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Enantioselective Automultiplication of Chiral Molecules by Asymmetric Autocatalysis

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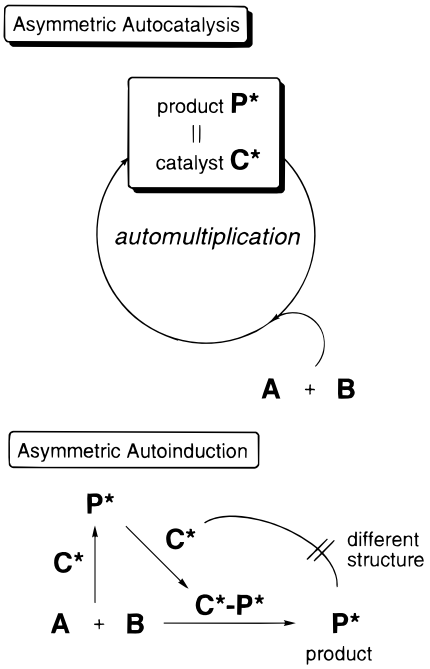
ABSTRACT

Asymmetric autocatalysis is a process of automultiplication of a chiral compound in which chiral product acts as a chiral catalyst for its own production. The discovery and the development of asymmetric autocatalysis of pyrimidyl-, quinolyl-, and pyridyl-alkanols are described in the enantioselective additions of diisopropylzinc to the corresponding nitrogen-containing aldehydes. (Alkynylpyrimidyl)alkanols automultiply with a yield of over 99% and over 99.5% ee. Asymmetric autocatalysts with extremely low ee's automultiply with significant amplification of ee's without the need for any other chiral auxiliaries. Small enantiomeric imbalances of chiral molecules induced by physical factors can be amplified by the present asymmetric autocatalysis.

Introduction

Chirality plays a central role in the chemical, biological, pharmaceutical, and material sciences. Due to recent advances in asymmetric catalysis,[1] catalytic enantioselective synthesis has become one of the most efficient methods for the preparation of enantiomerically enriched compounds. An increased amount of enantiomerically enriched product can be obtained from an asymmetric reaction using a small amount of an asymmetric catalyst. In conventional asymmetric catalysis, however, the structures of the products are different from those of the asymmetric catalysts and the chiral products per se never act as asymmetric catalysts.

Scheme 1



On the other hand, asymmetric *autocatalysis* is defined as an enantioselective synthesis in which the chiral product acts as an asymmetric catalyst for its own production (Scheme 1). Asymmetric autocatalysis is an efficient method for the catalytic enantioselective automultiplication of a chiral molecule without the need for any other chiral auxiliaries. Does any chiral organic compound serve as an asymmetric autocatalyst? Although Frank proposed a mathematical mechanism of asymmetric autocatalysis in 1953,[2] and the implications of asymmetric autocatalysis have been described,[3] no organic molecule which acts as an asymmetric autocatalyst has yet been found. Thus, it has been a challenge to find a chiral molecule which possesses asymmetric autocatalytic ability.

Asymmetric *autocatalysis* described above should be distinguished from asymmetric *autoinduction* which was described by Alberts and Wynberg.[4a] In asymmetric *autoinduction*, a chiral product, which itself does not possess catalytic activity, participates in the formation of a chiral complex with the enantioselective catalyst to effect asymmetric induction (Scheme 1).[4] For example, the enantioselective hydrocyanation of an aldehyde is catalyzed by a chiral cyclic dipeptide;[4d] the enantioselectivity of the chiral complex formed from the cyclic dipeptide (catalyst) and the chiral cyanohydrin (product) is higher than that with the chiral catalyst alone.

Kenso Soai was born in Hiroshima, Japan, in 1950. He received his B.S. (1974) and Ph.D. (1979) degrees in chemistry from the University of Tokyo, working with Professor Teruaki Mukaiyama. He moved to the University of North Carolina at Chapel Hill as a postdoctoral fellow with Professor Ernest L. Eliel in 1979. He began his independent career as a lecturer at the Science University of Tokyo in 1981, and he was promoted to Associate Professor in 1986 and Professor in 1991. His research interest includes asymmetric autocatalysis, asymmetric synthesis using homogeneous and heterogeneous catalysts, and the origin of chirality in biomolecules. He has received a Progress Award in Synthetic Organic Chemistry (1988), a Chisso Award in Synthetic Organic Chemistry (1990), an Inoue Prize for Science (2000), and The Divisional Award of The Chemical Society of Japan for 1999.

Takanori Shibata was born in Tokyo, Japan, in 1966. He received his B.S. (1989) and Ph.D. (1994) degrees in chemistry from the University of Tokyo, working with Professor Koichi Narasaka. After working for a year at Kitasato University as a research associate, he joined Soai's group at the Science University of Tokyo in 1995 as a research associate. He was appointed as Associate Professor of Chemistry at Okayama University in 1999. He received a Daicel Award in Synthetic Organic Chemistry in 1997.

Itaru Sato was born in Iwate, Japan, in 1971. He received his B.S. (1994) and Ph.D. (1999) degrees in chemistry from the University of Tohoku, working with Professor Masahiro Hirama. He was also a research fellow of the Japan Society for the Promotion of Science (1998−1999). He joined Soai's group at the Science University of Tokyo as a research associate in 1999. He received a Daicel Award in Synthetic Organic Chemistry in 2000.

