

# Gold-Catalyzed Rearrangements and Beyond

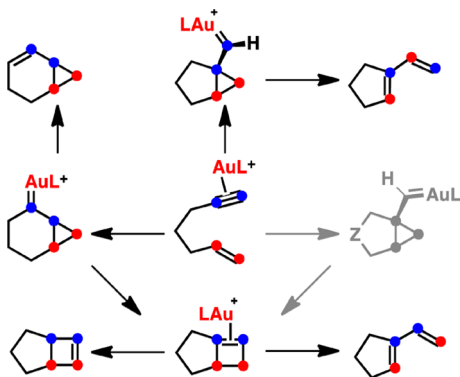
CARLA OBRADORS AND ANTONIO M. ECHAVARREN\*

*Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16,  
43007 Tarragona, Spain*

RECEIVED ON JULY 29, 2013

## CONSPECTUS

Cycloisomerizations of enynes are probably the most representative carbon–carbon bond forming reactions catalyzed by electrophilic metal complexes. These transformations are synthetically useful because chemists can use them to build complex architectures under mild conditions from readily assembled starting materials. However, these transformations can have complex mechanisms. In general, gold(I) activates alkynes in the presence of any other unsaturated functional group by forming an ( $\eta^2$ -alkyne)–gold complex. This species reacts readily with nucleophiles, including electron-rich alkenes. In this case, the reaction forms cyclopropyl gold(I) carbene-like intermediates. These can come from different pathways depending on the substitution pattern of the alkyne and the alkene. In the absence of external nucleophiles, 1,*n*-enynes can form products of skeletal rearrangement in fully intramolecular reactions, which are mechanistically very different from metathesis reactions initiated by the [2 + 2] cycloaddition of a Grubbs-type carbene or other related metal carbenes.



In this Account, we discuss how cycloisomerization and addition reactions of substituted enynes, as well as intermolecular reactions between alkynes and alkenes, are best interpreted as proceeding through discrete cationic intermediates in which gold(I) plays a significant role in the stabilization of the positive charge. The most important intermediates are highly delocalized cationic species that some chemists describe as cyclopropyl gold(I) carbenes or gold(I)-stabilized cyclopropylmethyl/cyclobutyl/homoallyl carbocations. However, we prefer the cyclopropyl gold(I) carbene formulation for its simplicity and mnemonic value, highlighting the tendency of these intermediates to undergo cyclopropanation reactions with alkenes.

We can add a variety of hetero- and carbonucleophiles to the enynes in the presence of gold(I) in intra- or intermolecular reactions, leading to the corresponding adducts with high stereoselectivity through stereospecific anti-additions. We have also developed stereospecific syn-additions, which probably occur through similar intermediates. The attack of carbonyl groups at the cyclopropyl carbons of the intermediate cyclopropyl gold(I) carbenes initiates a particularly interesting group of reactions. These trigger a cascade transformation that can lead to the formation of two C–C and one C–O bonds. In the fully intramolecular process, this stereospecific transformation has been applied for the synthesis of natural sesquiterpenoids such as (+)-orientalol F and (–)-englerin A.

Intra- and intermolecular trapping of cyclopropyl gold(I) carbenes with alkenes leads to the formation of cyclopropanes with significant increase in the molecular complexity, particularly in cases in which this process combines with the migration of propargylic alkoxy and related OR groups. We have recently shown this in the stereoselective total synthesis of the antiviral sesquiterpene (+)-schisanwilsonene by a cyclization/1,5-acetoxy migration/intermolecular cyclopropanation. In this synthesis, the cyclization/1,5-acetoxy migration is faster than the alternative 1,2-acyloxy migration that would result in racemization.

## 1. Introduction

Cycloisomerizations of enynes proceed by mechanistically complex, multistep transformations and can lead to complex architectures by fully intramolecular processes. The pioneering work on the electrophilic activation of enynes was carried out by the group of Trost in the 1980s using

palladium catalysts.<sup>1</sup> These early studies were followed by several groups that examined other electrophilic metals, mainly ruthenium<sup>2</sup> and platinum.<sup>3–7</sup> The potential of gold catalysis in organic synthesis was demonstrated with the development of efficient additions of alcohols and water to alkynes under mild conditions by Teles<sup>8</sup> and Tanaka,<sup>9</sup> as

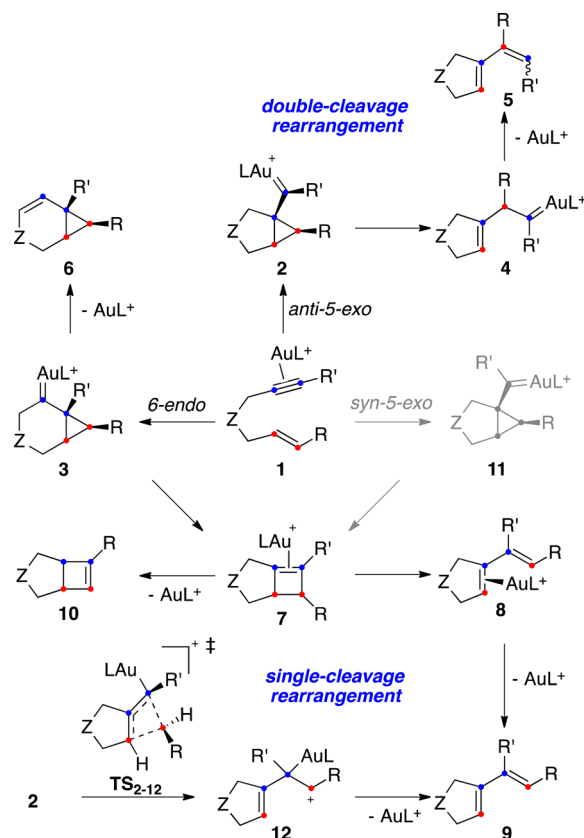
well as by the phenol synthesis discovered by Hashmi using gold(III).<sup>10</sup> This synthesis of phenols by cyclization of furans with alkynes was shown to be mechanistically related to some metal-catalyzed cycloisomerization reactions.<sup>11,12</sup> In 2004, our group<sup>13</sup> and those of Fürstner<sup>14</sup> and Toste<sup>15</sup> reported that gold(I) complexes were the most active and selective catalysts for the cycloisomerization of enynes. A mechanistically related gold(I)-catalyzed Conia-ene reaction of  $\beta$ -ketoesters with alkynes was also reported by Toste in 2004.<sup>16</sup> Henceforth, homogeneous gold(I) catalysis experienced an outburst leading to the discovery of a phenomenal amount of new synthetically useful transformations. In addition to the important synthetic achievements made in the past decade in this area, the nature of the gold–carbon bond in intermediates of type  $[\text{LAuCHR}]^+$ , which are involved in many gold(I)-catalyzed transformations, has inspired certain debate on the role played by gold(I) in the stabilization of these carbocationic species.<sup>17–19</sup>

Several reviews have covered synthetic and mechanistic aspects of homogeneous gold catalysis.<sup>20–28</sup> In this Account, we focus on the developments of gold(I) catalytic transformations derived from our early studies on the cycloisomerization of simple enynes that have led to the discovery of complex cascade reactions.

## 2. Gold(I)-Catalyzed Cyclization of Enynes

Broadly, gold(I) selectively activates alkynes in the presence of alkenes and other functional groups.<sup>20</sup> The high alkynophilicity of gold(I) does not reflect any thermodynamic preference for its coordination to alkynes, but it correlates with the higher reactivity of the resulting ( $\eta^2$ -alkyne)–gold(I) complexes toward nucleophilic attack.<sup>29</sup> In analogy to that shown in related cyclizations catalyzed by platinum(II),<sup>3–6</sup> activation of the alkyne functionality by gold(I) forms an ( $\eta^2$ -alkyne)–metal complex **1** that reacts as an electrophile with the alkene to form cyclopropyl gold(I) carbene-like intermediates **2** or **3** by an *anti*-5-*exo-dig* or a *6-endo-dig* cyclization, respectively (Scheme 1).<sup>13,30–33</sup> Intermediates **2** can evolve to generate new rearranged carbenes **4** by the formal insertion of the terminal alkene carbon into the alkyne carbons. These new carbenes **4** undergo  $\alpha$ -proton elimination to yield 1,3-dienes **5**, the products of an overall double-cleavage rearrangement. In this process, both the alkyne and the alkene have been cleaved in an intramolecular transformation. Although products with both configurations have been observed in this rearrangement, often compounds Z-**5** (R = H) are obtained.<sup>34,35</sup> On the other hand, intermediates **3** of *6-endo-dig* cyclization can lead to

