



An efficient and practical preparation of optically active *syn*-1-vinyl-2-amino alcohol derivatives by the regio- and diastereoselective addition reaction of (γ -alkoxyallyl)titaniums with chiral imines. Formal synthesis of statine

Sentaro Okamoto, Kohki Fukuhara and Fumie Sato*

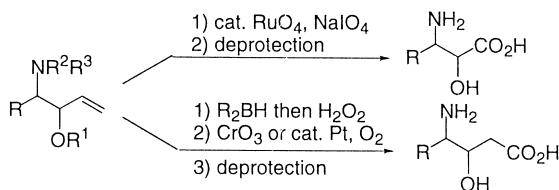
Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

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Abstract

(γ -Alkoxyallyl)titaniums **1**, generated by the reaction of acrolein dialkyl acetals and a divalent titanium reagent (η^2 -propene)Ti(O-*i*-Pr)₂, react readily with chiral imines **2**, prepared from aldehydes and optically active 1-phenylethyl amine, in a regiospecific manner to give optically active *syn*-1-vinyl-2-amino alcohol derivatives **3** with diastereoselectivity of more than 80% in good yield. By using the adduct **3d** thus obtained, statine was formally synthesized. © 2000 Elsevier Science Ltd. All rights reserved.

Synthesis of optically active 1-vinyl-2-amino alcohols and their derivatives has attracted much interest because they can work as useful intermediates in organic synthesis.¹ For example, they can be readily converted into optically active α -hydroxy- β -amino acids^{1a} and β -hydroxy- γ -amino acids^{1a,b,d} as shown in Scheme 1, both skeletons of which are widely found as the main unit or subunit in naturally occurring and man-made biologically important compounds.²

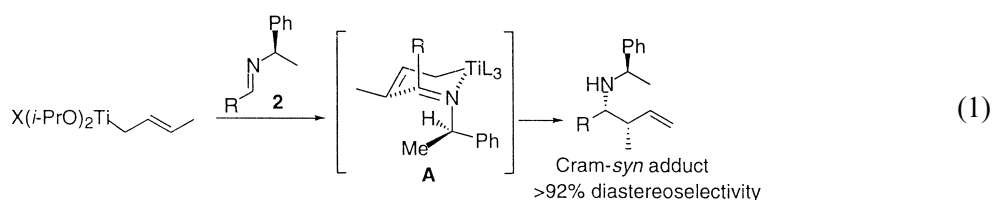


Scheme 1.

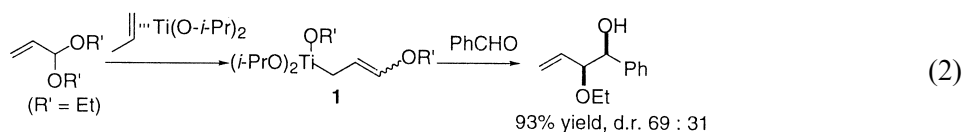
* Corresponding author.

The regio- and diastereoselective addition of α -alkoxyallylic anions to chiral imines seems to afford a straightforward method for synthesizing chiral 1-vinyl-2-amino alcohols. However, no report has appeared so far even for the reaction with an achiral imine.³ Herein, we report that this type of transformation can be attained by using (alkoxyallyl)titaniums **1**, thus opening up an efficient entry to optically active 1-vinyl-2-amino alcohol derivatives with *syn*-stereochemistry.

Recently, we have reported an efficient method for generating allyltitanium compounds by the reaction of allylic alcohol derivatives with a divalent titanium reagent (η^2 -propene)Ti(O-*i*-Pr)₂ generated in situ from Ti(O-*i*-Pr)₄ and 2 equiv. of *i*-PrMgCl, and their stereoselective addition reaction with carbonyl compounds and imines.^{4,5} During these studies, as shown in Eq. (1), we reported that the crotyltitanium complex thus prepared reacts with chiral imines **2**, prepared from aldehydes and optically active 1-phenylethylamine, to afford Cram-*syn* addition products highly predominantly,^{4b} where the reaction may proceed via a six-membered chair-like transition structure **A** which is based on the extended Cram's model proposed by Yamamoto.⁶



Quite recently, we found that (γ -alkoxyallyl)-titaniums **1** can be prepared from (η^2 -propene)-Ti(O-*i*-Pr)₂ and acrolein dialkyl acetal and that their reaction with carbonyl compounds proceeds regiospecifically to afford 1,2-diol derivatives with a diastereomeric ratio of 69:31, where the *syn*-isomer is major, as shown in Eq. (2).^{4h} With these results in hand, we anticipated that the reaction of **1** with **2** might open up an efficient entry to optically active 1-vinyl-2-amino alcohols.



