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Recent advances in syntheses of carbocycles and heterocycles via homogeneous gold catalysis. Part 2: Cyclizations and cycloadditions

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Contents

1. Introduction

As a new frontier in organic synthesis, gold catalysis consists of two types: heterogeneous and homogeneous. Heterogeneous gold catalysts typically exist as nanoparticles or solid-support gold alloy, thus allowing the catalysts to be in a different phase from the reactants and products.[1] Although the utility of heterogeneous gold catalysis has already been demonstrated in industry, the field of homogeneous gold catalysis has only recently drawn attention from academia since the late 1990s.[2] The understanding of gold catalysis has been facilitated by the theories of frontier orbitals,[2n] relativistic effects,[2m] and π-acidity.[2n] The strong σ-donor and weak π-acceptor properties of alkynes render gold-complexed alkynes electrophilic.[3] The unusual reactivity of gold catalysts, namely unsaturated C–C bond activation, leads to the evolution of powerful

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methods to efficiently assemble diverse structures. Of particular interest to organic and medicinal chemists is methodology development towards the syntheses of carbocycles and heterocycles.

Gold-catalyzed reactions have several unique features. Unlike the majority of transition metal-catalyzed processes, the high oxidation potential of gold(I) to gold(III) allows most gold(I)-catalyzed reactions to proceed without requiring air-excluding precautions. Unlike many Lewis acids, gold catalysts are exceptionally alkynophilic, but not oxophilic. Thus oxygen, water, and alcohols are often well tolerated, in sharp contrast to most air- and moisture-sensitive Lewis acid or transition metal-catalyzed reactions. In addition to convenient procedures, gold-catalyzed reactions also provide efficient access to diverse structures from simple starting materials. Furthermore, the non-classical carbocation/carbene nature of intermediates involved in gold-catalyzed transformations frequently results in well-controlled reactivity and selectivity, as demonstrated in several gold-catalyzed cyclization and cycloaddition reactions. Lastly, gold catalysis often demonstrates highly substrate-dependent reaction manifolds.

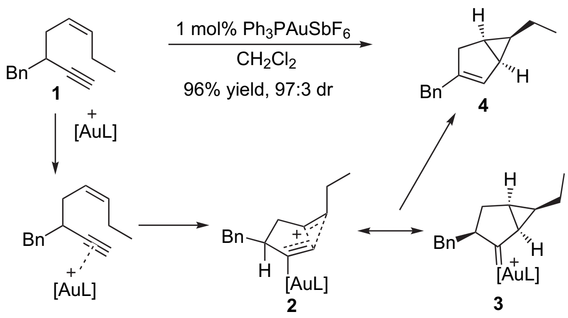
This review, as a second part on homogeneous gold catalysis to form heterocycles and carbocycles,[2t] highlights the most recent advances in gold-catalyzed cyclizations and cycloadditions involving at least two unsaturated C–C bonds. Reaction categories, mechanisms, and selectivity including chemo-, regio-, diastereo-, and enantioselectivity are subject of discussion. Meanwhile, the most interesting influences on reaction pathway through subtle structural changes of substrates and sometimes catalysts are also highlighted.

2. Cyclizations

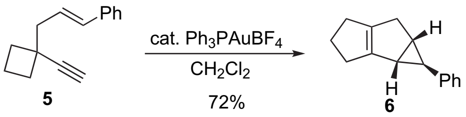
2.1. Enyne cyclizations

Gold-catalyzed cyclizations, in particular cycloisomerization reactions of alkynes, alkenes, and allenes, have emerged as powerful methods to construct carbocycles and heterocycles. Distinct from the enyne cyclizations catalyzed by Pd, Rh, Ru, and Ni complexes,[4] the gold-activated electrophilic alkynes lead to non-classical carbocation and/or carbenoid formation, which often triggers skeletal rearrangements. In addition, there have been no observations of β-hydride elimination in gold-catalyzed reactions. Furthermore, a striking impact of alkene/alkyne substitution and/or choice of ligands on the reaction outcome have been commonly observed. The gold-catalyzed cyclizations have captured vast research interests because of their immense substrate scope, diverse product portfolio, and intriguing mechanistic pathways.

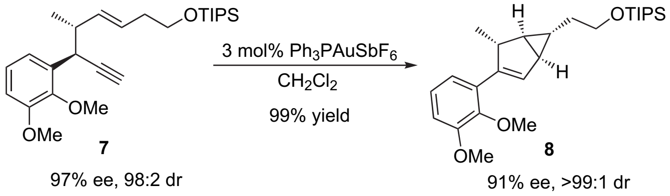
Among enyne substrates, gold-catalyzed isomerization reactions of 1,5- and 1,6-enyne have been most extensively studied and utilized to form various cyclic skeletons.



Scheme 1.



Scheme 2.



Scheme 3.

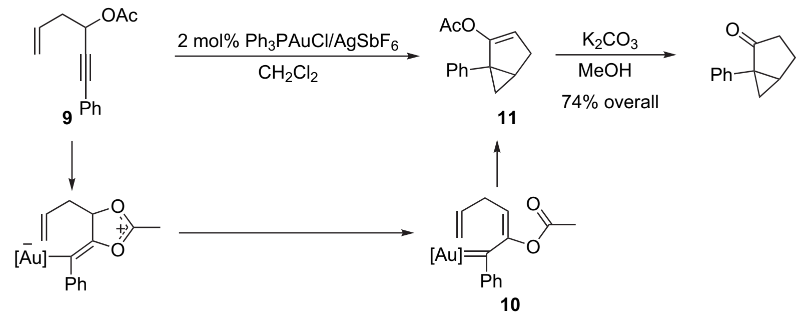
2.1.1. 1,5-Enynes

Departing from the conventional cyclopropanation methods[5] employing ylides, diazo compounds, or Simmons–Smith reaction, the gold-catalyzed 1,5-enyne cyclization pioneered by the Toste and Fürstner groups has offered yet another avenue to cyclopropanes. With a remarkable control of diastereoselectivity, 1,5-enyne **1** led to high yield of bicyclo[3.1.0]hexene **4** using 1 mol % of gold(I) catalyst.[6] The reaction was complete within 5 min at room temperature (Scheme 1). The proposed reaction intermediates have features of both cations and carbenoids (**2** and **3**), which are consistent with the observation that a 1,2-alkyl shift occurred with substrate **5** to afford tricyclic product **6** (Scheme 2). The alkene geometry dictated the stereochemical outcome of the products, with (*Z*)-olefin **1** favoring the formation of the *cis*-cyclopropane **4**, and the (*E*)-olefin **7** the *trans*-cyclopropane **8** (Scheme 3). In addition, excellent chirality transfer was achieved for the formation of compound **8**. Fürstner and co-workers reported the cyclization of enyne acetate **9** to a similar bicyclo[3.1.0] system presumably through carbenoid intermediate **10** after the 1,2-migration of acetyl group (Scheme 4).[7] The utility of this method was later demonstrated in an elegant synthesis of (−)-cubebol (**12**) by the Fehr group (Scheme 5).[8]

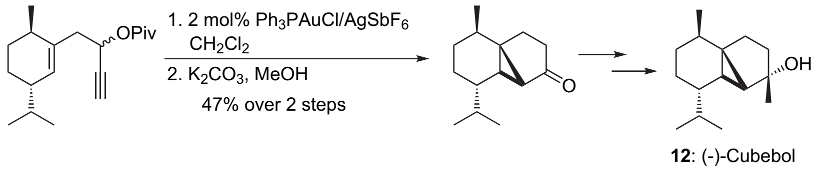
The Nolan group explored the use of *N*-heterocyclic carbenes as ligands in gold(I)-catalyzed enyne cycloisomerizations.[9] They found that the nature of the ligand on gold and the counterion both played a significant role on the reaction outcome (Scheme 6). For example, substrate **13** containing both 1,5-enyne and 1,6-enyne moieties gave a mixture of three products. With the BF_4 counterion, the triphenyl phosphine ligand favored the formation of bicyclo[4.1.0]heptene **14**, whereas IMes and IPr ligands favored the unprecedented bicyclo[3.1.0]hexene **16** as the product. With the IPr ligand, the OTf counterion led to a higher yield of product **14** than the BF_4 counterpart.

Gagosz discovered an intriguing cyclization of 1,5-enyne **17**, which generated novel alkylidene-cyclopentene **18** through a sequential carbocation rearrangement (Scheme 7).[10] This transformation serves as another example of high substrate dependency of gold-catalyzed enyne cycloisomerizations. This reaction is also noteworthy for its remarkable efficiency, high yield, and good selectivity.

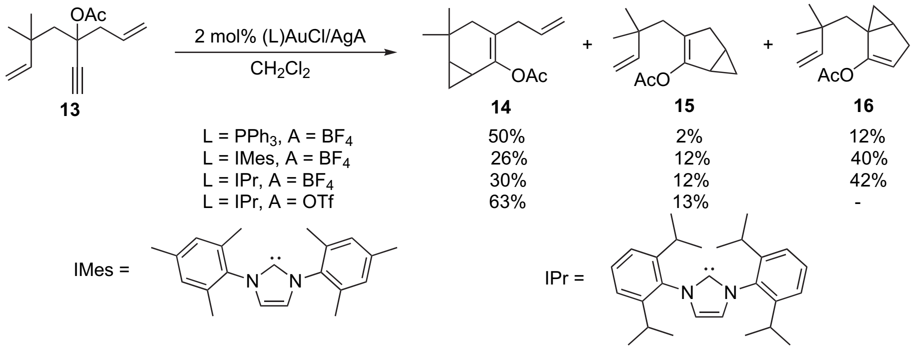
Exploiting similar cyclopropyl gold carbenoid intermediates, the Kozmin group utilized pendant oxygen or nitrogen nucleophiles for tandem cyclizations, presumably via a concerted (**A**) instead of a stepwise (**B**) process (Scheme 8).[11] A wide array of fused bicyclic, bridged, and spirocyclic structures were constructed with excellent diastereoselectivity (Scheme 9). In addition, the olefin geometry governed the cyclization mode. While a 6-*endo-dig* cyclization was favored for cis-olefin **19** leading to fused cis-oxabicyclic product **20**, trans-olefin **21** underwent a 5-*endo-dig* cyclization to give tetrahydrofuran **22**, thereby avoiding the formation of a strained *trans*-oxabicyclo[4.4.0]decene via the 6-*endo-dig* cyclization (Scheme 10).



Scheme 4.

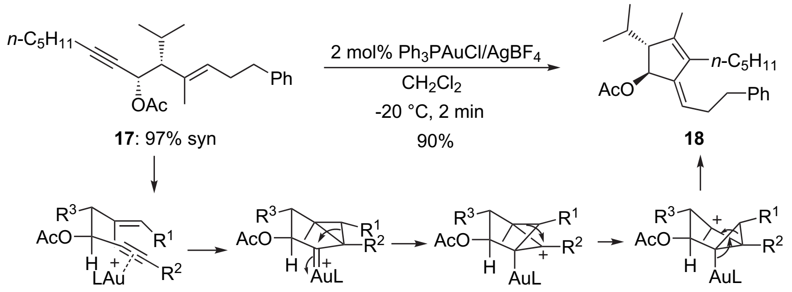


Scheme 5.



	14	15	16
L = PPh$_3$, A = BF$_4$	50%	2%	12%
L = IMes, A = BF$_4$	26%	12%	40%
L = IPr, A = BF$_4$	30%	12%	42%
L = IPr, A = OTf	63%	13%	-

Scheme 6.



Scheme 7.

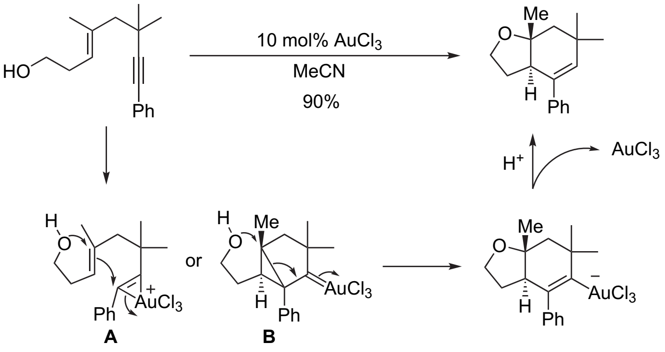
The Gagosz group discovered that cyclopropyl gold carbenoid intermediate **24** derived from 1,5-enyne acetate **23** could be intermolecularly trapped with methanol or water.[12] This strategy provided an efficient approach to functionalized cyclopentenes such as compound **25** with a complete control of diastereoselectivity (Scheme 11).

An allylic OBoc group in a 1,5-enyne system may also intercept cyclopropyl gold carbenoid intermediates. Thus, an efficient gold(I)-catalyzed tandem C–C and C–O bond formation sequences produced densely functionalized cyclohex-4-ene-1,2-diol derivatives with good diastereoselectivity (Scheme 12).[13]

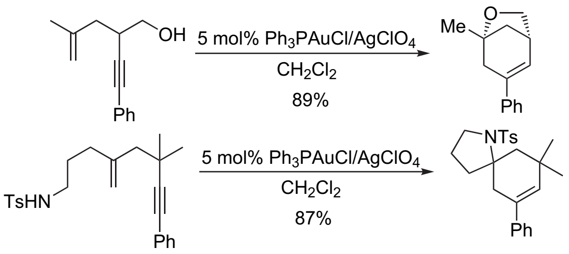
Introducing a siloxy-substituted alkyne in 1,5-enynes made possible an efficient AuCl-catalyzed skeletal rearrangement to yield cyclohexadienes.[14] A plausible mechanism incorporates two sequential 1,2-shifts with the first being driven by the formation of siloxy-stabilized cation intermediate **27** and the lower migratory aptitude of *C*3-substituents (Scheme 13).

If a siloxy group is placed at the allylic position of a 1,5-enyne system, cyclopentenes bearing an aldehyde substituent could be formed via a tandem cyclization and pinacol rearrangement.[15] This novel strategy also provided diverse fused bicyclic and spirocyclic ring systems containing a ketone moiety (Scheme 14).