**SCHEME 1.** General Pathways for the Gold(I)-Catalyzed Cycloisomerization of 1,6-Enynes



bicyclo[4.1.0]hept-2-ene derivatives **6** by  $\alpha$ -proton elimination.<sup>36–39</sup> Alternatively, isomerization of **3** by ring expansion of the cyclopropane gives ( $\eta^2$ -cyclobutene)–gold(I) complexes **7**. The opening of these gold(I) complexes can form complexes **8**, precursor of 1,3-dienes **9**, in a transformation in which only the alkene has been cleaved. Highly strained bicyclo[3.2.0]hept-5-enes, which are the free ligands of **7**, have been isolated only in a few cases.<sup>30,40,41</sup> Less strained cyclobutenes resulting from a formal [2 + 2] cycloaddition have been obtained in the cyclization of 1,7- and 1,8-enynes.<sup>6,30,31,37,42</sup> Intermediates **7** can also undergo isomerization to give bicyclo[3.2.0]hept-2-ene derivatives **10**.<sup>36,37</sup> Similarly, 1,5-<sup>43,44</sup> and 1,7-enynes undergo rearrangements with gold(I) catalysts by somewhat related pathways.<sup>30,45</sup>

According to DFT calculations, the *syn*-5-*exo-dig* cyclization via intermediates **11** does not compete with the other two pathways.<sup>30,31</sup> Exocyclic carbene intermediate **2**, formed in the *anti*-5-*exo-dig* pathway, can also give rise to products of single-cleavage rearrangement **9** through transition state **TS**<sub>2–12</sub> and intermediates **12**.<sup>30</sup>

The pathway followed by a particular enyne is highly dependent on its substitution pattern. Thus, 1,6-enyne **13a**

with a terminal alkyne and a disubstituted alkene reacts with a cationic catalyst formed in situ from  $[\text{Au}(\text{PPh}_3)\text{Cl}]$  and  $\text{AgBF}_4$  to form exclusively single-cleavage rearrangement diene **14a** (Scheme 2).<sup>13,30</sup> An identical product **14a** was obtained from 1,6-enyne **13b**, with the methyl substituent at the alkyne, in an equally highly selective double-cleavage rearrangement.<sup>37</sup> Although the gold(I)-catalyzed single-cleavage rearrangement is usually a stereospecific process in which the configuration of the alkene is retained,<sup>13,30,46</sup> reaction of (*E*)-1,6-enynes such as **13c–f**, bearing strongly electron-donating substituents at the terminal alkene carbon, react anomalously with cationic gold(I) catalyst **A**<sup>36,47,48</sup> to give selectively *Z*-configured dienes **14b–e**.<sup>49</sup> The same *Z*-preference was observed with other highly electrophilic gold(I) or platinum(II) catalysts. The *Z*-isomers of enynes **13c** and **13d** also give rise to *Z*-dienes with gold(I) or platinum(II) catalysts.<sup>49</sup> The stereochemically anomalous rearrangement remains mechanistically puzzling.

It is important to emphasize that, in contrast to Pd(II)<sup>1</sup> and Pt(II),<sup>5,50,51</sup> gold(I) does not promote Alder–ene cycloisomerizations of 1,*n*-enynes.<sup>30</sup> The Alder–ene cycloisomerization would require the simultaneous coordination of gold(I) to the alkyne and the alkene, which is not favorable for a metal that prefers a linear bicoordination. Furthermore, the oxidation of gold(I) to form a gold(III) metallacycle, a

mandatory step in an Alder–ene cycloisomerization, is also a very unlikely process.<sup>37,52</sup>

Conventionally, we prefer to depict complexes of type **2** as cyclopropyl gold(I) carbenes, to highlight their propensity to undergo cyclopropanation reactions, although DFT calculations showed that these are highly delocalized species that can also be described as gold(I)-stabilized cyclopropylmethyl/cyclobutyl/homoallyl carbocations.<sup>20,30</sup> The bond between Au and C in gold(I) carbenes  $[\text{LAu}=\text{CHR}]^+$  has been described as a half-double bond.<sup>19</sup>

Cyclizations of 1,5-enynes also proceed through species that are intermediate between a bicyclic gold(I) carbene and an open carbocation.<sup>53</sup> The highly electrophilic carbene of the intermediate species formed in these cycloisomerizations can even undergo formal C–H insertion reactions at  $\beta$ -C–H bonds leading to new cyclopropanes.<sup>54</sup>

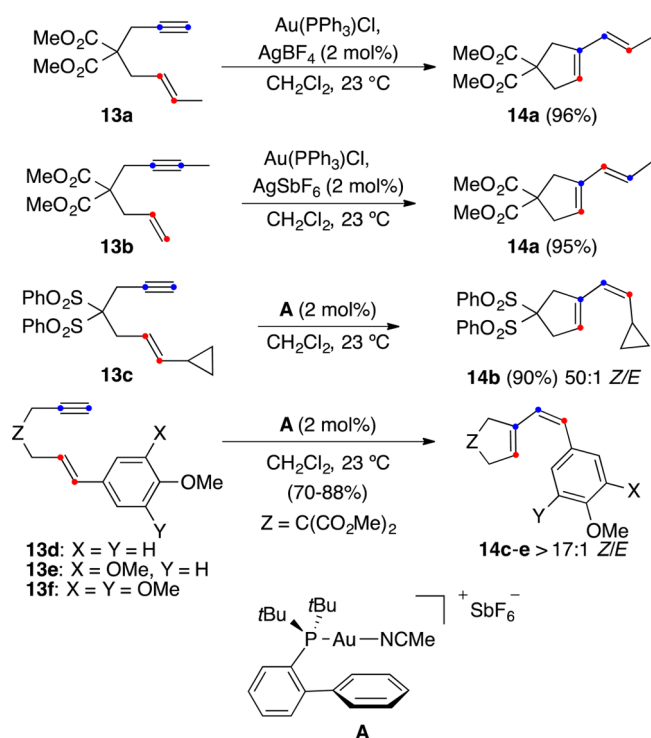
### 3. Gold(I)-Catalyzed Nucleophilic Additions to Enynes

In the presence of alcohols or water, gold(I) catalyzes the addition of these nucleophiles to the enynes leading to products of alkoxy- or hydroxycyclization (Scheme 3).<sup>13,30</sup> The overall process is an anti addition of an electrophile (the ( $\eta^2$ -alkyne)–gold(I) complex) and a heteronucleophile to an alkene. Therefore, this reaction is stereospecific, as illustrated in the methoxycyclizations of diastereomers **13g** and **13h**, which afford diastereomeric adducts **15a** and **15b**, respectively, by attack of MeOH to intermediate **16a** (Scheme 3). In these transformations, the catalyst was generated by protonolysis of the gold(I)–carbon bond of precatalyst  $[\text{Au}(\text{PPh}_3)\text{Me}]$  with a strong Brønsted acid. These processes follow the Markovnikov regiochemistry, which is further illustrated by the reaction of substrate **13i** in MeOH to form six-membered ring **15c** through intermediates of type **16b**. Related additions to 1,5-enynes are also stereospecific.<sup>55–57</sup>

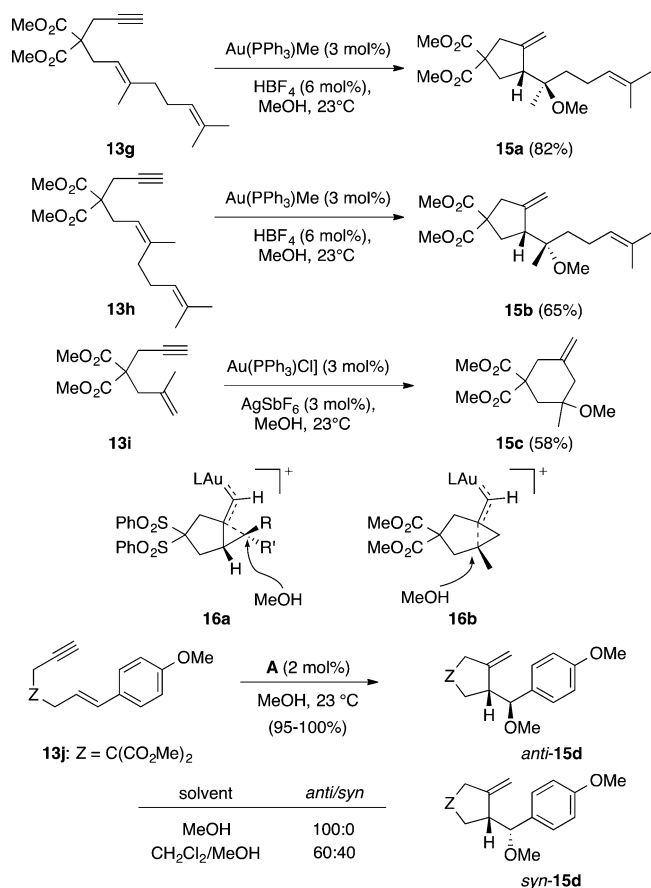
A few exceptions have been observed with the most polarized substrates. Thus, whereas reaction of enyne **13j** in MeOH as solvent gives the product of methoxycyclization **15d** as a single anti isomer, in agreement with the general behavior observed by other 1,6-enynes in similar reactions catalyzed by gold<sup>13,30</sup> or platinum,<sup>6</sup> when the reaction of **13j** was performed with only 5 equiv of MeOH, adduct **15d** was obtained as a 3:2 *anti/syn* mixture of stereoisomers (Scheme 3).<sup>49</sup>

