ORGANIC LETTERS

2005
Vol. 7, No. 19
4129−4132

Unusual Gold(I)-Catalyzed Isomerization of 3-Hydroxylated 1,5-Enynes: Highly Substrate-Dependent Reaction Manifolds

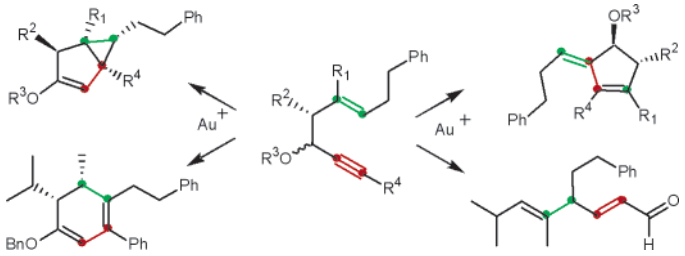
Fabien Gagosz*

Laboratoire de Synthèse Organique, Ecole Polytechnique, 91128 Palaiseau, France

gagosz@dcso.polytechnique.fr

Received June 16, 2005

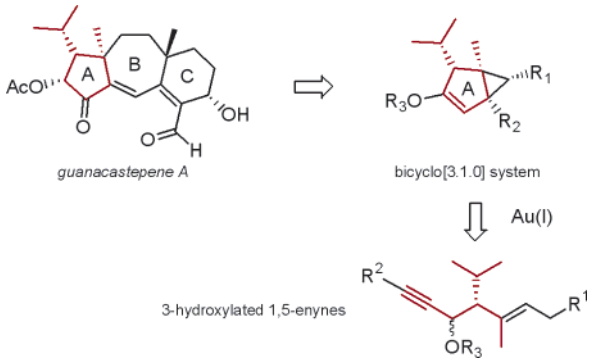
ABSTRACT



The gold(I) isomerization of diversely substituted 3-hydroxylated enynes has led to the discovery of three new unreported skeletal rearrangements furnishing structures such as alkylidene-cyclopentenes, cyclohexadienes or α,β-unsaturated aldehydes under very mild conditions.

Gold(I) complexes have recently emerged as efficient and mild catalysts for the transformation of substrates possessing an alkyne functionality into a range of useful structural motifs.[1] The potential of such catalysts has been mostly highlighted by various studies related to the conversion of enynes into cycloisomerized products.[2] In this respect, we were particularly intrigued by the possibility that ring A of the bioactive guanacastepene A[3] could be synthesized using a gold(I)-catalyzed cycloisomerization of a well defined enyne (Scheme 1). Actually, this approach would allow the early introduction of most of the functionalities present on ring A, while the presence of the cyclopropyl ring could serve as a springboard for the construction of ring B. We herein report results concerning these studies that led to the discovery of three new unusual gold(I)-catalyzed isomerizations of 3-hydroxylated 1,5-enynes.[4]

Scheme 1. Retrosynthesis of Guanacastepene A



(1) For a review on homogeneous catalysis by gold, see: Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65.

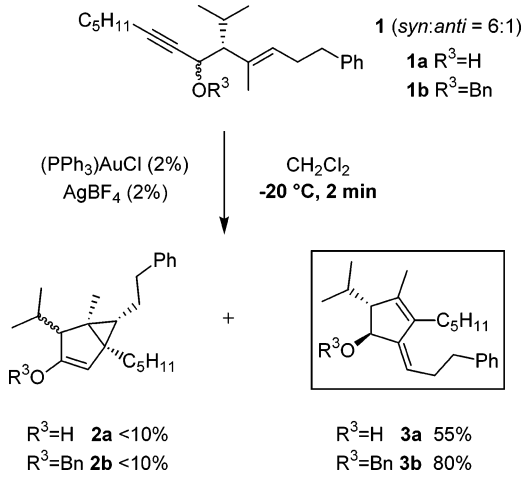
(2) (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553−11554. (b) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178−6179. (c) Muñoz, M.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293−1300. (d) Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155−3164. (e) Nieto-Oberhuber, C.; Muñoz, M.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406. (f) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803. (g) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859. (h) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978−15979. (i) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350−5352. (j) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527. (k) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807. (l) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−6963.

(3) Brady, S. F.; Singh, M. P.; Janso, J.; E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116−2117.

