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Amplification of chirality as a pathway to biological homochirality

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ABSTRACT

Amplification of enantiomeric enrichment is a key feature for the chemical evolution of biological homochirality from the origin of chirality. The aggregations of the enantiomers by diastereomeric interactions enable the modification of their enantiomeric excess during some chemical processes. Fluorine-containing chiral compounds possess large amplification effect *via* distillation, sublimation and achiral chromatography by self-disproportionation. Asymmetric amplifications in enantioselective catalysis occur by the differential formation and reactivity between homochiral and heterochiral aggregate in solution.

We described the amplification of ee in asymmetric autocatalysis of 5-pyrimidyl alkanol in the reaction between diisopropylzinc and pyrimidine-5-carbaldehdye. During the reactions extremely low ee (*ca.* 0.00005% ee) can be amplified to achieve more than 99.5% ee. Since the proposed origins of chirality such as CPL, quartz, chiral organic crystals of achiral compounds and statistical fluctuation of ee can initiate the asymmetric autocatalysis with amplification of ee, the proposed origin of chirality can be linked with enantiopure organic compound in conjunction with amplification of ee by asymmetric autocatalysis. In addition, we described that the carbon isotopically chiral compound triggers the asymmetric autocatalysis of 5-pyrimiodyl alkanol to afford the enantioenriched product with the absolute configuration correlated with that of carbon isotope chirality, that is, isotope chirality including hydrogen isotopes can control the enantioselectivity of asymmetric addition of alkyl metal reagent to aldehyde.

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1. Introduction

Chirality is one of the most fascinating research topics in many scientific areas and has been continuously studied to expand its intriguing and important abilities. There are many chiral systems, *i.e.*, systems that cannot be superposed on their mirror images. The representative chiral system in chemistry is chiral molecules [1,2]. Tetrahedral molecules with four different substituents on their asymmetric carbon atom are archetypal cases in which molecules have chirality [3,4]. The simple amino acid, alanine, is a tetrahedral chiral molecule, having hydrogen, methyl, carboxyl and amino groups on the carbon center (Fig. 1); thus, there are two enantiomeric alanines with opposite handedness, *i.e.*, *S*-configured L-alanine and *R*-configured D-alanine, which are nonsuperposable molecules. In the case that the molecule has two (or more) substituents on its carbon center that are the same, it becomes achiral, being superposable on its mirror image. The simplest amino acid, glycine, is illustrated in Fig. 1 as an example of an achiral molecule.

There are many chiral biologically related compounds. For example, limonene has two enantiomers, the *l*-isomer with *S*-configuration on the chiral carbon center and the *d*-isomer with *R*-configuration (Fig. 2). In general, the two enantiomers of chiral molecules show different biological activities, *e.g.*, *l*-limonene smells like a lemon; in contrast, the *d*-form smells like an orange. These differences between the biological activities of two enantiomers have often been observed in pharmaceuticals. An example is the fluoroquinolone anti-infective, levofloxacin, which has one asymmetric carbon in its structure. The previous commercial drug was a racemic mixture, which included almost the same amount of *S*- and *R*-enantiomers. However, it was discovered that the *S*-enantiomer is more active than the *R*-enantiomer [5]. Thus, the present drug has been constituted only from the *S*-enantiomer. In general, the major reason for the different recognition of two enantiomers by biological cells is the homochirality of biomolecules such as L-amino acids and D-sugars. The diastereomeric interaction between the enantiomers of a bioactive compound and the receptor formed from a chiral protein can cause different physiological responses.

The production technology of enantiomerically enriched bioactive compounds corresponding to biological homochirality

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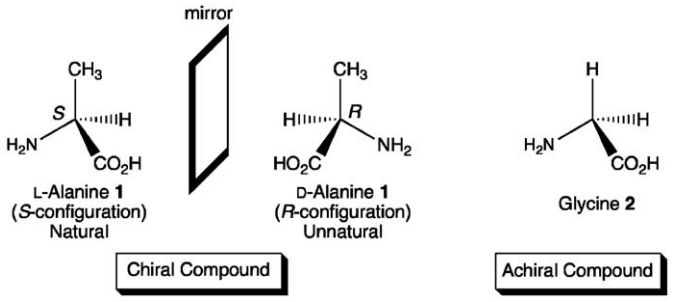

Fig. 1. Tetrahedral structure of chiral alanine and achiral glycine.

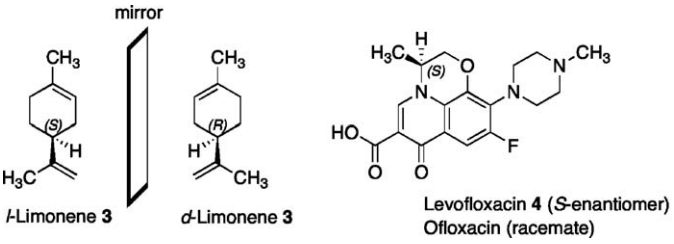

Fig. 2. Enantiomeric forms of limonene and the single enantiomer drug, levofloxacin.

is one of the significant topics in chemistry [6–9]. There is great interest in how and when biomolecules achieved high enantioenrichment, including the origin of chirality from the standpoint of chiral chemistry [10].

Living organisms use only one enantiomer of chiral molecules, such as the L-amino acids and the D-sugars. To date, several mechanisms have been proposed for elucidating the origins of the chirality of organic compounds, such as circularly polarized light (CPL) [11–13] and quartz [14,15]. Although the initial enantiomeric imbalance from an achiral condition can be introduced *via* these proposed mechanisms, a suitable amplification process for chirality is required to reach single-handedness of biological organic compounds (Fig. 3).

