Straightforward Synthesis of Dihydrobenzo[*a*]fluorenes through Au(I)-Catalyzed Formal [3+3] Cycloadditions
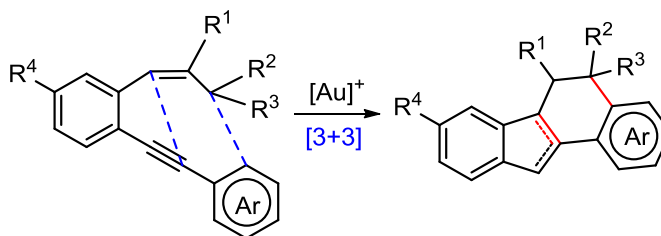
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ABSTRACT

Dihydrobenzo[*a*]fluorene derivatives have been prepared by a formal intramolecular [3+3] cycloaddition of *o*-(alkynyl)styrenes bearing a secondary alkyl group at the β-position of the styrene moiety. The process, catalyzed by a cationic gold(I) complex, involves a 1,2-hydride migration as the key step. 6,11-Dihydro-5*H*-benzo[*a*]fluorenes could be obtained from the initially generated 6,6a-dihydro-5*H*-benzo[*a*]fluorenes by subsequent heating of the reaction mixture under gold(I) or Brønsted acid-catalysis, or directly by conducting the reactions at high temperature.

Benzo[*a*]fluorene and, in particular, its polyhydro derivatives, are cores frequently found in diverse natural products possessing biological activity (Figure 1). This tetracyclic skeleton is present, for instance, in isoprekinamycin,[1] veratramine[2] or nakiterpiosinone[3] and is the structural base of whole families of compounds such as the dasyscyphins,[4] walsuchocins[5] or fluostatins.[6]

Moreover, synthetic polyhydrobenzo[*a*]fluorenes have also shown interesting properties, for example as bone loss inhibitors[7] or estrogen receptors.[8]

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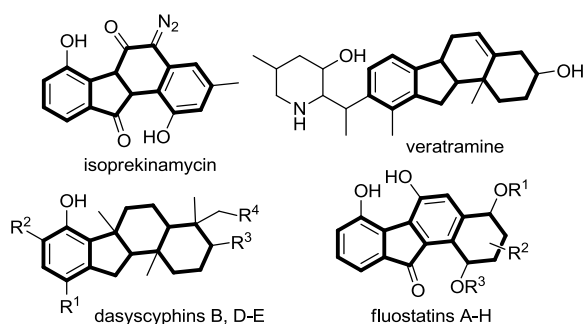
Figure 1. Selected natural products containing the polyhydrobenzo[*a*]fluorene skeleton

On the other hand, transition metal-catalyzed cyclization of functionalized unsaturated substrates has emerged in the last years as a fundamental tool for the synthesis of a wide array of cyclic structures not easily prepared by conventional methodologies.[9] Particularly interesting in this field are gold and platinum-catalyzed cycloisomerizations of enynes, that generally entail a rapid increase in structural complexity from readily available precursors under mild conditions.[10]

In this regard, we have recently described a gold-catalyzed cycloisomerization of *o*-(alkynyl)styrenes that provides an easy enantioselective access to the indene skeleton and is proposed to proceed via carbocation **I** (Scheme 1, *via a*).[11] Continuing with our ongoing interest in implementing new applications of gold-catalyzed reactions of 1,3-dien-5-ynes,[12] we envisioned that those compounds could be appropiate substrates for the development of a new route to benzo[*a*]fluorene derivatives.[13] Thus, we considered that if a rearrangement of carbocation **I** by hydride migration to the adjacent carbon would be possible, the trapping of the new intermediate **II** by intramolecular nucleophilic attack of an aromatic group could be favoured (Scheme 1, *via b*). The overall transformation would therefore lead to the formation of the dihydrobenzo[*a*]fluorene skeleton through a formal [3+3] cycloaddition.[14,15] The success of

the proposed reaction would obviusly depend on the appropiate selection of groups R[1] and R[2], that should be able to favour the formation of carbocation **II** from the initially generated carbocation **I**.

