Gold-Catalyzed Synthetic Strategies towards Four-Carbon Ring Systems

Guillermo Otárola, Juan J. Vaquero, Estibaliz Merino * and Manuel A. Fernández-Rodríguez *

Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química “Andrés M. del Río” (IQAR), Facultad de Farmacia, Campus Científico-Tecnológico, Universidad de Alcalá (IRYCIS), Autovía A-II, Km 33.1, 28805 Alcalá de Henares, Madrid, Spain; guilleotarola@yahoo.es (G.O.); juanjose.vaquero@uah.es (J.J.V.)
* Correspondence: estibaliz.merino@uah.es (E.M.); mangel.fernandezr@uah.es (M.A.F.-R.)

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Abstract: Four carbon ring systems are frequently present in natural products with remarkable biological activities such as terpenoids, alkaloids, and steroids. The development of new strategies for the assembly of these structures in a rapid and efficient manner has attracted the interest of synthetic chemists for a long time. The current research is focused mainly on the development of synthetic methods that can be performed under mild reaction conditions with a high tolerance to functional groups. In recent years, gold complexes have turned into excellent candidates for this aim, owing to their high reactivity, and are thus capable of promoting a wide range of transformations under mild conditions. Their remarkable efficiency has been thoroughly demonstrated in the synthesis of complex organic molecules from simple starting materials. This review summarizes the main synthetic strategies described for gold-catalyzed four-carbon ring formation, as well as their application in the synthesis of natural products.

Keywords: gold; catalysis; four-membered ring; cyclobutane; cyclobutene; cyclobutanone; [2+2] cycloaddition; ring expansion; allene; alkene; alkyne; pinacol rearrangement; Wagner-Meerwein rearrangement

1. Introduction

Cyclobutanes have been known for more than a century, but their use in organic synthesis has been explored in the last 50 years. Despite being the second most strained saturated carbocycle, it is a structural motif present in many complex natural products [1–6]. Thus, this skeleton can be found among secondary metabolites such as terpenoids [7–9], alkaloids [10,11], or polyketides [12] (Figure 1), many of them with remarkable biological properties such as antibacterial, antiviral, cytotoxic, and immunosuppressive activities. This natural occurrence, the benefits accompanying their use in medicinal chemistry discovery programs, as improving physicochemical and pharmaco-kinetic properties of candidates, as well as its usefulness as building blocks in organic synthesis, have encouraged the development of new methodologies for the construction of these scaffolds. A variety of methods have been described to synthesize cyclobutanes, being thermal and photochemical [2+2] cycloadditions the most common [13–18]. Other methods used for cyclobutane synthesis are: Brook rearrangement of 1,4-dicarbonyl compounds [19], ring expansion of cyclopropanes via pinacol-type rearrangements [20–22], and ring closure [23,24]. Recently, syntheses based on transition metal catalyzed processes have been shown as efficient methods to access cyclobutanes [25–30]. In this context, the development of chiral catalysts has spurred the development of stereoselective methodologies for the synthesis of four-carbon ring systems [31–39]. Furthermore, mainly due to their inherent reactivity,
cyclobutanes, cyclobutenes, and cyclobutanones can also be used as precursors of more complex molecules through ring-opening, ring-expansion, and ring-contraction reactions [40–64].

Gold(I) catalysts behave as soft Lewis π-acids over unsaturated C–C bonds, activating them as electrophiles withdrawing their electron density. There is a significantly higher reactivity over gold-coordinated allenes and alkynes, rather than alkenes [65–80]. Besides, these catalysts are reactive enough to work under mild conditions. Both features define gold(I) complexes as exceptional candidates for late-stage synthesis [81–83]. Therefore, gold catalysts promote chemical transformations unavailable using other metal-derived catalysts or have higher activity and selectivity than less expensive catalysts, thus allowing the reactions to be run at low temperatures and catalyst loadings. Additionally, high regio- and diastereoselective gold-catalyzed processes and the application in asymmetric synthesis have been reported [84–99].

Unsaturated systems activated by gold(I) neutral and cationic complexes can trigger a wide range of nucleophilic additions, processes often understood as cationic stepwise cascade mechanisms in which vinyl-gold species are commonly generated (Figure 2). These intermediates can further react with other nucleophiles, such as double or triple bonds, oxygenated functional groups, or strained cycles through 1,2-alkyl rearrangements. In this context, gold(I) complexes have emerged as efficient catalysts towards four-carbon rings synthesis. As of now, mainly two approaches to access these carbocycles using gold(I) catalysts have been developed: [2+2] cycloadditions and ring expansions. Interestingly, the key step of biosynthetic routes oriented to obtain these rings relies on carbocationic cyclization/cycloisomerization processes, which in general involve [2+2] cycloadditions or occasionally ring expansions, either in a concerted or a stepwise fashion [100].

Figure 1. Natural products containing four-membered rings in their skeleton.
A proper choice of the ligands tethered to the gold atom is needed to obtain satisfactory results. The most used ligands in gold-catalyzed four-carbon ring synthesis are shown in Figure 3. Commonly, the catalysts derived from these ligands are presented as neutral complexes bearing a halogenide, which are used accompanied by silver salts. Under those conditions, silver halogenides precipitate, generating the reactive cationic gold complex. In other cases, preformed cationic catalysts with low or non-coordinating counterions such as hexafluoroantimoniate, hexafluorophosphate, triflate or bis(trifluoromethane)sulfonimide have been employed, avoiding the use and drawbacks related to silver presence. Nevertheless, the assumption that cationic gold species are the unique activators has been questioned, and existing evidences for various processes suggest more complex mechanisms and a key role for silver and other activation factors [101].

On the other hand, the main drawback when applying gold(I) chemistry to asymmetric catalysis is the linear coordination geometry of this metal. It implies that the long distance (approx. 5 Å) between the substrate and chiral ligand does not allow the transfer of chiral information. An additional complication is the nucleophilic attack to the activated substrates out of the coordination sphere. In this context, the development of enantioselective gold(I) catalyzed transformations turns out to be a
challenge. To save these drawbacks, two main approaches involving different types of chiral ligands have been studied: (1) dinuclear biphosphine complexes and (2) monodentate bulky ligands, mainly phosphoramidite derivatives.

This review focuses on gold-catalyzed synthesis of four-carbon ring systems and is organized in three sections. The first section focuses on [2+2] cycloaddition approaches, the second covers Pinacol-and Wagner-Meerwein-like ring expansions, and other cyclizations are covered in the third section.

2. [2+2] Cycloadditions

[2+2] Cycloaddition reaction has been the classical strategy to build four carbon rings. It is understood as a combination of two unsaturated C–C bonds, where the cleavage of 2 π-bonds and the formation of 2 stronger σ-bonds are involved, thus being a thermodynamically driven process. Enynes, allenenes, bisalkynes, and bisallenenes are suitable substrates for gold(I)-catalyzed intramolecular [2+2] cycloadditions through a cationic stepwise cyclization mechanism. Some of the evidences that support this mechanism are regioselectivity, the requirement of a carbocation-stabilizing substituent at the alkene, the intermediate-trapping experiments with nucleophiles, as well as theoretical calculations. The intermolecular version of these transformations is a challenge, since in these cases gold catalyst can promote olefin dimerization and polymerization. Additionally, two unsaturated substrates are involved and can compete for the binding to the gold catalyst.

The classification of this section is based on the combination of alkynes, alkenes, and allenenes.

2.1. Allene–Alkene

The preparation and reactivity of allenes have been extensively studied [102–113]. This type of compound has been used in the synthesis of interesting natural and non-natural products [114–116].

