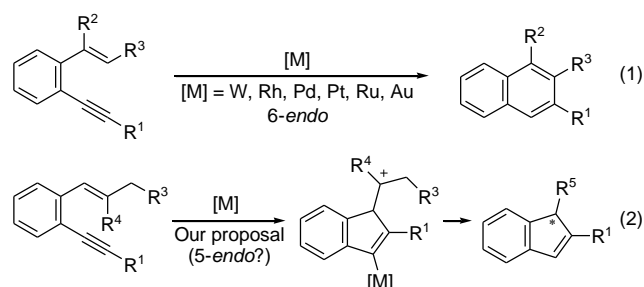


Au(I)-Catalyzed Enantioselective Synthesis of Functionalized Indenes

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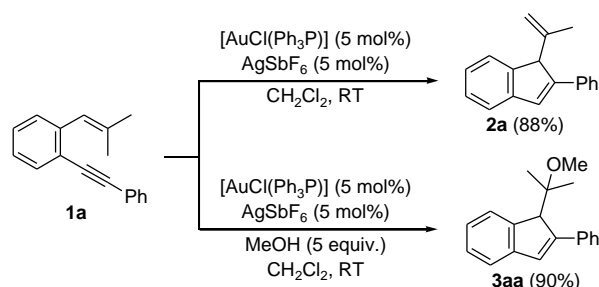
Molecules containing the 1*H*-indene scaffold show a wide range of biological activities,^[1] and possess great interest as functional materials,^[2] as well as precursors of metallocene complexes as for catalytic polymerization processes.^[3] So, several methodologies have been developed for their synthesis.^[4] Despite the unquestionable interest of optically active indenenes bearing the C-1 as stereogenic center, as far as we know, only two closely related strategies for the enantioselective synthesis of these compounds from achiral substrates have been published.^[5-8] Both of them are based on the use of boronic acid derivatives as starting materials and dicationic Pd(II) complexes as catalyst. Thus, enantioenriched 1-arylindenenes have been obtained in a cascade 1,4-addition-aldol condensation process,^[5] whereas 1*H*-indenenes bearing a CH₂COR group at the C-1 position are formed from *ortho*-boronate substituted cinnamic ketones and internal alkynes.^[6,7] The scarcity of general methods for the synthesis of optically active indenenes (in particular from achiral substrates) aimed us to initiate a project in this field. Our premise was the use of easily available starting materials and, therefore, we fixed our attention on the catalytic cyclization of *ortho*-(alkynyl)styrenes. In this context, it should be taken into consideration that the skeletal rearrangement of *ortho*-(alkynyl)styrenes catalyzed by several metallic complexes has been described to afford naphthalene derivatives through a 6-*endo* cyclization process (Scheme 1, eq. 1).^[9-13] However, a careful examination of all these publications showed that reactions with *o*-(alkynyl)styrenes where the terminal carbon of the alkene was disubstituted were not reported. So, we envisaged that *o*-(alkynyl)styrenes possessing a highly substituted alkene moiety and an internal acetylene could favour the 5-*endo* reaction pathway, due to a better stabilization of the exocyclic carbocationic intermediate, to form the desired indene skeleton with a stereogenic center at C-1 (Scheme 1, eq. 2).^[14] Herein we report our success on this unprecedented metal-catalyzed 5-*endo-dig* cyclization of *o*-(alkynyl)styrenes and the application of this reaction in the synthesis

of enantiomerically-enriched indenenes.



Scheme 1. Skeletal rearrangement of *ortho*-(alkynyl)styrenes. Previous work and proposed pathway.

For the initial assays we selected 2',2'-dimethyl *o*-(phenylethynyl)styrene **1a** as a model substrate (Scheme 2). Due to their excellent ability to activate alkynes,^[15] several complexes derived from coinage metals and platinum were tested as catalysts for the desired transformation. However, no reaction was observed with metal complexes such as AgSbF₆, PtCl₂, [PtCl₂(cod)], CuI, AuCl₃, AuCl or [AuCl(Ph₃P)]. Encouragingly, the reaction proceeded to completion within 30 min to yield the indenyl derivative **2a** in a high isolated yield (88%), when it was performed in dichloromethane at room temperature in the presence of the cationic gold(I) complex generated in situ from 5 mol% of [AuCl(Ph₃P)] and 5 mol% of AgSbF₆.^[16] Moreover, when this reaction was conducted in the presence of 5 equivalents of methanol we observed the formation of compound **3aa** in excellent yield (90%) (Scheme 2). The high selectivity of these reactions should be remarked as we did not observe the formation of naphthalene derivatives coming from a 6-*endo-dig* type cyclization or any other product coming from 5-*exo* additions of the alkene to the triple bond.



