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Chiral indenes

Gold(I)-Catalyzed Enantioselective Synthesis of Functionalized Indenes**

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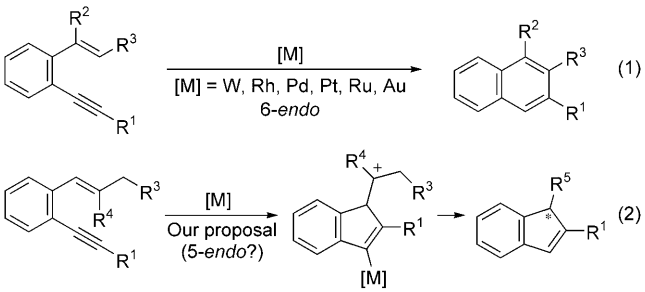
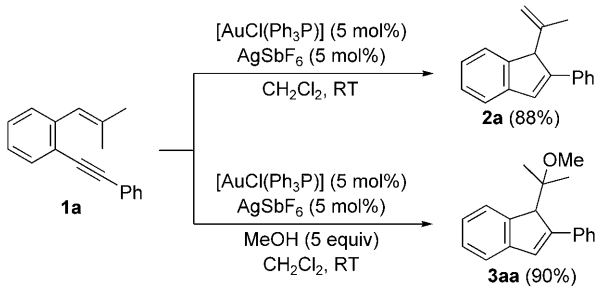
Molecules containing the 1*H*-indene scaffold show a wide range of biological activities,[1] and possess great interest as functional materials[2] as well as precursors of metallocene complexes for catalytic polymerization processes.[3] As a result, several methods have been developed for their synthesis.[4] Despite the unquestionable interest of optically active indenes bearing a stereogenic center at C1, 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 strategies are based on the use of boronic acid derivatives as starting materials and dicationic Pd^{II} complexes as the catalyst. Thus, enantioenriched 1-arylindenes have been obtained in a cascade 1,4-addition-aldol condensation process,[5] whereas 1*H*-indenes bearing a CH_2COR group at the C1 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 indenes (in particular from achiral substrates) motivated 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)styrene derivatives. 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 atom 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 favor the 5-*endo* reaction pathway—owing to better stabilization of the exocyclic carbocationic intermediate—to form the desired indene skeleton with a stereogenic center at C1 [Scheme 1, Eq. (2)].[14] Herein we report our results 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 indenes.



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

For the initial experiments we selected 2′,2′-dimethyl *o*-(phenylethynyl)styrene **1a** as a model substrate (Scheme 2). As a result of 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 us $AgSbF_6$, $PtCl_2$, $[PtCl_2(cod)]$, CuI, $AuCl_3$, AuCl, or $[AuCl(Ph_3P)]$ (cod = cycloocta-l,5-diene). Encouragingly, the reaction proceeded to completion within 30 minutes to yield the indenyl derivative **2a** in a high yield (88% of isolated product), when it was performed in CH_2Cl_2 at room temperature in the presence of the cationic gold(I) complex generated in situ from 5 mol% of $[AuCl(Ph_3P)]$ and



Scheme 2. Initial experiments and proof of concept.

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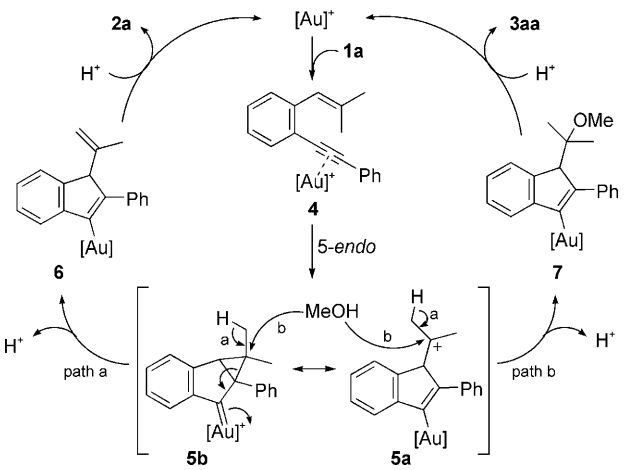
5 mol% of $AgSbF_6$.[16] Moreover, when this reaction was conducted in the presence of five equivalents of methanol we observed the formation of compound **3aa** in excellent yield (90%; Scheme 2). The high selectivity of these reactions should be noted as we did not observe the formation of naphthalene 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.

