CHEMISTRY
A EUROPEAN JOURNAL

.FULL PAPER

DOI: 10.1002/chem.200((will be filled in by the editorial staff))

Gold(I)-Catalyzed Cycloisomerizations and Alkoxycyclizations of *ortho*-(Alkynyl)styrenes

Ana M. Sanjuán,[a] Muhammad A. Rashid,[a,b] Patricia García-García,[a] Alberto Martínez-Cuezva,[a,c] Manuel A. Fernández-Rodríguez,[a] Félix Rodríguez,[d] and Roberto Sanz*[a]

Abstract: Indenes and related polycyclic structures have been efficiently synthesized by gold(I)-catalyzed cycloisomerizations of appropriate *ortho*-(alkynyl)styrenes. Disubstitution at the terminal position of the olefin was demonstrated to be essential to obtain products originating from a formal 5-*endo*-*dig* cyclization. Interestingly, a complete switch in the selectivity of the cyclization of *o*-(alkynyl)-α-methylstyrenes from 6-*endo* to 5-*endo* was observed by adding an alcohol to the reaction media. This allowed the synthesis of interesting indenes bearing an all-carbon quaternary center at C-1. Moreover, dihydrobenzo[*a*]fluorenes can be obtained from substrates bearing a secondary alkyl group at the *β*-position of the styrene moiety by a tandem cycloisomerization/1,2-hydride migration process.

In addition, diverse polycyclic compounds were obtained by an intramolecular gold-catalyzed alkoxycyclization of *o*-(alkynyl)styrenes bearing a nucleophile in their structure. Finally, the use of a chiral gold complex allowed access to elusive chiral 1*H*-indenes in good enantioselectivities.

Keywords: cycloisomerization • cyclization • gold • indenes • asymmetric catalysis

Introduction

Transition metal-catalyzed cyclization of polyunsaturated substrates has nowadays become one of the most valuable tools for the straightforward synthesis of cyclic compounds under mild conditions.[1] These processes frequently provide a significant increase in structural complexity furnishing functionalized molecules not easily accessible by conventional methodologies from rather simple precursors. Among all these strategies, the π-activation of alkynes by carbophilic Lewis acids, mainly gold or platinum derived complexes, towards attack by different nucleophiles has prompted the development of an impressive array of catalytically useful transformations.[1,2] In this context, the use of olefins as internal nucleophiles has been extensively studied and therefore, a wide number of synthetically and mechanistically attractive metal-catalyzed cycloisomerizations of enynes have been described.[3] The outcome of these rearrangements is determined by diverse factors, including the reaction conditions, the catalyst and the nature and position of the different substituents of the enyne.[4]

In particular, 1,3-dien-5-ynes, including *ortho*-(alkynyl)styrenes, although less studied than parent 1,5-enynes,[5] have exhibited interesting transformations. Simple conjugated dienynes afford benzene derivatives through varied cycloaromatization mechanisms[6] regardless of the dienyne and the catalyst employed.[7] In contrast, the substitution pattern of the olefin plays a critical role in the cycloisomerization of *ortho*-(alkynyl)styrenes (Scheme 1). Thus, the skeletal rearrangement of *o*-(alkynyl)styrenes *α*-substituted and mono- or non-*β*-substituted to produce naphthalenes through a 6-*endo* cyclization process has been described using complexes derived from several metals such as W,[8]

[a] A. M. Sanjuán, Dr. M. A. Rashid, Dr. P. García-García, Dr. A. Martínez-Cuezva, Dr. M. A. Fernández-Rodríguez, Prof. Dr. R. Sanz
Área de Química Orgánica, Departamento de Química
Facultad de Ciencias, Universidad de Burgos
Pza. Misael Bañuelos s/n, 09001-Burgos (Spain)
Fax: (+34) 947-258831
E-mail: rsd@ubu.es
Homepage: http://www2.ubu.es/ginves/cien_biotec/sintorg/uk/index.htm

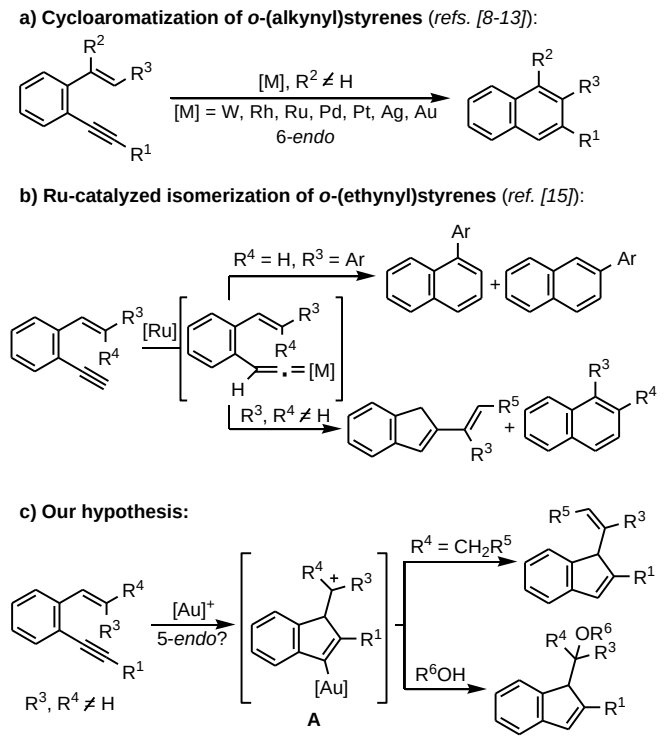
[b] Dr. M. A. Rashid
Current address: Department of Chemistry
University of Agriculture, Faisalabad (Pakistan)

[c] Dr. A. Martínez-Cuezva
Current address: Departmento de Química Orgánica, Facultad de Química
Regional Campus of International Excellence "Campus Mare Nostrum",
Universidad de Murcia, Murcia (Spain)

[d] Dr. F. Rodríguez
Instituto Universitario de Química Organometálica "Enrique Moles",
Universidad de Oviedo, C/Julián Clavería, 8, 33006, Oviedo (Spain)

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Full experimental procedures and characterization data for all the new compounds reported in this work.

Rh,[9] Ru,[9] Pd,[9-11] Pt,[9,11] Ag[12] or Au[9,13] as catalysts (Scheme 1a). Related cycloaromatizations of *o*-(alkynyl)biaryls also occurred allowing the efficient preparation of substituted phenanthrenes and other polycyclic heteroarenes.[14] Notably, a total 6-*endo* selectivity is usually achieved in these reported cyclizations and only in particular examples the 5-*exo* adducts are formed,[13a,c] whereas no products derived from a 5-*endo* cyclization are even detected. Moreover, Liu and co-workers have studied the ruthenium-catalyzed isomerization of *o*-(ethynyl)styrenes to give different products by a cascade reaction proceeding via formation of a vinylidene species (Scheme 1b).[15]



Scheme 1. Transition metal-catalyzed cycloisomerizations of *o*-(alkynyl)styrenes.

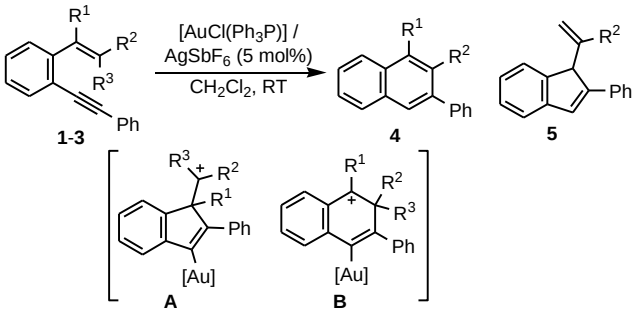
In this scenario we considered that *o*-(alkynyl)styrenes could evolve through a different reaction pathway to give 1*H*-indenes derivatives (Scheme 1c). Thus, our experience in the field of gold-catalysis[16] led us to suggest that *o*-(alkynyl)styrenes possessing an internal acetylene and a disubstituted alkene (R^3, $R^4 \neq H$) should evolve through a 5-*endo-dig* cycloisomerization to give intermediate **A**. An elimination reaction from this cationic intermediate or treatment with an appropriate nucleophile (i.e. an alcohol) should deliver the desired 1*H*-indenes derivatives. Therefore, in a recent publication we have reported the gold(I)-catalyzed cyclization and alkoxycyclization of *o*-(alkynyl)styrenes disubstituted at the terminal position of the olefin. This work proved our hypothesis and it allowed us to develop an efficient method to get functionalized 1*H*-indenes (Scheme 1c).[17] In addition, we have also described an efficient synthesis of dihydrobenzo[*a*]fluorenes from substrates bearing a secondary alkyl group at the *β*-position of the styrene moiety.[18] Herein, we wish to report a detailed study on the evolution of *o*-(alkynyl)styrenes under gold catalysis.

