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Review

Role of Asymmetric Autocatalysis in the Elucidation of Origins of Homochirality of Organic Compounds

Kenso Soai [1,*], Tsuneomi Kawasaki [1] and Arimasa Matsumoto [2]

1 Department of Applied Chemistry, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan; tkawa@rs.tus.ac.jp

2 Department of Chemistry, Biology and Environmental Science, Nara Women's University, Kita-Uoya Nishi-machi, Nara 630-8506, Japan; a-matsumoto@cc.nara-wu.ac.jp

* Correspondence: soai@rs.kagu.tus.ac.jp; Tel.: +81-(0)3-5228-8261

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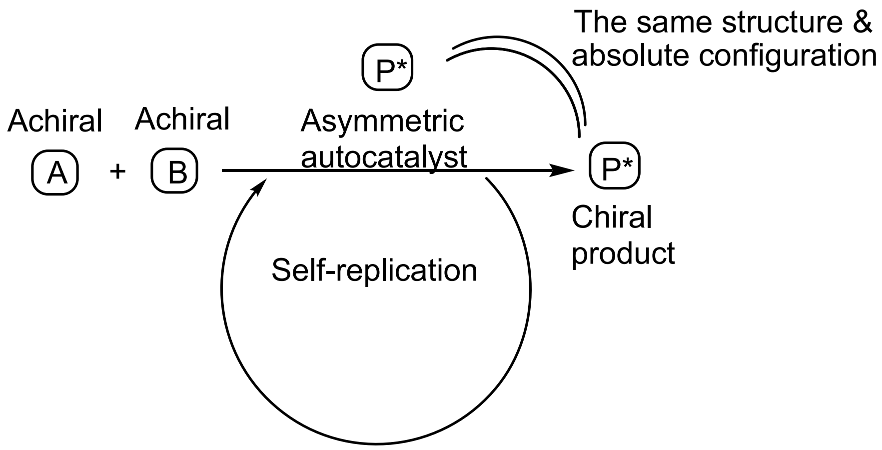
Abstract: Pyrimidyl alkanol and related compounds were found to be asymmetric autocatalysts in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde and related aldehydes. In the asymmetric autocatalysis with amplification of enantiomeric excess (ee), the very low ee (ca. 0.00005%) of 2-alkynyl-5-pyrimidyl alkanol was significantly amplified to >99.5% ee with an increase in the amount. By using asymmetric autocatalysis with amplification of ee, several origins of homochirality have been examined. Circularly polarized light, chiral quartz, and chiral crystals formed from achiral organic compounds such as glycine and carbon ($^{13}C/^{12}C$), nitrogen ($^{15}N/^{14}N$), oxygen ($^{18}O/^{16}O$), and hydrogen (D/H) chiral isotopomers were found to act as the origin of chirality in asymmetric autocatalysis. And the spontaneous absolute asymmetric synthesis was also realized without the intervention of any chiral factor.

Keywords: asymmetric autocatalysis; homochirality; chirality; asymmetric synthesis; Soai reaction

1. Introduction

The origins of biological homochirality of L-amino acids and D-sugars have attracted considerable attention ever since Pasteur discovered molecular dissymmetry in 1848 [1]. Although several theories of the origins of homochirality of organic compounds have been proposed [2–10], the enantiomeric excesses induced by these have usually been very low. For organic compounds to achieve homochirality, an amplification process from low enantiomeric excess (ee) to very high ee is required [11–23]. Therefore, asymmetric autocatalysis with amplification of chirality has been envisaged as the efficient process. We describe the discovery of asymmetric autocatalysis with amplification of ee. We also describe the study on the elucidation of the origin of homochirality of organic compounds by using asymmetric autocatalysis [24–36].

Asymmetric autocatalysis involves a process where a chiral product serves as the catalyst for its own production (Scheme 1). The reaction is a catalytic self-replication, i.e., automultiplication of a chiral compound. The superiority of asymmetric autocatalysis over the conventional non-autocatalytic asymmetric catalysis is as follows: (1) Because of the process of self-replication, the efficiency is high. (2) During the reaction, the amount of catalyst increases as the product increases. The catalytic activity and amount of catalyst does not decrease. (3) Because the structure of the product and the catalyst is the same, the separation of product from catalyst is not necessary.

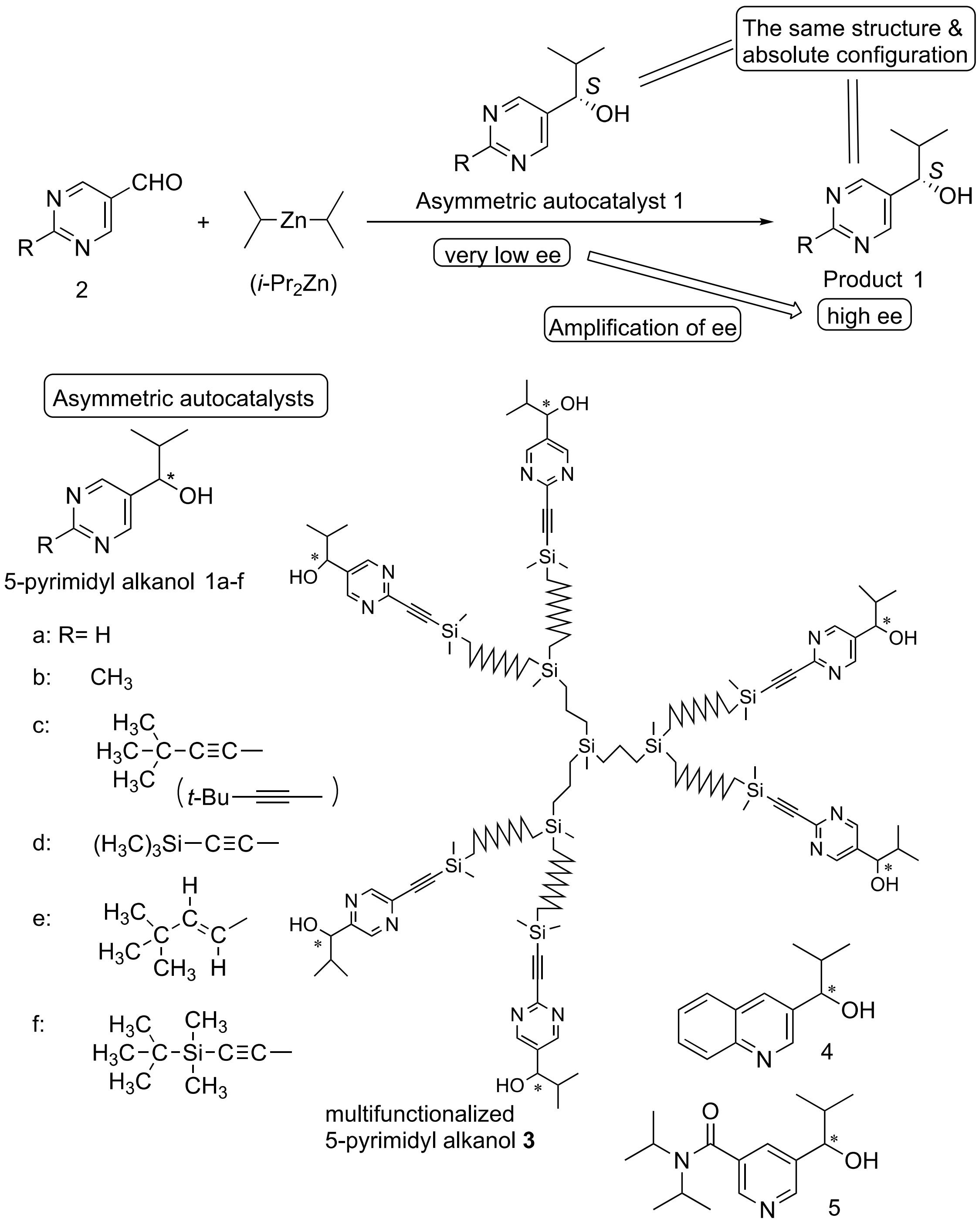


Scheme 1. Principle of asymmetric autocatalysis.