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Meanwhile, almost all of the α-amino acids in proteins of living organisms are the L type, while sugars in RNA and DNA are the D type. Considerable attention has been focused on the origin of the chirality of biomolecules.[5] Several mechanisms have been proposed as possible origins of enantiomeric imbalances in organic molecules. However, the imbalances in chiral organic molecules induced by the proposed mechanisms are usually too small to account for the large enantiomeric imbalances in naturally occurring compounds.[5] Thus, a chemical link is needed to fill the gap between these small and large enantiomeric imbalances in organic molecules.[6]

Over the past decade, the amplification of enantiomeric excess in enantioselective reactions has been reported in Sharpless epoxidation,[7] alkylation of aldehydes,[8] and other reactions:[9] in these reactions the ee's of the products are higher than those of the asymmetric catalysts used. However, since these enantioselective reactions are *not* autocatalytic, the ee of the product obtained in one reaction cannot be further increased by repeating the same reaction.

What will happen if an organic molecule serves as an asymmetric autocatalyst which shows asymmetric amplification? The major unique advantage of the amplification of ee by asymmetric autocatalysis may be that the enantiomerically enriched product in each reaction can be used as the asymmetric autocatalyst for the next run. Thus, an extremely small imbalance in chirality in the initial compound, even if it is too small to be detected by contemporary analytical methods, might be amplified to a large extent by asymmetric autocatalysis along with an amplification of ee.

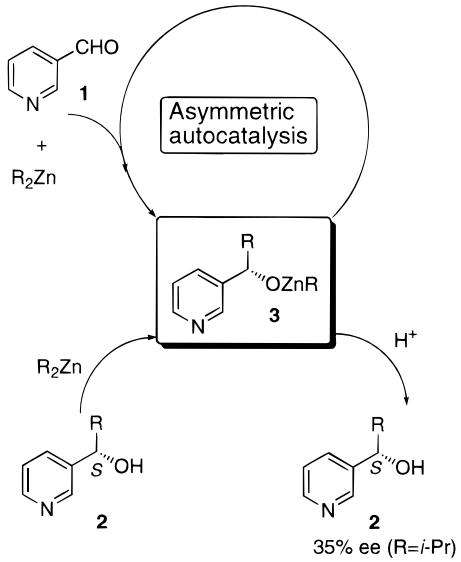
Mukaiyama et al. (including K.S.) reported that various organometallics add to benzaldehyde in the presence of a *β*-amino alcohol,[10] and we and others have developed chiral *β*-amino alcohols as catalysts for the highly enantioselective addition of dialkylzincs to aldehydes, to give enantiomerically enriched *sec*-alcohols.[11]

In this Account, we describe our success at the highly enantioselective automultiplication of chiral *sec*-alkanols, asymmetric autocatalysis with an amplification of enantiomeric excess,[12] and the amplification of slight enantiomeric imbalances in molecules based on asymmetric autocatalysis.

The First Asymmetric Autocatalysis of Chiral Pyridyl Alkanol

In the course of our continuing study on the catalytic enantioselective addition of dialkylzincs to aldehydes using chiral *β*-amino alcohols,[13] chiral piperazines,[14] and chiral phosphoramidates,[15] we examined the enantioselective addition of dialkylzincs to pyridine-3-carbaldehyde and benzaldehyde, respectively, using *N*,*N*-dibutylnorephedrine[13b] as a chiral catalyst. We observed that the addition reaction of diethylzinc to pyridine-3-carbaldehyde in the presence of *N*,*N*-dibutylnorephedrine is

Scheme 2



complete within 1 h at 0 °C,[16] while the reaction of benzaldehyde requires 16 h to complete at 0 °C.[13b] The fact that the reaction of pyridine-3-carbaldehyde is faster than that of benzaldehyde suggests that the chiral product of the former reaction, i.e., the ethylzinc alkoxide of 3-pyridylalkanol formed in situ, may act as an asymmetric autocatalyst.

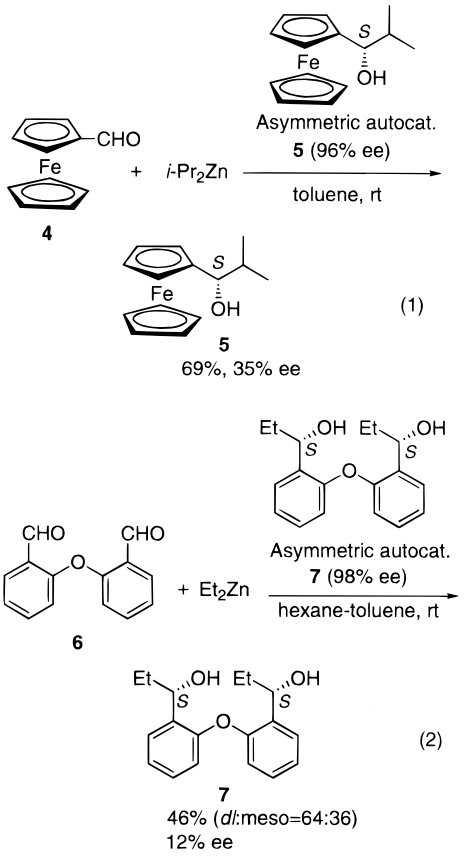
In 1990, we reported the first asymmetric autocatalysis in the enantioselective addition of diisopropylzinc (*i*-Pr_2-Zn) to pyridine-3-carbaldehyde (**1**) using a catalytic amount of (*S*)-2-methyl-1-(3-pyridyl)-1-propanol (**2**) with 86% ee (Scheme 2).[17] (*S*)-Pyridylalkanol **2** automultiplied, and the newly formed product **2** possessed the same structure (67% yield) and the same configuration (*S* enantiomer; 35% ee) as the catalyst. Chiral isopropylzinc alkoxide **3** formed in situ from **1** and *i*-Pr_2Zn is considered to catalyze the enantioselective addition of *i*-Pr_2Zn to aldehyde **1** and to form itself.

