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Golden Times for Allenes: Gold-Catalyzed Cycloisomerization of β-Hydroxyallenes to Dihydropyrans

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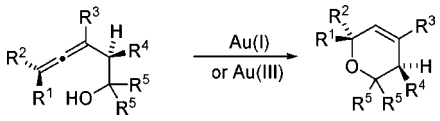
ABSTRACT



The gold(I)-catalyzed 6-*endo* cycloisomerization of β-hydroxyallenes provides a mild and efficient access to chiral functionalized dihydropyrans which were obtained at room temperature in good chemical yields with axis-to-center chirality transfer. The method was extended to the β-aminoallene 12, which afforded tetrahydropyridine 13 in good yield as well.

Chiral tetrahydropyrans and piperidines are an important class of heterocyclic target molecules because of their occurrence as structural units in a variety of natural products and biologically active compounds (Figure 1).

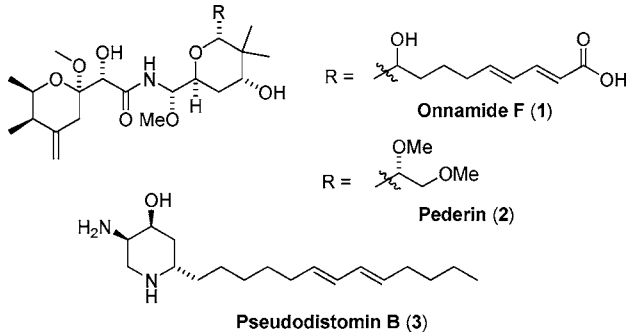


Figure 1. Examples of naturally occurring tetrahydropyrans and piperidines.

These include the antifungal and nematocidal compound onnamide F (**1**),[1] the insect chemical defense agent pederin (**2**),[2] as well as the cytotoxic and calmodulin-antagonistic agent pseudodistomin (**3**).[3]

Among various methods for the synthesis of these and related heterocycles, transition-metal-catalyzed transformations of allenes play an important role, e.g., cyclizations of β-hydroxyallenes with Pd,[4] Ag,[5] or Ru,[6] as well as the gold-catalyzed cyclization of γ- and δ-functionalized allenes.[7−9]

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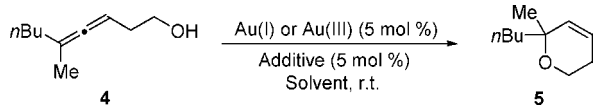
We have already reported on the highly efficient and stereoselective gold-catalyzed[10] cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans,[11] a method that was recently extended to the corresponding cyclization of α-aminoallenes to 3-pyrrolines,[12] as well as of α-thioallenes to 2,5-dihydrothiophenes.[13] Based on this work, we now disclose the first results on the corresponding cycloisomerization of *β*-hydroxyallenes to dihydropyrans and of *β*-aminoallenes to tetrahydropyridines.

The starting materials of our study were prepared in two different ways. The terminally disubstituted *β*-hydroxyallenes **4** and **7** were obtained by 1,6-cuprate addition to 2-en-4-ynoates,[14] followed by reduction of the *β*-allenic ester, whereas the diastereomerically pure allenols **9** were formed by copper-mediated S_N2'-substitution of propargylic oxiranes.[11,15] The *β*-aminoallene **12** was prepared from the corresponding *β*-hydroxyallene **4** by Mitsunobu reaction.[12]

We started our study with the *β*-hydroxyallene **4** which was treated with various gold precatalysts in different solvents (Table 1). Both gold(I) and gold(III) were found to be competent precatalysts and afforded the 6-*endo* cyclization product **5** with ca. 60% yield (entries 1−5). No trace of the 5-*exo* isomer could be detected.[16] Interestingly, the yield was hardly affected by the solvent and the presence of silver salts, which leads to the formation of cationic gold species. The reactivity, however, could be increased by addition of 3-hydroxypropionitrile (entry 2) or $AgBF_4$ (entries 4 and 5), indicating the formation of a more reactive gold catalyst. In the case of gold(I) chloride, also the addition of pyridine or 2,2′-bipyridine induced a remarkable increase of the reactivity (entry 6) or chemical yield (entry 7). In contrast to this, $AgBF_4$ alone, as well as the less Lewis acidic precatalysts $Au(OAc)_3$ and Ph_3PAuCl, did not afford any cyclization product (entries 8−10).

