aziridine) were discussed.

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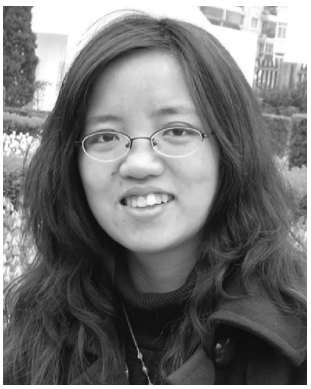
## 2. Small homocycles

### 2.1. Cyclopropane

Since the discovery of cyclopropane in 1882 by Freund,[4] more and more chemists are attracted by this amazing small three-membered carbocycle. Natural products containing cyclopropyl groups always have a lot of significant biological properties. Moreover, owing to their ready accessibility and good reactivity,[5] cyclopropanes were also widely used as a building block in organic synthesis, especially in organometallic chemistry.



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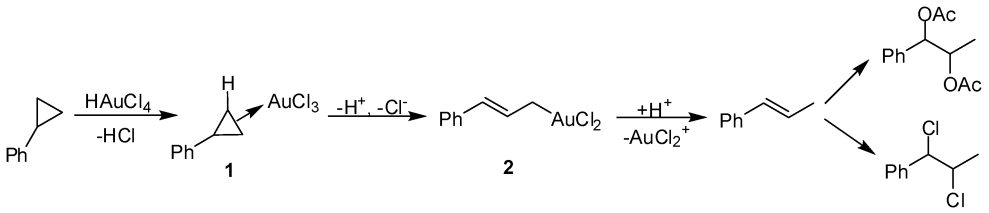
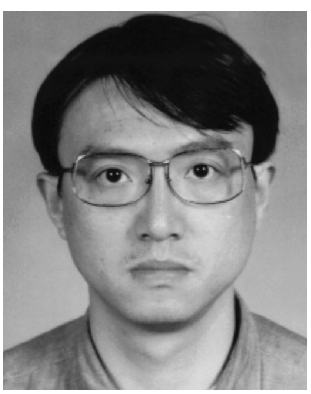



**Scheme 1** $HAuCl_4$-mediated transformation of cyclopropane to 1,2-adducts.

As we have known, oxidation of cyclopropanes by lead(IV), thallium(III), or mercury(II) resulted in 1,3-organometallic adducts, which could undergo other transformations through carbon–metal bond cleavage to get the versatile and useful molecules.[6] However, different from these results, Thomas *et al.* found that when cyclopropanes were catalyzed by tetrachloroauric acid in acetic acid, the products were not the expected 1,3-adducts but instead, as deduced from mass spectra, were 1,2-addition products (Scheme 1).[7] A partial explanation of these interesting reaction outcomes was provided. From the resulting volatile products, the author detected a substantial quantity of *trans*-l-phenylpropene, from which the mentioned 1,2-adducts could be derived.[8] $Au^{III}$ therefore appeared to have the unexpected ability to isomerize cyclopropanes to alkenes. The most likely isomerization route might involve three sequential steps: decomposition of a gold(III)–cyclopropane complex **1** along with loss of a proton, formation of an allylic gold compound **2** and protodeauration of the allylic gold intermediate.

Recently, an efficient synthetic route to pyrrolidines **5** from cyclopropyl methanols **3** and sulfonamides was reported by Rao and Chan. The mechanism was suggested to involve the activation of cyclopropyl methanols **3** by the AuCl/AgOTf catalyst, which caused ring opening of the cyclopropyl moiety trapped by the sulfonamide nucleophile. The resultant aminated acyclic intermediate **4** underwent subsequent intramolecular hydroamination to give **5** (Scheme 2).[9]

Unactivated vinylcyclopropanes are potentially good substrates for transition metal-catalyzed reactions involving ring-opening processes. Some classical rearrangements, cycloadditions, coupling



**Min Shi**

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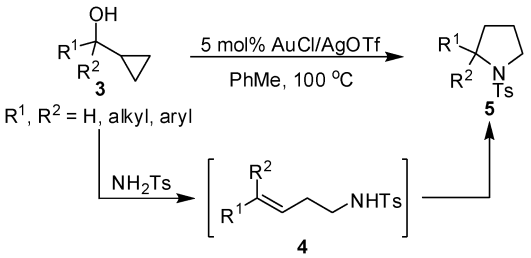



**Scheme 2** Gold-catalyzed domino reactions starting from cyclopropyl methanols.

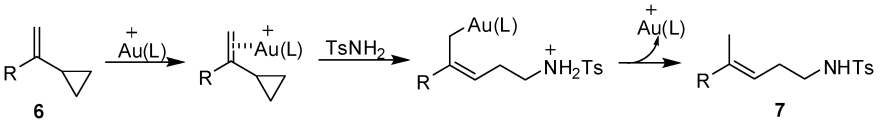
reactions and silaboration reactions have been reported.[10] Recently, Togni *et al.* found a new gold(I)-catalyzed intermolecular ring-opening of unactivated vinylcyclopropanes **6** with sulfonamides, constituting an efficient synthetic access to useful derivatives of homoallylic amines **7**.[11] The possible reaction mechanism is shown in Scheme 3. It should be noted that the same reaction could be also efficiently catalyzed by HOTf.[12] There was no significant difference between gold catalyst and HOTf to catalyze the reaction when R (R = aryl) had an electron-donating group. However, when R (R = aryl) contained an electron-withdrawing group, the reaction rate was much faster when the reaction was catalyzed by gold catalyst.

### 2.2. Cyclopropanol

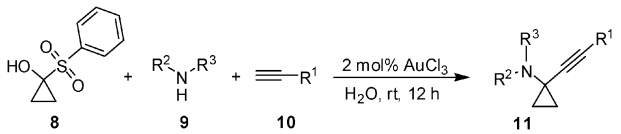
Cyclopropanol, which can be easily obtained from the cyclopropanone hemiacetals, is another kind of important and extensively used small homocycles.[13] It can be used as a surrogate for cyclopropanone, which is less stable compared with cyclopropanol under most conditions. Chen and his co-workers developed an efficient $AuCl_3$-catalyzed three-component reaction to synthesize 1-alkynylcyclopropylamine products **11** using 1-(arylsulfonyl)cyclopropanols **8**, secondary amines **9** and alkynes **10** (Scheme 4).[14] Unlike previous cyclopropanone derivatives,[13b,15] this new surrogate 1-(arylsulfonyl)cyclopropanol exhibited relatively higher reactivity. The mechanism in this reaction was similar to the coupling reaction of $AuCl_3$-activated terminal alkyne with aldehydes reported by Wei and Li.[16] Cyclopropanone, *in situ* generated from compound **8**, would react with **9** to provide an imine cation, which was then coupled with **10** to yield 1-alkynylcyclopropylamine **11**.

### 2.3. Methylenecyclopropane

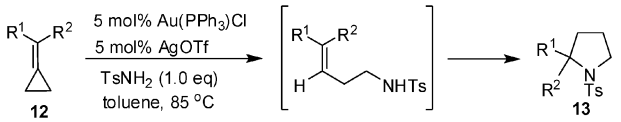
Transition metal-catalyzed (Pd, Rh, Ru, Pt *etc.*) reactions of methylenecyclopropanes have been widely explored in this area of study over the past several decades. The attractive feature of these compounds is their surprising stability in spite



**Scheme 3** Mechanism for the $Au^{I}$-catalyzed ring-opening of vinylcyclopropanes.



**Scheme 4** Three-component reactions catalyzed by $Au^{III}$.

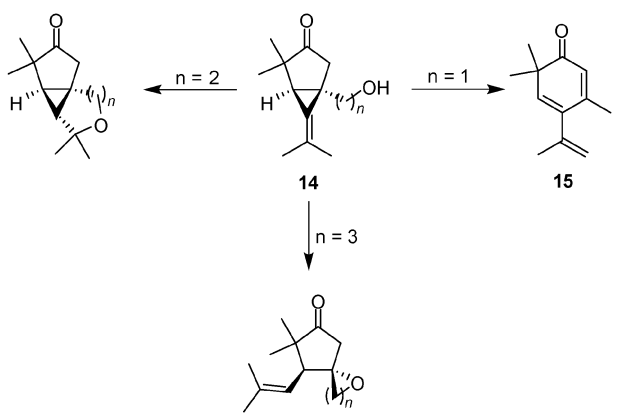


**Scheme 5** Hydroamination of methylenecyclopropanes.

of their high level of strain.[17] In the process of studying the characteristics of methylenecyclopropanes, Shi *et al.* have developed a facile synthetic route to pyrrolidine derivatives **13** *via* domino ring-opening and ring-closing hydroamination of methylenecyclopropanes **12** with sulfonamides catalyzed by gold(I) (Scheme 5).[18]

An interesting structure-dependent rearrangement of methylenecyclopropanes **14** was described by Fensterbank and Malacria *et al.* (Scheme 6).[19] They found that the length of the methylene spacer was the critical reason for the outcome of the reaction. When $n = 1$, this compound rearranged into the more stable α,β,γ,δ-unsaturated ketone **15**. With a longer tether ($n = 2$ or 3), nucleophilic attack of the double bond, or of the cyclopropyl ring by the alkoxyl group became faster, which resulted in different kinds of products.

Multiple-component reactions are always attractive, because they can build complex molecular structures in a single step. A gold-catalyzed three-component intermolecular domino reaction using 2-(arylmethylene)cyclopropylcarbinols **16**, terminal arynes **17** and alcohols **18** leading to 3-oxabicyclo[3.1.0]hexanes **19** and **19′** in high yields and moderate diastereoselectivities under mild conditions was reported by Shi's group (Scheme 7).[20] A plausible mechanism based on an intermolecular tandem hydroalkoxylation/Prins-type reaction pathway has been proposed.



**Scheme 6** Gold-catalyzed transformations of methylenecyclopropanes.

The alkyne–gold(I) complex was attacked by substrate **16** to produce vinyl-gold species **20**, which underwent protodemetalation to furnish intermediate **21**. A subsequent Prins-type reaction catalyzed by gold occurred to afford intermediate **22** stereospecifically. This process might proceed *via* a chair-like transition state, which could account for the stereoselectivity. Trapping the organogold cation **22** by an alcohol and the following protodemetalation delivered the three-component adducts and regenerated the gold(I) catalyst.

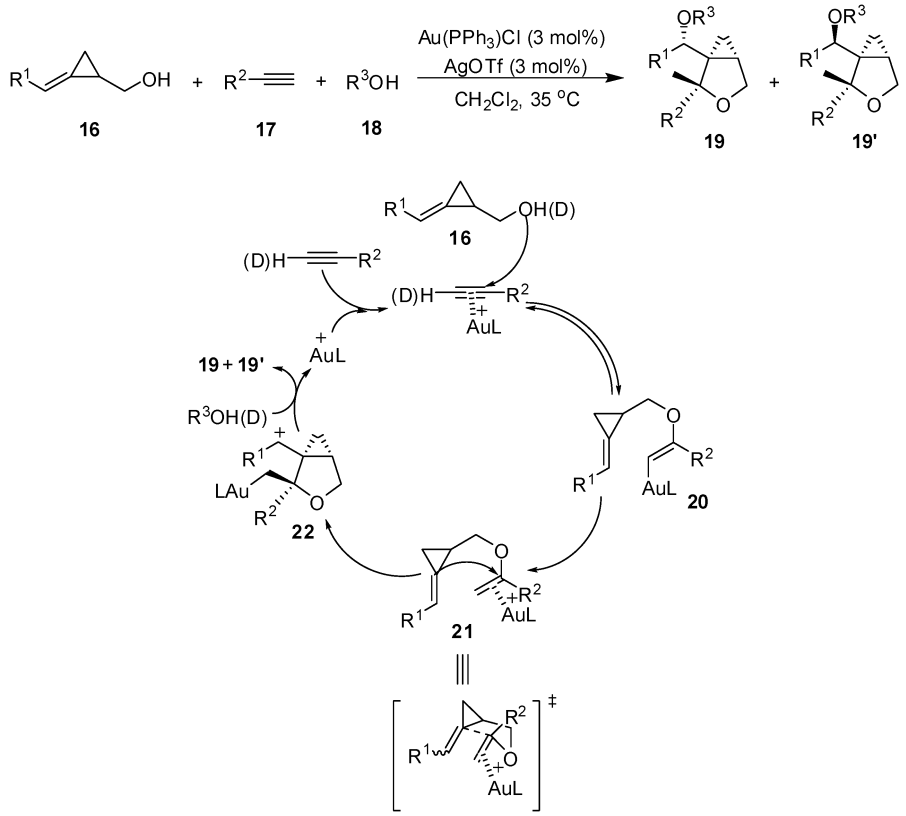
Metal-catalyzed tandem C–H bond and C–C bond activation has received considerable attention from many organometallic chemists due to its fundamental scientific interest and potential utility in organic synthesis.[21] Recently, Shi *et al.* developed an interesting and alternative way to attain biaryl derivatives **24** in good yields *via* $Au(PPh_3)Cl/AgOTf$-cocatalyzed tandem intramolecular C–H and C–C bond activation (Scheme 8).[22] The reaction might undergo dehydrogenative rearrangement of methylenecyclopropanes **23** containing a cyclohexyl group by transferring three hydrogen atoms from the cyclohexyl ring to the cyclopropane ring intra/intermolecularly. The mechanism had also been carefully investigated by deuterium labeling experiments and DFT calculations.