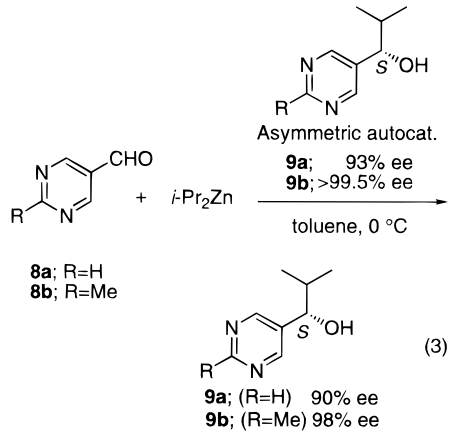
Asymmetric Autocatalysis of Ferrocenylalkanol and Diol

In addition to the nitrogen-containing alkanol, chiral ferrocenylalkanol **5** and diol **7** have also been shown to serve as asymmetric autocatalysts. Chiral (*S*)-ferrocenylalkanol **5** with 96% ee automultiplies in the enantioselective addition of *i*-Pr_2Zn to ferrocenecarbaldehyde **4** to give (*S*)-**5** in 69% yield and 35% ee (eq 1).[18] Chiral diol **7** also automultiplies during the addition reaction of Et_2Zn to the corresponding dialdehyde **6** (eq 2).[19]

Highly Enantioselective Asymmetric Autocatalysis of Chiral Pyrimidylalkanol

Chiral pyrimidylalkanol **9a**,**b** was found to be the first highly enantioselective asymmetric autocatalyst. Very high ee's were observed when highly enantiomerically enriched pyrimidylalkanol **9a**,**b** was used as an asymmetric auto-

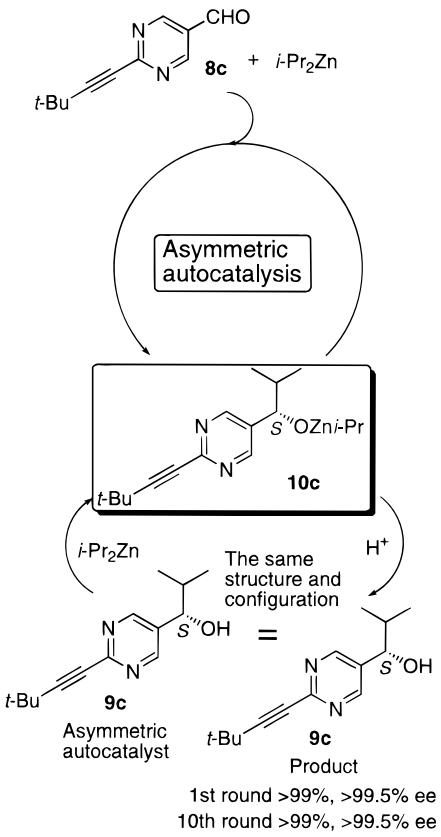




catalyst in the enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehydes **8a,b** (eq 3).[20] When chiral (*S*)-pyrimidylalkanol **9a** with 93% ee was used as an asymmetric autocatalyst, the newly formed (*S*)-**9a** had an ee of 90%. When chiral (*S*)-pyrimidylalkanol **9b** with 95% ee was used as an asymmetric autocatalyst, (*S*)-**9b** automultiplied without any loss of enantiomeric purity (96% ee). The ee of the newly formed alkanol (*S*)-**9b** reached 98% when asymmetric autocatalyst (*S*)-**9b** with >99.5% ee was used.

The benefits of asymmetric autocatalysis from the standpoint of enantioselective synthesis are as follows: (1) The use of an asymmetric catalyst with a structure different from that of the chiral product is not necessary. (2) The chiral product automultiplies exponentially according to the increase in the amount of chiral product, which serves as an asymmetric catalyst for its own production. (3) The autocatalysts do not deteriorate due to the continuous formation of new catalyst during the reaction. (4) Separation of the chiral product from the autocatalyst is not necessary.

