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Gold-catalyzed cyclopropanation reactions by carbenoid precursor toolbox

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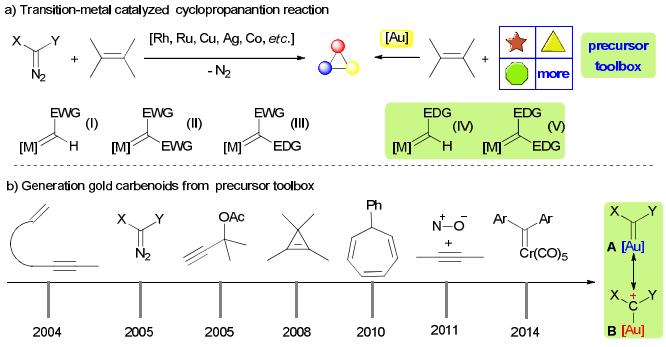
Homogenous gold-catalyzed cyclopropanation has emerged as a powerful method in organic synthesis due to its rich chemistry and fascinating reactivity. This thriving strategy is remarkable for its mild conditions, good selectivity, and high efficiency, which provides complementarity and orthogonality to traditional metal-catalyzed cyclopropanation. This review summarizes recent advances in gold-catalyzed cyclopropanation divided by the type of carbenoid precursors. Besides commonly used *diazo compounds*, current approaches enable readily available *enynes*, *propargyl esters*, *cyclopropenes*, *cycloheptatrienes*, *alkynes*, *and sulfonium ylides* as safer surrogates in the realm of gold carbenoid chemistry. Meanwhile, these reactions allow for the rapid building of molecular complexity including synthetically useful and intricate cyclic, heterocyclic, and polycyclic skeletons. The combination of the new reactivity of gold complexes with their capability to catalyze cyclopropanations may lead to myriad opportunities for the design of new reactions. Furthermore, the synthetic utilities of such superior methods have also been illustrated by selected natural and biologically interesting product total syntheses and the asymmetric formation of challenging target molecules.

1. Introduction

Cyclopropane is the smallest carbocycle with unique properties and reactivities.[1] This structural unit is tremendously important because of its wide occurrence in bioactive natural products and pharmaceuticals, use as conformationally restricted biological probes, and due to their versatility in organic synthesis as building blocks.[2] Among those methods to cyclopropanes, the transition-metal catalyzed selective cyclopropanation of olefins is straightforward and efficient.[3] Although rhodium represents the most commonly used transition metal for those cyclopropanations *via* decomposition of diazo compounds, the air and moisture stability of gold complexes currently makes them particularly appealing catalysts for effective cyclopropanations using diverse precursors (precursor toolbox, Scheme 1), which brings new "gold rush" for reactivity discovery.

Over the past decade, homogeneous gold catalysis,[4] including enantioselective gold catalysis,[5] has experienced explosive development from little known "ugly duckling" to now a "beautiful golden swan" in organic synthesis due to its rich chemistry and fascinating reactivity. Gold carbenoids, *i.e.*, gold carbenes **A** or gold-stabilized carbocations **B**, in these transformations are usually proposed as key reactive intermediates, which can undergo various synthetically challenging yet highly valuable transformations such as C–H insertion, ylide formation, and cyclopropanation reactions.[4-6] Significantly, these transformations offer enhancement of molecular complexity and diversity from simple molecules, which are often accompanied by high degrees of chemo-, regio-, diastereo-, and enantioselectivity. In particular, cyclopropanation, the standard reference reaction, has been used to evaluate new catalysts system.

In general, the reactivity profile of metallocarbenes is dependent on the metallocarbene structure,[3] which has led to the classification of these metallocarbenes according to the substituents



Scheme 1 Transition-metal catalyzed cyclopropanantion reaction. X, Y = EWG (acceptor group), EDG (donor group).

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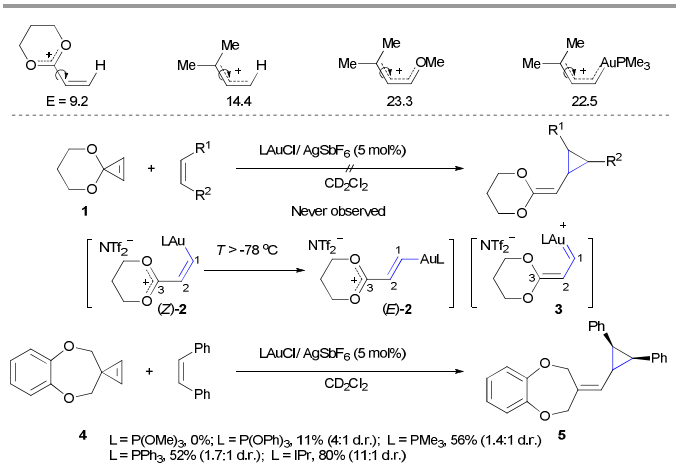
adorning the carbene. Thus, olefin cyclopropanations with metallocarbenes can be divided into three major groups: acceptor (I), acceptor/ acceptor (II), and donor/acceptor (III), as illustrated in Scheme 1. The dediazotization of diazo compounds is a common method in the generation of metal carbenes, but some diazo reagents are shock-sensitive, especially those without acceptor groups as stabilized elements. Therefore, cyclopropanation of olefins with metallocarbenes derived from donor- (IV) and donor/donor-diazo (V) species is much more challenging and has not been investigated much before and there are few successful examples.[3] In contrast, the precursor toolbox of gold offer a golden entry to new types of both metal-stabilized acceptor and donor carbenoids, which broaden the range of synthetic cyclopropanations available for these useful intermediates. Moreover, gold catalyzed cyclopropanation is notable for its mild conditions, good selectivity, and high efficiency, which provides complementarity and orthogonality to traditional metal-catalyzed cyclopropanation systems (*e.g.*, Rh chemistry). Additionally, the initial products of these reactions are often themselves highly reactive and can engage in cascade sequences that lead to the rapid construction of complex products. In this review, we focus on the stereoselective cyclopropanation reactions *via* gold carbenoids, which are generated from diverse precursors: 1) 1,*n*-enynes *via* cycloisomerization reaction, 2) diazo compounds *via* gold-catalyzed decomposition, 3) propargyl esters initiated by acyloxy migration reaction, 4) the cyclopropenes *via* gold-catalyzed ring-opening, 5) 1,3,5-cycloheptatrienes *via* the retro-Buchner reaction, 6) alkynes *via* oxidation/nitrene transfer reactions (Scheme 1). In addition, the latest model of gold-catalyzed cyclopropanation reaction by sulfonium ylides is also discussed.

Undoubtedly, the methodologies highlighted in this review could become a highly versatile tool for obtaining cyclopropanation products that cannot be easily attained by other methods. We hope this review will serve as a handy reference for chemists interested in using gold catalysis in organic synthesis and those interested in discovering new types of cyclopropanation reactions.

2. Nature of the Gold Carbenoid

Generally, reactions of olefins with metallocarbenes are the principle and most reliable strategy to access cyclopropane structures.[3] The "push–pull" dual reactivity of gold complexes



Scheme 2 Cyclopropanation based on theoretical and experimental studies.

renders them versatile species for alkene cyclopropanation, because it allows the use of gold-carbenoid-type reactivity.[4-6] Despite the early debut of gold carbenoids, the direct proof of the existence of such an intermediate is largely missing and mostly relies on indirect evidence and computational data.[6-9] Theoretical investigations and experimental observations have polarized the discussion surrounding the carbene (**A**) or cationic (**B**) character of organogold species, mostly in support of their carbocationic character.[6-9] However, gold complexes and salts have been applied successfully to perform cyclopropanation reactions that are traditionally carried out with carbenic systems. Unlike traditional metal carbene chemistry, the cyclopropanation can occur both in a concerted or stepwise fashion depending on the substrates and gold species.

In 2008, Fürstner and co-workers took advantage of the ring-opening of cyclopropenone acetals such as **1** to generate related organogold species.[7] The observed data by NMR spectroscopy pointed towards a high degree of double bond character for the C1–C2 bond, and not the C2–C3 bond, in the organogold species (*e.g.*, **2**), with a marginal contribution of the carbene form **3**. Furthermore, an in-depth theoretical analysis of the bond rotation energy for different carbocations demonstrates that LAu has a similar stabilizing effect as methoxy group on an allyl carbocation.[6c] The bond length between gold and the carbene carbon decreased with stronger

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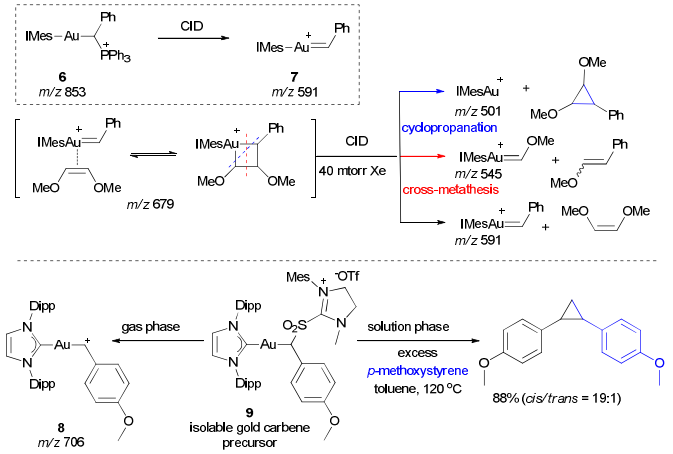
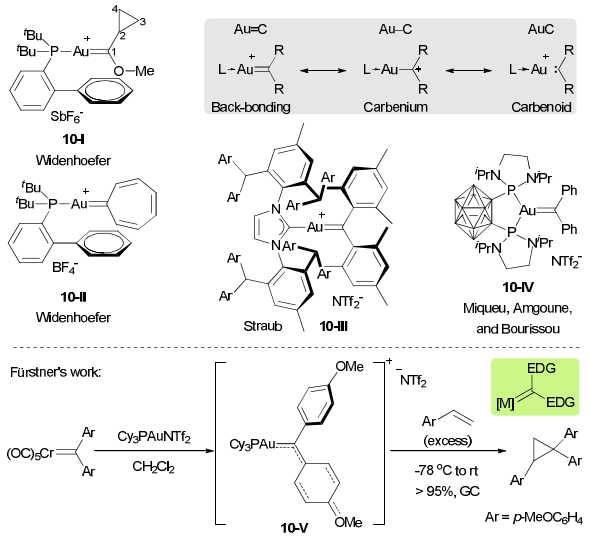
Prof. Junliang Zhang obtained his PhD from the Chinese Academy of Sciences in 2002 under the supervision of Prof. Shengming Ma. Then he worked as a postdoctoral fellow successively in University of Cologne (Humboldt Fellowship) and then University of Chicago. In 2006, he joined East China Normal University as a full professor. His research interests include developing novel synthetic methodology, asymmetric catalysis. He has published more than 80 papers and three book chapters.

σ-donating ligands such as chloride or *N*-heterocyclic carbenes and increased with less donating, π-acidic ligands such as phosphines or phosphites by reducing the back-donation to the substrate. This study suggests that the character of the organogold(I) species lies on a continuum between carbenes **A** and cations **B**, depending on the particular substitution patterns and the ligands on gold. Toste *et al.* examined experimentally the impact of cationic versus carbene-like species on the reactivity in olefin cyclopropanation. In the presence of an olefin and a cationic gold(I) catalyst, cyclopropenone acetal **1** did not provide any cyclopropanation product, which is in agreement with the fact that the organogold species generated by ring-opening of **1** should instead react as a gold-stabilized carbocation due to the cationic intermediate stabilized by the oxygen atoms. In contrast, cyclopropene **4** could indeed react with *cis*-stilbene leading to the cyclopropane product, but the yield and the diastereoselectivity were highly dependent on the ancillary ligand. As anticipated from the structural studies, π-acidic phosphites that increase cation-like reactivity gave little or none of the cyclopropanation product **5**. Conversely, the strong σ-donor and weak π-acceptor *N*-heterocyclic carbene IPr was indeed as anticipated to give an organogold with a higher carbene-like reactivity which favors olefin cyclopropanation (Scheme 2, bottom).



Scheme 3 Gas- and solution-phase studies for gold-catalyzed cyclopropanation. CID = collision-induced dissociation. IMes = 1,3-bis(2,4,6-trimethylphenyl) imidazol-2-ylidene. Dipp = 2,6-diisopropylphenyl.

Chen and co-workers examined reactivity of gold carbenoid **7** from gold benzylidene precursor **6** with *cis*-1,2-dimethoxyethylene and *cis*-3-hexene (Scheme 3, top).[8a] The typical reactions associated with metal carbenoids such as cyclopropanation and metathesis are observed, indicating the carbene nature of **7** and hence meaningful back donation by the gold center. Hammett correlations suggest that the resonance form **6** significantly contributes to the ground-state structure, although a final conclusion as to whether the positive charge resides on carbon or on gold (**7**) could not be drawn. In 2013, another elegant example of combined gas- and solution-phase studies for a catalytic cyclopropanation reaction was reported by the same group.[8b] They rationally designed a robust, isolable, and well-defined gold carbene precursor **8**, which is capable of effecting cyclopropanation of *p*-methoxystyrene in a range of different solvents at 120 °C. These studies also revealed that the cyclopropanation of olefins with gold carbenoids, though stereospecific, likely proceed in a stepwise rather than in a concerted manner (Scheme 3, bottom). The observed cyclopropane yields are dependent on the rate of gold carbene formation, which in turn is influenced by the ligand and substituent. By collision-induced dissociation threshold measurements, along with DFT calculations, the donation of electron density to the carbene carbon by the *p*-methoxy benzyl substituent and [NHC] ligand stabilizes the gold carbene intermediate and lowers the dissociation barrier.[8c]



Scheme 4 Isolation of gold carbenoid. Cy = cyclohexyl.

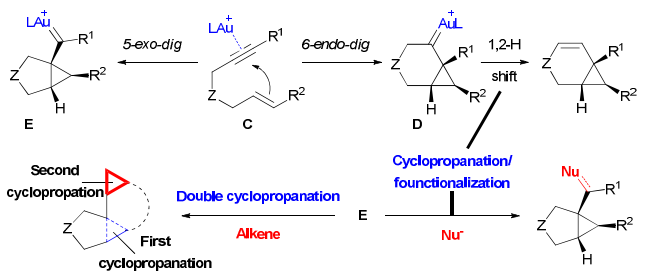
It is complementary and direct evidence that for the existence of a gold(I) carbene species has only very recently been accomplished by the isolation of a Fischer-type gold carbene.[9] As illustrated by Brooner and Widenhoefer,[9b] X-ray analysis of the gold cyclopropyl(methoxy) carbene complex **10-I** and comparison to extant protonated cyclopropyl ketones indicates that electron donation from the LAu fragment to the electron-deficient C1 atom is similar to that provided by a cyclopropyl group (Scheme 4, top). Three examples of non-heteroatom-stabilized complexes have also been reported. In complex **10-II**,[9c] the carbene moiety is incorporated into an aromatic cycloheptatrienylidene framework and is thereby stabilized by π delocalization. In complex **10-III**,[9d] the dimesityl carbene moiety $CMes_2$ is combined with a bulky $[(NHC)Au]^+$ fragment, thus resulting in very strong steric shielding of the gold carbenoid motif. With respect to complex **10-IV**,[9e] enhanced π-backdonation from the $[(DPCb)Au]^+$

(DPCb = *o*-carborane diphosphines) results in a significant contribution from the gold fragment to the stabilization of the carbene center. Inspired by these results, the detection and even isolation of highly reactive gold–carbene complexes with even more pronounced gold–carbene back-bonding seems possible. As a rule of thumb, strong metal–carbene bonds favor alkene metathesis reactions, while weak metal–carbene bonds lead to the cyclopropanation of alkene substrates. For example, transmetalation from chromium to gold allowed the formation of gold carbenoid species **10-V** in crystalline form (Scheme 4, bottom).[9f] The structure in the solid state suggests that there is only little back donation of electron density from gold to the carbene center and hence very modest Au–C double bond character; instead, the organic ligand framework is responsible for stabilizing this species by resonance delocalization of the accumulated positive charge. Complex **10-V** is a close relative of a series of putative gold benzylidene species of type $[ArCHAuL]^+$ (*e.g.*, **8**) that were implicated in cyclopropanation reactions of various olefins. Indeed, **10-V** is capable of cyclopropanating *p*-methoxystyrene even at low temperature, the discussion of its structure is deemed relevant for a better understanding of the mechanisms of π-acid catalysis in general.

