

Silicon-assisted propargylic transfer to aldehydes†

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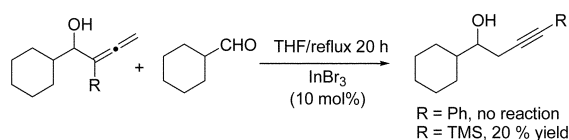
A new and efficient method of obtaining homopropargylic alcohols via homopropargylic transfer from the allenic alcohol to various aldehydes in the presence of Lewis acid catalysts is described; stereochemical studies have shown that this process is the first oxonium [3,3]-sigmatropic rearrangement of an allenic alcohol to a homopropargylic alcohol in the presence of aldehydes and Lewis acid.

Allenic and propargylic alcohols are attractive intermediates in organic synthesis because of their unique structural characteristics and versatile natures.¹ They have been used extensively as important building blocks for the synthesis of many biologically active natural products such as 3-deoxy-D-glycero-D-galacto-2-ulosonic acids (KDN),² (±)-9-deoxygoniopyrone³ and mono-THF acetogenins.⁴ Accordingly, there has been much interest in the development of new methods for the synthesis of these classes of compounds. Among the methods available, the metal-mediated propargylation/allenylation of carbonyl compounds is the most common approach.⁵ However, these methods are plagued with problems of regioselectivities and enantioselectivities. Therefore, a general and efficient method of obtaining this class of compounds is still highly desirable. In this paper, we report an efficient method for the propargylic transfer to carbonyl compounds based on an unusual oxonium-Claisen rearrangement of 2-trialkylsilyl allenic alcohols with aldehydes.

In our initial investigations, studies on THF solutions of various 2-substituted allenic alcohols^{3a} in the presence of 10 mol% indium tribromide (InBr₃) under reflux conditions were carried out to investigate whether allenic alcohols can rearrange to afford homopropargylic alcohols (Scheme 1).

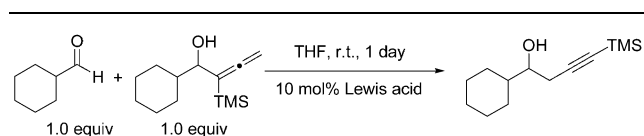
Unfortunately, no desired corresponding homopropargylic alcohols were obtained when 2-phenyl-substituted α -allenic alcohols were treated with various aldehydes under these conditions. To our surprise, when one equivalent of the corresponding aldehyde⁶ was introduced to 2-trimethylsilyl allenic alcohol in the presence of InBr₃ (10 mol%), the desired homopropargylic alcohol was obtained in 20% yield together with the recovery of 30% of the starting allenic alcohol. With this promising result, the α -trimethylsilyl cyclohexyl allenic alcohol, in the presence of the corresponding aldehyde, was treated with various Lewis acids. The results are shown in Table 1.

It is interesting to note that the use of indium triflate with more Lewis acidity afforded the desired homopropargylic alcohol in moderate yield (entry 6). Next, different α -trimethylsilyl allenic alcohols were subjected to the rearrangement using this condition



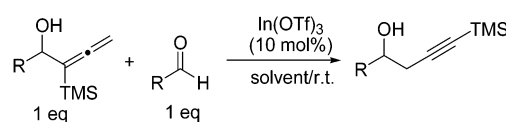
Scheme 1

† Electronic supplementary information (ESI) available: spectroscopic and analytical data for all compounds and the representative procedure. See <http://www.rsc.org/suppdata/cc/b411653d/>

Table 1 Effect of Lewis acids^a

Entry	Lewis acid	Yield ^b (%)
1	InCl ₃	—
2	Cu(OTf) ₂	—
3	InBr	5
4	InBr ₃	20 ^c
5	Sc(OTf) ₃	26
6	In(OTf) ₃	51

^a All reactions were carried out on 0.5 mmol scale at room temperature in THF (2 mL). ^b Isolated yield. ^c Recovered 30% of the starting material.

Table 2 Rearrangement of various allenic alcohols^a

Entry	R	Conditions	Yield ^b (%)
1	PhCH ₂ CH ₂	THF/24 h	30
2	C ₈ H ₁₇	THF/24 h	45
3	Ph	THF/24 h	50
4	c-C ₆ H ₁₁	THF/24 h	51
5	c-C ₆ H ₁₁	CH ₂ Cl ₂ /1 h	89

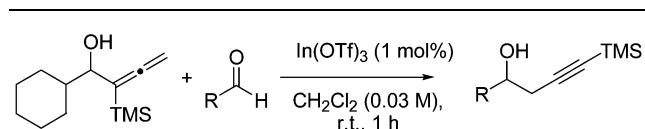
^a All reactions were carried out on 0.5 mmol scale at room temperature in solvent (2 mL). ^b Isolated yield.

(Table 2). Compared with other α -trimethylsilyl allenic alcohols, we found that cyclohexyl allenic alcohol afforded the cross-over product in higher yield, probably due to the higher steric hindrance of cyclohexyl allenic alcohol.

Next, using these optimized conditions, the cross-over reactions of α -trimethylsilyl cyclohexyl allenic alcohol and various aldehydes were carried out in CH₂Cl₂ in the presence of 1 mol% of In(OTf)₃. The results are shown in Table 3. In this reaction, complete conversions of cross-over products were obtained. The selectivity between cross-over and self-rearranged product can be improved when the reaction is carried out using 2 to 4 equivalents of aldehyde in the presence of 1 mol% of indium triflate. After the reaction, the excess aldehyde can be recovered in quantitative yield through flash column chromatography. The isolated yields were good, and only small amounts of the self-rearranged products were detected.