We describe herein the processes of asymmetric amplification as candidates for the mechanism of the chemical evolution of biological homochirality, which include asymmetric autocatalysis with amplification of enantiomeric excess (ee).

2. Amplification of ee by self-disproportionation of enantiomers

As we can see in the differential biological activities of the two enantiomers, which are caused by diastereomeric interaction with the receptor in the chiral protein, diastereomeric interactions have also worked in some enantiomeric mixtures. Although the enantiomers with *S*- and *R*-configuration show the same physical properties except for their optical rotation, if these enantiomers preferentially form a dimeric (or greater) aggregations such as *S*·*S* (or *R*·*R*) and *S*·*R*, the aggregates possess different physical properties. Several examples of such observations have been reported. Although the optical rotations of chiral compounds are linearly related to their ee in general, nonlinearity has been observed in several compounds because of a diastereomeric association [16]. There are examples in NMR studies in which different signals can be observed in enantiomerically pure and racemic mixtures [17]. In distillation [18], sublimation [19] and column chromatography (using achiral silica gel) [20] experiments, these self-associations of enantiomeric mixtures were observed with fractional changes in enantiomeric purity.

The enantiomers of fluorine compounds strongly associate with each other through hydrogen bonds; thus, fluorinated chiral

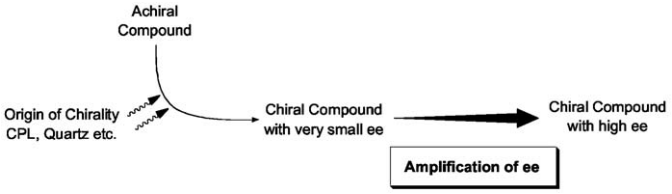

Fig. 3. A schematic outline of the evolution of chirality.

compounds often show a strong effect in these experiments. In the distillation of isopropyl trifluorolactate with 74% ee, when half the amount of distillate had been produced the ee was enhanced to 82% and the residue showed a reduced ee of 66% [21] (Fig. 4). The difference between the boiling points of racemic (93 °C) and enantiopure (136 °C) isopropyl trifluorolactate is 43 °C.

Racemic and enantiopure compounds show significant differences in the crystalline state, which result in different melting points, solubilities and sublimation rates. Recently, Soloshonok has reported the self-purification process of moderately enantioenriched α-(trifluoromethyl)lactic acid to achieve an almost enantiomerically pure form based on the faster sublimation rate of the racemic crystal compared with that of the enantiopure crystal [22]. The initial sample with 80% ee perfectly purified to reach >99.9% ee after 56.5 h simply by being stored in the open air (Fig. 4).

Furthermore, separation of racemate from the excess enantiomer has been observed in achiral chromatography using moderately enantioenriched compound with a trifluoromethyl substituent on the asymmetric carbon center as the starting substrate [23–25] (Fig. 5). After fractionation, the initial 67% ee of fluorinated compound **7** amplified to be >99.9% ee. Because the first fraction shows 8.1% ee, the difference in enantiomeric purity between the first and final 18th fraction is *ca.* 92% ee. The hydrogen bond between the enantiomers induced strong associations of fluorinated compound **7** to form homochiral and heterochiral macromolecular arrangements. The repulsive effect of the trifluoromethyl group in heterochiral interactions makes the aggregation size smaller than for homochiral interactions. These effects are considered as one of the reasons for the optical separation.

As described, under achiral conditions an organic compound with moderate ee can exhibit the optical self-purification phenomenon to afford enantiomerically amplified compound *via* the self-disproportionation of enantiomers induced by diastereomeric interactions. Thus, these chemical processes are considered as one of the pathways by which very small prebiotic ee achieved highly enantioenriched materials.

3. Amplification of ee in asymmetric catalysis

There are reactions in which the enantiopurity of the product is higher than that of the chiral catalyst and such phenomena are referred to as positive nonlinear effects [26]. Although in general, the ee of the chiral product should be proportional to that of the catalyst, when dimeric or higher aggregates of the chiral ligand are preferentially formed, the relationship possibly deviates from

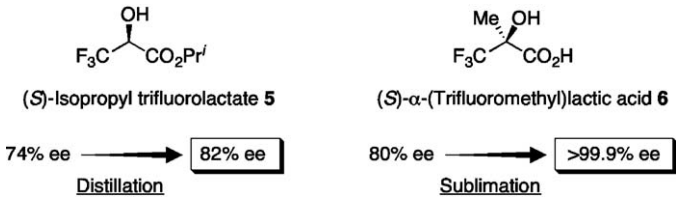

Fig. 4. Self-purification of trifluoro-derivatives of lactic acid.

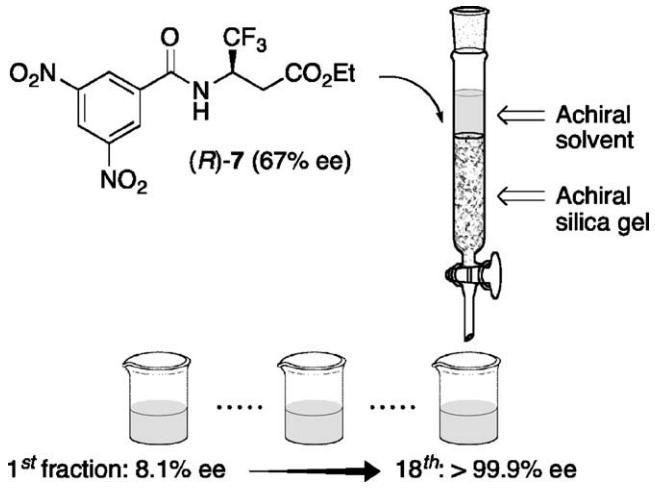

Fig. 5. Fractional separation of enantiomer **7** in achiral silica gel column chromatography.

linearity because of these diastereomeric interactions between the enantiomers of the catalyst monomer.

