Unlocking the 5-*exo* Pathway with the Au(I)-Catalyzed Alkoxycyclization of 1,3-Dien-5-ynes

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Abstract: The first general regio- and stereoselective 5-*exo* gold(I)-catalyzed alkoxycyclization of a specific class of 1,5-enynes such as 1,3-dien-5-ynes has been described, despite 1,5-enynes being known to almost invariably proceed via *endo* cyclizations under gold-catalysis. The configuration of the terminal alkene in the starting 1,3-dien-5-yne plays a crucial role on the regiochemical outcome of the reaction. A wide variety of interesting alkoxy-functionalized alkylidencyclopentenes have been synthesized from 1-monosubstituted (*E*)-1,3-dien-5-ynes. Contrary, the corresponding *Z* isomers evolve affording formal 6-*endo* cyclization products. In addition, mechanistic exploration supports a highly stabilized carbocation as a key intermediate instead of a highly constrained cyclopropyl gold carbene from *E* isomers, and also accounts for the well differentiated reactivity observed between both *E/Z* geometrical isomers as well as for the stereochemical outcome of the reaction.
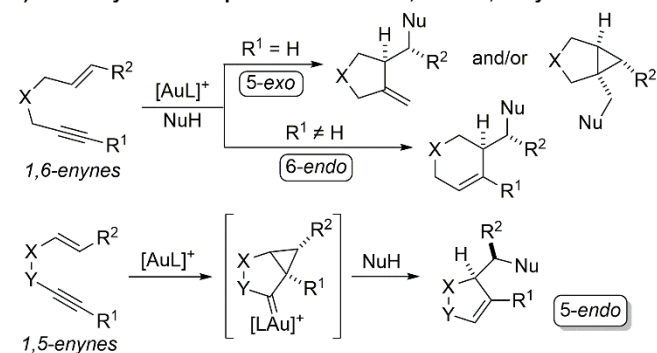
Introduction

The gold-catalyzed activation of 1,*n*-enynes toward the inter or intramolecular attack of nucleophiles is nowadays a well-established strategy for the construction of densely functionalized carbocyclic scaffolds, which usually operates in a highly selective manner.[1] Whereas 1,6-enynes could react through 5-*exo-dig* or 6-*endo-dig* processes,[2] mainly depending on the terminal or internal nature of the alkyne and the substituents of the alkene, as well as the nature of the metal ligands, 1,5-enynes almost exclusively evolve via *endo-dig* cyclizations.[3] Moreover, the addition of nucleophiles on enynes, mainly the addition of alcohols and water (alkoxy- and hydroxycyclizations), nicely expands the versatility of gold(I)-catalyzed reactions allowing the preparation of functionalized carbo and heterocyclic compounds.[4] This reactivity is likely favoured by the low oxophilicity of gold(I) complexes. Despite of the abundant studies in gold-catalyzed cyclization of 1,5-enynes, the elusive 5-*exo* cyclization was described only in two examples and merely as a by-product of the most favored *endo* pathway (Scheme 1a).[5,6] This scenario is likely due to the fact that the generation of bicyclo[3.1.0]hexanes, derived from *endo*

cyclizations, is strongly favoured over the formation of bicyclo[2.1.0]pentanes, resulting from the alternative *exo* pathway.[7]
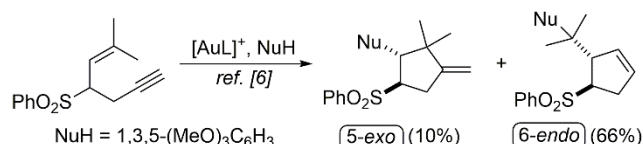
Along the last years, there has been some controversy about the nature of the reactive intermediates, mainly regarding the Au–C bond, in this type of gold-catalyzed cyclizations, ranging from simple carbocations till gold carbene complexes.[8] Based on thorough mechanistic studies, Fürstner suggested that organogold intermediates have a highly cationic character.[8a,c] Toste and Goddard proposed a description for the gold carbene bonding in which strongly σ-donating and weakly π-acidic ligands, such as NHCs, were expected to increase the carbene-like reactivity.[9] Recently, Echavarren has characterized spectroscopically cationic gold(I) carbenes for first time in solution.[10] Moreover, DFT calculations have been carried out to rationalize some of the observed experimental results,[11] and the direct isolation or in situ detection of intermediates is also helping to shed light on this matter.[12]

