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Perspective

The Soai reaction and its implications with the life's characteristic features of self-replication and homochirality

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ABSTRACT

Asymmetric autocatalysis is a reaction in which chiral product acts as a chiral catalyst for its own production. The process is a self-replication of chiral molecules with amplification of enantiomeric excess (ee). In the Soai reaction, (*S*)-pyrimidyl alkanol with extremely low ee acts as asymmetric autocatalyst in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde to afford more of the (*S*)-pyrimidyl alkanol of the same structure with significantly enhanced greater than 99.5% ee. The Soai reaction is capable of absolute asymmetric synthesis. Thus, the reaction between achiral diisopropylzinc and pyrimidine-5-carbaldehyde without the intervention of any chiral factor affords enantioenriched pyrimidyl alkanol with stochastic distribution. The proposed origins of homochirality such as quartz and circularly polarized light are correlated to highly enantioenriched compound by using the Soai reaction. The implications of the Soai reaction is described in the selected life's characteristic features of self-replication and homochirality.

Contents

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1. Introduction

1.1. *Characteristic features of life (selected) and those of asymmetric autocatalysis: self-replication and homochirality*

Among the characteristic features of life, the most typical one would be its ability of self-replication, a feature that has long been recognized. Over 2300 years ago, Aristotle (384–322 BCE) noted his conception that means "Human being is born from human being. Chair bed is not born from chair bed" (Fig. 1a) [1]. Even the most human-like modern robot is not considered to be a living creature mainly because that is not capable of self-replication so far.

Another characteristic feature of life is that the essential molecules of life such as amino acids and sugars exhibit overwhelming one-handedness of enantiomers, e.g., L-amino acids and D-sugars. The characteristic of handedness is the same in all species on Earth. This phenomenon is often called biological homochirality [2]. Biological homochirality is not a mere phenomenon; it has been considered to be an essential prerequisite for the emergence and function of life. Proteins are formed from the peptide condensation of L-amino acids. If D-amino acids are involved irregularly in proteins, then the structures of the proteins will become diastereomers with different chemical and physical behaviors. Subsequently, the proteins will lose the capability to perform, for example, enzyme functions. It is known that DNA is composed of D-deoxyribose (Fig. 1a). If DNA incorporates L-sugar in random manner, the conformation of the DNA changes and the transfer of genetic information to the next generation becomes very difficult. Indeed, Eschenmoser described that the reaction of the self-assemble by ligative oligomerization of tetrameric D-pyranosyl-RNA (analogues of RNA) is slower by at least two orders of magnitude when one of the components is substituted by the L-enantiomer [3].

Biological homochirality was first noted in the 19th century, which is recent compared with life's feature of self-replication. In the 19th century, many biologically related compounds were found to exhibit optical rotation of plane polarized light. In 1848, Pasteur crystallized two hemihedric crystal forms from a solution of racemic sodium ammonium tartrate and isolated each crystal form [4]. Solutions of each form exhibited opposite directions of optical rotation. Pasteur's discovery proved that the optically active molecules have dissymmetry, *i.e.*, chirality in contemporary terminology, in their molecular structures.

Asymmetric autocatalysis is a reaction in which chiral product acts as chiral catalyst for its own production (Fig. 1b). The process is an automultiplication (self-replication) of a chiral molecule with amplification of enantiomeric excess (ee).

Asymmetric autocatalysis has the following advantages over conventional asymmetric catalysis: (1) The efficiency is high, because automultiplication is a system that life adopts; (2) In sharp contrast to conventional catalysis, no decrease in the quantity and deterioration of catalyst is observed because the newly formed product becomes new catalyst; (3) Separation process of the product from catalyst is not necessary because their structure is the same.

1.2. *Studies on the self-replication of molecules without producing any stereogenic center*

Successful research on one characteristic feature of life, *i.e.*, self-replication at a molecular level, has been reported. von Kiedrowski devised ligative self-replicating oligonucleotides [5a] and Ghadiri devised ligative self-replicating oligopeptides [5b]. Rebek reported self-replicating achiral organic compounds based on molecular recognition [5c], and Otto devised supramolecular organic self-replicator [5d]. Although these works demonstrated elegant self-replication systems, the reactions do not produce any new stereogenic centers.

1.3. *Studies on the origins of homochirality*

Since Pasteur's discovery of molecular chirality, its origin in organic compounds has attracted much attention among a wide range of scientists [6]. According to his lecture record [7], Pasteur himself conducted experiments to induce chirality in organic

