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Recent advances in syntheses of heterocycles and carbocycles via homogeneous gold catalysis. Part 1: Heteroatom addition and hydroarylation reactions of alkynes, allenes, and alkenes

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Contents

1. Introduction

Despite the extensive use of gold and gold salts in heterogeneous catalysis since the 1960s,[1] the golden era of homogeneous gold catalysis has begun at the end of the 20th century, evident by the dramatically increased number of publications in this field.[2]

The booming of gold catalysis has been enabled by the understanding of fundamental principles in frontier orbitals, relativistic effects,[2a] and π-acidity.[2b] As the alkyne is a strong σ-donor and a weak π-acceptor toward the gold species, the gold-complexed alkyne is intrinsically electrophilic. The weakened alkyne C–C π-bond can be visualized by the X-ray crystal structures of gold–cyclic alkyne complexes, with a substantial C–C bond length increase, and an alkyne IR stretching vibration shift.[3a] By tethering a strongly coordinating phosphine and a labile alkyne or alkene, Toste and Shapiro were able to crystallize the first gold(I)–phosphine η^2-coordinated alkyne and alkene complexes, representing the most recent breakthrough in the field.[3b] However, the similar alkyne C–C bond length for Au(I), Cu(I) and Ag(I)–alkyne complexes, and the most significant alkyne linearity deviation for the Cu(I)–alkyne complex, does not explain why Au(I) catalysts are often most effective on alkyne activation. At least two reasons were proposed by the authors to account for the unique activity of gold catalysts. The first lies in the more propensity for Au(I) to undergo an η^2 to η^1 migration with respect to Cu(I). The second is the largest bonding energy difference between the alkyne π to metal σ-donation and the metal to alkyne π* back donation for Au(I) complex, which is revealed by a DFT study.

Gold-catalyzed reactions have displayed several unique features. Specifically, with an electron configuration of

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$[Xe]4f^{14}5d^{10}6s^1$ for the gold atom, gold catalysts mainly exist in +1 and +3 oxidation states. The high oxidation potential of Au(I) to Au(III) allows most Au(I)-catalyzed reactions to proceed without precautions to exclude air. In addition, gold catalysts are exceptionally alkynophilic, but not as oxophilic as most Lewis acids. Thus oxygen, water, and alcohols are often well-tolerated, in sharp contrast to most air- and moisture-sensitive Lewis acid or transition metal-catalyzed transformations. Besides convenient procedures without the concern of air and moisture, gold-catalyzed reactions often provide efficient access to structures of immense diversity and/or complexity from much simpler starting materials. Furthermore, distinct from classical carbocations, the non-classical carbocation or carbenoid feature of intermediates involved in gold-catalyzed transformations often leads to well-controlled product selectivity. Lastly, carbon–gold bonds are labile toward protodeauration, but not susceptible to β-hydride elimination, which frequently occurs in other transition metal-catalyzed reactions, thereby increasing the product selectivity.

To foster the application of gold catalysis in medicinal chemistry and total synthesis of natural products, this review identifies recent significant advances in heterocycle and carbocycle formations through two general classes of gold-catalyzed reactions. The first involves the addition of a heteroatom to alkynes, alkenes, and allenes. The second is the hydroarylation reaction of alkynes, alkenes, and allenes. The major focuses herein are the reaction mechanisms and selectivity, including chemo-, regio-, diastereo-, and enantioselectivity. The forthcoming second review (part 2) will focus on gold-catalyzed enyne cycloisomerizations and cycloadditions as another powerful tool to access carbocycles and heterocycles.

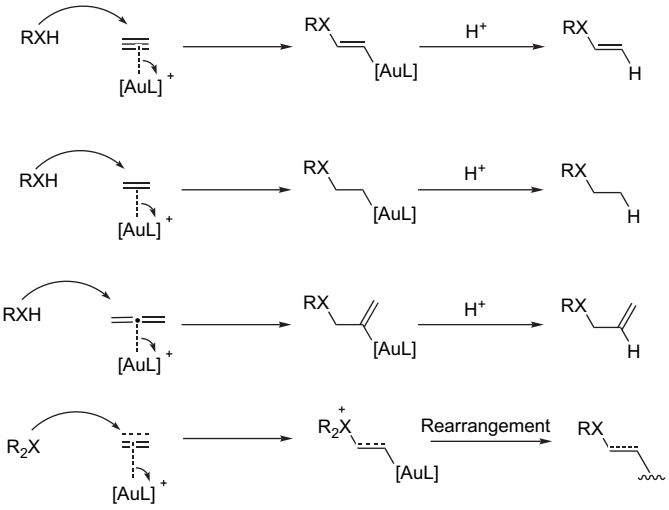
2. Heteroatom addition to unsaturated C–C bonds

Gold-activated alkynes and allenes, and occasionally alkenes are good electrophiles for both sp^2- and sp^3-hybridized heteroatom nucleophiles. If a heteroatom X is sp^3-hybridized and HXR serves as a nucleophile, the proposed mechanism involves a trans heteroatom auration in most cases and the ensuing protodeauration (Scheme 1). Typically an intramolecular C–X bond formation followed by protodeauration leads to an X-containing heterocycle. In the cases where R_2X (X=O, S) is used as a nucleophile, the resulting X cation often leads to a subsequent rearrangement reaction.

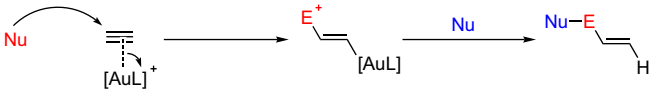
When X is sp^2 hybridized, particularly in the cases of ketones, aldehydes, and imines, upon the addition of X to gold-activated unsaturated C–C bonds, the resulting X cation, as an electrophile, could thereby trigger the addition of another nucleophile (Scheme 2).

Of particular interest is the third reaction mode in which the nucleophile also bears a leaving group thus setting the stage to generate a gold carbenoid (Scheme 3), a versatile intermediate for further transformations.

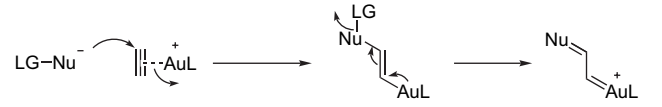
The regioselectivity of these reactions is often excellent, and high enantioselectivity has been accomplished in cyclization reactions of alcohols and amine derivatives with allenes.



Scheme 1.



Scheme 2.



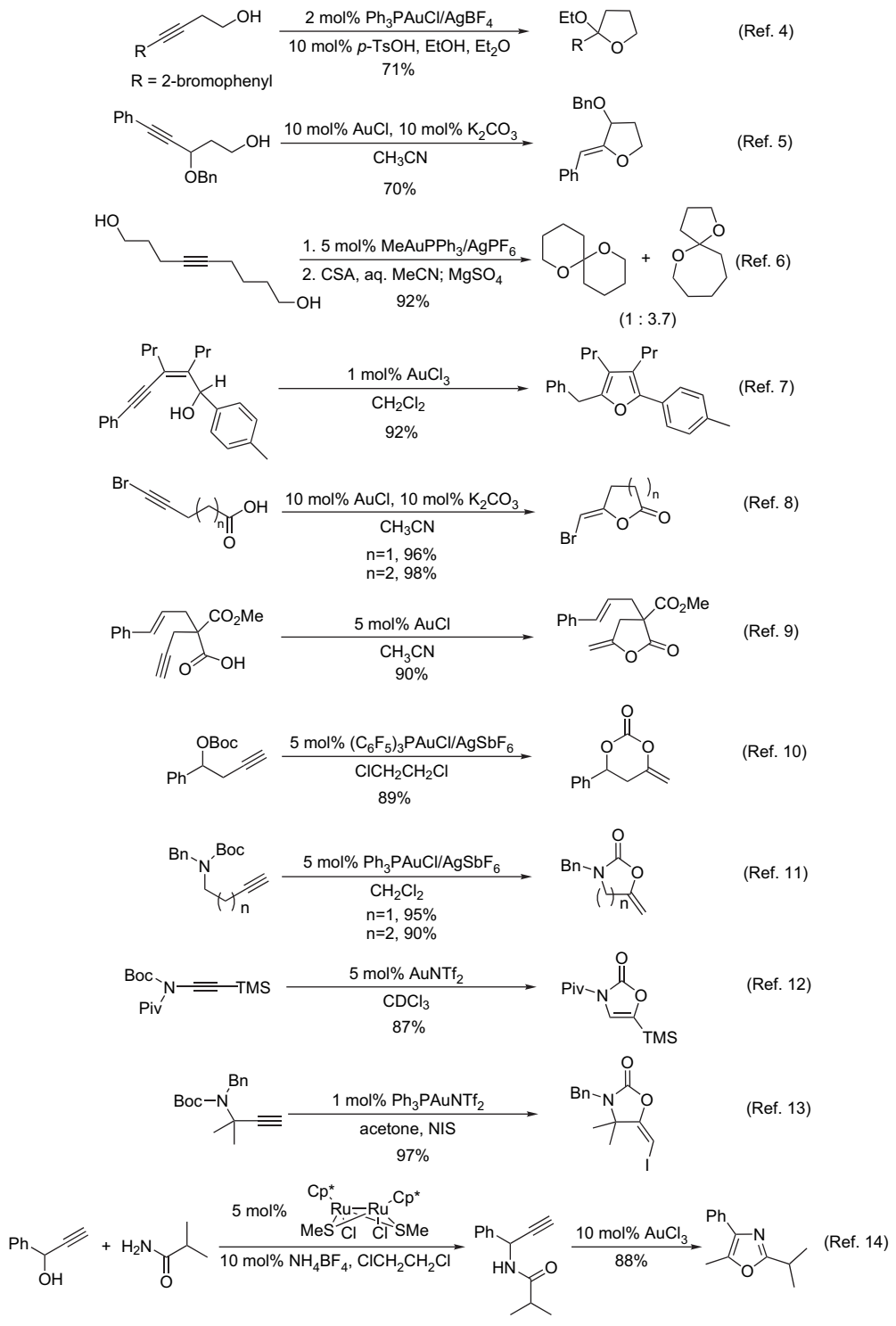
Scheme 3.