The first remarkable example of asymmetric amplification was reported in 1986 in Sharpless epoxidation, *i.e.*, titanium tartrate-catalyzed asymmetric epoxidation of allylic alcohols [27] (Fig. 6). Moreover, a large amplification effect has been reported in diethylzinc addition to benzaldehyde using chiral β-amino alcohols as the chiral ligand [28,29] (Fig. 6). Detailed mechanistic investigations demonstrated the reaction to be as follows: the heterochiral dimer is thermodynamically more stable than the homochiral dimer, and the enantiomerically enriched remaining monomer controls the enantioselectivity acting as an asymmetric catalyst [30]. Thus, the ee of the product is higher than that of the catalyst.

Recently, proline has been developed as an efficient chiral organocatalyst in various asymmetric reactions. Hayashi reported a large amplification effect in a proline-catalyzed α-aminoxylation reaction [31]. When the filtrate of the equilibrated proline solution of chloroform with 10% ee was used as the catalyst, a product with 96% ee was obtained in 93% yield. Because of the large difference between the solubility of the racemic and chiral crystals of proline, the dissolution and crystallization process amplifies the ee of the catalyst in the solution. Blackmond reported a detailed investigation of the phenomenon of asymmetric amplification of amino acids in a solid/solution system [32]. The amino acid-catalyzed sugar synthesis with amplification of ee has been proposed as a chemical model for the evolution of biological homochirality [33].

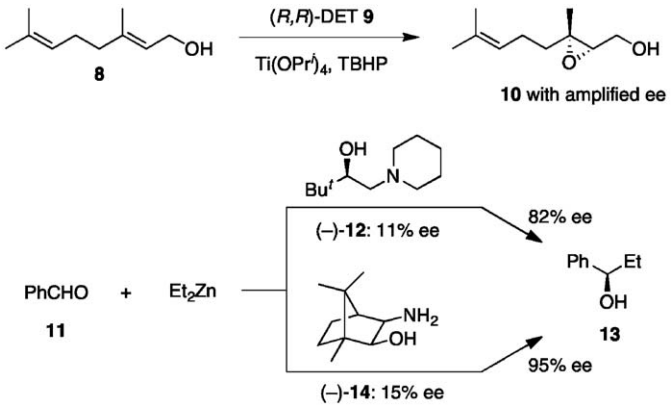

Fig. 6. Amplification of ee in asymmetric catalysis.

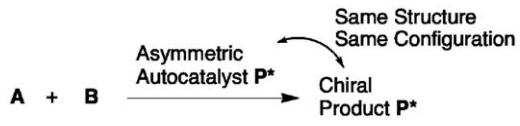

Fig. 7. The concept of asymmetric autocatalysis.

4. Asymmetric autocatalysis with amplification of ee

In the process of asymmetric autocatalysis, a chiral product **P*** serves as a chiral catalyst **P*** for its own formation in the reaction with achiral substrates **A** and **B**, *i.e.*, chiral product and chiral catalyst have identical structures, including their absolute configurations (Fig. 7). The process is automultiplication of chiral product **P***. In 1953, Frank proposed a mechanism of asymmetric autocatalysis with amplification of ee without mentioning any chemical structure in which the chiral product acts as anticatalyst of the production of the opposite enantiomer [34].

Conventional asymmetric catalysis produces a chiral product with a different structure from that of the chiral catalyst. We and others have extensively studied enantioselective addition of dialkylzincs to aldehydes using β-amino alcohols as the chiral catalyst to afford *sec*-alcohols with high ee [35–37]. Using *N*,*N*-dibutylnorephedrine (DBNE **15**) [38–40] and diphenyl-(1-methylpyrrolidin-2-yl)-methanol (DPMPM **16**) [41,42] as chiral catalysts, enantioselective addition of dialkylzincs to aldehydes can afford the chiral alcohols in high yield and high ee (Fig. 8).

During the course of the research, chiral 3-pyridyl alkanol **18** was found to act as the first example of asymmetric autocatalyst in the addition of diisopropylzinc (*i*-Pr_2Zn) to pyridine-3-carbaldehyde **17** [43] (Fig. 8). (*S*)-3-Pyridyl alkanol **18** with 86% ee acts as an asymmetric autocatalyst to afford the same compound (*S*)-**18** with 35% ee. The produced pyridyl alkanol **18** has the nitrogen containing alcohol moiety that should act as the chiral ligand for the next reaction, *i.e.*, catalyze its own formation. However, the ee value of the chiral product is lower than that of the chiral catalyst.

Further structural investigation has disclosed that the pyrimidyl alkanol **20** serves as a highly enantioselective asymmetric autocatalyst for the addition of *i*-Pr_2Zn to the corresponding aldehyde **19** [44] (Fig. 9). When (*S*)-pyrimidyl alkanol **20** with 99% ee was employed as an autocatalyst, (*S*)-**20** with 95% ee composed of both the newly formed and the initially submitted **20** was obtained. By subtracting the amount of catalyst loading from the obtained mixture, the yield and ee of newly formed product **20** was calculated to be a highly enantioenriched 93% with 67% yield.