Scheme 2. Initial experiments. Proof of concept.

A catalytic cycle that explains the formation of indenenes **2a** and **3aa** is shown in Scheme 3.^[17] The reaction is initiated by coordination of the cationic gold complex to the triple bond of the starting *o*-(alkynyl)styrene **1a** to give intermediate **4**. Intramolecular addition of the alkene moiety selectively leads to the cationic intermediate **5**, which can be represented as the two resonance structures **5a** and **5b**, through a 5-*endo-dig* cyclization as we

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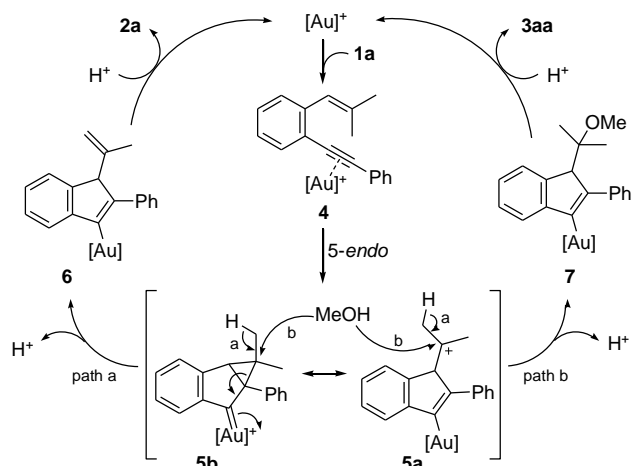
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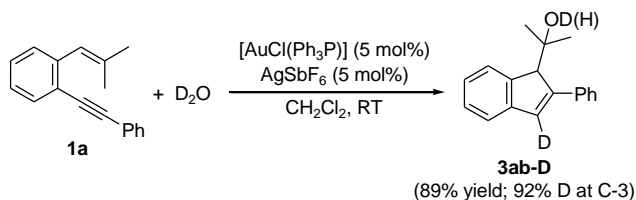
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anticipated. Elimination of a proton in **5** (path a) furnishes the vinyl-gold intermediate **6**, which after a protodemetalation reaction gives the indene **2a**. Alternatively, in the presence of methanol, trapping of the carbocation **5a** or a nucleophilic attack on **5b** accounts for the formation of vinyl-gold intermediate **7**. Further protodemetalation furnishes compound **3aa** regenerating the catalytic species.



Scheme 3. Proposed mechanisms for the synthesis of indenenes.

To support the proposed mechanism we performed the labelling experiment shown in Scheme 4. Thus, when compound **1a** was reacted in the presence of 5 equivalents of D₂O under the catalytic conditions previously commented we observed the exclusive formation of the deuterated compound **3ab-D** in 89% yield (92% deuterium incorporation at C-3). Interestingly, this experiment also served to demonstrate that water could be used as nucleophilic partner in this new reaction.



Scheme 4. Labelling experiment.

Once we had demonstrated the feasibility of our method for the preparation of indenenes through a gold-catalyzed *5-endo-dig* cyclization,^[18] we faced our original goal, the control of the C-1 stereogenic center. In this context it should be noted that despite the use of gold in homogeneous catalysis has witnessed tremendous activity in recent years, asymmetric gold-catalyzed reactions are still scarce.^[19] Most of these stereoselective processes are related to the enantioselective π -activation of allenes^[20] and very few examples have been reported about asymmetric gold-catalyzed processes involving alkyne activation.^[21] To the best of our knowledge, no examples have been reported about the enantioselective cycloisomerization or alkoxylation of *o*-(alkynyl)styrenes.^[22]

