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Novel Diastereo- and Enantioselectivities in the Chiral Oxazaborolidinone-Promoted Asymmetric Aldol Reaction of Highly Hindered Aldehydes Having a Quaternary Carbon at α Position and Limitations Observed on Catalyst (Promoter) Control[1]

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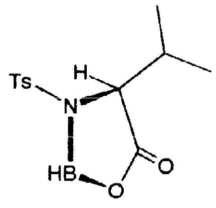
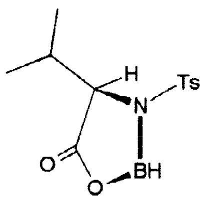
Abstract: The chiral oxazaborolidinone (**1** and **2**) -promoted asymmetric aldol reaction of pivalaldehyde with silyl nucleophile **3** resulted in excellent *syn* selectivity of the corresponding aldol with 96% ee. The catalyst (promoter) control was examined in the reaction with highly hindered aldehydes, **4** and **9**. The reaction of **4** in the presence of **2** gave almost enantiopure aldol **7** (>50 : 1) with *syn* selectivity (4 : 1) in good yield. © 1998 Elsevier Science Ltd. All rights reserved.

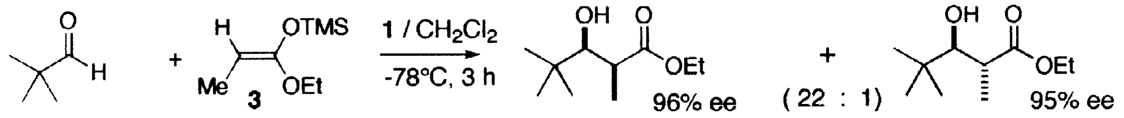
During the development of the chiral oxazaborolidinone (**1** and **2**)-promoted asymmetric aldol reaction, we have reported an interesting "catalyst (promoter) control" of reaction stereochemistry,[2] in which the new stereogenic center is definitely created by the effect of the stereochemistry of the catalyst (promoter) almost independent of that of the substrate aldehyde even in the presence of an α-chiral center in the aldehyde.[3] This catalyst (promoter) control has proved to be remarkably straightforward for achieving enantioselective acyclic stereoselection.[4] When our attention was focused on aldehydes having a formyl group adjacent to a quaternary carbon in searching for the scope and the limitations of the catalyst control, we found novel enhanced diastereo- and enantioselectivities on the catalyst control in our chiral oxazaborolidinone-promoted asymmetric aldol reaction. We disclose herein crucial results bound with the effectiveness in constructing complex acyclic sequences involving marine macrolides, e.g., bryostatin, aplasmomycin, epothilone, and actiphycin.



(*S*)-Oxazaborolidinone **1**



(*R*)-Oxazaborolidinone **2**



(1)

The first result is concerned with an unexpected switching of diastereoselectivity along with very high enantioselectivity in the reaction with pivalaldehyde. We have already reported that the asymmetric aldol reaction

