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ON THE STEREOCHEMICAL COURSE OF VINYLOXYBORANE-IMINE CONDENSATION -THE STEREOSELECTIVE FORMATION OF THREO β-AMINO ACID DERIVATIVES-

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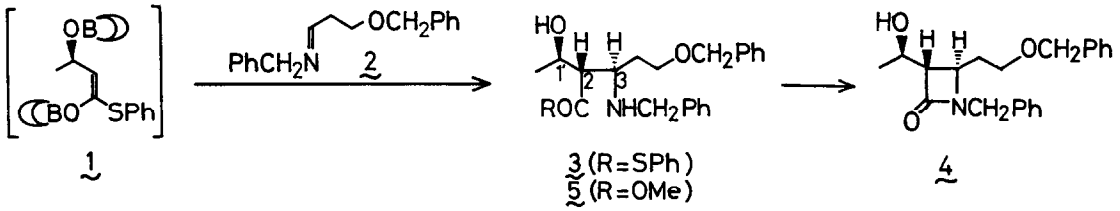
Summary: While reaction of Z(O)[1]-vinyloxyboranes with aldehydes gives erythro aldols highly selectively, it has been found that condensation of Z(O)-vinyloxyboranes with imines provides threo β-amino acid derivatives in a highly selective manner.

The condensation of esters and imines to afford β-lactams was first reported by Gilman and Speeter in 1943.[2] Since this report, considerable attention has been given to the development and utilization of this β-lactam forming reaction.[3] Most notably, this ester-imine condensation route to β-lactams has been recently applied to the synthesis of carbapenem antibiotics. Among these studies, several groups reported that lithium enolates of 3-hydroxybutanoates, which are easily available in an optically active form, reacted with some imines to afford β-lactams in a one step process.[3b,4] However, unfortunately in these cases the stereoselectivity (cis β-lactam selectivity) was undesirable for the synthesis of thienamycin and related antibiotics. On the contrast of these findings, we found that the reaction of the boron enolate **1** derived from 3(R)-hydroxybutyric acid with the imine **2** and following cyclization afforded the stereochemically desired β-lactam **4** in ca. 90% selectivity.[5] We became interested in the difference of stereoselectivity between boron enolates and lithium ones, and describe here some features of the stereoselectivity in vinyloxyborane-imine condensation reaction.

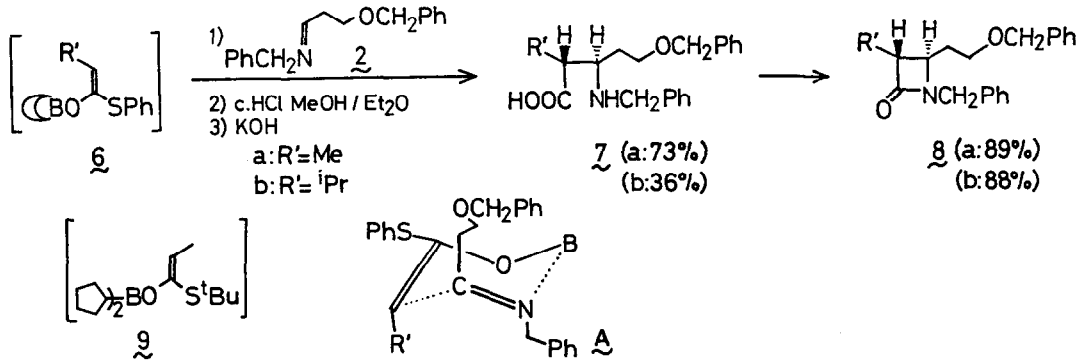


1 **3** (R=SPh), **5** (R=OMe), **4**

In order to explain the stereochemical course rationally [3(R)-hydroxybutyric acid→**4**] in terms of the recent general idea of aldol condensations,[6] we initially surmised that epimerization at C-2 might occur at the β-lactam cyclization stage.[5] Therefore, first of all we investigated the likely epimerization process in detail. The condensation product **3** was converted to the methyl ester **5** by treatment with sodium methoxide in CH_3OD. No deuterium incorporation at C-2 in **5** was observed by means of ^1H NMR analysis. Then, the methyl ester **5** was further subjected to a Grignard-mediated cyclization, in which no epimerization was observed in a synthesis of the cis carbapenem (carpetimycin A),[7] giving the β-lactam **4** and its stereoisomers in the same ratio as we previously reported.[5] These observations indicate strongly that the stereoselectivity in the vinyloxyborane-imine condensation is reflected in the stereochemistry of the major isomer **4** obtained after β-lactam cyclization.