In this field we have described the gold-catalyzed methoxycyclization reactions of 1,1-disubstituted 1,3-dien-5-ynes[13] that selectively undergo 5-*endo* cyclizations,[14] leading to 5-alkoxymethyl cyclopentadienes (Scheme 1b).[15] Related *ortho*-(alkynyl)styrenes, a particular type of 1,3-dien-5-ynes, also led to interesting cycloisomerization processes under gold-catalysis triggered by an initial 5-*endo* cyclization (Scheme 1b).[16] Additionally, we have recently reported the regio and diastereospecific 5-*endo* nucleophilic cyclization of β-monosubstituted *o*-(alkynyl)styrenes (Scheme 1c).[17] In our experience, the involved gold intermediates are well described as homoallylically stabilized carbocations with different degrees of gold carbene-type contribution mainly due to the substrate structure but not to the ancillary ligand electronic properties. Herein, we report the first general example of a gold(I)-catalyzed 5-*exo* cyclization of 1,5-enynes consisting on the alkoxycyclization of 1-monosubstituted 1,3-dien-5-ynes[18] that takes place in a regio- and diastereospecific manner thus initially supporting the intermediacy of an elusive cyclopropyl gold carbene on a strained bicyclo[2.1.0]pentane skeleton (Scheme 1d).
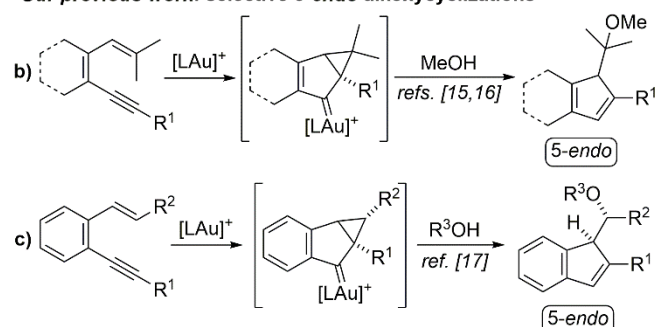
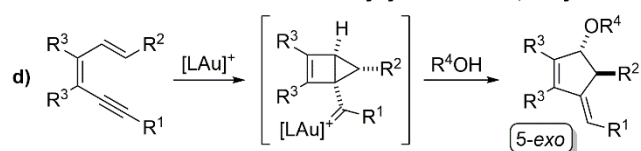## a) Au-catalyzed nucleophilic additions to 1,6- and 1,5-enynes:

Scheme 1. 5-*endo* Nucleophilic additions to 1,5-enynes (well-known reactivity). Alkoxycyclizations of 1,1-disubstituted-1,3-dien-5-ynes and β-monosubstituted *o*-(alkynyl)styrenes (our prior work). 5-*exo* Alkoxycyclizations of (*E*)-1-monosubstituted 1,3-dien-5-ynes (this work).

Results and Discussion

We selected dienyne **1a**, bearing an internal alkyne moiety, as model substrate for which the expected *endo*-cyclization would give rise to a cyclopropylgold carbene intermediate **A** that could lead to different products derived from formal 6-*endo* or 5-*endo* cyclization modes. Considering our previous results (see Scheme 1b,c),[15-17] α-methoxybenzyl cyclopentadiene **2´a** should be the preferred product (Scheme 2). An alternative *exo*-cyclization would lead to a highly strained cyclopropylgold carbene intermediate **B** and was unprecedented in the literature (Scheme 2).

Surprisingly, when we submitted (*E*)-**1a** to our standard methoxycyclization conditions under gold-catalysis,[17] we selectively obtained methoxyalkylidencyclopentene derivative **2a** instead of the cyclopentadiene derivative **2´a** resulting from the expected 5-*endo* alkoxycyclization (Scheme 2). This result clearly suggested that a 5-*exo* cyclization had taken place. In addition, although four diastereoisomers could be generated in
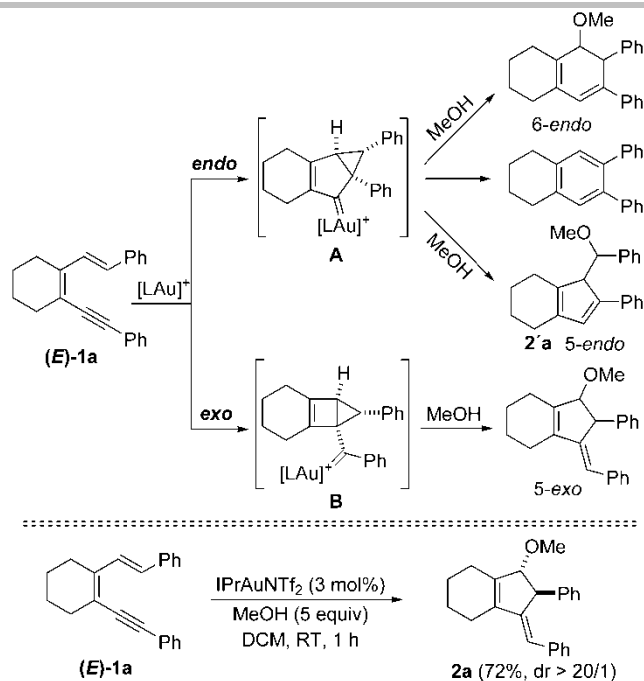
Scheme 2. Initial approach and preliminary result with enyne (*E*)-**1a**.

this methoxycyclization, only one was obtained indicating an exquisite control of the stereoselectivity of the reaction.

Based on this result, we decided to evaluate a variety of gold(I) catalysts (Table 1). First, different bis(triflimidate) gold(I) complexes were tested (entries 1–4). Although the 5-*exo* product was obtained as single stereoisomer in all cases, phosphine-based ligands (entries 2–4) performed less efficiently than a NHC-carbene ligand such as IPr (entry 1), and only the use of JohnPhosAuNTf₂ achieved comparable yields (entry 3). Nevertheless, a related cationic acetonitrile gold(I) complex bearing a bulkier biarylphosphine like XPhos (entry 5) was proved to be less efficient. We also evaluated the nature of the counteranion by treating IPrAuCl with silver salts as chloride scavengers (entries 6–9). Best results were obtained by using tosylate and particularly hexafluoroantimoniate as weakly coordinating counteranion providing access to the desired 5-*exo* product almost quantitatively (entries 8 and 9). The catalytic system IPrAuCl/AgSbF₆ has demonstrated to be highly efficient even in toluene (entry 10) or neat methanol (entry 11).

