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Accounts

Discovery and Development of Asymmetric Autocatalysis

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Asymmetric autocatalysis occurs when a chiral product operates as an asymmetric catalyst for its own production. We have discovered an asymmetric autocatalytic reaction in the enantioselective addition of dialkylzinc to pyridine-3-carbaldehyde, where the product, 3-pyridyl alkanol, acts as an asymmetric autocatalyst. A diol, ferrocenyl alkanol, 5-pyrimidyl alkanol, and 3-quinolyl alkanol were also found to be asymmetric autocatalysts for the enantioselective isopropylation of the corresponding aldehydes. Of these compounds, 5-(2-alkynyl)pyrimidyl alkanol was the best asymmetric autocatalyst, and the asymmetric autocatalytic isopropylation of the corresponding pyrimidine-5-carbaldehyde proceeded quantitatively (>99%), affording itself as a near enantiomerically pure (>99.5% ee) chiral product. When an asymmetric autocatalyst with an extremely low ee was used, the asymmetric autocatalytic reaction proceeded along with amplification of the ee, and a highly enantiomerically enriched product was obtained. When the enantioselective isopropylation of pyrimidine-5-carbaldehydes was examined in the presence of chiral organic compounds with a very low ee acting as chiral initiators, then highly enantiomerically enriched 5-pyrimidyl alkanols were obtained. Their absolute configurations were dependent upon the slight excess of enantiomer in the chiral initiators. Chiral inorganic crystals, such as quartz and sodium chlorate, also act as chiral initiators. In conjunction with asymmetric autocatalysis, the chirality of organic compounds with a high enantiomeric excess has been correlated for the first time with the circularly polarized light and chiral inorganic crystals. Moreover, when an enantioselective isopropylation was examined in the absence of a chiral initiator, asymmetric induction above the detection level was observed in the product, with the ratio of the resulting predominant *S*- and *R*-isomers being almost equal. This result fulfills one of the conditions necessary for spontaneous absolute asymmetric synthesis.

The enantioselective addition of alkylmetals to aldehydes in the presence of chiral ligands yields enantiomerically enriched secondary alcohols. Mukaiyama et al. (including K. S.) reported in 1979 that the highly enantioselective alkylation of alkyllithium to aldehydes proceeded using β-amino alcohols derived from proline as chiral ligands, and that various secondary alcohols were obtained in a high ee.[1] It was also found that the addition of chiral ligands, i.e., β-amino alcohols, enhanced the nucleophilicity of diethylzinc, enabling the ethylation of aldehydes to occur.[1] This is because dialkylzincs were known to be much more sluggish to react with aldehydes than alkyllithiums and Grignard reagents.

Alkylation of aldehydes by dialkylzinc was applied for the enantioselective reaction using chiral β-amino alcohols. The highly enantioselective addition of dialkylzincs to aldehydes has been reported using various chiral β-amino alcohols acting as asymmetric catalysts, and it has become one of the most reliable and efficient methods for preparing chiral secondary alcohols.[2] We have previously reported on the use of chiral β-amino alcohols, such as diphenylprolinol derivatives and *N*,*N*-dialkylnorephedrines, as efficient chiral catalysts, and have realized a very high enantioselectivity in the asymmetric alkylation of both aromatic and aliphatic aldehydes.[3]

In this account, we describe the first asymmetric autocatalytic reaction in which the asymmetric catalyst and the product have the same structure and absolute configuration.[4]

1. Implication of Asymmetric Autocatalysis and the First Example

In a conventional asymmetric catalytic reaction, the structures of the chiral catalyst C* and the product P* are generally different. In contrast, in an asymmetric autocatalytic reaction, the structures and the absolute configurations of the asymmetric autocatalyst P* and the product P* are the same (Scheme 1).

Asymmetric autocatalysis intrinsically has the following advantages:

(1) A high reaction efficiency: The concentration of the chiral catalyst dramatically increases as the reaction proceeds, and therefore the reaction concludes promptly.

(2) Easy purification of the product: The product and the cata-

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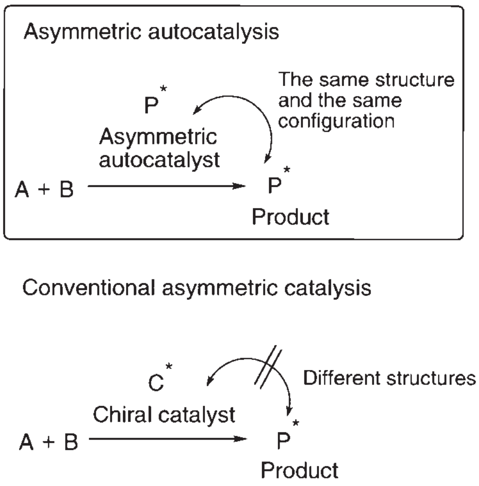


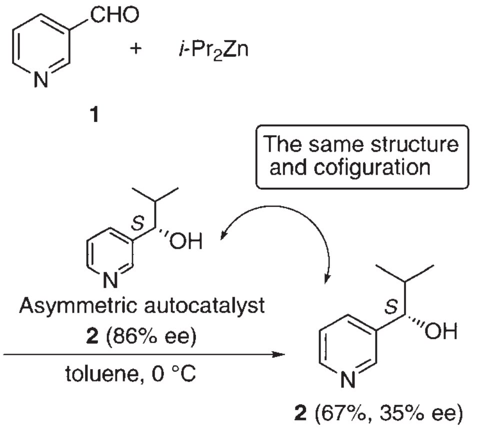
Scheme 1.

lyst are identical, and therefore separation of the product from the catalyst is not needed.

(3) Consecutive reaction: The product is a chiral catalyst, and therefore the product can be used as an asymmetric autocatalyst for the next reaction. This means that the chiral product can be provided semi-permanently from trace amounts of an asymmetric autocatalyst.

These advantages are realized by asymmetric autocatalysis, but not by asymmetric non-autocatalysis.