10.1021/ol051397k CCC: $30.25
Published on Web 08/18/2005

Compound **1** was first chosen as a model substrate to validate the above-described approach (Scheme 2). To this

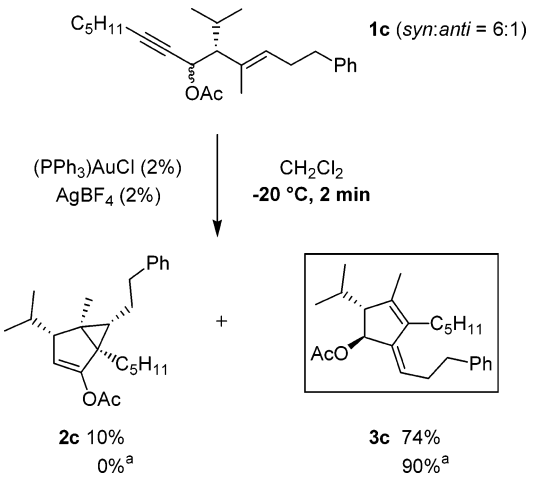
Scheme 2. Cycloisomerization of Enynes **1a** and **1b**



end, treatment of a mixture of *syn*- and *anti*-enynes **1a** with 2 mol % $(PPh_3)AuBF_4$ at room temperature was attempted.

However, a rapid decomposition of the substrate was observed under these conditions, and only traces of desired **2a** were detected.[5] Interestingly, lowering the temperature to −20 °C addressed the problems of degradation and led to a fast conversion of the substrate. However, conversion

Scheme 3. Cycloisomerization of Enyne **1c**

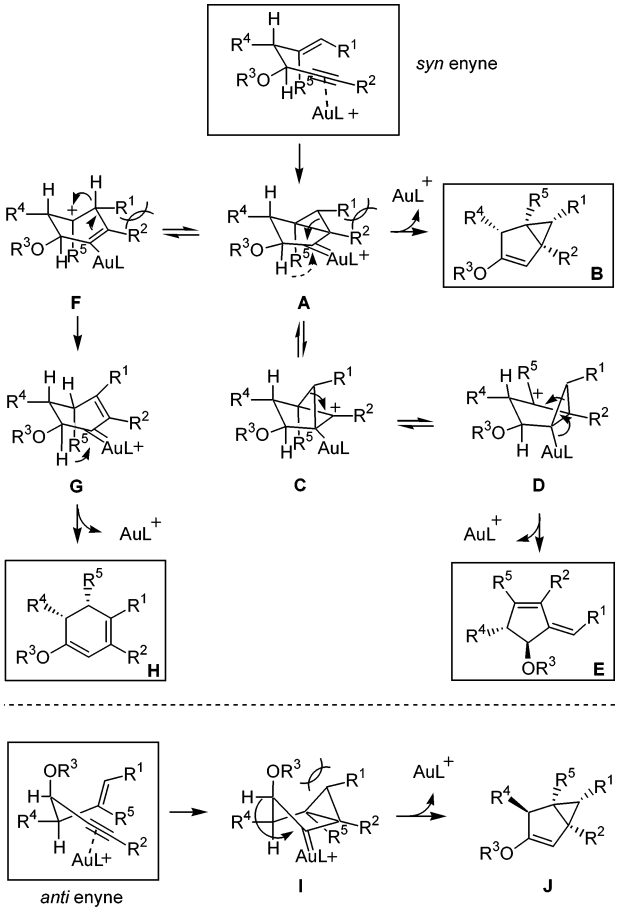


[a] Yields obtained when >97% pure syn isomer **1c** was used.

of **1a** into **2a** was not improved, and we were surprised to observe instead the formation of alkylidene-cyclopentene **3a**, which was isolated in 55% yield. This compound, whose structure and stereochemistry were confirmed by full NMR analyses, is produced by an unreported skeletal rearrangement and formally corresponds to an *endo*-metathesis-type compound. The yield of this new rearranged product was improved to 80% when the reaction was performed starting from benzyl ether **1b** as the substrate. Even in the case of enyne **1c**, a type of compound known to undergo a rapid 1,2-shift of the acetate moiety, the reaction furnished the corresponding alkylidene-cyclopentene **3c** in 74% yield (90% starting from >97% pure syn **1c**) (Scheme 3).

To determine more precisely the influence of the substitution pattern of the starting enynes on the course of the new