Scheme 3



Practically Perfect Asymmetric Autocatalysis: (2-Alkynyl-5-pyrimidyl)alkanol

To find a better asymmetric autocatalyst, we examined several 5-pyrimidylalkanols possessing an alkynyl group at their 2-positions as asymmetric autocatalysts. We found that 1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methylpropanol (**9c**) is a very efficient asymmetric autocatalyst (Scheme 3). (*S*)-Pyrimidylalkanol **9c** (20 mol %) with >99.5% ee automultiplied in >99% isolated yield and >99.5% ee during the enantioselective addition of *i*-Pr_2Zn to 2-(*tert*-butylethynyl)pyrimidine-5-carbaldehyde (**8c**) in cumene at 0 °C.[21] Chiral isopropylzinc alkoxide **10c** formed in situ from **8c** and *i*-Pr_2Zn is considered to catalyze the enantioselective addition of *i*-Pr_2Zn to aldehyde **8c** and to form itself. The reaction was repeated using the product of one reaction as an asymmetric autocatalyst for the next reaction. The (*S*)-product **9c** of the 10th reaction possessed an enantiomeric purity of >99.5% and was obtained in a yield of >99%. In each reaction, the amount of compound was amplified 6-fold. Thus, for 10 successive asymmetric autocatalytic reactions, the overall amplification factor was calculated, in principle, to be 6^{10} (ca. 6×10^7). On the other hand, when (*R*)-pyrimidylalkanol **9c** with >99.5% ee,

instead of (*S*)-**9c**, was used as an asymmetric autocatalyst, (*R*)-**9c** with >99.5% ee was obtained in >99% isolated yield.

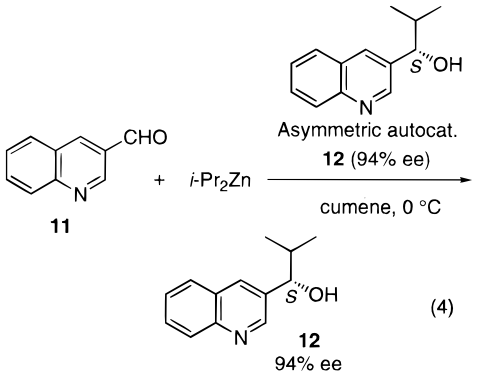
These extremely high yields and ee's may be attributed partly to the moderate electron-withdrawing effect that arises from the alkynyl group and an appropriate degree of steric hindrance of the alkyne. Thus, practically perfect asymmetric autocatalysis was established with (2-alkynyl-5-pyrimidyl)alkanol **9c**.

The nucleophilicity of the isopropyl moiety of *i*-Pr_2Zn may be enhanced by the coordination with the zinc alkoxide of **10**. However, the mechanism of asymmetric induction using **10** seems to be different from those proposed for β-amino alcohols, because **10** is not derived from a β-amino alcohol. The enantioselectivity of **10** in *i*-Pr_2Zn addition to pyrimidine-5-carbaldehyde **8** is very high. On the other hand, the enantioselectivity is moderate in the addition to benzaldehyde. These results suggest that, in addition to the coordination of *i*-Pr_2Zn with **10**, a nitrogen atom of aldehyde **8** may also be incorporated in the formation of a reactive intermediate.

Asymmetric Autocatalysis of Chiral 3-Quinolylalkanol and Chiral (5-Carbamoyl-3-pyridyl)alkanol

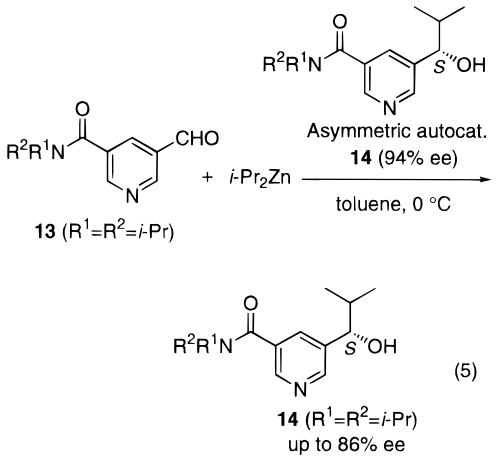
During the course of our search for highly enantioselective asymmetric autocatalysts other than pyrimidylalkanols **9a**−**c**, chiral 3-quinolylalkanol **12** and chiral (5-carbamoyl-3-pyridyl)alkanol **14** were also found to be highly enantioselective asymmetric autocatalysts.

Thus, (*S*)-3-quinolylalkanol **12** with 94% ee catalyzes the enantioselective addition of *i*-Pr_2Zn to quinoline-3-carbaldehyde (**11**) to afford itself (*S*)-**12** with 94% ee with the same configuration as the catalyst (eq 4).[22]



(4)

As we described above, the enantioselectivity of our first asymmetric autocatalyst (i.e., chiral pyridylalkanol **2**) was not sufficiently high. However, by introducing a carbamoyl group at the 5-position of the pyridine ring, we found that chiral (5-carbamoyl-3-pyridyl)alkanols **14** serve as asymmetric autocatalysts with high enantioselectivities (eq 5). Indeed, chiral ((*S*)-5-carbamoyl-3-pyridyl)alkanol **14** (R^1 = R^2 = *i*-Pr) (94% ee) catalyzes the enantioselective addition of *i*-Pr_2Zn to 5-carbamoyl-3-pyridinecarbaldehyde **13** to give itself in up to 86% ee with the same configuration as the catalyst.[23] Among the (5-carbamoyl-3-pyridyl)alkanols examined, pyridylalkanol **14** (R^1 = R^2 = *i*-Pr), which has isopropyl substituents on the nitrogen atom of the carbamoyl group, is the most highly enantioselective asymmetric autocatalyst. Unlike chiral pyrimidylalkanols, both quinolyl- and (5-carbamoyl-3-pyridyl)-alkanols have only one nitrogen atom on the aromatic ring.