Gold-catalyzed cycloisomerization of allenes 1 to alkylidene-cyclobutanes 2 through [2+2]-cycloaddition reaction was first published by Toste’s group [117]. This transformation provides access to enantioenriched bicyclo[3.2.0] structures 2 using chiral dinuclear gold(I) biaryl phosphine complex (R)-DTBM-SEGPHOS(AuCl)₂. The proposed mechanism proceeds through the reversible cyclization of activated substrate 3 to produce cis- or trans-vinyl-gold species 4. This carbocationic intermediate, not stabilized by gold, evolved to the final cyclobutyl derivatives 2 by cyclization, through the cis-form. However, the kinetically formed trans-carbocation is the intermediate involved when methanol is added to the reaction media, thus producing trans-cyclopentane cycloadduct 5 as a major product (Scheme 1).

![Scheme 1. Gold-catalyzed enantioselective [2+2] cycloaddition of allenes and main intermediates proposed for the general mechanism.](image-url)
In the same way, phosphoramidite ligands have been shown to be useful for these diastereo- and enantioselective gold(I)-catalyzed cycloadditions of allenenes (Scheme 2) [118–120]. A computational study supports a stepwise mechanism in which the alkene adds to the gold coordinated allene, generating a vinyl-gold intermediate. Two possible stereochemical rearrangements through cis-7 and trans-9 can be proposed considering the relative position of substituents on the formed cyclopentane ring. In both pathways, an interaction between the carbocation and gold forming a five membered metallacycle is suggested by the calculations. On the cis pathway, the intermediate evolves to the formation of cyclobutene derivatives 8 through demetalation, whereas carbocationic intermediate trans-9 is kinetically trapped with methanol to deliver 3,4-disubstituted pyrrolidines 10 possessing three contiguous stereogenic centers. Experimentally, the irreversible formation of 8 was demonstrated since alkoxycyclization product 10 was not observed by its exposition to (PhO)$_3$PAuBF$_4$ in the presence of methanol. This conclusion is in contrast with Fürstner’s work, where related cyclobutenes 8’ in the presence of a N-heterocyclic carbene 12 AuCl complex undergoes a rearrangement to give thermodynamically favored ring-expansion bicyclic [3.3.0] products through carbocation 11 [121].

Moreover, in contrast to the cationic stepwise mechanism commonly proposed [122,123], a recent work suggests a concerted pathway that precludes the intermediacy of vinyl-gold species 7 [124].

Related indolyl-allenes 15 are suitable substrates for the simple and straightforward synthesis of indole-fused heterocycles 16 under mild conditions and in an atom economical way, through formal [2+2] cycloaddition. Highly regioselective exo [2+2] cycloaddition is observed in the presence of IPrAuCl/AgNTf$_2$, in which allene serves as a 2C synthon. Nevertheless, an all-carbon quaternary stereocenter is generated through formal [3+2] cycloaddition affording...
diazabenzo[a]cyclopaenta[cd]azulenes 17 when JohnPhosAuCl/AgNTf$_2$ is employed as catalyst (Scheme 3) [125].

![Scheme 3](image)

Diastereoselective [2+2] and [3+2] intramolecular cycloadditions of allenes with indoles.

Recently, chiral HelPhos-V gold (I) complexes based on new chiral phosphathiahelicenes have been used as catalysts in the enantioselective [2+2] cyclization of N-homoalleny1 tryptamine derivatives 18 to afford polycyclic indole derivatives 19 with three contiguous stereogenic centers in good yields and up to 92% ee (Scheme 4) [126]. Related phospha [6] helicenes have also shown high efficiency in terms of enantioselectivity and catalytic activity in this type of [2+2] cycloaddition reaction [127].

![Scheme 4](image)

Diastereoselective [2+2] cycloadditions of indolyl-allenes 18.

In general, switching from intramolecular to intermolecular processes implies drawbacks related to loss of regio- and stereoselectivity. However, similar conditions to those used in the intramolecular version allow for the maintaining of similar levels of regio- and enantioselectivity in gold-catalyzed intermolecular [2+2] cycloadditions of allenamides with alkenes [128–131]. In all the reported examples, the presence of an adjacent nitrogen in the allene moiety favors the regioselectivity by polarity induction generating, after coordination of the catalyst, a vinyl-gold conjugated acyliminium intermediate 20 that then evolves by nucleophilic addition of an electron-rich alkene (Scheme 5).

Chen’s group first reported an efficient and selective intermolecular [2+2] cycloaddition approach to cyclobutane scaffolds using terminal allenamide 21 and alkenes 22 substituted by electron-donor groups, as enol ethers, in the presence of catalytic amounts of JohnphosAuCl/AgSBF$_6$. Under these conditions, the corresponding products 23 with Z configuration are obtained (Scheme 6) [129].
Scheme 5. General mechanism for gold-catalyzed [2+2] cycloaddition between allenamides and electron-rich alkenes.

Scheme 6. Gold-catalyzed [2+2] cycloaddition between allenamides 21 and activated alkenes 22.

The use of a phosphite-based gold(I) catalyst allows for extending the scope to internal allenyl sulfonamides 24 (Scheme 7) with the exclusive formation of the cis adducts 25 [130]. Aryl, alkyl, or benzyl substitution at the nitrogen atom is well tolerated, as well as cyclic and acyclic enol ethers.

Scheme 7. Gold-catalyzed [2+2] cycloaddition between internal N-allenylsulfonamides and enol ethers.

In addition, the behaviour of α,β-unsaturated N,N-alkyl hydrazones 26 in gold-catalyzed [2+2] cycloadditions with allenamides has been studied (Scheme 8). This transformation provides densely substituted cyclobutanes 27 with an all-carbon quaternary stereocenter. Excellent levels of regio- and diastereoselectivity and good yields are obtained, although in some cases mixtures of E/Z isomers were observed. Of note, the configuration of the alkene substrate is preserved in the final product, which is associated with steric factors [132].
Gold complexes with phosphoramidite ligands 30–33 have shown satisfactory control of the enantioselectivity in reactions of N-allenylsulfonamides 28 with styrenes 29. The reaction works at low temperature due to the high reactivity of the allenes. The cycloaddition is compatible with electron withdrawing and electron donating substituents on the aromatic ring and no effect is observed with substitution at the different positions. In addition, the reaction conditions have allowed the synthesis of cyclobutanes containing challenging all-carbon quaternary stereocenters (Scheme 9) [133].

Scheme 9. Gold-catalyzed [2+2] cycloaddition between styrenes and allenyl sulfonamides.
3-(Propa-1,2-dien-1-yl)oxazolidin-2-one has been shown to be an efficient two carbon partner in a complete regio- and stereocontrolled intramolecular gold-catalyzed [2+2] cycloaddition with alkenes (Scheme 10). Trans isomer 35 is obtained regardless of alkene configuration. A stepwise cationic pathway involving cationic intermediates is proposed as mechanism. The nucleophilic attack of the alkene to a second cationic intermediate 34 would be the regioselectivity-determining step, favoring the formation of more stabilized benzylic or iminium cation [128,134]. Gold complex 36 with chiral 1,2,3-triazolylidene ligand has proven successful for enantioselective transformations over these substrates [135].

\[
R^1 = -\text{N(Me)}-\text{CO}_2\text{Bn}, -\text{N(nPr)}-\text{CO}_2\text{Me}, \text{N-oxazolidinonyl}, \text{N-pyrrolidin-2-onyl}, \text{Ar}
\]

\[
R^1:R^2 = -\text{N(Boc)}-\text{oPr}, -\text{N(Boc)}-\text{(CH}_2)_2-, R^1:R^2 = \text{H}, -\text{(CH}_2)_2-, R^1:R^2 = \text{H, Me}, R^1 = \text{H, Me, Ph}
\]

\[
\text{[2,3-(Bu)]}_2\text{C}_2\text{H}_3\text{Cl]}\text{PAuCl (2 mol %)} \quad \text{AgSbF}_6 (2 \text{ mol %}) \quad \text{DCM, } -15 \degree \text{C}
\]

33–96%

\[
4\text{-OMeCH}_3\quad 63–85\%
\]

\[
9–99\% \text{ ee}
\]

Scheme 10. Gold-catalyzed [2+2] cycloaddition between allenamides and alkenes.