Table 1. Optimization of the gold-catalyzed methoxycyclization of (*E*)-**1a**.[a]

Entry	Catalyst	Solvent	Conversion[b]	Yield [%][b]
1	IPrAuNTf₂	CH₂Cl₂	100	77
2	Ph₃PAuNTf₂	CH₂Cl₂	60[c]	34
3	(*t*-Bu)₃PAuNTf₂	CH₂Cl₂	100	37
4	JohnPhosAuNTf₂	CH₂Cl₂	100	69

5	XPhos(MeCN)AuSbF$_6$	CH$_2$Cl$_2$	100	27
6	IPrAuCl/AgNTf$_2$	CH$_2$Cl$_2$	100	64
7	IPrAuCl/AgBF$_4$	CH$_2$Cl$_2$	100	67
8	IPrAuCl/AgOTs	CH$_2$Cl$_2$	100	85
9	IPrAuCl/AgSbF$_6$	CH$_2$Cl$_2$	100	90
10	IPrAuCl/AgSbF$_6$	Toluene	100	88
11	IPrAuCl/AgSbF$_6$	MeOH	100	79

[a] Reaction conditions: (*E*)-1a (0.1 mmol), MeOH (0.5 mmol), catalyst (3 mol%), solvent (1 mL), RT, 20 min. [b] Calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Complete conversion was achieved after 1 h.

With the optimized reaction conditions in hand we proceeded to study a wide range of enynes (*E*)-1 (Scheme 3). Aryl, heteroaryl, alkyl, and even a carboxylate substituent on the alkyne are well tolerated and the reaction proceeds smoothly (**2a-d**). Although the terminal alkyne **1e** also evolved through the 5-*exo* cyclization pathway, the formation of the expected methoxyalkylidene **2e** product was not observed. Instead, isomerization of the double bonds into inner positions takes place affording **2'e** along with a minor amount of ketone **3**, derived from a competitive addition of methanol to the terminal alkyne and subsequent hydrolysis (Scheme 3). Curiously, when the starting dienyne (*E*)-1f, bearing a TMS-substituted alkyne, was used, compound **2e** was obtained.[19] We also evaluated the nature of the substituent on the terminal alkene moiety (R^2). The transformation has shown to be general with phenyl rings bearing different functional groups **2g-j**, as well as other arenes such as naphthyl **2k** or heteroarenes such as thienyl **2l**. Remarkably, when R^2 is a methyl group the reaction also proceeds, with only a minor loss of the stereochemical control of the process, giving rise to **2m** in 77%. The methoxycyclization was successfully accomplished with other alkyl groups as R^2 substituents such as cyclopropyl, **2n**, or even with dienyne **1o**, possessing a hydroxymethyl substituent (Scheme 3). We also varied the nature of substituents R^3 on the internal alkene of the starting enyne (*E*)-1. In this regard, modification of the cyclohexane unit into a tetrahydropyran or *N*-tosyl-tetrahydropyridine ring provides access to the hydrocyclopenta[*c*]pyran (**2p,q**) and hydrocyclopenta[*c*]pyridine (**2r**) cores in good yields. In addition, the X-ray structure of compound **2r** could be obtained further supporting the proposed stereochemistry.[20] Importantly, the presence of a cyclic structure on the internal alkene in the starting enyne (*E*)-1 is not required to promote the reaction as demonstrated with the 5-*exo* methoxycyclization of linear enynes **1t** and **1u**, which afforded the expected methoxyalkylidencyclopentene derivatives **2t** and **2u** in high yields (Scheme 3).

