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Gold(I)-Catalyzed Rearrangement of Propargyl Benzyl Ethers: A Practical Method for the Generation and in Situ Transformation of Substituted Allenes

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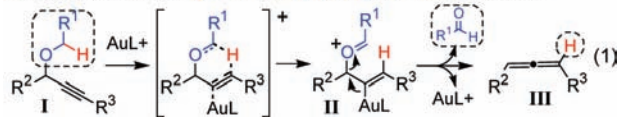
Allenes are useful structural motifs that can serve as substrates or intermediates in countless transformations.[1] It is therefore not surprising that numerous synthetic methodologies to access such compounds have been developed.[2] For instance, allenes can be produced from propargylamine derivatives following an internal redox process in which the tertiary amine serves as a hydride donor. This transformation was initially discovered by Crabbé for the formation of monosubstituted allenes by reaction of a terminal alkyne with formaldehyde and diisopropylamine in the presence of CuBr.[3] Several modifications have recently been reported[4] that allow either better efficiency[4c] or the formation of disubstituted[4a,b,d] or chiral allenes[4b,d] by modifying the metal catalyst (Zn,[4a] Ag,[4b] Au[4d]) and/or the amine moiety.[4a−d] However, these transformations still suffer some limitations, as they generally require a long reaction time (6−24 h), a high temperature (40−150 °C), and/or a high catalyst loading (10−80 mol %) and cannot be used to produce trisubstituted allenes.

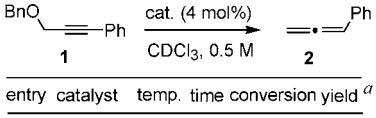
On the basis of our recent investigations of gold-catalyzed 1,5-hydride shifts onto alkynes,[5] we conceived that a propargylic ether **I** might be a valuable precursor for the synthesis of allene **III**, following a hydride transfer/fragmentation sequence (eq 1).[6−8] The 6-endo activation of the alkyne by a gold(I) catalyst might indeed induce a 1,5-hydride transfer, leading to oxonium intermediate **II**. Allene **III** could finally be obtained after the loss of an aldehyde molecule with concomitant regeneration of the catalyst.

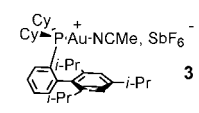
■ *Propargylic ethers: hydride transfer / fragmentation sequence*

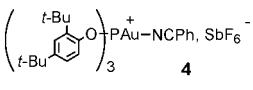


Simple propargyl benzyl ethers were naturally considered as potential candidates for performing this sequence. Benzyl ethers are indeed not only easily accessible from the corresponding alcohols, thus allowing the possible development of a practical allene formation procedure, but also known to be suitable hydride donor groups.[9]

Table 1. Optimization of the Catalytic System with Benzyl Ether **1**[10]





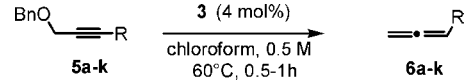


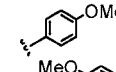
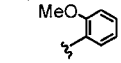
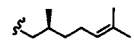
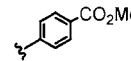
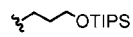
entry	catalyst	temp.	time	conversion	yield [a]
1	3	20°C	2.5h	18%	7%
2	4	20°C	3.5h	46%	19%
3	**3**	**60°C**	**0.5h**	**100%**	**67%** [b]
4	4	60°C	0.5h	—	— [c]

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield. [c] Degradation.

In the first attempts, primary benzyl ether **1** was reacted with 4 mol % [XPhosAu(NCCH$_3$)SbF$_6$] (**3**)[11,12] or the more electrophilic catalyst [(2,4-*t*-BuPhO)$_3$PAu(NCPh)SbF$_6$] (**4**) at 20 °C in CDCl$_3$ (Table 1, entries 1 and 2). However, while the desired transformation did occur, allene **2** was formed in low yield and prolonged reaction times were required to reach completion.[10] Heating the reaction mixture at 60 °C was beneficial when complex **3** was used as the catalyst (entry 3). Under these conditions, substrate **1** was rapidly consumed (0.5 h) and smoothly converted into allene **2**, which was isolated in 67% yield. The use of a PMB ether susbstrate did not give better results.[10]

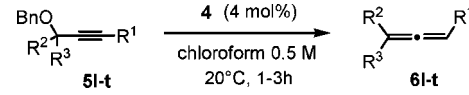
Table 2. Substrate Scope: Primary Benzyl Ethers