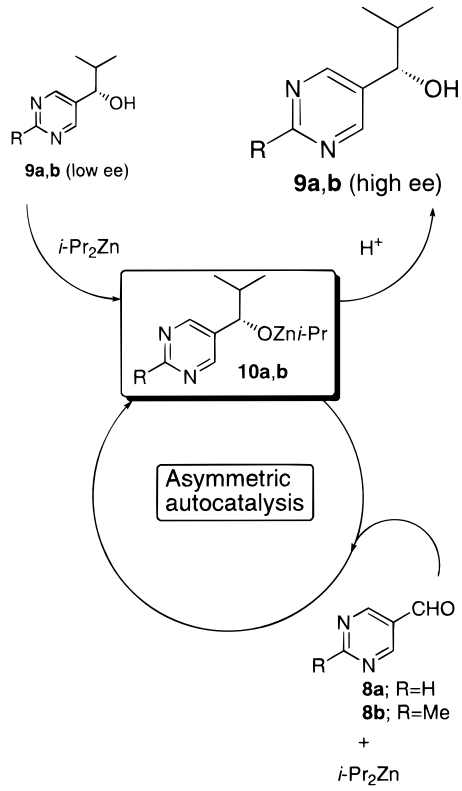


(5)

Asymmetric Autocatalysis with Amplification of Enantiomeric Excess

As an asymmetric autocatalyst, (*S*)-pyrimidylalkanol **9a** with only 2% ee was found to give (*S*)-**9a** consisting of the initial and newly formed alkanol **9a** with an increased ee of 10% in the reaction between *i*-Pr_2Zn and aldehyde **8a** (Scheme 4, Figure 1).[24] One of the advantages of asymmetric autocatalysis with an amplification of ee over

Scheme 4



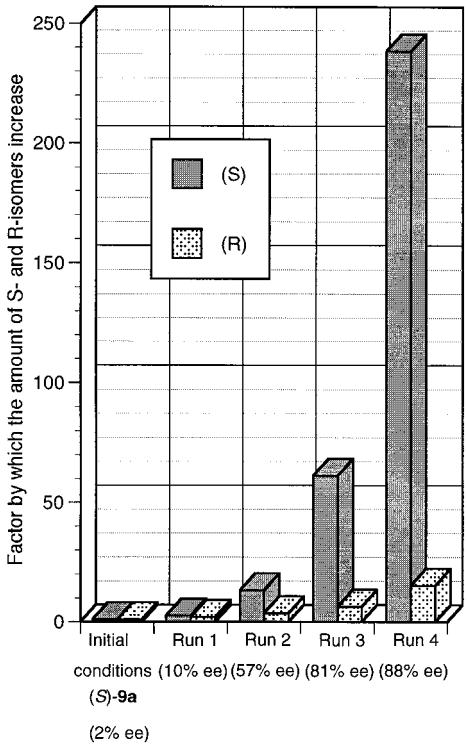


FIGURE 1. Change of the amount of *S*- and *R*-isomers of **9a** in consecutive asymmetric autocatalytic reactions.

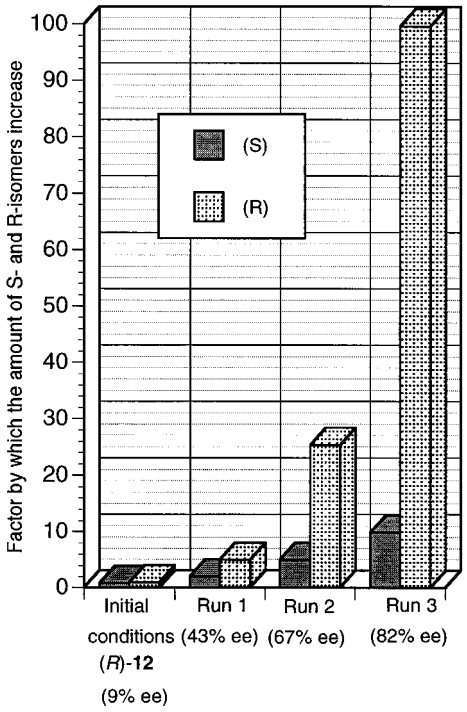


FIGURE 2. Change of the amount of *R*- and *S*-isomers of **12** in consecutive asymmetric autocatalytic reactions.

*non*autocatalytic amplification reactions is that *consecutive* asymmetric autocatalytic reactions are possible. Thus, successive asymmetric autocatalytic reactions were performed, with the product of one round serving as the asymmetric autocatalyst for the next. The ee of the product (and asymmetric autocatalyst) **9a** increased sequentially to 57% ee, 81% ee, and then 88% ee.[24] This is an unprecedented asymmetric autocatalytic reaction with an amplification of ee. As shown in Figure 1, during the first four successive asymmetric autocatalytic reactions, (*S*)-**9a** in the initial catalyst increases 239-fold. On the other hand, (*R*)-**9a** increases only 16-fold.