3. 1,*n*-Enynes *via* Cyclization

The π-acidic carbophilic gold, coupled with its ability to stabilize carbocation intermediates, is an especially useful catalyst in cycloisomerization reactions.[4j] Pioneering work from the group of Echavarren on cationic gold(I) catalysts in this field opened the way to a number of highly powerful synthetic methods and applications in organic syntehesis.[10] 1,*n*-Enynes undergo a variety of skeletal rearrangements in the presence of gold catalysts rather than the common observed Alder-ene type rearrangements under the catalysis of palladium and rhodium complexes. These skeletal rearrangements often share the formal cyclopropanation step *via* the *endo*/ *exo-dig* cyclizations of 1,*n*-enynes (*e.g.*, 1,6-enynes) to form cyclopropyl gold(I) carbene-like intermediates **D** or **E** (Scheme 5).[4j,11] The mechanism is thought to proceed by initial η-coordination of the gold to the alkyne followed by the cyclopropanation, leading to reactive gold-carbenes **D** or **E,** which can undergo further diverse transformations. For example, gold-carbenes **D** can afford bicyclo[4.1.0]heptanes *via* a 1,2-hydride shift. On the other hand, intermediates **E** can be trapped by nucleophiles to generate functionalized bicyclic products. Alternatively, a second cyclopropanation process can take place when another intramolecular alkene moiety is at suitable position or external alkene exists.

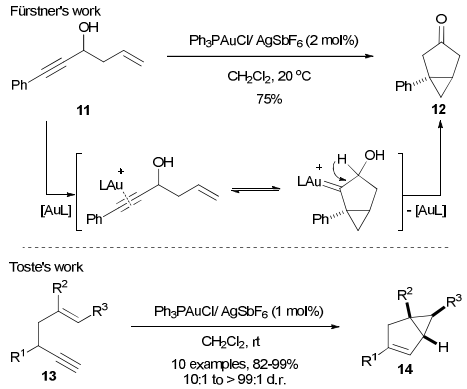
So far, many aspects of gold-catalyzed cycloisomerization reactions have already been highlighted by Echavarren,[4j,11a] Zhang,[11b] Toste,[11c] and others,[11d-f] including mechanistic and asymmetric aspects of the reaction. To avoid the overlap, this review will endeavor to survey recent representative advance for the synthesis of intricate cyclopropane scaffolds in this area except some typical examples.



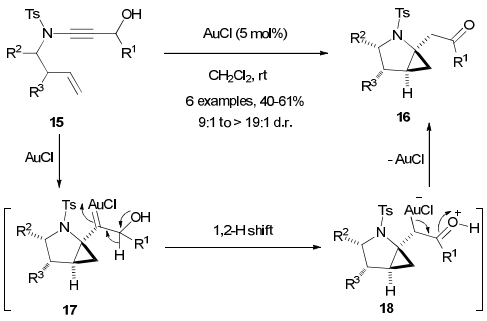
Scheme 5 Gold-catalyzed 1,*n*-Enyne cycloisomerization reaction.

3.1 Cascade Reactions Initiated by Cyclopropanation

In 2004, Fürstner[12] and Toste[13a] reported the first cationic gold(I)-catalyzed cycloisomerizations of 1,5-enynes to [3.1.0]bicyclic products (Scheme 6). During the course of Pt(II)-catalyzed cycloisomerization reaction of hydroxylated 1,5-enyne **11**, Fürstner found that $Ph_3PAuCl/AgSbF_6$ was also efficient to catalyze this reaction, leading to cyclic ketones **12**.[12] Toste immediately demonstrated that the catalytic activity of cationic gold complex was superior to that of platinum.[13a] In the presence of gold(I) catalyst, a highly efficient *endo-dig* cyclization takes place with a variety of substrates even if the 1,5-enynes do not contain any heteroatom in the tether between two unsaturated bonds (*e.g.*, **13**). In the course of investigating a related cycloisomerization of 6-siloxy-1,5-enynes to form cyclohexadienes, Kozmin also disclosed that AuCl could catalyze the formation of [3.1.0]bicycles from 1,5-enynes.[13b]



Scheme 6 Gold(I)-catalyzed cycloisomerization of 1,5-enynes to [3.1.0]bicyclic products.

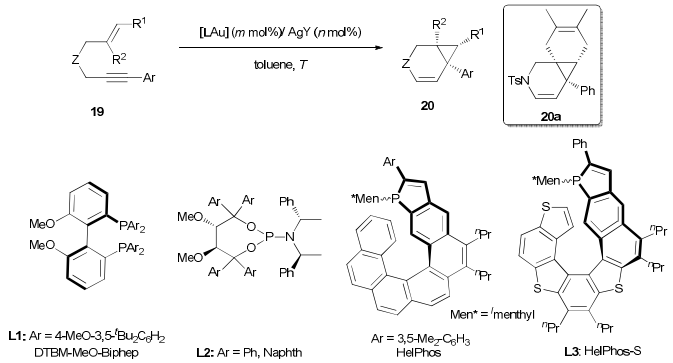


Scheme 7 Gold-catalyzed cycloisomerizations of 1,6-ene-ynamides.

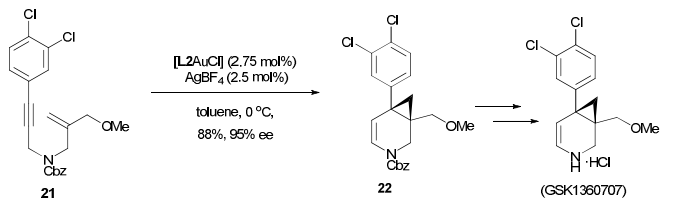
In 2009, Couty, Meyer and Cossy reported an interesting gold-catalyzed cycloisomerization of 1,6-ene-ynamides having a propargylic alcohol moiety to 2-aza-bicyclo[3.1.0]hexane derivatives **16** with high diastereoselectivities.[14] By analogy with the behavior of the non-heterosubstituted 1,5-enyne **11**, the corresponding cyclopropyl gold carbenes **17** could also undergo a rapid 1,2-hydride shift leading, after demetalation, to the desired products bearing a carbonyl subunit (Scheme 7).

Recently, Michelet and co-workers have developed an enantioselective gold(I)-catalyzed cyclopropanation reaction of 1,6-enynes *via* cycloisomerization.[15] In this case, bimetallic gold(I) complexes derived from chiral ligand (*R*)-4-MeO-3,5-di-tert-butyl-Biphep (**L1**) as catalyst in toluene at room temperature provided enantioenriched bicyclo[4.1.0]heptenes **20** (Table 1). Although high enantioselectivities were obtained, the yields were not good with only two examples above 60%. Noteworthy, the acyclic TADDOL derived phosphoramidites **L2**, developed by Fürstner group, also proved competent in the cycloisomerization of a range of enynes.[16] Direct application of TADDOL-phosphoramidite-AuCl complex to the synthesis of the important antidepressive GSK136070721 was finally highlighted, *via* stereoselective cycloisomerization of enyne **21**

Table 1 Gold-catalyzed asymmetric cyclopropanation of 1,6-enynes



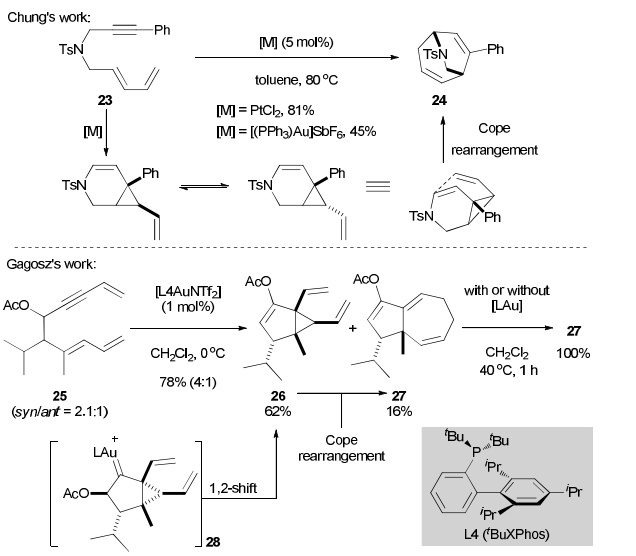
[LAu] (*m*)	AgY (*n*)	Z	Yield (%)	*ee* (%)
[**L1**$(AuCl)_2$] (3) *ref.* 15, 2009	AgOTf or $AgNTf_2$ (6)	NTs, O; 13 examples	8-64	13-99
[**L2**AuCl] (5.5) *ref.* 16, 2010	$AgBF_4$ or $AgNTf_2$ (5)	NTs, NMs, NCbz, NCO_2Me, O; 11examples	53-94	38-98
[HelPhosAuCl] (4) *ref.* 17*a*, 2014	$AgBF_4$ (4)	NTs (Ar = Ph, R^1 = R^2 = H)	95	84
[**L3**AuCl] (4) *ref.* 17*b*, 2014	$AgNTf_2$ (4)	NTs (**20a**)	91	93



Scheme 8 Gold-catalyzed asymmetric cyclopropanation for synthesis of GSK136070721.

(Scheme 8).[16*c*] Most recently, Voituriez, Marinetti and co-workers designed a new type of phosphahelicene series, so called "HelPhos" and "HelPhos-S" (**L3**) ligands to achieve both high catalytic activity and good enantiomeric excesses.[17]

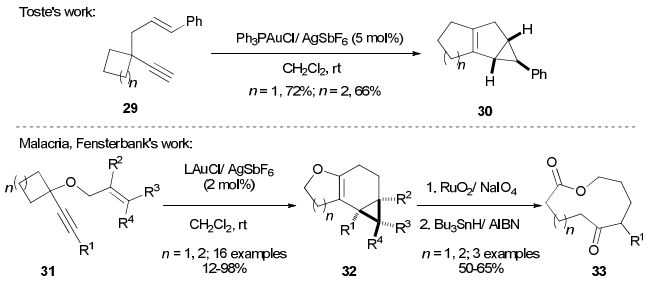
Introduction of a vinylcyclopropane (VCP) group is a very commonly used strategy for rendering the [3,3]-sigmatropic rearrangement, *i.e.*, Cope rearrangement, available. Enyne isomerizations with electrophilic metal catalysts allows the in situ generation of divinyl cylclopropanes. For example, treatment of dienyne **23** with catalytic $PtCl_2$ or $[(PPh_3)Au]SbF_6$ led to isolation of the bicyclo[3.2.2]nonadiene **24** (Scheme 9, top).[18*a*] Another example comes from the group of Gagosz who successfully realized a gold(I)-catalyzed tandem cycloisomerization/Cope rearrangement process which allows the formation of complex polycyclic frameworks from easily accessible linear trienyne substrates (Scheme 9, bottom).[18*b*] The resulting bicyclic compounds (*e.g.*, **27**) possess the basic structure found in a series of natural products with interesting biological activities. It should be noted that while **25** was used as a mixture of *syn* and *anti* isomers, only a single *trans* isomer **27** was obtained. In this case, a 1,2-OAc shift occurred during the cycloisomerization step to intermediately produce the cyclopropanated compound **26**. Furthermore, the control experiment indicates that the gold complex is not involved in the Cope rearrangement.



Scheme 9 Gold(I)-catalyzed tandem cycloisomerization/Cope rearrangement.

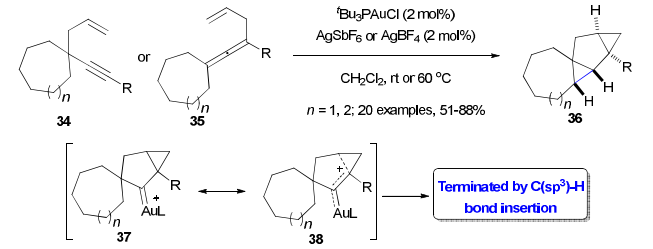
In the absence of β-hydrogen for the 1,2-hydride shift, the gold-carbenoid would undergo diverse transformations, *e*.g., ring expansion. In 2004, Toste and co-workers found that substrates **29** undergo cyclopropanation concomitant with ring expansion to form the tricyclic compound **30** (Scheme 10, top).[13*a*] In a similar vein, Malacria, Fensterbank and co-workers combined the gold-catalyzed cycloisomerization/ring expansion reaction with the $RuO_2/NaIO_4$-oxidation and reductive ring-opening to realize a new strategy for synthesis of macrocyclic

lactones **33** from *O*-tethered 1,6-enynes **31** (Scheme 10, bottom).[19]

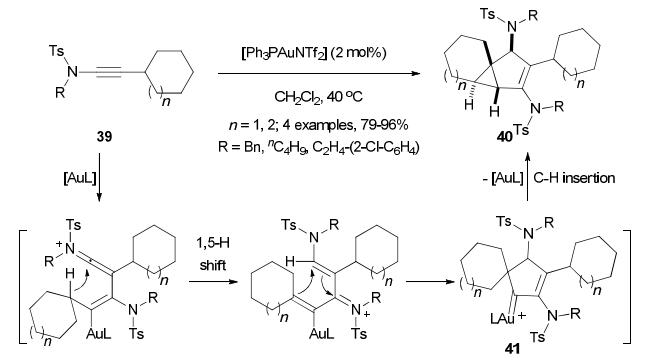


Scheme 10 Gold-catalyzed cascade cyclopropanation/ring expansion of 1,*n*-enynes. L = IPr, JohnPhos: [2-(di-*t*-butylphosphino)biphenyl].

In 2009, Toste and co-workers demonstrated the elegant gold-catalyzed cycloisomerization of a range of diverse 1,5-enynes **34** or 1,4-enallenes **35** for cascade construction of tetracycles **36** in moderate to high yields (Scheme 11).[20a] In this case, gold carbenoid **37**/**38** may involve the insertion of adjacent unreactive C(sp^3)–H bond. Subsequently, D. Zhang *et al.* carried out the DFT calculations[20b] to further identify that the formation of intermediate **37** was the rate-determining step. In addition, theoretical calculations also revealed that the ring-size of the cycloalkyl substitutions was crucial for the success of C(sp^3)–H insertion. If the ring size of cycloalkyl was less than seven, intermediate **37** would undergo ring expansion process rather than C(sp3)–H insertion. Alternatively, for 7- or 8-membered cycloalkyl substituted substrates, the C(sp^3)–H insertion was favored.



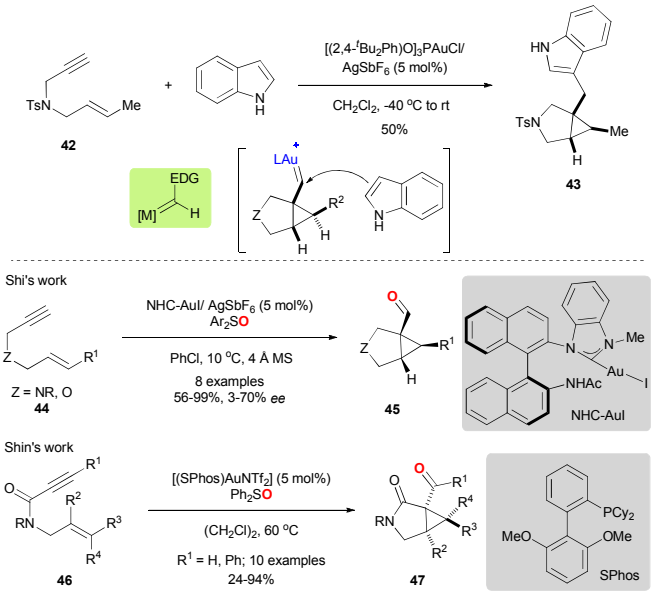
Scheme 11 Gold-catalyzed cascade cycloisomerization/C–H insertion of 1,5-enynes and 1,4-enallenes.



Scheme 12 Gold-catalyzed alkyne dimerization of ynamides.

However, 6-membered cycloalkyl rings could indeed undergo the C–H insertion rather than the ring-expansion in some cases. For instance, in 2011, Gagosz, Skrydstrup and co-workers found that ynamides **39** could play the role of both the electrophilic and nucleophilic partner to produce various nitrogen-containing tricycles **40** in the presence of a gold(I) complex (Scheme 12).[21] In analogy with intermediate **37**/**38**, gold carbenoid **41** was generated by a dimerization, 1,5-hydride shift, and metalla-Nazarov reaction sequence. Then, insertion of the gold carbenoid into a C(sp^3)–H bond of the adjacent spirocycloalkyl fragment would lead to a fused tricyclic product.

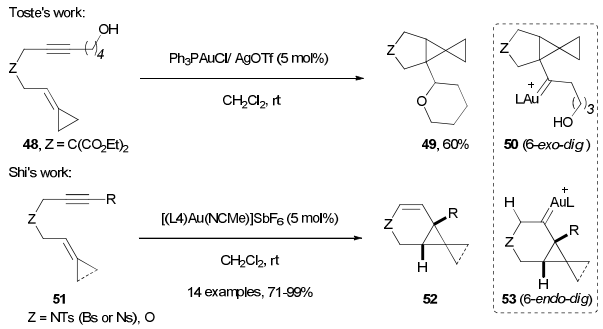
Intermolecular trapping of the proposed cyclopropyl gold carbenoid intermediate with nucleophiles has also been explored. For example, C–H insertion of the indole takes place to give functionalized cyclopropane **43** (Scheme 13, top).[22] In 2007, Toste and co-workers documented the oxidation of gold carbenoid intermediates generated from the cyclosiomerization of 1,6-enynes in the presence of diphenylsulfoxide.[23a] In 2011, Shi *et al.* developed a new class of axially chiral NHC ligands using optically active BINAM as the starting material.[23b] This chiral NHC ligand was successfully applied in the asymmetric gold-catalyzed oxidative rearrangement of 1,6-enynes, for the first time, to give the corresponding cyclopropyl aldehyde products **45** in moderate *ee*. Enantioselectivities for this transformation were heavily dependent on the solvent as well as the structure of substrate. Analogously, the intramolecular oxidative cyclopropanation of allyl propiolamides **46** has been developed by Shin *et al.*,[23c] leading to synthetically useful cyclopropanes **47** (Scheme 13, bottom).



