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Catalyst Control in a Chiral Borane-Mediated Aldol Reaction. Both *syn*- and *anti*-Aldols in Almost Optically Pure State Obtained from One Racemic Aldehyde

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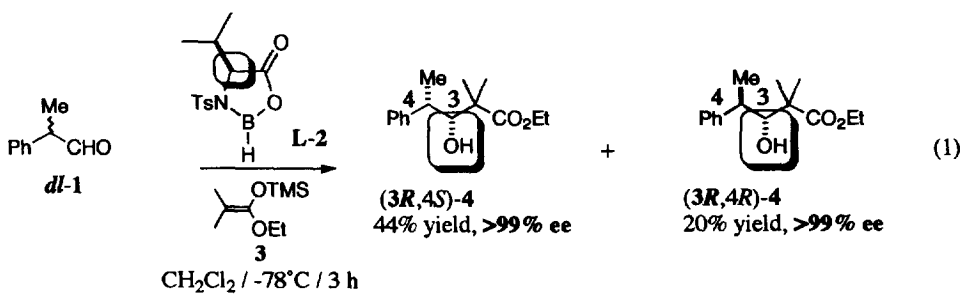
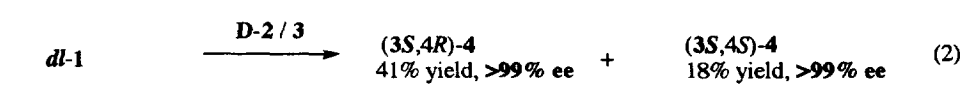
Abstract : **Chiral borane (L-2 and D-2)-mediated aldol reaction proceeded with chiral aldehydes (1, 5, and 9) in a manner of "catalyst control". Both enantiomers were obtained from one racemic aldehyde in almost optically pure state.** Copyright © 1996 Elsevier Science Ltd

Diastereofacial selection on α-chiral aldehydes has aroused interest widely for stereoselective construction of carbon-carbon bonds.[1] Stereochemical control in reactions involving α-chiral aldehydes has been generally explained by both "substrate control" and "reagent control".[2] These controls, however, are not discrete and occasionally work as "double stereodifferentiation".[3] An example has recently been reported in which reagent control completely overcame substrate control in an aldol reaction.[4] A third way of stereochemical control should be addressed to "catalyst control"[5] where the stereochemical environment of the catalyst mainly affects the stereochemical outcome of the reaction; this is especially remarkable in catalyst-promoted asymmetric reactions.





There have been dramatic developments in asymmetric Mukaiyama aldol reactions through the use of several kinds of chiral Lewis acids.[6] Our chiral borane-mediated aldol reaction using *N*-sulfonyl amino acid as a chiral ligand is one of them, which can be characterized by its simple experimental procedure accompanied with high chemical yield and excellent enantioselectivity.[6e,f, 7] The asymmetric aldol reaction with 1-(trimethylsiloxy)-1-ethoxy-2-methyl-2-propene (**3**) was utilized as a key reaction for constructing the quarternary carbon system contained in a natural product, ***calyculins***.[8] The success of this application is based upon the fact that the completely enantioselective outcome of the reaction is independent of the stereochemistry of the substrate. We further investigated the scope of "catalyst control" in the chiral borane-mediated aldol reaction using α-chiral aldehydes.

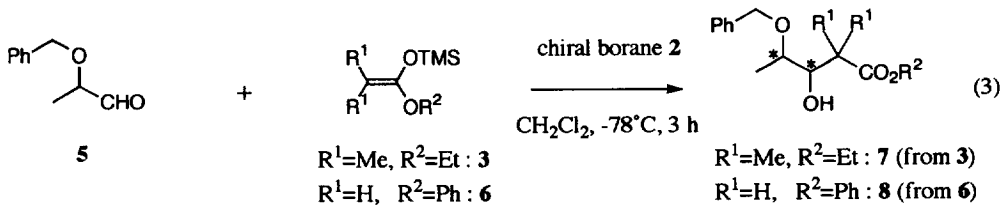


Table 1. Catalyst Control in Chiral Borane-Mediated Asymmetric Aldol Reactions with α-Benzyloxypropionaldehyde

Entry	Aldehyde	Silyl ketene acetal (chiral borane)	Aldol products[a] (% yield) % ee[b]	
1	***dl*-5**	**3** (L-2)	(3*S*,4*S*)-**7** (45) 93% ee	(3*S*,4*R*)-**7** (43) 93% ee
2	***dl*-5**	**3** (D-2)	(3*R*,4*R*)-**7** (47) 94% ee	(3*R*,4*S*)-**7** (40) 93% ee
3	***dl*-5**	**6** (L-2)	(3*S*,4*S*)-**8** (35) 80% ee	(3*S*,4*R*)-**8** (31) 66% ee
4	***S*-5**	**3** (L-2)	(3*S*,4*S*)-**7** (83) 94% ee	(3*S*,4*R*)-**7** (6)[c] 93% ee

[a] The relative stereochemistry of **7** was determined by NOE experiment of the cyclized derivatives from **7** (see ref **11**). The relative stereochemistry of **8** was determined on the basis of chelation control experiment with $SnCl_4$ (see ref **10**) where the *syn*- and *anti*-isomers could not be separated.