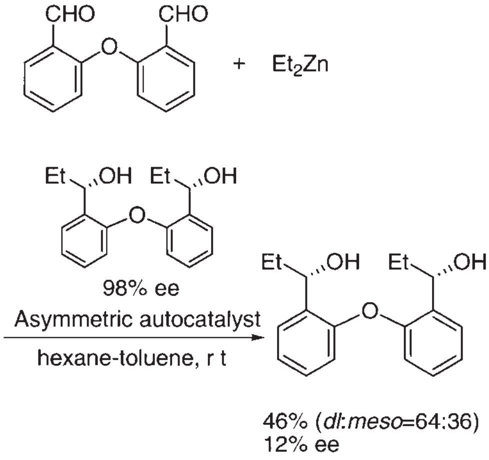
We have comprehensively examined the asymmetric alkylation of various aldehydes using chiral *β*-amino alcohols as chiral catalysts, and noticed that the asymmetric ethylation of pyridine-3-carbaldehyde using *N*,*N*-dibutylnorephedrine (DBNE) proceeded much more smoothly than that of benzaldehyde. (The reaction concluded within 1 h for pyridine-3-carbaldehyde, and within 16 h for benzaldehyde.[5]) We considered that the acceleration was due to the participation of the product, i.e., the alkylzinc alkoxide of 3-pyridyl alkanol, in the catalytic cycle acting as an asymmetric catalyst (or asymmetric autocatalyst). Based on this assumption, we examined the enantioselective addition of diisopropylzinc to pyridine-3-carbaldehyde **1** using the product, (*S*)-3-pyridyl alkanol **2** (86% ee), as an asymmetric autocatalyst, and obtained 3-pyridyl alkanol **2** in a 67% yield with 35% ee in the *S*-form (Eq. 1).[6] This is the first example of an asymmetric autocatalysis in which the product and the chiral catalyst have the same structure and the same absolute configuration.



(1)

2. Highly Enantioselective Asymmetric Autocatalysis

Chiral diols[7] having a diphenyl ether skeleton and a chiral ferrocenyl alkanol[8] were found to serve as asymmetric autocatalysts in the enantioselective alkylation of the corresponding aldehydes (Eqs. 2 and 3).[7,8] In these reactions, however, the ee of the products was lower than that of the asymmetric autocatalysts. To improve the enantioselectivity of the asymmetric autocatalytic reaction, we concentrated on the molecular symmetry of the asymmetric catalyst (product) and the aldehyde, and on the electrophilicity of the aldehyde.



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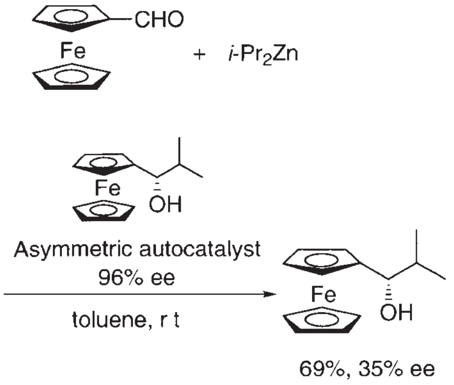
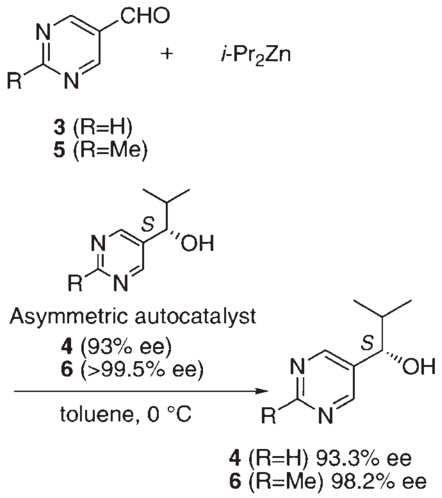


(3)

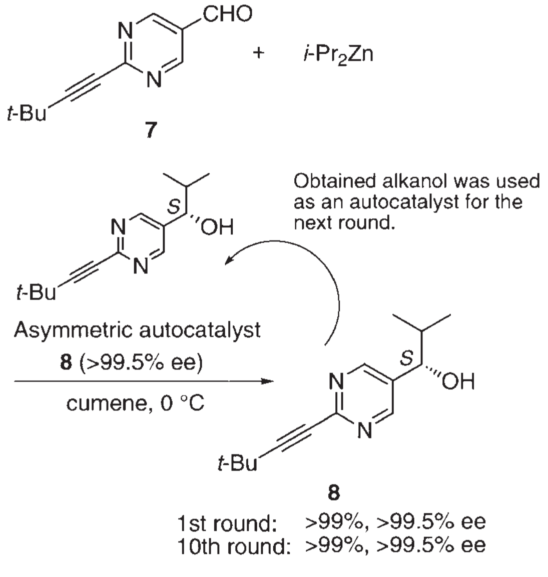
2.1 5-Pyrimidyl Alkanols.

We chose a pyrimidine ring, which has two nitrogen atoms on the aromatic ring, to replace the pyridine ring as a fundamental skeleton. After a thorough investigation of the reaction conditions, including the reaction temperature, concentration, and concentration of dialkylzinc, we realized the first example of a highly enantioselective asymmetric autocatalysis.[9] In the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde **3** using (*S*)-5-pyrimidyl alkanol **4** as an asymmetric autocatalyst, (*S*)-alkanol **4**, which has the same structure and absolute configuration as the catalyst, was newly formed in a 93% ee (Eq. 4). Next, we used 5-pyrimidyl alkanol **6** with a methyl group on the 2-position as an asymmetric autocatalyst, and examined the enantioselective isopropylation of the corresponding aldehyde **5** under the same reaction conditions. The ee of 5-pyrimidyl alkanol **6** reached 98% when the almost enantiomerically pure catalyst **6** was used (Eq. 4).[9]



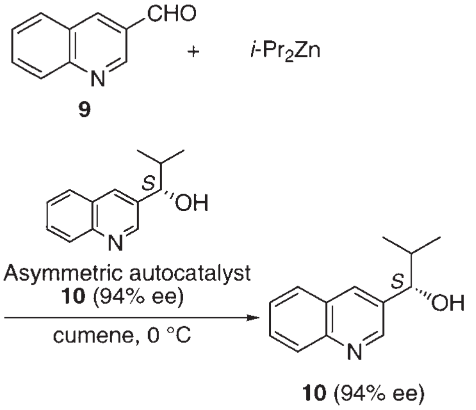
(4)