These intermolecular [2+2] cycloadditions of allenamides have been extended to the employment of indoles as olefin counterpart. In this regard, Bandini developed an enantioselective gold-catalyzed dearomative [2+2] cycloaddition of allenamides with indoles (Scheme 11a). This transformation enables direct access to methylenecyclobutane-fused indolines 37, featuring two consecutive quaternary stereogenic centers with excellent stereocchemical control. The ring-closing event is favoured by the combined use of indoles carrying an electron withdrawing group at the N(1)-position, which increases the electrophilicity of the dearomatized indolinine intermediate, and electron rich phosphines, which increase the nucleophilicity of alkenyl-gold species. DFT calculations support a polar non-concerted mechanism. Under kinetic conditions, tricyclic compound 38 is obtained, whereas isomeric cycloadduct 39 is generated under thermodynamic conditions (Scheme 11b). In both cases, the dearomatization process is the rate determining step [136,137].

Moreover, the reaction of 3-styrylindoles with N-allenamides grants enantiocinriched cyclobutane derivatives and tetrahydrocarbazoles using H8-BINOL-derived phosphoramidite 40 and Me2SAuCl/AgNTf2. This transformation is highly dependent on the electronic nature of the indolic nitrogen. Enantiomeriched non-fused cyclobutane derivatives are obtained with indoles bearing electron donating groups at the nitrogen, whereas tetrahydrocarbazoles are provided with electron withdrawing groups at that position. These results have been rationalized by DFT calculations (Scheme 12) [138].
Scheme 11. (a) Asymmetric intermolecular [2+2] cycloaddition between allenamides and indoles. (b) Mechanistic considerations.

Scheme 12. Tuneability of the cycloaddition process towards [2+2] or [4+2] products regarding the N-substituent at the indole substrate.

Xiang-Phos ligand 41 bearing two bulky adamantyl groups on the P atom gave the best results in the reaction of 3-styrylindoles with N-allenyl oxazolidinone (Scheme 13) [139].
When a second allene molecule takes part in the cyclization process instead of an alkene, cyclobutanes with two exocyclic double bonds are achieved, which can be modified in further reactions.
A combination of N-heterocyclic carbene gold(I) catalyst IPrAuCl and a silver salt efficiently transforms N-tethered 1,5-bisallenes 48 to 6,7-dimethylen-3-azabicyclo[3.1.1]heptanes 49 (Scheme 15). DFT calculations support a stepwise mechanism in which the twisted head-to-head cycloaddition is more favourable than tail-to-tail or head-to-tail cyclizations [141].

![Scheme 15. Gold-catalyzed [2+2] cycloaddition of bisallenes.](image)

A selective homodimerization of N-allenylsulfonamides to produce dialkylidencyclobutanes 50 occurs in good yields when alleneamide substrates are mixed with only 0.5 mol% of a gold catalyst. The reaction time decreases, and the yield increases with phosphite gold complexes as catalysts in combination with norbornene at 50 °C (Scheme 16) [130].

![Scheme 16. Gold-catalyzed cyclodimerization of allenamides toward dialkylidencyclobutanes.](image)

### 2.3. Alkene–Alkyne

The alkene–alkyne system has been extensively studied to generate cyclobutanes, cyclobutenes, and cyclobutanones through [2+2] cycloaddition in both intra- and intermolecular fashions [142].

1,6-[143–152], 1,7-[153–156], 1,8-[150,157,158] and 1,9-[158] enynes have been used as substrates affording a variety of different bicycles owing four-membered carbon rings. Most of these unsaturated systems required the use of bulky phosphines as ligands, mainly biarylphosphines. Some examples incorporating additionally 9- to 15-membered ring macrocycles has been also reported [159,160].

Regarding intramolecular [2+2] cycloaddition of enynes, alkene’s addition to gold-activated alkynes afford cyclopropyl methyl carbenes as common intermediates in these processes. Several competing pathways arise, and their prevalence is regulated by the substitution pattern, catalysts, and conditions employed. The substrate may evolve through an exo-dig or endo-dig cyclization to render cyclobutenes. A general map for 1,6-enynes reactivity under gold catalysis is depicted in Scheme 17 [147,161,162].
The high energy activation from anti-52 to syn-52 (24.7 kcal/mol for R\(^1\) = H and R\(^2\) = Me) can be explained by the loss of conjugation between the gold carbene and the cyclopropane since there is a shortening of the cyclopropane and C=Au bonds, as well as a lengthening of the C-C bond connecting the cyclopropane and the gold carbene in the transition state [153]. Hence, such isomerization is rather unlikely under the reaction conditions. Nevertheless, an aryl group tethered to the carbene facilitates rotation around the cyclopropane carbene bond by conjugation of the cyclopropane with the phenyl ring showing a low rotational barrier (8.6 kcal/mol) [147]. Direct formation of syn-52 can be achieved through an alternative pathway by syn-type attack of the alkene to the (alkyne)gold intermediate.

Syn-52 expands to form 54 with an activation energy of 11.9 kcal/mol. These results point to the anti to syn isomerization pathway possibly competing with the opening of anti-52. Afterwards, 54 can be obtained by a proton-elimination followed by protonolysis of the C–Au bond. 1,6-Enynes are reluctant to afford 53 due to the unstable configuration that represents an endo trans ring, thus isomerizing rapidly through 1,3-hydrogen migration to exo-54 analogue through acid catalysis [163,164].

Frequently, 1,3-diienes 55 are obtained as a result of a single-cleavage rearrangement, understood as a formal insertion of the alkene between the carbons belonging to the alkene. Alternatively, a double-cleavage rearrangement is prone to happen, leading to products 56 in which both unsaturations have suffered C–C bond cleavage.

On the other hand, different cyclobutane derivatives can be obtained depending on the substrate substitution and the presence of other reagents on the reaction media. Thus, gold-catalyzed cycloisomerization of substituted 1,6-ene-ynamides 57 allows for access to cyclobutanones 60, through hydrolysis of the corresponding cyclobutenes initially formed, as reported by Cossey [145,148] and Yeh (Scheme 18) [152]. As trimethylsilyl-ynamides do not undergo fast protosilylation in the presence of AuCl, the mechanistic proposal involves the loss of the trimethylsilyl group by protonation of the double bond of the initially formed trimethylsilyl-substituted cyclobutene intermediate 58 with formation of trimethylsilanol. The compound 59 in the presence of H\(_2\)O leads to cyclobutanone 60.
Moreover, the presence of an electron-rich arene as nucleophile grants access to 6,6-diarylbicyclo[3.2.0]heptanes 62 bearing a quaternary center, through a tandem gold-catalyzed cycloaddition/hydroarylation of 7-aryl-1,6-enynes 61 (Scheme 19) [151]. Several mono-, di-, and trisubstituted arenes undergo this transformation in good yields obtaining mixtures of endo/exo diastereoisomers in ranges from 1:7 to >25:1.