### 2.4. Vinylidenecyclopropane

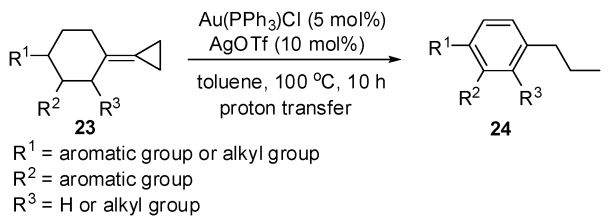
Vinylidenecyclopropanes are highly strained but readily accessible and reasonably stable molecules that can serve as useful building blocks in organic synthesis.[23] Thus far, it has been known that vinylidenecyclopropanes can undergo a variety of ring-opening/cycloaddition reactions upon heating or photoirradiation as well as in the presence of Lewis acids because the relief of ring strain provides the kinetic driving force to initiate the unleashing of the strain. Shi *et al.* previously reported a novel intramolecular rearrangement of vinylidenecyclopropane **25** to give an unexpected naphthalene derivative *via* an intramolecular Friedel–Crafts reaction in the presence of hard Lewis or Brønsted acids, such as $Sn(OTf)_2$ or HOTf, along with the release of a propene molecule.[24] Further investigation revealed that when gold(I) (soft Lewis acid) was used as a catalyst, a functionalized 1,2-dihydronaphthalene derivative **30** was formed selectively (Scheme 9).[25] A plausible rearrangement mechanism was proposed. The corresponding cyclopropyl ring-opened zwitterionic intermediate or the resonance-stabilized zwitterionic intermediate **27** was formed from the initial zwitterionic intermediate **26**. Intramolecular Friedel–Crafts reaction with the adjacent aromatic group took place to produce the corresponding zwitterionic intermediate **28**, which afforded the corresponding intermediate **29** by deprotonation. Subsequent protonation of the intermediate **29** produced the corresponding 1,2-dihydronaphthalene derivative **30** along with the release of the Au(I) catalyst to initiate the next catalytic cycle.

A novel gold(I)-catalyzed tandem oxidative ring-opening/C–C bond cleavage reaction of vinylidenecyclopropanes **31**



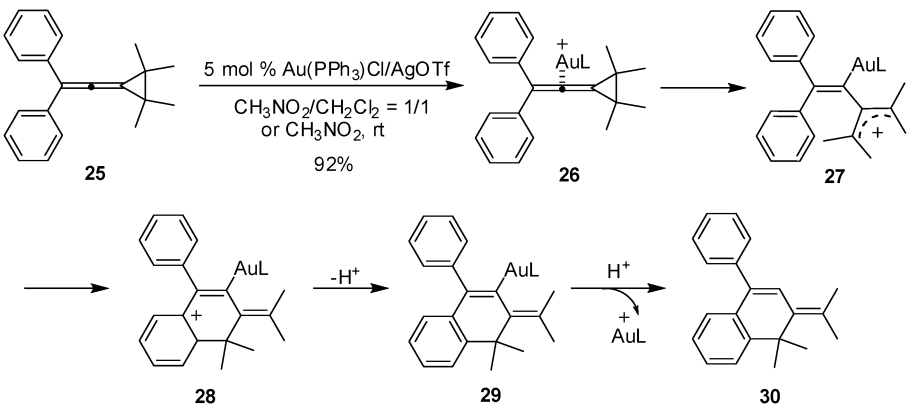

**Scheme 7** Gold-catalyzed three-component intermolecular domino reaction.



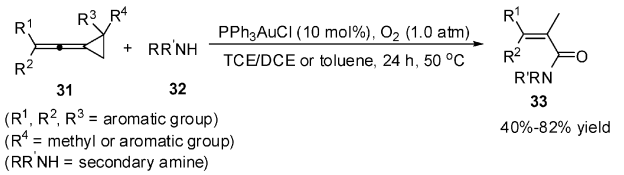

**Scheme 8** Gold-catalyzed tandem C–H and C–C bond activation of methylenecyclopropanes.

with a variety of secondary amines **32** was developed by Lu and Shi, leading to the corresponding fully substituted acrylamides **33** in moderate to good yields under an oxygen atmosphere (Scheme 10).[26] On the mechanistic investigations, three control experiments were conducted, suggesting that the reaction did not proceed through a radical mechanism and molecular oxygen was involved in a much earlier stage. The other two deuterium labeling experiments indicated that an isomerization of the cyclopropane indeed took place and the allylic gold(I) species most likely existed in the reaction system.

Instead of simple arylvinylidenecyclopropanes, functionalized vinylidenecyclopropanes **34** tethered with primary alcohol chains were designed and synthesized recently by Shi's group. Then a new intramolecular tandem addition/ring-opening reaction of this novel vinylidenecyclopropane was established for the synthesis of allene-containing tetrahydropyran derivatives **36** in the catalysis of $[(Ph_3PAu)_3O]BF_4$ and AgOTf (Scheme 11).[27]




**Scheme 9** Plausible mechanism for the formation of **30**.




**Scheme 10** Gold(I)-catalyzed tandem oxidative ring-opening/C–C bond cleavage reaction.

This reaction could occur through two possible pathways: gold cation activated the allene functionality (path 1); gold(I) catalyzed the ring-opening (path 2). Subsequent intramolecular nucleophilic addition by the hydroxyl group gave the same intermediate **35**, which produced the corresponding tetrahydropyran derivatives **36**.

Moreover, Shi *et al*. synthesized another type of functionalized vinylidenecyclopropanes **37** containing an additional secondary alcohol chain and found that in the presence of gold(I), vinylidenecyclopropanes **37** could undergo intramolecular nucleophilic addition, rearrangement, and ring-opening of the cyclopropane to give enone derivatives **38** in moderate to good yields under mild conditions (Scheme 12).[28] The reaction mechanism had also been discussed on the basis of $^{18}O$-isotope labeling experiments.

### 2.5. Cyclopropene

Cyclopropenes display a diverse range of reactivities, thus presenting unique opportunities for organic synthesis.[29] In 2008, Shi and his co-workers described an efficient synthetic protocol for the construction of indene derivatives through the gold(I)-catalyzed cycloisomerization of arylvinylcyclopropenes.[29k,30] Later, Wang *et al*. demonstrated another efficient one-pot, two-step reaction to give indene derivatives from simple cyclopropenes in the catalysis of gold(I).[29k,31] Moreover, a rapid and stereoselective gold-catalyzed ring-opening rearrangement of cyclopropenylmethyl acetates to *Z*-acetoxydienes was reported by Ariafard and Hyland *et al*.[29k,32]

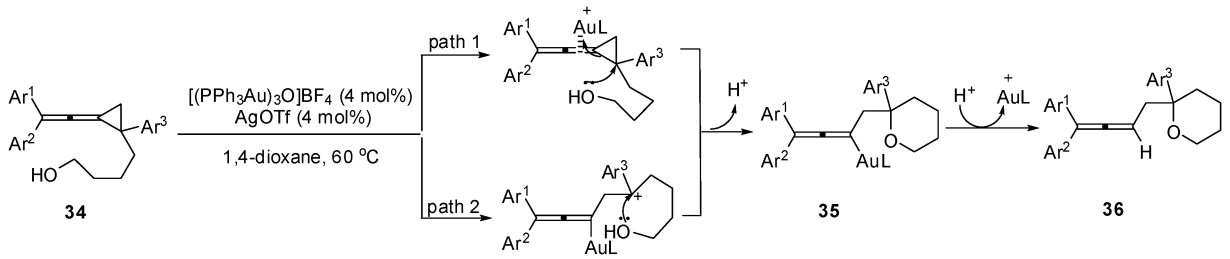
In 2010, Meyer, Cossy and co-workers reported a novel gold-catalyzed intramolecular cycloisomerization of allyl 3,3-dimethylcyclopropenylcarbinyl ethers or sulfonamides leading to 5-isopropylidene-3-oxa and 3-azabicyclo[4.1.0]heptanes with high diastereoselectivities.[29k,33]

In addition to the domino cycloisomerizations, Lee and co-workers described the first gold(I) catalyzed ring-opening addition of cyclopropenes with a series of alcohols in a mild and highly regioselective manner, yielding the corresponding *tert*-allylic ethers.[29k,34] In the later full article, the author expanded on the substrate scope, possible mechanism and regioselectivity issues of this reaction and found that excess alcohol was crucial for achieving high regioselectivities.[29k,35]

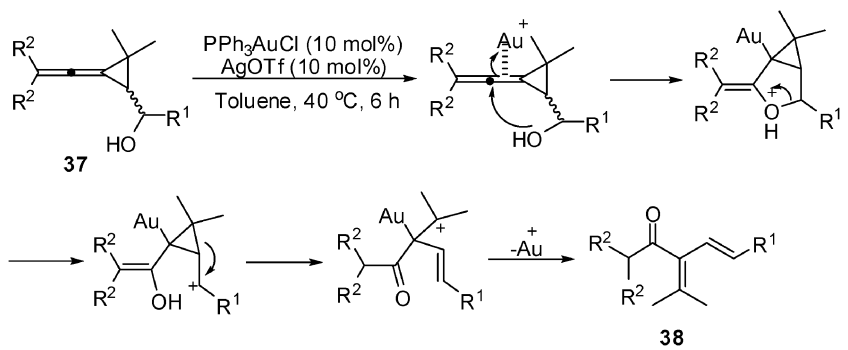
During Lee group's ongoing study of gold-catalyzed transformations with cyclopropenes **39**, they found that furans **40** could also be used as a nucleophile to form a series of functionalized trienes **41** and **41′** in high yields (Scheme 13).[36] When the substituents on the cyclopropene were sterically or electronically differentiated, (*EEE*)-trienes could be isolated in good yields and excellent stereoselectivities.

### 2.6. Strained small homocycles bearing alkynyl groups

Substrates which contain both an alkyne and a three-membered ring are particularly suitable for domino transformations catalyzed by transition metals, since ring cleavage or ring enlargement and subsequent cyclization usually result in the formation of complex and useful structures. Recently, gold salts or gold complexes were also applied to cyclopropylalkyne cascade reactions. The first example was reported by Toste's group, providing a versatile and stereoselective gold(I)-catalyzed ring expansion of 1-alkynylcyclopropanols **42** to alkylidenecycloalkanones **43** (Scheme 14).[37]

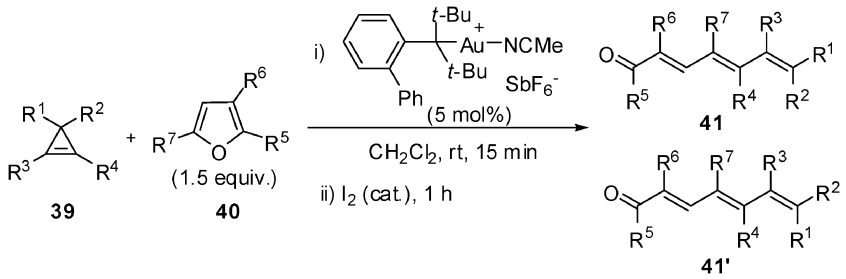



**Scheme 11** Gold-catalyzed tandem addition/ring-opening reaction of vinylidenecyclopropanes.

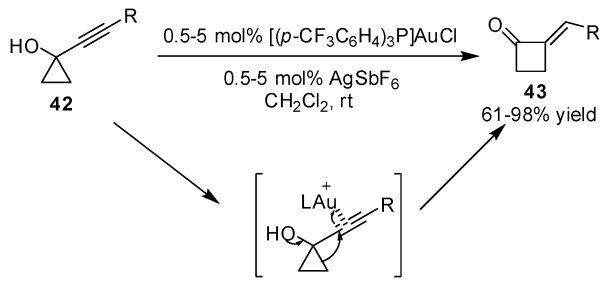



**Scheme 12** Gold-catalyzed intramolecular rearrangement of vinylidenecyclopropanes.



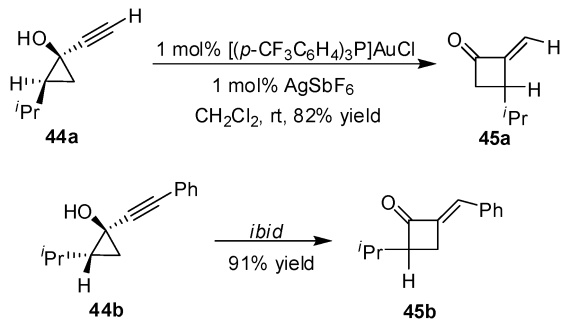

**Scheme 13** Gold(I)-catalyzed furans addition to cyclopropenes.




**Scheme 14** Gold-catalyzed ring expansion of 1-alkynylcyclopropanols.

A mechanism involving migration of a carbon–carbon σ-bond onto a gold(I)-activated alkyne accounted for the observed stereoselectivity and migratory aptitude in substituted cycloalkanols. Upon replacement of the alkynyl group with an allenic group, Kleinbeck and Toste achieved an asymmetric ring expansion reaction of 1-allenylcyclopropanols catalyzed by chiral phosphine-gold(I) complexes. Moreover, this method constituted the first report of an enantioselectively gold-catalyzed 1,2-alkyl migration.[38]