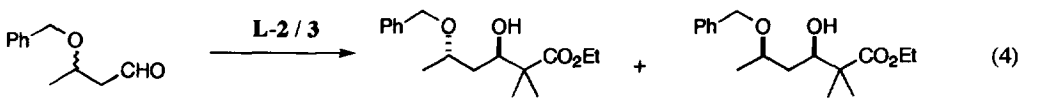
[b] The enantiomeric excess of **7** and **8** was determined by HPLC using DAICEL OD column.

[c] The minor isomer was obtained owing to the purity of the starting aldehyde.

2-Phenylpropanal (***dl*-1**) has frequently been employed as a reference aldehyde for judging the level of Cram and *anti*-Cram selectivity.[5, 9] Reaction of ***dl*-1** with **3** in the presence of one mole equivalent of $BF_3 \cdot OEt_2$ gave predominantly the Cram product (*syn*-isomer), (3***RS***,4***RS***)-**4**, in the ratio of 4 to 1. When to this aldehyde (***dl*-1**) was applied a chiral borane complex (**L-2**)(a stoichiometric amount), prepared *in situ* from *N*-*p*-toluenesulfonyl-(***S***)-valine and $BH_3 \cdot THF$ complex, as a promoter, a mixture was obtained consisting of *syn*- and *anti*-isomers in the ratio of 2 to 1 (eq. 1). *To our surprise, both aldols turned out to be completely optically pure*. The optical purity of **4** was determined by HPLC using DAICEL CHIRAL AD and OD columns. As shown in eq. 2, the reverse result also was obtained in the presence of **D-2**, prepared from (***R***)-valine. The fact that both pure enantiomers were derived from a racemic chiral aldehyde suggests that the reaction exclusively proceeded under catalyst control (*si* facial selectivity).

Next we turned to the aldehydes (**5** and **9**), acceptable for chelation with Lewis acid[10], in order to ascertain the catalyst control in the reactions (eqs. 3 and 4). A part of the results of the reaction with **5** is shown in Table 1. Reaction of ***dl*-5** with **3** in the presence of chiral borane resulted in formation of both *syn*- and *anti*-aldols in similar, satisfactory yields along with excellent high level of enantioselectivity. Obviously, this reaction also proceeds under catalyst control. We were able to obtain all four enantiomeric aldols from one racemic aldehyde in almost optically pure state by using chiral complexes **L-2** and **D-2** (entries 1 and 2). When optically active aldehyde (***S***)-**5** was used, the expected enantiomer could be obtained in the presence of chiral complex **L-2**, but along with a small amount of the counter isomer owing to the purity of the starting aldehyde (entry 4). Reaction of silyl ketene acetal **6** gave (3***R***,4***R***)- and (3***R***,4***S***)-**8** with considerably lower enantiomeric excess than that of **3**, but catalyst control still works (entry 3).

Reaction of **9** with **3** gave both *syn- and anti*-aldols in similar yields without any Cram selectivity (eq. 4). The relative stereochemistry of 1,3-diol system was determined on the basis of chelation control experiments (1,3-*anti* selectivity) with $SnCl_4$.[10] The optical purity of products was determined by ^{19}F NMR measurement of their MTPA esters prepared with (***R***)-(-)-methoxytrifluoromethylphenylacetyl chloride. The enantiomeric excess of *syn*-isomer was somewhat lower than that of *anti*-isomer but the catalyst control worked well ever in this 1,3-diol system.



(4)

9

(3***R***,5***S***)-**10**
46% yield, **98% ee**

(3***R***,5***R***)-**10**
42% yield, **82% ee**

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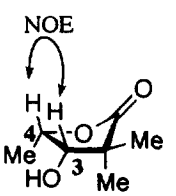
11. Hydrogenation of **7** with Pd-C gave γ-lactone **11** in 90% yield. A NOESY experiment of **11** derived from one of the diastereomers showed that the stereochemistry was (3*S*,4*S*)-configuration which corresponds to that of (3*S*,4*S*)-**7** (*syn*-aldol).



(3*S*,4*S*)-**11**

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