![Scheme 18](image1.png)

**Scheme 18.** Gold-catalyzed cycloisomerization of trimethylsilyl substituted 1,6-ene-ynamides.

Propargylic esters 63, a particular type of 1,7-enynes, can be used as a mean to generate allenes 64 in situ, stemming from a syn 1,3-migration of the carboxylic ester group. Thus, alkylidencyclobutanes 65 are obtained through a formal [2+2] cycloaddition of allenes, as reported by Zhang and Chang et al. [165–167]. Interestingly, the unsaturation thought to be activated by the gold catalyst is not the allene, but the alkene moiety to avoid unfavourable steric interactions (Scheme 20).

![Scheme 19](image2.png)

**Scheme 19.** Gold-catalyzed tandem [2+2] cycloaddition/hydroarylation of enynes.
Scheme 20. [3,3]-Rearrangement of propargylic esters towards allenenes followed by gold-catalyzed intramolecular [2+2] cycloaddition.

On the other hand, the intermolecular version of [2+2] cycloaddition of alkynes with alkenes has been widely studied [169,170]. Potential problems with this approach lie in the competitive coordination of the alkene to the catalyst forming Au(I)-alkene complexes. These compounds lead to complex reaction mixtures or polymerizations in the presence of Au(I) complexes. Sterically hindered cationic Au(I) complexes minimize the competitive pathways.

Terminal alkynes are preferred due to the low reactivity associated to internal alkynes. Bulky Au(I)biphenylphosphine complexes form isolable σ,π-dicoordinated digold complexes 70 in the presence of phenylacetylene. These complexes catalyze an intermolecular [2+2] cycloaddition between phenylacetylene and α-methylstyrene with almost complete selectivity and higher yield for the cyclobutene compared to the corresponding mono Au(I) complex precursor (Scheme 22). In the presence of the latter, the Brønsted acid generated from the counteranion triggers α-methylstyrene dimerization and degradation of cyclobutene [170]. Later, it was shown that [tBuXPhosAu(MeCN)]+ complex with the bulky and soft anion [BAR_4]^(-) (3,5-bis(trifluoromethyl)phenylborate) improves the yields of [2+2] cycloaddition [171].
Weakly- to moderately-coordinating [IMP-R] anions, such as [IMP-CF₃]⁻, [IMP-NO₂]⁻, and [IMP-CO₂Me]⁻, are compatible with gold catalysis in [2+2] cyclization of α-methyl styrene and phenylacetylene showing slightly lower yields and reaction rates than [iBuXPhosAu(MeCN)][BAr₄F], [iBuXPhosAu(MeCN)][BIMP] and [iBuXPhosAu(MeCN)][SbF₆] (Figure 4).
In this context, substituted cyclobutenes are synthesized in a regioselective fashion by intermolecular gold(I) catalyzed [2+2] cycloaddition with terminal electron-rich alkynes and aromatic or aliphatic alkenes. The mechanistic proposal based on kinetic studies and DFT calculations support as first intermediates cyclopropyl gold(I) carbenes and the involvement of an associative ligand exchange between the gold-coordinated alkene and the alkyne as the rate-limiting step [172]. The scope of the reaction includes reactions of 1,3-butadiynes 71 with alkenes 72. In these cases, a chemoselective [2+2] cycloaddition takes place only through the terminal alkyne to give alkynyl cyclobutenes 73, resulting from the coupling of the more substituted carbon of the alkyne with the secondary carbon of the alkyne (Scheme 23) [172].

Figure 4. Gold complexes with imidazolyl-phenyl (IMP) anions.

In the same way, 1-vinyl-3-substituted cyclobutenes 74 can be synthesized by reactions of alkenes with the corresponding 1,3-enynes [173] (Scheme 24).

Recently, [2+2] cycloaddition of chloroalkynes 75 with monosubstituted unactivated alkenes 76 has been described with excellent regioselectivities. The reaction is largely stereospecific with 1,2-disubstituted unactivated alkenes (Scheme 25) [174]. The synthetic utility of the
1-chlorocyclobutene derivatives 77 has been demonstrated by their successful employment as substrates in cross-coupling reactions.

\[
\begin{align*}
\text{R}^1 &= \text{Ph, 4-MeC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, \\
\text{R}^2, \text{R}^3 &= \text{H, }-(\text{CH}_2)_n,-(\text{CH}_2)_n,-(\text{CH}_2)_n,-\text{Bu, C}_6\text{H}_{13}, -(\text{CH}_2)_2\text{OTIPS}, \\
&\quad -(\text{CH}_2)_2\text{OTIPS}, -(\text{CH}_2)_2\text{OTIPS}, -(\text{CH}_2)_2\text{Br}, -(\text{CH}_2)_2\text{CO}_2\text{Et}, \text{cyclohexyl}
\end{align*}
\]

\[
\begin{align*}
\text{75} &\text{ } + \text{ } \text{76} \xrightarrow{\text{iPrAuCl (5 mol %) NaBAR}_{6} (10 mol %)} \text{DCE, 40 °C or 60 °C, 12 h} \text{77} \\
\text{R}^1 &= \text{Ph, 4-MeC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, \\
\text{R}^2, \text{R}^3 &= \text{H, }-(\text{CH}_2)_n,-(\text{CH}_2)_n,-(\text{CH}_2)_n,-\text{Bu, C}_6\text{H}_{13}, -(\text{CH}_2)_2\text{OTIPS}, \\
&\quad -(\text{CH}_2)_2\text{OTIPS}, -(\text{CH}_2)_2\text{OTIPS}, -(\text{CH}_2)_2\text{Br}, -(\text{CH}_2)_2\text{CO}_2\text{Et}, \text{cyclohexyl}
\end{align*}
\]

Scheme 25. Gold-catalyzed [2+2] cycloadditions of chloroalkynes with unactivated alkenes.

The first enantioselective example has been performed over di- and trisubstituted alkenes 78 with a gold catalyst bearing Josiphos ligand and [BARF] \(^{6-}\) counterion in order to reduce the amount of digold species formed (Scheme 26) [175]. Remarkably, this approach has been applied to the enantioselective total synthesis in 9 steps of Rumphellone A, a terpenoid known for its cytotoxicity against human tumour cells.

\[
\begin{align*}
\text{78} \xrightarrow{(R,Sp)-\text{Josiphos-AuCl}_2 (5 \text{ mol %}) NaBAR}_{6} (5 \text{ mol %})} \text{MeCl (0.5 M), 14-72 h} \text{79} \\
\text{R}^1 &= \text{Ph, p-Br-C}_6\text{H}_4, p-\text{BuC}_6\text{H}_4, p-\text{Cl-C}_6\text{H}_4, \\
\text{R}^2 &= \text{Me, Et, }-(\text{CH}_2)_2\text{C}_6\text{H}_5
\end{align*}
\]

Scheme 26. Enantioselective [2+2] cycloaddition between terminal alkynes and trisubstituted alkenes.

The same reaction has been used to test a new atropisomeric teraryl monophosphine ligand, Joyaphos by Sparr et al. [176]. The results of this investigation have shown that (Sa)-Ph\(_2\)JoyaphosAuCl and Cy\(_2\)JoyaphosAuCl (Figure 5) combined with AgSbF\(_6\) can be used to promote the desired reaction, although moderate yields and poor enantioselectivity are achieved.
Recently, Echavarren’s group has reported other enantioselective synthesis of Rumphellaone A, in 12 steps (ca. 8% yield), and Hushinone a norsesquiterpenoid found in the essential oils from the buds of Betula pubescens, in 16 steps (ca. 1.1% yield) [160]. The key step is a diastereoselective gold(I)-catalyzed [2+2] macrocyclization of 1,10-enzyme 79 to build the cyclobutene moiety (Scheme 27).

