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Gold-Catalyzed Tandem Cycloisomerization–Hydroalkoxylation of Homopropargylic Alcohols

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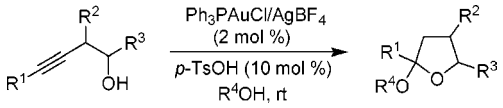
ABSTRACT



The tandem cycloisomerization–hydroalkoxylation of various homopropargylic alcohols in the presence of an alcohol and a dual catalyst system, consisting of a gold precatalyst and a Brønsted acid, provides an efficient route to tetrahydrofuranyl ethers under mild reaction conditions. The reaction can be carried out in various solvents, including alcohol, with both terminal and internal alkynes as the substrate.

Tetrahydrofuranyl ethers are important building blocks in organic synthesis. In addition to their function as protecting groups,[1] these cyclic acetal skeletons occur in a variety of natural products that possess diverse biological activities (Figure 1).

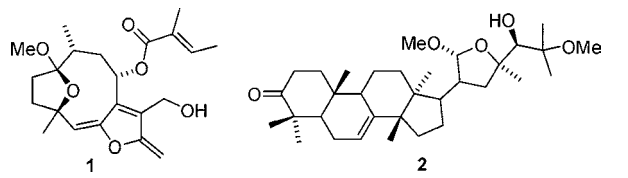


Figure 1. Naturally occurring tetrahydrofuranyl ethers.

These include cytotoxic compounds such as vernolide-A (**1**)[2] and the methoxylated protolimonoid (**2**),[3] which shows inhibitory activity against trypomastigote forms of *Trypanosoma cruzi*. Furthermore, oxidation of the cyclic acetal[4] offers a convenient access to substituted γ-lactones, which are also important structural units of many natural products.[5] Thus, it is not surprising that numerous pathways for the synthesis of cyclic acetals have been developed. Besides the radical cyclization of haloacetals,[6] transition metal catalysis has been utilized frequently for this purpose, for example, in the Pd-catalyzed coupling of allylic alcohols and vinyl ethers,[7] as well as the Ir-catalyzed cycloisomerization−hydroalkoxylation of bis-homopropargylic alcohols.[8]

Because of their unique ability to activate carbon−carbon multiple bonds, the use of gold catalysts plays an important role in modern transition metal catalysis.[9] Of particular value are cycloisomerization reactions, which are perfect examples for atom efficiency.[10] Recent instances of these include the gold-catalyzed cycloisomerization of α-hydroxyallenes,[11]

(1) (a) Kruse, C. G.; Broekhof, N. L. J. M.; Van der Gen, A. *Tetrahedron Lett.* **1976**, 1725. (b) Ochiai, M.; Sueda, T. *Tetrahedron Lett.* **2004**, *45*, 3557.

(2) Kuo, Y.-H.; Kuo, Y.-J.; Yu, A.-S.; Wu, M.-D.; Ong, C.-W.; Yang Kuo, L.-M.; Huang, J.-T.; Chen, C.-F.; Li, S.-Y. *Chem. Pharm. Bull* **2003**, *51*, 425.

(3) Biavatti, M. W.; Vieira, P. C.; Da Silva, M. F. G. F.; Fernandes, J. B.; Albuquerque, S. *J. Nat. Prod.* **2002**, *65*, 562.

(4) (a) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050. (c) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351.

(5) Review: Koch, S. S. C.; Chamberlin, A. R. *Stud. Nat. Prod. Chem.* **1995**, *16*, 687.

(6) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63. (d) Villar, F.; Equey, O; Renaud, P. *Org. Lett.* **2000**, *2*, 1061.

(7) (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809. (b) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367.

(8) Genin, E.; Antoniotti, S.; Michelet, V.; Genet, J.-P. *Angew. Chem.* **2005**, *117*, 5029; *Angew. Chem. Int. Ed.* **2005**, *44*, 4949.