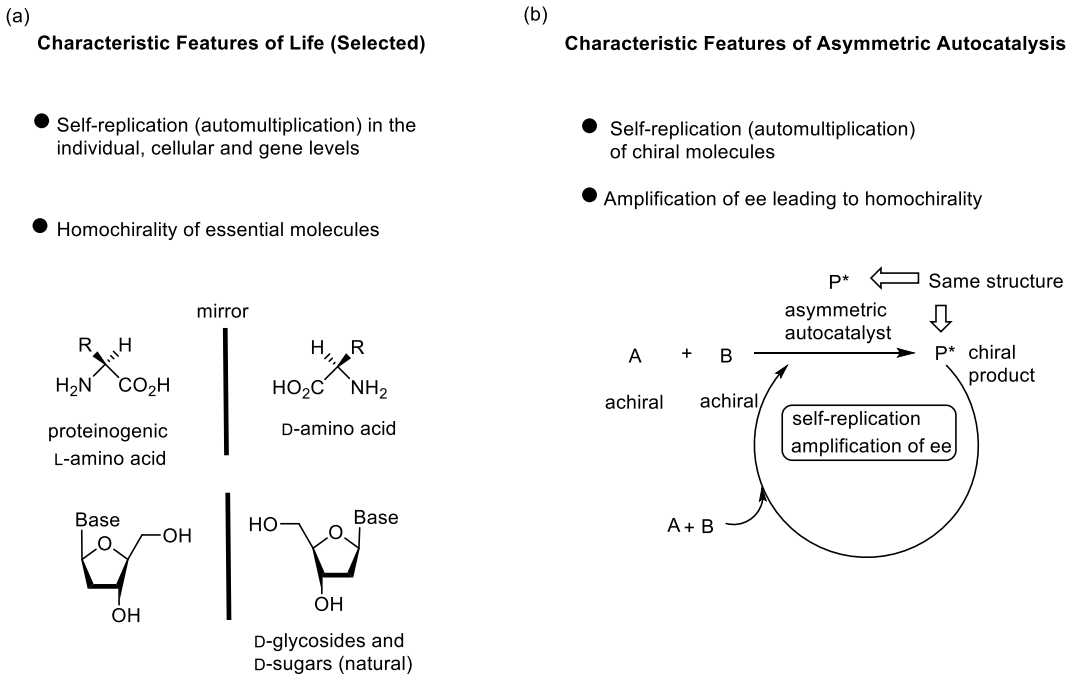
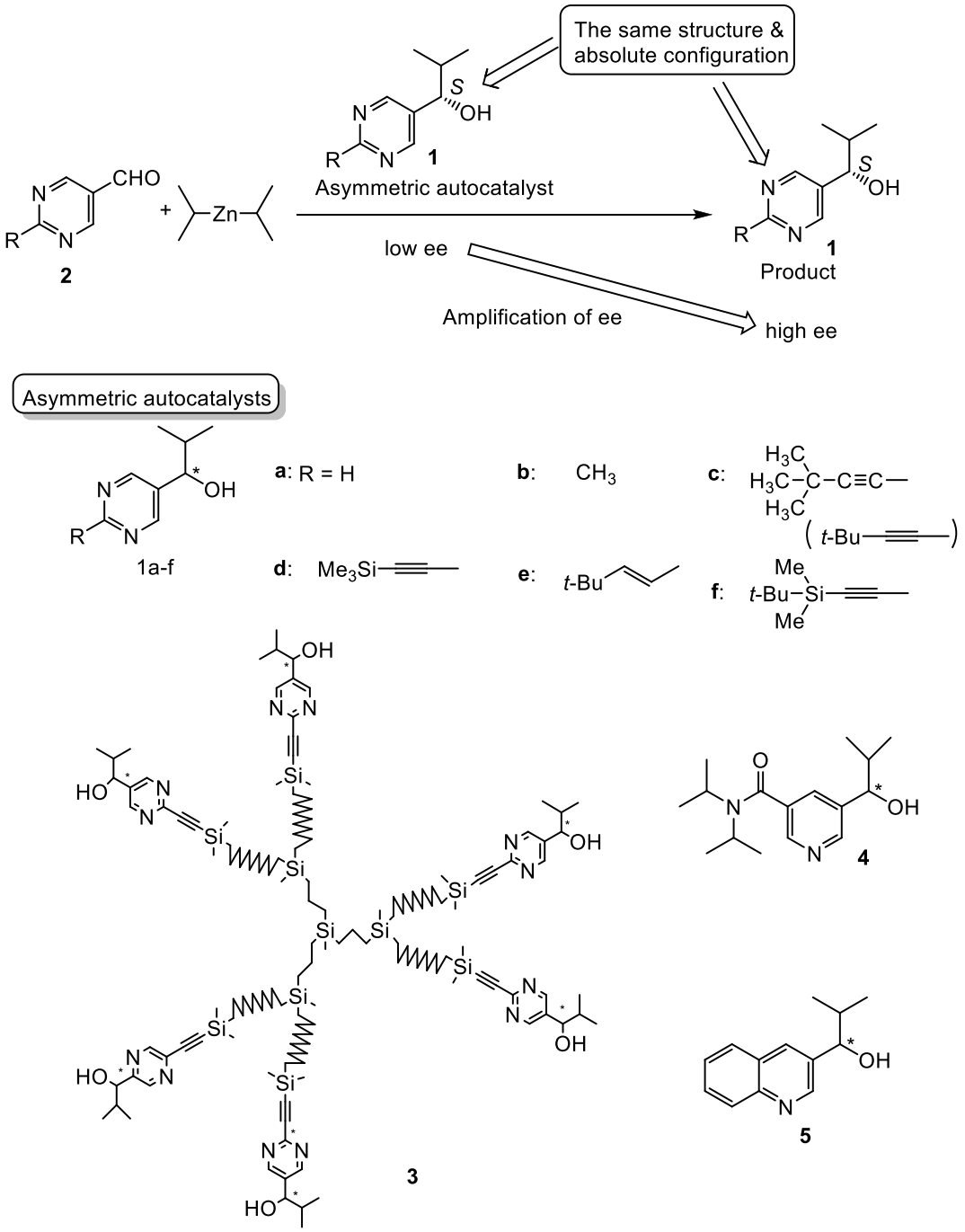


Fig. 1. Comparison between (a) the characteristic features of life (selected) and (b) asymmetric autocatalysis: The Soai reaction.