After screening the substituted pyrimidines, it was found that the substituent on the 2-position of the pyrimidine ring was very important in achieving high enantioselectivity and efficiency as an asymmetric autocatalyst, and that the alkynyl[10a] and alkenyl[10b] groups were the best for this purpose. In the presence of (*S*)-5-pyrimidyl alkanol **8** (which has a *t*-butylethynyl group on the 2-position of the pyrimidine ring) as an asymmetric autocatalyst, the enantioselective alkylation of pyrimidine-5-carbadehyde **7** was examined using 1.7 equivalents of diisopropylzinc in cumene as a solvent. (*S*)-5-Pyrimidyl alkanol **8** was obtained in a near quantitative yield (>99%) and in an almost enantiomerically pure form (>99.5% ee) (Eq. 5). The high yield and enantioselectivity were realized in 10 consecutive asymmetric autocatalytic reactions, in which the obtained product (*S*)-**8** was used as an asymmetric autocatalyst for the next run, and therefore a practically perfect asymmetric autocatalysis could be established. During the 10 consecutive reactions, the initial (*S*)-5-pyrimidyl alkanol **8** was automultiplied by a factor of about 60000000.[10a] Trimethylsilylethenyl and 3,3-dimethyl-1-butenyl groups also exhibit high enantioselectivities.[10b]



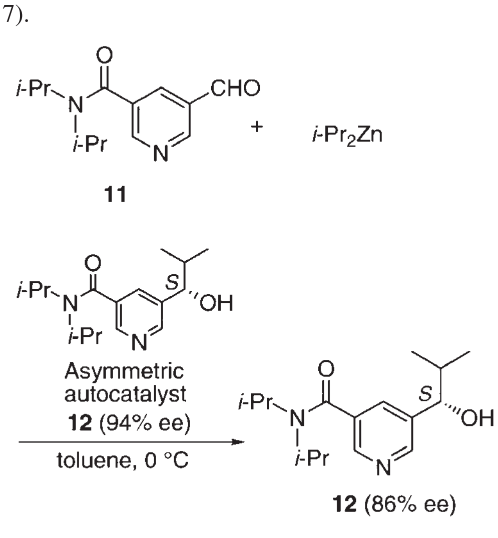
(5)

2.2 3-Quinolyl Alkanol and 5-Carbamoyl-3-pyridyl Alkanol. 3-Quinolyl alkanol, which has one nitrogen atom on the ring, is also an efficient asymmetric autocatalyst, as is 5-pyrimidyl alkanol, which has two nitrogen atoms on the ring. When (*S*)-3-quinolyl alkanol **10** with a 94% ee was examined as an asymmetric autocatalyst using cumene as a solvent, the asymmetric isopropylation of quinoline-3-carbaldehyde **9** proceeded to give (*S*)-3-quinolyl alkanol **10** with the same 94% ee as the catalyst (Eq. 6).[11]



(6)

As described in the previous section, 3-pyridyl alkanol exhibits asymmetric autocatalytic activity, but the enantioselectivity is not very high. Introduction of a carbamoyl group at the 5-position of the pyridine ring enhances the enantioselectivity dramatically.[12] Pyridyl alkanol **12**, which possesses two isopropyl substituents on the nitrogen atom of the carbamoyl group, could induce an ee as high as 86% in the asymmetric isopropylation of the corresponding pyridine-3-carbaldehyde **11** (Eq. 7).



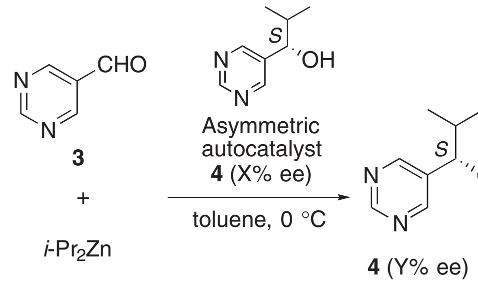
(7)

3. Asymmetric Autocatalysis with the Amplification of Enantiomeric Excess

3.1 Pyrimidyl Alkanols. We also studied asymmetric autocatalysis using asymmetric autocatalysts with a lower ee. (*S*)-Pyrimidyl alkanol **4** with 2% ee was used as an asymmetric autocatalyst for the enantioselective isopropylation of aldehyde **3**. The ee of the resulting alkanol **4**, which included the initial catalyst and the newly formed product, increased to 10% ee (Table 1, Entry 1).[13]

In a non-autocatalytic reaction, Kagan et al. first reported on

Table 1. Asymmetric Autocatalytic Reaction with Amplification of ee



Entry	Asymmetric autocatalyst **4**	Autocatalyst and Product **4**		Product **4**
	X/% ee	Yield/%	Ee/%	Y/% ee
1	2	38	10	16
2	10	63	57	74
3	57	67	81	89
4	81	63	88	90
5	88	66	88	88

asymmetric amplification in a Katsuki–Sharpless epoxidation, in which the ee of the product is higher than that of the chiral catalyst.[14] Asymmetric amplification has been reported in other reactions,[4b,15] including the enantioselective addition of diethylzinc to aldehyde using β-amino alcohols as a chiral catalyst. In all these cases, however, the structure of the chiral catalyst was different from that of the product. Therefore, when the reaction was quenched, further amplification of the ee of the product was not possible.

In contrast, in our asymmetric autocatalysis route, consecutive amplification of the ee is possible by using the product as an asymmetric autocatalyst for the next run. The asymmetric autocatalytic reaction using the above reagents obtained the pyrimidyl alkanol **4** with a 10% ee, which, serving as an asymmetric autocatalyst, increased its ee to 57% ee in the same asymmetric isopropylation reaction (Table 1, Entry 2). The ee of **4** increased to 81% ee, and then to 88% ee by the third and fourth consecutive asymmetric autocatalytic reactions, respectively (Entries 3 and 4 in Table 1).[13] During the four consecutive asymmetric autocatalytic reactions, the (*S*)-pyrimidyl alcohol **4**, which was the major enantiomer in the initial asymmetric autocatalyst mixture by a slight margin, automultiplied by a factor of 238, while the slightly minor enantiomer, the (*R*)-pyrimidyl alcohol **4**, multiplied by a factor of 16 (Fig. 1).[13]

It is noteworthy that, even when an asymmetric autocatalyst with an extremely low ee was used as the initial catalyst, an almost enantiomerically pure product, i.e., asymmetric autocatalyst, could be obtained by consecutive asymmetric autocatalyses. The slightly (*S*)-enriched 5-pyrimidyl alkanol **8** with ca. 0.00005% ee (*S* isomer:*R* isomer = 50.000025:49.999975) was used as an initial catalyst, and almost enantiomerically pure (>99.5% ee) **8** was obtained after three consecutive enantioselective isopropylations of the aldehyde **7** (Eq. 8).[16] During the three consecutive asymmetric autocatalytic reactions, the (*S*)-pyrimidyl alcohol **8** was automultiplied by a factor of about 630000, while the (*R*)-pyrimidyl alcohol **8** was automultiplied by a factor of less than 1000 (Fig. 2). These results have significant scientific importance, in that the initial tiny enantiomeric excess and the amount of chiral compound increased without the assistance of any other chiral auxiliary.