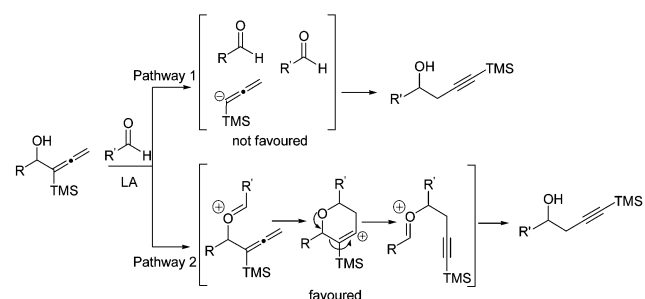
Two possible reaction pathways (Scheme 2) can be envisaged to occur during this rearrangement. Pathway 1 involves the reaction of an intermolecular allenic anion (generated in the reaction) with

Table 3 Cross-over reactions of allenic alcohol and aldehydes in CH₂Cl₂ with In(OTf)₃^a



Entry	R	Yield ^b (%)
1	c-C ₆ H ₁₁ -	98
2	PhCH ₂ CH ₂ -	79
3	BnO(CH ₂) ₃ -	78
4	C ₈ H ₁₇ -	77
5	C ₂ H ₅ CH=CHC ₂ H ₄ - (<i>cis</i>)	77
6	BnO(CH ₂) ₂ -	73 ^c
7	(CH ₃) ₂ CHCH ₂ -	73
8	C ₅ H ₁₁ -	71
9	CH ₂ =CHCH ₂ O(CH ₂) ₄ -	70

^a Unless otherwise noted, all reactions were carried out on 0.2 mmol scale in CH₂Cl₂ (0.03 M) for 1 h at room temperature. ^b Isolated yield. ^c 100% recovery of the excess aldehyde.



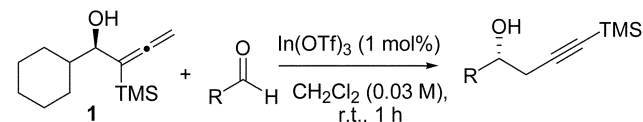
Scheme 2 Proposed mechanism for rearrangement/cross-over of allenic alcohol.

the aldehyde. On the other hand, pathway 2 involves an unprecedented oxonium [3,3]-sigmatropic rearrangement of the allenic alcohol in the presence of aldehyde and Lewis acid catalyst. In order to further understand the mechanism involved in this reaction, we carried out stereochemical studies using enantiomerically enriched allenic alcohol **1** (92% *ee*).⁷ The results are summarized in Table 4.

The cross-over experiments with a few aldehydes were carried out under the same conditions. In all cases, the products were obtained in high enantioselectivities (88% to 97% *ee*, corrected based on 92% *ee* of the starting material). Furthermore, the products were obtained in the opposite configuration as compared to the starting material. With these results, we believe that this allenic alcohol undergoes a 2-oxonia [3,3]-sigmatropic rearrangement in the presence of aldehyde to give the homopropargylic adduct. The requirement of the silicon substituent at the 2-position of the allenic alcohols was probably due to the more stepwise nature of this reaction where the silicon stabilized the β -carbocation. It is also possible that the rearrangement could be fully concerted where the silicon group stabilises the transition state without a vinyl cation intermediate.⁸

In conclusion, a new and efficient method of obtaining homopropargylic alcohols *via* homopropargylic transfer from the

Table 4 Rearrangement using optically active allenic alcohol **1**^{7,9}



Entry	R	% <i>ee</i> ^d (%) ^e	[α] _D ²⁵ , CHCl ₃	Configuration
1	PhCH ₂ CH ₂ -	85 ^b (92)	-17.7 (<i>c</i> 1.0)	<i>R</i> ^c
2	Ph-	89 ^b (97)	+43.6 (<i>c</i> 0.5)	<i>R</i> ^d
3	BnO-C ₂ H ₄ -	81 ^b (88)	+13 (<i>c</i> 0.05)	<i>R</i> ^c

^a Enantiomeric excess was determined by chiral HPLC. ^b Determined from (*R*)-1-cyclohexyl-2-trimethylsilylbuta-2,3-dien-1-ol with 92% *ee*. ^c Predicted based on d. ^d Based on ref. 10. ^e Corrected value.

allenic alcohol to various aldehydes in the presence of Lewis acid catalysts has been accomplished. This represents the first oxonium [3,3]-sigmatropic rearrangement of an allenic alcohol to the homopropargylic alcohol in the presence of aldehydes and Lewis acid. The following are the characteristics of this method: (1) This reaction works with a wide variety of aldehydes, affording a wide variety of homopropargylic alcohols in good to excellent yields. (2) Only 1 mol% of the Lewis acid catalyst is required to catalyze the reaction and the excess aldehyde used in the reaction can be recovered in quantitative yield. (3) The reaction has also been shown to proceed with high enantioselectivities when optically active allenic alcohol was used as the starting material. (4) Silicon seems to play an important role in this type of rearrangement.

Effort to design a practical enantioselective version of this reaction is in progress.

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