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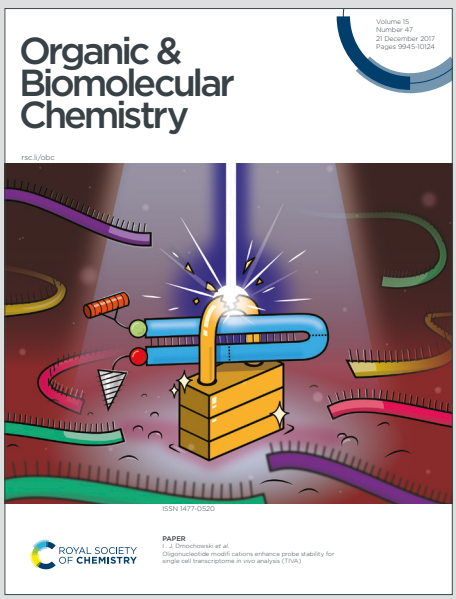

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ARTICLE

Gold(I)-catalyzed nucleophilic cyclization of β-monosubstituted *o*-(alkynyl)styrenes: a combined experimental and computational study†

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The stereospecific gold(I)-catalyzed nucleophilic cyclization of β-monosubsituted *o*-(alkynyl)styrenes to produce C-1 functionalized 1*H*-indenes including challenging substrates and nucleophiles, such as β-(cyclo)alkyl-subsituted *o*-(alkynyl)styrenes and a variety of alcohols as well as selected electron-rich aromatics, is reported. DFT calculations support the stereochemical outcome of the process that involves the formation of a key cyclopropyl gold carbene intermediate through a regiospecific 5-*endo* cyclization.

Introduction

The ability of gold(I) to act as a soft carbophilic Lewis acid to activate alkynes for a subsequent inter or intramolecular nucleophilic attack has led to the development of a plethora of useful synthetic methodologies during the last years.[1]

In this field, cycloisomerizations of enynes are one of the most representative transformations catalyzed by gold complexes, allowing the construction of complex structures under very mild conditions usually involving simple and readily available starting materials.[2] Favoured by the low oxophilicity of gold(I) complexes, the nucleophilic cyclization of enynes in the presence of alcohols or water, alkoxy- or hydroxycyclization reactions respectively, is a useful strategy that allows the formation of functionalized carbo and heterocyclic compounds.[3]

For 1,5-enynes, 5-*endo* cyclizations are almost always involved likely due to the much more favourable generation of a bicyclo[3.1.0]hexane intermediate compared to a bicyclo[2.1.0]pentane system that would arise from a *exo*-cyclization.[4] In many cases, divergent reaction pathways are observed depending on the substitution pattern of the enyne.[5] In this area, our group has being studying along the last years the behaviour of *o*-(alkynyl)styrenes, a particular type of 1,3-dien-5-ynes.[6] Although most of the previously reported chemistry for these substrates are devoted to the synthesis of naphthalene derivatives through 6-*endo* cyclizations,[7] in 2010 we first showed that 5-*endo* cycloisomerizations and alkoxycyclizations are also possible by using β,β-disubstituted styrenes.[8] With this methodology alkoxy- and hydroxy-functionalized indene derivatives, which are relevant scaffolds due to their appearance in biologically active molecules and their applications in materials science,[9] could be efficiently obtained. Considering the presence of the two substituents at the β-position, we had proposed a gold-stabilized homoallylic carbocation as a likely key intermediate (Scheme 1a).[10] Varying the nature of the two substituents at the β-position of the *o*-(alkynyl)styrenes, we have also achieved the synthesis of dihydrobenzo[*a*]fluorenes[11] and dihydroindeno[2,1-*a*]indenes.[12] After our pioneering work, other authors have also developed related 5-*endo* cyclizations of β,β-disubstituted *o*-(alkynyl)styrenes under gold-, other transition metal-, and even metal free-catalysis.[13]

In this context we decided to study the gold-catalyzed nucleophilic cyclizations of β-monosubstituted *o*-(alkynyl)styrenes.[14] With this goal in mind, we have recently reported the methoxycyclization of β-aryl *o*-(alkynyl)styrenes that takes place in a regiospecific 5-*endo* mode (Scheme 1b).[15] However, for these substrates the regiochemistry of the potential cyclization is not obviously predicted.[16] Considering the carbocationic-like intermediates that would account for the competitive 5-*endo* and 6-*endo* cyclizations, both types of ring closures must locate the positive charge at secondary carbon atoms (Scheme 1c). In fact, at least for β-alkyl-substituted substrates (R^1 = Alk), the 6-*endo* cyclization should give rise to a more stabilized intermediate. In addition, although the analysis of the stereospecificity of these

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. See DOI: 10.1039/x0xx00000x

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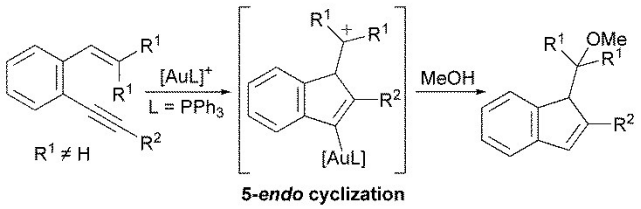
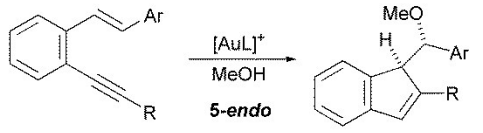
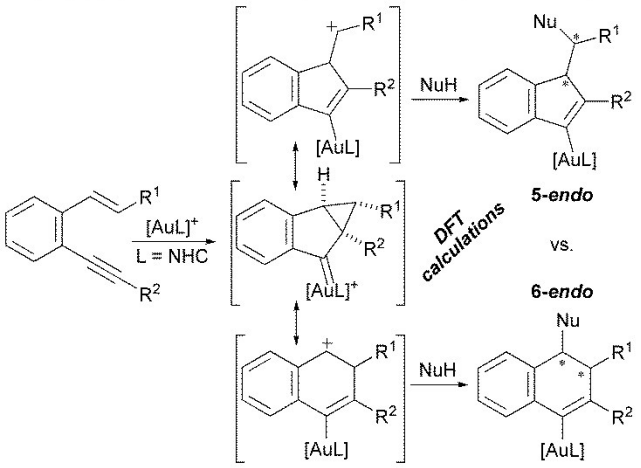
(a) **Our previous work**: Au(I)-catalyzed alkoxycyclizations of β,β-disubstituted *o*-(alkynyl)styrenes [refs. 8 and 10a]



