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J. Am. Chem. Soc., **2004**, 126 (35), 10858-10859• DOI: 10.1021/ja046248w • Publication Date (Web): 13 August 2004

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COMMUNICATIONS

Published on Web 08/13/2004

Catalaytic Isomerization of 1,5-Enynes to Bicyclo[3.1.0]hexenes

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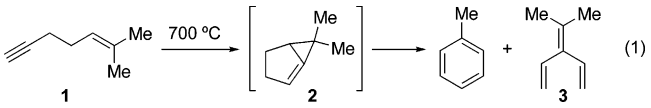
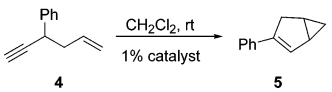
Transition metal-catalyzed isomerization and rearrangement reactions of unsaturated systems provide access to structural motifs not accessible through their thermal counterparts. This is exemplified by the numerous applications of transition metal-catalyzed Alder-ene reactions of 1,6- and 1,7-enynes for the synthesis of cyclopentyl and cyclohexyl ring systems.[1] The corresponding skeletal rearrangements of simple 1,5-enynes are much less studied. Berson and co-workers conjectured that the thermal rearrangement of 1,5-enyne **1** proceeds via bicyclo[3.1.0]hexene **2** to afford toluene and triene **3** as the major constituents of a complex mixture.[2] Scattered reports of transition metal-catalyzed isomerizations of 1,5-enynes[3] exist; however, these generally employ enol ethers as the ene component.[4,5] While enols are expected to be excellent nucleophiles,[6] we were intrigued by the possibility that metal−alkyne complexes could be electrophilic enough to react even with simple olefins and catalyze processes related to the thermal rearrangement.



To this end, treatment of 1,5-enyne **4** with 1 mol % palladium(II) or platinum(II) complexes returned mainly starting material (eq 2). Both silver(I) tetrafluoroborate and triphenylphosphinegold(I) chloride failed to catalyze the rearrangement of **4**. On the other hand, the combination of these two complexes[7] rapidly (5 min) and cleanly produced bicyclo[3.1.0]hexene[8] **5**, an olefin isomer of the proposed intermediate (**2**) in the thermal isomerization. In sharp contrast to the gold(I)-catalyzed cyclizations of ω-alkynyl β-ketoesters,[9] none of the competing 5-*exo*-*dig* cyclization to afford an *exo*-methylene product was observed. Finally, gold(III) chloride also catalyzed this reaction, however, with significantly lower conversion. On the other hand, 5% $AuCl_3$ with 15% AgOTf gave complete conversion; however, this was accompanied by a substantial amount of decomposition.

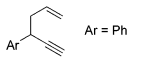
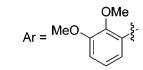
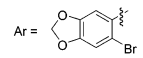
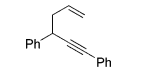
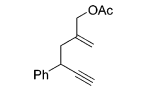
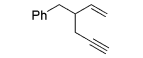
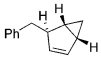
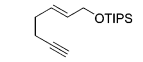
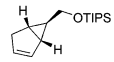
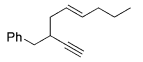
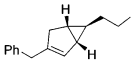
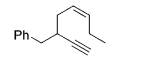
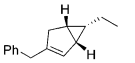
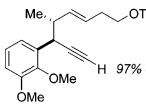
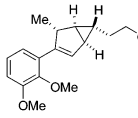


catalyst	*conversion*
$(CH_3CN)_2PdCl_2$, 24h	~ 4%
$PtCl_2$, 24h	~ 4%
$PtCl_2$, $AgBF_4$ 24h	~ 5%
$AgBF_4$, 24h	trace
$(PPh_3)AuCl$, $AgBF_4$, 5 min.	100%
$(PPh_3)AuCl$, 24h	0%
$AuCl_3$, 3h.	50%

(2)

A range of 1,5-enynes undergo the triphenylphosphinegold(I)-catalyzed rearrangement (Table 1). The propargylic position can be unsubstituted (entry 6) or substituted with aryl (entries 1−5) or alkyl substituents (entries 8 and 9). Additionally, potentially nucleophilic aromatic groups (entry 2) do not interfere with the reaction.[10] Introduction of an alkyl group at the allylic position is also tolerated, producing bicyclo[3.1.0]hexene **15** as a 10:1 mixture of diastereomers[11] (entry 6). The rearrangement proceeds when the 1,5-enyne (**16**) is unsubstituted at both the allylic and propargylic positions, albeit with slightly decreased efficiency (entry 7).