Reactions are generally conducted under very mild conditions, with excellent efficiency and functional group compatibility.

2.1. Heteroatom addition to alkynes

The gold-catalyzed 5-*endo-dig*, 5-*exo-dig* or 6-*exo-dig* cyclization reactions of heteroatom nucleophiles onto alkynes followed by protodeauration provide straightforward and efficient approaches to various five- and six-membered heterocycles. The nucleophiles can be the oxygen atom of alcohols,[4–7] carboxylic acids,[8,9] carbonates,[10,11] carbamates,[12,13] and amides[14] (Scheme 4), and the nitrogen atom of amines,[15] carbamates,[16] trichloroacetimidates,[17] and anilines[18] (Scheme 5). It should be noted that vinyl gold species can also be trapped with electrophilic reagents such as NIS to afford vinyl iodide with well-controlled stereochemistry of the resulting olefin (Ref. 13, Scheme 4). A ruthenium- and gold-catalyzed sequential reaction leads to the facile synthesis of substituted oxazoles from propargylic alcohols and amides (Ref. 14, Scheme 4).

Gold-catalyzed sequential or tandem reactions involving the addition of oxygen nucleophiles to alkynes constitute efficient strategies to assemble oxygen-containing heterocycles (Schemes 6–21). For example, Barluenga and co-workers reported the $AuCl_3$-catalyzed intramolecular hydroalkoxylation

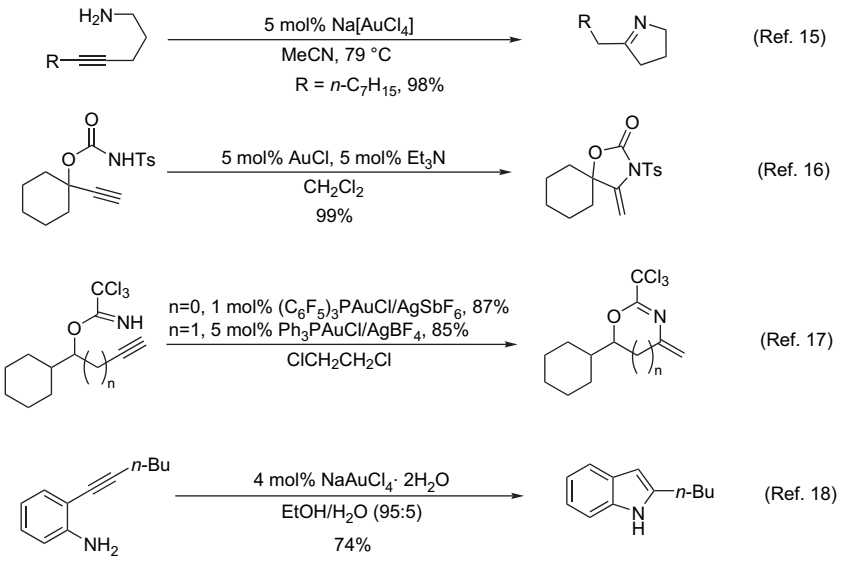


Scheme 4.

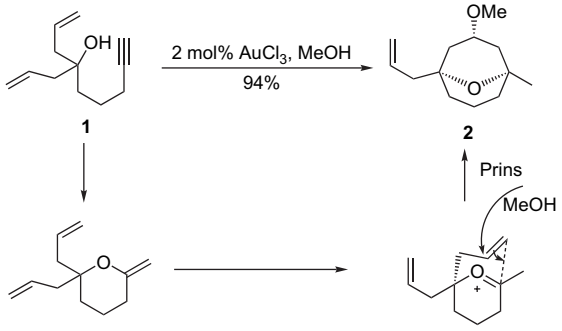
of alkyne **1** coupled with a Prins cyclization to provide the bridged bicyclic compound **2** (Scheme 6).[19]

Floreancig and Jung have utilized homopropargylic or propargylic ethers to prepare five- and six-membered heterocycles via a cascade of gold-catalyzed hydration, β-elimination of methanol, and gold-promoted 1,4-addition sequence as shown in Scheme 7.[20] The reaction yields and diastereoselectivity are excellent for the formation of tetrahydropyrans and piperidines. This method has been applied in the total synthesis of (+)-andrachcinidine **5**. A similar reaction sequence also leads to tetrahydrofurans.

An efficient three-component reaction of 2-(arylmethylene)cyclopropylcarbinol such as **6**, with alkyne **7** and alcohol **8**, affords 3-oxabicyclo[3.1.0]hexane **9** in excellent yield (Scheme 8).[21] In this transformation, the gold catalyst serves dual roles by promoting both the hydroalkoxylation of alkyne



Scheme 5.



Scheme 6.

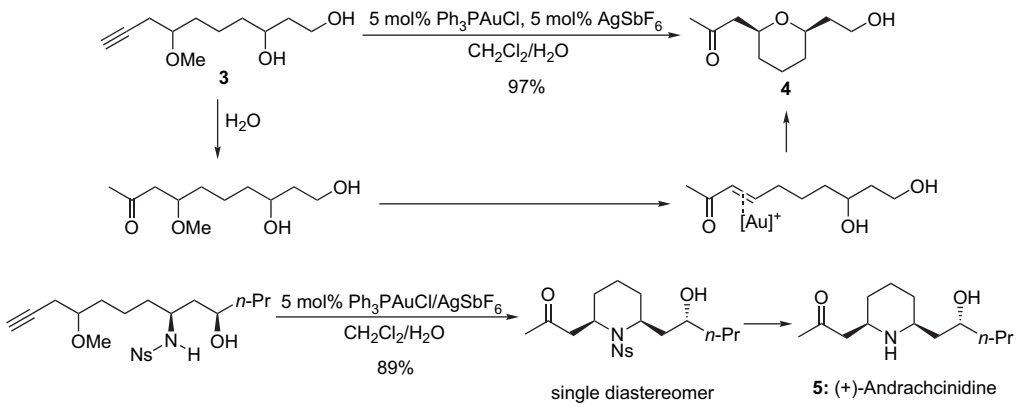
and the ensuing cyclization to generate the tetrahydrofuran ring.

An alkynyl alcohol intermediate **11** derived from the gold-catalyzed ring-opening of epoxide **10**, can undergo highly regio- and diastereoselective cascade additions of two alcohols to the alkyne to form substituted morpholine **12** (Scheme 9).[22]

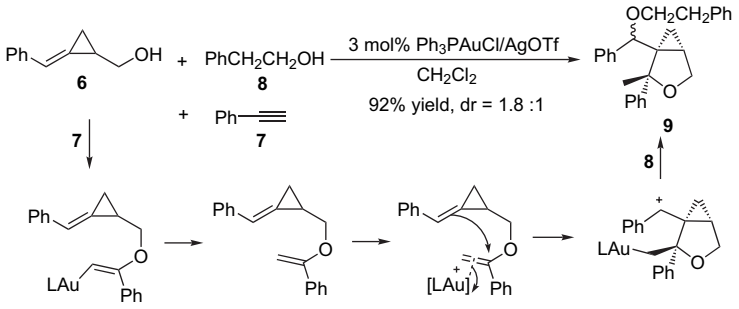
Liu and co-workers discovered an intriguing gold-catalyzed cascade cyclization/oxidative cleavage reaction of enyols with molecular oxygen, which formally cleaves a C–C triple bond (Scheme 10).[23] The first step presumably involves a 5-*exo-dig* cyclization to afford intermediate **14**, which is then oxidized in the presence of oxygen to form butenolide **15**. Both steps require the use of gold catalyst, and the second step is presumably a radical process since radical scavengers have completely suppressed the reaction.

An elegant gold(I)-catalyzed *N*-acyl iminium ion cyclization cascade has recently been developed by Dixon and co-workers (Scheme 11).[24] The carboxylic acid cyclization onto alkyne forms activated ester **18**, thus facilitating the subsequent aminolysis to yield amide **19**. Then the gold(I)- and/or acid-promoted Pictet–Spengler type of cyclization through acyl iminium ion **20** furnishes the tetracyclic framework of product **21**.

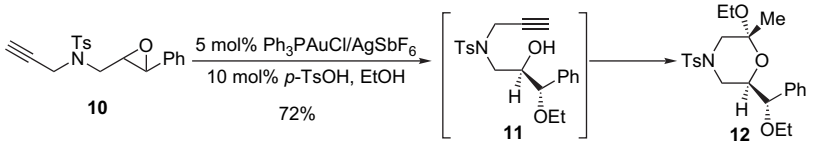
Toste and Dubé investigated the synthesis of indenyl ketals, indenyl ethers, and cycloalkene ethers, such as compound **23**, **25**, and **27**, respectively, via a gold(I)-catalyzed intramolecular carboalkoxylation of alkynes (Scheme 12).[25] The mechanistic rationale involves an alkyne activation followed by C–O bond cleavage, instead of ionization of benzylic ether. This hypothesis is supported by a double label crossover experiment, and



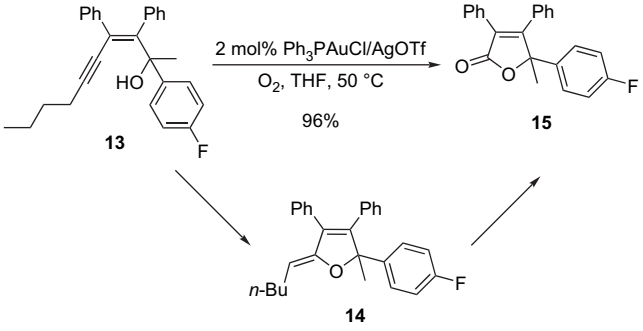
Scheme 7.