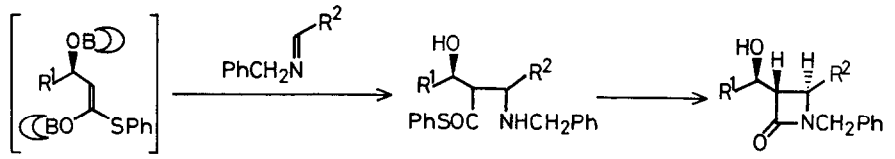
In the above-mentioned condensation reaction, two types of stereoselections took place at the same time. One between C-2 and C-3 corresponds to erythro-threo selectivity in well-known aldol condensations.[6] If chemistry of aldol condensations can be extended directly to vinyloxyborane-imine condensations, erythro selectivity leading to cis β-lactams should be observed because the stereochemistry of **1** should be assigned the Z(O)[1]-vinyloxyborane on the basis of the report by Masamune.[8] Threo selectivity leading to trans β-lactams observed in our case suggested the possibility of E(O)[1]-geometry of **1** or the different transition state from the case of aldol condensations. Therefore, relationship between boron enolate geometry and erythro-threo selectivity was next examined carefully.

The Z(O)-vinyloxyborane **6a**, which was reported to give erythro selectivity in aldol condensations,[8c] was subjected to the condensation with the imine **2**, affording the β-amino acid **7a** in 73% yield after hydrolytic work-up.[9] Cyclization [Ph_3P-$(PyS)_2$ in CH_3CN][10] of thus obtained β-amino acid **7a** provided the trans β-lactam **8a** selectively (threo selectivity 6:1). It strongly suggested that the stereoselection was occurred via the different transition state from that of aldol condensations. The vinyloxyborane **6b** was also found to afford the trans β-lactam **8b** in a highly selective manner (9:1). On the other hand, reaction of the E(O)-vinyloxyborane **9**, which gave high threo selectivity in aldol condensations,[8a] with the imine also afforded the threo isomer[9] slightly predominantly (2:1). These results are quite complex to imagine a general transition state model of vinyloxyborane-imine condensations. However, only in the case of the Z(O)-vinyloxyborane,[11] we can say that the transition state like **A** in which $CH_2CH_2OCH_2Ph$ group is located at axial position plays an important role to give high threo selectivity. This transition state (**A**) might be rationalized by considering the stereoelectronic effect of the imino group.[12] Although the similar transition state model has been already proposed by Yamamoto in the reaction of allylic organometallic compounds with imines,[12] and also by Hart in erythro-selective lithium E(OLi)-enolate-imine condensations,[3b,13] the present reaction offers a new general method for the stereoselective synthesis of threo β-amino acid derivatives.[14]



Next, with a view to show broader generality of this stereoselective condensation reaction, we carried out a couple of reactions using 3(R)-hydroxybutyric acid. The result are summarized in Table I. The condensation of boron enolates with imines except sterically hindered ones proceeded in moderate to good yields to give β-aminothiol esters, which were converted to β-lactams by a sequence of hydrolysis and cyclization . As expected, desired stereoisomers were produced with 80-90% selectivity in every case, showing broader generality of threo selective vinyloxyborane-imine condensations.

Table I



run	R^1	R^2	condensation y.	cyclization y.	selectivity
1	Me	OCH_2Ph	36%	72%	88%[a]
2	Me	OCH_2Ph	--	--	
3	Me	Ph	43%	43%	92%[b]
4	Me	Ph	--	--	
5	Me	TMS*	55%	76%	89%[c] (80%, 93%)[b,15]
6	Et	TMS*	49%	79%	77%[b]

* TMS group was removed at the hydrolysis step.

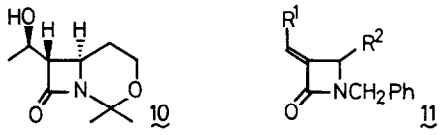
The stereoselectivity was determined as follows.

a. The isomers were converted to their TBDMS ethers and separated on a silica gel column chromatography.

