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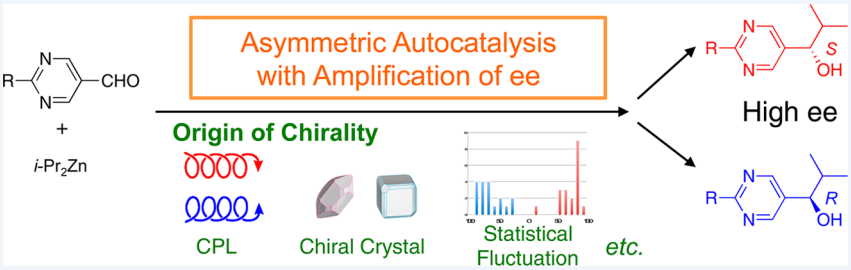
Asymmetric Autocatalysis of Pyrimidyl Alkanol and Its Application to the Study on the Origin of Homochirality

Kenso Soai,*[,†,‡] Tsuneomi Kawasaki,[‡,§] and Arimasa Matsumoto[†]

[†]Department of Applied Chemistry, and [‡]Research Center for Chirality, Research Institute for Science and Technology, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

[§]Department of Materials Science and Engineering, University of Fukui, Bunkyo, Fukui 910-8507, Japan



CONSPECTUS: Amplification of enantiomeric excess (ee) is a key feature for the chemical evolution of biological homochirality from the origin of chirality. We describe the amplification of ee in the asymmetric autocatalysis of 5-pyrimidyl alkanols in the reaction between diisopropylzinc (*i*-Pr_2Zn) and pyrimidine-5-carbaldehydes. During the reaction, an extremely low ee (ca. 0.00005% ee) can be amplified to >99.5% ee, and therefore, the initial slightly major enantiomer is automultiplied by a factor of ca. 630000, while the initial slightly minor enantiomer is automultiplied by a factor of less than 1000. In addition, pyrimidyl alkanols with various substituents at the 2-position of the pyrimidine ring, 3-quinolyl alkanol, 5-carbamoyl-3-pyridyl alkanol, and large multifunctionalized pyrimidyl alkanols also act as highly efficient asymmetric autocatalysts in the addition of *i*-Pr_2Zn to the corresponding aldehydes.

The asymmetric autocatalysis of pyrimidyl alkanol can discriminate the chirality of various compounds. Chiral substances such as alcohols, amino acids, hydrocarbons, metal complexes, and heterogeneous chiral materials can act as chiral triggers for asymmetric autocatalysis to afford pyrimidyl alkanols with the corresponding absolute configuration of the initiator. This recognition ability of chiral compounds is extremely high, and chiral discrimination of a cryptochiral quaternary saturated hydrocarbon was established by applying asymmetric autocatalysis.

By using the large amplification effect of the asymmetric autocatalysis, we can link various proposed origins of chirality with highly enantioenriched organic compounds in conjunction with asymmetric autocatalysis. Thus, a statistical fluctuation in ee of racemic compounds can be amplified to high ee by using asymmetric autocatalysis. Enantiomeric imbalance induced by irradiation of circularly polarized light can affect the enantioselectivity of asymmetric autocatalysis. The asymmetric autocatalysis was also triggered by the morphology of inorganic chiral crystals such as quartz, sodium chlorate, and cinnabar. Chiral organic crystals of achiral compounds also act as chiral initiators, and during the study of a crystal of cytosine, enantioselective chiral crystal phase transformation of the cytosine crystal was achieved by removal of the water of crystallization in an achiral monohydrate crystal. Enantioselective C−C bond formation was realized on the surfaces of achiral single crystals based on the oriented prochirality of achiral aldehydes. Furthermore, asymmetric autocatalysis of pyrimidyl alkanols is a highly sensitive reaction that can recognize and amplify the significantly small effect of a chiral compound arising solely from isotope substitution of hydrogen, carbon, and oxygen (D/H, $^{13}C/^{12}C$, and $^{18}O/^{16}O$). These examples show that asymmetric autocatalysis with an amplification of chirality is a powerful tool for correlating the origin of chirality with highly enantioenriched organic compounds. Asymmetric autocatalysis using two *β*-amino alcohols reveals a reversal of enantioselectivity in the addition of *i*-Pr_2Zn to aldehyde and is one approach toward understanding the mechanism of asymmetric dialkylzinc addition, where heteroaggregates act as the catalytic species.

1. INTRODUCTION

The origin of biological homochirality, such as that seen in L-amino acids and D-sugars, has been a subject of considerable attention. If proteins include random enantiomers, then they cannot construct a specific steric structure and cannot act as, for example, enzymes. Therefore, homochirality is an essential feature in biology to keep their function. Many theories have been postulated on the origin of homochirality,[1−5] which may give insights into the origin of life. Proposed mechanisms, such as circularly polarized light (CPL),[6,7] quartz,[8] and spontaneous absolute asymmetric synthesis[9] can induce, where possible, only

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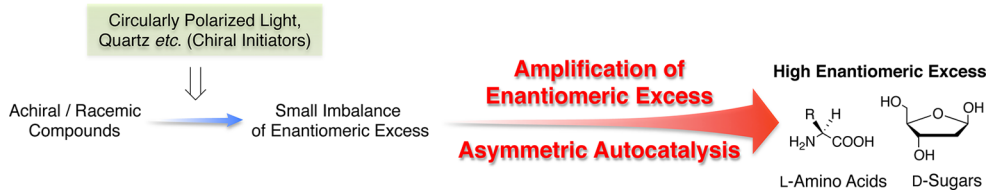
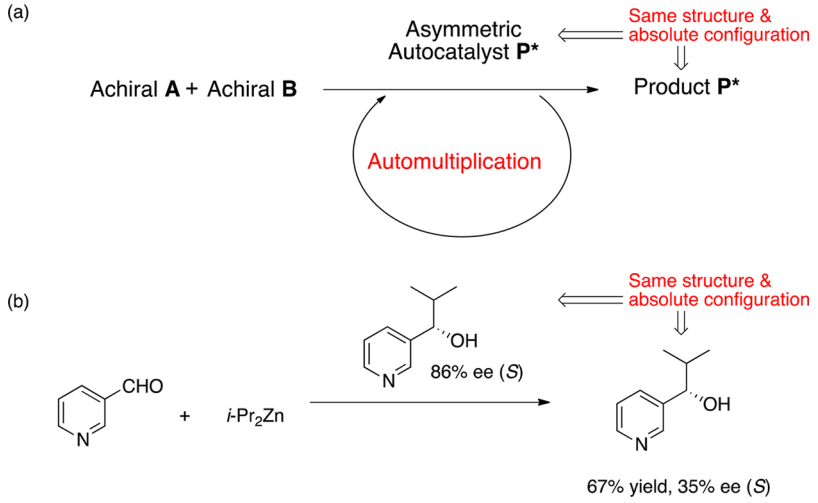
Scheme 1. Proposed Route to Homochirality



Scheme 2. (a) General Description of Asymmetric Autocatalysis and (b) the First Report on Asymmetric Autocatalysis of 3-Pyridyl Alkanols



a very low enantioimbalance, and therefore, an amplification pathway is needed to achieve the high enantioenrichment seen in biological compounds (Scheme 1).

