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# Gold-Catalyzed Reactions via Cyclopropyl Gold Carbene-like Intermediates

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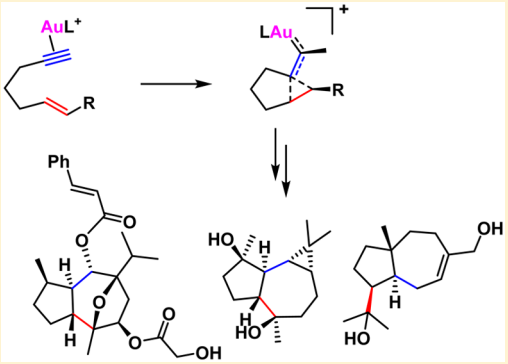
**ABSTRACT:** Cycloisomerizations of 1,*n*-enynes catalyzed by gold(I) proceed via electrophilic species with a highly distorted cyclopropyl gold(I) carbene-like structure, which can react with different nucleophiles to form a wide variety of products by attack at the cyclopropane or the carbene carbons. Particularly important are reactions in which the gold(I) carbene reacts with alkenes to form cyclopropanes either intra- or intermolecularly. In the absence of nucleophiles, 1,*n*-enynes lead to a variety of cycloisomerized products including those resulting from skeletal rearrangements. Reactions proceeding through cyclopropyl gold(I) carbene-like intermediates are ideally suited for the bioinspired synthesis of terpenoid natural products by the selective activation of the alkyne in highly functionalized enynes or polyenynes.




## 1. INTRODUCTION

Homogeneous gold catalysis is a relatively new field of research that became popular in the early years of this century. Although there were a few scattered papers describing reactions of aromatic compounds with gold salts, the first signals of the synthetic potential of gold in homogeneous catalysis came with the work of Teles[1] and Tanaka[2] on the addition of alcohols and water to alkynes.

Many reviews have covered different aspects of homogeneous gold catalysis.[3−12] Here, we focus on the developments of synthetic methods that were inspired on our initial studies of platinum(II)-catalyzed reactions and, in particular, on the multifaceted nature of cyclopropyl metal carbenes, key electrophilic intermediates formed by the activation of alkynes in functionalized 1,*n*-enynes and related substrates.

Inspired by the seminal work of the group of Trost on the electrophilic activation of enynes using palladium(II) complexes as catalysts,[13] which was followed by related work by Murai and Chatani using ruthenium(II)[14,15] and by the synthesis of phenols by intramolecular reactions of furans with alkynes developed by Hashmi,[16] we initially examined the intramolecular reaction of allylsilanes and allylstannanes with alkynes, discovering that $PtCl_2$ was the best catalyst, although palladium(II), ruthenium(II), and silver(I) salts and complexes could also be used.[17,18] Several other groups had almost concurrently found that platinum(II) also catalyzed the skeletal rearrangement of 1,6-enynes and other cycloisomerizations under relatively mild conditions.[19−24] We also found that $PtCl_2$ was an excellent catalyst for the addition of water and alcohols (hydroxy- and alkoxycyclization) to 1,6-enynes such as **1a−d**, a process that proceeds stereospecifically (Scheme 1).[25] Although these reactions proceed by an *exo-dig* pathway, the alternative *endo-dig* cyclization mode was also observed in other cases.[26]

The formation of five- or six-membered ring compounds **2a−c** or **3**, respectively, was rationalized by the competitive opening of a common intermediate **4** by attack of the nucleophile at the most electrophilic site, which was dictated by the substitution of the alkene following the Markovnikov rule, a hypothesis that was supported by DFT calculations (Scheme 2).[27] Intermediates **4** can be described as cyclopropyl platinum(II) carbenes, although the contribution of a charge-separated resonance form corresponding to metal stabilized homoallyl carbocations is also significant. It is important to note that the involvement of very similar reactive intermediates was already suggested in the palladium(II)-[13,28] and ruthenium(II)-catalyzed[15] reactions of 1,6-enynes.

In a parallel work, we also examined the synthesis of phenols by cyclization of furans with alkynes using platinum(II) catalysts[29,30] instead of gold(III), as originally reported by Hashmi,[16] concluding that this transformation is mechanistically related to metal-catalyzed cycloisomerization of enynes in which the furan ring acts as an electron-rich alkene (Scheme 3). According to the DFT studies performed for the platinum(II)-catalyzed reaction, the attack of the furan to the $\eta^2$-alkyne metal complex **5** leads to a cyclopropyl metal carbene **6**, which opens up to form **7**. Cyclization to **8**, followed by elimination of the metal generates oxepine **9**, in tautomeric equilibrium with arene oxide **10**, which leads to phenols **11**. Although almost all the examples reported concerned with the intramolecular reaction of furanynes, we recently developed an intermolecular version using cationic gold(I) catalysts.[31]

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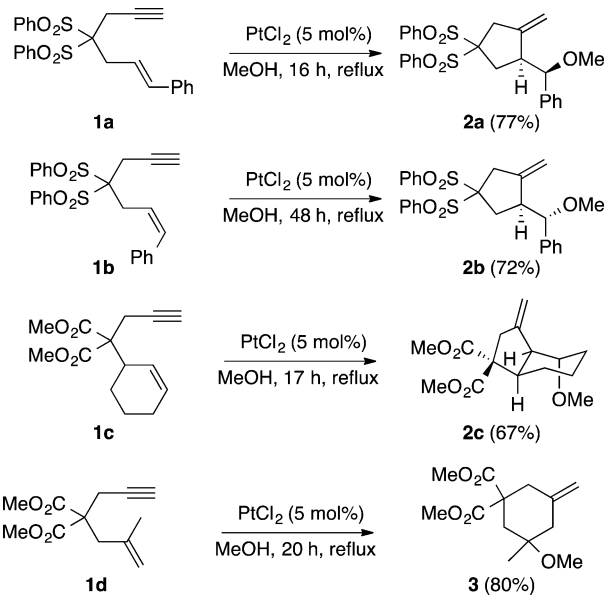
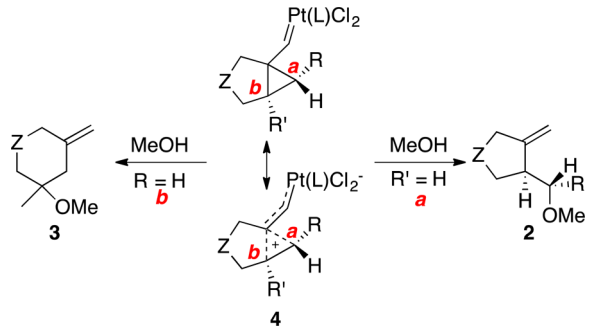
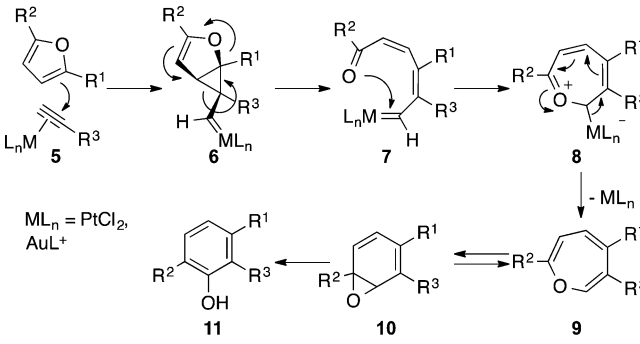
**Scheme 1. Platinum(II)-Catalyzed Methoxycyclization of 1,6-Enynes**




**Scheme 2. Mechanistic Rationale for the Regioselectivity Observed in the *Exo-Dig* Cyclization of Platinum(II)-Catalyzed Methoxycyclizations of 1,6-Enynes**