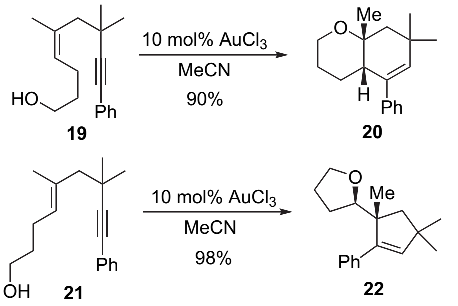
With an allylic acetate present in 1,5-enynes, a different reaction pathway was observed (Scheme 15).[16] In this scenario, gold(III) catalyst **29** promoted the migration of the allylic acetoxy group of **28** to generate zwitterion intermediate **30**, which then underwent



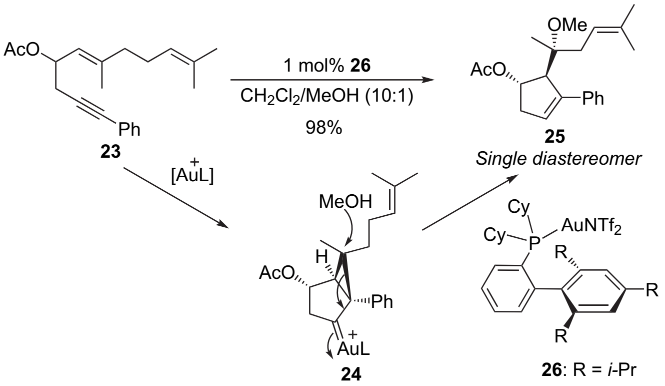
Scheme 8.



Scheme 9.



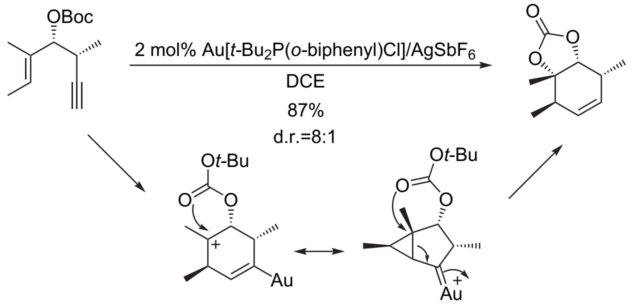
Scheme 10.



Scheme 11.

a ring closure to from 1,4-diene **31**. The subsequent DDQ oxidation then smoothly converted the diene to the corresponding arene.

For propargylic alcohol in 1,5-enynes such as **32**, a gold(I) catalyst induced an interesting cyclization to afford substituted benzenes (Scheme 16).[17] It was proposed that a 6-*endo-dig* cyclization of enyne **32** produced intermediate **33**, which then gave tetrahydronaphthalene **34** via deprotonation and dehydration.



Scheme 12.

A gold(I)-catalyzed [1,7]-hydrogen shift in 3,5-dien-1-ynes is another manifold of the cyclization reaction to establish aromatic systems.[18] Supported by a series of elegant studies with deuterium-labeled substrates, a plausible mechanism is depicted in Scheme 17. It has been speculated that the metal alkyne complex **36** has more of an sp^2 character with respect to alkyne **35** alone, thereby facilitating the allylic deprotonation by increasing the acidity of the *C*7-hydrogen. The resulting intermediate **37** upon protodeauration led to dienyl allene **38**, which was followed by a 6-π-electrocylic ring closure and a 1,3-hydrogen shift to give the corresponding tetrahydronaphthalene **39**.

With a cationic gold(I) catalyst, 1,5-enyne substrates bearing an aromatic ring tether and an internal alkyne favored the 6-*endo-dig* cyclization to form substituted naphthalene **40** (Scheme 18).[19] In contrast, terminal alkynes or iodoalkynes preferentially underwent the 5-*exo-dig* cyclization to form indene derivatives (**41**).

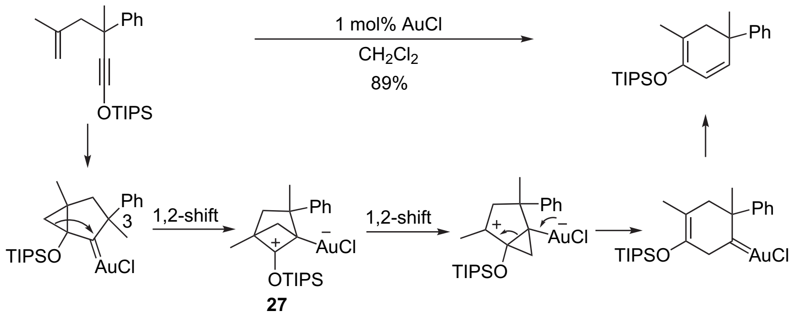
An interesting gold(I)-catalyzed Claisen rearrangement of propargyl vinyl ether **42**, a 1,5-enyne containing an oxygen atom linker, provided β-allenic aldehyde **44**, likely through the oxo-carbenium intermediate (**43**).[20] Alternatively, this intermediate could be trapped with an exogenous or internal nucleophile, thereby offering an efficient synthesis of dihydropyrans **45** (Scheme 19).[21] This transformation is highly diastereoselective as shown by the conversion of substrate **46** to hydroxypyran **47**, in which water served as a nucleophile (Scheme 20). With a pendant hydroxyl group in substrate **48**, the anomerically stabilized [6,6]-spiroketal **49** was formed with complete relative stereochemical control of three chiral centers (Scheme 21).

2.1.2. 1,6-Enynes

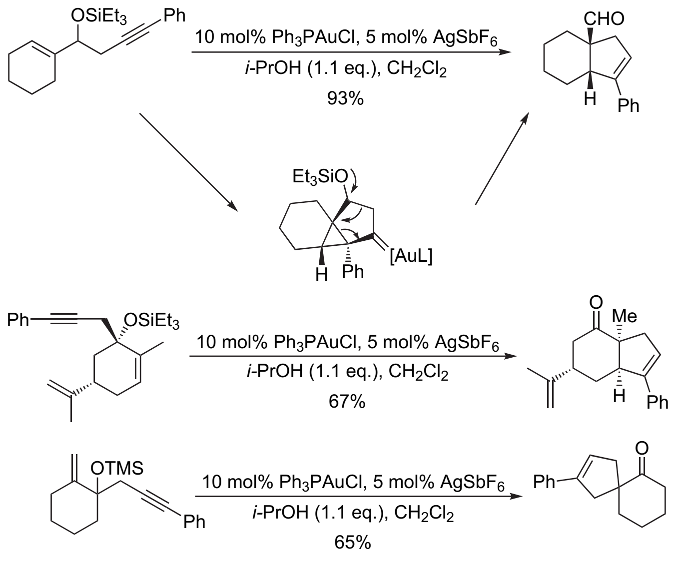
Gold-catalyzed cycloisomerizations of 1,6-enynes have been pioneered by the Echavarren group (Scheme 22). The reaction outcome is dependent upon the alkene and alkyne substitutions in the starting material. For example, enyne **50**, containing a 1,2-disubstituted alkene, underwent a skeletal rearrangement to generate the formally enyne metathesis product **52**. In contrast, terminal alkene substrate **51** led to cyclohexene **53** as the major product (Scheme 23).[22] Towards the formation of 1,3-diene **52**, DFT calculations supported the involvement of gold(I)-catalyzed skeletal rearrangement of the cyclopropyl carbenoid intermediate (**54**) instead of the ring opening of a cyclobutene intermediate (**55**).[23]

When a nitrogen or oxygen atom is incorporated into the tether between an internal alkyne and an alkene, such as substrate **56**, the *endo*-cyclic product **57** can be formed (Scheme 24).[22c,24] It has also been discovered that gold-catalyzed formal [4+2] and [2+2] cycloadditions can take place for structurally related substrates (see section 3 vide infra).

Echavarren's group also harnessed allyl silane nucleophiles for cyclization reactions to form 1,4-dienes (Scheme 25).[22c,25] Again, a cyclopropyl carbenoid intermediate (**58**) was proposed and desilyation assisted by methanol presumably occurred at this stage.

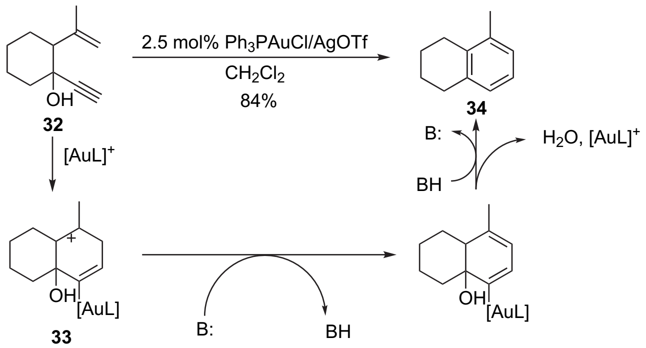


Scheme 13.

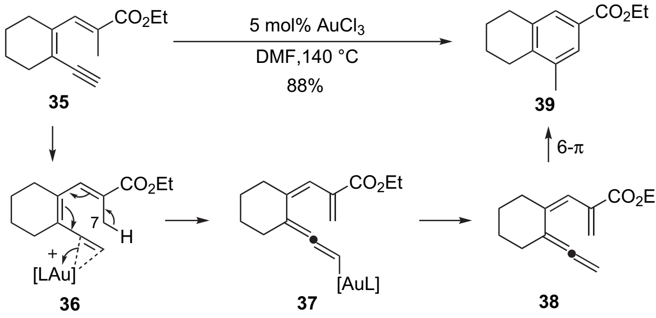


Scheme 14.

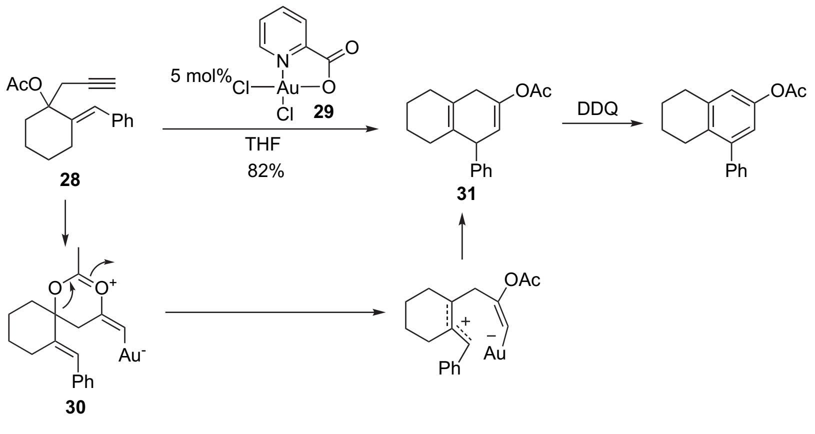
Not only can a gold(I)-catalyzed enyne cycloisomerization intermediate be intercepted by a nucleophile, but the gold carbenoid may also be oxidized by diphenyl sulfoxide (Scheme 26).[26] The *N*-heterocyclic carbene gold complex IPrAuCl gave the best results for these reactions. Starting with substrate **59**, the facile oxidation of cyclopropane carbenoid **60** afforded cyclopropyl aldehyde **61** in excellent yield, and without further skeletal rearrangement leading to diene product **62**. However, for 1,1-disubstituted alkene **63**, the gold-catalyzed oxidative cyclization generated the corresponding cyclopentenyl aldehyde **64** without detection of any cyclopropyl aldehyde product (Scheme 27).



Scheme 16.

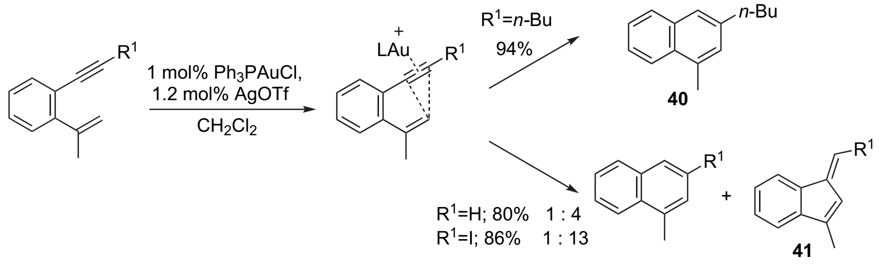


Scheme 17.

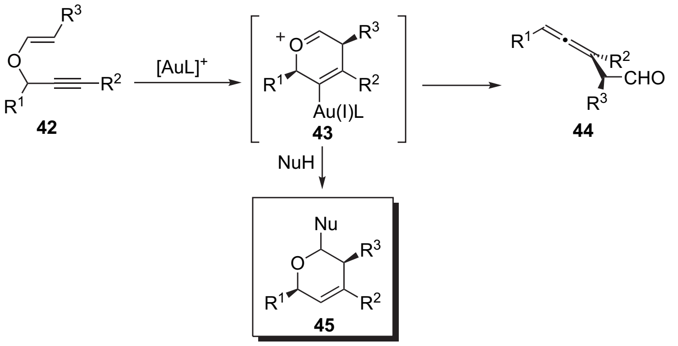


Scheme 15.

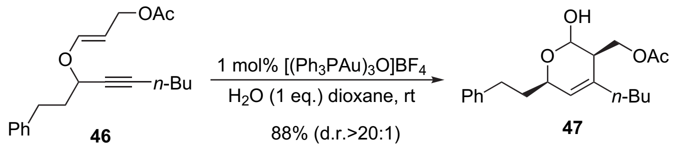
By installing a propargyl acetate in 1,6-enyne **65**, Fürstner and Hannen discovered a gold-catalyzed Ohloff–Rautenstrauch rearrangement reaction. This reaction produced vinyl acetate **67**, which is structurally related to isosesquicarene (**68**) (Scheme 28).[27] The



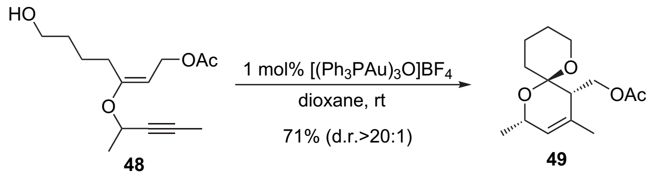
Scheme 18.



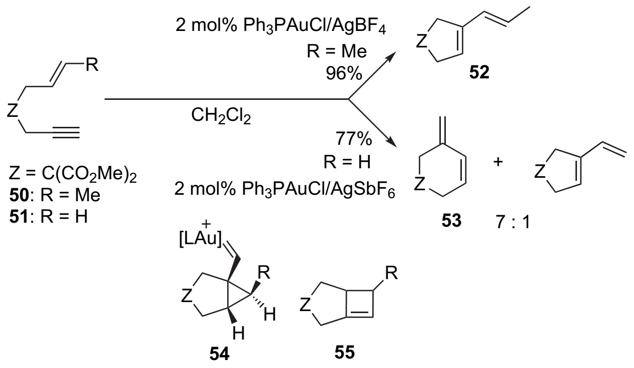
Scheme 19.



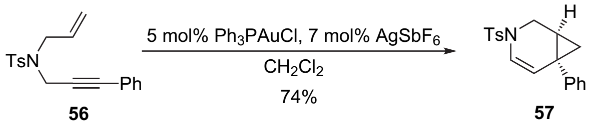
Scheme 20.