Results and Discussion

Preliminary results:

To test our hypothesis regarding the influence of the substitution pattern at the olefin moiety on the outcome of the cycloisomerization, representative *o*-(phenylethynyl)styrenes **1-3** were prepared. Starting from the simplest *o*-(alkynyl)-styrene **1a** ($R^1 = R^2 = R^3 = H$) we did not observe reaction in the presence of the cationic gold(I) complex generated in situ from 5 mol% of [$AuCl(Ph_3P)$] and 5 mol% of $AgSbF_6$ (Table 1, entry 1). By using the β-monosubstituted (R^2 = Me) *o*-(phenylethynyl)styrene **1b**, a mixture of unidentifiable compounds was formed (Table 1, entry 2). Next, we tried the reaction with the α-substituted (R^1 = Me) *o*-(phenylethynyl)styrenes **2a-c** (Table 1, entries 3–5). Considering previous reports (see Scheme 1a) and also the stability of the two possible formal intermediates **A** and **B** formed after activation of the alkyne and further attack of the olefin, we expected in these cases the formation of the corresponding 6-*endo* cyclization products. In fact, we isolated the naphthalene derivatives **4a-c** in very high yield. Finally, a key experiment was performed with the β,β-dibsubstituted ($R^2 = R^3$ = Me) *o*-(phenylethynyl)styrene **3a** (Table 1, entry 6). As previously commented, we thought that in this case the reaction should proceed through intermediate **B** to give the 5-*endo* product. Pleasantly, our plan came true and accordingly we observed how the reaction cleanly evolved to afford the indenyl derivative **5a** in a very high yield (88%).[19] Remarkably, the reaction took place with complete regioselection as we did not observe the formation of products coming from 6-*endo* or 5-*exo* additions of the alkene to the carbon−carbon triple bond. A catalyst screening showed that several cationic gold(I) complexes, either preformed (such as [$AuNTf_2(Ph_3P)$]) or generated in situ with silver salts, were able to promote the indene formation within 30 min whereas no reaction was observed with metal complexes such as $AgSbF_6$, $PtCl_2$, [$PtCl_2$(cod)], CuI, $AuCl_3$, AuCl or [$AuCl(Ph_3P)$].[20]

Table 1. Gold(I)-catalyzed cycloisomerization of model *o*-(alkynyl)styrenes **1-3**.[a]



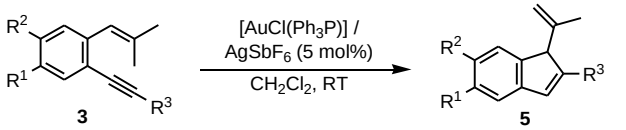
entry	enyne	R^1	R^2	R^3	product	yield [%][b]
1	**1a**	H	H	H	–[c]	–
2	**1b**	H	Me	H	–[d]	–
3	**2a**	Me	H	H	**4a**	83
4	**2b**	Me	Me	H	**4b**	84
5	**2c**	Me	Ph	H	**4c**	88
6	**3a**	H	Me	Me	**5a**	88

[a] Reactions conducted using 0.5 mmol of *o*-(alkynyl)styrene derivative **1-3** in CH_2Cl_2 (1 mL) at RT. [b] Yield of isolated product based on starting material **1-3**. [c] Starting material was recovered. [d] Unidentifiable mixture of products based on ^{1}H NMR analysis of the crude.

Synthesis of 1*H*-indenes by cycloisomerization of 2′,2′-disubstituted *o*-(alkynyl)styrenes 3:

The previous study allowed us to identify the structural requirements of the initial *o*-(alkynyl)styrenes to get 1*H*-indene derivatives.[21] At this point, the importance of developing new methods to synthesize this skeleton should be remarked. Thus, 1*H*-indenes are found in pharmaceuticals,[22] functional materials[23] or as ligands in metal catalysis.[24] Therefore, the present novel transformation seemed of interest and then, a deeper study on its scope and limitations was performed. First, reactions of 2´,2´-dimethyl *o*-(alkynyl)styrenes **3** with diverse substitution at the central phenyl ring as well as in the alkyne terminus were conducted under the optimized conditions; the results are given in Table 2. These data show that the formation of the corresponding indene derivatives is compatible with the presence of both electron-withdrawing (entries 2–3) and electron-donating groups (entries 4 and 8) at the aromatic ring. Moreover, different substituents at the alkyne (R^3), including aromatic (entries 1–4), heteroaromatic (entry 5), cycloalkenyl (entry 6), linear- and cyclo-alkyl (entries 7–10), and heteroatomic moieties (entry 11), are well tolerated. However, substrates bearing R^3 groups such as H, I or TMS gave only decomposition products under these conditions.

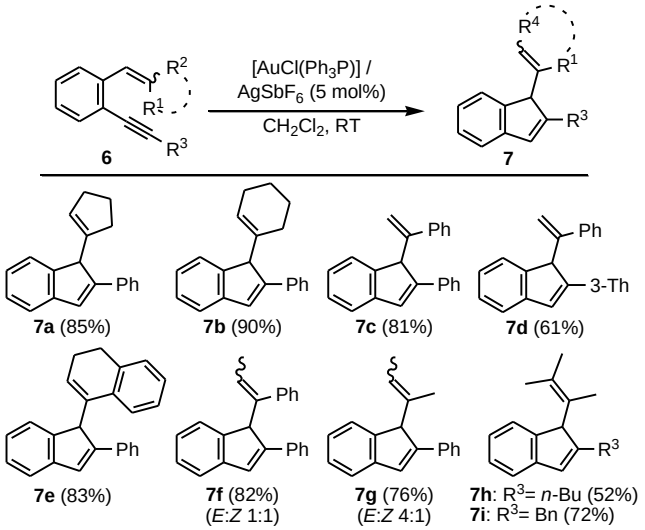
Table 2. Gold(I)-catalyzed cycloisomerization of 2´,2´-dimethyl *o*-(alkynyl)styrenes **3**.[a]



entry	**3**	R^1	R^2	R^3	**5**	yield [%][b]
1	**3a**	H	H	Ph	**5a**	88
2	**3b**	H	F	Ph	**5b**	80
3	**3c**	H	Br	Ph	**5c**	88
4	**3d**	-OCH$_2$O-		Ph	**5d**	70
5	**3e**	H	H	3-Th[c]	**5e**	94
6	**3f**	H	H	*c*-C$_6$H$_9$[d]	**5f**	40[e]
7	**3g**	H	H	*n*-Bu	**5g**	73
8	**3h**	OMe	OMe	*n*-Bu	**5h**	64
9	**3i**	H	H	*c*-C$_3$H$_5$[f]	**5i**	76
10	**3j**	H	H	*c*-C$_6$H$_{11}$[g]	**5j**	87
11	**3k**	H	H	SPh	**5k**	83

[a] Reactions conducted using 0.5 mmol of *o*-(alkynyl)styrene derivative **3** in CH_2Cl_2 (1 mL) at RT. [b] Yield of isolated product based on starting material **3**. [c] 3-Thienyl. [d] Cyclohexenyl. [e] Using [AuNTf$_2$(Ph$_3$P)] as catalyst; partial decomposition of the product and/or substrate accounts for the low yield obtained. [f] Cyclopropyl. [g] Cyclohexyl.

Next, we decided to explore the regio- and stereoselectivity of the cycloisomerization with regard to the substitution at the terminal carbon atom of the alkene. So, *o*-(alkynyl)styrenes **6** possessing different aliphatic and aromatic groups at this position were prepared and their reactions under the optimized conditions were conducted. As a result, several indenes **7** with both (hetero)aromatic and aliphatic groups at C2 were accessible from dienynes **6** with total regioselection and in good yields (Scheme 2). For instance, reactions of *o*-(alkynyl)styrenes **6a-b** possessing an aliphatic ring as R^1-R^2 substituent at the terminal position of the olefin, as well as **6c-f** with mixed aliphatic-aromatic substitution at the same carbon, efficiently furnished the corresponding carbocycles **7a-f**. Moreover, substrates **6g-i** bearing two different acyclic aliphatic groups at the *β*-position of the styrene moiety also produced the indene derivatives **7g-i**. In those cases where the formation of two *Z*/*E* isomers was possible (7**f**,**g**) we observed mixtures of these two isomers, the *Z*/*E* ratio of which was independent of the substrate stereochemistry. As expected, formation of internal alkenes was preferred. Thus, in the reaction to get indenes **7g-i** we only observed the formation of less than 10% of the alternative isomeric indenes having a terminal alkene.

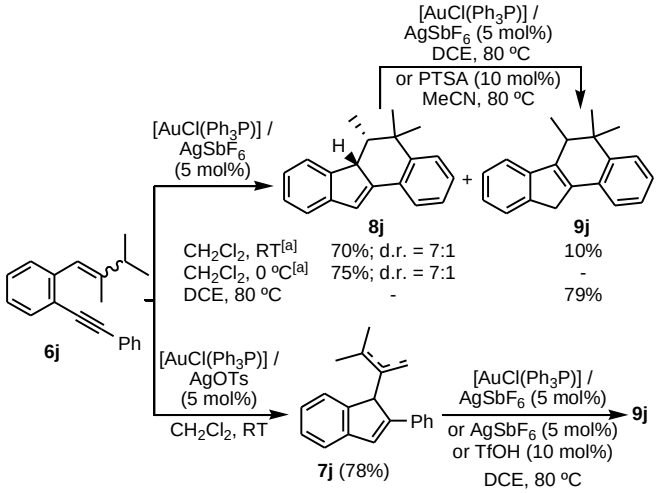


Scheme 2. Gold(I)-catalyzed cycloisomerization of *o*-(alkynyl)styrenes **6** bearing different substituents at the olefin. 3-Th = 3-Thienyl

It should be noted that all the reactions depicted in Table 2 and Scheme 2 exclusively afforded in high yields the corresponding indene derivatives as a result of a 5-*endo* cycloisomerization and not even traces of regioisomeric 6-*endo* or 5-*exo* adducts were detected.

Interestingly, a new reaction pathway was observed for *o*-(alkynyl)styrene **6j** having an isopropyl and a methyl at the terminal position of the alkene (Scheme 3). Thus, its reaction under the developed optimized conditions gave less than 10% of the expected indene derivative **7j**. Instead, we observed the formation of a mixture of the tetracyclic compounds **8j** (70%) and **9j** (10%). Interestingly, these regioisomeric dihydrobenzo[*a*]fluorenes are the result of a formal gold-catalyzed [3+3] cycloaddition.[25] After screening several reaction parameters,[18] we determined that **8j** was selectively obtained as a ca. 7:1 mixture of diastereoisomers[26] in a 75% yield when conducting the reaction at 0 ºC. In addition, **9j** was exclusively isolated in 79% yield by performing the reaction in 1,2-dichloroethane (DCE) at 80 ºC. Remarkably, our initially desired indene derivative **7j** could be selectively isolated (78% yield) when the reaction was performed with the catalyst generated in situ from [AuCl(Ph$_3$P)] and silver tosylate (Scheme 3). In addition, indene derivative **7j** could be transformed into the dihydrobenzo[*a*]fluorene **9j** by its treatment with our initial catalytic system ([AuCl(Ph$_3$P)] / AgSbF$_6$) but at 80 ºC in 1,2-dichloroethane (DCE). On the contrary, when this experiment was performed at room temperature we did not observe the formation of the regioisomer **8j** indicating that this fluorene derivative is not directly derived from indene **7j**. Moreover, compound **9j** could also be obtained from **7j** by its treatment with catalytic amounts of AgSbF$_6$ (5 mol%) or triflic acid (10 mol%) in DCE at 80 ºC. In a similar way, isolated dihydrobenzo[*a*]fluorene **8j** could be transformed into its regioisomer **9j** under the initial reaction conditions that imply the use [AuCl(Ph$_3$P)] / AgSbF$_6$ (5 mol%), but raising the temperature to 80 ºC. Also, the same transformation could be observed under acidic catalytic conditions

(10 mol% of PTSA) at 80 ºC (Scheme 3). All these experiments seem to indicate that formation of compound **9j** is the result of a simple isomerization reaction of the initially formed compound **8j** under acid conditions. In a similar way, the transformation of **7j** into **9j** seems to be a protic acid catalyzed process.[27]



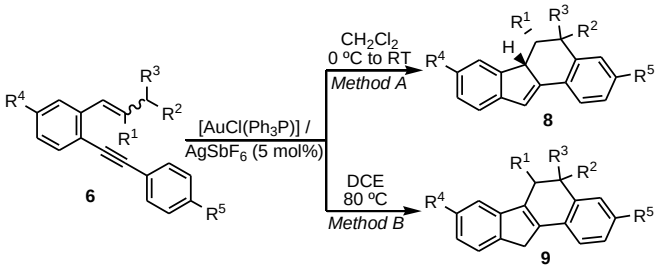
Scheme 3. Gold(I)-catalyzed cycloisomerization of *o*-(alkynyl)styrene **6j**. [a] <10% of **7j** were also formed under these reaction conditions.