Next, other alcohols other than methanol were also tested as nucleophiles (Table 2). Under standard reaction conditions, a diverse range of alkoxyalkylidencyclopentene derivatives **4** are easily obtained in good yields by reaction of model enyne (*E*)-1a with simple primary alcohols such ethanol or butanol (entries 1 and 2), as well as others more functionalized such as allyl alcohol or ethyleneglycol, bearing an alkene or an extra hydroxyl group, respectively (entries 3 and 4). To further demonstrate the general applicability of these alcohols in the 5-*exo* cyclization, selected enynes (*E*)-1 bearing different R^2 substituents were evaluated as reaction partners (entries 5–9). In all cases the reaction proceeds efficiently. In addition, the cyclohexane ring is not required to promote the 5-*exo* cyclization, as linear dienyne **1t** successfully underwent the alkoxycyclization with ally alcohol (entry 9).
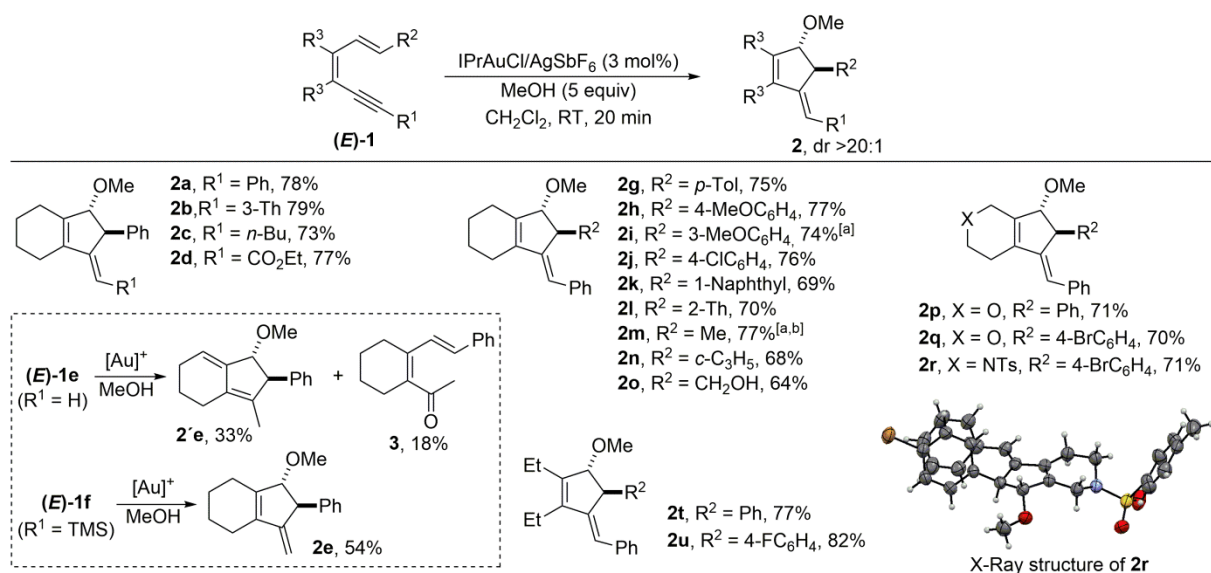
Scheme 3. 5-*exo* Methoxycyclization of 1,3-dien-5-ynes (*E*)-1. Synthesis of alkylidencyclopentenes **2a-u**. Yields are of isolated material after column chromatography. [a] The starting enyne **1** was used as a 20:1 mixture of geometrical isomers. [b] Obtained as a ca. 14:1 mixture of diastereoisomers.

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Table 2. Alkoxycyclization reactions of (**E**)-**1**. Synthesis of alkoxyalkylidencyclopentenes **4**.[a]
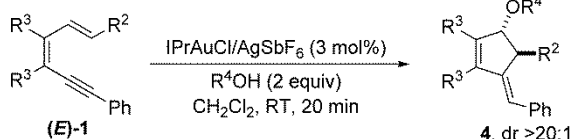
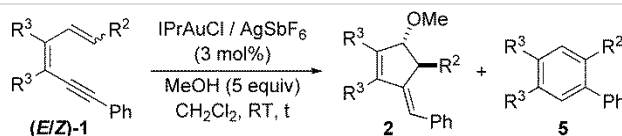| Entry	Enyne	R^2	R^3	R^4	Product	Yield [%][b]
1	**1a**	Ph	–(CH$_2$)$_4$–	Et	**4aa**	61
2	**1a**	Ph	–(CH$_2$)$_4$–	*n*-Bu	**4ab**	72
3	**1a**	Ph	–(CH$_2$)$_4$–	CH$_2$=CHCH$_2$	**4ac**	70
4	**1a**	Ph	–(CH$_2$)$_4$–	HO-(CH$_2$)$_2$	**4ad**	74
5	**1h**	4-MeOC$_6$H$_4$	–(CH$_2$)$_4$–	Et	**4ha**	71
6	**1h**	4-MeOC$_6$H$_4$	–(CH$_2$)$_4$–	HO-(CH$_2$)$_2$	**4hd**	68
7	**1k**	1-naphthyl	–(CH$_2$)$_4$–	*n*-Bu	**4kb**	60
8	**1k**	1-naphthyl	–(CH$_2$)$_4$–	HO-(CH$_2$)$_2$	**4kd**	61
9	**1t**	Ph	Et	CH$_2$=CHCH$_2$	**4tc**	79

[a] Reaction conditions: (**E**)-**1** (0.3 mmol), R^{4}OH (0.6 mmol), IPrAuCl/AgSbF$_6$ (3 mol%), CH$_2$Cl$_2$ (1 mL), RT, 20 min. [b] Isolated yield after column chromatography.

Taking into account our recent report about the diastereospecific alkoxycyclization of β-monosubstituted *o*-(alkynyl)styrenes,[17] in which the configuration of the starting alkene was transferred to the final cyclized product, we wondered at this point what could be the result when using starting dienynes **1** as a mixture of geometrical isomers. So, as enyne **1s** was obtained as a 7/1 mixture of *E/Z* isomers, we decided to subject this product to the reaction conditions to explore the influence of the configuration of the terminal alkene on the reaction outcome. Interestingly, two well-differentiated main products were observed: the 5-*exo* methoxycyclized product **2s** and the tetrahydronaphthalene derivative **5s** resulting from a formal 6-*endo* cycloisomerization (Scheme 4). These compounds were obtained in a similar ratio corresponding to the mixture of geometrical isomers of the starting enyne **1s**. Formation of compound **5s** could be reasoned by a direct 6-*endo* cycloisomerization or alternatively by an initial 5-*endo* cyclization affording a bicyclo[3.1.0]hexane intermediate (see Scheme 2), which rapidly evolves through ring expansion followed by aromatization to deliver the tetrahydronaphthalene derivative, similarly to the reported cycloisomerization reaction of the related 1,1-disubstituted 1,3-dien-5-ynes.[14a] According to this result, we hypothesized that enyne (**E**)-**1** would provide exclusively the 5-*exo* product **2** whereas, by contrast, tetrahydronaphthalene **5** would arise from the *Z*-isomer of **1**.