**Scheme 3. Mechanism for the Pt(II)- or Au(I)-Catalyzed Reaction of Furans with Alkynes To Form Phenols**

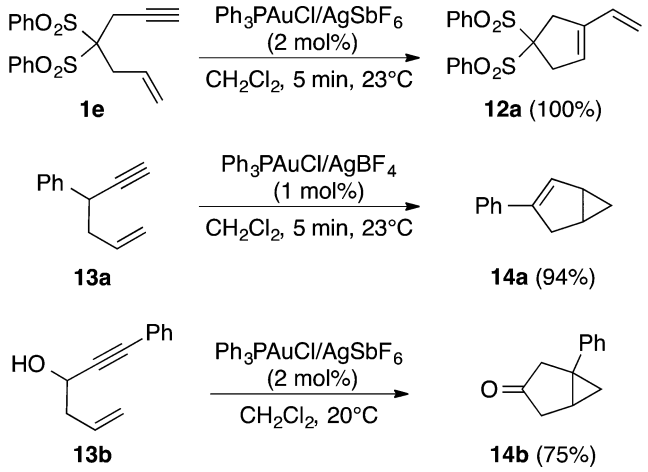



## 2. GOLD(I)-CATALYZED CYCLIZATIONS OF 1,*N*-ENYNES

During our initial studies focused on the use of platinum(II) complexes as catalysts, we also found that highly Lewis acidic $AuCl_3$ could be used as a catalyst in some cases.[26] However, we soon realized that cationic phosphine gold(I) complexes were more convenient catalysts, actually being the most active and selective for reactions of alkynes, outperforming platinum(II) and all the other metal catalysts that we had examined for the addition of heteronucleophiles, cycloisomerizations of 1,6-enynes, and similar transformations.[32,33] First, we generated in situ the reactive cationic gold(I) complexes by protonolysis of neutral complex $Ph_3PAuMe$, which leads to the formation of methane.[32] However, this method introduces a strong Brønsted acid into the reaction medium, which may promote unwanted side reactions. More convenient proved to be the use of $Ph_3PAuCl$ and a silver(I) salt with a noncoordinating anion such as $AgSbF_6$.[32,33] Recently, we found that the mode of activation of the LAuCl precatalysts with silver(I) salts has an important effect in catalysis.[34] Thus, if complexes LAuCl are allowed to react with AgX in poorly coordinating solvents and in the absence of the substrate, dinuclear chloride-bridged species $[LAuClAuL]^+X^-$ are readily formed, regardless of the counterion. These very robust complexes are poor catalysts, so that their formation significantly reduces the reaction rate. The formation of $[LAuClAuL]^+X^-$ can be minimized by premixing LAuCl with the substrate, followed by addition of silver salts, allowing formation of complexes $[LAu(substrate)]^+X^-$, which can directly enter the catalytic cycles. Of course, the formation of dinuclear chloride-bridged complexes can be entirely circumvented by the use of silver-free, cationic $[LAuL']^+X^-$, where L′ is a weakly coordinating ligand, which are often the alternative of choice in gold(I) catalysis.

Along with our initial study in 2004 on the cycloisomerization of 1,6-enynes such as **1e** to form 1,3-diene **12a** by skeletal rearrangement,[32] the groups of Fürstner[35] and Toste[36] reported related examples of cycloisomerization of 1,5-enynes of type **13a,b** to give bicyclo[3.1.0]hex-2-ene derivatives **14a,b**, respectively, under almost identical conditions using $Ph_3PAuCl$ and a silver salt (Scheme 4). A gold(I)-catalyzed Conia–ene

**Scheme 4. Gold(I)-Catalyzed Skeletal Rearrangement of 1e[32] and Cycloisomerizations of 1,5-Enynes 13a[35] and 13b[36]**




reaction of *β*-ketoesters with alkynes was also reported by Toste.[37]

In general, cationic gold(I) complexes activate selectively alkynes[3,12] even in the presence of other potentially coordinating functional groups as alkenes.[38] It is important to remark that, unlike other transition metals, gold(I) does not promote Alder–ene cycloisomerizations of 1,*n*-enynes, which require the unfavorable coordination of gold(I) to both the alkyne and the alkene. The oxidative cyclometalation of gold(I) to form a gold(III) metallacycle, is also a very unlikely process.[33,39] In the case of 1,6-enynes, gold(I) forms ($\eta^2$-alkyne)metal complexes



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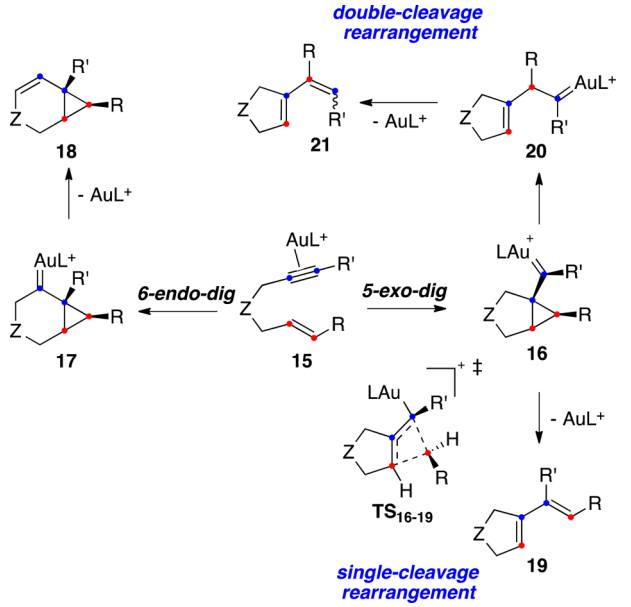
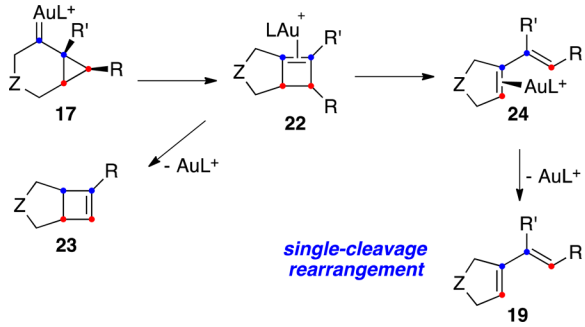
**Scheme 5. Main Pathways for the Gold(I)-Catalyzed Cycloisomerization of 1,6-Enynes**




**Scheme 6. Alternative Mechanism for the Gold(I)-Catalyzed Single-Cleavage Rearrangement of 1,6-Enynes**




**15**[40] that react intramolecularly with the alkene to form cyclopropyl gold(I) carbene-like intermediates **16** and/or **17** by 5-*exo-dig* or 6-*endo-dig* cyclization, respectively (Scheme 5).[32,41−44] Similar pathways are followed by 1,5-,[45−47] 1,7-,[41,48] and higher enynes[49−52] in the presence of gold(I) catalysts. According to DFT calculations, intermediates **16** and **17** are even more delocalized cationic structures than their Pt(II) counterparts, although for convenience, we prefer to represent these complexes as cyclopropyl gold(I) carbenes to highlight their propensity to undergo cyclopropanation reactions. However, although the back-donation from gold(I) to the cationic centers in these metal carbene-like structures is low,[53−55] it still provides sufficient stabilization[56,57] as has recently been shown in a few well-characterized gold carbenes $[LAu{=}CR_2]^+$ and $[L_2Au{=}CR_2]^+$.[58,59] The bond between Au and C in these gold(I) carbenes has been described as a half-double bond.[56] Terminologically, we recommend using the term gold carbenes rather than gold carbenoids for these species[57] since genuine gold(I) carbenoids $LAu{-}CH_2{-}X$ (X = Cl, SPh) have been structurally characterized.[60,61] These neutral complexes can be considered as formal precursors of gold methylidene complex $[LAu{=}CH_2]^+$ by an $\alpha$-elimination of the X group.

Intermediates **17** usually lead to bicyclo[4.1.0]hept-2-ene derivatives **18** by $\alpha$-proton elimination (Scheme 5).[62−64] On the other hand, intermediates **16** of 5-*exo-dig* cyclization afford 1,3-dienes **19** by a skeletal rearrangement (single-cleavage) in an interesting process that gives rise directly the $\eta^2$-coordinated gold(I) diene complex and involves a 1,3-suprafacial migration of the terminal carbon of the alkene via transition state $\mathbf{TS_{16-19}}$.[41] Intermediates **16** can also undergo a slightly different migration (double-cleavage rearrangement) by the formal insertion of the terminal alkene carbon into the alkyne carbons that forms a new gold(I) carbene **20**. Carbenes **20** then undergo $\alpha$-proton elimination to give 1,3-dienes **21**. Compounds **21** (R = H) with *Z* configuration usually predominate, although both *E*- and *Z*-configured products have been observed.[65−67]

The scenario shown in Scheme 5 is a simplification, as other similar pathways may also be possible depending on the substitution pattern of the substrate. Thus, intermediates **17** of *endo*-dig cyclization can undergo ring expansion to give ($\eta^2$-cyclobutene)gold(I) complexes **22**, which can evolve to form bicyclo[3.2.0]hept-2-ene derivatives **23** (Scheme 6).[62,63,68,69] Highly strained bicyclo[3.2.0]hept-5-enes have only been isolated in a few cases.[42,70] Intermediates **22** can also open up to form **24** and then dienes **19** in an overall single-cleavage process.[42]