Synthesis of dihydrobenzo[*a*]fluorenes 8 and 9 from *o*-(alkynyl)styrenes 6j-w:

Considering the novelty and interest of this transformation, as well as the common occurrence of the benzo[*a*]fluorene core in natural products possessing biological activity[28] we decided to explore the extent of its scope. Thus, two methods *A* and *B* were employed to selectively obtain dihydrobenzo[*a*]fluorenes **8** and **9** (Table 3). As previously observed for **6j** (entry 1), under the method *A* reaction conditions (0 ºC or RT depending on the substrate) 6,6a-dihydro-5*H*-benzo[*a*]fluorenes **8j-t** could be obtained in good yields from *o*-alkynylstyrenes **6j-t**.[29] High diastereoselectivities, ranging from 5:1 to >20:1, were observed in all cases. In the other hand, by using the method *B* reaction conditions a series of 6,11-dihydro-5*H*-benzo[*a*]fluorenes **9** were synthesized with total selectivity and very good yields (Table 3).

It should be noted that the process works nicely with either electron-withdrawing (entries 3–4) or electron-donating (entries 5–6) aryl substituents at the triple bond of the starting material, as well as with diverse substitution patterns at the alkene, provided that one of these groups is a secondary alkyl (entries 7–13). Particularly remarkable is the reaction of substrates **6r-t** (entries 14–19). These substrates are monosubstituted at the β-carbon of the styrene moiety (R^1 = H) and it should be noted that this type of substituted enyne derivatives did not give positive results in our initial experiments (see Table 1, entry 2). Here, for the first time we observed a clean evolution of these compounds to efficiently afford the corresponding formal [3+3] cycloadducts.

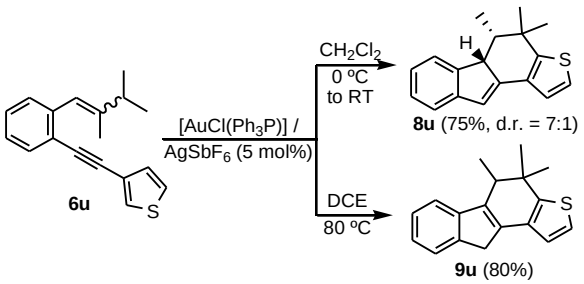
Table 3. Synthesis of dihydrobenzo[*a*]fluorenes **8** and **9**.[a]



ent.	**6**	R^1	R^2	R^3	R^4	R^5	d.r.[b]	yield (**8**) [%][c]	yield (**9**) [%][c]
1	**6j**	Me	Me	Me	H	H	7:1	75	79
2	**6k**	Me	Me	Me	H	Cl	5:1	81[d]	81
3	**6l**	Me	Me	Me	H	OMe	6:1	79	86[d]
4	**6m**	Me	Me	Et	H	H	[e]	68[d]	–[f]
5	**6n**	Me	–$(CH_2)_5$–		H	H	>20:1	75[d]	84
6	**6o**	Et	Me	Me	H	H	5:1	71[d]	–[f]
7	**6p**	Ph	Me	Me	H	H	>20:1	70[d]	71
8	**6q**	Ph	–$(CH_2)_5$–		H	H	–	–[g]	80
9	**6r**	H	Me	Me	H	H	–	72	72
10	**6s**	H	–$(CH_2)_5$–		H	H	–	67	78
11	**6t**	H	Me	Me	Br	H	–	76	83

[a] Reactions conducted using 0.5 mmol of *o*-(alkynyl)styrene derivative **6** in CH_2Cl_2 (1 mL) at 0 ºC to RT (*Method A*) or in DCE (1 mL) at 80 ºC (*Method B*). [b] Diastereomeric ratio of the corresponding product **8** determined by ^{1}H NMR of the crude reaction mixture. [c] Yield of isolated product based on starting material **6**. [d] Reaction conducted throughout at RT. [e] Obtained as a ca. 6:3:2:1 mixture of diastereomers. [f] Reaction not performed under *Method B*. [g] Reaction not performed under *Method A*.

We have also studied the applicability of these reactions for the construction of other polycyclic frameworks by changing the substituent at the triple bond (Scheme 4). In this sense, *o*-alkynylstyrene **6u** bearing a thienyl group reacted efficiently to afford the corresponding tetracyclic adducts **8u** and **9u** under conditions *A* and *B*, respectively. Nevertheless, reactions of substrates **6v-w**, possessing indolyl and cyclohexenyl groups linked to the triple bond and carried out under method *A* conditions, gave mixtures of the desired polycyclic compounds **8** and the corresponding indene derivatives **7** (see Supporting Information). In these cases, thermal conditions *B* led to low yields probably due to partial decomposition and, surprisingly, did not improve the proportion of [3+3] adduct over indenes **7**.

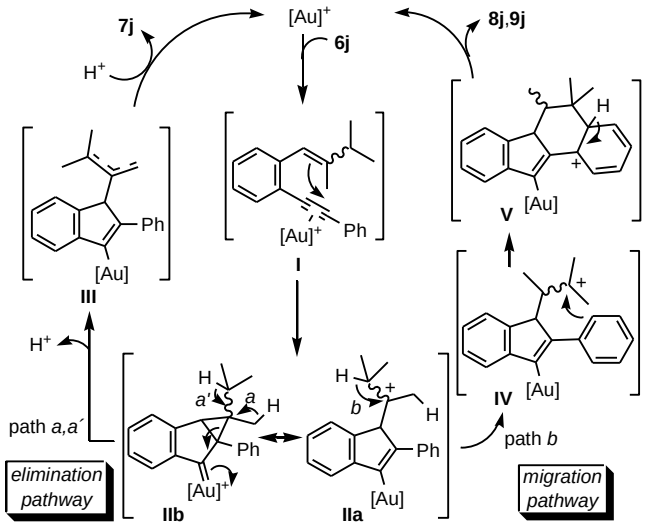


Scheme 4. Gold(I)-catalyzed cycloisomerization of *o*-(alkynyl)styrenes **6u**.

Mechanism of cycloisomerization of *o*-(alkynyl)styrenes:

According to all these results we propose the mechanism shown in Scheme 5 to explain the formation of indenes **5** and **7** and

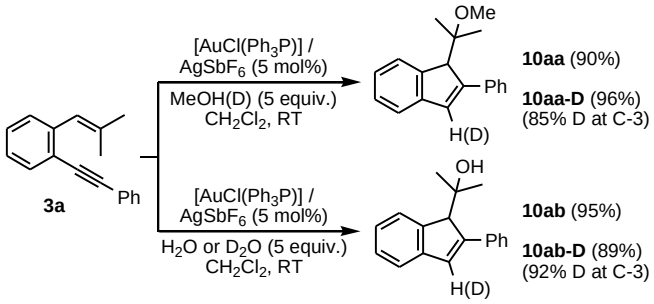
dihydrobenzo[*a*]fluorenes **8** and **9**. The proposal is illustrated for the model substrate **6j**.[30] Thus, we suppose that the reaction is initiated by coordination of the cationic gold complex to the triple bond of the starting *o*-(alkynyl)styrene **6j** to give intermediate **I**. An intramolecular nucleophilic attack by the olefin leads to the cationic intermediate **II**, which can be represented as the contribution of resonance structures **IIa** and **IIb** that delocalize the positive charge along different positions of the molecule. Elimination of a proton in this intermediate, (path *a*/*a'*; elimination pathway), furnishes the vinyl-gold intermediate **III**, which after a protodemetalation reaction gives indene **7j** and releases the gold catalyst for a new cycle. On the other hand, intermediate **II** could also undergo a hydride migration, giving rise to cationic intermediate **IV** (path *b*; migration pathway). The subsequent Friedel–Crafts-type alkylation reaction affords the dihydrobenzo[*a*]fluorene derivative **V**, which after protodemetalation furnishes compound **8j**, regenerating the catalytic species.[31] So, the different behaviour observed for *o*-(alkynyl)styrene **6j**, which leads to **7j** or **8j** depending on the counterion of the gold complex, could be understood considering that the carbocationic intermediate **II** would evolve through the elimination pathway to afford **7j**, when the relatively basic tosylate anion is used. On the contrary, in the presence of less basic SbF_6^- anion the 1,2-hydride migration would predominantly take place to finally produce **8j**. Also, formation of fluorene derivative **9j** from indene **7j** can be easily explained through a protic acid–catalyzed reaction implying the protonation of the alkene,[27] which would afford a cationic gold-free intermediate analogous to **IV**, followed by a Friedel–Crafts-type alkylation reaction. Finally, it should be noted that the formation of indene derivatives **5** from (alkynyl)styrenes **3** could be understood through a mechanism analogue to that shown for the formation of indene derivative **7j**.



Scheme 5. Proposed mechanisms for the formation of adducts **7**-**9** illustrated for model substrate **6j**.