![Figure 5. JoyaphosCl complexes.](image)

Scheme 27. Key step employed as an approach towards Rumphellaone A and Hushinone total syntheses.

A convergent approach to the core bridged tricyclic BCD ring system of norditerpenoid alkaloids and Racemulsonine has been developed by Xu et al. through gold(I)-catalyzed [2+2] enyne cycloaddition and pinacol rearrangement (Scheme 28) [155].

![Scheme 28. Approach to the core bridged tricyclic BCD ring system.](image)

### 2.4. Alkyne-Alkyne

In contrast to 1,1,1-triynes, 1,1,1-triynes has been barely used as precursors of four-membered rings under gold catalysis. In fact, all the examples described entail the initial generation of an allene moiety that then evolve by formal [2+2] cycloaddition.

In this arena, alkyne-propargylic pivaloates 80 have been shown to be suitable substrates to promote a gold-catalyzed [2+2] cyclization. Fused cyclobutene compounds 83, containing a ketone moiety, can be obtained through an allene intermediate 81. Then, this intermediate can undergo condensation with one of the gold-activated triple bonds and subsequent cyclization through pathway A to deliver 83. Alternatively, in the pathway B, the formation of intermediate 82 by [2+2] cycloaddition of 81 is proposed, which would afford cyclobutane 83 upon hydrolysis (Scheme 29) [177].
Access to functionalized naphtho[β]cyclobutenes 85 with high stereoselectivity can be achieved by gold-catalyzed cascade cyclization of 1,7-diyn-3,6-bis(propargyl) carbonates 84. The cascade sequence involves a double 3,3-rearrangement forming bis(allenyl)carbonate 86. This is followed by a 6π-electrocyclic reaction to deliver a naphthyl derivative 87 that can be represented as a highly stabilized biradical 88 which by spontaneous cyclization affords cyclobutanyl dicarbonate 89. Finally, a decarbonylative cyclization provides 85 (pathway A). Alternatively, intramolecular nucleophilic attack of the allenic moiety on the gold-activated allene is proposed in pathway B affording oxocarbenium intermediate 90. Subsequent nucleophilic attack of the Au-C(sp²) bond on the carbonyl moiety gives 89 which evolves in a similar sequence that in pathway A towards 85 (Scheme 30) [178].

On the other hand, intramolecular gold-catalyzed cycloisomerization of stable alkylidene tethered diynes 91 gives access to cyclobutene-fused azepines 92. A plausible mechanism has been proposed based on 1H NMR studies (Scheme 31). Initially, nucleophilic addition of alkene to activated alkyne occurs through a 6-endo-dig attack supported by the nitrogen lone pair. The cleavage of C=N bond in 93 leads to an allylic cation 94 and consequent removal of the metal forms the allene 95. Finally, activation of the vicinal alkyne triggers a [2+2] cycloaddition with the former allene [179].
Scheme 30. Gold-catalyzed [2+2] cycloaddition of diynes towards naphtho[b]cyclobutenes.

Scheme 31. Gold-catalyzed [2+2] cycloaddition of diynes towards cyclobutene-fused azepines.

Other examples of alkylidencyclobutene cores such as azabicyclo[4.2.0]octadienes 97 have been synthesized by Chan et al. from diyne substrates 96 through 1,3-migration/6-exo-dig cyclization/Prins-type [2+2]-cycloaddition [167]. A complete control of the product selectivity is gained by the study of the steric interactions between the alkyne moieties with the gold catalyst. Later,
the same authors described the gold-catalyzed cycloisomerization of 1,6-diyne esters \(^98\) to prepare chemoselectively bicyclo[3.2.0]hepta-1,5-dienes \(^99\) (Scheme 32) \(^{180}\).

\[\text{Scheme 32. Gold-catalyzed intramolecular } [2+2] \text{ cycloaddition of diynes towards alkylidencyclobutenes.}\]

Finally, an intermolecular approach has been reported by Shi et al. in which allenes are generated in situ from activated propargylic esters, using a silver-free gold catalyst. \([2+2]\) Cycloaddition works under mild conditions with high efficiency. The silver-free condition is crucial for the success of the transformation since the presence of a silver cation can activate the pyvaloate group as a leaving group, giving acyclic dimer \(^{100}\) as the only observed product (Scheme 33). The \([2+2]\) cycloaddition reaction is substrate-dependent and it was confirmed that it is a thermal reaction and, therefore, gold activation is not required for the cycloaddition event \(^{181}\).

\[\text{Scheme 33. Carbophilicity and oxophilicity competition in Au/Ag catalysis.}\]

3. Ring Expansion

A recurrent approach to access four-membered rings via gold(I) catalysis is the ring expansion of activated cyclopropane derivatives, taking advantage of the large ring strain associated to these carbocycles. This strategy to build the cyclobutane core typically implies the formation of a cyclopropylmethyl cation intermediate and a subsequent 1,2-alkyl migration. The noticeable \(\pi\)-character
of the cyclopropyl group is responsible for its hyperconjugation, thus stabilizing these species as non-classical carbocations. In this context, vinylidene-, alkynyl- and alkylidencyclopropanes and vinyl-, alkynyl- and allenylcyclopropanes are suitable substrates to react through a gold(I) catalyzed ring expansion to afford cyclobutane scaffolds. Considering this behavior, most of the examples reported can be categorized in pinacol-like or Wagner-Meerwin rearrangements.

3.1. Pinacol-Like Transformations

Cyclopropanols and related cyclopropyl ethers are suitable starting materials to produce cyclobutanes through gold-catalyzed ring expansion. Such a process relies on a 1,2-alkyl shift triggered by activation of a vicinal unsaturation. This alkyl migration is also assisted by the electron density donation from the lone pair of the oxygen.

In 2005, Toste’s group reported the first examples of this kind of gold(I)-catalyzed ring expansion using 1-alkynylcyclopropanols 101 to render alkylidencyclobutanones 103 in high yields and as single olefin isomers (Scheme 26) [182]. The process is tolerant of diverse substitution at the alkyne moiety and allows the employment of silyl ethers as substrates if 2 equivalents of methanol are added to the reaction media. In the mechanistic proposal, the coordination of cationic gold(I) to the alkyne induces a selective 1,2-alkyl shift of the most substituted chain in species 102, which is consistent with the experimental data. In this way, E isomer is obtained in a stereoselective and, remarkably, stereospecific manner regarding substituents on the ring. Related cycloalkylidencyclobutanones 106 could be prepared from cyclopropanols 104 bearing a 1,6-diyne. This cascade process is proposed to entail a diyne cycloisomerization and the cyclopropyl expansion (Scheme 34) [183]. On the other hand, a single example of the preparation of an allyl cyclobutanone from a cyclopropanol bearing an allylic alcohol is included in a more general work that describes the ring expansion of 1,4-allylic diol derivatives under gold catalysis [184].

![Scheme 34. Gold-catalyzed ring expansion of cyclopropanols: Synthesis of alkylidencyclobutanones.](image)

In the presence of a cationic gold complex and an oxidant such as a pyridine N-oxide, 1,3-diketones can be constructed in a regioselective fashion from spirocyclic propargylic alcohols [185]. In the case of alkynylcyclopropanol 107, the corresponding β-keto cyclobutanone 109 is obtained, although in moderate yield due to its instability upon column chromatography (Scheme 35). Notably, the oxidative cycloisomerization is completely selective and the formation or intermediacy of (E)-2-benzylidencyclobutanone is discarded. The plausible mechanism supported by NMR studies points out a favored coordination of gold to the N-oxide over coordination with the alkyne. The complex
formed suffers oxidative addition at the alkyne moiety, leading to \( \alpha \)-oxo gold-carbene species 108 which, after pinacol-like ring expansion, generates 1,3-diketone 109.