Consistent with the expected migratory aptitude, gold(I)-catalyzed rearrangement of **44a** affords only **45a**. The rearrangement of **44b**, however, selectively yields **45b** because of the larger strain in the transition state for cyclization expected in the mechanism owing to the interaction between the phenyl group and the isopropyl substituent (Scheme 15).[39] In agreement with experimental findings, calculations render the Gibbs energy barrier for the migration of the nonsubstituted carbon atom 2.8 kcal $mol^{-1}$ lower than that for the substituted one, which thus predicts that the only product obtained from the rearrangement of **44b** will be **45b**. Moreover, on the basis of computational results, Ardura *et al.* found that the gold-catalyzed rearrangement of 1-alkynylcyclopropanols to



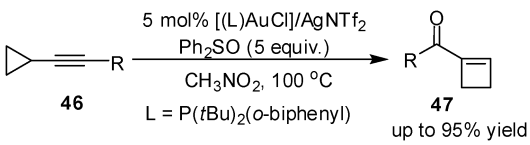

**Scheme 15** Substituent effect of the reaction.

alkylidenecycloalkanones in $CH_2Cl_2$ solution is a two-step process. In the first step, the cationic gold(I) complex coordinates to the alkyne moiety. The second step consists of a 1,4-H shift, which requires the assistance of a second molecule of cyclopropanol to be easily accessible. The assisting cyclopropanol molecule plays a very efficient bifunctional catalytic role by accepting the H atom from the oxygen atom of the formed cyclobutanone and simultaneously transferring its hydrogen on the hydroxyl group to the ethylidene carbon atom. Interestingly, when the hydroxyl group of alkynylcyclopropanol is replaced by *tert*-butyl carbonate, different from the above reported 1,2-alkyl transfer, 6-*endo*-*dig* cyclization is preferred to provide six-membered cyclized carbonates as the main products.[40]

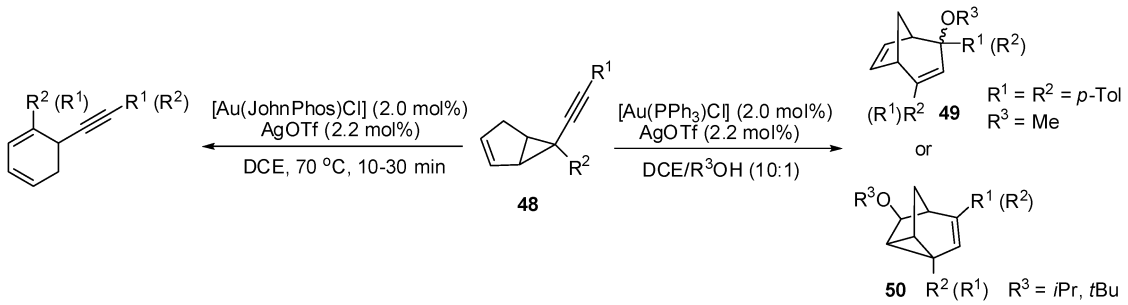
Cyclobutene derivatives are significant subunits in many natural products, but efficient methods for their synthesis are limited. Liu's group described a gold-catalyzed oxidative ring-expansion of alkynylcyclopropanes **46** to cyclobutenyl ketones **47** using an external oxygen donor (Scheme 16).[41] This catalysis allowed the high regioselective generation of a ketone group at the alkynyl carbon atom, along with the expansion of a cyclopropyl ring. Participation of gold α-carbonylcarbenoid intermediates was excluded based on the crossover experiments. Meanwhile, Yu's group also reported a powerful method to construct synthetically useful four-membered carbocycles from the ring expansion of alkynylcyclopropanes trapped by sulfonamides.[42]

Constraining the alkenyl function of the alkynylcyclopropanes in a cyclic substructure would likely impose new reaction pathways. Recently, Barluenga's group disclosed a novel gold(I)-catalyzed cycloisomerization of alkynyl, cyclopentene-fused cyclopropanes **48**. This reaction involved cleavage of the bridging C–C bond and formal [1,2]-alkynyl shift which resulted in five-to-six-membered ring expansion (Scheme 17).[43] Moreover, divergent structural rearrangements were observed to provide bicyclo[3.2.1]octadiene **49** and bicyclo[3.2.1.$0^{2,7}$]octane derivatives **50** through a cationic allyl-gold complex.

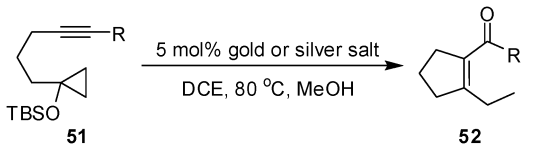
In addition to the structures with adjacent cyclopropyl and alkynyl groups, Ban and his co-workers found that long




**Scheme 16** Gold-catalyzed oxidative ring-expansion of alkynylcyclopropanes.




**Scheme 17** Gold-catalyzed cycloisomerization of 1-alkenyl-2-alkynylcyclopropanes.



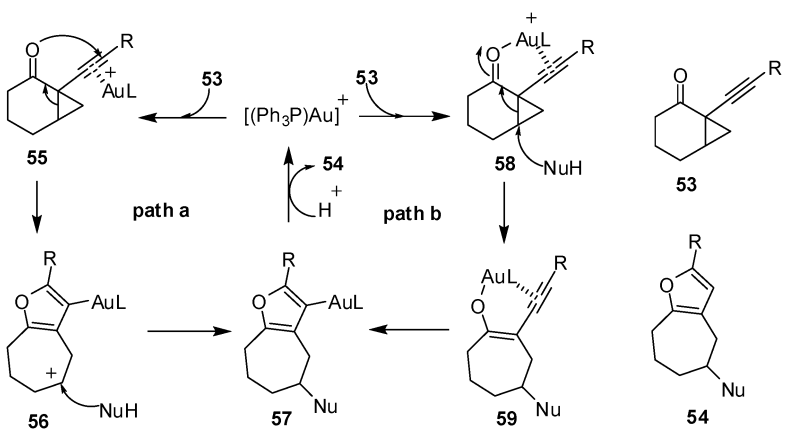

**Scheme 18** Gold or silver salts catalyzed intramolecular carbocyclization.

carbon chain tethered with internal alkynylcyclopropanol silyl ethers such as compounds **51** in the presence of catalytic amount of cationic gold or silver salt afforded the corresponding α,β-unsaturated enones **52** in moderate yields (Scheme 18).[44]

Zhang and Schmalz reported that subjecting 1-(1-alkynyl)-cyclopropyl ketones **53** to the solution of $(Ph_3P)AuOTf$ in $CH_2Cl_2$ in the presence of nucleophiles efficiently gave highly substituted furans **54** (Scheme 19).[45] Lewis acids such as $Cu(OTf)_2$, $In(OTf)_3$, $Ga(OTf)_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$ were also active, but only modest yields were obtained after prolonged reaction time. Two plausible mechanisms have been envisioned for this novel $Au^I$-catalyzed transformation. In path a, a cationic $Au^I$ species first coordinates to the triple bond to generate an intermediate **55**. Nucleophilic attack of the carbonyl oxygen atom on the activated triple bond with concomitant cleavage of the cyclopropane would generate a carbocation **56**, which can be trapped by nucleophiles. Protonolysis of the resulting organogold intermediate **57** gives products **54** and regenerates the $Au^I$ catalyst. Alternatively, a chelate complex **58** is transformed to an Au-enolate **59** through a regioselective homo-Michael-type addition, and subsequent cycloisomerization affords intermediate **57** (path b). Zhao and his co-workers further demonstrated the reaction mechanism through computations.[46a] They found that the key step in the catalytic cycle was the attack of the oxygen atom of $CH_3OH$ on the C–C σ bond of the cyclopropane moiety to yield new organogold intermediates through formation of a C–O bond and cleavage of a C–C bond. Similar results were also reported by Li *et al.*[46b]

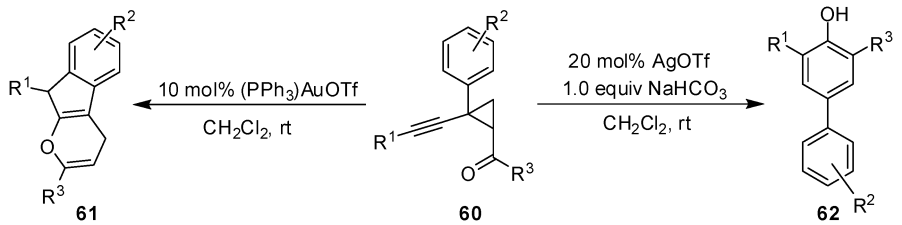
Tu and Zhang *et al*. discovered two tandem rearrangements of *cis*-2-acyl-1-alkynyl-1-aryl cyclopropanes **60** in the presence of gold or silver catalysts. When gold(I) was used as the catalyst, a 5-*exo*-*dig* attack of the gold-activated triple bond by the carbonyl group was preferred. After cleavage of the cyclopropane, the gold carbene intermediate underwent an intramolecular Friedel–Crafts reaction and protodemetallation to yield pyran-fused indenes **61**. While in the silver-catalyzed process, coordination of AgOTf with both the triple bond and the ketone oxygen led to the cleavage of the cyclopropane. Further cycloisomerization resulted in 2,4,6-trisubstituted phenols **62** (Scheme 20).[47]

Cyclization of cyclopropylenyne **63** assisted by a sterically encumbered phosphine for preparation of tricycles had been reported by Echavarren and his co-workers in 2006 (Scheme 21).[48] Interestingly, *syn*-**64′** was favored with catalyst **65** in the presence of a small amount of water, whereas the use of AuCl led to formation of *anti*-**64**, although the reaction rate was relatively slow. An alkenylgold intermediate formed in the cyclization of enynes could be trapped in 5-*exo*-*dig* or 6-*endo*-*dig* Prins reactions to form an additional C–C bond. The concerted pathway was favored with AuCl as the catalyst, whereas the cationic $Au^I$ complex **65** apparently favored a non-concerted reaction *via* a cyclopropyl-stabilized cation,[49]

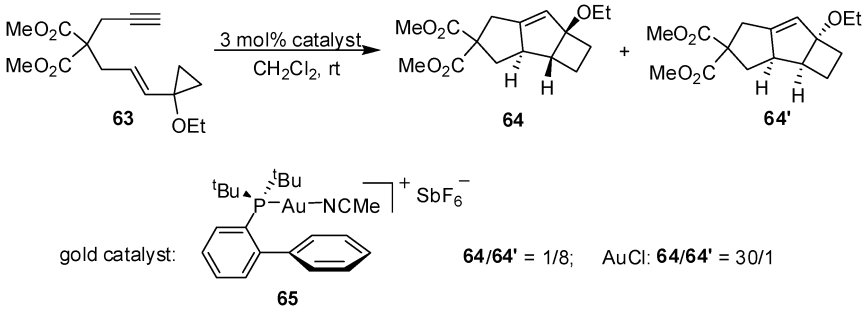



**Scheme 19** $Au^I$-catalyzed ring expansion/cyclization of **53** with different nucleophiles.




**Scheme 20** Different tandem reactions catalyzed by gold(I) and silver(I).




**Scheme 21** Cyclization of cyclopropylenynes.

which underwent a non-stereospecific ring expansion to give mixtures of stereoisomers.

A novel Au-catalyzed homo-Rautenstrauch rearrangement of 1-cyclopropylpropargylic esters to give cyclohexenones such as **68** and cyclopentenyl ketones such as **73** under mild conditions was reported by Wang and his co-workers (Scheme 22).[50] When terminal alkyne **66** was used, 1,2-migration of the acetate afforded a vinyl metal species, which could result in the formation of the gold carbene species **69** or the bond-tautomeric zwitterionic intermediate **70** to produce the corresponding compound **67**. However, substitution at the terminal position of the acetylene unit might initiate a 6-*endo*-*dig*-like 1,3-migration of the carboxylate group to give intermediate **74** or **75**. Then compound **72** could be subsequently formed from these intermediates. In addition, enantiomerically enriched cyclohexenones and cyclopentenyl ketones could be prepared by the gold-catalyzed cyclization of optically active propargyl acetates. Although the rearrangements were cationic in nature, the high degree of chirality transfer in these reactions suggested that gold-stabilized nonclassical carbocations with a certain configurational stability were involved.