(b) Au(I)-catalyzed methoxycyclization of β-aryl *o*-(alkynyl)styrenes [ref. 15]



(c) **This work**: Nucleophilic cyclizations of β-monosubstituted *o*-(alkynyl)styrenes. Combined experimental and computational study



Scheme 1 Au(I)-catalyzed alkoxycyclizations of β,β-disubstituted *o*-(alkynyl)styrenes (previous work) and nucleophilic cyclization of β-monosubstituted *o*-(alkynyl)styrenes.

processes could facilitate the mechanistic proposal regarding the nature of the involved gold intermediates, whose structures are typically described as intermediates between cyclopropyl gold carbenes and gold-stabilized homoallyl carbocations,[4] we have also carried out DFT calculations in order to further understand the source of regio- and stereoselectivity in these processes.

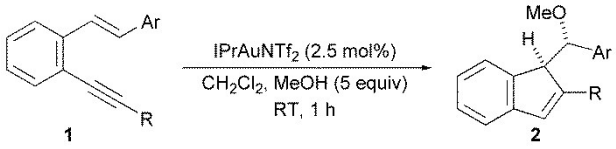
Herein, we report a detailed experimental and computational study on the nucleophilic cyclizations of β-monosubstituted *o*-(alkynyl)styrenes under gold catalysis, including β-alkyl substituted substrates and a variety of O- and C-centered nucleophiles.

Results and discussion

Methoxycyclization reactions

As reported in our prior publication,[15] we had described the regiospecific 5-*endo* methoxycyclization of selected β-aryl *o*-(alkynyl)styrenes **1** that diastereospecifically led to 1-methoxybenzyl-1*H*-indenes **2** in high yields and typically short reaction times (Table 1, entries 1–3, 5–7, 11–14, 16, 19, 20 and 22–24).[15] We established IPrAuNTf$_2$,[17] bearing a NHC ligand and the weakly coordinating counteranion Tf_2N^- as the best catalyst, whereas complexes possessing phosphine or phosphite ligands provided lower conversion and/or yields (see ESI for further details). Herein we have expanded the scope of this process to new substrates such as **1e,f,m** (entries 9, 10 and 21), as well as to different mixtures of geometrical isomers of starting materials (entries 4, 8, 15, 17 and 18). So, different starting substrates **1a-g**, bearing a representative selection of aromatic substituents at the alkene, including electron-donating and electron-withdrawing groups, were suitable for this methoxycyclization (entries 1–11). In addition, apart from a phenyl group, the alkyne moiety can also support (cyclo)alkyl, heteroaromatic, alkenyl, and arylthio groups as substituents (entries 12–24). Remarkably, starting from geometrically pure (*E*)-**1** the corresponding 1-methoxybenzyl-1*H*-indenes **2** were obtained as single diastereoisomers. Control experiments using a variety of enynes **1** as ~1/1 mixtures of geometrical isomers led to the corresponding indenes **2** as ~1/1 mixtures of diastereoisomers (entries 2, 4,

Table 1 Au(I)-catalyzed methoxycyclization of β-aryl *o*-(alkynyl)styrenes **1**.[15] Stereospecific synthesis of 1-methoxybenzyl-1*H*-indenes **2**.[a]



Entry	1	Ar	R	*E*/*Z*	2	dr[b]	yield [%][c]
1	**1a**	Ph	Ph	>20/1	**2a**	>20/1	93
2	**1a**	Ph	Ph	1/1	**2a**	1/1	86
3	**1b**	4-MeC_6H_4	Ph	>20/1	**2b**	>20/1	86
4	**1b**	4-MeC_6H_4	Ph	1/1	**2b**	1/1	93
5	**1c**	4-MeOC_6H_4	Ph	>20/1	**2c**	16/1	86
6	**1c**	4-MeOC_6H_4	Ph	1/8	**diast-2c**	5/1	79
7	**1d**	4-ClC_6H_4	Ph	>20/1	**2d**	>20/1	85
8	**1d**	4-ClC_6H_4	Ph	1/8	**diast-2d**	8/1	80
9	**1e**	4-FC_6H_4	Ph	>20/1	**2e**	>20/1	92
10	**1f**	3-MeOC_6H_4	Ph	6/1	**2f**	5,5/1	71
11	**1g**	1-Naphthyl	Ph	>20/1	**2g**	>20/1	88
12	**1h**	Ph	*n*-Bu	>20/1	**2h**	>20/1	91
13	**1h**	Ph	*n*-Bu	<1/20	**diast-2h**	>20/1	87
14	**1i**	4-MeC_6H_4	*n*-Bu	>20/1	**2i**	>20/1	75
15	**1i**	4-MeC_6H_4	*n*-Bu	1/1	**2i**	1/1	90
16	**1j**	4-MeOC_6H_4	*n*-Bu	9/1	**2j**	9/1	70
17	**1j**	4-MeOC_6H_4	*n*-Bu	1/1	**2j**	1/1	80
18[d]	**1k**	4-ClC_6H_4	*n*-Bu	>20/1	**2k**	>20/1	74
19[e]	**1k**	4-ClC_6H_4	*n*-Bu	<1/20	**diast-2k**	>20/1	88
20	**1l**	1-Naphthyl	*n*-Bu	>20/1	**2l**	>20/1	91
21	**1m**	4-MeC_6H_4	*c*-C_3H_5	>20/1	**2m**	>20/1	90
22[f]	**1n**	Ph	*c*-C_6H_9[g]	>20/1	**2n**	>20/1	82
23	**1o**	Ph	3-Th[h]	>20/1	**2o**	>20/1	87
24	**1p**	Ph	SPh	>20/1	**2p**	>20/1	90