Further experiments with cationic gold catalysts in noncoordinating solvents made it possible to decrease the reaction time considerably (entries 11−13 and 17−19). Yields of **5** around 60% were obtained with Ph_3PAuCl and $AgBF_4$ or $AgSbF_6$, as well as with the stable cationic Au(I) complex **6**[17] after 60−90 min at room temperature. With these precatalysts, the temperature (entry 17) or the catalyst loading (entries 18−19) could be decreased without compromising the chemical yield. Only in coordinating solvents such as THF, diethyl ether, or acetonitrile were very slow conversions observed, probably because of the decreased Lewis acidity of the gold catalyst in these solvents (entries 14−16).

Table 1. Gold-Catalyzed Cycloisomerization of *β*-Hydroxyallene **4** to 5,6-Dihydro-2*H*-pyran **5**

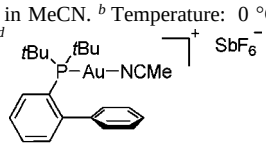


4 **5**

entry	Au salt	additive	solvent	time	yield (%)
1	$AuCl_3$[a]		toluene	6 d	58
2	$AuCl_3$[a]	3-hydroxypropionitrile	toluene	1 d	62
3	AuCl		CH_2Cl_2	5 d	50
4	AuCl	$AgBF_4$	CH_2Cl_2	3 d	60
5	AuCl	$AgBF_4$	toluene	3 d	62
6	AuCl	pyridine	CH_2Cl_2	4.5 h	64
7	AuCl	2,2′-bipyridine	CH_2Cl_2	5 d	86
8		$AgBF_4$	toluene	5 d	–
9	$Au(OAc)_3$		toluene	14 d	–
10	Ph_3PAuCl		toluene	14 d	–
11	Ph_3PAuCl	$AgSbF_6$	toluene	25 min	54
12	Ph_3PAuCl	$AgBF_4$	toluene	1 h	60
13	Ph_3PAuCl	$AgBF_4$	CH_2Cl_2	1.5 h	60
14	Ph_3PAuCl	$AgBF_4$	THF	3 d	46
15	Ph_3PAuCl	$AgBF_4$	Et_2O	4 d	56
16	Ph_3PAuCl	$AgBF_4$	MeCN	27 d	62
17	Ph_3PAuCl	$AgBF_4$	toluene[b]	1.25 h	66
18	Ph_3PAuCl[c]	$AgBF_4$[c]	toluene	6.5 h	61
19	Au(I) complex **6**[c,d]		toluene	1.5 h	66

[a] 0.195 M solution in MeCN. [b] Temperature: 0 °C. [c] 1 mol %.

[d]



6

We next extended the scope of the reaction to the sterically more hindered and ester-functionalized *β*-hydroxyallenes **7** (Table 2). Not surprisingly, slower cyclizations and decreased chemical yields of the dihydropyrans **8** were noted for the substrates **7a** and **7b** bearing a *tert*-butyl group at the allene terminus, as well as for the tertiary alcohol **7c** (entries 1−4). Nevertheless, a completely regioselective 6-*endo* cyclization was still observed in these cases. The reactivity difference between substrates **7a** and **7b** is striking and indicates a strong influence of the steric properties of the substrate. Similar to the model substrate **4**, the precatalyst combination $Ph_3PAuCl/AgBF_4$ gave faster reactions, but not necessarily higher yields of the products **8a**−**c**, than AuCl/pyridine. For the ester-substituted *β*-hydroxyallene **7d**, on the other hand, the former precatalyst afforded no cyclization product at all (entry 5), whereas the latter provided the desired heterocycle **8d** with good chemical yield (84%) and complete axis to center chirality transfer (entry 6).