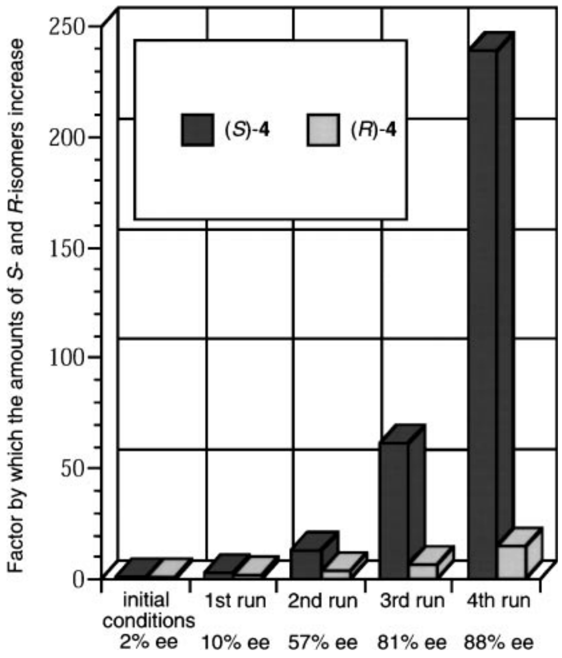
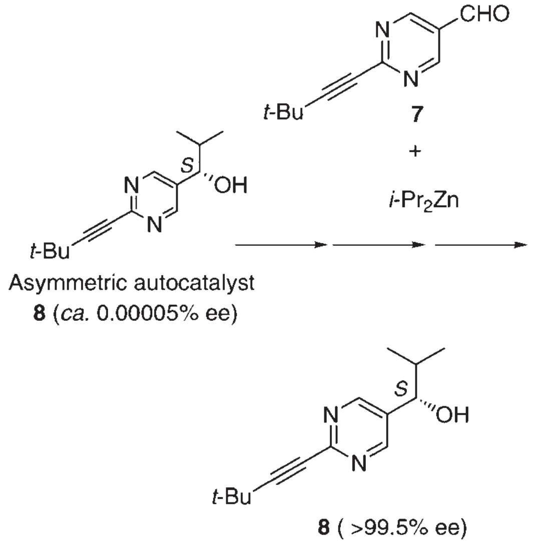


Fig. 1. The increase in the amounts of (*S*)- and (*R*)-isomers of alkanol **4** in consecutive asymmetric autocatalytic reaction.



(8)

3.2 The Relationship between the Reaction Time, Yield, and Enantiomeric Excess. Kinetics analysis was carried out to elucidate the relationship between the reaction time and the product yields of the enantioselective addition of diisopropylzinc to 2-alkynylpyrimidine-5-carbaldehyde using the corresponding 5-pyrimidyl alkanol as an asymmetric autocatalyst.[17] The reaction was proven to be autocatalytic, and the simulated plots were best fitted to the experimental plots when the simulation was second order with respect to the alkylzinc alkoxide of the 5-pyrimidyl alkanol, and first order with respect to the aldehyde and diisopropylzinc (Fig. 3).[17]

Moreover, the second-order model for asymmetric autocatalyst of the alkylzinc alkoxide of the 5-pyrimidyl alkanol could

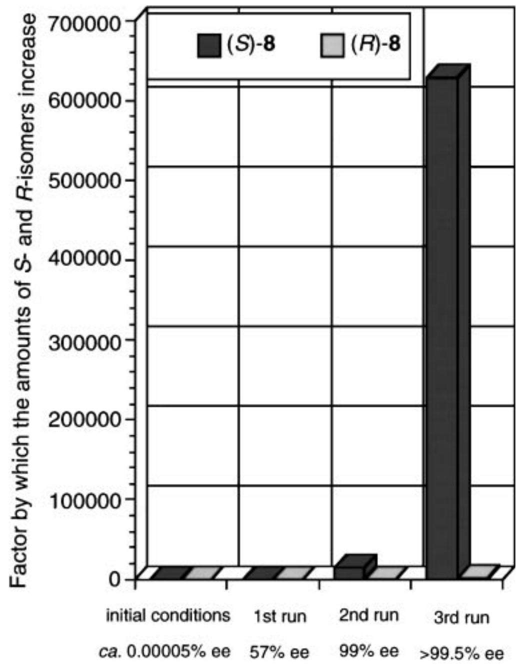


Fig. 2. The increase in the amounts of (*S*)- and (*R*)-enantiomers **8** in consecutive asymmetric autocatalytic reaction.

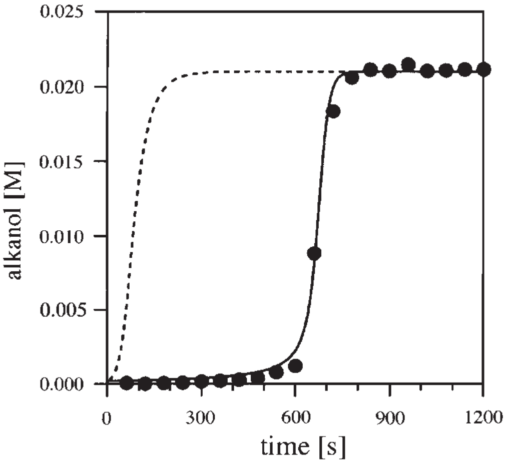
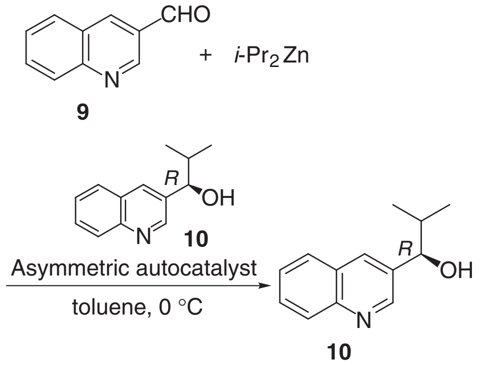