Taking into account the relative success on the use of chiral biphosphines with biphenyl skeletons as ligands in gold-catalyzed enantioselective reactions, we prepared several dinuclear chiral gold(I) catalysts with (*R*)-BINAP (**L1**), (*S*)-H₈-BINAP (**L2**), (*S*)-SEGPHOS (**L3**), (*S*)-3,5-xylyl-SEGPHOS (**L4**), (*S*)-DTBM-

SEGPHOS (**L5**), MeOBIPHEP (**L6**), (*S*)-3,5-xylyl-MeOBIPHEP (**L7**), and (*S*)-DTBM-MeOBIPHEP (**L8**) as ligands (Figure 1), according to known procedures.^[21a]

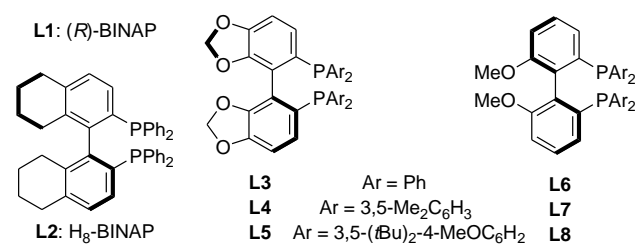


Figure 1. Chiral ligands (**L1-L8**) screened in the gold(I)-catalyzed enantioselective cycloisomerization of *o*-(alkynyl)styrenes **1**.

Initial efforts were focused on the optimization of an efficient chiral catalyst for the transformation of *o*-(alkynyl)styrene **1a** into 1-alkenyl-1*H*-indene **2a** (Table 1). We were pleased to find that the use of all tested chiral gold complexes associated with the silver salt AgSbF₆ allowed completed conversions in one hour at room temperature (entries 1-8). The best result regarding the enantiomeric excess was found by using the gold complex bearing the ligand 3,5-xylyl-MeOBIPHEP (**L7**) (entry 7). So, further optimization was performed with this complex. The influence of the silver salt was then investigated (entries 7, 9, 10), silver tosylate giving the best result. Finally, by lowering the temperature to -30 °C we were able to obtain the indene **2a** with a pleasant 82% enantiomeric excess in a reasonable reaction time (entries 10-13). At lower temperature only a slight improvement in the enantioselectivity was observed, while the reaction became sluggish (entry 14).

Table 1: Optimization of the reaction conditions for the asymmetric synthesis of indene **2a**.^[a]

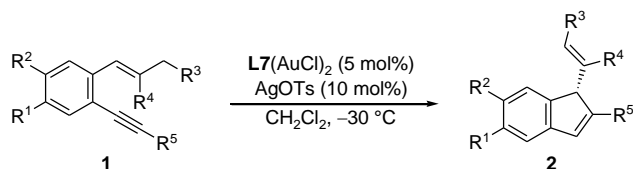
Entry	L*/AgX	x mol%	T [°C]	t [h]	ee [%] ^[b]
1	L1 / AgSbF ₆	2.5	25	1	-10
2	L2 / AgSbF ₆	2.5	25	1	35
3	L3 / AgSbF ₆	2.5	25	1	24
4	L4 / AgSbF ₆	2.5	25	1	40
5	L5 / AgSbF ₆	2.5	25	1	24
6	L6 / AgSbF ₆	2.5	25	1	36
7	L7 / AgSbF ₆	2.5	25	1	41
8	L8 / AgSbF ₆	2.5	25	1	29
9	L7 / AgOTf	2.5	25	3	50
10	L7 / AgOTs	2.5	25	6	60
11	L7 / AgOTs	5	0	24	70
12	L7 / AgOTs	5	-20	48	76
13	L7 / AgOTs	5	-30	80	82
14	L7 / AgOTs	5	-40	120	85 ^[c]

[a] Reactions conducted using 0.05 mmol of 2',2'-dimethyl *o*-(phenylethynyl)styrene **1a**, in CH₂Cl₂ (0.2 mL) until complete conversion. [b] Determined by HPLC analysis (column: Chiralcel-OJ, eluent: hexane/*i*PrOH 90:10, flow: 1 mLmin⁻¹). [c] 77% conversion as estimated by ¹H-NMR.