[a] Reaction conditions: **1** (0.3 mmol) in CH_2Cl_2 (1 mL) at RT. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of the product based on the starting material. [d] Reaction conditions = 2 h at refluxing DCE. Conducting the process at RT the competitive attack of methanol to the triple bond takes place. [e] Reaction time = 6 h. [f] Reaction time = 48 h. [g] Cyclohexen-1-yl. [h] 3-Thienyl.

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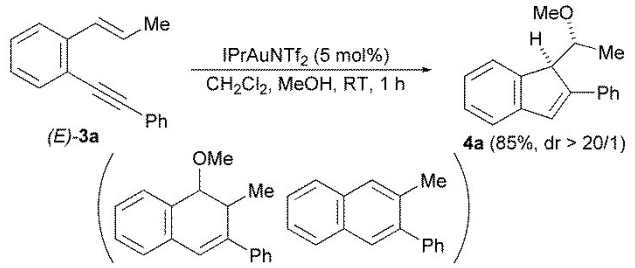

Scheme 2 Selective 5-*endo* Au(I)-catalyzed methoxycyclization of (*E*)-**3a** to indene **4a**.

15 and 17). Moreover, when selected (*Z*)-**1** styrenes were submitted to the same reaction conditions, the other diastereoisomer of **2** (**diast-2**) was selectively obtained (entries 6, 8, 13 and 19). These results prove the diastereospecificity of the process as the stereochemical information of the alkene is transferred to the final product.[18]

Then, we turned our attention to β-alkyl monosubstituted *o*-(alkynyl)styrenes **3**. (*E*)-**3a**, bearing a methyl group as substituent at the β-position, was selected as model substrate and submitted to the same reaction conditions prior described for β-aryl *o*-(alkynyl)styrenes **1**. In this case, a preliminary analysis of the most likely way of cyclization, simply considering the stability of the presumed carbocationic intermediates, reveals that the carbocation arising from a 6-*endo* ring closure (secondary benzylic, Scheme 1b) should be more stable than the corresponding carbocation resulting from the 5-*endo* cyclization (secondary alkylic, R^1 = Me in Scheme 1b). Nevertheless, 1-methoxyalkyl-1*H*-indene derivative **4a** was selectively obtained in high yield as a single diastereoisomer, and without the presence of competitive naphthalene derivatives derived from a competitive 6-*endo* cyclization (Scheme 2). The stereochemistry of **4a** was established considering our previous and related results,[16] which involve a net anti addition of a heteroatomic nucleophile and an activated alkyne to the olefin.[3]

So, we proceeded to study the methoxycyclization of a series of β-alkyl *o*-(alkynyl)styrenes **3**. As shown in Table 2, the process proceeded efficiently for a variety of starting enynes **3a-h** bearing different (cyclo)alkyl substituents at the olefin as well as aryl or (cyclo)alkyl groups at the alkyne (entries 1–11). Regarding the stereospecific nature of this cyclization, starting from the pure (*E*) isomer the corresponding 1-(1-methoxy)alkyl indene derivatives **4** were obtained as single diastereoisomers (entries 1, 3, 5–9 and 11), whereas the use of *o*-(alkynyl)styrenes **3** as mixtures of geometrical isomers led to the isolation of the corresponding indenes **4** with the same diastereomeric ratio as the starting enynes (entries 2, 4 and10). It is worthy to note the reactivity of β-cyclopropyl substituted *o*-(alkynyl)styrenes **3i** and **3j**, as the competitive attack of methanol on the cyclopropyl ring does not interfere with the addition to the more hindered β-position, although this type of cyclopropyl ring opening has been well-established.[19] In this way, the corresponding 1-(1-methoxy-1-cyclopropylmethyl)-1*H*-indenes **4i,j** were diastereospecifically obtained in high yields (entries 12–14). It is also interesting to point out that the intramolecular [4+2] cycloaddition of 6-aryl-

Table 2 Au(I)-catalyzed methoxycyclization of β-alkyl *o*-(alkynyl)styrenes **3**. Stereospecific synthesis of 1-methoxyalkyl-1*H*-indenes **4**[a]

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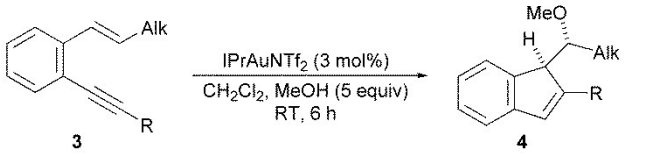