Fig. 3. Comparison of the simulation with experimetal results. Temperature: 0 °C, toluene solution. Initial concentration of aldehyde: 2.08×10^{-2} M, initial concentration of i-Pr_2Zn: 3.13×10^{-2} M, initial concentration of alkanol: 2.08×10^{-4} M. Filled circle: observed. Solid line: simulation. A broken curve represents the simulation assuming the first-order autocatalytic reaction.

also rationalize the amplification from a moderate ee to a high ee.[17b,18] The amplification from a very low ee to a high ee suggests the involvement of an additional aggregation of substrates.[17b]

3.3 Asymmetric Autocatalysis with Amplification of ee Using 3-Quinolyl Alkanol and 5-Carbamoyl-3-pyridyl Alkanol. The 3-quinolyl alkanol **10** is also an asymmetric autocatalyst with amplification of ee (Table 2).[19] Starting from (*R*)-**10** with 9% ee, (*R*)-**10** with 88% ee was obtained after six consecutive asymmetric autocatalytic reactions between quinoline-3-carbaldehyde **9** and i-Pr_2Zn. During the course of these reactions, the amount of the major (*R*)-**10** component in the initial catalyst increased about 7600-fold, while that of the minor (*S*)-**10** component in the initial catalyst increased only about 580-fold.[19]

Table 2. Asymmetric Autocatalytic Reaction Using Quinolyl Alkanol **10** with Amplification of ee



Entry	Asymmetric autocatalyst **10**	Autocatalyst and Product **10**	
	Ee/%	Yield/%	Ee/%
1	8.9	47	43.3
2	43.3	56	67.0
3	67.0	43	81.6
4	81.6	60	85.5
5	85.5	65	86.2
6	86.2	53	88.1

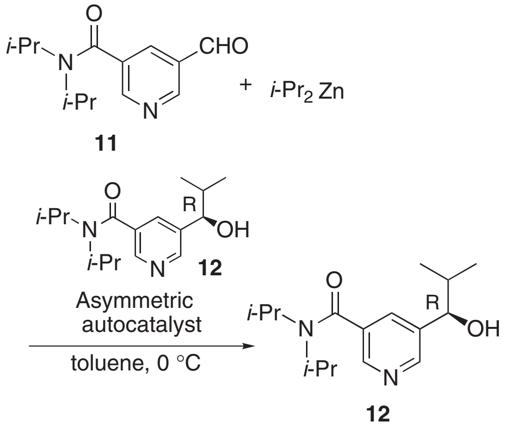
5-Carbamoyl-3-pyridyl alkanol **12** can also operate as an asymmetric autocatalyst with an amplification of ee in the enantioselective addition of i-Pr_2Zn to aldehyde **11**. Over eight consecutive asymmetric autocatalytic reactions, the ee of 3-pyridyl alkanol **12** increased from 4% ee to 87% ee (Table 3).[20]

4. Asymmetric Autocatalysis Using Chiral Initiators

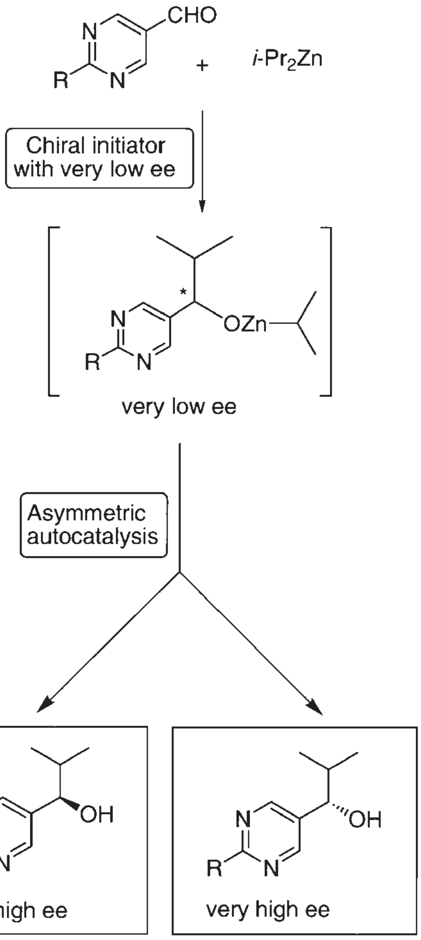
4.1 Asymmetric Autocatalysis Using Chiral Organic Compounds as Chiral Initiators. The asymmetric autocatalysis with amplification of ee starting from pyrimidyl alkanols with an extremely very low ee has a significant implication from a scientific point of view: a slight enantiomeric imbalance in the pyrimidyl alkanols was recognized and amplified to a large enantiomeric imbalance by asymmetric isopropylation of aldehydes based on asymmetric autocatalysis. Even when asymmetric isopropylation of pyrimidine-5-carbaldehyde was carried out in the presence of a chiral organic compound with a very low ee (denoted here as a “chiral initiator”) other than a pyrimidyl alkanol, a slight enantiomeric imbalance was induced in the initial product, i.e., isopropylzinc alkoxide of pyrimidyl alkanols. The slight enantiomeric imbalance would be dramatically amplified by the subsequent asymmetric autocatalysis (Scheme 2).

Initially, we chose mandelic acid ester as the chiral initiator.[21] In the presence of (*S*)-methyl mandelate ((*S*)-methyl 2-hydroxy-2-phenylacetate) with ca. 0.1% ee, the asymmetric addition of diisopropylzinc to pyrimidine-5-carbaldehyde **5** gave (*R*)-5-pyrimidyl alkanol **6** in ca. 70% ee. On the other hand, (*S*)-

Table 3. Asymmetric Autocatalysis Using Pyridyl Alkanol **12** with Amplification of ee



Entry	Asymmetric autocatalyst **12**	Autocatalyst and Product **12**	Product **12**	
	Ee/%	Ee/%	Yield/%	Ee/%
1	4	11	33	16
2	11	25	34	33
3	25	52	34	67
4	52	66	32	76
5	66	76	63	79
6	76	83	58	86
7	83	84	57	85
8	84	86	53	87



The configurations of chiral initiators decide those of pyrimidyl alcohol

Scheme 2.

