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COMMUNICATION

Gold(I)-catalyzed diastereoselective synthesis of 1-α-oxybenzyl-1*H*-indenes†

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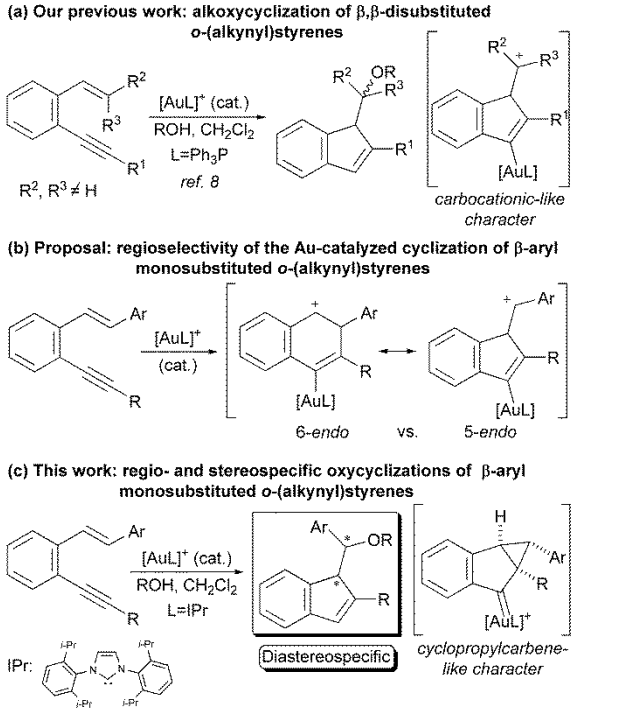
The gold(I)-catalyzed oxycyclization of β-aryl monosubstituted *o*-(alkynyl)styrenes gives rise to 1-α-methoxy or 1-α-hydroxybenzyl-1*H*-indenes in a diastereospecific way. In contrast with β,β-disubstituted *o*-(alkynyl)styrenes, the stereochemical outcome of the process, diastereospecific reactions, supports the higher contribution of a gold intermediate with cyclopropylcarbene-like character.

Gold-catalyzed cycloisomerization reactions of 1,n-enynes have received a good deal of attention in the last years providing versatile routes to interesting carbocyclic structures not easily prepared by classical methods.[1] In this context, 1,5-enyne cycloisomerizations involving almost always 5-*endo*-*dig* cyclizations[2] have been less developed, despite their synthetic usefulness for the preparation of interesting cyclopentene derivatives.[3] In this field, our group and others have been specially interested in the study of the reactivity of *o*-(alkynyl)styrenes,[4] as a particular type of 1,3-dien-5-ynes.[5] Although most of the previously reported cycloisomerizations of *o*-(alkynyl)styrenes led to naphthalene derivatives through formal 6-*endo* cyclizations,[6] considering Gagosz and co-workers´ report about the synthesis of cyclopentenes through 5-*endo* alkoxycyclization of 3-acetoxy-1,5-enynes,[7] we first demonstrated that the corresponding 5-*endo* cyclization pathway could be induced by a proper selection of the olefin substitution pattern. We found that β,β-disubstituted *o*-(alkynyl)styrenes undergo selectively 5-*endo* cyclizations, using cationic gold complexes bearing triphenyl phosphine as ligand both in the presence or absence of silver salts.[8] In this way, indene derivatives, which are privileged scaffolds mainly due to their applications in materials science and as ligands for metallic catalysts,[9] are easily accessed from simple starting materials.[10] After our seminal work, different authors have reported related 5-*endo* cyclizations of β,β-disubstituted *o*-(alkynyl)styrenes under gold- and other transition metal-catalysis.[11] Using these β,β-disubstituted *o*-(alkynyl)styrenes, and external oxygen nucleophiles, we have been able to prepare 1-alkoxy- or 1-hydroxy-dialkylmethyl-1*H*-indenes. However, when these starting materials possess two different groups at the β-position the stereoselectivity of the cyclization had not been properly established in our previous work, and we assumed that the oxycyclization was not stereospecific likely due to a high contribution of a gold-stabilized homoallylic carbocation species as intermediate (Scheme 1a).[8c] At this point, we decided to explore the gold-catalyzed nucleophilic additions to β-aryl-monosubstituted *o*-(alkynyl)styrenes.[12] In this case two major issues, regio- and stereoselectivity, should be addressed. Firstly, for the initial



Scheme 1 Gold(I)-catalyzed alkoxycyclization of β,β-disubstituted *o*-(alkynyl)styrenes (previous work) and β-monosubstituted *o*-(alkynyl)styrenes (this work).