To test our hypothesis, the reactivity of a selection of dienynes **1**, as mixtures *E/Z* isomers, was studied under the standard protocol (Table 3). In all cases, both compounds **2** and **5** were obtained in a proportion comparable to the *E/Z* ratio of the starting material, and only minimal differences are noticeable. Remarkably, some examples implied a significant increase in the reaction time. These results clearly indicate that the *E/Z* ratio determines the final outcome. Notably, the nature of the substi-
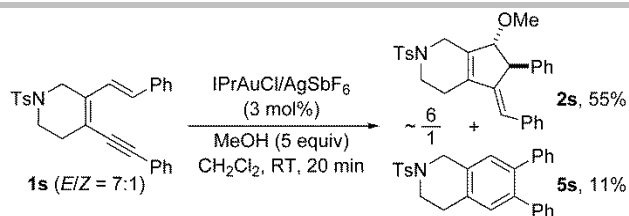
Scheme 4. Cyclization of dienyne (**E,Z**)-**1s**. Isolation of methoxyalkylidencyclopentene **2s** and tetrahydronaphthalene **5s**.

tuent R^2 of the enyne possesses a minimal influence. For instance, phenyl group provides unaltered ratio (entries 1, 4 and 5). When halogen- or methoxy-substituted aryl rings were tested only a slightly changed ratio of products was detected. Even when R^2 is a less bulky group, such as methyl (entries 3 and 6), the **2**:**5** proportion is determined by the *E/Z* ratio of the starting enyne **1**.
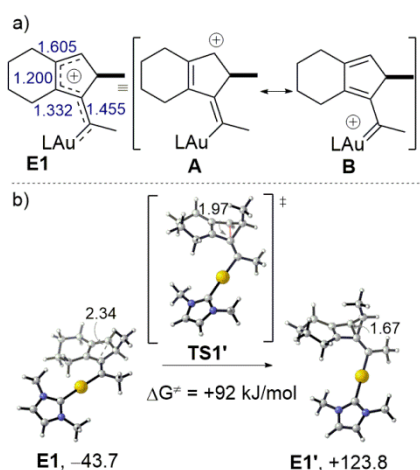
Table 3. Au(I)-catalyzed cyclization of dienynes (**E/Z**)-**1**. Selective access to methoxyalkylidencyclopentenes **2** and tetrahydronaphthalenes **5**.[a]

Entry **1**	R^2	R^3	*E/Z*	t (min)	**2**:**5**[b]	Yield [%][c] **2**	**5**
1 **1a**	Ph	–(CH$_2$)$_4$–	1.2/1	10	1.3/1	41	38
2 **1i**	3-MeOC$_6$H$_4$	–(CH$_2$)$_4$–	1/10	60	1/8	9	64
3 **1m**	Me	–(CH$_2$)$_4$–	1.2/1	10	1.1/1	40[d]	35
4 **1s**	Ph	–CH$_2$(NTs)(CH$_2$)$_2$–	1/20	10	1/20	–	68
5 **1t**	Ph	Et	2/1	10	1.7/1	51	33
6 **1v**	Me	Et	1/1.2	10	1/1.6	33[d]	47
7 **1w**	3-ClC$_6$H$_4$	–(CH$_2$)$_4$–	3/1	60	2.5/1	51	21
8 **1x**	2-FC$_6$H$_4$	–(CH$_2$)$_4$–	2.5/1	240	2.5/1	52	33

[a] Reaction conditions: (**E/Z**)-**1** (0.3 mmol), MeOH (1.5 mmol), IPrAuCl/AgSbF$_6$ (3 mol%), CH$_2$Cl$_2$ (1 mL), RT. [b] Calculated by ^{1}H NMR in the crude reaction mixture. [c] Isolated yield after column chromatography. [d] Obtained as a ca. 13:1 mixture of diastereoisomers.

In summary, according to the observed results, there is a correlation between the proportion of 5-*exo* and 6-*endo* products and the ratio of *E/Z* geometrical isomers of the starting enyne **1**. The position of the substituent in the terminal alkene moiety therefore plays a decisive role into favouring the 5-*exo* or the 6-*endo* pathway. Whereas (*E*)-enynes prefer the 5-*exo* cyclization mode affording methoxyalkylidencyclopentene **2**, the (*Z*)-enynes, similarly to their parent 1,1-disubstituted 1,3-dien-5-ynes,[14a] give rise to the benzene derivatives **5**.

Aiming to shed light onto the different reactivity displayed by 1,3-dien-5-ynes (**E**)-**1** and (**Z**)-**1** and to provide reasonable mechanisms ruling their transformations toward compounds **2** and **5**, respectively, we performed a thorough computational study at the DFT level. We are including here only the lowest energy mechanistic pathway and a brief account of the key steps of the alternative routes, i.e. 5-*exo*, 5-*endo* and 6-*endo*

cyclization modes of the starting gold-complexes (**SC$_E$** and **SC$_Z$**) and of the role of methanol present in the reaction medium (Scheme 5). Full mechanistic disclosure with greater level of detail is provided in the Supporting Information.