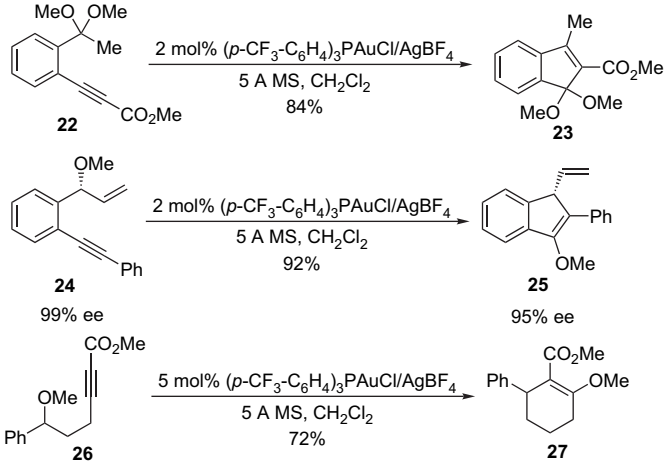
Scheme 8.



Scheme 9.



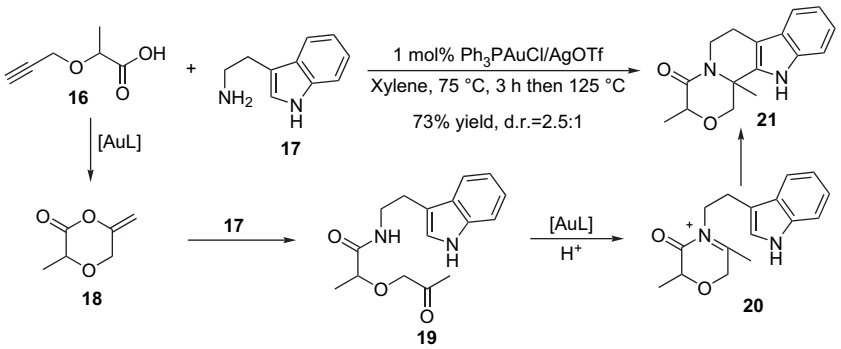
Scheme 10.



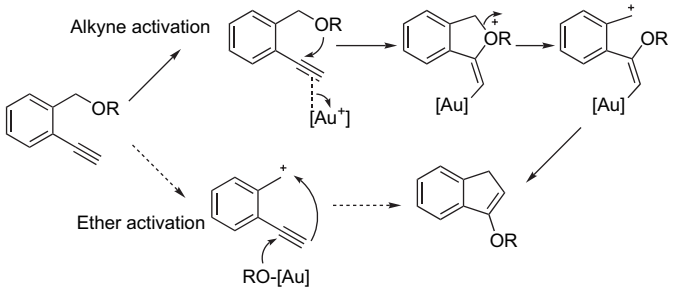
Scheme 12.

an excellent chirality transfer likely due to a 'memory effect' (**24** to **25**). The resulting carbocation could be trapped with vinyl gold intermediate to give the indene adduct (Scheme 13).

The use of alkynones for furan formation was demonstrated in three scenarios. First, Hashimi reported a gold-catalyzed reaction sequence containing one C–C and two C–O bond formations in the transformation of compound **28** to tricyclic spirocycle **30** (Scheme 14).[26] The authors favor the 5-*endo-dig* cyclization of a ketone carbonyl over the corresponding cyclization of a secondary alcohol by proposing structure **29** as the intermediate. Second, the gold-catalyzed sequential nucleophilic domino attack onto a metal-complexed alkyne has been employed to prepare highly substituted furans from enyne ketones by Larock and co-workers (Scheme 15).[27] Two possible mechanistic pathways are proposed. In the first proposal, the ketone addition to gold–alkyne complex (**32**) proceeds prior to the trapping of the resulting cation by methanol to yield product **34**. Alternatively, a gold-promoted

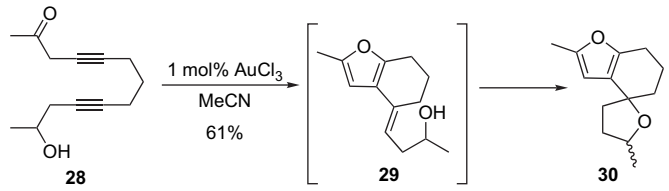


Scheme 11.

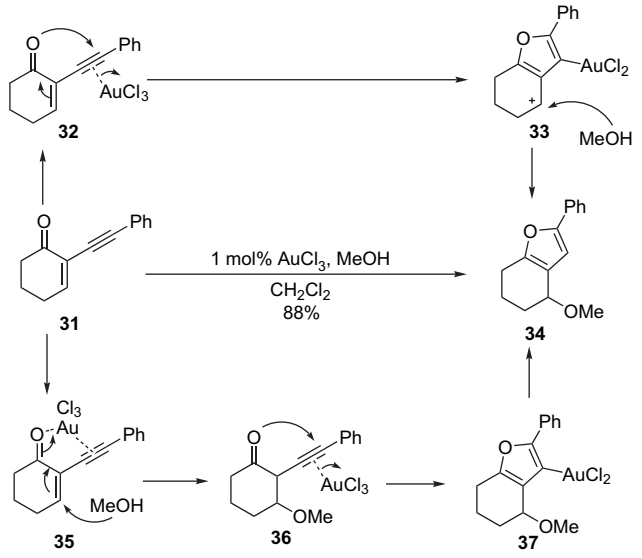


Scheme 13.

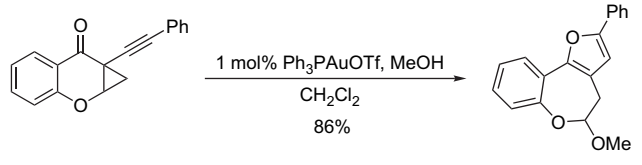
conjugate addition of alcohol to enone (**35**) may lead to intermediate **36**, which then undergoes a ketone addition to alkyne. The third example is the analogous chemistry with cyclopropyl alkynyl ketones revealed by Schmalz and Zhang (Scheme 16).[28]



Scheme 14.

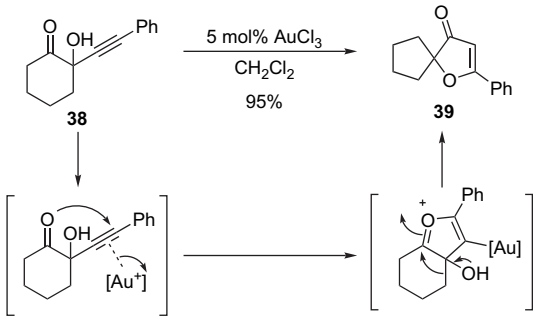


Scheme 15.

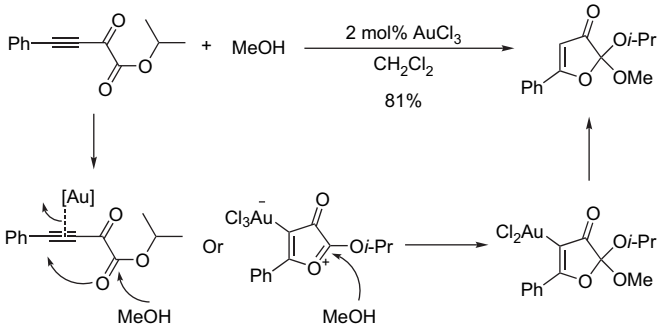


Scheme 16.

Furanone compounds can also be obtained from alkynones, adding another utility of the oxonium ion formed upon the addition of a carbonyl oxygen to an alkyne. For example, with an α-hydroxy group, alkyne ketone substrate **38** can be converted to novel spirofuranone **39** using $AuCl_3$ as the catalyst through a domino heterocyclization and 1,2-migration (Scheme 17).[29] In addition, 3(2*H*)-furanones can be derived from 2-oxo-3-butynoates or disubstituted 1,2-diones via the gold-catalyzed cyclization and nucleophilic addition sequence (Scheme 18).[30]

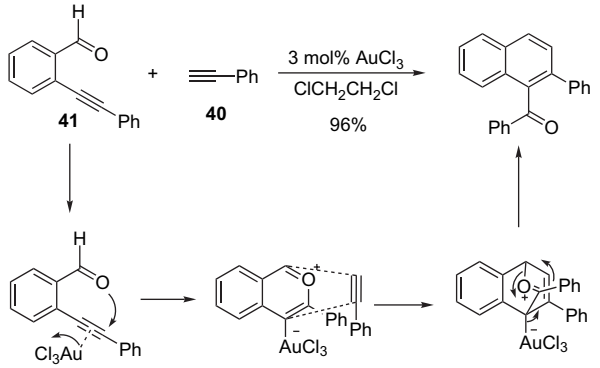


Scheme 17.



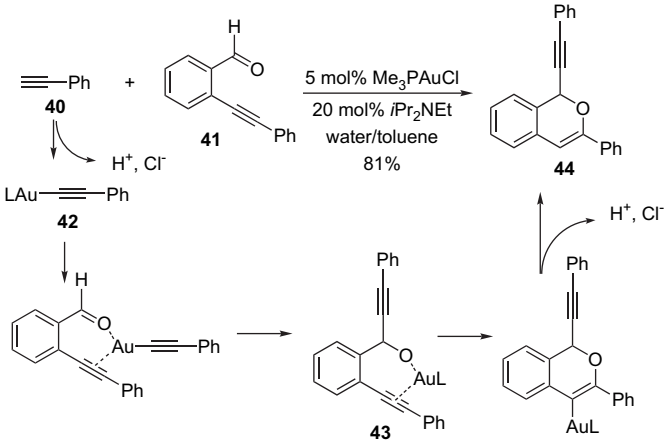
Scheme 18.

In contrast to the gold-catalyzed benzannulation reaction pioneered by Yamamoto and co-workers (Scheme 19),[31] which has been thoroughly reviewed,[31a] Li reported a water-triggered and gold-catalyzed cascade addition/cyclization of identical substrates utilized in Yamamoto's benzannulation chemistry. In this reaction, terminal alkynes **40** reacted with *ortho*-alkynylaryl aldehyde **41** to generate isochromene **44**,



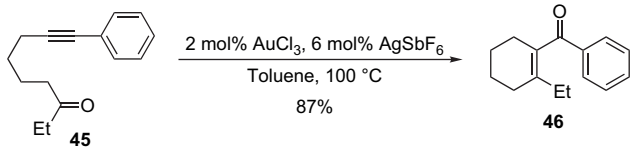
Scheme 19.

employing base and a catalytic amount of Me_3PAuCl (Scheme 20).[32] Presumably, alkynyl gold intermediate **42** formed in the presence of base could add to aldehyde **41**. The resulting secondary alcohol **43** then undergoes an intramolecular trans oxyauration, and protodeauration to deliver the resulting isochromene **44**.