As described above, we found that chiral pyrimidylalkanol **9** with a low ee as an asymmetric autocatalyst gives **9** with the same configuration but with higher ee in the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **8**. We emphasize one of the most important implications of the present asymmetric autocatalytic amplification of ee: Even when the initial ee of the asymmetric autocatalyst is extremely low, it can be amplified considerably by consecutive asymmetric autocatalysis without the need for any other chiral auxiliaries. Thus, (*S*)-pyrimidylalkanol **9c** with an ee as low as 0.6% automultiplied during four consecutive asymmetric autocatalytic reactions, and the ee of (*S*)-**9c** reached >99.5% ee.[25a]

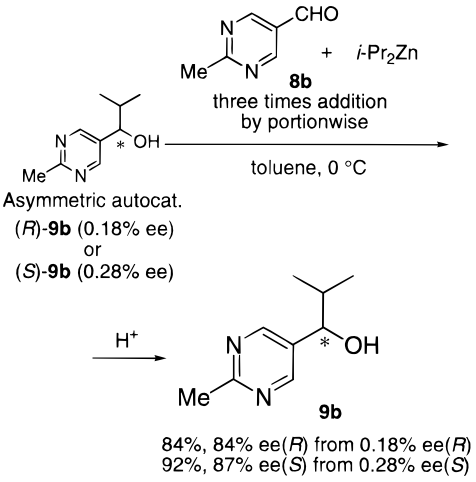
Chiral isopropylzinc alkoxides **10** formed in situ from (*S*)- and (*R*)-pyrimidylalkanols **8** and *i*-Pr_2Zn are thought to serve as asymmetric autocatalysts (Scheme 4). In fact the relation between the yield of the product **10** and the reaction time shows a sigmoid curve,[25b] which is typically observed in autocatalytic reaction. For the amplification of ee, an inhibition mechanism should be present to suppress the activity of the minor enantiomer of the catalyst. Kagan formulated the inhibition mechanism of the amplification of ee in nonautocatalytic reactions by the aggregations of chiral ligands.[9a] We postulate aggregations of the catalysts, however, the elucidation of the inhibition mechanism of the present asymmetric autocatalysis requires further investigation.

In addition to pyrimidylalkanols, enantiomerically enriched 3-quinolylalkanol **12** also acts as an asymmetric autocatalyst with an amplification of ee (Figure 2).[26] Thus, the ee of (*R*)-**12** increases from 9% ee to 88% ee during six successive asymmetric autocatalytic reactions, where the amount of major (*R*)-**12** in the initial catalyst increases 7628-fold, while that of minor (*S*)-**12** in the initial catalyst increases only 586-fold. (5-Carbamoyl-3-pyridyl)alkanol **14** was also found to be an asymmetric autocatalyst with an amplification of ee.[25c]

One-Pot Asymmetric Autocatalysis with Amplification of Enantiomeric Excess

The consecutive asymmetric autocatalytic reactions with an amplification of ee described above are quenched by adding acid and purified after each run. If one-pot asymmetric autocatalysis with an amplification of ee works effectively, it would be a more convenient method. Indeed, we found that chiral pyrimidylalkanol also works in one-pot asymmetric autocatalysis with an amplification of ee. Chiral (*R*)-pyrimidylalkanol **9b** (R = Me) with 6.4% ee is increased (84% yield) with an amplification of ee (92% ee) in one pot by portionwise addition (three portions) of 2-methylpyrimidine-5-carbaldehyde (**8b**) and *i*-Pr_2Zn.[27] Even using (*R*)-**9b** with an ee as low as 0.18% as an initial autocatalyst, the ee was enhanced to 84% by

Scheme 5



the three portionwise additions of aldehyde **8b** and *i*-Pr_2-Zn (Scheme 5). Conversely, (*S*)-pyrimidylalkanol **9b** (0.28% ee) with the opposite configuration automultiplied to give itself with an amplified ee of 87% (Figure 3). Thus, very tiny enantiomeric imbalances in pyrimidylalkanol are dramatically amplified by one-pot asymmetric autocatalysis.

Amplification of a Slight Enantiomeric Imbalance Induced by Physical Factors Based on Asymmetric Autocatalysis: A Link between the Origin of Chirality and Organic Compounds with High Enantiomeric Excess

The origins of the chirality and homogeneity of natural products remain an unsolved mystery.[5] The ee's of chiral molecules induced by several physical mechanisms that have been proposed as origins of chirality, such as circularly polarized light (CPL),[28] have usually been very low. The chemical process which links the slight enantiomeric imbalance of organic molecules induced by chiral physical factors to chiral molecules with high enantiomeric imbalances found in nature is not known.

In the preceding sections, we described the asymmetric autocatalysis of pyrimidylalkanols with a significant amplification of ee using a catalytic amount of an asymmetric autocatalyst of very low ee in the initial conditions. If a chiral molecule with very low ee is used in the initial conditions instead of an asymmetric autocatalyst, the chiral molecule may serve as a chiral initiator, and a slight enantiomeric imbalance may be induced in the initially formed zinc alkoxide of pyrimidylalkanol. Then, the induced slight enantiomeric imbalance, even though it is extremely small, may be expected to be enhanced by the subsequent one-pot asymmetric autocatalysis of pyrimidylalkanol with an amplification of ee.