Enantiomers are mirror images of each other and are not superimposable. They show the same physical properties, except for their sign of specific optical rotation. However, considering the formation of a dimer, such as an *S*·*S* homodimer (or *R*·*R* homodimer) and an *S*·*R* heterodimer, such diastereomeric aggregates possess different physical properties. Thus, several amplification processes based on diastereomeric differences have been reported. Enantiomeric self-purification via self-disproportionation has been observed in both distillation[10] and sublimation.[11]

Moreover, there are catalytic asymmetric reactions in which the enantiopurity of the product is higher than that of the catalyst. Kagan reported on a titanium tartrate-catalyzed asymmetric epoxidation to afford a chiral product with an amplified enantiomeric excess (ee) higher than that of the catalyst.[12] Large amplification phenomena have been reported in dialkylzinc addition reactions using chiral amino alcohols as the ligand.[13] An amplification of ee in proline-catalyzed α-aminoxylation[14] and amino acid-catalyzed sugar synthesis[15] has been reported. Viedma reported on the amplification of crystal ee in the formation of enantiomorphs of sodium chlorate after grinding,[16] which was applied to a conglomerate of chiral amino acid derivatives.[17] Amplification of chirality has been observed via a cooperative effect in polymer helicity.[18]

Our approach to correlate the origin of chirality with highly enantioenriched organic compounds is to use asymmetric autocatalysis with an amplification of enantiopurity.[19−21] Thus, the proposed chiral factors for the origin of chirality can possibly induce an enantiomeric imbalance to provide, after the amplification of ee, a near enantiopure product in conjunction with asymmetric autocatalysis (Scheme 1).

2. DISCOVERY OF ASYMMETRIC AUTOCATALYSIS WITH AMPLIFICATION OF ENANTIOMERIC EXCESS

Asymmetric autocatalysis is defined as a reaction in which the chiral product acts as a chiral catalyst for its own production. In the reaction between achiral **A** and achiral **B**, the chiral catalyst **P*** affords the chiral product **P*** with the same structure and absolute configuration; that is, the chiral product **P*** acts as a chiral catalyst **P*** for its own multiplication (Scheme 2a). Thus, the reaction is an automultiplication of chiral molecules.

In 1953, Frank proposed a kinetic model for asymmetric autocatalysis, without mentioning any particular chemical structure, in which a chiral product acted as a chiral catalyst for its own production and suppressed the formation of its enantiomer.[22] However, no actual reaction was known until our first report on the asymmetric autocatalysis of 3-pyridyl alkanols, which involved the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to pyridine-3-carbaldehydes (Scheme 2b).[23]

After searching various nitrogen-containing substrates, in 1995 we discovered the amplification of ee during the asymmetric autocatalysis of 5-pyrimidyl alkanol in the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde.[24] Then, we showed that the effect of the substituent at the 2-position of pyrimidine was significant.[25] Thus, using a substrate with an alkynyl substituent at the 2-position, asymmetric amplification from as low as ca. 0.00005% ee to an almost enantiopure (>99.5% ee) product **1** was achieved in only three consecutive asymmetric autocatalysis reactions, as shown in Figure 1.[26] The first round of asymmetric autocatalysis using (*S*)-**1** with ca. 0.00005% ee gave the same (*S*)-**1** in a 96% yield with an enhanced ee of 57%. The second round of the reaction using (*S*)-**1** with the obtained 57% ee amplified the ee of **1** to 99%, and the third round of the reaction finally gave (*S*)-**1** with significantly amplified near

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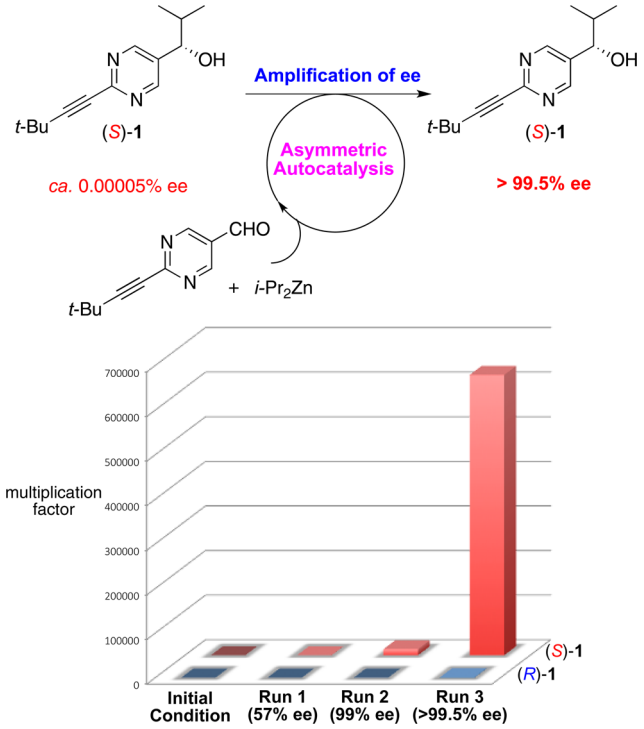

Figure 1. Amplification of ee in the asymmetric autocatalysis of 5-pyrimidyl alkanols **1**.

enantiopure >99.5% ee. During these three consecutive reactions, the initial only slightly major (*S*)-enantiomer **1** was automultiplied by a factor of ca. 630000, whereas the multiplication factor of the initial only slightly minor (*R*)-enantiomer was less than 1000 (Figure 1). The initial very small enantioimbalance in (*S*)-**1** represented only a few molecules difference in the 10-million racemic molecules of **1**. Therefore, it was demonstrated that asymmetric autocatalysis with amplification of ee enables chiral compounds with a slight bias in chirality to become highly enantioenriched without the assistance of any chiral chemical auxiliary or asymmetric physical field.

