Gold-Catalyzed Homogeneous (Cyclo)Isomerization Reactions

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Gold is currently one of the most used metals in organometallic catalysis. The ability of gold to activate unsaturated groups in different modes, together with its tolerance to a wide range of functional groups and reaction conditions, turns gold-based complexes into efficient and highly sought after catalysts. Natural products and relevant compounds with biological and pharmaceutical activity are often characterized by complex molecular structures. (Cyclo)isomerization reactions are often a useful strategy for the generation of this molecular complexity from synthetically accessible reactants. In this review, we collect the most recent contributions in which gold(I)- and/or gold(III)-catalysts mediate intramolecular (cyclo)isomerization transformations of unsaturated species, which commonly feature allene or alkyne motifs, and organize them depending on the substrate and the reaction type.

Keywords: gold, catalysis, isomerization, allenes, 1,n-enynes, 1,n-diynes

1. INTRODUCTION

Historically, most civilizations have considered gold as synonym of power, purity, beauty and wealth. In contrast, for a long time, gold was chemically ignored and misconceived as an inert element. It was only at the end of the twentieth century and the beginning of the twenty first when a “gold rush” in synthesis started with the publication of the original works of Fukuda (Fukuda and Utimoto, 1991), Teles (Teles et al., 1998), and Tanaka (Mizushima et al., 2002) on the homogeneous gold-catalyzed addition of water and alcohol to alkynes. The seminal contributions that sparked the interest in gold catalysis in the ending years of the twentieth century were due to Hashmi et al. who showed the catalytic reactivity of AuCl$_3$ on cycloisomerization reactions of alkyne-based compounds leading to furans and arenes (Hashmi et al., 2000; Stephen et al., 2000). Since then the interest on this metal has increased notably as revealed by the vast number of publications on gold catalysis$^1$. Located in group 11 of the periodic table, gold behaves as a soft carbophilic Lewis acid with the ability to stabilize an adjacent carbocation through back-donation. Relativistic effects in this atom promote the contraction of its 6s orbital, which becomes the main reason for this relatively uncommon behavior across the periodic table (Gorin and Toste, 2007; Faza and López, 2015). Nevertheless, gold complexes are usually poorly-reactive in their precatalytic state and they need prior transformation in-situ, most commonly through the abstraction of one ligand, generally a chloride group. Among others, silver salts are the most used agents for this purpose (Ranieri et al., 2015). Furthermore, both the electronic nature of ligands (Wang et al., 2012; Ebule et al., 2016; Gong et al., 2016; Ferrer and Echavarren, 2018a) and of the counterion (Homs et al., 2014; Giancalleoni et al., 2015; Jia and Bandini, 2015; Rocchigiani et al., 2015; Gatto et al., 2016; Yuan et al., 2018; Schießl et al., 2018a,b) have a significant influence on the reactivity of the gold-catalyzed processes.
Thus, gold(I)- and gold(III)-complexes are mostly intended for the activation of unsaturated groups, such as allene and alkyne derivatives (Jones, 2015; Blons et al., 2018). Figure 1 shows the possible activation modes exerted by a generic cationic gold complex [Au]⁺ toward common starting materials which will be the subject of revision in this report. Four possibilities have been described for the coordination of gold to an allene moiety: \( \eta^2 \)-coordinated complexes (2), zwitterionic carbenes (3), \( \sigma \)-allylic cations (4) or \( \eta^1 \)-coordinated bent allenes (5) (Soriano and Fernández, 2014). Cumulenic derivatives could also be formed under gold activation. The \( \sigma \)-coordination of gold to the alkynyl group of an ynamide substrate 6 promotes the formation of an electrophilic keteniminium ion 7 susceptible to a nucleophilic attack. Propargylic carbonate/ester substrates 8 are prone to rearrange under gold-catalysis, usually trough a 1,3- or 1,2-migration of the carbonate/ester group over the \( \pi \)-system toward either the alkyne intermediate 9 or the gold-carbene 10, respectively (Ghosh et al., 2014; Swift and Gronert, 2016). Alkynes containing and internal nucleophilic functional group 11 can cyclize either in an \textit{exo-dig} or \textit{endo-dig} fashion leading to 12 and 13. Otherwise, it is possible that two gold complexes coordinate simultaneously to the terminal alkyne 11 forming a \( \sigma_2 \pi \)-digold alkyne and then furnishing intermediates 14 and 15 (Cheong et al., 2008; Larsen et al., 2015). Cyclopropane gold carbene-like intermediates 17 and 18 are, respectively, achieved through an \textit{endo-dig} and an \textit{exo-dig} carbocyclization of the enyne 16 (Obradors and Echavarren, 2014). Two internal alkynes placed 2The Scopus database returns 30,000 entries when looking for gold catalyst, gold catayis or gold-mediated keywords (search performed in January 2019) in an alkyne 19 can react onto each other under gold-\( \pi \)-activation forming a conjugated vinyl cation intermediate 20. Recently, the possibility of dual gold-activation has started to garner attention. It is a reactivity pattern for diyne systems, in which one gold center simultaneously enhances the nucleophilic character of the terminal alkyne through a \( \sigma \)-bond while a second gold center turns the other alkyne motif more electrophilic trough a classical \( \pi \)-coordination (Cheong et al., 2008; Odabachian et al., 2009; Stephen et al., 2012; Ye et al., 2012; Hashmi, 2014). This reactivity is represented in the transformation of diyne 21 toward intermediate 22. The diversity in the activation patterns shown by gold opens a large window of possibilities for the use of this metal as a powerful tool in the design and synthesis of relevant compounds in different fields. In fact, an increasing number of structurally complex molecules, such as natural products, biologically active compounds or polycyclic systems are reachable from synthetically accessible alkyne, allene and allene reagents under metal-mediated isomerization process (Aubert et al., 2011; Yamamoto, 2012; Zhang et al., 2012; Stathakis et al., 2016; Hu et al., 2017; Herndon, 2018). In this sense, gold shines over other metals mostly due to its tolerance to diverse functional groups, low toxicity and the usually mild thermal conditions that are required to run these kind of transformations, in some occasions even showing tolerance to aqueous media or green solvents (Gatto et al., 2018).