Mechanistic studies of a similar reaction involving cyclopropylpropargyl acetates were carried out by Toste and his co-workers (Scheme 23).[51] These studies provided an experimental evidence for the reversibility of the rearrangement in the case of propargylic ester **76a**. In contrast, the Au(I)-catalyzed [3,3]-sigmatropic rearrangement of propargyl vinyl ether **76b** was irreversible and proceeded in a concerted mode. Moreover, they found that the cationic nature of the Au(I)-coordinated allenes formed after the rearrangement and the electron-donating abilities of the allene substituents heavily influenced their structure–reactivity, which determined the $\eta^1$- or $\eta^2$-allene character of $Au^I$-coordinated allenes. A similar report and DFT calculation of the Au(I) and Au(III) catalyzed reaction of 3-cyclopropyl propargylic carboxylates was described by Nevado and his co-workers in 2010.[52]

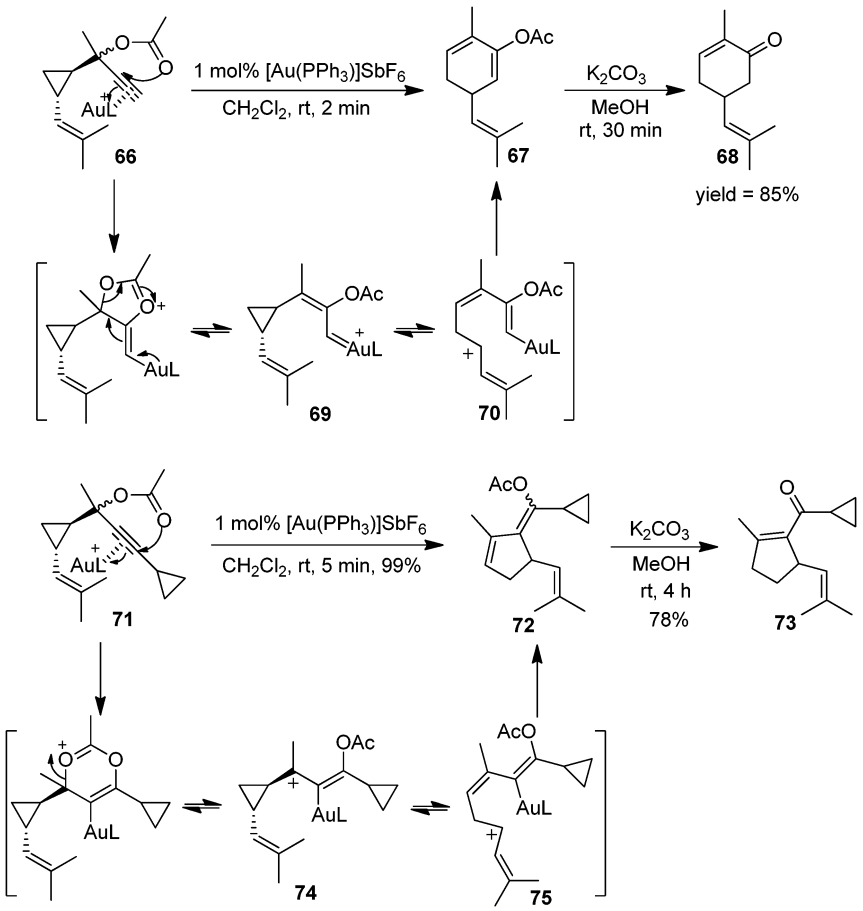
In 2010, Wang *et al*. reported the first gold-catalyzed rearrangement reaction of propargyl cyclopropenes containing both triple-bond and cyclopropene moieties, which afforded benzene derivatives in high yields.[29k,53]

The intramolecular indole/alkyne cyclizations were interesting due to the versatile reaction modes occurring in this system. Gold-catalyzed intramolecular reactions of 3-alkynyl-bearing indoles **77** with cyclopropane and hydroxyl groups were demonstrated by Liu's group in 2010, which led to highly functionalized 3-allenylindoles **78** with good efficiency (Scheme 24).[54] This process likely involved cascade cyclization/heterolytic fragmentation/elimination reactions, which resulted in 1,5-indole migration and C-3 allenylation of the indole moiety.

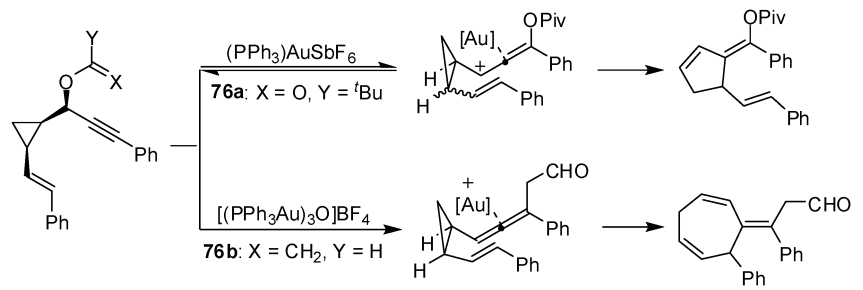
In addition to the above intramolecular rearrangement reactions, Zhang and his co-workers advanced a novel concept of Au-containing all-carbon 1,4-dipoles and applied it in [4+2] annulations of alkynylcyclopropyl ketones **79** with dipolarophiles to form 6-membered carbo/heterocycles-containing furans in good efficiencies and excellent regioselectivities (Scheme 25).[55] The high regioselectivities observed with substituted alkynylcyclopropyl ketones suggested that instead of oxocarbenium, the Au-containing all-carbon 1,4-dipole **80** was preferred to be the reactive intermediate for the annulations as nucleophilic attack of the methine group of the cyclopropane ring in oxocarbenium was expected to be sterically disfavored.

Similarly, a Au- or Cu-catalyzed sequential intermolecular cycloisomerization/formal [4+3] cycloaddition of 1-(1-alkynyl)-cyclopropyl ketones **81** and nitrones **82** was developed by Wang *et al*. (Scheme 26).[56] In this process, a new type of oxazepine-based 5/7-bicyclic heterocycles **83** could be isolated in good yields and excellent stereoselectivities.

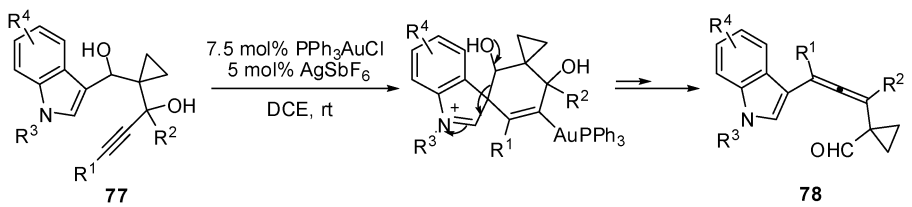
Then, Zhang *et al*. found an interesting regioselective control in the cycloaddition reactions of 1-(1-alkynyl) cyclopropyl ketones **81** with nitrones **82**. When using $Sc(OTf)_3$/1,10-phenanthroline as the catalyst, the formal [3+3] cycloaddition products tetrahydro-1,2-oxazines **84** were obtained. Whereas, in




**Scheme 22** Cyclization of cyclopropylpropargyl acetates.




**Scheme 23** Two different reactivity patterns in vinylcyclopropyl-substituted substrates.

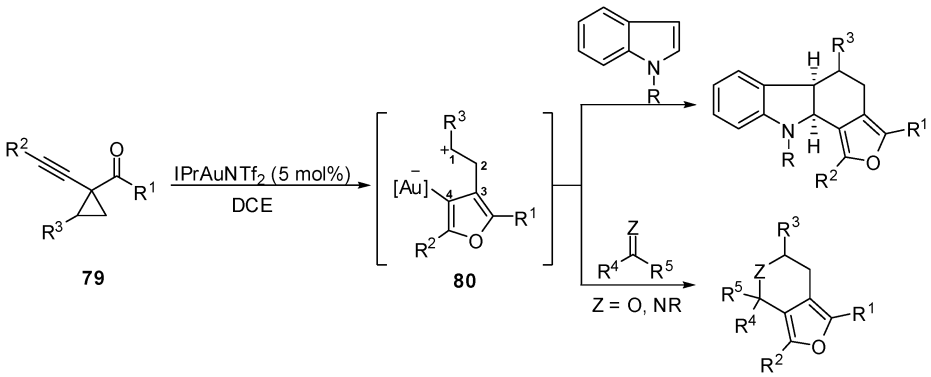



**Scheme 24** Gold-catalyzed 1,5-migration of indoles.

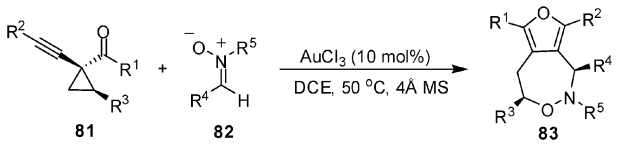
the presence of gold(I) catalyst, [4 + 3] cycloaddition products 5,7-fused bicyclic furo[3,4-*d*]-[1,2]oxazepines **83** could be afforded (Scheme 27).[57]

They proposed two plausible mechanisms for this gold(I)-catalyzed [4 + 3] cycloaddition. In cycle I, the cationic gold(I) species coordinated to the alkyne, and subsequent nucleophilic attack gave the oxonium-containing vinyl-gold intermediate **85**. The following regioselective homo-Michael addition of nitrones **82** produced furanyl-gold intermediate **86**, which underwent ring closure to obtain the final products **83**. In cycle II, nucleophilic




**Scheme 25** [4 + 2] annulations of alkynylcyclopropyl ketones and dipolarophiles by gold(I).




**Scheme 26** [4 + 3] cycloaddition of 1-(1-alkynyl)cyclopropyl ketones and nitrone.

addition of the nitrones **82** to the key carbocationic furanyl-gold intermediate **87** would also produce intermediate **86**, which underwent the same ring closure step as in cycle I to give compounds **83**. In order to verify this mechanism, a kinetic resolution experiment of a racemic mixture of **81a** and a transformation experiment of optically active *ent*-**81a** were performed. The results provided strong supporting evidence for the proposed cycle (cycle I) and the carbocationic mechanism (cycle II) could be ruled out (Scheme 28).

## 3. Small heterocycles

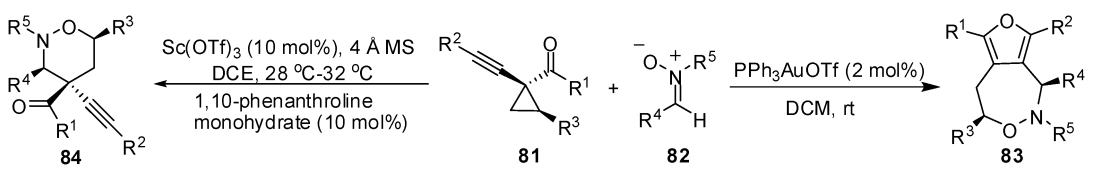
### 3.1. Epoxide

Epoxide, one of the smallest heterocycles, exhibits a synthetically useful balance between stability and reactivity. Plenty of methods have been developed to the ring-opening and ring-rearrangement of epoxides.[58] In 2004, He's group discovered a gold-catalyzed stereospecific alkylation of arenes with epoxides. Treating (phenoxymethyl)oxiranes **88** with $AuCl_3$/3AgOTf (2.5 mol% based on gold) in 1,2-dichloroethane yielded exclusively the *endo* addition product 3-chromanols **89** in good yields. An intermolecular reaction of trimethoxybenzene with 3 equiv. of propylene oxide in the presence of 5 mol% $AuCl_3$/3AgOTf in 1,2-dichloroethane at 83 °C was also examined, leading to product 1-(2,4,6-trimethoxyphenyl)-2-propanol **90** in 52% isolated yield after 24 h (Scheme 29).[59] The addition of the trimethoxybenzene to the less hindered primary carbon atom of the epoxide revealed that the reaction seemed to be a unique feature associated with the catalytic system described here and suggested that the reaction proceeded through an $S_N2$ type mechanism. A similar result was also reported by Yang and his co-workers employing the thiourea/$AuCl_3$/AgOTf catalytic system.[60]