Scheme 1. Previously reported synthesis of indenes and proposed synthesis of dihydrobenzo[*a*]fluorenes
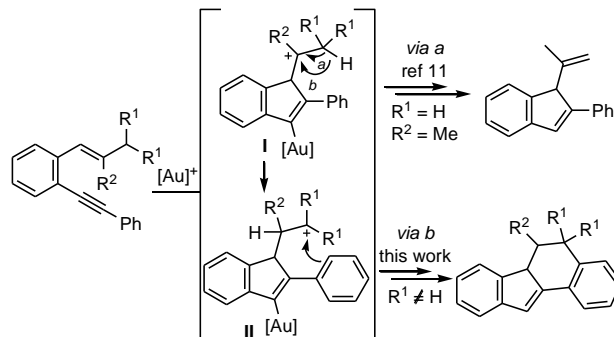
To check our hypothesis we selected as a model substrate *o*-(alkynyl)styrene **1a** (4:1 mixture of geometrical isomers), having an isopropyl group linked to the double bond, that would generate a rather favored tertiary carbocation upon migration to form an intermediate of type **II**. At the outset, we tested its reactivity in the presence of different cationic gold complexes and solvents (Table 1). We were glad to find that by performing the reaction in CH_2Cl_2 using 5 mol% of AuPPh$_3$Cl/AgSbF$_6$ as catalyst a high selectivity to the formation of the dihydrobenzo[*a*]fluorene products **2a** and **iso-2a** was obtained, with less than 10% of indene derivatives **3a** and **iso-3a** formed (entry 1). Minor influence of the ligand of the gold complex was observed (entries 1−4), while the counterion plays a crucial role in the outcome of the reaction (entries 1 vs. 5−9) as indene derivatives **3a** and **iso-3a** are primarily or even exclusively obtained with triflate (entry 8) or tosylate (entry 9) counterions. The solvent also has a significant influence in the selectivity of the reaction (entries 1 vs. 10−13) with CH_2Cl_2 being the best for promoting the formal [3+3] cycloaddition (entry 1), whereas ethereal solvents lead mainly to the formation of indene derivatives (entries 12 and 13). It is remarkable how an appropriate selection of the reaction conditions allows the selective isolation in good yields of either dihydrobenzo[*a*]fluorene (entry 1) or indene derivatives (entry 9).

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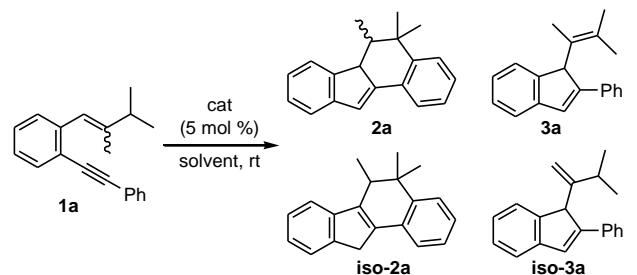
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[14] It is worth noting that the unique properties of gold complexes have allowed the disclosure of new types of cycloaddition reactions that

were previously unfeasible. For a recent revision on gold-catalyzed cycloaddition reactions: López. F.; Mascareñas, J. L. *Beilstein J. Org. Chem.* **2011**, *7*, 1075–1094.

[15] For other gold-catalyzed cycloaddition reactions involving 1,3-dien-5-ynes see: a) Barluenga, J.; Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764–2765. b) Fernández-García, J. M.; Fernández-Rodríguez, M. A.; Aguilar, E. *Org. Lett.* **2011**, *13*, 5172–5175.

Table 1. Effect of the catalyst and the solvent in the selectivity

entry	catalyst	solvent	2a + iso-2a yield (%)[a]	3a + iso-3a yield (%)[a]
1	AuPPh₃Cl/AgSbF₆	CH₂Cl₂	94 (80)[b]	6
2	AuPEt₃Cl/AgSbF₆	CH₂Cl₂	93	7
3	IPrAuCl/AgSbF₆	CH₂Cl₂	80	17
4	AuP(OPh)₃Cl/AgSbF₆	CH₂Cl₂	91	7
5	AuPPh₃NTf₂	CH₂Cl₂	80	20
6	AuPPh₃Cl/AgBF₄	CH₂Cl₂	75	25
7	AuPPh₃Cl/AgPF₆	CH₂Cl₂	45	50
8	AuPPh₃Cl/AgOTf	CH₂Cl₂	7	93
9	AuPPh₃Cl/AgOTs	CH₂Cl₂	–	100 (78)
10	AuPPh₃Cl/AgSbF₆	MeNO₂	80	14
11	AuPPh₃Cl/AgSbF₆	toluene	80	16
12	AuPPh₃Cl/AgSbF₆	DME	38	55
13	AuPPh₃Cl/AgSbF₆	THF	8	82

[a] Determined by ¹H-RMN of the crude mixture using 1,3,5-trimethoxybenzene as internal standard; in brackets isolated yield. [b] **2a** was obtained as a ca. 7:1 mixture of diastereoisomers.