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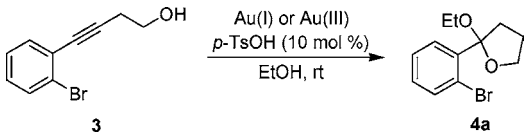
α-aminoallenes,[12] and α-thioallenes,[13] which provide an efficient and stereoselective access to chiral five-membered heterocycles. More recently, these transformations have been extended to the gold-catalyzed cyclization of *β*-hydroxy- and *β*-aminoallenes to the corresponding dihydropyrans and tetrahydropyridins, respectively.[14] In contrast to this, the gold-catalyzed cycloisomerization of hetero-substituted alkynes usually leads to aromatic heterocycles,[15] even though Genet and co-workers[16] have recently reported the gold-catalyzed cycloisomerization of bis-homopropargylic diols to strained bicyclic ketals. Herein we report an unprecedented tandem cycloisomerization−hydroalkoxylation of homopropargylic alcohols to tetrahydrofuranyl ethers using a dual catalyst system consisting of a gold precatalyst and a Brønsted acid.[17]

The starting materials of our study are readily available by Sonogashira coupling[18] of but-3-yn-1-ol with various aryl halides, as well as by Yamaguchi−Hirao alkynylation[19] of oxiranes. Initial experiments were performed using alcohol **3** as model substrate, which was treated with catalytic amounts of a gold salt and *p*-TsOH in ethanol as solvent at room temperature (Table 1).

Table 1. Gold-Catalyzed Tandem Cycloisomerization−Hydroalkoxylation of Homopropargylic Alcohol **3** to Tetrahydrofuranyl Ether **4**



3 **4a**

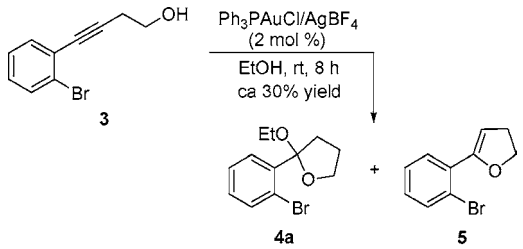
entry	mol %	Au salt	additive	time	yield (%)
1	2	Ph_3PAuCl	–	5 d	–
2	5	Ph_3PAuCl	$AgBF_4$	1 h	77
3	2	Ph_3PAuCl	$AgBF_4$	1 h	76
4	0.1	Ph_3PAuCl	$AgBF_4$	2 h	64
5	2	Ph_3PAuCl	$AgSbF_6$	2 h	74
6	2	AuCl	–	3 h	53
7	2	AuCl	pyridine	4 h	67
8	2	$Au(OH)_3$	–	12 h	30
9	2	$Au(OAc)_3$	–	4 h	76
10	2	$AuCl_3$	–	6 h	54
11	2	$HAuCl_4$[a]	–	8 h	67
12	2	$NaAuCl_4$	–	5 h	–
13	–[a]	–[a]	$AgBF_4$	4 d	–
14	–	–	$AgBF_4$	4 d	–
15	–	–	–	5 d	–

[a] Without addition of *p*-TsOH.

Both gold(I) and gold(III) precatalysts were found to be active and afforded the cyclic acetal **4a** in moderate to good yields. Whereas Ph_3PAuCl alone was unreactive (entry 1), formation of a cationic gold species by addition of silver salts led to a clean and rapid formation of the desired product **4a** in good yield (entry 2). Decreasing the catalyst loading from 5 to 2 or 0.1 mol % only marginally affected the reaction time and chemical yield (entries 3−5). Compared to the cationic system, other gold precatalysts were less reactive and afforded lower yields of the acetal **4a** (entries 6−11). With gold(I) chloride, an increase of the yield from 53% to 67% was observed in the presence of pyridine; this might indicate an activation of the hydroxy group by the base. Not surprisingly, $HAuCl_4$ acts both as gold source and Brønsted acid, so that the presence of *p*-TsOH is not required with this precatalyst (entry 11). In contrast to this, sodium tetrachloroaurate is inactive (entry 12), as are $AgBF_4$ or *p*-TsOH alone (or a combination of both; entries 13−15), ruling out the possibilty of a simple silver- or acid-catalyzed process.