Additions of carbon nucleophiles to enynes can also be carried out in the presence of gold(I).<sup>58–61</sup> Thus, for example, reaction of 1,6-enyne **13k** with indole, an electron-rich

**SCHEME 2.** Single- and Double-Cleavage Rearrangement of 1,6-Enynes



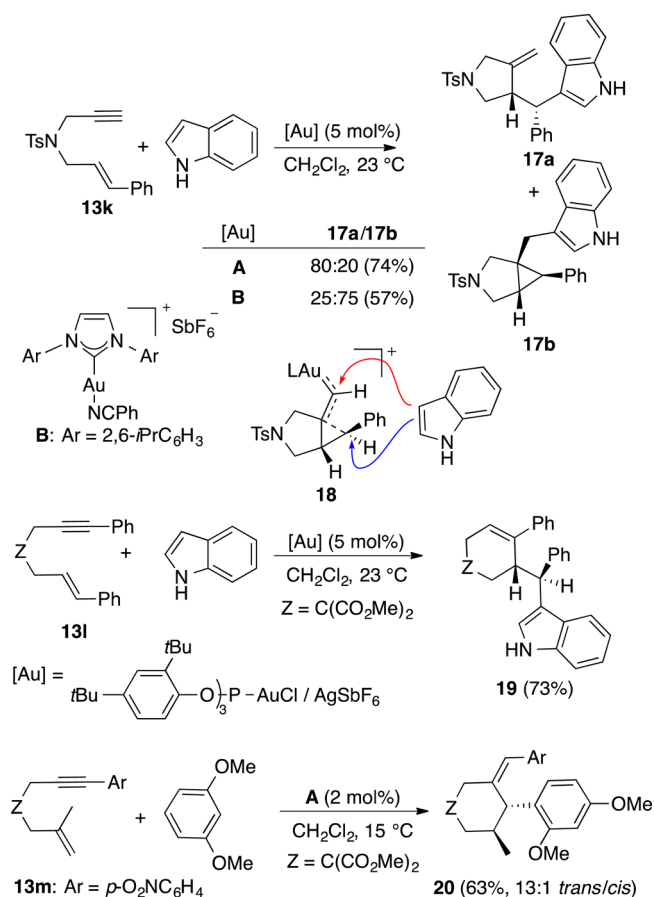
## SCHEME 3. anti-Addition of Heteronucleophiles to 1,6-Enynes



heteroarene, leads to adducts **17a** and **17b** by nucleophilic attack at the cyclopropyl or carbene carbons, respectively, of intermediate **18** (Scheme 4).<sup>58,59</sup> Adduct **17a** was favored using phosphine–gold(I) complex **A**, whereas complex **B** with an NHC ligand directed the nucleophilic attack at the carbene carbon, leading to adduct **17b**. This result can be explained by the enhancement of the carbene-like character of the intermediate **18** by the highly donating NHC ligand. The 6-*endo-dig* cyclization pathway predominates in the case of the addition of indole to phenyl-substituted enyne **13l**, which leads stereospecifically to adduct **19**, while in the case of substrate **13m**, the electron-rich arene attacks at the most substituted alkene carbon leading to **20**.<sup>59</sup> The addition of 1,3-dicarbonyl compounds and allyl silanes to 1,6-enynes, as well as similar additions of diverse carbon nucleophiles to 1,5-enynes are also catalyzed by cationic gold(I) catalysts.<sup>59</sup>

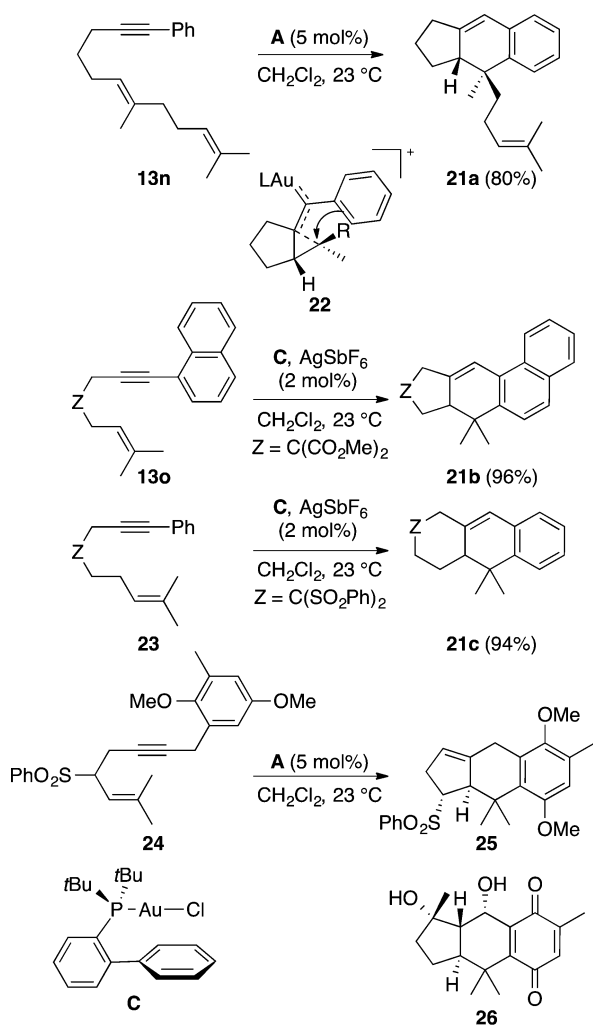
Related intramolecular arylations of 1,6-enynes,<sup>62,63</sup> as well as additions of carboxylic acids to enynes,<sup>17</sup> have been proposed to take place in a concerted manner following the Stork–Eschenmoser model for cyclizations of squalene and

## SCHEME 4. Addition of Arenes and Heteroarenes to 1,6-Enynes



oxidosqualene. However, the results of Schemes 3 and 4 and other related studies<sup>64</sup> are best accommodated if distorted cationic cyclopropyl gold(I) carbenes are involved as discrete intermediates. A similar type of intermediate is probably also involved in processes in which two carbon bonds are formed by electrophilic *syn*-addition to the alkene. An illustrative case is the intramolecular [4 + 2] cyclization of aryl alkynes with alkenes to form tricyclic derivatives (Scheme 5).<sup>36,38</sup> This reaction of 1,6-enynes such as **13n** is stereospecific and, according to DFT calculations, proceeds stepwise through intermediate **22**, which evolves by a Friedel–Crafts-type reaction to form the final tricyclic derivative **21a**.<sup>38</sup> Similarly, 1-naphthyl substituted 1,6-enyne **13o** gives tetracyclic derivative **21b**, and a related 1,7-enyne **23** gives rise to **21c**. Recently, we have obtained enantiomeric excesses up to 88% in the same [4 + 2] cycloadditions of aryl-substituted 1,6-enynes using chiral gold(I) phosphite complexes derived from 3,3'-bis(triphenylsilyl)-1,1'-bi-2-naphthol.<sup>65</sup> Chiral biphosphine gold(I) catalysts had also been used for this type of [4 + 2] cycloadditions of aryl-substituted 1,6-enynes.<sup>66</sup> The reaction of benzyl-substituted

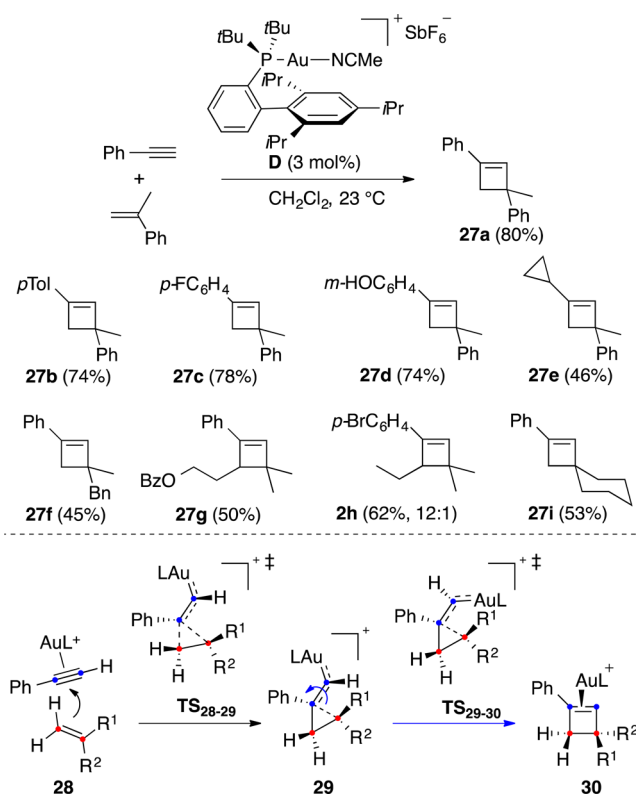


**SCHEME 5.** Formal [4 + 2] Cycloaddition of Arylalkynes with Alkenes

1,5-enyne **24** also occurs in a similar manner to afford **25**,<sup>53</sup> with the skeleton of the natural product (+)-pyncnanthuquinone **C** (**26**).