Entry	3	Alk	R	*E*/*Z*	4	dr[b]	yield [%][c]
1	**3a**	Me	Ph	>20/1	**4a**	>20/1	85
2	**3a**	Me	Ph	1/2	**diast-4a**	2/1	88
3[d]	**3b**	Me	*n*-Bu	>20/1	**4b**	>20/1	87
4[d]	**3b**	Me	*n*-Bu	1/1	**diast-4b**	1,5/1	81
5	**3c**	*n*-Pr	Ph	>20/1	**4c**	>20/1	73
6[d]	**3d**	*n*-Pr	*c*-C_3H_5	>20/1	**4d**	>20/1	84
7	**3e**	*n*-Bu	Ph	>20/1	**4e**	>20/1	72
8[d]	**3f**	*n*-Bu	*c*-C_3H_5	>20/1	**4f**	>20/1	87
9	**3g**	*n*-C_6H_{13}	Ph	>20/1	**4g**	>20/1	84
10	**3g**	*n*-C_6H_{13}	Ph	1/1	**4g**	1/1	89
11	**3h**	*c*-C_6H_{11}	Ph	>20/1	**4h**	>20/1	90
12	**3i**	*c*-C_3H_5	Ph	>20/1	**4i**	>20/1	85
13[d]	**3j**	*c*-C_3H_5	*n*-Bu	>20/1	**4j**	>20/1	88
14[d]	**3j**	*c*-C_3H_5	*n*-Bu	1,6/1	**4j**	1,6/1	83

[a] Reaction conditions: **3** (0.3 mmol) in CH_2Cl_2 (1 mL) at RT. The reaction times can be reduced up to 1–2 h by using 5 mol% of catalyst. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of the product based on the starting material. [d] Reaction time = 2 h.

1,6-enynes, developed by Echavarren and co-workers,[20] resulted stereospecific except for substrates bearing cyclopropyl groups as substituents of the alkene,[21] whereas in our case this type of alkene moiety does not interfere in the stereoinformation transfer.

Computational results: reaction mechanism

Aiming to shed light into the experimentally observed stereospecificity of the methoxycyclization reaction of both β-aryl- and β-alkyl-monosubstituted *o*-(alkynyl)styrenes **1** and **3**, as well as to elucidate its mechanism, we performed a thorough computational study at the M06/Def2-SVP theoretical level selecting a simplified *o*-(alkynyl)styrene **3** with Alk = R = Me as theoretical model. The influence of the solvent was taken into account via the polarizable continuum model (PCM, employing dichloromethane parameters).

A number of alternative mechanistic pathways were explored and only the lowest energy one is shown here, non-competitive alternatives can be found in the ESI. Computational results indicate that (*S**,*S**)-1*H*-indene for this substitution pattern (as in **diast-4** in Table 1, but considering Alk = R = Me) is thermodynamically more stable than the (*S**,*R**)-diastereoisomer (as in **4** in Table 1, also considering Alk = R = Me) by 13.8 kJ mol^{-1} (see ESI). This thermodynamic preference could be in agreement with the isolated 1*H*-indene derivatives formed when starting from the (*Z*)-*o*-(alkynyl)styrenes **3** but cannot explain why, when (*E*)-isomers are employed as reactants, the (*S**,*R**)-1*H*-indenes **4** are the isolated products. This seems to indicate that the observed

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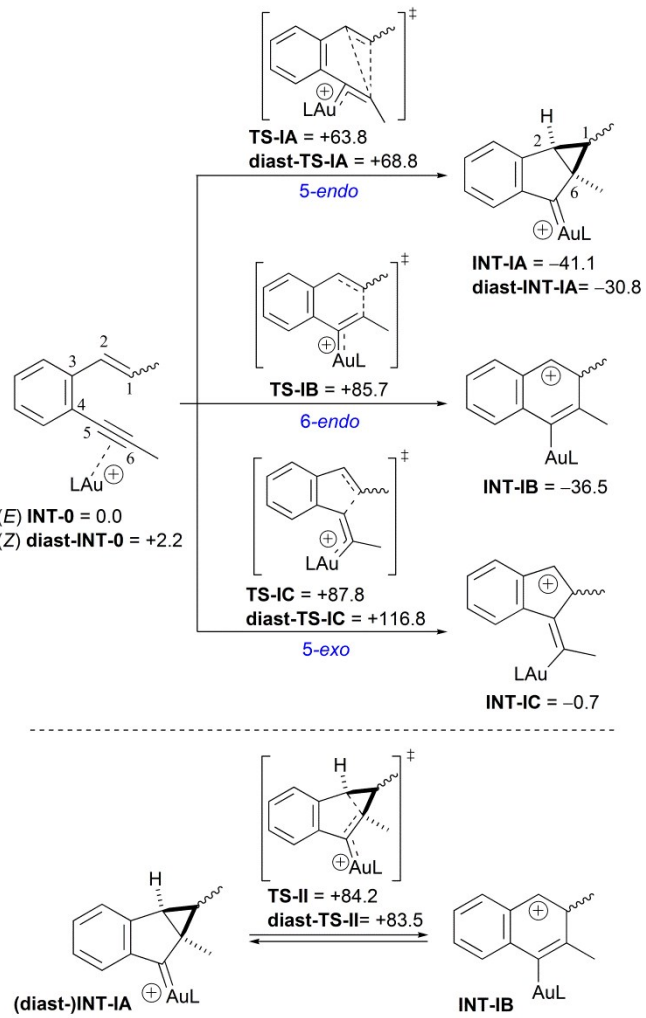

Scheme 3 Computed initial plausible *5-endo*, *6-endo* and *5-exo* cyclizations of **INT-0** and **diast-INT-0** at the PCM(DCM)/M06/Def2-SVP theoretical level. Gibbs free energies are reported, in kJ mol^{-1} (1 atm and 298 K), relative to **INT-0** (**diast-INT-0** does not proceed through a 6-*endo* TS according to our calculations).

