

# Process Development of a Key Building Block for Anti-AIDS Drugs by Organocatalyzed Enantioselective Direct Cross-Aldol Reaction

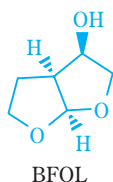
Sumitomo Chemical Co., Ltd.  
Fine Chemicals Research Laboratory  
Tetsuya IKEMOTO  
Yosuke WATANABE

We have been trying to apply environmentally benign organocatalysts to the synthesis of various kinds of pharmaceutical compounds. We herein report a practical synthesis of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol (BFOL), a key building block for HIV protease inhibitors. The route is based on an enantioselective proline catalyzed direct cross-aldol reaction between aldehydes.

This paper is translated from R&D Report, "SUMITOMO KAGAKU", vol. 2008-II.

## Introduction

Since List, Barbas, et al. reported a direct asymmetric cross-aldol reaction using proline in 2000<sup>1)</sup>, organocatalysis have attracted attention.<sup>2)-6)</sup> We have focused on organocatalysis from the beginning, and have been working on development of applications with efficient methods for synthesizing pharmaceutical products.<sup>7), 8)</sup> This time we have developed a practical production method for (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol (abbreviated as BFOL) (Fig. 1), which is a common intermediate for anti-AIDS drugs using a direct asymmetric cross-aldol reaction where L-proline, which is inexpensive and environmentally friendly, is the organocatalyst.<sup>9)</sup>



**Fig. 1** Chemical Structure of BFOL

## Research on Synthesizing the Anti-AIDS Drug Intermediate (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol

### 1. Course of development

Since around 2000 the (3*R*,3*aS*,6*aR*)-hexahydro-

furo[2,3-*b*]furan-3-yl group has frequently been seen as a building block for the next generation of HIV protease inhibitors,<sup>10)-14)</sup> and there has been interest in its characteristic structure. This intermediate has three asymmetric centers. It was presumed that synthesis would not be easy, and upon investigation, it was difficult to say whether the method for synthesis, which was not known at the time, was an industrial production method. Therefore, assuming that if it could be produced inexpensively on an industrial scale, it would give rise to great business potential, we started the research.

### 2. Introduction to known synthesis methods

When we first started the research, only methods (1), (2), and (5) were known, but after that there were reports of various other methods for synthesis, so in the following we will give an introduction to the synthesis methods that have been reported in academic papers up to now, including recent reports.

#### (1) Ghosh et al. method (i)<sup>15)</sup> (Fig. 2)

This is a kinetic optical resolution using an enzyme. Synthesis of the racemate is a comparatively short process, and this is a superior method for synthesis of small amounts, but it includes radical cyclization and ozone oxidation and is not suitable for synthesis in large volumes.

(2) Ghosh et al. method (ii)<sup>16</sup> (Fig. 3)

This is a chiral pool method that uses unnatural D-ethyl maleate as the starting material. In addition to the process being long, LDA, LiAlH<sub>4</sub> and other expensive reagents are used. Ozone oxidation is also included.

(3) Ghosh et al. method (iii)<sup>17</sup> (Fig. 4)

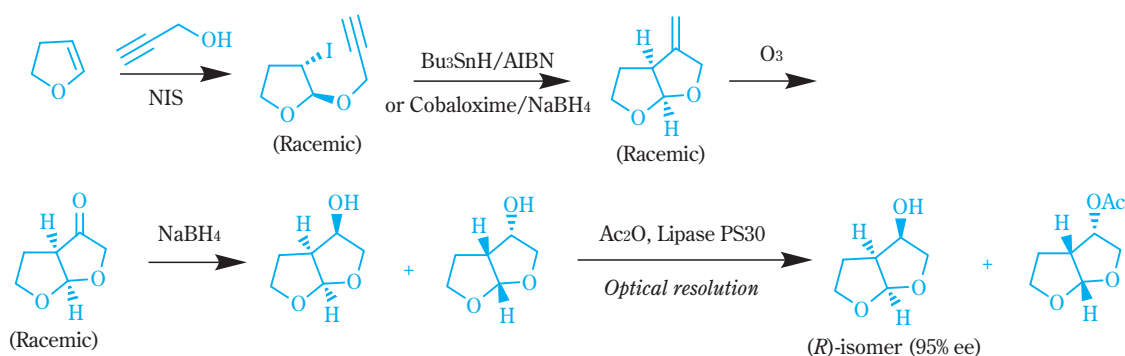
This is a method for synthesis via olefin metathesis using Grubbs' catalyst and an optical radical addition reaction (*S*)-1-(benzyloxy)-3-butene-2-ol obtained from a kinetic optical resolution using an enzyme as the raw

material. It is a production method that is interesting academically.