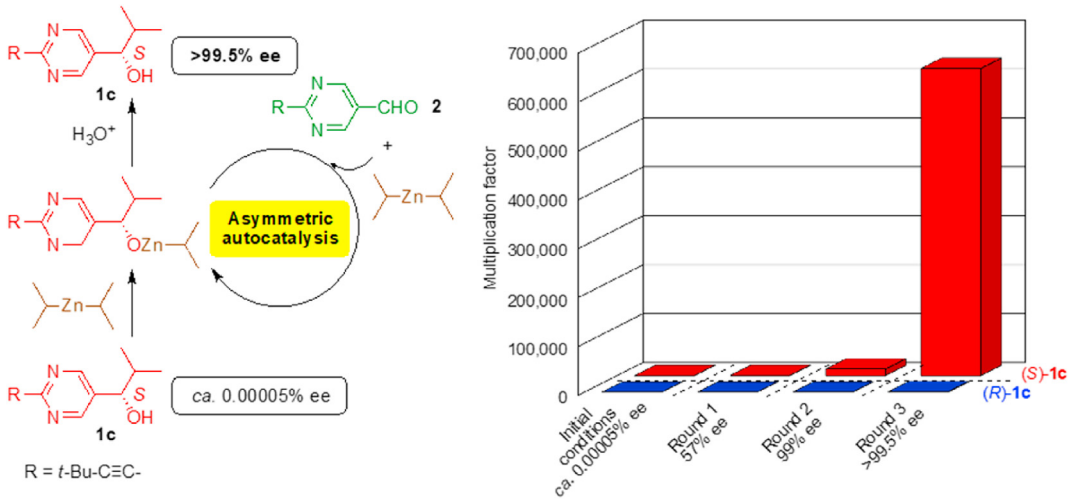
compounds; a plant was irradiated with sunlight so the plant experienced the movement of sunlight from west to east, the opposite direction of light movement on northern hemisphere. He also conducted crystallization under a strong magnetic field. Although he did not come to any definite conclusion, it is noteworthy that research in the origin of homochirality of organic compounds was initiated by this giant of chemistry.

Thus, the research in the origins of homochirality has attracted the attention of many scientists. Quartz is an inorganic crystal of SiO_2 that occurs naturally as hemihedric enantiomorphs. The rotation of polarized light, called optical activity, was found with quartz. Thus, quartz has been proposed as the origin of chirality of organic compounds and several studies claim to have reported the induction of a small extent of ee of organic compound by using quartz. However, the only report that has been generally accepted as valid is the small extent of enantioselective adsorption of racemic amino acid detected by a sensitive radioisotopic method [6a]. Hazen *et al.* reported the enantioselective adsorption of racemic aspartic acid on enantiotopic surfaces of calcite [6b]. Circularly polarized light (CPL) can also generate chirality, and has thus been proposed as the origin of chirality of organic compounds. Irradiation of racemic leucine with CPL resulted in a 2% enantiomer enrichment of this amino acid [6c].

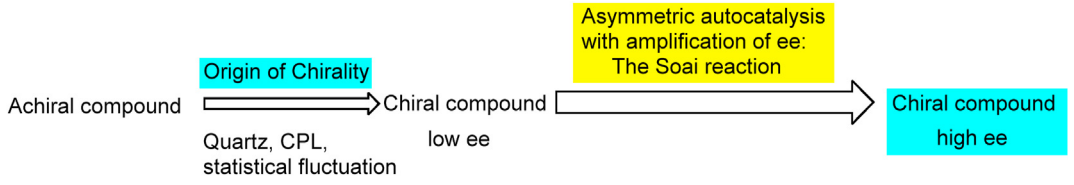
The proposed origins of chirality of organic molecules can



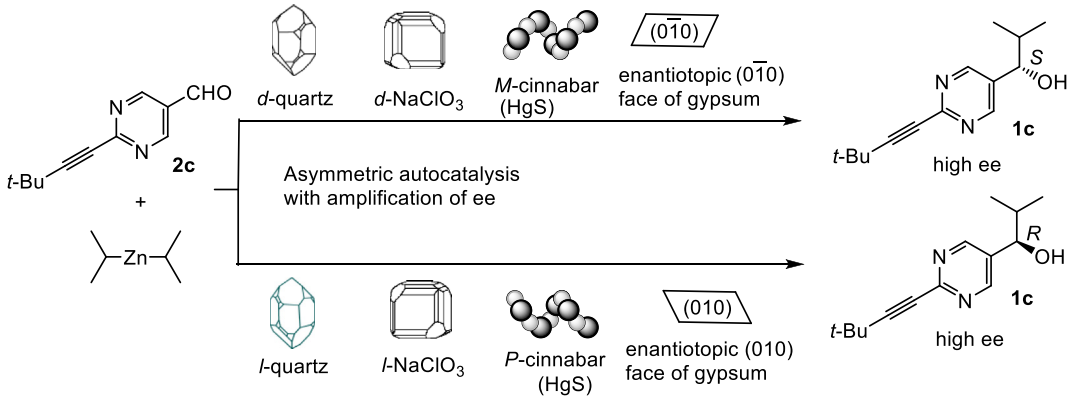
Scheme 1. Asymmetric autocatalysis of 5-pyrimidyl alkanol **1**, multi functionalized pyrimidyl alkanol **3**, 5-carbamoyl-3-pyridyl alkanol **4** and 3-quinolyl alkanol **5** with amplification of enantiomeric excess (ee): The Soai reaction.