Scheme 20.

First reported by Yamamoto and Jin, substituted cyclic enone **45** could be formed through a novel gold-catalyzed intramolecular carbocyclization of alkyne ketone **46** (Scheme 21).[33] The reaction outcome is equivalent to an alkyne–aldehyde metathesis.



Scheme 21.

Similar to the oxygen nucleophiles, nitrogen nucleophiles can undergo the same type of addition to gold-activated alkynes. For instance, enamines resulting from the hydroamination of amine[34] or aniline,[35] readily cyclize onto alkynes to form pyrroles or indoles (Scheme 22). Alternatively, the gold-catalyzed cyclization of 2-alkynylaniline **47** can generate indolyl-gold species **49**, which then adds to α,β-unsaturated ketone, or through a gold-catalyzed Friedel–Crafts-type process to form C-3-functionalized indole **50** (Scheme 23).[36]

The intramolecular imine addition to alkyne in substrate **51** forms a gold-containing azomethine ylide **53**, which then undergoes a [3+2] cycloaddition with electron-rich vinyl ether **52** leading to carbene intermediate **54** (Scheme 24). The subsequent 1,2-migration eventually affords tricyclic compound **55**.[37]

With pentenynyl allyl tosylamides, the gold(I)-catalyzed nucleophilic addition of the nitrogen of tosylamide to alkyne forms a cationic vinyl gold intermediate **57**, which initiates an aza-Claisen-type rearrangement followed by aromatization to generate substituted pyrrole **58** (Scheme 25).[38] Depending on substrates, the reaction is typically complete within 5–45 min. This reaction also allows the formation of a quaternary carbon after the [3,3]-sigmatropic rearrangement.

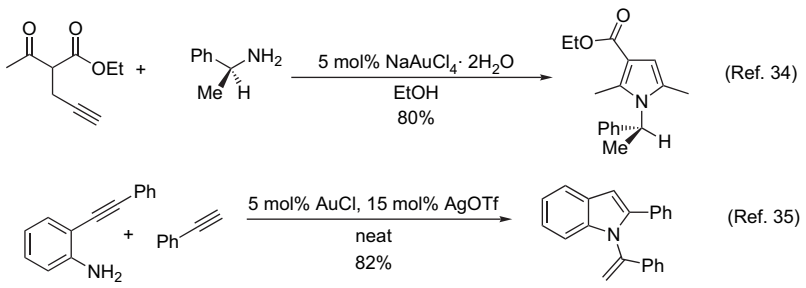
Cyclic ketone-fused indoles such as **63** can be obtained via a sequential Au/Pt-catalyzed cyclization, 1,2-acyl migration, and 1,2-migration of *n*-butyl group (**60**–**61**–**62**–**63**, Scheme 26). Alternatively, an intramolecular Friedel–Crafts reaction following the Au/Pt-catalyzed cyclization leads to a tricyclic system **66** without the migration of *n*-butyl group (**61**–**65**–**66**).[39] The use of $PtCl_4$ catalyst gives better yields and selectivity for the formation of **63**, and a gold catalyst bearing heterocyclic carbene ligand affords a mixture of two products.

A variant of the reaction mode described in Scheme 2 is to apply enamides or ensulfonamides as nucleophiles to establish a quaternary carbon center through a C–C bond formation.[40] The resulting iminium species can be trapped with methanol to form aminal isomers in situ (Scheme 27), which are further reduced to spiropiperidines.

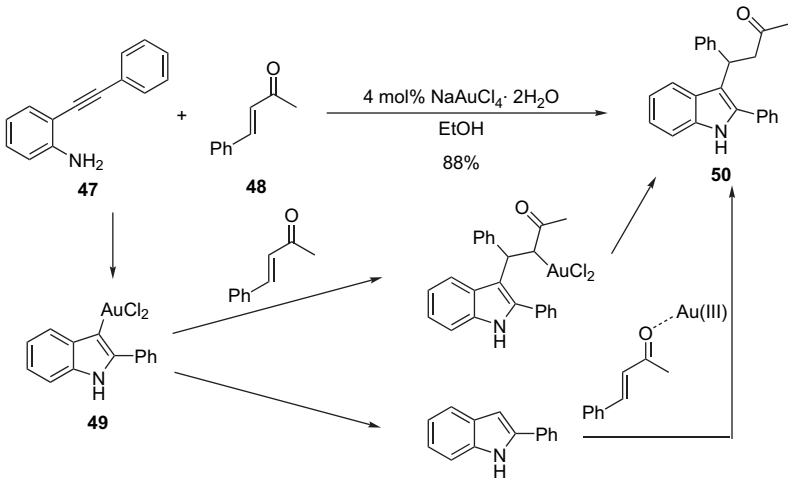
Various novel fused pyrrole heterocycles (**71**) have been prepared by Gevorgyan and Seregin via gold vinylidene intermediates resulting from the1,2-migration of trialkyl silicon, tin, and germanium group of propargyl silyl ether **67**. The ensuing addition of nitrogen to gold vinylidene (**68**), and a series of 1,2-hydride shifts (**69**, **70**) furnish the bicyclic ring structure (Scheme 28).[41] The presence of silicon, tin, and germanium group at the C-2 position of pyrrole allows further functionalization of these novel heterocycles.

Besides oxygen and nitrogen nucleophiles, sulfur nucleophiles can also add to alkynes. For example, Nakamura coworkers reported an intramolecular carbothiolation of alkynes (**72** to **73**) followed by 1,3-rearrangement of the sulfonium species (**73** to **74**) to produce benzothiophenes (Scheme 29).[42]

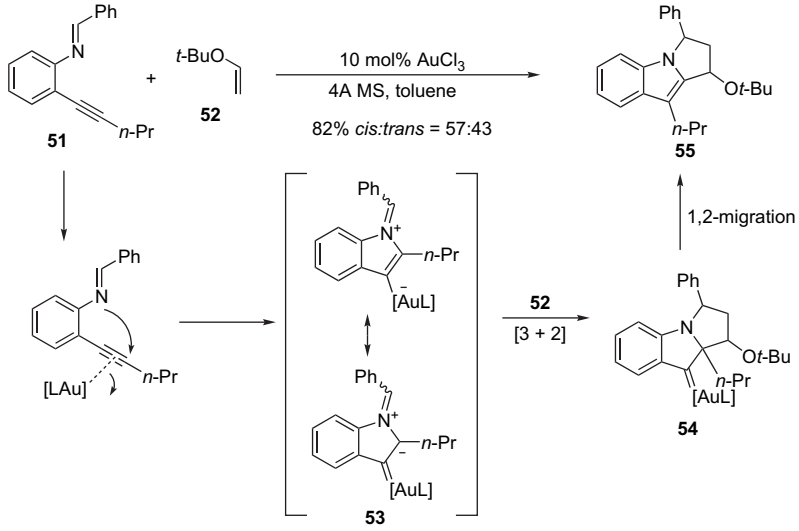
A rather unusual [2+2+1] type of cycloaddition of 2 equiv of phenylacetylene and 1 equiv of nitric acid affords isoxazole



Scheme 22.



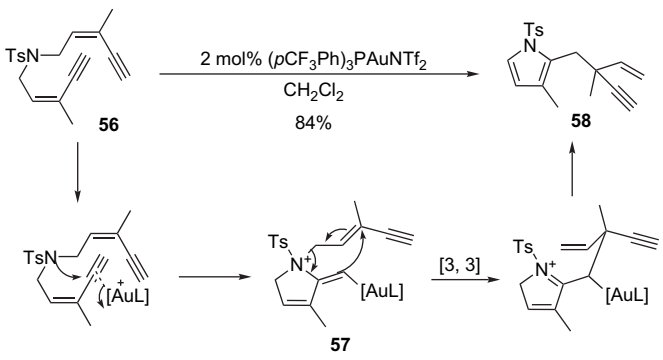
Scheme 23.



Scheme 24.

75 catalyzed by *n*-Bu_4NAuCl_4 (Scheme 30).[43] The reaction is believed to proceed through the addition of nitrite to an alkyne followed by a dipolar cycloaddition to furnish the isoxazole moiety.

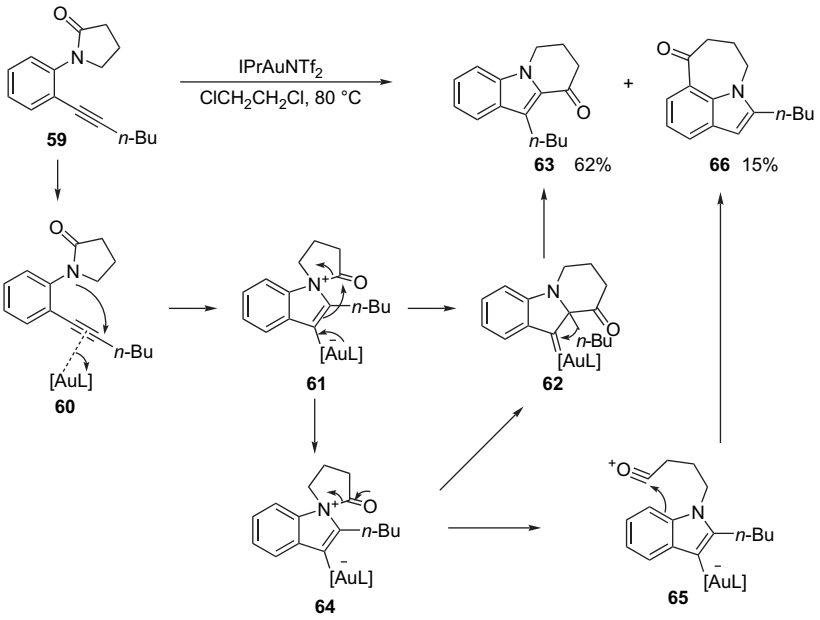
As one example to illustrate the reaction mode depicted in Scheme 3, the oxygen of a nitro group in substrate **76** could undergo an intramolecular addition to an alkyne to form the intermediate auric ate complex **77** (Scheme 31). The positively-charged nitrogen then acts as an electrophile to facilitate the hydration to generate nitroso species **78**. The subsequent series of cyclization and dehydration generate both isatogen **79** and anthranil **80**.[44]



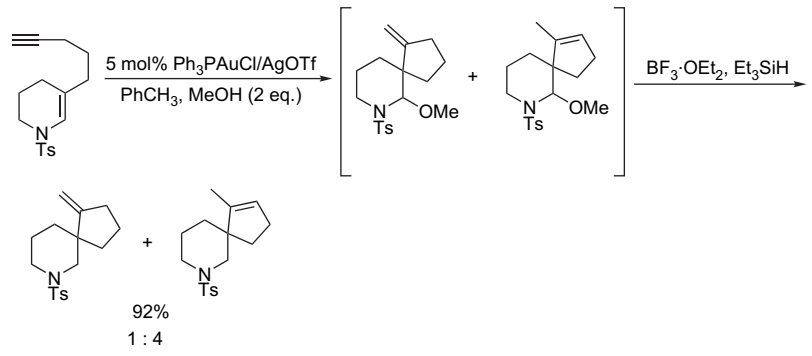
Scheme 25.

