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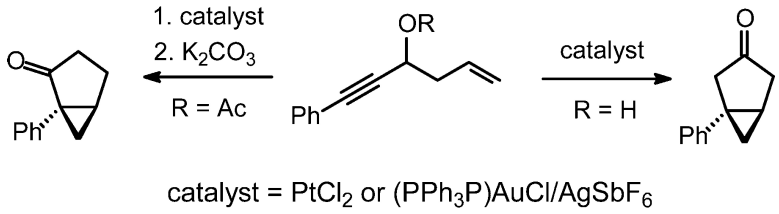

catalyst = $PtCl_2$ or $(PPh_3P)AuCl/AgSbF_6$

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Platinum- and Gold-Catalyzed Cycloisomerization Reactions of Hydroxylated Enynes

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Complexation of enynes to $PtCl_2$ engenders a host of selective cycloisomerization reactions that likely involve cyclopropyl platinum carbenes as reactive intermediates (Scheme 1).[1−3] Such species are best viewed as latent cyclopropyl methyl cations that can evolve along different pathways.[4] The overall transformations are inherently atom economical, result in a substantial increase in structural complexity, and are simple, safe, and convenient to perform and therefore meet many of the stringent criteria imposed upon contemporary organic synthesis.[1]

In pursuit of previous investigations in this field,[4,5] we envisaged that enynes bearing an −OH group at the propargylic position might undergo an as yet unknown transformation. The evolving platinum carbene is expected to trigger an irreversible 1,2-hydrogen shift[6] with formation of a bicyclo[3.1.0]hexanone skeleton as shown in Scheme 2. Since this structural motif is present in a large number of terpenes,[9] a concise entry into this important class of natural products might ensue.

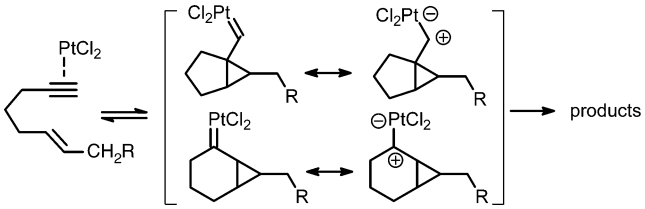
To probe this concept, alcohol **2**-D_1 was prepared from the deuterated aldehyde **1**-D_1 and allylmagnesium bromide (Scheme 3). Treatment of this enyne with $PtCl_2$ in toluene at 60 °C furnished the bicyclic ketone **3**-D_1 in 75% yield. In line with the proposed mechanism, the deuterium label in the product appears exclusively at the C-atom α to the newly formed carbonyl group.

Next, it was attempted to integrate the allylation and the cycloisomerization into a "one-pot" transformation. This seemed possible since previous investigations from this laboratory had shown that aldehydes react with allyl chlorosilane **4** in the presence of $PtCl_2$ to afford the corresponding homoallylic alcohols via "halophilic activation" of the donor.[7] In fact, treatment of alkynal **1** with **4** and $PtCl_2$ catalyst in MeCN at 80 °C engendered a reaction cascade comprising an allylation followed by in situ rearrangement of the resulting enyne and delivered the bicyclic product **3** in 55% yield (Scheme 3). This outcome compares well to the two-step protocol (60% overall) and shows that $PtCl_2$ can act as dual−specific catalyst.

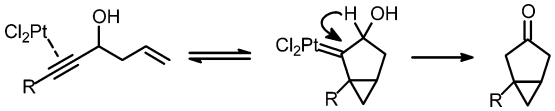
Table 1 illustrates the generality of this novel skeletal reorganization reaction of hydroxylated enynes. It is noteworthy that the propargylic alcohol unit in the substrates can also be remote from the alkene as exemplified by the conversion of **13** (R = Me, Ph) into the bicyclic products **14** bearing the newly formed ketone in the lateral chain. Moreover, it was found that $PtCl_2$ can be replaced by $(PPh_3)AuCl/AgSbF_6$ as the catalyst;[8] the resulting cationic gold complex is particularly reactive and induces the isomerization even at ambient temperature (entry 1, footnote b).

The favorable profile of this rearrangement became apparent from a concise approach to sabinone **18** and the two isomeric sabinols **19** (Scheme 4), characteristic terpenes found in various *Artemisia*, *Juniperus*, and *Thuja* species.[9] Lewis acid-catalyzed addition of the allenyl silane **16** to aldehyde **15** afforded the labile 1,3-butadienyl derivative **17**,[10] which delivered sabinone **18** on exposure to catalytic amounts of $PtCl_2$ in benzene in good yield. This example shows that an additional double bond in the substrate does not interfere with the skeletal reorganization of the hex-1-en-5-yn-4-ol backbone. Reduction of **18** with $NaBH_4/CeCl_3$ afforded *cis*- and *trans*-sabinol **19** as a 1:1 mixture, which was separated by preparative GC.