In the case of (**E**)-**1**, after the coordination of the gold complex to the alkyne moiety forming **SC$_E$**, the initial 5-*exo* transition structure **TS$_{E5exo}$** leading to the intermediate **E1** is less energetic in 14.3 and 21.3 kJ mol^{-1} than those involving a 5-*endo* (**TS$_{E5endo}$**) and 6-*endo* (**TS$_{E6endo}$**) cyclization mode, respectively. We will discuss later the reasons behind this preference. An analysis of the Wiberg indices at **E1** revealed that this structure should be envisioned as a hybrid of two resonant forms of the gold-carbene **A** and the allylic carbocation **B** (Scheme 6a). This may be the main reason for the non-observation of 5-*exo* cyclizations of structurally related β-monosubstituted *o*-(alkynyl)styrenes, since the stability due to aromaticity would be jeopardized during the cyclization step, incurring in a higher energetic penalty.[17] It is noteworthy that our computational studies predict that the strained cyclopropyl carbene isomer, the bicyclo[2.1.0]pentane intermediate **E1′** (123.8 kJ mol^{-1}), would not be formed during the reaction course (Scheme 6b). In fact, we computed this isomerisation step finding that it requires to

overcome an energy barrier of 92 kJ mol^{-1} (**TS1′**) hence resulting non-competitive with respect to alternative computed pathways.

The mechanism would then evolve with the interception of the carbocation intermediate **E1** by a methanol molecule. Our results envisaged a clear preference between the two suitable approach trajectories of methanol onto the most reactive allylic position C2. Thus, methanol would approach through the opposite side of the molecular plane in which the methyl group is placed since it is less cluttered therefore minimizing the steric contacts at the transition structure (ΔG_{TSE2} = 42.7 kJ mol^{-1} vs. $\Delta G_{TS'E2}$ = 67.9 kJ mol^{-1}). In line with the experimental evidence, the computed trajectory selectivity in the methanol attack affords the alkoxycyclopentene derivative **E3** in which both methoxy and methyl group are placed in *trans* relative spatial disposition. Interestingly, both **TS$_{E2}$** and **E3** are almost isoenergetic,[21] the reverse process, the departure of MeOH being a competitive step. However, this reversibility is satisfactorily solved with the excess of MeOH (2−5 equiv) in the reaction medium. The subsequent proton capture by the Tf$_2$N$^-$ counteranion at the **E3** affords intermediate **E4** which finally affords diastereoisomer **2a** after a protodeauration step.

Scheme 5. Proposed mechanism for the gold(I)-mediated formation of the alkylidenecyclopentene **E4** and the tetrahydronaphthalene **Z4** from the 1,3-dien-5-ynes **SC$_E$** and **SC$_Z$** at the PCM(DCM)/M06/Def2-SVP theoretical level. Gibbs free energies are reported in kJ mol^{-1} (1 atm and 298 K), relative to **SC$_E$**. Tf$_2$N$^-$ was chosen as counteranion to allow for a comparative analysis with the computational results of previous studies.[17] Colours refer to the alternative initial cyclizations: 5-*exo* (red), 5-*endo* (blue), 6-*endo* (green).

Scheme 6. a) Resonance forms of intermediate **E1**; b) computed transformation of intermediate **E1** into the strained cyclopropyl carbene isomer **E1′**. Energies are shown in kJ mol^{-1} and distances in angstroms (Å).

On the contrary, for the **(Z)-1** dienyne, the 5-*exo* cyclization of **SC$_Z$** is disfavoured compared to the alternative 5-*endo* mode ($\Delta G_{TSZ5exo}$ = 104.0 kJ mol^{-1} and $\Delta G_{TSZ5endo}$ = 88.0 kJ mol^{-1}, respectively). The transition structure for a seemingly straightforward 6-*endo* cyclization could not be located on the potential energy surface. At this point, the resulting bicycle **Z1** is prone to either react with a methanol molecule or undergo a ring expansion. Opposite to that observed for *o*-(alkynyl)styrene compounds,[17] the ring expansion process, involving the cleavage of the C2−C6 single bond on route to **Z3**, is highly favoured with respect to the nucleophilic attack by methanol onto C1 (Δ_{TSZ2} = 37.0 kJ mol^{-1} and $\Delta G_{TS'Z2}$ = 74.0 kJ mol^{-1}, respectively). This can easily be justified resorting to the gain of aromaticity at the 6-memberred ring occurring after the deprotonation of **Z3**, which affords the tetrahydronaphthalene derivative, **Z4**. Then, upon protodeauration, this latest intermediate would afford tetrahydronaphthalene **5**.

Our calculations revealed that for both simulated reaction profiles the initial cyclization step is the rate-determining: the 5-*exo* cyclization involving the (*E*)-dienyne-gold complex **SC$_E$** and the 5-*endo* one for its diastereoisomer.

In this scenario, we wondered why the 5-*exo* cyclization is not competitive for the **(Z)-1** species under gold(I)-catalysis. To answer this question, we analyzed both transition structures for the 5-*exo* cyclization, **TS$_{E5exo}$** and **TS$_{Z5exo}$** (Figure 1).