Scheme 21.



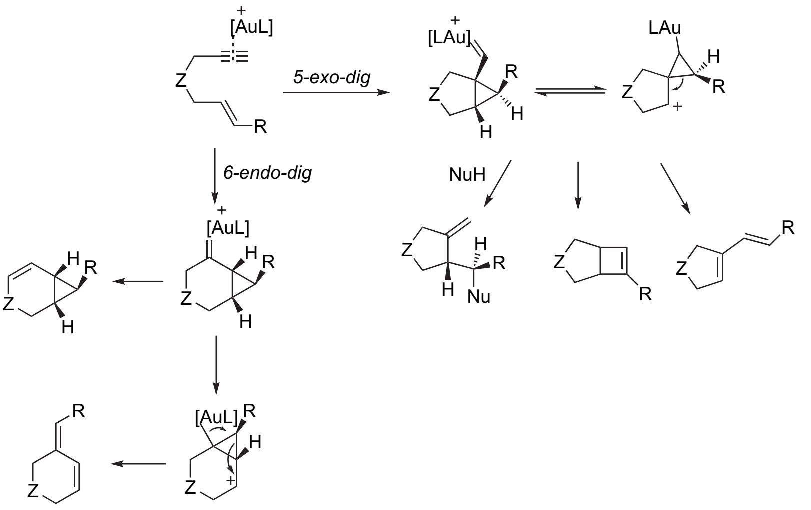
Scheme 23.



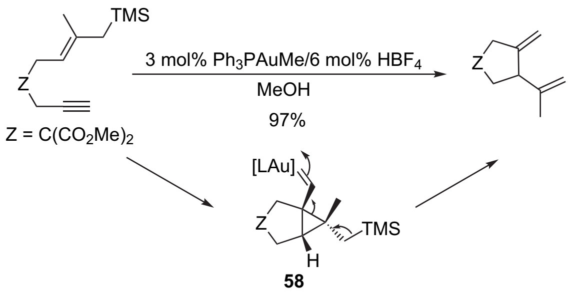
Scheme 24.

proposed metallocarbenoid **66** was formed via the 1,2-rearrangement of acetate, although the authors also suggested the possibility that cyclopropanation proceeded prior to the acetyl group migration.

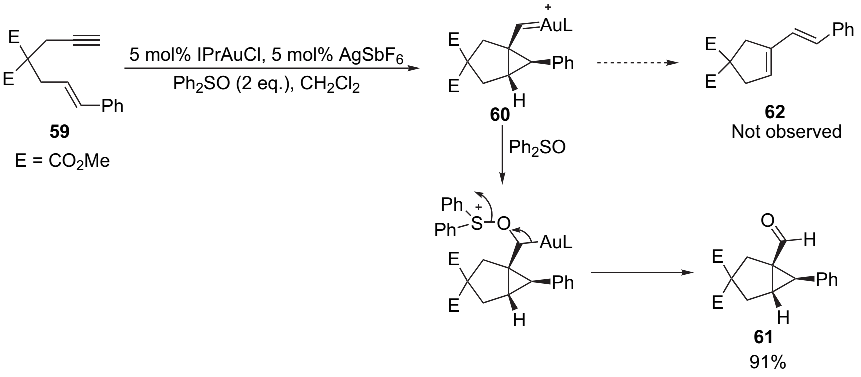
A gold(I)-catalyzed tandem three-step reaction sequence of dienyne substrates provides an expedient approach to polycyclic scaffolds.[28] As shown in Scheme 29, stirring only for 5 min at room temperature afforded a complex tetracyclic product **73**, obtained as a single diastereomer in almost quantitative yield. This reaction



Scheme 22.



Scheme 25.

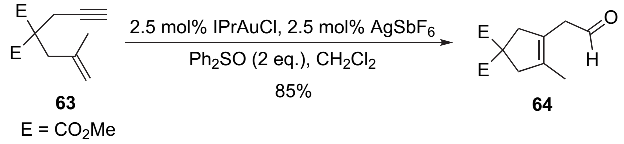


Scheme 26.

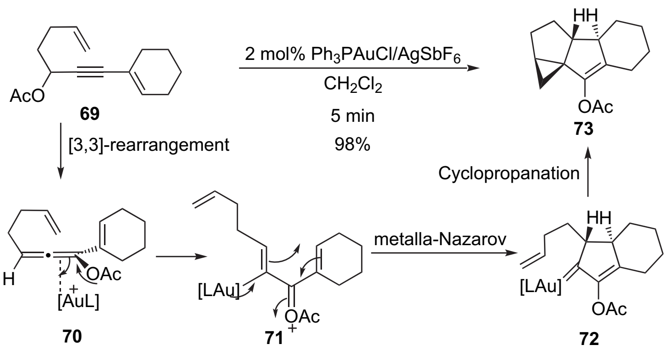
cascade entails the [3,3]-rearrangement of propargyl acetate **69** to allenyl acetate **70**, a metalla-Nazarov cyclization (**71** to **72**), and the successive intramolecular cyclopropanation of carbenoid **72** to yield tetracyclic product **73**.

With an embedded cyclopropyl ether in 1,6-enynes such as substrate **74**, the cyclopropyl group of the carbenoid intermediates **75** could be opened by the adjacent cyclopropyl ether nucleophile, thus forming two diastereomeric vinyl gold species **76** and **77** (Scheme 30). The resulting oxocarbenium ion then initiated a Prins-type cyclization to furnish the tricyclic structures.[29] In a similar fashion as shown in Scheme 31, the methyl ketones could also act as a nucleophile to open the cyclopropyl group of carbenoid **78**, leading to oxocarbenium intermediate **79**. A subsequent Prins cyclization resulted in the formation of tricyclic product **80** virtually as a single diastereomer. Besides cyclopropyl ethers and ketones, aldehydes were also employed to trap gold carbenoids. For example, gold carbene intermediate **81** reacted with an aldehyde to generate oxocarbenium ion **82**, which led to novel tricyclic product **83** (Scheme 32).[30] The examples depicted in Schemes 26, 31, and 32 have showcased the oxophilic character of gold carbenoid species, which will surely see more applications in the future.

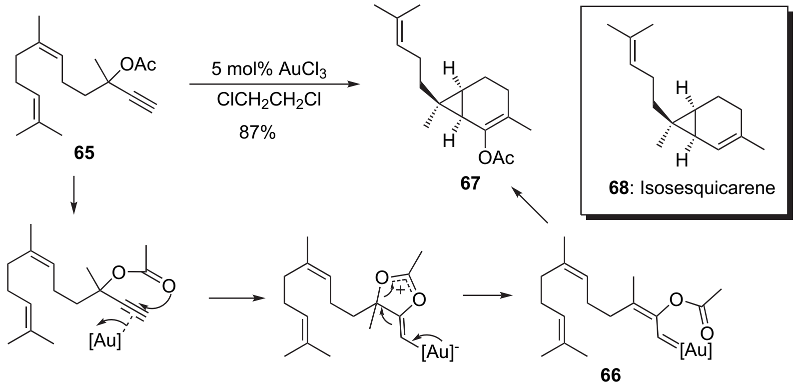
Another strategy to capture cyclopropyl carbenoid intermediates is a second cyclopropanation, either intra- or intermolecularly as depicted in Schemes 33 and 34, respectively.[31] Interesting contiguous cyclopropyl products were formed with high diastereoselectivity, arising from the proposed well-organized transition state in the second cyclopropanation step.



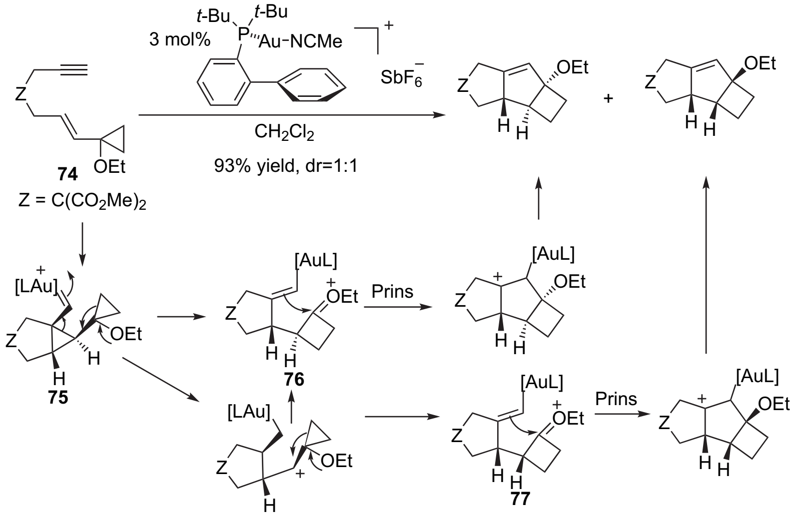
Scheme 27.



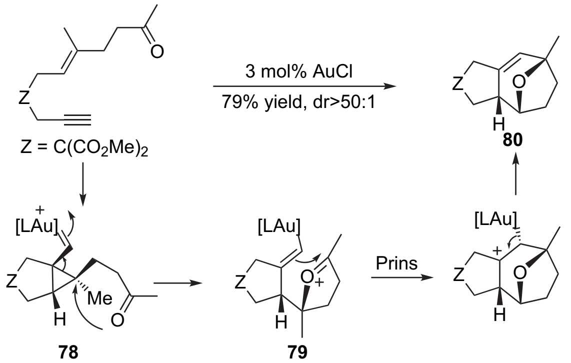
Scheme 29.



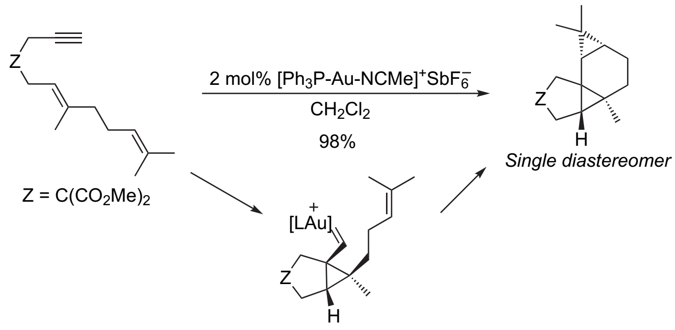
Scheme 28.



Scheme 30.



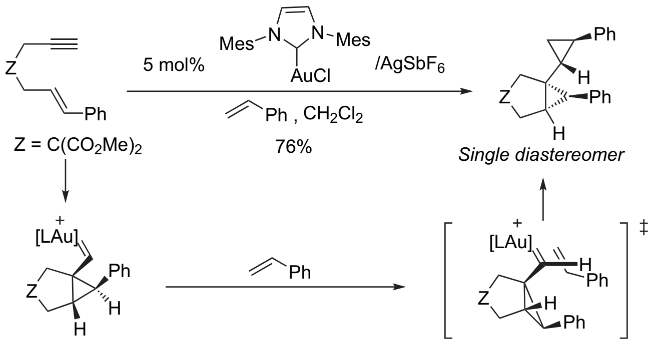
Scheme 31.



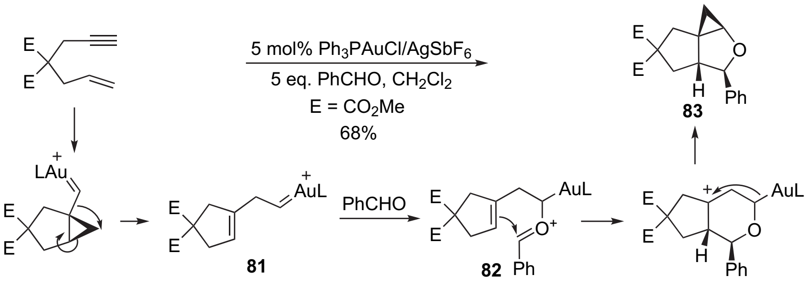
Scheme 33.

The gold carbenoid derived from 1,6-enyne **84** could be trapped with methanol to yield cyclopentane **85** with good enantioselectivity using a chiral BINAP-derived bisphosphine-gold catalyst.[32] Besides alcohol nucleophiles, it was found that nitrogen nucleophiles including carbamates or anilines could also be employed for this type of transformation (Scheme 35).[33] Alternatively, Genêt and co-workers demonstrated that an electron-rich aromatic ring such as indole allowed a highly diastereoselective Friedel–Crafts reaction in excellent yield (Scheme 36).[34]

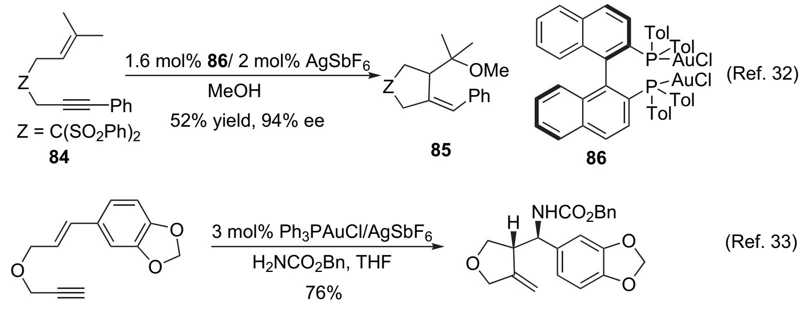
Taking advantage of the gold-catalyzed tandem cyclization and [3,3]-sigmatropic rearrangement of 1,6-enynes (**87**), cycloheptenones could be formed efficiently (Scheme 37).[35] As oxonium intermediate **88** was involved in the Claisen rearrangement, the reaction was complete in 2 min at −15 °C, whereas a typical thermal Claisen rearrangement in the absence of a Lewis acid would



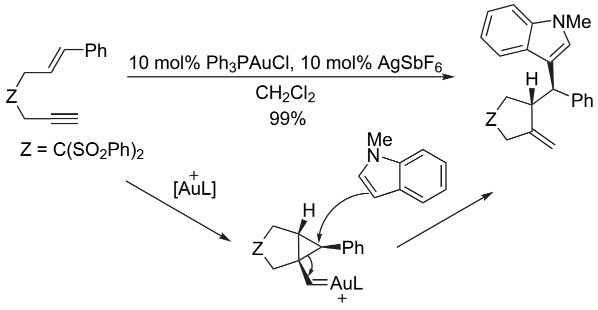
Scheme 34.



Scheme 32.