The enantioselectivity observed in this autocatalytic reaction should be high enough to expect a remarkable phenomenon, *i.e.*, asymmetric autocatalysis with amplification of ee [45–61], which

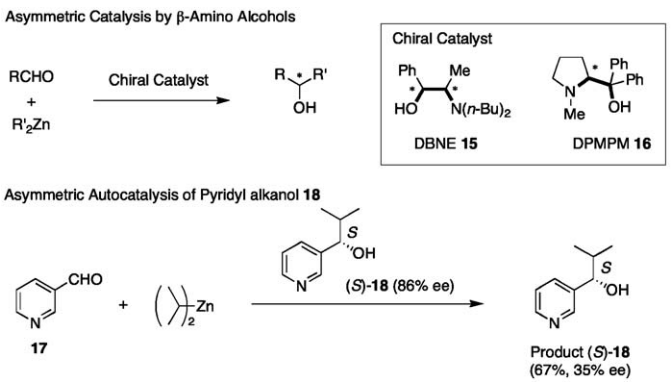

Fig. 8. Amino alcohol catalyzed asymmetric addition of dialkylzinc and asymmetric autocatalysis of pyridyl alkanol.

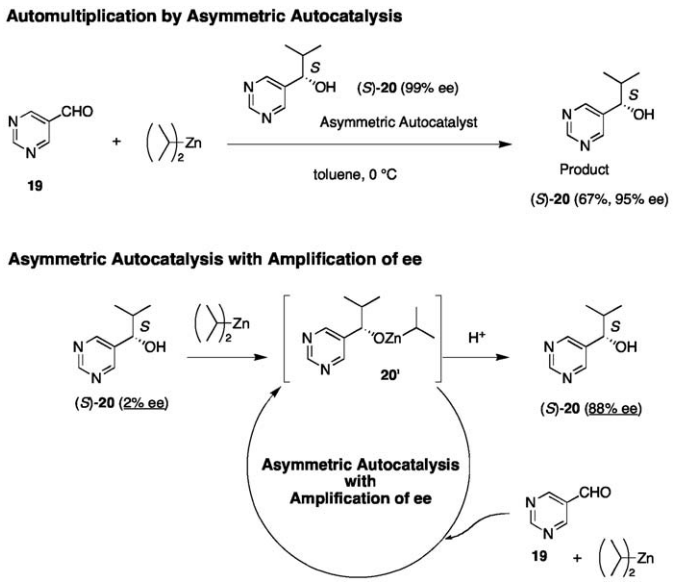

Fig. 9. Asymmetric autocatalysis of 5-pyrimidyl alkanol **20** and amplification of ee.

prompted the examination of the reaction using an autocatalyst with a low ee. As a result, we found for the first time that the initial small 2% ee was significantly amplified to a high enantioenrichment (88% ee) [44] (Fig. 9). When the (*S*)-pyrimidyl alkanol **8** (20 mol%, 2% ee) was employed as an asymmetric autocatalyst, (*S*)-**8** with 10% ee was obtained in 46% yield as a mixture of newly formed product and initial catalyst. Because the structure of the catalyst and product are the same, as required for asymmetric autocatalysis, the reaction proceeded successively by using the product of one reaction as the autocatalyst of the next round of reactions. Further enhancement of ee was observed to reach the final ee value up to 88% after four rounds of consecutive reactions. Starting from compound **20** with 2% ee, the enantioenrichment was enhanced to reach 88% ee during the course of automultiplication of chiral compound **20** without the assistance of any other chiral auxiliary. This is the first realization of the chemical process of asymmetric autocatalysis with amplification of ee [44].

An investigation of the substituent effect at the pyrimidine ring shows that substrate **22** having a *tert*-butylethynyl group at the 2-position possessed a significant asymmetric autocatalytic activity in the *i*-Pr_2Zn addition to pyrimidine-5-carbaldehyde **21**. When (*S*)-2-(*tert*-butylethynyl)-5-pyrimidyl alkanol **22** with >99.5% ee was employed as an asymmetric autocatalyst, (*S*)-**22** with >99.5% ee was obtained as a mixture of the newly formed and initially added **12** [62] (Fig. 10). The yield of the newly formed **12** was calculated to be >99%. To take advantage of asymmetric autocatalysis, the obtained **12** in the first round was used as an asymmetric autocatalyst for the next round. Even after the 10th round, the yield of **12** was >99% and the ee was >99.5% without any decrease in reactivity and enantioselectivity of the asymmetric autocatalyst; thus, 2-(*tert*-butylethynyl)-5-pyrimidyl alkanol **22** served as a practically perfect asymmetric autocatalyst.

Moreover, we found that compound **22** shows remarkable amplification of enantiomeric purity from as low as approximately 0.00005% ee to near enantiomerically pure (>99.5% ee) product **22** in only three consecutive asymmetric autocatalyses [63] (Fig. 10).

The initial round of asymmetric autocatalysis using (*S*)-**22** with *ca.* 0.00005% ee gave (*S*)-**22** in 96% yield with an extremely amplified 57% ee (Fig. 11). The second round of the reaction using (*S*)-**22** with 57% ee afforded the product with an ee value of 99%. The third and final round of asymmetric autocatalysis gave (*S*)-**22** with almost enantiopure >99.5% ee. During these three consecutive reactions, the initial slightly major (*S*)-enantiomer of **22** has automultiplied by a factor of *ca.* 630,000. In contrast, the multiplication factor for the slightly minor (*R*)-enantiomer **22** was less than 1,000 [63].