Synthesis of oxygen-functionalized 1*H*-indenes:

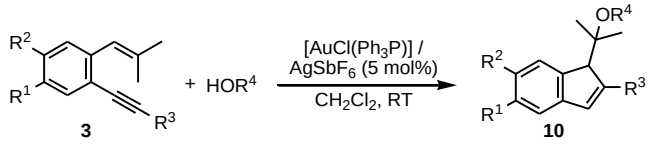
Considering the above mechanism (Scheme 5), we thought that intermediate **II** could be trapped by the addition of an appropriate external nucleophile to the reaction media, and thus, new products with enhanced complexity could be easily obtained. Pleasantly, reactions of the model substrate **3a** conducted under the optimized conditions in the presence of 5 equivalents of methanol or water exclusively afforded the oxygen functionalized 1*H*-indenes **10aa** and **10ab** in excellent yields (Scheme 6). Moreover, parallel reactions using MeOD or D_2O as the nucleophile gave the deuterated compounds **10aa-D** and **10ab-D** that displayed, respectively, 85% and 92% deuterium incorporation at C-3.



Scheme 6. Gold(I)-catalyzed alkoxycyclization of *o*-(alkynyl)styrene **3a**.

The scope of the alkoxycyclization process[32] to produce functionalized indenes[33] was then analyzed. First we found that besides methanol and water (Table 4, entries 1–2) other primary alcohols, including functionalized ones such as allylic alcohol or 2-bromoethanol, could be successfully employed as external nucleophiles in this transformation (entries 3–5). Even the isopropoxy derivative **10af** was obtained as the major adduct in 81% yield by using 20 equivalents of isopropanol as the nucleophile, though the competitive formation of **5a** took place in a small amount (entry 6). Then, using methanol and/or water as nucleophile a variety of functionalized indenes **10** with selected substitution at R^1, R^2 and R^3 were synthesized (entries 7–19). As expected by the results obtained in the cycloisomerization in the absence of nucleophile the reaction tolerates both electron-withdrawing (entries 7–10) and electron-donating (entries 11–12) groups at the internal phenyl ring as well as a broad range of substituents at the triple bond including (hetero)aromatic (entries 7–14), (cyclo)alkyl (entries 15–18), and heteroatomic moieties (entry 19). All these reactions were completely selective and we did not observe the formation of additional products derived from other possible reaction pathways. Thus, the corresponding indenes **10** were isolated in good to excellent yields.

Table 4. Gold(I)-catalyzed synthesis of oxygen-functionalized 1*H*-indenes **10**.[a]



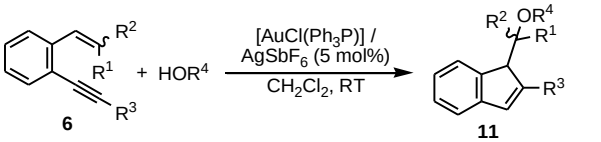
entry	**3**	R^1	R^2	R^3	R^4	**10**	yield [%][b]
1	**3a**	H	H	Ph	Me	**10aa**	90
2	**3a**	H	H	Ph	H	**10ab**	95
3	**3a**	H	H	Ph	Et	**10ac**	85
4	**3a**	H	H	Ph	allyl	**10ad**	93
5	**3a**	H	H	Ph	$(CH_2)_2Br$	**10ae**	85
6[c]	**3a**	H	H	Ph	*i*-Pr	**10af**	81[d]
7	**3b**	H	F	Ph	Me	**10ba**	95
8	**3b**	H	F	Ph	H	**10bb**	76
9	**3c**	H	Br	Ph	Me	**10ca**	87
10	**3c**	H	Br	Ph	H	**10cb**	78[e]
11	**3d**	$–OCH_2O–$		Ph	Me	**10da**	98
12	**3d**	$–OCH_2O–$		Ph	H	**10db**	72

13	**3e**	H	H	3-Th[f]	Me	**10ea**	94
14	**3e**	H	H	3-Th[f]	H	**10eb**	84
15	**3g**	H	H	*n*-Bu	Me	**10ga**	81
16	**3g**	H	H	*n*-Bu	H	**10gb**	78[e]
17	**3i**	H	H	*c*-C_3H_5[g]	Me	**10ia**	77
18	**3j**	H	H	*c*-C_6H_{11}[h]	Me	**10ja**	80
19	**3k**	H	H	SPh	Me	**10ka**	84

[a] Reactions conducted using 0.5 mmol of *o*-(alkynyl)styrene derivative **3** and 5 equiv. of nucleophile in CH_2Cl_2 (1 mL) at RT. [b] Isolated yield. [c] Reaction performed using 20 equiv. of *i*-PrOH. [d] 8% of **5a** was also formed. [e] Using $AuNTf_2(Ph_3P)$ as catalyst. [f] 3-Thienyl. [g] Cyclopropyl. [h] Cyclohexyl.

To further test the scope of the process we explored the reaction with starting materials where the substitution at the alkene terminal carbon atom was different from two methyl groups. Some conclusions could be extracted from the results obtained and depicted in Table 5. The alkoxycyclization is completely selective with *o*-(alkynyl)styrenes 2´,2´-disubstituted by either aliphatic or aromatic groups allowing the preparation of several functionalized indenes **11** in good to excellent yields (entries 1–4). Moreover, and no surprisingly, the addition of the external nucleophile to the terminal carbon of the olefin was affected by the steric hindrance at that position as it was revealed for substrates **6g** and **6j**. Thus, reaction of **6g**, where a methyl group was replaced by an ethyl group, furnished the desired indene **11ga** in a moderate 55% yield with the concomitant formation of **7g** as a mixture of isomers and in a 29% yield (entry 5). In the case of substrate **6j**, bearing a methyl and an *iso*-propyl group at the olefin, the incorporation of methanol in the final adduct was totally suppressed and, therefore, a mixture of compounds **7**-**9j** was detected (entry 6). On the other hand, regarding the stereoselectivity of the methoxycyclization, the experiment conducted with a single isomer of **6c** gave methoxy-functionalized indene **11ca** as a 3:1 mixture of diastereoisomers (entry 3). In the same way, the reaction of **6d**, enriched in one geometrical isomer (6:1), produced the product **11da** with a lower diastereoselectivity (d.r. = 3:1) (entry 4). These results clearly revealed that the alkoxycyclization is not diastereospecific.

Table 5. Gold(I)-catalyzed alkoxycyclization of *o*-(alkynyl)styrenes **6** bearing different substituents at the terminal position of the olefin.[a]

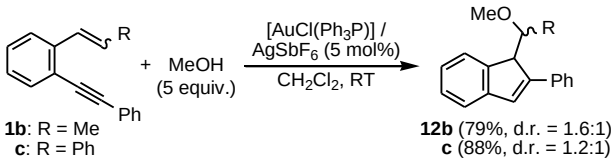


6 **11**

ent.	**6**	d.r. (*E*:*Z*)	R^1	R^2	R^3	R^4	**11**	d.r	yield [%][b]
1	**6a**	–	$-(CH_2)_4-$		Ph	Me	**11aa**	–	96
2	**6a**	–	$-(CH_2)_4-$		Ph	H	**11ab**	–	71
3[c]	**6c**	1:0	Ph	Me	Ph	Me	**11ca**	3:1	88
4[c]	**6d**	6:1	Ph	Me	3-Th[d]	Me	**11da**	3:1	75
5[e]	**6g**	1.5:1	Me	Et	Ph	Me	**11ga**	1.5:1	55[f]
6	**6j**	4:1	Me	*i*Pr	Ph	Me	**–**	–	–[g]

[a] Reactions conducted using 0.5 mmol of *o*-(alkynyl)styrene derivative **6** and 5 equiv. of MeOH or 20 equiv of H_2O (entry 2) in CH_2Cl_2 (1 mL) at RT. [b] Isolated yield. [c] Using $[AuNTf_2(Ph_3P)]$ as catalyst. [d] 3-Thienyl. [e] Performed with 100 equiv. of MeOH. [f] 29% of **7g** was also formed. [g] A mixture of adducts **7**-**9j** was obtained.

While working on the generalization of this reaction we obtained some unexpected results. Thus, as shown in Table 1 (entry 2), the reaction of enyne derivative **1b** monosubstituted at the *β*-position of the styrene led to a mixture of unidentified products when the reaction was performed under the conventional reaction conditions. Surprisingly, the same reaction performed in the presence of methanol (5 equiv.) led to the formation of methoxy-functionalized indene **12b** in good yield (Scheme 7). In the same sense, *o*-(phenylethynyl)-*β*-phenylstyrene **1c** reacted in the presence of methanol to afford **12c** in high yield (Scheme 7).

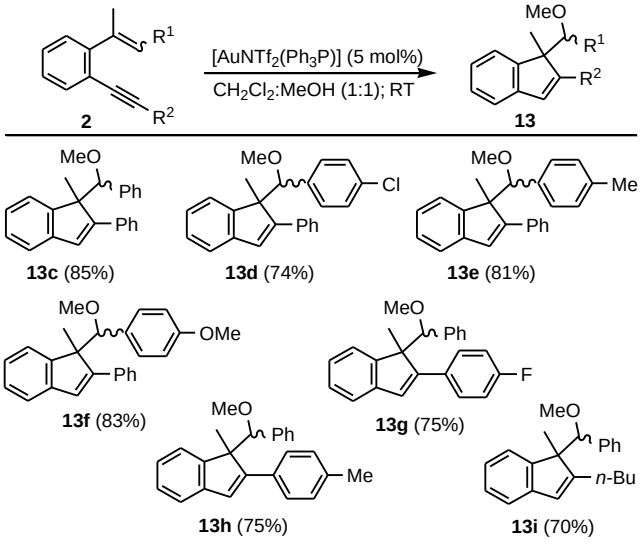


1b: R = Me
c: R = Ph

12b (79%, d.r. = 1.6:1)
c (88%, d.r. = 1.2:1)

Scheme 7. Gold(I)-catalyzed alkoxycyclization of *o*-(alkynyl)styrenes **1**, monosubstituted at the terminal position of the olefin.