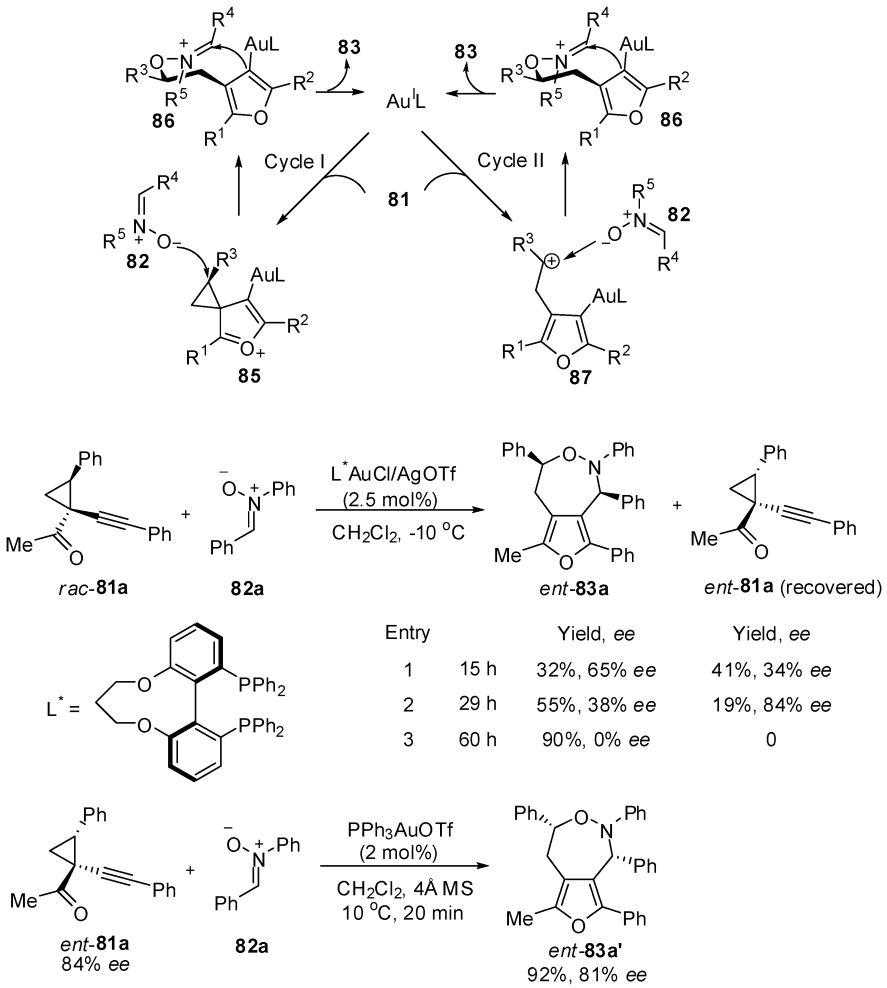
α-Hydroxy epoxides were very attractive substrates, which could be easily synthesized by simple steps and transformed to various new skeletals. In 2009, a novel rearrangement of α-hydroxy epoxides in the presence of a gold catalyst was investigated by Liang *et al*. Various 1,5 or 1,6-diketones and monoketones were afforded efficiently under mild conditions (Scheme 30).[61] The substituents and the ring strain effects controlled the selective formation of the two products. The process for the formation of monoketone **92** involved a semi-pinacol rearrangement of the α-hydroxy epoxide **91** and elimination of one molecule of aldehyde (path a). On the other hand, the formation of diketone **93** underwent a bond cleavage and a keto–enol tautomerism process (path b).

Since the discovery that highly dispersed nanogold particles supported on metal oxides could be highly active catalysts, there has been an explosion in the interest for the catalysis by gold nanoparticles.[62] Recently, Stratakis *et al*. found that gold nanoparticles supported on $TiO_2$ could be used as a practical heterogeneous catalyst for the isomerization of epoxides **94** to allylic alcohols **95**. The reaction proceeded smoothly to give the products in high yields and the selectivities of the products were often remarkable (Scheme 31).[63]

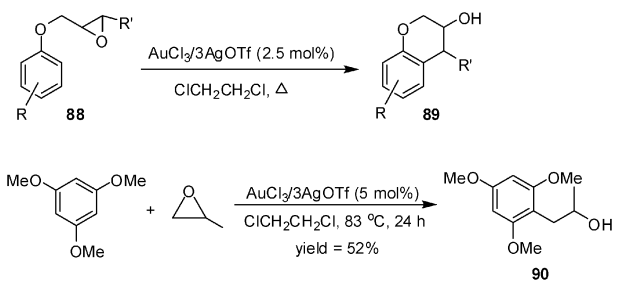
It has been proposed that the $TiO_2$ surface stabilized cationic gold species, such as $Au^I$, which were detectable by X-ray photoelectron spectroscopy. These species acted as Lewis acid sites to activate the epoxide, whereas the surrounding oxygen atoms from the $TiO_2$ support could act as basic sites and catalyze the isomerization. The reaction occurred through a concerted mechanism (Scheme 32).




**Scheme 27** Controlled cycloaddition of 1-(1-alkynyl)cyclopropyl ketones and nitrone.




**Scheme 28** Mechanism for gold(I)-catalyzed [4 + 3] cycloaddition.



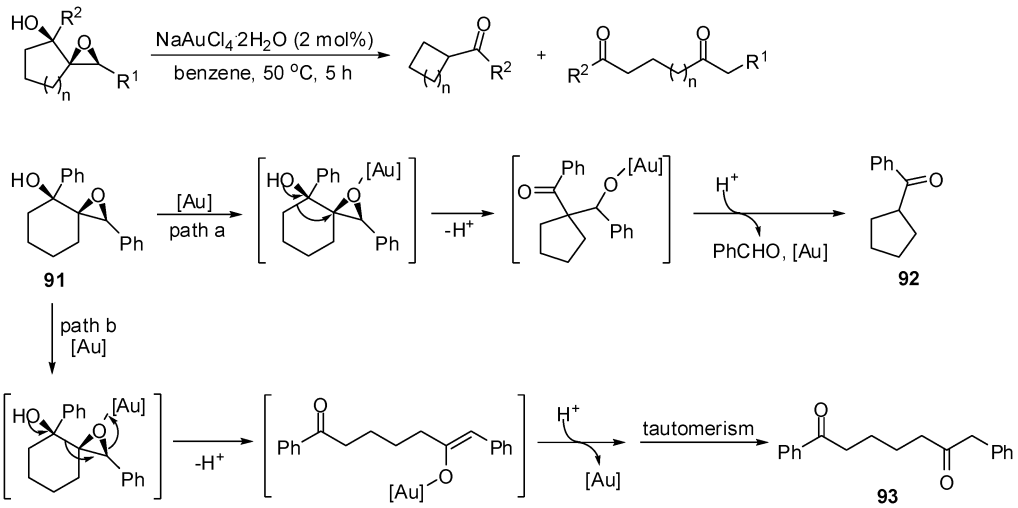

**Scheme 29** Gold$^{III}$-catalyzed alkylation of arenes with epoxides.

Coordination to the epoxide functionality to the $Au^I$ species on the $TiO_2$ surface resulted in the simultaneous hydrogen atom abstraction from one of the *gem* carbon atoms by the oxygen atoms of $TiO_2$.

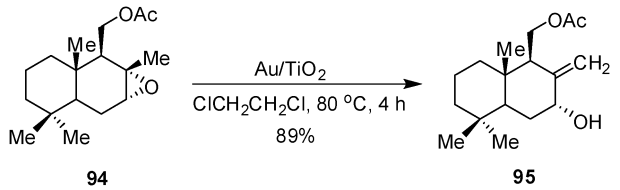
Deng's group found that polymer-immobilized nanogold could be a highly effective catalyst for activation of carbon dioxide, which reacts with epoxides **96** to yield cyclic carbonates **97** with TOF $>$ 50 000 mol mol$^{-1}$ h$^{-1}$ (Table 1).[64] The synergism between the nanogold species and the peculiar microenvironment of the polymer surface led to the exclusive catalytic activity for the reaction. The catalytic performance was determined much more by the particle size of the nanogold than gold loading. Polymer has been used as the support to immobilize the nanogold catalysts because the polymer-immobilized catalysts were closer to homogeneous catalysts in chemical character and were attractive for technological applications.

The traditional deoxygenation of epoxides to alkenes by using stoichiometric reagents suffered from low activity and low atom efficiency. Consequently, the development of an efficient catalytic system for the selective deoxygenation of epoxides to the corresponding alkenes was still desired. Kaneda's group has just discovered two efficient and selective heterogeneous gold and silver nanoparticle (NP)-catalyzed methods to synthesize alkenes by deoxygenation of epoxides, using 2-propanol[65] or $CO/H_2O$[66] as reductants. Recently, they demonstrated another highly selective ($>$99%) deoxygenation of epoxides **98** to alkenes **99** catalyzed by hydrotalcite-supported gold catalyst with $H_2$ as an ideal "green" reducing reagent (Scheme 33).[67] Moreover, after the reaction, solid Au/HT could be reused without loss of activity or selectivity. They proposed a concerted effect between the basic sites of HT and the Au nanoparticles, which meant that heterolytic cleavage of $H_2$ occurred at the interface between Au NPs and HT as a macroligand of Au NPs to give $[Au–H]^-$ and $[HT–H]^+$ species. These hydrogen species would selectively

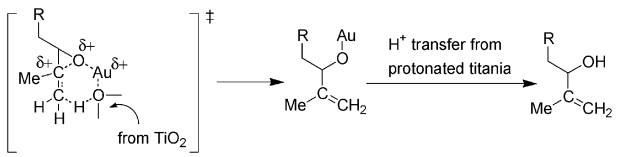
 




**Scheme 30** Proposed mechanism for the formation of monoketone **92** and diketone **93**.

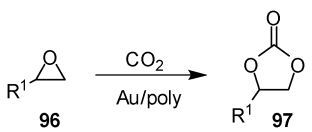


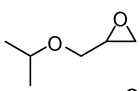
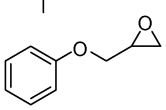
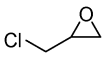

**Scheme 31** Transformation of epoxides into allylic alcohols catalyzed by $Au/TiO_2$.



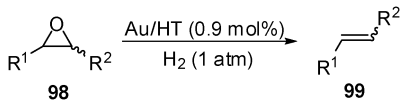

**Scheme 32** A concerted mechanism.

**Table 1** Cyclization reactions of epoxides with $CO_2$ over 0.05 wt% Au/Poly

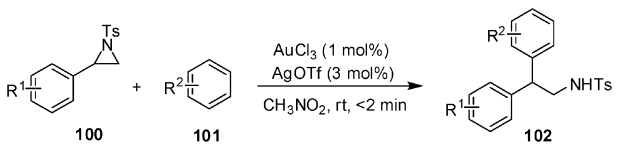



| Entry | Epoxides | GC yields (%) | TOF |
|---|---|---|---|
| 1 |  | 90 | 11 600 |
| 2 |  | 93.2 | 10 400 |
| 3 |  | 93.7 | 6300 |

deoxygenate the epoxides **98** to form the corresponding alkenes **99** and water without further reduction of the C=C bonds in the products.




**Scheme 33** Transformation of epoxides to alkenes catalyzed by Au/HT.



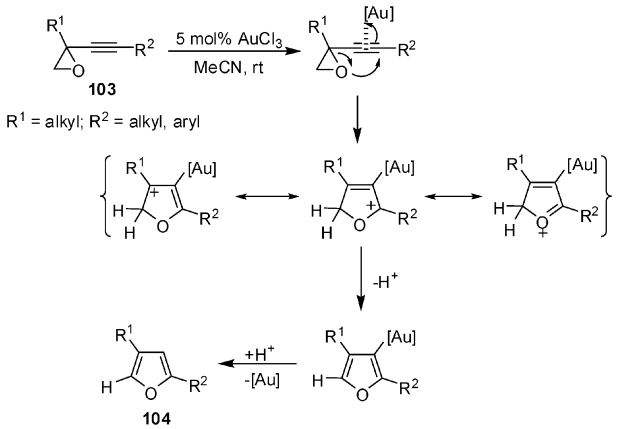

**Scheme 34** $AuCl_3/AgOTf$-catalyzed ring-opening reaction of aziridines with arenes.

### 3.2. Aziridine

It is well-known that aziridine is a versatile building block for the synthesis of many nitrogen-containing biologically active molecules. Among the procedures of ring opening of aziridines, a nucleophilic ring-opening reaction is one of the major routes to access highly functionalized compounds.[68] $BF_3{\cdot}OEt_2$ promoted reactions of aziridines with allylsilanes or arenes have been previously reported.[69] However, 1.0 equiv. of $BF_3{\cdot}OEt_2$ had to be used. Indium triflate was also employed for the reaction of aziridines with arenes.[70] The reaction usually completed within several hours in the presence of catalytic amount of $In(OTf)_3$ and afforded the product as a mixture of regioisomers in most cases. Wu *et al.* described a highly efficient and regiospecific ring-opening reaction of aziridines **100** with electron-rich arene **101** catalyzed by gold(III) chloride/silver triflate, which provided a facile and convenient route for the synthesis of β-arylamines **102** (Scheme 34).[71] The advantages of this method include high efficiency, excellent regioselectivity, experimentally operational ease, mild conditions and low catalytic loading.