In addition, 2-methyl-5-pyrimidyl alkanol **23** [64,65], 3-quinolyl alkanol **24** [66,67] and 5-carbamoyl-3-pyridyl alkanol

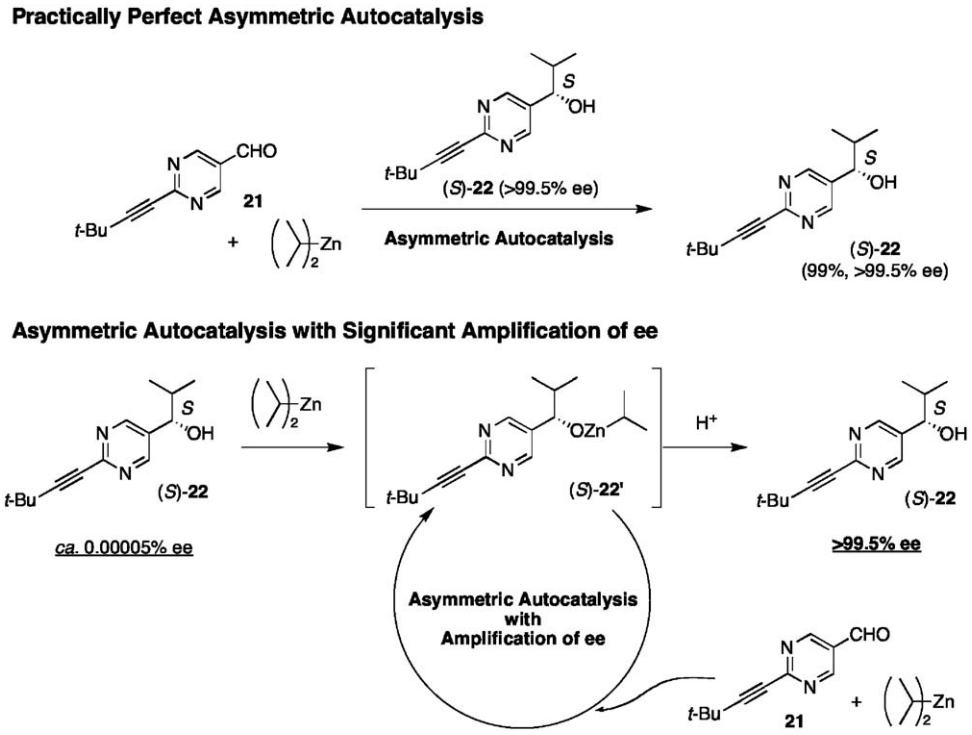

Fig. 10. Practically perfect asymmetric autocatalysis of 2-(*tert*-butylethynyl)-5-pyrimidyl alkanol **22** and amplification of ee from extremely low (*ca.* 0.00005% ee) to almost enantiopure (>99.5% ee).

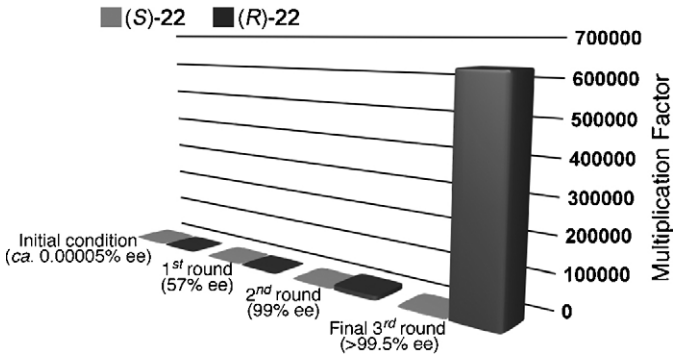

Fig. 11. The multiplication factor of *S*- and *R*-enantiomers of pyrimidyl alkanol **22** during three consecutive asymmetric autocatalyses with amplification of ee.

25 [68] are also highly efficient asymmetric autocatalysts with amplification of ee (Fig. 12). Derivatization of the terminal groups of 2-ethynyl substituents at the 2-position expanded the applicable compounds for asymmetric autocatalysis with amplification of ee [62]. The activities of each compound were examined by the use of an autocatalyst with low ee value. The *n*-butylethynyl derivative **26** with 5.8% ee amplifies to 21% ee after one round of reaction. Trimethylsilylacetylene-substituted pyrimidyl alkanol **27** with 8.4% ee was efficiently enhanced to 74% ee by one asymmetric autocatalysis. The phenyl analogue was also effective, although the efficiency of amplification was lower than for the *t*-butylethynyl group-substituted **22**. We have reported that the initially employed ferrocene-containing pyrimidyl alkanol with 8% ee was enhanced to 67% ee by a single round of the addition reaction. After consecutive cycles of reaction, the enantioenrichment was amplified to >99% ee [69]. Pyrimidyl alkanol **30** possessing an alkenyl group at the 2-position also displays a significant autoamplification factor [70]. Thus, extremely low enantioenrichment of pyrimidyl alkanol could be autoamplified to very high ee by consecutive reactions.

A possible mechanistic framework for the asymmetric autocatalysis has been studied by kinetic experiments using chiral HPLC [71] and a reaction microcalorimeter [72], NMR [73] and computational molecular modeling [74–76], which showed that the chiral dimer of alkoxide **3** acts as a reactive species for the production of the next product **3** with the same absolute configuration as the catalyst.

