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Gold and Brønsted Acid Catalyzed Hydride Shift onto Allenes: Divergence in Product Selectivity

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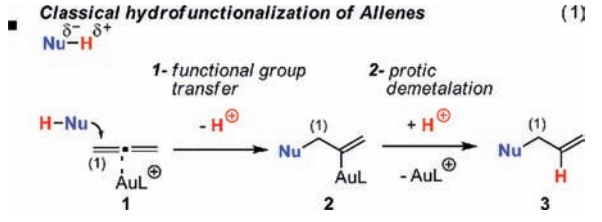
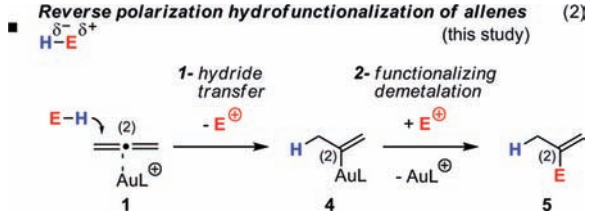
Supporting Information

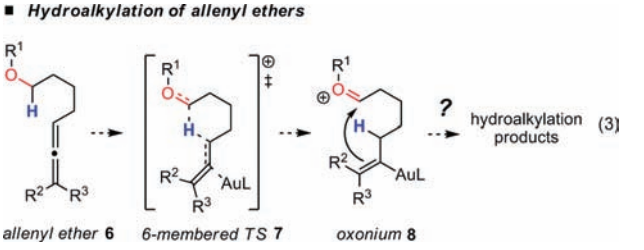
ABSTRACT: A series of allenyl ethers can be transformed into various fused or spiro tetrahydrofurans and tetrahydropyrans following a hydride shift/cyclization sequence. A divergence in product selectivity, which depends on the nature of the catalyst used (Au(I) complex or Brønsted acid), was observed.

During the past 10 years, an impressive number of studies have highlighted the utility of gold catalysis in organic synthesis.[1] A multitude of structural motifs of various nature and complexity have thus been assembled using gold-catalyzed transformations involving the addition of a nucleophile onto a π-system such as an alkyne, allene, or alkene. Among the various classes of transformations which have been developed, the *hydrofunctionalization* of π-systems has attracted particular attention.[1] In the case of allenes, this process allows a rapid and efficient access to a large variety of allylic derivatives **3** by a formal inter- or intramolecular addition of the Nu−H bond of a carbon, oxygen, or nitrogen nucleophile across one of the C=C bonds of the allene (eq 1).[2] From a mechanistic point of view, this transformation involves first a *nucleophilic transfer of the functional group* Nu on the gold-activated allene **1** followed by a *protic demetalation* of the intermediate vinyl-gold species **2**.





In conjunction with our recent investigations in the field of gold-catalyzed hydride transfers,[3] we were intrigued by the possibility of developing *a reverse polarization hydrofunctionalization of allenes* (eq 2). By contrast with a classical hydrofunctionalization, such a process would first involve the *transfer of a hydrogen atom as a hydride* onto the gold-activated allene **1**. The resulting vinyl-gold species **4** would then be functionalized in a final *electrophilic demetalation* step to furnish compound **5**. Interestingly, this process would be complementary to that presented in eq 1 since it would allow a functionalization at the central carbon C(2) of the allene. We decided to study the feasibility of this process in an intramolecular hydroalkylation of allenes using allenyl ethers of type **6** as substrates (eq 3). We indeed conceived that a 6-*exo* gold activation of the allene in compound **6** might induce a 1,5-hydride shift proceeding through a six-membered transition state of type **7**.[4,5] The resulting oxonium **8** could then be trapped by the pendant vinyl-gold species to furnish hydroalkylation products.