Scheme 13 Intermolecular trapping of the proposed cyclopropyl gold carbenoid intermediate with nucleophiles.

Intramolecular O–H insertion of a pendant alcohol to a gold-stabilized cyclopropyl carbene has been realized by Toste *et al.* in 2008 (Scheme 14).[24a] During the course of gold(I)-catalyzed ring-expanding enyne cycloisomerization reactions,

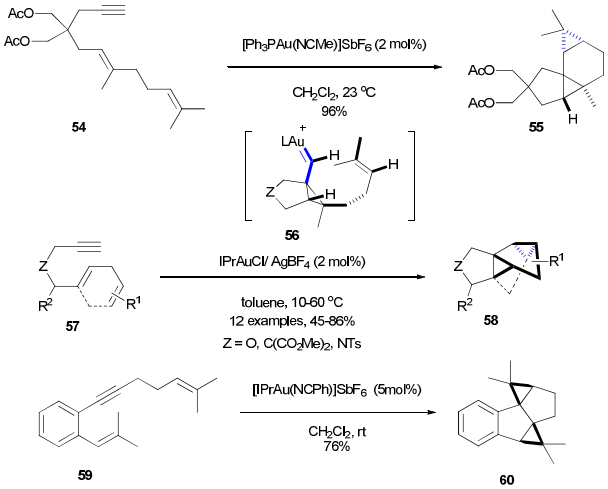
they observed that pyran-derived tricyclic compound **49** was formed in 60% yield. The resulting intermediate **50** by a 6-*exo-dig* cyclization can undergo an intramolecular addition with the pendant alcohol, which occurs faster than cyclopropane ring expansion. In 2012, Zhang, Wei and Shi reported a complementary gold(I)-catalyzed cycloisomerization of *N*- and *O*-tethered methylenecyclopropanes (MCPs) to provide easy access to tricyclic compounds or bicyclo[4.1.0]heptane derivatives **52** in high yields under mild conditions.[24b] In contrast to the 6-*exo-dig* cyclization in Toste's work, the rearrangement of *N*- and *O*-tethered MCPs **51** is initiated by a 6-*endo-dig* process. Intermediate **53** is expected to undergo a facile 1,2-hydride shift, followed by elimination of Au(I) complex to give product.



Scheme 14 Gold-catalyzed cycloisomerization of methylenecyclopropanes.

3.2 Double Cyclopropanation of 1,*n*-Enynes

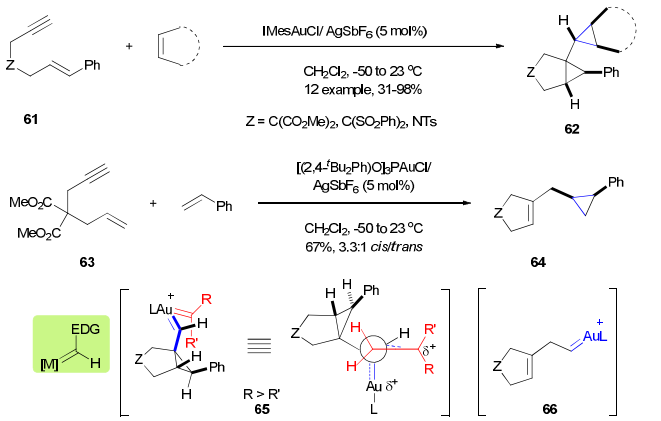
The carbene-like character of the intermediates **E** formed in gold-catalyzed cycloisomerizations can be trapped by intra- and intermolecular alkenes to make another cyclopropane. Echavarren and co-workers reported the pioneering study that reaction of dienyne **54** with gold(I) complex leads stereoselectively to tetracyclic adduct **55** (Scheme 15).[25] The second cyclopropanation occurs through intermediate **56** in a concerted although highly asynchronous manner. Subsequently,



Scheme 15 Gold-catalyzed intramolecular double cyclopropanation.

Chung *et al.*[26] demonstrated that the highly strained tetracyclo [3.3.0.0^{2,8}.0^{4,6}]octane derivatives **58** were obtained from a double intramolecular cyclopropanation of 1,6-enynes **57**, which possess a 1,4-cyclohexadiene core, *via* the initially formed cyclopropyl gold carbenes. Similar to 1,6-enynes, 1,5-enynes (*e.g.*, **59**) also proceed double cyclopropanations in the presence of a gold catalyst.[27]

The gold(I)-catalyzed intermolecular cyclopropanation of alkenes with 1,6-enynes is an electrophilic process, which is mechanistically related to the well-known Simmons–Smith reaction proceeding through zinc carbenoids (Scheme 16).[28] Recent DFT calculations reveal that this cyclopropanation occurs stepwise with more polarized alkenes such as styrenes, although the overall process is still stereospecific since the formation of the second C–C bond occurred with a very small activation energy.[28b] For simple aliphatic olefins such as propene and ethylene, the authors located transition states for concerted carbene transfer computationally. According to the proposed model **65**, the regio- and stereochemistry are mainly controlled by the substituent at C1 of the alkene, in which the cyclopropanation takes place at the less sterically hindered alkene to form **62**. Other theoretical calculations also suggest that the cyclopropanation of electron-rich alkenes with gold(I) carbenes proceeds *via* a stepwise mechanism.[28c] Interestingly, enyne **63** reacts with styrene to give **64** *via* a new type of gold carbene **66**.

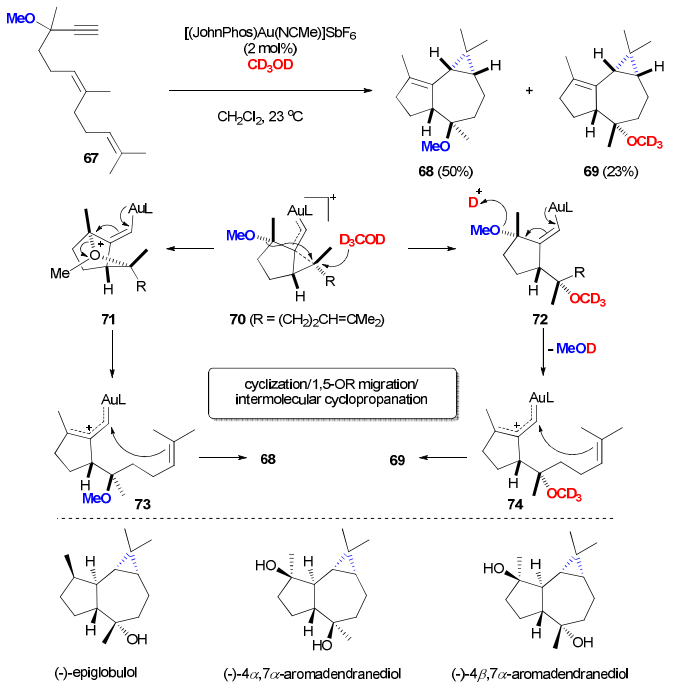


Scheme 16 Gold-catalyzed intramolecular/intermolecular double cyclopropanations.

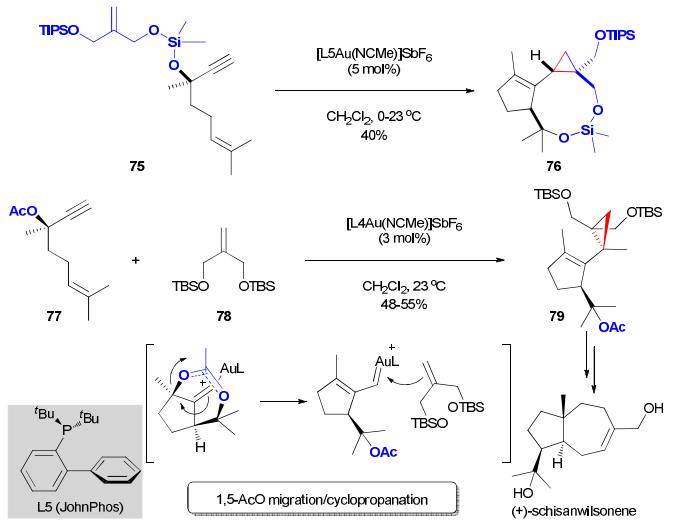
3.3 Cascade 1,5-OR Migration/Cyclopropanation of 1,*n*-Enynes

Dienynes substituted with OR groups at the propargylic position such as **67** undergo a tandem reaction in the presence of competing CD_3OD to form tricyclic compounds **68** and **69** (Scheme 17).[29a] This result is consistent with a reaction occurring *via* intermediate **70**, in which the OR group attacks the cationic center to form bridged system **71**. Opening of **71** then leads to an *α,β*-unsaturated gold carbene/gold-substituted allylic carbocation **73** (DFT calculations are more consistent with latter form), which undergoes intramolecular cyclopropanation with the alkene at the side chain to give **68**. In the presence of CD_3OD, intermolecular addition of this external

nucleophile to **70** leads to **72**, which then gives rise to **74** and inturn the final product **69**. By the application of this method, three natural sesquiterpenes including (-)-epiglobulol, (-)-4α,7α-aromadendranediol, and (-)-4*β*,7*α*-aromadendranediol have been synthesized in seven steps, respectively, from commercially available (*E*,*E*)-farnesol.[29b]



Scheme 17 Gold(I)-catalyzed cyclopropanation with 1,5-migration of OR groups in dienynes. JohnPhos = 2-(di-*t*-butylphosphino)biphenyl.

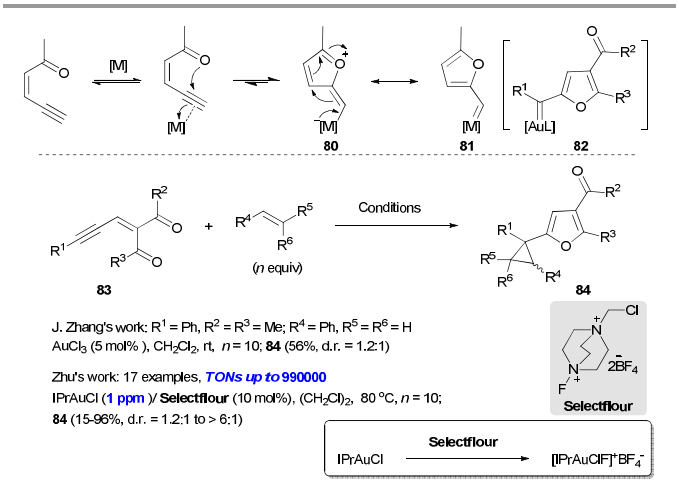


Scheme 18 Gold(I)-catalyzed cyclopropanation with 1,5-migration of OR groups in 1,6-enynes.

By analogy, 1,6-enyne **75** with an alkene group through a silicon tether gave stereoselectively tricyclic compound **76** by tandem cyclization, 1,5-migration, and an intramolecular cyclopropanation. In an intermolecular variant of this process, reaction of 1,6-enyne **77** with alkene **78** produced **79**, which was applied to total synthesis of the antiviral sesquiterpene (+)-schisanwilsonene. In this scenario, it is interesting to remark that the cyclization/1,5-acetoxy migration is faster than the alternative 1,2-acyloxy migration that would lead to racemization (Scheme 18).[30]

3.4 Tandem Cycloisomerization/Cyclopropanation of Yne−Enones

The transition-metal-catalyzed cycloisomerization of yne-enones has recently attracted renewed attention, due to its fundamental scientific interest and great applications in organic synthesis.[4w,31] In these transformations, the alkyne moiety is activated by a transition metal, which is then attacked by the carbonyl oxygen through 5-*exo*-*dig* cyclization to form zwitterionic intermediate **80** or its resonance structure, metal (2-furyl)carbene complex **81** (Scheme 19, top). Complex **81** can subsequently participate in various transformations, such as ylide formation, X−H insertion, cross-coupling reaction, and cyclopropanation.



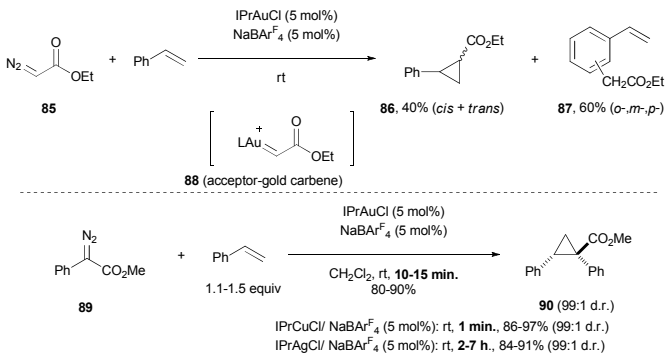
Scheme 19 Gold-catalyzed tandem cycloisomerization/ cyclopropanation of yne−enones.

In 2010, Wang and J. Zhang reported a novel efficient approach to 3-acylfuran derived cyclopropane **84** through $AuCl_3$-catalyzed tandem cycloisomerization/cyclopropanation of yne-enone **83** in the presence of styrene.[32a] In this reaction, the gold (2-furyl)carbene species **82** was proposed as key intermediate. Very recently, Zhu *et al.* found that the combination of NHC−gold complex and Selectfluor is a highly efficient catalyst system for such type of reaction, with the turnover number (TON) up to 990000 and the turnover frequency (TOF) up to 82500 h^{-1}.[32b] The reaction probably proceeded through a cationic $Au(III)^+$ species, which was generated in situ from the oxidation of IPrAuCl with Selectfluor (Scheme 19, botom).

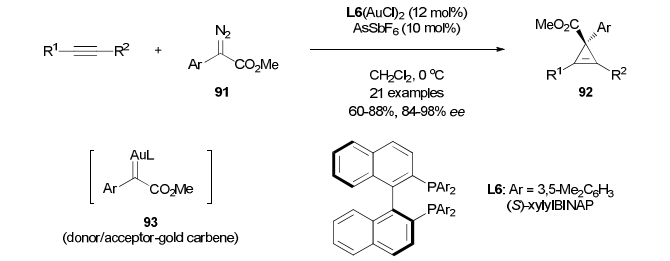
4. Diazo Compounds *via* Decomposition

The metal-catalyzed decomposition of diazo compounds to generate transient metallocarbenes has been exploited in a wide array of useful synthetic transformations.[3] However,

homogeneous gold-catalyzed carbene transfer reactions of diazo reagents were unknown until Nolan, Díaz-Requejo, Pérez, and coworkers reported the first example of cyclopropanation in 2005.[33] As shown in Scheme 20, the presumed acceptor-gold carbene intermediate **88** from decomposition of ethyl diazoacetate (EDA) **85** with IPrAuCl/NaBAr$^F_4$ [Ar^F = 3,5-(CF$_3$)$_2$Ph], reacts with styrene leading to competing cyclopropanation and C–H insertion products, as opposed to the Cu-catalyzed reaction with only cyclopropanation products formation. Later, several gold complexes derived from either phosphine, phosphate or NHC ligands were examined by Pérez, Echavarren and coworkers for the cyclopropanation of styrene or cyclohexene with ethyl 2-phenyldiazoacetate **89** (Scheme 20, bottom).[34] A comparative study with related copper and silver complexes as catalysts was also presented. Consequently, very high conversions and complete diastereoselectivity toward the *trans*-isomer have been achieved with gold- as well as copper-based catalysts. However, silver catalysts display a considerably lower activity than their copper or gold counterparts.



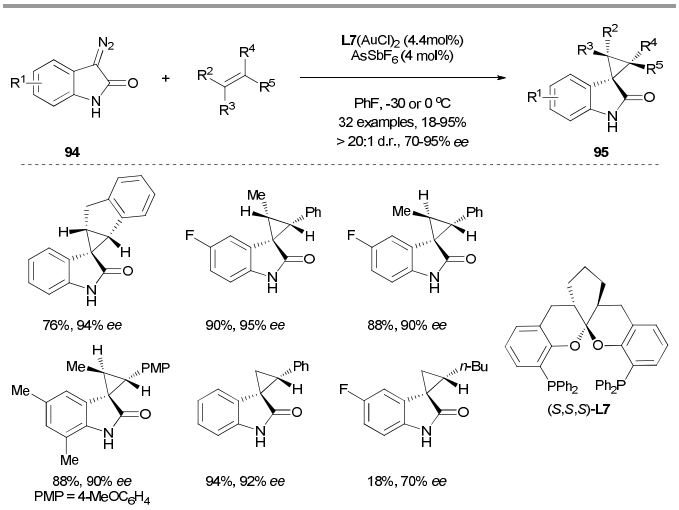
Scheme 20 Gold-catalyzed olefin cyclopropanation using diazo compounds.



Scheme 21 Enantioselective cyclopropenation of internal alkynes with aryldiazoacetates.