Isomeric 1,6-enynes **1f** and **1g**, which differ in the substitution pattern of the alkyne, react with gold(I) to form the same 1,3-diene **12b** by two different mechanisms, single- and double-cleavage rearrangement, respectively (Scheme 7).[32,33,41] Other 1,6-enynes bearing terminal alkynes such as **1d** and **1h** give 1,3-dienes **12c,d** by single-cleavage rearrangement.[32,33]

Somewhat surprisingly, *E*-1,6-enynes such as **1j−l**, with strongly electron-donating substituents at the terminal alkene carbon, react with cationic gold(I) catalyst **25a** to give *Z*-configured dienes **12f−h** (Scheme 7).[71] This *Z*-selectivity was also found using different electrophilic gold(I) or platinum(II) catalysts. This is rather mechanistically puzzling, since both the platinum(II)- and the gold(I)-catalyzed single-cleavage rearrangements are in the vast majority of cases stereospecific processes in which the configuration of the alkene is retained.[32,41,65,72] Complexes of gold(I) bearing commercially available bulky dialkyl biphenyl phosphines such as **25a**,[73] proved to be particularly useful in homogeneous gold(I) catalysis. Experimental and theoretical studies confirmed that gold(I) does not interact significantly with the closest arene ring of the ligand.[74]

## 3. GOLD(I)-CATALYZED INTERMOLECULAR REACTIONS OF ALKYNES WITH ALKENES

We examined the intermolecular reaction between alkynes and electron-rich alkenes with many different gold(I) catalysts, although only complex mixtures of oligomers were obtained. In addition, electron-rich alkenes are very good ligands for gold(I),[38] thus competing with the alkyne for the coordination to the metal. However, by using cationic gold(I) complex **25b** with a very bulky phosphine, cyclobutenes **26** were finally obtained regioselectively for a variety of electron-rich alkenes (Scheme 8).[75] Interestingly, the isolated yields were improved in most cases by changing the anion from $SbF_6^-$ to softer $BAr_4^{F-}$, presumably by minimizing the formation of unproductive $\sigma,\pi$-digold(I) alkyne digold(I) complexes, an undesired side reaction in many gold-catalyzed reactions of terminal alkynes.[76] The same improvement was observed in the intramolecular [2 + 2] cycloaddition of alkynes with alkynes in substrates of type **27** to form macrocycle **28** (Scheme 9).[76,77]

The regioselective formation of cyclobutenes by [2 + 2] cycloaddition probably proceeds by electrophilic addition of the



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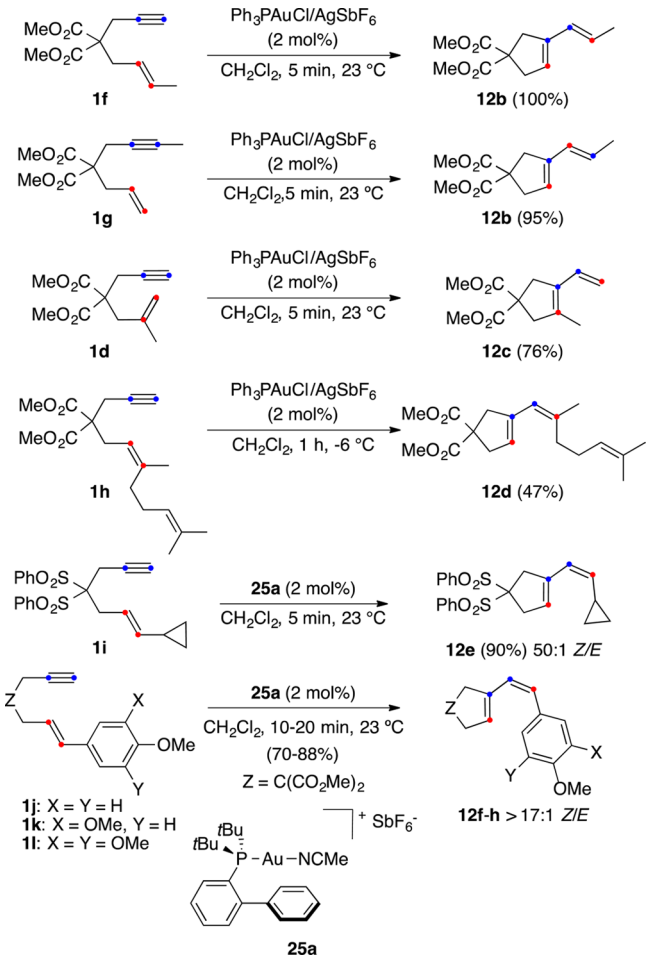
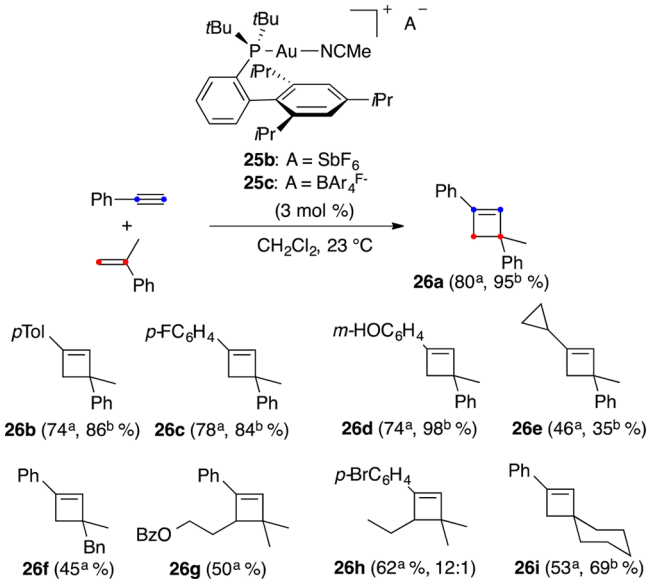
**Scheme 7. Single- and Double-Cleavage Rearrangement of 1,6-Enynes**



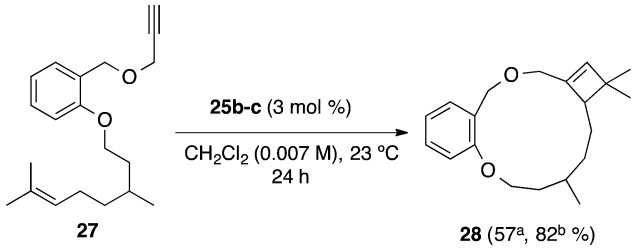

**Scheme 8. [2 + 2] Cycloaddition of Arylalkynes with Alkenes**




[a]Reaction performed with catalyst **25b**. [b]Reaction performed with catalyst **25c**.

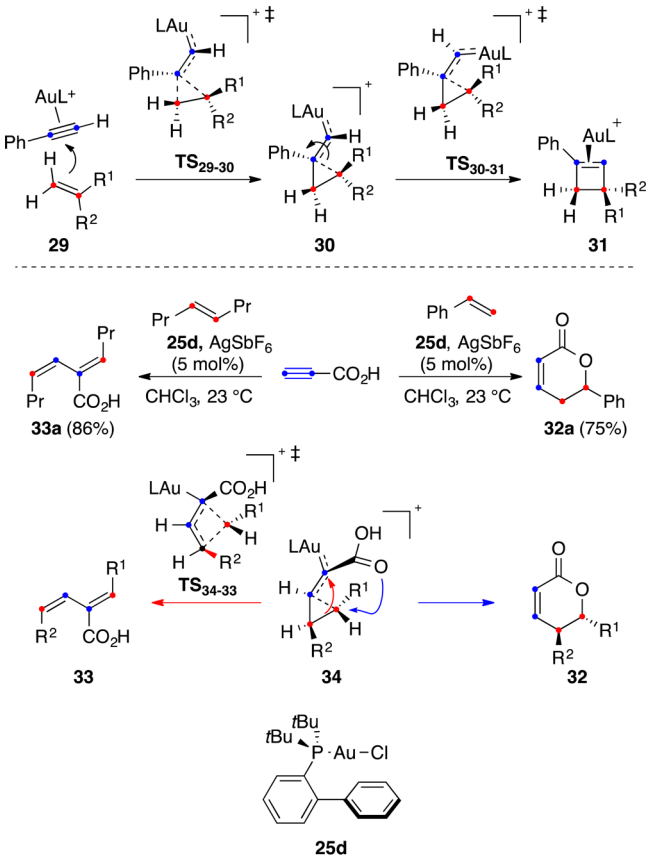
($\eta^2$-alkyne)gold(I) complex to the alkene via $\mathbf{TS_{29-30}}$ to form a cyclopropyl gold(I) carbene **30** very similar to intermediate **16**

**Scheme 9. Macrocyclization via [2 + 2] Cycloaddition of Alkynes with Alkenes**




[a]Reaction performed with catalyst **25b**. [b]Reaction performed with catalyst **25c**.