![Scheme 35. Synthesis of 2-benzoylcyclobutan-1-one 109 by oxidative catalyzed ring expansion of 1-(phenylethynyl)cyclopropan-1-ol 107.](image)

More recently, \( O \)-substituted alkynylcyclopropyl allyl ethers 110 have also proven to be effective reactants for the construction of highly substituted alkylidencyclobutanones 113 using the same gold catalyst (Scheme 36) [186]. The reactions are accelerated by the presence of water and occur in moderate to good yields with broad scope. A thorough mechanistic study on the reported process has been accomplished including \( D \) and \( ^{18}O \) labelling experiments and DFT calculations. The authors propose that the gold carbene intermediate 111 formed after the initial ring expansion (102, Scheme 34), evolves through an intramolecular \([3,3] \)-sigmatropic rearrangement. The subsequent \([1,2] \)-allyl migration in 112, assisted by the presence of catalytic amount of water, produces the observed cyclobutanone 113.

![Scheme 36. Synthesis of alkylidencyclobutanones by gold-catalyzed ring expansion of alkynylcyclopropyl allyl ethers.](image)

Alkenylecpropanols and their ether derivatives are also precursors of cyclobutenones under gold catalysis. In an early work, Echavarren and coworkers reported that alkenyl cyclopropanol ethyl ethers 114 in which the olefin is part of a terminal 1,6-enzyme produce, in the presence of catalytic amounts of gold and water, variable mixtures of isomeric cyclobutane-fused tricyclic compounds 115 and 115a (Scheme 29) [187]. The isomeric ratio is mainly dependent on the catalyst employed: \( syn \) cycloadduct 115a is slightly favored in reactions conducted with cationic \([\text{JohnPhosAu(NCMe)}]_{s} \text{SbF}_6 \) catalyst, whereas \( anti \) tricyclic skeleton 115 is almost exclusively formed with AuCl.

This methodology has been employed as the key step of the total synthesis of Repraesentin F, using as starting material a cyclopropyl silyl ether 116 bearing an enyne system with an internal alkyne (Scheme 37). In this particular case, the higher selectivity to the desired tricyclic steroisomer is achieved with a cationic gold(I) catalyst derived from \( f \text{BuXPhos} \) biphenyldiphosphine ligand and with \( \text{[BAr}_{4}^{\text{F}} \)\] as counterion [188].
The mechanism of these transformations is proposed to proceed through the well-established formation of cyclopropane carbene intermediate 117 (Scheme 38). Then, ring expansion to give oxonium species 118 occurs via a concerted pathway with AuCl as catalyst, whereas cationic gold(I) complexes trigger a non-stereospecific stepwise process through the intermediacy of carbocation 119. Finally, Prins-like reaction followed by demetalation affords the corresponding products 115 and/or 115a.

Scheme 38. Proposed mechanism to access tricyclic compounds 115.

However, studies accomplished by Voiturez’s group on the enantioselective cyclization of related substrates 120 reveal a different behaviour. Under their optimized conditions that involve the use of a chiral bis(phosphine)digold(I) complex and wet toluene as solvent, selective evolution of the formation of cyclobutanones 121 occurs instead of the production of tricyclic adducts 115 (Scheme 39) [189]. The reactions take place with good yields and enantioselectivities although variable syn/lanti diastereoselectivities are reached.
A related reaction of substrate 122 having a cis-disubstituted cyclopropanol integrated in an 1,6-enyne chain, gives bicyclic ketone 123 in excellent yield (Scheme 40) [190]. Cycloisomerization of cyclic olefin analogues 124 provides the corresponding tricyclic systems 125 in good yields and with total diastereoselection. Notably, the utility of this methodology for the rapid assembly of polycyclic ring systems is illustrated by its use in a key step of the total synthesis of the angular triquinane Ventricosene (Scheme 40).

Efficient access to the tricyclic framework of protoilludanes 127 was described by Echavarren et al. through a related gold-catalyzed cycloisomerization of allene-alkenylcyclopropane derivatives 126 [191]. The process is also stereospecific, as demonstrates the different outcome of Z- and E-126 (Scheme 41).
On the other hand, analogous cyclopropyl enlargements to build the 4-membered ring are possible starting from 1-allylencyclopropanols 128. In this sense, Toste reports the use of chiral dinuclear gold phosphine complexes for the construction of cyclobutanones 129 possessing a vinyl-substituted quaternary stereogenic center (Scheme 42) [192]. These reactions occur with good yields and enantioselectivities, displaying broad scope and tolerance to functional groups.

More recently, the same research group has combined visible light photoredox and gold catalysis to develop a novel approach to cyclic ketones from cycloalkanols through a ring expansion-oxidative arylation reaction in the presence of aryl diazonium salts. By this dual catalysis, using alkenyl or allenyl cycloalkanols 130, functionalized cyclobutanones 131 are furnished (Scheme 43) [193]. Mechanistic studies strongly suggest the initial formation of gold(III)-Ar species, by formal oxidative addition of aryl diazonium salts to gold(I), and the subsequent activation of the alkene or allene by this electrophilic gold(III) intermediate.

### 3.2. Wagner-Meerwein-Like Transformations

Polysaturated systems having a non-functionalized cyclopropane ring in their structure have also been proven as valuable precursors of cyclobutane containing cycloadducts in the presence of gold catalysts [75]. These processes typically involve an initial cycloisomerization upon metal activation of the alkyn e and subsequent Wagner-Meerwein shift over the cyclopropylmethyl cation produced. In this sense, Min Shi’s group described the gold(I)-catalyzed synthesis of cyclobutene-fused carbazoles 133 by cycloisomerization of 1-(indol-3-yl)-3-alkyn-1-ols 132, a particular type of cyclopropyl embedded 1,5-enynes (Scheme 44) [194]. The authors proposed the key formation of a gold carbene intermediate 134 via nucleophilic attack of the indolyl group to the activated alkyne followed by 1,2-alkyl migration and posterior water elimination. Then, a ring expansion takes place that gives the tetracyclic skeleton and the final product after metal elimination.
The same group later reported that gold(I) catalysts are able to transform simple 1,5-enynes containing a cyclopropane ring in the alkyl chain into a variety of cyclobutane-fused cycloadducts depending on the substrate substitution, the temperature and the gold catalyst used [195,196]. Thus, reaction of (hetero)aryl-substituted 1,5-enynes 135 in dichloromethane at 0 °C using [JohnPhosAu(MeCN)]SbF₆ as catalyst gives cyclobutane-fused 1,4-cyclohexadienes 136 in very high yields (Scheme 45). Moreover, the corresponding benzocyclobutenes 137 can be efficiently achieved by conducting the reactions under oxidative conditions. On the other hand, by simply controlling the reaction temperature and the gold(I) catalyst employed, three different products: biscyclopropanes 135, cyclobutane-fused 1,3-cyclohexadienes 139 and tricyclic cyclobutenes 140 can be selectively synthesized from 1,5-enynes 135, provided that an ortho-substituted arene is installed at their alkyne terminus (Scheme 45).

**Scheme 44.** Gold(I)-catalyzed synthesis of cyclobutene-fused carbazoles from suitable indolylalkynols.

**Scheme 45.** Gold(I)-catalyzed ring expansion of 1,5-enynes tethered with a cyclopropane moiety towards diverse cyclobutene scaffolds.
A plausible mechanism that accounts for all these observations is proposed based on deuterium-labeling, intermediate trapping experiments, and supported by DFT calculations. The proposal suggests a classical enyne cycloisomerization that produces bicyclopentyl gold carbene species 141 and subsequent Wagner-Merwein shift to form key cyclobutene-fused intermediate 142, which undergoes different transformations to furnish the observed products (Scheme 46). These studies also revealed that both tricyclic cycloadducts 138 and 140 are intermediates for the formation of bicyclic derivatives 139.