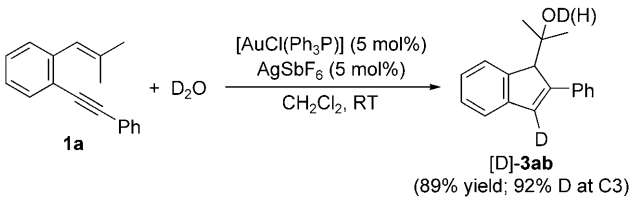
A catalytic cycle that explains the formation of indenes **2a** and **3aa** is shown in Scheme 3.[17] The reaction is initiated by coordination of the cationic gold complex to the triple bond of



Scheme 3. Proposed mechanisms for the synthesis of indenes.

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 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** (path b) accounts for the formation of vinyl gold intermediate **7**. Further protodemetalation furnishes compound **3aa** and thus regenerating the catalytic species.

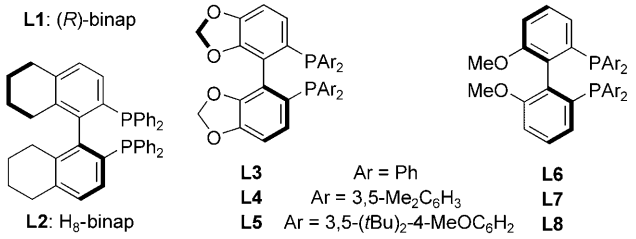
To support the proposed mechanism we performed the labeling experiment shown in Scheme 4. Thus, when **1a** was treated in the presence of five equivalents of D_2O under the catalytic conditions previously described we observed the exclusive formation of the deuterated compound [D]-**3ab** in 89% yield (92% deuterium incorporation at C3). Interestingly, this experiment also served to demonstrate that water could be used as a nucleophilic partner in this new reaction.



Scheme 4. Labeling experiment.

Once we had demonstrated the feasibility of our method for the preparation of indene derivatives through a gold-catalyzed 5-*endo-dig* cyclization,[18] we turned to our original goal, the control of the stereogenic center at C1. In this context it should be noted that despite the tremendous activity in the use of gold in homogeneous catalysis, 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 on the enantioselective cycloisomerization or alkoxycyclization of *o*-(alkynyl)styrenes.[22]

Taking into account the relative success with 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*)-H_8-binap (**L2**), (*S*)-segphos (**L3**), (*S*)-3,5-xylyl-segphos (**L4**), (*S*)-DTBM-segphos (**L5**), MeO-biphep (**L6**), (*S*)-3,5-xylyl-MeO-biphep (**L7**), and (*S*)-DTBM-MeO-biphep (**L8**) as ligands (Scheme 5), according to known procedures.[21a]



Scheme 5. Chiral ligands (**L1**–**L8**) screened in the gold(I)-catalyzed enantioselective cycloisomerization of *o*-(alkynyl)styrenes **1**.

Initial efforts were focused on selecting an efficient chiral catalyst for the transformation of *o*-(alkynyl)styrene **1a** into 1-alkenyl-1*H*-indene **2a** (Table 1). Pleasingly, all chiral gold complexes tested associated with the silver salt $AgSbF_6$ allowed complete conversions to **2a** in one hour at room temperature (Table 1, entries 1–8). The best result with respect to the *ee* value was obtained using the gold complex bearing the ligand **L7** (Table 1, entry 7). So, further optimization was performed with this complex. The influence of the silver salt was then investigated (Table 1, entries 7, 9, and 10), and silver tosylate gave the best result. Finally, by lowering the temperature to −30°C we obtained the indene **2a** with 82% *ee* in a reasonable reaction time (Table 1, entries 10–13). At lower temperature only a slight improvement in the enantioselectivity was observed, while the reaction became sluggish (Table 1, entry 14).

