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Gold(I)-Catalyzed Propargyl Claisen Rearrangement

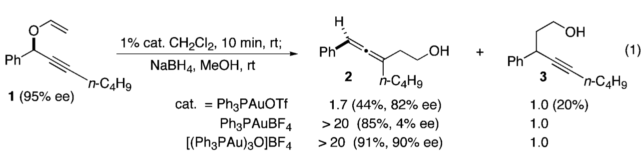
Benjamin D. Sherry and F. Dean Toste*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

Received September 6, 2004; E-mail: fdtoste@uclink.berkeley.edu

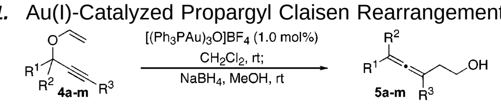
The [3,3]-sigmatropic rearrangement of allyl vinyl ethers[1] is an indispensable tool in organic synthesis, and catalysis of this reaction has further strengthened its impact.[2] In general, Lewis acid catalysis of the Claisen rearrangement can be divided into two classes: hard Lewis acids, which catalyze the reaction by coordination to the oxygen atom,[3] and soft Lewis acids, in particular those based on Hg(II) and Pd(II), which catalyze the reaction through coordination to the π-bonds.[4] The latter mode of catalysis is often limited by binding of the electrophilic metal to the strongly nucleophilic vinyl ether, thus preventing activation of the allylic olefin. Recent reports of Au(I)-catalyzed additions to alkynes,[5] suggest that this limitation might be absent in a Au(I)-catalyzed acetylenic Claisen rearrangement.[6] Importantly, a general catalytic version of the Claisen rearrangement of propargyl vinyl ethers has yet to be developed.[7]

In light of our previous success employing $Ph_3PAuOTf$ for carbon−carbon bond formation,[5a] we chose this catalyst system in preliminary studies of the acetylenic Claisen rearrangement. While $Ph_3PAuOTf$ did afford the desired allene **2**,[8] a substantial amount of the product derived from competing [1,3]-rearrangement was also formed (eq 1). Interestingly, changing the counterion from triflate to tetrafluoroborate addressed the problems of regiocontrol; however, the use of Ph_3PAuBF_4 as a catalyst provided almost racemic homoallenic alcohol **2** from enantioenriched propargyl vinyl ether **1**.[9] Our interest in catalysis with metal−oxo complexes[10] led us to consider the gold−oxo complex, $[(Ph_3PAu)_3O]BF_4$,[11] as an alternative means by which to access electrophilic Au(I) species.[12] In the event, treatment of enantioenriched propargyl vinyl ether **1** with 1 mol % $[(Ph_3PAu)_3O]BF_4$ afforded homoallenic alcohol **2** in 91% yield and with nearly complete chirality transfer.



With optimized reaction conditions in hand, we set out to define the scope of the catalytic acetylenic Claisen rearrangement. The Au(I)-catalyzed reaction is effective for a diverse collection of propargyl vinyl ethers (Table 1). Specifically, substrates containing electron-rich and electron-deficient aryl groups at the propargylic position afforded good to excellent yields of the desired homoallenic alcohols (entries 1−6). A range of alkyl groups can also be incorporated at the propargylic position, including linear and branched aliphatic moieties (entries 7−11). Substitution at the alkyne terminus is equally tolerated, spanning hydrogen (entry 1), aryl (entries 7 and 8), and alkyl substituents (entries 2−6 and 9−13). Importantly, the reaction is tolerant of commonly employed protecting groups, such as silyl ethers (entries 2 and 9) and pivolate ester (entry 3). Furthermore, tertiary propargyl vinyl ethers can be employed in the reaction, at slightly elevated temperatures, to afford tetrasubstituted allenes in good to excellent yield (entries 12 and 13). Notably, the efficiency of the reaction is illustrated by the

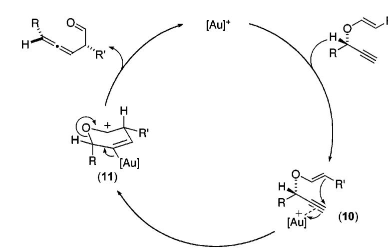
Table 1. Au(I)-Catalyzed Propargyl Claisen Rearrangement



entry	cmpd	R^1	R^2	R^3	time	yield[a]
1	a	Ph	H	H	5 h	78%
2	b	Ph	H	$(CH_2)_3OTBS$	0.5 h	89%
3	c	Ph	H	CH_2OPiv	25 h	81%
4	d	p-MeO-C_6H_4	H	n-C_4H_9	12 h	89%
5	e	p-F_3C-C_6H_4	H	Me	19 h	86%
6[b]	f	o-Br-C_6H_4	H	n-C_4H_9	6.5 h	96%
7[b]	g	n-C_5H_{11}	H	Ph	5 h	93%
8[b]	h	i-Pr	H	Ph	6 h	87%
9	i	$TBSOCH_2CH_2$	H	n-C_4H_9	23 h	76%
10	j	Me	H	$(CH_2)_3Ph$	12 h	84%
11[b]	k	n-C_5H_{11}	H	c-C_3H_5	6 h	90%
12[c]	l	$PhCH_2CH_2$	Me	Me	1 h	91%
13[c]	m	—$(CH_2)_5$—		$(CH_2)_3Ph$	1 h	61%

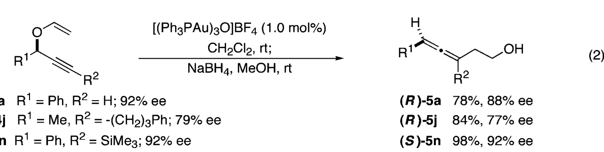
[a] Isolated yield after column chromatography. [b] Run with 0.1 mol % $[(Ph_3PAu)_3O]BF_4$. [c] Run at 75 °C in 1,2-dichloroethane.