Scheme 4. Mechanistic Proposal for Alkylidene-cyclopentene Formation

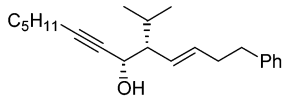
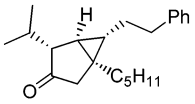
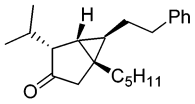
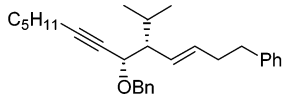
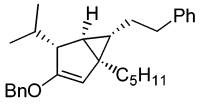
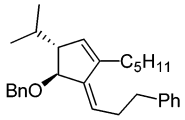
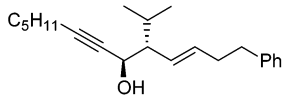
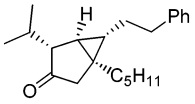
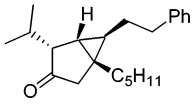
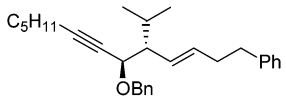
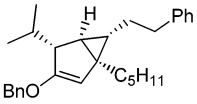
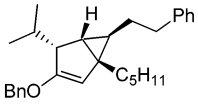
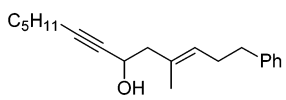
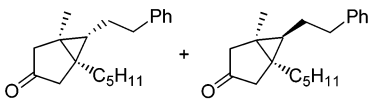
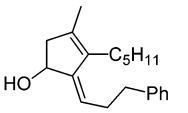
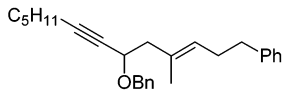
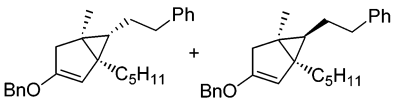
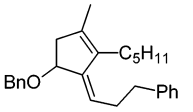
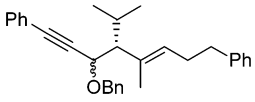
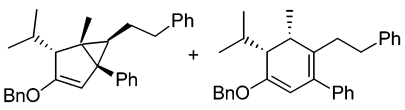
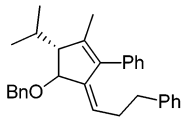


skeletal reorganization, various enynes **1d**−**j** were synthesized and subjected to gold(I)-catalyzed isomerization. The results are summarized in Table 1. We first turned our attention to enynes **1d**−**g**, lacking the methyl group at the vinylic position. It is interesting to note that the isomerization required in these cases a longer reaction time and a higher temperature to reach completion. This may be attributed to the reduced nucleophilicity of the alkene compared to

(4) For related studies, see: (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (b) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mouries, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656−8657.

(5) A fast coloration of the solution and the formation of very apolar products were observed. Under the same reaction conditions, product **3a** led to the formation of the same byproducts.

Table 1. Isomerizations of Various 3-Hydroxylated 1,5-Enynes[a]

substrate	temperature	time	products and yields	dr [b]
1d 	20 °C	5 min	 **2d** 66%  **3d** 14%	**2d**:**3d** = 4.2:1
1e 	-10 °C	15 min	 **2e** 54% [c]  **3e** 27%	
1f 	20 °C	5 min	 **2d** 17%  **3d** 70%	**2d**:**3d** = 1:4.1
1g 	-10 °C	15 min	 **2e** 15% [c]  **3g** 63% [c]	**2e**:**3g** = 1:4.1
1h 	-20 °C	5 min	 **2h** 63% **3h**  **4h** 29%	**2h**:**3h** = 2.3:1
1i 	-20 °C	5 min	 **2i** 30% [c] **3i**  **4i** 57%	**2i**:**3i** = 2.3:1
1j  *syn*:*anti* = 5:1	-20 °C	5 min	 **2j** 33% [c] **3j**  **4j** 54%	**2j**:**3j** = 1:3.3

[a] Reaction conditions: 0.1 M enyne in DCM with 2% $(PPh_3)AuBF_4$. [b] Ratio determined by ^1H NMR. [c] Isolated as the deprotected enol form.

analogues **1a**−**c**.[6] We were further surprised to observe that such a simple structural modification had a very significant influence on the course of the reaction. For example, the rearrangement leading to the alkylidene-cyclopentene skeleton was only observed in the case of the syn isomer **1e**, but the corresponding alkylidene-cyclopentene **3e** was isolated in only 27% yield. Moreover, a reversal in selectivity was observed when the reaction was performed using either *syn*-enyne **1d** or isomeric *anti*-enyne **1f**.[7] These results suggest that the hydroxyl group can indeed act as a stereodirecting element in this transformation.

Enynes **1h** and **1i** smoothly reacted at −20 °C, affording the corresponding alkylidene-cyclopentenes **4h** and **4i** in 29 and 57% yields, respectively. The presence of an alkyl group at the allylic position of the substrate is apparently not of crucial importance for the obtention of alkylidene-cyclopentene-type products but facilitates their formation probably through steric compression. We were, however, surprised by the formation of compounds **3h** and **3i** since the reaction was performed starting from a substrate possessing an olefin with a trans configuration. We next examined the influence of the lateral chain of the alkyne moiety on the course of the reaction. An experiment was performed on substrate **1j** possessing a bulkier phenyl group at the terminal position of the alkyne. In that case, alkylidene-cyclopentene **4j** was obtained in 54% yield along with 25% of cyclohexadiene **3j** generated by a new unreported isomerization pathway.