This review focuses on homogeneous gold-mediated intramolecular (cyclo)isomerizations without the direct intervention of external agents in the intermediate mechanistic steps, except water in some unavoidable cases. It is organized according to both the kind of substrates to be activated by the gold complex: Allenes, 1,\( n \)-diynes and 1,\( n \)-diynes and to the first mechanistic step in the global transformation such as carbocyclization, nucleophilic attack or carbonate/ester group rearrangement processes. Due to the overwhelming number of studies and the recently published reviews about gold-mediated isomerization reactions (Belmont and Parker, 2009; Fensterbank and Malacria, 2014; Yang and Hashmi, 2014; Dorel and Echavarren, 2015; Asiri and Hashmi, 2016; Day and Chan, 2016; Maes et al., 2016; Quintavalla and Bandini, 2016; Siva Kumari et al., 2016; Wei and Shi, 2016; García-Morales and Echavarren, 2018; Lee and Kumar, 2018; McGee et al., 2018; Toullec and Michelet, 2018), we will include here the most relevant contributions of the last years.

2. GOLD-CATALYZED ISOMERIZATION PROCESSES INVOLVING ALLENES

Allenes are cumulenic compounds in which one carbon atom stabilishes a \( \pi \)-bond with two adjacent carbon centers, adopting an ideal bond angle of 180° (Patel and Bharatam, 2011; Soriano and Fernández, 2014). Both the structural architecture of this triatomic system and the electronic nature of the substituents on it direct the metal coordination modes and therefore the reactivity of the activated allene (Figure 1). In addition, the initial mode in which gold coordinates to the cumulenic motif, and the further transformations, determines the spatial disposition

FIGURE 1 | Gold activation reaction patterns toward different unsaturated substrates.

Gold-activated substrates
of the substituents observed in the isomeric products (Yang and Hashmi, 2014) and even turns the mechanistic pathway away from that of the uncatalyzed reaction (Mandal and Datta, 2018). Interestingly, gold complexes are able to catalyze the racemization of 1,3-disubstituted allenes, a process which has been theoretically studied for the particular case of IPrAuOTf acting as the catalyst (Li et al., 2016).

In 2018, Guinchard et al. reported an elegant thermal ring closure of enantionenriched N-allyltryptamines 23 catalyzed by the Echavarren catalyst, [JohnPhosAuNCMe]SbF$_6$ (Figure 2A). The initial gold(I)-activation of the allene motif promotes the tandem 6-exo-dig/aza-Cope rearrangement process affording intermediates 24. The nature of the R$^1$ and R$^2$ substituents placed at both the original allene and alkene groups direct the subsequent evolution of 24 toward the different indolo[2,3-$a$]quinazolines 25, 26, and 27. Thus, for R$^1$ = H 24 undergoes an isomerization process of the exocyclic C—C double bond yielding 25 whereas when R$^1$ = alkyl, aryl the mechanism evolves trough a [3,3]-Cope rearrangement to afford compounds 26. Pentacyclic substrates 27 were isolated for the special case of R$^1$ = aryl and R$^2$ = H (Gobé et al., 2018). In the same line, the (non-)substitution at the terminal position of the alkylene group contained in the initial indole-tethered amino allenynes 28 is the responsible for the divergent synthesis of the fused polycyclic indoles 29 and 30 (Figure 2B). [IPrAu]$^+$ would activate the allene motif toward a 6-endo-carboauration at the C3 atom of the indole ring as initial step whereas the subsequent hydroamination process over the N-pendant terminal alkylene ends in the hexacycle 29. This process does not occur in the case of alkynes bearing bulky R$^2$ groups. Pentacycles 30 are therefore accessed in these latter transformations (Alcaide et al., 2018).

Other gold-mediated carbocyclization reactions have been described for allenes. Daphnane/tigliane diterpene natural products contain a common scaffold based on a 5-7-6 carbotricyclic ring system. In this sense, Li et al. published a gold(I)-mediated sequential transformation of allenynes 31 into the polycyclic ethers 33 (Figure 3A). The authors noted that the overall direct gold-catalyzed process was unfruitful, requiring the optimization of a two-step sequence under different reaction conditions and gold(I)-complexes. Thus, [PPh$_3$Au]$^+$ promotes the initial 5-exo-dig hydroalkoxylation onto the alkylene group toward intermediates 32 (Riedel et al., 2017) which subsequently undergo a furan-allene (4+3) cycloaddition under thermal treatment (60°C), and with the participation of [tBuXPhosAu]$^+$, to afford the isomeric mixture of the desired product 33 plus 33’. This last step is highly influenced by the nature of the R$^1$ substituent at the allene site. Terminal allenes (R$^1$ = H) are poor substrates for this (4+3) cycloaddition, producing a complex mixture of products whereas tricyclic systems 33b and 33c are obtained in good yields and with a moderate isomeric ratio for the target product 33 vs. the undesired ether (Li et al., 2017b).

In 2017, the combination of gold(I) and copper(II) complexes was reported as an efficient catalyst to promote the site- and regiocontrolled carbocyclization of a racemic mixture of allenes 34. In order to explain the mechanistic sequence behind these transformations Schomaker et al. proposed a double metal activation in which Cu(OTf)$_2$ would form a Cu-enolate chelate whereas [R$_3$PAu]$^+$ (R = Ph or Cy) would activate the allene motif (35) to then furnish the cyclopentene species 36 in >1:1 dr (antis: syn of the two starred carbon centers). Remarkably, the stereochemistry at the junction of the two 5-member rings at 36 remains syn during the process. The different dr observed in
products 36 respect to the 1:1 dr in the initial mixture of allenes 34 is reasoned assuming that the rate of the gold-activated allene epimerization is faster than that of the carbocyclization process at the intermediate 35 (Figure 3B) (Reeves et al., 2017).