To further expand the scope of gold catalysis beyond just electrophilic activation, Toste and co-workers employed nucleophiles with labile leaving groups to generate carbenoid intermediates, which could be followed by either a formal H-shift, C–H insertion, or oxidation to give the requisite products. At least two examples of this concept have been reported, including acetylenic Schmidt reaction, and the preparation of sulfur-containing heterocycles via sulfoxides.

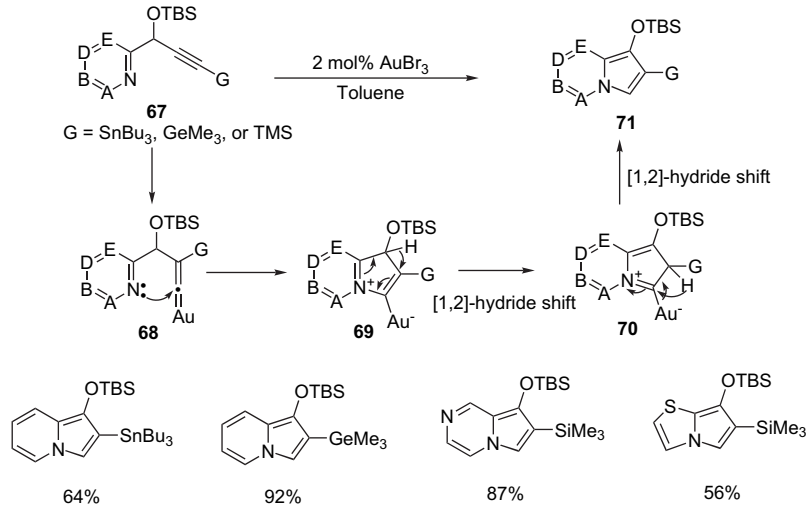
In the acetylenic Schmidt reaction (Scheme 32),[45] following the nucleophilic attack of the proximal nitrogen of azide at the gold-activated alkyne (**81**), the exclusion of dinitrogen in intermediate **82** gives a gold carbenoid intermediate **83**. A formal 1,2-shift of **83** produces 2*H*-pyrrole **84**, which readily tautomerizes to the corresponding 1*H*-pyrrole **85**. In the case



Scheme 26.



Scheme 27.

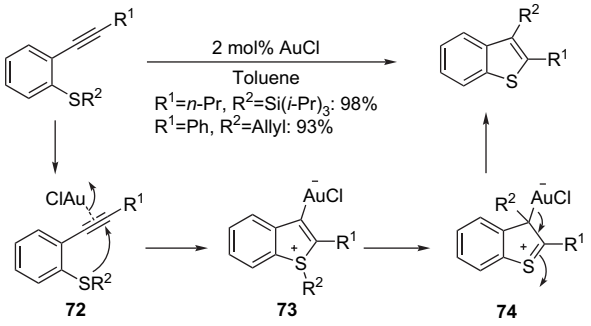


Scheme 28.

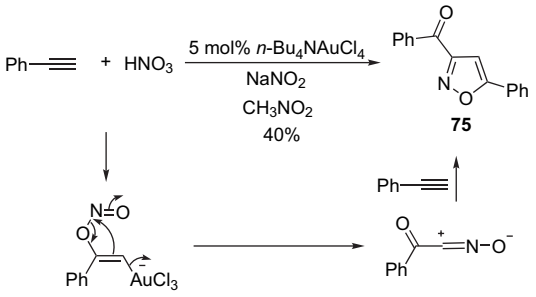
of substrate **86**, the tandem cyclization and ring expansion through an alkyl shift (**87**) allow the formation of bicyclic tetrasubstituted pyrrole **88**.

The gold carbenoid intermediates may also undergo facile oxidation employing diphenyl sulfoxide as the oxidant (Scheme 33).[46] *N*-Heterocyclic carbene gold complex IPrAuCl gives the best results for these reactions. In all cases, oxidation proceeds once gold carbenoid is formed, with no further skeletal rearrangement. For example, Schmidt reaction of compound **89** and triazene cyclization of substrate **91** can be intercepted to give the corresponding carbonyl compounds **90** and **92**, respectively.

Analogous to the azide cyclization, the gold(I)-catalyzed rearrangement of alkynyl sulfoxides takes advantage of the nucleophilicity of sulfoxide oxygen and the latent sulfonium generated in situ as a leaving group.[47] Internal alkyne substrate **93** favors the 6-*endo-dig* cyclization (Scheme 34), whereas 5-*exo-dig* cyclization is preferred for terminal alkyne **96** (Scheme 35). The resulting carbenoid intermediates in both cases (**94** and **97**) undergo a C–H insertion with the phenyl moiety to yield bicyclic structures **95** and **98**, respectively.



Scheme 29.



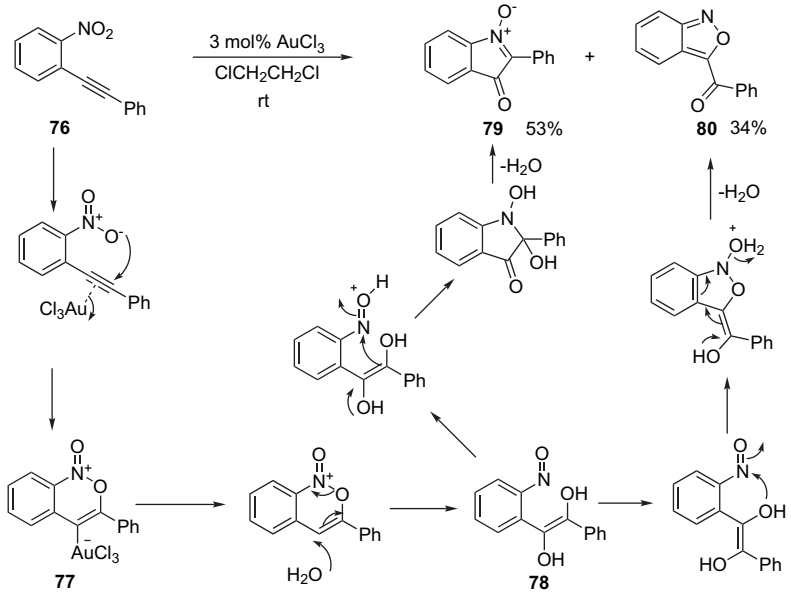
Scheme 30.

2.2. Heteroatom addition to allenes

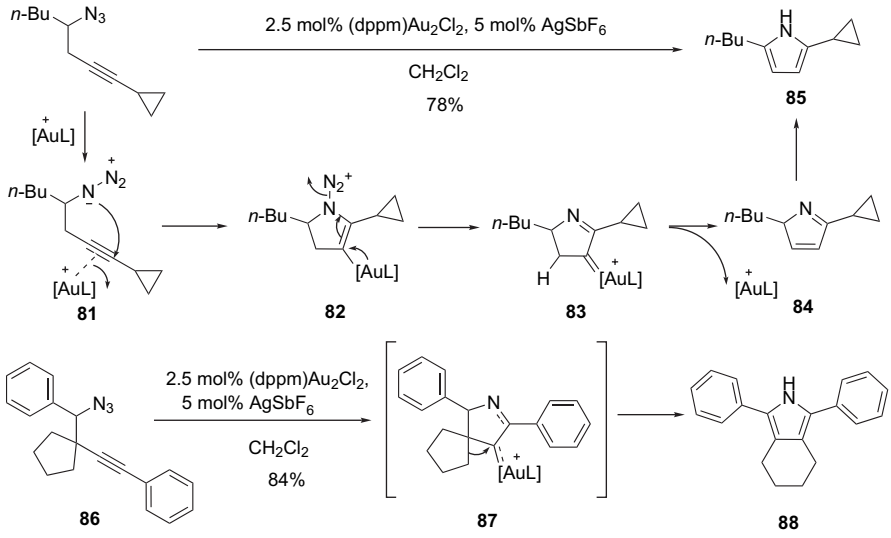
A series of five- and six-membered heterocycle can be constructed using the gold-catalyzed annulation of allenes with pendant nucleophiles including alcohols,[48–51] esters,[52,53] ketones,[54] thiols,[55] amines,[56] sulfonamides,[57] amides,[58] and enamines[59] formed in situ (Scheme 36). In the cyclization of substrate **99**, an interesting product selectivity dependence on the gold catalyst oxidation state was observed (Scheme 37).[60] While $AuCl_3$ favors the formation of 3-bromofuran **101** likely initiated by the activation of the carbonyl group (**100**), the lower oxidation state catalyst Et_3PAuCl interacts with allene preferentially to trigger the carbonyl oxygen cyclization (**102**) leading to **103**.