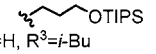


entry	substrate	R	product	yield [a]	entry	substrate	R	product	yield [a]
1	**5a**	C_5H_{11}	**6a**	98% [b]	8	**5g**		**6g**	68%
2	**5b**	C_4H_9	**6b**	61% [b]					
3	**5c**		**6c**	89%	9	**5h**		**6h**	71%
4	**5d**		**6d**	82%	10	**5i**		**6i**	76%
5	**5e**		**6e**	70%					
6	**1**	Ph	**2**	67%	11	**5j**		**6j**	84% [b]
7	**5f**		**6f**	80%	12	**5k**		**6k**	57%

[a] Isolated yield. [b] Volatile product; ^{1}H NMR yield.

Table 3. Substrate Scope: Secondary and Tertiary Benzyl Ethers



entry	substrate		product	yield [a]
1		R^3= C_5H_{11}	**6l**	94%
2	R^1=Ph, R^2=H	R^3= 	**6m**	93%
3		R^3= 	**6n**	89%
4 [b]		R^3= Ph	**6o**	85%
5	R_2=H, R^3=R^1= 		**6p**	87%
6	R^1=  OTIPS, R^2=H, R^3=*i*-Bu		**6q**	76%
7	R^1=Ph	R^2=Me, R^3=Et	**6r**	85%
8		R^2-R^3= -$(CH_2)_5$-	**6s**	69%
9 [c]	R^1=H	R^2-R^3= -$(CH_2)_5$-	**6t**	78% [d]

[a] Isolated yield. [b] Using 4 mol % XPhosAuNTf$_2$ in chloroform at 60 °C. [c] Using 4 mol % **3** in chloroform at 60 °C. [d] Volatile product; ^{1}H NMR yield.

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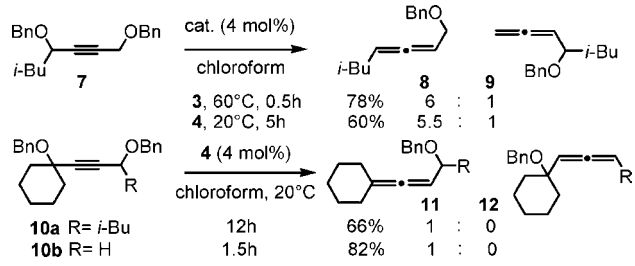
To underline the practicality and efficiency of this new gold(I)-catalyzed process, a series of other primary propargyl benzyl ethers **5a**−**k** were reacted in chloroform at 60 °C with 4 mol % **3**. The reaction proved to be general, and various monosubstituted allenes **6a**−**k** were formed in moderate to good yields (57−98%) (Table 2). Notably, the transformation was rapid (0.5−1 h) and tolerated the presence of various functional groups (alkyl, aryl, alkene, silyl ether, cyanide, ester, halogen).

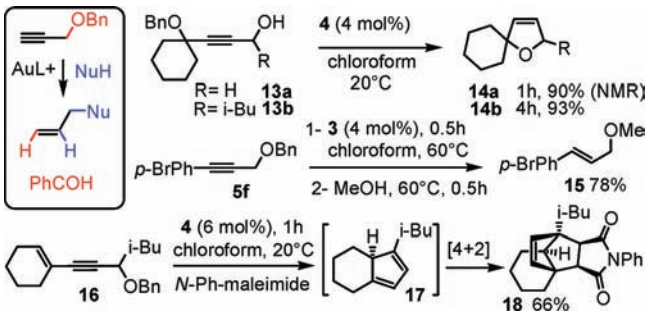
We next turned our attention to the possibility of generating allenes from secondary and tertiary propargyl benzyl ethers. For such substrates, the transformation was expected to be more favorable because of a Thorpe−Ingold effect induced by the presence of additional substituents at the propargylic position. This was actually the case, and substrates **5l**−**t** were rapidly transformed (1−3 h) into allenes **6l**−**t** under generally milder reaction conditions (4 mol % **4** in chloroform at 20 °C) (Table 3). Disubstituted allenes **6l**−**q** bearing alkyl or aryl groups were produced in high yields (76−94%) (entries 1−6). The formation of trisubstituted allenes **6r** and **6s** is remarkable, as elimination of the acid-sentivitive tertiary benzyl ether was hardly observed (entries 7 and 8).[13] The transformation was further compatible with terminal alkynes such as **5t**, which furnished allene **6t** in 78% yield (entry 9).