In the last few years many chemists have focused their efforts in developing enantioselective reactions, which is currently one of the most active arenas in the field of gold catalysis (Wang et al., 2014). An illustrative example is that published by Voituriez et al. in the course of the total synthesis of the natural product (-)-rhazinilam. They reported the use of a digold(I) complex attached to the chiral biphenyl-phosphine ligand L to mediate in the enantioselective 6-exo-trig cycloisomerization of the allene-functionalized pyrrole 37, which leads to the tetrahydroindolizine derivative 38 in 89% yield and 83% ee. This reaction is conducted in a solution of mesitylene at room temperature (Figure 4A) (Magné et al., 2017).
In the same line, asymmetric gold-catalysis via the combined use of a non-spectator chiral ligand and a metal center has been described for the cyclization of the 4-allen-1-ol substrates 39 affording chiral 2-substituted tetrahydrofurans 40 (>90% ee, Figure 4B). The pendant amide group at the chiral binaphtyl-based ligand (R)-L2 seems to play a crucial role in the rate acceleration of the reaction due to its abilities to act as a general base. Authors propose that the preferred gold-allene coordination is that in which that amide group is placed close to the alcohol group, whereby forming a hydrogen bond C=O⋅⋅⋅H-O which increases the nucleophilicity of the oxygen atom and thus the rate of the reaction (Wang et al., 2017a).

Furthermore, the highly stereoselective cycloisomerization of optically active 4,5-alkadienoic acids leading to gamma-butyrolactones has been reported to occur under catalysis of chiral gold-complexes (Zhou et al., 2018a). Also, non-chiral gold catalysts have been reported to promote related cycloisomerizations of cumulenols (Alcaide et al., 2016) or allenols (Lempke et al., 2016). For this later example, the effects governing the mechanism of the gold-catalyzed attack mode of hydroxylamines onto allenes yielding either dihydrooxazine or N-hydroxypyrroline derivatives (that is O-vs. NH-attack and 5- vs. 6-member ring formation) were computationally studied and described in detail by Silva and coworkers in 2017 (Kiriakidi et al., 2017).

3. GOLD-CATALYZED ISOMERIZATION PROCESSES INVOLVING AN INITIAL ALKYNE ACTIVATION

Most of the studies on gold-mediated isomerization reactions are devoted to the transformation of alkynes bearing a second unsaturation (an alkene or alkyne group), that is 1,\(n\)-enynes and 1,\(n\)-diynes substrates (Jiménez-Núñez and Echavarren, 2008; Asiri and Hashmi, 2016; Day and Chan, 2016; Lee and Kumar, 2018). Nonetheless, cycloisomerization processes have also been described in molecules containing solely a reactive alkyne or alkyne group. This is the case of the gold(I)-directed ring-contraction process of cyclooctyne to 5-member bicyclic alkenes (Das et al., 2016) or the intramolecular hydroamination of 6-alkenyl-2-pyridones to yield 1,6-carboannulated 2-pyridones (Timmerman et al., 2017). In those circumstances where both types of unsaturations are present, the well-known preference of gold for alkyne over alkene groups is rationalized in terms of the HOMO-LUMO energy gap of the coordinated \(\pi\)-systems rather than through intrinsic considerations of the metal itself (Gorin and Toste, 2007). Henceforth, (cyclo)isomerization processes initiated by the gold activation of an alkyne group will be described.

3.1. Gold-Catalyzed Cycloisomerization of Ynamides

Ynamides are special amines substituted by an alkyne group and an electro-withdrawing group which modulate its stability and reactivity (Pan et al., 2016). Yeh et al. reported the gold(I)-catalyzed double cyclization of the 3-enynamides 41 in dichloromethane at room temperature (Figure 5A). The authors propose an initial cyclization involving the gold-activated alkyne motif and the pendant endocyclic C=C bond that provides vinyl cation 42. This cationic intermediate 42 could cyclize forming either a 6-member ring, by attack of the pendant phenyl ring...
onto the deficient carbon center (path \(a\) toward 43, traces) or a 4-member ring, involving the exocyclic alkene (path \(b\) leading to 44). The strained cyclodibutene compounds 44 are quickly oxidized when exposed to air, affording the respective 1,4-diketones compounds 45, which are isolated as major products (Zhong et al., 2017).

In 2018, Liu et al. designed a new route toward benzo[\(b\)]carbazoles 49 involving the [JohnPhosAuNCMe]\(^{1+}\)-catalyzed cycloisomerization of the ynamide-ynes 46 via a formal dehydro-Diels-Alder reaction at room temperature (Figure 5B). Initial gold-activated keteniminium ions 47 undergo a cyclization affording the vinyl cations 48 which evolve toward the final tetracycles 49 by a benzoannulation reaction (Xu et al., 2018). The same catalyst, [JohnPhosAuNCMe]SbF\(_6\), mediates the transformation of ynamides 50 into tetrahydro[\(g\)]quinolines 52 (Figure 5C). An initial [3,3]-sigmatropic rearrangement of the acetyl group and activation of the ynamide group would yield the keteniminium ion 51 which would experiment a formal [4+2]-cycloaddition yielding 52. This protocol is efficient even in the presence of air and moisture, indicating the tolerance of the gold catalysts to diverse reaction conditions (Chen et al., 2018).

A very interesting case is that of \(N\)-substituted ynamides decorated with functional groups with migratory abilities. Figure 5D shows the unconventional thermal transformation of \(N\)-sulfonyl ynamides 53 to 4-sulfonlated pyrrol derivatives 56 in presence of XPhosAuNTf\(_2\) catalyst. The authors proposed a mechanism initiated by a [1,3]-sulfonyl migration from the \(N\) atom to the distal carbon atom of the alkyne fragment resulting in intermediate 54. The subsequent gold-activation of the alkyne moiety promotes an umpolung at the unsaturations and facilitates a 5-endo-dig cyclization toward 55, which is transformed into the indole 56 via a deaurative [1,5]-sulfynylation process. This kind of sulfonyl/sulfinyl shift proceeds in a regioselective fashion. These results were also supported by a computational study (Sahoo et al., 2018).