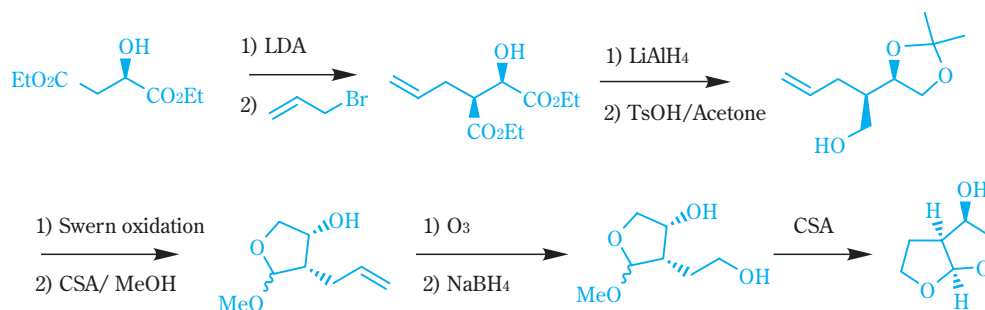
(4) Ghosh et al. method (iv)<sup>18</sup> (Fig. 5)

This is a method that uses a chiral auxiliary group and has a diastereoselective titanium aldol reaction as the key reaction.

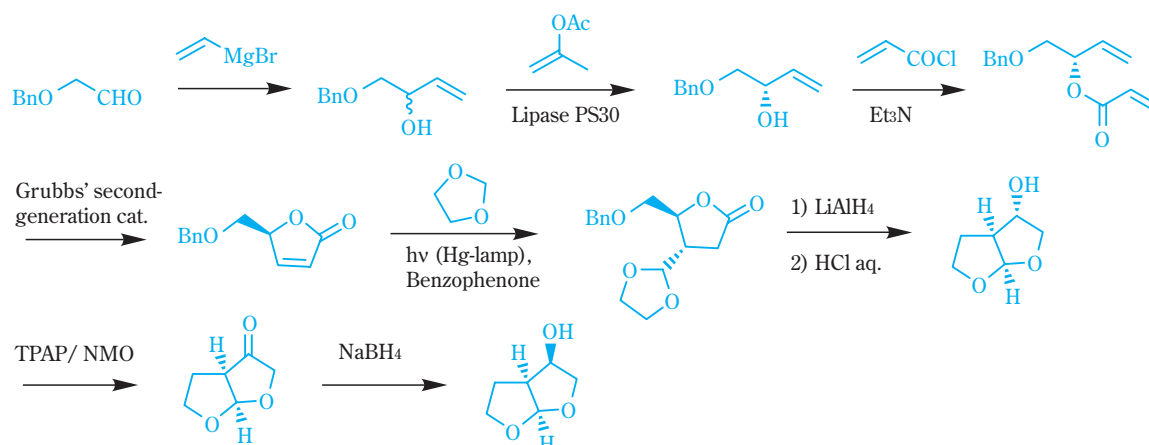
It includes Swern oxidation and ozone oxidation, and the chiral auxiliary group that is stoichiometrically required is expensive.



**Fig. 2** Synthetic method by Ghosh's group (i)



**Fig. 3** Synthetic method by Ghosh's group (ii)



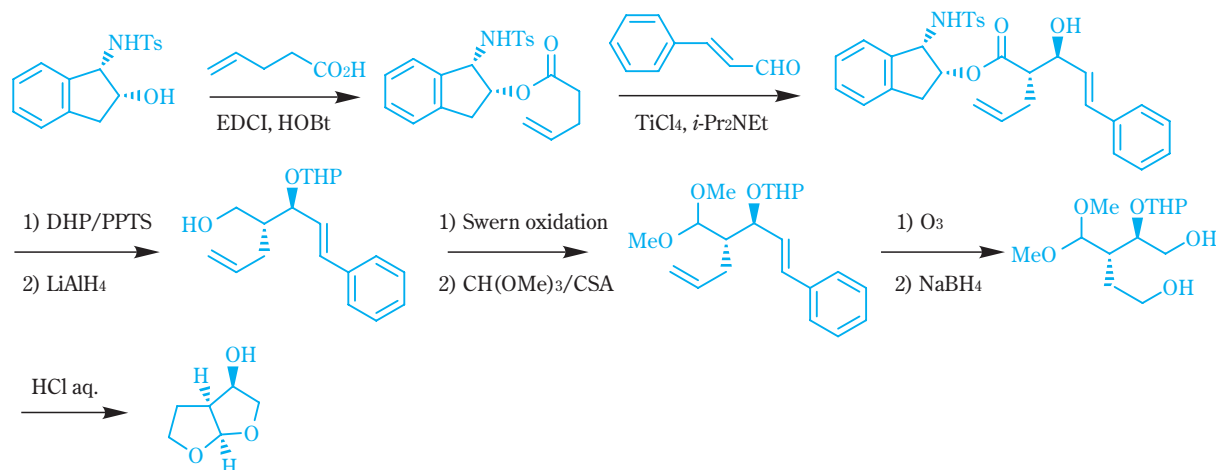
**Fig. 4** Synthetic method by Ghosh's group (iii)

(5) Uchiyama et al. method<sup>19</sup> (Fig. 6)