Under the optimized catalytic conditions, [**L7**$(AuCl)_2$] associated with the silver salt AgOTs in CH_2Cl_2, 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 (R^1, R^2), at the alkene terminal carbon atom (R^3, R^4), and at the alkyne moiety (R^5). High yields and enantioselectivities were observed for starting materials **1a–f**

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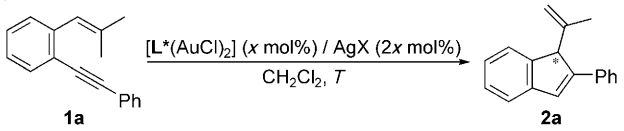
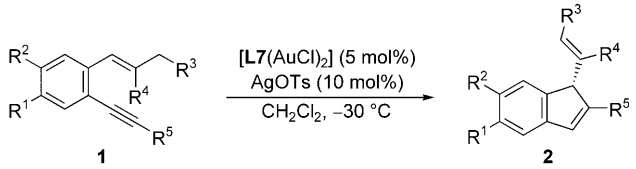
Table 1: Optimization of the reaction conditions for the asymmetric synthesis of indene **2a**.[a]



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 conditions: 2′,2′-dimethyl *o*-(phenylethynyl)styrene **1a** (0.05 mmol) in CH_2Cl_2 (0.2 mL) until complete conversion. [b] Determined by HPLC on a chiral stationary phase using a Chiracel OJ column (eluent: *n*-hexane/*i*PrOH (90:10), flow: 1 mL min^{-1}. [c] 77% conversion as estimated by ^1H NMR spectroscopy.

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



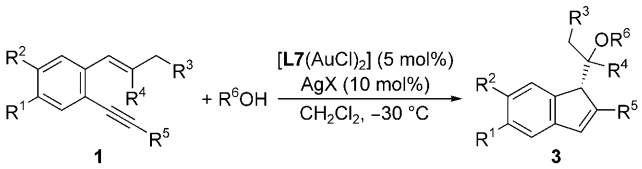
Entry	**1**	R^1	R^2	R^3	R^4	R^5	**2**	Yield [%][b]	*ee* [%][c]
1	**1a**	H	H	H	Me	Ph	**2a**	81	82
2[d]	**1b**	H	F	H	Me	Ph	**2b**	84	77
3[d]	**1c**	-OCH_2O-		H	Me	Ph	**2c**	84	86
4	**1d**	H	H	-$(CH_2)_3$-		Ph	**2d**	93	81
5	**1e**	H	H	-$(CH_2)_4$-		Ph	**2e**	96	80(92)
6	**1f**	H	H	H	Me	3-Th	**2f**	81	68
7[d]	**1g**	H	H	H	Me	*n*Bu	**2g**	80	20

[a] Reactions conditions: *o*-(alkynyl)styrene derivative **1** (0.3 mmol) in CH_2Cl_2 (0.6 mL) at −30°C for 3–4 days. [b] Yield of isolated product based on the starting material **1**. [c] Determined by HPLC on a chiral stationary phase, see the Supporting Information; *ee* value after recrystallization in brackets. [d] Reaction conducted at −20°C. 3-Th = 3-thienyl, Ts = 4-toluenesulfonyl.

where R^5 is an aromatic or heteroaromatic group (Table 2, entries 1–6). However, for alkyl-substituted alkyne **1g** a lower enantioselectivity was observed (Table 2, entry 7). In addition, the possibility of increasing the enantiomeric excess value of the final products by a simple recrystallization has been demonstrated (Table 2, entry 5).

We have also examined the enantioselective alkoxycyclization of *o*-(alkynyl)styrenes **1** (Table 3). Again, high yields and enantioselectivities were observed for aryl-substituted

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*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_2O-		H	Me	Ph	Me	**3ca**	98	84(>98)
9	**1c**	-OCH_2O-		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	Me	**3fa**	90	75(>98)
13	**1f**	H	H	H	Me	3-Th	H	**3fb**	91	78(>98)
14	**1g**	H	H	H	Me	*n*Bu	Me	**3ga**	88	30
15	**1g**	H	H	H	Me	*n*Bu	H	**3gb**	90	28
16	**1h**	H	Br	H	Me	Ph	Me	**3ha**	95	80(>98)
17	**1h**	H	Br	H	Me	Ph	H	**3hb**	94	80(>98)

[a] Reactions conditions: *o*-(alkynyl)styrene derivative **1** (0.3 mmol), nucleophile (30 equiv), X = OTs with ROH and X = SbF_6 with H_2O, in CH_2Cl_2 (1.2 mL) at −30°C for 2–4 days. [b] Yield of isolated product based on starting material **1**. [c] Determined by HPLC on a chiral stationary phase, see the Supporting Information; *ee* value after recrystallization in brackets. [d] Reaction conducted at −20°C. [e] 12% of **2a** was also formed.

alkynes **1a–f,h** in the presence of several alcohols (Table 3, entries 1, 3–6, 8, 10, 12, and 16) or water (Table 3, 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 the nucleophile, the isopropoxy derivative **3ae** was obtained with the highest *ee* value, though the competitive formation of **2a** occurred to a small extent. As expected, alkyl-substituted alkyne **1g** led to lower enantioselectivities (Table 3, entries 14 and 15). Gratifyingly, oxygen-functionalized 1*H*-indenes **3** can be obtained as a single enantiomer by recrystallization (Table 3, entries 1, 5, 6, 8, 9, 12, 13, 16, and 17). Moreover, the absolute configuration of product **3ha** was determined to be *R* by using single-crystal X-ray analysis,[23] and the configuration of the remaining products were assigned by analogy.