Table 1. Au(I)-Catalyzed Synthesis of Bicyclo[3.1.0]hexenes[a]

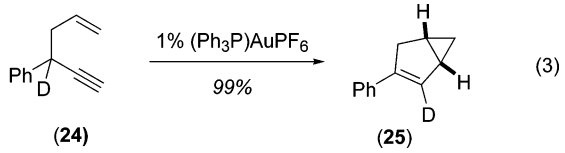
entry	substrate	(mol%) catalyst	product	yield
1	 Ar = Ph (**4**)	1% $(Ph_3P)AuPF_6$	(**5**)	99%
2	 Ar = (**6**)	2% $(Ph_3P)AuPF_6$	 (**7**)	99%
3	 Ar = (**8**)	1% $(Ph_3P)AuSbF_6$	(**9**)	95%
4	 (**10**)	1% $(Ph_3P)AuSbF_6$	 (**11**)	94%
5	 (**12**)	3% $(Ph_3P)AuSbF_6$	 (**13**)	96%
6	 (**14**)	3% $(Ph_3P)AuSbF_6$	 (**15**)	82% (10:1 dr)[b]
7	 (**16**)	2% $(Ph_3P)AuSbF_6$	 (**17**)	61%[c] (>99:1 dr)[b]
8	 (**18**)	1% $(Ph_3P)AuSbF_6$	 (**19**)	98% (>99:1 dr)[b]
9	 (**20**)	1% $(Ph_3P)AuSbF_6$	 (**21**)	96% (97:3 dr)[b]
10	 (**22**) *97% ee, 98:2 dr*	3% $(Ph_3P)AuPF_6$	 (**23**)	99% 91% ee, >99:1 dr[b]

[a] Reaction conditions: 0.5 M 1,5-enyne in dichloromethane, rt. [b] Diastereomeric ratio determined by ^1H NMR. [c] Starting material (19%) was recovered.

Terminal and internal alkynyl substrates (entry 4) react with equal facility, the latter producing an allylic quaternary center. Substrates containing either 1,1- (entry 5) or 1,2-disubstituted (entries 8−10) olefins cleanly undergo the gold(I)-catalyzed isomerization. For example, 3 mol % triphenylphosphinegold(I) hexafluoroantimonate smoothly catalyzes the formation of **13** by the rearrangement of 1,1-disubstituted olefin **12**.

To gain insight into the mechanism of this transformation, we studied the stereochemical course of the rearrangement. We found that the gold(I)-catalyzed reaction of substrates containing 1,2-disubstituted olefins is stereospecific. For example, (*E*)-olefin **18** selectively affords *trans*-cyclopropane **19** (entry 8), while (*Z*)-olefin **20** produces a 97:3 mixture of diastereomers in favor of *cis*-cyclopropane **21** (entry 9). Additionally, enantioenriched 1,5-enyne **22** is isomerized to **23** with excellent chirality transfer (entry 10).[12] Finally, deuterium-labeled 1,5-enyne **24** underwent gold(I)-catalyzed conversion to a bicyclo[3.1.0]hexene (**25**) in which the deuterium was selectively incorporated at the vinyl position (eq 3).

