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Mimicking Polyolefin Carbocyclization Reactions: Gold-Catalyzed Intramolecular Phenoxycyclization of 1,5-Enynes

Patrick Yves Toullec, Thomas Blarre, and Véronique Michelet*

Laboratoire Charles Friedel, UMR 7223, Ecole Nationale Supérieure de Chimie de Paris, 11, rue P. et M. Curie, 75231 Paris Cedex 05, France

veronique-michelet@enscp.fr

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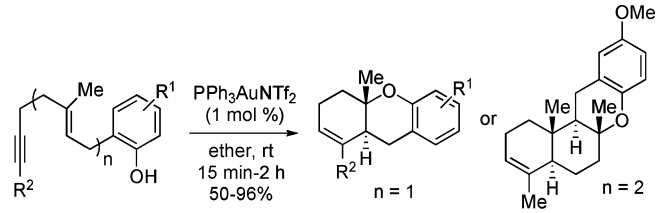
ABSTRACT



R^1 = H, Me, Cl, Br, OCH_2O, OMe, OBn
R^2 = Me, Ph, H

PPh_3AuNTf_2 promotes highly efficient intramolecular phenoxycyclization reactions on 1,5-enynes under mild conditions. The original tricyclic and functionalized heterocycles were isolated in good to excellent yields. The 6-*endo* cyclization process is predominant and operates via a biomimetic cascade cation−olefin process. The efficiency of this system was further demonstrated in the cycloisomerization reaction of a 1,5,9-dienyne.

Since the introduction of the Stork−Eschenmoser postulate[1] more than 50 years ago, polyolefin carbocyclizations have been a field of constant interplay between biologists and chemists.[2] From a synthetic point of view, the involved enzyme-like domino processes[3] have attracted a lot of attention due to the ability of these transformations to allow the construction of polycyclic functionalized structures in a highly selective manner mainly featuring the 6-*endo* mode of cyclization. Synthetic strategies involving chiral iodonium ion-[4] and Lewis acid-mediated[5] polyprenoid cyclizations have appeared as an alternative due to the analogy of their reactivity with one of the protons toward alkenes. Among them, the development of the first enantioselective Brönsted−Lewis acid catalyst by Yamamoto et al. represents a major advance in the field.[6] Cationic carbophilic late transition metal complexes, such as Pt or Hg,[7]

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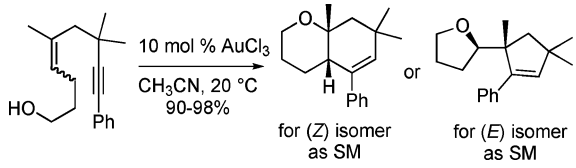
also promote stoichiometrically, and very recently, catalytically[8] in the case of platinum, the polyenes' cyclization. From the organometallic perspective, we postulated that the replacement of the terminal alkene moiety by an alkyne function would release a highly reactive vinyl−metal intermediate prone to protodemetalation.[9] Whereas several reports have been devoted to the late transition carbophilic Lewis acid catalyzed cycloisomerization of 1,6-enynes,[9,10] few reports deal with 1,5-enynes.[11,12] The Kozmin group reported the formation of bicyclic ethers upon cycloisomerization of 1,5-enynes possessing an internal hydroxyle or amine function (Scheme 1).[11c] They reported a strong influence of the stereochemistry

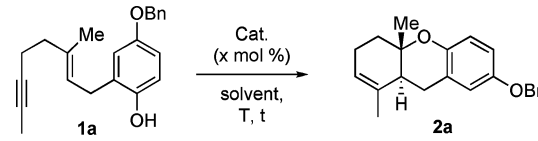
Scheme 1. Au-Catalyzed Cycloisomerization of 1,5-Enynes



of the alkene on the regioselectivity of the cyclization event: whereas *Z* alkenes lead to the obtention of products resulting from a *6-endo* cyclization, *E* alkenes produces bicyclic *5-endo* compounds. As part of our ongoing program devoted to the development of atom-economical metal-catalyzed cycloisomerization reactions[13] and considering the biological and medicinal importance of the hexahydroxanthene core,[14] we engaged in the application of the tandem nucleophilic addition/cycloisomerization reaction to the synthesis involving 1,5-enynes and oxygen nucleophiles. The tricyclic arrangement is indeed present in a family of hydroquinone-containing sesquiterpenes containing more than a hundred isolated natural products of marine origin.[15] These natural products along with synthetic analogues featuring the same structural architecture have attracted attention from synthetic chemists in line with the discovery of promising biological properties.[16] In this paper, we describe a highly efficient gold-catalyzed *6-endo-dig* intramolecular phenoxycyclization of 1,5-enynes and 1,5,9-dienynes.