**Scheme 10. Divergent Pathways in the Gold(I)-Catalyzed Intermolecular Reactions of Alkynes with Alkenes**




involved in the cyclization of enynes (Scheme 10).[75] Ring expansion of **30** through $\mathbf{TS_{30-31}}$ would give ($\eta^2$-cyclobutene)-gold(I) complex **31**. Intermediate **30** was also trapped intramolecularly with an alkene to form the corresponding cyclopropane.

The intermolecular reaction of propiolic acid and related alkynes with strongly electron-withdrawing groups gives dihydropyrones **32** or 1,3-dienes **33** via a similar mechanism, although the initial attack of the alkene to the ($\eta^2$-alkyne)gold(I) complex occurs with the opposite regiochemistry (Scheme 10).[78] Thus, cyclopropyl gold(I) carbene intermediate **34**, with gold bonded to the internal carbon of the alkyne, evolves by intramolecular opening to form **32** by attack of the carboxylic acid to the most substituted carbon of the alkene. On the other hand, in the reaction of alkenes with two very similar



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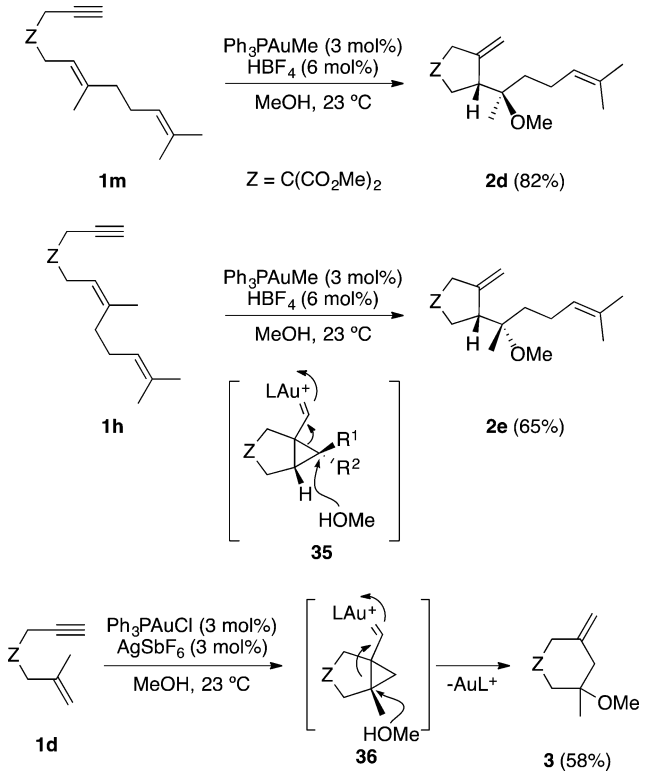
substituents, intermediate **34** undergoes a 1,3-migration similar to that found in the single-cleavage rearrangement to form stereospecifically 1,3-dienes **33**. A transition state similar to $\mathbf{TS}_{34-33}$ has been proposed in the reaction of cyclopropyl gold(I) carbenes generated by retro-Buchner reaction of 7-cyclopropyl 1,3,5-cycloheptatrienes.[79]

## 4. GOLD(I)-CATALYZED NUCLEOPHILIC ADDITIONS TO ENYNES

**4.1. Additions of Heteronucleophiles.** Gold(I) complexes are able to catalyze the addition of amines, alcohols, or water to 1,*n*-enynes affording products of amino-, alkoxy-, or hydroxycyclization under much milder conditions than other metal catalysts.[26,32,33,62,80−82] These additions are stereospecific, as illustrated by the alkoxycyclization of diastereomeric enynes **1m** and **1h**, and proceed via opening of cyclopropyl gold(I) carbene intermediates **35** by attack of the nucleophile to the cyclopropane ring (Scheme 11). Thus, the overall process is an *anti*

**Scheme 11. *Anti*-Addition of Nucleophiles to 1,6-Enynes**

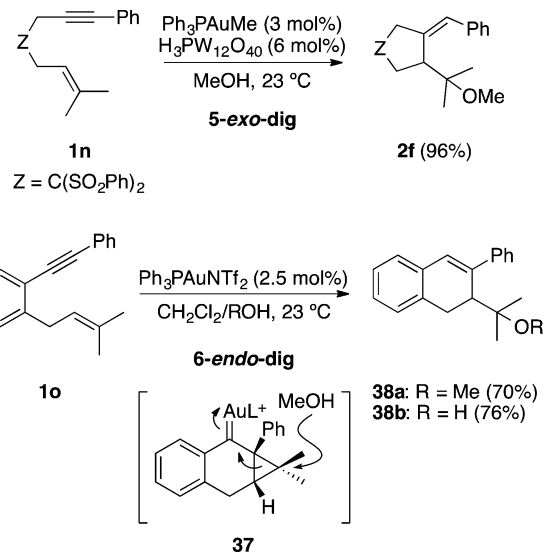



addition of the alkyne−gold(I) complex and the heteronucleophile to an alkene following the Markovnikov regiochemistry, which is further demonstrated by the reaction of enyne **1d** with gold(I) in the presence of MeOH to form six-membered ring **3** via intermediate **36**. Analogous additions of heteronucleophiles to 1,5-[80,83] and 1,7-enynes[48] are also stereospecific.

1,6-Enynes such as **1n** bearing an aryl substituent at the alkyne terminus undergo an analogous 5-*exo* methoxycyclization to afford **2f** in the presence of gold(I) and MeOH (Scheme 12).[33] However, similar 1,6-enyne **1o** tethered by a benzene ring undergoes gold(I)-catalyzed hydroxy- or alkoxycyclizations preferentially via 6-*endo-dig* pathway through intermediates **37** giving rise to dihydronaphthalenes **38**.[84]

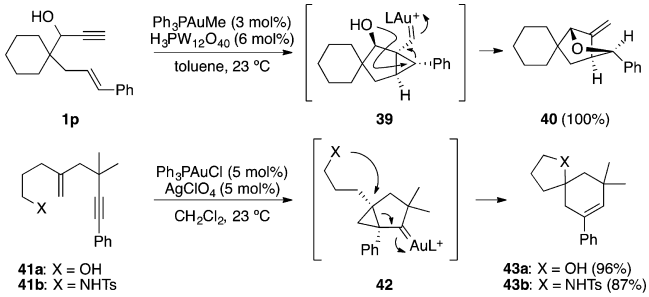
Amino- and alkoxycyclizations can also take place intramolecularly starting from amino- or hydroxy-1,*n*-enynes.[33,85,86]

**Scheme 12. Hydroxy- and Alkoxycyclization of 7-Aryl-Substituted 1,6-Enynes**




Thus, 1,6-enyne **1p** containing a propargylic alcohol gave **40** quantitatively upon treatment with gold(I) as a result of an intramolecular attack of the hydroxyl group to cyclopropyl gold carbene intermediate **39** (Scheme 13).[33] In a mechanistically

**Scheme 13. Cyclizations of Amino- And Hydroxy-1,*n*-enynes**




related transformation, amino- or hydroxy-1,5-enynes **41** afforded in the presence of gold(I) spirofused heterobicyclic compounds **43** through intermediates of type **42**.[85] In a similar vein, 1,*n*-enynes bearing nucleophilic moieties such as carboxylic acids,[53,87] carbamates,[88] or carbonates[89] are also prone to undergo gold-catalyzed tandem cyclizations, giving rise to a variety of complex molecular architectures.