Furthermore, gold(III)-complexes are able to promote the activation of ynamides toward cycloisomerization reactions. In 2018, Ye et al. reported the practical synthesis of indeno[1,2-c]pyrroles 59 in good yields under mild conditions from \(N\)-propargyl ynamides 57 and with gold(III) catalysis. In contrast to the usual metal-catalyzed cyclization of \(n\)-tethered ynamides over the central \(\alpha\)-carbon atom, authors reported a regioselective attack on the \(\beta\)-carbon of the ynamide 57 leading to the vinyl cation 58, mostly associated to a lower ring strain of the formed pentacycle with respect to the four-member ring alternative (Figure 5E) (Shen et al., 2018).

### 3.2. Gold-Catalyzed Cycloisomerization of 1,\(n\)-dienyes and 1,\(n\)-diynes Containing a Propargyl Carbonate/Ester

In the last 3 years a great number of studies devoted to gold-mediated cyclizations of compounds containing a propargyl carbonate/ester motif have been reported. It is worth to note that the usual initial carboxy rearrangement determines the fate and further transformations that encompass this chemistry. For this reason substrate design is key to successfully obtain the desired target molecule through these reactions. Recently, Zhang et al. introduced the application of frustrated Lewis pairs as a synthetic strategy, that is, basic tertiary amine as ligands to design gold cationic complexes which improve the regio- and stereoselective ratios of propargyl ester isomerizations (Wang et al., 2017b). In this sense, related \(1,\(n\)-enyne derivatives are well-exploited reactants and powerful synthetico tools to build carbonyl-based compounds. Figure 6A describes the diasterospecific synthesis of cyclopentanones 62 owning two contiguous stereogenic carbons published by Tius et al. The authors use a gold(I) complex to catalyze a tandem [1,3]-OAc shift/cyclization/acetate hydrolysis process. This cycloisomerization reaction can be conducted at room temperature with substrates 60 bearing different functional groups such as esters, -CF\(_3\) or alkyl chains. The high diastereoselectivity observed in the transformation is related to the rapid alkenyl isomerization of the pentadienyl intermediate 61 (Congdon and Tius, 2018).

A couple of years earlier, the preparation of benzazocines 66 was accomplished from terminal 1,9-enynyl esters 63 through a gold-catalyzed cascade reaction. Xie et al proposed the initialization of the mechanism with a 1,2-acloxy shift that further evolves with a O-cyclization to yield 1,3-dipolar intermediates 64. These 64 species engage in a [3+2] cycloaddition reaction involving the terminal alkene to afford the polycyclic scaffolds 65, which convert into the final substituted benzocines 66 by a hydrolysis process. Two different diastereoisomers were isolated and fully characterized, the trans isomers 66 being the major products of the reaction (Figure 6B) (Feng et al., 2016). The same group has reported on the successful attempts to obtain complex tetracyclic frameworks by applying a similar gold-catalyzed protocol on related linear enynyl esters (Sun et al., 2017).

Liu et al. published the gold(I)-mediated diastereoselective formation of 8-oxabicyclo[3.2.1]octanes 70 from glycal bearing propargyl esters 67 (Figure 6C). The authors proposed that the [PPPh\(_3\)+Au]\(^{1+}\) catalyst has a dual role during the course of the reaction. First, the gold(I)-complex activates the alkyne group to facilitate a 1,3-acloxy migration leading to the allene intermediates 68. Further along into the mechanistic pathway, the metal acts as Lewis acid promoting the intramolecular Ferrier reaction with the departure of the alcoxy group, which is integrated as a new ligand in the gold complex [Au]OR\(^2\) furnishing the oxocarbenium species 69. Lastly the bicyclic structure of 70 is formed by cyclization and formation of AcOR\(^2\) as a by-product (Liao et al., 2017).

In conjunction with the latter works, functionalized anthracenes 73 can also be generated under thermal conditions (50°C) with bulky gold(I)-catalysts promoting the cyclization of 2-(2-ethynylbenzyl)furan featuring propargyl carbonate or ester groups 71. Intermediates 72 are proposed to be formed after a 3,3-rearrangement of the propargyl carbonate OR\(^2\) moiety, and then evolve to products 73 via a [4+2]-cycloaddition between the furanyl system and the distal C=C double bond of the allene. A similar protocol was applied in the cycloisomerization of the related 1,5-furan-ynes 74 to obtain
antracen-1(2H)ones 75; in this case a late 1,2-R¹ shift is required after the [4+2]-cycloaddition step to afford the final ketone (Figure 7A) (Sun et al., 2016).

An unusual chemoselective gold-activation of alkenes over allenes using sterically bulky ligands as di²BuXphos has been described by Shi et al. Substituted bicyclic[4.4.0]dihyronaphthalenes 78 were accessed from the dienynes 76 through an initial 1,3-OPiv rearrangement and subsequent alkene-activation at intermediate 77, which then experiments an allene-ene cyclization and hydrolysis. Interestingly, the pivaloyl group (Piv) migrates selectively during the formation of hydrobenzopyranes (78, X = O) as indicated in Figure 7B (Thummanapelli et al., 2016).

As in the case of 1,n-enynes, reactions initiated by migration of a carbonate or ester group have been subject of study in related 1,n-diyne derivatives (Day and Chan, 2016; Li et al., 2017a). Chan et al. reported in two different studies the gold(I)-mediated cycloisomerization of 1-en-4,n-enynes 79 (Chen et al., 2016a) and 1-en-3,9-enynes 81 (Figure 8A) (Rao et al., 2016). Both reactions were conducted under the same solvent and temperature conditions (DCE, 80°C) but with different gold catalysts. Thus, for the conversion
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**FIGURE 7** | Gold-mediated cycloisomerization of 1,6-dienynes started by an acyloxy shift process.