5-pyrimidyl alkanol **6** in 70% ee could be synthesized by using (*R*)-methyl mandelate with ca. 0.1% ee (Table 4, Entries 1 and 2). These results imply that the slight enantiomeric imbalance (50.05:49.95) in methyl mandelate was recognized and amplified in the pyrimidyl alkanol **6** via the asymmetric isopropylation of pyrimidine-5-carbaldehyde **5**. Even a methyl mandelate with a lower ee of ca. 0.05% could be used (Entries 3 and 4). Chiral initiators, such as carboxylic acid and an amine also work effectively (Entries 5–8).[21] Moreover, (*S*)-2-butanol with ca. 0.1% ee serves as a chiral initiator to give (*S*)-pyrimidyl alkanol **6** with an ee of 73%, while (*R*)-2-butanol affords (*R*)-**6**. It is noteworthy that a chirality with only a slight difference between the methyl and ethyl groups bonded to an asymmetric carbon in 2-butanol with a low ee could be recognized (Entries 9 and 10).

Next, we chose leucine as the chiral initiator. In the presence of L-leucine with an ee of ca. 2%, the asymmetric isopropylation of pyrimidine-5-carbaldehyde **5** with diisopropylzinc provided (*R*)-pyrimidyl alkanol **6** with an amplified ee of 21%. When D-leucine with ca. 2% ee was used instead of L-leucine, (*S*)-pyrimidyl alkanol **6** with a 22% ee was obtained (Scheme 3).[21] These ee values are easily amplified by further asymmetric autocatalysis.

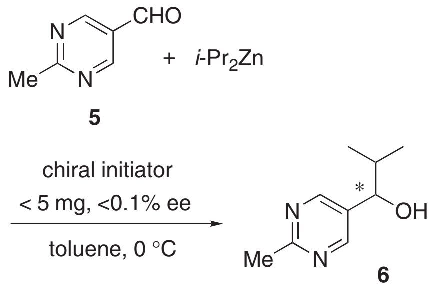
Further, we examined the use of [6]helicene (hexahelicene) as a chiral initiator. In the presence of (*P*)-[6]helicene with a 0.13% ee, the reaction between 2-alkynylpyrimidine-5-carbaldehyde **7** and *i*-Pr$_2$Zn gave (*S*)-pyrimidyl alkanol **8** with a 56% ee. In contrast, (*R*)-pyrimidyl alkanol **8** with a 62% ee was formed using (*M*)-[6]helicene with an ee of 0.54% (Scheme 4).[22] The moderate enantiomeric excesses of (*R*)- and (*S*)-**8** (56% and 62% ee, respectively) were increased to >99.5% ee by the subsequent asymmetric autocatalysis.

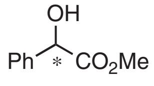
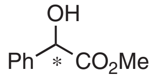
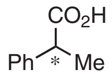
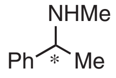
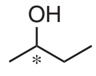
Asymmetric photolysis using circularly polarized light (CPL) of racemic leucine provides enantiomerically-enriched leucine with an ee of ca. 2%,[23] and asymmetric photosynthesis of prochiral compounds affords chiral hexahelicene with an ee of ca. 0.2%.[24] Therefore, the implication of the above results is that, in combination with asymmetric autocatalysis, an organic compound with a high enantiomeric excess can be produced using CPL as a physical chiral source.

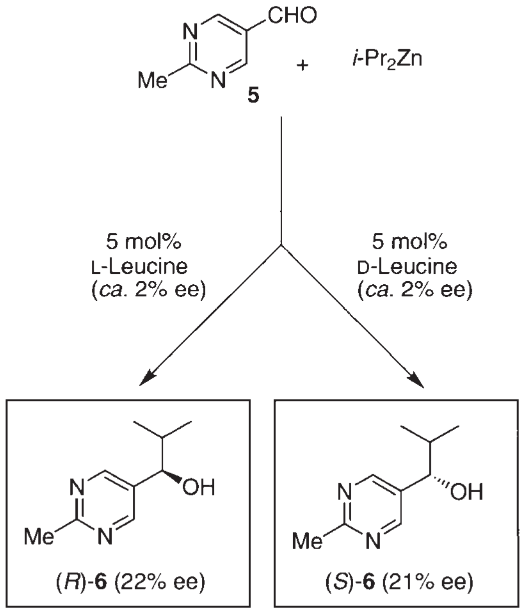
In biomolecules, only one of the two possible enantiomers plays a pivotal role. e.g., L-amino acids in proteins and D-sugars in DNA or RNA. In the course of chemical evolution, which led to the emergence of life, just how the enantiomeric imbalances were induced in organic compounds, and how these imbalances were amplified is an enigma. One of the candidates for the origin of chirality is CPL, and indeed, strong radiation of CPL from the star formation region has been observed recently.[25] Therefore, our results on the first correlation of a high ee in an organic compound using CPL is scientifically significant.

Deuterium-substituted chiral compounds acting as chiral initiators are a new challenge. In the presence of (*S*)-benzyl alcohol-α-d^1 (R = Ph, >99.5% ee), the asymmetric isopropylation of pyrimidine-5-carbaldehyde **7** with diisopropylzinc affords

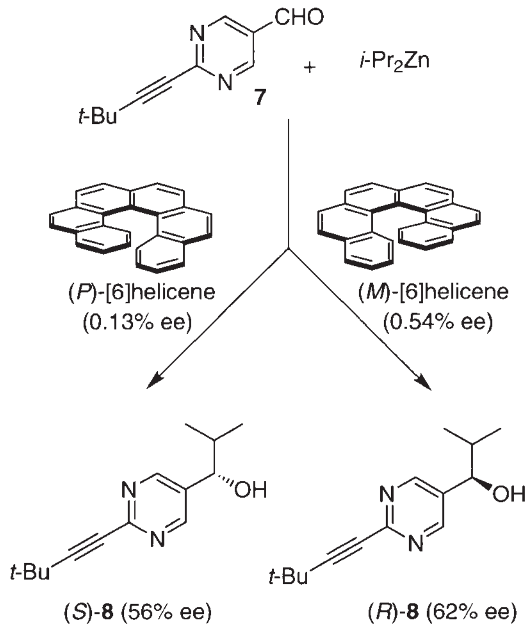
Table 4. Asymmetric Autocatalysis Using Chiral Initiators