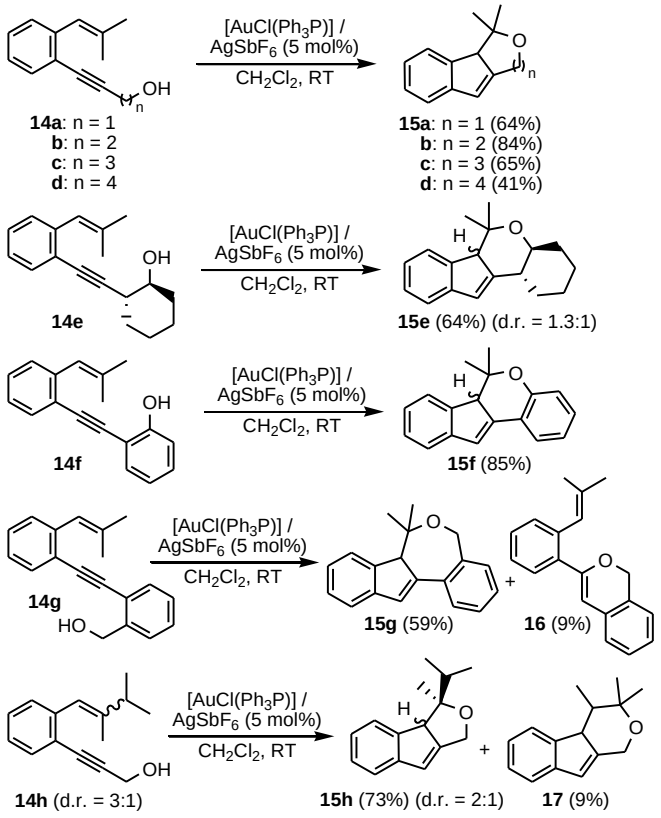
Other surprising results were found with enyne derivatives **2** substituted at the *α*-position of the styrene. Under conventional reaction conditions (see Table 1) these reagents selectively evolve to give naphthalene derivatives through a 6-*endo* cyclization process. However, an interesting switch of selectivity was observed when the reactions were performed with methanol as cosolvent of the process (Scheme 8).[34] Under these conditions 1*H*-indenes **13c-i** were isolated in high yields (ca. 2–1.5:1 mixture of diastereoisomers) as a result of a 5-*endo*-*dig* cyclization process.[35] Notably, the alkoxycyclization occurred regardless the electronic nature of the aromatic groups at both the *β*-carbon of the styrene moiety and the alkyne terminus. In addition, the methodology also allowed the synthesis of alkyl-substituted indenes at C-2 as demonstrated for **13i** (Scheme 9). Interestingly, in this reaction an all-carbon quaternary stereocenter is generated at C-1.



Scheme 8. Gold(I)-catalyzed synthesis of oxygen-functionalized 1*H*-indenes **13** bearing a quaternary centre at C-1.

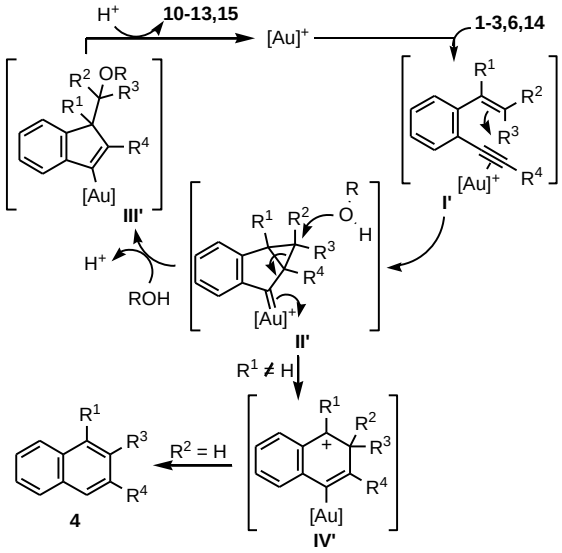
With the aim of accessing diverse polycyclic compounds we also tried the alkoxycyclization in an intramolecular fashion. To this end, we synthesized *o*-(alkynyl)styrenes **14a-h** possessing a hydroxy group in their structure. Pleasantly, reaction of substrates **14a-c** proceeded smoothly under the standard conditions, generating indenes fused to 5-, 6- and 7-membered oxygen-containing

heterocycles in good to high yields (Scheme 9). Even **15d**, a tricyclic compound with a fused oxocane ring, could be obtained in a moderate 41% yield. Moreover, *o*-(alkynyl)styrenes **14e-g**, where the nucleophile is appended to an additional cycle, also partook efficiently in the intramolecular alkoxycyclization reaction, giving rise to the corresponding tetracycles. All these reactions were highly selective, and only in the case of **14g** formation of minor amounts of the product **16**, coming from direct attack of the alcohol to the triple bond was observed.[36] Finally, we tried the reaction with the *o*-(alkynyl)styrene **14h**, possessing an isopropyl group at the terminal carbon of the olefin. It should be noted that the reaction of substrates with this type of substitution pattern did not react in an intermolecular fashion with an alcohol (MeOH) as demonstrated in our attempt shown in Table 5 (entry 6). However, the reaction of **14h** afforded as major product the furan derivative **15h** along with a very minor amount of pyran derivative **17** (Scheme 9).



Scheme 9. Synthesis of polycyclic compounds **15** by gold(I)-catalyzed intramolecular alkoxycyclization of *o*-(alkynyl)styrenes **14**.

The mechanism of all these alkoxycyclization processes would initially follow a mechanism similar to that commented before for the simple cycloisomerization reaction (see Schemes 5 and 10). Thus, the reaction would start by coordination of the cationic gold complex to the triple bond of starting *o*-(alkynyl)styrenes **1-3, 6** or **14**, followed by intramolecular nucleophilic attack of the olefin leading to cationic gold carbeonid intermediate **II'**.[37] However, in the presence of water or an alcohol, instead of the proton elimination suggested in Scheme 5, this intermediate **II'** would be trapped by the nucleophile generating vinyl gold intermediate **III'**. After a protodemetalation reaction, compounds **10**-**13** or **15** are formed and the catalytic species are regenerated (Scheme 10). As previously noted, a switch in the selectivity of the cyclization is observed for *o*-(alkynyl)-α-methylstyrenes **2** and thus, indenes are obtained in the presence of methanol and naphthalenes in its absence. These facts could be explained by supposing that in the presence of methanol the corresponding intermediate **II'** (R^2 = H; R^1, $R^3 \neq$ H) rapidly reacts with the nucleophile at the less hindered position to afford the indene derivatives **13**. However, in the absence of an appropriate nucleophile, a ring opening reaction of intermediate **II'** gives the more stable benzylic cation **IV'**, which finally produces the naphthalene derivative **4** by proton elimination and subsequent protodeauration (Scheme 10). In addition, the generation of a minor amount of pyran derivative **17** (Scheme 9) could be easily explained through the formation of intermediate **IV** (see Scheme 5 and Supporting Information).



Scheme 10. Proposed mechanism for the alkoxycyclization of *o*-(alkynyl)styrenes.

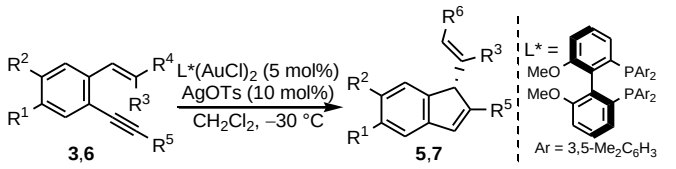
Enantioselective synthesis of 1*H*-indenes:

Once we had established the versatility of *o*-(alkynyl)styrenes as precursors of indene derivatives we thought on the possibility of preparing these adducts in an enantioselective fashion by using chiral gold catalysts. Remarkably, the synthesis of optically active indenes remains a challenge with only two recent strategies for the enantioselective synthesis of these compounds from achiral substrates having been published.[38] Both approaches are based on the use of boronic acid derivatives as starting materials and their coupling in tandem reactions catalyzed by chiral palladium complexes producing the corresponding indenes in good yields and variable enantioselectivities.[39]

In this context, it should be noted that although gold catalysis has witnessed tremendous activity in recent years, its application in asymmetric synthesis is an underdeveloped area.[40] Particularly, gold-catalyzed enantioselective processes involving alkyne activation are relatively scarce.[35,41]. Therefore, we were pleased to find that, after some optimization,[42] we were able to obtain indene derivatives with good enantiomeric excess using the combination (*S*)-3,5-xylyl-MeOBIPHEP-$(AuCl)_2$ / AgOTs as catalyst in dichloromethane at –30 ºC (Table 6). Under these optimized catalytic conditions we found high yields and enantioselectivities for *o*-(alkynyl)styrenes **3a-e,6a-b** where R^5 is an aromatic or heteroaromatic group (entries 1–4, 10–11). Interestingly, the possibility of increasing the enantiomeric excess of the final

products by a simple recrystallization has been demonstrated for indene **7b** that we were able to isolate with 92% *ee* (entry 11). However, starting materials **3f-k** having alkenyl, aliphatic or heteroatomic substitution in the alkyne lead to low enantiomeric excess (entries 5–9).

Table 6. Enantioselective synthesis of 1-alkenyl-1*H*-indenes **5** and **7**.[a]

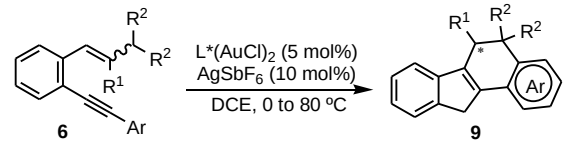


3,**6** **5**,**7**

entry	**3,6**	R^1	R^2	R^3	R^4	R^5	**5,7**	Yield [%][b]	*ee* [%][c]
1	**3a**	H	H	Me	Me	Ph	**5a**	81	82
2[d]	**3b**	H	F	Me	Me	Ph	**5b**	84	77
3[d]	**3d**	-OCH_2O-		Me	Me	Ph	**5d**	84	86
4	**3e**	H	H	Me	Me	3-Th[e]	**5e**	81	68
5	**3f**	H	H	Me	Me	*c*-C_6H_9[f]	**5f**	71	24
6[d]	**3g**	H	H	Me	Me	*n*-Bu	**5g**	80	20
7[d]	**3i**	H	H	Me	Me	*c*-C_3H_5[g]	**5i**	75	11
8[d]	**3j**	H	H	Me	Me	*c*-C_6H_{11}[h]	**5j**	43[i]	14
9[d]	**3k**	H	H	Me	Me	SPh	**5k**	77	5
10	**6a**	H	H	-$(CH_2)_4$-		Ph	**7a**	93	81
11	**6b**	H	H	-$(CH_2)_5$-		Ph	**7b**	96	80(92)

[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **3** or **6** in CH_2Cl_2 (0.6 mL) at −30 ºC for 3–4 days. [b] Isolated yield. [c] Determined by HPLC analysis, see Supporting Information; in brackets *ee* after recrystallization. [d] Reaction conducted at −20 ºC. [e] 3-Thienyl. [f] Cyclohexenyl. [g] Cyclopropyl. [h] Cyclohexyl. [i] 62% conversion.