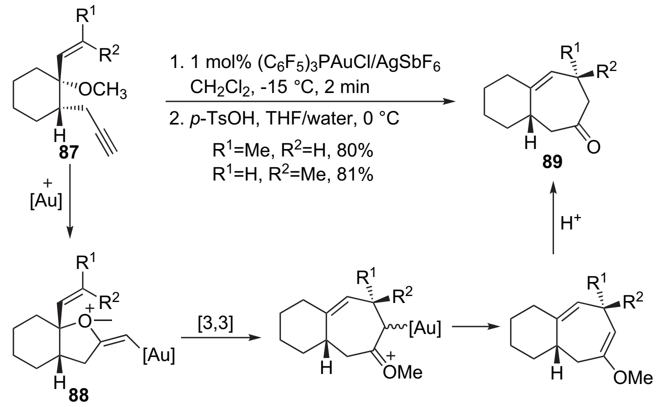


Scheme 35.



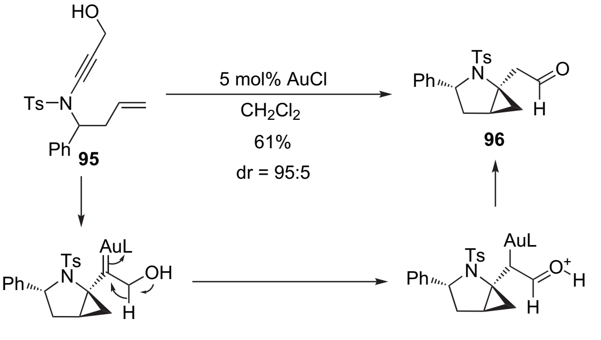
Scheme 36.

require heating for a substantially longer time. The olefin geometry elicited the diastereoselectivity control by placing the substituent R^2 in substrate **87** in a cis relationship with respect to the angular hydrogen in the product (**89**).

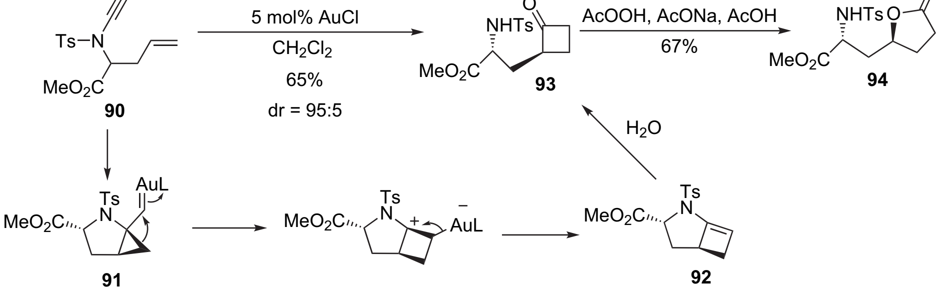


Scheme 37.

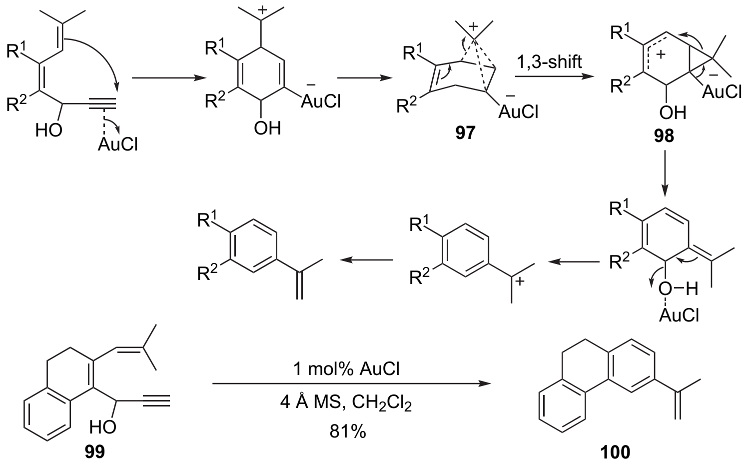
Incorporating a nitrogen atom linker, enyne sulfonamide substrates such as substrate **90** adopted a very different reaction pathway to form cyclobutanones catalyzed by AuCl (Scheme 38).[36] It was proposed that ynamides underwent a diastereoselective formal [2+2] cycloaddition through cyclopropyl gold carbenoid **91** to give cyclobutene intermediate **92**. Upon exposure to atmospheric moisture, cyclobutene **92** was hydrolyzed to cyclobutanone **93**, a precursor of a functionalized γ-lactone **94**. With a propargylic alcohol in substrate **95**, the 1,2-hydride shift is more facile than the cyclopropyl ring expansion, thereby affording cyclopropyl aldehyde **96** with a 95:5 diastereoselectivity (Scheme 39).



Scheme 39.

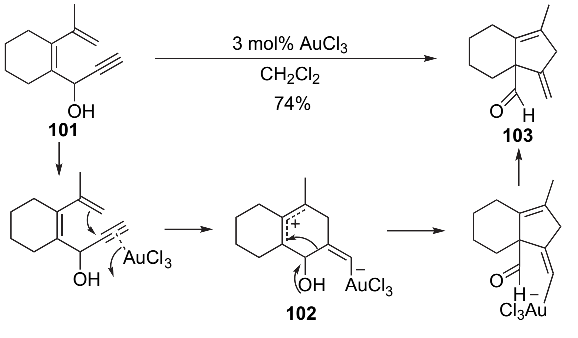


Scheme 38.



Scheme 40.

Gold-catalyzed 4,6-dien-1-yne-3-ol rearrangement may involve a 1,3-alkylidene migration (**97** to **98**), which has been established through ^{13}C-labeling experiments and product identification of the corresponding platinum catalysis (Scheme 40).[37] A sequential cyclopropyl ring opening and dehydration then gave rise to a styrene derivative. For example, dienyl propargyl alcohol **99** undertook a facile cyclization to form tricyclic product **100**. Yet another reaction manifold of structurally similar substrates such as **101** entailed a 6-*exo-dig* cyclization to give allyl cation **102**, which was followed by a pinacol rearrangement to provide reorganized cyclopentenyl aldehyde **103** (Scheme 41).



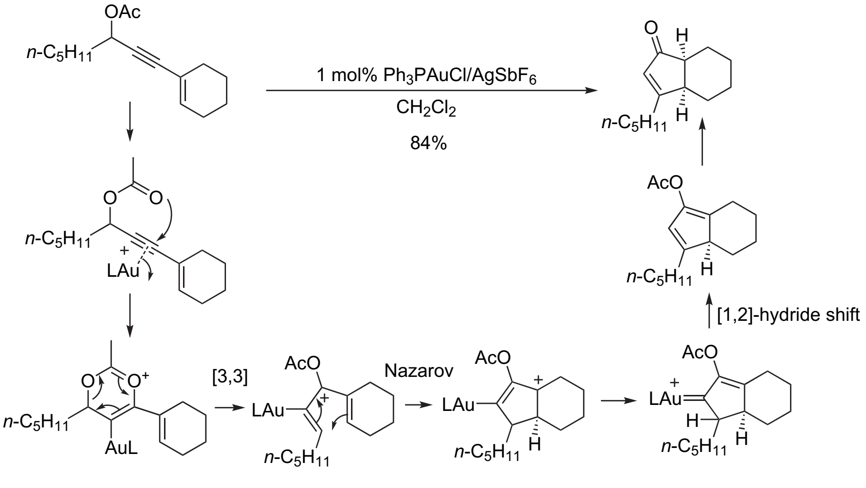
Scheme 41.

2.1.3. 1,3-Enynes

1,3-Enyne substrates can also be engaged in gold-catalyzed transformations. For example, the Zhang group discovered a new strategy leading to cyclopentenone formation via a cascading gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction/[1,2]-hydride shift sequence (Scheme 42).[38] The author observed that adventitious water expedited the reaction. Subsequent DFT studies by the Yu group revealed that water may act as a proton shuttle to facilitate the [1,2]-hydride shift, presumably the rate-limiting step, through a hydrogen-bonding network.[39]

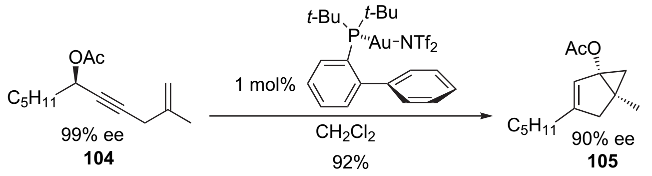
2.1.4. 1,4-Enynes

1,4-Enyne systems containing a distal or proximal propargyl ester with respect to the alkene moiety can both undergo gold(I)-catalyzed cycloisomerizations, as shown in Schemes 43 and 45, respectively. In the former case, placing an enantiomerically pure propargyl acetate in the 1,4-enyne substrate (**104**) allows the gold(I)-catalyzed formation of bicyclo[3.1.0]hexene **105** with two adjacent quaternary centers at the ring junction (Scheme 43), with only a modest erosion on ee.[40] The proposed mechanism consists of a [3,3]-sigmatropic rearrangement of the gold–alkyne complex to generate allenyl acetate intermediate **106**, which then cyclizes in a 6-*endo-trig* fashion to form carbocation **107** (Scheme 44). The electron-rich phosphine ligand may increase the back bonding nature of the gold species, thereby assisting the trapping of carbocation by vinyl gold to afford gold carbenoid **108**. This is followed

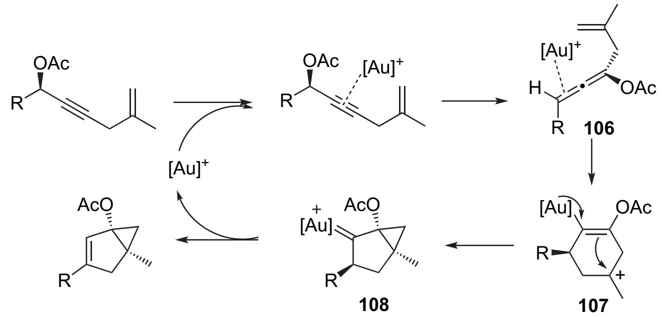


Scheme 42.

by a 1,2-hydride shift to yield the product and regenerate the catalyst.

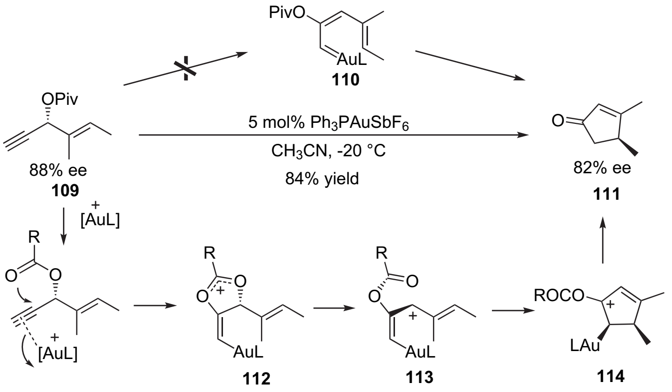


Scheme 43.



Scheme 44.

In the case where an ester group resides between the alkyne and the alkene of a 1,4-enyne, the gold(I)-catalyzed Rautenstrauch rearrangement proceeds to generate 2-cyclopentenones (Scheme 45).[41] This reaction features an unexpected chirality transfer from starting material to product, which rules out the possibility of a reaction intermediate like carbenoid **110**. The origin of the 'memory effect' has been further investigated by computational methods.[42] The data suggest that the gold(I)-induced ester group transfer to the vicinal alkyne likely occurs prior to the diastereoselective C–C bond formation. Presumably, it is the helicity of the pentadienyl cation intermediate, which imparts the chirality of the starting material (**109**) to that of the product (**111**). This overall center-to-helix-to-center chirality transfer (**112**–**113**–**114**) thus accounts for the stereochemistry of product **111**.



Scheme 45.

2.1.5. 1,7-Enynes

1,7-Enynes were also studied for cycloisomerization reactions.[43] The proposed key intermediate is cyclopropyl gold carbenoid **115**, which can either undergo a skeletal rearrangement to afford 1,3-diene **116**, a formal enyne metathesis product, or react with an alcohol nucleophile to generate tertiary alcohol **117** with complete inversion of the carbon center (Scheme 46). While the water/acetone solvent mixture favored the diene product (**116**), the more nucleophilic methanol solvent produced predominantly the tertiary ether (**117**).

2.1.6. 1,9-Enynes

With an emphasis on generating skeletal diversity, Porco and co-workers explored a very unusual gold-catalyzed 1,9-enyne cyclization to form the 10-membered macrocycle **119** (Scheme 47).[44] Typically, an enyne cyclization would entail a cyclopropyl intermediate formed by the addition of the alkene to the cation in intermediate **118**, which would be followed by ring opening to generate 1,3-diene product **120**. The authors reasoned that the presence of the aryl group might facilitate the elimination of intermediate **118** to afford 1,4-diene **119** instead.

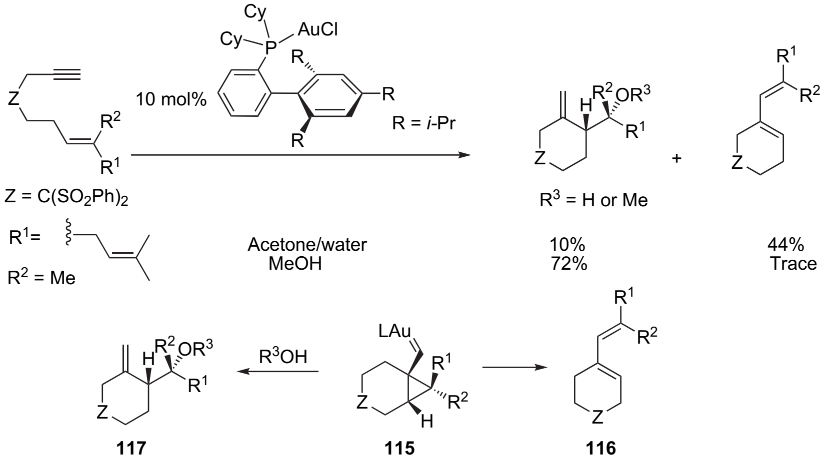
2.1.7. Cyclizations involving enols, silyl enol ethers, enamines, and enamides

Gold-activated alkynes can also react with nucleophiles including enols, silyl enol ethers, enamines, and enamides to form C–C bonds, thus significantly broadening the scope of gold catalysis. The Toste group reported a mild gold(I)-catalyzed Conia-ene reaction of β-ketoesters with terminal alkynes to form cyclopentanes via a 5-*exo-dig* cyclization mode (Scheme 48).[45] This reaction could essentially be considered an enyne cycloisomerization, as the cyclization of enol alkyne intermediate **121** is the key step. Deuterium labeling experiments supported a mechanism involving trans-carboauration. From an operation point of view, the mild 'open-flask' reaction conditions are superior to the thermal or transition metal-catalyzed version of this reaction. The efficiency of this method is showcased by the examples in Scheme 49. First, substrate **122** gave nearly quantitative yield of the bridged product **123** with only 1 mol % of catalyst and the reaction was complete in 5 min at room temperature. In addition, [5,5], [6,5], and [7,5] bridged bicyclic products could be formed by this reaction. One such example is the formation of bicyclic compound **125**, in which two quaternary centers were adjacent at ring junctions.