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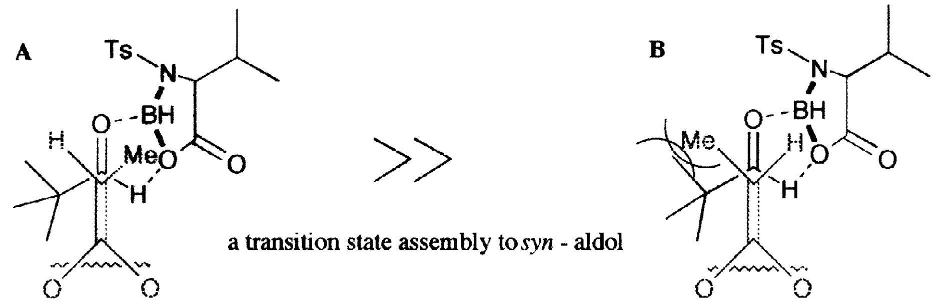
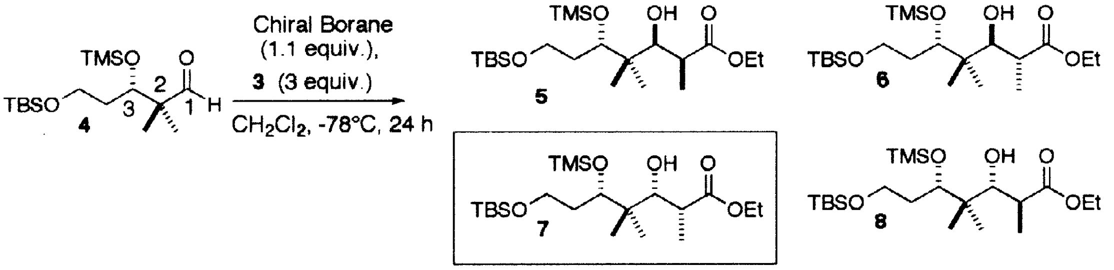
of a variety of aldehydes with a silyl nucleophile derived from phenyl propionate (*E*-isomer 98%) resulted in moderate *anti*-diastereoselectivity with relatively low enantioselectivity.[6] Contrary to the generality, when we used pivalaldehyde and silyl nucleophile **3** (***E*/*Z*** = 85 : 15), the *syn* isomer was obtained as a major product (22 : 1) with 96% ee, as shown in eq. 1.[7] The result is really surprising. This unexpected switching of diastereoselectivity observed in the reaction of the bulky aldehyde can be rationally explained by merging Corey's hydrogen bond model between the aldehyde hydrogen and the catalyst borane-ring oxygen[8] and Yamamoto's extended transition model[9] as **A** depicted in Fig. 1 where **B** is destabilized by the gauche interaction between the methyl and *tert*-butyl groups.[10]

Fig. 1



a transition state assembly to *syn* - aldol



(2)

Table 1 Chiral Oxazaborolidinone-Promoted Aldol Reaction with Aldehyde **4**

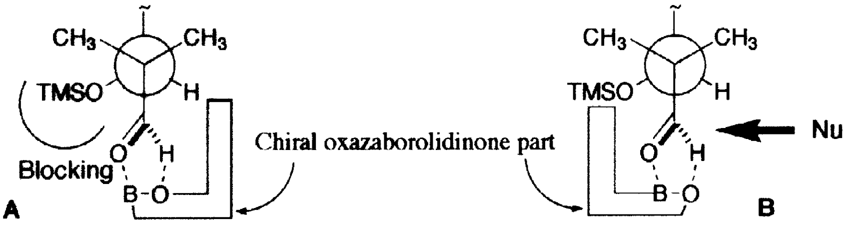
Chiral Borane	% Yield	*syn* / *anti*[a]	*syn*[b] **7** / **5**	*anti*[b] **8** / **6**
1 (L-Valine)	34	2:1	7:5	5:3
2 (D-Valine)	87	4:1	>50:1	>50:1

a) The *syn/anti* ratio (**5** + **7** / **6** + **8**) is corresponding to the diastereoselectivity of the reaction. b) The each *syn* (**7** / **5**) and *anti* (**8** / **6**) ratio is corresponding to the enantioselectivity of the reaction.