Like indenes **5** and **7**, [3+3]-tetracyclic compounds **9** exhibit a stereogenic center in their structure and, therefore, we also attempted their enantioselective synthesis. Thus, under the best reaction conditions found,[43] selected dihydrobenzo[*a*]fluorenes **9** were prepared in good yields although with modest enantiomeric excess (Scheme 11). The significant decrease in the enantioselectivity compared with the analogous indenes could be at least partially explained considering the higher temperatures needed for the formation of the [3+3] adducts, as well as the lack of complete diastereoselectivity in the formation of adducts **8**.



6 **9**

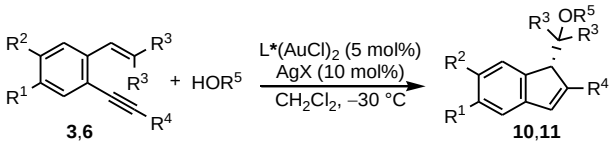
$R^1 = R^2$ = Me; Ar = Ph — **9j** (80% yield, 42% *ee*)
$R^1 = R^2$ = Me; Ar = *p*-$MeOC_6H_4$ — **9l** (89% yield, 32% *ee*)
R^1 = Me; R^2–R^2 = –$(CH_2)_5$–; Ar = Ph — **9n** (80% yield, 42% *ee*)
R^1 = Ph; R^2 = Me; Ar = Ph — **9p** (82% yield, 36% *ee*)
$R^1 = R^2$ = Me; Ar = 3-Thienyl — **9u** (79% yield; 34% *ee*)

Scheme 11. Enantioselective synthesis of [3+3] adducts **9**.

We also performed the enantioselective alkoxycyclization of *o*-(alkynyl)styrenes **3** and **6** (Table 7). The model substrate **3a** cyclizes in the presence of water and primary alcohols affording the corresponding functionalized indenes in high yields and good enantioselectivities (entries 1–4), that can be further improved by recrystallization, allowing the isolation of the final product even as a single enantiomer when methanol is used as the nucleophile. By using isopropanol as the nucleophile, the isopropoxy derivative **10af** was obtained with the highest *ee*, although as in the racemic reaction the competitive formation of **5a** took place in a small amount. Next, we carried out the alkoxycyclization of several *o*-alkynylstyrenes in the presence of water or methanol. Again, we obtained the corresponding indenes in good to excellent yields and high enantioselectivities when the substituent of the triple bond was an (hetero)aromatic ring, independently of the substitution in other positions of the substrate (entries 6–13 and 17–18). As expected by the results obtained in the cycloisomerization in the absence of an external nucleophile, non-aromatic alkyne substituted *o*-(alkynyl)styrenes **3g-k** led to lower enantioselectivities (entries 14–16). Unfortunately, all the efforts made to produce 1*H*-indenes **13** bearing an all-carbon quaternary enatioenriched centre at C-1 failed, we observed no reaction at low temperature and very low *ee* (<10%) and moderate yield at room temperature.

It is noteworthy that most of the functionalized indenes that have been synthesized could be isolated as a single enantiomer after recrystallization. Moreover, the absolute configuration of product **10ca** was determined to be *R* by using single crystal X-ray diffraction,[44] and the rest were assigned by analogy.

Table 7. Enantioselective synthesis of oxygen-functionalized 1*H*-indenes **10** and **11**.[a]



3,**6** **10**,**11**

ent	**3,6**	R^1	R^2	R^3	R^4	R^5	**10,11**	yield [%][b]	*ee* [%][c]
1	**3a**	H	H	Me	Ph	Me	**10aa**	99	88(>98)
2	**3a**	H	H	Me	Ph	H	**10ab**	93	86
3[d]	**3a**	H	H	Me	Ph	Et	**10ac**	88	81
4[d]	**3a**	H	H	Me	Ph	allyl	**10ad**	94	80
5[d]	**3a**	H	H	Me	Ph	*i*-Pr	**10af**	72[e]	92(98)
6	**3b**	H	F	Me	Ph	Me	**10ba**	93	82(>98)
7	**3b**	H	F	Me	Ph	H	**10bb**	88	86
8	**3c**	H	Br	Me	Ph	Me	**10ca**	95	80(>98)
9	**3c**	H	Br	Me	Ph	H	**10cb**	94	80(>98)
10	**3d**	–OCH_2O–		Me	Ph	Me	**10da**	98	84(>98)
11	**3d**	–OCH_2O–		Me	Ph	H	**10db**	80	88(>98)
12	**3e**	H	H	Me	3-Th[f]	Me	**10ea**	90	75(>98)
13	**3e**	H	H	Me	3-Th[f]	H	**10eb**	91	78(>98)
14	**3g**	H	H	Me	*n*-Bu	Me	**10ga**	88	30
15	**3g**	H	H	Me	*n*-Bu	H	**10gb**	90	28
16	**3k**	H	H	Me	SPh	Me	**10ka**	69	4
17	**6a**	H	H	–$(CH_2)_4$–	Ph	Me	**11aa**	87	80
18	**6a**	H	H	–$(CH_2)_4$–	Ph	H	**11ab**	77	84

[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **3** or **6**, 30 equiv. of nucleophile, AgOTs as silver salt with ROH and $AgSbF_6$ with H_2O, in CH_2Cl_2 (1.2 mL) at −30 ºC for 2–4 days. [b] Isolated yield. [c] Determined by HPLC analysis, see Supporting Information; in brackets *ee* after recrystallization. [d] Reaction conducted at −20 ºC. [e] 12% of **5a** was also formed. [f] 3-Thienyl.

Conclusion

In summary, we have shown that *ortho*-(alkynyl)styrenes are valuable precursors of indene derived compounds by gold-catalyzed

formal 5-*endo-dig* cycloisomerizations and alkoxycyclizations. Thus, reactions of *o*-(alkynyl)styrenes disubstituted at the β-position of the styrene moiety selectively afford 1*H*-indene derivatives in high yields whereas substrates bearing a secondary alkyl group at the terminal carbon of the olefin efficiently produce dihydrobenzo[*a*]fluorenes through a formal [3+3] cycloaddition. Moreover, parallel reactions in the presence of oxygen-centered nucleophiles such as water and alcohols provide the corresponding functionalized indene derivatives. These gold-catalyzed alkoxycyclizations are also observed with *o*-(alkynyl)-α-methylstyrenes which allows the preparation of indenes bearing an all-carbon quaternary centre at C-1. Notably, the later results implies a critical effect of the alcohol in the outcome of the cycloisomerization by switching the selectivity from a 6-*endo* to 5-*endo* cyclization. In addition, we have also accomplished the selective synthesis of polycyclic compounds by a related intramolecular gold-catalyzed alkoxycyclization of appropriate substituted *o*-(alkynyl)styrenes. Finally, we have developed the asymmetric synthesis of 1*H*-indenes and dihydrobenzo[*a*]fluorenes using a chiral gold complex derived from electron-rich ligand 3,5-xylyl-MeOBIPHEP. Notably, the enantiomerically-enriched functionalized indenes are obtained in high yields and with *ee* values up to 92%, that can be improved to >98% after a simple recrystallization.

Experimental Section

Typical procedure for the gold(I)-catalyzed synthesis of 1*H*-indenes 2 and 8. Synthesis of 2-phenylsulfanyl-1-(prop-1-en-2-yl)-1*H*-indene (5k): $AgSbF_6$ (5.0 mol%, 8.5 mg) was added to a solution of [AuCl(Ph$_3$P)] (5.0 mol%, 12.3 mg) in CH_2Cl_2 (1.0 mL) and the reaction mixture was stirred 5–10 minutes. A solution of *o*-(alkynyl)styrene derivative **3k**[45] (0.5 mmol, 132 mg) in CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred at RT until complete disappearance of the styrene derivative was observed by TLC or GC-MS. The mixture was filtered through silica gel, the solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel using hexane as eluent to afford indene **5k** (109 mg, 83%) as a yellow oil; R_f = 0.28 (hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.38 (bs, 3H), 4.23 (bs, 1H), 5.10–5.17 (m, 1H), 6.48–6.50 (m, 1H), 7.05–7.36 (m, 5H), 7.38–7.45 (m, 3H), 7.58–7.67 (m, 2H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 16.7 (CH_3), 60.9 (CH), 116.2 (CH_2), 119.6 (CH), 123.1 (CH), 124.5 (CH), 127.2 (CH), 128.2 (CH), 128.8 (C), 129.3 (2 x CH), 133.1 (C), 133.5 (2 x CH), 143.0 (C), 144.1 (C), 145.7 (C), 146.7 (C) ppm; LRMS(EI): *m/z* (%): 265 [(M+1)$^+$, 16], 264 (M$^+$, 78), 155 (100); HRMS (EI) calcd for $C_{18}H_{16}S$: 264.0973; found: 264.0968.

General procedure for the gold(I)-catalyzed enantioselective synthesis of 1*H*-indenes 5,7 and 10-11: $AgSbF_6$ (10.0 mol%, 5.1 mg) or AgOTs (10.0 mol%, 8.4 mg) was added to a solution of **L***$(AuCl)_2$ (5.0 mol%, 17.4 mg) in dry CH_2Cl_2 and the reaction mixture was stirred 5–10 minutes and cooled to –30 ºC or –20 ºC (see Tables 6 and 7 for the suitable Ag salt and temperature for each substrate). The nucleophile (30 equiv., 9 mmol), when appropriate, was added, followed by a solution of the corresponding *o*-(alkynyl)styrene derivative **3** or **6** (0.3 mmol) in dry CH_2Cl_2. The resulting reaction mixture was stirred until complete disappearance of starting material, as monitored by TLC or GC-MS. The mixture was diluted with hexanes and filtered through a pad of silica gel, the solvent was removed and the crude mixture was purified by flash chromatography on silica gel using mixtures of hexane and EtOAc as eluents. The corresponding 1*H*-indenes **5**, **7**, **10** or **11** were isolated in the yields and enantioselectivities reported in Tables 6 and 7.