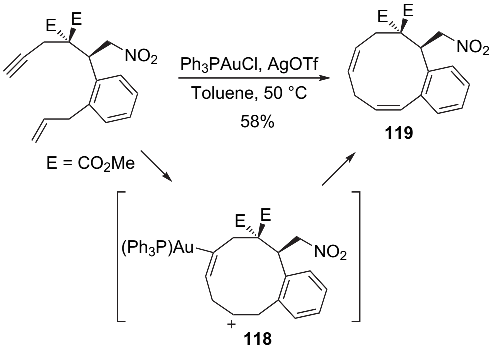
Subsequently, the Toste group also disclosed a complementary gold(I)-catalyzed 5-*endo-dig* cyclization to form cyclopentenes using biscarbonyl compounds bearing an internal alkyne.[46] Dienes, vinyl iodides, fused ring systems, and heterocyclic structures could be generated by this strategy (Scheme 50). By invoking a steric argument, the authors reasoned that the 5-*exo-dig* Conia-ene reaction only occurred with terminal alkynes, whereas 5-*endo-dig* cyclization worked for both terminal and internal alkynes (Scheme 51). In the case of 5-*exo-dig* Conia-ene reaction (n=3), the 1,3-allylic strain caused by the steric interaction of R with OH developed in the transition state can only accommodate a small R group such as H, and the placement of a gold center with an alkyl R group leads to unfavorable interaction. Conversely, the R group in the 5-*endo-dig* cyclization (n=2) has no such issues as the gold species is located adjacent to an alkyl-substituted carbon without inhibiting the cyclization.

The ligand cavity can also play an important role in the gold catalysis, which is illustrated by the unprecedented gold(I)-catalyzed 6-*exo-dig* cyclization of acetylenic ketoester **126** using the sterically encumbered ligand **127** (Scheme 52).[47] In stark contrast to the dismal yield (3% by NMR) after the same reaction time (1.5 h) with triphenyl phosphine as ligand, ligand **127** gave quantitative NMR yield of the cyclization product **128**. Such effect on reactivity was also observed with substrate **129**, which underwent a 7-*exo-dig* cyclization and olefin isomerization to furnish cycloheptenone **130** with a superior yield when ligand **127** was utilized (Scheme 53).

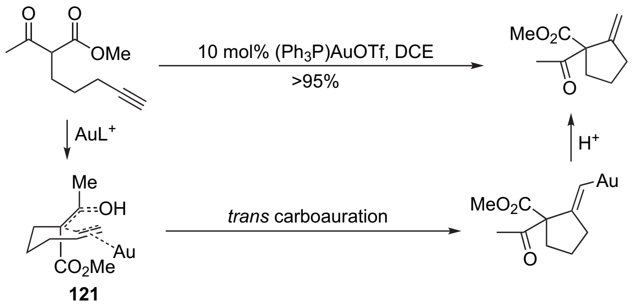
In addition to biscarbonyl compounds serving as nucleophiles, silyl enol ethers[48] and silyl ketene amides[49] can also add to a gold-activated alkyne to form carbocyles and heterocycles (Scheme 54). Depending on the substrates, 5-*exo-dig*, 5-*endo-dig*, or 6-*endo-dig* cyclization products were obtained with complete control of regioselectivity. This method has played a critical role in recent total



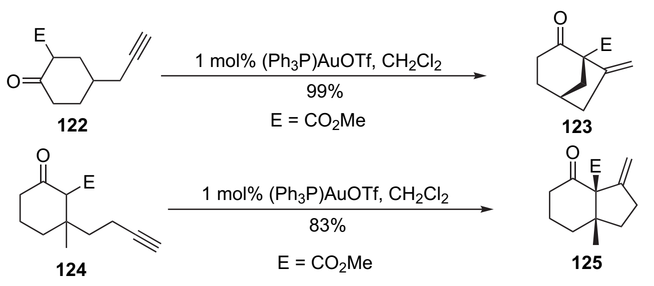
Scheme 46.



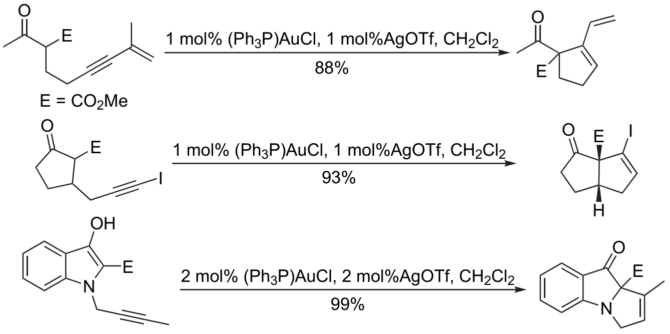
Scheme 47.



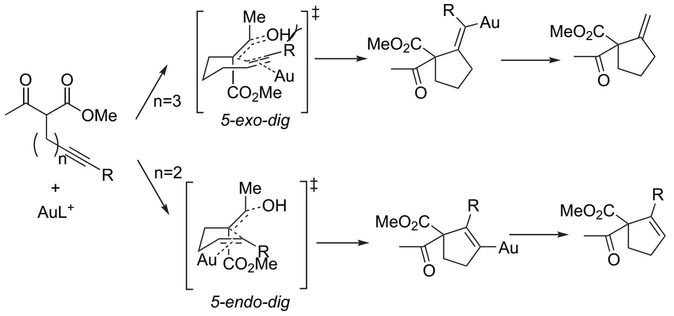
Scheme 48.



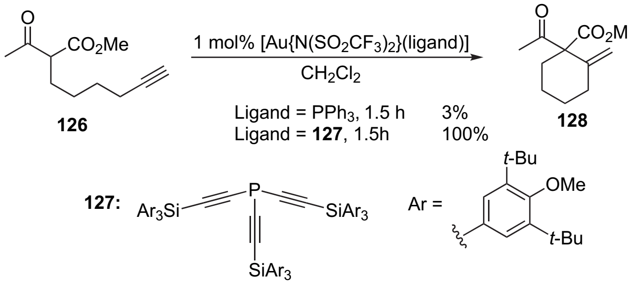
Scheme 49.



Scheme 50.



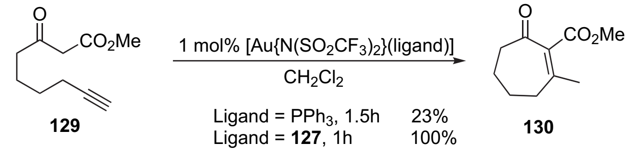
Scheme 51.



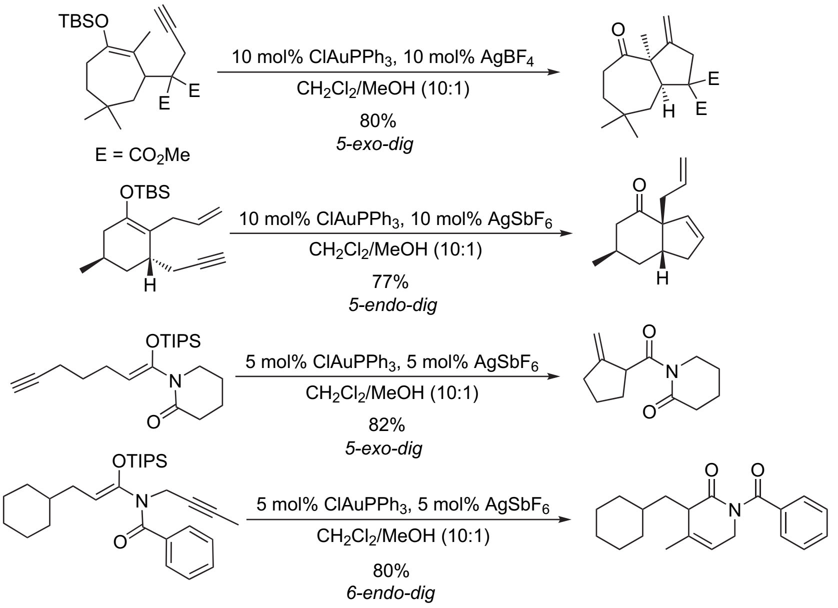
Scheme 52.

syntheses of (+)-lycopladine A,[39] (+)-fawcettimine,[50] and platencin,[51] with the gold-catalyzed silyl enol ether alkyne cyclization being a key step. In the first two cases, the resulting vinyl iodides also provided useful handles for further functionalizations (Scheme 55).

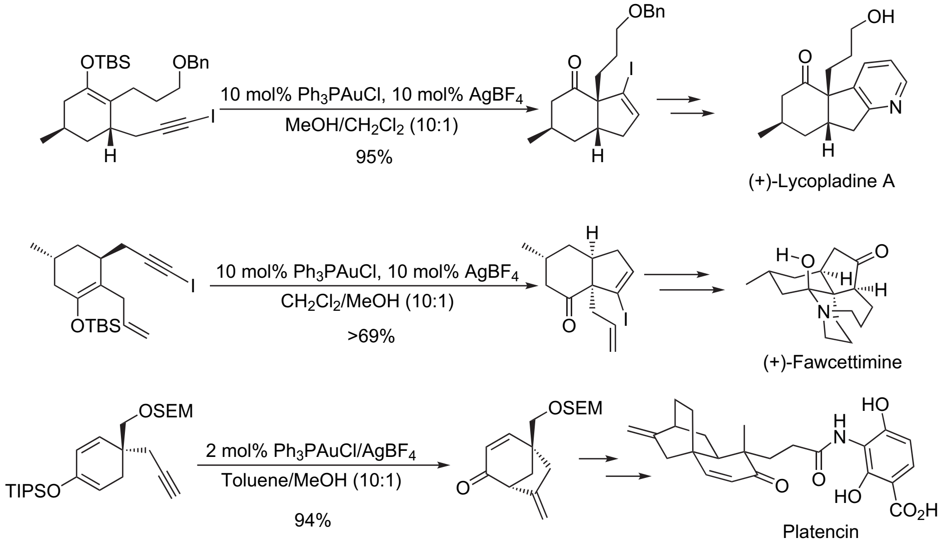
Besides silyl enol ethers, enamines formed in situ from ketones or enones with propargylic amine could undergo a 6-*endo-dig* cyclization to form functionalized pyridines (Scheme 56).[52] In contrast, enamines generated from aldehydes bearing two α-alkyl



Scheme 53.



Scheme 54.



Scheme 55.

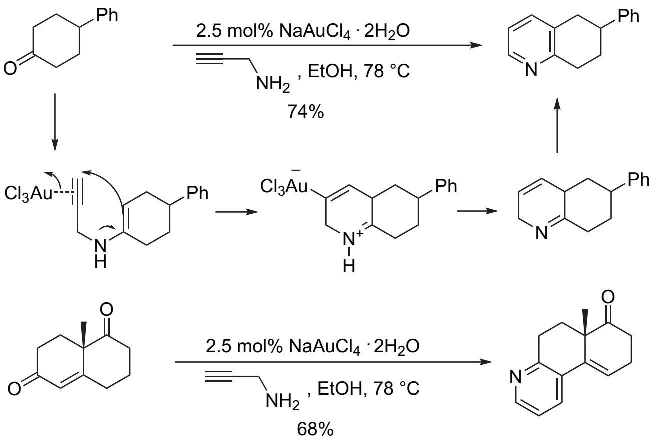
groups and a catalytic amount of secondary amines took a different reaction pathway by forming cyclopentanes via a 5-*exo-dig* cyclization (Scheme 57).[53] It should be noted that these reactions all proceeded at elevated temperatures.

2.2. Diyne cyclizations

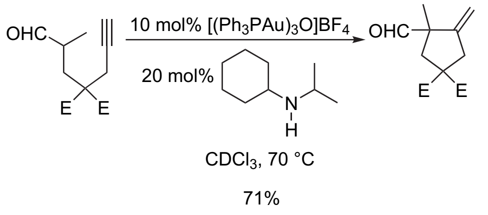
In the presence of a gold catalyst, a propargyl acetate can be readily converted to an allenyl acetate via a [3,3]-sigmatropic rearrangement, thus allowing further transformations. In the case of diyne substrate **131**, allenyl alkyne intermediate **132** was engaged in a second gold(I)-catalyzed cyclization to form aryl ketone **133** (Scheme 58).[54] The overall process is also referred as Myers–Saito cyclization. Similarly, the allenyl intermediate **134** arising from the [3,3]-sigmatropic rearrangement of a diyne ester can undergo a 6-*endo-dig* cyclization to generate oxocarbenium intermediate **135**. Subsequent trapping with an indole nucleophile yields a functionalized α-pyrone (Scheme 59).[55] During the transformation, the enantiomeric excess of the substrates is completely lost leading to racemic products.

Diyne propargyl alcohols can also undergo gold-catalyzed cycloisomerizations to afford aryl ketones (Scheme 60).[56] Despite the similarity with the starting material and product shown in Scheme 58, the underlying mechanism is, however, very different. As depicted in Scheme 61, a hydroxyl-directed gold complexation with the proximal alkyne in substrate **136** triggers the 6-*endo-dig* cyclization to form highly electrophilic carbocation **138**.

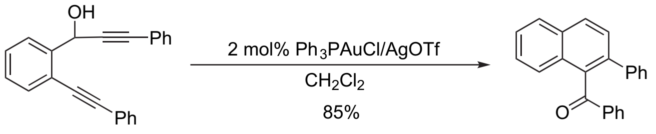
Subsequent addition and dehydration lead to aryl ketone **139**. Simple diaryl diynes in the absence of either propargylic ester or hydroxy substitution have been shown to participate in an *endo* cyclization to generate formal [3+2] cycloaddition products (vide infra).



Scheme 56.