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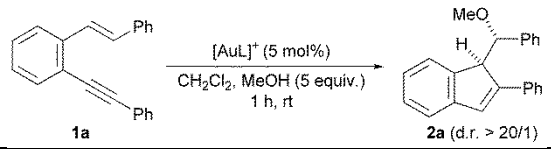
† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, NMR spectra of all products. CCDC 1585617 for **3i**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

olefin attack, triggered by the gold-activation of the alkyne, a regioisomeric 6-*endo* cyclization could be competitive with the previously reported 5-*endo* as the positive charge would be located at secondary carbons in the carbocationic-like intermediate for both types of ring closures (Scheme 1b). Secondly, the stereochemical outcome of these reactions, i.e. stereospecific or non-stereospecific nature of the process, could contribute to shed light about the controversial character of the involved gold intermediates, which could be also influenced by the nature of the ligands on the gold catalyst.[13] Herein, we want to report our results about the nucleophilic additions to β-aryl-monosubstituted *o*-(alkynyl)styrenes under gold-catalysis, which take place selectively through 5-*endo* cyclizations and in a diastereospecific manner leading to a new family of functionalized indene derivatives (Scheme 1c).

To perform our goal, we selected (*E*)-β-phenyl *o*-(alkynyl)styrene **1a** as model substrate and treated it with an excess of MeOH in CH_2Cl_2 under the catalysis of a selection of gold complexes (Table 1). In a first attempt, **1a** was treated with $Ph_3PAuNTf_2$ and after 1 h we observed the partial but stereospecific formation of 1-α-methoxybenzyl-1*H*-indene **2a** (entry 1). A similar result was obtained when using the catalytic system $Ph_3PAuCl/AgSbF_6$ that we had previously used for the methoxycyclization of β,β-disubstituted *o*-(alkynyl)styrenes (entry 2). A slightly better result was displayed by gold catalyst bearing a phosphite ligand (entry 3), whereas complete conversions were obtained when gold complexes with bulky biarylphosphines as ligands were employed (entries 4–6). However, the best yield was obtained using the NHC-gold(I) complex $IPrAuNTf_2$, possessing the weakly coordinating counteranion Tf_2N^- and a highly electron-donating ligand (entry 7). Moreover, the catalyst load could be halved without a serious impact on the reaction outcome (entry 8), supporting its remarkably high activity for a wide variety of Au-catalyzed transformations that had been elegantly shown by Gagosz and co-workers.[14] A brief silver salt screening showed no beneficial silver effect or improvement for this process (entries 9–11). Remarkably, in all the tests only one diastereoisomer of indene **2a** was observed in the ^{1}H NMR of the crude reaction mixture, whose stereochemistry was initially assigned based on previous literature reports.[7a]

Table 1 Effect of the gold catalyst on the methoxycyclization of (*E*)-β-phenyl *o*-(alkynyl)styrene **1a**[a]



1a **2a** (d.r. > 20/1)

Entry	Catalyst	Conversion (%)[b]	Yield (%)[c]
1	$Ph_3PAuNTf_2$	76	51
2	$Ph_3PAuCl/AgSbF_6$	66	54
3	$[(3,5\text{-}t\text{-}Bu)_2C_6H_3O_3]_3AuCl/AgNTf_2$	97	65
4	$XPhosAuNTf_2$	100	76
5	$BrettPhosAuNTf_2$	100	62
6	$JohnPhosAuNTf_2$	100	84
7	$IPrAuNTf_2$	100	89
8[d]	$IPrAuNTf_2$	100	84
9	$IPrAuCl/AgNTf_2$	100	63
10	$IPrAuCl/AgSbF_6$	100	79
11	$IPrAuCl/AgBF_4$	100	86

[a] Reactions conducted using 0.1 mmol of **1a** in CH_2Cl_2 (0.8 mL). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by ^{1}H NMR using CH_2Br_2 as internal standard. When the NMR yield is significantly lower than the conversion several unidentified products were observed. [d] Carried out with 2.5 mol% of catalyst.