stereospecifity is kinetically governed. With this in mind, we started to explore the competitive initial cyclizations of both (*E*)- and (*Z*)-alkynyl-gold complexes **INT-0** and **diast-INT-0**, respectively. All the geometrically plausible modes for the cyclization of this conjugated system have been considered computationally: *5-endo*, *6-endo* and also the *5-exo* modes were calculated (Scheme 3, top). It is worth noting that the first two modes, 5-*endo* and 6-*endo*, have been broadly observed in similar substrates both experimentally and through computational exploration,[22] the *5-exo* mode is usually disregarded as a non-competitive mechanistic branch. We nevertheless included the three routes for the sake of completeness. At the starting intermediate the **INT-0** stereoisomer is more stable by 2.2 kJ mol^{-1} with respect to **diast-INT-0**. Both *5-endo* cyclization transition states toward cyclopropylcarbenes **INT-IA** and **diast-INT-IA** are ~20 kJ mol^{-1} less energetic than the alternative *6-endo* cyclization furnishing the dihydronaphthalenes **INT-IB** and its enantiomer. The formation of the intermediate **(diast-)INT-IA** from enynes is well-known and has been reported in similar cycloisomerizations.[22] In fact, the related homoallyl carbocation, postulated as intermediate for transformations of β,β-disubstituted *o*-(alkynyl)styrenes (see Scheme 1), is computed to be ~50–60 kJ mol^{-1} less stable than **(diast-)INT-IA**, therefore, strongly suggesting the occurrence of a cyclopropyl carbene as a more likely intermediate (see ESI).

In good agreement with previous studies, our computational results predict that a starting *5-exo* cyclization of **INT-0** and **diast-INT-0** towards the carbocation intermediate **INT-IC** (and its enantiomer) results in higher energies than the *endo* alternative, particularly for the *Z* isomer, with an associated activation energy almost 40 kJ mol^{-1} higher than what is needed for the (*Z*)-*5-endo* cyclization (**diast-TS-IC**).

Lastly, we also considered as a viable route the interconversion between (diast-)**INT-IA** and **INT-IB** via transition structure **TS-II** and **diast-TSII**. This process is nevertheless very costly as the computed energy barriers reveal. For the transformation **(diast-)INT-1A** → **INT-IB**, the computed barriers are $\Delta G_{TS\text{-}II}^{\neq}$ = 125.3 and $\Delta G_{diast\text{-}TS\text{-}II}^{\neq}$ = 114.3 kJ mol^{-1}, respectively, and for the reverse sequence **INT-1B** → **(diast-)INT-IA**: $\Delta G_{TS\text{-}II}^{\neq}$ = 120.7 and $\Delta G_{diast\text{-}TS\text{-}II}^{\neq}$ = 120.0 kJ mol^{-1} (Scheme 3, bottom).

This initial exploration strongly suggests that the formation of either the dihydronaphthalene **INT-IB** or the indene derivative **INT-IC**, and a subsequent methanol attack is unfavourable and the alternative pathway through the cyclopropylcarbene **INT-IA** and **diast-INT-IA** operates in the experiment.

Once **INT-IA** and **diast-IA** are formed, which already contain the indene core, two alternative paths are conceivable to furnish the observed 1-metoxyalkyl-1*H*-indene derivatives **4**. **(diast-)INT-IA** could either cleave its C1-C6 bond leading to a homoallylic secondary carbocation intermediate, prone to be intercepted by a methanol molecule or, in contrast, methanol could attack directly onto the cyclopropylcarbene intermediate **(diast-)INT-IA** in an S_N2-like reaction featuring an intramolecular leaving group. It is worth noting that loss of stereoespecificity would be observed, should the homoallylic cation be involved in the reaction mechanism, due to **4** and **diast-4** becoming available via rotation of the C1–C2 bond. Gratifyingly, our simulations predict that the methanol attack onto the C1 atom of intermediate **(diast-)INT-IA** is kinetically more favourable than the proposed cyclopropyl ring-opening process (see ESI). Two transition structures were located for this S_N2 process since methanol can attack onto any of the two faces of the C1 atom: one in which the nucleophile approaches opposite to gold in an *anti*-S_N2 trajectory (**TS-III**), and the less common *syn*-S_N2 alternative **TS´-III** (Scheme 4). Our results indicate that the methanol attacks onto any of both diastereoisomers, **INT-IA** and **diast-INT-IA**, and proceeds following the *anti*-S_N2 trajectory (**TS-III**) rather than the *syn*-S_N2 alternative (**TS´-III**). Similar reactions have been previously studied and the authors also found the same methanol approach preference, the larger orbital overlap, whereby, a stronger interaction, between C1 and the incoming oxygen atom from methanol seems to be the responsible of this selective *anti* path.[23]

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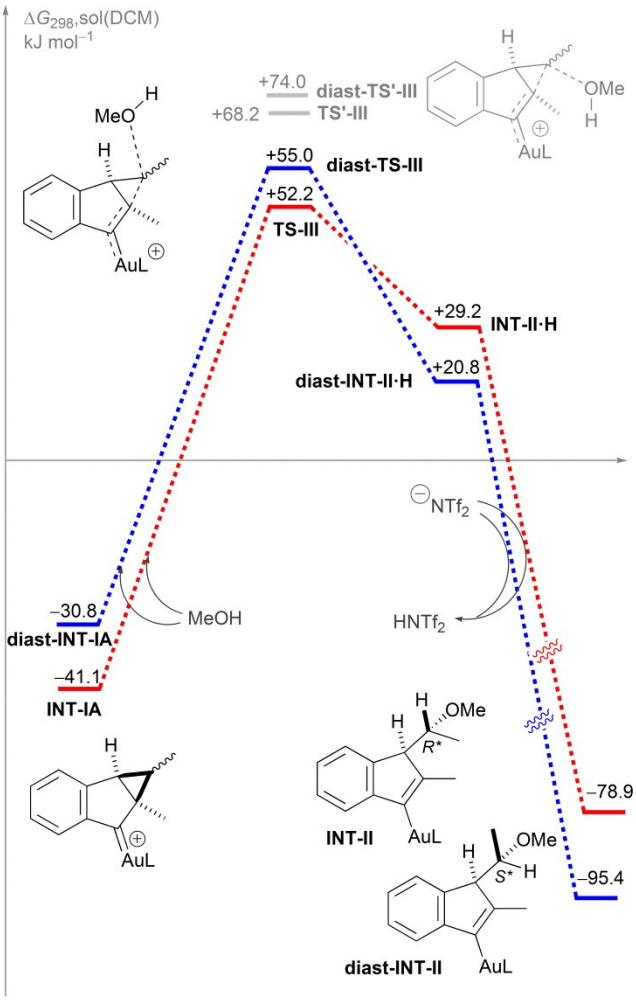