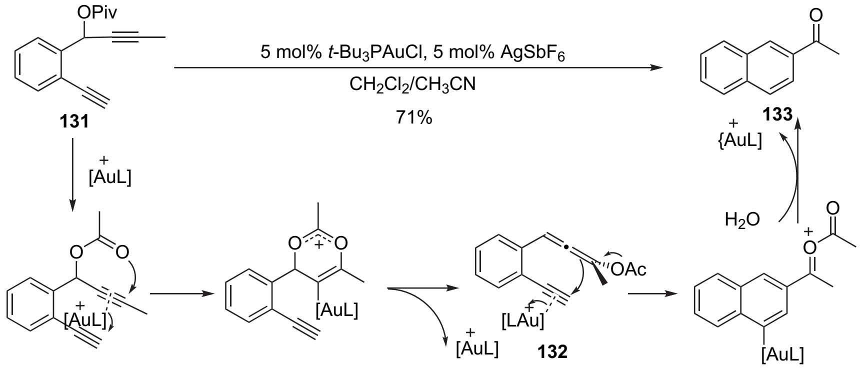
Scheme 57.



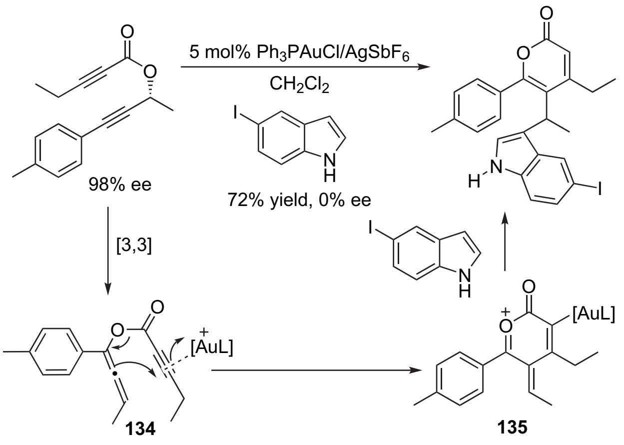
Scheme 60.

2.3. Alleneyne cyclizations

Alleneynes can also be applied to gold(I)-catalyzed cycloisomerizations with the allene being the nucleophile to cyclize onto a gold-activated alkyne. Furthermore, minor changes in substrates or catalysts could lead to distinct reaction pathways towards products of different structural classes. This has been exemplified in the cycloisomerizations of alleneyne substrates **140** and **143** (Scheme 62).[57] Under identical reaction conditions using $Ph_3PAuSbF_6$ as the catalyst, alleneyne **140** bearing a terminal alkyne substrate gave only the Alder-ene type product **142** presumably through a 1,5-proton shift, whereas alleneyne **143** containing an internal alkyne led to vinyl allene **144** likely via a 1,5-hydride shift (Scheme 63). On the other hand, the choice of catalysts may also have a profound impact on the reaction outcome. For terminal alkyne **140**, $AuCl_3$ predominantly favored the formation of bicyclic compound **141**, yet $Ph_3PAuSbF_6$ offered only the Alder-ene product **142**. Conversely, internal alkyne **143** gave the same vinyl allene product **144** using either a gold(I) or a gold(III) catalyst. In the case of alleneyne substrate **145** consisting of a terminal alkyne, a formal metathesis reaction took place to provide allenene product **146** (Scheme 64).[58]



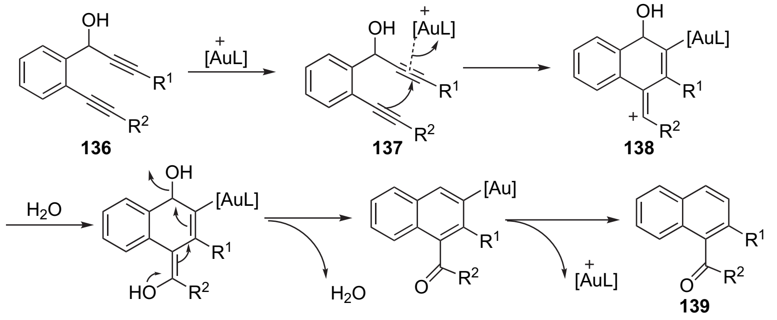
Scheme 58.



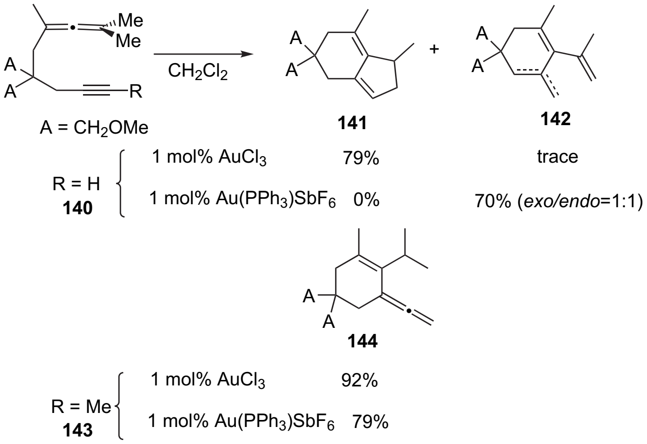
Scheme 59.

The gold(I)-catalyzed cycloisomerization of alleneyne **147** generated bicyclo[4.3.0]nonadiene derivative **148** via a tandem 6-*endo-dig*/Nazarov cyclization reaction (Scheme 65).[59] This remarkably efficient process was complete within 1 h at 0 °C.

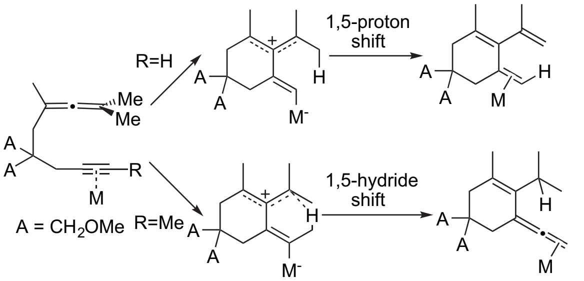
A more recent report on gold-catalyzed alleneyne cycloisomerization leading to cross-conjugated trienes revealed an interesting dual activation of an ene reaction (Scheme 66). In addition to the computational study, three experiments supported the double activation of phosphine-gold(I).[60] First, internal alkynes failed to participate in the reaction. Second, deuterium exchange took place at the terminal alkyne position. Lastly, transient formation of phosphine-gold acetylide was observed. It appears that



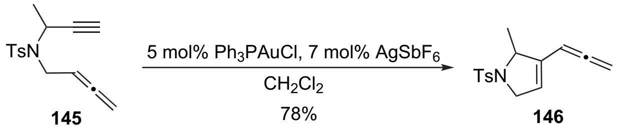
Scheme 61.



Scheme 62.



Scheme 63.



Scheme 64.

the nucleophilic addition of an allene to a phosphine–gold complexed phosphine–gold acetylide **149** is preferred over either oxidative cyclization involving metallocyclic species or simple nucleophilic addition of the allene to phosphine–gold complexed substrate. The resulting *gem*-disubstituted vinyl gold species **150** then participated in a 1,5-hydrogen atom shift and protodeauration to form the triene products.

2.4. Allenene cyclizations

Gold(I)-catalyzed cycloisomerization of vinyl allenes constitutes a novel approach to substituted cyclopentadienes (Scheme 67).[61] The pentadienyl cation **152**, generated by coordination of gold catalyst with allene **151**, underwent an electrocyclic ring closure to form allyl cation **153**. A subsequent intramolecular 1,2-hydrogen shift then led to the formation of cyclopentadiene **154**. This facile reaction gave nearly quantitative yield of cyclopentadiene almost instantaneously even at 0 °C.

Allenenes can also be engaged in the gold(I)-catalyzed cycloisomerization to dienes with moderate enantioselectivity as reported by the Gagné group (Scheme 68).[62] This reaction tolerated substrates bearing 1,1-disubstituted alkenes, which are often not acceptable for the cyclizations catalyzed by other transition metal complexes. The proposed mechanism invokes the cyclization of an alkene onto a gold-activated allene to form cationic species, which is subjected to further eliminations (Scheme 63). Subsequently, the same group reported a related hydroarylation of allenes using $(PhO)_3PAuCl/AgX$ catalysts.[63]

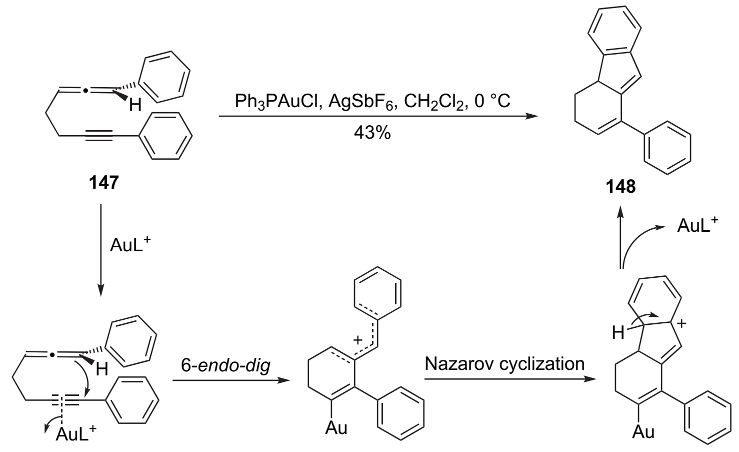
2.5. Diene cyclization

Building a highly functionalized cyclopentene framework can be a daunting task, yet the Liu group successfully developed an elegant gold-catalyzed deoxygenative cyclization of *cis*-2,4-diene-1-als with regioselective addition of two nucleophiles,[64] overcoming the thermally reversible 6-π-electrocyclization of the dienal starting material (Schemes 69 and 70). As depicted in Scheme 69, the gold catalyst acted as a Lewis acid to promote the olefin addition to an aldehyde. The resulting stabilized allyl cation **156** could then be intercepted by a nucleophile such as an allyl silane. The departure of the gold alkoxy group generated a second allyl cation **157**, thus allowing the ensuing nucleophilic attack of the olefin to furnish the intricate bridged cyclic product **158**. By using a variety of nucleophiles either inter- or intramolecularly, the 6,5-fused bicyclic product **155** or more elaborate polycyclic skeletons (**158**–**161**) could be constructed with good to excellent diastereoselectivity. Thus, different annulation strategies allowed for rapid increase of structural complexity.

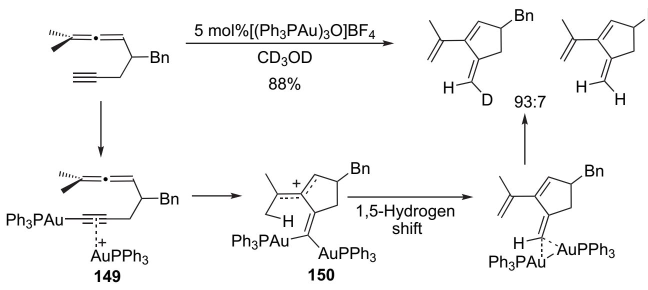
The Echavarren group discovered a conceptually novel gold-catalyzed allyl–allyl coupling reaction, in which five- or six-membered carbocycles and hetereocycles could be formed.[65] For example, in the presence of catalyst **164**, both 1,4-*trans*- and *cis*-cyclohexene substrates **162** and **163** cyclized to afford a single diastereomer **165** in excellent yield (Scheme 71). In contrast, the Rh-catalyzed cyclization only worked with the cis substrate, while the Pd-catalyzed cyclization only proceeded with the trans substrate, highlighting that the gold-catalyzed bis-allyl coupling was mechanistically very different from the corresponding Pd and Rh catalyses. Furthermore, both Rh- and Pd-catalyzed reactions gave inferior yields of **165**.

3. Cycloadditions

Transition metal-catalyzed cycloaddition reactions are powerful tools to construct carbocycles and heterocycles[66] in an atom-

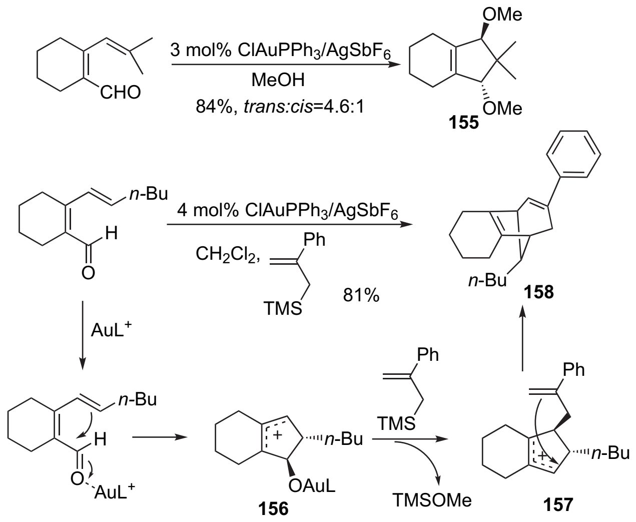


Scheme 65.

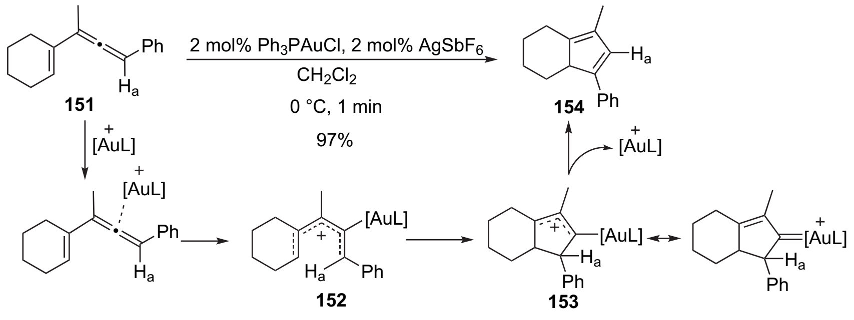


Scheme 66.

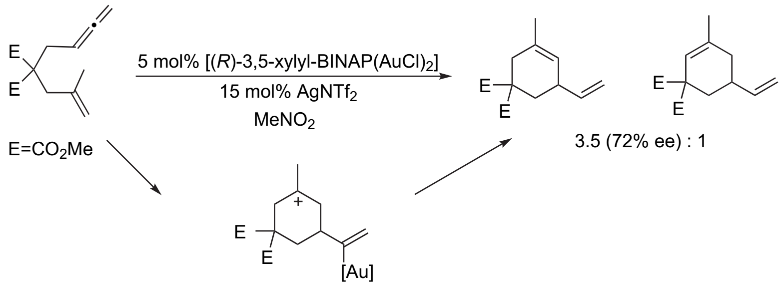
economic fashion.[67] The repertoire of transition metal-catalyzed cycloaddition has been expanded significantly by the gold-catalyzed reactions, due to the unique reactivity of gold catalysts. So far, [2+1], [2+2], [3+2], [4+2], [4+3], and [6+2] cycloadditions, including the corresponding formal cycloadditions, have been reported.



