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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

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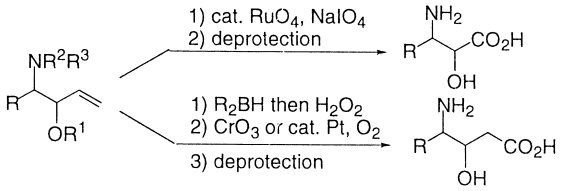
Abstract

(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.

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.

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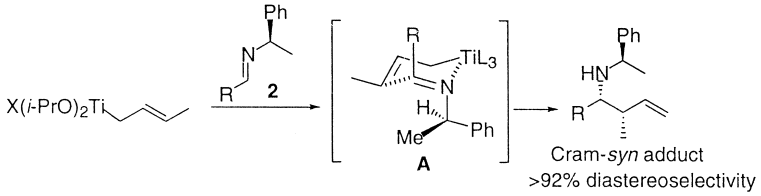
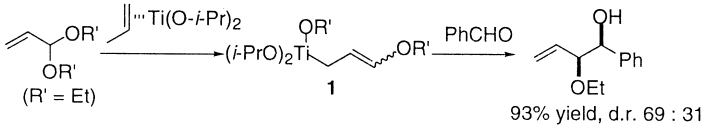
The regio- and diastereoselective addition of α-alkoxyallylic anions to chiral imines seems to afford a straightforward method for synthesizing chiral 1-vinyl-2-amino alcohols. However, no report has appeared so far even for the reaction with an achiral imine.[3] Herein, we report that this type of transformation 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]



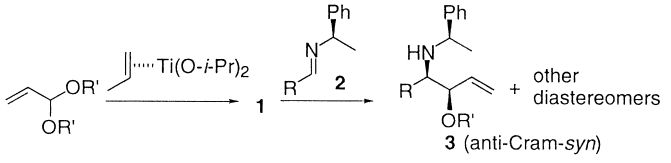
(1)

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.



(2)

The results of the reaction of **1** with **2** (Eq. (3)) are summarized in Table 1.[7] Allyltitanium complex **1** prepared from acrolein dibenzyl[8] 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).



(3)

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=*n*-C_7H_{15}	76	80 : 20	**3c**[e]	58
	d : R=$(CH_3)_2CHCH_2$	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

[a]Isolated yield of the resulting 1-vinyl-2-aminoalka-1-yl ethers. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Stereochemistry was confirmed by converting to the known compound, 4-methyl-5-ethyl-2-oxazolidone. See footnote.† [d]Other isomers could not be separated by column chromatography on silica gel. [e]Stereochemistry was assigned in anology with compounds **3a** and **3d**. [f]Stereochemistry was confirmed by converting to the known compound, 4-(2-hydroxy)ethyl-5-(2-methyl)propyl-2-oxazolidone. See Scheme 2. [g]^{1}H 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).

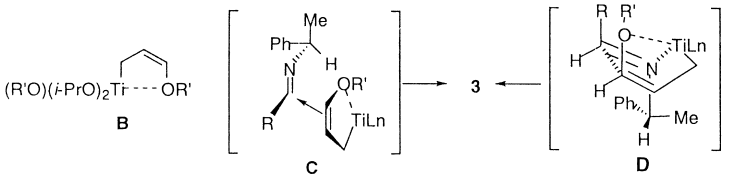
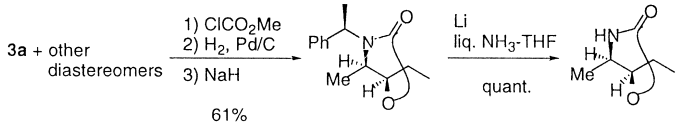


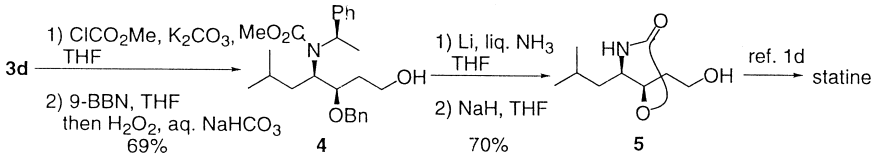
Figure 1.

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 $[\alpha]_D$ value with that reported for the (*S,S*)-isomer.[13]



$H_2O_2/NaHCO_3$ to afford primary alcohol **4** in 69% yield. The compound **4** was then converted to **5** in 70% yield by debenzylation 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, $CHCl_3$), lit.[1b] for (*S*,*S*)-**5**: $[\alpha]_D^{20}$ –75.2 (*c* 1.76, $CHCl_3$)).



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.

References

1. (a) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-J.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (b) Shinozaki, K.; Mizuno, K.; Oda, H.; Masaki, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1737. (c) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677. (d) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150. (e) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360. See also Ref 3a.
2. Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman: London, 1985; pp. 55–138.
3. The Lewis acid mediated stereoselective addition reactions of γ-alkoxyallylic stannanes with *N*-acyliminium intermediates providing 1-alkenyl-2-amino alcohol derivatives have been reported: (a) Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1311. (b) Marshall, J. A.; Gill, K.; Seletsky, B. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 953. Intramolecular cyclization of chiral imines having γ-alkoxyallylstannyl moiety in the presence of Lewis acid affording α-vinyl-β-amino cyclic ethers has been reported: (c) Park, J.-Y.; Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4901.
4. (a) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (b) Gao, Y.; Sato, F. *J. Org. Chem.* **1995**, *60*, 8136. (c) Kasatkin, A.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2848. (d) Hikichi, S.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 2867. (e) Teng, X.; Kasatkin, A.; Kawanaka, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8977. (f) Teng, X.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 6927. (g) Matsuda, S.; An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7513. (h) Teng, X.; Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916.
5. Reviews for synthetic reactions mediated by (η^2-propene)Ti(O-*i*-Pr)$_2$: (a) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511. (b) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. (c) Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 424.
6. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
7. Typical reaction procedure: To a solution of acrolein dibenzyl acetal (254 mg, 1.9 mmol) and Ti(O-*i*-Pr)$_4$ (675 μL, 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. $NaHCO_3$ (0.5 mL), NaF (1.2 g) and Celite (1.2 g), the mixture was filtered though 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.
8. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett*. **1980**, *21*, 1357.
9. Although it seemed that the reactions using **1** derived from the diethyl acetal would give somewhat better diastereoselectivity as observed in the reaction with **2b**, we mainly carried out the reaction of **1** derived from the dibenzyl acetal because the benzyl group of the resulting products **3** can be easily deprotected.
10. Yamamoto, Y.; Nishii, S. *J. Org. Chem*. **1988**, *53*, 3597. Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett*. **1992**, *33*, 7873.
11. Hallett, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun*. **1995**, 657.
12. Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc*. **1986**, *108*, 7778.
13. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett*. **1987**, *28*, 6331.