

PRACTICAL METHOD FOR SYNTHESIS OF OPTICALLY PURE PROPARGYLIC ALCOHOLS

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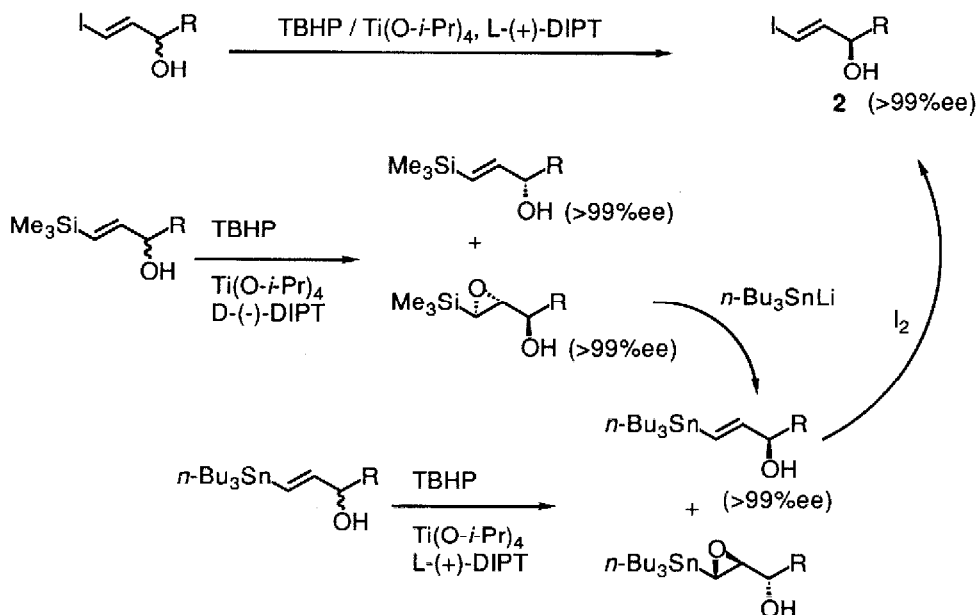
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Summary: Highly efficient practical method for synthesis of optically pure propargylic alcohols is described which involves the synthesis of chiral γ -iodo allylic alcohols by the Sharpless kinetic resolution of secondary γ -hetero substituted allylic alcohols and their 1,2-dehydrohalogenation reaction.

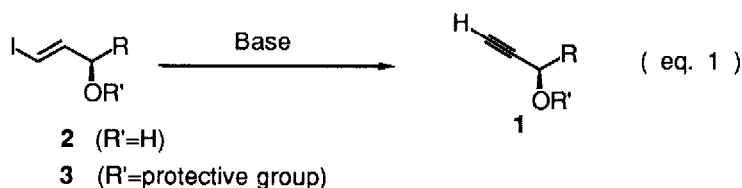
The optically active propargylic alcohols (**1**) have been recognized as versatile synthetic intermediates of a variety of natural products. Various synthetic methods for preparation of **1** in a chiral form have been developed which include optical resolution of the racemic alcohols,^{1a} microbial asymmetric hydrolysis of the corresponding acetates,^{1b} asymmetric reduction of acetylenic ketones,^{1c} the reductive cleavage of chiral acetylenic acetals,^{1d} and the asymmetric alkynylation of aldehydes.^{1e} However, these methods suffer from some disadvantages such as rather low optical purity, requirement of stoichiometric amounts of the chiral substrates or reagents, and/or lack of generality, and thus, there still exists a need for developing practical methods for synthesis of optically pure propargylic alcohols.

Recently we have developed highly efficient general method for synthesis of secondary γ -halo allylic alcohols (**2**) with trans configuration by using the Sharpless kinetic resolution as the key step (Scheme 1).² The Sharpless kinetic resolution of racemic γ -iodo allylic alcohols affords direct method for preparation of optically pure (E)- γ -iodo allylic alcohols in excellent yields.^{2a} The kinetic resolution of γ -trimethylsilyl allylic alcohols or γ -tributylstannyl allylic alcohols followed by the conventional reactions of the resulting products affords another efficient approach to (E)- γ -iodo allylic alcohols.^{2b,c} Thus it is now possible to prepare various kinds of optically pure (E)- γ -iodo allylic alcohols in large quantity by using the above reactions property.

Scheme 1.



Since iodo alkenes can be readily converted into the corresponding alkynes by treatment with base,³ it occurred to us naturally that the combination of this dehydrohalogenation reaction with that of Scheme 1 provides practical method for preparation of optically pure propargylic alcohols. However, since no one ever has carried out the transformation of γ -iodo allylic alcohols into propargylic alcohols, we were concerned whether the reaction shown in eq.1 proceeds without racemization or not.