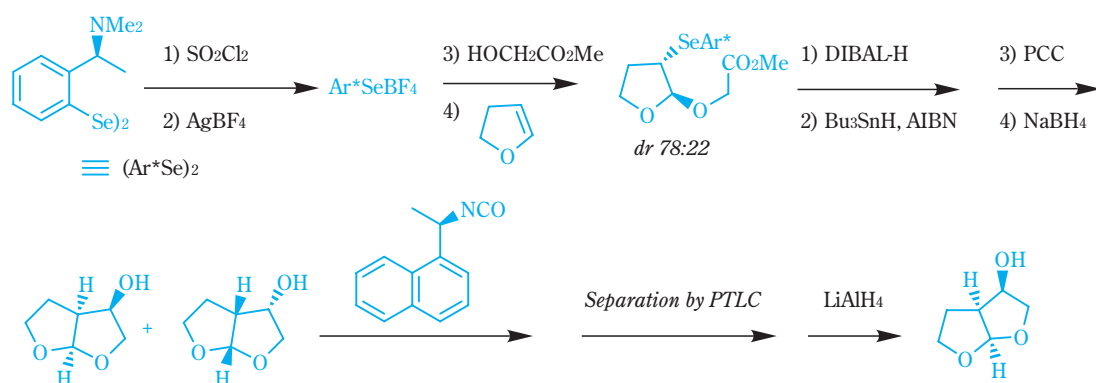
This is an academically interesting reaction, but it uses an organic selenium compound and is not suitable as an industrial method.

(6) Quaedflieg et al. method<sup>20</sup> (Fig. 7)

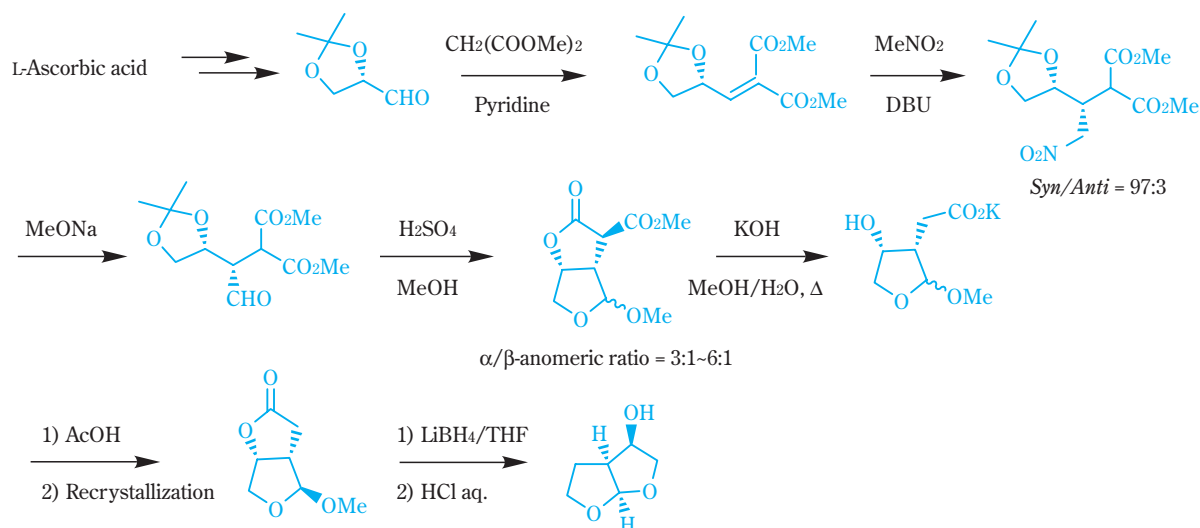
This is a chiral pool method that uses (*S*)-2,2-dimethyl-1,3-dioxolan-4-carbaldehyde, which can be derived from L-ascorbic acid, as the starting material.



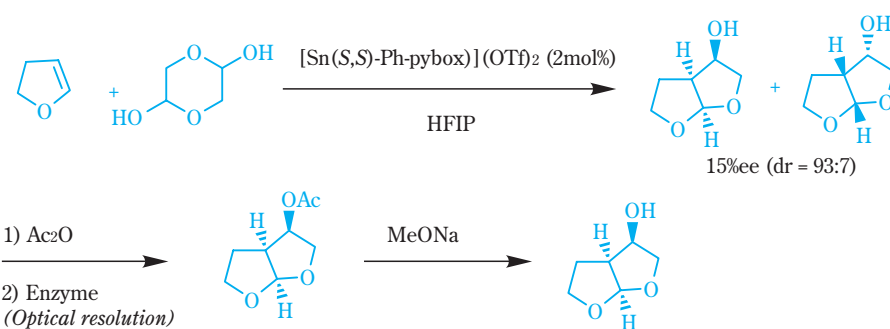
**Fig. 5** Synthetic method by Ghosh's group (iv)



**Fig. 6** Synthetic method by Uchiyama's group



**Fig. 7** Synthetic method by Quaedflieg's group



**Fig. 8** Synthetic method by Canoy's group

This is an attractive production method, but the processes are somewhat long. Expensive  $\text{LiBH}_4$  is used, and reagents such as nitromethane, for which there should be concerns in terms of safety, are used.