On the basis of these observations and previously described rearrangements of 1,5-enynes,[2] we propose the sequence

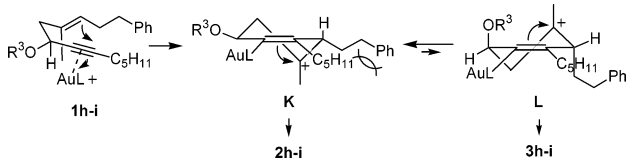
(6) For a review on π-nucleophilicity in C−C bond formation, see: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

(7) The reason for such a selectivity is still unclear, and studies to rationalize this result are underway.

shown in Scheme 4 as the most likely mechanism for the formation of the new cycloisomerized products. In the case of *syn*-enynes, the nucleophilic attack of the olefin onto the gold(I)−alkyne complex produces the gold-stabilized carbocation **A**, which normally collapses to **B** by a 1,2-hydride shift and release of gold(I). The presence of bulky substituents on the cyclopropyl ring (R^1, R^2, and R^3) dramatically alters the normal reaction pathway leading to **B**. A double 1,2-alkyl shift process, favored by a decrease of steric congestion in **A**, can operate instead and lead to intermediate **C** and then **D**.[2k] The latter finally fragments to regenerate the catalyst and furnish alkylidene-cyclopentenes **E**. Alternatively, steric interactions may sufficiently reduce the rate of the cyclopropyl ring formation and therefore stabilize carbocationic intermediate **F**. A competitive diastereoselective 1,2-hydride shift leading to **G** may then be involved, which would explain the formation of a six-membered cycle in **3j** and justify the stereochemistry of the final compound. Cyclohexadiene **H** is generated by subsequent 1,2-hydride shift followed by elimination of the gold(I) catalyst. This rearrangement seems to be unlikely in the case of the corresponding anti isomers due to a disfavored interaction between the OR^3 group and the cyclopropane moiety in intermediate **I**.

Therefore, the 1,2-hydride shift occurs to afford compounds **J**. In the case of enynes **1i**−**j**, the formation of isomers **2i**−**j** and **3i**−**j** may be explained by a fast equilibrium between conformers **K** and **L** driven by a plausible decrease of the steric interactions in intermediate **K** (Scheme 5). In this way, both epimers **2h**:**3h** and **2i**:**3i** can be produced

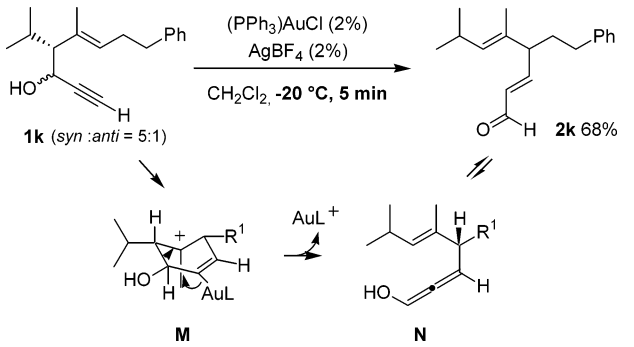
Scheme 5. Formation of Epimers **2h**:**3h** and **2i**:**3i**



despite the unique geometry of the starting olefins **1h** and **1i**.

A final experiment was performed on terminal alkyne **1k** (Scheme 6). No alkylidene-cyclopentene was formed in this case due to the unlikely possibility of a 1,2-alkyl shift leading

Scheme 6. Cycloisomerization of Enyne **1k**



to the corresponding intermediate **D**. However, we were pleased to isolate instead aldehyde **2k** in 68% yield, whose formation may be rationalized by the mechanism proposed in Scheme 6.

A 6-*endo*-dig attack of the olefin onto the gold(I)−alkyne complex results in the formation of intermediate **M**. Subsequent Grob-type fragmentation affords allenol **N**, which spontaneously tautomerizes to aldehyde **2k**. This unreported transformation corresponding to an acetylenic oxy-Cope rearrangement is remarkable since it operates rapidly under very mild conditions and *without* isomerization of the dienic system.[8]

In summary, we have demonstrated that the gold(I)-catalyzed isomerization of 3-hydroxylated 1,5-enynes may follow highly divergent reaction pathways depending on the substitution pattern and the relative configuration of the substrate since three unreported types of skeletal rearrangement have been discovered. Further studies related to the exploitation of these new synthetically useful transformations are underway and will be reported in due course.

Acknowledgment. The author wishes to thank Prof. S. Z. Zard, Dr. B. Quiclet-Sire, Dr. I. Hanna, Dr. P. Le Floch and Dr. N. Mézailles for helpful discussions.

Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051397K

(8) For an example of the silver(I)-catalyzed acetylenic oxy-Cope process, see: Bluthe, N.; Gore, J.; Malacria, M. *Tetrahedron* **1986**, *42*, 1333−1344.