While Yamamoto showed that the axial chirality of allenes could be transferred to the tetrahedral chirality of products via gold-catalyzed hydroamination of allenes (Ref. 57, Scheme 36), Toste and co-workers[61] and Widenhofer and Zhang[62] independently reported gold(I)-catalyzed intramolecular enantioselective hydroamination and hydroalkoxylation of allenes (Scheme 38). Both groups utilized chiral dinuclear gold–phosphine complexes to obtain excellent enantioselectivity.

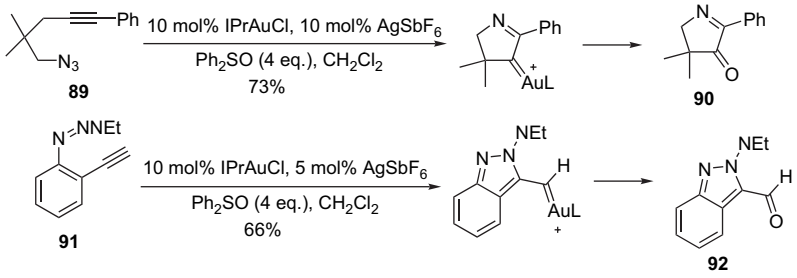
As one exceedingly rare example of a dynamic kinetic asymmetric transformation (DYKAT) involving axially chiral



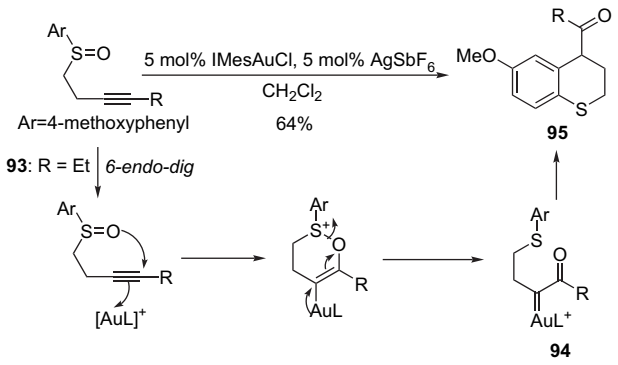
Scheme 31.



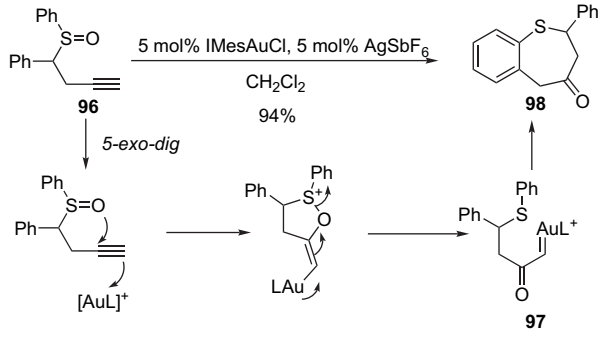
Scheme 32.



Scheme 33.



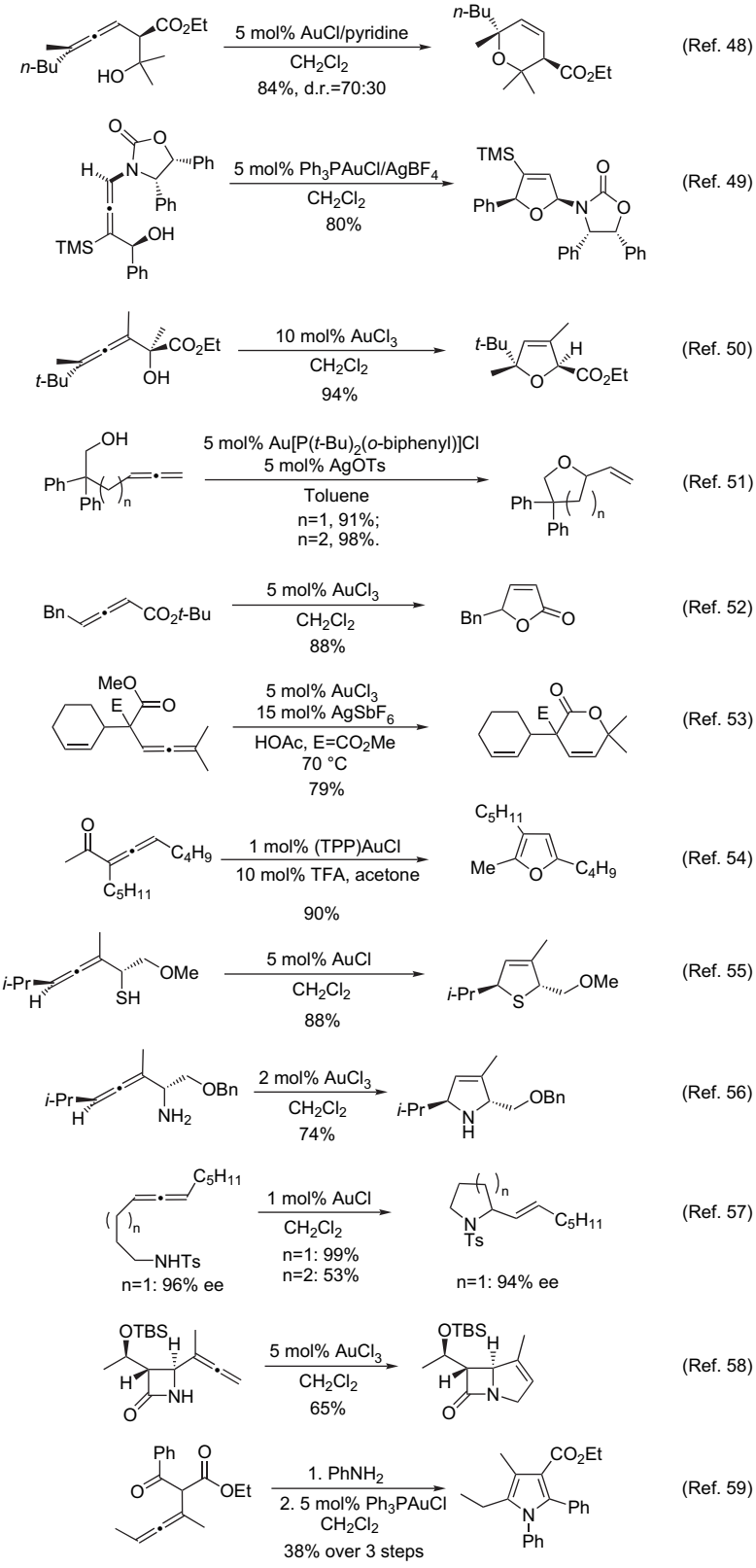
Scheme 34.



Scheme 35.

allenes, Widenhoefer demonstrated a novel enantioselective dynamic kinetic hydroamination of racemic allenes (Scheme 39).[63] This reaction worked well with trisubstituted allenes, which may slow down the C–N bond formation with respect to rapid allene racemization.

Despite limited success in gold-catalyzed enantioselective transformations, a recent milestone work of Toste and coworkers depicted a powerful chiral counterion strategy, which could potentially expand the scope of asymmetric gold catalysis.[64] They envisioned that chiral anionic counterions such as phosphate **106**, paired with cationic metal catalysts could provide a chiral environment for asymmetric transformations. The effectiveness of this strategy has been demonstrated in the intramolecular hydroalkoxylation, hydroamination, and hydrocarboxylation reactions (Scheme 40). There was a pronounced solvent polarity effect on the ee of the reaction, with the less polar solvent such as benzene giving higher ee. Dinuclear gold complex containing bis(diphenylphosphinomethane) (dppm) was adopted for the cyclization of substrate **105** and offered the best ee. Another interesting approach is to combine chiral gold–phosphine cations and chiral phosphate anions, which leads to the observation of dramatic matched and mismatched pairing effects on the asymmetric induction, as demonstrated in the transformation of allenyl acid **107** to lactone **109**. Clearly,

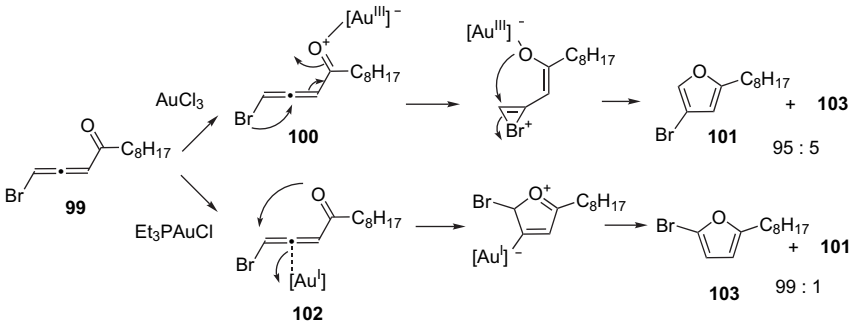


Scheme 36.

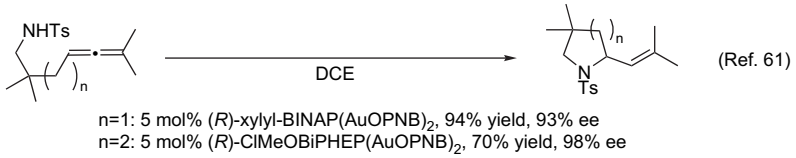
synergistic effects were obtained with proper matching of ligand and counterion. This strategy can be potentially applied to a wide range of metal cation-catalyzed asymmetric transformations.

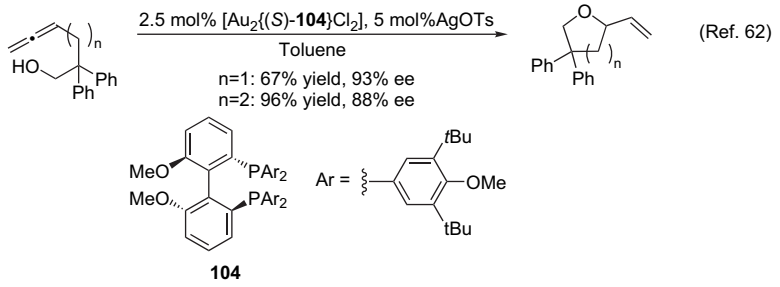
2.3. Heteroatom addition to alkenes

The gold(I)-catalyzed addition of 1,3-dicarbonyl compound to an unactivated alkene was recently reported by Che and

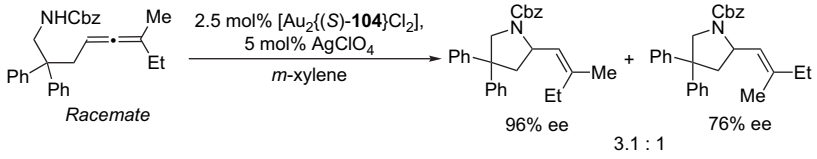


Scheme 37.