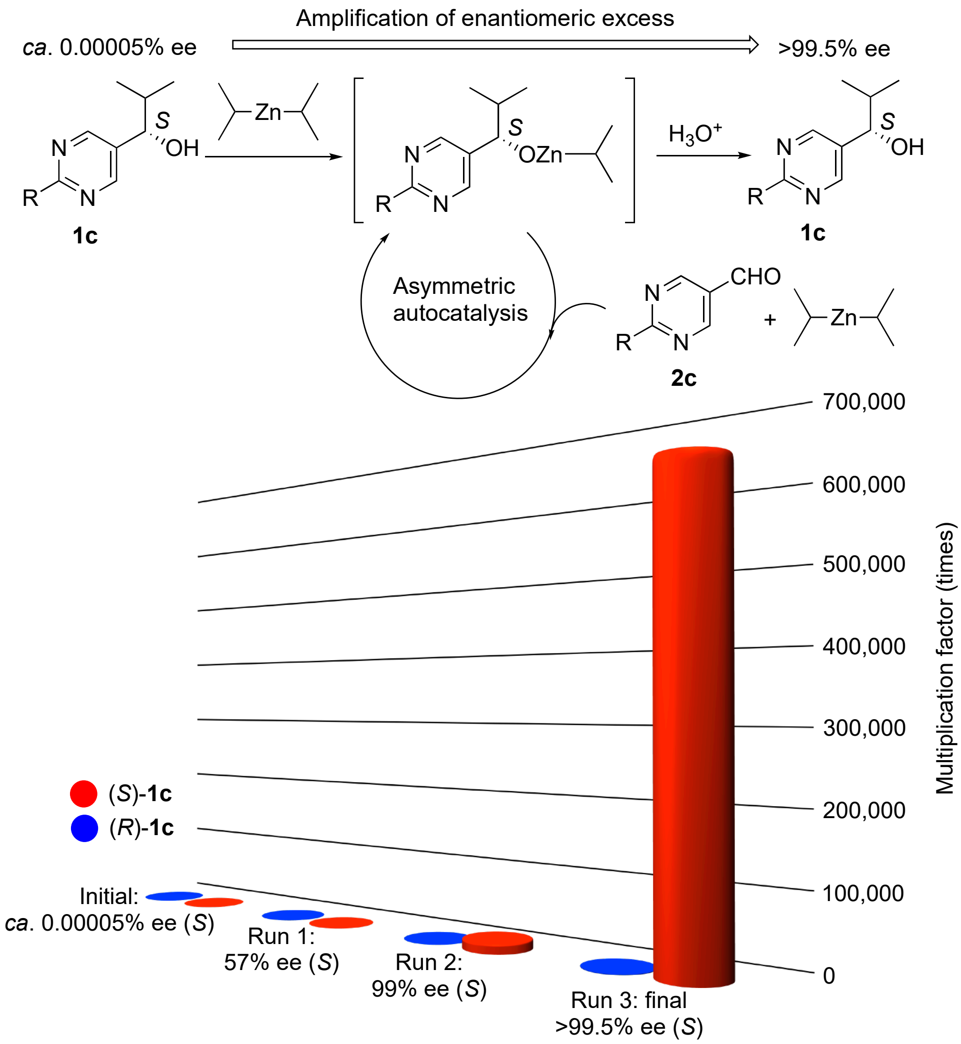
Frank proposed a mechanism, i.e., a mathematical equation, of asymmetric autocatalysis without showing any chemical structure in 1953 [21]. However, no real asymmetric autocatalysis had been reported until we first reported on the asymmetric autocatalysis of 3-pyridyl alkanol in 1990 [37].

2. Discovery of Asymmetric Autocatalysis with Amplification of Enantiomeric Excess

After the examination of the chiral diol system [38], we found in 1995 an efficient asymmetric autocatalysis of 5-pyrimidyl alkanol **1** with amplification of ee from 2% ee to 88% ee in the reaction between diisopropylzinc (i-Pr_2Zn) and pyrimidine-5-carbaldehyde **2a** (Scheme 2) [39,40]. In that reaction, pyrimidyl alkanol **1a** with 2% ee serves as an asymmetric autocatalyst to produce more of itself with an amplified ee. The consecutive asymmetric autocatalysis enables the amplification from 2 to 88% ee [39]. 2-Alkynylpyrimidyl alkanol **1c** with >99.5% ee was found to be an efficient asymmetric autocatalyst affording itself, **1c**, with >99.5% ee and with >99% yield [41]. It was also found that the asymmetric autocatalysis of pyrimidyl alkanol **1c** exhibit significant amplification of ee (Scheme 3). Indeed, starting from a very low (ca. 0.00005%) ee of (*S*)-pyrimidyl alkanol **1c** as an asymmetric autocatalyst, three cycles of asymmetric autocatalysis enabled the amplification of ee of alkanol **1c** to >99.5%. During the reaction, the amount of (*S*)-**1c** increased by a factor of ca. 630,000 times [42]. 2-Alkenylpyrimidyl alkanol **1e** [43], 3-quinolyl alkanol **4** [44–46], and 5-carbamoylpyridyl alkanol **5** [47,48] are also highly enantioselective asymmetric autocatalysts with amplification of ee (Scheme 2). The unique aspect of amplification of ee by asymmetric autocatalysis is that it is accomplished without the intervention of any other chiral factor. The only chiral factor is the initial enantiomeric imbalance of alkanol **1** itself as an asymmetric autocatalyst. In addition, asymmetric autocatalytic self-multiplication of multi-functionalized pyrimidyl alkanol **3** [49] and ultra-remote intramolecular asymmetric autocatalysis [50] were reported.



Scheme 2. Asymmetric autocatalysis. Structures of the autocatalysts of pyrimidyl alkanols **1a**–**f**, multi-functionalized pyrimidyl alkanol, **3**; 3-quinolyl alkanol, **4**; and 5-carbamoyl-3-pyridyl alkanol, **5**.



Scheme 3. Asymmetric autocatalysis of 5-pyrimidyl alkanol, **1c**, with amplification of enantiomeric excess from ca. 0.00005% to >99.5% ee.

Thus, it was proved that a chemical reaction exists in which very low enantioenrichment is amplified to almost enantiopure (>99.5% ee).

3. Study on the Mechanism of Asymmetric Autocatalysis

As described in the preceding section, asymmetric autocatalysis exhibits enormous amplification of ee during the self-replication. Thus, mechanistic insights into the asymmetric autocatalysis have attracted great attention. For the non-autocatalytic, non-linear effect in asymmetric catalysis, the dimer mechanism by Noyori [51] and MLn mechanism by Kagan [52] have been proposed.

We revealed the relationship between the reaction time and yield in the asymmetric autocatalysis using pyrimidyl alkanol **1c** with >99.5% ee [53]. A sigmoidal curve of product formation was observed. We also reported the relationship between the time, yield, and ee of the product by using chiral HPLC [54], which suggested dimeric or higher order aggregated catalytic species.