The results of the reaction of **1** with **2** (Eq. (3)) are summarized in Table 1.⁷ Allyltitanium complex **1** prepared from acrolein dibenzyl⁸ or diethyl acetal reacts readily with methylimine **2a**, primary alkylimines **2b**, **2c** and **2d** to afford the corresponding 1-vinyl-2-amino alcohol derivatives regiospecifically in good yields; however, secondary alkylimine **2e** and arylimine **2f** scarcely react presumably due to their steric requirement. Although four diastereomeric products are possible for the reaction of **1** with **2**, to our satisfaction, 1-vinyl-2-amino alcohol derivative **3** having an anti-Cram-*syn* structure is produced, without exception, in a synthetically useful selectivity of more than 80% ds (Eq. (3) and Table 1).⁹ Moreover, the major product **3**, except for **3a**, can be readily separated from other diastereomers by column chromatography: thus pure **3** can be isolated in good yield (Table 1).

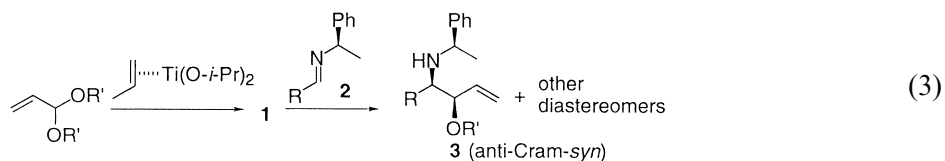


Table 1
Reaction of (γ -alkoxyallyl)titaniums **1** with chiral imines **2** shown in Eq. (3)

Acetal	2	Products		
		Total Yield, % ^a	D.r., 3 : others ^b	Isolated Yield of 3, %
R'=Bn	a : R=Me	72	83 : 17	3a ^c ^d
	b : R=Et	69	80 : 20	3b ^e 55
	c : R= <i>n</i> -C ₇ H ₁₅	76	80 : 20	3c ^e 58
	d : R=(CH ₃) ₂ CHCH ₂	60	84 : 16	3d ^f 48
	e : R=(CH ₃)CH	<10 ^g	-	-
	f : R=Ph	<5 ^g	-	-
R'=Et	2b	70	86 : 14	3b(R'=Et) ^e 59

^aIsolated yield of the resulting 1-vinyl-2-aminoalka-1-yl ethers. ^bDetermined by ¹H NMR analysis of the crude mixture. ^cStereochemistry was confirmed by converting to the known compound, 4-methyl-5-ethyl-2-oxazolidone. See footnote.[†] ^dOther isomers could not be separated by column chromatography on silica gel. ^eStereochemistry was assigned in analogy with compounds **3a** and **3d**. ^fStereochemistry was confirmed by converting to the known compound, 4-(2-hydroxy)ethyl-5-(2-methyl)propyl-2-oxazolidone. See Scheme 2. ^g¹H NMR analysis.

Since both enantiomers of **2** are readily available and the auxiliary group is easily removed, the present finding opens an easy and practical route to both enantiomers of *syn*-1-vinyl-2-amino alcohol derivatives. Noteworthy here is the fact that **3** has an anti-Cram-*syn* structure, and not Cram-*syn*, which was the structure of the major product for the reaction of Eq. (1). Predominant production of **3** can be explained by assuming that allyltitaniums **1** may exist as its *Z*-form **B** which is stabilized by the chelation between the alkoxy group and the titanium,¹⁰ and the reaction proceeds via an open-chain transition state **C**¹¹ or, alternatively, via a six-membered boat-like transition structure **D**¹² (Fig. 1).