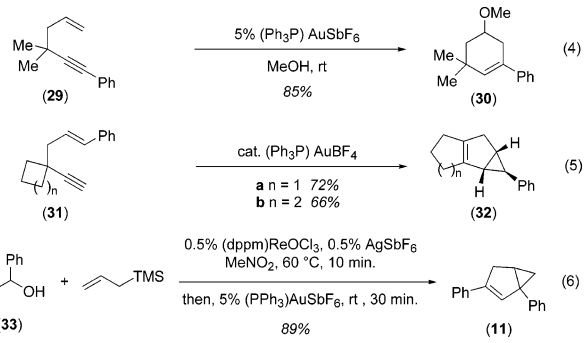
10.1021/ja046248w CCC: $27.50



(3)

On the basis of these data, we propose the process detailed in Scheme 1 as the most likely mechanism for this transformation. Coordination of cationic gold(I) to the alkyne followed by nucleophilic addition of the pendant olefin produces cyclopropylcarbinyl[13] cation **27**, which may have some gold(I) carbene character (**28**). The bicyclo[3.1.0]hexene product is generated by a 1,2-hydrogen shift onto a cation or a gold(I) carbene. The stereoselectivity and stereospecificity of the reaction can be accounted for by considering half-chair transition states, with the large groups occupying pseudoequatorial positions, similar to those proposed for the acetylenic Cope rearrangement.[14]

The proposed mechanism suggests that cationic intermediate **27**/**28** could potentially be trapped in the presence of a nucleophile. In accord with this hypothesis, cyclohexenyl methyl ether **30** was produced when the gold(I)-catalyzed reaction of enyne **29** was carried out in methanol (eq 4).[15] Notably, for this reaction the presence of a quaternary carbon at the propargylic position is necessary to prevent competing formation of the bicyclo[3.1.0]-hexene; however, in the absence of nucleophile, a 1,2-alkyl shift is observed. For example, 1,5-enynes **31a** and **31b** undergo a gold-(I)-catalyzed tandem cycloisomerization−ring enlargement process[16] to afford tricyclic structure **32a** and **32b** in 72 and 66% yield, respectively (eq 5).

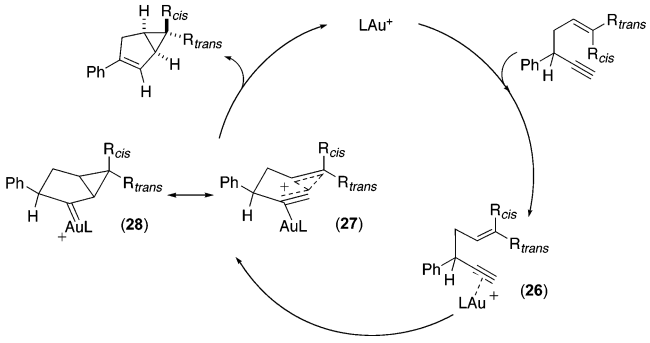


In conclusion, we have developed a transition metal-catalyzed rearrangement of 1,5-enynes that produces bicyclo[3.1.0]hexenyl products that are isomeric to those produced as intermediates in the thermal reaction. The gold(I)-catalyzed reaction can be conducted under "open-flask" conditions and as such can be combined with our rhenium-catalyzed propargylic allylation[17] to provide a one-pot synthesis of bicyclo[3.1.0]hexenes from propargyl alcohols (eq 6). This carbon−carbon bond-forming reaction provides a stereospecific method for the synthesis of a variety of cyclopropane containing carbocycles, including tricyclic structures prepared by a tandem cycloisomerization−ring enlargement reaction. Development of gold(I)-catalyzed[18] carbon−carbon bond-forming reactions, including an enantioselective version of this cycloisomerization, is ongoing and will be reported in due course.

Acknowledgment. We gratefully acknowledge the University of California, Berkeley, Merck Research Laboratories, and Amgen, Inc., for financial support. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member and Novartis Pharma as a Supporting Member.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 1. Mechanistic Proposal for Au(I)-Catalyzed Cycloisomerization



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(11) Major diastereomer was assigned on the basis of the NOE measurements detailed in Supporting Information.

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JA046248W