79→80 [JohnPhosAuNCMe]^+ was the active cationic gold species which provided the best results, whereas in the case of the cycloisomerization of the diyne 81 [LAuCHPh]^+ was employed. In the latter, therefore, a cationic catalyst featuring a N-heterocyclic carbene ligand is used. In both cases the mechanistic route would be initiated by the gold-activation of the propargyl moiety promoting a 1,3-acyloxy transfer followed by several cyclizations. In fact, the relative position of the olefine moiety determines whether the evolution of the mechanism at the first cyclization occurs through either a 1,4-eneallene cycloisometization toward 80 or a metallo-Nazarov cyclization toward the tetracycles 82. In 2018, the synthesis of naphtho[2,3-c]furan-1(3H)-ones 84 was reported via cycloisomerization of propargylic ynoates 83, under thermal conditions with BrettPhosAuCl as catalyst and in presence of NaBARf4 as an activator of the gold complex (Figure 8B) (Li et al., 2018a). The reaction mechanism would involve a [3,3]-rearrangement of the propargyl ester leading to a carboxyallene intermediate followed by an intramolecular Diels-Alder cyclization. The authors were able to synthesize up to 24 examples of 84 combining diverse alkyl and aryl substituents and they also describe a new method for the in-situ generation of carboxyallene intermediates.

An interesting formation of primitive dendrimer systems containing bicyclic structures from substrates incorporating two sets of dialkynes were described by Oh et al. The hydrated NaAuCl4 mediates in the thermal cycloisomerization of 85 through a dual 1,3- and 1,2-acyloxy transposition at the terminal and inner alkyne moieties, respectively, followed by
an annulation process leading to the benzo-fused 7-member cycles 86 (Figure 8C) (Lee et al., 2016). In a related work, the [Ph3PAu]+-activation of propargyl ester motifs promotes the 1,3-acyl shift/[2+2]/hydrolysis cascade reaction of the diynes 87 furnishing a diastereomeric mixture of the polycyclic systems 88 (Figure 8D). The authors were able to resolve the diastereomeric mixture and even extend this protocol to other diynes in which the pivaloate substituents are located at positions 3 and 3’ (Lee et al., 2018).

### 3.3. Gold-Catalyzed Cycloisomerization Processes of 1,\(n\)-enynes and 1,\(n\)-diynes Initiated by a Nucleophilic Attack Onto the Alkyne Group

Gold is able to activate an alkyne group toward a nucleophilic addition and, for instance, make it susceptible to act as the receptor motif in a hydride shift reaction (Xie et al., 2014; Nahide et al., 2018). In this sense, Wong et al. reported the gold-alkyne activation of 1,5-enynes 81 toward a rare 1,6-hydride shift leading to the gold-activated oxonium intermediate 90, which then experiments a Prins-type cascade forming two new C—C bonds and furnishing the final tricyclic system 91 (Figure 9A) (Lu et al., 2018). This mechanistic proposal is supported by deuterium-labeling cross-over experiments. According to the authors, there is no precedent of cycloisomerizations initiated by a gold-catalyzed 1,6-hydride transfer reaction. This protocol provides rapid access to fused polycyclic compounds presented in many bioactive natural products as Nominine or Walsuranin B.

An activated alkyne group could act as electrophile in an intramolecular nucleophilic attack if a functional group present within the system has such nature. An experimental gold(I)-mediated double 6-endo cascade cyclization strategy of enynes...
FIGURE 9 | Gold-mediated cycloisomerization reactions of 1, n-eneynes containing an internal atom-centered nucleophile.

92 to form benzoxyanthrene and benzoacridone derivatives 93 has been described by Cheng et al. (Figure 9B). The tandem process starts with an X-attack (X = O, N) to the alkyne moiety and further carbocyclization involving the pendant alkene motif, ending with the formation of both C—N and C—C bonds and releasing a methanol molecule. This reaction is conducted in toluene at 80 °C under microwave irradiation; this provides a better yield when compared with conventional thermal treatment (Xiong et al., 2018). Before this study, the same group had reported a similar protocol to obtain benzo[a]carbazoles via gold(I)-mediated cycloisomerization of structurally related ortho-alkynylanilines in toluene at 100 °C (Peng et al., 2017). Likewise, gold(III)-complexes have been reported to be excellent catalysts in similar transformations. Kumar et al. developed an elegant gold(III)-mediated strategy for the synthesis of substituted thiopyrano[2,3-b]indoles 95. This implies that enyne tethered indole sulfides 94 undergo a tandem σ-bond migration/6-endo-trig cyclization/oxidative aromatization process. The authors highlight the significance of the Z orientation of the C=C bond to assist the rearrangement step (Figure 9C) (Jha et al., 2017).

Besides, the use of bimetallic complexes has become more popular in gold chemistry during the last years (El Sayed Moussa et al., 2016; Trommenschlager et al., 2017; Arif et al., 2018). The synthesis of the (+)-conolidine alkaloid has been reported via a gold(I)-catalyzed cascade cyclization of the conjugated enyne 96. The bulky bimetallic gold complex (R)-MeO-DTBM-BIPHEP(AuCl)2 bearing a chiral ligand is used as effective precatalyst to form the ketone intermediate 97 (32% yield and 88% ee) (Figure 9D) (Naoe et al., 2016). Recently, Zi et al. achieved the first desymmetrization of prochiral bisphenols via gold(I)-catalyzed enantioselective hydroetherification of alkynes. This protocol was applied successfully in (di)alkyne compounds bearing P-stereogenic...
Several reports pivoting about cycloisomerization reactions of enyne-lactones by gold(I)-catalysis have been published by Zhu et al. (Figure 10). Under [Ph₃PAu]⁺ catalysis, the lactone-enynes 98 and 100 are proposed to experiment a ring-expansion reaction of the lactone ring affording the previously unknown 2-oxoninium intermediate 102a which exists in equilibrium with 102b. The presence of the benzo-fused ring at intermediates 102b displaces the equilibrium reaction toward the most stable 2-oxoninium 102a, whereas, in its absence, intermediate 102b is the preferred product. Both intermediates 102a and 102b then undergo an interesting 6π electrocyclization reaction and subsequent aromatization process toward compounds 99 and 101, respectively. The addition of one equivalent of water is required for the formation of 99 whereas the diester 101 is isolated even in anhydrous media (Figure 10A) (Luo et al., 2017). On the other hand, the nature of the ligand at the gold(I)-catalyst seems to have a high influence in the evolution of the mechanism allowing the transformation of related enyne-lactones 103. Thus, benzo-fused polycyclic compounds 105 are achieved using a carbene derivate gold complex as precatalyst (SIPrAuCl) in presence of the activating partner AgBF₄ (Figure 10B). The authors reasoned that an initial vinyl ether addition onto the activated-alkyne toward the 104 motif might be favored rather than an oxygen attack, as in the previous transformations, mostly due to the strong σ-donor and weak π-acceptor nature of the SIPr ligated gold center (Luo et al., 2018). If the lactone motif is replaced by a tetrahydrofuran group as in compound 106, then the bicyclo 107 is obtained via a gold(I)-catalyzed 5-exo-dig/[1,3] O-to-C tandem process in a diastereoselective fashion (Figure 10C) (Zhang et al., 2018a). With this set of papers Zhu
et al. demonstrated the versatility of diverse gold(I) complexes in the ring-expansion process of lactones and related structural motifs via a nucleophilic attack onto an activated alkyne group. 1,6-Diynes are prone to be transformed into valuable heterocyclic systems through the attack of an internal nucleophile, in particular -NH, -CO, or -OH groups, when present, either onto one or both of the gold π-activated C–C triple bonds. Lamellarins are a group of pyrrole alkaloids based in a pyrano[3,4-b]pyrrol-7(1H)-one scaffold which present anticancer activity. Thibonett et al. designed a gold(I)-catalyzed cycloisomerization of the 1,4-diynes 108 furnishing the substituted pyrano-pyrrolones 109 via two consecutive intramolecular 5-endo-dig and 6-endo-dig additions to both activated alkyne motifs (Figure 11A). The former cyclization proceeds involving the amine group in the formation of the pyrrol ring, whereas in the latter it is one of the ester groups which is involved in the formation of the pyranone ring (Delaye et al., 2017).