Scheme 38.

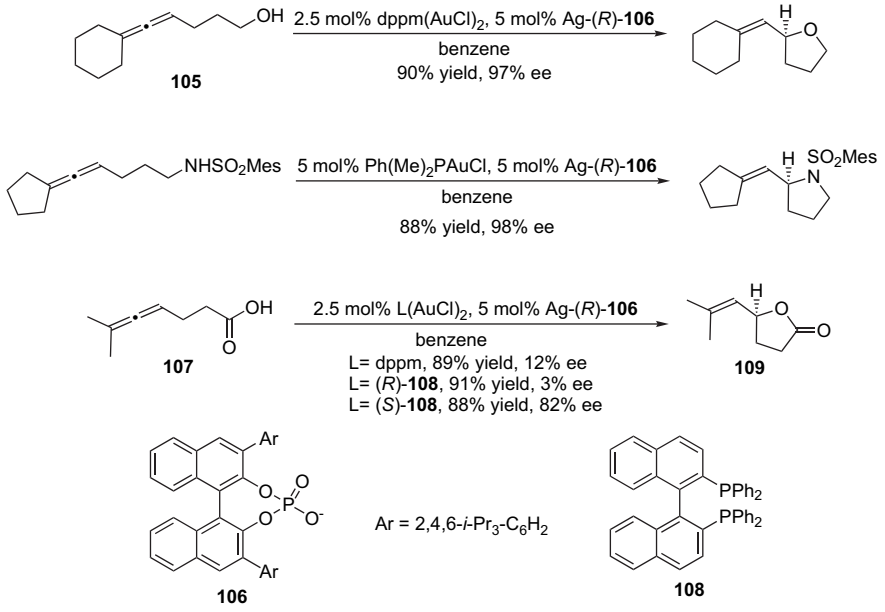


Scheme 39.

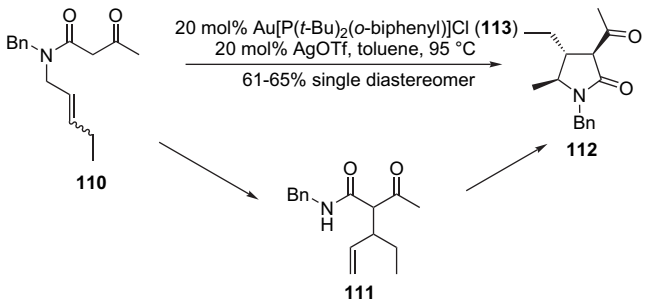
Zhou (Scheme 41).[65] They found that β-ketoamide **110** gave highly functionalized lactam **112** with excellent diastereoselectivity using sterically bulky phosphine ligand **113**. Interestingly, both *cis*-**110** and *trans*-**110** olefin isomers afford the same product **112** as a single diastereomer, which can be explained by invoking the initial Claisen rearrangement to give the same intermediate **111**, which then lead to the product via a gold-catalyzed hydroamination.

Li and Skouta disclosed a novel approach to isoflavanones (**116**)[66] and azaisoflavanones (**119**) with potential biological significance (Scheme 42).[67] Starting with aryl-substituted alkynes **115** and **118**, and 2-hydroxybenzaldehyde **114** and 2-tosylaminobenzaldehyde **117**, this type of reaction allows rapid assembly of the requisite heterocycles incorporating all atoms of the starting material with 100% theoretical atom economy in the presence of 1 mol % of AuCN and 25–50 mol % of PBu_3. Unfortunately, alkyl-substituted terminal alkynes fail to react under the reaction conditions. The proposed mechanism invokes a C–H activation of aldehyde **114** followed by its addition to an alkyne. The subsequent 1,4-addition of pendant nucleophile to the resulting enone in intermediate **120** may also be promoted by the gold catalyst (Scheme 43).

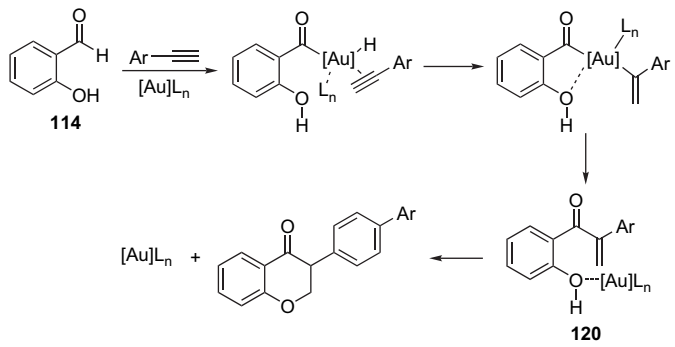
Hydroamination of unactivated olefin remains a challenge in organic synthesis. He and co-workers discovered that both inter- and intramolecular hydroamination in the presence of gold catalysts proceeded with sulfonamides (Scheme 44).[68] Amines and anilines, however, failed to react under the given conditions. The double deuterium-labeled substrate **121** gave products **122** and **123**, demonstrating that the nucleophile presumably attacks from the opposite face of a gold(I)–alkene complex affording a trans-addition product (Scheme 45). Similar gold-catalyzed intramolecular hydroamination of carbamates[69] and amides,[70] and addition of alcohols to olefin[71] were also reported. Subsequently, Widenhoefer reported



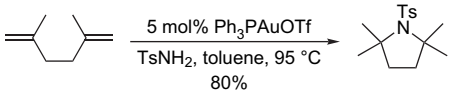
Scheme 40.



Scheme 41.

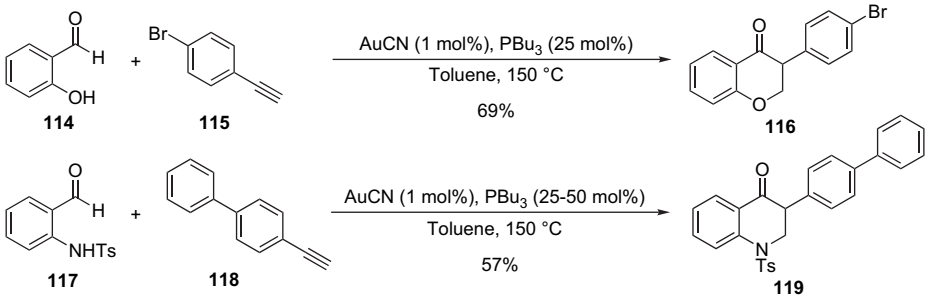


Scheme 43.

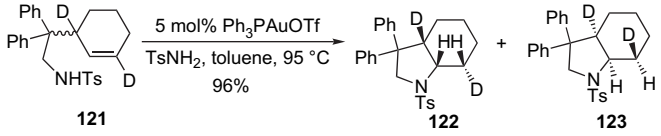


Scheme 44.

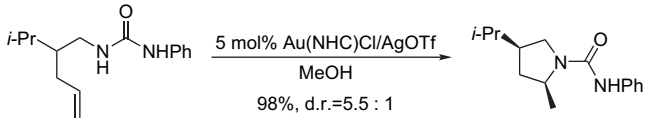
a room temperature hydroamination reaction of *N*-alkenyl ureas using gold complex bearing an electron-rich and bulky *N*-heterocyclic carbene ligand (Scheme 46).[72] The mechanistic details of hydroamination of alkenes were later studied by density functional theory combined with polarizable continuum models to reveal a striking role of counterion-assisted proton shuttling process.[73] In addition to metal triflate-catalyzed processes, Hartwig reported that hydroamination and hydroalkoxylation could also be catalyzed by triflic acid.[74] The comparable reaction rates and product regiochemistry posed a question whether the addition of weakly basic substrates with N–H and O–H bonds to alkenes was catalyzed by gold triflate alone or by the protic acid generated in situ.



Scheme 42.



Scheme 45.

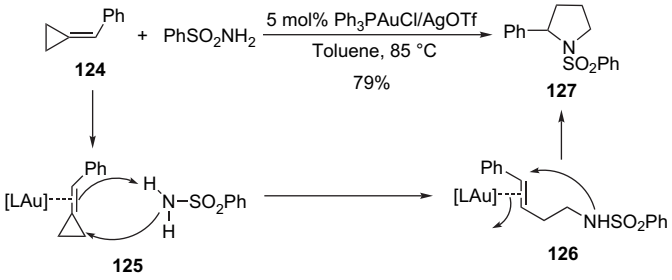


Scheme 46.

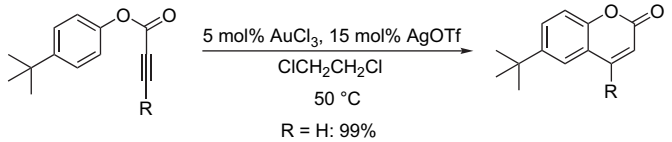
Shi and co-workers took advantage of the hydroamination reaction of gold-activated methylenecyclopropane **124** to accomplish the synthesis of pyrrolidine **127** (Scheme 47). The authors attributed the product formation to a domino ring-opening (**125**) and ring-closing sequence (**126**), both of which were presumably facilitated by gold activation.[75]

3. Hydroarylation

The hydroarylation of gold-activated alkynes, allenes, and alkenes can be characterized as Friedel–Crafts reaction mechanistically. In these cases, an electron-rich aromatic system, is more prone to reaction as a nucleophile.



Scheme 47.