The development of an enantioselective variant of this type of reactions remained elusive until Davies and co-workers reported a highly enantioselective cyclopropenation of internal alkynes with aryldiazoacetates **91** (Scheme 21).[35] A cationic Au(I)/xylylBINAP was found efficiently to induce high enantioselectivity and the desired cyclopropenes **92** were obtained in good yields. The scope of the method encompasses a variety of aryl disubstituted alkynes and several donor/acceptor aryldiazoacetates **91**. The reactivity of the donor/acceptor-gold carbenoids **93** is similar to the silver carbenoids. Most notably, the gold carbenoids have a very different reactivity profile compared to the corresponding rhodium carbenoids, and are much less susceptible to steric interference.

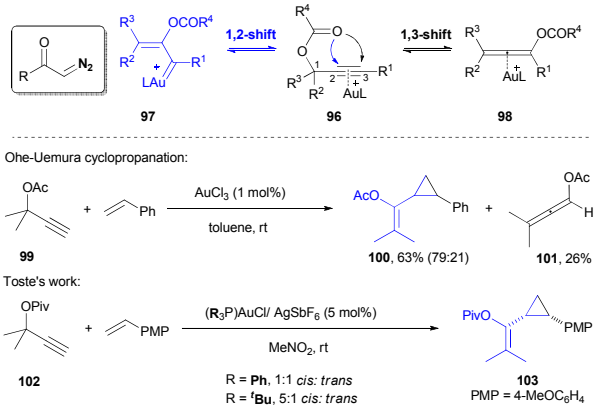
In 2013, Zhou *et. al* presented the first example of highly enantioselective gold-catalyzed cyclopropanation reaction by using donor/acceptor diazo species as a precursor of gold carbenes (Scheme 22).[36] Importantly, the authors demonstrated that the chiral spiroketal bisphosphine structure **L7,** developed by the group of Ding, was a very efficient ligand for the asymmetric cyclopropanation between diazooxindoles **94** and various alkenes. The resulting spirocyclopropyloxindoles **95**, which are obtained generally in good to excellent yields and enantioselectivities, are appealing structures in medicinal research.



Scheme 22 Enantioselective cyclopropanation of alkenes with diazooxindoles.

5. Propargyl Esters *via* Acyloxy Migration

The ready accessibility of propargyl esters makes them very attractive building blocks. Gold-catalyzed 1,2- or 1,3-acyloxy migration of propargylic esters to form a gold vinyl carbenoid species **97** or a gold allene species **98** are the representative transformations (Scheme 23, top).[4k,6e] As a rule of thumb, if esters **96** possess terminal alkynes (R^1 = H) and electronically biased internal alkynes (R^1 = EWG), the 1,2-shift takes place.

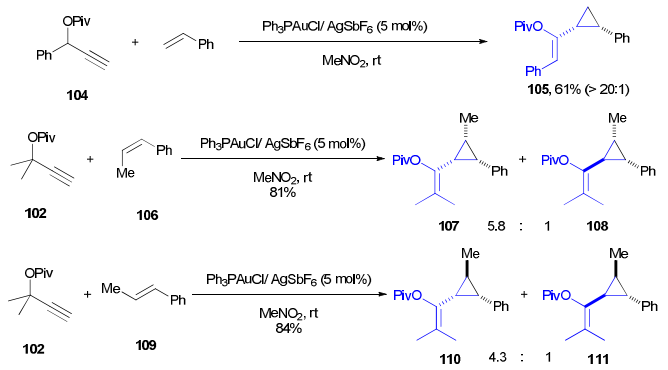


Scheme 23 Competitive 1,2- or 1,3-migration of propargylic esters.

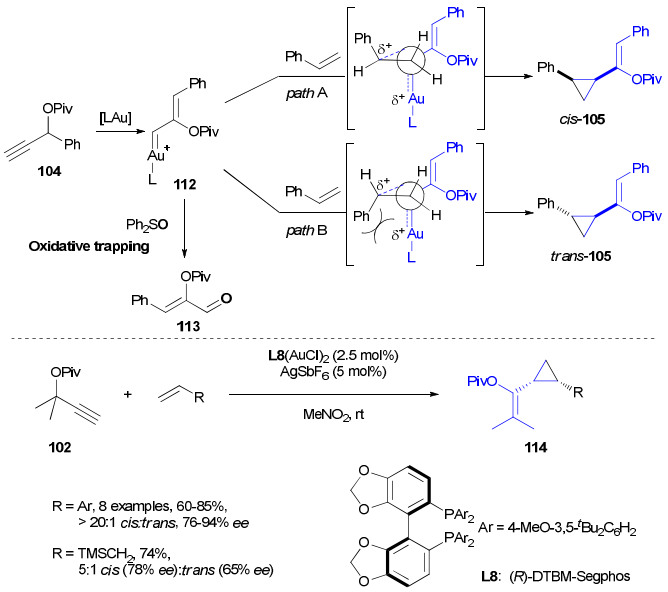
In contrast, for tertiary or benzyl alcohol derived substrate, possessing electronically unbiased internal alkynes ($R^1 \neq H$), the 1,3-shift, accurately, 3,3-rearrangement,[4m] is preferred.

5.1. Intermolecular Cyclopropanation *via* 1,2-Acyloxy Migration

In 2003, as the logical extension study on the Ru-catalyzed cyclopropanation of alkenes from propargyl esters with alkenes, Ohe and Uemura found that gold(III) complex could also catalyze the reaction of propargyl acetate **99** with styrene to give the desired cyclopropane **100** along with 26% yield of the allenyl ester **101**.[37] Subsequently, Toste *et al.* disclosed a Au(I)-catalyzed variant of the Ohe-Uemura cyclopropanation in which ligand effects were manifest in the diastereoselectivity of the transformation of **102** to **103** (Scheme 23, bottom).[38] Based on these seminal observations, numerous studies have demonstrated that a propargyl ester entity constitutes a convenient and safe synthetic equivalent to an α-diazoketone for inter- or intramolecular cyclopropanation processes. Given



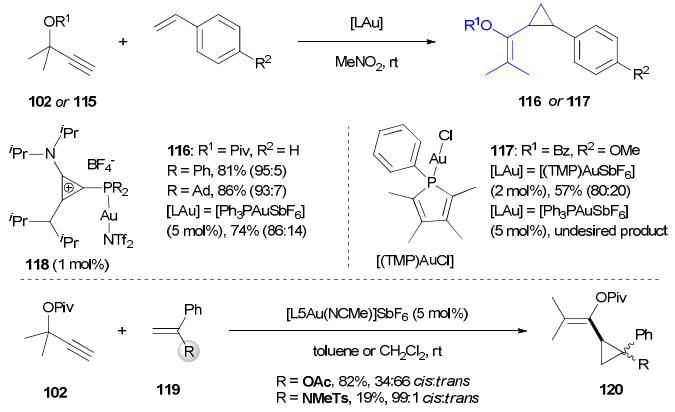
Scheme 24 Gold-ctalyzed cyclopropanation of alkenes with propargyl esters.



Scheme 25 Gold-catalyzed enantioselective cyclopropanation of alkenes with propargyl esters.

the high steric bulk of $(^tBu)_3P$ and the observation that phenyl propargyl pivaloate **104** provided the product *cis*-**105** as a single olefin isomer (Scheme 24, top), a stereochemical model accounting for the diastereoselectivity was proposed. Cyclopropanation is proposed to occur *via* the less sterically encumbered Au carbenoid to provide the *Z*-olefin isomer due to steric clash between the ligand on Au and the substituent on the incoming olefin (Scheme 25, top). The high stereospecificity in the Au(I)-catalyzed cyclopropanation reaction of *cis*- and *trans*-β-methyl styrenes lends additional support to a mechanism that involves concerted carbene transfer from a gold(I)-carbenoid intermediate (Scheme 24, bottom). In addition, the proposed gold(I)-carbenoid **112** intermediate could be trapped by external nucleophilic oxidants, specifically diphenyl sulfoxide.[23a] Importantly, the authors demonstrated that the process could also be rendered enantioselective by exploiting chiral digold complexes derived from (*R*)-DTBM-Segphos, which represents the first example to propose an asymmetric gold system suitable for the synthesis of chiral cyclopropanes. Usually, high levels of enantioselectivity could be achieved when the propargylic system features sterically demanding esters such as pivaloates, or the alkene component contains large aromatic substituents.

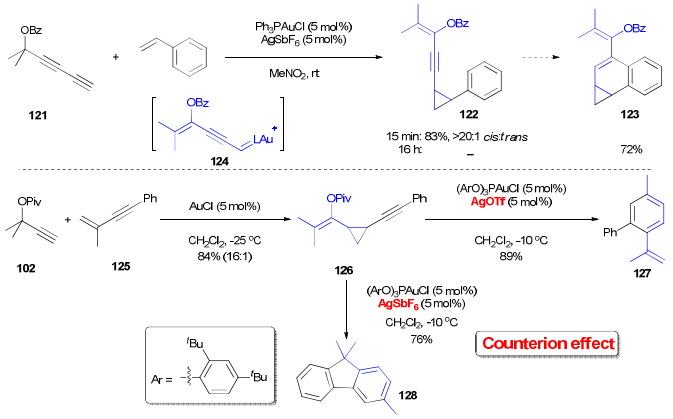
As a model reaction, Toste's cyclopropanation has been used to evaluate new catalyst system. Recently, gold complexes with cyclopropenylylidene-stabilized phosphenium compounds [39a] and tetramethylphosphole (TMP)[39b] have been synthesized and showed higher activity in cyclopropanation than the corresponding phosphine-based complexes (Scheme 26, top). On the other hand, trapping different propargyl esters with olefins directly connected to a heteroatom, such as vinyl acetates and vinyl sulfonamides, has also successfully realized, thus leading to highly substituted cyclopropane derivatives **120** in low to excellent diastereoselectivity (Scheme 26, bottom).[39c]



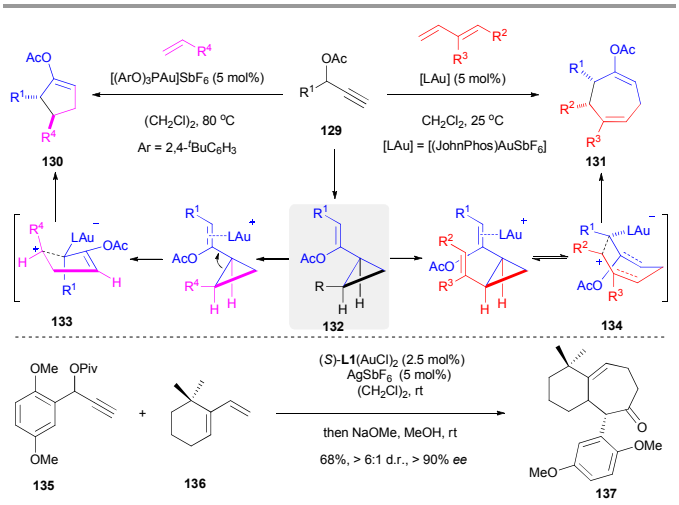
Scheme 26 New gold catalysis system for cyclopropanation of alkenes with propargyl esters.

Transition metal-catalyzed sequential carbon-carbon bond-forming reactions provide a strategy to increase synthetic efficiency.[40] In 2006, Toste and co-workers reported a facile access to benzonorcaradienes **123** from conjugated diynyl-propargyl esters **121** and vinylarenes (Scheme 27, top).[41a] The

proposed mechanism involved the formation of the gold carbenoid **124**, which reacted with the styrene leading to cyclopropanes **122**. A similar strategy is employed in the annulation of enynes **125** with propargyl esters **102** to form styrenes **127** or fluorenes **128**. Notably, the product selectivity was controlled through selection of the catalyst counterion (Scheme 27, bottom).[41b]



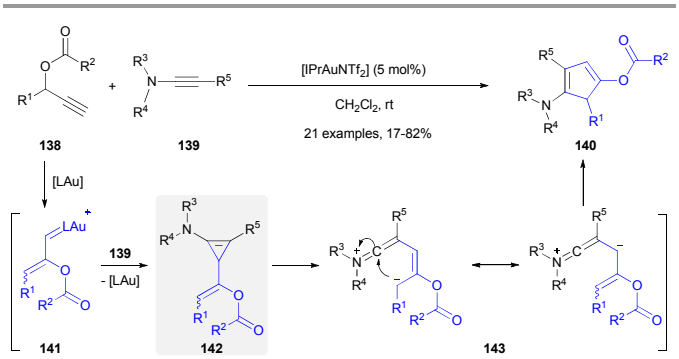
Scheme 27 Gold(I)-catalyzed tandem cyclopropanation/cyclization squence.



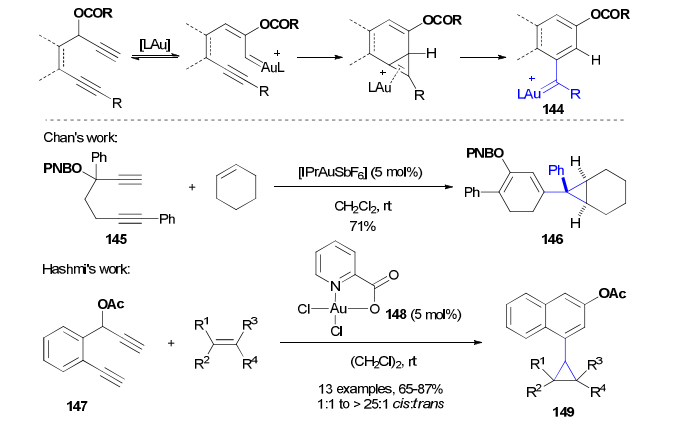
Scheme 28 Gold-catalyzed tandem cyclopropanation/Cope rearrangement.

In 2011, the group of Nevado demonstrated that propargyl acetates **129** react with alkenes or dienes in the presence of a gold catalyst to give five or seven membered rings **130** and **131**, respectively.[42] As shown in Scheme 28, the same gold-mediated 1,2-acyloxy migration as above generates a gold–carbenoid species, which cyclopropanates a C–C double bond to form a *cis*-cyclopropane intermediate **132**. When alkenes are used, subsequent gold reactivation of the vinyl acetate moiety results in cyclopropyl ring-opening forming intermediate **133**. An envelope conformation is proposed for the transition state to minimize torsional/steric interactions yielding the *trans*-2,3-disubstituted cyclopentannulation products **130**. In contrast, employing 1,3-dienes as reacting partners, a subsequent gold-catalyzed Cope rearrangement through a boat-like transition state would deliver the *cis*-2,3-disubstituted cyclohepta-dienyl acetates **131**. Furthermore, treatment of pivaloate **135** with 6,6-dimethyl-1-vinylcyclohexene in the presence of the chiral gold catalyst (*S*)-MeO-DTBM-Biphep(AuCl)$_2$/AgSbF$_6$, followed by in situ hydrolysis, allowed the construction of the basic bicarbocyclic core of Frondosins (*e.g.*, **137**) in 68% yield and 90% *ee* (Scheme 28, bottom). Since this bicyclic enone was previously elaborated into Frondosin A and B, the approach represented a streamlined formal enantioselective synthesis of both molecules.

In addition, Hashmi and co-workers found that highly substituted cyclopentadienes can be obtained by intermolecular cyclization of ynamides **139** and propargylic carboxylates **138**.[43] As depicted in Scheme 29, a cyclopropenation reaction of gold carbenoids **141** derived from propargylic acetates with electron-rich ynamides was proposed. The next step comprises a ring opening which is triggered by the lone pairs at the nitrogen atom. The resulting zwitterionic keteniminium cation/allylic anion **143** then undergoes ring closure to form the final product **140**. An alternative pathway comprising a stepwise reaction in which the nucleophilic carbon atom of the ynamide attacks the electrophilic carbene to deliver the keteniminum intermediate is also possible.



Scheme 29 Gold-catalyzed tandem cyclopropanation/ring closure reaction.



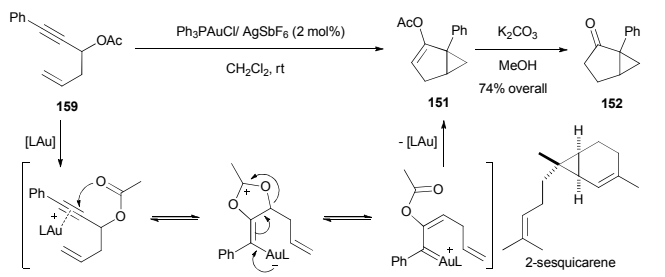
Scheme 30 Gold-catalyzed tandem 1,2-acetate migration/intermolecular cyclopropanation reaction.