### 3.3. Strained small heterocycles bearing alkynyl groups

**3.3.1. Epoxy alkyne.** Cyclizations of epoxy alkynes have provided rapid access to complex molecular structures in an easy one-pot process in which a wide range of metal salts can

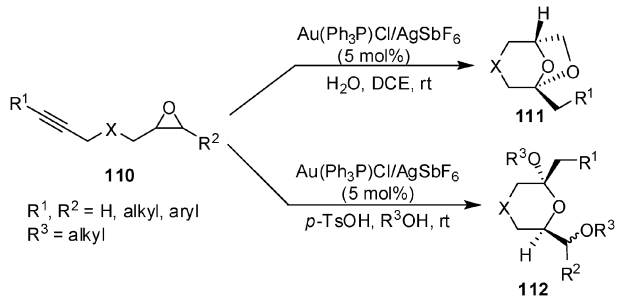


**Scheme 35** Gold-catalyzed isomerization of epoxy alkynes to furans.

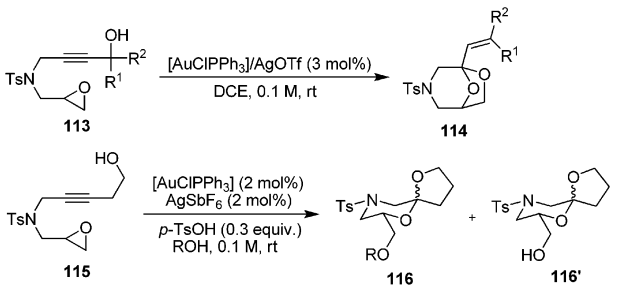
be used, either in a stoichiometric or a catalytic manner. For example, Marson *et al*. reported an efficient $Sn(OTf)_2$, $TiCl_4$ or $SnBr_4$-induced alkyne-epoxy alcohol cyclization leading to a seven-membered carbocyclic ring, however, the reaction generally requires an excess of the metal reagents.[72] Gansäuer found that a catalytic amount of Ti(III) complexes sufficed to implement radical epoxide–alkyne cyclization in the presence of excess manganese powder.[73] In addition, McDonald and Schultz described a $Mo(CO)_6$-catalyzed cyclization of α-ethynylepoxides to give furans.[74] The first intermolecular alkyne–epoxide reductive coupling was recently reported by Molinaro and Jamison with the use of the Ni(0)–$PBu_3$ catalyst.[75] Later on, Liu and his co-workers achieved a cascade alkyne–epoxide cyclization of (*o*-ethynyl)phenyl epoxides catalyzed by Ru complexes.[76]

The first example of gold-catalyzed isomerization of epoxy alkynes **103** to furans **104** under mild conditions was reported by Hashmi and Sinha in 2004 (Scheme 35).[77] In this case, the gold complex activated C–C triple bond for the addition of a nucleophile, and the epoxide oxygen would attack at the distal position of the alkyne. The most important feature of the substrates **103** was that the alkynyl group was placed adjacent to epoxide, which made the epoxide more reactive.

Echavarren *et al*. found that enyne **105**, bearing an epoxy group at the alkenyl side chain, could be transformed to oxotricyclic derivative **109** in the presence of $Au^I$ catalysts (Scheme 36).[48] The reaction proceeded through intermediate



**Scheme 37** Gold-catalyzed isomerization of epoxy alkynes to ketals.

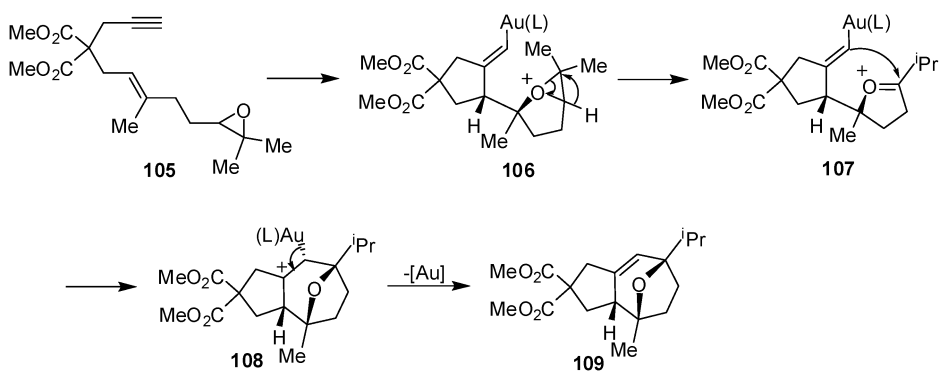


**Scheme 38** Gold-catalyzed isomerizations of epoxy propargylic/homopropargylic alcohols.

**106**, which suffered C–O bond cleavage followed by a 1,2-hydrogen shift to form **107**. Intermediate **107** underwent Prins reaction to give intermediate **108**. Elimination of the metal fragment of intermediate **108** afforded tricyclic product **109**.

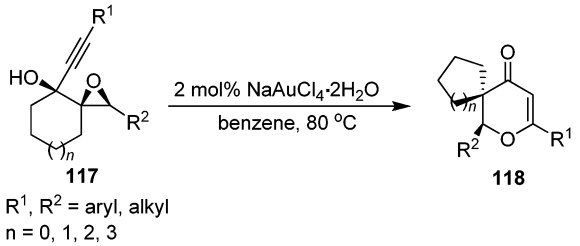
Subsequently, Shi *et al*. developed a novel access to ketal skeletons **111** or **112** through highly regio- and diastereoselective intermolecular addition of water and alcohols to alkynyl epoxides **110** catalyzed by gold(I) (Scheme 37).[78] This transformation involved a domino sequence with a three-membered ring-opening, 6-*exo*-*dig*-cycloisomerization and subsequent intra- or intermolecular nucleophilic addition to a double bond.

In their later report, an efficient gold-catalyzed cycloisomerization of epoxy propargylic/homopropargylic alcohols to ketals/spiroketals was described (Scheme 38).[79] The formation of ketals **114** probably involved a Meyer–Schuster rearrangement of the epoxy propargylic alcohols **113** exclusive involvement of an oxonium ion intermediate. Moreover, they demonstrated that the ring-opening reaction of oxirane was probably the rate-determining step in the transformation of the epoxy



**Scheme 36** Gold-catalyzed isomerization of an enyne bearing an epoxy group.




**Scheme 39** Gold-catalyzed isomerization of cyclic 1-alkynyl-2,3-epoxy alcohols.

homopropargylic alcohols **115** to spiroketals **116** and **116′**. Similar gold(I)-catalyzed cascade cyclization of allenyl epoxides to polyether skeletons was also reported by Lee and Gagné *et al.*[80] By subjecting oxygen tethered alkynyl epoxides in acetone in the presence of gold(I) catalyst, Balamurugan *et al.* found that bicyclic ketals could be successfully afforded under mild conditions and the water formed from the acetone solvent played a crucial role in the cyclization of the acetonide on the triple bond.[81]

Cycloisomerizations of esters of acyclic 1-alkynyl-2,3-epoxy alcohols to form furan derivatives in the presence of a variety of nucleophiles were reported by Liang and his co-workers.[82] Direct nucleophilic attack of the epoxide oxygen atom to the gold-coordinated alkynes resulted in the formation of a key oxonium ion intermediate. However, when water was used as a nucleophile, difurylmethane was formed in high yield.[83] By further investigating the isomerization of cyclic 1-alkynyl-2,3-epoxy alcohols **117**, Liang and his co-workers found that spiropyranones **118** were formed through a tandem cyclization/[1,2]-alkyl migration process (Scheme 39).[82b,84a] Similar researches on the transformation of acyclic 1-alkynyl-2,3-epoxy alcohols to bisfurans were also reported by Shi and his co-workers. The substituent effect on this isomerization was systematically analyzed.[84b]

Pale *et al.* have developed a catalytic approach to functionalized divinyl ketones **120** through an $Au^I$-catalyzed rearrangement of (3-acyloxyprop-1-ynyl)oxiranes **119**.[85] Theoretical calculations of this reaction were carried out by Faza and his co-workers. Three competing paths for the rearrangement of both cyclic and acyclic **119** had been taken into account (Scheme 40).[86] These proposed mechanisms were characterized by the following: (a) the nucleophilic attack of the oxirane to an allene intermediate that originated from 1,3-ester migration; (b) gold mediation occurring *via* carbenoid chemistry through an initial 1,2-rearrangement;[87] (c) the pathway proposed by Pale and his co-workers, proceeding through a plausible oxirane activation. The three competing paths for the rearrangement of **119** evidenced the multifaceted character of gold as a catalyst. The preferred mechanism for this facile synthetic transformation involved a sequence of more than eight steps where the dense functionalization of the substrate's backbone was the key of the reactivity: all the groups acted in synergy, and sequential gold coordination to the π-system and the lone pairs of oxygen atom was needed for the rearrangement. Moreover, the transformation of a cyclized precursor was slightly kinetically favored because of the ring strain released in the rate-limiting step.

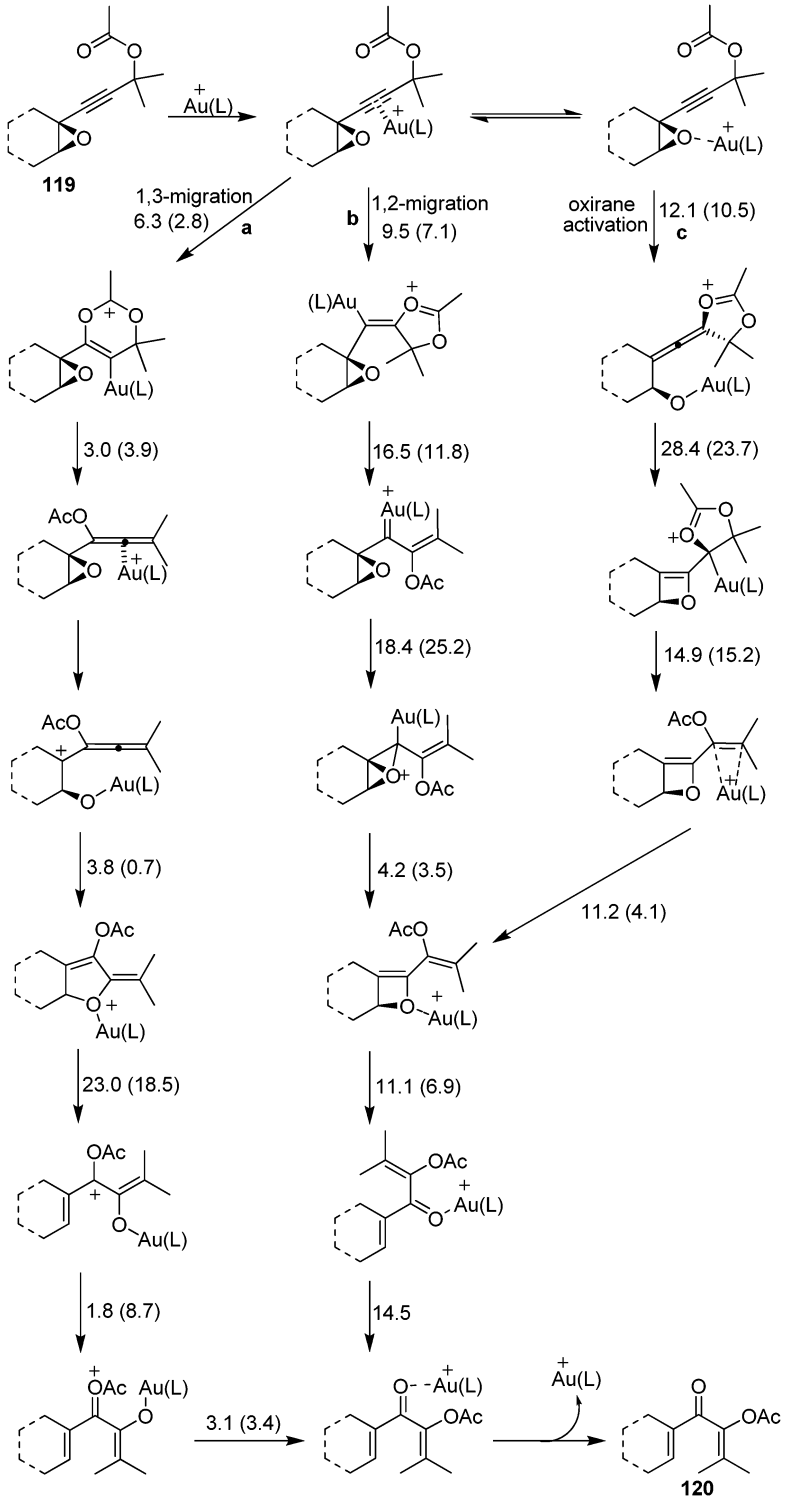
Meanwhile, Pale's group developed the isomerization reactions of alkynyloxiranes to furans in the presence of an external nucleophile and in the catalysis of silver or gold salts. The mechanism investigations revealed that such reactions proceeded through an addition–cyclization–elimination cascade of events.[88] After that, they found that acetoxylated alkynyloxiranes and -aziridines **121** could be rearranged into various highly substituted furans and pyrroles **122** by treating with various nucleophiles.[89] A plausible mechanism involving 1,2-acyl migration concomitant with oxirane opening, nucleophilic addition, cyclization and elimination has been proposed in this literature (Scheme 41).

Gold-catalyzed isomerization of 2-alkynylaryl epoxides **123** was first reported by Hashmi *et al.* (Scheme 42).[90] This new conversion nicely complemented the few known routes to 3-acylindenes **124**.[91] The tentative mechanistic study pointed towards a pentadienyl cation to cyclopentenyl cation cyclization as a key step and not a hydrated carbocyclization or the participation of vinylidene-metal species. Isotope labeling of the epoxide oxygen indicated an intramolecular oxygen transfer.