Echavarren and co-workers had established that gold complexes with highly electron-donating ligands, such as NHCs, enhance the carbene-like character of the gold intermediates in cyclizations of 1,5-enynes.[13] Considering this fact in the context of the ligand effects in gold catalysis,[15] these preliminary results seem to support that the reactions of these β-aryl monosubstituted *o*-(alkynyl)styrenes **1** would take place through an intermediate that requires a higher retrodonation of gold to stabilize the initially generated carbocation and so, they proceed more efficiently with complexes bearing donor ligands.

With the optimized reaction conditions in hand, we proceeded to evaluate the behaviour of a series of β-aryl *o*-(alkynyl)styrenes **1**. As shown in Table 2, the transformation was suitable for a variety of starting substrates **1a-e** bearing different substituents at the triple bond, including (hetero)aromatic, alkyl, alkenyl, and arylthio groups (entries 1–7). Interestingly, starting from geometrically pure *E*-isomers of the *o*-(alkynyl)styrenes **1a-e**, the corresponding methoxybenzyl indenes **2a-e** were obtained in high yields, and as single diastereoisomers in all the cases, showing the potential of this reaction as a wide variety of groups are allowed to be present in the starting alkyne. In addition, we have also checked that the stereoinformation of the alkene is finely transferred to the final cyclizated product, as using **1a** as a ca. 1/1 mixture of geometrical isomers led to the corresponding indene **2a** as a ca. 1/1 mixture of diastereoisomers (entry 2). Moreover, using (*Z*)-**1b** as starting material the other diastereoisomer of **2b** (**diast-2b**) was selectively formed (entries 3 vs. 4), thus proving the stereospecificity of the reaction. Regarding the aryl substituent at the β-position of the olefin, *p*-tolyl- as well as 1-naphthyl-substituted *o*-(alkynyl)styrenes **1f-i** behaved the same way as parent **1a** providing high yields of the corresponding indene derivatives **2f-i** and with complete control of the stereochemical outcome of the reactions determined by the stereochemistry of the starting enyne (entries 8–11). Moreover, substrates bearing functionalized aryl groups, such as **1j** and **1k**, also methoxycyclized leading to the corresponding indenes **2j** and **2k** in good yields and in a diastereospecific manner (entries 12–13). Interestingly, with *o*-(alkynyl)styrene **1k** possessing a butyl group as alkyne substituent the methoxycyclization of the *E*-isomer was found to be slower than the *Z*-isomer leading, in the first case, to competitive addition of methanol to the triple bond (entry 13). Finally, *o*-(alkynyl)styrenes **1l** and **1m**, functionalized with an electron-rich 4-methoxyphenyl group at the β-position, were

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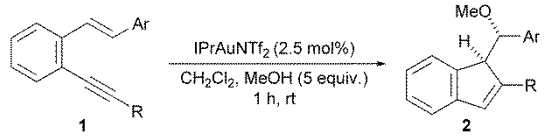
Table 2 Gold-catalyzed methoxycyclization of β-aryl *o*-(alkynyl)styrenes **1**. Diastereospecific synthesis of 1-methoxybenzyl-1*H*-indenes **2**[a]