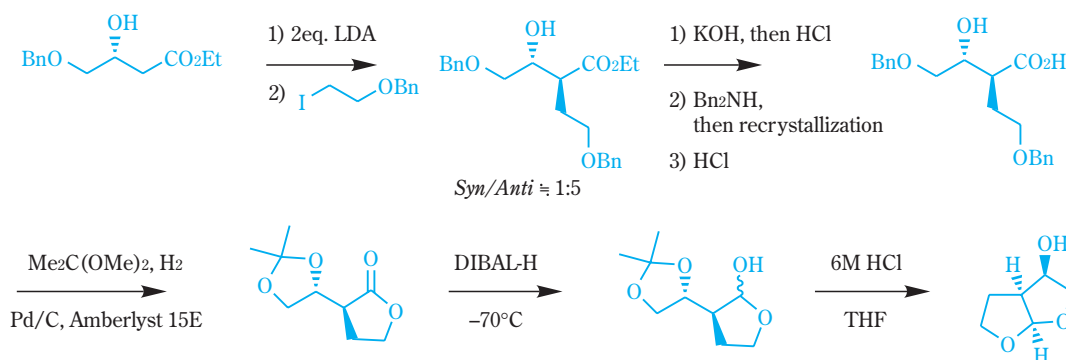
(7) Yu, Canoy et al. method<sup>(21), (22)</sup> (Fig. 8)

These are attractive methods that have been independently reported by two groups recently. These aim at asymmetric synthesis using a BOX asymmetric catalyst, but while both of them have a high diastereoselectivity, the optical yield is low, so an optical resolution process that uses enzymes, etc., is necessary.

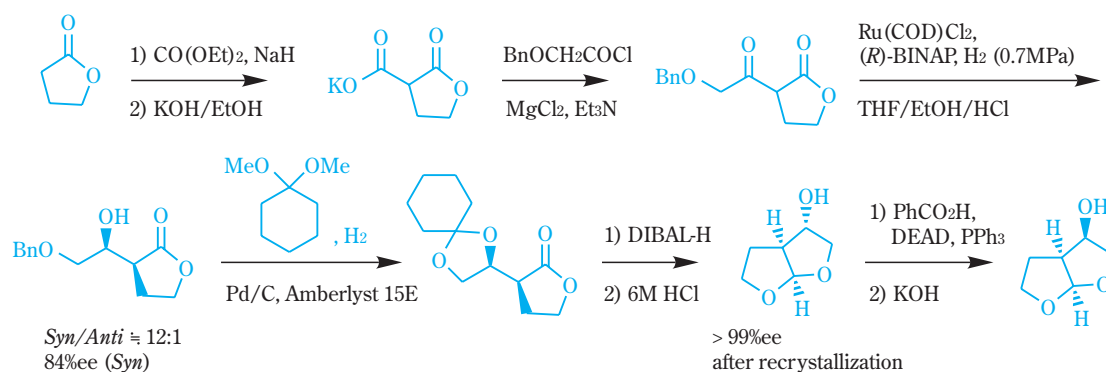
### 3. Our approach

(1) Diastereoselective alkylation<sup>(23)</sup> (Fig. 9)

We developed a method where, after diastereoselective alkylation by the method of Seebach et al.,<sup>(24)</sup> using ethyl (*R*)-4-benzyloxy-3-hydroxybutyrate, which is easily obtained by asymmetric reduction of ethyl-4-benzyloxy acetoacetate, as the starting material, acetonide protection of diol was carried out while deprotecting the benzyl groups, and next, BFOL was obtained by DIBAL reduction and cyclization. While BFOL can be obtained by a comparatively short process from ethyl (*R*)-4-benzyloxy-3-hydroxybutyrate, which can be



**Fig. 9** Our synthetic approach (1) *via* diastereoselective alkylation



**Fig. 10** Our synthetic approach (2) *via* DKR asymmetric hydrogenation

obtained industrially, there were problems in that there was a need for recrystallization using hydrolyzed carboxylic acid after the alkylation to improve the *syn/anti* selectivity, and there was a need to use a double equivalent of expensive LDA in the first half of the process.

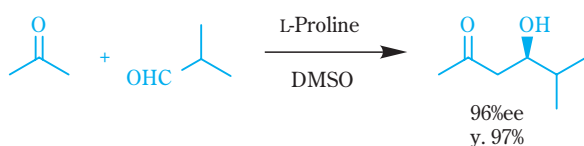
#### (2) DKR asymmetric hydrogenation<sup>25)</sup> (Fig. 10)

To avoid using LDA, which was a problem in (1), we developed a method with asymmetric hydrogenation using dynamic kinetic resolution (DKR) of  $\alpha$ -benzylacetyl- $\gamma$ -butyrolactone using a BINAP catalyst as the key reaction where the diastereoselectivity and the enantioselectivity were controlled at the same time. We discovered a method for easily synthesizing  $\alpha$ -(benzyloxy)acetyl- $\gamma$ -butyrolactone, which is the reducing substrate, from  $\gamma$ -butyrolactone, making it possible to start from an inexpensive raw material. However, since we had the *syn* form after asymmetric hydrogen reduction, there was a problem in that an inversion process was required for the hydroxyl groups afterwards.

### 4. Development of new production method using organocatalyst

#### (1) Organocatalyst

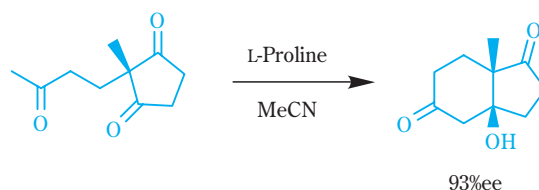
Since List, Lerner, Barbas, et al. reported a direct asymmetric cross-aldol reaction using proline in 2000<sup>1)</sup> (Fig. 11), organocatalysts that do not contain metals, of which proline is representative, have attracted attention<sup>2)-6)</sup>.