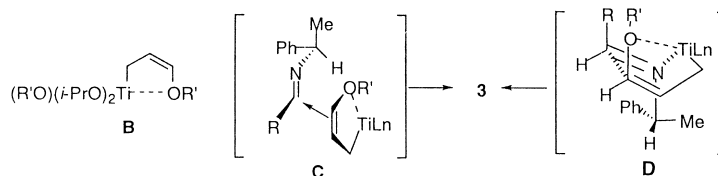
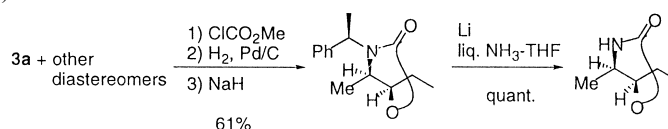


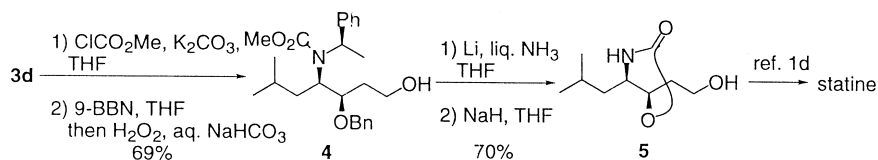
Figure 1.

The compound **3d** thus obtained was converted to 4-(2-hydroxy)ethyl-5-(2-methyl)propyl-2-oxazolidone (**5**),^{1b,d} the known synthetic precursor of statine which is a key element of pepstatin, a naturally occurring aspartic protease inhibitor, as shown in Scheme 2. The product **3d**, after protection of the amino group as its methyl carbamate, was successively treated with 9-BBN and

[†] The stereochemistry of **3a** was confirmed by converting to the known compound, 4-methyl-5-ethyl-2-oxazolidone, by reaction sequences shown below. The absolute configuration was confirmed to be *R,R* by comparing its [α]_D value with that reported for the (*S,S*)-isomer.¹³



H₂O₂/NaHCO₃ to afford primary alcohol **4** in 69% yield. The compound **4** was then converted to **5** in 70% yield by debenzylolation under Birch reduction conditions and the following cyclization using NaH in THF. Spectroscopic data of **5** thus obtained was in good agreement with those reported in the literature^{1b} and its absolute configuration was confirmed to be *R,R* based on its $[\alpha]_D$ value ($[\alpha]_D^{25} +73.2$ (*c* 0.531, CHCl₃), lit.^{1b} for (*S,S*)-**5**: $[\alpha]_D^{20} -75.2$ (*c* 1.76, CHCl₃)).



Scheme 2.

In summary, we have developed an efficient method for preparing optically active *syn*-1-vinyl-2-amino alcohol derivatives **3** from γ -alkoxy allyltitaniums **1** and chiral imines **2**. Since **1** is easy to prepare from readily available and inexpensive starting materials, and both enantiomers of **2** are readily accessible, the reaction is highly practical and will find applications in organic synthesis such as the preparation of α -hydroxy- β -amino- and β -hydroxy- γ -amino acids.

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- Typical reaction procedure: To a solution of acrolein dibenzyl acetal (254 mg, 1.9 mmol) and Ti(O-*i*-Pr)₄ (675 μ L, 2.28 mmol) in diethyl ether (14 mL) was added *i*-PrMgCl (4.38 mL, 1.04 M in ether, 4.56 mmol) at -50°C . The resulting mixture was stirred for 1.5 h at -50 to -40°C . To this was added imine **2b** (161 mg, 1.0 mmol) at -40°C . The resulting mixture was allowed to warm to room temperature over 8 h. After addition of aq. sat. NaHCO₃ (0.5 mL), NaF (1.2 g) and Celite (1.2 g), the mixture was filtered through a pad of Celite. The filtrate was

concentrated in vacuo and passed through a short silica gel column to give a mixture of adducts (270 mg) in 69% total yield. Pure **3b** (169 mg) was isolated in 55% yield by column chromatography on silica gel.

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