The designed transformation was first attempted with model allene **9** possessing a tetrahydrofuran moiety as the potential hydride donor group (Table 1). Its treatment with 4 mol % of the gold complex $[(XPhos)Au(NCCH_3)SbF_6]$[6] **12** in refluxing $CHCl_3$ for 4 h did not lead to an efficient reaction but validated our proposal since the formation of spiro compound **10** could be observed (9%, entry 1). Remarkably, the use of the phoshite gold complex **13** in CH_2Cl_2 at 20 °C greatly improved the efficiency of the reaction (entry 2). Under these conditions, the conversion of allene **9** was rapid (0.5 h) and a mixture of spiro compound **10** and fused bicyclic compound **11** was obtained in in 30% and 61% yields respectively.

Interestingly, the selectivity was reversed when the Brønsted acid $HNTf_2$ was used instead of gold-complex **13** (entry 3). Under these conditions, the transformation was slower but furnished exclusively compound **10** in an excellent 95% yield. The reaction could also be performed using $PtCl_2$ as the catalyst, even if a longer reaction time and a higher temperature were required (entry 4). The formation of compound **10** under gold(I) or Brønsted acid catalysis is remarkable, since it proceeds under very mild conditions in a stereoselective manner.[7] Notably, two new contiguous asymmetric centers, one of them quaternary, are formed during the process. The formation of

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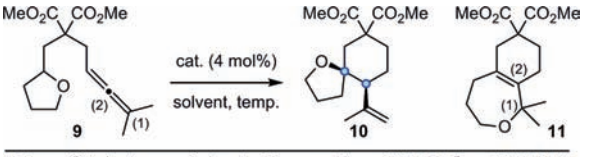
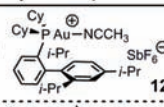
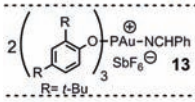
Table 1. First Attempt of Hydroalkylation with Allene 9



Entry	Catalyst	Solvent	Temp.	Time	Yield 10 [a]	Yield 11 [a]
1	 12	$CHCl_3$	60°C	4h	9% [b]	0%
2	 13	CH_2Cl_2	20°C	0.5h	30%	(1:2.2) [c] 61%
3	$HNTf_2$	CH_2Cl_2	20°C	22h	95%	0%
4	$PtCl_2$	toluene	110°C	24h	29%	(1.4:1) [c] 21%

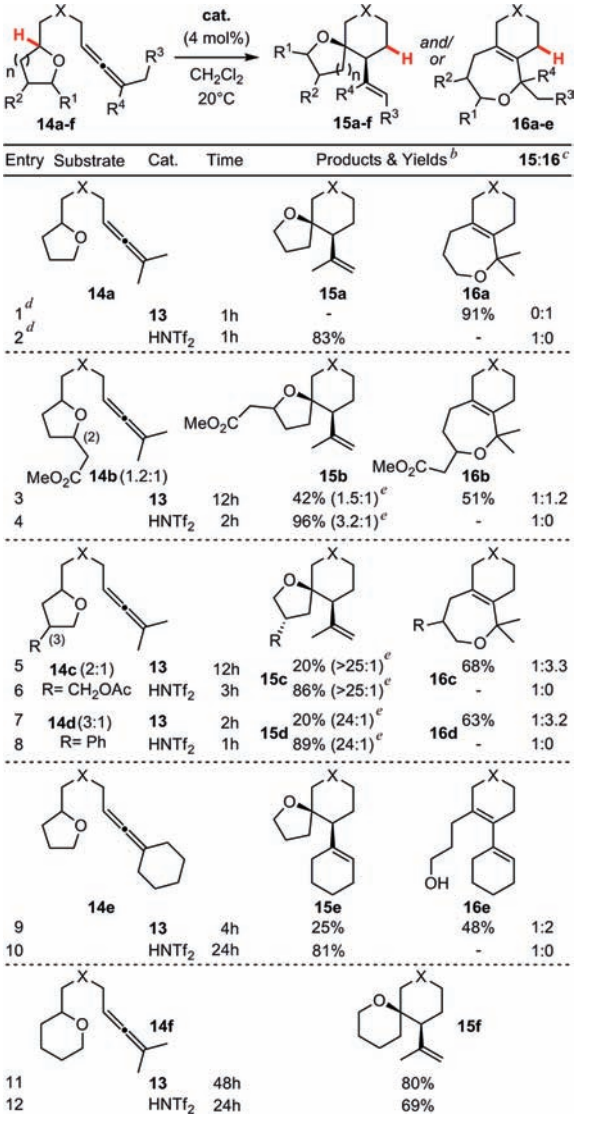
[a] Isolated yield. [b] NMR yield. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