We examined the asymmetric autocatalysis of pyrimidylalkanol **9b** using leucine with a low ee as a chiral initiator. We chose leucine as a chiral initiator because it is a biologically important α-amino acid and because L- or D-leucine with ca. 2% ee is obtained by the asymmetric photolysis of racemic leucine with right or left CPL.[28a] In

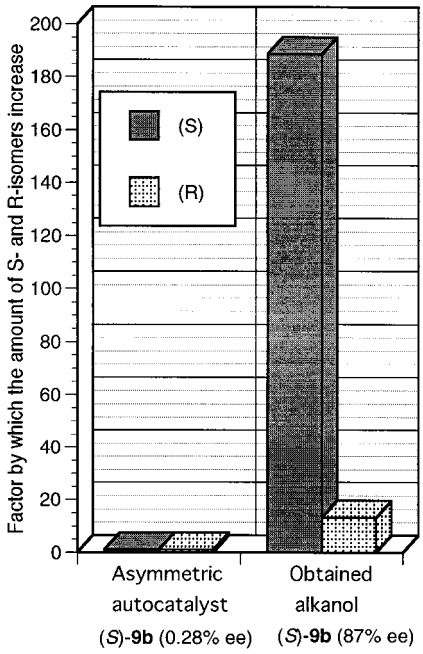
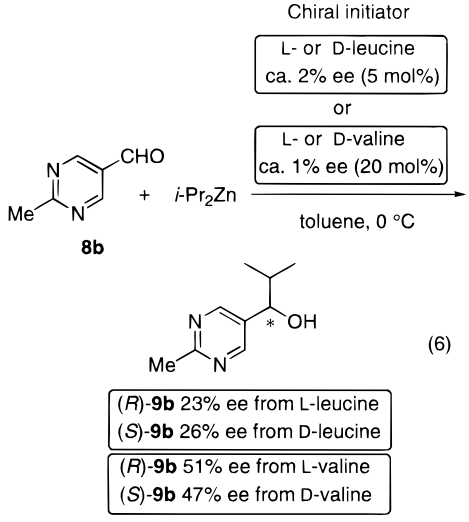


FIGURE 3. Change of the amount of *S*- and *R*-isomers of **9b** in one-pot asymmetric autocatalytic reaction.

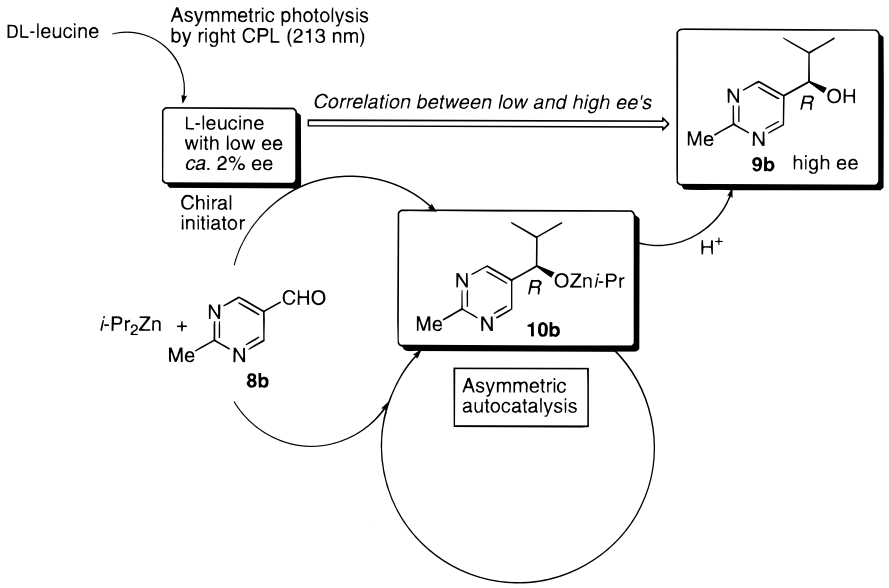
addition, a recent report disclosed that strong CPL is observed in an area of star formation.[29]

In the presence of L-leucine (5 mol %) with ca. 2% ee, *i*-Pr_2Zn and 2-methylpyrimidine-5-carbaldehyde (**8b**) were added in three portions, one after another. (*R*)-2-Methyl-1-(2-methyl-5-pyrimidyl)propan-1-ol (**9b**) with an amplified ee of 23% was obtained in 83% yield (eq 6).[30] On the



other hand, in the presence of D-leucine, (*S*)-**9b** with an amplified ee of 26% was obtained. These results clearly show that the absolute configuration of the resulting pyrimidylalkanol **9b** was determined by the absolute configuration of the only slightly more predominant enantiomer of L- or D-leucine. We also found that, in the presence of L- and D-valine (20 mol %) with ca. 1% ee, (*R*)- and (*S*)-pyrimidylalkanols **9b** with amplified ee's of 51% and 47% were obtained, respectively, from the addition of *i*-Pr_2Zn and aldehyde **8b** in two portions (eq

Scheme 6



6).[30] The ee of pyrimidylalkanol **9b** is readily increased to >95% by further asymmetric autocatalysis of pyrimidylalkanol **9b**,[24,27] as described in the preceding sections.