Both **TS$_{E5exo}$** and **TS$_{Z5exo}$** are found to be structurally very close and with characteristics reminiscent of a C=C double bond attack to the central carbon atom of a gold-activated allene.[22] The forming C−C bond lengths are comparable (2.13 and 2.17 Å, for **TS$_{E5exo}$** and **TS$_{Z5exo}$**, respectively), however, the spatial orientation of the methyl group differs notably. Whereas in **TS$_{E5exo}$** the methyl group at C1 is located *out* of the forming ring, that group turns *in* in the case of **TS$_{Z5exo}$**, therefore increasing the steric hindrance around the reactive site. This steric factor would be enough to avoid the 5-*exo* cyclization of **(Z)-1**, as well as in the cases of related 1,1-dialkyl substituted 1,3-dien-5-ynes, as reported previously,[14] and to favour the 5-*endo* alternative that is less sterically congested. Although electronic effects derived from the substitution pattern of the alkene have been
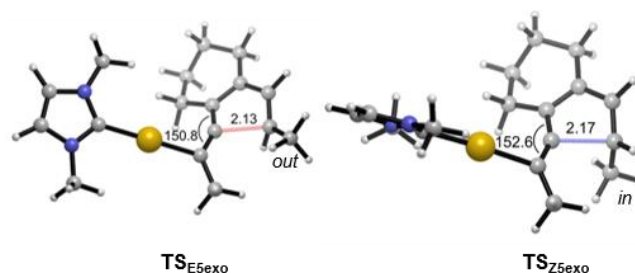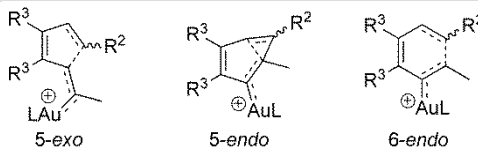

Figure 1. Computed transition structures **TS$_{E5exo}$** and **TS$_{Z5exo}$**. Distances are shown in angstroms (Å) and angles in degrees (°).

pointed as a key factor in determining the cyclization modes in gold-catalyzed enyne cycloisomerization reactions,[8] rarely steric factors have been decisive. Remarkably, in this case, the position (*E/Z*) of the substituent has a crucial role in determining the cyclization mode.

For the sake of completeness, we also explored the influence of the size of the substituent at the alkene moiety and the presence of the cyclohexene fragment in the bicyclic system in the energetic barriers of the three possible initial cyclization modes (Table 4). We observed that the 5-*exo* cyclization mode is favourable in all (*E*)-1,3-dien-5-enynes studied regardless of the substitution at C1. Remarkably, the energetic barrier decreases as the size of the substituent increases. This could be related to the electron delocalization along the polyene at the transition structure, which is greater when a phenyl group is present. Additionally, such electron delocalization would be the main reason behind the preference of 5-*exo* with respect to the 5-*endo* transition structure, where the electron delocalization is lower. In all cases, the transition structure involving a 6-*endo* cyclization mode is the highest energy one. Likewise, the 5-*endo* cyclization is preferred rather than the 5-*exo* for (*Z*)-diastereoisomers due to steric congestion around the reactive site. Interestingly, and contrary to the observed tendency with (*E*)-enynes, (*Z*)-enynes with bulkier substituents such as phenyl group (Table 4, entry 3) have a higher energetic barrier for the 5-*exo* cyclization over the related (*Z*)-methyl substituted enyne despite of the electron delocalization effect of this substituent. This clearly supports that **TS$_{Z5exo}$**, bearing a substituent in position *in*, is considerably much more exposed to steric factors than **TS$_{E5exo}$** possessing the substituent in position *out*. We also decided to study the possible effect of the cyclohexane moiety (Table 4, entry 4). In absence of a cyclic structure including the central double bond, computational results predict that the 5-*exo* cyclization is even easier for the corresponding (*E*)-1 whereas similar energetic barriers are computed for the 5-*endo* transition structure (entries 2 vs. 4).

Table 4. Gibbs free energies (kJ mol⁻¹) of the transition structures of the three possible cyclization modes of gold(I)-activated 1,5-enynes (*E*)-**1** and (*Z*)-**1**. *E* and *Z* refers to the stereoisomerism of the C1–C2 double carbon bond at the initial 1,5-enyne. Energies are relative to the corresponding previous intermediate **SC**.

5-*exo* 5-*endo* 6-*endo*

Entry	R²	R³	$\Delta G_{5\text{-}exo}$		$\Delta G_{5\text{-}endo}$		$\Delta G_{6\text{-}endo}$	
			E	*Z*	*E*	*Z*	*E*	*Z*
1	H	–(CH₂)₄–	79.6		105.6		96.7	
2	Me	–(CH₂)₄–	72.7	104.0	87.3	88.0	94.0	–[a]
3	Ph	–(CH₂)₄–	69.3	112.0	86.4	91.1	94.0	–[a]
4	Me	Me	56.1	96.5	87.5	89.6	95.3	–[a]

[a] Computational results predict that the cyclization does not proceed involving this transition structure.

Finally, we explored a likely derivatization of new compounds **2**. Into this regard, we envisioned that an oxidation of the methoxy-substituted allylic position will provide access to valuable 2-cyclopentenone derivatives. Initial tests with **2a** demonstrated that the use DDQ as oxidant at room temperature affords the desired 4-alkylidenecyclopentenone **6a** in high yields (Scheme 7).[23]
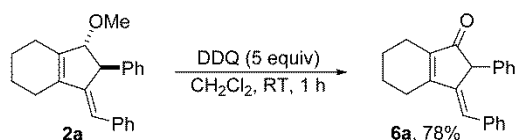
Scheme 7. Oxidation of methoxyalkylidencyclopentene **2a**. Synthesis of unsaturated ketone **6a**.