Scheme 4 Proposed mechanism for the gold(I)-mediated formation of 1-methoxyalkyl-1*H*-indenes **INT-II** and **diast-INT-II** from cyclopropylcarbene **INT-IA** and **diast-INT-IA** at the PCM(DCM)/M06/Def2-SVP theoretical level. Gibbs free energies are reported, in kJ mol^{-1} (1 atm and 298 K), relative to **INT-0.** Some structures and connections are not shown for clarity. In order to study the transfer of stereochemical information the computational study was performed with the diastereoisomers shown in this scheme, the corresponding enantiomeric forms would report analogous profiles.

Both computed favoured transition structures **TS-III** and **diast-TS-III** are shown in Figure 1. Our computational results predict that the distance of the forming O—C bond is shorter in **TS-III** species than in **diast-TS-III** (2.05 and 2.22 Å, respectively), in contrast, this situation is inverted when comparing the breaking C—C bond, which is longer in **TS-III** than in **diast-TS-III**. It is remarkable that this favoured trajectory is independent on the absolute configuration of the C1 atom since it determines the absolute configuration of the stereogenic centers present at subsequent intermediates **INT-II·H** and **diast-INT-II·H**, and, therefore, the stereospecifity of the process. Whereas transition structure **TS-III** evolves towards intermediate **INT-II·H**, its diastereoisomer **diast-INT-II·H** is obtained from **diast-TS-III**. It is noteworthy that this situation would be inverted in the case of proceeding through **TS'-III** and **diast-TS´-III**. The subsequent proton capture step by the counteranion Tf_2N^- leads to the corresponding intermediates **INT-II** and **diast-INT-II**, that afford the 1*H*-

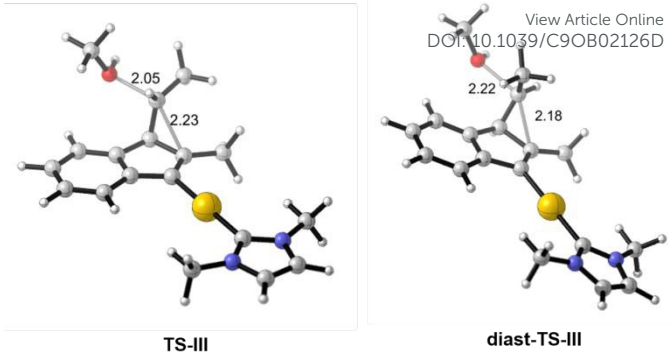

Figure 1. Computed transition structures **TS-III** and **diast-TS-III** at the PCM(DCM)/M06/Def2-SVP theoretical level. Relevant distances are shown in angstroms.

indenes derivatives **4** and **diast-4**, which show the stereospecifity observed experimentally after a protodeauration process (for full mechanism, see ESI).

Other nucleophilic cyclizations

Considering the stereospecific nature of the methoxycyclization of β-monosubstituted *o*-(alkynyl)styrenes **1** and **3**, we wondered at this point if other nucleophiles could also be suitable for this transformation thus allowing diastereoselective access to a variety 1-functionalized indenes. With enyne (*E*)-**1a** as model substrate different *O*-centered nucleophiles were essayed under the same reaction conditions as described for methanol (Table 3, entries 1–9).[24] Successful results were obtained employing a selection of primary alcohols, which gave rise to alkoxy-functionalized indenes **5a-d** in high yields and with high diastereospecificity (entries 1–4). Secondary alcohols were also able to efficiently participate in the alkoxycyclization process although slightly longer reaction times were required (entries 5 and 6). With *s*-BuOH an almost equimolecular mixture of diastereoisomers was obtained due to the new stereogenic center introduced by the external alcohol (entry 6). Interestingly, a carboxylic acid like acetic acid also turned out to be a suitable nucleophilic partner giving rise to acetate **5g** in high yield (entry 7). In addition, 1,3-cyclohexanedione selectively led to the *O*-functionalized product **5h** without competitive *C*-alkylation (entry 8).[25] Finally, when ethyl L-lactate was employed as nucleophile a mixture of diastereoisomers with respect to the new stereocenter introduced by the lactate moiety was obtained. However, we were able to isolate the major diastereoisomer in pure form thus allowing the preparation of enantiopure **5i**, although its absolute configuration was not determined (entry 9). Then, other β-aryl or β-alkyl *o*-(alkynyl)styrenes **1** or **3** were treated with selected alcohols, also leading to the corresponding *O*-functionalized indenes **5j-o** (entries 10–15).