Several groups also investigated the mechanism of asymmetric autocatalysis. Heat flow measurement by microcalorimeter revealed the relationship between a reaction rate and the progress of the reaction. This suggested the dimeric catalyst model [55]. The dimeric and tetrameric species were proposed by the NMR measurement of the reaction solution [56,57]. The structure of catalyst aggregates has been proposed by density functional theory (DFT) calculation [58–61]. Reaction models have also been presented based on spontaneous mirror-symmetry breakage. These works proposed the mechanistic frameworks of asymmetric autocatalysis of pyrimidyl alkanol [62–69]. We clarified the crystal structures of asymmetric autocatalyst **1c** based on X-ray diffraction [70,71]. It was revealed that the structures are either tetrameric or oligomeric. The tetrameric crystal structure is formed in the presence of an excess molar amount of *i*-Pr_2Zn, while the higher order aggregate is formed in the presence of an equimolar or slightly excess amount of *i*-Pr_2Zn. Recently, reaction modeling was reported which suggests that the tetramer or higher order aggregates work for the asymmetric autocatalysis [72]. The clarification of the entire reaction pathway of asymmetric autocatalysis awaits further investigation.

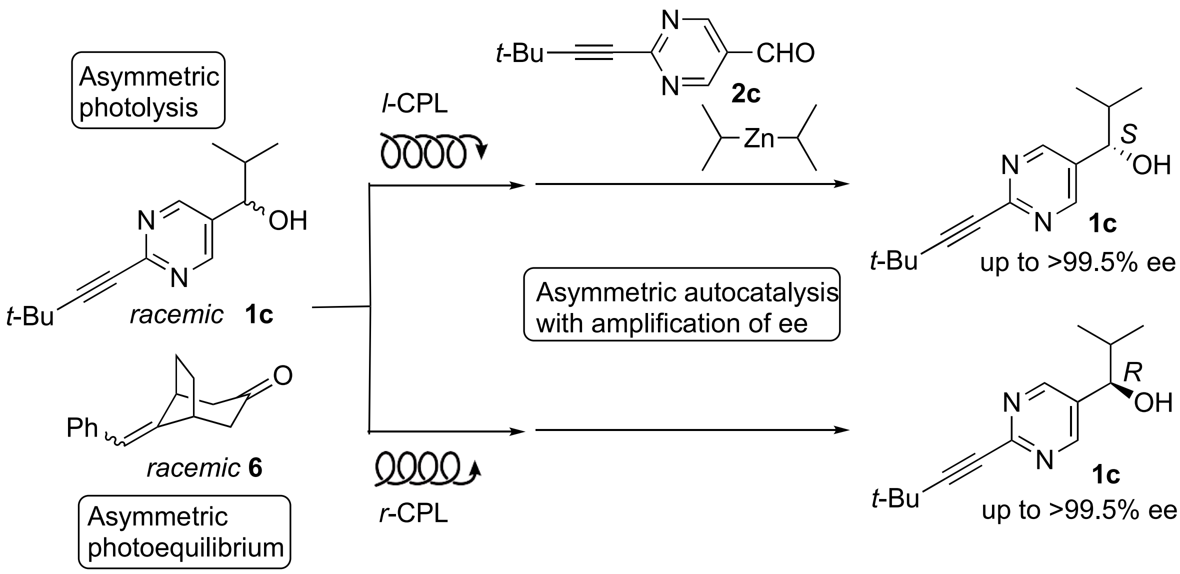
4. Elucidation of the Origins of Homochirality by Using Asymmetric Autocatalysis

As described in the preceding section, asymmetric autocatalysis amplified ee from very low to very high. We then examined the origins of homochirality by using asymmetric autocatalysis. We envisaged that the low ee induced by the origin of chirality could be amplified by asymmetric autocatalysis. The origins of chirality so far proposed have usually induced only very low ees. To explain the very high ees observed in nature, the amplification of very low ee of organic compounds is necessary. We employed asymmetric autocatalysis of amplification of ee to examine the several proposed mechanisms of the origin of chirality.

4.1. Circularly Polarized Light

One of the representative chiral physical forces is circularly polarized light (CPL). Left (*l*) and right (*r*)-CPL have long been considered as the origin of chirality. In some of the star-forming regions, the occurrence of relatively strong CPL has been observed [73]. It is known that only ca. 2% ee is induced by irradiation of CPL to racemic organic compounds such as leucine. Asymmetric photosynthesis of hexa-helicen by CPL irradiation has been reported [5]. The induced low ee in leucine was correlated, for the first time, to the very high ee of organic compounds by using asymmetric autocatalysis [74].

The direct irradiation of *l*-CPL to racemic (*rac*) pyrimidyl alkanol **1c**, and the subsequent asymmetric autocatalysis, gave (*S*)-alkanol **1c** with >99.5% ee (Scheme 4) as a result of the amplification of ee [75]. On the other hand, *r*-CPL irradiation affords (*R*)-**1c** with >99.5% ee. The relationship between the handedness of *l*- and *r*-CPL and (*S*)-**1c** and (*R*)-**1c** is explained by the following consideration: The cotton effects of the circular dichroism (CD) spectra of the solid state of (*R*)-**1** and (*S*)-**1c** are plus (+) and minus (-) at 313 nm, respectively. Thus, when *l*-CPL is irradiated on *rac*-**1c**, the asymmetric photodecomposition of (*R*)-**1c** is induced because *l*-CPL is absorbed preferentially. Then, the less reactive (*S*)-**1c** becomes the predominant enantiomer over (*R*)-**1c**. The asymmetric autocatalysis of the remaining alkanol increases the ee of (*S*)-**1c** to >99.5% ee. Thus, the direct correlation is accomplished between the handedness of CPL and that of highly enantioenriched organic compound.



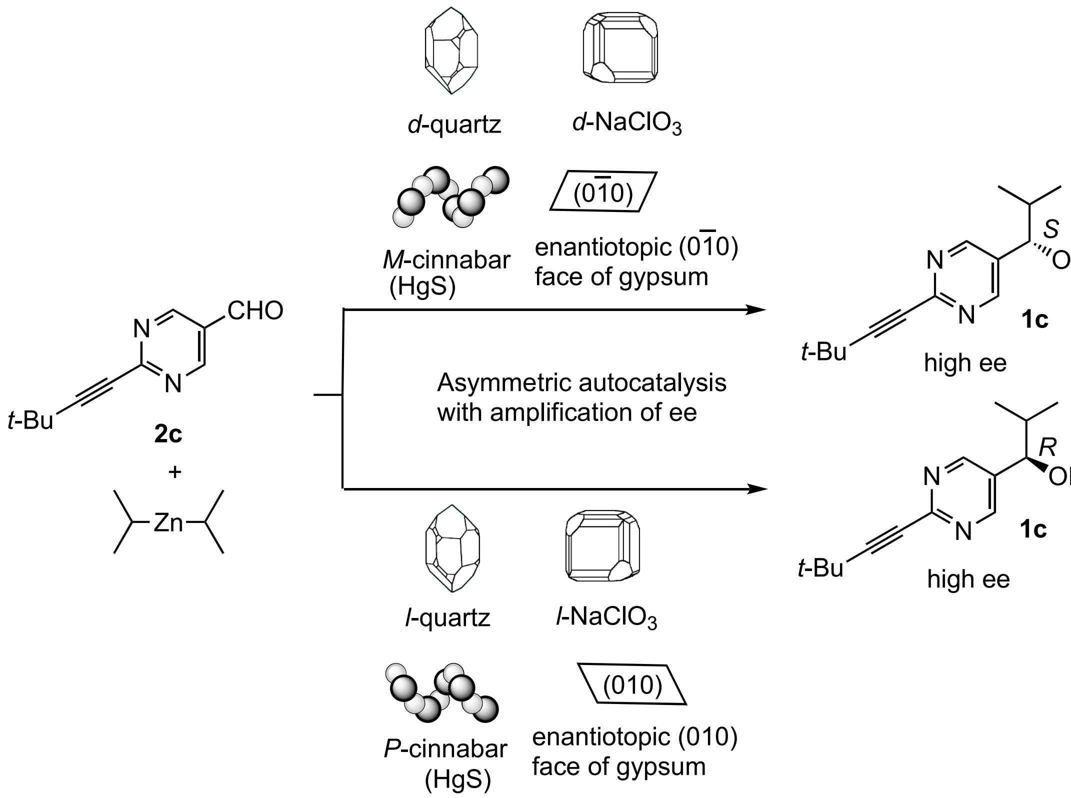
Scheme 4. Circularly polarized light (CPL) triggers asymmetric autocatalysis.