Thus, the best conditions for accomplishing the formal [3+3] cycloaddition pathway consist of the use of AuPPh₃Cl/AgSbF₆ as catalyst in CH₂Cl₂ as solvent. Under these conditions we were able to isolate 80% of a ca. 7:1 mixture of 6,6a-dihydro-5*H*-benzo[*a*]fluorene **2a** and 6,11-dihydro-5*H*-benzo[*a*]fluorene **iso-2a**, differing in the position of the double bond.[16]

Gratifyingly, selective formation of either **2a** or **iso-2a** could be achieved by simply controlling the temperature of the reaction (Scheme 2a). So, 75% of **2a** was isolated as a ca. 7:1 mixture of diastereoisomers[17] when the reaction was performed at 0 ºC, whereas 79% of **iso-2a** was obtained at 80 ºC in DCE. These results suggest that **iso-2a** could be formed by a thermal rearrengment of **2a**, which was confirmed by the transformation in good yield of isolated **2a** into **iso-2a** upon heating under the reaction conditions or in the presence of a Brønsted acid (Scheme 2a). Moreover, we observed that when the reaction was carried out at 80 ºC not even traces of indene derivatives **3a** or **iso-3a** were formed. Therefore, we checked out the possibility that indene derivatives could cyclize under these reaction conditions to afford **iso-2a**, which turned out to be the case (Scheme 2b). However, no transformation of **3a**/**iso-3a** was observed in the presence

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[16] Variable amounts of **iso-2a** were obtained for all entries in Table 1 where the [3+3] cycloaddition pathway was observed.

[17] The relative stereochemistry of the major isomer of **2a** was established by a NOESY experiment and resulted in *syn*. The same *syn*-selectivity was also observed and determined for cycloadducts **2b-h** described later in this paper. See Supporting Information for details.

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of the cationic gold complex at room temperature, which evidence that these are not intermediates in the synthesis of **2a** at low temperature, but the result of a different reaction pathway.

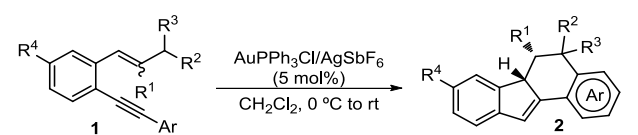**Scheme 2.** Effect of the temperature in the selectivity
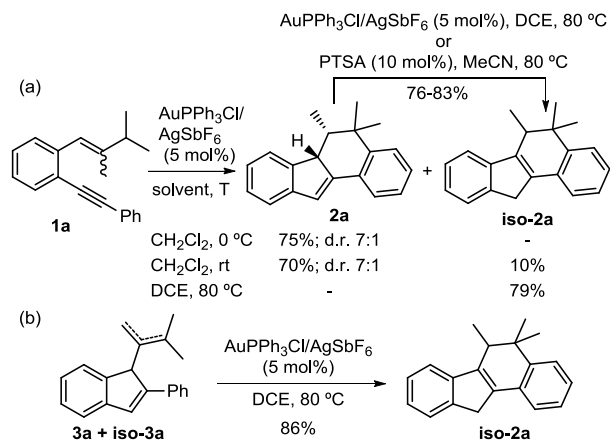
Accordingly with these results and based on our experience in the cycloisomerization of 1,3-dien-5-ynes we propose the following mechanism (Scheme 3).