compound **11** is also of interest since it corresponds to the formal insertion of the C−O bond of the tetrahydrofuran ring into the $C_{(1)}$=$C_{(2)}$ bond of the allene combined with a migration of the $C_{(2)}$=$C_{(3)}$ bond.

Given the novelty of this transformation and its synthetic potential,[8] we explored its scope using either **13** or $HNTf_2$ as the catalyst. As seen from the results compiled in Table 2, a series of other allenes **14a**−**f** could be used as substrates. In all cases, the transformation proved to be efficient with overall yields in hydroalkylated products ranging from 69% to 96%. The reaction could be performed with substrates possessing another type of linker (entries 1 and 2), a substituted tetrahydrofuran (entries 3−8), a differently substituted allene (entries 9 and 10),[9] or a tetrahydropyran as the hydride donor group (entries 11 and 12). The same trend in selectivity was observed: the use of $HNTf_2$ as the catalyst led to the exclusive formation of spiro compounds **15** while the use of gold complex **13** generally furnished mixtures of compounds **15** and **16**, the latter being the major component. Exceptionally, when allenes **14a** and **14f** were used as the substrates, the gold catalysis led to the exclusive formation of compounds **16a** and **15f**, which were isolated in respectively 91% and 80% yields (entries 1 and 11). Notably, while the conversion of 2-substituted tetrahydrofuran **14b** into spiro compound **15b** was moderately selective (entries 3 and 4), the transformations of 3-substituted tetrahydrofurans **14c** and **14d**, used as diastereoisomeric mixtures, were conversely extremely selective (entries 5−8).[10] The corresponding spiro compounds **15c** and **15d**, containing three asymmetric centers, were indeed obtained with diasteroisomeric ratios greater than 24:1. In the gold-catalyzed hydroalkylation of allene **14e**, the conjugated diene **16e** was the major product instead of the regular fused bicyclic compound.[11]

A mechanistic proposal for the gold and Brønsted acid catalyzed formations of spiro compounds **10** and/or fused bicyclic compounds **11** from allene **9** is presented in Scheme 1. The acid or gold activation of the allene moiety in substrate **9** induces a 1,5-hydride shift that produces oxonium **17**, a common intermediate in the formation of compounds **10** and **11**. In the gold-catalyzed process (A = AuL^+), intermediate **17** evolves into spiro compound **18** by the direct reaction of the oxonium with the C−Au bond.[12,13] Compound **18** may also be produced in a two-step sequence from oxonium **17** by elimination of the

Table 2. Substrate Scope: Cyclic Ethers as Hydride Donor Groups[a]



Entry	Substrate	Cat.	Time	Products & Yields [b]		15:16 [c]
1 [d]	14a	13	1h	15a -	16a 91%	0:1
2 [d]		$HNTf_2$	1h	83%	-	1:0
3	14b (1.2:1)	13	12h	15b 42% (1.5:1) [e]	16b 51%	1:1.2
4		$HNTf_2$	2h	96% (3.2:1) [e]	-	1:0
5	14c (2:1)	13	12h	15c 20% (>25:1) [e]	16c 68%	1:3.3
6	R= CH_2OAc	$HNTf_2$	3h	86% (>25:1) [e]	-	1:0
7	14d (3:1)	13	2h	15d 20% (24:1) [e]	16d 63%	1:3.2
8	R= Ph	$HNTf_2$	1h	89% (24:1) [e]	-	1:0
9	14e	13	4h	15e 25%	16e 48%	1:2
10		$HNTf_2$	24h	81%	-	1:0
11	14f	13	48h	15f 80%		
12		$HNTf_2$	24h	69%		