**Fig. 11** Proline catalyzed intermolecular asymmetric direct cross-aldol reaction between ketone and aldehyde

Approximately 30 years before the report by List et al., Hajos, Parrish, Eder, Sauer, and Wiechert had already reported on an intramolecular asymmetric aldol reaction using proline<sup>26), 27)</sup> (Fig. 12). However, since it was probably recognized as an exceptional reaction, it did not attract attention for close to 30 years afterwards. However, with the report by List et al., asymmetric organocatalysis, for which proline is representative, began to get attention all at once. Speaking of asymmetric catalysts, organometallic complex catalysts

as a whole were being studied at the time. Since the design of these catalysts was on a single track toward greater complexity, the authors themselves also remember being dumbfounded after reading a paper about the simple amino acid L-proline providing optical purity that outstripped masterfully designed organometallic complex catalysts under extremely mild conditions. After that and up to the present time, various organocatalysts have been designed, and at present, it is developed to where there has been a branching off of the area of investigation from organometallic catalysts.



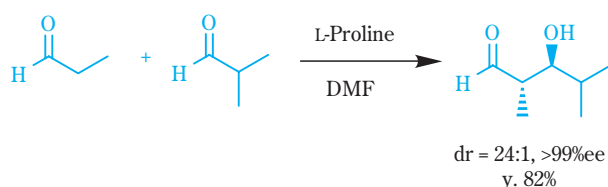
**Fig. 12** Proline catalyzed intramolecular aldol reaction between ketones

#### (2) Attractiveness of organocatalysts for synthesis of pharmaceutical products

When metal complex catalysts are used, there is a problem in that Pd, Rh and other heavy metals remain in the final drug substance in the order of ppm, but organocatalysts do not contain metals from the beginning, so this problem does not arise. The reaction conditions are generally mild, and high temperature and low temperature reactions are not required. In addition, work-up is generally simple, so there are few limitations in terms of equipment. In addition, a strong point of organocatalysts is addition reactions that do not produce byproducts beyond the reaction equations for aldol reactions, Mannich reactions, Henry reactions, aza-Henry reactions, Michael reactions, Morita-Baylis-Hillman reactions and Diels-Alder reactions. They are also attractive from the standpoint of green chemistry. On the other hand, since organocatalytic reactions are mild, the activity is typically low. There is a problem in that completion of the reactions requires time, and this is one of the problems when considering industrialization.

#### (3) Direct asymmetric cross-aldol reaction between aldehydes

In 2002, two years after the report by List et al., MacMillan et al. reported good progress in yield and



**Fig. 13** Proline catalyzed intermolecular asymmetric direct cross-aldol reaction between aldehydes

optical purity with a direct asymmetric cross-aldol reaction between aldehydes<sup>28)</sup> (Fig. 13).

On top of the report by List et al., this report was an amazing report that leveled what had been common sense up to that point. So said, common sense said that we should think of direct asymmetric cross-aldol reactions between aldehydes as not normally being selective. This is because it was thought that reactions of this sort that occur in the body could not progress at all with good yields based on organic chemistry if they were not enzymatic reactions. However, according to this report, a cross-aldol adduct could be obtained with a good yield and an extremely high optical purity of 99% ee or better with the extremely simple catalyst proline.

Along with immediately replicating this reaction, we attempted synthesis using various substrates that we could think of. However, while it certainly went well with the substrates introduced in the reference, combinations of substrates did not necessarily give satisfactory results when we actually carried out the reaction. We found that it was a reaction with a high degree of substrate specificity. In addition, we felt there would be the following problems when attempting to apply this reaction industrially.

i) At a glance it seems like the yield is good, but use of a large excess of one of the aldehydes is necessary, and the actual content of the target substance in the reaction solution is low.

ii) Since the byproducts are mainly self-aldol adducts, various cross-aldol adducts and their elimination products the physical properties are similar, and it can be assumed that they will be difficult to separate.

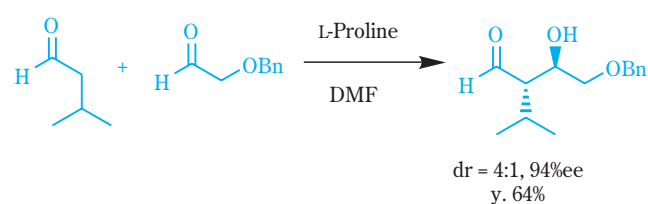
iii) The target substance is an unstable  $\beta$ -hydroxyaldehyde.

Therefore, even if separation using chromatography in the laboratory is possible, it can be assumed that industrial separation would be extremely difficult.