Scheme 3. Proposed mechanism
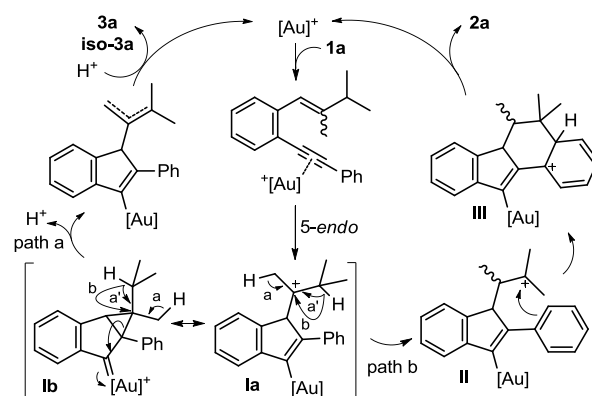
The reaction would be initiated by coordination of the gold complex to the triple bond of the starting dienyne **1a** followed by an intramolecular 5-*endo-dig* nucleophilic attack of the terminal olefin, leading to an intermediate that can be represented as the contribution of two resonance structures **Ia** and **Ib**. As previously proposed, elimination of a proton in **I** (path a/a′) furnishes a vinyl gold intermediate, which after protodemetalation gives the indene **3a** or **iso-3a**, depending on which proton has been eliminated. On the other hand, intermediate **I** can undergo a hydride migration giving rise to intermediate **II** (path b). This new carbocation would be subsequently

trapped by nucleophilic attack of the aromatic ring, a Friedel-Crafts alkylation,[18] affording dihydrobenzo[*a*]fluorene derivative **III** which after protodemetalation furnishes compound **2a** regenerating the catalytic species.[19]

Table 2. Synthesis of 6,6a-dihydro-5*H*-benzo[*a*]fluorenes **2**

entry	**1**	R^1	R^2	R^3	R^4	Ar	**2**	yield (%)[a]	dr
1[b]	**1b**	Me	Me	Me	H	*p*-ClC$_6$H$_4$	**2b**	81	5:1
2	**1c**	Me	Me	Me	H	*p*-MeOC$_6$H$_4$	**2c**	79	6:1
3	**1d**	Me	Me	Me	H	3-Th	**2d**	75	7:1
4[b]	**1e**	Me	Me	Et	H	Ph	**2e**	68	[c]
5[b]	**1f**	Me	−(CH$_2$)$_5$−		H	Ph	**2f**	75	>20:1
6[b]	**1g**	Et	Me	Me	H	Ph	**2g**	71	5:1
7[b]	**1h**	Ph	Me	Me	H	Ph	**2h**	70	>20:1
8	**1i**	H	Me	Me	H	Ph	**2i**	72	–
9	**1j**	H	−(CH$_2$)$_5$−		H	Ph	**2j**	67	–
10	**1k**	H	Me	Me	Br	Ph	**2k**	76	–

[a] Isolated yield. [b] Reaction conducted at rt. [c] Obtained as a ca. 6:3:2:1 mixture of diastereoisomers.

Once we had established the optimum conditions for directing the cycloisomerization of *o*-(alkynyl)styrenes **1** to the [3+3] cycloaddition pathway, we checked the potential of this methodology for the synthesis of a family of dihydrobenzo[*a*]fluorenes **2** and **iso-2**. Gratifyingly, reaction of easily accessible *o*-(alkynyl)styrenes **1a-k** at 0 ºC[20] afforded 6,6a-dihydro-5*H*-benzo[*a*]fluorenes **2a-k** in good yields and with high diastereoselectivities (Table 2). The method is compatible with the presence of both a halogen (entry 1) and an electron-donating group (entry 2) in the nucleophilic aromatic ring, that can also be heteroaromatic (entry 3). Moreover, diverse substitution paterns are well tolerated at the double bond of the starting material, as long as one of the groups is a secondary alkyl (entries 4−7). *o*-(Alkynyl)styrenes **1i-k**, having a monosubstituted olefin, are also appropriate substrates for this reaction (entries 8−10). In addition, further functionality can also be introduced in the central aromatic ring of the starting material (entry 10).
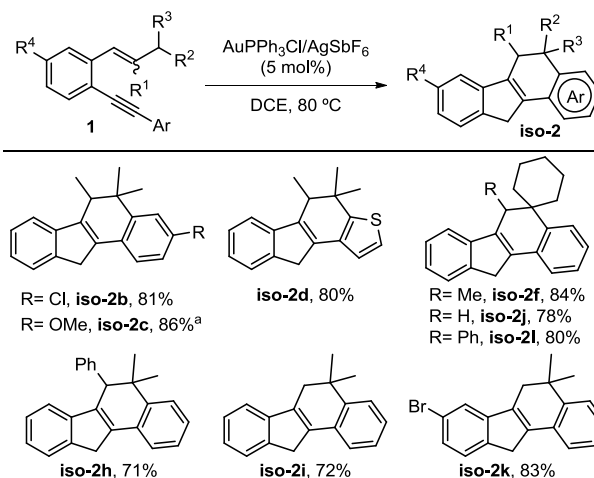
On the other hand reaction of selected *o*-alkynylstyrenes **1** at 80 ºC allowed for the synthesis of 6,11-dihydro-5*H*-benzo[*a*]fluorenes **iso-2** with very good yields and again with a wide scope regarding the substitution in all the possible different positions (Scheme 4).