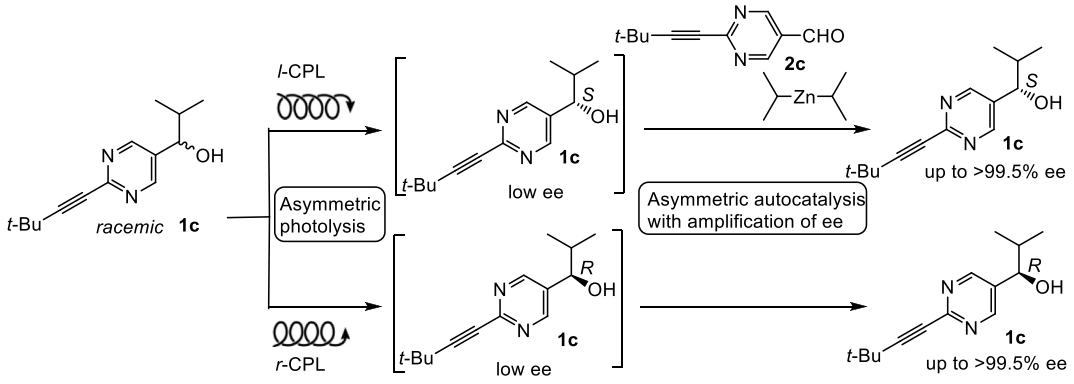
Scheme 2. The Soai reaction of pyrimidyl alkanol **1c** with significant amplification of ee from extremely low (*ca.* 0.00005%) ee to greater than 99.5% ee.



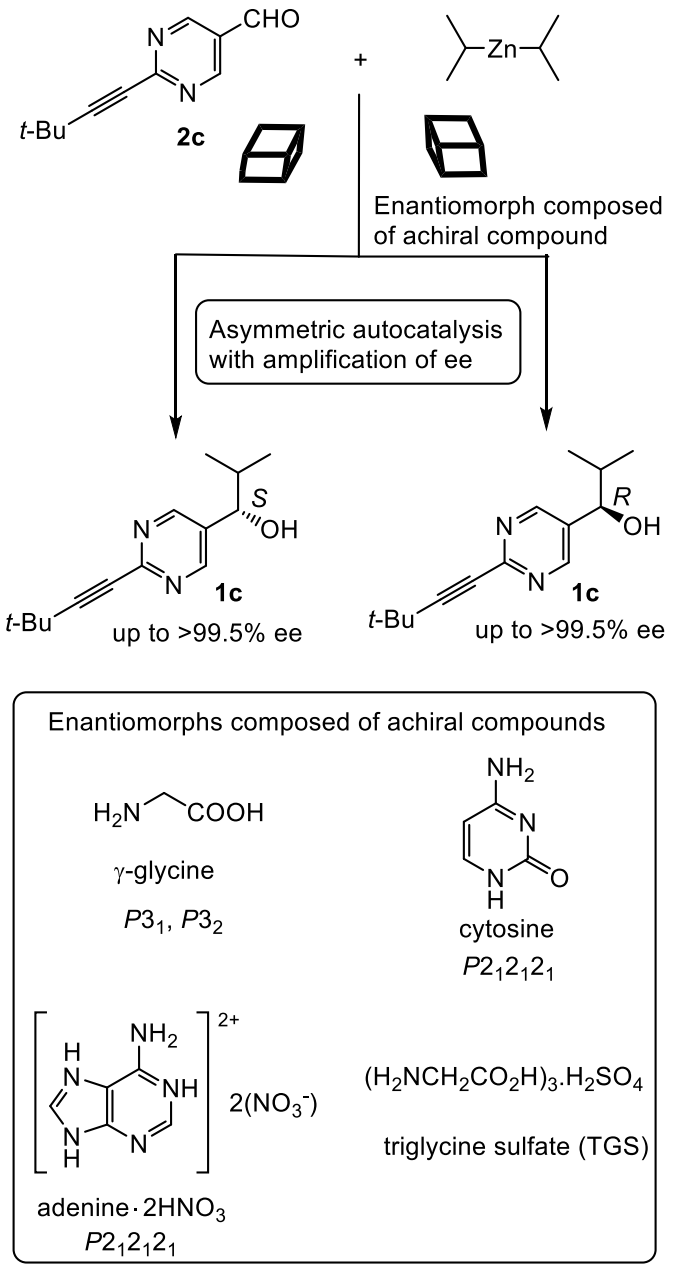
Scheme 3. Correlation of the origin of chirality with chiral compound of high ee by using asymmetric autocatalysis with amplification of ee.



Scheme 4. Asymmetric autocatalysis triggered by chiral inorganic crystals and by enantiotopic face of achiral gypsum crystal.



Scheme 5. Asymmetric photolysis of racemic pyrimidyl alkanol **1c** by irradiating CPL and the subsequent asymmetric autocatalysis with amplification of ee.



Scheme 6. Asymmetric autocatalysis triggered by chiral crystals composed of achiral organic compounds.

usually induce only low ee in chiral molecules [6] with a few exceptions involving physical crystallizations [6,l,m,n]. Thus, the linkage between these very low ee and high ee observed in life has been missing.

It has long been accepted that without the intervention of a chiral factor, when a reaction that transforms an achiral compound into chiral forms, the product is composed of equal amounts of left- and right-handed enantiomers, *i.e.*, a racemate. Absolute asymmetric synthesis is a reaction that would produce an enantioenriched chiral compound without the intervention of a chiral factor [8a,b]. At first glance, this clearly contradicts the equal amounts model. In the late 19th century, Pearson noted the idea that the chiral compound formed in the initial stage self-replicates to afford enantioenriched product [9a]. In 1953, Frank proposed a reaction scheme, without describing a specific chemical structure, by which autocatalysis and inhibition in replicating chiral molecules can amplify an initially small ee to high ee [9b]. However, no experimental examples were known until 1995 when Soai *et al.* reported asymmetric autocatalysis with amplification of an ee [10a].