With this result in hand, we decided to evaluate the feasibility of a one-pot procedure to synthesize 4-alkylidenecyclopentenones in one single operational step from enynes **1**. So, after the initial methoxycyclization, the oxidation would take place sequentially upon addition of DDQ to the reaction media (Table 5). To our delight this protocol was successful in providing a variety of interesting 4-alkylydinecyclopentenones **6**. Enynes **1** bearing on the alkene moiety an aryl (neutral or moderately deactivate, entries 1, 2, and 6), a thienyl (entry 3) or a (cyclo)alkyl group (entries 4 and 5) are well tolerated. As expected, when a mixture of *E/Z*-isomers was used, the tetrahydronaphthalenes **5m** and **5x**, derived from the *endo* cyclization of the corresponding enynes (*Z*)-**1** (entries 4 and 6), were also observed.

Table 5. Au(I)-catalyzed methoxycyclization of selected enynes **1** followed by DDQ-mediated oxidation. One-pot synthesis of unsaturated ketones **6**.[a]
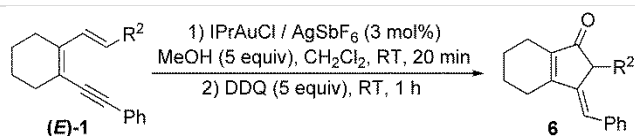
Entry	Enyne	R²	Product	Yield [%][b]
1	**1a**	Ph	**6a**	68
2	**1j**	4-ClC₆H₄	**6j**	62
3	**1l**	2-Th	**6l**	63
4[c]	**1m**	Me	**6m**	36[d,e]
5	**1n**	*c*-C₃H₅	**6n**	61
6[f]	**1x**	2-FC₆H₄	**6x**	47[d]

[a] Reaction conditions: (*E*)-**1** (0.3 mmol), MeOH (1.5 mmol), IPrAuCl/AgSbF₆ (3 mol%), DCM (1 mL), RT, 20 min; then, DDQ (1.5 mmol), RT, 1h. [b] Isolated yield after column chromatography. [c] Used as a 1.2:1 mixture of (*E/Z*)-isomers. [d] The corresponding tetrahydronaphthalenes **5m** and **5x** were also obtained derived from the corresponding (*Z*)-**1**. [e] Obtained as a ca.10:1 mixture of geometrical isomers likely due to subsequent isomerisation of the final unsaturated ketone. [f] Used as a 2.5:1 mixture of (*E/Z*)-isomers.

Conclusion

Herein we have described the first general 5-*exo* Au(I)-catalyzed alkoxycyclization of a specific class of 1,5-enynes, such as 1.3-dien-5-ynes, in a selective manner. This chemistry has been hereby exploited to form a wide range of densely decorated (bi)cyclic systems from a variety of 1-monosubstituted (*E*)-1,3-dien-5-ynes. Furthermore, our protocol is compatible with substituents of different nature at almost all possible positions of the starting material and it even allows the formation of heterocyclic systems. Mechanistic exploration has provided a rationale for this unexpected chemistry, offering a complete picture which explains the different reactivity of 1,3-dien-5-ynes depending on their substitution pattern and the configuration of the terminal alkene. Theoretical calculations has suggested the intermediacy of a different organogold compound instead of previously proposed bicyclo[2.1.0]pentane intermediate. This species has a strong carbocationic contribution. This chemistry has been found to be governed by a delicate balance of electron delocalization and steric factors resulting in a manifold of competing pathways which allows the reaction to be drastically steered to the formation of different products via subtle changes at the starting material. Remarkably the (*Z*)-1,3-dien-5-ynes react into a divergent pathway affording tetrahydronaphthalene 6-*endo* products, so a change in the geometry of the terminal double bond determines the cyclization mode. The origin of this differential reactivity was disentangled pointing to steric factors in the positions *in* and *out* of the key decisive 5-*exo* intermediate. Finally, two-step one-pot derivatization of the 5-*exo* products is possible and it has been exemplified through the formation of alkylidenecyclopentenones, a desirable structural motif.
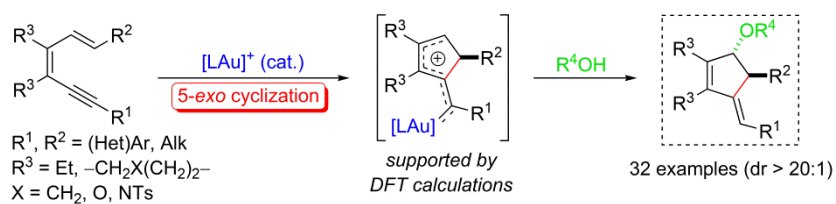
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Entry for the Table of Contents

R^1, R^2 = (Het)Ar, Alk
R^3 = Et, $-CH_2X(CH_2)_2-$
X = CH_2, O, NTs

supported by DFT calculations

32 examples (dr > 20:1)

Whereas *endo* processes are ubiquitous for the cyclizations of 1,5-enynes under Au(I)-catalysis, this work describes the first general 5-*exo* alkoxycyclization. (*E*)-1,3-Dien-5-ynes undergo a regio- and stereoselective 5-*exo* Au(I)-catalyzed cyclization delivering alkylidencyclopentenes, whereas their *Z*-isomers evolve via a formal 6-*endo* cyclization. DFT calculations predict that a highly stabilized carbocation plays a crucial role in the outcome of the process.