Scheme 4. Synthesis of 6,11-dihydro-5*H*-benzo[*a*]fluorene **iso-2**

R= Cl, **iso-2b**, 81%
R= OMe, **iso-2c**, 86%[a]

iso-2d, 80%

R= Me, **iso-2f**, 84%
R= H, **iso-2j**, 78%
R= Ph, **iso-2l**, 80%

iso-2h, 71%

iso-2i, 72%

iso-2k, 83%

[a] Reaction conducted at rt

Finally, taking advantage of our previously reported enantioselective synthesis of indenes by using dinuclear chiral gold(I) catalysts,[11,21] we explored the possibility of obtaining enantioenriched dihydrobenzo[*a*]fluorenes. Thus, under the best reaction conditions found,[22] we synthesized some dihydrobenzo[*a*]fluorenes **iso-2** in an enantioselective fashion in good yields although with modest enantiomeric excess (Scheme 5).[23]

Scheme 5. Enantioselective synthesis of benzo[*a*]fluorenes **iso-2**

R^1= R^2 = Me, Ar= Ph → **iso-2a** (80% yield, 42% ee)
R^1= R^2 = Me, Ar= *p*-MeOC$_6$H$_4$ → **iso-2c** (89% yield, 32% ee)
R^1= R^2 = Me, Ar= 3-Thienyl → **iso-2d** (79% yield; 34% ee)
R^1= Me, R^2-R^2 = −(CH$_2$)$_5$−, Ar = Ph → **iso-2f** (80% yield, 42% ee)
R^1= Ph, R^2= Me, Ar= Ph → **iso-2h** (82% yield, 36% ee)

In conclusion, we have developed an efficient synthesis of dihydrobenzo[*a*]fluorenes through a novel gold-catalyzed intramolecular formal [3+3] cycloaddition of simple *o*-(alkynyl)styrenes. Reactions take place through

[18] For a mechanistically related gold reaction to give fluorenes, see: Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736−3737.

[19] Proton elimination from intermediate **II**, that would lead to **3a** after protodemetalation, could also be posible.

[20] Reactions of **1b,e-h** occurred at rt without significant formation of **iso-2** adducts, whereas increasing amounts of indenes **3** were observed at 0 ºC, and therefore these reactions were performed at rt.
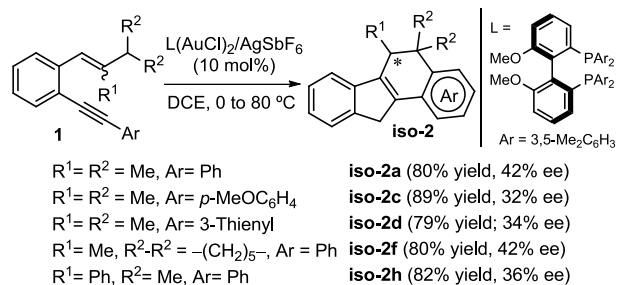
[21] For gold(I)-catalyzed enantioselective cycloisomerizations of 1,n-enynes see: a) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319−1323. b) Brazeau, J.-F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742−2749 and references therein. For reviews, see: c) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884−4908. d) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, DOI: 10.1039/c2sc20542d.

[22] See Supporting Information for a detailed study.

[23] Compared with our previous results (ref. 11), the observed modest enantioselectivity could be partially explained considering that the reaction that affords **2** is not totally diastereoselective.

a tandem 5-*endo* cyclization−[1,2]-hydride migration−Friedel-Crafts alkylation to afford the corresponding cycloadducts in good yields. Efforts to identify new reaction pathways of *o*-(alkynyl)styrenes that could provide selective and straihgtforward access to other relevant policyclic compounds are currently underway.

Supporting Information Available. Experimental procedures, and characterization data for all new compounds. Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org