In addition to the initial report of asymmetric amplification using asymmetric autocatalyst **3** without a substituent at the 2-position,[24] it was found that the 2-methyl-5-pyrimidyl alkanol **4**[27] and the 5-pyrimidyl alkanols **5**−**12** possessing alkenyl[28] and alkynyl groups[25,29,30] at the 2-position, including **1**, also exhibited a significant automultiplication functionality (Figure 2). The 3-quinolyl alkanols **13**−**15**[31] and 5-carbamoyl-3-pyridyl alkanol **16**[32] are also highly efficient asymmetric autocatalysts. Recently, we reported on the asymmetric autocatalysis of the large chiral molecule **17**, in which multiple asymmetric stereogenic centers are attached at the periphery of the alkylsilane backbone.[33] This large molecule possesses the capability to self-replicate and self-improve the ee and diastereomeric ratio.

We have reported the kinetic analysis of the relationship between the time and yield[34] including ee of the product of asymmetric autocatalysis using chiral HPLC,[35] which suggested the aggregate as catalytic species by comparing the yield and ee between experimental and simulated values. In addition, it was also indicated that a suppression pathway of the minor enantiomer existed and higher order (oligomeric) stable and unstable aggregates were formed. Mechanistic studies of asymmetric autocatalysis were also investigated in several groups with various methods. Measurement of heat flow by microcalorimeter provided a detailed reaction rate as a function of time, which explained the dimeric catalyst model.[36] NMR experiments proposed the presence of dimeric and tetrameric species by the direct observation of the reaction solution.[37,38] And computational molecular modeling revealed the detailed structure of catalyst aggregates at the molecular level, and the authors proposed the transition state of the reaction including substituent effects to discuss the enantioface selectivity of asymmetric autocatalysis.[39−42] Reaction models based on the effect of spontaneous mirror-symmetry breaking have been reported, and these approaches also suggested the mechanistic framework of asymmetric autocatalysis of pyrimidyl alkanol.[43−46]

One of the important aspects of asymmetric autocatalysis of pyrimidyl alkanols is that various chiral substances can trigger the reaction. Thanks to the large amplification effect, the initial induced enantiomeric imbalance can be amplified efficiently by

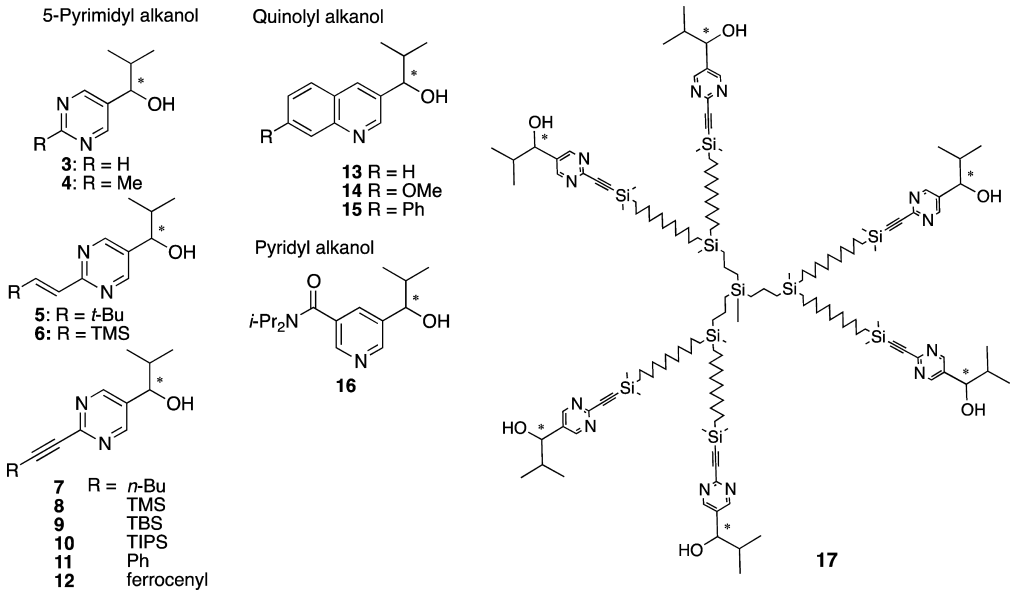

Figure 2. Asymmetric autocatalysts in reactions with corresponding aldehydes and *i*-Pr_2Zn with amplification of ee.

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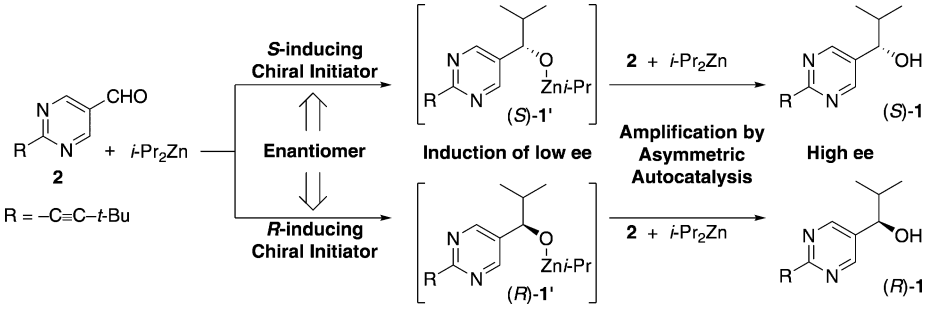
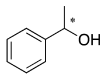
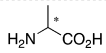
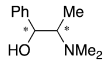
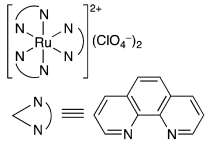
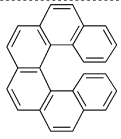
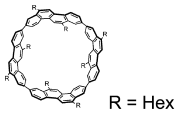
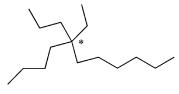
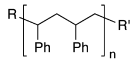
Table 1. Enantioselective *i*-Pr$_2$Zn Addition to Pyrimidine-5-Carbaldehyde 2 Initiated Using Chiral Compounds Followed by Asymmetric Autocatalysis



