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Gold(III) Chloride Catalyzed Cyclization of α-Hydroxyallenes to 2,5-Dihydrofurans

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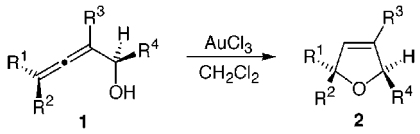
ABSTRACT



Functionalized α-hydroxyallenes 1 were smoothly converted into the corresponding 2,5-dihydrofurans 2 by using 5–10 mol % of gold(III) chloride as catalyst. This mild and efficient cyclization method can be applied to alkyl- and alkenyl-substituted allenes at room temperature, furnishing tri- and tetrasubstituted dihydrofurans in good to excellent chemical yields and with complete axis to center chirality transfer.

As a result of their reactivity and inherent chirality, allenes and especially allenic alcohols have become versatile synthetic precursors in modern organic chemistry. Hence, several applications of allenic compounds, e.g., in natural product synthesis, have been published over the past years.[1] During our own studies toward the use of functionalized allenes in target-orientated synthesis, we were recently able to show that 2-hydroxy-3,4-dienoates, e.g., **1a**, can be smoothly converted into the corresponding tri- and tetrasubstituted 2,5-dihydrofurans by simple treatment with HCl gas in chloroform[2] (Figure 1). This transformation proceeds under perfect

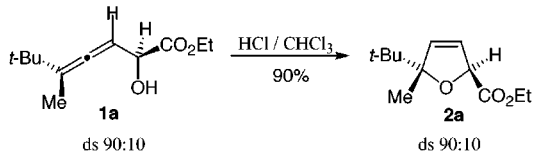


Figure 1. HCl gas promoted cyclization of 2-hydroxy-3,4-dienoate **1a** to 2,5-dihydrofuran **2a**.

chirality transfer, furnishing the desired heterocycles in good chemical yields and diastereoselectivities of up to 90%.

2,5-Dihydrofurans and derivatives thereof constitute pivotal structural elements of a variety of natural products with intriguing biological activities, e.g., mycotoxins[3] and polyether antibiotics.[4] Thus, the stereoselective preparation of suitably functionalized 2,5-dihydrofurans is of particular interest.

We were therefore pleased to find that 2-hydroxy-3,4-dienoate **1a** can be more conveniently cyclized to heterocycle **2a** by using acidic Amberlyst 15 resin in refluxing dichloromethane[5] (Table 1, entry 1). Again, the obtained NMR spectra reveal that reaction takes place under complete axis to center chirality transfer and in quantitave yield.

However, acid-labile substrates or those that would readily undergo elimination reactions to the corresponding vinylallenes (as a result of conformational rigidity or steric hindrance that hampers the desired cyclization) are incom-

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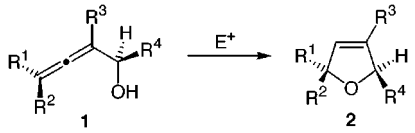
Table 1. Electrophilic Cyclization of α-Hydroxyallenes **1** to 2,5-Dihydrofurans **2**



1 2

entry	hydroxyallene	R^1	R^2	R^3	R^4	electrophile	amount (mol %)	dihydrofuran (yield)
1	**1a**	*t*-Bu	Me	H	CO_2Et	Amberlyst 15		**2a** (quant)
2	**1a**	*t*-Bu	Me	H	CO_2Et	$AuCl_3$	5	**2a** (74%)
3	**1b**	*t*-Bu	Me	Me	CO_2Et	$AuCl_3$	10	**2b** (94%)
4	**1c**	*t*-Bu	*n*-Bu	H	CO_2Et	$AuCl_3$	8	**2c** (quant)
5	**1d**	*t*-Bu	H	Me	CO_2Me	$AuCl_3$	5	**2d** (78%)
6	**1e**	*t*-Bu	Me	H	CH_2OH	$AuCl_3$	5	**2e** (24%)
7	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AuCl_3$	7	**2f** (95%)
8	**1f**	*t*-Bu	H	Me	CH_2OTBS	$AgNO_3$	22	**2f** (mixture)
9	**1g**	H	Me	Me	CH_2OTBS	$AuCl_3$	10	**2g** (77%)
10	**1h**	H	*n*-Hex	Me	CH_2OTBS	$AuCl_3$	5	**2h** (65%)
11	**1i**	*t*-Bu	Me	Me	CH_2OMe	$AuCl_3$	10	**2i** (90%)
12	**1j**	$H_2C{=}CH(CH_2)_2$	Me	Me	CH_2OMe	$AuCl_3$	10	**2j** (86%)

patible with this method. To overcome this limitation, we focused our efforts on the use of gold(III) chloride as an electrophile, since it was known that catalytic amounts of Au(III) induce the cyclization of allenyl ketones to furans.[6] Indeed, with 5−10 mol % of $AuCl_3$ (99%, Aldrich) in dry dichloromethane at room temperature we were able to obtain the ester-substituted 2,5-dihydrofurans **2a**−**d** with good to excellent chemical yields (Table 1, entries 2−5).

As in the case of the acid-induced cyclizations, GC analysis and NMR spectra proved that all reactions proceeded under perfect stereocontrol; hence, dihydrofuran **2a** was again obtained with 90% ds. Moreover, compared to the well-established Ag(I)-promoted method,[7] the use of gold(III) chloride not only increases the reaction rate but also allows the transformation of notoriously difficult substrates, e.g., alcohols and silyl ethers. Thus, diol **1e**, accessible through S_N2' ring opening of a propargylic epoxide with an organocuprate[7b] or Grignard reagent,[8] furnished the corresponding dihydrofuran **2e**, albeit in low yield (entry 6). This may be due to complexation since protection of the primary hydroxy group as a *tert*-butyldimethylsilyl or simple methyl ether provided dihydrofurans **2f**−**j** in good chemical yields.[9] In contrast, the cyclization of α-hydroxyallene **1f** with $AgNO_3$ in acetone/water[7] proceeded sluggishly; even after 24 h only a mixture of substrate and product was obtained, whereas the corresponding Au(III)-catalyzed cyclization provided **2f** after 3 h with 95% chemical yield.

Furthermore, the reaction is hardly influenced by the substitution pattern of the allenic entity, furnishing both tri- and tetrasubstituted 2,5-dihydrofurans equally well. Thus, α-hydroxyallenes with sterically demanding alkyl groups, as well as an alkenyl group, are smoothly converted into the corresponding dihydrofurans (entries 7−12); these are not accessible by conventional methods. Besides its mildness and efficiency, this catalytic cyclization represents a very user-friendly protocol, since no aqueous workup is required. Hence, the desired heterocycles are obtained spectroscopically pure just after evaporation of the solvent, followed by short flash column chromatography to remove the metal catalyst.

In summary, we present a new efficient gold(III)-catalyzed cyclization reaction of highly functionalized α-hydroxyallenes to the corresponding 2,5-dihydrofurans. The scope and limitations of this transformation, as well as its application in natural product synthesis, are currently under investigation.

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Supporting Information Available: Experimental procedure and ^1H and ^{13}C NMR data of 2,5-dihydrofurans. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) With the more Lewis acid labile trimethylsilyl or triethylsilyl ether, however, no cyclization but cleavage of the protection group was observed.