Oxo-1,6-enynes **44** also react in the presence of gold(I) by a formal [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition to afford predominantly oxatricyclic compounds **48**, together with minor amounts of dienes **49** (Scheme 14).[90] These reactions proceed via intramolecular attack of the carbonyl to cyclopropyl gold carbenes **45** to form oxonium cations **46**, which undergo a Prins-type cyclization to give intermediates **47**. Demetalation from **47** forms oxatricycles **48**, whereas an alternative elimination with fragmentation of the seven-membered ring leads to dienes **49**. Oxo-1,5-enynes also undergo an intramolecular gold(I)-catalyzed reaction to form oxatricyclic adducts.[91]

We exploited gold(I)-catalyzed intramolecular [2 + 2 + 2] alkyne/alkene/carbonyl cycloadditions in the synthesis of several oxygen-bridged sesquiterpenoids. Thus, ketoenynes **44d** and **44e** were respectively converted into oxatricycles **48d** and **48e**, which are key intermediates in the total syntheses of (+)-orientalol F



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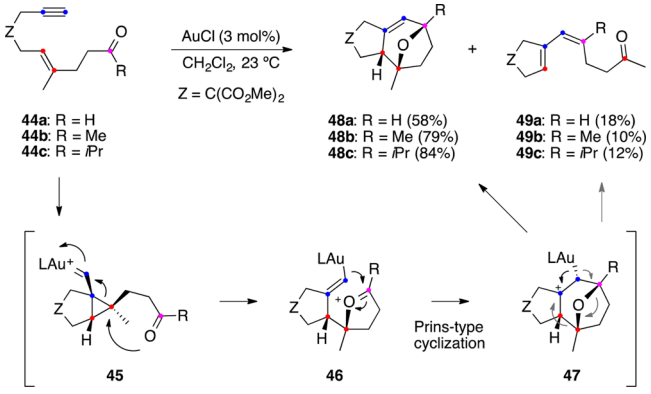
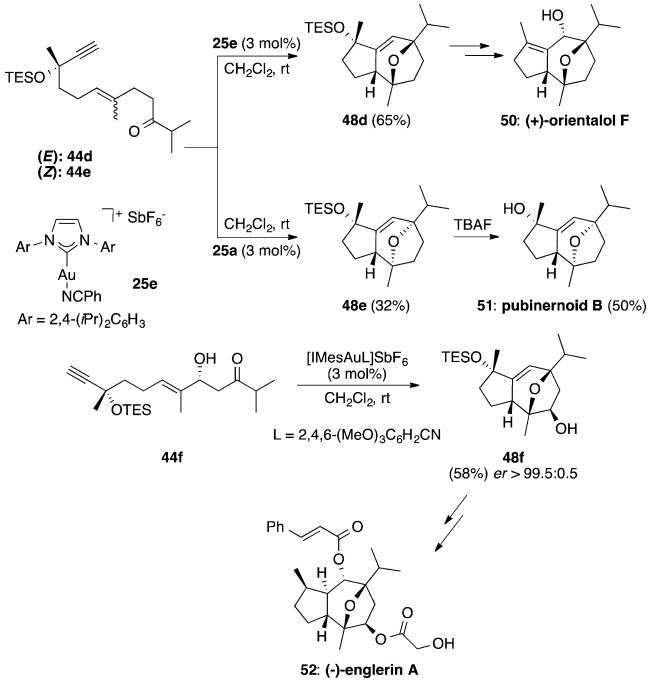
**Scheme 14. Intramolecular [2 + 2 + 2] Alkyne/Alkene/Carbonyl Cycloaddition of Oxo 1,6-Enynes**



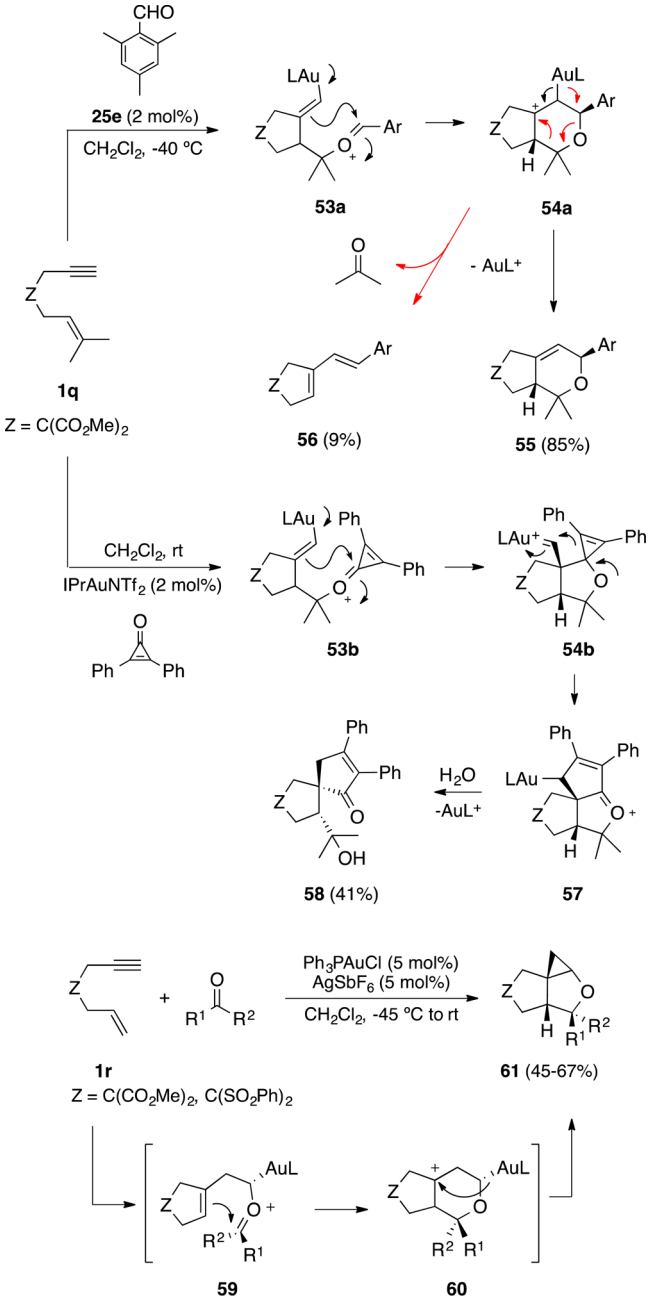

**Scheme 15. Intramolecular [2 + 2 + 2] Cycloadditions of Oxo 1,6-Enynes in Total Synthesis**




(**50**) and pubinernoid B (**51**) (Scheme 15).[92] Oxo-1,6-enyne **44f** was analogously cyclized to form **48f**, which was subsequently converted into (−)-englerin A (**52**).[93] Another total synthesis of **52** included a very similar gold(I)-catalyzed cyclization as the key step.[94] Remarkably, an unprotected aldol subunit could be used in both syntheses as the substrate for the gold-catalyzed reaction.

1,*n*-Enynes also react intermolecularly with carbonyl compounds giving rise to a wide range of products depending on the substitution pattern of the alkene and the nature of the carbonyl compound. 1,6-Enynes such as **1q** react with aromatic aldehydes in a formal [2 + 2 + 2] cycloaddition to give oxabicyclic adducts of type **55** together with dienes **56**, which result from a metathesis-type reaction of the enyne with the aldehyde (Scheme 16).[95] The formation of these products can be explained by attack of the aldehyde to the cyclopropyl gold carbene intermediate to form **53a**, which undergoes a Prins-type cyclization followed by either demetalation to form **55** or fragmentation to give **56**. This mechanism is analogous to that

**Scheme 16. Intermolecular Cycloadditions of 1,6-Enynes and Carbonyl Compounds**




proposed for the intramolecular [2 + 2 + 2] cycloaddition of oxo-1,6-enynes (Scheme 14).[90] 1,7-Enynes also undergo [2 + 2 + 2] cycloadditions with carbonyl compounds to give analogous products.[96] On the other hand, following a related mechanism, 1,6-enyne **1q** reacts with cyclopropenones in a ring-expanding spiroannulation to afford spirocyclic cyclopentenones **58** after incorporation of a molecule of water to rearranged intermediate **57**.[97] 1,6-Enynes **1r** bearing a monosubstituted alkene react with aldehydes and ketones in a different way to form tricyclic compounds **61**.[98,99] This transformation presumably proceeds via trapping of the rearranged carbene that results from the enyne to form oxonium cation **59**, followed by Prins cyclization and demetalation.