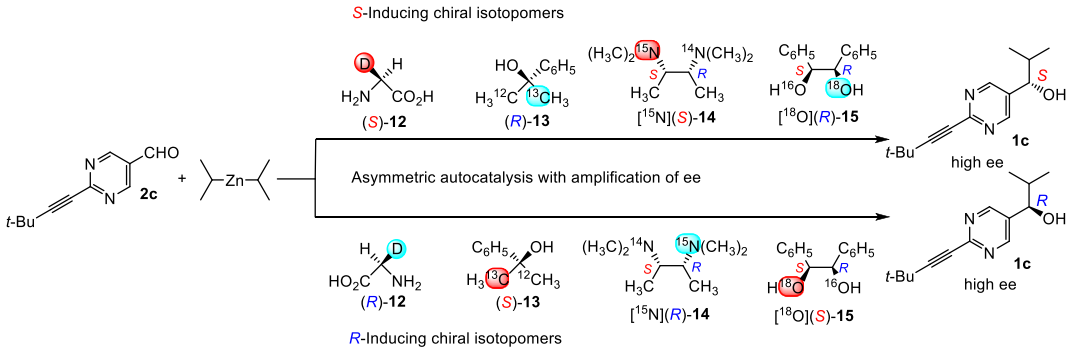
2. Asymmetric autocatalysis: the Soai reaction with amplification of ee [10,11]

2.1. Prologue to the discovery of asymmetric autocatalysis

In the course of our continuing study on the enantioselective addition of organometallic reagents to aldehydes [12a,b], we observed that absolute configurations of the chiral alkanol products are controlled by the absolute configurations of alkanol moiety of chiral β-amino alkanol catalysts [12c]. We also observed that pyridine-3-carbaldehyde, an aldehyde containing a nitrogen atom, reacts faster than benzaldehyde with diethylzinc to afford enantioenriched 3-pyridyl alkanol in a reaction in which the same chiral catalyst, *i.e.*, (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine, is used [12d].

Based on these observations, we got an idea that chiral nitrogen-containing alkanol with the suitable structure may become asymmetric autocatalyst in the enantioselective addition of dialkylzincs to the corresponding nitrogen-containing aldehyde. Is it possible to devise a chiral molecule that possesses both characteristic features of life, *i.e.*, autocatalysis and homochirality? Wynberg challenged chemists to realize asymmetric autocatalysis [13].

In 1990, we found the first example of asymmetric autocatalysis of 3-pyridyl alkanol in the enantioselective addition of dialkylzincs to pyridine-3-carbaldehyde [10b]. In this reaction, 3-pyridyl alkanol automultiplies to yield predominantly the identical compound with the same enantiomeric configuration.



Scheme 7. Asymmetric autocatalysis triggered by chiral hydrogen (D/H) **12**, carbon ($^{13}C/^{12}C$) **13**, nitrogen ($^{15}N/^{14}N$) **14** and oxygen ($^{18}O/^{16}O$) **15** isotopomers.

2.2. Discovery of asymmetric autocatalysis with amplification of ee: The Soai reaction

In 1995, we found that 5-pyrimidyl alkanol acted as an asymmetric autocatalyst for amplification of ee in the reaction between pyrimidine-5-carbaldehyde **2a** and diisopropylzinc (Scheme 1) [10a].

Starting with (*S*)-5-pyrimidyl alkanol **1a** with 2% ee, the first asymmetric autocatalysis resulted in the identical pyrimidyl alkanol **1a** with 10% ee. Subsequent asymmetric autocatalyses with 10% ee resulted in a progression from 10% to 57%, then to 81%, and finally to 88% ee. The unique aspects of the amplification were that the origin of chiral amplification was the initial small enantiomeric imbalance of asymmetric autocatalyst **1a** and that no other chiral factor was necessary.

It was also found that 2-alkynyl-5-pyrimidyl alkanol **1c** was a near-perfect asymmetric autocatalyst in the enantioselective addition of diisopropylzinc to 2-alkynylpyrimidine-5-carbaldehyde. (*S*)-2-Alkynyl-5-pyrimidyl alkanol **1c** with >99.5% ee automultiplied to maintain the enrichment with a yield >99% [10c]. Moreover, (*S*)-2-alkynyl-5-pyrimidyl alkanol **1c** with only *ca.* 0.00005% ee acted as an asymmetric autocatalyst in consecutive asymmetric autocatalyses to generate the same (*S*)-alkanol **1c** with a successive increased ee of 57%, 99%, and then >99.5% (Scheme 2) [10d]. During these consecutive asymmetric autocatalyses, the initial slightly major (*S*)-enantiomer automultiplied by the factor of *ca.* 630,000 times, while the initial slightly minor (*R*)-enantiomer did so less than 1000 times. These results demonstrated that there is an actual chemical reaction in which the initial small enantiomeric imbalance is amplified to >99.5% ee by asymmetric autocatalysis. Mislow named the reaction the Soai reaction [8a].

It was also found that 5-carbamoyl-3-pyridyl alkanol **4** [10e,f][10e,f] and 3-quinolyl alkanol **5** [10g,h] were asymmetrically autocatalytic with amplification of ee (Scheme 1). Multifunctional pyrimidine-terminated large chiral molecule **3** was also found to act as asymmetric autocatalysis with amplification of ee [10i].