[a] Unless otherwise noted, X = $C(CO_2Me)_2$. [b] Isolated yield. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] X = $C(CH_2OBn)_2$. [e] d.r. determined by ^{1}H NMR spectroscopy.

cationic gold fragment in an intermediate carbocation **20**. This latter species could be formed by the alternative trapping of oxonium **17** by the C=C bond of the vinyl-gold species. A gold-catalyzed tetrahydrofuran ring-opening in spiro compound **18** produces an allylic carbocation that subsequently ring-closes to produce oxepane **11**. A proton loss/protodeauration sequence on carbocation **20** *via* gold compound **21** would account for the competitive formation of spiro compound **10**.[14]

In the Brønsted acid catalyzed process (A = H^+), oxonium **17** would be trapped by the pendant alkene to produce carbocation **20**. A subsequent proton loss would furnish spiro compound **10**.[15] It is interesting to note that intermediate **18** (leading to product **11**) and product **10** possess isomeric structures that only differ in the position of the C=C double bond. The generally observed divergence in product selectivity might be explained by the preferential direct and/or stepwise formation of the isopropylidene intermediate **18** under gold catalysis, while, under

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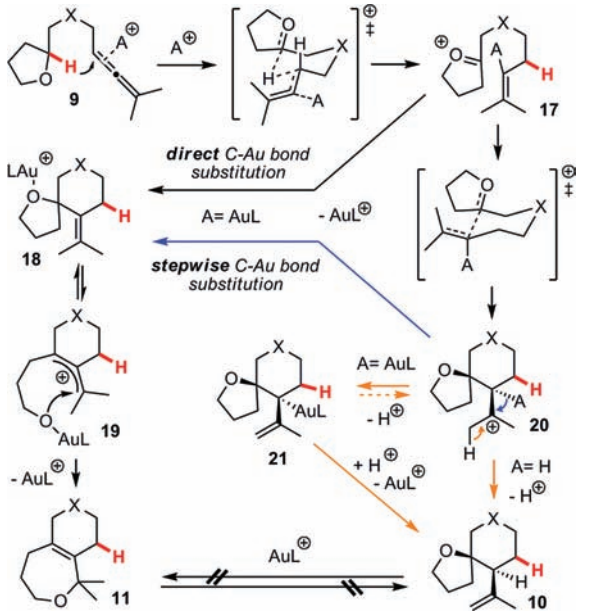
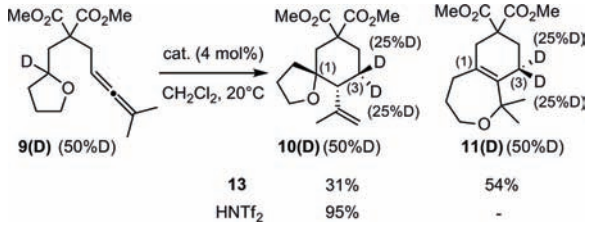
Scheme 1. Mechanistic Proposal (X = $C(CO_2Me)_2$, A = H^+ or LAu^+)



Scheme 2. Hydroalkylation with Deuterium-Labeled Allene 9(D)



Brønsted acid catalysis, a regiospecific proton loss proceeding on intermediate **20** would lead exclusively to the isopropenyl compound **10**. This mechanistic proposal is supported by the reactions of deuterium-labeled allene **9(D)** with gold catalyst **13** or $HNTf_2$, which furnished compounds **10(D)** and **11(D)** with the deuterium next to the oxygen in the tetrahydrofuran ring being transferred to position $C_{(3)}$ of the newly formed six-membered cycle (Scheme 2).[16]

We next attempted the hydroalkylation process on substrates possessing a benzylether moiety as the hydride donor group.[3a] We were delighted to see that a complete divergence in product selectivity was observed when allene **22** was treated with either gold complex **13** or $HNTf_2$ (Scheme 2). Under gold catalysis, tetrahydropyran **24** was obtained in 94% yield, while tetrahydropyran **23** was produced in 84% yield when $HNTf_2$ was used as the catalyst.[17] A mechanism analogous to that presented in Scheme 1, involving a common oxonium intermediate **25**, accounts for the selective production of tetrahydropyrans **23** and **24** (Scheme 3).