After generation of a vinyl carbenoid of type **97**, if a second alkyne is intramolecularly offered, a subsequent reaction takes place to generate a new carbenoid **144** (*i.e.*, carbene transfer, Scheme 30).[44] These highly reactive species are allowed to react with differently substituted alkenes in a cyclopropanation fashion. In 2013, Chan *et al.* disclosed an example involving tandem 1,2-acetate migration/intermolecular

cyclopropanation to support the formation of gold carbenoid **144**.[44a] In the case of aromatic backbones, 1-naphthyl-carbenoids are finally generated. Hashmi and co-workers demonstrated that even a simple 1:1 ratio of the starting materials delivered the corresponding cyclopropylnaphthalenes in high yields by the use of a Au(III) catalyst **148** (Scheme 30, bottom).[44b]

5.2. Intramolecular Cyclopropanation *via* 1,2-Acyloxy Migration

As an extension of the platinum-catalyzed cycloisomerization of hydroxylated enynes, the group of Fürstner demonstrated gold-catalyzed intramolecular cyclopropanation using propargyl acetates as carbene precursor (Scheme 31).[12] It was observed that substrate **150** underwent a smooth 1,2-acyloxy migration and then cyclopropanation in the presence of gold(I) catalyst. Treatment of **151** with a base provides bicyclo[3.1.0]hexanone **152**, which is present in a large number of terpenes. For example, a cyclization of this type catalyzed by $AuCl_3$ was used for the diastereoselective synthesis of 2-sesquicarene and related terpenes.[45a] The reaction allows the configuration of the substrate to be translated with high fidelity into the resulting cyclopropane product. This salient feature was recently highlighted by the preparation of no less than 10 members of the sesquisabina and sesquithuja terpene families from only two diastereomeric precursors **153** (Figure 1).[45b]



Scheme 31 Gold-catalyzed intramolecular cyclopropanation of propargyl acetate.

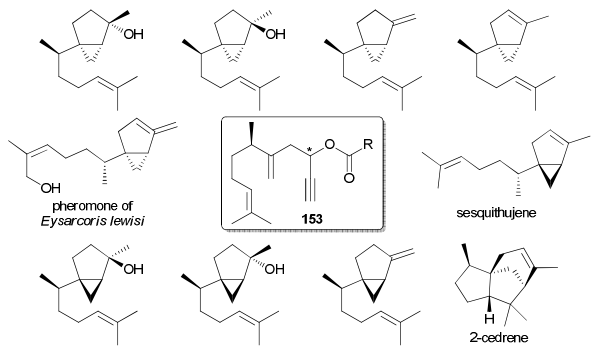
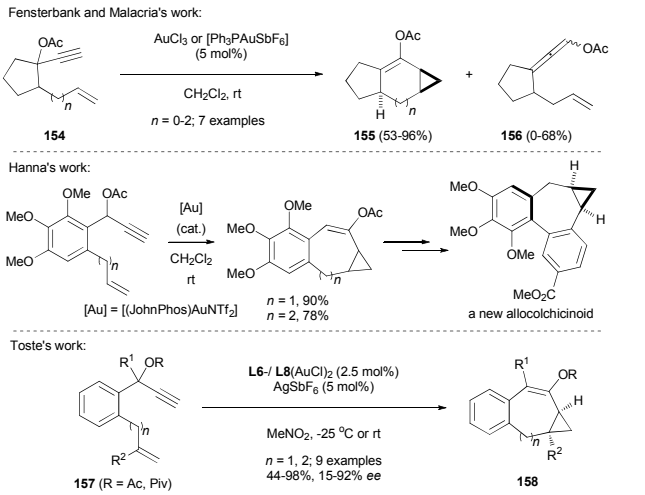
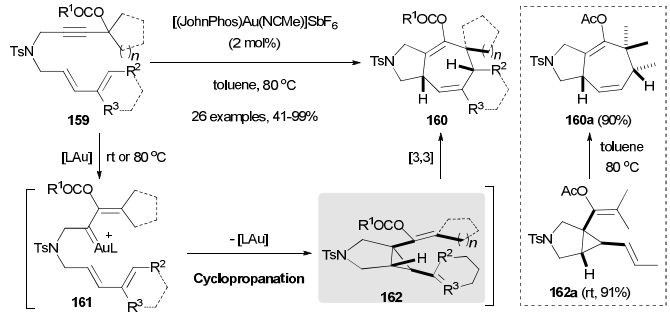


Figure 1 Set of naturally occurring sesquiterpenes accessed by gold-catalyzed intramolecular cyclopropanation of the diastereomeric substrates **153**.

In 2008, Fensterbank, Malacria and co-workers described an interesting intramolecular cyclopropanation in Au-catalyzed rearrangements of propargyl esters (Scheme 32, top), providing a variety of tricyclic products **155** accompanied by allenyl esters **156** as byproducts.[46a] This study concluded that both Au(I) and Au(III) are effective catalysts for the transformation. It is also remarkable that running some of these reactions under solvent-free conditions or in ionic liquids are reasonable.[46b] Later, Hanna *et al.* reported an impressive gold(I)-catalyzed cycloisomerization of 1,7- and 1,8-enyne propargylic acetates afforded cyclopropyl derivatives containing 7- and 8-membered rings, respectively. This methodology was applied to the synthesis of a new class of allocolchicinoids (Scheme 32, middle).[47a] Subsequently, Toste *et al.* extended the utility of this cyclopropanation reaction to an asymmetric process that allows enantioselective synthesis of medium-sized rings.[47b] Synthetically challenging polycarbocyclic skeletons embedding 7- and 8-membered rings **158** were obtained in high yields with good enantioselectivities by employment of (*R*)-xylyl-BINAP (**L6**) and (*R*)-DTBM-Segphos (**L8**) as chiral ligands. Noteworthy, these results extend the scope of enantioselective transition metal catalyzed enyne cycloisomerization reactions, which have been traditionally limited to the synthesis of 5- and 6-membered rings (Scheme 32, bottom).



Scheme 32 Gold-catalyzed intramolecular cyclopropanation for synthesis of achiral and chiral medium-sized rings.



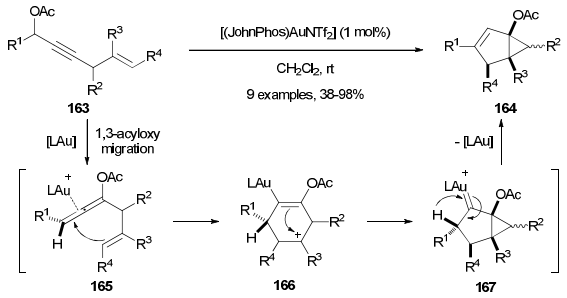
Scheme 33 Gold-catalyzed tandem cyclopropanation/Cope rearrangement of 1,6,8-dienyne carbonates and esters.

In 2014, Chan *et al.* developed a gold(I)-catalyzed efficient and selective synthetic route to *cis*-cyclohepta-4,8-diene-fused pyrrolidines **160** from readily accessible acyclic 1,6,8-dienyne carbonates and esters **159** (Scheme 33).[48] Starting carbonates and esters with a pendant alkyl group on the

terminal alkenyl carbon center were found to favor tandem 1,2-acyloxy migration/cyclopropanation followed by Cope rearrangement of the resulting *cis*-3-aza-bicyclo[3.1.0]hexane intermediate **162**. This formal gold(I)-catalyzed [4C+3C] cycloaddition approach represents an attractive alternative to previously reported metal-catalyzed reactions both in terms of atom economy and functional group tolerance.

5.3. Intramolecular Cyclopropanation *via* 1,3-Acyloxy Migration

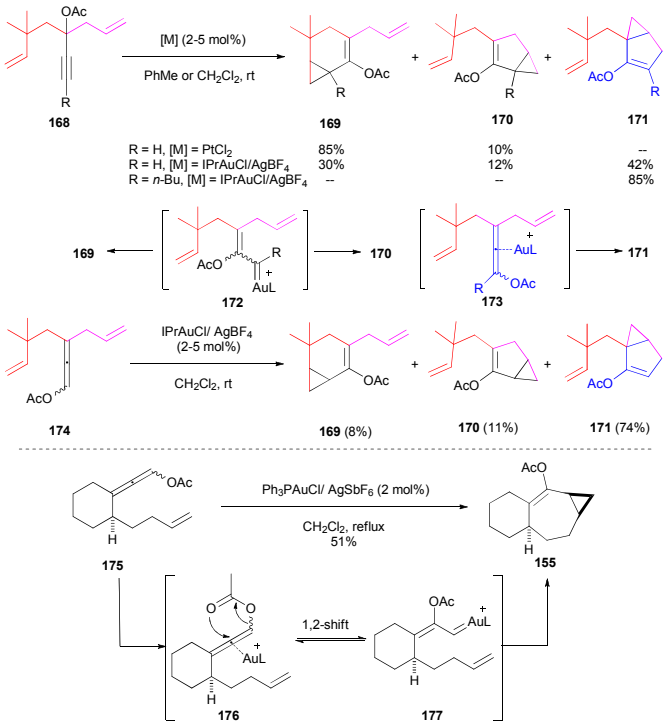
In 2006, Buzas and Gagosz demonstrated an efficient gold-catalyzed synthesis of bicyclic framework **164** from propargyl acetates (Scheme 34).[49] Treatment of substrates **163** with the gold catalyst initiates 1,3-acyloxy migration to form the allene species **165**, which further undergoes a nucleophilic attack of the pendant alkene at the metal-activated allene *via* a 6-*endo*-*trig* cyclization to produce cyclohexyl carbocation **166**. Subsequent formation of the cyclopropane afforded the gold(I) carbenoid **167**. Finally, a 1,2-hydride shift and dissociation would produce the bicyclo[3.1.0]hexenes. The whole process can be considered as a tandem 1,3-acyloxy migration and 1,*n*-allene-ene cycloisomerization, which is strongly supported by the chirality transfer experiment.



Scheme 34 Gold-catalyzed intramolecular cyclopropanation *via* 1,3-migration.

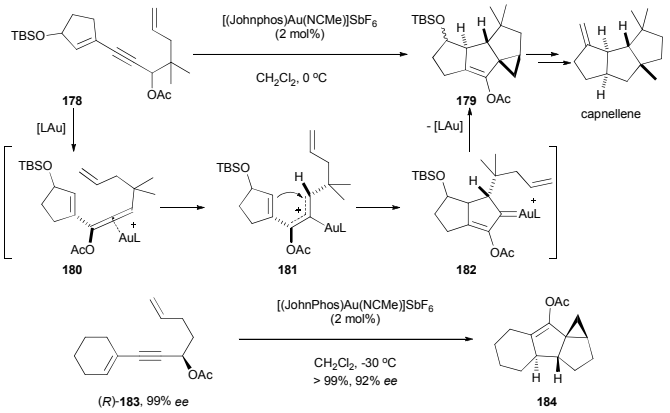
As an extension of previous work using $PtCl_2$, Nolan *et al.* in 2006 successfully realized the cycloisomerization of the dienynepropargyl acetate **168** (Scheme 35, top).[50a] A substantial part of this work dealt with the competition between two intramolecular cyclopropanations in the presence of NHC–gold complexes, leading to [3.1.0]- and [4.1.0]bicycle, respectively. Additionally, both gold precatalyst and counterion were found to impact the outcome of the reaction. The cycloisomerization reaction of **168** leading to **171** would occur by a 1,3-OAc shift/allene–ene cyclization/1,2-OAc shift sequence. To support this hypothesis, the allenyl acetate **174** was prepared and subjected to the reaction conditions, which indeed afforded a greater proportion of **171** over **169** and **170**. To prove "retro-migration" of the ester, allenyl ester **175** was subjected to typical cyclization conditions in the presence of gold catalyst. As expected, the tricyclic compound **155** was observed, which can be explained by invoking a 1,2-acyloxy shift from **176** to afford a vinyl gold carbenoid **177** (Scheme 35, bottom).[50b]

Manifestly, exploiting a dual gold catalysis process starting from propargyl acetates to generate allenylester precursors is benefit to limit the number of reaction steps. Based on this step-economic principle, Fensterbank, Malacria



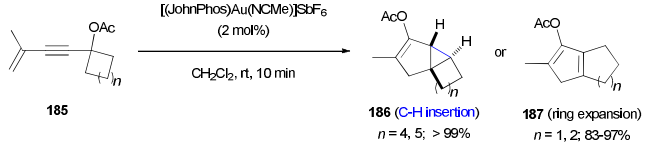
Scheme 35 Gold-ctalyzed competitive intramolecular cyclopropanation *via* 1,2- or 1,3-migration.

and co-workers reported an even more complex process by assembling a second alkene unit to trap the gold carbenoid **182** (Scheme 36).[51] The resulting product **179** was finally elaborated into the sesquiterpene natural product capnellene.[51b] The process was later shown to proceed with axis-to-center chirality transfer, with the stereochemical information being maintained in both η^2-allene and bent η^1-allene complexes (from **183** to **184**). Finally, DFT calculations suggested that the metalla-Nazarov pathway will take place with an attack of the vinyl group *anti* to the metal fragment on the configurationally stable intermediates **181**, providing gold carbenoid **182**.[51]



Scheme 36 Gold-ctalyzed 1,3-migration/Nazarov cyclization/cyclopropanation cascade reaction of propargyl acetates.

Then, the same group examined the possible evolution of carbenes of type **182** in the absence of a pendant olefin on cyclic precursors of type **185** (Scheme 37).[51b] The tricyclic product **186** was isolated nearly quantitatively as a single diastereomer. The ring size of cycloalkyl substitutions was also crucial to C(sp^3)–H insertion process, and the smaller (less than seven-membered) ring would result in a ring expansion to **187** (see Scheme 10). Furthermore, DFT calculations suggest that as *n* increases, the energy to reach the ring fusion transition state decreases from 29.6 to 16.4 kcal·mol^{-1}. Conversely, the ring expansion activation energies increase from 11.9 to 26 kcal·mol^{-1}. For *n* = 3, both processes require activation energies above 22 kcal·mol^{-1}, favoring the elimination pathway. All these evolutions also illustrate a continuum between a carbene and a carbocation in the nature of intermediates of type **A** and **B**, which has been the matter of intense debate.[6]

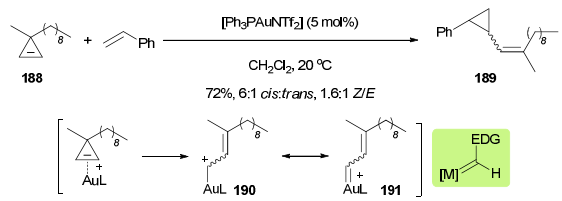


Scheme 37 Gold-ctalyzed competitive C-H insertion and ring expansion reaction of propargyl acetates.

6. Cyclopropenes *via* Gold-catalyzed Ring-opening

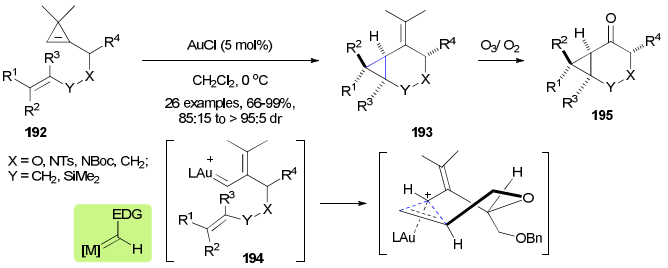
Cyclopropenes are highly strained but readily accessible substances, which entered the field of gold catalysis in 2008 and have proven to be valuable partners in a variety of gold-catalyzed reactions.[1c,52]

During the Lee group's ongoing study of gold-catalyzed transformations of cyclopropenes, in 2008, they disclosed the generation of gold carbenoid **190** by ring-opening of cyclopropene **188**.[53a] The alkenyl cyclopropane **189** was isolated in 72% yield as a 6:1 mixture of *cis*/*trans* diastereomers and a 1.6:1 mixture of *Z*/*E*-geometric isomers in the presence of excess amount of styrenes (Scheme 38). Later, a more detailed study of the nature of alkenyl gold carbenoids came from the group of Toste (see section 2).[6c] Interestingly, Angelici, Woo, and co-workers also investigated the intermolecular cyclopropanation of styrene by the surface bound gold carbenoid generated from cyclopropene, albeit with only low yield.[53b]



Scheme 38 Gold-catalyzed intermolecular cyclopropanation from cyclopropenes.

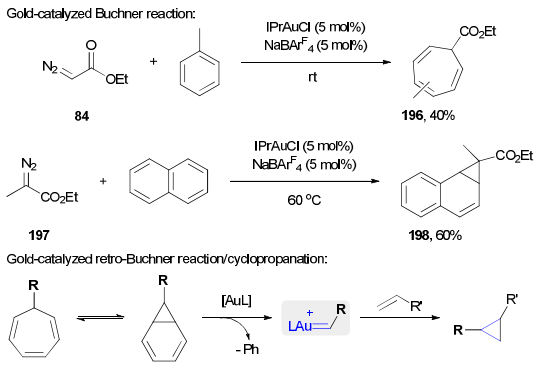
Recently, Meyer, Cossy *et al.* reported the intramolecular isomerisation of tethered 1,6-cyclopropene-ene **192** (Scheme 39).[54] In the presence of gold(I) chloride, the cycloisomerization proceeds with regioselective electrophilic ring opening of the cyclopropene and subsequent intramolecular cyclopropanation of the remote olefin with the generated vinyl gold carbenoid **194**. The reaction allows highly efficient access to 3-oxa- or 3-azabicyclo[4.1.0]heptanes **193** in good to excellent yields and usually with high levels of diastereoselectivity, as well as to substituted bicyclo[4.1.0] heptan-3-ol derivatives. The indispensable *gem*-dimethyl group, which was crucial for substrate stability, presumably has a marked influence not only on the regioselectivity but also on the diastereoselectivity *via* a twist-boat-like transition state. In addition, the 3,3-dimethylcyclopropene moiety can be viewed as a synthetically useful *α*-diazoketone surrogate, because the isopropylidene substituent can be readily converted into a carbonyl group by ozonolysis.