The asymmetric photoequilibrium of *rac*-olefin **6** using CPL, and the subsequent asymmetric autocatalytic reaction, gave pyrimidyl alkanol **1c** of the correlated absolute configuration to CPL [76]. Recently, under CPL irradiation, a Viedma-type racemization-crystallization of an amino acid derivative was reported [77].

4.2. Chiral Inorganic Crystals of Quartz, Sodium Chlorate, Cinnabar, and Retgersite, and the Enantiotopic Face of the Achiral Crystal of Gypsum

A chiral single crystal of silicon dioxide is known as quartz, and it exhibits enantiomorphism. Chiral minerals including quartz have been proposed as the origin of homochirality [6]. There are many reports attempting to induce chirality in organic compounds by using quartz [78]. However, no significant asymmetric induction has yet been reported by using quartz.

We thought that the asymmetric autocatalysis amplifies significantly the very low ee of the product initially induced by chiral *d*- and *l*-quartz [79]. Indeed, in the presence of *d*-quartz, asymmetric autocatalysis using pyrimidine-5-carbaldehyde **2c** and *i*-Pr_2Zn afforded (*S*)-**1c** with 97% ee in a yield of 95% (Scheme 5). On the other hand, *l*-quartz afforded (*R*)-**1c** with 97% ee. It was clearly shown by these results that *d*- and *l*-quartz act as chiral initiators of asymmetric autocatalysis. The initially formed slightly enriched (S)-(zinc alkoxide) of pyrimidyl alkanol **1c** serves as an asymmetric autocatalyst and automultiplies with amplification of ee. Thus, the chirality of *d*- and *l*-quartz is correlated to the chirality of a near enantiopure organic compound.



Scheme 5. Asymmetric autocatalysis triggered by chiral quartz, sodium chlorate, cinnabar and enantiotopic face of achiral crystal of gypsum.

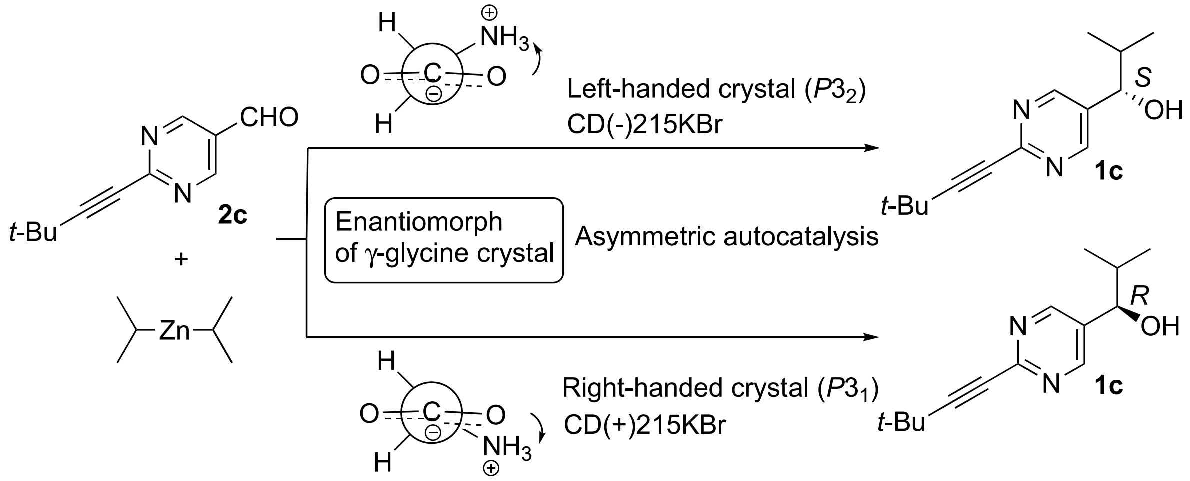
Sodium chlorate ($NaClO_3$) and sodium bromate ($NaBrO_3$) are chiral inorganic ionic crystals [14,80,81]. It was also found that *d*-$NaClO_3$ triggers asymmetric autocatalysis to give (*S*)-**1c**, while *l*-$NaClO_3$ gives (*R*)-**1c** [82]. On the other hand, *d*-$NaBrO_3$ and *l*-$NaBrO_3$ trigger the formation of (*R*)- and (*S*)-**1c**, respectively [83]. Note that *d*-$NaClO_3$ and *l*-$NaBrO_3$ with the opposite signs of optical activity have the same type of enantiomorph. Enantiomorphic *P*- and *M*-crystals of cinnabar, mercury(II) sulfide (HgS), are composed of –Hg–S–Hg–S helical chains. We found that *P*-cinnabar acts as a chiral trigger of asymmetric autocatalysis to give (*R*)-**1c**. In contrast, *M*-HgS triggers the formation of (*S*)-**1c** [84]. Retgersite ($NiSO_4$ $6H_2O$) of [CD(+)390_{Nujol}] triggers asymmetric autocatalysis to afford (*S*)-**1c**. In contrast, retgersite of [CD(−)390_{Nujol}] affords (*R*)-**1c** [85].

Gypsum (calcium sulfate dihydrate) is a common mineral which has been widely used. The crystal structure is not chiral. However, gypsum exhibits two-dimensional enantiotopic cleavage (010) and (0−10) face. Pyrimidine-5-carbaldehyde **2c** was put on the enantiotopic (010) face. Then, the reaction of aldehyde **2c** on gypsum with the vapor of *i*-Pr_2Zn gave (*R*)-pyrimidyl alkanol **1c** [86]. In contrast, the reaction by exposing on the opposite (0−10) face gave (*S*)-alkanol **1c**. Thus, it was shown that the enantiotopic face of achiral gypsum works as an origin of chirality.

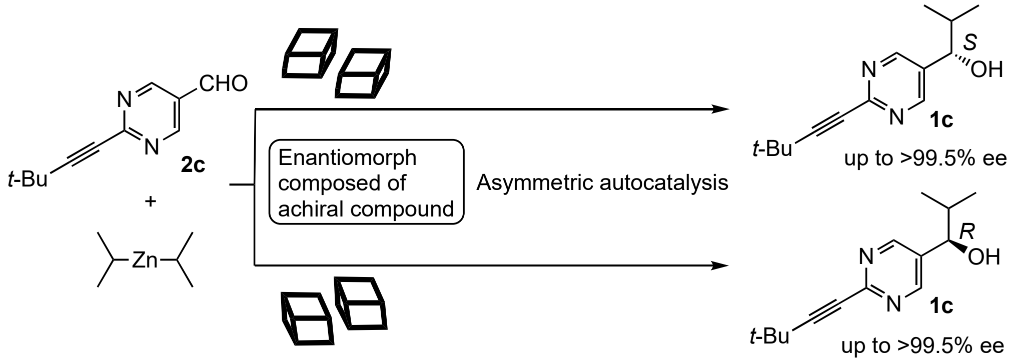
In combination with asymmetric autocatalysis, chiral inorganic crystals serve as the origin of chirality to give enantioenriched organic compounds of the correlated absolute configurations.