Under the optimized catalytic conditions, the use of (*S*)-3,5-xylyl-MeOBIPHEP-(AuCl)₂ associated with silver salt AgOTs in CH₂Cl₂, we examined the scope of this enantioselective reaction (Table 2). As shown, the reaction is tolerant towards a variety of *o*-(alkynyl)styrenes **1** bearing different substituents at the aromatic ring (R¹, R²), at the alkene terminal carbon (R³, R⁴), and at the

alkyne moiety (R^5). High yields and enantioselectivities were observed for starting materials **1a-f** where R^5 is an aromatic or heteroaromatic group (entries 1-6). However, for alkyl-substituted alkyne (**1g**) a lower enantioselectivity was observed (entry 7). In addition, the possibility of increasing the enantiomeric excess of the final products by a simple recrystallization has been demonstrated (entry 5).

Table 2. Gold(I)-catalyzed enantioselective synthesis of 1-alkenyl-1*H*-indenes **2**.^[a]

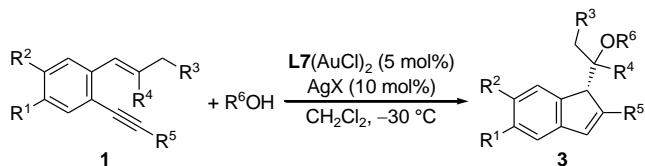


Entry	1	R^1	R^2	R^3	R^4	R^5	2	Yield [%] ^[b]	ee [%] ^[c]
1	1a	H	H	H	Me	Ph	2a	81	82
2 ^[d]	1b	H	F	H	Me	Ph	2b	84	77
3 ^[d]	1c	-OCH ₂ O-	H	H	Me	Ph	2c	84	86
4	1d	H	H	-(CH ₂) ₃ -	H	Ph	2d	93	81
5	1e	H	H	-(CH ₂) ₄ -	H	Ph	2e	96	80(92)
6	1f	H	H	H	Me	3-Th ^[f]	2f	81	68
7 ^[d]	1g	H	H	H	Me	<i>n</i> -Bu	2g	80	20

[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **1** in CH₂Cl₂ (0.6 mL) at -30 °C for 3-4 days. [b] Yield of isolated product based on starting material **1**. [c] Determined by HPLC analysis, see Supporting Information; in brackets *ee* after recrystallization. [d] Reaction conducted at -20 °C. [e] 12% of **2a** was also formed. [f] 3-Thienyl.

We have also examined the enantioselective alkoxylation of *o*-(alkynyl)styrenes **1** (Table 3). Again, high yields and enantioselectivities were observed for aryl-substituted alkynes **1a-f,h** in the presence of several alcohols (entries 1, 3-6, 8, 10, 12, and 16) or water (entries 2, 7, 9, 11, 13, and 17). Primary and secondary alcohols, as well as water, were successfully employed as nucleophiles in this transformation. By using isopropanol as nucleophile, the isopropoxy derivative **3ae** was obtained with the highest *ee*, though the competitive formation of **2a** took place in a small amount. As expected, alkyl-substituted alkyne **1g** led to lower enantioselectivities (entries 14, and 15). Gratifyingly, oxygen-functionalized 1*H*-indenes **3** can be obtained as a single enantiomer by recrystallization (entries 1, 5-6, 8-9, 12-13, and 16-17). Moreover, the absolute configuration of product **3ha** was determined to be *R* by using single crystal X-ray diffraction,^[23] and the rest were assigned by analogy.

Table 3. Gold(I)-catalyzed enantioselective synthesis of oxygen-functionalized 1*H*-indenes **3**.^[a]



Entry	1	R^1	R^2	R^3	R^4	R^5	R^6	3	Yield [%] ^[b]	ee [%] ^[c]
1	1a	H	H	H	Me	Ph	Me	3aa	99	88(>98)
2	1a	H	H	H	Me	Ph	H	3ab	93	86
3 ^[d]	1a	H	H	H	Me	Ph	Et	3ac	88	81
4 ^[d]	1a	H	H	H	Me	Ph	allyl	3ad	94	80
5 ^[d]	1a	H	H	H	Me	Ph	<i>i</i> -Pr	3ae	72 ^[e]	92(98)
6	1b	H	F	H	Me	Ph	Me	3ba	93	82(>98)
7	1b	H	F	H	Me	Ph	H	3bb	88	86
8	1c	-OCH ₂ O-	H	H	Me	Ph	Me	3ca	98	84(>98)