Entry	Chiral Initiator		5-Pyrimidyl Alkanol **1**		Ref.
	Structure	Config.	Config.	ee (%)	
1		*S*	*S*	93	47
		R	*R*	96	
2		*S*	*S*	92	48
		R	*R*	90	
3		(1*S*,2*R*)	*S*	99	49,50
		(1*R*,2*S*)	*R*	99	
4	Helical silica	Right-handed	*S*	96	51
		Left-handed	*R*	97	
5		Δ	*S*	91	52
		Λ	*R*	88	
6		*P*	*S*	95	53
		M	*R*	95	
7		*M*	*S*	91	54
		P	*R*	91	
8		*R*	*S*	97	55
		S	*R*	97	
9		–	*S*	94	56
		–	*R*	92	

further reactions. Thus, even chiral compounds without any catalytic activity can serve as chiral initiators to afford enantioenriched pyrimidyl alkanols, with their absolute configurations related to those of the chiral initiators (Table 1). As shown in entries 1−3 of Table 1, in the presence of chiral compounds, enantioselective addition of *i*-Pr$_2$Zn to pyrimidine-5-carbaldehydes gave alkanols with a high ee with the corresponding absolute configurations.[47−50] Heterogeneous chiral materials, including helical silica (entry 4)[51] and chiral metal complexes with topological chirality (entry 5)[52] can also serve as a chiral trigger for asymmetric autocatalysis to provide the enantioenriched alkanol **1** with a high enantioenrichment.

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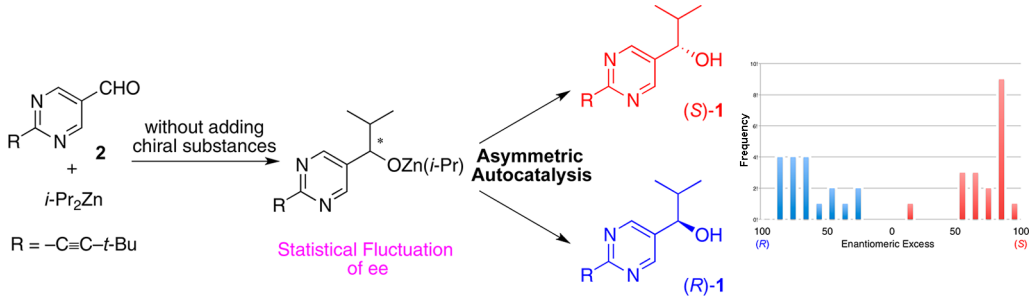
Scheme 3. Enantioselective Synthesis without the Intervention of a Chiral Substance



In addition, chiral hydrocarbons, such as helicenes[53] and finite single-wall carbon nanotube molecules,[54] and even cryptochiral compounds, such as a saturated quaternary and tertiary hydrocarbons[55] and isotactic polystyrene,[56] can also act as chiral triggers of asymmetric autocatalysis (entries 6–9). Therefore, these sequences of the reaction represent a highly sensitive discrimination of hidden chirality. Further study should be directed to understand how chiral source induced the initial imbalance of ee including the absolute handedness before starting the amplification cycle in asymmetric autocatalysis.[57]

3. SPONTANEOUS ABSOLUTE ASYMMETRIC SYNTHESIS

The synthesis of enantioenriched compounds without the assistance of any chiral factors is called spontaneous absolute asymmetric synthesis.[9] It is widely believed that without the intervention of a chiral factor, the molecular ratio of (*R*)- and (*S*)-products is 1:1. However, based on the theory of statistics, the so-called racemate does not contain exactly the same numbers of each enantiomer. Therefore, when a system involves asymmetric autocatalysis with an amplification of ee, an initial bias in ee resulting from a fluctuation in the racemate would be enhanced to produce an enantioenriched product (Scheme 3).

The reaction of achiral pyrimidine-5-carbaldehyde **2** with *i*-Pr_2Zn without adding any chiral substance has been examined. The subsequent consecutive asymmetric autocatalysis afforded pyrimidyl alkanol **1** with either an *S* or *R* configuration.[58−60] The absolute configurations show an approximate stochastic distribution of *S* and *R* enantiomers (19 times resulting in the formation of *S* and 18 times resulting in the formation of *R*). The approximate stochastic distribution in the formation of the alkanol fulfills one of the conditions necessary for chiral symmetry breaking via spontaneous absolute asymmetric synthesis.[43] This reaction is a strong candidate for the origin of homochirality[61−64] and differs from spontaneous chiral crystallization in that it enables an increase in both ee and the amount of a chiral compound.

4. CORRELATION BETWEEN CPL AND HIGHLY ENANTIOENRICHED COMPOUNDS

CPL is a chiral physical force and has been proposed as an origin of chirality.[65] Because of the very small anisotropy factors of organic compounds, only very low enantioenrichment has been induced by asymmetric photoequilibrium and photoreactions from irradiation using CPL. However, if these chiral compounds with a low ee can act as a chiral initiator for asymmetric autocatalysis, then highly enantioenriched compounds would be obtained to construct a chemical system that connects the chirality of the CPL with the high ee chiral compound.

Leucine,[66] helicene,[53] and chiral olefins[67] with a small ee, which can be obtained via irradiation with CPL, have been submitted to asymmetric autocatalysis as a source of chirality to give enantioenriched alkanols with the corresponding absolute configurations to those of the chiral initiators (Scheme 4a). Moreover, it should be assumed that direct irradiation with CPL of racemic alkanol **1** would induce asymmetric photodegradation to give a slightly enantioenriched **1**. Indeed, direct irradiation of racemic **1** by *l*-CPL or *r*-CPL (313 nm) and a subsequent asymmetric autocatalysis produces (*S*)- or (*R*)-alkanol **1** with >99.5% ee, respectively, corresponding to the handedness of CPL (Scheme 4b).[68] This process provides, for the first time, a direct correlation of the handedness of CPL with a near enantiopure organic compound.