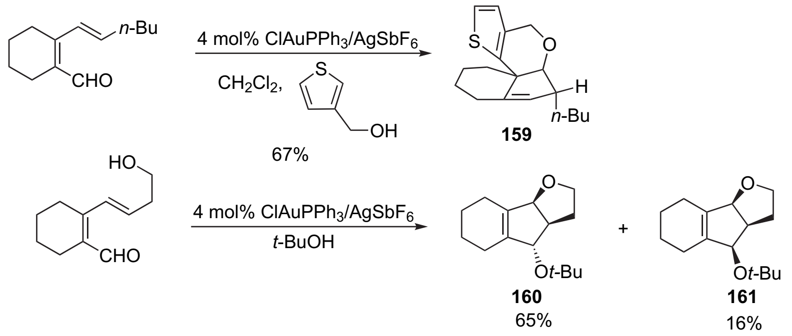
Scheme 69.



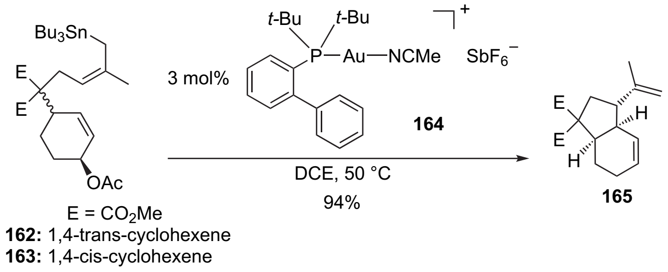
Scheme 67.



Scheme 68.



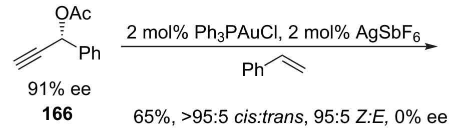
Scheme 70.



Scheme 71.

3.1. [2+1] Cycloaddition (intermolecular cyclopropanation)

The gold(I)-catalyzed stereoselective intermolecular olefin cyclopropanation is a powerful method that has been added to the arsenal of existing cyclopropanation methods (Scheme 72).[68] In this transformation, the enantiomerically enriched acetate **166** was converted into vinyl cyclopropane **167**, with excellent control of the cyclopropane stereochemistry and olefin geometry, despite the complete loss of ee. The lack of *trans*-cyclopropane formation lies in the disfavored steric interaction between the gold catalyst and the phenyl group in transition state **169** leading to the trans isomer, which is otherwise absent in transition state **168** leading to the cis isomer (Scheme 73). The use of chiral ligands such as **170** caused exclusive cis-cyclopropanation and excellent enantioselectivity with substrates containing a sterically demanding pivaloate (Scheme 74).

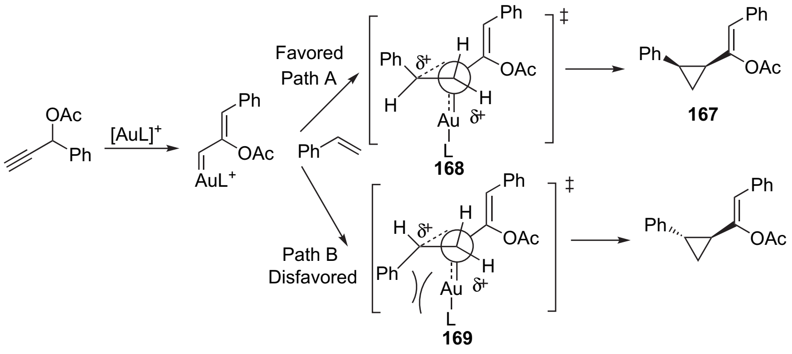


Scheme 72.

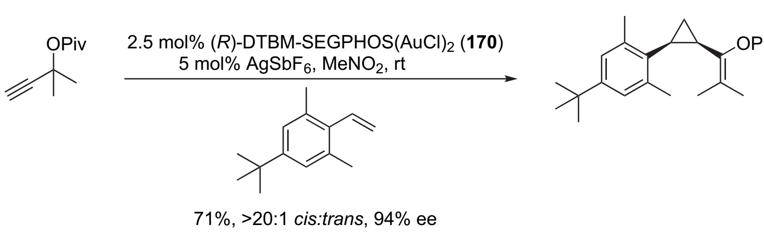
3.2. [2+2] Cycloaddition

Echavarren's group first reported a gold(I)-catalyzed formal [2+2] cycloaddition of enyne substrates to construct cyclobutenes (Scheme 75), which presumably involved the ring expansion of *syn*-cyclopropyl gold carbenoids (Scheme 22).[22,69]

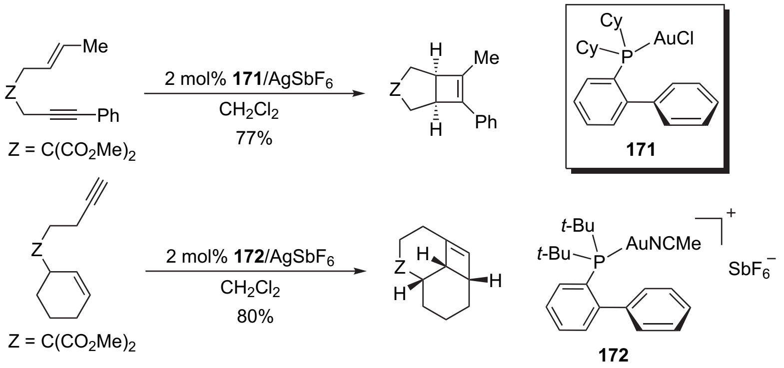
Zhang developed a gold(I)-catalyzed tandem process of [3,3]-rearrangement of propargyl esters and an ensuing formal [2+2] cycloaddition of the resulting indole allenyl ester **173** (Scheme 76).[70] As a result, the unusual tetracyclic structure **174** was obtained almost quantitatively.



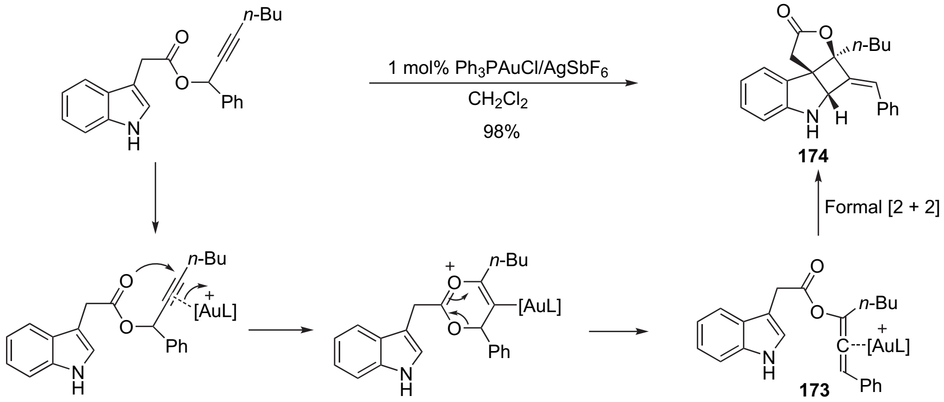
Scheme 73.



Scheme 74.



Scheme 75.



Scheme 76.

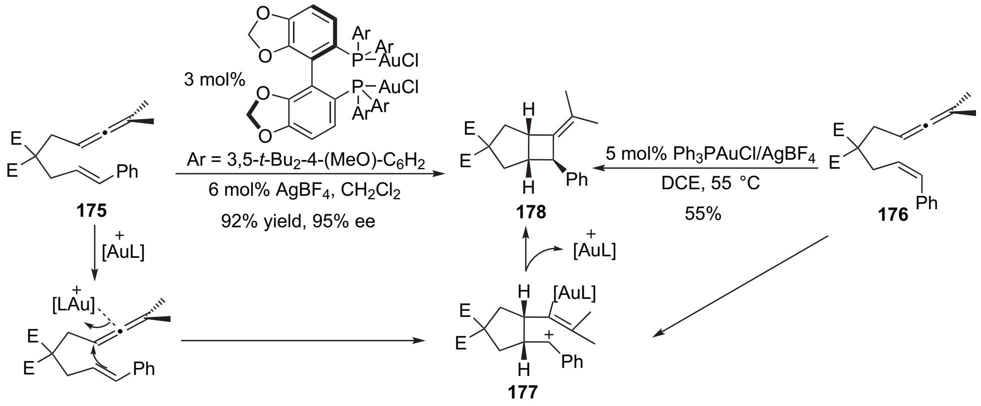
A [2+2] allene–alkene cycloaddition could also be achieved asymmetrically to form cyclobutanes with excellent enantioselectivity using a bisphosphine chiral ligand (Scheme 77).[71] An interesting aspect of this method was that the substrate **176**, the cis-alkene isomer of **175**, also led to product **178**, supporting the mechanism involving benzyl cation **177** as the common intermediate derived from trans- and cis-olefin isomers **175** and **176**.

3.3. [3+2] Cycloaddition

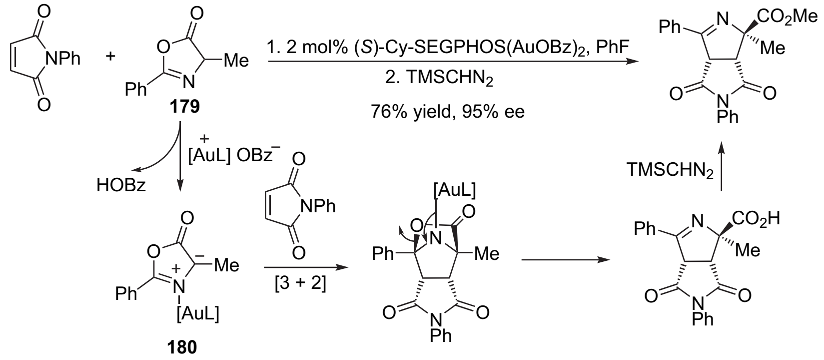
A paradigm shift from the π-bond activation by gold catalysts to other reaction manifolds was evident in a recent report by the Toste group of the 1,3-dipolar cycloaddition of münchnone **180** with electron-deficient alkenes. In this reaction, the chiral gold species was associated with dipole **180** and in turn dictated the stereochemical outcome of the reaction (Scheme 78).[72] High regio-, diastereo-, and enantioselectivity was achieved using the (*S*)-Cy-SEGPHOS(AuOBz)$_2$ catalyst.

The Liu group reported an unprecedented [3+2] cycloaddition of arenyne–ynes to efficiently construct polycyclic ring systems at ambient temperature.[73] The proposed mechanism is depicted in Scheme 79. The cyclization was presumably initiated by the nucleophilic addition of arene onto the alkyne–gold complex **181**. The electron-rich intermediate might be protonated to form a vinyl cation species **182**, which then generated tricyclic product **183** via a 5-*exo-dig* or Nazarov type of cyclization.

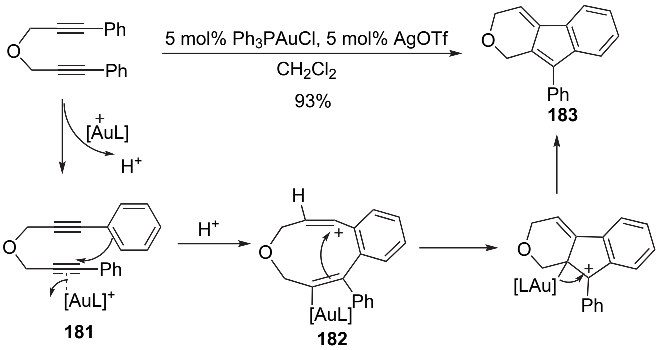
Zhang and Huang developed an elegant formal [3+2] cycloaddition of enones/enals and allenyl MOM ethers to obtain cyclopentanone enol ethers containing an all-carbon quaternary center (Scheme 80).[74] The mechanistic proposal is that a gold catalyst may



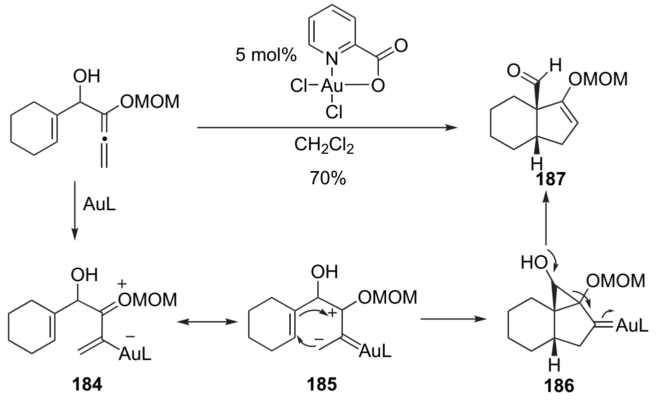
Scheme 77.



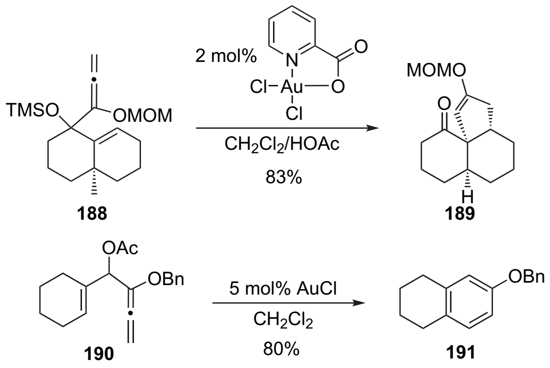
Scheme 78.



Scheme 79.



Scheme 80.