Scheme 46. Some intermediates proposed for the formation of cycloadducts 137–140 from enynes 135.

In the same way, methylene-, vinylidene-, and alkylidencyclopropane enyne derivatives are also useful precursors for the construction of elaborated compounds containing a four-membered ring in their structure. This strategy was first illustrated in the transformation of 1,6-enyne 143 to fused cyclobutane 144 (Scheme 47) [190]. Interestingly, the introduction of aryl groups as alkyne substituents triggers a divergent evolution of the gold(I)-stabilized allyl cation intermediates to the diastereoselective construction of tetracyclic scaffolds 145 as a result of a final Nazarov-type electrocyclization (Scheme 47).

Scheme 47. Gold(I)-catalyzed ring expansion of 1,6-enynes containing a cyclopropane unit towards cyclobutane scaffolds.

The bicyclo[4.2.0]octane skeleton is also accessible from homologous methylidencyclopropyl 1,5-enynes 146 through a related mechanistic pathway. Thus, Gagné et al. described that these substrates undergo a 6-endo-dig cyclization followed by a Wagner-Merwein migration and 1,2-hydrogen shift, over carbocation allylic species 147, to give bicyclo dienes 148 (Scheme 48) [197]. Good yields and moderate enantioselectivities are reached, being substitution at the cyclopropylidene moiety crucial.
for the enantioselection. Of note, Carreira et al. have further demonstrated the usefulness of this methodology in the total synthesis of a Harziane diterpenoid [198] (Scheme 48). Interestingly, also Gagné reported that particular 1,5-dienes containing a cyclohexane with an exocyclic cyclopropylidene are suitable substrates towards the construction of the bicyclo[4.2.0]oct-1-ene core [199].

![Scheme 48. Gold(I)-catalyzed ring expansion of 1,5-enynes containing a cyclopropane unit towards cyclobutane scaffolds.](image)

Moreover, cationic intermediates 147 could be diastereoselectively trapped by addition of MeOH or aldehydes to the reaction media, thus producing functionalized bicyclo[4.2.0]octanes 149 or terpene-like polycyclic scaffolds 150 (Scheme 48) [200]. The later reactions work nicely with aliphatic and electron deficient aromatic aldehydes, although it is limited to enynes with highly activated arenes at the alkyne.

In contrast, 1,5-enynes 146a bearing an additional alkynyl group directly attached to the methylencyclopropane unit, selectively produce tricyclic cycloadducts 151 as single diastereomers as a result of a complex cycloisomerization process of the initially formed bicyclic compounds 148 (Scheme 49) [201].

![Scheme 49. Gold(I)-catalyzed ring expansion of diynes containing a cyclopropylidene unit.](image)

The corresponding 1,7-enynes possessing a methylenecyclopropane moiety are also suitable precursors of cyclobutene containing scaffolds through related mechanisms initiated by gold-alkyne activation. In this context, Min Shi’s group has recently reported the preparation of cyclobutenyl substituted 1,2-dihydroquinolines 153 in moderate yields from aniline tethered 1,7-enynes 152 (Scheme 50) [202]. The process is limited to substrates bearing a terminal alkyne and aryl substituents at the methyldiene unit. Moreover, reactions are not completely selective and the cyclobutenes are obtained accompanied with minor quantities of methylenecyclopropane isomers, which are selectively formed when using a silver catalyst. On the contrary, analogous ortho-(propargyloxy) aryl methylenecyclopropanes 154 (R = H) evolve through an intramolecular hydroarylation, instead of a
6-exo enyne cycloisomerization, followed by the ring enlargement to generate cyclobutene substituted 2H-chromenes 155 in good yields (Scheme 50) [203]. When blocking the reactive position of the arene to inhibit the hydroarylation process (R ≠ H) a new reaction occurs that efficiently provide cyclobutane fused dihydrobenzofuranes 156 (Scheme 50) [204]. This process is proposed to proceed via the initial ring expansion of the cyclopropane that generates a cyclobutene gold carbenoid species. This intermediate undergoes the nucleophilic attack of the oxygen followed by [2,3]-sigmatropic rearrangement and metal dissociation to give the observed tricyclic adducts. The process exhibits broad scope at both the arene and the alkyne moieties and only substrates bearing a terminal acetylene and bulky groups at the ortho position evolve through a different reaction pathway. Interestingly, the tricyclic adducts 156 could be also enantiomerically obtained using a chiral gold catalyst.

Scheme 49. Gold(I)-catalyzed ring expansion of diynes containing a cyclopropylidene unit.

Scheme 50. Gold(I)-catalyzed ring expansion of aniline or benzyloxy tethered 1,7-enynes containing a cyclopropane unit towards cyclobutene scaffolds.
Different heteropolycyclic scaffolds possessing a benzoazepine-fused cyclobutene core are furnished from related alkynylamide tethered methylenecyclopropanes 157 (Scheme 51) [205]. These reactions proceed via an initial 7-exo enyne cycloisomerization followed by the cyclopentylmethyl to cyclobutyl ring expansion that gives a tricyclic carbocationic intermediate 158, whose evolution is determined by the gold catalyst employed. Thus, deprotonation using PPh3AuCl/AgOTf triggers the selective production of tricyclic compounds 159, whereas the use of JohnphosAuCl/NaBArF catalytic system promotes a selective intramolecular Friedel-Crafts type cyclization that finally delivers spirocyclic adducts 160.

![Scheme 51. Gold(I)-catalyzed ring expansion of alkynylamide linked methylenecyclopropanes.](image)

Interestingly, azepine-fused cyclobutanes with an aryl group at the bridgehead 162 could be prepared in an enantioselective manner from 1,6-enynes 161. These reactions occur with good yield and enantioselective although display limitations at the substitution at both the alkyne and olefin of the enyne (Scheme 52) [206]. The process involves asymmetric cyclopropanation of the methyleniden unit, C–C cleavage and Wagner-Meerwein rearrangement. DFT calculations show that the chirality of the final product from the first cyclopropanation step is lost in the subsequent bond cleavage but is then regenerated in the Wagner–Meerwein rearrangement.

![Scheme 52. Enantioselective synthesis of azepine-fused cyclobutanes from cyclopropylidene 1,6-enynes.](image)

Suitable functionalized vinylidencyclopropanes 163–165 are also valuable precursors of diverse cyclobutene-fused cycloadducts, in a similar fashion as the latter mentioned methylenecyclopropanes. In this case, alkylidene cyclobutyl carbene species 166, formed by ring expansion, are proposed as key intermediates and their evolution is governed by the substrate substitution (Scheme 53). Thus, vinylidencyclopropanes 163 having a pendant olefin, and a hydrogen or fluor substituent at C-4,
selectively deliver benzocycloctane-fused cyclobutenes 167 via the intramolecular cyclopropanation of carbene intermediate 166a (Scheme 53a) [207]. Moreover, related aromatic substrates 164 furnish benzocycloheptane-fused cyclobutenes 168 through an intramolecular C–H insertion provided that a strong electron withdrawing group is present at the para position of the pendant arene (Scheme 53b) [208]. These processes display broad scope and, remarkably, their enantioselective versions have been also developed. However, competitive nucleophilic addition to the carbene intermediate are observed from most of the substrates substituted at C-4 and, therefore, no cyclobutane scaffolds are obtained with these substrates. Furthermore, intramolecular nucleophilic addition of oxygen nucleophiles to the carbene intermediate 166c yields methylene cyclobutanones 169 when vinylidencyclopropanes bearing both an alkyl substituent (R₁) and an aryl methyl ether are employed (Scheme 53c) [209]. Interestingly, both E and Z isomers 169 can be selectively obtained by controlling the gold ligand and the reaction conditions. In addition, alkylidene cyclobutanones are also accessible by reaction of unfunctionalized vinylidencyclopropanes with pyridine N-oxides via an intermolecular addition of the oxide to the alkylidene cyclobutenyl gold carbene species 166 initially generated [210].