Thus, the overall process constitutes the first synthetic correlation between a slight CPL-induced imbalance in the chirality of an organic compound and significant enantiomeric enrichment in a chiral molecule (Scheme 6). In addition, it should be mentioned that (*R*)-pyrimidylalkanol **9b** can be transformed into a chiral naturally occurring compound in a stereospecific manner without any loss of its enantiomeric purity.[31]

Chiral Recognition of Various Molecules with a Slight Enantiomeric Imbalance Based on Asymmetric Autocatalysis

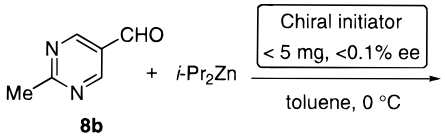
Apart from α-amino acids, various chiral organic molecules with an ee as low as ca. 0.05−0.1% can serve as chiral initiators in the asymmetric autocatalysis of pyrimidylalkanol **9b**.[30] As shown in Table 1, (*S*)-methyl mandelate with 0.1% ee directed the formation of (*R*)-pyrimidylalkanol **9b** with 68% ee, and vice versa ((*S*)-pyrimidylalkanol **9b** with 70% ee was obtained from (*R*)-methyl mandelate) (entries 1 and 2). Methyl mandelate with ca. 0.05% ee can also be used as a chiral initiator (entries 3 and 4). Chiral carboxylic acid (entries 5 and 6) and amine (entries 7 and 8) also act as chiral initiators. Even the very small steric difference between methyl and ethyl substituents on the asymmetric carbon atom of simple (*S*)-2-butanol with only ca. 0.1% ee is sufficient to induce chirality in the resulting pyrimidylalkanol **9b** (entries 9 and 10).

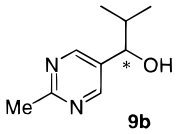
Thus, enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **8b** can recognize slight enantiomeric imbalances in various chiral molecules.

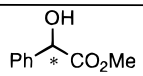
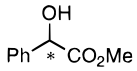
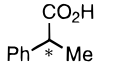
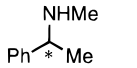
Conclusion

Chiral (zinc alkoxides of) 5-pyrimidyl-, 3-pyridyl-, and 3-quinolylalkanols are asymmetric autocatalysts which automultiply in the enantioselective addition of *i*-Pr_2Zn to the corresponding aldehydes. Practically perfect asym-

Table 1. Amplification of Ee of Pyrimidylalkanol 9b Induced by Chiral Initiators





entry[a]	chiral initiator	ee (%)	alkanol **9b** ee (%)
1		ca. 0.1 (*S*)	68 (*R*)
2		ca. 0.1 (*R*)	70 (*S*)
3		ca. 0.05 (*S*)	54 (*R*)
4		ca. 0.05 (*R*)	38 (*S*)
5		ca. 0.1 (*S*)	76 (*R*)
6		ca. 0.1 (*R*)	73 (*S*)
7		ca. 0.1 (*S*)	79 (*R*)
8		ca. 0.1 (*R*)	85 (*S*)
9		ca. 0.1 (*S*)	73 (*S*)
10		ca. 0.1 (*R*)	76 (*R*)

[a] The molar ratio of chiral initiator:aldehyde **8b**:diisopropylzinc is 0.01−0.02:1.0:2.4. Aldehyde **8b** and diisopropylzinc were added in three portions.

metric autocatalysis which exhibits high enantioselectivity (>99.5% ee) and high yield (>99%) is attained with (2-alkynyl-5-pyrimidyl)alkanol. In principle, consecutive asymmetric autocatalysis can infinitely automultiply chiral compounds with high ee. Asymmetric autocatalysis provides an ideal method of asymmetric synthesis: no chiral catalyst is needed other than itself, the amount of the product increases exponentially, and there is no need to separate the product from the catalyst.

Consecutive asymmetric autocatalysis enables 5-pyrimidyl- and 3-quinolylalkanols with even extremely low ee's to automultiply with a significant amplification of ee without the need for any other chiral auxiliaries. When a chiral compound with only a slight enantiomeric imbalance is present as a chiral initiator, the absolute configuration of the pyrimidylalkanol with high ee formed by asymmetric autocatalysis is determined by that of the chiral initiator. In the presence of L-leucine with low ee induced by asymmetric degradation using CPL, asymmetric autocatalysis affords (*R*)-pyrimidylalkanol with high ee's, and vice versa. Thus, asymmetric autocatalysis with an amplification of ee serves as a mediator which links a slight enantiomeric imbalance in molecules induced by CPL to high enantiomeric purities of organic molecules.

As described, we have discovered highly enantioselective asymmetric autocatalysis and asymmetric autocatalysis with amplification of ee. These are the beginning of the experimental achievement on asymmetric autocatalysis. We believe that our asymmetric autocatalysis with an amplification of ee may become a powerful tool for examining the validity of various mechanisms that have been proposed as the origin of the chirality of organic molecules.[32]

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