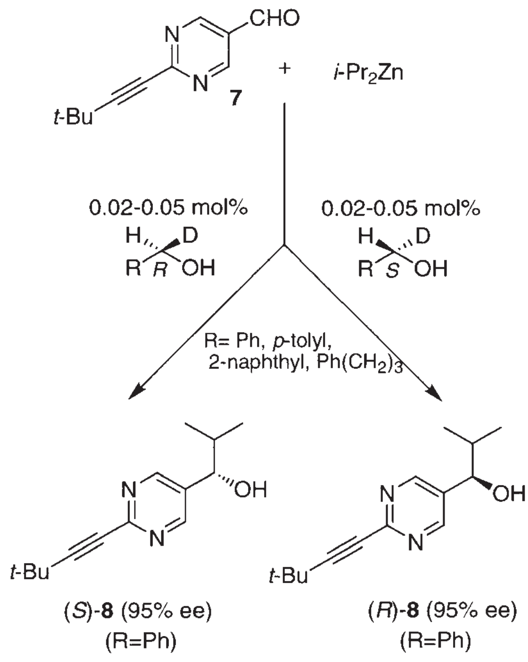
Entry	Chiral initiator		Obtained alkanol **6**
		Ee/%	Ee/%
1		ca. 0.1 *(S)*	68 *(R)*
2		ca. 0.1 *(R)*	70 *(S)*
3		ca. 0.05 *(S)*	54 *(R)*
4		ca. 0.05 *(R)*	38 *(S)*
5		ca. 0.1 *(S)*	76 *(R)*
6		ca. 0.1 *(R)*	73 *(S)*
7		ca. 0.1 *(S)*	79 *(R)*
8		ca. 0.1 *(R)*	85 *(S)*
9		ca. 0.1 *(S)*	73 *(S)*
10		ca. 0.1 *(R)*	76 *(R)*



Scheme 3.



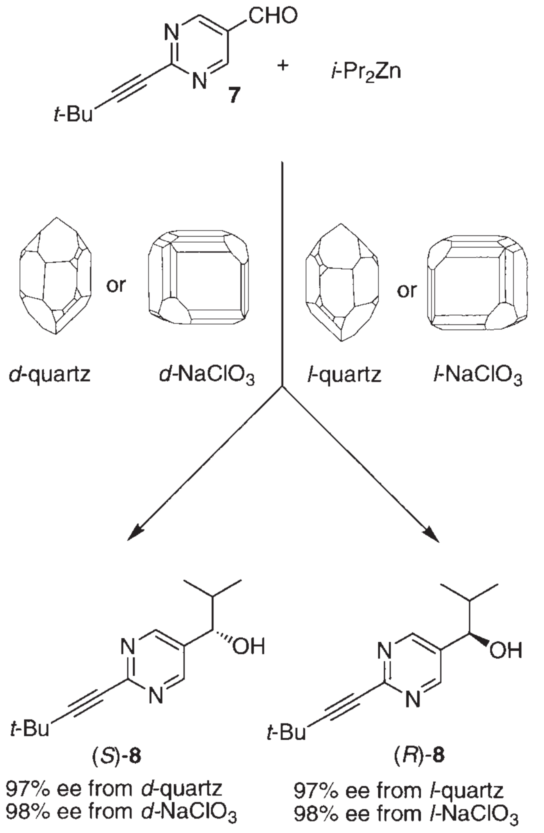
Scheme 4.



Scheme 5.

(*R*)-pyrimidyl alkanol **8** in ee values as high as 95%.[26] On the other hand, when (*R*)-benzyl alcohol-α-d^1 (R = Ph, >99.5% ee) was used, (*S*)-pyrimidyl alkanol **8** with 95% ee was obtained (Scheme 5). *p*-Tolylmethanol-α-d^1, 2-naphthylmethanol-α-d^1, and 3-phenyl-1-propanol-α-d^1 can also be used as chiral initiators, and the correlation between the absolute configuration of the chiral deuterium alcohols and the obtained pyrimidyl alkanol **8** is the same.[26] These results are the first examples of highly enantioselective reactions using chiral compounds due to isotopic substitution as the chiral source.

4.2 Asymmetric Autocatalysis Using Chiral Inorganic Crystals as Chiral Initiators. In place of the above-mentioned chiral organic compounds, we examined quartz (SiO_2) as a chiral initiator, because quartz exhibits morphologically chiral inorganic crystals in both dextrorotatory (*d*) and levoro-



Scheme 6.

tatory (*l*) enantiomorphs that exist in nature. It is one of the candidates for the origin of chirality of organic compounds.[27] Asymmetric adsorption of radioactive amino acids on quartz has been reported.[28] However, no apparent asymmetric synthesis using quartz as a chiral source has been reported.[29]

The asymmetric isopropylation of pyrimidine-5-carbaldehyde **7** with *i*-Pr_2Zn was examined in the presence of *d*- or *l*-quartz powder (average particle size = 3–8 μm). (*S*)-Pyrimidyl alkanol **8** was obtained from *d*-quartz and (*R*)-pyrimidyl alkanol **8** from *l*-quartz in a high yield and a high ee (95 and 97% ee, respectively) (Scheme 6).[30]

Next, we chose sodium chlorate ($NaClO_3$) as a chiral initiator for the asymmetric isopropylation of pyrimidine-5-carbaldehyde **7** with *i*-Pr_2Zn. *d*-$NaClO_3$ (particle size = 5–12 μm) afforded (*S*)-pyrimidyl alkanol **8** with a 98% ee, and *l*-$NaClO_3$ afforded (*R*)-**8** with a 98% ee (Scheme 6). When the same reaction was examined using a mixture of *d*- and *l*-$NaClO_3$ (*d*:*l* = 3:1), the excess enantiomorph (*d*-$NaClO_3$) determined the absolute configuration of the product, and (*S*)-pyrimidyl alkanol **8** was obtained.[31] It should be noted that the stirred crystallization of $NaClO_3$ from an aqueous solution is reported to give stochastically *d*- or *l*-highly enantiomerically enriched $NaClO_3$ crystals.[32]

It was also found that sodium bromate ($NaBrO_3$) acted as a chiral initiator.[31b] In the case of $NaBrO_3$, unlike that of $NaClO_3$, *d*-$NaBrO_3$ afforded (*R*)-**8** and *l*-$NaBrO_3$ afforded (*S*)-**8**. However, these results can be rationalized by the fact that the configuration of the crystal structures of *d*-$NaBrO_3$ and *l*-$NaClO_3$ are the same.[31b]

5. Stochastic Production of *S*- and *R*-Enantiomers without Adding a Chiral Source: Spontaneous Absolute Asymmetric Synthesis