Entry	1	Ar	R	*E*/*Z*	2	d.r.[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**	Ph	*n*-Bu	>20/1	**2b**	>20/1	91
4	**1b**	Ph	*n*-Bu	<1/20	**diast-2b**	>20/1	87
5[d]	**1c**	Ph	*c*-C_6H_9[e]	>20/1	**2c**	>20/1	82
6	**1d**	Ph	3-Th[f]	>20/1	**2d**	>20/1	87
7	**1e**	Ph	SPh	>20/1	**2e**	>20/1	90
8	**1f**	4-MeC_6H_4	Ph	>20/1	**2f**	>20/1	86
9	**1g**	4-MeC_6H_4	*n*-Bu	>20/1	**2g**	>20/1	75
10	**1h**	1-naphthyl	Ph	>20/1	**2h**	>20/1	88
11	**1i**	1-naphthyl	*n*-Bu	>20/1	**2i**	>20/1	91
12	**1j**	4-ClC_6H_4	Ph	>20/1	**2j**	>20/1	85
13[g]	**1k**	4-ClC_6H_4	*n*-Bu	<1/20	**diast-2k**	>20/1	88
14	**1l**	4-MeOC_6H_4	Ph	>20/1	**2l**	16/1	86
15	**1l**	4-MeOC_6H_4	Ph	1/8	**2l**	1/5	83
16	**1m**	4-MeOC_6H_4	*n*-Bu	9/1	**2m**	9/1	70

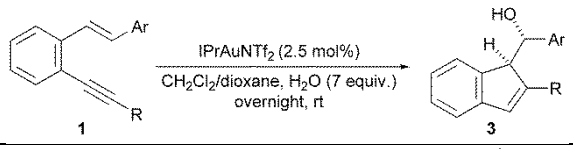
[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **1** in CH_2Cl_2 (1 mL) at RT. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of product based on starting material **1**. [d] Reaction time = 48 h. [e] Cyclohexen-1-yl. [f] 3-Thienyl. [g] Reaction time = 4 h. When the reaction was carried out with (*E*)-**1k** sub-products derived from competitive attack of MeOH to the triple bond were also formed, although **2k** was also formed with d.r. > 20/1.

subjected to the standard conditions giving rise to the methoxy-functionalized indene derivatives **2l** and **2m** in high yields (entries 14–16). The reactions of **1l** take place with a minor loss of the stereospecificity (entries 14–15), likely due to a competitive contribution of the carbocationic like-character of the gold intermediate considering the ability of the 4-methoxyphenyl group to stabilize carbocations at the benzylic position. A similar observation had been reported by Echavarren et al. in the alkoxycyclization of 1,6-enynes.[16]

As we had previously demonstrated that water could also be a useful nucleophile for the hydroxycyclization reactions of β,β-disubstituted *o*-(alkynyl)styrenes,[8c] we decided to check if this process also works with β-aryl *o*-(alkynyl)styrenes **1**. After some experimentation with model **1a** we found that the use of a mixture of CH_2Cl_2 and dioxane as solvent allows external water to participate in the cyclization leading to the formation of 1-(α-hydroxybenzyl)-1*H*-indene **3a** that was obtained in good yield and as a single diastereoisomer (Table 3, entry 1). Remarkably, in the optimization study for this process we observed no hydroxycyclization for **1a** in the presence of $Ph_3PAuNTf_2$ or $(PhO)_3PAuCl/AgSbF_6$ as catalysts,[17] showing again the superior activity of the gold complex bearing the NHC ligand for the cyclizations of β-monosubstituted *o*-(alkynyl)styrenes. Taking into account the potential synthetic interest of 1-(α-hydroxybenzyl)-1*H*-indenes for further transformations, we decided to prepare a variety of hydroxycyclizated products **3**. A selection of starting (*E*)-β-aryl *o*-(alkynyl)styrenes **1** efficiently underwent the hydroxycyclization under the standard conditions, resulting in formation of the expected alcohols **3** in high yields and in a stereospecific manner. As established above, the nucleophilic addition of water to (*E*)-**1a** afforded one diastereoisomer of **3a**, whereas starting from a mixture of geometrical isomers of **1a** led to hydroxyindene derivative **3a** as a mixture of diastereoisomers (entries 1 vs. 2). A similar result was observed for *o*-(alkynyl)styrene **1b** bearing a butyl group as substituent of the triple bond (entries 3 vs. 4). Starting enynes **1c-e**, possessing different groups at the triple bond, also efficiently underwent the hydroxycyclization reaction giving rise to the corresponding alcohols as single diastereoisomers although with **1e** no complete conversion was achieved under these conditions (entries 5–7). In addition, selected starting *o*-(alkynyl)styrenes **1**, bearing different aryl groups at the β-position of the olefin, **1h,i,l,m** also provided access to the corresponding 1-(α-hydroxybenzyl)indenes **3** in good yields (entries 8–11), although with butyl-substituted starting *o*-(alkynyl)styrene **1i** complete conversion was again not achieved (entry 9). Analogous to what was observed in its methoxyclization, when *o*-(alkynyl)styrene **1l**, bearing an electron-rich 4-methoxyphenyl group as aryl substituent of the alkene, was used as starting material the diastereospecificity was practically lost and the corresponding hydroxyindene derivative **3l** was obtained as a mixture of diastereoisomers (entry 10). Moreover, in order to unambiguously establish the relative stereochemistry of the diastereoisomer generated in these gold-catalyzed methoxy- and hydroxycyclizations of *o*-(alkynyl)styrenes **1**, the structure of **3i** was further assigned by X-ray analysis.[18]