In 2017, Xu et al. reported an elegant gold(I)-catalyzed cyclization/carbonylation cascade reaction of diynes containing an amide group which operates under mild reaction conditions. Thus, 1,6-diynes 110 undergo a 6-exo-dig cyclization with the carbonyl oxygen of the amide group leading to the 1,3-oxazine gold intermediate 111, which is then intercepted by the remaining alkyne affording the intermediate 112. After protodeauration and hydration β,γ-unsaturated ketones 113 are obtained in good yields (Figure 11B) (Bao et al., 2017). Otherwise, 1,6-diynes bearing ortho-benzyl alcohols 114 evolve to dihydroisobenzofuran derivatives 116 through a gold(I)-catalyzed protocol initiated by two consecutive unusual 5-exo-dig hydroxyalkylation processes and a further Prins-like cyclization. Authors reasoned the formation of the 5-exo-dig cyclized product taking into account the more favorable six-membered ring chelated gold complex 115 when compared to the alternative bigger chelate, which would result in a more usual 6-endo-O-cyclization (Figure 11C) (Hashmi et al., 2007). This kind of transformation has not only been described as regioselective but also as stereoselective at the spiro-quaternary center placing the oxygen atom in the axial disposition (Cao et al., 2016).

Chan et al. designed an efficient method to prepare azacycle-fused pyroles 121-123 by gold(I)-catalyzed dehydrative cycloisomerization of β-amino-1,6-diylnos 117. The mechanistic sequence would be initiated with the formation of the pyrrole ring (118) promoted by the nucleophilic attack of the amine toward the closer gold-activated alkyne and departure of a water molecule. A subsequent gold activation of the remaining alkyne motif would promote a cyclization leading to the intermediates 119 and 120. The type of cyclization depends on both the length of the alkyl chain and the nature of the X linker (X = -NTs, O or CH₂), as is shown in Figure 11D. Furthermore, the intermediate 119 is the precursor of the fused pyroles 121 and 122 whereas pyroles 123 result from the expansion and further protodeauration of 120 (Kothandaraman et al., 2016). The nature of the substituents of the amide groups at the diynes 124 direct the gold(I)-catalyzed formation of the lactams 125 and 126. Thus, for a bulky R3 group and an electron-rich migrating R3 group path a is more favorable and involves a tandem NR3-nucleophilic cyclization/1,3-R3 migration/1,5-ene cyclodimerization process to yield 125. In contrast, if R3 is a poor shifting group, the dienynes 124 evolve through a cascade hydromination/Michael addition reaction (path b) to afford the spirocycle 126 (Figure 11E) (Li et al., 2018b).

3.4. Gold-Catalyzed Carbocyclization Processes of 1,6-enynes and 1,6-diynes

Those processes in which 1,6-enyne substrates are transformed into isomeric products through an initial carbocyclization step are very well documented. In 2018, Percy et al. have shown for the first time the intramolecular carbocyclization of difluorinated enol acetals bearing a pendant unsaturated group 127 leading to the cyclohexanone scaffolds 128 in a moderate diastereoisomeric ratio (Figure 12A). The reaction is conducted in a mixture of dichloromethane and methanol solvents at 40 °C in presence of PdAuCl as precatalyst and Ag₂SbF₆ as activator agent of the previous one. The carbonyl group is further reduced to obtain difluorinated diols. Besides, a mixture of difluorinated pyran scaffolds 130 and 131 are isolated, the gemdiol derivate 131 being the major product when using propargyl ethers 129 as starting reactants and 2-MeTHF as solvent (McCarter et al., 2018).

In a very recent publication, Echavarren et al. reported the gold(I)-catalyzed cascade cyclization reaction of oxime-tethered 1,6-enynes 132 furnishing the substituted oxazines (n = 1) and dihydroisoxazoles (n = 0) 133 in a diastereospecific fashion and very good yields (Figure 12B). The mechanism ruling this transformation has been proposed to proceed stepwise through an intramolecular addition of the O atom of the oxime onto the transient gold-carbene intermediate, as revealed by the DFT computations performed. The Z orientation at the C=N bond of the oxime group is determined to obtain 133, otherwise, with the E-oxide variant, dihydropyrrole N-oxides are isolated. The latter substrates resulted from the initial N-attack of the oxime onto the gold-carbene intermediate (Muratore et al., 2018).