#### 4. Gold(I)-Catalyzed Intermolecular Reactions of Alkynes with Alkenes

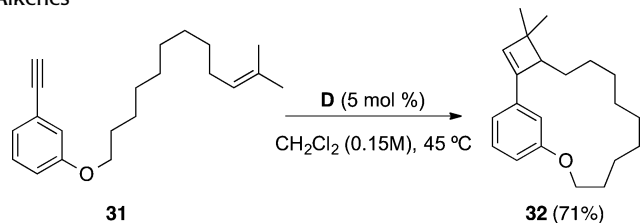
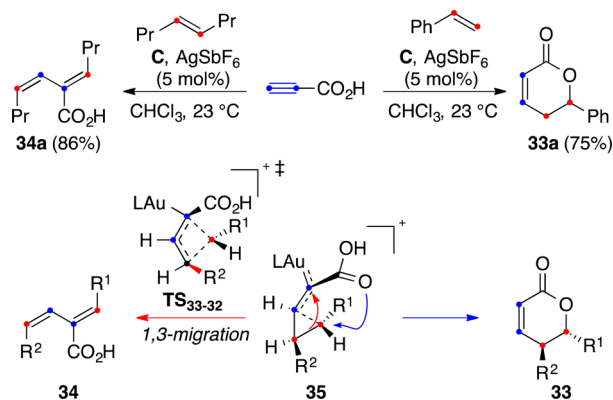
The parent intermolecular reaction between alkynes and alkenes catalyzed by gold(I) was a challenge since all the conceivable products are themselves substituted alkenes, which can compete with the initial alkene leading to oligomerization products. In addition, electron-rich alkenes, which would be the best partners for this reaction, would coordinate preferentially with gold(I), thus reducing the concentration of the active ( $\eta^2$ -alkyne)–gold(I) complex. After much experimentation with different gold(I) complexes, cyclobutenes **27** were obtained as the products of this intermolecular reaction by using cationic gold(I) complex **D** with a very bulky phosphine (Scheme 6).<sup>67</sup>

**SCHEME 6.** [2 + 2] Cycloaddition of Arylalkynes with Alkenes

The observed regiochemistry of this [2 + 2] cycloaddition is consistent with a reaction proceeding by electrophilic addition to the alkene via **TS**<sub>28–29</sub> to form a highly distorted cyclopropyl gold(I) carbene **29**, which undergoes ring expansion through **TS**<sub>29–30</sub> to give ( $\eta^2$ -cyclobutene)–gold(I) complex **30**. Intermediate **29** was also trapped intramolecularly with an alkene to form the corresponding cyclopropane.<sup>67</sup> This process has been extended for the synthesis of large macrocycles such as **32** from enyne **31** by intramolecular [2 + 2] cycloaddition (Scheme 7).<sup>68</sup>

Interestingly, the intermolecular reaction of propiolic acid with alkenes proceeds through regioisomeric cyclopropyl gold(I) carbene intermediates **35**, in which gold bonds to the internal carbon of the alkyne (Scheme 8).<sup>69</sup> Asymmetrically substituted alkenes, such as styrene, give lactones **33** by attack of the carboxylic acid to the most substituted carbon of the alkene. On the other hand, alkenes with two identical, or very similar, substituents evolve by 1,3-migration to form stereospecifically 1,3-dienes **34**.

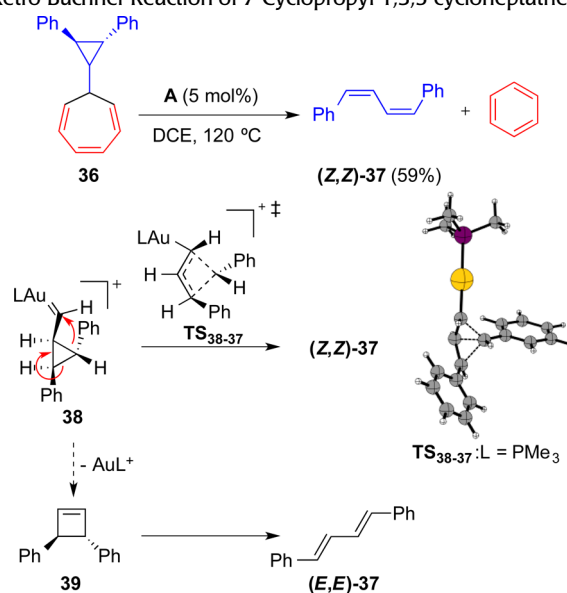
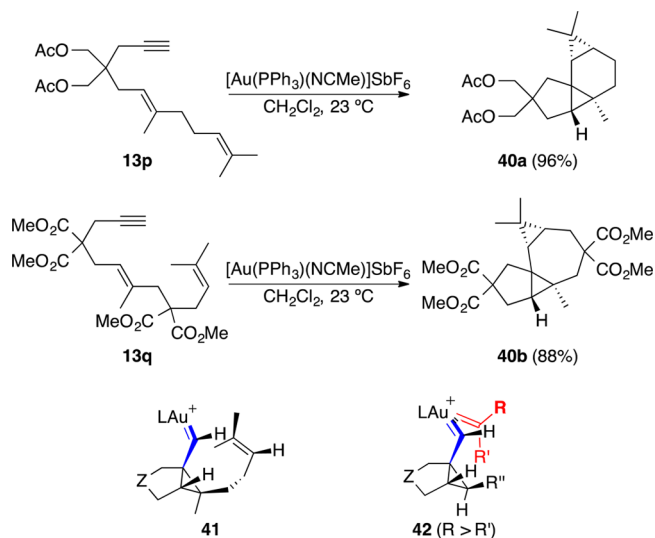
It is interesting that a very similar transition state to **TS**<sub>34–35</sub> for the formation of 1,3-dienes from propiolic acid<sup>69</sup> had been also proposed in a seemingly different context. Electrophilic gold(I) catalysts promote the retro-Buchner reaction of 7-substituted 1,3,5-cycloheptatrienes,

**SCHEME 7.** Macrocyclization via [2 + 2] Cycloaddition of Alkynes with Alkenes**SCHEME 8.** Divergent Pathways in the Reaction of Propiolic Acid with Alkenes

generating substituted gold(II) carbenes and a molecule of benzene.<sup>70</sup> This reaction proceeds by retrocyclopropanation of the norcaradienes, which are in tautomeric equilibrium with the cycloheptatrienes. Other related retrocyclopropanations have been observed in the presence of gold(I).<sup>71,72</sup> In the case of 7-cyclopropylcycloheptatriene **36**, the reaction leads selectively to *Z,Z*-1,4-diphenyl-1,3-butadiene (*Z,Z*-**37**), whose formation can be rationalized by the evolution of cyclopropyl gold(II) carbene **38** through **TS**<sub>38-37</sub> by 1,3-shift of a CHPh fragment (Scheme 9). This transition state is also very similar to that involved in the single cleavage rearrangement (**TS**<sub>2-12</sub>, Scheme 1). The ring expansion of **38** to form cyclobutene **39**, which would have afforded *E,E*-**37** by conrotatory opening, was not observed in this system.<sup>70</sup>

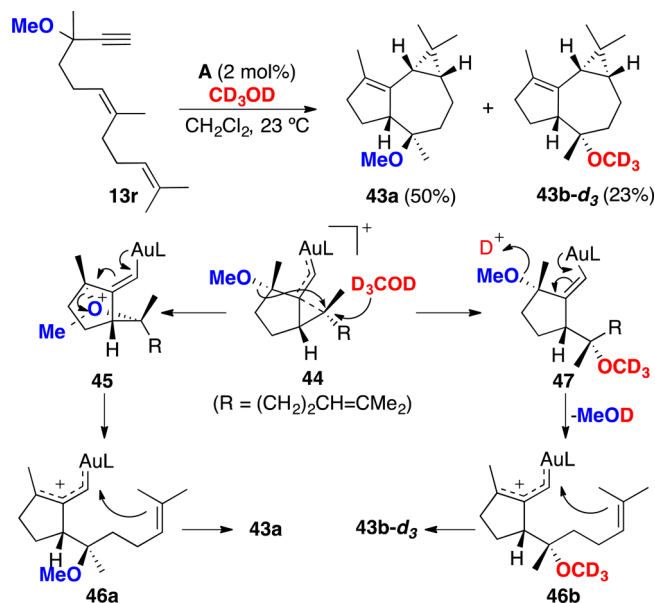
## 5. Gold(I)-Catalyzed Cyclopropanation of Enynes

The carbene-like character of the intermediates formed in metal-catalyzed cycloisomerizations is more clearly manifested in intra- and intermolecular cyclopropanation of alkenes.<sup>2,7,73</sup> Thus, reaction of dienynes **13p** and **13q** with gold(I) leads stereoselectively to tetracyclic compounds **40a** and **40b** (Scheme 10). These cyclopropanations occur through intermediates such as **41** or **42** for intermolecular processes,<sup>74,75</sup> in a concerted although highly asynchronous