5. ENANTIOSELECTIVE SYNTHESIS INDUCED BY CHIRAL INORGANIC CRYSTALS

In the Earth's crust, there are a wide variety of chiral minerals that may have served as accessible chiral surfaces in the prebiotic evolution of chiral compounds.[8]

We examined asymmetric autocatalysis triggered by *d*- and *l*-quartz. When pyrimidine-5-carbaldehyde **2** was treated with *i*-Pr_2Zn in the presence of *d*- and *l*-quartz powder, enantiomers (*S*)- and (*R*)-**1** with a high enantioenrichment were obtained using an ensuing asymmetric amplification (Scheme 5).[69] In addition, chiral ionic crystals of sodium chlorate can also act as a chiral trigger.[70]

Cinnabar, a chiral mineral of mercury(II) sulfide, mediates asymmetric autocatalysis.[71] Enantiomorphic *P* and *M* crystals of cinnabar act as chirality triggers for asymmetric autocatalysis to afford enantiomers (*R*)- and (*S*)-**1**, respectively. These results clearly show that chiral inorganic crystals trigger asymmetric autocatalysis, and the induced enantioimbalance is amplified efficiently to a high level by subsequent asymmetric autocatalysis.

6. CHIRAL CRYSTALS COMPOSED OF ACHIRAL ORGANIC COMPOUNDS

6.1. Asymmetric Autocatalysis Induced by Chiral Crystals of Achiral Organic Compounds

There are achiral organic compounds that form enantiomorphic crystals. Spontaneous chiral crystallization of achiral organic compounds and their subsequent stereospecific reactions using crystals as substrates has been considered as being one of the important candidates for the origin of homochirality.[72] Our approach was to use chiral crystals as chiral triggers, instead of using them as substrates, in asymmetric autocatalysis (Table 2).

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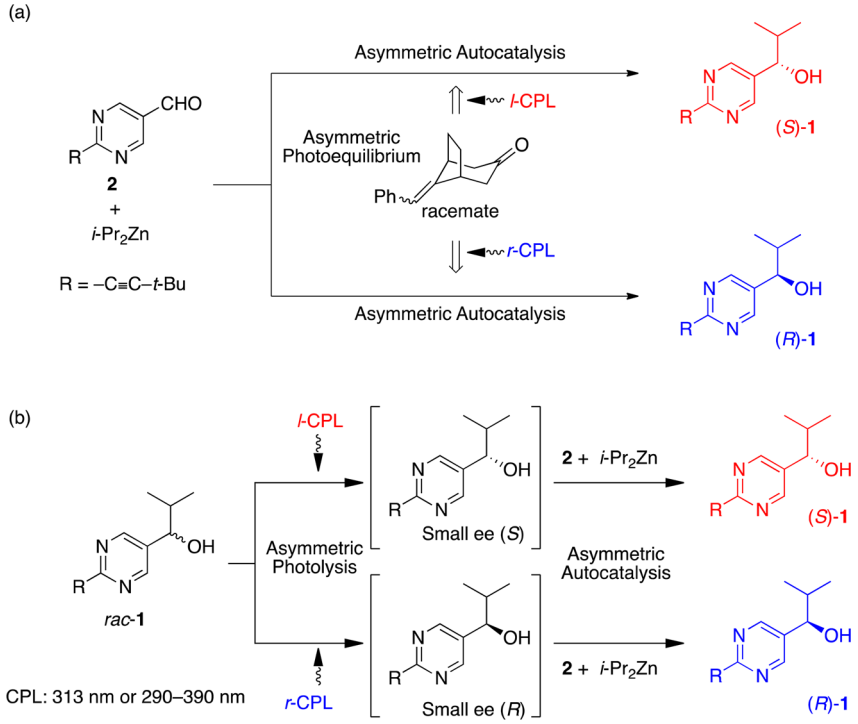
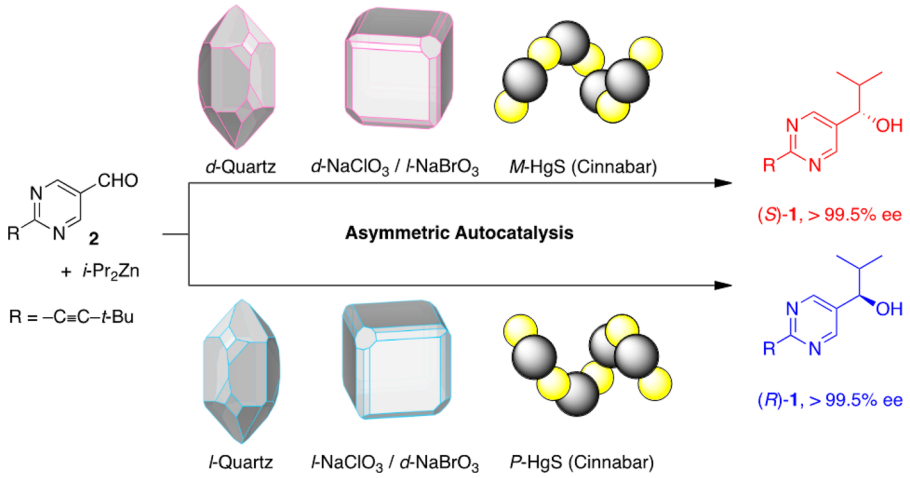
Scheme 4. Asymmetric Autocatalysis Triggered by Irradiation with CPL Mediated with (a) Asymmetric Photoequilibrium of Chiral Keto-olefin and (b) Direct Photodegradation of Asymmetric Autocatalyst



Scheme 5. Asymmetric Autocatalysis Initiated Using Chiral Inorganic Crystals



The nucleobase cytosine is an achiral flat molecule that spontaneously crystallizes from methanol into a chiral form ($P2_12_12_1$). The enantiomorphs of cytosine can be obtained spontaneously using stirred crystallization.[73] In the presence of [CD(−)310$_{Nujol}$]-cytosine crystals, the reaction between aldehyde **2** and *i*-Pr_2Zn gives enantioenriched (*S*)-**1** in conjunction with asymmetric autocatalysis, as shown in Table 2 (entry 1).[73] In contrast, [CD(+)310$_{Nujol}$]-cytosine crystals trigger the production of (*R*)-**1**. Adenine dinitrate also forms chiral crystals and triggers asymmetric autocatalysis (entry 2).[74] Moreover, enantiomorphous crystals composed of achiral hippuric acid,[75] *N*-(2-thienylcarbonyl)glycine,[57] and chiral cocrystals[76] can effectively act as chiral triggers for asymmetric autocatalysis (entries 3−5). These results show that spontaneously generated crystal chirality of achiral compounds including nucleobases can provide large yields of chiral organic compounds with high ee by asymmetric autocatalysis. The initial enantioselection is considered to occur under the influence of the chiral surface of the crystals. The computational results[57] indicate that the enantioface-selective adsorption of aldehyde **2** followed by the *i*-Pr_2Zn addition and enantioselective adsorption of the initially formed isopropylzinc alkoxide, which can induce an enantiomerically imbalanced asymmetric autocatalyst.