We were also able to perform hydroxycyclization reactions with some new β-aryl *o*-(alkynyl)styrenes **1** and selected β-alkyl *o*-(alkynyl)styrenes **3d** and **3e** (entries 16–19). In these cases, a mixture of CH_2Cl_2/dioxane as solvent was required to favour water participation, as well as longer reaction times

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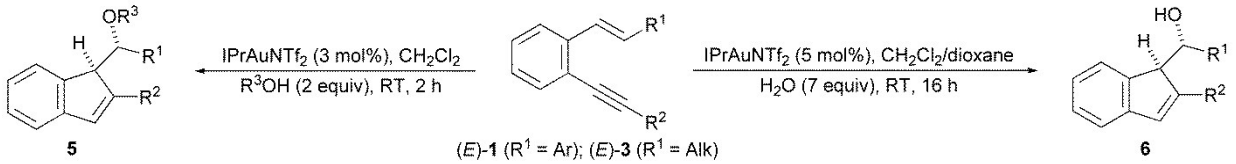
Table 3 Au(I)-catalyzed alkoxy and hydroxycyclization of β-monosubstituted *o*-(alkynyl)styrenes (*E*)-**1** and (*E*)-**3**. Synthesis of alkoxy- and hydroxy-functionalized 1*H*-indenes **5** and **6**[a]



5 (*E*)-**1** (R^1 = Ar); (*E*)-**3** (R^1 = Alk) **6**

Entry	Starting material	R^1	R^2	R^3OH	product	dr[b]	yield [%][c]
1	**1a**	Ph	Ph	EtOH	**5a**	>20/1	91
2	**1a**	Ph	Ph	*n*-BuOH	**5b**	>20/1	86
3	**1a**	Ph	Ph	H_2C=$CHCH_2OH$	**5c**	>20/1	82
4	**1a**	Ph	Ph	$PhCH_2OH$	**5d**	>20/1	71
5[d]	**1a**	Ph	Ph	*i*-PrOH	**5e**	>20/1	80
6[d]	**1a**	Ph	Ph	*s*-BuOH	**5f**	1,1/1[e]	73
7	**1a**	Ph	Ph	AcOH	**5g**	>20/1	80[k]
8[f]	**1a**	Ph	Ph	$-(CH_2)_3C(O)CH=C(OH)-$	**5h**	>20/1	86
9[g]	**1a**	Ph	Ph	(*S*)-$MeCH(CO_2Et)OH$	**5i**	1,4/1[h]	70[i]
10[d]	**1h**	Ph	*n*-Bu	H_2C=$CHCH_2OH$	**5j**	>20/1	84
11[j]	**1h**	Ph	*n*-Bu	AcOH	**5k**	>20/1	71[k]
12[g,j]	**1h**	Ph	*n*-Bu	(*S*)-$MeCH(CO_2Et)OH$	**5l**	1,5/1[h]	69[i]
13[j]	**3e**	*n*-Bu	Ph	H_2C=$CHCH_2OH$	**5m**	>20/1	72
14[j]	**3e**	*n*-Bu	Ph	AcOH	**5n**	>20/1	72[k]
15	**3f**	*n*-Bu	*c*-C_3H_5	H_2C=$CHCH_2OH$	**5o**	>20/1	82
16[l]	**1e**	4-FC_6H_4	Ph	H_2O	**6a**	>20/1	62
17[l]	**1m**	4-MeC_6H_4	*c*-C_3H_5	H_2O	**6b**	>20/1	74
18	**3d**	*n*-Pr	*c*-C_3H_5	H_2O	**6c**	>20/1	63
19[l]	**3e**	*n*-Bu	Ph	H_2O	**6d**	>20/1	68

[a] Reaction conditions: **1** or **3** (0.3 mmol), R^3OH (0.6 mmol) in CH_2Cl_2 (1 mL) at RT, or H_2O (2.1 mmol) in a 1:1 mixture of CH_2Cl_2/1,4-dioxane (1.6 mL) at RT. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield of the product based on the starting material **1**. [d] Reaction time = 3 h. [e] This dr refers to the mixture of diastereoisomers with respect to the new stereogenic center introduced by the *s*-BuOH. The two other minor diastereoisomers were also observed (<10%). [f] 1,3-Cyclohexanedione was used as R^3OH [g] (*S*)-Ethyl lactate was used as R^3OH. [h] This dr refers to the mixture of diastereoisomers with respect to the new stereogenic center introduced by the ethyl lactate. The two other minor diastereoisomers were also observed (<10%). [i] Referred to the overall yield for the two major independently isolated and enantiomerically pure diastereoisomers. [j] Reaction time = 6 h. [k] Minor amounts (~10%) of the corresponding hydroxycyclized compounds **6** were also obtained. [l] 3 mol% of catalyst was used.

with a higher amount of the catalyst in some cases. In these hydroxycyclizations a most clear superior activity of $IPrAuNTf_2$, compared with gold complexes bearing Ph_3P or $(PhO)_3P$ ligands, was observed.[26] In this way, several 1-(α-hydroxyalkyl)-1*H*-indenes **6a-d** were synthesized in good yields and also in a stereospecific way.

We then shifted our attention towards nucleophilic counterparts that could give rise to the formation of new C–C bonds. With enyne (*E*)-**1a** as model substrate electron-rich aromatic compounds such as 1,3,5-trimethoxybenzene, 1,3-dimethoxybenzene, and 3,5-dimethoxyphenol resulted useful nucleophiles able to participate in these Au-catalyzed cyclizations (Scheme 5). Whereas the nucleophilic cyclization with 1,3,5-trimethoxybenzene gave rise selectively to indene **7a** in high yield and as single diastereoisomer, the use of 1,3-dimethoxybenzene as the nucleophilic counterpart led to indene **7b** as a ~8:1 mixture of diastereoisomers. Moreover, when using 3,5-dimethoxyphenol as external nucleophile, a regioisomeric mixture of **7c** and **7´c** (~2:1) was generated due to the presence of two competitive nucleophilic positions in the aromatic core. Nevertheless, single diastereoisomers of these indene derivatives were obtained and the major one, **7c**, could be isolated in pure form (Scheme 5). Finally, this reaction was successfully extended to a selection of *o*-(alkynyl)styrenes (*E*)-**1** that provide useful access to 1-diarylmethyl-1*H*-indenes **7d-g** as single diastereoisomers in good yields by their treatment with 1,3,5-trimethoxybenzene (Scheme 5).[27]