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(16) In some cases, small amounts of acyclic isomerization products (conjugated dienes) of allene **4** were observed as side products.

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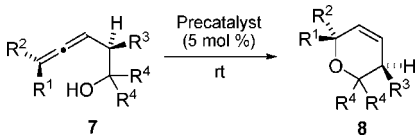
Table 2. Au(I)-Catalyzed Cycloisomerization of Sterically Demanding or Ester-Functionalized β-Hydroxyallenes **7** to Dihydropyrans **8**



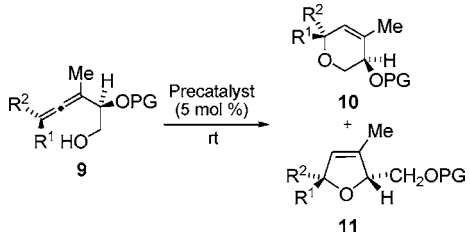
7 **8**

entry	**7**	R^1	R^2	R^3	R^4	conditions[a]	**8** (yield, %)
1	**7a**	*t*Bu	Me	H	H	A	22 h	**8a** (42)
2	**7b**	*t*Bu	*n*Bu	H	H	A	10 d	**8b** (36[b])
3	**7c**	Me	*n*Bu	H	Me	A	24 h	**8c** (32)
4	**7c**	Me	*n*Bu	H	Me	B	6 d	**8c** (46)
5	**7d**[c]	Me	*n*Bu	COOEt	Me	A	4 h	**8d** (−)
6	**7d**[c]	Me	*n*Bu	COOEt	Me	B	13 d	**8d** (84[c])

[a] Conditions A: $Ph_3PAuCl/AgBF_4$ in toluene. Conditions B: AuCl/pyridine in CH_2Cl_2. [b] 67% conversion of **7b**. [c] dr = 70:30.

Further investigations of the chirality transfer and the tolerance toward functional groups were carried out with the diastereomerically pure β-hydroxyallenes **9** (Table 3). Treatment of the alkyl-substituted allenols **9a**−**d** with $Ph_3PAuCl/AgBF_4$ afforded the diastereomerically pure dihydropyrans **10a**−**d** with moderate yields for sterically demanding substrates (entries 1, 2, and 4), whereas better yields were achieved for less bulky allenols (entries 5 and 6). Thus, these cycloisomerizations took place with complete chirality transfer, too. It is interesting to note that the β-hydroxyallene **9b** gave a higher yield than its diastereomer **9a**; this may be explained by steric hindrance between the *tert*-butyl and acetoxy groups during the cyclization of **9a**. Another interesting observation is the formation of the 2,5-dihydrofurans **11b**/**c** as side products (entries 4 and 5) which may be formed by (gold-catalyzed?) acetate migration from the secondary to the primary hydroxy group, followed by gold-catalyzed cycloisomerization of the α-hydroxyallene.[11,15] By using gold(III) chloride as the precatalyst, a clean, albeit extremely slow, conversion of the β-hydroxyallene **9a** into the dihydrofuran **11a** could be achieved (entry 3).

Table 3. Gold-Catalyzed Cycloisomerization of the Diastereomerically Pure β-Hydroxyallenes **9**



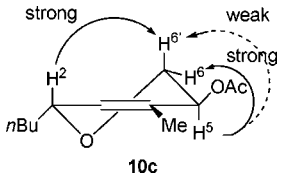
9 **10** **11**

entry	**9**[a]	R^1	R^2	PG	conditions[a]	**10** (yield, %)	**11** (yield, %)
1	**9a**	*t*Bu	H	Ac	A, 30 min	**10a** (30[b])	**11a** (−)
2	**9a**	*t*Bu	H	Ac	B, 16 h	**10a** (34[b])	**11a** (−)
3	**9a**	*t*Bu	H	Ac	C, 55 d	**10a** (−)	**11a** (78[b])
4	**9b**	H	*t*Bu	Ac	A, 30 min	**10b** (50[b])	**11b** (11[b])
5	**9c**	H	*n*Bu	Ac	A, 20 min	**10c** (84[b])	**11c** (8[b])
6	**9d**	H	*n*Bu	Me	A, 15 min	**10d** (68[b])	**11d** (−)
7	**9e**	H	Ph	Ac	A, 1 h	**10e** (65[c])	**11e** (10[c])
8	**9e**	H	Ph	Ac	B, 8 d	**10e** (66[c])	**11e** (−)
9	**9f**	H	Ph	Me	B, 9 d	**10f** (60[c])	**11f** (−)