Having determined that the methoxycyclization reaction of β-aryl *o*-(alkynyl)styrenes **1** is stereospecific, i.e. the stereoinformation is completely transferred in most of the

Table 3 Gold-catalyzed hydroxycyclization of β-aryl *o*-(alkynyl)styrenes **1**. Synthesis of 1-(1-hydroxybenyl)-1*H*-indenes **3**[a]

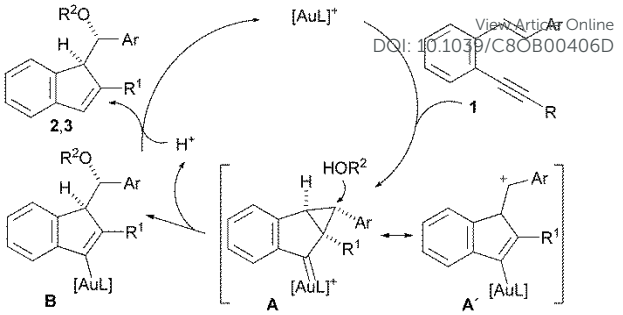


Entry	1	Ar	R	*E*/*Z*	3	d.r.[b]	Yield (%)[c]
1[d]	**1a**	Ph	Ph	>20/1	**3a**	>20/1	76
2	**1a**	Ph	Ph	1/1	**3a**	1/1	76
3	**1b**	Ph	*n*-Bu	>20/1	**3b**	>20/1	77
4	**1b**	Ph	*n*-Bu	1/1	**3b**	1/1	72
5	**1c**	Ph	*c*-C_6H_9[e]	>20/1	**3c**	>20/1	70
6	**1d**	Ph	3-Th[f]	>20/1	**3d**	>20/1	75
7	**1e**	Ph	SPh	>20/1	**3e**	>20/1	60[g]
8	**1h**	1-naphthyl	Ph	>20/1	**3h**	>20/1	79
9	**1i**	1-naphthyl	*n*-Bu	>20/1	**3i**	>20/1	53[h]
10	**1l**	4-MeOC_6H_4	Ph	>20/1	**3l**	3.5/1	65
11	**1m**	4-MeOC_6H_4	*n*-Bu	>20/1	**3m**	>20/1	63

[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **1** in a 1:1 mixture of CH_2Cl_2 and 1,4-dioxane (1.6 mL) at rt. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of product based on starting material **1**. [d] Reaction time = 4 h. [e] Cyclohexen-1-yl. [f] 3-Thienyl. [g] ~80% conversion. [h] ~65% conversion despite an additional load of 2.5 mol % of the catalyst was added.