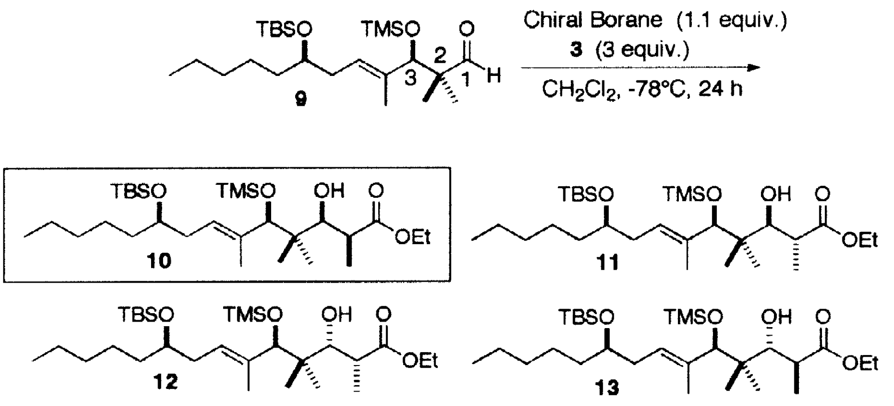
Second, we deal with important limitations observed on the catalyst control in the reactions with highly sterically hindered aldehydes involving a chiral hydroxy function at the β-position. The aldehydes, **4** and **9**, were selected as models of such complex bulky aldehydes. In the presence of a stoichiometric amount of chiral borane, **1** and **2**, aldehyde **4** underwent the aldol condensation with 3 equiv. of **3** at -78°C in 24 h, as shown in eq. 2.[11] The results are summarized in Table 1. When chiral borane **1** was used, the diastereo- and enantioselectities were less satisfactory. However, by using chiral borane **2**, derived from D-valine, the reaction proceeded more smoothly to give the corresponding aldols with moderate *syn* selectivity (**7** is predominant) in 87% yield. ***Surprisingly, each isomer obtained was almost enantiomerically single.*** The spatial orientation of the siloxy group at C-3 presumably fixed by the introduction of two methyl groups at C-2 affects the whole conformation of the aldehyde and when the chiral borane coordinates to the aldehyde, an adequate fitness between the stereocenters of the catalyst and the substrate (at C-3) might be requested for the stereochemical outcome expected from the catalyst control. The reaction with **1** (from L-valine) lost the catalyst control because of the stereochemically mismatching interactions. However, even in such a complex case, the reaction with **2** gave the products with the stereochemistry at

C-3 which is the same as that expected from the catalyst control. An effective approach of the silyl nucleophile may take place *via* a path like **B** in Fig.2.[12]

Fig. 2



Next, we shifted our attention to the reaction of more complex aldehyde **9**, in which the arrangement of the trimethylsiloxy group is more compressed by an allylic strain from the back olefin (eq. 3).[11] The enhanced steric



(3)

Table **2** Chiral Oxazaborolidinone-Promoted Aldol Reaction with Aldehyde **9**

Chiral Borane	% Yield	*syn* / *anti* [a]	*syn* [b] **10** /**12**	*anti* [b] **11** /**13**
1 (L-Valine)	92	10:1	12:1	10:1
2 (D-Valine)	54	4.5:1	4:1	1.5 :1

a) The *syn/anti* ratio (**10** + **12** /**11** + **13**) is corresponding to the diastereoselectivity of the reaction. b) The each *syn* (**10** / **12**) and *anti* (**11** / **13**) ratio is corresponding to the enantioselectivity of the reaction.

bulkiness slightly depressed both diastereo- and enantioselectivities, as summarized in Table 2. However, chiral borane **1** underwent the condensation to give the aldols with rather high *syn* selectivity (10 : 1) in 92% yield. The facial selectivity of each *syn* and *anti* isomer was still considerably high (>10 : 1). This result is also a case of the catalyst control; here the stereochemistry at C-3 of aldehyde **9** is reverse to that of aldehyde **4** so that the catalyst control appeared in the reaction with **1**, according to the same mutual stereochemical relationship, as shown in Tables 1 and 2.

The most impressive feature of this report is the finding of the limitations of the catalyst control in the chiral oxazaborolidinone-promoted asymmetric aldol reaction, which will allow us to use in safety the catalyst control for a variety of aldehydes in practical cases of synthesis. Further studies to develop this methodology in the synthesis of macrolides are underway in our laboratories.

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References and Notes

(1) Enantioselective Acyclic Stereoselection Under Catalyst Control 4. For part 3; see Kiyooka, S. -i.; Maeda, H. *Tetrahedron: Asymmetry*, **1997**, *8*, 3371 - 3374.

(2) (a) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis* ; Pergamon, Oxford, 1996.
(b) Kiyooka, S. -i. ***Development of a Chiral Lewis Acid-Promoted Asymmetric Aldol Reaction Using Oxazaborolidinone***, in ***Reviews on Heteroatom Chemistry***, **1997**, *17*, 245 - 270. The ***catalyst*** as a term in this paper involves the meaning of a promoter used in stoichiometric amounts. The chiral oxazaborolidinones, **1** and **2**, were used as a promoter in the reaction of bulkyl aldehydes although catalytic conditions are available for simple aldehydes by controlling the reaction conditions.