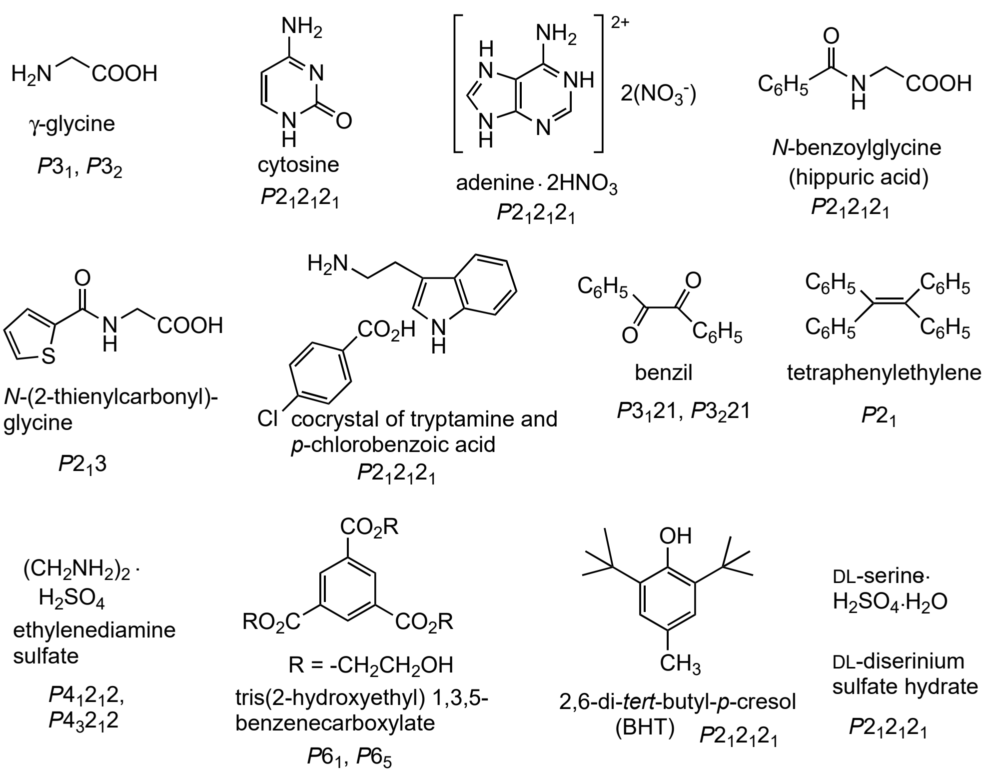
4.3. Chiral Crystals Formed from Achiral Organic Compounds

Achiral organic compounds often form achiral crystals. However, it is known that some of the achiral organic compounds form chiral crystals [87]. In some stereospecific reactions, these chiral organic crystals have been used as reactants [10]. However, in enantioselective synthesis, chiral crystals composed of achiral organic compounds have seldom been used as inducers. We used chiral crystals formed from achiral organic compounds as chiral inducers of asymmetric autocatalysis (Schemes 6 and 7).



Scheme 6. Asymmetric autocatalysis triggered by chiral γ-polymorph of achiral glycine.





Scheme 7. Asymmetric autocatalysis initiated by chiral crystals composed of achiral organic compounds.

Natural proteinogenic amino acids, except glycine, exhibit L-form. Glycine stands as the only achiral amino acid that possesses no asymmetric carbon atoms. Although it is known that the stable crystal structure of the γ-glycine polymorph is chiral, it took years to determine the absolute crystal structure of the γ-glycine polymorph. Recently, the absolute crystal structure of the γ-glycine polymorph was correlated with optical rotatory dispersion (ORD) [88]. Guillemin reported CD spectra of γ-glycine [89].

We have correlated the absolute crystal structure of γ-glycine and have used the γ-glycine crystal as a chiral trigger of asymmetric autocatalysis [90]. It was found that the $P3_2$ crystal (left-handed) of γ-glycine triggers the formation of (*S*)-pyrimidyl alkanol **1c** with up to >99.5% ee (Scheme 6). In contrast, the $P3_1$ crystal afforded (*R*)-alkanol **1c** with up to >99.5% ee.

Thus, in conjunction with asymmetric autocatalysis, achiral glycine as its chiral γ-polymorph acts as the origin of homochirality.

Cytosine is a nucleobase and achiral. It may be formed under plausible prebiotic conditions [91]. When cytosine is crystallized from methanol, chiral crystals form. Chiral crystals of cytosine trigger asymmetric autocatalysis. When cytosine crystals of [CD(+)310_{Nujol}] were used as chiral initiators of the reaction of aldehyde **2c** with *i*-Pr_2Zn, (*R*)-alkanol **1c** was formed in combination with asymmetric autocatalysis (Scheme 7). In contrast, a [CD(−)310_{Nujol}]-cytosine crystal afforded (*S*)-**1c** [92]. Thus, the chiral cytosine crystal serves as the origin of chirality.

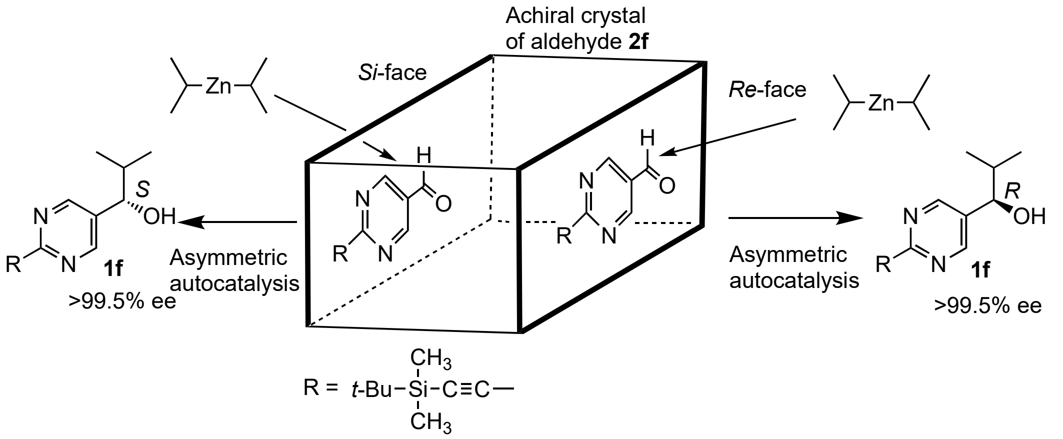
Cytosine forms achiral crystals of cytosine monohydrate when it is crystallized from water. When it is heated from one of the enantiotopic faces, the crystal water is eliminated by heating and chiral dehydrated cytosine is formed [93]. Interestingly, the chirality of the dehydrated crystal is determined by the enantiotopic face of the crystal from which the heating is applied. It is worth noting that the dehydration of the crystal water of cytosine monohydrate under reduced pressure conditions [94] also gives the chiral cytosine crystal with the opposite chirality to that dehydrated by heating. Thus, by removal of crystal water from an achiral crystal of cytosine monohydrate either by heating or under reduced pressure, the formation of chiral crystals with controlled absolute chirality was achieved.

Adenine is another achiral nucleobase. Chiral crystals of adenine dinitrate act as chiral initiators of asymmetric autocatalysis (Scheme 7) [95]. Thus, achiral nucleobases, i.e., cytosine and adenine, can serve as the origin of homochirality in conjunction with asymmetric autocatalysis.