In conclusion, we have developed an asymmetric gold-catalyzed cycloisomerization or alkoxycyclization of *o*-(alkynyl)styrenes that provides enantiomerically enriched functionalized 1*H*-indene derivatives in high yields and with *ee* values of up to 92%, which 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 (**L7**) and silver salts, efficiently promotes this enantioselective cyclization under mild reaction conditions. Notably, the reactions reported here represent the first examples of metal-catalyzed

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cyclizations of *o*-(alkynyl)styrenes through a 5-*endo*-*dig* mechanism. *o*-(Alkynyl)styrene derivatives had been widely used as precursors of naphthalene derivatives and this work further expands the utility of these starting materials, thus demonstrating their ability to act as simple precursors of (enantiopure) indenes.

Experimental Section

General procedure for the gold(I)-catalyzed enantioselective synthesis of 1*H*-indenes **2** and **3**: $AgSbF_6$ (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 CH_2Cl_2 and the mixture was stirred for 5–10 min and cooled to −30°C or −20°C (see Table 2 and Table 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 CH_2Cl_2. The resulting reaction mixture was stirred until complete consumption of starting material **1** (as evident by TLC or GC-MS analysis). The mixture was diluted with hexanes and filtered through a pad of silica gel, the solvent was removed and the crude residue was purified by flash chromatography on silica gel using mixtures of hexanes and EtOAc as eluents. The corresponding yields and enantioselectivities of 1*H*-indenes **2** or **3** are reported in Table 2 and Table 3, respectively.

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[16] A similar result was obtained using 5 mol% of the bis(trifluoromethanesulfonyl)imidate derivative $[AuNTf_2(Ph_3P)]$ (Tf = trifluoromethanesulfonyl).
[17] For related mechanisms, see: a) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859; b) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963; c) A. K. Buzas, F. M. Istrate, F. Gagosz, *Angew. Chem.* **2007**, *119*, 1159–1162; *Angew. Chem. Int. Ed.* **2007**, *46*, 1141–1144; d) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811.
[18] The scope of this new transformation was briefly investigated using different *o*-alkynyl styrenes **1a–h**. See the Supporting Information for the synthesis of racemic 1-alkenyl-1*H*-indenes **2a–g** and 1-oxygen-functionalized-1*H*-indenes **3aa–3hb**. In addition, we also looked at the behavior of the corresponding terminal alkyne, 2′,2′-dimethyl *o*-(ethynyl)styrene, though the reaction was sluggish and gave decomposition products.
[19] For reviews, see: a) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391; b) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181.
[20] For recent examples, see: a) A. Z. González, F. D. Toste, *Org. Lett.* **2010**, *12*, 200–203; b) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner, F. D. Toste, *Angew. Chem.* **2010**, *122*, 608–611; *Angew. Chem. Int. Ed.* **2010**, *49*, 608–611, and references therein.
[21] a) M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293–1300; b) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003; c) C.-M. Chao, M. R. Vitale, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Chem. Eur. J.* **2009**, *15*, 1319–1323; d) C.-M.

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Chao, D. Veltrami, P. Y. Toullec, V. Michelet, *Chem. Commun.* **2009**, 6988–6990; see also: L. Charruault, V. Michelet, R. Taras, S. Gladiali, J.-P. Genêt, *Chem. Commun.* **2004**, 850–851, for a conceptually related platinum-catalyzed alcoxycyclization of 1,6-enynes.

[22] *ortho*-(Alkynyl)styrenes could be considered in some way as 1,5-enynes. As far as we know neither the gold-catalyzed enantioselective cycloisomerization of *o*-(alkynyl)styrenes neither of 1,5-enynes has been reported. In contrast, gold-catalyzed enantioselective reactions of 1,6-enynes have been described (see references [21a,c,d]).

[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.

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