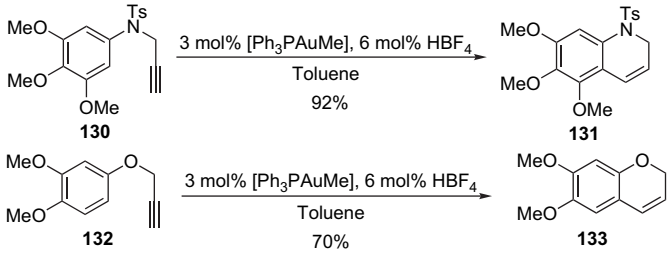


Scheme 48.

3.1. Hydroarylation of alkynes

The intramolecular hydroarylation reactions of aryl alkynoates proceed smoothly to form coumarins using $AuCl_3$/AgOTf (Scheme 48).[76] The intermolecular version of this reaction could be achieved under solvent-free conditions.

The intramolecular hydroarylation of substrate **128** involving an alkyne and an indole moiety was achieved with remarkable regioselectivity. While the gold(I) catalyst **129** favors the 7-*exo-dig* cyclization, the gold(III) catalyst $AuCl_3$ promotes the 8-*endo-dig* cyclization (Scheme 49).[77] With *N*-propargyl *N*-tosylaniline **130** or *O*-propargyl aryl ether **132**, the 6-*endo-trig* cyclization reactions are preferred to give 1,2-dihydroquinoline **131** and chromene **133**, respectively (Scheme 50).[78]

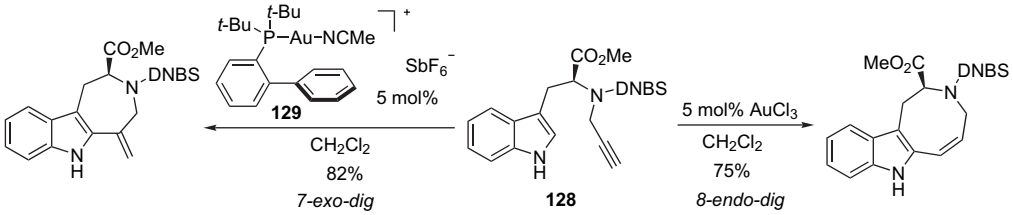


Scheme 50.

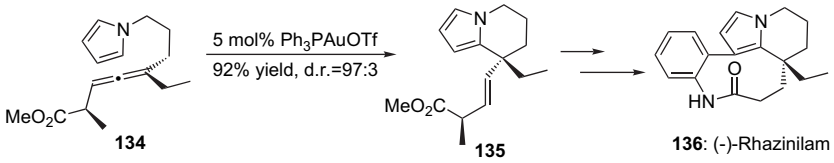
3.2. Hydroarylation of allenes

The gold-catalyzed reactions were incorporated as the key steps leading to several natural products. One example is the enantioselective total synthesis of (−)-rhazinilam (**136**) by Nelson and co-workers, in which a gold(I)-catalyzed annulation of pyrrole with allene in substrate **134** established a chiral quaternary center with excellent transfer of chirality to intermediate **135** (Scheme 51).[79] In contrast, $(CH_3CN)_2PdCl_2$ gave the cyclization product with a very moderate diastereoselectivity. The presence of the pendant ester group may direct the coordination of gold catalyst from one π face of allene, thus the nucleophilic attack occurred from the opposite face and established the desired stereochemistry. Moreover, Widenhofer and Liu conducted an asymmetric gold(I)-catalyzed intramolecular hydroarylation of allenes with indoles using chiral phosphine ligand and dinuclear gold complex (Scheme 52).[80] Both six- and seven-membered ring can be formed with good enantioselectivity.

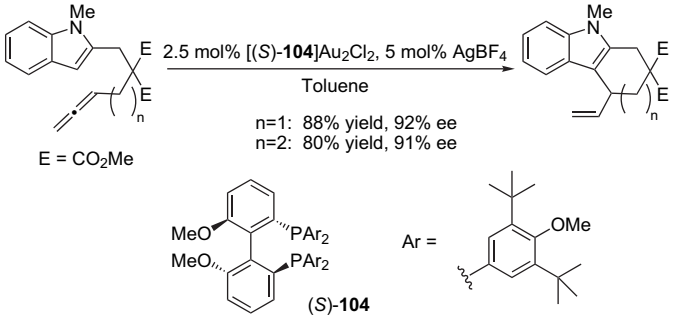
The gold-catalyzed hydroarylation of allenic aniline **137** was highly regioselective to generate dihydroquinoline **139**



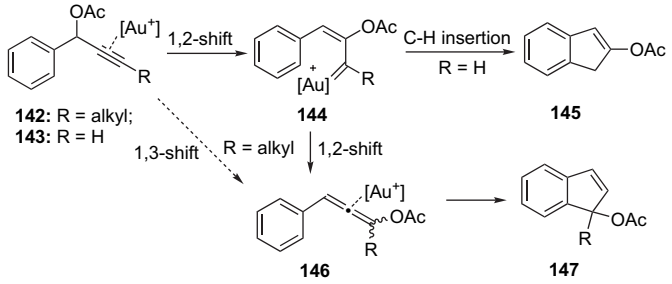
Scheme 49.



Scheme 51.

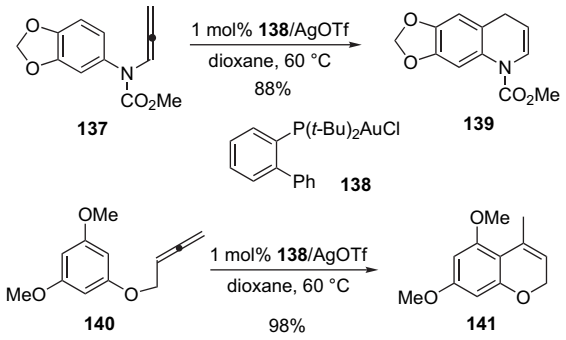


Scheme 52.



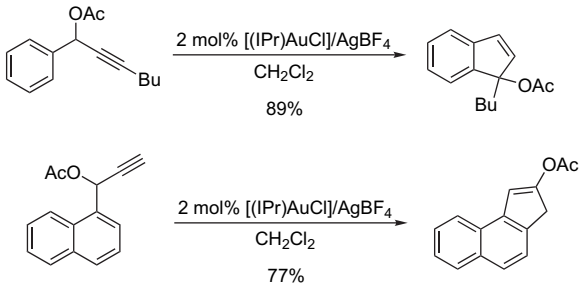
Scheme 55.

(Scheme 53),[81] which could be further converted to quinoline using Pd/C in the presence of oxygen. Under the same reaction conditions, phenol allenyl ether **140** led to the formation of chromene **141**.



Scheme 53.

The heterocyclic carbene gold complex can catalyze tandem processes of [3,3] rearrangement and intramolecular hydroarylation of allene intermediates to form substituted indenes (Scheme 54).[82] This remarkably efficient reaction is typically complete within 5 min at rt. With internal alkyne substrate **142**, a sequential 1,2-shift rather than a 1,3-shift as supported by a recent computational study,[83] leads to aryl allene intermediate **146**, which is followed by a gold-promoted hydroarylation to form indene **147**. With terminal alkyne substrate **143**, after one 1,2-shift, a C–H insertion of intermediate **144** occurs to furnish the indene product **145** (Scheme 55).



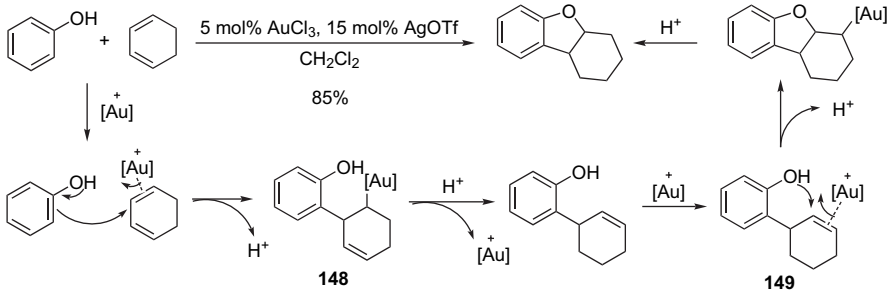
Scheme 54.

3.3. Hydroarylation of alkenes

A highly efficient gold-catalyzed annulation of phenols with dienes to construct tricyclic scaffolds was reported by Li and co-workers (Scheme 56).[84] The reaction contains two gold-catalyzed processes including a Friedel–Crafts reaction (hydroarylation of a diene) to form intermediate **148**, and a subsequent hydrophenoxylation of intermediate **149**.

4. Conclusion

The homogeneous gold catalysis represents a new frontier in organic synthesis as numerous novel reactions have been discovered. Understanding the mechanism of these reactions has enabled the discovery of unprecedented reaction modes. The utility of these methods has been demonstrated in various heterocycle and carbocycle syntheses. These reactions are all based upon a common platform, namely, the activation of alkynes, allenes, and sometimes alkenes by the gold species. The gold-catalyzed transformations are convenient, and often accomplished under remarkably mild conditions. In addition to high level control of chemo-, regio-, and diastereoselectivity of many reactions, highly enantioselective gold catalysis has also emerged. Finally, the broad substrate scope and diverse product scaffolds of these reactions will undoubtly increase their impact on medicinal chemistry and natural product synthesis.



Scheme 56.

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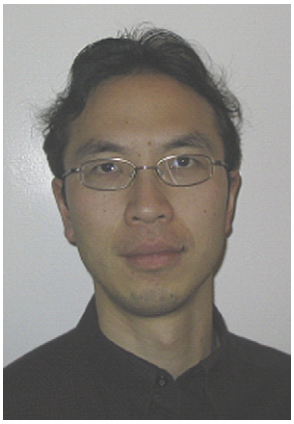
Biographical sketch



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 guidance of Professor Yunhua Ye. Hong Shen subsequently moved to University of Minnesota, where he developed a formal [3+3] cycloaddition under the direction of 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 having his Ph.D. degree in 2003, Hong Shen became a medicinal chemist at Merck Research Laboratories, Rahway, New Jersey. He is currently a research fellow working on the discovery of novel drugs for the treatment of cardiovascular and metabolic diseases. He has authored over 24 papers and 8 patents.