2.3. Mechanistic studies on the Soai reaction

The mechanisms and the reaction schemes of the Soai reaction have attracted the broad attentions [14a-p]. The structure and the aggregation states of catalyst, *i.e.*, the isopropylzinc alkoxides of pyrimidyl (or pyridyl) alkanols, have been investigated by using calorimetry [14a], HPLC [14b,c], NMR [14,g,h,m], DFT calculation [14i,k], single crystal X-ray crystallography [14l], NMR (and IR) [14m], *in situ* MS [14n], CD [14o] and by constructing the reaction models [14d,e,f,g]. The structure and the aggregation states of catalyst, *i.e.*, dimer, tetramer, oligomer, hemiacetal [14h,q], and the equilibrium [14o] between dimer and tetramer have been reported. The whole mechanism of the Soai reaction has been under current discussions [11i,j,k,14p].

3. Research on the origins of homochirality in conjunction with asymmetric autocatalysis

The proposed origins of chirality of organic molecules can usually induce only low ee in chiral molecules. The Soai reaction can link the weak origins of chirality with highly enantioenriched organic molecules (Scheme 3).

As examples of this, chiral inorganic crystals such as quartz [15a], cinnabar [15b], sodium chlorate [15c], enantiotopic face of achiral gypsum [15d] can induce enantiomeric imbalances in the newly formed pyrimidyl alkanol (isopropylzinc alkoxide) in the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc (Scheme 4). The subsequent asymmetric autocatalysis with amplification of ee affords highly enantioenriched pyrimidyl alkanols with the corresponding absolute configurations matching those of the original chirality. By asymmetric autocatalysis, the chirality of inorganic crystals is correlated to the chirality of highly enantioenriched organic molecule for the first time.

Similarly, asymmetric photolysis by irradiation of CPL to racemic 5-pyrimidyl alkanol **1c** followed by asymmetric autocatalysis yields

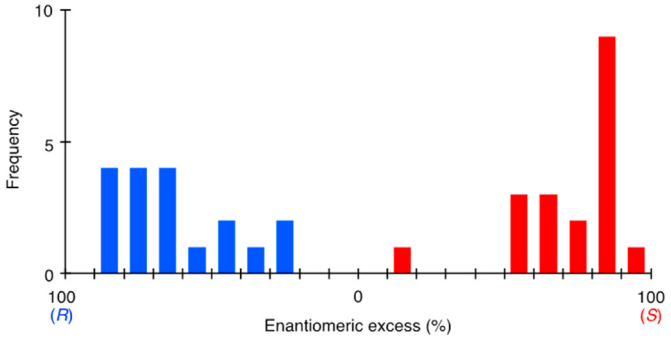
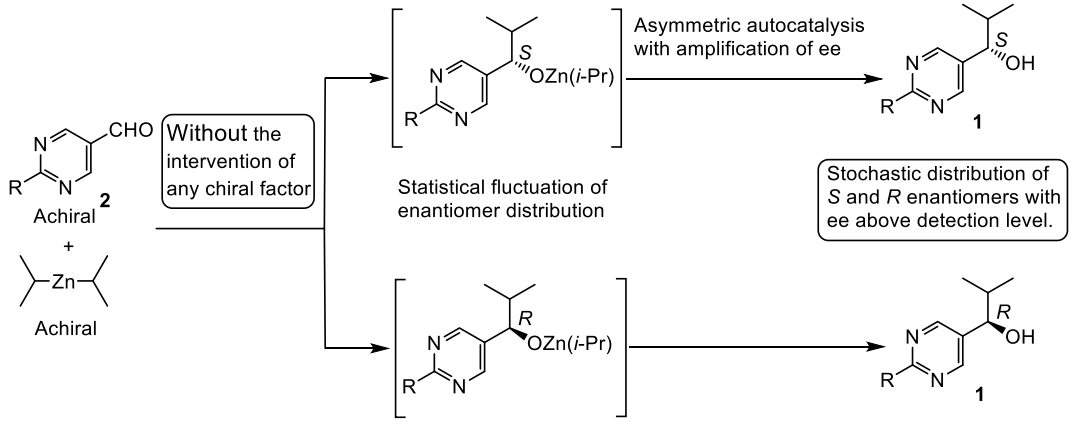


Fig. 2. Stochastic distribution of (*R*) and (*S*)-pyrimidyl alkanol **1c** formed in absolute asymmetric synthesis using pyrimidine-5-carbaldehyde **2c** and *i*-Pr_2Zn in toluene-ether [18b].



Scheme 8. Absolute asymmetric synthesis in the Soai reaction.

highly enantioenriched 5-pyrimidyl alkanol (Scheme 5) [15e].

Chiral organic crystals composed of achiral compounds such as cytosine can act as chiral triggers of asymmetric autocatalysis (Scheme 6) [16a,b].

Surprisingly, chiral compounds **12**-**15** due to the D/H [16c], $^{13}C/^{12}C$ [16d], $^{15}N/^{14}N$ [16e], $^{18}O/^{16}O$ [16f] isotope chirality trigger asymmetric autocatalysis to yield highly enantioenriched pyrimidyl alkanol with the absolute configurations matching those of isotopomers (Scheme 7). Because the differences of atomic weights of carbon, nitrogen, and oxygen isotopes are so small, asymmetric induction by these isotopomers are unprecedented. Even artificially designed helical silica [17a] and helical mesoporous silica [17b] trigger asymmetric autocatalysis.