The intermolecular reaction of terminal alkynes with oxoalkenes **62** leads to 8-oxabicyclo[3.2.1]oct-3-enes **64** as a result of



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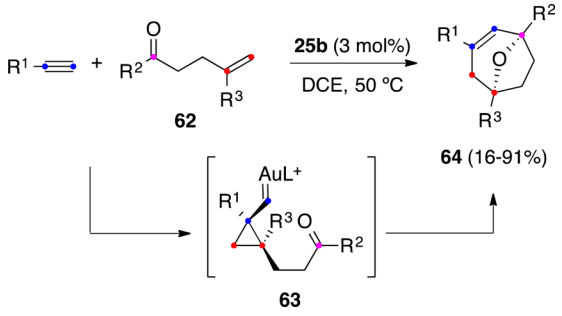
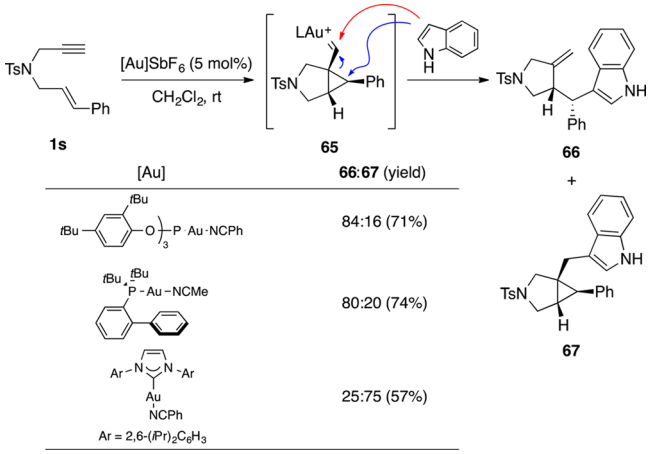
**Scheme 17. Intermolecular [2 + 2 + 2] Alkyne/Alkene/Carbonyl Cycloaddition of Terminal Alkynes and Oxoalkenes**




a formal [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition via cyclopropyl gold carbene intermediates **63** (Scheme 17).[100]

**4.2. Additions of Carbonucleophiles.** Electron-rich aromatic and heteroaromatic compounds can act as nucleophiles reacting with 1,6-enynes.[101−104] Cyclopropyl gold(I) carbenes that result as intermediates in the cyclization of 1,6-enynes can act as bifunctional electrophiles, reacting with arenes either at the carbene or at the cyclopropane.[101] Hence, indole reacted with 1,6-enyne **1s** in the presence of different gold(I) complexes to give two different adducts **66** and **67** (Scheme 18). We found that

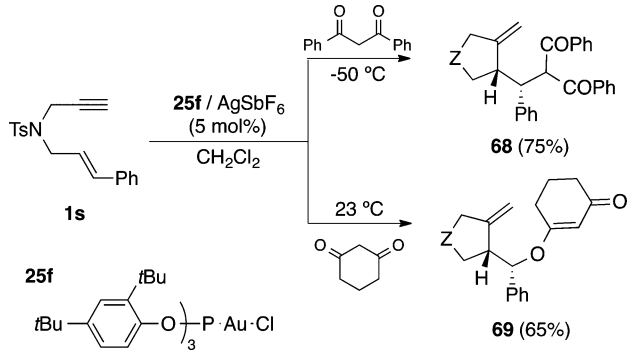
**Scheme 18. Regiodivergent Addition of Indole to 1,6-Enynes**




the more electrophilic gold(I) complexes with less donating phosphite or phosphine ligands favored the attack to the cyclopropane ring to give **66**, whereas complexes with more donating NHC ligands favored the formation of **67** by attack at the metal carbene. An analogous reaction in the presence of a gold(I) catalyst generated in situ from $Ph_3PAuCl/AgSbF_6$ was reported to give exclusive formation of products of type **66** by attack to the cyclopropane ring.[103]

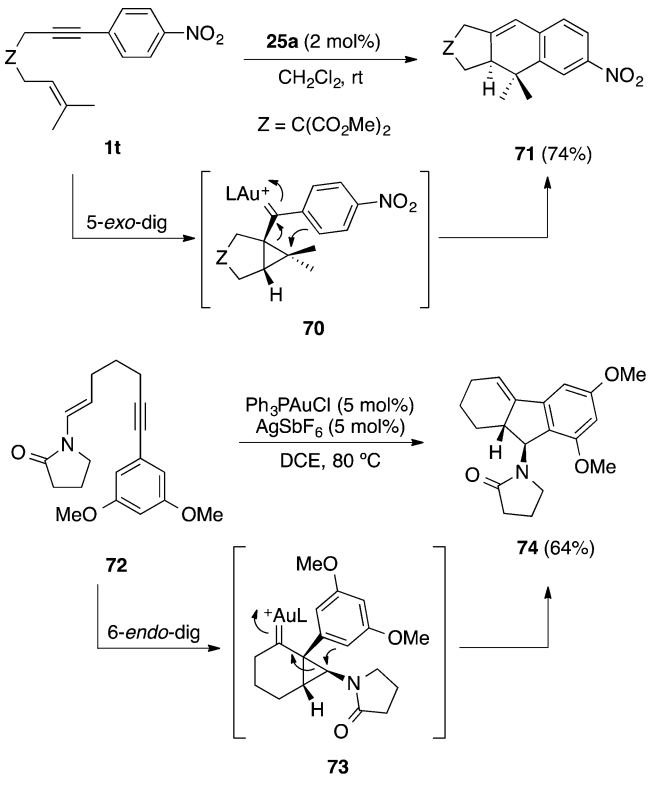
1,3-Dicarbonyl compounds can also add to 1,6-enynes such as **1s** acting as carbonucleophiles through their enol tautomer to give compounds **68** (Scheme 19).[102] However, some dicarbonyl compounds such as 1,3-cyclohexadione may act as *O*-nucleophiles to form adduct **69**. As in the addition of heteronucleophiles to 1,6-enynes, products derived from the attack at the carbene carbon are favored with more donating ligands, whereas more electrophilic complexes favor the attack to the cyclopropane. Gold(I) also catalyzes the addition of allyl silanes to 1,6-enynes, as well as the addition of a variety of carbonucleophiles to 1,5-enynes.[102]

**Scheme 19. Addition of 1,3-Dicarbonyl Compounds to 1,6-Enynes**




Intramolecular attack of aryl groups in 1,6-enynes of type **1t** leads stereospecifically to tricyclic products such as **74** of intramolecular formal [4 + 2] cycloaddition (Scheme 20).[62,63,105]

**Scheme 20. Intramolecular Friedel−Crafts-Type Additions to 1,6-Enynes**




This is a very general reaction that proceeds via initial *exo*-cyclization of the enyne followed by opening of the cyclopropyl gold(I) carbene **70** by a Friedel−Crafts-type reaction. These cycloadditions can be performed enantioselectively in the presence of chiral phosphine[106] or phosphite[107] gold(I) complexes. The *endo*-cyclization of the 1,6-enyne also takes place in certain cases, being the preferred pathway for arylalkynes bearing enesulfonamides or enamines such as **72** to afford tricycles **74**.[108]

Benzyl-substituted 1,5-enynes such as **13c** also undergo a formal [4 + 2] cycloaddition via 5-*endo-dig* cyclization to afford tricyclic product **75**.[47] In contrast, 1,5-enynes **13d** with an aryl substituent at the alkyne react with gold(I) through a different



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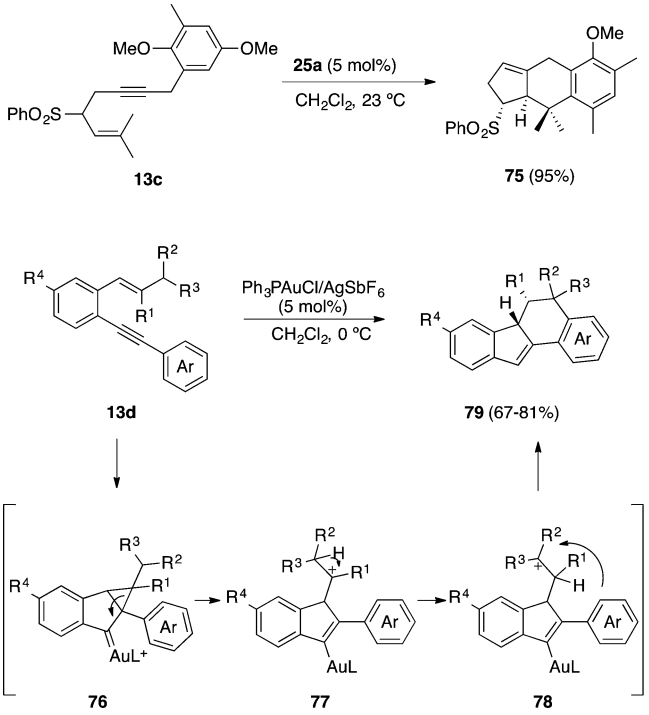
**Scheme 21. Intramolecular Friedel–Crafts-Type Additions to 1,5-Enynes**