Scheme 39 Gold-catalyzed intramolecular cyclopropanation from cyclopropenes.

7. 1,3,5-Cycloheptatrienes *via* Retro-Buchner Reaction

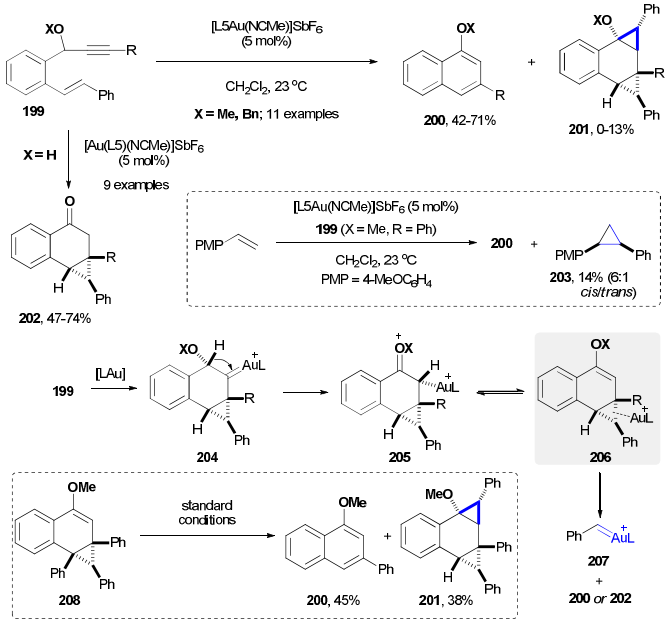
The Buchner reaction of gold carbenes derived from diazo species with arenes takes place.[33,55] Interestingly, the gold(I) carbenoid could also be regenerated from 1,3,5-cycloheptatrienes in an overall retro-Buchner process found by Echavarren *et al.* in 2010.[56] This novel strategy relies on a gold-promoted retro-cyclopropanation and is driven by the restoration of aromaticity, which can obviate the use of shock-sensitive diazo derivatives to generate reactive metal carbenes. In the presence of external alkenes and tethered alkenes, in-situ generated gold carbenoid can subsequently undergo efficient cyclopropanation reactions (Scheme 40).



Scheme 40 Gold-catalyzed Buchner and retro-Buchner reaction.

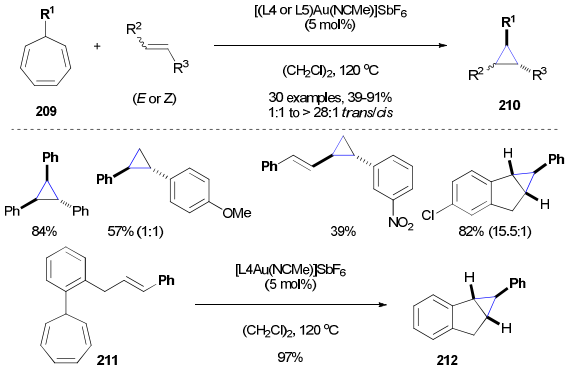
In the context of the synthesis of 1,3-disubstituted naphthalenes, Solorio-Alvarado and Echavarren explored the first example of a retro-cyclopropanation promoted by gold(I) in solution.[56] As shown in Scheme 41, 1,6-enynes **199** bearing OMe/OBn and OH substituents at the propargyl position undergo different transformations to afford the annulation/

fragmentation products **200** and **202** in the presence of cationic Au(I) catalyst, respectively. Interestingly, the biscyclopropanes **201** was also isolated, indicating metal carbene is formed in the fragmentation process. Indeed, when the gold(I)-catalyzed annulation of **199** was performed in the presence of *p*-methoxystyrene, cyclopropane **203** was obtained. These results are consistent with a mechanism proceeding by the 6-*endo*-*dig* gold(I)-promoted cyclization of enynes **199** to form **204**, followed by a 1,2-H shift to form alkenylgold(I) species **205**. The isomer of **206** with LAu^+ in the convex face would be formed similarly from the C1 epimer of intermediate **204**. Retro-cyclopropanation *via* **206**, presumably by stepwise cleavage by electrophilic LAu^+, would then give products **200**/**202** and generate gold(I) carbenoid **207**. Further experimental support for this proposal was obtained by treatment of enol ether **208**, which led cleanly to a mixture of **200** and biscyclopropane **201**. In addition, a similar process was also proposed in the gas-phase cleavage of 1-ethoxy-2-methoxycyclopropane with $[AuIMes]^+$ on the basis of collision-induced dissociation (CID) experiments and theoretical calculations.[28c,57]



Scheme 41 Gold-catalyzed 1,6-enyne cyclization involving retro-Buchner reaction.

In 2011, the same group demonstrated that cationic gold(I) complexes promote the retro-Buchner reaction of 1,3,5-cycloheptatrienes **209**/**211** to in-situ generate gold(I) carbenoids [LAu = CH**R**^{1}], which can be trapped by inter- or intramolecular olefins (Scheme 42).[58a] 1,2,3-Trisubstituted cyclopropanes **210**/**212**, which are not easily prepared by other methods, can be synthesized from 1,2-substituted alkenes and readily available 7-substituted 1,3,5-cycloheptatrienes. According to current DFT calculations, the gold-catalyzed retro-Buchner process occurs in a stepwise manner, although the two C−C cleavages occur on a rather flat potential energy surface.[57,58b] The intermediates generated by the retro-Buchner reaction behave more like metal carbenes of rhodium or copper or even free carbenes than benzylic carbocations.

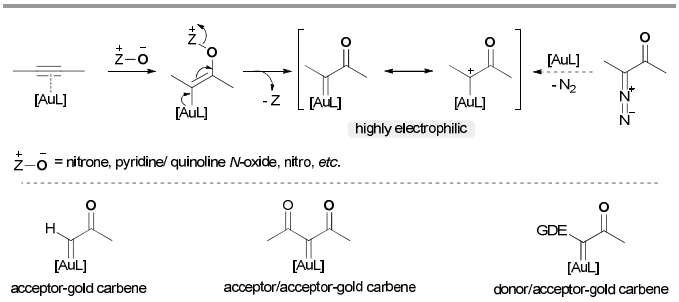


Scheme 42 Gold-catalyzed cyclopropanation by retro-Buchner reaction.

8. Alkynes *via* Oxidation/Nitrene Transfer Reaction

8.1 Alkynes *via* Oxidation Reaction by *N*-Oxides

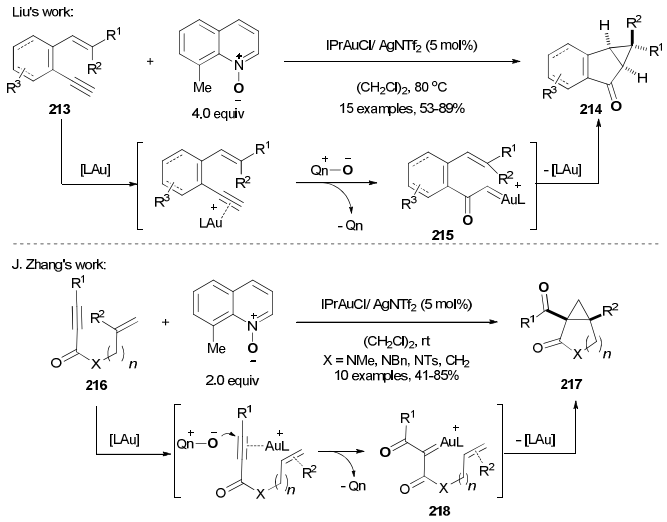
Recently, gold-catalyzed oxidative reactions of alkynes have received considerable attention, since they provide efficient access to functionalized carbo- and heterocycles.[6e,59] L. Zhang,[60a-c] Shin,[60d] Liu,[60e] and Yamamoto[60f] have independently done seminal works by exploiting different oxidants in this field. The key reaction sequence, illustrated in Scheme 43, is initiated by the attack of a nucleophilic oxygen atom of the oxidant on the gold-activated alkyne, followed by the elimination of a neutral organic unit with concomitant formation of highly electrophilic *α*-oxo gold carbenoid. This strategy makes stable, benign, and often commercially available alkynes safe surrogates for *α*-diazoketones, which offer a new entry to metal carbenoids, especially acceptor-gold carbenoids. In this context, those intermediates, generated *via* gold-catalyzed oxidation alkynes by pyridine/quinoline *N*-oxides, can undergo various synthetically challenging yet highly valuable transformations such as X−H (X = O, N, C) insertion, ylide formation, and cyclopropanation reactions.



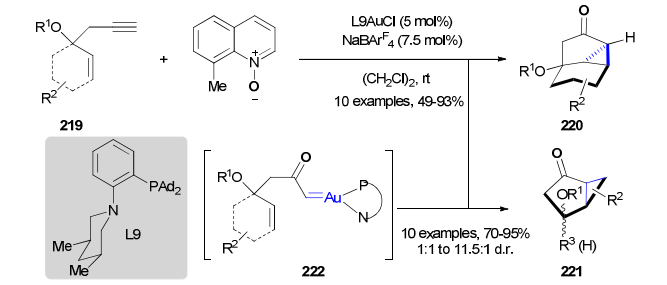
Scheme 43 Gold-catalyzed alkyne oxidation.

In 2011, Liu's[61] and J. Zhang's[62] groups independently realized the oxidative cyclopropanations of 1,*n*-enynes with 8-methylquinoline *N*-oxide as an external oxidant (Scheme 44). For 1,5-enynes **213** bearing a terminal electron-rich alkyne, Liu *et al*. found that the gold-catalyzed oxidative cyclopropanation proceeded smoothly to produce the corresponding cyclopropyl indanone compounds **214** stereoselectively.[61] Qian and J.

Zhang demonstrated that electron-deficient 1,6-enynes **216** could also undergo a oxidative cyclopropanation under the catalysis of gold(I) complex, affording the carbo- and hetero[*n*.1.0] bicyclic framework **217** in moderated to good yields, which are widely found in natural products and pharmaceutics.[62] This transformation involves the selective formation of two C–C bonds to afford annulated cyclopropyl ketone derivatives, allowing for facile construction of adjacent quaternary centers. On the basis of experimental data, both reactions are most likely to proceed through prior oxidations of alkyne to form *α*-carbonyl gold(I) carbenoid **215**/**218**, followed by intramolecular cyclopropanation with a pedant alkene. An alternative pathway involving sequential enyne cycloisomerization and oxidation of the gold carbenoid intermediate was ruled out.



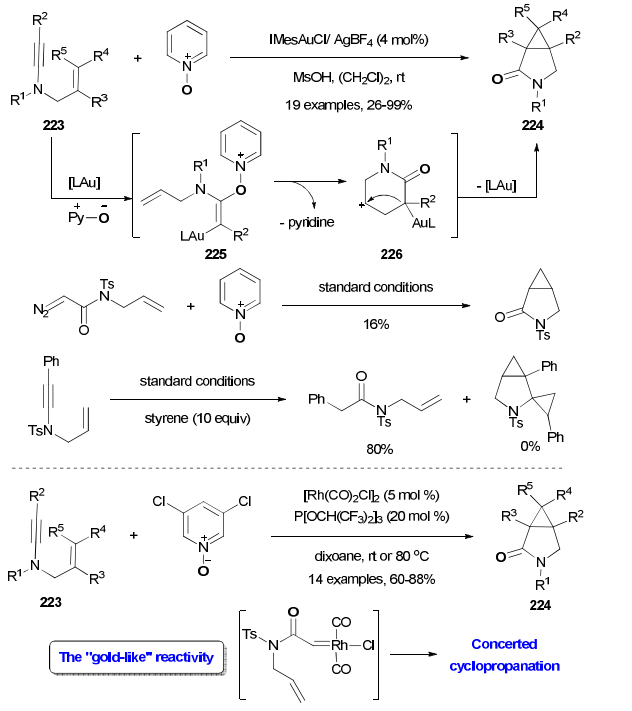
Scheme 44 Gold-catalyzed oxidative cyclopropanation of 1,*n*-enynes.



Scheme 45 Gold-catalyzed oxidative cyclopropanation of 1,*5*-enynes.

Very recently, by utilizing a conformationally rigid P,*N*-bidentate ligand, Ji and L. Zhang demonstrated a highly efficient intramolecular oxidative cyclopropanation reactions with flexible and electronically neutral terminal alkynes **219** (Scheme 45).[63] Bicyclic/tricyclic functionalized cyclopropyl ketones **220**/**221** are isolated in good yields in three steps from readily available enones/enals. The optimal ligand facilitates the reaction by attenuating the reactivity of the highly electrophilic *α*-oxo gold carbenoid *via* the formation of tri-coordinated gold carbene intermediate **222** and by offering better steric shielding due to conformational rigidity.

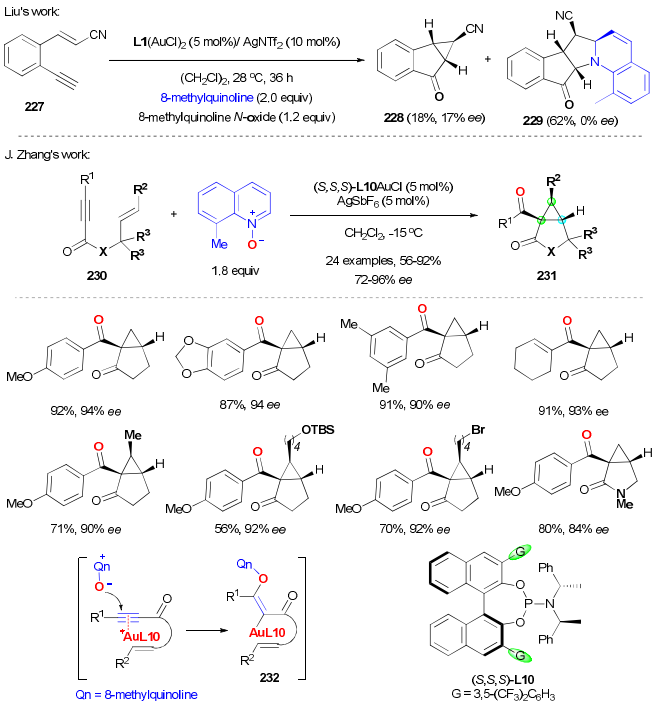
Another synthetically useful 3-aza-bicyclo[3.1.0]-hexan-2-one derivatives **224** can be easily prepared *via* gold-catalyzed oxidative cyclopropanation of *N*-allyl ynamides **223** (Scheme 46, top).[64a] The substrate is readily accessible, and various substituents such as an ester, aryl, or acyl group are well tolerated. However, the introduction of an electron-rich aromatic ring to the alkyne moiety (R^2) resulted in 1,2-dicarbonyl compound as the major product. Protecting groups (R^1) such as Ms, Ns, SES, *p*-$MeOC_6H_4SO_2$, and *p*-$BrC_6H_4SO_2$ are compatible in this transformation. Moreover, the mechanistic study excludes the gold carbene as the key intermediate, which reveals the complexity of the mechanism of the gold-catalyzed oxidative reaction. Consequently, Li *et al*. proposed that gold-activated **223** was attacked by pyridine *N*-oxide to afford intermediate **225**. Subsequent intramolecular nucleophilic addition of an alkenyl moiety and loss of pyridine would lead to the formation of **226**, which would undergo cyclization to afford the final product **224**. Soon after, the "gold-like'' reactivity was found in Rh(I) complexes with appropriate ligands by Tang and co-workers (Scheme 46, bottom).[64b] They demonstrated that Rh(I) carbenoid produced from oxidation ynamides could also react with various substituted alkenes to afford the above 3-azabicyclo[3.1.0] hexane structures. Their DFT calculations indicated that this process is most likely to occur *via* a concerted cyclopropanation pathway.



Scheme 46 Gold-catalyzed oxidative cyclopropanation of *N*-allylynamides.