4. Absolute asymmetric synthesis, *i.e.*, symmetry breaking, by the Soai reaction

Asymmetric autocatalysis with amplification of ee overturns the common understanding in organic chemistry that the reaction of achiral compounds into chiral compounds without using any chiral factor always gives the product with below detection level of optical rotation value, *i.e.*, of equal amounts of left- and right-handed enantiomers, *i.e.*, racemates.

The Soai reaction was found to be capable of achieving absolute asymmetric synthesis of enantioenriched compounds without the intervention of a chiral factor (Scheme 8) [8a,18]. Reaction between pyrimidine-5-carbaldehyde and diisopropylzinc without a chiral factor yielded enantioenriched (*S*)- or (*R*)-pyrimidyl alkanol with ee above the detection level [18a,b,c]. The distribution of the formation of absolute configurations of pyrimidyl alkanol was stochastic (Fig. 2). Likewise, absolute asymmetric synthesis in the presence of amorphous achiral silica gel [18d] and achiral amines [18e] also gave enantioenriched (*S*)- or (*R*)-pyrimidyl alkanol with stochastic distribution of the absolute configurations.

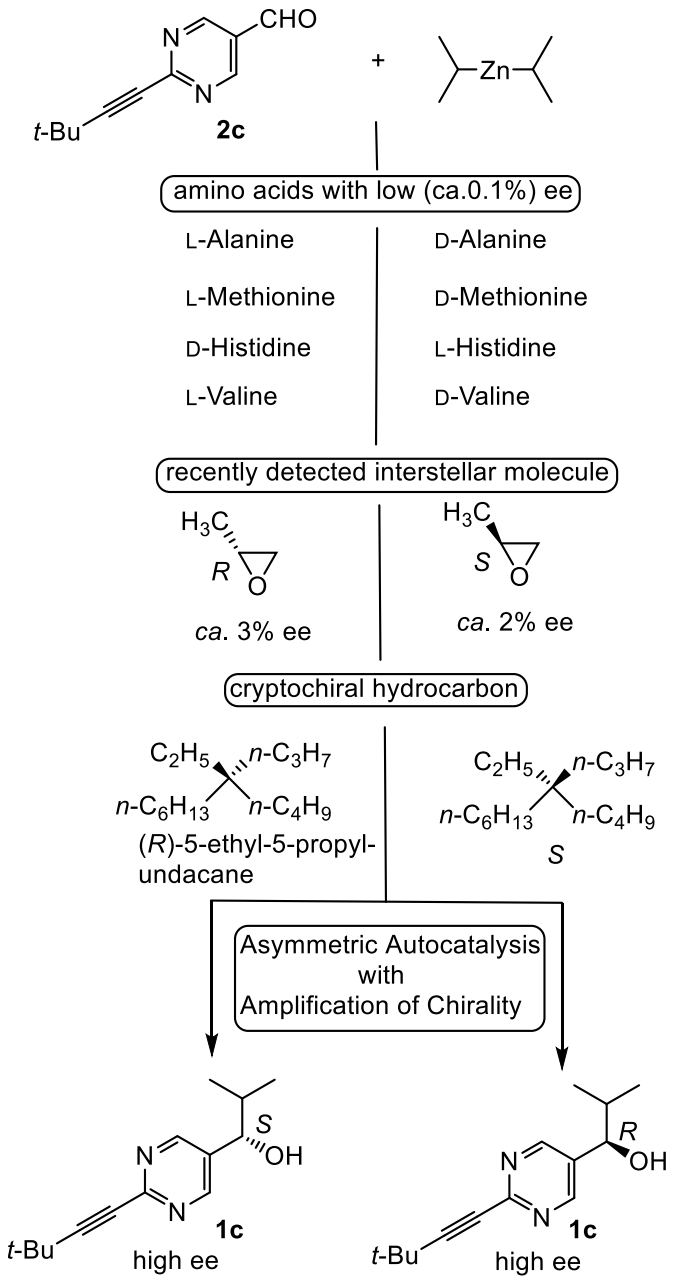
In usual organic reactions that form chiral products from achiral compounds without a chiral factor, the formed (*S*)- or (*R*)-chiral product always remains largely static. When the number of product molecules becomes large, due to the law of large numbers, the ratio of these enantiomers essentially becomes one to one, *i.e.*, a racemate. Unlike in usual organic reactions, as shown in the extraordinary amplification of ee from extremely low enrichment to >99.5% ee [10d], the Soai reaction is unique in that the slightly enriched chiral product molecules are dynamic and act as an asymmetric autocatalyst to automultiply and simultaneously suppress the formation of its slightly depleted enantiomer.

Let us consider the initial situation of the Soai reaction without the intervention of chiral factor: when 99 molecules are formed, the possible minimum ee should be 50 molecules of one enantiomer and 49 of the other. That is $(50-49)/(50+49) = 1/99$. This corresponds to *ca.* 1.01% ee, which is well above the threshold of the Soai reaction (*ca.* 0.00005% ee) [10d].

Moreover, these 99 molecules are not considered to be formed at the same moment. More or less, time lags should exist. Unlike usual reactions, the product in the Soai reaction does not remain calm, but increases its quantity and ee by asymmetric autocatalysis. Chiral molecules with certain *S* chirality, for example, formed spontaneously in the very initial moment would begin to automultiply with enhancing its ee. The molecule with the opposite *R* configuration is formed spontaneously after some interval and it begins to automultiply. In this case, the first *S* enantiomer has already automultiplied, and the whole mixture is not racemate but *S* predominant. Under these autocatalytic conditions, chiral symmetry breaking at molecular level would occur rather naturally.