In the absence of a chiral substance, nucleophile attack on a prochiral aldehyde on the *re*- or *si*-face occurs with a theoretical equal probability, providing stochastic yields of *S* and *R* molecules. However, the exact numbers of the two enantiomers in chiral adducts are not equal in most cases. Mislow[33a] described the inevitability of enantiomeric enrichment in absolute asymmetric synthesis. According to the theory of statistics, it is expected that a fluctuation in the ratio of the *S*- and *R*-isomers becomes more and more obvious as the amount of the mixture become smaller.[34] For example, if 100000 chiral molecules are formed under reaction conditions where the probability of the formation of two enantiomers is equal, then half of the groups will contain a statistical excess of more than 212 molecules of one of the enantiomers (i.e., >0.21% ee). Thus, even if we examine the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde without adding any chiral substance, extremely small fluctuations would induce a slight enantiomeric imbalance (the magnitude of this small imbalance cannot be detected by modern ee analysis techniques) in the initially formed zinc alkoxide of the pyrimidyl alkanol. The imbalance would be enlarged by consecutive asymmetric autocatalytic reactions with an amplification of the ee.

Indeed, the reaction of pyrimidine carbaldehydes and *i*-Pr_2Zn without the addition of a chiral substance after the subsequent asymmetric autocatalysis with amplification of ee, produces pyrimidyl alkanols with an ee that is above the detection level.[35a] The reaction of pyrimidine-5-carbaldehyde **7** with *i*-Pr_2Zn in a mixed solvent of diethyl ether and toluene gave optically active (*S*)- and (*R*)-pyrimidyl alkanol **8** with detectable ee values (15–91%). To examine the statistical distribution of the absolute configurations of compound **8** formed, an additional 36 experiments were carried out under the same reaction conditions. In all cases, the ee values were above detection level in the products. As shown in Fig. 4, the absolute configurations of the pyrimidyl alkanol **8** showed an approximate stochastic distribution (19 times the formation of *S*, and 18 times the formation of *R*).[35b] Other solvents, e.g., a mixture of ether–toluene, dibutyl ether alone, and a mixture of diethyl ether–dibutyl ether, also facilitate the stochastic formation of (*S*)- and (*R*)-**8**.[35c] Thus, ethereal solvents play an essential role in achieving the formation of pyrimidyl alkanol **8** in a stochastic manner: It should be noted that these results satisfy the necessary conditions for a spontaneous absolute asymmetric synthesis.

6. Conclusions

We have found that asymmetric autocatalysis occurs in the enantioselective addition of dialkylzincs to aldehydes. Chiral 5-pyrimidyl, 3-quinolyl, and 5-carbamoyl-3-pyridyl alkanols operate as efficient asymmetric autocatalysts for the asymmetric isopropylation of pyrimidine-5-, quinoline-3-, and 5-carbamoylpyridine-3-carbaldehydes, respectively. In particular, 2-alkynylnyl- and 2-alkenyl-5-pyrimidyl alkanols realized near perfect asymmetric autocatalysis, and the enantioselective isopropylation of the corresponding aldehydes proceeded almost quantitatively (>99% yield), exhibiting almost perfect enantio-

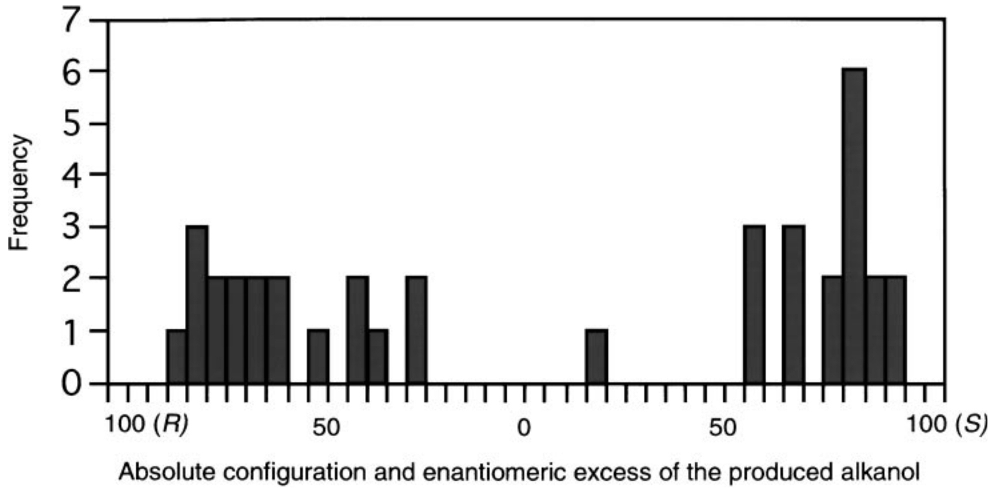


Fig. 4. Stochastic production of chiral (*S*)- and (*R*)-alkanol without adding any chiral substance.

selectivity (>99.5% ee).

Moreover, when asymmetric autocatalysts with a low ee was used, asymmetric amplification was observed. We took the best autocatalytic system and conducted consecutive reactions in which the product obtained was used as the catalyst for the ensuing reaction: Starting from pyrimidyl alkanol with ca. 0.00005% ee, we obtained an almost enantiomerically pure alkanol in significantly increased ee after only three consecutive reactions.

Chiral initiator-induced asymmetric autocatalysis was also realized. In the presence of chiral organic molecules with a low ee, the asymmetric diisopropylation of pyrimidine-5-carbaldehydes proceeded to afford chiral 5-pyrimidyl alkanols with a highly amplified ee. Circularly polarized light-induced chiral compounds, such as leucine and [6]helicene with a low ee, also operate as chiral initiators. Furthermore, chiral inorganic crystals, such as quartz and sodium chlorate, are also chiral initiators. The absolute configuration of the pyrimidyl alkanol is dependent on the *d*- or *l*-enantiomorph of the inorganic crystals used.

Even in the absence of a chiral initiator, enantiomerically enriched pyrimidyl alkanol was formed from the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc. The absolute configurations of the pyrimidyl alkanols formed in ether containing a solvent show approximate stochastic distributions. These results suggest that the reaction is a spontaneous absolute asymmetric synthesis.

Asymmetric autocatalysis is an efficient method for asymmetric synthesis and has significant advantages. It serves as an efficient tool for examining the validity of the theories of the origins of chirality.

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