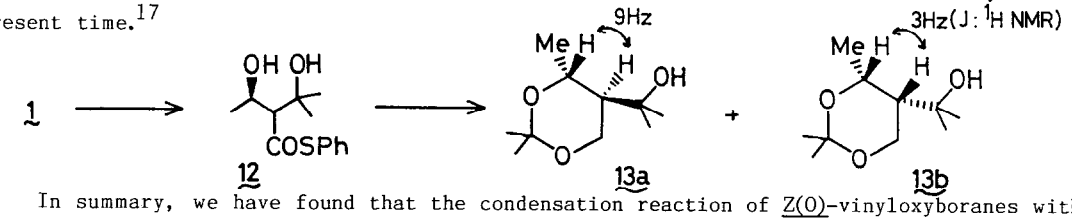
b. The cis and trans isomers were separated and the trans isomers were analyzed by 90MHz ^{1}H NMR.

c. The isomers were analyzed by 400MHz ^{1}H NMR.

The stereochemistry of major products was determined by converting to the bicyclic β-lactam **10**[16](run 1,5) or converting to ene lactams **11**[16](run 3,6).



Finally we wish to have a short comment concerning another stereoselectivity; that is, selection between C-1' and C-2. In an attempt to show generality of the stereoselection between C-1' and C-2, reaction of the vinyloxyborane **1** with acetone was carried out, giving **12** in 57% yield. The condensed product **12** was then transformed to the acetonide **13** in 3 steps [1) NaOMe in MeOH, 2) LAH in Et_2O, 3) dimethoxypropane, cat. TsOH in acetone.] (**13a:13b**=7.5:1). The result showed that the stereoselectivity was completely different from the case of imines. This phenomenon is extremely difficult to be illustrated clearly at the present time.[17]



In summary, we have found that the condensation reaction of Z(O)-vinyloxyboranes with imines proceeds in a threo selective manner, and provides a new method for the preparation of threo β-amino acid derivatives.

Acknowledgement. We are grateful to Kanegafuchi Chemical Ind. Co., Ltd. for providing us with 3(R)-hydroxybutyric acid and 3(R)-hydroxyvaleric acid.

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1) These descriptors proposed by Masamune are used for the unity of enolate geometry in this paper. Z(O) indicates that top priority is conferred on the element in the bracket in this special case, see: Masamune, S.; Kaiho, T.; Garvey, D.S. J. Am. Chem. Soc. **1982**, 104, 5521.

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6) For a review of the aldol reaction: Heathcock, C.H. "Asymmetric Synthesis," Vol 3. Morrison, D.J. Ed.; Academic Press: London, 1984; pp111-212.

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9) In these cases 9-BBN or dicyclopentylboron moiety could not be removed by oxidative work-up. So, acidic hydrolysis was used for N-O bond cleavage followed by basic hydrolysis of resulting ester.

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11) The structures of **1** and **6b** were tentatively assigned as Z(O) according to Masamune's chemistry. See reference 8.

12) a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. J. Am. Chem. Soc. **1984**, 106, 5031. b) Idem. J. Org. Chem. **1985**, 50, 3115.

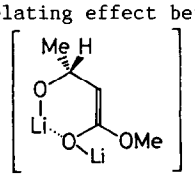
13) The reason why the erythro product was mainly produced from **i**[Z(OLi)] is unclear at present. See reference 3, 4.

14) For other β-amino acid syntheses employing enolate-imine condensations: a) Ohtsuka, M; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. Tetrahedron Lett. **1981**, 22, 2109. b) Ojima, I.; Inaba, S.; Yoshida, K. ibid. **1977**, 3643. c) Ikeda, K.; Achiwa, K.; Sekiya, M. ibid. **1983**, 24, 913. d) Idem. ibid. **1983**, 24, 4707. e) Okano, K.; Morimoto, T.; Sekiya, M. J. Chem. Soc., Chem. Commun. **1984**, 883. f) Colvin, E.W.; McGarry, D.G. ibid. **1985**, 539.

15) Selectivity changed slightly in every experiment. In one case rather low selectivity (ca. 80%) was observed. The reason is not clear at present.

16) Bouffard, F.A.; Johnston, D.B.R.; Christensen, B.G. J. Org. Chem. **1980**, 45, 1130.

17) It seems likely that the reaction of vinyloxyboranes with carbonyl compounds proceeds via the well-known transition state (**B** or **C**). On the other hand, it appears that the condensation with imines proceeds via the transition state **D** presumably owing to the chelating effect between a boron and an imine functionality.



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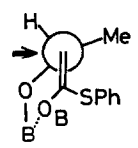
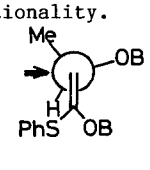
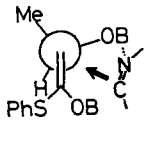


B (chelation)



C (allylic strain)



D ?