(3) (a) Kiyooka, S. -i.; Kira, H.; Hena, M. A. *Tetrahedron Lett.* **1996**, *37*, 2597 - 2600. (b) Kiyooka, S. -i.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A. *Ibid.* **1997**, *38*, 3553 - 3556.

(4) Kiyooka, S. -i.; Maeda, H. *Tetrahedron: Asymmetry*, **1997**, *8*, 3371 - 3374.

(5) (a) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741 - 750. (b) Corey, E. J.; Pan, B. -C.; Huo, D. H.; Deardrorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816 - 6818. (c) White, J. D.; Vedananda, T. R.; Kang, M.; Choudrhy, S. C. *Ibid.* **1986**, *108*, 8105 - 8107. (d) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D. -S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801 - 2803. (e) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Ibid.* **1997**, *36*, 166 - 168. (f) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Ibid.* **1997**, *36*, 523 - 524.

(6) Kiyooka, S. -i.; Kaneko, Y.; Kume, K. -i. *Tetrahedron Lett.* **1992**, *34*, 4927 - 4930.

(7) The structure of the *syn*- and *anti*-products was reconfirmed on the basis of NOE experiments of their acetonides derived from the aldol products.

(8) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351 - 4354.

(9) Ishihara, K.; Maruyama, T.; Mori, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483 - 3491.

(10) Gennari, C. *Selectivities in Lewis Acid Promoted Reactions*, Schinzer, D. Ed.: Kluwer Academic Publishers, Dordrecht, 1988; pp 53 - 71.

(11) Prolonged reaction time (> 20 h) is necessary to get acceptable yields along with the use of a stoichiometric amount of chiral oxazaborolidinones. The stereochemistry of all products was confirmed by using NOE experiments of the derived acetonides.
Aldol **7**: $[\alpha]^{D}_{24}$ -8.4 (c 0.48, $CHCl_3$). IR (neat): 3478, 1736, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.00 (s, 6H), 0.08 (s, 9H), 0.67 (s, 3H), 0.77 (s, 9H), 0.78 (s, 3H), 1.10 (d, 3H, J = 7.08), 1.13 (t, 3H, J = 7.08), 1.32 - 1.41 (m, 1H), 1.74-1.81 (m, 1H), 2.62 (dq, 1H, J = 5.36, 7.07), 2.83 (d, 1H, J = 3.90), 3.48 - 3.64 (m, 3H), 3.77 (dd 1H, J = 3.88, 5.12), 3.99 (q, 2H, J = 7.07). ^{13}C NMR (CDCl3, 100 MHz): δ (ppm) -5.8, 0.2, 12.9, 13.5, 17.7, 19.0, 19.5, 25.4, 35.3, 41.0, 42.2, 59.8, 60.4, 74.5, 76.1, 176.5.
Aldol **10**: $[\alpha]^{D}_{24}$ +22 (c 0.60, $CHCl_3$). IR (neat): 3485, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.05 (s, 3H), 0.06 (s, 3H), 0.10 (s, 9H), 0.70 (s, 3H), 0.89 (s, 9H), 0.88 (t, 3H, J = 7.07), 0.92 (s, 3H), 1.23 (d, 3H, J = 7.07), 1.25 (d, 3H, J = 7.07), 1.22 - 1.41 (m, 8H), 1.59 (s, 3H), 2.18 (br. t, 2H, J = 6.83), 2.65 (dq, 1H, J = 6.59, 7.07), 3.67 - 3.73 (m, 1H), 3.71 (d, 1H, J = 1.71), 3.93 (dd, 1H, J = 1.71, 6.59), 3.99 (s, 1H), 4.12 (m, 2H), 5.38 (t, 1H, J = 6.83). ^{13}C NMR (CDCl3, 100 MHz): δ (ppm) -4.5, -4.3, 0.0, 13.8, 14.1, 14.2, 16.9, 18.12, 21.51, 22.7, 25.2, 26.0, 32.0, 35.6, 36.7, 41.7, 43.0, 60.3, 71.8, 77.7, 87.4, 126.4, 136.35, 176.8.

(12) The aldol reaction of the TBS-protected aldehyde no longer proceeds because of over steric bulkiness. The evidence supports the mechanistic explanation with Fig. 2.