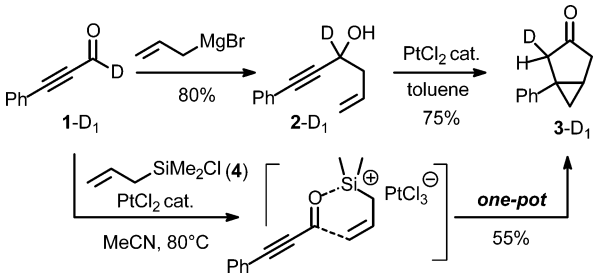
Scheme 1



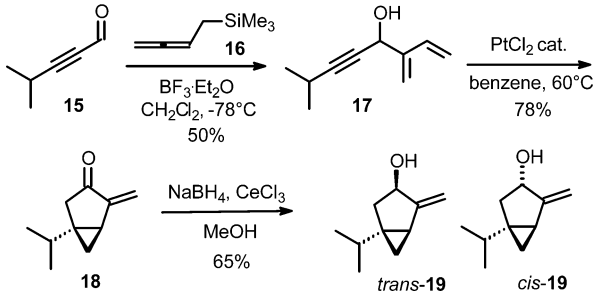
Scheme 2



Scheme 3



Scheme 4



To extend the scope of the method further, alcohol **2** was converted into the corresponding acetate **20**. As suggested by previous findings,[11] the ester might be able to participate in the rearrangement process by attacking the polarized metal−alkyne complex initially formed. Interception of the emerging carbene by the terminal double bond results in the formation of compound **21** in which the acetate has migrated, masking a ketone group at C-2 as the corresponding enol ester (Scheme 5). This simple method allows functionalization of this otherwise inaccessible position on the bicyclic skeleton and therefore complements the hydride shift process outlined above.

10.1021/ja048094q CCC: $27.50

Scheme 5

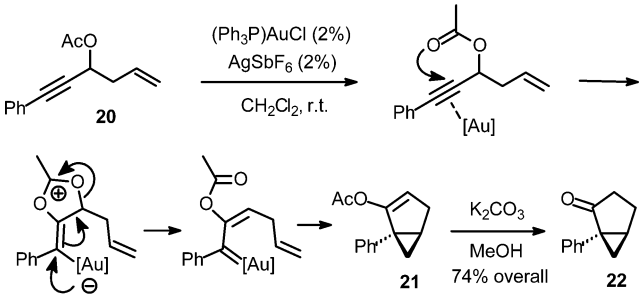
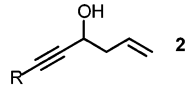
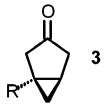
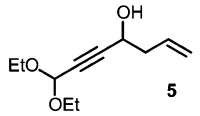
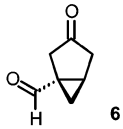
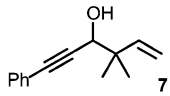
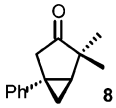
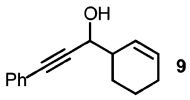
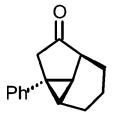
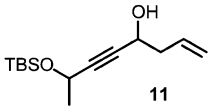
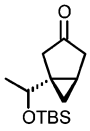
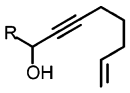
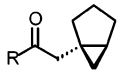


Table 1. Metal-Catalyzed Cycloisomerizations of Hydroxylated Enynes[a]

Substrate	Product	Yield
 2	 3	74%/75%[b] (R = Ph) 72% (R = C_5H_{11}) 81% (R = C_7H_{15})
 5	 6	60%[c]
 7	 8	66%
 9	 10	52%
 11	 12	94%[d]
 13	 14	62% (R = Me) 62% (R = Ph)

[a] All reactions were performed in toluene at 60−80 °C with $PtCl_2$ (5 mol %) unless stated otherwise. [b] Using $(PPh_3)AuCl/AgSbF_6$ (2 mol %) in CH_2Cl_2 at 20 °C. [c] After workup with aq HCl. [d] dr = 3:1.

Finally, the stereochemical implications of the novel rearrangement have been investigated (Scheme 6). Brown crotylation[12] of **1** afforded the homoallylic alcohols **23** in high optical purity, which were isomerized with $PtCl_2$ catalyst in toluene at 60 °C. In full accordance with the mechanistic proposal, the *diastereomeric* substrates *syn*-**23** and *anti*-**23** furnished the *enantiomeric* products **24**/**25** and *ent*-**24**/*ent*-**25**, respectively. The significantly higher dr in the *syn* series is likely explained by the fact that only carbene **A** is devoid of eclipsing interactions between the methyl branch, the adjacent alcohol, and the incipient cyclopropyl ring and should therefore be more favored over **B** than the diastereomeric intermediate **D** is favored over **C**.[13] Further studies to probe this and related aspects of the novel cycloisomerization are underway and will be reported in due course.

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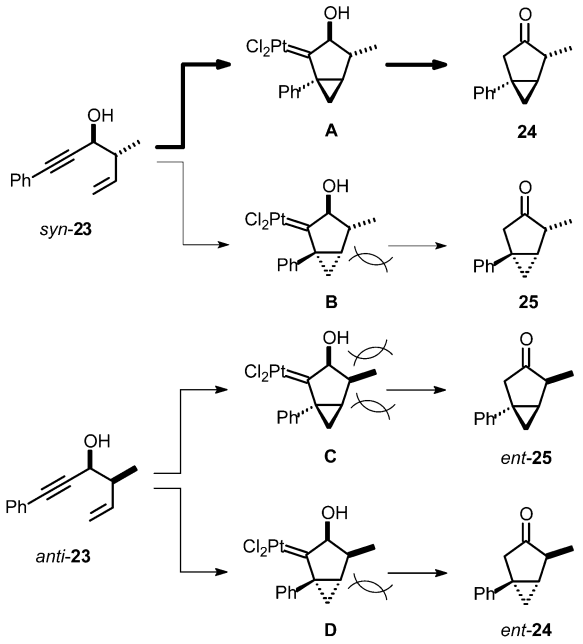
Scheme 6



Substrates			Products		
	d.e.	e.e	Yield	d.r.	ee
syn-**23**	94%	92%	65%	4.3:1	92% (**24**), 89% (**25**)
anti-**23**	86%	93%	63%	1.5 :1	78% (*ent*-**24**), 87% (*ent*-**25**)

Supporting Information Available: Experimental part including spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
(13) This interpretation assumes that the steric interactions in the carbene region are similar for **A**/**B** and **C**/**D** as suggested by molecular modeling.

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