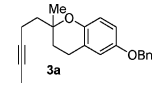
As a model reaction, we prepared 1,5-enyne **1a** (see the Supporting Information) and attempted its cyclization in the presence of various Bronsted or Lewis acid catalysts (Table 1). The use of hydrochloric acid as the electrophilic alkyne

Table 1. [M]-Catalyzed Cycloisomerization of 1,5-Enyne **1a**



entry	catalyst (%)	conditions	yield[a] (%)
1	HCl (50)	toluene/diethyl ether (4/1)	
2	$PdCl_2$ (5)	toluene, 80 °C, 16 h	
3	$PdCl_2$ (5), PPh_3 (10), $AgSbF_6$ (12.5)	dioxane, 60 °C, 16 h	
4	$PtCl_2$ (5)	toluene, 80 °C, 16 h	*b*
5	PPh_3AuCl (1), $AgSbF_6$ (1)	diethyl ether, 20 °C, 16 h	78
6	PPh_3AuNTf_2 (1)	diethyl ether, 20 °C, 1 h	95
7	PPh_3AuNTf_2 (1)	toluene, rt, 1 h	95
8	PPh_3AuNTf_2 (1)	CH_2Cl_2, rt, 1 h	95
9	$AuCl_3$ (10)	CH_3CN, rt	30[c]

[a] Isolated yield. [b] Presence of **2a** and **3a** detected. [c] 35% conversion.



activator did not lead to any conversion of the starting material (Table 1, entry 1). Palladium-based systems, in the presence or the absence of silver salts (Table 1, entries 2 and 3), did not engender any reactivity neither. The use of $PtCl_2$ led to the formation of a complex mixture of products including tetrahydroxanthene **2a** corresponding to the hydroxycyclization product and the chromane **3a**, resulting from the hydroalkoxylation of the alkene double bond.[17] (Table 1, entry 4). In the presence of cationic Au(I) complexes,[18] the clean formation of the bicyclic ether **2a** in 78% yield was this time observed under very mild conditions (Table 1, entry 5). The use of 1 mol %

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(11) For Hg-catalyzed carbocyclization (three examples), see: (a) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703. (b) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451. For Au-catalyzed alkoxy and aminocyclization, see: (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (d) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141. (e) Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*, 2617.

(12) During the preparation of this manuscript, the Gagné group reported the platinum-catalyzed phenoxycyclization of 1,5-enynes using 20 mol % of a dicationic pincer-ligated platinum complex (two examples); see: Nelsen, D. L.; Gagné, M. R. *Organometallics* **2009**, *28*, 950.

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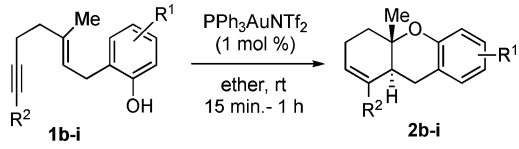
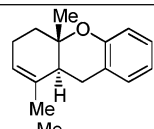
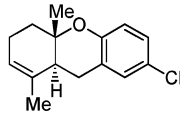
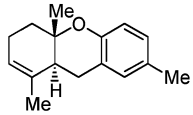
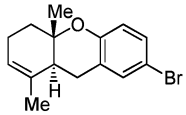
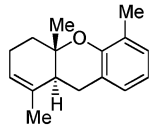
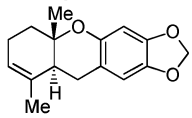
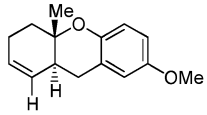
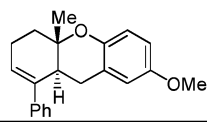
catalyst of the cationic gold complex $(PPh_3)AuNTf_2$,[19] allowed full conversion within 1 h at room temperature (Table 1, entry 6), the desired tricyclic product being isolated in 95% yield. The reaction can be conducted in a variety of solvents including diethyl ether, toluene, or CH_2Cl_2 (Table 1, entries 6−8). As a comparison with the Kozmin group's results (Scheme 1),[11c] the reaction was conducted in acetonitrile in the presence of $AuCl_3$ (Table 1, entry 9). A low conversion was observed, and **2a** was isolated in 30% yield.

The *6-endo* mode of cyclization has been proven on the basis of 2D NMR experiments conducted on compound **2c** (Table 2). These optimum conditions were applied to a variety of 1,5-enynes and dienynes substrates (Table 2 and Scheme 2). All of the reactions tested went to completion within 15 min to 1 h in the presence of 1 mol % of PPh_3AuNTf_2. The substitution of the phenol ring does not affect the yield of the transformation as both electron-donating (Table 2, entries 3 and 5−8) or electron-withdrawing groups (Table 2, entries 2 and 4) are well tolerated. The corresponding tricyclic derivatives **2b**−**i** were isolated in 76−96% yield. The cyclization takes place with the same order of reactivity when the phenol ring is substituted with a methyl group at the 2 position or at the 4 position (Table 2, entries 3, 5). The substitution on the alkyne can be either a methyl (Table 2, entries 1−6), a hydrogen (Table 2, entry 7), or an aromatic ring (Table 2, entry 8). It is remarkable to notice that the 6-*endo* cyclization of the 1,5-enyne fragment occurs irrelevantly of the substitution of the alkyne moiety (Table 2, entries 6−8).