Acknowledgements

We gratefully acknowledge the Ministerio de Economía y Competitividad (MINECO) and FEDER (CTQ2010-15358 and CTQ2013-48937-C2-1-P) and Junta de Castilla y León (BU237U13) for financial support. A. M. S. thanks the Junta de Castilla y León (Consejería de Educación) and the Fondo Social Europeo for a PIRTU contract. M.A.R. and P.G.-G. thank MEC for a ''Young Foreign Researchers'' (SB2009-0186) contract and MINECO for "Juan de la Cierva" contract, respectively.

[1] Selected recent reviews: a) L. Fensterbank, M. Malacria, *Acc. Chem. Res*. **2014**, *47*, 953–965; b) T. Cañeque, F. M. Truscott, R. Rodríguez, G. Maestri, M. Malacria, *Chem. Soc. Rev*. **2014**, 2916–2926; c) N. Krause, C. Winter, *Chem. Rev*. **2011**, *111*, 1994–2009; d) M. Bandini, *Chem. Soc. Rev*. **2011**, *40*, 1358–1367; e) C. Aubert, L. Fensterbank, P. García, M. Malacria, A. Simonneau, *Chem. Rev*. **2011**, *111*, 1954–1993; f) S. I. Lee, N. Chatani, *Chem. Commun*. **2009**, 371–384; g) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075–6089; h) S. M. Abu Sohel, R. S. Liu, *Chem. Soc. Rev*. **2009**, *38*, 2269–2281;

[2] Representative recent reviews on gold/platinum catalysis: a) A. S. K. Hashmi, *Acc. Chem. Res*. **2014**, *47*, 864–876; b) A. Fürstner, *Acc. Chem. Res*. **2014**, *47*, 925–938; c) F. Rodríguez, F. J. Fañanás, *Synlett* **2013**, 1757–1771; d) A. S. K. Hashmi, F. D. Toste, *Modern Gold Catalyzed Synthesis*, Wiley-VCH, Weinheim, **2012**; e) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev*. **2012**, *41*, 2448–2462; f) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675–691; g) A. Fürstner, *Chem. Soc. Rev*. **2009**, *38*, 3208–3221; h) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403.

[3] Selected revisions on enyne cycloisomerizations: a) C. Obradors, A. M. Echavarren, *Acc. Chem. Res*. **2014**, *47*, 902–912; b) E. Soriano, J. Marco-Contelles, *Acc. Chem. Res*. **2009**, *42*, 1026–1036; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev*. **2008**, *108*, 3326–3350; d) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; e) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. For pioneering work, see: f) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc*. **2000**, *122*, 11553–11554.

[4] A. S. K. Hashmi, *Pure Appl. Chem.* **2010**, *82*, 1517–1528.

[5] For leading references on the cycloisomeriation of 1,5-enynes see: a) F. Gagosz, *Org. Lett.* **2005**, *7*, 4129–4132; b) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807; c) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc*. **2004**, *126*, 10858–10859; d) Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouriès, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2004**, *126*, 8656–8657; e) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.

[6] For a review on dienyne cycloaromatization see: D. M. Hitt, J. M. O'Connor, *Chem. Rev*. **2011**, *111*, 7904–7922.

[7] a) P. García-García, A. Martínez, A. M. Sanjuán, M. A. Fernández-Rodríguez, R. Sanz, *Org. Lett.* **2011**, *13*, 4970–4973; b) P. García-García, M. A. Fernández-Rodríguez, E. Aguilar, *Angew. Chem.* **2009**, 121, 5642–5645; *Angew. Chem. Int. Ed*. **2009**, *48*, 5534–55377; c) J.-J. Lian, C.-C. Lin, H.-K. Chang, P.-C. Chen, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 9661–9667; d) J.-J. Lian, A. Odedra, C.-J. Wu, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 4186–4187; e) C. A. Merlic, M. E. Pauly, *J. Am. Chem. Soc*. **1996**, *118*, 11319–11320.

[8] a) T. Miura, N. Iwasawa, *J. Am. Chem. Soc*. **2002**, *124*, 518–519; b) K. Maeyama, N. Iwasawa, *J. Org. Chem.* **1999**, *64*, 1344–1346.

[9] J. W. Dankwardt, *Tetrahedron Lett.* **2001**, *42*, 5809–5812.

[10] a) N. Kadoya, M. Murai, M. Ishiguro, J. Uenishi, M. Uemura, *Tetrahedron Lett*. **2013**, *54*, 512–514; b) C. Feng, T.-P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 17710–17712.

[11] K. Saito, H. Sogou, T. Suga, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2011**, *133*, 689–691.

[12] T. Godet, P. Belmont, *Synlett* **2008**, 2513–2517.

[13] a) J. Aziz, G. Frison, P. Le Menez, J.-D. Brion, A. Hamze, M. Alami, *Adv. Synth. Catal.* **2013**, *355*, 3425–3436; b) C. Michon, S. Liu, S. Hiragushi, J. Uenishi, M. Uemura, *Synlett* **2008**, 1321–1324; c) T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, 411–414. For the gold-catalyzed synthesis of naphthalenes, see also recent work: d) A. S. K. Hashmi, *Acc. Chem. Res*. **2014**, *47*, 864–876; e) I. Braun, A. M. Asiri, A. S. K. Hashmi, *ACS Catal.* **2013**, *3*, 1902–1907; f) A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, *Organometallics* **2012**, *31*, 644–661.

[14] a) J. Carreras, G. Gopakumar, L. Gu, A. Gimeno, P. Linowski, J. Petuškova, W. Thiel, M. Alcarazo, *J. Am. Chem. Soc.* **2013**, *135*, 18815–18823; b) J. Carreras, M. Patil, W. Thiel, M. Alcarazo, *J. Am. Chem. Soc*. **2012**, *134*, 16753–16758; c) K. Komeyama, R. Igawa, K. Takaki, *Chem. Commun.* **2010**, *46*, 1748–1750; d) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575; e) B. Martín-Matute, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.

[15] a) R. J. Madhushaw, C.-Y. Lo, C.-W. Hwang, M.-D. Su, H.-C. Shen, S. Pal, I. R. Shaikh, R.-S. Liu, *J. Am. Chem. Soc.* **2004**, *126*, 15560–15565; b) H.-C. Shen, S. Pal, J.-J. Lian, R.-S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 15762–15763.

[16] a) E. Álvarez, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, *J. Org. Chem.* **2013**, *78*, 9758–9771; b) A. M. Sanjuán, A. Martínez, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, *Beilstein J. Org. Chem.* **2013**, *9*, 2242–2249; c) R. Sanz, E. Álvarez, D. Miguel, P. García-García, M. Fernández-Rodríguez, F. Rodríguez, *Synthesis* **2012**, 1874–1884; d) E. Álvarez, D. Miguel,

P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez, R. Sanz, *Beilstein J. Org. Chem.* **2011**, *7*, 786–793; e) R. Sanz, D. Miguel, M. Gohain, P. García-García, M. A. Fernández-Rodríguez, A. González-Pérez, O. Nieto-Faza, A. R. de Lera, F. Rodríguez, *Chem. Eur. J.* **2010**, *16*, 9818–9828; f) R. Sanz, D. Miguel, F. Rodríguez, *Angew. Chem.* **2008**, *120*, 7464–7467; *Angew. Chem. Int. Ed.* **2008**, *47*, 7354–7357.

[17] A. Martínez, P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez, R. Sanz, *Angew. Chem.* **2010**, *122*, 4737–4741; *Angew. Chem. Int. Ed.* **2010**, *49*, 4633–4637.

[18] P. García-García, M. A. Rashid, A. M. Sanjuán, M. A. Fernández-Rodríguez, R. Sanz, *Org. Lett.* **2012**, *14*, 4778–4781.

[19] More recently, same substrates were efficiently employed in gold(I)-catalyzed oxidative cycloadditions with nitrosobenzenes: a) C. H. Chen, Y. C. Tsai, R. S. Liu, *Angew. Chem.* **2013**, *125*, 4697–4701; *Angew. Chem. Int. Ed.* **2013**, *52*, 4599–4603. For related metal-catalyzed oxidative cyclizations of *o*-(alkynyl)styrenes see: b) H.-H. Hung, Y.-C. Liao, R.-S. Liu, *Adv. Synth. Catal.* **2013**, *355*, 1545–1552; c) D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das, R.-S. Liu, *Angew. Chem.* **2011**, *123*, 7043–7046; *Angew. Chem. Int. Ed.* **2011**, *50*, 6911–6914.

[20] See Table S1 in the Supporting Information for details.

[21] For other gold-catalyzed synthesis of indenes, see: a) Y. Wang, P. R. McGonigal, B. Herlé, M. Besora, A. M. Echavarren, *J. Am. Chem. Soc.* **2014**, *136*, 801–809; b) P. R. McGonigal, C. de León, Y. Wang, A. Homs, C. R. Solorio-Alvarado, A. M. Echavarren, *Angew. Chem.* **2012**, *124*, 13270–13273; *Angew. Chem. Int. Ed.* **2012**, *51*, 13093–13096; c) P. Nun, S. Gaillard, A. Poater, L. Cavallo, S. P. Nolan, *Org. Biomol. Chem.* **2011**, *9*, 101–104; d) A. S. K. Hashmi, M. Bührle, R. Salathé, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 2059–2064. See also ref. [16c-f].

[22] a) N. J. Clegg, S. Paruthiyil, D. C. Leitman, T. S. Scanlan, *J. Med. Chem.* **2005**, *48*, 5989–6003; b) A. Korte, J. Legros, C. Bolm, *Synlett* **2004**, 2397–2399.