Enantiomorphous crystals formed from achiral *N*-benzoylglycine (hippuric acid) [96], 2-thenoylglycine [97], certain chiral cocrystals consisting of two achiral compounds [98], benzil [99], tetraphenylethylene [100], ethylenediammonium sulfate [101], aromatic triester [102], and 2,6-di-*tert*-butyl-*p*-cresol (BHT) [103] serve as chiral initiators of asymmetric autocatalysis (Scheme 7). It should be added that a chiral crystal composed of a racemic serine initiates asymmetric autocatalysis. Asymmetric autocatalysis using the *M*-crystals of DL-diserinium sulfate hydrate as the chiral initiator afford (*R*)-pyrimidyl alkanol **1c**, while *P*-crystals afford (*S*)-alkanol **1c** [104].

4.4. Enantiotopic Face of Achiral Organic Crystal Composed of Achiral Organic Compound

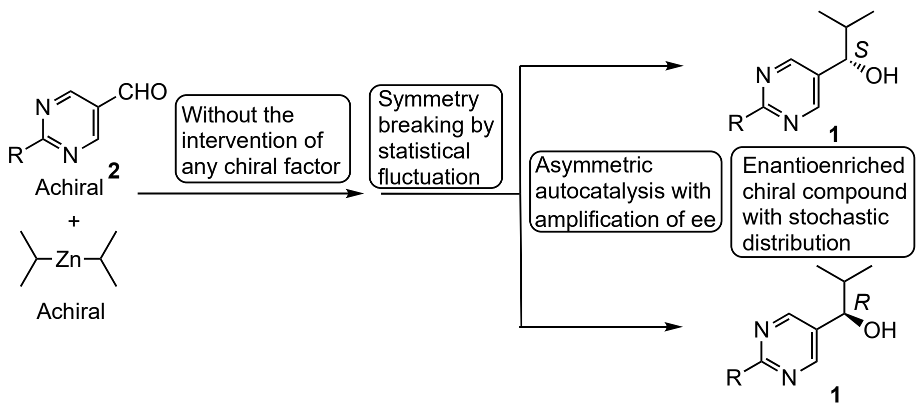
Some of the crystal faces of achiral organic crystals formed from achiral compounds become enantiotopic. Achiral 2-(*tert*-butyldimethylsilylethynyl) pyrimidine-5-carbaldehyde **2f** forms an achiral crystal (*P*-1) that has enantiotopic faces. When the *Re*-face of the crystal was exposed to *i*-Pr_2Zn, (*R*)-pyrimidyl alkanol, **1f** was formed (Scheme 8) [105]. In contrast, exposure of *i*-Pr_2Zn on the *Si*-face gave (*S*)-alkanol **1f**. The ees of alkanol **1f** were amplified to >99.5% ee by asymmetric autocatalysis. Thus, it was shown that the enantiotopic faces of achiral crystals act as the origin of homochirality in conjunction with asymmetric autocatalysis.



Scheme 8. Asymmetric autocatalysis initiated on the enantiotopic face of an achiral 2-(*tert*-butyldimethylsilylethynyl) pyrimidine-5-carbaldehyde **2f**.

4.5. Spontaneous Absolute Asymmetric Synthesis by Asymmetric Autocatalysis

As described in the preceding section, asymmetric autocatalysis of pyrimidyl alkanol enhances extremely low ca. 0.00005% ee to near enantiopure >99.5% ee [42]. We reasoned that if *i*-Pr_2Zn is reacted with pyrimidine-5-carbaldehyde **2** without using any chiral factor, the product with low ee based on the statistical fluctuation would form. The subsequent asymmetric autocatalysis may enhance the initial low ee to the detectable high ee (Scheme 9).



Scheme 9. Spontaneous absolute asymmetric synthesis by asymmetric autocatalysis without the intervention of any chiral factor.

Although the term "absolute asymmetric synthesis" had been used for the asymmetric synthesis "without the use of any chiral chemical substance," Mislow newly defined absolute asymmetric synthesis as "the formation of an enantioenriched compound from achiral compounds without the intervention of any chiral factor [3]." The spontaneous absolute asymmetric synthesis, based on the statistical fluctuation, has been thought of as one of the origins of chirality. However, it is known that the reaction between achiral reagents without any chiral factor always gives so-called racemic product. However, there are statistical fluctuations in the numbers of enantiomers [3]. Let us consider the situation of flipping a coin one hundred times: there is an 8% probability of 50 heads and 50 tails. The remaining 92% are results with either heads or tails being in excess: 49 to 51, 53 to 47, etc. Pályi et al. described the distribution of ee by statistical fluctuations of various amounts of so-called racemic molecules [106–108].

We found spontaneous absolute asymmetric synthesis in the reaction between pyrimidine-5-carbaldehyde **2** and *i*-Pr_2Zn without the addition of any chiral substance. In 1996, we applied patent for this absolute asymmetric synthesis [109,110]. The reaction afforded enantioenriched (*S*)-pyrimidyl alkanol **1** or (*R*)-alkanol **1** [109]. When aldehyde **2c** and *i*-Pr_2Zn were reacted in a mixed solvent of ether-toluene, enantioenriched product was formed in situ by statistical fluctuation. The subsequent asymmetric autocatalysis gave (*S*) or (*R*)-**1** with detectable enantioenrichments. The formation of (*S*)-alkanol **1c** occurred 19 times and (*R*)-**1c** occurred 18 times in a total of 37 reactions (Figure 1a) [110]. The absolute configurations of **1c** formed exhibits a stochastic distribution of *S* and *R* enantiomers. Moreover, by using achiral amorphous silica gel (Figure 1b) [111] and achiral amines (Figure 1c) [112], enantioenriched **1c** was obtained and the distribution of (*S*)- and (*R*)-handedness was stochastic. The absolute asymmetric synthesis has also been reported between pyrimidine-5-carbaldehyde **2b** and *i*-Pr_2Zn (*S*)-**1b** or (*R*)-**1b** in a stochastic distribution [113]. As described, the results fulfill the conditions necessary for spontaneous absolute asymmetric synthesis [62,65,114–117].