To shed light on the reaction mechanism, we treated homopropargylic alcohol **3** with $Ph_3PAuCl/AgBF_4$ for 8 h *in the absence* of a Brønsted acid and obtained a 1:3 mixture of the cyclic acetal **4a** and the dihydrofuran **5**, albeit in low yield (Scheme 1). Treatment of the reaction mixture (after 8 h reaction time) with catalytic amounts of *p*-TsOH for 45 min gave mainly tetrahydrofuranyl ether **4a** and only traces

Scheme 1



3 **4a** **5**

(9) Recent reviews on homogeneous gold catalysis in organic synthesis: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (b) Hashmi, A. S. K. *Angew. Chem.* **2005**, *117*, 7150; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990. (c) Arcadi, A.; Giuseppe, S. D. *Curr. Org. Chem.* **2004**, *8*, 795.

(10) (a) Trost, B. M. *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.

(11) (a) Hoffmann-Röder, A; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (b) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1758.

(12) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121.

(13) Morita, N.; Krause, N. *Angew. Chem.* **2006**, *118*, 1930; *Angew. Chem. Int. Ed.* **2006**, *45*, 1897.

(14) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.

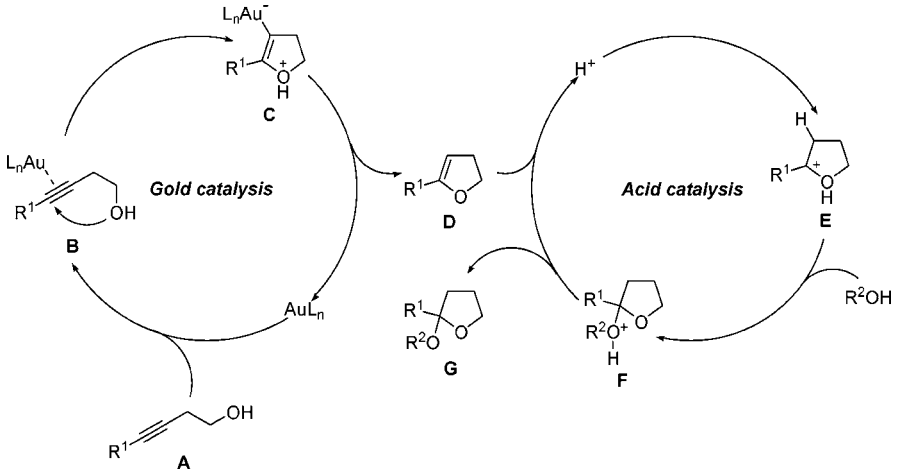
(15) (a) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (c) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610. (d) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (e) Liu, Y.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

(16) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. See also: Barluenga, J.; Dieguez, A.; Fernandez, A.; Rodriguez, F.; Fananas, F. J. *Angew. Chem.* **2006**, *118*, 2145; *Angew. Chem. Int. Ed.* **2006**, *45*, 2091.

(17) Examples for the gold-catalyzed intermolecular addition of nucleophiles to alkenes and alkynes: (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem.* **1998**, *110*, 1475; *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (b) Nguyen, R.-V.; Yao, X.-Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673. (c) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445. (d) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

(18) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Tykwinsky, R. R. *Angew. Chem.* **2003**, *115*, 1604; *Angew. Chem. Int. Ed.* **2003**, *42*, 1566.

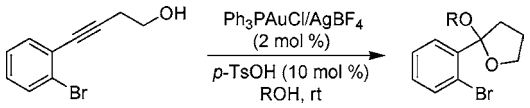
Scheme 2



of dihydrofuran **5**. Thus, the acetal **4a** is probably formed by gold-catalyzed cycloisomerization of **3** to the corresponding 2,3-dihydrofuran, followed by the known acid-catalyzed hydroalkoxylation[20] of the latter.