6.2. Absolute Control of Enantiomorphs of Cytosine from Dehydration of the Water of Crystallization

When cytosine is crystallized from water, it forms an achiral monohydrate crystal. We found that the removal of water of crystallization from enantiotopic crystal faces gave enantiomorphs of anhydrous cytosine crystals ($P2_12_12_1$) (Figure 3).[77]

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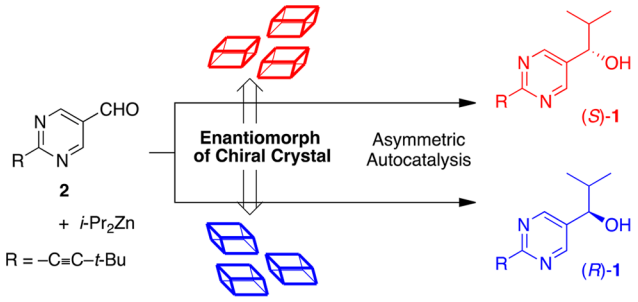
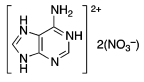
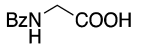
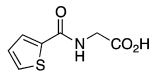
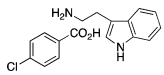
Table 2. Asymmetric Autocatalysis Initiated Using Chiral Organic Crystals Composed of Achiral Compounds



Entry	Enantiomorphous Crystal			5-Pyrimidyl Alkanol **1**		Ref.
		Space Group	Solid-state CD	ee	Config.	
1		$P2_12_12_1$	CD(–)310$_{Nujol}$	>99.5	*S*	73
			CD(+)310$_{Nujol}$	>99.5	*R*	
2		$P2_12_12_1$	CD(–)250$_{Nujol}$	>99.5	*S*	74
			CD(+)250$_{Nujol}$	>99.5	*R*	
3		$P2_12_12_1$	CD(+)260$_{Nujol}$	>99.5	*S*	75
			CD(–)260$_{Nujol}$	>99.5	*R*	
4		$P2_12_12_1$	CD(+)300$_{KBr}$	75	*S*	57
			CD(–)300$_{KBr}$	90	*R*	
5		$P2_12_12_1$	CD(–)225$_{Nujol}$	95	*S*	76
			CD(+)225$_{Nujol}$	96	*R*	

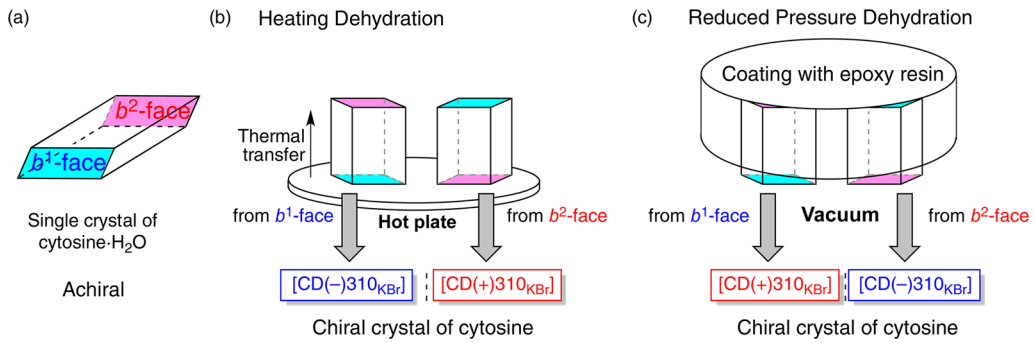


Figure 3. Enantioselective synthesis of a chiral crystal of achiral cytosine by the dehydration of the water of crystallization from cytosine monohydrate. (a) Enantiotopic face of achiral cytosine monohydrate. Formation of chiral crystal of achiral cytosine (b) under thermal condition and (c) under reduced pressure.

Cytosine monohydrate ($P2_1/c$) has enantiotopic b_1 and b_2 faces with nonsuperimposable parallelogram-shaped faces (Figure 3a). On heating, dehydration occurs on the b_1 face, and the resulting anhydrous crystal shows positive CD at 310 nm (CD(−)310$_{KBr}$) in the solid state (Figure 3b). In contrast, heat transfer from the b_2 face gives [CD(+)310$_{KBr}$] crystals. Furthermore, enantiomorphs of cytosine can be obtained from dehydration under reduced pressure (Figure 3c).[78] When the b_1 face is exposed to reduced pressure at room temperature, it gives [CD(+)310$_{KBr}$] cytosine. It should be noted that the resulting crystal chirality is opposite to that obtained from dehydration on heating. This is the first example of the formation of chiral crystals from an achiral compound in an absolutely controlled manner without using any chiral substance.[79]

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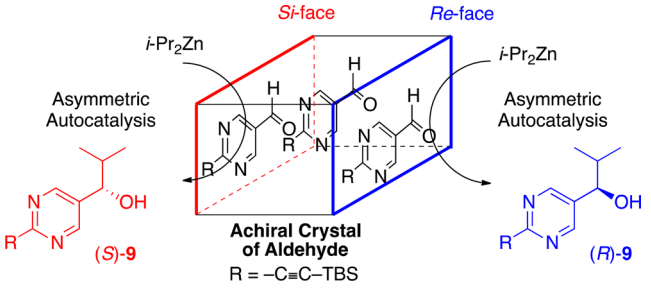
Scheme 6. Enantioface-Selective Reaction at the Oriented Surface of an Achiral Single Crystal



7. ADDITION OF DIISOPROPYLZINC TO THE ENANTIOTOPIC CRYSTAL FACE OF ACHIRAL PYRIMIDINE-5-CARBALDEHYDES

Because the reagents react directly with the oriented molecules in the crystal, the products are formed in a stereospecific manner to provide optically active compounds corresponding to the prochirality of the substrate at the crystal surface. Enantioface-selective oxidation[80] and reduction[81] with low-to-moderate ee at the enantiotopic surface has been reported. We describe the enantioselective formation of C–C bonds to form **9** on the face of single crystal pyrimidine-5-carbaldehyde using *i*-Pr_2Zn vapor (Scheme 6).[30]

Scheme 7. Molecular Chirality Arising from Hydrogen, Carbon, and Oxygen Isotopes Substitution

