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Gold(I) Catalyzed Isomerization of 5-en-2-yn-1-yl Acetates: An Efficient Access to Acetoxy Bicyclo[3.1.0]hexenes and 2-Cycloalken-1-ones

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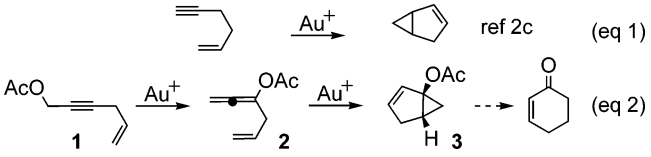
Gold(I) complexes have emerged as efficient and mild catalysts for the activation of alkynes toward addition by a variety of nucleophiles.[1] The potential of such catalysts has been highlighted by numerous studies related to the conversion of various enynes into cycloisomerized products.[2]

In this respect and by analogy with the isomerization of 1,5-enynes to bicyclo[3.1.0]hexenes (eq 1),[2c] we surmised that 5-en-2-yn-1-yl acetates such as **1** might be valuable precursors for the synthesis of acetoxy bicyclo[3.1.0]hexene (e.g., **3**) after a gold catalyzed sequence of allene (e.g., **2**) formation[3] and cycloisomerization (eq 2). This approach would be advantageous since the presence of the acetoxy functionality at the ring junction might allow the synthesis of more elaborate structures such as 2-cyclohexen-1-ones.

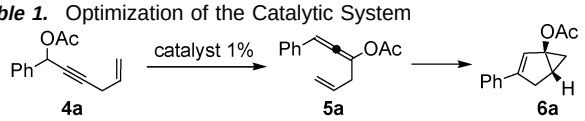


Following our recent success in using the air stable crystalline $Ph_3PAuNTf_2$ [4] catalyst for the formation of C−C or C−O bonds, we chose this catalytic system to validate this approach (Table 1).

Treatment of propargylic acetate **4a** with 1% of $Ph_3PAuNTf_2$ in CH_2Cl_2 at room temperature furnished the desired bicyclo[3.1.0]-hexene **6a** in 49% yield along with 41% of the postulated intermediate allene **5a** (entry 1). Heating the reaction mixture at 40 °C did not improve the yield (entry 2). At 60 °C, the reaction was faster and afforded **6a** in good yield (entry 3). Changing the electronic properties of the phosphine had a significant effect on the course of the transformation (entries 4 and 5). While the electron deficient $(p\text{-}CF_3Ph)_3PAuNTf_2$ catalyst[4c] gave **6a** in a modest 32% yield, the bulkier and more electron rich $Ad_2n\text{-}BuPAuNTf_2$ [4c] furnished **6a** in 78% yield. The yield could even be improved to 94% by using 1% of $Ad_2n\text{-}BuPAuNTf_2$ and heating the reaction mixture at 60 °C for 0.5 h (entry 6). We next turned our attention on the use of biphenylphosphine based catalysts (entries 7 and 8).[5] Remarkably, the use of **7** and **8** provided **6a** in excellent yields (98% and 96%) in CH_2Cl_2 at room temperature.[6] Furthermore, reacting allene **5a**[7] with 1% of **7** in CH_2Cl_2 at room temperature cleanly furnished **6a** in 98% yield, thus proving the intermediacy of allene **5a** in this transformation. It is worth notice that the use of Au(III), Pt(II), or Ag(I) catalysts did not furnish the desired bicyclo[3.1.0]hexene **6a**.[8] In light of these results, catalyst **7** was retained in the study of the scope of this transformation.

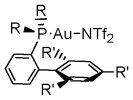
The reaction proved to be quite general and various substituted 5-en-2-yn-1-yl acetates **4b**−**j** reacted using 1% of **7** as the catalyst to furnish the corresponding bicyclo[3.1.0]hexenes **6b**−**j** in generally good yields (38%−99%) (Table 2). Substitution at the alkene was first examined. The reaction was exceptionally fast with methallyl derivative **4b** furnishing bicyclo[3.1.0]hexene **6b** in 97% yield (entry 1). Crotyl derivative **4c** reacted more slowly and gave **6c** as the sole product in 93% yield despite the fact that a cis/trans mixture of substrate was used (entry 2). Introduction of a methyl group at the allylic position was also tolerated, producing bicyclo-[3.1.0]hexene **6d** as a 1:2.8 mixture of diastereoisomers (entry 3).[9,11]