![Scheme 53. Gold-catalyzed cyclobutane formation from functionalized vinylidencyclopropanes: (a) via cyclopropanation; (b) via C–H insertion; (c) via nucleophilic addition](image-url)
On the other hand, particular examples of gold-catalyzed synthesis of cyclobutene-fused compounds from cyclopropyl alkynes with a tethered oxygen nucleophile have been reported. In this sense, Zhang has described the preparation of densely functionalized bicyclo[3.2.0]heptanes \( 171 \) by a gold-catalyzed intermolecular reaction between alkynyl cyclopropyl ketones \( 170 \) and excess of ethyl vinyl ether and subsequent treatment with a Brønsted acid in the presence of water (Scheme 54) [211]. A mechanism has been proposed involving the initial cycloisomerization upon activation of the alkyne, followed by a 1,3-dipolar cycloaddition with the enol ether. Then, the construction of the cyclobutane is proposed to occur via a Wagner-Meerwein ring enlargement. Moreover, reactions of related 1-epoxi-1-alkynylcyclopropanes in the presence of water catalyzed by gold catalysts furnish functionalized bicyclic oxacyclic alcohols with good yields and diastereoselectivities [212]. Notably, the addition of halonium salts (NBS or NIS) allows the introduction of a halogen in the cyclization products [213].

![Scheme 54](image)

**Scheme 54.** Gold-catalyzed synthesis of bicyclo[3.2.0]heptanes from alkynyl cyclopropyl ketones.

Unactivated cyclopropyl alkynes can also be useful substrates for the preparation of cyclobutanes under gold catalysis provided that an appropriate nucleophile is present in the reaction media. Thus, reactions of a wide range of internal cyclopropyl alkynes \( 172 \) with sulfonamides in the presence of a cationic gold catalyst produce cyclobutanamines \( 174 \) in moderate to good yields [214]. A plausible mechanism for this transformation implies the alkyne activation by gold and subsequent ring expansion that generates a gold-stabilized allylic cyclobutyl carbocation \( 173 \), which is trapped by the sulfonamide to finally render the observed cyclobutyl sulfonamides after demetalation (Scheme 55). Interestingly, the same transformation is achieved using a magnetic nanoparticle-supported phosphine gold(I) complex [215].

![Scheme 55](image)

**Scheme 55.** Gold-catalyzed ring expansion of simple alkynylcyclopropanes.

External oxidants such as sulfoxides are also suitable reagents to trigger cyclobutane formation reactions from cyclopropyl alkynes via the well-documented formation of \( \alpha \)-oxo gold-carbene species. So, Liu developed an efficient gold(I)-catalyzed transformation of internal cyclopropyl alkynes \( 172a \) to cyclobutenyl ketones \( 176 \) using an excess of diphenyl sulfoxide as reactant (Scheme 56) [216]. This process begins with the selective intermolecular oxidation of the alkyne at the \( \beta \) position respect to the cyclopropane thus producing \( \alpha \)-oxo gold-carbene intermediate \( 175 \), which then undergoes a Wagner-Meerwein migration and posterior demetalation that accounts for the cyclobutene formation.
An alternative concerted pathway in which the cyclopropyl expansion facilitates the cleavage of the O–S bond cannot be discarded.

Scheme 56. Gold-catalyzed ring expansion of alkynyl cyclopropanes in the presence of an external oxidant.

On the other hand, gold-catalyzed reaction of 4-methoxybut-2yn-1-ols 177 with two molecules of allytrimethylsilane affords bicyclo[3.2.0]heptanes 181 in high diastereoselectivity and good yields (Scheme 57) [217]. The proposed mechanism, based on deuterium-labeling experiments and the isolation of an intermediate, involves the formation of cyclopropyl alcohol 179 by propargylic substitution with an equivalent of allylsilane followed by enyne cyclosimerization. Then, the gold catalyst induces the formation of the cyclopropyl carboxylation 179, which undergoes the ring enlargement to generate bicyclic carboxylation 180 that gives the observed cycloadducts 181 by further reaction with the second unit of allylsilane.

Scheme 57. Gold-catalyzed synthesis of bicyclo[3.2.0]heptenes from allylsilane and methoxy substituted propargylic alcohols.

4. Other Cyclization Approaches

Herein, other types of cyclizations from those shown previously are exposed. The first, reported by Li’s group, involves the interaction of homopropargylic ethers 182 with pyridine N-oxide that gives α-oxo gold-carbene intermediates 183. These species are intramolecularly trapped by the pendant alkoxy group to produce oxonium ylides species 184, whose rearrangement affords the observed α-alkoxy cyclobutanones 185 in moderate yields (Scheme 58) [218]. The process is quite limited, as it only works with substrates bearing a terminal acetylene and electron-rich substituents at the homopropargylic position. Other substitution led to the formation of α,β-unsaturated carbonyl compounds [219], which are also obtained as side products with some of the suitable homopropargylic ethers 182.
Moreover, Hashmi’s group employed the previously introduced σ,π-digold species for the construction of a couple of benzofused cyclobutane scaffolds 188 from thiophene embedded diynes 186 possessing a terminal alkyne at C-3 and a tert-butyl group at the internal alkyne in C-2 (Scheme 59) [220]. In this transformation, the gold catalyst coordinates the external alkyne of the diyne system in a classical π-fasion whereas the terminal alkyne is σ-coordinated, thus producing the activated intermediate 187. Then, the cyclobutane core is obtained through a 6-endo cyclization followed by a carbene C–H insertion.

Finally, the synthesis of cyclobutanones from alkynyl ketones through a gold-catalyzed oxidative process has been recently developed [221]. Thus, reaction of tert-butyl alkynyl ketone 189 with 8-isopropylquinoline N-oxide in the presence of a cationic gold catalyst gives β-diketone-α-gold carbene intermediate 190, which then selectively evolves to observed cyclobutanones 191 by a C–H insertion (Scheme 60). Not surprisingly, variable selectivity to the desired cyclobutanones are achieved when more challenging substrates possessing different suitable hydrogens to undergo the C–H insertion are employed. For these substrates optimization of the gold catalyst is required.
Scheme 60. Synthesis of cyclobutanones from alkynyl ketones via oxidative gold catalysis.

5. Conclusions

The research recorded in this review highlights the great potential of gold catalysts for the construction of four carbon ring systems, a class of carbocycles widely present in natural products and very relevant intermediates in organic synthesis. Two main strategies have been developed in recent decades regarding on the reaction type: [2+2] cycloadditions and ring expansions. The progress of this field relies on the design and development of gold(I) catalysts to optimize yields, regio-, chemo- and stereoselectivities, as well as on the understanding of reaction mechanisms. These approaches allow to get complex cyclobutene derivatives under mild conditions, with high functional group tolerance and good yields, usually from easily available substrates. Enantioselective versions of some of these transformations employing gold complexes derived from chiral phosphine ligands have also been reported. In addition, examples of total synthesis of natural products following these methodologies have been shown to illustrate its relevance, advantages, and applications to access cyclobutane skeletons.

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