[a] Conditions A: $Ph_3PAuCl/AgBF_4$ in toluene. Conditions B: $Ph_3PAuCl/AgBF_4$ in THF. Conditions C: $AuCl_3$ in toluene. [b] dr > 95:5. [c] dr = 85:15.

In contrast to the allenols **9a**−**d**, the stereochemical information of the phenyl-substituted β-hydroxyallenes **9e/f** was partly lost during the cycloisomerization, giving the dihydropyrans **10e/f** as a 85:15 mixture of diastereomers (entries 7−9). A similar behavior has been observed previously in the gold-catalyzed cyclization of phenyl-substituted α-hydroxyallenes to 2,5-dihydrofurans and may be explained by formation of zwitterionic intermediates with a benzyl cation substructure.[18] Switching the solvent from toluene to THF served to suppress the acetate migration which gave **11e** as side product (entry 8 vs 7) but did not improve the chirality transfer.

The relative configuration of the dihydropyran **10c** was determined by observing strong NOEs between 5-H and 6-H, as well as between 2-H and 6′-H (Figure 2).

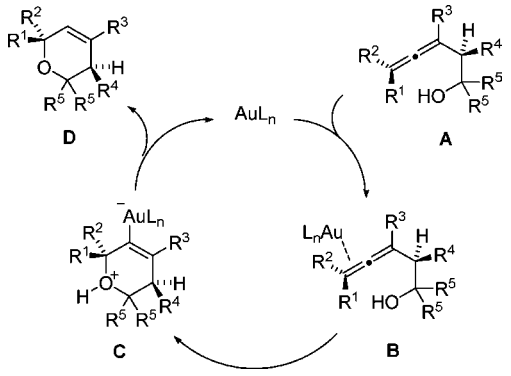


10c

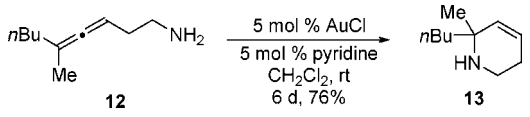
Figure 2. NOEs observed for dihydropyran **10c**.

The chirality transfer observed for the β-hydroxyallenes **9** to the dihydropyrans **10** can be explained with the mechanistic model shown in Scheme 1. Thus, coordination of the gold catalyst to the terminal double bond of the allene **A** gives rise to the formation of the intermediate **B** which,

Scheme 1



Scheme 2



upon nucleophilic attack of the oxygen, is transformed into the σ-gold complex **C**. Protodemetalation of the latter provides the heterocyclic product **D** and releases the gold catalyst into the catalytic cycle. At present, the exact nature of the catalytically active gold species is unknown.

To further demonstrate the efficiency and utility of the gold-catalyzed cycloisomerization of functionalized allenes, we treated the (unprotected) β-aminoallene **12** with 5 mol % each of gold(I) chloride and pyridine in dichloromethane and were delighted to observe a rather slow but clean conversion into the tetrahydropyridine **13**, which was isolated in a good yield of 76% (Scheme 2).

In summary, we have developed an efficient and stereoselective gold(I)-catalyzed 6-*endo* cycloisomerization of various β-hydroxyallenes to the corresponding chiral dihydropyrans. The method was extended to the cyclization of the β-aminoallene **12** to the tetrahydropyridine **13**. Further work will be devoted to corresponding stereoselective transformations of other functionalized allenes, 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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(18) Deutsch, C.; Krause, N. To be published.