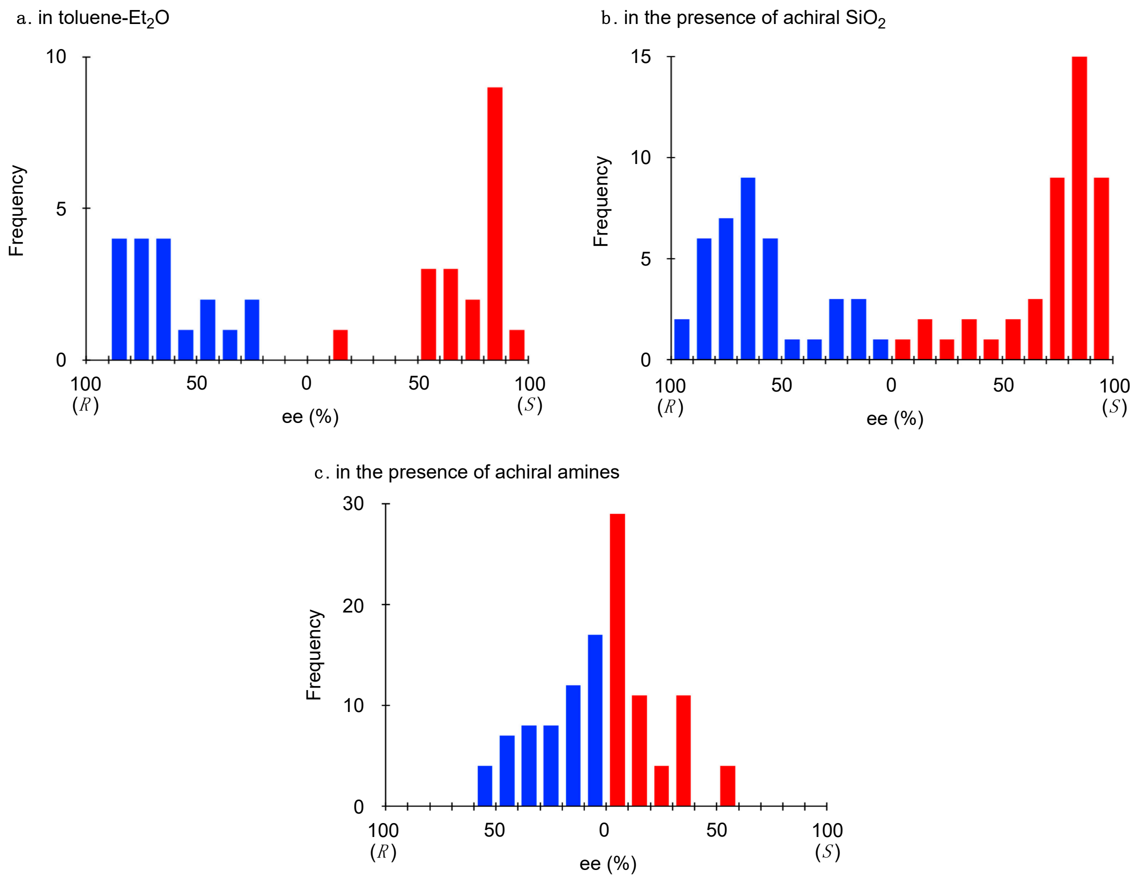
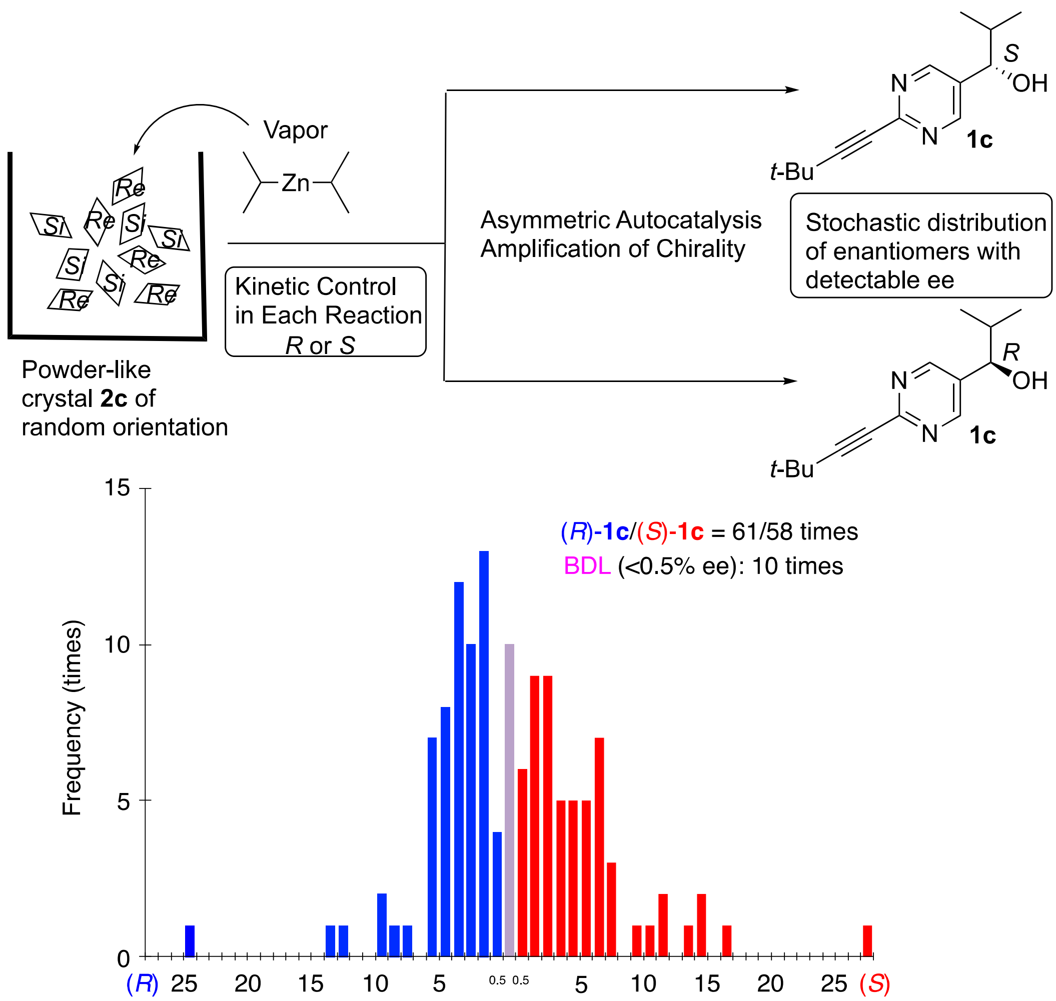


Figure 1. Spontaneous absolute asymmetric synthesis of pyrimidyl alkanol **1**. Histograms of the absolute configuration and ee of products.

Very recently, absolute asymmetric synthesis under heterogeneous solid-vapor phase conditions has been reported by us (Scheme 10) [118]. The powder of pyrimidine-5-carbaldehyde **2c** in test tubes was exposed to the vapor of *i*-Pr_2Zn and toluene in a desiccator. In 129 reactions, (*R*)-pyrimidyl alkanol **1c** was formed 61 times. On the other hand, (*S*)-alkanol **1c** was formed 58 times (10 times the formation of **1c** of <0.5% ee was assigned as below the detection level). Thus, the results show that the distribution of (*S*) and (*R*)-alkanol **1c** is stochastic. Although the ee values of alkanol **1c** varied, these ee could be enhanced to >99.5% ee during the subsequent asymmetric autocatalysis. The present heterogeneous absolute asymmetric synthesis under solid vapor phase conditions could be possible in a more spacious platform.