In the planning of further efficient asymmetric autocatalysts possessing high autoamplification ability, the key feature is the interaction between the enantiomers of the asymmetric autocatalyst. As mentioned in a previous section, fluorine-containing compounds are expected to interact with each other, which can lead to self-purification. There is a trend in fluorine-containing compounds for a larger difference between the energy of homochiral

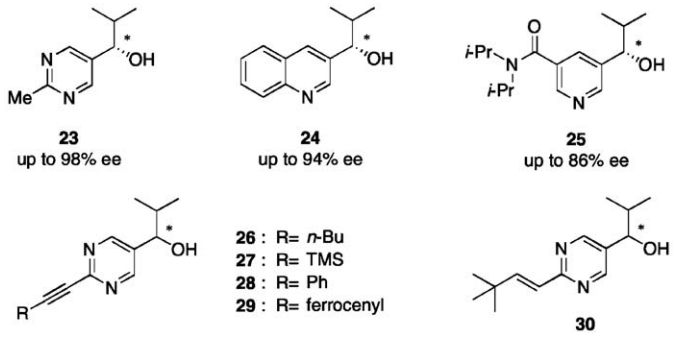

Fig. 12. Asymmetric autocatalysts, which produce amplification of ee in the enantioselective addition of *i*-Pr_2Zn to the corresponding aldehydes.

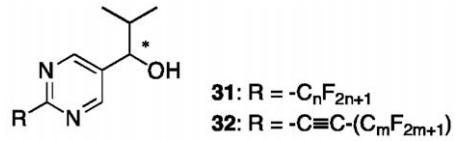

Fig. 13. Proposed structures of asymmetric autocatalysts modified with fluorinated substituents.

and heterochiral aggregates. Thus, one of the promising modifications of an asymmetric autocatalyst may involve the introduction of fluorine groups into the structure. In addition to the high coordination capability of zinc atoms toward heteroatoms such as nitrogen and oxygen in an asymmetric autocatalyst, the differentiation ability of fluorinated compounds between homochiral and heterochiral aggregates in their stability and catalytic activity may improve the amplification effect in asymmetric autocatalysis. In addition, electron-withdrawing fluorinated substituents may enhance the reactivity of pyrimidine-5-carbaldehyde. Structural modifications, *i.e.*, introduction of a fluorinated functional group, are proposed for further study as shown in Fig. 13.

Recently, asymmetric autocatalytic organocatalysis in Munnich reaction has been reported without amplification of ee [77].

5. Asymmetric autocatalysis with amplification of ee initiated by chiral factors as a source of chirality

As was mentioned in the above section, the significant enhancement of ee from the minute imbalance of enantiomer of an asymmetric autocatalyst, that is, asymmetric autocatalysis, could amplify the slight ee of *ca.* 0.00005% to almost enantiomerically pure >99.5% ee during consecutive reactions. Thus, if the enantioenrichment of the initially formed asymmetric autocatalyst could be introduced by an external chiral factor, we can obtain highly enantioenriched pyrimidyl alkanol as a product after the autocatalytic amplification of ee. The absolute configuration of the produced alkanol with high ee is controlled by, and thus correlated with, the initial enantioselection, *i.e.*, the configuration of the originally used external chiral factor determines the absolute configuration of the pyrimidyl alkanol with high ee.

In practice, various chiral compounds can initiate the asymmetric autocatalysis to induce the production of the zinc alkoxide of a pyrimidyl alkanol and the subsequent autocatalytic amplification of ee affords the highly enantioenriched alkanol (Fig. 14). Not only enantiomerically pure compounds, chiral compounds with very small ee can also act as chiral triggers for asymmetric autocatalysis. When (*S*)-butan-2-ol **33** with *ca.* 0.1% ee was used as a chiral initiator of asymmetric autocatalysis, (*S*)-pyrimidyl alkanol **23** with 73% ee was obtained [78]. In contrast, (*R*)-**33** with 0.1% ee induced the production of (*R*)-**23** with 76% ee. In the same manner, chiral compounds with amino, ester, carboxyl [78] and epoxy [79] functionalities with low ee can serve as chiral initiators of asymmetric autocatalysis to give pyrimidyl alkanol **22** or **23** with high ee. Chiral $Cr(acac)_3$ complexes having the chiral topology also induces asymmetric autocatalysis [80]. Further consecutive reactions enable the amplification of ee to produce the highly enantiomerically enriched alkanol **22** with the absolute configurations corresponding to that of the Δ- or Λ-$Cr(acac)_3$. The chiral hydrocarbons, 1,1′-binaphthyl [81], [6]- and [5]-helicenes [82] and allene [83] can act as chiral initiators of asymmetric autocatalysis.

Because of the lack of higher order helicity, isotactic polystyrene **42** with a molecular weight above *ca.* 5,000 exhibits no detectable value of specific optical rotation [84]. In addition, (*n*-butyl)ethyl(*n*-hexyl)(*n*-propyl)methane **43** is a saturated quaternary hydrocarbon, which possesses practically no optical rotation over the range 280–580 nm [85]. The chiral discrimination of these