Absolute asymmetric synthesis under solid-vapor phase conditions is also achieved. Powder crystal of pyrimidine-5-carbaldehyde is exposed to the vapor of *i*-Pr_2Zn/toluene. Subsequent asymmetric autocatalysis on the surface of crystal afforded (*R*) or (*S*)-pyrimidyl alkanol with stochastic distribution [18f]. Amedjkough *et al.* described absolute asymmetric synthesis of pyrimidyl alkanol under solid-vapor phase conditions in the presence of MOF [18g].

Thus, absolute asymmetric synthesis with apparent ee was achieved experimentally for the first time by the Soai reaction.



Scheme 9. Discrimination of absolute configurations of chiral compounds with low ee and of cryptochiral compound.

5. Discrimination of absolute configurations of chiral compounds with low ee by asymmetric autocatalysis

Asymmetric autocatalysis can be employed in the determination of absolute configurations of samples with low ee. The chirality of amino acids with low ee collected from meteorites and asteroids

has been a research focus from the standpoint of the origin of life (Scheme 9) [19a,b].

The Soai reaction is used for the discrimination of chirality of amino acids with low ee [19c,d]. Among 20 proteinogenic amino acids, 19 amino acids are chiral (L-form) and glycine is the only achiral one. Chiral amino acids with low ee were discriminated by the Soai reaction. On the other hand, the only achiral glycine has almost been neglected as the origin of homochirality. It should be noted that glycine forms a chiral stable γ-polymorph and that it triggers asymmetric autocatalysis [19e]. Thus, the absolute chirality of γ-glycine in meteorites and asteroids may be discriminated by the Soai reaction.

A recent report has revealed the presence of 2-methyloxirane (propylene oxide) in space [19f]. The chirality of 2-methyloxirane with low ee is discriminated by the Soai reaction [19g]. Moreover, cryptochiral saturated quaternary hydrocarbon [19h] and cryptochiral isotactic polystyrene [19i] could be discriminated by the Soai reaction. Chirality of various organic compounds can be detected by the Soai reaction [19j]. Chiral helical silica [19k] and chiral mesoporous silica [19l] also act as chiral triggers of asymmetric autocatalysis.

6. Summary and outlook

Self-replication (autocatalysis) and homochirality are two of the characteristic features of life. Asymmetric autocatalysis with amplification of enantiomer-enriched pyrimidyl alkanol—the Soai reaction—between pyrimidine-5-carbaldehyde and diisopropylzinc bears these two characteristic features. It enables absolute asymmetric synthesis, *i.e.*, the formation of enantioenriched compound without the intervention of any other chiral factor.

Asymmetric autocatalysis with amplification of ee was successfully implicated in asymmetric synthesis of *sec*-alkanols [20a] and alkynyl alkanols [20b]. The Soai reaction exhibits unusual reversal of the sense of enantioselectivity by mixing achiral catalyst to chiral catalyst [21]. Carreira *et al*. reported asymmetric autocatalytic synthesis of Efavirenz, a chiral drug for HIV [22].

Autocatalysis constitutes a part of emerging area of systems chemistry [23]. Carrol described that the simplest form of life exists in the form of self-amplifying autocatalytic reactions such as the Soai reaction [24]. Pross described about asymmetric autocatalysis as follows: “the kinetic power of replication which is responsible for the emergence of life could have well been responsible for one of life's most striking features – its homochiral character [25].”.

The best method for any material—molecules and living creatures, *etc*.—to endure over extended periods of time is the formation of an identical new entity by automultiplication. Even very solid rock or catalyst will deteriorate over time unless the same new rock or catalyst is formed by automultiplication. Life adopts the system of automultiplication and is termed self-replication in the case of life on Earth, and is the best system for life to exist as long as possible, not as individuals but as species.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Kenso Soai, born in Hiroshima, Japan in 1950. He obtained his Ph.D. degree in 1979 from the University of Tokyo with Professor Teruaki Mukaiyama. He was research associate with Professor Ernest L. Eliel at the University of North Carolina at Chapel Hill, USA. He joined the Faculty of Tokyo University of Science in 1981 and became PI. He was promoted to Associate Professor then to Full Professor (1991). He is currently Professor Emeritus.

His major research interests are new synthetic methods and origins of homochirality. Enantioselective addition of alkylmetal reagents to aldehydes, asymmetric conjugate addition of dialkylzinc to enone using chiral nickel catalyst, catalytic enantioselective addition of dialkylzincs to aldehydes, reduction of esters with sodium borohydride in *t*-BuOH-MeOH. In 1995, he discovered asymmetric autocatalysis of pyrimidyl alkanol with amplification of enantiomeric excess in the addition of diisopropylzinc to pyrimidine-5-carbaldehyde, *i.e.*, the Soai reaction. The reaction is self-replication of chiral compound. Initially very low ee of asymmetric autocatalyst is amplified to near enantiopure with the increase in the quantity. The reaction is capable of correlating the origins of homochirality such as quartz to highly enantioenriched compound.

His major awards include Chirality Medal (2005), Chemical Society of Japan Award (2010), Merit of Tokyo Metropolitan (2002), Inoue Prize for Science (2000), Molecular Chirality Award (2002), Medal for Scientific Achievement (National Academy of Sciences, Literatures and Arts, Modena, 2003), Synthetic Organic Chemistry Award (2003), Science and Technology Award (MEXT, 2007), Medal with Purple Ribbon (Japanese government, 2012), and Toray Science and Technology Award (2017).