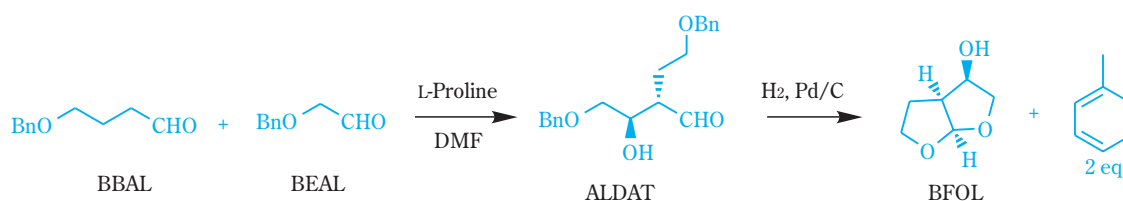
(4) Development of new production method using proline

Even though we thought that industrial reactions would be difficult with MacMillan's direct cross-aldol reaction, it was an extremely attractive reaction, so it was always in our heads when we thought about methods for synthesis on various themes. While this was going on, MacMillan et al. reported that benzyloxy acetaldehyde was a good aldol acceptor for direct cross aldol reactions<sup>29)</sup> (Fig. 14).

The instant we saw this paper, we had the gut feeling that MacMillan's aldol reaction could be applied to the industrial synthesis of BFOL. In other words, if it were possible to promote a cross-aldol reaction for BBAL and BEAL and obtain ALDAT as the main product, it would be possible to derive BFOL stereoselectively by deprotection and cyclization (Fig. 15). Since this has



**Fig. 14** Proline catalyzed intermolecular asymmetric direct cross-aldol reaction between benzyloxyacetaldehyde and isovaleraldehyde



**Fig. 15** Our approach for the synthesis of BFOL using proline catalyzed intermolecular asymmetric direct cross-aldol reaction

completely different properties from the self- and cross-aldol adducts and the substances these eliminate, we felt that industrial separation such as distillation would be possible.

Therefore we quickly attempted the cross-aldol reaction for BBAL and BEAL with L-proline as the catalyst, and next, attempted the deprotection and cyclization reactions. As a result, the yield was low at approximately 30%, but we found that we obtained good optical purity for the BFOL, and we started serious investigations.

## 5. Research aimed at industrialization

### (1) Asymmetric cross-aldol reaction

As a result of carrying out various investigations concerning the molar ratios for BBAL and BEAL, we found that to assure a yield of 60% or more based on the BBAL, the BEAL had to be at least a double equivalent of the BBAL. The reason for this was that, rather than being because the effect occurs in the presence of an excess, there is self-condensation of the BEAL during the reaction and it is consumed, so in the latter stages of the reaction BEAL becomes insufficient. When a double equivalent of BEAL or more is used, there is certainly an increase in the yield for the BBAL, but in terms of the yield for the BEAL, it clearly tends to be reduced. As a result, the target substance content in the reaction solution drops.

With regard to the amount of the catalyst, if the amount of L-proline added was 30 mol% or greater, there was an increasing trend in byproducts such as elimination products, and when it was 15 mol% or less, the reaction was not completed. With regard to the timing of addition, there was a tendency for the yield to improve with split addition rather than adding all of the catalyst in a batch at the beginning. We think that this is because the L-proline becomes inactive during the reaction.

### (2) Deprotection and cyclization reactions

The aldol adduct obtained in this manner is extracted first and condensed. Next it is introduced into the deprotection and cyclization process. However, when we obtained its thermal stability during condensation, ALDAT was unstable as predicted, and even at 30°C, it was clear that it gradually decomposed over a long period of time. Therefore, we determined that condensation is difficult, and using as little as possible of an extracting solvent, we stored it as is at a low temperature without condensation and introduced it to the next

process.

For the deprotection and cyclization process, we added an acid in the presence of a Pd/C catalyst, and by carrying out a contact hydrogenation reaction, we found that it progressed all at once to cyclization. We examined various acid catalysts, but we obtained the best results with hydrochloric acid. A hydrogen pressure of 0.5MPa was necessary to obtain a practical hydrogenation speed, but with the normal method of feeding hydrogen to a vessel where all of the reagents had been prepared, the yield and purity dropped as the reaction time was extended. The reason for this was that in the presence of an acid catalyst, the aldol adduct decomposed over time, and it could be assumed that it would be difficult to increase the scale. Therefore, we thought that there might be a solution to this problem with titration of the substrate under pressurized conditions from our experience with other research projects. In other words, when 0.5MPa is applied in advance to a reaction vessel where all of the reagents except the aldol adduct have been placed, we thought it would be possible to bring it to cyclization of stable BFOL simultaneously with the titration when the aldol adduct was also titrated at a pressure exceeding that.

Therefore, when we quickly tested it, the yield and quality were fixed even when we extended the titration time, and it was possible to increase the scale.

By distilling this crude form that included the BFOL obtained in this manner, it was possible to roughly separate out a mixture of the BFOL and its epimer *epi*-BFOL from the other aldol adducts. However, the separation of BFOL and *epi*-BFOL was difficult even with rectification.

Therefore, we tested various methods including kinetic resolution, but we did not make it to where we found good conditions. However, even if we assumed that separation would be possible, it would mean disposing of the epimer, so we wondered if there weren't some method for using it.

### (3) Oxidation and reduction purification

If we assume that, since the BFOL obtained from this reaction has sufficiently high optical purity at 99% ee, that the steric configuration of the condensed ring of its epimer, the *epi*-BFOL (96% ee), is the same as the BFOL, we thought that it might be possible to bring it back to BFOL while substantially maintaining the optical purity by first oxidizing the mixture, deriving ketone from BFON and stereoselectively reducing it.