**SCHEME 9.** Generation and Evolution of a Cyclopropyl Gold(II) Carbene by Retro-Buchner Reaction of 7-Cyclopropyl-1,3,5-cycloheptatriene **36****SCHEME 10.** Cyclopropanation of Alkenes via Cyclopropyl Gold(II) Carbene Intermediates

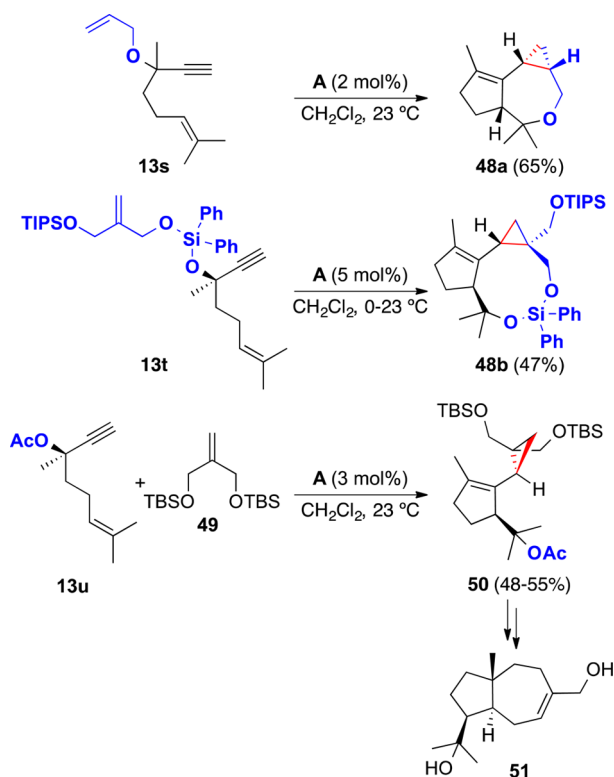
manner. Intramolecular cyclopropanations of 1,5-enynes proceed similarly through an *endo*-carbene.<sup>53</sup> However, cyclopropanation of 1,6-enynes occurs stepwise for more polarized alkenes such as styrenes, although the overall process is still stereospecific since formation of the second carbon–carbon bond occurred with a very small activation energy.<sup>75</sup> Other theoretical calculations also suggest that the cyclopropanation of electron-rich alkenes by gold(II) carbenes proceeds by a stepwise mechanism.<sup>76</sup>

Dienynes such as **13r** substituted with OR groups at the propargylic position react with gold(II) catalysts by

**SCHEME 11.** Gold(I)-Catalyzed 1,5-Migration of OR Groups in Dienyne **13r**

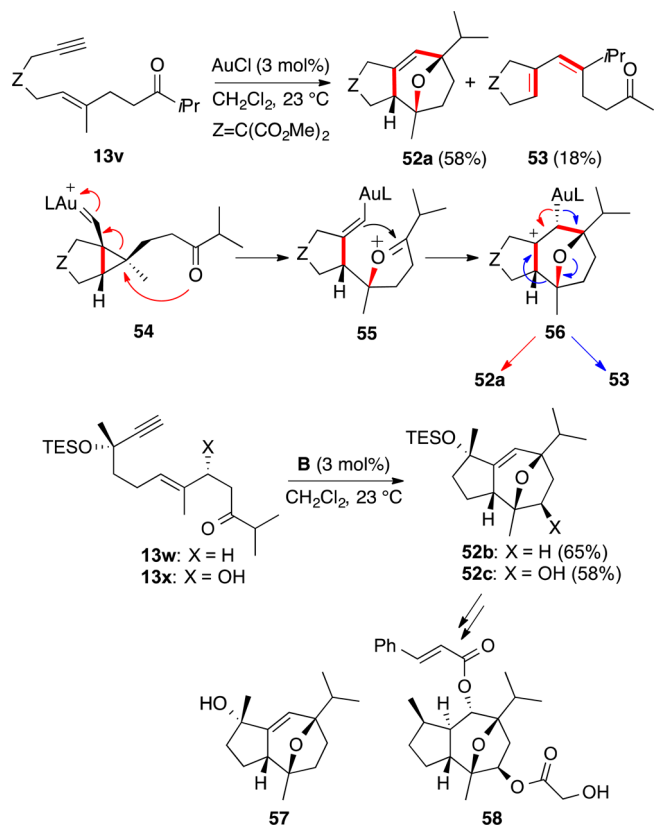
intramolecular 1,5-migration of OR groups to form tricyclic compounds **43a,b**, which are structurally related to the sesquiterpenes globulol and epiglobulol (Scheme 11).<sup>77</sup> This result is consistent with a reaction occurring via intermediate **44**, in which the OR group attacks the cationic center to form bridged system **45**. Opening of **45** then leads to an  $\alpha,\beta$ -unsaturated gold carbene/allyl gold cation **46a**, which undergoes intramolecular cyclopropanation with the alkene at the side chain to give **43a**. In the presence of  $\text{CD}_3\text{OD}$ , intermolecular addition of this external nucleophile to **44** leads to **47**, which then gives rise to **43b-d<sub>3</sub>** via **46b**.

Other 1,6-enynes bearing different OR groups at the propargylic position react similarly to form  $\alpha,\beta$ -unsaturated gold carbenes/allyl-gold cations related to **46**. Thus, enyne **13s** with an allyloxy group gave stereoselectively tricyclic compound **48a** by cyclization, 1,5-migration, and, finally, an intramolecular cyclopropanation (Scheme 12).<sup>73</sup> By appending the alkene to the 1,6-enyne through a silicon tether in substrate **13t**, we also obtained cyclic siloxane **48b** with high stereoselectivity.<sup>78</sup> In an intermolecular variant of this process, reaction of 1,6-enyne **13u** with alkene **49** gave **50**, which was converted into the antiviral sesquiterpene (+)-schisanwilsonene (**51**) by a stereoselective route that includes a divinyl cyclopropane rearrangement. In this last example, it is interesting to remark that the cyclization/1,5-acetoxy migration is faster than the alternative 1,2-acetoxy migration that would lead to racemization.<sup>78</sup>

**SCHEME 12.** Reactions of 1,6-Enynes via 1,5-Migration of OR

## 6. Gold(I)-Catalyzed Cascade Reactions of Oxoenynes

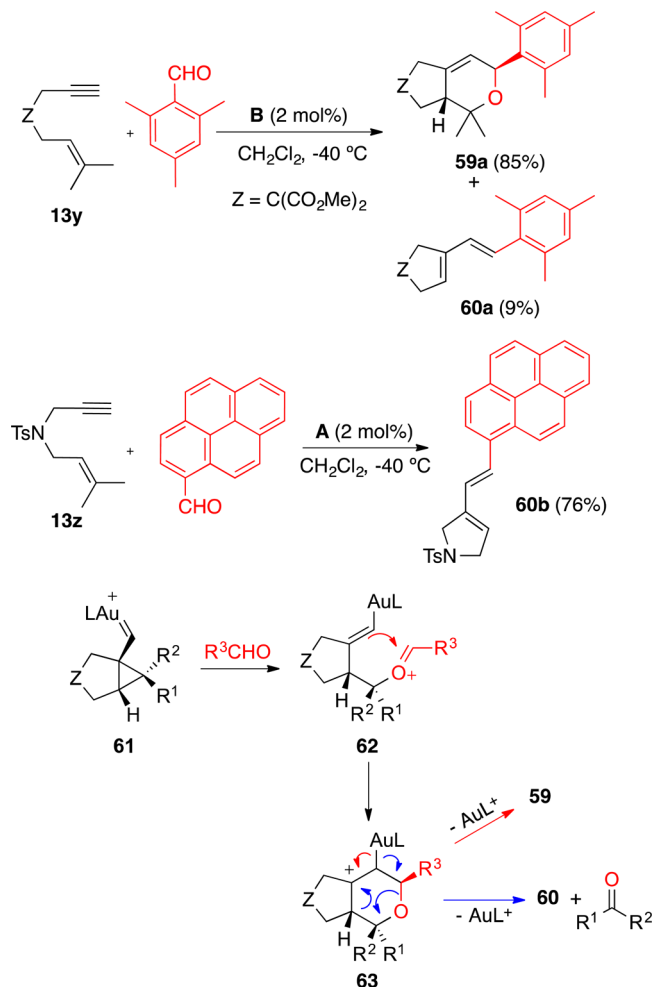
1,6-Enyne **13v** with a carbonyl group at the alkenyl side chain reacts in the presence of gold(I) to give oxatricyclic derivative **52a** by a cascade [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition in which two C–C and one C–O bonds are formed (Scheme 13).<sup>79</sup> Diene **53** was also obtained as a minor product. This reaction probably takes place by nucleophilic opening of the cyclopropane ring of intermediate **54** by the carbonyl group to form an oxonium cation **55**, which gives **56** by a Prins-type intramolecular reaction closing a seven-membered ring. Intermediate **56** then gives oxatricyclic derivative **52a** by metal elimination or diene **53** by a fragmentation process. The [2 + 2 + 2] cycloaddition of substrates **13w** and **13x** led to more functionalized tricyclic products **52b** and **52c**, which were transformed into the natural products (+)-orientalol F (**57**)<sup>80</sup> and (–)-englerin A (**58**).<sup>81</sup> Another total synthesis of **58** used a very similar gold(I) catalyzed reaction as the key step.<sup>82</sup> The remarkable stereochemical control exerted by the propargylic stereocenter in the cyclizations of substrates **13w** and **13x** is identical to that observed in the cyclization proceeding via 1,5-OR migration through intermediate **44** (Scheme 11).<sup>77</sup> Interestingly, attack of a carbonyl group to

**SCHEME 13.** Intramolecular [2 + 2 + 2] Alkyne/Alkene/Carbonyl Cycloaddition of Oxo-1,6-enynes

the cyclopropyl gold carbene is faster than the 1,5-migration of the propargylic OR groups.