Despite significant achievements in oxidative functionalization of alkynes, the catalytic enantioselective version was

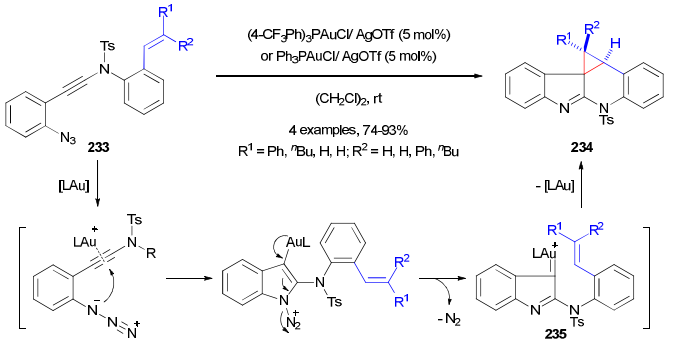
unprecedented until Liu *et al.*[65] disclosed a single example of asymmetric intramolecular cyclopropanation of 1,5-enyne, yet unfortunately to afford the cyclopropane **228** as a byproduct with only 17% *ee* (Scheme 47, top). In 2014, J. Zhang and co-workers[66] successfully realized a highly diastereo- and enantioselective intramolecular cyclopropanation of 1,6-enynes **230** *via* gold(I)-catalyzed alkyne oxidation with the use of chiral phosphoramidite as ligand, leading to optically active bicyclo[3.1.0]hexane-2-ones **231** bearing three contiguous quaternary and tertiary chiral centers with up to 96% *ee*. This new method features a practical one-pot protocol without slow addition of substrates, *i.e.*, ynones can be visualized as a safe and reliable surrogates of acceptor/acceptor diazo compounds. More importantly, control experiments reveal that the *β*-gold vinyloxyquinolinium intermediate **232** rather than the generally proposed gold carbene is involved in the enantiodetermining step. Using tandem mass spectrometry and ion spectroscopy in conjunction with quantum-chemical calculations, Roithová *et al.* also observed that the primarily formed *β*-gold vinyloxypyridinium complexes *via* the intermolecular oxidation reactions can readily undergo rearrangement, dependent on their substituents, to either *α*-oxo gold carbenenoids (a synthetic surrogate of the *α*-oxo carbenes) or pyridine adducts of gold enone complexes in the condensed phase.[67]



Scheme 47 Gold-catalyzed enantioselective alkyne oxidation/cyclopropanation.

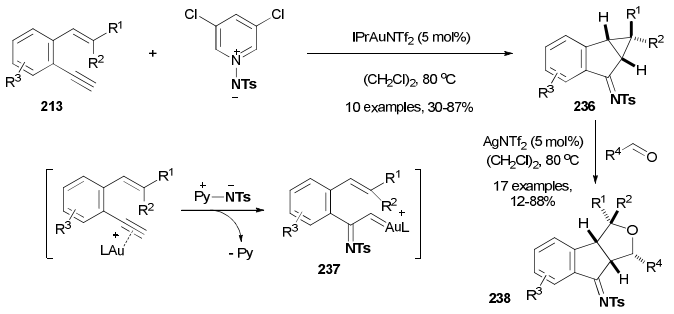
8.2 Alkynes *via* Nitrene Transfer Reaction

Besides oxidation, nitrene transfer to alkynes under gold catalysis could generate *α*-imino gold carbenes. In 2005, Toste *et al*. reported the use of azide as an effective nitrene equivalent for the generation of a gold-carbenoid species in their synthesis of pyrroles.[68a] Following on from this pioneering work, Gagosz[68b] and L. Zhang[68c] independently reported the elegant synthesis of indoles from alkynyl azides by the nucleophilic addition of alcohols or arenes to gold carbenoids. Most recently, Fujii, Ohno and co-workers[69] developed a novel entry to cyclopropane-derived indoloquinoline frameworks **234** *via* the gold-catalyzed cascade cyclization of (azido)ynamides (Scheme 48). An *α*-amidino gold carbenoid **235** was formed in this reaction, which could be intramolecularly trapped by the alkene.



Scheme 48 Gold-catalyzed cascade cyclization of (azido)ynamides.

With the nitrogen counterpart of pyridine *N*-oxides, iminopyridinium ylides as the nitrene-transfer reagent, *α*-imino gold carbenoids could be generated *via* gold-promoted nitrenation of alkynes.[70a] Liu *et al.*[70b] reported a related reaction, gold-catalyzed iminocyclizations of 1,5-enynes **213**, leading to cyclopropyl-indanimines **236** (Scheme 49). In this transformation, an *α*-imino gold carbenoid **237** was postulated as the key intermediate. Furthermore, a silver-catalyzed stereoselective [3+2] cycloadditions between cyclopropylindanimines **236** bearing a strained bicyclo[3.1.0]hexane framework and aldehydes would take place. The stereochemical course of this cycloaddition is rationalized with a cyclic transition state.

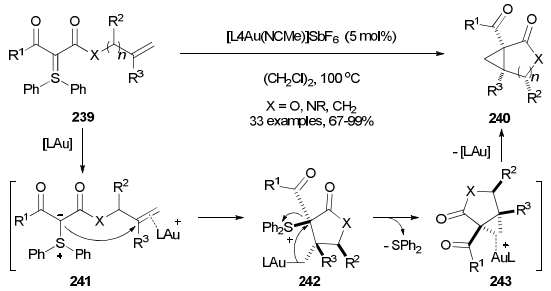


Scheme 49 Gold-catalyed nitrenation/cyclopropanation of 1,5-enynes.

9. Cyclopropanation of Sulfonium Ylides

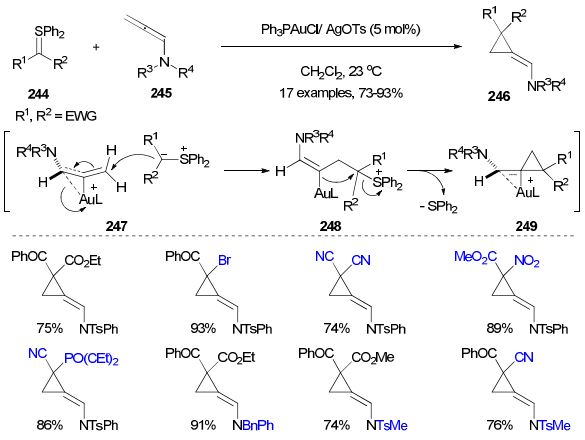
In contrast to the in-situ generated metallocarbene pathways, a novel instance of gold-catalyzed intramolecular cyclopropanation of olefins through sulfonium ylides was described by Maulide and co-workers in 2011 (Scheme 50).[71] Generally, a range of densely functionalized heterobicycles and carbocycles **241** were produced in high yields with high stereoselectivity starting from readily available and easily handled sulfonium

ylides **239**. Computational and experimental investigations suggested the initial cationic Au(I) species based electrophilc activation of the C = C bond, with consequent nucleophilic attack by the ylidic carbon onto the internal carbon of the double bond (**241**). Next, the intermediate lactone **242** underwent cyclopropanation, delivering SPh_2 as a leaving group. The catalytic cycle is closed by a ligand exchange reaction, with release of the product and addition of a new substrate molecule. All steps of the calculated mechanism are thermodynamically favorable, and the rate limiting step corresponds to lactone ring formation (from **241** to **242**).



Scheme 50 Gold-catalyzed intramolecular cyclopropanation by sulfonium ylides.

Quite recently, the same group successfully expanded their strategy to the intermolecular version (Scheme 51).[72] Consequently, a stereoselective gold(I)-catalyzed intermolecular cyclopropanation of allenamides with stabilized sulfonium ylides was developed. This process proceeds under very mild conditions through allene activation supported by DFT calculations, leading to a variety of diacceptor methylenecyclopropanes in good yields and with remarkable *E*-selectivity. As shown in intermediate **247**, intermolecular attack of the ylidic carbon atom on the terminal allene C atom results in the gold–vinyl complex **248** (the rate-limiting step). Subsequently, loss of SPh_2 and nucleophilic attack of the metallic C(sp^2) back onto the original ylidic carbon leads to the formation of complex **249**. Finally, ligand exchange with release of the product and addition of a new molecule complete the catalytic cycle. Stereochemical constraints force the two consecutive C–C bond formation steps to occur as far as possible away from the *N* atom and from its bulky substituents, leading to exclusive formation of the *E* isomer of the product.



Scheme 51 Gold-catalyzed intermolecular cyclopropanation by sulfonium ylides.

4. Conclusions

In comparison with traditional transition metals (*e.g.*, Rh, Ru, Cu, Ag, and Co), despite in its infancy, gold-catalyzed cyclopropanation reactions has emerged as a new platform to develop new tandem reactions and construct unprecedented molecular architectures from relatively simple and readily available starting materials. The efficiency of several representative precursors such as alkynes, propargyl esters, cyclopropenes, and sulfonium ylides as safe surrogates of diazo compounds for gold catalyzed cyclopropanation has been highlighted. Moreover, the scope and versatility of previously reported transition metal catalyzed cyclopropanation reactions (*e.g.*, Rh catalysts) could be enhanced by using new gold catalysts, which may further stimulate the development of new cyclopropanation reactions. With respect to the myriad synthetic and theoretical studies devoted to catalytic cyclopropanation, only a few examples of asymmetric reactions have been developed to date.

From this literature overview, only a few guidelines can be sketched for the development of the current gold catalyzed cyclopropanation toolbox:

★ High catalyst efficiency can be attained in these reactions by the choice of appropriate catalyst–precursor pairs.

★ Gold complexes derived from the electronic-rich and steric-bulky ligands (*e.g.*, IPr, JohnPhos) seem to have quite general applicability.

★ The gold-catlyzed cyclopropanation *via* decomposition of diazo reagents has been extremely less explored with comparison to that with other noble metals (*e.g.*, Rh, Ru, and Cu).

★ The cyclopropanation processes can occur both in a concerted or stepwise fashion depending on the substrates and generated gold-carbenoid species.

★ In some cases, the initial products of these reactions are often themselves highly reactive and can engage in cascade sequences, *e.g.,* tandem cyclopropanation/Cope rearrangement, leading to the rapid construction of complex skeletons.

★ Although several chiral backbones are emerging as successful ligands to induce high enantioselective cyclopropanation, none of them is general at present.

In the future, breakthroughs in several fronts are desirable: (1) better understanding of the reactivity modes of gold carbenoids via extensive mechanistic investigations and DFT calculations; (2) the development of more atom-economic and greener precursors enables gold carbenoids to generate; (3) lowering the catalyst loading (≤ 0.5 mol%) so that operations of industrial scale could become affordable; (4) expanding the current toolbox of cyclopropanation reactions, and in particular the number of enantioselective variants promoted by chiral gold complexes, to prepare new and challenging molecular targets; (5) Application to the synthesis of natural products and functional molecules. Furthermore, the coupling of the new

reactivity of gold complexes with their capability to catalyze cyclopropanations should offer ample opportunities for the design of new reactions. A more extensive development of synthetic applications, including the synthesis of natural and biologically active compounds, can be easily anticipated.

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Notes and references

1 (*a*) *The Chemistry of the Cyclopropyl Group*, ed. S. Patai and Z. Rappoport, John Wiley and Sons, New York, 1987; (*b*) *Small Ring Compounds in Organic Synthsis VI*, ed. A. de Meijere, Springer, Berlin, Germany, 2000; (*c*) B.-L. Lu, L. Dai and M. Shi, *Chem. Soc. Rev.*, 2012, **41**, 3318–3339.

2 (*a*) R. J. Breckenridge and C. J. Suckling, *Tetrahedron*, 1986, **42**, 5665–5677; (*b*) J. Salaun, *Chem. Rev*., 1989, **89**, 1247-1270; (*c*) J. Salaün, *Top. Curr. Chem.*, 2000, **207**, 1–67; (*d*) W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589–8627; (*e*) R. Faust, *Angew. Chem., Int. Ed.*, 2001, **40**, 2251–2253; (*f*) L. A. Wessjohann, W. Brandt and T. Thiemann, *Chem. Rev*. 2003, **103**, 1625-1648; (*g*) J. A. Bull and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 1895–1902; (*h*) D. Y.-K. Chen, R. H. Pouwer and J.-A. Richard, *Chem. Soc. Rev.*, 2012, **41**, 4631–4642.

3 (*a*) A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385−5453; (*b*) *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, ed. M. P. Doyle, M. A. McKervey and T. Ye, Wiley-Interscience, New York, 1998; (*c*) M. P. Doyle and D. C. Forbes, *Chem. Rev*., 1998, **98**, 911–936; (*d*) H. M. L. Davies and E. G. Antoulinakis, *Org. React*., 2001, **57**, 1–326; (*e*) H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev*., 2003, **103**, 977–1050; (*f*) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev*., 2003, **103**, 2861–2904; (*g*) G. Maas *Chem. Soc. Rev.*, 2004, **33**, 183–190; (*h*) H. Pellissier, *Tetrahedron*, 2008, **64**, 7041–7095; (*i*) *Contemporary Carbene Chemistry*, ed. R. A. Moss and M. P. Doyle, Wiley, New York, 2014.

4 (*a*) A. S. K. Hashmi, *Gold Bull*. 2004, **37**, 51-65; (*b*) N. Marion and S. P. Nolan, *Angew. Chem., Int. Ed*., 2007, **46**, 2750–2752; (*b*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395–403; (*c*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211; (*d*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun*., 2007, 333–346; (*e*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed*., 2007, **46**, 3410–3449; (*f*) A. Duschek and S. F. Kirsch, *Angew. Chem., Int. Ed*., 2008, **47**, 5703–5705; (*g*) R. Skouta and C.-J. Li, *Tetrahedron*, 2008, **64**, 4917–4938; (*h*) Z. Li, C. Brouwer and C. He, *Chem. Rev*., 2008, **108**, 3239–3265; (*i*) A. Arcadi, *Chem. Rev*., 2008, **108**, 3266–3325; (*j*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev*., 2008, **108**, 3326–3350; (*k*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev*., 2008, **108**, 3351–3378; (*l*) N. T. Patil and Y. Yamamoto, *Chem. Rev*., 2008, **108**, 3395–3442; (*m*) S. Wang, G. Zhang and L. Zhang, *Synlett*, 2010, 692–706; (*n*) H. Schmidbaur and A. Schier, *Organometallics*, 2010, **29**, 2–23; (*o*) F. López and J. L. Mascareñas, *Beilstein J. Org. Chem*., 2011, **7**, 1075–1094; (*p*) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev*., 2011, **111**, 1657–1712; (*q*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994–2009; (*r*) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev*., 2011, **40**, 1910–1925; (*s*) M. Bandini, *Chem. Soc. Rev*., 2011, **40**, 1358–1367; (*t*) Matthias Rudolph and A. Stephen K. Hashmi, *Chem. Soc. Rev*., 2012, **41**, 2448–2462; (*u*) L.-P. Liu, G. B. Hammond, *Chem. Soc. Rev*. 2012, **41**, 3129–3139; (*v*) A. S. K. Hashmi, *Acc. Chem. Res.*, 2014, **47**, 864–876; (*w*) D. Qian and J. Zhang, *Chem. Rec.*, 2014, **14**, 280–302; (*x*) J. Xie, C. Pan, A. Abdukader and C. Zhu, *Chem. Soc. Rev*., 2014, **43**, 5245–5256.

5 (*a*) R. A. Widenhoefer, *Chem. Eur. J.*, 2008, **14**, 5382–5391; (*b*) N. Bongers and N. Krause, *Angew. Chem., Int. Ed*., 2008, **47**, 2178–2181; (*c*) S. Sengupta, X. Shi, *ChemCatChem*, 2010, **2**, 609–619; (*d*) A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis*, 2011, 1501–1514; (*e*) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.*, 2014, **47**, 889–901.

6 (*a*) A. S. K. Hashmi, *Angew. Chem., Int. Ed*., 2008, **47**, 6754–6756; (*b*) A. M. Echavarren, *Nat. Chem*., 2009, **1**, 431–433; (*c*) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard III and F. D. Toste, *Nat. Chem*., 2009, **1**, 482–486; (*d*) A. S. K. Hashmi, *Angew. Chem., Int. Ed*., 2010, **49**, 5232–5241; (*e*) *Modern Gold Catalyzed Synthesis*, ed. A. S. K. Hashmi and F. D. Toste, Wiley-VCH, Weinheim, 2012; (*f*) C. Obradors, A. M. Echavarren, *Chem. Commun*., 2014, **50**, 16–28.

7 A. Fürstner and L. Morency, *Angew. Chem., Int. Ed*., 2008, **47**, 5030–5033.

8 (*a*) A. Fedorov, M.-E. Moret and P. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 8880–8881; (*b*) D. H. Ringger and P. Chen, *Angew. Chem., Int. Ed*., 2013, **52**, 4686–4689; (c) D. H. Ringger, I. J. Kobylianskii, D. Serra and Peter Chen, *Chem. Eur. J*., 2014, **20**, 14270–14281.

9 (*a*) M. Fañanás-Mastral and F. Aznar, *Organometallics*, 2009, **28**, 666–668.; (*b*) R. E. M. Brooner and R. A. Widenhoefer, *Chem. Commun*., 2014, **50**, 2420–2423; (*c*) R. J. Harris and R. A. Widenhoefer, *Angew. Chem., Int. Ed*. 2014, **53**, 9369–9371; (*d*) M. W. Hussong, F. Rominger, P. Krämer and B. F. Straub, *Angew. Chem., Int. Ed*., 2014, **53**, 9372– 9375; (*e*) M. Joost, L. Estévez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune and D. Bourissou, *Angew. Chem., Int. Ed*., 2014, **53**, DOI: 10.1002/anie.201407684; (*f*) G. Seidel and A. Fürstner, *Angew. Chem., Int. Ed*., 2014, **53**, 4807–4811

10 C. Nieto-Oberhuber, M. Paz Munoz, E. Bunuel, C. Nevado, D. J. Cardenas and A. M. Echavarren, *Angew. Chem., Int. Ed*., 2004, **43**, 2402–2406.