Table 2. 1,5-Enyne and 1,5,9-Dienyne Cyclizations Catalyzed by PPh_3AuNTf_2

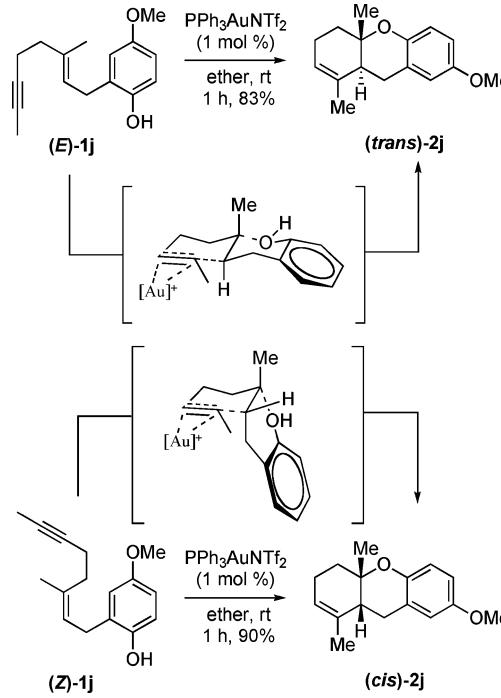


1b-i **2b-i**

entry	R^1	R^2	product		yield[a] [%]
1	H	Me		**2b**	76
2	4-Cl	Me		**2c**	80
3	4-Me	Me		**2d**	80
4	4-Br	Me		**2e**	89
5	2-Me	Me		**2f**	88
6	3,5-OCH_2O	Me		**2g**	88
7	4-MeO	H		**2h**	96
8	4-MeO	Ph		**2i**	83

[a] Isolated yields. Small amounts (0−10%) of a minor isomer, presumably resulting from the 5-*endo* cyclization, were obtained as byproduct.

Scheme 2. Au-Catalyzed Cycloisomerization of (*E*)- or (*Z*)-1,5-Enynes



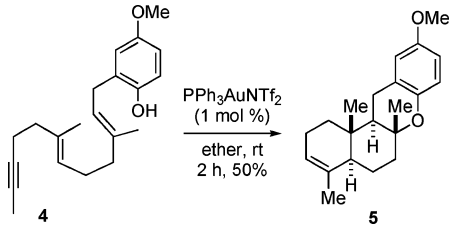
The *6-endo* mode of cyclization being observed for all enynes possessing an (*E*)-alkene (**1a**−**i**), we decided to investigate the reactivity of substrates **(*E*)-1j** and **(*Z*)-1j** possessing respectively a (*E*)- or (*Z*)-alkenyl side chain (Scheme 2). As expected the hexahydroxanthene **(*trans*)-2j** was obtained in 83% isolated yield. We were pleased to see that the **(*cis*)-2j** derivative possessing a *cis* ring junction was obtained as a single regio- and diastereoisomer in 90% yield.

Mechanistically, a reasonable initial η^2 coordination of cationic gold(I) fragment on the alkyne function would then trigger a double-cyclization process. The 6-*endo* cyclization process is in complete accordance with a Stork−Eschenmoser-type carbocationic cyclization and in complete coherence with Fürstner's group[20] results on the carboxycyclization of 1,6-

enynes. As depicted in Scheme 2, the *cis* or *trans* relationship of the corresponding hexahydroxanthene results from a chairlike cyclization process.

To further probe the gold-catalyzed biomimetic cascade cation−olefin cyclization, the reactivity of dienyne **4** was also attempted: we were pleased to find that the expected cyclization smoothly occurred leading to the tetracyclic derivative **5** featuring the *trans*−*trans* arrangement[21] in 50% yield (Scheme 3). Although tricycles **2a**−**j** have been obtained in high yields

Scheme 3. Au-Catalyzed Cycloisomerization of 1,5,9-Dienyne **4**



with a high degree of diastereoselectivity (>20/1), the low yield observed for the formation of **5** may be rationalized as an evidence of an alternative mechanism involving stepwise cation−olefin cyclization.[7c,12]

In summary, we have showed that PPh_3AuNTf_2 efficiently promotes intramolecular phenoxycyclization reactions on 1,5-enynes under mild conditions. The original tricyclic and functionalized heterocycles were isolated in good to excellent yields. We have showed that the 6-*endo* cyclization process is predominant and operates via a biomimetic cascade cation-olefin process. The efficiency of this system was further demonstrated in the cycloisomerization reaction of 1,5,9-dienyne. This process paves the way for further applications in enantioselective tandem nucleophile addition/cycloisomerization reactions. Current efforts are focused on expanding the scope of this methodology to other classes of nucleophiles.

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Supporting Information Available: Experimental procedure, full analyses of **1a**−**j**, **2a**−**j**, **4**, and **5**, and 2D and NOESY experimental analysis of **2c** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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