Table 1. Optimization of the Catalytic System



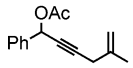
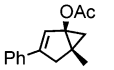
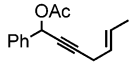
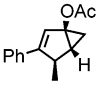
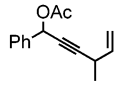
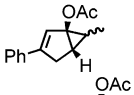
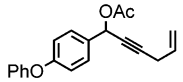
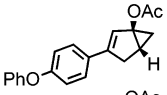
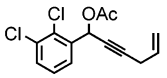
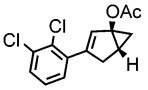
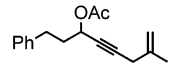
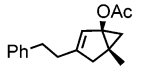
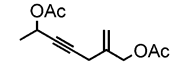
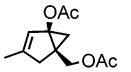
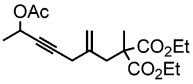
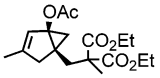
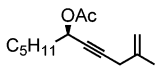
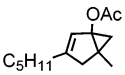
entry	catalyst	conditions	time	yield (**4a** / **5a** / **6a**)[a]
1	Ph_3AuNTf_2	CH_2Cl_2, rt	6h	0% / 41% / 49%
2	Ph_3AuNTf_2	CH_2Cl_2, reflux	6h	0% / 37% / 48%
3	Ph_3AuNTf_2	1,2-DCE, 60°C	2h	0% / 4% / 82%
4	$(pCF_3Ph)_3PAuNTf_2$	CH_2Cl_2, rt	6h	0% / 53% / 32%
5	$Ad_2n\text{-}BuPAuNTf_2$	CH_2Cl_2, rt	6h	0% / 21% / 78%
6	$Ad_2n\text{-}BuPAuNTf_2$	1,2-DCE, 60°C	0.5h	0% / 0% / 94%
7	**7**	**CH_2Cl_2, rt**	**1h**	**0% / 0% / 98%**
8	**8**	CH_2Cl_2, rt	5h	0% / 0% / 96%

[a] isolated yields



7 R= *t*-Bu, R'= H
8 R=Cy, R'= *i*-Pr

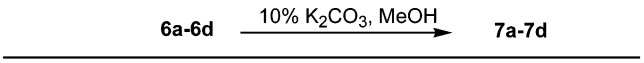
Table 2. Gold(I) CatalyzedFormation of Bicyclo[3.1.0]hexenes

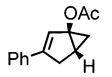
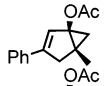
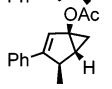
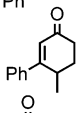
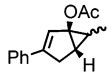
entry	substrate	product	time	yield[b]
1		**4b**  **6b**	5 min	97%
2		**4c** (E:Z=85:15)  **6c**	5 h	93%
3		**4d** (dr=1:1)  **6d**	30 min (exo:endo =1:2.8)	98%
4		**4e**  **6e**	2 h	99%
5		**4f**  **6f**	2 h	38%[c]
6		**4g**  **6g**	20 min	99%
7		**4h**  **6h**	2.5 h	72%
8		**4i**  **6i**	15 min	96%
9		**4j** 99% ee  **6j**	15 min	92% 90% ee

[a] Reaction conditions: 0.25 M substrate in CH_2Cl_2, 1% of **7**, rt. [b] Isolated yields. [c] A total of 44% of the corresponding allene were also isolated.

10.1021/ja064223m CCC: $33.50

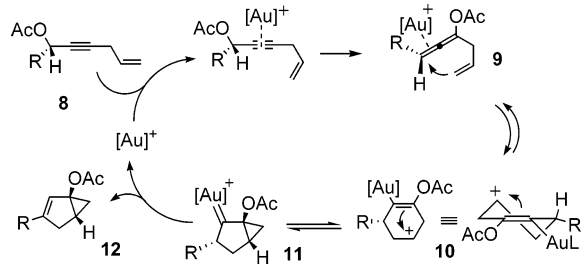
Table 3. Formation of 2-cycloalken-1-ones



Entry	Substrate		Product		Yield [a]
1		**6a**		**7a**	94%
2		**6b**		**7b**	89%
3		**6c**		**7c**	96%
4		**6d**		**7d**	98%

[a] Isolated yields.

Scheme 1. Proposed Mechanism

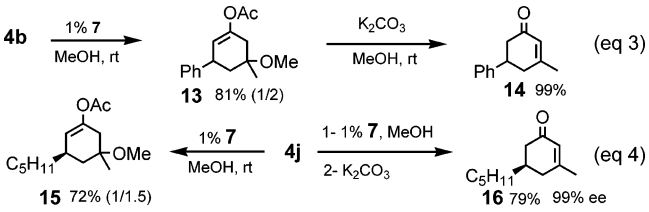


The aromatic ring could be substituted, but with a decrease in efficiency when the 2,3-dichlorophenyl derivative **4f** was used as the substrate (entries 4 and 5). The rearrangement proceeded as well when the propargylic position of the enyne was substituted with an alkyl chain (entries 6−9). Various substituted bicyclo[3.1.0]-hexenes **6g**−**j** possessing two adjacent quaternary centers at the ring junction were thus obtained in yields ranging from 72% to 99%. Finally, the cycloisomerization of enantioenriched substrate **4j** was attempted. We were pleased to observe the rapid formation of bicyclo[3.1.0]hexene **6j** which was isolated in 92% yield. Interestingly, the stereochemical information of the substrate was nearly completely transferred to the final product.[10]

