# 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.
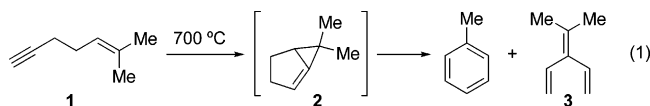
To this end, treatment of 1,5-enyne **4** with 1 mol % palladium-(II) or platinum(II) complexes returned mainly starting material (eq 2). Both silver(I) tetrafluoroborate and triphenylphosphinegold(I) chloride failed to catalyze the rearrangement of **4**. On the other hand, the combination of these 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.
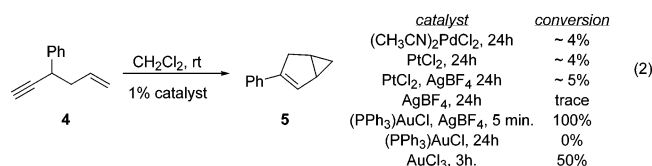
A range of 1,5-enynes undergo the triphenylphosphinegold(I)-catalyzed rearrangement (Table 1). The propargylic position can be unsubstituted (entry 6) or substituted with aryl (entries 1−5) or alkyl substituents (entries 8 and 9). Additionally, potentially nucleophilic aromatic groups (entry 2) do not 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 = MeO, OMe	(6)	2% $(Ph_3P)AuPF_6$		(7)	99%
3	Ar = (O,O, Br)	(8)	1% $(Ph_3P)AuSbF_6$		(9)	95%
4	Ph, Ph	(10)	1% $(Ph_3P)AuSbF_6$	Ph, Ph	(11)	94%
5	OAc, Ph	(12)	3% $(Ph_3P)AuSbF_6$	OAc, Ph	(13)	96%
6	Ph	(14)	3% $(Ph_3P)AuSbF_6$	Ph	(15)	82% (10:1 dr)[b]
7	OTIPS	(16)	2% $(Ph_3P)AuSbF_6$	OTIPS	(17)	61%[c] (>99:1 dr)[b]
8	Ph	(18)	1% $(Ph_3P)AuSbF_6$	Ph	(19)	98% (>99:1 dr)[b]
9	Ph	(20)	1% $(Ph_3P)AuSbF_6$	Ph	(21)	96% (97:3 dr)[b]
10	Me, OTIPS, OMe, OMe (22) 97% ee, 98:2 dr		3% $(Ph_3P)AuPF_6$	Me, OTIPS, OMe, OMe	(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 ^{1}H 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).

$$(3)$$

Scheme 1. Mechanistic Proposal for Au(I)-Catalyzed Cycloisomerization
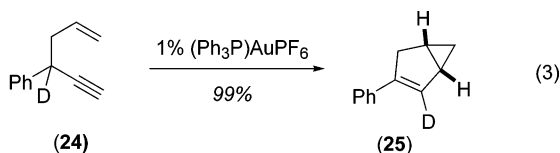
On the basis of these data, we propose the process detailed in Scheme 1 as the most likely mechanism for this transformation. Coordination of cationic gold(I) to the alkyne followed by nucleophilic addition of the pendant olefin produces cyclopropylcarbinyl[13] cation **27**, which may have some gold(I) 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).


$$(4)$$

$$(5)$$

$$(6)$$
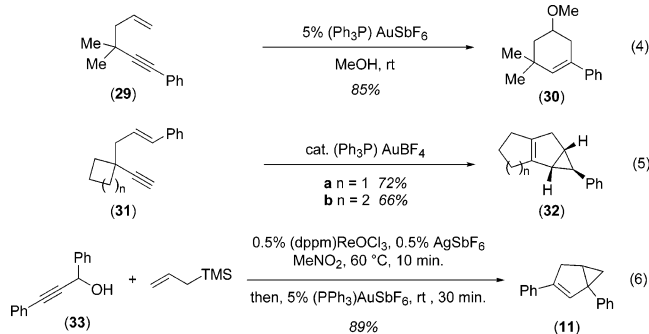
In conclusion, we have developed a transition metal-catalyzed rearrangement of 1,5-enynes that produces bicyclo[3.1.0]hexenyl products that are isomeric to those produced as intermediates in the thermal reaction. The gold(I)-catalyzed reaction can be conducted under "open-flask" conditions and as such 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.

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.
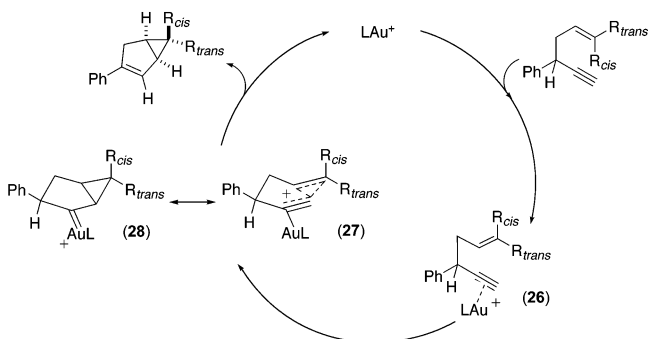
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