Therefore, when we attempted a TEMPO oxidation reaction, which is an industrial oxidation reaction that we frequently use, we found that both the BFOL and the *epi*-BFOL were oxidized, and we got BFON with approximately 98% ee.

In addition, we were also lucky in that we found that BFON is a crystal, and with a single recrystallization, optical purity improves to 99.9% ee.

With regard to the ketone reduction, there was already a report<sup>15)</sup> from Ghosh et al. previously on this reaction, so we foresaw that reduction could be done stereoselectively to some extent, but there was no accurate description of the fraction generated. Therefore, when we actually attempted it, it exhibited a high selectivity with a dr of 98 : 2 under conditions of NaBH<sub>4</sub> and -15°C as shown in **Table 1**. The diastereomeric ratio was also sufficient, but aiming at a further improvement, we examined various other conditions. When the reducing agent was limited to NaBH<sub>4</sub>, we

found that little improvement in selectivity was seen even at low temperatures, but when the reaction was carried out at -70°C using K-Selectride<sup>®</sup> as the reducing agent, we found that it exhibited a high selectivity of dr 99.9 : 0.1.

## Conclusion

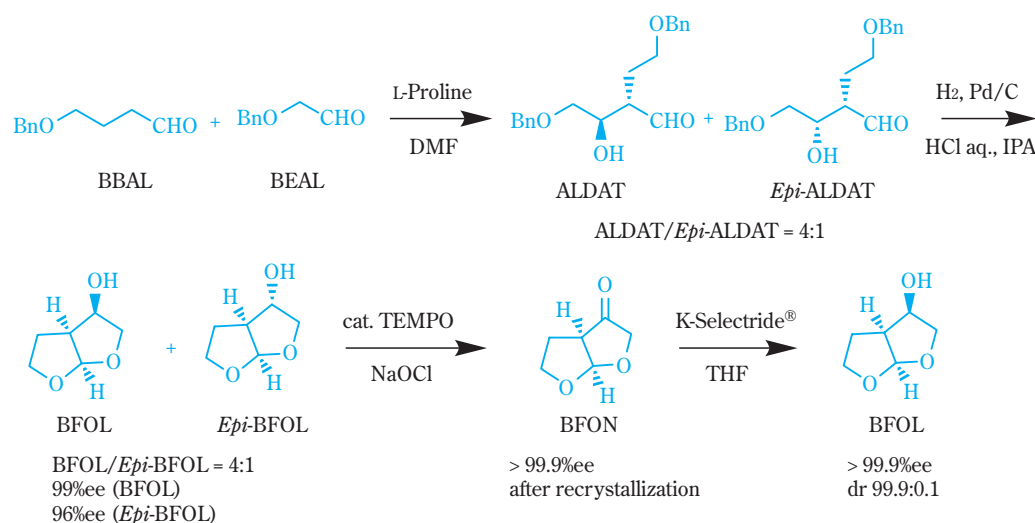
We first focused on the importance of organocatalysts, and have worked on developing applications for efficient synthesis methods for pharmaceutical products. However, this time we used the inexpensive and environmentally friendly organocatalyst L-proline, and established a simple industrial synthesis method for the complex anti-AIDS drug intermediate BFOL, which has three asymmetric carbon centers (**Fig. 16**). This reaction only has a byproduct of 2 mol of toluene according to the reaction equation (**Fig. 15**), and it is also an ideal reaction system from the standpoint of green chemistry.

While the world's major pharmaceutical companies are already developing their own processes, it is possible to reduce the number and cost of processes by proposing methods using the process that we have developed when compared with existing production methods. It goes without saying that it is a process that will be competitive in the future, but moving forward, we would like to be recognized as a company that carries out the development of processes on a higher plane, taking into consideration the environment with the catalysts themselves being environmentally friend-

**Table 1** Reduction condition of BFON

Reducing agent	Solvent	Temperature	Diastereomeric ratio <sup>a)</sup>
NaBH <sub>4</sub>	EtOH	-15°C	98.0/2.0
NaBH <sub>4</sub>	EtOH	-70°C	98.4/1.6
NaBH(OAc) <sub>3</sub>	EtOH	-70°C	98.7/1.3
( <i>n</i> -Bu) <sub>4</sub> NBH <sub>4</sub>	EtOH	-70°C	98.0/2.0
K-Selectride <sup>®</sup>	THF	-70°C	99.9/0.1
BH <sub>3</sub> /THF	THF	-70°C	97.2/2.8
LiAlH <sub>4</sub>	THF	-70°C	99.5/0.5
DIBAL-H	THF	-70°C	98.4/1.6

a) Determined by GC analysis



**Fig. 16** Our method for the synthesis of BFOL using proline catalyzed intermolecular asymmetric direct cross-aldol reaction



ly and there being little waste product in the reaction equations themselves.