The stereoselective formation of compound **23**,[18] containing four asymmetric centers, two being formed during the hydroalkylation process, may be explained by considering the highly ordered chairlike transition state **26** leading to carbocation **27** from oxonium **25**. The relative *trans* relationship between the

Scheme 3. Hydride Shift from Benzyl Ether 22

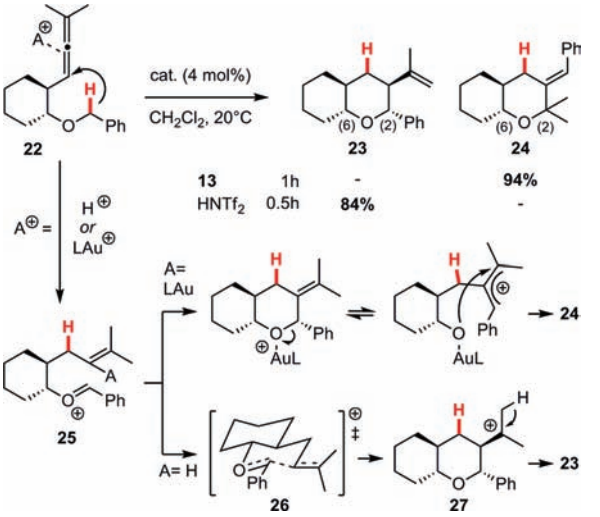
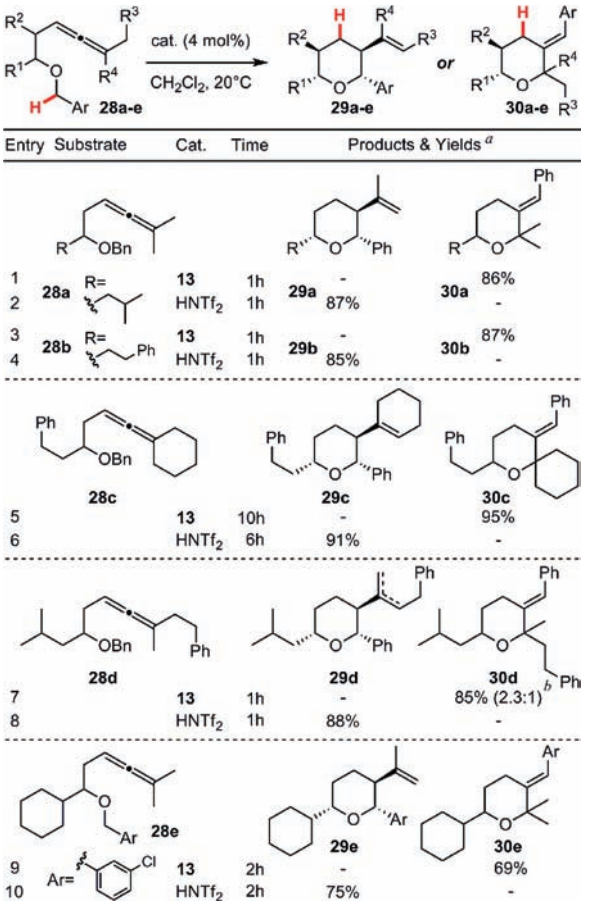


Table 3. Substrate Scope: Benzyl Ethers as Hydride Donor Groups



Entry	Substrate	Cat.	Time	Products & Yields [a]		
1	28a R=	13	1h	29a -	30a 86%	
2		$HNTf_2$	1h	87%	-	
3	28b R= Ph	13	1h	29b -	30b 87%	
4		$HNTf_2$	1h	85%	-	
5	28c	13	10h	29c -	30c 95%	
6		$HNTf_2$	6h	91%	-	
7	28d	13	1h	29d -	30d 85% (2.3:1) [b]	
8		$HNTf_2$	1h	88%	-	
9	28e Ar= Cl	13	2h	29e -	30e 69%	
10		$HNTf_2$	2h	75%	-	

[a] Isolated yield. [b] d.r. determined by ^1H NMR spectroscopy.

phenyl and isopropenyl substituents in product **23** results from the pseudoequatorial positions of the phenyl and isopropylidene group in transition state **26**. An analogous disposition accounts

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for the *cis* relationship between the phenyl group and the alkyl substituent at carbon $C_{(6)}$.