First we carried out the elimination reaction of **2** ($\text{R} = n\text{-C}_5\text{H}_{11}$) under several conditions, and found that no racemization occurred when the reaction was carried out by using LDA in THF (run 1 in Table 1), while use of LiNH_2 in liquid ammonia resulted in partial racemization (run 2). The reaction condition of LiNH_2 / liq- NH_3 is very attractive for carrying out the reaction in large quantity, we, therefore, carried out the elimination reaction after converting **2** into **3** (protection of the hydroxyl group) (eq.1), and found that the reaction proceeded without loss of stereochemical integrity (run 3,4). With these results in

hand, we have carried out the 1,2-dehydrohalogenation reaction of various **2** and **3** under these conditions and the results are summarized in Table 1. As can be seen from the table, the reaction proceeds without loss of stereochemical integrity regardless of the substituent R. Thus, in summary, the combination of the Sharpless kinetic resolution of secondary γ -hetero substituted allylic alcohols with 1,2-dehydrohalogenation reaction provides general and practical synthetic method for preparation of optically pure propargylic alcohols.

Table 1: 1,2-Dehydrohalogenation reaction of **2** or **3**

Run	Substrate (2 or 3)		Condition	1		
	R	R' ^a		Yield (%) ^b	ee (%) ^c	$[\alpha]_D$ (temp., c, solvent)
1 ^d	<i>n</i> -Am	H	LDA / THF, 0 °C	84	>99	+22.0° (21 °C, 1.10, ether) ^e
2	<i>n</i> -Am	H	LiNH ₂ / NH ₃ , -78 °C	85	97	
3	<i>n</i> -Am	TBS	LiNH ₂ / NH ₃ , -78 °C	95 ^f	>99	+43.1° (20 °C, 1.06, ether)
4 ^g	<i>n</i> -Am	EE	LiNH ₂ / NH ₃ , -78 °C	93 ^h	>99	
5	Me	H	LDA / THF, 0 °C	74	>99	+51.2° (20 °C, 1.06, dioxane) ⁱ
6	Me	H	LiNH ₂ / NH ₃ , -78 °C	73	96	
7	<i>c</i> -Hex	H	LDA / THF, 0 °C	93	>99	+13.8° (21 °C, 1.0, ether) ^j
8	Ph	EE	LiNH ₂ / NH ₃ , -78 °C	88 ^h	>99	
9	CH ₂ OCH ₂ Ph	EE	LiNH ₂ / NH ₃ , -78 °C	81 ^h	>99	

a) TBS=*t*-butyldimethylsilyl, EE= ethoxyethyl. b) Isolated yield by column chromatography. c) Determined by ¹H-NMR (200 MHz) and/or HPLC analysis of the corresponding MTPA ester. d) The reaction was carried out as described in note 4. e) lit.^{6a} +20° (21°C, c 1.0, ether). f) Treatment with *n*-Bu₄NF afforded the corresponding propargylic alcohol in quantitative yield, +22.1° (21°C, c 1.30, ether). g) The reaction was carried out as described in note 5. h) Treatment with PPTS in *i*-PrOH provided the corresponding propargylic alcohol in 90-92% yield. The optical rotations of the alcohols obtained are as follows : R=*n*-Am ; +21.7° (21°C, c 1.18, ether), R=Ph ; +20.1° (25°C, c 1.37, dioxane), lit.^{6b} +20.8° (25°C, c 4.3, dioxane), R=CH₂OCH₂Ph ; +4.9° (21°C, c 1.10, dioxane), lit.^{6c} -4.8° (21°C, c 2.9, dioxane) for R configuration. i) lit.^{6d} +52° (20°C, c 2.3, dioxane). j) lit.^{6e} +11.2° (25°C, c 1, ether).

References and Notes.

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- 4) To a solution of diisopropylamine (8.0 g, 78.7 mmole) in THF (100 ml) was added BuLi (2.10 N in hexane solution, 30 ml) at 0 °C. After 20 min, to this solution was added a solution of iodo allylic alcohol **2** (R=C₅H₁₁, R'=H; 4.0 g, 15.7 mmole) in THF (5 ml). The mixture was stirred for 30 min at 0 °C then poured into saturated aqueous NH₄Cl. The organic layer was separated and the aqueous layer was extracted with ether (3 x 30 ml). The combined organic layers were dried (MgSO₄) and concentrated to give an oil, which was purified by column chromatography on silica gel to afford the propargylic alcohol **1** (R=C₅H₁₁, R'=H; 1.7 g, 84 % yield).
- 5) To a freshly prepared LiNH₂ in liq.NH₃ (prepared from 1.39 g of lithium metal and 50 mg of FeNO₃•9H₂O in ca. 120 ml of NH₃) was added dropwise a solution of allylic ether **3** (R=C₅H₁₁, R'=ethoxyethyl; 16.0 g, 49.1 mmole) in THF (30 ml). After 1 h, ether (50 ml) and solid NH₄Cl (20 g) was added, and ammonia was allowed to evaporate. The residue was partitioned between water (400 ml) and hexane (200ml) and the organic layer was separated and dried (MgSO₄). After concentration of the organic layer, the resulting oil was purified by silica gel column chromatography to provide 9.0 g of the propargylic ether **1** (93 % yield).
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