Intermolecular reactions of 1,6-enynes with carbonyl compounds in the presence of gold(I) catalysts lead to a variety of products depending on the substitution pattern of the alkene.<sup>83–85</sup> Thus, for example, 1,6-enyne **13y** reacts with 2,4,6-trimethylbenzaldehyde to give the product of formal [2 + 2 + 2] cycloaddition **59a**, along with diene **60a**, resulting from a metathesis-type reaction (Scheme 14).<sup>83</sup> When the reaction was performed with **13z** and 1-pyrene-carboxaldehyde, 1,3-diene **60b** was obtained as the major compound. Formation of the [2 + 2 + 2] cycloaddition products of type **59** can be explained by attack of the aldehyde to cyclopropyl gold(I) intermediate **61** to give oxonium cation **62**, followed by Prins cyclization to form tetrahydropyranyl cation **63** and metal elimination. Metathesis-type products **60** could be formed by a fragmentation of **63**, analogous to that observed in the intramolecular gold(I)-catalyzed reaction of oxo-1,6-enynes (Scheme 13).<sup>79</sup>

Oxo-1,5-enynes such as *E*- and *Z*-**64** also undergo gold(I)-catalyzed cyclization to form tricyclic derivatives **65a** and **65b**, respectively (Scheme 15).<sup>86</sup> When gold(I) complexes

**SCHEME 14.** Intermolecular [2 + 2 + 2] Alkyne/Alkene/Carbonyl Cycloaddition of 1,6-Enynes with Aldehydes

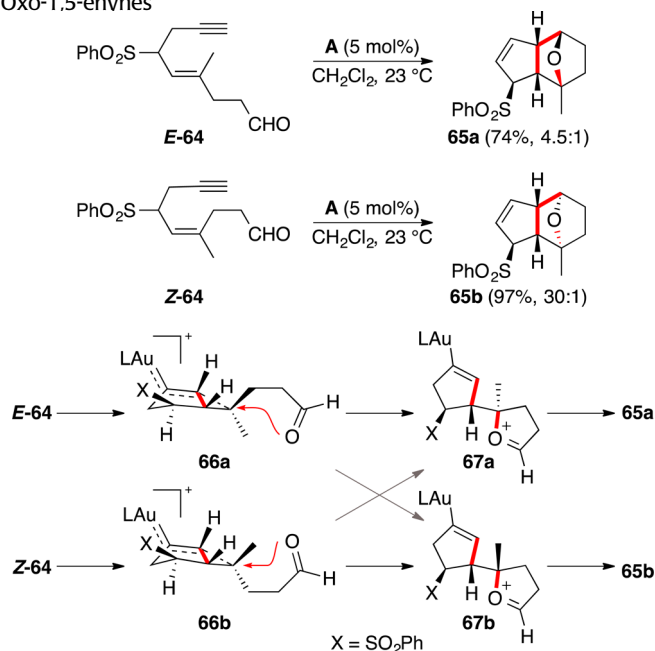
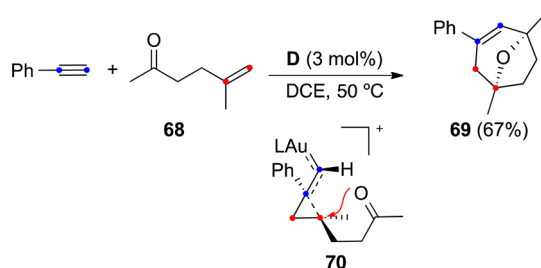
with donating ligands are used as catalysts, the major cycloisomerization pathway proceeding through intermediates **66** and **67** is stereospecific. However, the stereoselectivity is only moderate in the case of *E*-**64**, which is consistent with the existence of two competitive pathways, supporting again the proposal for stepwise processes via discrete intermediates in gold(I) catalyzed cascade reactions.

The intermolecular gold(I)-catalyzed reaction of terminal alkynes with oxoalkenes of type **68** leads to 8-oxabicyclo-[3.2.1]oct-3-enes **69** by a similar [2 + 2 + 2] cycloaddition process through intermediates **70** in which two C–C and one C–O bonds are formed (Scheme 16).<sup>87</sup>

## 7. Concluding Remarks

Many reactions of 1,*n*-enynes and related substrates catalyzed by gold(I) bear certain resemblance with carbocationic processes promoted by Brønsted or Lewis acids. However, gold(I) catalysts orchestrate complex reactions with



**SCHEME 15.** Intramolecular Alkyne/Alkene/Carbonyl Cycloaddition of Oxo-1,5-enynes**SCHEME 16.** Intermolecular [2 + 2 + 2] Alkyne/Alkene/Carbonyl Cycloaddition of Alkynes with Oxoalkenes

exquisite regio- and stereocontrol, by stabilizing the key reactive cationic intermediates. Although in a few cases the reactions proceed through open carbocations, most transformations are stereospecific. The basic mechanistic pathways involved in the cycloisomerization of 1,*n*-enynes are reasonably well understood, although still the factors that control the many competitive pathways are still rather obscure, particularly in intermolecular reactions. Nevertheless, complex cascade transformations can now be designed based on relatively simple principles. This journey to gain mechanistic insight into this family of complex transformations has also led to the discovery of robust, yet highly reactive cationic catalysts such as **A** and **D** bearing bulky phosphines, which are among the most useful gold(I) catalysts.

We thank the MICINN (Grant CTQ2010-16088/BQU), the AGAUR (Grant 2009 SGR 47), the European Research Council (Advanced

Grant No. 321066), and the ICIQ Foundation for financial support. C.O. acknowledges the receipt of a FPU fellowship from the Ministry of Education and Science. We also thank the past and present graduate students of our group at the Universidad Autónoma de Madrid (UAM) and the ICIQ, notably Carolina Fernández-Rivas, María Méndez, Belén Martín-Matute, M. Paz Muñoz-Herranz, Cristina Nevado, Cristina Nieto-Oberhuber, Catalina Ferrer, Eloísa Jiménez-Núñez, Elena Herrero-Gómez, Patricia Pérez-Galán, Verónica López-Carrillo, Mihai Raducan, Nicolas Delpont, César Rogelio Solorio-Alvarado, Núria Huguet, Morgane Gaydou, Yahui Wang, and Anna Homs, as well as our theoretical collaborators Diego J. Cárdenas (UAM), Elena Buñuel (UAM), Feliu Maseras (ICIQ), and Maria Besora (ICIQ) for their contributions to the understanding of the complex mechanisms triggered by gold catalysts.

#### BIOGRAPHICAL INFORMATION

**Carla Obradors** was born in Manresa (Catalonia, Spain) in 1987. She completed her B.Sc. in Chemistry (2010) at the Universitat Autònoma de Barcelona (UAB) and joined the group of Prof. Antonio M. Echavarren at the Institute of Chemical Research of Catalonia (ICIQ) with a FPU fellowship. She received a Special Master Thesis Award from the Universitat Rovira i Virgili (Tarragona) in 2012.

**Antonio M. Echavarren** was born in Bilbao in 1955 (Basque Country, Spain) and obtained his Ph.D. 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 (1984–86). 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, where he stayed until 1992. That year he returned to the UAM as a Professor of Organic Chemistry. He is also Professor of Research of the CSIC since 2004. He moved in 2004 to Tarragona as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ). He received the 2004 Janssen-Cytag Award in Organic Chemistry and the 2010 Gold Medal of the Royal Spanish Chemical Society.

#### FOOTNOTES

\*To whom correspondence should be addressed. E-mail: aecharvarren@icq.es. The authors declare no competing financial interest.