The use of gold-homogeneous catalysis to achieve complex poly-annulated-cyclic systems is also gaining attention as, for instance, in the formation of the biologically active compound (+)-aureol (Wildermuth et al., 2016). In this sense, stable functionalized hydroxenoenes 135 are easily accessible up to nine rings trough a gold(I)-catalyzed cyclization of aryl-tethered 1,7-enynes 134, under mild reaction conditions (Figure 12C). A great number of different substituents R1 and R2 decorating the aryl motifs or even fused aromatic rings are compatible with the conditions, revealing the high synthetic value of this protocol (Dorel et al., 2016).

In 2016, Sanz et al. demonstrated that β,β-diaryl-o-(alkynyl)-styrnes 136 are transformed at 80 °C into dihydroindeno[2,1-a]indenenes 137 under gold(I)-catalysis whereas benzofulvenes 138 are obtained at 0 °C. The formation of the tetracycles 137 implies a formal [4+1] cycloaddition trough a tandem 5-endo-cyclization-diene/iso-Nazarov cyclization process (Figure 12D) (Sanjuán et al., 2016). A computational study for related gold(I)-mediated transformations in which the initial styrenes bear alkyl groups at the β positions has been reported by Zhou et al.
FIGURE 11 | Gold-mediated cycloisomerization of 1,n-dynes containing an internal atom-centered nucleophile.
The authors concluded that the reaction would evolve through a [1,2]-H shift on the isopropyl moiety rather than a cyclopropane expansion, as suggested in the experimental work (Sanjuán et al., 2015).

The Van der Eycken research group has reported the elegant one-pot synthesis of spirocyclic pyrrol-2-one-dienones 140 via a gold(I)-catalyzed intramolecular Friedel-Craft reaction of the Ugi adducts 139 (Figure 12E). Two diastereomeric dienones were isolated depending on both the gold-catalyst and the reaction conditions. Taking the 140 yields into account and supported by a conformational theoretical analysis, the authors concluded that the isomer 140a resulting from the catalytic treatment with Ph3PAuCl is energetically more favorable than that derived from the bulkier JhonPhosAuCl precatalyst (140b) (Nechaev et al., 2018b).
Continuing with carbocyclization processes, it was reported that several gold(I) salts (L = t-Bu, P, IPr; X = [OTf]−, [NTf2]−, [SbF6]−) activate the 1,5-enynes 141 toward gold-allenes 142 via a [3,3]-rearrangement. The subsequent tandem Nazarov cyclization/[1,2]-H shift process allows the formation of the fused cyclopentadienes 143, which were exposed to a further reduction to obtain primary alcohols 144 (Figure 13A). The position of the two double bonds at the final cyclopentadiene ring strongly depends on the size and type of the fused cycle, mostly carbocycles and N-heterocycles (Rinaldi et al., 2018). Bandini et al. described a related [3,3]-sigmatropic rearrangement for the site-selective gold(I)-mediated dearamatization of napthylpropynol derivatives toward dihydrofurynaphthalen-2(1H)-ones (An et al., 2017).

In 2018, Nakamura et al. published the gold(I)-catalyzed intramolecular 5-endo-Ar reaction of isoxazoles 145 substituted by a propargyl amine or ether at C4 position. This cycloisomerization furnishes the fused isoxazole substrates 146 in good yields at 60°C (Figure 13B). Moreover, the authors demonstrated that the addition of an external hydride acceptor as N-phenylbenzaldimine increased the yield in the synthesis of isoxazolopyridines (146, X = NH). Remarkably, the use of bulky gold(I)-complexes, such as [JhonPhosAu]+, is essential for the satisfactory formation of products (Morita et al., 2018).

Gold-catalyzed cyclizations in 1,6-enynes on indole scaffolds have also been reported in the last years (Pérez-Galán et al., 2016). Figure 13C shows a recent example in which N-substituted indoles 147 containing an alkene-tethered diyne cycloisomerize to eight-membered ring indazole derivatives 148 under gold(I)-catalysis. Shi et al. described the use of bulky-phosphine gold complexes to promote, under thermal treatment (80°C), two intramolecular nucleophilic attacks at the C2 and C3 centers of the indole moiety of both activated internal alkynes. Interestingly, compounds 148 exhibit yellow-green fluorescence, so they may have potential applications in the field of OLEDs (Liu et al., 2018). Related gold(I)-mediated carbocyclizations of enynes involving an eight-membered ring formation have been described recently in the synthesis of dibenzo[h,e][1,4]diazocines (Ito et al., 2018). Likewise, gold(III) complexes have been reported to be able to promote carbocyclization processes. Thus, bis(indoyl)methyl alkynyls 149 are transformed into substituted carbazoles 150 under catalysis of hydrated NaAuCl4 (Figure 13D). The mechanism for this transformation was found computationally to proceed via an unusual 1,2-migration of an indolymethyl moiety as key step (Suárez et al., 2017). 1,2- And 1,3-quinoxalinone fused pyrroles 152 and 154 were achieved involving a AuCl3-mediated cycloisomerization of alkynyl pyrroles 151 and 153 (Figure 13E). 1,2-Quinoxalinolines 152 are formed via an initial 1,3-R3 rearrangement followed by a 6-exo-trig cyclization involving the pendant pyrrol ring at 151, while 153 is transformed into 154 directly through a 6-exo-dig cyclization onto the terminal alkene unit (Wei et al., 2018). Nevertheless, related structurally pyrroles bearing a non-terminal alkene experiments a 7-endo-dig cyclization rather than a 6-exo-dig (Kong et al., 2018).

Reactants containing a cyclopropane unit have gained considerable attention lately, and a number of remarkable transformations using this kind of substrates have been achieved through gold-chemistry. The cis-to-trans isomerization of cyclopropane rings has been experimental and computationally studied under gold(I) and gold(III) catalysis, concluding that chiral bisoxazoline-Au(III) complexes are the best catalysts for promoting this isomerization (Reiersolmoen et al., 2018).