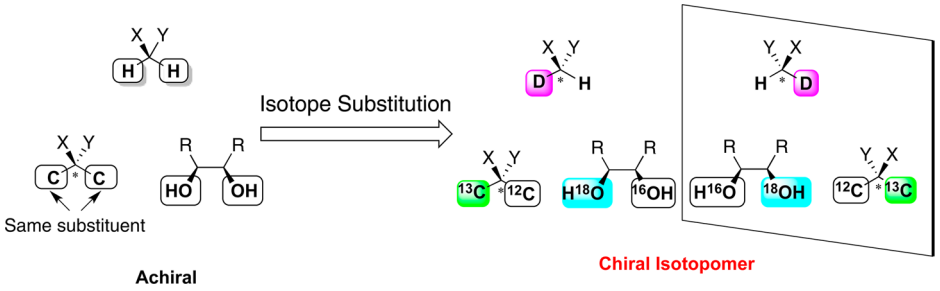
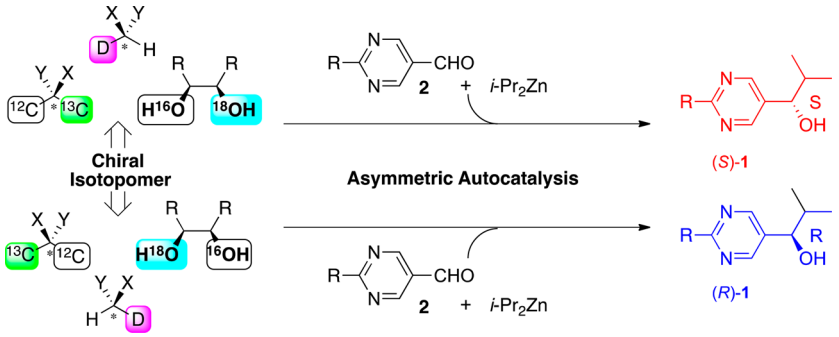
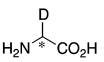
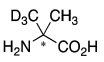
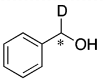
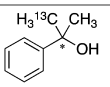
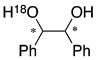
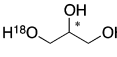


Table 3. Asymmetric Autocatalysis Triggered by Chiral Compounds Arising from Isotope Substitution



Entry	Isotope Labeled Chiral Compound		5-Pyrimidyl Alkanol **1**		Ref.
	Structure	Config.	ee	Config.	
1		*S*	96	*S*	82
		R	93	*R*	
2		*R*	99	*S*	82
		S	99	*R*	
3		*R*	95	*S*	83
		S	96	*R*	
4		*R*	94	*S*	85
		S	96	*R*	
5		*S*	97	*S*	86
		R	92	*R*	
6		*R*	94	*S*	87
		S	97	*R*	

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2-*tert*-Butyldimethylsilylethynylpyrimidine-5-carbaldehyde crystallizes in an achiral form ($P\bar{1}$), and when the crystal structure is projected perpendicular to the *c*-axis, either the *Si* or *Re* face of the formyl group is oriented toward the outside of the crystal. These opposite enantiotopic faces were treated with *i*-Pr_2Zn vapor to perform alkylation on the single-crystal surface. When one face was exposed to *i*-Pr_2Zn vapor for the addition reaction, (*R*)-alkanol **9** was isolated. On the other hand, when the opposite face was exposed, the (*S*)-**9** alkanol was produced. The ee was amplified further to >99.5% ee by a subsequent asymmetric autocatalysis.

Thus, the two-dimensional orientation of prochiral molecules on an achiral single crystal can also act as a source of chirality in the enantioselective formation of enantioenriched compounds.

8. ASYMMETRIC AUTOCATALYSIS TRIGGERED BY CHIRAL COMPOUNDS ARISING FROM ISOTOPE SUBSTITUTION (D/H, $^{13}C/^{12}C$, AND $^{18}O/^{16}O$)

Chiral isotopomers have rarely been employed as chiral auxiliaries in asymmetric synthesis because the chirality is extremely slight and originates from the very small difference in electronic states between the isotopes. However, we found that chiral hydrogen, carbon, and oxygen isotopomers (Scheme 7) trigger asymmetric autocatalysis to afford highly enantioenriched products.

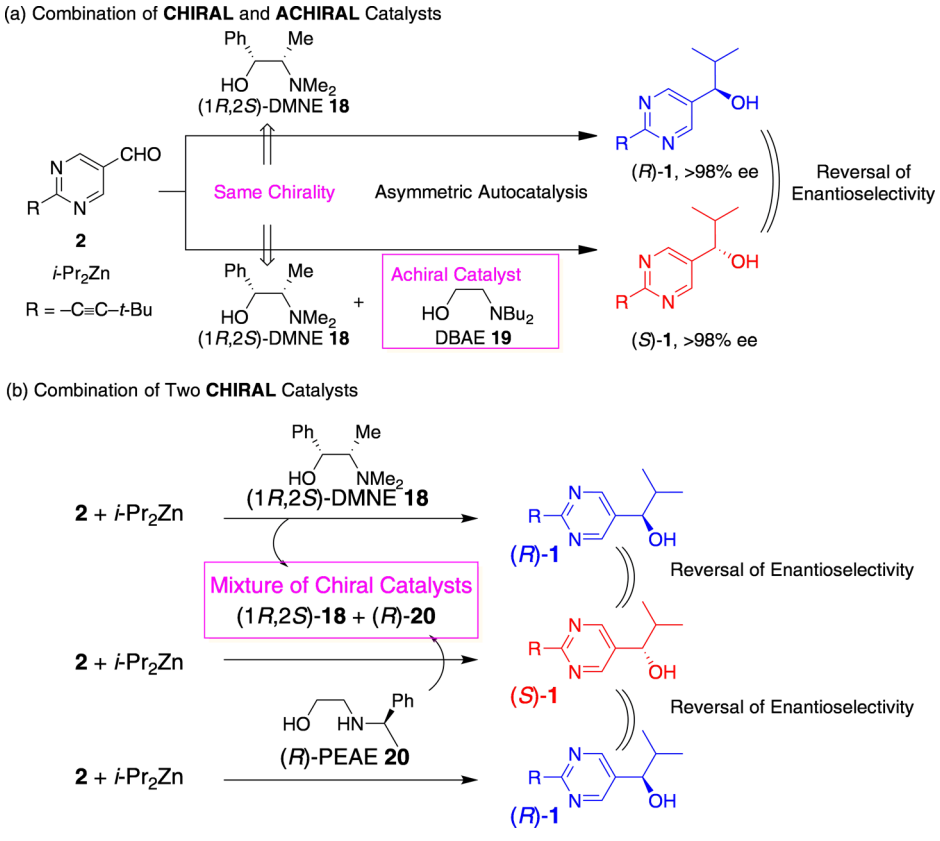
Glycine and α-methylalanine become chiral upon deuteration of one of the hydrogen atoms of the enantiotopic methylene group of glycine or one of the methyl groups of α-methylalanine. We used the chiral isotopomer of glycine-α-*d* and α-methyl-d_3-alanine as the chiral initiators in asymmetric autocatalysis. The absolute configuration of the corresponding alkanol **1** was controlled by the chirality resulting from the hydrogen isotope substitution, as shown in Table 3 (entries 1 and 2).[82] In addition, chirally deuterated primary alcohols can be discriminated by applying asymmetric autocatalysis (entry 3).[83]