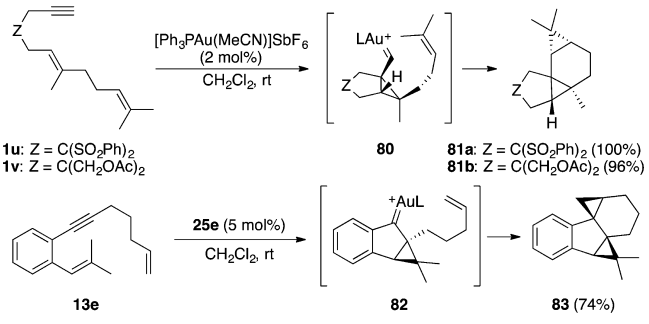

mechanism to form dihydrobenzofluorenes **78** in a formal [3 + 3] cycloaddition.[109] This transformation can be explained by a 1,2-H shift in intermediate 77, followed by a Friedel–Crafts alkylation (Scheme 21).

## 5. CYCLOPROPANATION REACTIONS

The carbene-like character of the intermediates formed in metal-catalyzed cycloisomerizations of enynes is more clearly exhibited in intra- and intermolecular cyclopropanations of alkenes.[110−112]

**5.1. Intramolecular Cyclopropanations of Enynes.** Formation of tetracyclic compounds **81a,b** by cyclization of dienynes **1u,v** at room temperature nicely illustrates the high reactivity and stereoselectivity usually exerted by gold catalysts (Scheme 22).[112] This reaction, which was first reported using

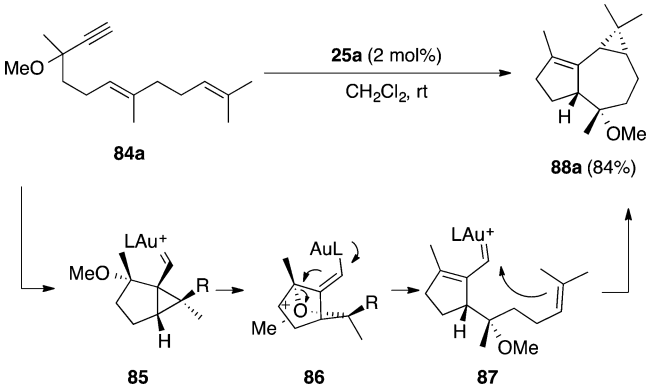
**Scheme 22. Intramolecular Cyclopropanation of 1,*n*-Enynes**



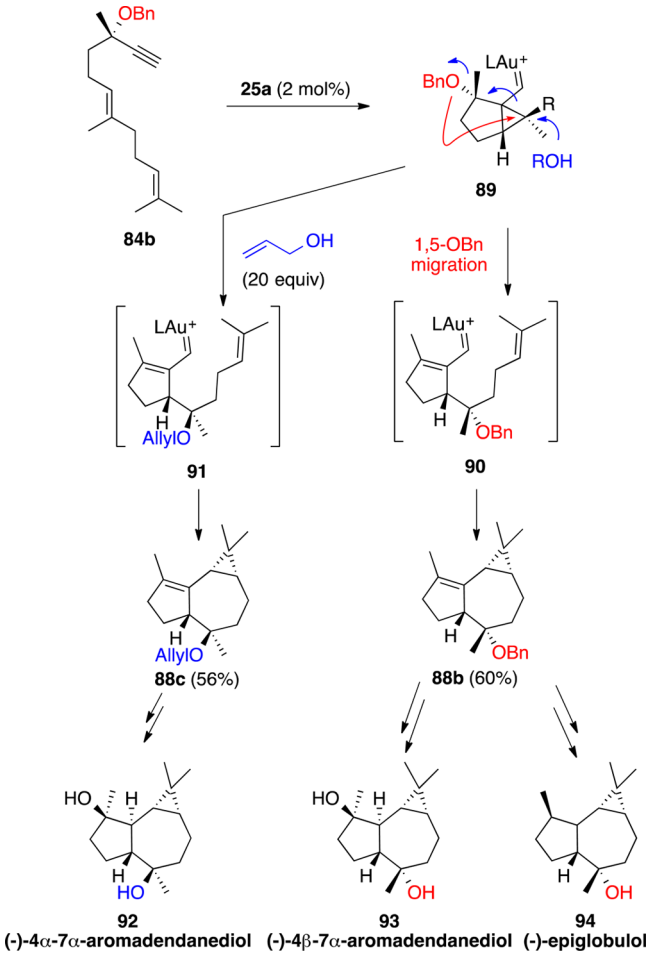

ruthenium(II) complexes under more forcing conditions (80 °C, toluene),[15] proceeds by a 5-*exo-dig* cyclization followed by cyclopropanation of the resulting cyclopropyl gold(I) carbene **80**. When the starting dienynes are cyclic substrates these intramolecular cyclopropanations lead to very complex ring systems.[113] 1,5-Dienynes such as **13e** react similarly to afford pentacyclic product **83** through *endo*-carbene **82**.[47]

Dienynes bearing a methoxy or other OR group at the propargylic position such as **87a** undergo an intramolecular 1,5-OR migration in the presence of gold(I) to form tricyclic compounds **88a** (Scheme 23).[114] This reaction presumably takes

**Scheme 23. 1,5-Migration of Propargyl OR Groups in Dienynes**




**Scheme 24. Synthesis of Aromadendrane Sesquiterpenes**




place via cyclopropyl gold(I) carbene intermediate **85**, which leads to bridged system **86** by attack of the OR group at the cyclopropane. Opening of **86** results in the formation of *α,β*-unsaturated gold(I) carbene **87**, which is prone to undergo intramolecular cyclopropanation with the alkene at the side chain to form **88a**.



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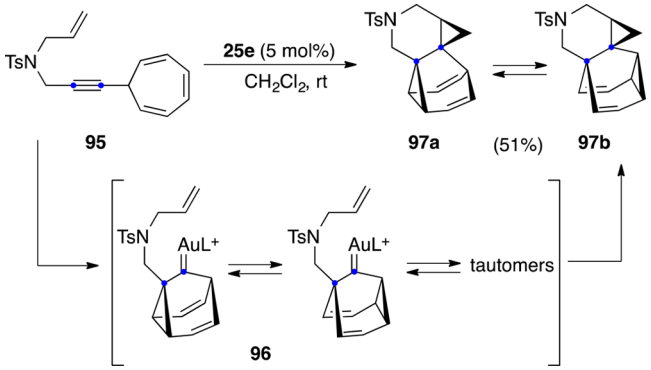
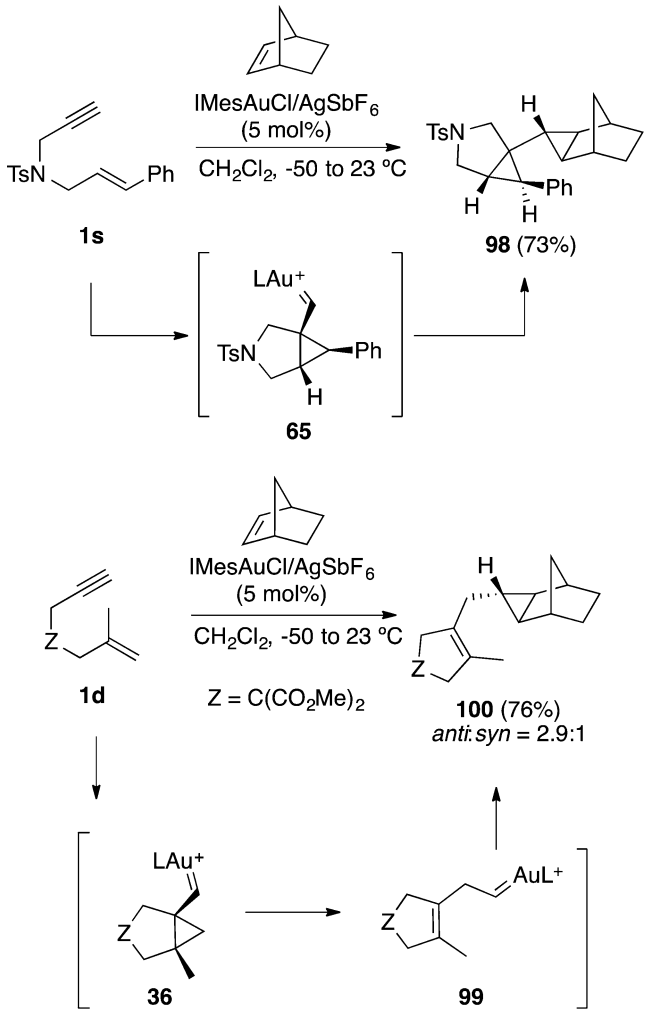
**Scheme 25. Intramolecular Cyclopropanation from 7-Alkynylcyclohepta-1,3,5-heptatrienes**