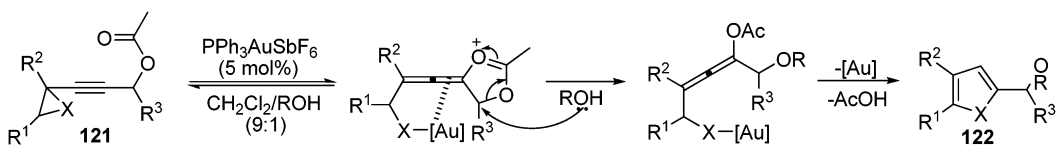
Besides the aromatic systems, the nonaromatic systems were also investigated by Liu and his co-workers (Scheme 43).[92] Starting from **125**, the key intermediate **127** was formed by a 6-*exo*-*dig* attack of the epoxide at the alkyne of π-intermediate **126**, and its structure was best represented by its gold-carbenoid resonance form **128**, which triggered a Nazarov-type cyclization to give the observed product **129**. The carbenoid character of species **128** was verified by a trapping experiment with $Ph_2SO$ oxidation.[93]

Although the gold-catalyzed isomerization of 2-alkynylaryl epoxides has been reported by Hashmi and Liu before, successful precedent using epoxide bearing an electron-withdrawing substituent has never been disclosed. Shi and his co-workers have reported a novel combination of gold complex with $Yb(OTf)_3$ to catalyze the rearrangements of epoxy alkynes **130**, affording interesting functionalized indene derivatives **131** (Scheme 44).[94] Double transfer of the carbonyl group in a five-carbocyclic system or intramolecular [1,3]-migration of an acyl group could be observed in this process. $Yb(OTf)_3$ played an important role in the reaction: (1) promote the rearrangement of epoxides twice; (2) activate the alkyne–gold complex during the reaction. Upon further increasing the atom number between the epoxide and the alkyne, two kinds of six and seven-membered heterocycles were obtained through selective carbon or oxygen nucleophilic addition on alkynes depending on the structures of substrates.[95]

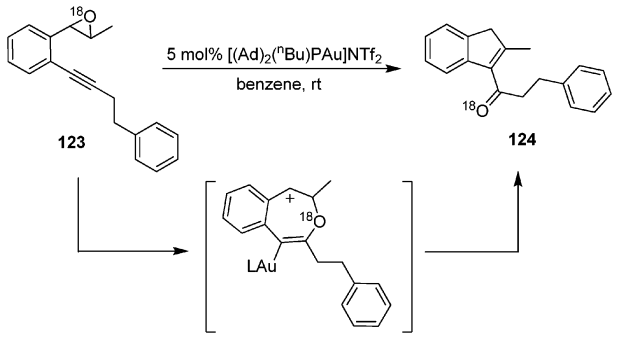
In addition to the intramolecular cycloisomerizations of epoxy alkynes, gold-catalyzed [3 + 2] cycloadditions of gold α-carbonylcarbenoids (generated from 2-epoxy-1-alkynylbenzenes) with alkenes were demonstrated by Liu's group, affording 2,3-dihydrofuran products efficiently. Deuterium-labeling experiments indicated a stepwise ionic mechanism for the [3 + 2] cycloaddition.[96] Their further investigations revealed that *cis*-1-epoxy-1-alkynylcyclopropanes **132** could undergo an unprecedented [4 + 2] cycloaddition of epoxyalkynes with enones or dienes to produce complex oxacyclic compounds **135** with excellent diastereoselectivity. The strong s character of the carbocation associated with the cyclobutyl carbon of 1-oxyallyl cation **133** played an important role in this novel annulation. Tricyclic oxonium species **134** reacted with water



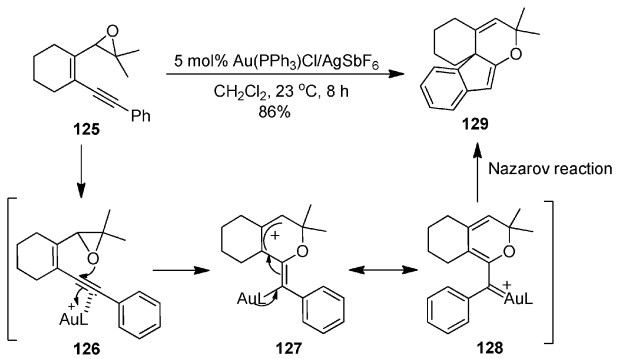

**Scheme 40** $Au^{I}$-catalyzed rearrangement of (3-acyloxyprop-1-ynyl)oxiranes.



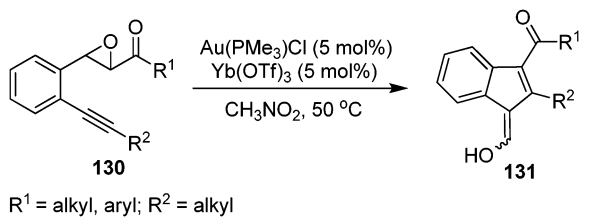

**Scheme 41** Mechanism for the formation of furans or pyrroles.




**Scheme 42** Gold-catalyzed conversion of 2-alkynylaryl epoxide **123**.




**Scheme 43** Gold-catalyzed cycloisomerization of nonaromatic epoxide to polycyclic 2*H*-pyran.



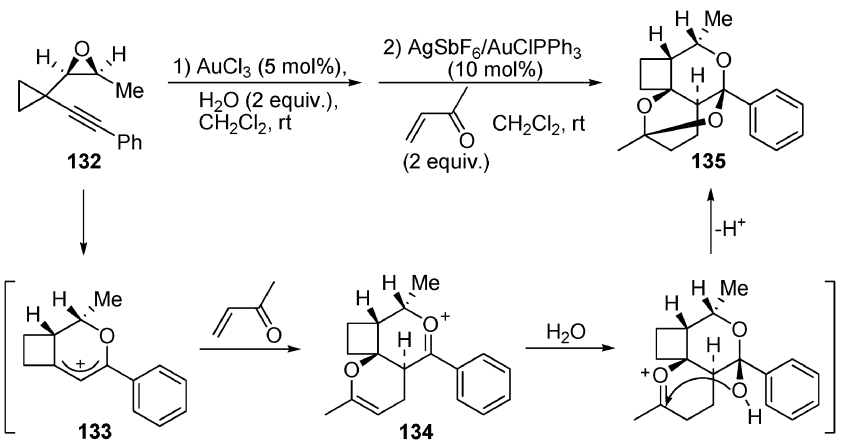

**Scheme 44** Domino rearrangement of epoxy alkynes.

through a bifunctional oxonium–enol (acid–base) pair, ultimately giving the tricyclic oxacyclic compound **135** along with the release of one proton (Scheme 45).[97a] Then, they observed different chemoselectivities for the gold-catalyzed transformation of the same substrates *cis*-1-epoxy-1-alkynylcyclopropanes into various cyclohalogenated products with *N*-halosuccinimide (halo = chloro, bromo and iodo).[97b]

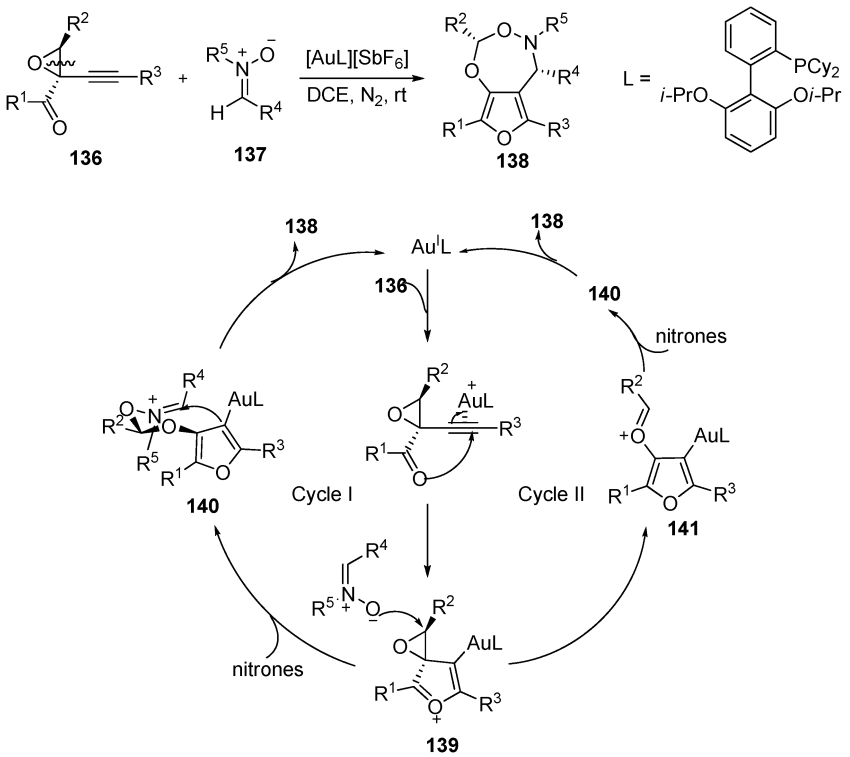
The first example of gold-catalyzed, chemoselective C–C bond cleavage of epoxides **136** by introducing an alkyne was successfully developed by Wang and Zhang (Scheme 46).[98] The hetero-bicyclics **138** could be efficiently prepared in a highly diastereoselective fashion from readily available 1-(1-alkynyl)-oxiranyl ketones **136** and nitrones **137**. The process probably involved two different cycles having the same oxonium-containing vinyl-gold intermediate **139**. In cycle I, the regioselective homo-Michael addition of nitrones at the $C_\beta$ position of the epoxy motif would generate furanyl-gold intermediate **140**, which underwent the favored chairlike conformation to give the corresponding products diastereoselectively. In cycle II, aromatization of intermediate **139** could produce furanyl-gold intermediate **141** with an oxygen-stabilized carbocation. Subsequent reaction with nitrones would give the same intermediate **140** as in cycle I.

**3.3.2. Aziridine alkyne.** Davies and his co-workers found great counterion effects in a gold-catalyzed synthesis of pyrroles from alkynyl aziridines **142** (Scheme 47).[99] The atom-economic formation of 2,5-disubstituted pyrroles **143a** proceeded in quantitative yields and avoided extractive workup or lengthy purification with $PPh_3AuOTs$ as the catalyst. A novel reaction pathway was accessed on changing the catalyst system to $PPh_3AuOTf$, affording 2,4-disubstituted pyrroles **143b**. The author explained these results by considering the basicity of the counterion and the solvent. When basic counterion tosylate was used, proton elimination from intermediate **144** was facilitated to form 2,5-disubstituted pyrroles **143a**, regardless of the reaction solvent. In the absence of such a basic counterion, an aromatic or otherwise weakly Lewis basic solvent could also mediate the proton transfer pathway, at a sufficient rate to see formation of **143a**. When both counterion and solvent were insufficiently basic, an alternative pathway *via* 1,2-aryl transfer took precedence to form 2,4-substituted pyrroles **143b**. Similar results have also been reported by Hou *et al.*[100a] and Liu *et al.* recently.[100b]

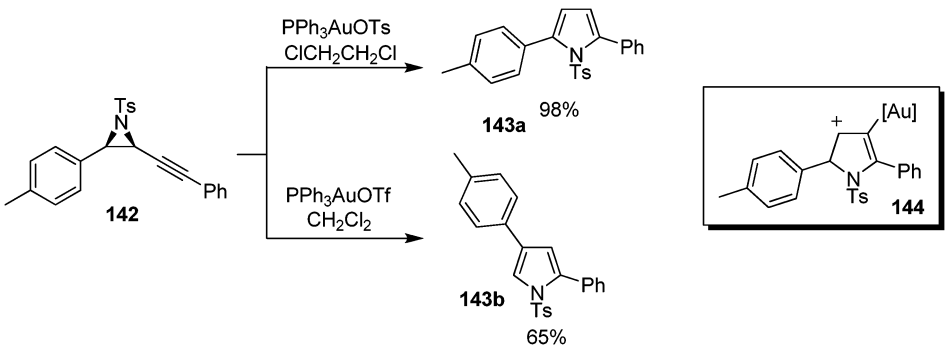
Subsequently, Tu *et al*. reported the gold-catalyzed rearrangement of propargylic aziridine **145** to form trisubstituted and