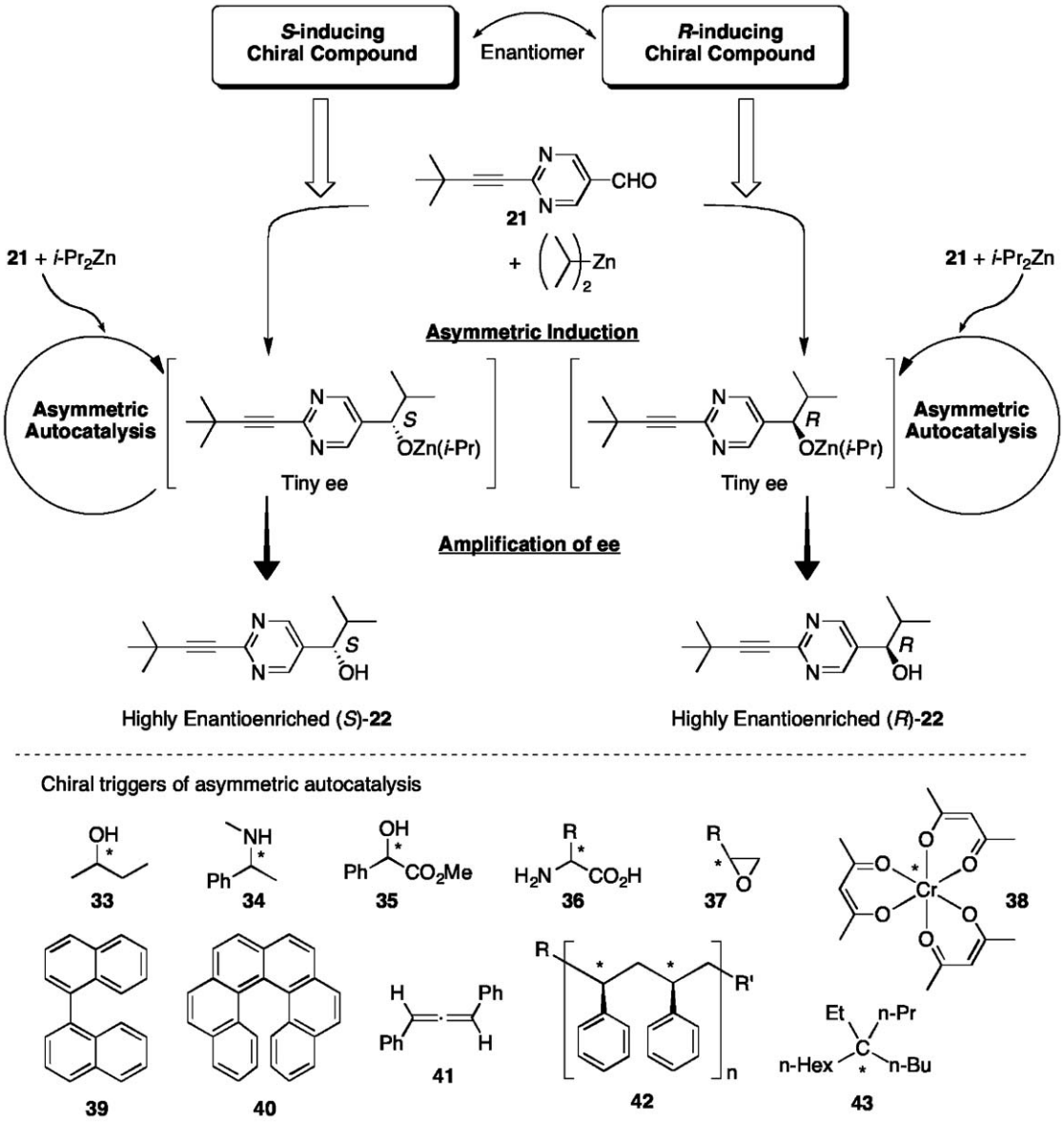

Fig. 14. Asymmetric autocatalysis initiated by chiral compounds.

enantiomers poses the utmost difficulty. Their enantiomeric forms cannot be distinguished by applying any contemporary technique and are called cryptochiral. Thus, asymmetric autocatalysis triggered by cryptochiral compounds has been examined. Isotactic polystyrene **42** induced enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **21** to afford the pyrimidyl alkanol **22** with the corresponding absolute configurations to that of cryptochiral polystyrene **42** and its enantiomer *ent*-**42** [86]. In addition, the reaction between pyrimidine-5-carbaldehyde **21** and *i*-Pr_2Zn in the presence of (*R*)-**43** formed (*S*)-pyrimidyl alkanol **22** with high ee, whereas in the presence of (*S*)-**43**, the opposite (*R*)-alkanol **22** was obtained [87]. We have demonstrated that the achiral catalyst can reverse the enantioselectivity of chiral catalyst in asymmetric autocatalysis initiated with the mixture of chiral and achiral β-amino alcohols [88]. The results bring the mechanistic insight in β-amino alcohols catalyzed addition of dialkylzincs to aldehydes [89]. Asymmetric autocatalysis can be utilized to elucidate the steric discrimination of the substituents of chiral secondary alcohols [90].

So far, several chiral factors have been proposed as the origins of the chirality of organic compounds, including circularly polarized light (CPL) [11–13], inorganic crystals such as quartz [14,15] and sodium chlorate [91,92], enantiomorphous organic crystals formed from achiral organic molecules [93–96] and spontaneous absolute asymmetric synthesis [97]. The enantiomeric imbalances that were induced by these proposed mechanisms have usually been very small; therefore, a suitable amplification process is required to reach homochirality of biological organic compounds. Asymmetric autocatalysis with amplification of ee gives a strong correlation between the origin of chirality and the homochirality of organic compounds, *i.e.*, asymmetric autocatalysis can be initiated by these proposed origins of chirality. We have reported the enantioselective synthesis, in combination with asymmetric autocatalysis, triggered by CPL [98,99], quartz [100] and enantiomorphous organic crystals formed from achiral compounds [101] and a spontaneous absolute asymmetric synthesis [102] (Fig. 15).