Shi and co-workers reported a set of works on gold(I)-catalyzed cycloisomerization of enynes containing methylenecyclopropanes. The IPrAuSbF6 catalyst is able to activate the alkene motif of enynes toward an intramolecular cyclization and further ring expansion of the methylenecyclopropane scaffold. For instance, aniline-linked 1,6-enynes bearing a cyclopropane ring 155 can be converted into 1,2-dihydroquinolines 156 and 157 under thermal conditions in a solution of dichloroethane. Under gold-catalysis, products 156, containing a cyclobutene ring were the major product compared to compounds 157, in which the cyclopropane is not expanded (Figure 14A). This product ratio is inverted when using AgSbF6 as catalyst (jiang et al., 2018). This methodology was extended to methylenecyclopropane-contained ynamides 158. Thus, substrates 158 evolve at room temperature to the polycyclic system 159 using Ph3PAuCl as catalyst whereas spirocyclics 160 were obtained by using a more sterically bulky catalyst, such as JhonphosAuCl. In both cases the gold-catalyst promotes the expansion of the alkylidencyclopropane to a four-member ring but only in the latter the catalyst facilities the subsequent intramolecular Friedel-Crafts process in the formation of 160 (Figure 14B) (Zhang et al., 2018b). A similar situation is reported for the intramolecular hydroarylation of the enynes 161 toward oxacycles 162 and 163. Thus, whereas both catalysts, IPrAuSbF6 and (p-CF3C6H4)3PAuSbF6, promote the carbocyclization step, only the former promotes the methylenecyclopropane expansion to a cyclobutene ring (Figure 14C). The authors reasoned this different reactivity attending to the inability of the gold complex containing electron-deficient phosphine ligands to activate the alkene moiety toward the ring expansion process (Fang et al., 2016). Temperature can also be a determining factor in these reactions, as shown in the isomerization of 1,5-enynes containing a cyclopropane ring, 164. These systems cycloisomerize to related bicyclic or spirobicyclic compounds depending on the catalyst and the thermal conditions. For instance, 164 furnishes 165 in presence of IPrAuNTf2 at -30°C. However, substrate 165 is converted into the bicycloprenanes 166 at 0°C under catalysis of the bulky gold complex [JhonPhosAu(MeCN)]SbF6 whereas bicycles 167 can be obtained at 60°C in a good diastereoisomeric ratio (Figure 14D). The authors proposed a catalytic cycle in which compounds 165 and 166 are precursors of 167 (Chen et al., 2016b). In the same line, Voituriez et al. described the enantioselective synthesis of cyclobutanone derivatives 169 via gold(I)-catalyzed cycloisomerization of enyne-methylenecyclopropanes 168. The most broadly tested catalyst was a binuclear gold complex bearing a bulky...
FIGURE 13 | Gold-mediated cycloisomerization of 1,6-enynes.
chiral-phosphine ligand, as represented in Figure 14E. The major isolated products are those with substituents R² and R³ presenting cis configuration (Wu et al., 2017). A similar approach was used as the key step in the total synthesis of the sesquiterpene Repraesentin F. Echavarren et al. reported a highly diastereoselective gold(I)-mediated cyclization of the 1,6-ene 170 via a tandem cycloisomerization/Prins-type reaction furnishing the tricyclic systems 171 containing the unusual skeleton of this natural product. Through this protocol the diastereoisomer with the desired anti ring fusion configuration...
is obtained as major product in a 7.2:1 ratio with respect to that with the syn fusion (Figure 14F) (Ferrer and Echavarren, 2018b).

The reactivity pattern of 1,ₙ-diynes has also been smartly exploited toward the construction of complex highly π-conjugated polycyclic systems (Asiri and Hashmi, 2016). In this sense, the works from Hashmi stand out with several remarkable publications on this topic in the last years (Tšupova et al., 2017; Wurm et al., 2017, 2018). A representative example is shown in Figure 15A. They described the gold-mediated cycloisomerization of 1,₅-diynes building on an aromatic ring toward aromatic polycyclic-annulated systems. The reaction mechanism involves a vinyl cation intermediate and operates under mild reaction conditions. Interestingly, optical properties have been described in this kind of annulated-pentalene compounds making them potential candidates for future optoelectronic devices (Sekine et al., 2018). Another example by Hashmi et al. was reported in 2017 and was highlighted as the first intramolecular trapping of dually gold-activated intermediates with an olefinic C(sp²)-H bond (Figure 15B). 1,₅-Diynes bearing an allyl-substituted alkene attached to an aromatic skeleton (175) could also be converted into fluorene derivatives via a dehydrogenative dual gold-catalyzed activation at reflux of tetrahydrofuran (Bucher et al., 2017). In this sense, dual-gold catalysis has been implemented in the cycloaromatization of unconjugated (E)-enedynes toward isoidolines 181 by using the trigold oxo complex [(Ph₃PAu)₃O]BF₄ as catalyst (Figure 15C). Both specific experiments with deuterated reactants and a detailed theoretical study indicate that the most feasible mechanistic pathway is that involving the very reactive allenyl-gold/gold-vinylidene.
intermediate 180, which is generated from a dual-gold activated substrate 179 via a 5-exo-trig cyclization. The subsequent carboxylation and rearomatization afforded the enantioenriched isoidolines 181 in good yields (Zamani et al., 2019).

4. CONCLUSIONS

In this review, the interest on gold and its relevance in intramolecular isomerization reactions is confirmed by taking into account the vast number of studies reported in the last 3 years and covered here. Most of the isomerization processes included in this review are initiated by three main different kind of transformations at allene and alkyne sites: nucleophilic attack onto the activated alkylene, 1,3 or 1,2- rearrangement of a carbonate/ester group over the π-system or a carbocyclization process. As we have shown, structurally complex molecules can be synthesized from easily reachable reactants under gold-catalysis and mild reaction conditions. Fewer in number but still important, some studies have developed gold(III)-catalysts although gold(I)-complexes seem to be more versatile, effective and preferred in this kind of reactions. Nowadays, enantioselective synthesis is a paramount goal, particularly when chemists are involved in biologically relevant molecules. Accordingly, the number of studies involving gold-complexes containing chiral ligands is growing notably. Although we can consider gold as a “young” metal, chemically speaking, it is clear that this metal center has many advantages to take into account when designing and performing innovative, complexity oriented and efficient chemical transformations.

AUTHOR CONTRIBUTIONS

CS, ON, and MM-L contributed conception of the review article, scope and structure. MM-L drafted the article. CS and ON revised its scientific and formal content.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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