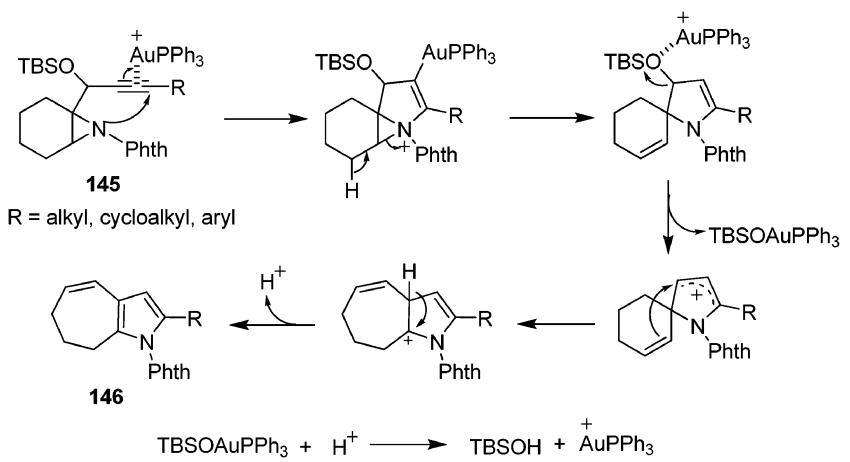

**Scheme 45** [4 + 2] cycloaddition of epoxy alkynes with enones.




**Scheme 46** [4 + 3] cycloaddition of epoxy alkynes **136** with nitrones.

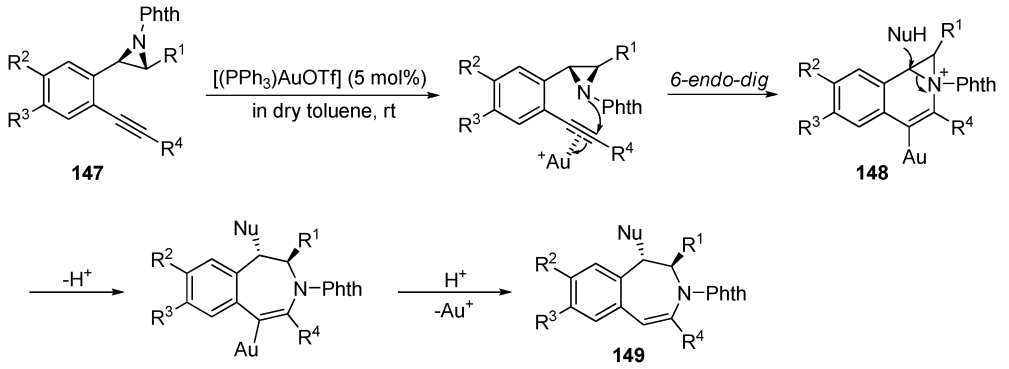



**Scheme 47** Counterion effects in a gold-catalyzed synthesis of pyrroles from alkynyl aziridines.

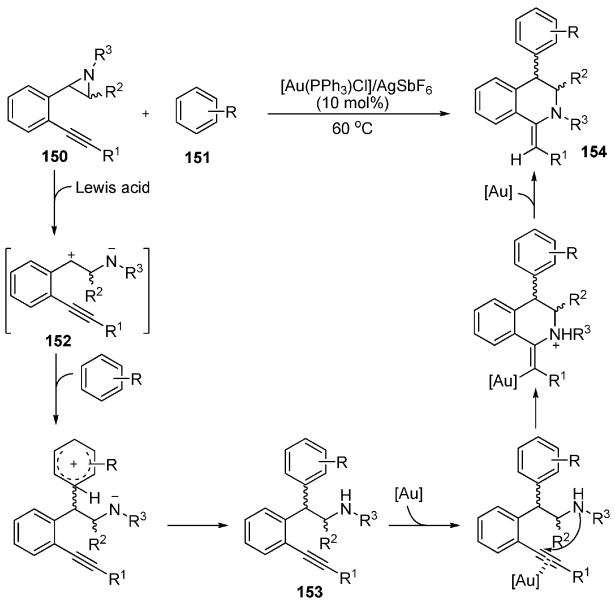



**Scheme 48** The rearrangement of propargylic aziridine.




**Scheme 49** Formation of 3-benzazepine derivatives.

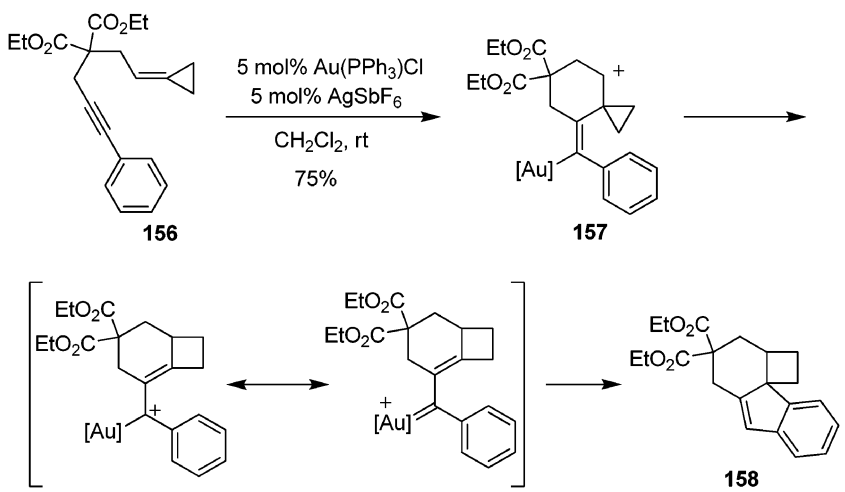



**Scheme 50** Domino reaction of aziridinyl alkynes with arenes.

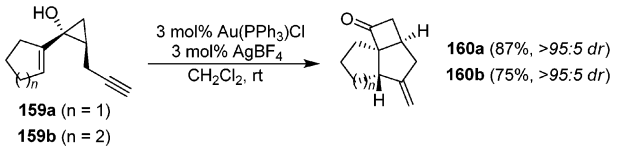
cycloalkene-fused pyrroles **146** involving an unusual tandem cyclization, ring-opening and Wagner–Meerwein process (Scheme 48).[101]

Additionally, a gold-catalyzed ring-opening cyclization of (*o*-alkynyl)phenyl aziridines **147** assisted by external heteronucleophiles was developed by Liu's group, which could afford functionalized benzazepines **149** in high regio- and stereoselectivities. This reaction likely proceeded through a regioselective 6-*endo-dig* cycloaddition to form an aziridinium ion intermediate **148**. Furthermore, it should be also noted that the existence of the electron-withdrawing group on the aziridine ring was crucial for the regioselective benzylic C3–N1 bond cleavage of the aziridine ring (Scheme 49).[102] In intermediate **148**, the positive charge accommodation of the benzylic C3–N1 bond was better than the C2–N1 bond having an ester substituent, thus it got easier to be broken toward the attack of the nucleophile.

A highly regiospecific gold(III) chloride/silver triflate catalyzed ring-opening reaction of aziridines by electron-rich arenes had been reported by Wu's group, affording β-arylamines in good yields.[71] Later on, Shi and his co-workers reported a novel gold(I)-catalyzed domino reaction of aziridinyl alkynes **150** with various arenes **151** that led to 1,2,3,4-tetrahydroisoquinoline and 3,4-dihydroisoquinoline structural motifs under mild conditions, with *syn*-stereoselectivities favored. A plausible mechanism that proceeded through a benzylic cation was presented on the basis of deuterium-labeling and control experiments as well as the observed diastereoselectivities. The moderate to high




**Scheme 51** Cyclization of aryl ynylidenecyclopropane.



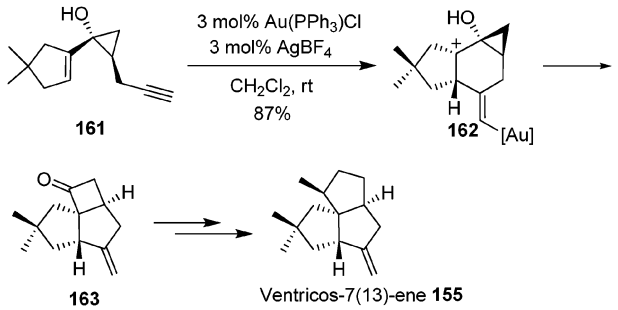

**Scheme 52** Cyclopropanol cycloisomerization.

*syn*-diastereoselectivities could be rationalized by using the Friedel–Crafts reaction mechanism of a benzylic cation **152**. The preferred direction of attack from ArH should correlate to the preferred conformation of the benzylic cation **152** and occur from the bottom face of the plane due to steric hindrance. The initial breaking of the C–N bond in the presence of Lewis acid gave intermediate **152**, which underwent Friedel–Crafts reaction with arenes and intramolecular proton transfer to form intermediate **153**. The final product **154** could be obtained by intramolecular nucleophilic addition and elimination of the gold catalyst (Scheme 50).[103]

## 4. Application of gold-catalyzed reactions using strained small rings

Ventricos-7(13)-ene **155**, a novel triquinane containing an unprecedented rearranged pentalenene skeleton, is an angular tricyclic ring system, bearing a hindered all-carbon quaternary center and remote *exo*-methylene. This product was extracted from the essential oil of the liverwort *Lophozia ventricosa* belonging to the family of Lophoziaceae and investigated by means of GC-MS and extensive NMR measurements.[104] Before describing this novel total synthesis, the gold-catalyzed enyne cycloisomerization should be mentioned. Toste *et al.* have developed two new gold-catalyzed ring-expanding cycloisomerization reactions of enynes containing an embedded cyclopropane unit that offer an opportunity to synthesize complex polycyclic ring systems rapidly.[105]

Enyne cycloisomerization of alkylidenecyclopropane **156** would lead to a spirocyclic cyclopropylmethyl cation **157**

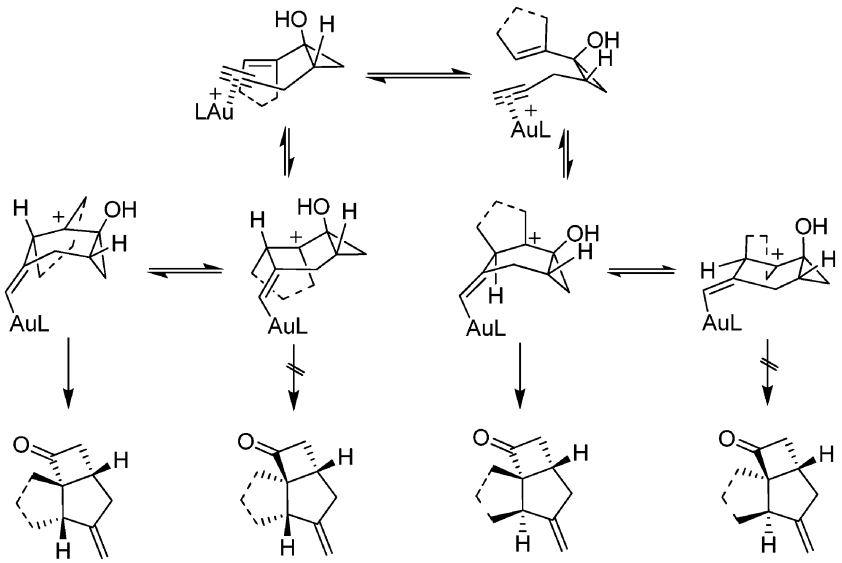



**Scheme 54** Synthesis of ventricos-7(13)-ene **155**.

bearing a vinylogous gold substituent. In this case, σ-bond migration might be aided by electron-donation from gold. The formed gold(I)-stabilized allylic cation would participate in a Nazarov-type electrocyclization to give the corresponding product **158** in 75% yield (Scheme 51).

An alternative approach to the generation of the cyclopropylmethyl cation involved the cyclization of enynes bearing an internal cyclopropanol unit. Gold(I)-catalyzed cycloisomerization of cyclic olefin substrates **159a** and **159b** provided diastereomerically pure angular tricyclic systems **160a** and **160b** in good yields under mild conditions (Scheme 52). A stereochemical analysis for the gold(I)-catalyzed reactions is presented in Scheme 53.

The first total synthesis of (±)-ventricos-7(13)-ene **155** has been completed in 11 steps. Gold(I)-catalyzed reaction of **161** proceeded smoothly at room temperature *via* cyclopropylcarbinyl cation **162** to furnish cyclobutanone **163** in 87% yield as a single diastereomer. Subsequent ring expansion steps from cyclobutanone **163** to the angular triquinane ring were easily achieved (Scheme 54). Employing gold-catalyzed enyne cycloisomerizations enabled the rapid synthesis of (±)-ventricos-7(13)-ene **155**, illustrating the increasing utility of this methodology as a tool to access complex molecular frameworks.




**Scheme 53** Stereochemical analysis of cyclopropanol cycloisomerization.

## 5. Conclusions

The manifold synthetic methods and their applications presented in this review demonstrate considerably growing interest in gold-catalyzed transformations of strained small rings. Employing heterogeneous or homogeneous gold catalysts enabled the discovery of unprecedented reaction modes. By virtue of their unique ability to coordinate to carbon–carbon multiple bonds and heteroatoms and further activate these functional groups, gold complexes have been utilized as highly efficient catalysts for the domino reactions involving in strained small ring-containing molecules to construct various useful molecules. Furthermore, these reactions are always finished under remarkably mild conditions in a short time with low catalyst loadings, and give the products with level control of chemo-, regio-, and diastereoselectivity.

Looking at the speed at which the field is expanding today, we believe that the applications of these synthetic methods in total synthesis will be developed rapidly in the future.[106] The possibility of gold catalysts in industrial applications is worth anticipating.

## Acknowledgements

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