The hydroalkylation process was further extended to substituted allenes **28a**−**e** (Table 3). The transformations proved to be efficient, and a range of tetrahydropyrans were obtained in yields ranging from 69% to 95%. The gold catalysis produced exclusively compounds of type **30**, while the Brønsted acid catalysis delivered only compounds of type **29** in a stereoselective manner. Notably, the transformation could be performed with an aryl-substituted benzyl ether substrate (entries 9 and 10).

In summary, we have shown that a range of allenyl ethers can be transformed into various spiro tetrahydrofurans and tetrahydropyrans following a hydride shift/cyclization sequence catalyzed by a gold(I) complex or a Brønsted acid. This transformation, which corresponds to a formal hydroalkylation of an allene, proceeds under mild experimental conditions and is applicable to substrates possessing various hydride donor groups. It also represents a powerful method to stereoselectively convert a secondary or tertiary sp^3 C−H bond into a new C−C bond.[19] Importantly, a clear-cut divergence in product selectivity was observed when the reaction was catalyzed either by the gold complex or by the Brønsted acid. Further studies related to gold and Brønsted acid catalyzed hydride transfers onto π-systems are underway.

■ ASSOCIATED CONTENT

Supporting Information. 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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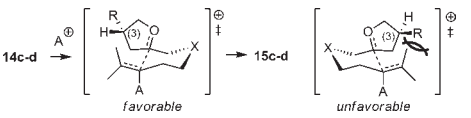
(6) For the synthesis of gold complexes **12** and **13**, see: Amijs, C. H. M.; López-Carrillo; Raducan, V. M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.

(7) The stereochemistry of **10** was determined by ^{1}H NMR spectroscopy.

(8) The spiroether structural unit is found in a number of natural products.

(9) The reaction could not be performed with monosubstituted allenes.

(10) This selectivity may be explained by considering the possible steric interactions between the substituent on the THF ring at $C_{(3)}$ and the pendant alkene group in the chairlike transition state leading to intermediate **20** (see Scheme 1).



(11) Compound **16e** corresponds to an open form of the bicyclic compound generally obtained. Its formation probably results from a gold-catalyzed oxepane ring opening.

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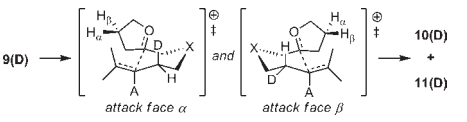
(13) The formation of intermediate **18** could not be observed when the reaction of **9** with gold catalyst **13** was monitored by ^{1}H NMR spectroscopy.

(14) Compounds **10** and **11** remain unchanged when they were separately treated with gold catalyst **13** thus precluding the formation of **11** from **10** and **10** from **11**.

(15) Under $HNTf_2$ catalysis, and even after prolonged reaction times, compound **10** was not transformed into compound **11** thus precluding an isomerization of **10** into **18** via **20**.

(16) The deuteration at carbon $C_{(3)}$ in products **10(D)** and **11(D)** was equally shared between the two available positions. This specific pattern tends to show that no memory of chirality is involved in the hydroalkylation of allene **9**. The nucleophilic trapping of oxonium **17** should proceed in this case with no facial selectivity.



(17) For a (3,5) oxonium-ene type cyclization leading to tetrahydropyrans of types **23** and **24**, see: Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669.

(18) No other diastereoisomer could be detected by ^{1}H NMR spectroscopy of the crude reaction mixture.

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