#### REFERENCES

- Trost, B. M. Palladium-Catalyzed Cycloisomerizations of Enynes and Related Reactions. *Acc. Chem. Res.* **1990**, *23*, 34–42.
- Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. Construction of Novel Polycyclic Ring Systems by Transition-Metal-Catalyzed Cycloisomerization of Ene-Ene-Ynes. Interception of a Carbenoid Intermediate in Skeletal Reorganization of Enynes. *J. Am. Chem. Soc.* **1998**, *120*, 9104–9105.
- Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. PtCl<sub>2</sub>-Catalyzed Conversion of 1,6- and 1,7-Enynes to 1-Vinylcycloalkenes. Anomalous Bond Connection in Skeletal Reorganization of Enynes. *Organometallics* **1996**, *15*, 901–903.
- Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. Cationic Platinum-Complex-Catalyzed Skeletal Reorganization of Enynes. *Organometallics* **2001**, *20*, 3704–3709.

- 5 Fürstner, A.; Szillat, H.; Stelzer, F. Novel Rearrangements of Enynes Catalyzed by  $\text{PtCl}_2$ . *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786.
- 6 Méndez, M.; Muñoz, M. P.; Echavarren, A. M. Platinum-Catalyzed Hydroxy- and Alkoxy-cyclization of Enynes. *J. Am. Chem. Soc.* **2000**, *122*, 11549–11550.
- 7 Mainetti, E.; Mourriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. The Effect of a Hydroxy Protecting Group on the  $\text{PtCl}_2$ -Catalyzed Cyclization of Dienes—A Novel, Efficient, and Selective Synthesis of Carbocycles. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135.
- 8 Teles, J. H.; Brode, S.; Chabanas, M. Cationic Gold(I) Complexes: Highly Efficient Catalysts for the Addition of Alcohols to Alkynes. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415–1418.
- 9 Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. Highly Efficient Au<sup>I</sup>-Catalyzed Hydration of Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563–4565.
- 10 Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. Highly Selective Gold-Catalyzed Arene Synthesis. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
- 11 Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. Pt(II)-catalyzed Intramolecular Reaction of Furans with Alkynes. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754–4757.
- 12 Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Intramolecular Reactions of Alkynes with Furans and Electron Rich Arenes Catalyzed by  $\text{PtCl}_2$ : The Role of Platinum Carbenes as Intermediates. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.
- 13 Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Cationic Gold(I) Complexes: Highly Alkynophilic Catalysts for the exo- and endo-Cyclization of Enynes. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406.
- 14 Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. Platinum- and Gold-Catalyzed Cycloisomerization Reactions of Hydroxylated Enynes. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.
- 15 Luzung, M. R.; Markham, J. P.; Toste, F. D. Catalytic Isomerization of 1,5-Enynes to Bicyclo[3.1.0]hexenes. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859.
- 16 Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. Gold(I)-Catalyzed Conia-Ene Reaction of  $\beta$ -Ketoesters with Alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527.
- 17 Fürstner, A.; Morency, L. On the Nature of the Reactive Intermediates in Gold-Catalyzed Cycloisomerization Reactions. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033.
- 18 Hashmi, A. S. K. "High Noon" in Gold Catalysis: Carbene versus Carbocation Intermediates. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754–6756.
- 19 Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III; Toste, F. D. A Bonding Model for Gold(I) Carbene Complexes. *Nat. Chem.* **2009**, *1*, 482–486.
- 20 Zhang, L.; Sun, J.; Kozmin, S. A. Gold and Platinum Catalysis of Enyne Cycloisomerization. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.
- 21 Jiménez-Núñez, E.; Echavarren, A. M. Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. *Chem. Rev.* **2008**, *108*, 3326–3350.
- 22 Gorin, D. J.; Sherry, B. D.; Toste, F. D. Ligand Effects in Homogeneous Au Catalysis. *Chem. Rev.* **2008**, *108*, 3351–3378.
- 23 Michelet, V.; Toullec, P. Y.; Genêt, J. P. Cycloisomerization of 1,n-Enynes: Challenging Metal-Catalyzed Rearrangements and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.
- 24 Fürstner, A. Gold and Platinum Catalysis—a Convenient Tool for Generating Molecular Complexity. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.
- 25 Shapiro, N. D.; Toste, F. D. A Reactivity-Driven Approach to the Discovery and Development of Gold-Catalyzed Organic Reactions. *Synlett* **2010**, 675–691.
- 26 Liu, L.-P.; Hammond, G. B. Recent Advances in the Isolation and Reactivity of Organogold Complexes. *Chem. Soc. Rev.* **2012**, *41*, 3129–3139.
- 27 Rudolph, M.; Hashmi, A. S. K. Gold Catalysis in Total Synthesis—an Update. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462.
- 28 Obradors, C.; Echavarren, A. M. Intriguing Mechanistic Labyrinths in Gold(I) Catalysis. *Chem. Commun.* **2013**, *1039/C3CC45518A*.
- 29 García-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramírez, J.; Lopez, N. Selective Homogeneous and Heterogeneous Gold Catalysis with Alkynes and Alkenes: Similar Behavior, Different Origin. *ChemPhysChem* **2008**, *9*, 1624–1629.
- 30 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. Divergent Mechanisms for the Skeletal Rearrangement and [2 + 2] Cycloaddition of Enynes Catalyzed by Gold. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146–6148.
- 31 Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. The Role of Cyclobutenes in Gold(I)-Catalyzed Skeletal Rearrangement of 1,6-Enynes. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111.
- 32 Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. Missing Cyclization Pathways and New Rearrangements Unveiled in the Gold(I) and Platinum(II)-Catalyzed Cyclization of 1,6-Enynes. *Tetrahedron* **2007**, *63*, 6306–6316.
- 33 Soriano, E.; Marco-Contelles, J. Mechanistic Insights on the Cycloisomerization of Polyunsaturated Precursors Catalyzed by Platinum and Gold Complexes. *Acc. Chem. Res.* **2009**, *42*, 1026–1036.
- 34 Ota, K.; Chatani, N. Rh(II)-catalyzed skeletal reorganization of enynes involving selective cleavage of C—C triple bonds. *Chem. Commun.* **2008**, 2906–2907.
- 35 Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. Rh(II)-Catalyzed Skeletal Reorganization of 1,6- and 1,7-Enynes through Electrophilic Activation of Alkynes. *J. Am. Chem. Soc.* **2009**, *131*, 15203–15211.
- 36 Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. Intramolecular [4 + 2] Cycloadditions of 1,3-Enynes or Arylalkynes with Alkenes with Highly Reactive Cationic Phosphine Au(I) Complexes. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.
- 37 Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. Gold(I)-Catalyzed Cyclizations of 1,6-Enynes: Alkoxy-cyclizations and exo/endo Skeletal Rearrangements. *Chem.—Eur. J.* **2006**, *12*, 1677–1693.
- 38 Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. Gold(I)-Catalyzed Intramolecular [4 + 2] Cycloadditions of Arylalkynes or 1,3-Enynes with Alkenes: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 269–279.
- 39 Lee, Y. T.; Kang, Y. K.; Chung, Y. K. Au(I)-Catalyzed Cycloisomerization Reaction of Amide- or Ester-Tethered 1,6-Enynes to Bicyclo[3.2.0]hept-6-en-2-ones. *J. Org. Chem.* **2009**, *74*, 7922–7934.
- 40 Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. Au(I)-Catalyzed Cyclization of Enynes Bearing an Olefinic Cycle. *J. Org. Chem.* **2006**, *71*, 9366–9372.
- 41 Brooner, R. E. M.; Brown, T. J.; Widenhoefer, R. A. Direct Observation of a Cationic Gold(I)—Bicyclo[3.2.0]hept-1(7)-ene Complex Generated in the Cycloisomerization of a 7-Phenyl-1,6-enyne. *Angew. Chem. Int. Ed.* **2013**, *52*, 6259–6261.
- 42 Odabachian, Y.; Gagosz, F. Cyclobutenes as Isolable Intermediates in the Gold(I)-Catalyzed Cycloisomerization of 1,8-Enynes. *Adv. Synth. Catal.* **2009**, *351*, 379–386.
- 43 Zhang, L.; Kozmin, S. Gold-catalyzed cycloisomerization of siloxy enynes to cyclohexadienes. *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807.
- 44 Sun, J.; Conley, M.; Zhang, L.; Kozmin, S. Au- and Pt-Catalyzed Cycloisomerizations of 1,5-Enynes to Cyclohexadienes with a Broad Alkyne Scope. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710.
- 45 Cabello, N.; Rodríguez, C.; Echavarren, A. M. Gold-Catalyzed Cyclizations of 1,7-Enynes. *Synlett* **2007**, 1753–1758.
- 46 Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. The Mechanistic Puzzle of Transition Metal-Catalyzed Skeletal Rearrangements of Enynes. *Chem.—Eur. J.* **2006**, *12*, 5916–5923.
- 47 Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. Cationic  $\eta^1/\eta^2$ -Gold(I) Complexes of Simple Arenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455–5459.
- 48 Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. Metal-Arene Interactions in Dialkylbiarylphosphane Complexes of Copper, Silver, and Gold. *Chem.—Eur. J.* **2010**, *16*, 5324–5332.
- 49 Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. cis-Selective Single-Cleavage Skeletal Rearrangement of 1,6-Enynes Reveals the Multifaceted Character of the Intermediates in Metal-Catalyzed Cycloisomerizations. *Angew. Chem., Int. Ed.* **2008**, *47*, 7892–7895.
- 50 Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Reaction of Enol Ethers with Alkynes Catalyzed by Transition Metals: 5exo-dig versus 6endo-dig Cyclizations via Cyclopropyl Platinum or Gold Carbene Complexes. *Chem.—Eur. J.* **2003**, *9*, 2627–2635.
- 51 Nevado, C.; Charrault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J. P.; Echavarren, A. M. On the Mechanism of Carbohydroxy-palladation of Enynes. Additional Insights on the Cyclization of Enynes with Electrophilic Metal Complexes. *Eur. J. Org. Chem.* **2003**, 706–713.
- 52 Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. Unlikelihood of Pd-Free Gold(I)-Catalyzed Sonogashira Coupling Reactions. *Org. Lett.* **2010**, *12*, 3006–3009.
- 53 López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. Nature of the Intermediates in Gold(I)-Catalyzed Cyclizations of 1,5-Enynes. *Chem.—Eur. J.* **2011**, *17*, 10972–10978.
- 54 Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. Au(I)-Catalyzed Cycloisomerizations Terminated by  $\text{sp}^3$  C—H Bond Insertion. *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811.
- 55 Zhang, L.; Kozmin, S. Gold-Catalyzed Assembly of Heterobicyclic Systems. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963.
- 56 Böhringer, S.; Gagosz, F. Gold(I)-Catalyzed [4 + 2] Annelation/Nucleophilic Addition Sequence: Stereoselective Synthesis of Functionalized Bicyclo[4.3.0]nonenes. *Adv. Synth. Catal.* **2008**, *350*, 2617–2630.
- 57 Buzas, A.; Istrate, F.; Le Goff, X. F.; Odabachian, Y.; Gagosz, F. Gold(I)-Catalyzed [4 + 2] Cycloaddition of N-(Hex-5-enynyl) tert-Butyloxycarbamates. *J. Organomet. Chem.* **2009**, *694*, 515–519.
- 58 Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. Gold(I)-Catalyzed Arylation of 1,6-Enynes: Different Site Reactivity of Cyclopropyl Gold Carbenes. *Chem. Commun.* **2007**, 698–700.
- 59 Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. Gold(I)-Catalyzed Intermolecular Addition of Carbon Nucleophiles to 1,5- and 1,6-Enynes. *J. Org. Chem.* **2008**, *73*, 7721–7730.