We next extended the scope of the tandem cycloisomerization−hydroalkoxylation to different alcohols and solvents (Table 2). The cyclic acetals **4b**−**d** were obtained in 58−78% yield by using the $Ph_3PAuCl/AgBF_4$/*p*-TsOH catalyst in methanol, 2-propanol, or 2-methoxyethanol (entries 1−3). Only in the presence of the bulky *tert*-butyl alcohol, the starting material remained unchanged even after 5 days at room temperature.

Table 2. Synthesis of Tetrahydrofuranyl Ethers **4** Using Different Alcohols and Solvents



3 **4**

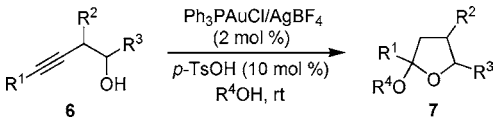
entry	ROH	solvent	time	**4** (yield, %)
1	MeOH		1 h	**4b** (68)
2	*i*PrOH		3 h	**4c** (58)
3	$MeO(CH_2)_2OH$		3 h	**4d** (78)
4	*t*BuOH		5 d	–
5	EtOH[a]	toluene	45 min	**4a** (69)
6	EtOH[a]	CH_2Cl_2	1 h	**4a** (46)
7	EtOH[a]	THF	2 h	**4a** (66)
8	EtOH[a]	Et_2O	2 h	**4a** (71)
9	EtOH[a]	MeCN	3 h	–

[a] Two equivalents.

The gold- and acid-catalyzed tandem cycloisomerization−hydroalkoxylation can also be carried out in non- or weakly coordinating solvents. Treatment of substrate **3** with 2 equiv of ethanol afforded the cyclic acetal **4a** with yields ranging from 46% to 71% in toluene, dichloromethane, THF, or diethyl ether as the solvent (Table 2, entries 5−8). These conditions may be advantageous for valuable or solid alcohols. Only the strongly coordinating acetonitrile failed to give any cyclization product (entry 9), probably because of deactivation of the gold catalyst.

To further examine the scope of the tandem cycloisomerization−hydroalkoxylation, we treated various homopropargylic alcohols **6** with the dual catalyst system and different alcohols as the solvent (Table 3). Electronically diverse aryl groups at the alkyne terminus are tolerated (entries 1−8) with electron-rich systems giving the lowest yield (entry 2). Again,

Table 3. Gold- and Acid-catalyzed Synthesis of Tetrahydrofuranyl Ethers **7**



6 **7**

entry	R^1	R^2	R^3	R^4	**7** (yield/%)
1	4-MeC_6H_4	H	H	Et	**7a** (50)
2	4-$MeOC_6H_4$	H	H	Et	**7b** (36)
3	4-$MeO_2CC_6H_4$	H	H	Et	**7c** (67)
4	4-$MeO_2CC_6H_4$	H	H	Me	**7d** (71)
5	4-$MeO_2CC_6H_4$	H	H	*i*Pr	**7e** (63)
6	Ph	H	H	Et	**7f** (63)
7	Ph	Ph	H	Et	**7g** (69[a])
8	Ph	H	Ph	Et	**7h** (72[a])
9	*n*Bu	H	Me	Et	**7i** (44[a])
10	*t*Bu	H	Me	Et	–
11	Me_3Si	H	Me	Et	–

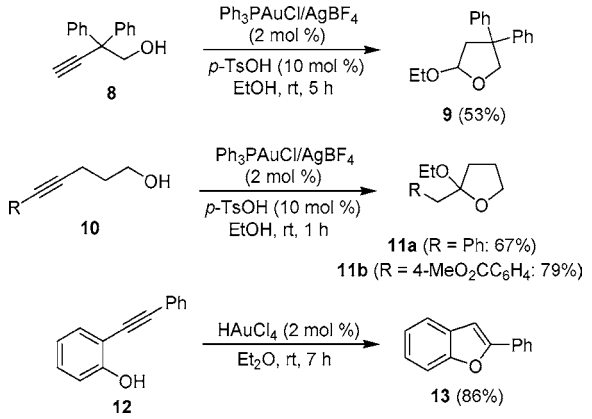
[a] dr = 60:40.