The functionalized acetoxy bicyclo[3.1.0]hexene products lend themselves to a number of useful transformations. For example they can be efficiently converted into 2-cycloalken-1-ones by simple treatment with K_2CO_3 in methanol thus highlighting the general utility of this transformation (Table 3). The cleavage of the cyclopropane ring seems to be directed by the substitution pattern of the cylopropyl ring. Bicyclo[3.1.0]hexenes **6a**, **6c**, and **6d** afforded the corresponding 2-cyclohexen-1-ones **7a**, **7c**, and **7d**, while bicyclo[3.1.0]hexene **6b** bearing a methyl group at the ring junction gave 2-cyclopenten-1-one **7b**.

To account for these observations, a mechanistic manifold for the formation of the bicyclo[3.1.0]hexenes is proposed in Scheme 1. Gold(I) activation of the triple bond in alkyne **8** promotes the formation of allene **9** through a [3,3]-sigmatropic rearrangement. A further gold(I) activation of the allene induces the nucleophilic attack of the pendant alkene resulting in the formation of the cationic vinyl-gold species **10**.[11] Subsequent formation of the cyclopropyl ring assisted by electron donation from gold(I) affords gold(I) carbene **11**. A final 1,2-hydride shift regenerates the gold(I) catalyst and produces bicyclo[3.1.0]hexene **12**.

The proposed mechanism suggests that intermediate **10** could be trapped by a nucleophile. In agreement with this hypothesis, cyclohexene **13** was formed in 81% yield as a 1:2 mixture of diastereoisomers when the rearrangement of **4b** was performed in MeOH (eq 3). Interestingly, the nucleophilic addition of the alkene onto the gold(I) activated allene seems to be faster than the addition of methanol onto the same activated allene. Subsequent basic treatment of **13** afforded 2-cyclohexen-1-one **14** in 99% yield. Furthermore, treatment of enantioenriched propargylic acetate **4j** furnished **15** in 72% yield as a 1:1.5 mixture of epimers under the same experimental conditions (eq 4). A one-pot cycloisomerization deprotection sequence was also attempted and led to the formation of the corresponding 2-cyclohexen-1-one **16** with a complete retention of the chiral information. Note that the cyclohexenones obtained by that route (e.g., **16**) are regioisomeric with those generated by opening the cyclopropane as in Table 3.



In summary, we have developed an efficient gold(I) catalyzed cycloisomerization of 5-en-2-yn-1-yl acetates that provides an efficient access to acetoxy bicyclo[3.1.0]hexenes which can be further transformed into 2-cycloalken-1-ones. Cyclohexenones are key building blocks in numerous total syntheses. Further studies related to this new gold(I)-catalyzed process as well as its application to the synthesis of natural products are underway.

Acknowledgment. The authors wish to thank Prof. S. Z. Zard 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.

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(2) For selected examples of Au^+ cycloisomerization of 1,n enynes, see (1,3-enyne): (a) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442−1443. 1,4-enyne: (b) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803. 1,5-enyne: (c) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859. (d) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978−10979. (e) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129−4132. (f) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−16963. (g) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807. 1,6-enyne: (h) Nieto-Oberhuber, C.; Munoz, M. P.; Lopez, S.; Jiménez-Nùnez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677−1693.

(3) For examples of Au^+ catalyzed 3,3-rearrangements of propargylic esters, see: (a) ref 2a. (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805. (c) Marion, N.; Diez-Gonzales, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1−5

(4) (a) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957−1959. (b) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515−518. (c) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.

(5) Lopez, S.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178−6179.

(6) Interestingly, aromatic groups do not interfere in the reaction (ref 3c).

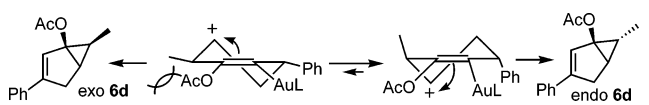
(7) Allene **5a** was obtained in 89% yield by reaction of **4a** with 10% of $AgNTf_2$ in CH_2Cl_2 at room temperature for 30 min.

(8) In CH_2Cl_2 for 6 h; 5% $AuBr_3$: 0% **4a**, 0% **5a**, 0% **6a**. 5% $PtCl_2$: 80% **4a**, 17% **5a**, 0% **6a**. 10% $AgNTf_2$: 0% **4a**, 89% **5a**, 0% **6a**.

(9) The stereochemistry of the major endo isomer was assigned on the basis of NMR experiments.

(10) The enantiomeric excess was determined by chiral HPLC analysis. However, the configuration of the major enantiomer was not determined.

(11) A equilibrium between two conformers may explain the stereochemistry observed for **6d**:



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