9	1c	-OCH ₂ O-	H	Me	Ph	H	3cb	80	88(>98)
10	1d	H	H	-(CH ₂) ₃ -	Ph	Me	3da	87	80
11	1d	H	H	-(CH ₂) ₃ -	Ph	H	3db	77	84
12	1f	H	H	H	Me	3-Th ^[f]	3fa	90	75(>98)
13	1f	H	H	H	Me	3-Th ^[f]	3fb	91	78(>98)
14	1g	H	H	H	Me	<i>n</i> -Bu	3ga	88	30
15	1g	H	H	H	Me	<i>n</i> -Bu	3gb	90	28
16	1h	H	Br	H	Me	Ph	3ha	95	80(>98)
17	1h	H	Br	H	Me	Ph	3hb	94	80(>98)

[a] Reactions conducted using 0.3 mmol of *o*-(alkynyl)styrene derivative **1**, 30 equiv. of nucleophile, AgOTs as silver salt with ROH and AgSbF₆ with H₂O, in CH₂Cl₂ (1.2 mL) at -30 °C for 2-4 days. [b] Yield of isolated product based on starting material **1**. [c] Determined by HPLC analysis, see Supporting Information; in brackets *ee* after recrystallization. [d] Reaction conducted at -20 °C. [e] 12% of **2a** was also formed. [f] 3-Thienyl.

In conclusion, we have developed an asymmetric gold-catalyzed cycloisomerization or alkoxylation of *o*-(alkynyl)styrenes that provides enantiomerically-enriched functionalized 1*H*-indene derivatives in high yields and with *ee* values up to 92%, that can be improved to >98% after a simple recrystallization. The combined catalytic system consisting of a gold complex with the atropisomeric electron-rich ligand 3,5-xylyl-MeOBIPHEP and silver salts efficiently promotes this enantioselective cyclization under mild conditions. It should be also remarked that the reactions here reported represent the first examples of metal catalyzed cyclizations of *o*-(alkynyl)styrenes through a 5-*endo-dig* mechanism. *o*-(Alkynyl)styrenes had been widely used as precursors of naphthalene derivatives and so this work further expands the utility of these starting materials demonstrating its ability as simple precursors of (enantiopure) indenes.

Experimental Section

General procedure for the gold(I)-catalyzed enantioselective synthesis of 1*H*-indenes **2 and **3**:** AgSbF₆ (10 mol%, 5.1 mg) or AgOTs (10 mol%, 8.4 mg) was added to a solution of L7(AuCl)₂ (5 mol%, 17.4 mg) in dry CH₂Cl₂ and the reaction mixture was stirred 5-10 minutes and cooled to -30 °C or -20 °C (see Tables 2 and 3 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 **1** (0.3 mmol) in dry CH₂Cl₂. The resulting reaction mixture was stirred until complete disappearance of starting material **1**, as monitored by TLC or GC-MS. The mixture was diluted with hexanes and filtered through a pad of silica gel, 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 **2** or **3** were isolated in the yields and enantioselectivities reported in Tables 2 and 3.

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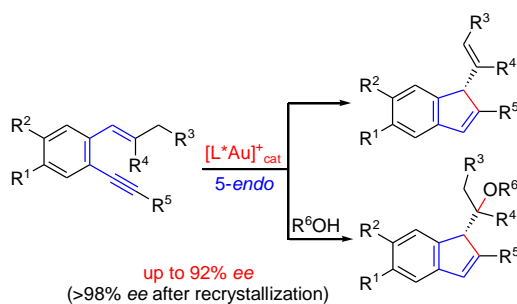
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- [23] CCDC 766525 (**3ha**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Chiral indenenes

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Au(I)-Catalyzed Enantioselective Synthesis of Functionalized Indenes



An asymmetric synthesis of functionalized 1*H*-indenenes from easily available *ortho*-(alkynyl)styrene derivatives under mild conditions is reported. The reactions proceed through an unprecedented and selective 5-*endo-dig* gold(I)-catalyzed cycloisomerization or alkoxy cyclization, if water or an alcohol is present. The indenenes are obtained in high yields and with ee values up to 92% that can be even improved to >98% after recrystallization.