(19) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(20) (a) Brown, C. D. S.; Simpkins, N. S. *Tetrahedron Lett.* **1993**, *34*, 131. (b) Barton, D. H. R.; Launay, F. *Tetrahedron* **1997**, *43*, 14565. (c) Toyooka, N.; Nagaoka, M.; Sasaki, E.; Qin, H.; Kakuda, H.; Nemoto, H. *Tetrahedron* **2002**, *58*, 6097. (d) El-Seedi, H. R.; Yamamura, S.; Nishiyama, S. *Tetrahedron* **2002**, *58*, 7485.

different alcohols can be used without compromising the yield of the tetrahydrofuranyl ether **7** (entries 3−5). Substitutents at C-1 and C-2 did not cause any problems (entries 7−9). Secondary alcohols afforded the corresponding acetals **7h**/**i** as 60:40 mixture of diastereomers (entries 8 and 9), indicating that there is almost no stereocontrol in the hydroalkoxylation of the chiral 2,3-dihydrofuran formed in the cyclization step. The latter example shows that the method can also be applied to substrates with an alkyl substituent at the triple bond. However, the cyclization is sensitive to steric hindrance at this position since the *tert*-butyl- or trimethylsilyl-substituted substrates did not react under the standard conditons. (entries 10 and 11).

Further extensions of gold-catalyzed cyclization are shown in Scheme 3. The transformation of homopropargylic **8** alcohol into the cyclic acetal **9** shows that the tandem cycloisomerization-hydroalkoxylation is not restricted to internal alkynes but can be applied to terminal acetylenes as well. Compared to substrates bearing a bulky substituent at the triple bond (Table 3, entries 10 and 11), this reaction also demonstrates that steric hindrance in alkyl chain does not prevent the tandem cycloisomerization−hydroalkoxylation. Increasing the distance between the triple bond and hydroxy group is also possible: the bis-homopropargylic alcohols **10** afforded the tetrahydrofuranyl ethers **11** with good yield under the same conditions as the homopropargylic alcohols **3**/**6**. Finally, we were delighted to observe a clean cycloisomerization the 2-alkynylphenol **12** to the benzofuran **13** in the presence of AuCl, $AuCl_3$, or $HAuCl_4$; the latter gave the highest yield of 86%. Because of its mildness and efficiency, our method competes well with known protocols for this transformation.[21]

Scheme 3



Based on the assumption that the tandem cycloisomerization−hydroalkoxylation of homopropargylic alcohols to tetrahydrofuranyl ethers takes place via 2,3-dihydrofurans (see Scheme 1), we propose the mechanism shown in Scheme 2. Coordination of the gold catalyst to the triple bond of the substrate **A** gives rise to the formation of the π-complex **B**, which upon nucleophilic attack of the oxygen is transformed into the σ-gold complex **C**. Protodemetalation of the latter affords the 2,3-dihydrofuran **D** and releases the gold catalyst into the first catalytic cycle. The dihydrofuran enters the second catalytic cycle and is transformed into the intermediates **E** and **F** by protonation and nucleophilic attack of the alcohol R^2OH, respectively. Finally, deprotonation closes the second catalytic cycle and releases the cyclic acetal **G**.

In summary, we have developed a mild and efficient tandem cycloisomerization−hydroalkoxylation of homopropargylic alcohols to tetrahydrofuranyl ethers in the presence of an alcohol and a dual catalyst system, consisting of a gold precatalyst and a Brønsted acid. The method was applied to the cyclization of the bis-homopropargylic alcohols **10**, as well as to the 2-alkynylphenol **12**. The reaction can be carried out in various solvents, including alcohol, with both terminal and internal alkynes as the substrate. Further work will be devoted to the extension of the method to other functionalized alkynes, as well as to the application of the method in target-oriented synthesis.

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Supporting Information Available: Experimental procedure and NMR data of cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (b) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381. (c) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437.