Scheme 81.

promote the formation of intermediate **184** and its resonance structure, the 1,3-dipole **185**, thereby allowing a formal [3+2] cycloaddition. The resulting gold carbenoid cycloadduct **186** bearing a strained bicyclo[3.1.0] system undergoes fragmentation followed by protodeauration leading to aldehyde **187**. A variety of fused bicyclic, spirocyclic, and tricyclic ring systems have been obtained with excellent diastereo- and regioselectivity. As shown in Scheme 81, tertiary silyl ether **188** could also undergo a formal cycloaddition and in situ hydrolysis to provide ketone **189**. Interestingly, with an acetate present at the allylic position (**190**), a formal [3+3] cyclization proceeded to afford an aromatic ring resulting from the elimination of acetate (**191**).[75]

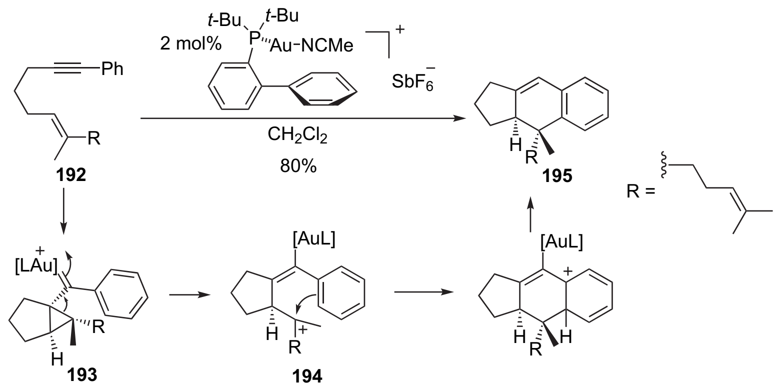
3.4. [4+2] Cycloaddition

In contrast to the aforementioned [2+2] enyne cycloaddition (Scheme 75), a gold-catalyzed formal [4+2] cycloaddition could occur for substrates bearing an aryl or vinyl substituted alkyne (Scheme 82).[76] Despite the lack of *gem*-substitution at the tether in substrate **192** (Thorpe–Ingold effect), the reaction still proceeds smoothly. Importantly, the reaction is also stereospecific with the olefin geometry dictating the stereochemical outcome of products. DFT calculations support a stepwise mechanism by the initial formation of *anti*-cyclopropyl gold carbenoid **193**, followed by its ring opening to generate an aryl group-stabilized carbocation **194**, which undergoes a Friedel–Crafts-type reaction to form cycloadduct **195**.

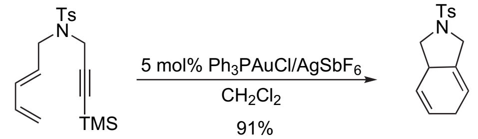
The activation of alkynes by gold(I) has also been utilized in the intramolecular Diels–Alder reaction, despite the absence of an electron-withdrawing group to activate the alkyne dienophile. With gold and silver catalysts, the reaction could proceed at room temperature (Scheme 83).[77] Upon work-up, the silyl group was lost due to silver-assisted silyl cleavage.

Hashmi and co-workers have published a series of papers on phenol synthesis via a formal [4+2] cycloaddition reaction utilizing a gold-catalyzed cyclization of furan alkyne substrates.[78] One such example is the synthesis of tetrahydroisoquinoline shown in Scheme 84. Their mechanistic studies suggested the involvement of arene oxides as intermediates.[79]

Enynes and propargyl esters can be selectively converted into styrenes or fluorenes under catalyst control in formal [4+2] cycloaddition reactions (Scheme 85).[80] The first step of the reaction sequence is a gold-catalyzed cyclopropanation. While $Ph_3PAuNTf_2$ leads to the formation of trans-cyclopropyl products, the less reactive AuCl gives predominantly cis-cyclopropyl intermediate **196**, which then assumes a 5-*endo* cyclization to introduce bicyclic intermediate **197**. The following ester migration and cyclopropyl ring opening establishes the arene core. The reaction selectivity leading to either styrenes or fluorenes is solely based on the counterion effect, with OTf anion favoring the formation of styrene **198**, and SbF_6 anion the exclusive generation of fluorene **199** under otherwise identical reaction conditions.

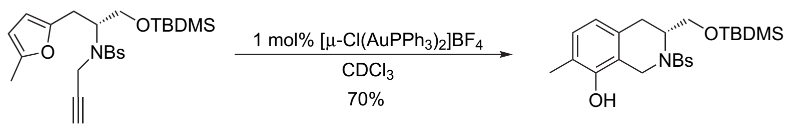


Scheme 82.

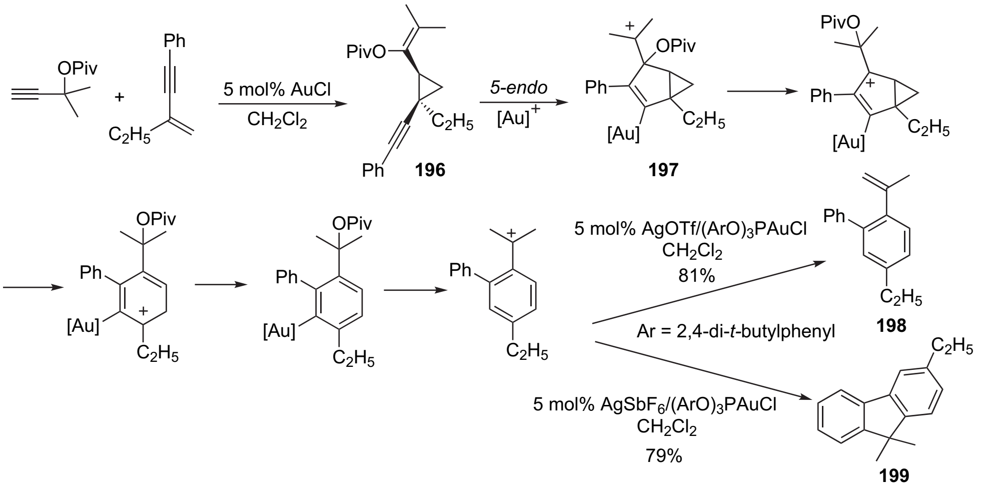


Scheme 83.

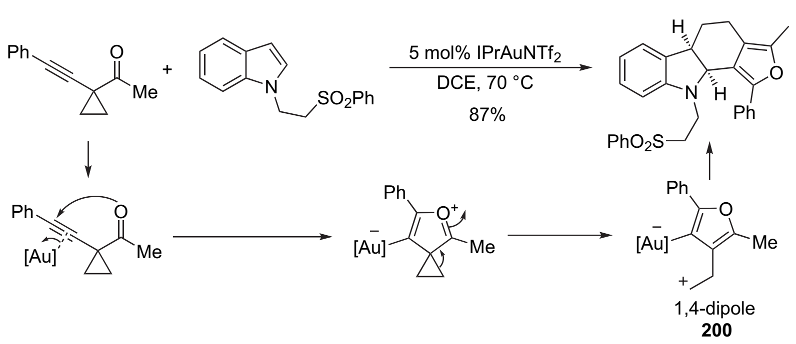
Another formal [4+2] cycloaddition to access unusual heterocyclic systems was reported by Zhang and co-workers (Scheme 86).[81] The proposed mechanism invokes gold-containing all-carbon 1,4-dipoles, formulated after the ring opening of cyclopropyl group (**200**). The resulting formal 1,4-dipoles were engaged in subsequent annulation with indoles, ketones, aldehydes, imines, or



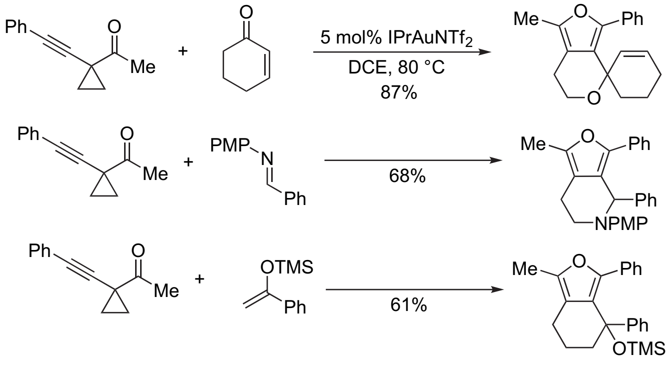
Scheme 84.



Scheme 85.



Scheme 86.



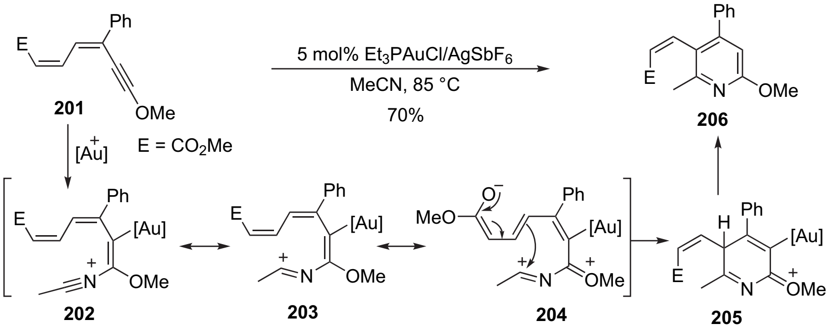
Scheme 87.

silyl enol ethers to give a wide range of novel fused heterocycles (Scheme 87).

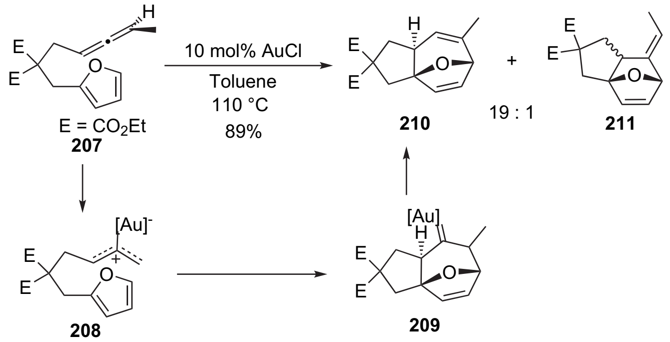
Most recently, Barluenga and co-workers discovered a gold-catalyzed hetero-dehydro-Diels–Alder cycloaddition of captodative dienynes with nitriles as a regioselective approach to pyridines (Scheme 88).[82] In their mechanistic proposal, the dienyne substrate **201** was activated by a gold catalyst to induce nucleophilic addition of acetonitrile, in which the regioselectivity was guided by the polarization of the substrate. The ensuing cyclization may occur with resonance structures (**202**–**204**). The resulting dihydropyridine **205** then yielded the corresponding pyridine **206**.

3.5. [4+3] Cycloaddition

A novel [4+3] cycloaddition of allenyl dienes was discovered to form a polycyclic system containing a seven-membered ring (Scheme 89).[83] It was presumed that the activation of the allene in substrate **207** by AuCl could form an allyl cation–metal complex **208**, setting up the stage for cycloaddition to yield gold carbenoid **209**. The ensuing 1,2-hydrogen shift gave seven-membered carbocycle **210** as the major product, accompanied with a small amount of [4+2] cycloadduct **211**.



Scheme 88.

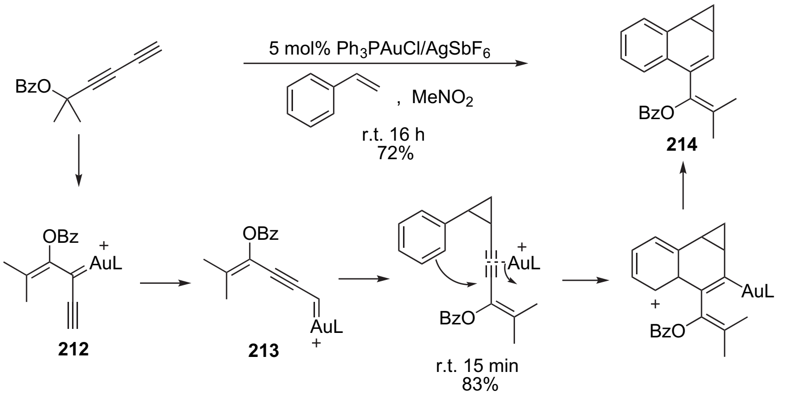


Scheme 89.

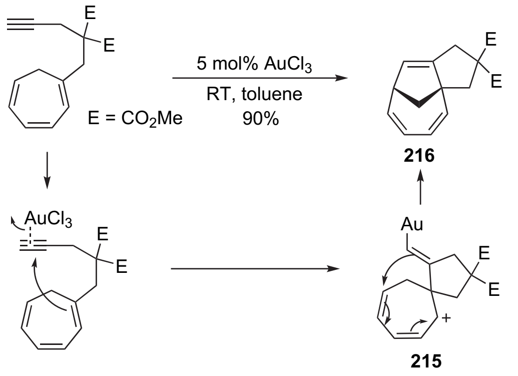
Another original gold(I)-catalyzed [4+3] annulation strategy provided an access to benzonorcaradienes (Scheme 90).[84] This process included the formation of carbenoid **213** via a 1,3-metallotropic rearrangement (**212** to **213**) or a cumulene intermediate. The ensuing cyclopropanation with styrene and the gold-promoted intramolecular cyclization afforded product **214** containing the benzonorcaradiene scaffold.

3.6. [6+2] Cycloaddition

An interesting platinum- or gold-catalyzed [6+2] cycloaddition of alkynes tethered to cycloheptatriene allows the formation of tricyclic bridged systems (Scheme 91).[85] The proposed mechanism entailed a stepwise *exo* cyclization of alkene onto the gold-activated alkyne, and the cyclization of the resulting pentadienyl



Scheme 90.



Scheme 91.

cation species **215** to afford the unusual bridged tricyclic product **216**.

4. Conclusion

Since the milestone work of Ito and co-workers on gold(I)-catalyzed asymmetric aldol reactions two decades ago,[86] homogeneous gold catalysis has demonstrated its utility in various C–C and C–X (X=O, N, S, etc.) bond formations, particularly in the context of cyclization and cycloaddition reactions. Summarized in this review are powerful methods in homogeneous gold catalysis developed in recent years as innovative strategies to construct a wide range of carbocycles and hetereocycles. Mechanistically distinct from most other transition metal catalysis, gold catalysis may offer products that are often difficult to obtain via conventional methods. As new methods of gold catalysis emerge on a weekly basis, the pursuit of novel reactivity and selectivity will continue to be the driving force in this field, with enormous impact and more forthcoming applications in organic synthesis.

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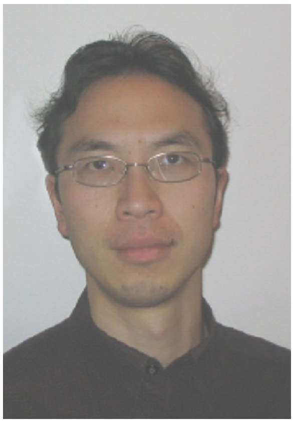
Biographical sketch



Hong C. Shen was born in Chengdu, China in 1974. In 1997, he received his B.S. degree in chemistry from Peking University under the direction of Professor Yunhua Ye. Hong C. Shen subsequently moved to University of Minnesota, where he developed a formal [3+3] cycloaddition with Professor Richard Hsung, and obtained his M.S. degree in 1998. Hong Shen then joined the research group of Professor Barry Trost at Stanford University. His work spanned from Ru- and Pd-catalyzed reactions to their applications in total syntheses of natural products. After obtaining his Ph.D. degree in 2003, Hong C. Shen assumed a senior research chemist position at Merck Research Laboratories, Rahway, New Jersey. He is currently a research fellow working on the discovery of novel drugs for treatment of cardiovascular and metabolic diseases. He has authored close to 30 publications and 9 patents.