11 (*a*) C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 864–876; (*b*) L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal*., 2006, **348**, 2271–2296; (*c*) I. D. G. Watson and F. D. Toste, *Chem. Sci.* 2012, **3**, 2899–2919; (*d*) V. Michelet, P. Y. Toullec and J.-P.

Genet, *Angew. Chem., Int. Ed*., 2008, **47**, 4268–4315; (*e*) A. Fürstner, *Chem. Soc. Rev*., 2009, **38**, 3208–3221; (*f*) A. Marinetti, H. Jullien and A. Voituriez, *Chem. Soc. Rev*., 2012, **41**, 4884–4908.

12 V. Mamane, T. Gress, H. Krause and A. Fürstner, *J. Am. Chem. Soc*., 2004, **126**, 8654–8655.

13 (*a*) M. R. Luzung, J. P. Markham and F. D. Toste, *J. Am. Chem. Soc*. 2004, **126**, 10858–10859; (*b*) L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc*. 2004, **126**, 11806–11807.

14 S. Couty, C. Meyer and Janine Cossy, *Tetrahedron*, 2009, **65**, 1809–1832.

15 (*a*) C.-M. Chao, D. Beltrami, P. Y. Toullec and V. Michelet, *Chem. Commun*., 2009, 6988–6990; (*b*) A. Pradal, C.-M. Chao, P. Y. Toullec and V. Michelet, *Beilstein J. Org. Chem*., 2011, **7**, 1021–1029.

16 (*a*) H. Teller, S. Flügge, R. Goddard and A. Fürstner, *Angew. Chem., Int. Ed*., 2010, **49**, 1949–1953; (*b*) H. Teller and A. Fürstner, *Chem. Eur. J*., 2011, **17**, 7764–7767; (*c*) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel and A. Fürstner, *J. Am. Chem. Soc*., 2012, **134**, 15331–15342.

17 (*a*) K. Yavari, P. Aillard, Y. Zhang, F. Nuter, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem., Int. Ed*., 2014, **53**, 861–865; (*b*) P. Aillard, A. Voituriez, D. Dova, S. Cauteruccio, E. Licandro and A. Marinetti, *Chem. Eur. J.,* 2014, **20**, 12373–12376.

18 (*a*) S. Y. Kim, Y. Park and Y. K. Chung, *Angew. Chem., Int. Ed*., 2010, **49**, 415–418; (*b*) Z. Cao and F. Gagosz, *Angew. Chem., Int. Ed*., 2013, **52**, 9014–9018.

19 A. Simonneau, Y. Harrak, L. Jeanne-Julien, G. Lemière, V. Mouriès-Mansuy, J.-P. Goddard, M. Malacria and L. Fensterbank, *ChemCatChem*, 2013, **5**, 1096–1099.

20 (*a*) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda and F. D. Toste, *J. Am. Chem. Soc*., 2009, **131**, 2809–2811; (*b*) Y. Liu, D. Zhang, J. Zhou and C. Liu, *J. Phys. Chem. A*, 2010, **114**, 6164–6170.

21 S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2011, **50**, 5090–5094.

22 (*a*) C. H. M. Amijs, C. Ferrer and A. M. Echavarren, *Chem. Commun*., 2007, 698–700; (*b*) C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer and A. M. Echavarren, *J. Org. Chem*., 2008, **73**, 7721–7730.

23 (*a*) C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc*., 2007, **129**, 5838–5839; (*b*) W. Wang, J. Yang, F. Wang and M. Shi, *Organometallics*, 2011, **30**, 3859–3869; (*c*) H.-S. Yeom and S. Shin, *Org. Biomol. Chem*., 2013, **11**, 1089–1092.

24 (*a*) S. G. Sethofer, S. T. Staben, O. Y. Hung and F. D. Toste, *Org. Lett*., 2008, **10**, 4315–4318; (*b*) D.-H. Zhang, Y. Wei and M. Shi, *Chem. Eur. J*., 2012, **18**, 7026 –7029.

25 C. Nieto-Oberhuber, S. López, M. P. Muñoz, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas and A. M. Echavarren, *Chem. Eur. J*., 2006, **12**, 1694–1702.

26 S. M. Kim, J. H. Park, S. Y. Choi and Y. K. Chung, *Angew. Chem., Int. Ed.*, 2007, **46**, 6172–6175.

27 V. López-Carrillo, N. Huguet, Á. Mosquera and A. M. Echavarren, *Chem. Eur. J*., 2011, **17**, 10972–10978.

28 (*a*) S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber and A. M. Echavarren, *Angew. Chem., Int. Ed*., 2006, **45**, 6029–6032; (*b*) P. Pérez-Galán, E. Herrero-Gómez, D. T. Hog, N. J. A. Martin, F. Maseras and A. M. Echavarren, *Chem. Sci*., 2011, **2**, 141–149; (*c*) L. Batiste, A. Fedorov and P. Chen, *Chem. Commun*., 2010, **46**, 3899–3901.

29 (*a*) E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio and A. M. Echavarren, *Angew. Chem., Int. Ed*., 2009, **48**, 6152–6155; (*b*) J. Carreras, M. Livendahl, P. R. McGonigal and A. M. Echavarren, *Angew. Chem., Int. Ed*., 2014, **53**, 4896–4899.

30 M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon and A. M. Echavarren, *Angew. Chem., Int. Ed*., 2013, **52**, 6396–6399.

31 (*a*) K. Miki, F. Nishino, K. Ohe and S. Uemura, *J. Am. Chem. Soc*., 2002, **124**, 5260–5261; (*b*) K. R. Vicente, J. González, L. Riesgo, J. González and L. A. López, *Angew. Chem., Int. Ed*., 2012, **51**, 8063–8067; (c) Y. Xia, S. Qu, Q. Xiao, Z.-X. Wang, P. Qu, L. Chen, Z. Liu, L. Tian, Z. Huang, Y. Zhang and J. Wang, *J. Am. Chem. Soc*., 2013, **135**, 13502−13511.

32 (*a*) T. Wang and J. Zhang, *Dalton Trans.,* 2010, **39**, 4270−4273; (*b*) J. Ma, H. Jiang and S. Zhu, *Org. Lett*., 2014, **16**, 4472–4475.

33 M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo and P. J. Pérez, *Angew. Chem., Int. Ed*., 2005, **44**, 5284–5288.

34 A. Prieto, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, P. Pérez-Galán, N. Delpont and Echavarren, A. M. *Tetrahedron*, 2009, **65**, 1790–1793.

35 J. F. Briones and H. M. L. Davies, *J. Am. Chem. Soc*., 2012, **134**, 11916–11919.

36 Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou and K. Ding, *J. Am. Chem. Soc*., 2013, **135**, 8197–8200.

37 (*a*) K. Miki, K. Ohe and S. Uemura, *Tetrahedron Lett*., 2003, **44**, 2019–2022; (*b*) K. Miki, K. Ohe and S. Uemura, *J. Org. Chem*., 2003, **68**, 8505-8513.

38 M. J. Johansson, D. J. Gorin, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc*., 2005, **127**, 18002–18003.

39 (*a*) J. Petuškova, H. Bruns and M. Alcarazo, *Angew. Chem., Int. Ed*., 2011, **50**, 3799–3802; (*b*) K. Fourmy, S. Mallet-Ladeira, O. Dechy-Cabaret and M. Gouygou, *Organometallics,* 2013, **32**, 1571−1574; (*c*) C. A. Sperger, J. E. Tungen and A. Fiksdahl, *Eur. J. Org. Chem*., 2011, 3719–3722.

40 (*a*) L. F. Tietze, *Chem. Rev*., 1996, **96**, 115–136; (*b*) J.-C. Wasilike, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev*., 2005, **105**, 1001–1020; (*c*) A. E. Allen and D. W. C. MacMillan, *Chem. Sci*., 2012, **3**, 633-658.

41 (*a*) D. J. Gorin, P. Dubé and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 14480–14481; (*b*) D. J. Gorin, I. D. G. Watson and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 3736–3737.

42 D. Garayalde, K. Krüger and C. Nevado, *Angew. Chem., Int. Ed*., 2011, **50**, 911–915.

43 E. Rettenmeier, A. M. Schuster, M. Rudolph, F. Rominger, C. A. Gade and A. S. K. Hashmi, *Angew. Chem., Int. Ed*., 2013, **52**, 5880 –5884.

44 (*a*) W. Rao, M. J. Koh, D. Li, H. Hirao and P. W. Chan, *J. Am. Chem. Soc*., 2013, **135**, 7926–7932; (*b*) T. Lauterbach, M. Ganschow, M. W. Hussong, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Adv. Synth. Catal*., 2014, **356**, 680–686.

45 (*a*) A. Fürstner and P. Hannen, *Chem. Eur. J*., 2006, **12**, 3006–3019; (*b*) A. Fürstner and A. Schlecker, *Chem. Eur. J*., 2008, **14**, 9181–9191.

46 (*a*) X. Moreau, J.-P. Goddard, M. Bernard, G. Lemière, J. M. López-Romero E. Mainetti, N. Marion, V. Mouriès, S. Thorimbert, L. Fensterbank and M. Malacria, *Adv. Synth. Catal*., 2008, **350**, 43–48; (*b*) X. Moreau, A. Hours, L. Fensterbank, J.-P. Goddard, M. Malacria and S. Thorimbert, *J. Organomet. Chem*., 2009, **694**, 561–565.

47 (*a*) F.-D. Boyer, X. L. Goff and I. Hanna, *J. Org. Chem*., 2008, **73**, 5163–5166; (*b*) I. D. G. Watson, S. Ritter and F. D. Toste, *J. Am. Chem. Soc*., 2009, **131**, 2056–2057.

48 W. Rao, Sally, S. N. Berry and P. W. H. Chan, *Chem. Eur. J*., 2014, **20**, 13174–13180.

49 A. Buzas and F. Gagosz, *J. Am. Chem. Soc*., 2006, **128**, 12614–12165.

50 (*a*) N. Marion, P. de Frémont, G. Lemière, E. D. Stevens, L. Fensterbank, M. Malacria and S. P. Nolan, *Chem. Commun.*, 2006, 2048–2050; (*b*) N. Marion, G. Lemière, A. Correa, C. Costabile, R. S. Ramon, X. Moreau, P. de Frémont, R. Dahmane, A. Hours, D. Lesage, J.-C. Tabet, J.-P. Goddard, V. Gandon, L. Cavallo, L. Fensterbank, M. Malacria and S. P. Nolan, *Chem. Eur. J*., 2009, **15**, 3243–3260.

51 (*a*) G. Lemière, V. Gandon, K. Cariou, T. Fukuyama, A. Dhimane, L. Fensterbank and M. Malacria, *Org. Lett*., 2007, **9**, 2207–2211; (*b*) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, and M. Malacria, *J. Am. Chem. Soc*. 2009, **131**, 2993–3006; (*c*) L. Fensterbank and M. Malacria, *Acc. Chem. Res.*, 2014, **47**, 953–965.

52 (*a*) F. Miege, C. Meyer and C. Cossy, *Beilstein J. Org. Chem*., 2011, **7**, 717–734; (*b*) Z.-B. Zhu, Y. Weib and M. Shi, *Chem. Soc. Rev*., 2011, **40**, 5534–5563; (*c*) D.-H. Zhang, X.-Y. Tang and M. Shi, *Acc. Chem. Res.*, 2014, **47**, 913–924.

53 (*a*) J. T. Bauer, M. S. Hadfield and A.-L. Lee, *Chem. Commun*., 2008, 6405–6407; (*b*) Y. Zhou, B. G. Trewyn, R. J. Angelici and L. K. Woo, *J. Am. Chem. Soc*., 2009, **131**, 11734–11743.

54 (*a*) F. Miege, C. Meyer and C. Cossy, *Org. Lett.,* 2010, **12**, 4144–4147; (*b*) F. Miege, C. Meyer and C. Cossy, *Chem. Eur. J.,* 2012, **18**, 7810–7822.

55 P. J. Pérez, M. M. Díaz-Requejo and I. Rivilla, *Beilstein J. Org. Chem*., 2011, **7**, 653–657.

56 C. R. Solorio-Alvarado and A. M. Echavarren, *J. Am. Chem. Soc*., 2010, **132**, 11881−11883.

57 (*a*) A. Fedorov and P. Chen, *Organometallics*, 2010, **29**, 2994−3000; (*b*) A. Fedorov, L. Batiste, A. Bach, D. M. Birney and P. Chen, *J. Am. Chem. Soc*. 2011, **133**, 12162−12171.

58 (*a*) C. R. Solorio-Alvarado, Y. Wang and A. M. Echavarren, *J. Am. Chem. Soc*., 2011, **133**, 11952**–**11955; (*b*) Y. Wang, P. R. McGonigal, B. Herle, M. Besora and A. M. Echavarren, *J. Am. Chem. Soc*., 2014, **136**, 801−809.

59 (*a*) J. Xiao and X. Li, *Angew. Chem., Int. Ed*., 2011, **50**, 7226–7236; (*b*) L. Zhang, *Acc. Chem. Res.,* 2014, **47**, 877–888; (*c*) H.-S. Yeom and S. Shin, *Acc. Chem. Res.,* 2014, **47**, 966–977.

60 (*a*) L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc*., 2010, **132**, 3258–3259; (*b*) B. Lu, C. Li and L. Zhang, *J. Am. Chem. Soc*., 2010, **132**, 14070–14072; (*c*) W. He, C. Li and L. Zhang, *J. Am. Chem. Soc.,* 2011, **133**, 8482–8485; (*d*) H. S. Yeom, J. E. Lee and S. Shin, *Angew. Chem., Int. Ed*., 2008, **47**, 7040–7043; (*e*) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15372–15375; (*f*) N. Asao, K. Sato and Y. Yamamoto, *Tetrahedron Lett.*, 2003, **44**, 5675–5677.

61 D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das and R.-S. Liu, *Angew. Chem., Int. Ed*., 2011, **50**, 6911–6914.

62 D. Qian and J. Zhang, *Chem. Commun*., 2011, **47**, 11152–11154.

63 K. Ji and L. Zhang, *Org. Chem. Front.,* 2014, **1**, 34–38.

64 (*a*) K.-B. Wang, R.-Q. Ran, S.-D. Xiu and C.-Y. Li, *Org. Lett*., 2013, **15**, 2374–2377; (*b*) R. Liu, G. N. Winston-McPherson, Z.−Y. Yang, X. Zhou, W. Song, I. A. Guzei, X. Xu and W. Tang, *J. Am. Chem. Soc*. 2013, **135**, 8201–8204.

65 D. B. Huple, S. Ghorpade and R.-S. Liu, *Chem. Eur. J*., 2013, **19**, 12965–12969.

66 D. Qian, H. Hu, F. Liu, B. Tang, W. Ye, Y. Wang and J. Zhang, *Angew. Chem., Int. Ed*., 2014, **53**, DOI: 10.1002/anie.201407717.

67 J. Schulz, L. Jašíková, A. Škríba and J. Roithová, *J. Am. Chem. Soc*., 2014, **136**, 11513–11523.

68 (*a*) D. J. Gorin, N. R. Davis and F. D. Toste, *J. Am. Chem. Soc*., 2005, **127**, 11260–11261; (*b*) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354–7358; (*c*) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8358–8362.

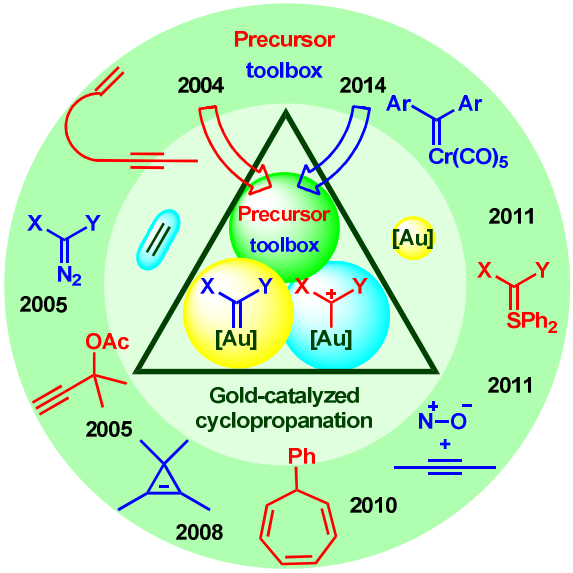
69 Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett*., 2014, **16**, 3138–3141.

70 (*a*) C. Li and L. Zhang, *Org. Lett*. 2011, **13**, 1738–1741; (*b*) H.-H. Hung, Y.-C. Liao and R.-S. Liu, *Adv. Synth. Catal*., 2013, **355**, 1545–1552.

71 X. Huang, S. Klimczyk, L. F. Veirosb and N. Maulide, *Chem. Sci*., 2013, **4**, 1105-1110.

72 J. Sabbatani, X. Huang, L. F. Veiros and N. Maulide, *Chem. Eur. J.,* 2014, **20**, 10636–10639.

TOC



A fruitful platform: This review highlights recent advances in gold-catalyzed selective cyclopropanation divided by the type of carbenoid precursors.