Experimentally, carbon isotopomers are more difficult to discriminate than those of hydrogen, because the chirality originates from the much smaller difference in atomic weight between ^{13}C and ^{12}C. Therefore, the possibility that isotopically substituted carbon chiral compounds could induce chirality in some enantioselective reactions had not been considered before.[84] By using asymmetric autocatalysis, we have achieved enantioselective reaction with carbon isotope chirality (entry 4).[85] When asymmetric autocatalysis was performed in the presence of (*R*)-dimethylphenylmethanol with carbon isotope chirality, production of (*S*)-**1** with 94% ee was observed. In turn, when (*S*)-isomer was used as chiral trigger, (*R*)-**1** with 96% ee was obtained. Moreover, it was also found that oxygen ($^{18}O/^{16}O$) isotopomers, such as hydrobenzoin and glycerin, could also trigger asymmetric autocatalysis (entries 5 and 6).[86,87] Thus, the neglected isotope chirality of many organic compounds can be discriminated using asymmetric autocatalysis.

9. REVERSAL OF ENANTIOSELECTIVITY IN ASYMMETRIC AUTOCATALYSIS INITIATED BY MIXTURES OF β-AMINO ALCOHOLS

In asymmetric catalysis, achiral additives can enhance the reactivity and enantioselectivity, and achiral cocatalysts can cooperatively participate when enantioface selection occurs. We observed an unexpected reversal of the enantiofacial selectivity

Scheme 8. Reversal of Enantioselectivity in Asymmetric Addition of *i*-Pr_2Zn to Aldehyde 2 by Mixing (a) Chiral and Achiral Catalysts and (b) Two Chiral Catalysts of β-Amino Alcohols



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of chiral β-amino alcohol catalysts in the dialkylzinc addition to aldehyde from the cooperative formation of a catalytically active mixed aggregate (Scheme 8).[50]

The addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **2** using chiral (1*R*,2*S*)-dimethylnorephedrine (DMNE, **18**) alone afforded (*R*)-alkanol **1** with a high ee in combination with asymmetric autocatalysis (Scheme 8a). Surprisingly, when the same reaction was catalyzed by a mixture of chiral (1*R*,2*S*)-DMNE **18** (0.5 mol %) and achiral *N*,*N*-dibutylaminoethanol (DBAE, **19**, 19.5 mol %), (*S*)-**1** was obtained instead of (*R*)-**1**. Thus, the presence of the achiral catalyst DBAE **19** reversed the sense of enantioselectivity of the chiral catalyst **18**.

Furthermore, a reversal of enantioselectivity was also found in the reaction using two chiral catalysts.[88] The enantioselective addition of *i*-Pr_2Zn to aldehyde **2** was catalyzed by a mixture of two chiral catalysts, DMNE **18** and 2-[(1-phenylethyl)amino] ethanol (PEAE, **20**) (Scheme 8b). Both (1*R*,2*S*)-**18** and (*R*)-**20**, when they are used independently, induce the formation of (*R*)-alkanol **1**. However, when a mixture of (1*R*,2*S*)-**18** and (*R*)-**20** was employed as a chiral inducer, the opposite enantiomer, (*S*)-**1**, was formed.

These findings show that the key catalytic species that determines the enantioselectivity of the reaction should be formed from the interaction between two β-amino alcohol catalysts.[89] Thus, not only the monomeric species but also the mixed aggregate is catalytically active in the β-amino-alcohol-catalyzed addition of dialkylzinc compounds.

10. CONCLUSIONS

We found that chiral 5-pyrimidyl alkanols are highly enantioselective asymmetric autocatalysts for the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehydes, and thus, a significantly large amplification from an extremely low to an almost enantiopure >99.5% ee was realized for the first time without the assistance of any other chiral auxiliary. Thanks to this large amplification effect, chiral substances including cryptochiral hydrocarbons and chiral isotopomers can act as chiral initiators of asymmetric autocatalysis to afford enantioenriched alkanols. By use of asymmetric autocatalysis, spontaneous absolute asymmetric synthesis was realized in the formation of enantioenriched pyrimidyl alkanol. Furthermore, without the addition of any chiral molecules, various sources of chirality, such as CPL, chiral crystals, and enantiotopic surfaces of achiral crystals have been directly correlated with near enantiopure pyrimidyl alkanol using asymmetric autocatalysis.

As described in this Account, the asymmetric autocatalysis of pyrimidyl alkanol is a unique and efficient reaction leading to a very high ee from an extremely low ee. Using asymmetric autocatalysis, several origins of chirality have been correlated to the almost enantiopure organic compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail: soai@rs.kagu.tus.ac.jp.

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Notes

The authors declare no competing financial interest.

Biographies

Kenso Soai obtained his Ph.D. degree from the University of Tokyo with Teruaki Mukaiyama. He was a research associate with Ernest. L. Eliel at the University of North Carolina at Chapel Hill. He joined the faculty of Tokyo University of Science in 1981. He has been a Full Professor since 1991.

Tsuneomi Kawasaki received a Ph.D. degree in 2004 from the University of Tokyo with Takeshi Kitahara. He then joined the group of Kenso Soai at Tokyo University of Science. In 2012, he was promoted to Associate Professor at the University of Fukui.

Arimasa Matsumoto obtained his Ph.D. degree in 2012 from the University of Tokyo under the direction of Eiichi Nakamura and then joined Kenso Soai's group.

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