[23] a) M. Enders, R. W. Baker, *Curr. Org. Chem.* **2006**, *10*, 937–953; b) J. Yang, M. V. Lakshmikantham, M. P. Cava, D. Lorcy, J. R. Bethelot, *J. Org. Chem.* **2000**, *65*, 6739–6742.

[24] a) A. Glöckner, H. Bauer, M. Maekawa, T. Bannenberg, C. G. Daniliuc, P. G. Jones, Y. Sun, H. Sitzmann, M. Tamm, M. D. Walter, *Dalton Trans.* **2012**, *41*, 6614–6624; b) B. Wang, *Coord. Chem. Rev.* **2006**, *250*, 242–258; c) R. Leino, P. Lehmus, A. Lehtonen, *Eur. J. Inorg. Chem.* **2004**, 3201–3222; d) H. G. Alt, A. Köppl, *Chem. Rev.* **2000**, *100*, 1205–1221.

[25] For a revision on gold-catalyzed cycloadditions see: a) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2011**, *7*, 1075–1094. For other gold-catalyzed cycloaddition reactions involving 1,3-dien-5-ynes, see: b) J. M. Fernández-García, M. A. Fernández-Rodríguez, E. Aguilar, *Org. Lett.* **2011**, *13*, 5172–5175; c) J. Barluenga, M. A. Fernández-Rodríguez, P. García-García, E. Aguilar, *J. Am. Chem. Soc.* **2008**, *130*, 2764–2765. For gold-mediated cycloadditions, see: d) R. Manzano, T. Wurm, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2014**, *20*, 6844–6848; e) A. S. K. Hashmi, D. Riedel, M. Rudolph, F. Rominger, T. Oeser, *Chem. Eur. J.* **2012**, *18*, 3827–3830; f) J. Barluenga, J. Calleja, A. Mendoza, F. Rodríguez, F. J. Fañanás, *Chem. Eur. J.* **2010**, *16*, 7110–7112.

[26] The relative stereochemistry of the major isomer of **8j** was established by a NOESY experiment as *syn*. The same *syn* selectivity was also observed and determined for cycloadducts **8** described latter in this paper.

[27] The role of Brønsted acids as true catalytic species in apparently metal-catalyzed reactions has been suggested before. See: a) T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353−9361; b) B. D. Kelly, J. M. Allen, R. E. Tundel, T. H. Lambert, *Org. Lett.* **2009**, *11*, 1381–1383; c) R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Adv. Synth. Catal.* **2006**, *348*, 1841–1845; d) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem.* **2006**, *118*, 807–810; *Angew. Chem. Int. Ed.* **2006**, *45*, 793–795; e) A. S. K. Hashmi, L. Schwarz, P. Rubenbauer, M. C. Blanco, *Adv. Synth. Catal.* **2006**, *348*, 705–708; f) M. Georgy, V. Boucard, J.-C. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181; g) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247–1252.

[28] See for instance: a) S. Gao, Q. Wang, L. J.-S. Huang, L. Lum, C. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 371–383; b) J. C. Liermann, H. Kolshorn, H. Anke, E. Thines, T. Opatz, *J. Nat. Prod.* **2008**, *71*, 1654–1656.

[29] It should be noted that as for the model reaction, formation of minor amounts (< 10%) of indenes **7** were detected in all the examples depicted in Table 3 performed under conditions *A*.

[30] For reports about the nature of proposed intermediates in gold catalysis and related mechanisms, see: a) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16–28; b) V. López-Carrillo, N. Huguet, Á. Mosquera, A. M. Echavarren, *Chem. Eur. J.* **2011**, *17*, 10972–10978; c) A. S. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; A. S. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; d) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811; e) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859.

[31] D. J. Gorin, I. D. G. Watson, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737.

[32] For related gold-catalyzed alkoxycyclizations of 1,5-enynes see: a) A. K. Buzas, F. M. Istrate, F. Gagosz, *Angew. Chem.* **2007**, *119*, 1159–1162; *Angew. Chem. Int. Ed.* **2007**, *46*, 1141–1144; b) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963.

[33] For alkoxycyclizations of particular *o*-(alkynyl)styrenes bearing an enolether as olefin that selectively produce naphthalenes see:Y. Liu, J. Guo, Y. Liu, X. Wang, Y. Wang, X. Jia, G. Wei, L. Chen, J. Xiao, M. Cheng, *Chem. Commun.* **2014**, *50*, 6243–6245.

[34] We have previously observed that the presence of an alcohol also led to a switch in the selectivity of the cyclization of 1,3-dien-5-ynes. See: A. M. Sanjuán, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, *Adv. Synth. Catal.* **2013**, *355*, 1955–1962 and ref. [7a].

[35] Starting from **2b**, the corresponding methoxy-functionalized indene **13b** was isolated in 34% yield (ca. 6:1 mixture of diastereoisomers) along with naphthalene derivative **4b** as the major product (55% isolated yield).

[36] For **14d** ca. 10% of the corresponding indene, where the intramolecular addition of the alcohol did not occur, was also formed.

[37] The open carbocationic resonance structure of **II'** is not explicitly drawn for clarity and also because in the case of $R^1 \neq H$ and $R^2 = H$ its contribution to the hybrid of resonance should be low.

[38] a) F. Zhou, M. Yang, X. Lu, *Org. Lett.* **2009**, *11*, 1405–1408; b) N. Miyaura, T. Nishikata, S. Kiyomura, Y. Yamamoto, *Synlett* **2008**, 2487–2490; c) T. Nishikata, Y. Kobayashi, K. Kobayshi, Y. Yamamoto, N. Miyaura, *Synlett* **2007**, 3055–3057.

[39] Related Pd or Rh catalyzed asymmetric synthesis of 1-indenols from acylboronic acids and internal alkynes were also described: a) M. Yang, X. Zhang, X. Lu, *Org. Lett.* **2007**, *9*, 5131–5133; b) R. Shintani, K. Okamoto, T. Hayashi, *Chem. Lett.* **2005**, *34*, 1294–1295. For a Rh-catalyzed enantioselective synthesis of indenyl amines from aryl ketenimines an internal acetylenes, see: c) D. N. Tran, N. Cramer, *Angew. Chem.* **2011**, *125*, 10824–10828; *Angew. Chem. Int. Ed.* **2011**, *50*, 11098–11102.

[40] For recent reviews see: a) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889–901; b) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2013**, *9*, 2250–2264; c) A. Pradal, P. Toullec, V. Michelet, *Synthesis* **2011**, 1501–1514; d) S. Sengupta, X. Shi, *ChemCatChem* **2010**, *2*, 609–619; e) A. S. K. Hashmi, *Nature* **2007**, *449*, 292–293. For reviews on enantioselective transition-metal-catalyzed cycloisomerizations see: f) A. Marinetti, H. Jullien, A. Voituriez, *Chem. Soc. Rev.* **2012**, *41*, 4884–4908; g) I. D. G. Watson, F. D. Toste, *Chem. Sci.* **2012**, *3*, 2899–2919.

[41] a) W. Zi, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 12600–12603; b) L. Huang, H.-B. Yang, D.-H. Zhang, Z. Zhang, X.-Y. Tang, Q. Xu, M. Shi, *Angew. Chem.* **2013**, *125*, 6899–6903; *Angew. Chem. Int. Ed.* **2013**, *52*, 6767–6771; c) J.-F. Brazeau, S. Zhang, I. Colomer, B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 2742–2749; d) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Furstner, *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342; e) A. K. Mourad, J. Leutzow, C. Czekelius, *Angew. Chem.* **2012**, *124*, 11311–11314; *Angew. Chem. Int. Ed.* **2012**, *51*, 11149–11152; f) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277; g) F. Liu, D. Qian, L. Li, X. Zhao, J. Zhang, *Angew. Chem.* **2010**, *122*, 6819–6822; *Angew. Chem. Int. Ed.* **2010**, *49*, 6669–6672; h) A. S. K. Hashmi, M. Hamzic, F. Rominger, J. W. Bats, *Chem. Eur. J.* **2009**, *15*, 13318-13322; i) C.-M. Chao, D. Beltrami, P. Y. Toullec, V. Michelet, *Chem. Commun.* **2009**, 6988–6990; j) C.-M. Chao, M. R. Vitale, P. Y. Toullec, J. P. Genêt, V. Michelet, *Chem. Eur. J.* **2009**, *15*, 1319–1323; k) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003; l) M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293–1300.

[42] See Table S2 in the Supporting Information for details.

[43] See Table S3 in the Supporting Information for details.

[44] CCDC 766525 (**10ca**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[45] R. Sanz, A. Martínez, P. García-García, M. A. Fernández-Rodríguez, M. A. Rashid, F. Rodríguez, *Chem. Commun.* **2010**, *46*, 7427–7429.

Received: ((will be filled in by the editorial staff))
Revised: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

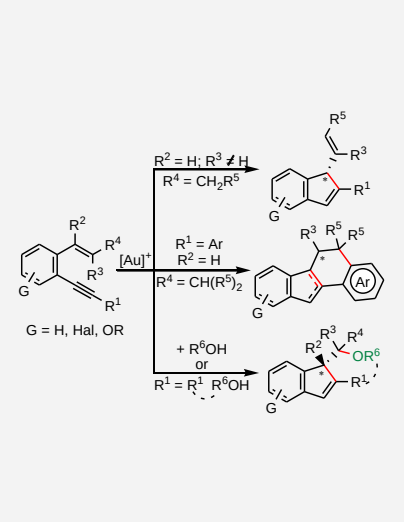
Entry for the Table of Contents

Cyclization

*A. M. Sanjuán, M. A. Rashid, P. García-García, A. Martínez-Cuezva, M. A. Fernández-Rodríguez, F. Rodríguez, R. Sanz**

…….…… Page – Page

Gold(I)-Catalyzed Cycloisomerizations and Alkoxycyclizations of *ortho*-(Alkynyl)styrenes



A full account for the gold(I)-catalyzed reactions of *ortho*-(alkynyl)styrenes is reported. Selective 5-*endo* cyclizations are achieved by control of substrate olefin substitution patterns, which give rise to a wide variety of interesting 1*H*-indenes. These compounds can be prepared in an enantioselective way by using a chiral gold complex. In the presence of alcohols the corresponding alkoxycyclization processes take place, even for α-substituted substrates that led to indenes bearing an all-carbon quaternary center at C-1.