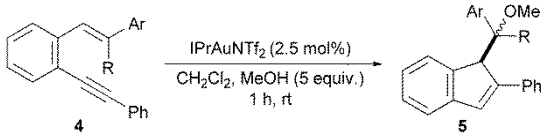
cases from the alkene to the final indene, we wondered if this fact is also true for β,β-disubstituted *o*-(alkynyl)styrenes **4** as it had not been properly established in our previous reports (Table 4).[8c] When (*Z*)-β-methyl-β-phenyl *o*-(alkynyl)styrene **4a** was used as starting enyne the corresponding methoxycyclizated indene **5a** was obtained as a single diastereoisomer, under the same conditions described for **1** (entry 1). Moreover, almost the same result was obtained using gold complexes bearing Ph_3P as ligand in the presence or absence of silver salts (entries 2–3). In this case, the similar reactivity of substrate **4a** in the presence of the gold catalyst, bearing both the NHC and the phosphine ligands, is not surprising due to the higher nucleophilic nature of the trisubstituted alkene that would contribute to stabilize the carbocationic-like character of the intermediate. However, submission of *o*-(alkynyl)styrene **4b**, with an ethyl substituent instead of a methyl one at the β-position, to the same conditions resulted in an almost complete loss of stereospecificity (entry 4). Intrigued by this result, other *o*-(alkynyl)styrenes **4** with different substituents at the β-positions were also tested. With **4c**, bearing a propyl group as R substituent, the corresponding methoxycyclizated product **5c** was obtained as a mixture of diastereoisomers clearly different from the mixture of geometrical isomers of the starting material (entry 5). A similar behaviour was observed for substrates **4d** (Ar = 4-FC_6H_4, R = Et), **4e** (Ar = 4-$MeOC_6H_4$, R = Me), and **4f** (Ar = 4-$MeOC_6H_4$, R = Et) (entries 6–8). These results seem to indicate that when starting from β,β-disubstituted *o*-(alkynyl)styrenes **4**, possessing a more nucleophilic trisubstituted alkene, their methoxycyclization reactions are not completely stereospecific in all cases, with variable degrees of stereoinformation loss that could also be influenced by steric hindrance issues.

By analogy with our previously reported mechanistic proposal for the methoxycyclization of β,β-disubstituted *o*-(alkynyl)styrenes[8c] and on the basis of other known gold-catalyzed enyne cyclizations,[13] a likely mechanism to account for the observed stereoselectivity issues is outlined in Scheme 2. An initial activation of the alkyne through coordination of cationic gold(I) triggers the attack of the olefin moiety through a 5-*endo* cyclization to give intermediate cyclopropyl carbene **A**, which has an alkenylgold carbocation mesomeric form **A´**. Whereas attack of the *O*-nucleophile to **A** would ensure a stereospecific process leading to the vinyl gold species **B** that would be subsequently protodemetalated to afford the functionalized indenes **2** and **3**, the competitive contribution of **A´** to the intermediate gold complex structure would lead to a partial loss of the stereoinformation from the configurationally defined alkene. When this stereoinformation is totally transferred to the final indene it seems to indicate a greater, or almost exclusive, contribution of the cyclopropyl gold carbene **A**, as well as its configurational stability. However, when the final functionalized indene derivative is obtained as a mixture of diastereoisomers in spite of starting from only one geometrical isomer of the alkene, as it is the case with most of the β,β-disubstituted *o*-(alkynyl)styrenes **4**, it seems to point out that a competitive contribution of the carbocationic intermediate **A´** is occurring, likely due to the higher stabilization of the positive charge at the β-carbon of the substrate caused by its tertiary nature. In agreement with Echavarren´s and Gagosz´s proposals,[7,13] our results with β-monosubstituted *o*-(alkynyl)styrenes support that the intermediates in these Au-catalyzed cyclizations are gold-stabilized homoallylic carbocations and not open carbocations, and are probably better represented as cyclopropyl gold carbenes instead of simple carbocations.[19] In addition, the rapid and stereospecific attack of the nucleophile to configurationally stable cyclopropyl gold carbene **A** accounts for the relative stereochemistry of the obtained indene derivatives. For substrates **4b-f**, as well as with **1l**, in which the reactions are not completely stereospecific, the bond rotation of the carbocationic intermediate should be faster than the attack of the methanol, likely due to the higher weakeness of the cleaved bond in these cases. The stereospecific reaction of **4a** shows that the homoallylic stabilization of the carbocation is significant even for a substrate in which the positive charge is highly stabilized by methyl and phenyl groups.



