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

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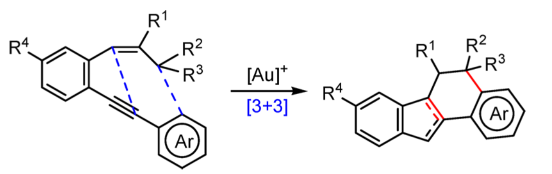
ABSTRACT



Dihydrobenzo[*a*]fluorene derivatives have been prepared by a formal intramolecular [3 + 3] cycloaddition of *o*-alkynylstyrenes 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]

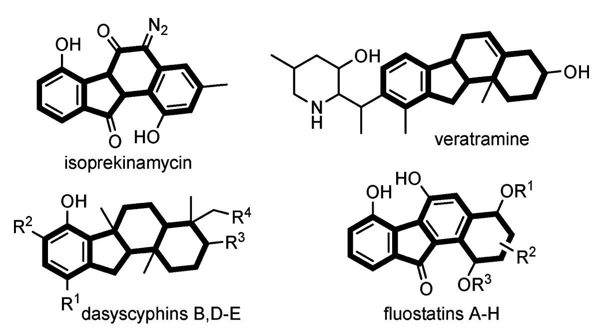


Figure 1. Selected natural products containing the polyhydrobenzo[*a*]fluorene skeleton.

On the other hand, transition-metal-catalyzed cyclization of functionalized unsaturated substrates has emerged

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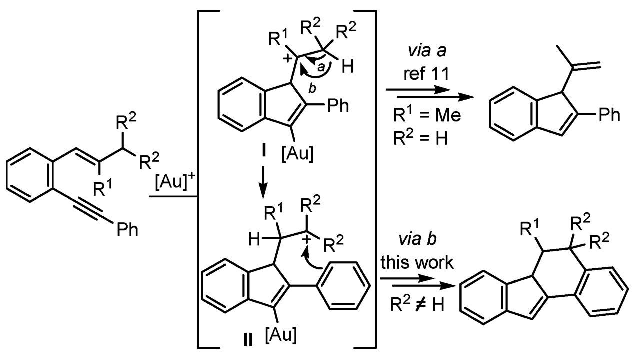
in recent years as a fundamental tool for the synthesis of a wide array of cyclic structures not easily prepared by conventional methodologies.[9] Particularly interesting in this field are gold- and platinum-catalyzed cycloisomerizations of enynes that generally entail a rapid increase in structural complexity from readily available precursors under mild conditions.[10]

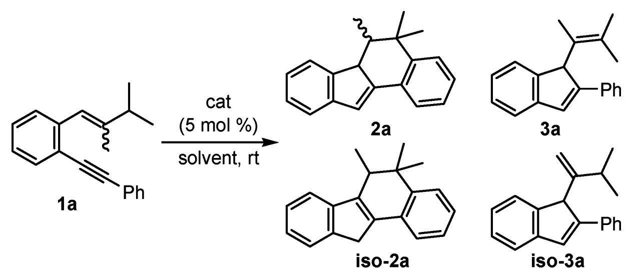
In this regard, we have recently described a gold-catalyzed cycloisomerization of *o*-alkynylstyrenes that provides an easy enantioselective access to the indene skeleton and is proposed to proceed via carbocation **I** (Scheme 1, via route *a*).[11] Continuing with our ongoing interest in implementing 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 favored (Scheme 1, via route *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 obviously depend on the appropiate selection of groups R^1 and R^2, which should be able to favor 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 test our hypothesis, we selected as a model substrate *o*-alkynylstyrene **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 $AuPPh_3Cl/AgSbF_6$ 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). A 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).

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	$AuPPh_3Cl/AgSbF_6$	CH_2Cl_2	94 (80)[b]	6
2	$AuPEt_3Cl/AgSbF_6$	CH_2Cl_2	93	7
3	$IPrAuCl/AgSbF_6$	CH_2Cl_2	80	17
4	$AuP(OPh)_3Cl/AgSbF_6$	CH_2Cl_2	91	7
5	$AuPPh_3NTf_2$	CH_2Cl_2	80	20
6	$AuPPh_3Cl/AgBF_4$	CH_2Cl_2	75	25
7	$AuPPh_3Cl/AgPF_6$	CH_2Cl_2	45	50
8	$AuPPh_3Cl/AgOTf$	CH_2Cl_2	7	93
9	$AuPPh_3Cl/AgOTs$	CH_2Cl_2		100 (78)
10	$AuPPh_3Cl/AgSbF_6$	$MeNO_2$	80	14
11	$AuPPh_3Cl/AgSbF_6$	toluene	80	16
12	$AuPPh_3Cl/AgSbF_6$	DME	38	55
13	$AuPPh_3Cl/AgSbF_6$	THF	8	82

[a] Determined by ^1H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard; isolated yield shown in parentheses. [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