## References

- 1) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, **122**, 2395 (2000).
- 2) Y. Hayashi, *J. Synth. Org. Chem. Jpn.*, **63**, 46 (2005).
- 3) A. Berkessel and H. Gröger, "Asymmetric Organocatalysis, From Biomimetic Concepts to Applications in Asymmetric Synthesis", VCH, Weinheim (2005).
- 4) P. I. Dalko, "Enantioselective Organocatalysis, Reactions and Experimental Procedures" VCH, Weinheim (2007).
- 5) B. List, *Chem. Rev.*, **107**, 5413 (2007).
- 6) H. Pellisser, *Tetrahedron*, **63**, 9267 (2007).
- 7) O. Tokuda, T. Kano, W. -G. Gao, T. Ikemoto and K. Maruoka, *Org. Lett.*, **7**, 5103 (2005).
- 8) T. Ikemoto, O. Tokuda and W. -G. Gao, SUMITOMO KAGAKU, **2005-II**, 27 (2005).
- 9) T. Ikemoto, Y. Watanabe, J. Tomokawa, T. Kawakami, Y. Uekita and I. Kurimoto, *Proceedings of the first international symposium on Process Chemistry*, 92 (2008).
- 10) A. K. Ghosh, J. F. Kincaid, W. Cho, D. E. Walters, K. Krishnan, K. A. Hussain, Y. Koo, H. Cho, C. Rudall, L. Holland and J. Buthod, *Bioorg. Med. Chem. Lett.*, **8**, 687 (1998).
- 11) A. K. Ghosh, D. W. Shin, L. Swanson, K. Krishnan, H. Cho, K. A. Hussain, D. E. Walters, L. Holland and J. Buthod, *Farmaco*, **56**, 29 (2001).
- 12) J. F. Miller, C. W. Andrews, M. Brieger, E. S. Furfine, M. R. Hale, M. H. Hanlon, R. J. Hazen, I. Kaldor, E. W. McLean, D. Reynolds, D. M. Sammond, A. Spaltenstein, R. Tung, E. M. Turner, R. X. Xu and R. G. Sherrill, *Bioorg. Med. Chem. Lett.*, **16**, 1788 (2006).
- 13) D. L. N. G. Surleraux, A. Tahri, W. G. Verschuere, G. M. E. Pille, H. A. de Kock, T. H. M. Jonckers, A. Peeters, S. De Meyer, H. Azijn, R. Pauwels, M. -P. de Bethune, N. M. King, M. Prabu-Jeyabalan, C. A. Schiffer and P. B. T. P. Wigerinck, *J. Med. Chem.*, **48**, 1813 (2005).
- 14) L. A. Soebera, J. Castaner and M. Bayés, *Drugs Future*, **30**, 441 (2005).
- 15) A. K. Ghosh and Y. Chen, *Tetrahedron Lett.*, **36**, 505 (1995).
- 16) A. K. Ghosh, J. F. Kincaid, D. E. Walters, Y. Chen, N. C. Chaudhuri, W. J. Thompson, C. Culberson, P. M. D. Fitzgerald, H. Y. Lee, S. P. McKee, P. M. Munson, T. T. Duong, P. L. Darke, J. A. Zugay, W. A. Schleif, M. G. Axel, J. Lin and J. R. Huff, *J. Med. Chem.*, **39**, 3278 (1996).
- 17) A. K. Ghosh, S. Leshchenko and M. Noetzel, *J. Org. Chem.*, **69**, 7822 (2004).
- 18) A. K. Ghosh, J. Li and R. S. Perali, *Synthesis*, **18**, 3015 (2006).
- 19) M. Uchiyama, M. Hirai, M. Nagata, R. Katoh, R. Ogawa and A. Ohta, *Tetrahedron Lett.*, **42**, 4653 (2001).
- 20) P. J. L. M. Quaedflieg, B. R. R. Kesteleyn, P. B. T. P. Wigerinck, N. M. F. Goyvaerts, R. J. Vijn, C. S. M. Liebregts, J. H. M. H. Kooistra and C. Cusan, *Org. Lett.*, **7**, 5917 (2005).
- 21) R. H. Yu, R. P. Polniaszek, M. W. Becker, C. M. Cook and L. H. L. Yu, *Org. Proc. Res. Dev.*, **11**, 972 (2007).
- 22) W. L. Canoy, B. E. Cooley, J. A. Corona, T. C. Lovelace, A. Millar, A. M. Weber, S. Xie and Y. Zhang, *Org. Lett.*, **10**, 1103 (2008).
- 23) Sumika Fine Chemicals, Jpn. Kokai Tokkyo Koho 2004-107315 (2004).
- 24) D. Seebach, J. Aebi and D. Wasmuth, *Org. Synth.*, **63**, 109 (1985).
- 25) Sumika Fine Chemicals, Jpn. Kokai Tokkyo Koho 2005-008530 (2005).
- 26) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974).
- 27) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **10**, 496 (1971).
- 28) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **124**, 6798 (2002).
- 29) A. B. Northrup, I. K. Mangion, F. Hettche and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, **43**, 2152 (2004).

PROFILE



*Tetsuya IKEMOTO*

Sumitomo Chemical Co., Ltd.  
Fine Chemicals Research Laboratory  
Senior Research Associate, Ph. D.



*Yosuke WATANABE*

Sumitomo Chemical Co., Ltd.  
Fine Chemicals Research Laboratory  
Senior Research Associate