**Scheme 26. Intermolecular Cyclopropanation of 1,6-Enynes**



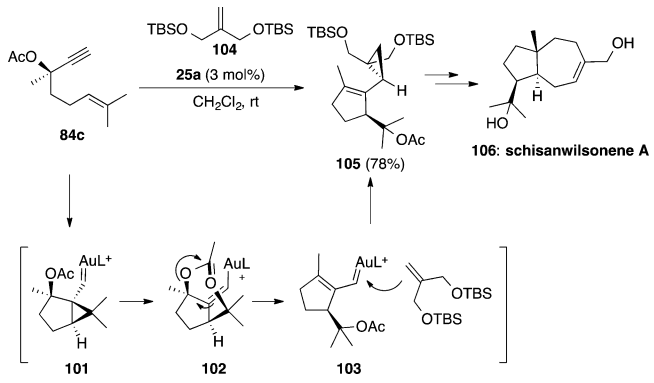

This cascade cyclization process is ideally suited for the total syntheses of sesquiterpenes (−)-4$\alpha$,7$\alpha$-aromadendranediol (**92**), (−)-4$\beta$,7$\alpha$-aromadendranediol (**93**), and (−)-epiglobulol (**94**) from a single dienyne **84b** by using a stereodivergent gold(I)-catalyzed reaction as the key step (Scheme 24).[115] In the absence of any external nucleophile, cyclopropyl gold(I) carbene intermediate **89** undergoes a 1,5-OBn migration followed by intramolecular cyclopropanation to form tricyclic compound **88b**, which is the precursor of **93** and **94**. On the other hand, by adding an external nucleophile such as allyl alcohol, intermediate **89** leads to **91** and then to **88c** after intramolecular cyclopropanation.

Intramolecular cyclopropanation of a gold(I) carbene can lead to very complex structures starting from 7-alkynylcyclohepta-1,3,5-trienes **95** (Scheme 25).[116] This reaction generates highly fluxional barbaralyl gold(I) cations **96** that can be trapped by the pending alkene to form **97a**,**b**, which are in equilibrium by Cope rearrangement both in the solid state and in solution.

**5.2. Intermolecular Cyclopropanations of Enynes.** Intermediate cyclopropyl gold(I) carbenes such as **65** resulting from the cyclization of 1,6-enynes can also be trapped intermolecularly by cyclic or acyclic alkenes to afford adducts **98** stereoselectively (Scheme 26).[117,118] 1,6-Enynes such as **1d** bearing a terminal alkene react differently yielding **100**, probably by rearrangement of cyclopropyl gold(I) carbene **36** to give carbene **99**. The involvement of carbene **99** in the trapping by the alkene also supports the involvement of this type of species as intermediates in the double-cleavage rearrangement (see Scheme 5).

In the presence of gold(I), 1,6-enyne **84c** undergoes a cyclization followed by 1,5-acetoxy migration to give $\alpha,\beta$-unsaturated carbene **103**, which reacts intermolecularly with alkene **104** giving rise to **105** with only 5% loss of enantiomeric excess (Scheme 27).[119] This transformation has been used as the key step in the total synthesis of antiviral sesquiterpene (+)-schisanwilsonene A (**106**). It is remarkable that the cyclization/1,5-acetoxy migration is faster than the alternative 1,2-acyloxy migration, which would lead to racemization.

**Scheme 27. Synthesis of (+)-Schisawilsonene A**




## 6. CONCLUDING REMARKS

Gold(I) catalysts trigger complex reactions of substituted 1,*n*-enynes by stabilizing the key reactive cationic intermediates, which can be viewed in a simplified form as cyclopropyl gold(I) carbenes. These intermediates react with diverse nucleophiles inter- or intramolecularly and cyclopropanate alkenes leading to complex structures with total atom economy. This work, along with that of many other groups, has promoted gold from a mere curiosity to the metal of choice for the activation of alkynes in complex molecular settings under homogeneous conditions. The same basic principles uncovered during the mechanistic study of gold(I)-catalyzed reactions of 1,*n*-enynes can also been extended for reactions of more complex systems as well as for the development of more challenging intermolecular transformations between alkynes and alkenes. In this regard, in order to fulfill the synthetic potential of intermolecular transformations, new types of gold(I) catalysts that selectively activate alkynes in reactions with highly functionalized alkenes are still required, particularly in the arena of enantioselective synthesis.



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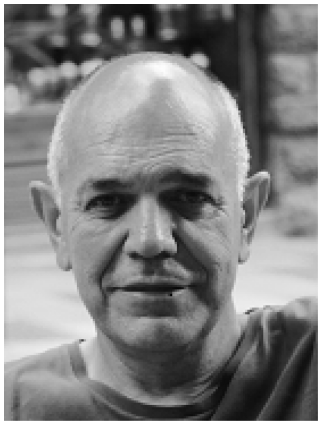
### Notes

The authors declare no competing financial interest.

### Biographies

Ruth Dorel was born in Zaragoza (Spain) in 1989. She graduated with a degree in Chemistry from the Universidad de Zaragoza in 2012. In 2013, she was awarded the Master of Synthesis and Catalysis Extraordinary Prize at the Universitat Rovira i Virgili (Tarragona, Spain). She has been carrying out her Ph.D. studies at the Institute of Chemical Research of Catalonia (ICIQ) since 2013 under the supervision of Prof. Antonio M. Echavarren, working on the synthesis of natural products and polycyclic aromatic hydrocarbons.



Antonio M. Echavarren was born in Bilbao in 1955 (Basque Country, Spain) and obtained his Ph.D. in 1982 at the Universidad Autónoma de Madrid (UAM, 1982) with Prof. Francisco Fariña. After a postdoctoral stay in Boston College with Prof. T. Ross Kelly, he joined the UAM as an Assistant Professor (1984−1986). Following a two-year period as a NATO fellow in the group of Prof. John K. Stille in Fort Collins (Colorado State University), he joined the Institute of Organic Chemistry of the CSIC in Madrid. In 1992, he returned to the UAM as a Professor of Organic Chemistry. He has also been a Professor of Research of the CSIC since 2004. In 2004, he moved to Tarragona as a Group Leader at the newly created Institute of Chemical Research of Catalonia (ICIQ). He has been Liebig Lecturer (Organic Division, German Chemical Society, 2006), Abbot Lecturer in Organic Chemistry (University of Illinois at Urbana—Campaign, 2009), Schulich Visiting Professor (Technion, Haifa, 2011), Sir Robert Robinson Distinguished Lecturer (University of Liverpool, 2011), and Novartis Lecturer in Organic Chemistry (Massachusetts Institute of Technology, 2015). In 2012, he received a European Research Council Advanced Grant, and in 2014 he was elected president of the 49th EUCHEM Conference on Stereochemistry (Bürgenstock conference). Prof. Echavarren is a member of the International Advisory Board of *ChemSusChem* (2007−), *Organic & Biomolecular Chemistry* (2008−), *Chemical Society Reviews* (2010−), *Advanced Synthesis and Catalysis* (2011−), and *Organic Letters* (2014−), member of the Editorial Board of *ChemCatChem* (2009−) and *Chemistry European Journal* (2014−), Associate Editor of *Chemical Communications* (2011−), and Fellow of the Royal Society of Chemistry. He received the 2004 Janssen−Cylag Award in Organic Chemistry and the 2010 Gold Medal of the Royal Spanish Chemical Society. In 2015, he received an Arthur C. Cope Scholar Award from the ACS. His current interests are the discovery of new catalytic methods based on the chemistry of transition metals as well as the synthesis of natural products and polyarenes.

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