- 60 Leseurre, L.; Chao, C.-M.; Seki, T.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. Synthesis of Functionalized Carbo- And Heterocycles via Gold-Catalyzed Cycloisomerization Reactions of Enynes. *Tetrahedron* **2009**, *65*, 1911–1918.
- 61 Böhringer, S.; Gagosz, F. Gold(I)-Catalyzed [4 + 2] Annulation/Nucleophilic Addition Sequence: Stereoselective Synthesis of Functionalized Bicyclo[4.3.0]nonenes. *Adv. Synth. Catal.* **2008**, *350*, 2617–2630.
- 62 Chao, C. M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J. P.; Michelet, V. Asymmetric Gold-Catalyzed Hydroarylation/Cyclization Reactions. *Chem.—Eur. J.* **2009**, *15*, 1319–1323.
- 63 Sethofer, S. G.; Mayer, T.; Toste, F. D. Gold(I)-Catalyzed Enantioselective Polycyclization Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277.
- 64 Pérez-Galán, P.; Martin, N. J. A.; Campaña, A. G.; Cárdenas, D. J.; Echavarren, A. M. Carbocations or Cyclopropyl Gold Carbenes in Cyclizations of Enynes. *Chem.—Asian J.* **2001**, *6*, 482–486.
- 65 Delpont, N.; Escofet, I.; Pérez-Galán, P.; Spiegl, D.; Raducan, M.; Bour, C.; Siniši, R.; Echavarren, A. M. Modular Chiral Gold(I) Phosphite Complexes. *Catal. Sci. Technol.* **2013**, *3*, 3007–3012.
- 66 Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. Asymmetric Gold-Catalyzed Hydroarylation/Cyclization Reactions. *Chem.—Eur. J.* **2009**, *15*, 1319–1323.
- 67 López-Carrillo, V.; Echavarren, A. M. Gold(I)-Catalyzed Intermolecular [2 + 2] Cycloaddition of Alkynes with Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.
- 68 Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A. M. Gold(I)-Catalyzed Macrocyclization of 1,*n*-Enynes. *Org. Lett.* **2013**, *15*, 1576–1579.
- 69 Yeom, H.-S.; Koo, J.; Park, H.-S.; Wang, Y.; Liang, Y.; Yu, Z.-X.; Shin, S. Gold-Catalyzed Intermolecular Reactions of Propiolic Acids with Alkenes: [4 + 2] Annulation and Enyne Cross Metathesis. *J. Am. Chem. Soc.* **2012**, *134*, 208–211.
- 70 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. Cyclopropanation with Gold(I) Carbenes by Retro-Buchner Reaction from Cycloheptatrienes. *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955.
- 71 Solorio-Alvarado, C. R.; Echavarren, A. M. Gold-Catalyzed Annulation/Fragmentation: Formation of Free Gold Carbenes by Retro-Cyclopropanation. *J. Am. Chem. Soc.* **2010**, *132*, 11881–11883.
- 72 Fedorov, A.; Batiste, L.; Bach, A.; Birney, D. M.; Chen, P. Potential Energy Surface for (Retro-)Cyclopropanation: Metathesis with a Cationic Gold Complex. *J. Am. Chem. Soc.* **2011**, *133*, 12162–12171.
- 73 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. Gold(I)-Catalyzed Intramolecular Cyclopropanation of Dienynes. *Chem.—Eur. J.* **2006**, *12*, 1694–1702.
- 74 López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. Gold(I)-Catalyzed Intermolecular Cyclopropanation of Enynes with Alkenes: Trapping of Two Different Gold Carbenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029–6032.
- 75 Pérez-Galán, P.; Herrero-Gómez, H.; Hog, D. T.; Martin, N. J. A.; Maseras, F.; Echavarren, A. M. Mechanism of the Gold-Catalyzed Cyclopropanation of Alkenes with 1,6-Enynes. *Chem. Sci.* **2011**, *2*, 141–149.
- 76 Batiste, L.; Fedorov, A.; Chen, P. Gold Carbenes via 1,2-Dialkoxycyclopropane Ring-Opening: A Mass Spectrometric and DFT Study of the Reaction Pathways. *Chem. Commun.* **2010**, *46*, 3899–3901.
- 77 Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. Evolution of Propargyl Ethers into Allylgold Cations in the Cyclization of Enynes. *Angew. Chem., Int. Ed.* **2009**, *48*, 6152–6155.
- 78 Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J.; Echavarren, A. M. Synthesis of (+)-Schisanwilsonene A by Tandem Gold-Catalyzed Cyclization-1,5-Migration-Cyclopropanation. *Angew. Chem., Int. Ed.* **2013**, *52*, 6396–6399.
- 79 Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. Prins Cyclizations in Au-Catalyzed Reactions of Enynes. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452–5455.
- 80 Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. Stereoselective Gold-Catalyzed Cycloaddition of Functionalized Ketoenynes: Synthesis of (+)-Orientalol F. *Chem. Commun.* **2009**, 7327–7329.
- 81 Molawi, K.; Delpont, N.; Echavarren, A. M. Enantioselective Synthesis of (–)-Englerins A and B. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517–3519.
- 82 Zhou, Q.; Chen, X.; Ma, D. Asymmetric, Protecting-Group-Free Total Synthesis of (–)-Englerin A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3513–3516.
- 83 Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. Gold-Catalyzed Reactions of 1,5- and 1,6-Enynes with Carbonyl Compounds: Cycloaddition vs. Metathesis. *Chem.—Eur. J.* **2009**, *15*, 5646–5650.
- 84 Schelwies, M.; Dempwolf, A. L.; Rominger, F.; Helmchen, G. Gold-Catalyzed Intermolecular Addition of Carbonyl Compounds to 1,6-Enynes. *Angew. Chem., Int. Ed.* **2007**, *46*, 5598–5601.
- 85 Schelwies, M.; Moser, R.; Dempwolf, A. L.; Rominger, F.; Helmchen, G. Gold-Catalyzed Intermolecular Addition of Carbonyl Compounds to 1,6-Enynes: Reactivity, Scope, and Mechanistic Aspects. *Chem.—Eur. J.* **2009**, *15*, 10888–10900.
- 86 Huguet, N.; Echavarren, A. M. Gold-Catalyzed Cyclizations of Oxo-1,5-enynes. *Synlett* **2012**, *23*, 49–53.
- 87 Obradors, C.; Echavarren, A. M. Intermolecular Gold-Catalyzed Cycloaddition of Alkynes with Oxalkenes. *Chem.—Eur. J.* **2013**, *19*, 3547–3551.