Conclusions

In summary, we have reported that gold-catalyzed nucleophilic cyclizations of β-monosubstituted *o*-(alkynyl)styrenes occur in

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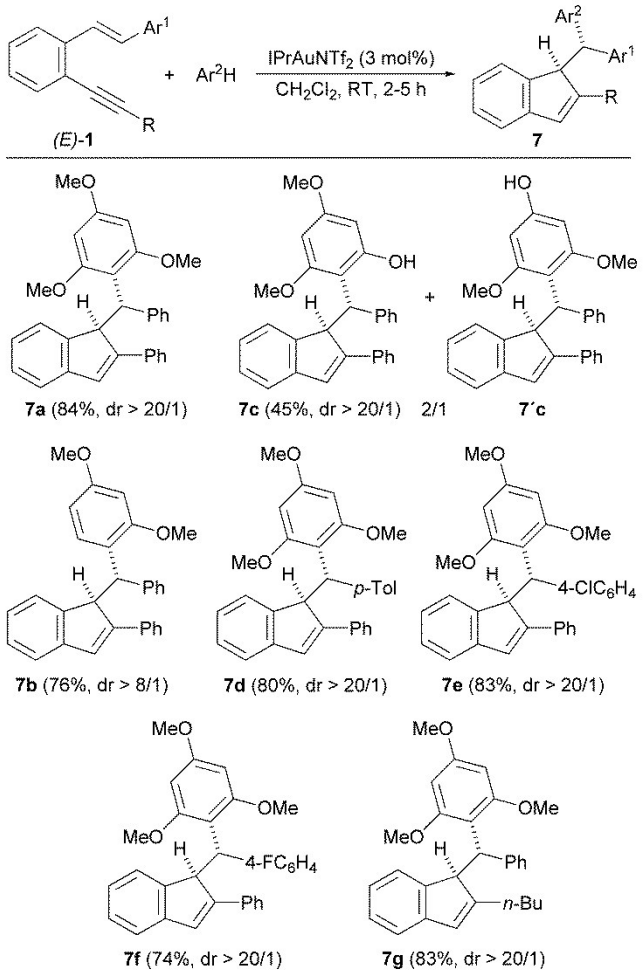

Scheme 5 Au-catalyzed nucleophilic additions of electron-rich arenes to (*E*)-**1**. Synthesis of 1-diarylmethyl-1*H*-indenes **7**.

a 5-*endo* regiospecific way regardless the nature of the substituent at the β-position, despite the fact that a 6-*endo* cyclization could be initially considered more favourable. The process exhibits broad scope both at the substrate and the nucleophile, including O-centred nucleophiles, such as functionalized primary and secondary alcohols and acetic acid, and C-centred nucleophiles such as electron-rich arenes. Remarkably, the reactions are generally stereospecific affording interesting functionalized 1*H*-indene derivatives in high yields and as single diastereoisomers, just by simply transferring the stereochemical information of the alkene moiety into the final product. The experimental results have been further supported by theoretical calculations whose conclusions are in agreement with the observed reactivity. So, a cyclopropyl gold carbene is proposed as the key intermediate for these reactions, which allows the positive charge to be greatly homoallylically stabilized. This intermediate evolves through an attack in *anti*-S_N2 trajectory of an O- or C-based nucleophile, yielding functionalized 1*H*-indenes. This cyclopropyl carbene intermediate also plays a decisive role in the stereospecifity of the process allowing the transfer of the stereochemical information of the alkene into the final products.

Experimental

General procedure for the methoxycyclization of *o*-(alkynyl)styrenes 1 and 3

To a 10 mL oven-dried vial containing a magnetic stirring bar, $IPrAuNTf_2$ (0.009 mmol, 7.8 mg, 3 mol%), CH_2Cl_2 (0.6 mL) and MeOH (1.5 mmol, 0.06 mL) were added in sequence at RT, and the mixture was stirred for 5 min. A solution of the corresponding starting *o*-(alkynyl)styrene **1** or **3** (0.3 mmol) in CH_2Cl_2 (0.4 mL) was subsequently added. The resulting reaction mixture was stirred at RT until complete consumption of the styrene derivative was observed by GC–MS (1–6 h). The mixture was filtered through a short pad of silica gel using a 100:1 mixture of hexane/EtOAc as eluent, the solvent was removed under reduced pressure, and the crude mixture was purified by flash column chromatography on silica gel using mixtures of hexane and EtOAc as eluents to obtain the corresponding 1-(α-methoxybenzyl)-1*H*-indenes **2**, and 1-(1-methoxyalkyl)-1*H*-indenes **4** in the yields reported in Tables 1 and 2.

Computational methods

All the structures and energies here reported have been optimized through the Kohn-Sham formulation of the density functional theory (DFT) [28] at the M06/Def2-SVP theoretical level.[29] This methodology has been found particularly efficient for the description of Au(I) catalytic cycles, including energy minima and transition structures.[30] Solvent effects were calculated with the PCM continuum solvation model with dichloromethane parameters.[31] The nature of all stationary points as minima or transition structures on the potential energy surface was confirmed by a frequency analysis at the same level of theory. At all the stationary points thermal contributions to the electronic energy were computed through the analytic second derivatives of the energy with respect to atomic displacements and the application of the rigid rotor and harmonic oscillator (RRHO) approximations to the partition functions. The stability of the resulting wavefunctions were checked for all the optimized structures.[32] All calculations were performed using the ultrafine grid implemented in Gaussian 09 E.01.[33]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Burgos and Junta de Castilla y León and FSE, respectively, for predoctoral contracts. M. M.-L. thanks Xunta de Galicia for a postdoctoral contract (ED418B 2016/166-0).

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