Scheme 1. Competitive Hydride Transfers



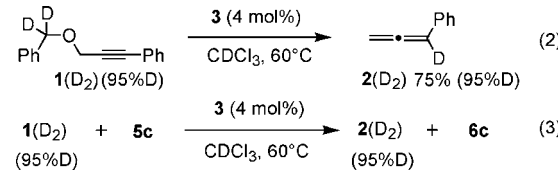
A series of competitive reactions were performed with substrates possessing two benzyl ether groups with different degrees of substitution at the propargylic position (Scheme 1). Not surprisingly, substrate **7** furnished allene **8** selectively, as the result of a Thorpe−Ingold effect favoring the hydride shift from the more substituted benzyl ether. The selectivity was even complete with ethers **10a** and **10b** bearing a tertiary benzyl ether moiety.

Scheme 2. Reductive Substitution Processes



We finally focused on the possibility of further reacting the allenes thus formed with a nuleophilic species. Such a cascade of gold-catalyzed transformations would be synthetically valuable, as it would correspond to an overall *reductive substitution process* of the starting propargyl benzyl ethers (Scheme 2). This concept was validated by the efficient formation of dihydrofurans **14a** and **14b**.[14a] The trapping could be performed in an intermolecular fashion, as shown by the conversion of **5f** into the allylic derivatives **15**.[14b] Cascade reactions could also be realized: the cycloisomerization of the allene generated from **16** furnished the intermediate cyclopentadiene **17**,[14c] which was trapped by *N*-phenylmaleimide to produce the [4 + 2] adduct **18** in 66% yield.

The 1,5-hydride shift mechanism proposed in eq 2 was supported by the deuterium labeling experiments shown in eqs 2 and 3. One of the deuterium atoms in benzyl ether **1**(D2) was indeed cleanly transferred to the position geminal to the phenyl group in **2**(D2) (eq 2). The internal delivery of the hydride was also supported by the crossover experiment shown in eq 3, since **2**(D2) and **6c** were the only detectable products formed during the reaction.



In summary, we have shown that a series of easily accessible benzyl propargyl ethers react readily with a gold(I) catalyst to furnish variously substituted allenes via a 1,5-hydride shift/fragmentation sequence. This transformation is rapid and practical. It can be performed under very mild conditions (room temperature or 60 °C) using terminal as well as substituted alkyne substrates bearing various substituents at the propargylic positions. The allenes thus formed can be reacted in situ with an internal or external nucleophile, corresponding to an overall *reductive substitution process*, to produce more functionalized compounds.

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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.

References

(1) For a book, see: (a) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. *1* and 2. For selected recent reviews, see: (b) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (c) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (e) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (f) Wei, L. L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (g) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (h) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (i) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133.

(2) For recent reviews of the synthesis of allenes, see: (a) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259. (b) Brummond, K. M.; Deforrest, J. E. *Synthesis* **2007**, 795. (c) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. Also see ref 1a.

(3) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859.

(4) (a) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786. (b) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213. (c) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763. (d) Lo, V. K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517.

(5) Dias Jurberg, I.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543.

(6) For recent selected reviews of Au and Pt catalysis, see: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (b) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (c) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (e) Li, Z.; Brower, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (g) Gorin, D. J.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (h) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (i) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(7) For recent contributions on gold catalysis from our group, see: (a) Odabachian, Y.; Le Goff, X.-F.; Gagosz, F. *Chem.—Eur. J.* **2009**, *15*, 8966. (b) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379.

(8) For gold-catalyzed formation of allenes from enamines and terminal alkynes, see: Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13569.

(9) (a) Shikanay, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. (b) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. (c) Jiménez-Núñez, E.; Raducan, M.; Lautenbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6152. (d) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (e)

McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972. (f) Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180.
(10) See the Supporting Information for more details.
(11) Complex **3** was previously found to be an effective catalyst for gold-catalyzed hydride transfers (see ref 5).
(12) For the synthesis of **3** and **4**, see: Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.
(13) Notably, no example of trisubstituted allene formation was reported using a Crabbé-type reaction (see refs 3 and 4).
(14) (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (b) Nishina, N.; Yamamoto, Y. *Tetrahedron* **2009**, *65*, 1799. (c) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912.

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