Scheme 2 Mechanistic proposal

Table 4 Gold-catalyzed methoxycyclization of β,β-disubstituted *o*-(alkynyl)styrenes **4**[a]



4 5

Entry	4	Ar	R	*E/Z*	5	d.r.[b]	Yield (%)[c]
1	**4a**	Ph	Me	<1/20	**5a**	>20/1	87
2[d]	**4a**	Ph	Me	<1/20	**5a**	16/1	89
3[e]	**4a**	Ph	Me	<1/20	**5a**	16/1	86
4	**4b**	Ph	Et	17/1	**5b**	3/1	78
5[f]	**4c**	Ph	*n*-Pr	8/1	**5c**	3/1	61
6	**4d**	4-FC_6H_4	Et	1/15	**5d**	5/1	60
7	**4e**	4-$MeOC_6H_4$	Me	<1/20	**5e**	13/1	88
8	**4f**	4-$MeOC_6H_4$	Et	1/18	**5f**	8/1	90

[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **4** in CH_2Cl_2 (2 mL) at rt. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield of product based on starting material **4**. [d] Carried out with $Ph_3PAuNTf_2$ as catalyst. [e] Carried out with $Ph_3PAuCl/AgSbF_6$ as catalytic system. [f] Carried out with an additional load of 2.5 mol % of catalyst and one hour more.

Conclusions

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In conclusion, we have reported the gold(I)-catalyzed methoxy- and hydroxy-cyclizations of β-aryl-monosubstituted *o*-(alkynyl)styrenes that take place in a regio- and stereospecific way leading to interesting functionalized indene derivatives in high yields and as single diastereoisomers. The obtained results support that the intermediates in these gold-catalyzed cyclizations are better described as cyclopropyl gold carbenes in which the positive charge is significantly stabilized homoallylically. Further attack of the external nucleophile to these intermediates is faster than the competitive rotation around the weakest bond of the cyclopropyl ring. Only with highly activated and/or sterically-encumbered substrates, which place the positive charge in a tertiary carbon, the cyclizations are not completely stereospecific.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 For selected reviews, see: (*a*) A. S. K. Hashmi, *Pure Appl. Chem.*, 2010, **82**, 1517; (*b*) C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902; (*c*) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028.

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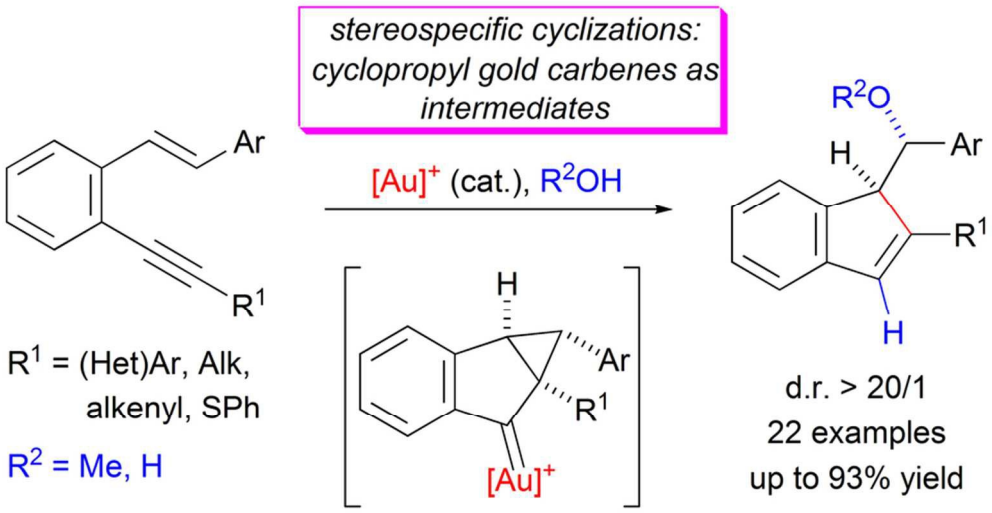

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