Scheme 1. Proposed Mechanism for the Au(I)-Catalyzed Rearrangement



ability to perform a number of reactions with as little as 0.1 mol % $[(Ph_3PAu)_3O]BF_4$ (entries 6−8 and 11).

Our preliminary experiments directed toward catalyst optimization revealed that $[(Ph_3PAu)_3O]BF_4$ was uniquely effective at transferring central chirality of the starting carbinol to axial chirality in the allene product (eq 1). We have found that this reaction is applicable to a variety of substrates providing access to enantiomerically enriched homoallenic alcohols[13] (eq 2). For example, Au(I)-catalyzed reaction of silylacetylene (R)-**4n** proceeds with complete chirality transfer to provide allenylsilane[14] (S)-**5n** in 98% yield after reduction of the intermediate aldehyde.



Employing β-substituted vinyl ethers in the Claisen rearrangement affords synthetically useful α-substituted carbonyl products.[15] To probe the diastereoselectivity of the acetylenic Claisen rear-

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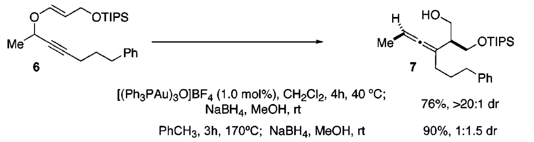
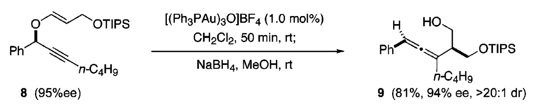
rangement, (*E*)-enol ether **6** was subjected to the Au(I)-catalyzed and thermal conditions. The catalytic reaction proceeds smoothly at 40 °C to afford a single diastereomer of **7**, while the thermal reaction required heating to 170 °C and produced a 1:1.5 mixture of diastereomers in favor of the opposite diastereomer (eq 3).[16] Additionally, allene **9** can be prepared enantio- and diastereoselectively from the rearrangement of vinyl ether **8** (eq 4).



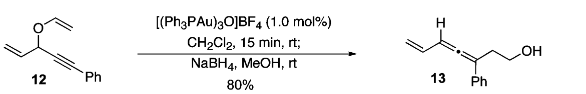
(3)



(4)

A mechanistic hypothesis based on a cyclization-induced rearrangement[4c] catalyzed by Au(I) is shown in Scheme 1. A 6-*endo*-dig addition of the enol ether onto gold(I)−alkyne complex **10** results in the formation of intermediate **11**. The diastereoselectivity of the rearrangement can be accounted for by considering the half-chair transition state[17] leading to **11**. The vinyl substituent (R′) occupies a pseudoequatorial position, and the propargylic group (R) adopts a pseudoaxial orientation in order to avoid $A^{1,2}$-strain with the vinyl gold substituent. Grob-type fragmentation of **11** affords the β-allenic aldehyde and regenerates the cationic Au(I) catalyst.

In accord with a mechanism involving alkyne activation, the Au(I)-catalyzed reaction of vinyl ether **12** shows a high degree of selectivity for the acetylenic Claisen over the allylic Claisen pathway (eq 5). This is in sharp contrast to reported hard Lewis acid-catalyzed[3b] and thermal rearrangements[18] that are selective for the allyl vinyl rearrangement.



(5)

In conclusion, we have developed an air- and moisture-tolerant Au(I) catalyst for the acetylenic Claisen rearrangement. The gold-catalyzed reaction provides access to a variety of homoallenic alcohols, which can be prepared enantioenriched when employing a nonracemic propargyl vinyl ether. The reaction is highly stereoselective and proceeds under mild conditions with low catalyst loading. Efforts aimed at utilizing Au(I) complexes as catalysts for other rearrangements and understanding the unique role of the trinuclear gold catalyst are ongoing in our laboratories.

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

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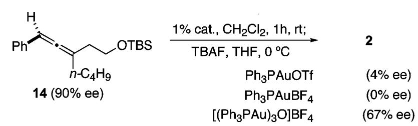
(8) Attempts to isolate the aldehyde met with substantial decomposition; therefore, intermediate aldehydes were reduced in situ to allow for product purification.

(9) We found that the poor chirality transfer is most likely a result of rapid (5 min) racemization of the allene catalyzed by Ph_3PAuBF_4. On the other hand, even after 1 h, a substantial amount of the allene's enantiomeric excess is retained in the presence of $[(Ph_3PAu)_3O]BF_4$.



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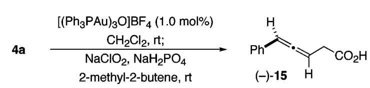
(12) The nature of the catalytically active Au(I) species is not known at this time. Both $(Ph_3P)_2AuBF_4$ and Ph_3PAuCH_2CHO are generated under the reaction conditions and were prepared independently. The former catalyzes the reaction at a much slower rate than does $[(Ph_3PAu)_3O]BF_4$, and the latter is not a competent catalyst.

(13) The allene absolute stereochemistry was assigned by comparison of the optical rotation of **15**: Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470.



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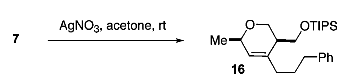
(16) The relative stereochemistry was determined by nOe measurements (see Supporting Information) on pyran **16**, obtained from the silver-catalyzed[13] cyclization of **7**.



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