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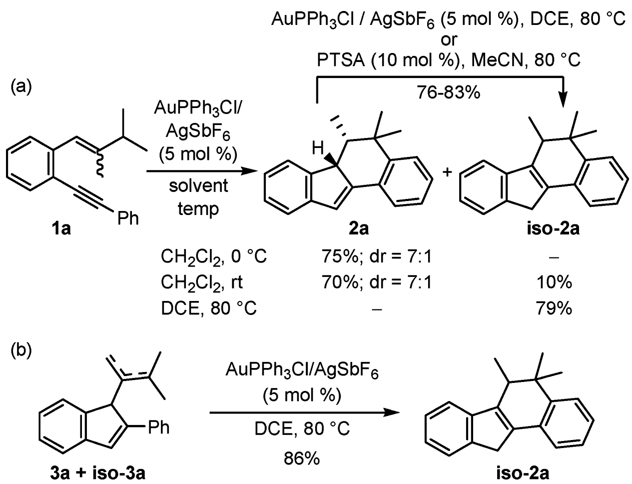
$AuPPh_3Cl/AgSbF_6$ as catalyst in CH_2Cl_2 as solvent. Under these conditions, we were able to isolate 80% of a ca. 7:1 mixture of 6,6a-dihydro-5*H*-benzo[*a*]fluorene **2a** and 6,11-dihydro-5*H*-benzo[*a*]fluorene **iso-2a**, differing in the position of the double bond.[16]

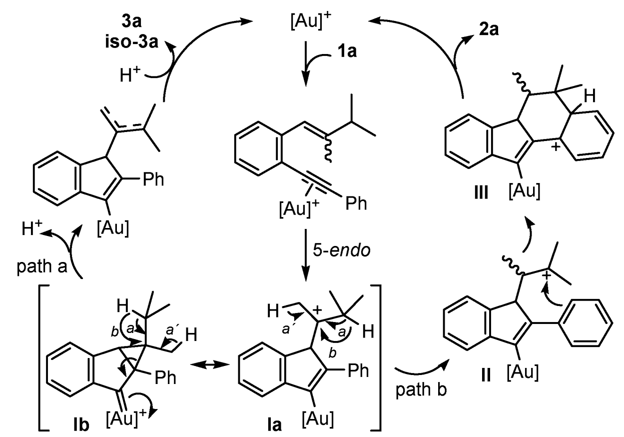
Gratifyingly, selective formation of either **2a** or **iso-2a** could be achieved by simply controlling the temperature of the reaction (Scheme 2a). So, 75% of **2a** was isolated as a ca. 7:1 mixture of diastereoisomers[17] when the reaction was performed at 0 °C, whereas 79% of **iso-2a** was obtained at 80 °C 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 °C 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 of the cationic gold complex at room temperature, which is 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



According to 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 that 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]

Once we had established the optimum conditions for directing the cycloisomerization of *o*-alkynylstyrenes **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*-alkynylstyrenes **1a**–**k** at 0 °C[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, which 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

(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, see: 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.

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

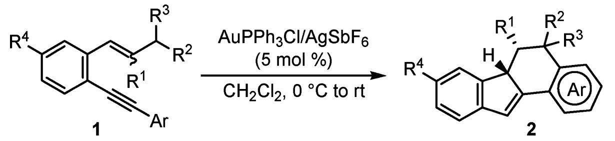
(17) The relative stereochemistry of the major isomer of **2a** was established by a NOESY experiment as *syn*. The same *syn* selectivity was also observed and determined for cycloadducts **2b**–**h** as described in this paper. See the Supporting Information for details.

(18) For a mechanistically related gold-catalyzed 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**, which would lead to **3a** after protodemetalation, could also be possible.

(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 °C, and therefore these reactions were performed at rt.

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_6H_4	**2b**	81	5:1
2	**1c**	Me	Me	Me	H	*p*-$MeOC_6H_4$	**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.

(entries 4–7). *o*-Alkynylstyrenes **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 °C 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).

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]

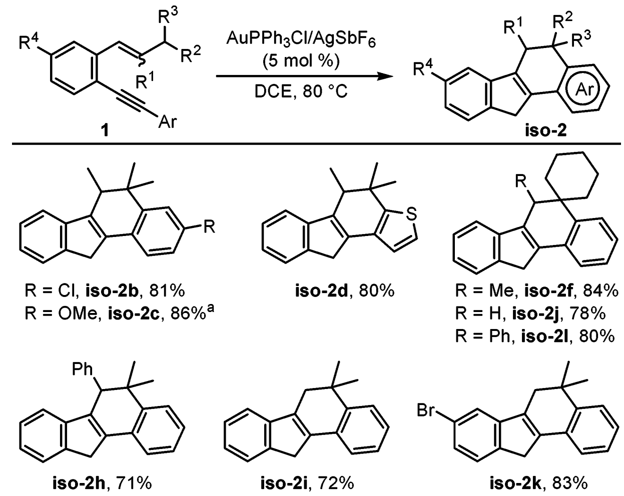
In conclusion, we have developed an efficient synthesis of dihydrobenzo[*a*]fluorenes through a novel gold-catalyzed intramolecular formal [3 + 3] cycloaddition of simple *o*-alkynylstyrenes. Reactions take place through a tandem 5-*endo* cyclization–[1,2]-hydride migration–Friedel–Crafts alkylation to afford the corresponding cycloadducts in good yields. Efforts to identify new reaction pathways of *o*-alkynylstyrenes that could provide selective and straightforward access to other relevant policyclic compounds are currently underway.

(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 the Supporting Information for a detailed study.

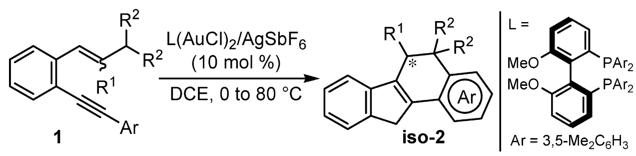
(23) Compared with our previous results (ref 11), the observed modest enantioselectivity could be partially explained considering that the reaction that affords **2** is not totally diastereoselective.

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



[a] Reaction conducted at rt.

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*-$MeOC_6H_4$	**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)

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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

The authors declare no competing financial interest.