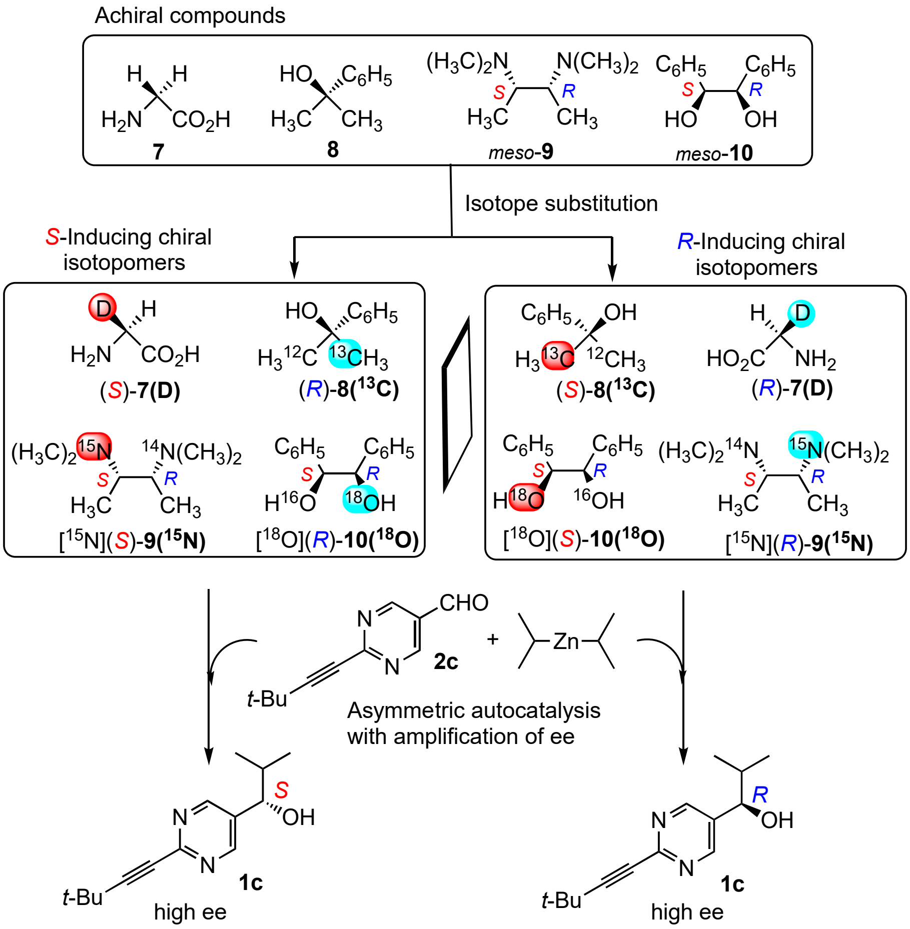
Scheme 10. Absolute asymmetric synthesis of pyrimidyl alkanol **1c** under solid-vapor phase conditions.

4.6. *Asymmetric Autocatalysis Triggered by Hydrogen, Carbon, Oxygen, and Nitrogen Chiral Isotopomers*

Many apparent achiral organic compounds become chiral by substitution of carbon (^{12}C), nitrogen (^{14}N), and oxygen (^{16}O) for their isotopes of ^{13}C, ^{15}N, and ^{18}O, respectively. For example, dimethylphenylmethanol **8** is an achiral compound because it has the same two methyl groups. However, when one of the carbon atoms of the methyl group is labelled with ^{13}C, the alkanol becomes a chiral (*R*)-alkanol **8**(^{13}C) or (*S*)-alkanol **8**(^{13}C) (Scheme 11). Because the difference of carbon (^{13}C/^{12}C) isotopomers between enantiomers is so small, no report has appeared before on the asymmetric induction by using chiral carbon (^{13}C/^{12}C) isotopomers.

We found that in the presence of chiral carbon (^{13}C/^{12}C) isotopomer and (*R*) or (*S*)-**8**(^{13}C), as a chiral trigger, pyrimidine-5-carbaldehyde **2c** reacts with *i*-Pr_2Zn to give pyrimidyl alkanol **1c** with a very high ee of the absolute configuration correlated to that of the carbon isotopomer (Scheme 11). (*R*)-Carbon isotopomer **8**(^{13}C) triggered the formation of (*S*)-pyrimidyl alkanol **1c** with high ee. In contrast, (*S*)-carbon isotopomer **8**(^{13}C) gave (*R*)-pyrimidyl alkanol [119]. Other carbon (^{13}C/^{12}C) isotopomers also serve as chiral triggers on asymmetric autocatalysis. Chiral nitrogen (^{15}N/^{14}N) isotopomer, [^{15}N](*S*) and [^{15}N](*R*)-diamine **9**(^{15}N) were also found to work as chiral triggers of asymmetric autocatalysis [120]. In addition, oxygen (^{18}O/^{16}O) isotopomer, [^{18}O](*R*), and [^{18}O](*S*)-diol **10**(^{18}O), trigger asymmetric autocatalysis to give pyrimidyl alkanol **1c** of high ee with the correlated absolute configuration to that of oxygen isotopomer [121,122]. As described, carbon, nitrogen, and oxygen isotopomers were found to act as the origin of homochirality in conjunction with asymmetric autocatalysis.

As to chiral hydrogen (D/H) isotopomers, there are a few examples of low asymmetric induction by hydrogen isotopomers [123,124]. It was found that chiral hydrogen isotopomers act as chiral initiators of asymmetric autocatalysis [125,126]. It should be noted that achiral glycine **7** becomes chiral by substituting one of the hydrogen atoms of the methylene group for deuterium (D). In the presence of chiral (*S*)-glycine-α-*d* **7**(D), (*S*)-pyrimidyl alkanol **1c** of high ee was formed with the correlated absolute configuration to that of chiral glycine-α-*d* [127].



Scheme 11. Asymmetric autocatalysis triggered by carbon ($^{13}C/^{12}C$), nitrogen ($^{15}N/^{14}N$), oxygen ($^{18}O/^{16}O$), and hydrogen (D/H) isotope chirality.

5. Various Chiral Compounds as Triggers of Asymmetric Autocatalysis

Various chiral compounds work as chiral initiators of asymmetric autocatalysis. Amino acids even with low ee [128], such as hexa-helicene [129], tetrathia-hepta-helicene [130], and 2-aza-hexa-helicene [131], initiate asymmetric autocatalysis to give alkanol **1c** of the correlated absolute configuration to those of the chiral initiators. It is known that the value of optical rotation of a chiral saturated quaternary hydrocarbon, 5-ethyl-5-propylundecane, is below detection level because the differences in the structures of the four substituents are so small. The compound is called cryptochiral. It was found that 5-ethyl-5-propylundecane triggers asymmetric autocatalysis [132]. Cryptochiral isotactic polystyrene also works as a chiral trigger [133]. Artificially designed helical [134] silica and mesoporous helical silica [135] are also chiral triggers.

6. Conclusions

Asymmetric autocatalysis of the enantioselective addition of i-Pr_2Zn to pyrimidine-5-carbaldehyde was discovered by us. In this reaction, the very low ca. 0.00005% ee of (*S*)-2-alkynylpyrimidyl alkanol

1 was enhanced to >99.5% ee by consecutive asymmetric autocatalyses. Mislow first mentioned this reaction as the Soai reaction [3]. The asymmetric autocatalysis with amplification of ee is unique because no chiral substance other than the asymmetric autocatalyst itself is required.

To elucidate the origins of homochirality, asymmetric autocatalysis with amplification of ee was applied. By using asymmetric autocatalysis, the initially induced low ee by the proposed origin of chirality was enhanced significantly by the asymmetric autocatalysis. The racemic pyrimidyl alkanol was irradiated with *l* or *r*-circularly polarized light. The subsequent asymmetric autocatalysis correlated the chirality of CPL with that of the formed alkanol **1**. Thus, for the first time, the correlation was made possible between the chirality of CPL and that of a chiral organic compound of very high ee. Chiral minerals such as quartz and cinnabar were found to act as chiral triggers of asymmetric autocatalysis. Thus, chirality of quartz was correlated to that of a highly enantioenriched organic compound. It was also found that chiral organic crystals composed of achiral compounds, i.e., glycine, cytosine, and adenine, serve as chiral triggers of asymmetric autocatalysis. Spontaneous absolute asymmetric synthesis without the intervention of any chiral factors was realized using the asymmetric autocatalysis of pyrimidyl alkanol with amplification of ee. Asymmetric autocatalysis was initiated by chiral compounds resulting from carbon ($^{13}C/^{12}C$), nitrogen ($^{15}N/^{14}N$), and oxygen ($^{16}O/^{18}O$) isotopomers. X-ray crystallographic analysis revealed the structure of asymmetric autocatalysts. It should be mentioned that bio-reactions should be studied looking for asymmetric autocatalysis.

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