Direct irradiation of racemic **22** by left-handed CPL and the subsequent asymmetric autocatalysis using the remaining alkanol as the chiral seed, produces highly enantioenriched (*S*)-alkanol **22** with >99.5% ee [99]. On the other hand, irradiation with right-handed (*r*) CPL, gave (*R*)-**22** with >99.5% ee. The process provides

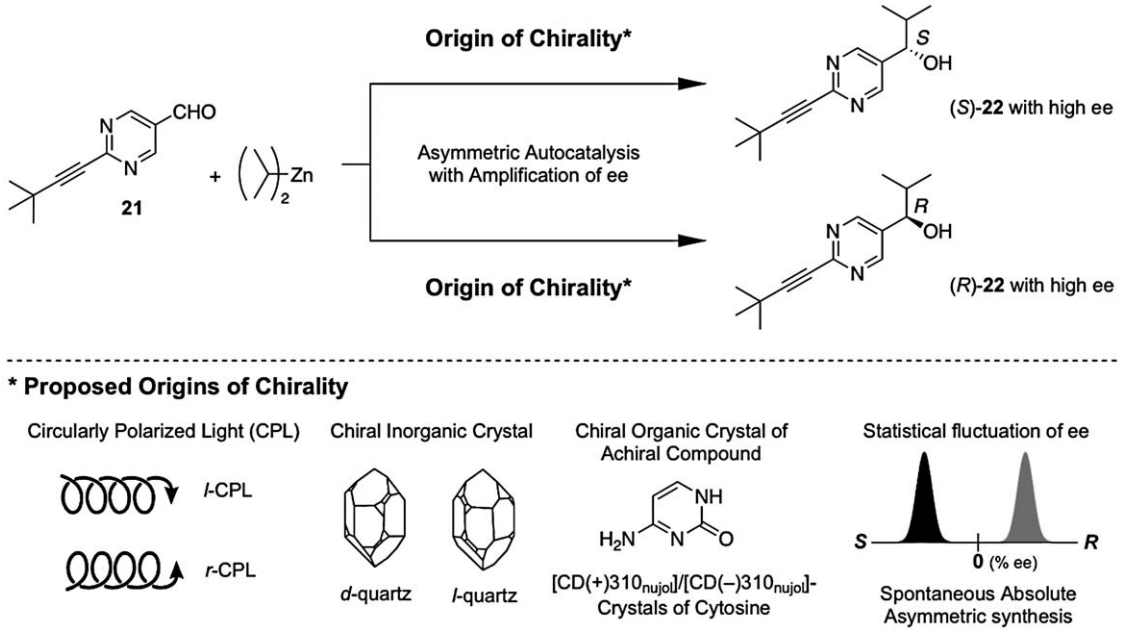

Fig. 15. Asymmetric autocatalysis induced by the proposed origins of chirality.

direct correlation of the handedness of CPL with that of the organic compound with high ee.

Enantiomorphous inorganic crystals of quartz are candidates for the origin of chirality. Thus, we performed an asymmetric autocatalysis triggered by quartz. When pyrimidine-5-carbaldehyde **21** was treated with *i*-Pr_2Zn in the presence of *d*-quartz powder, (*S*)-pyrimidyl alkanol **22** with 97% ee was obtained with a yield of 95% [100]. In contrast, in the presence of *l*-quartz, (*R*)-**22** with 97% ee was obtained with a yield of 97%. In addition, sodium chlorate [103] and sodium bromate [104] can also be subjected to asymmetric autocatalysis as the source of chirality to form enantiomerically enriched alkanol **22** with the corresponding absolute configurations.

Enantiomorphous organic crystals of achiral compounds can also act as the chiral source of asymmetric autocatalysis [101]. Cytosine is an essentially flat achiral molecule; however, cytosine in the crystalline state shows chirality. When aldehyde **21** and *i*-Pr_2Zn reacted in the presence of a [CD(+)310nujol]-crystal of cytosine, enantioenriched (*R*)-pyrimidyl alkanol **22** was obtained [105]. [CD(−)310nujol]-Cytosine crystal with the opposite chirality induced the production of enantioenriched (*S*)-alkanol **22**. Enantiomorphous crystals of the achiral quaternary ammonium salt tryptamine/*p*-chlorobenzoic acid [101], hippuric acid [106] and benzil [107] trigger asymmetric autocatalysis.

Asymmetric autocatalysis can amplify the spontaneously generated (under the achiral condition) slight enantiomeric excess, *i.e.*, the statistical fluctuation of chirality in the initially forming racemic zinc alkoxide of pyrimidyl alkanol **22** can be enhanced to a detectable ee [102,108]. When pyrimidine-5-carbaldehyde **21** was reacted with *i*-Pr_2Zn without adding any chiral substance, the following amplification afforded pyrimidyl alkanol **22** with either *S*- or *R*-configurations being formed with ee above the detection level (Fig. 15). An approximate stochastic distribution of the formation of either *S*- or *R*-enantiomers (19 times formation of *S* and 18 times *R*) of pyrimidyl alkanol **22** was observed [102]. These experimental outcomes meet one of the conditions necessary for a spontaneous absolute asymmetric synthesis. Theoretical discussions have been developed on the symmetry breaking in asymmetric autocatalysis [109–112].

6. Isotopically chiral compound triggers asymmetric autocatalysis with amplification of ee

Many apparently achiral organic molecules on Earth may be chiral because of the substitution of the naturally abundant carbon isotopes in an enantiotopic moiety within the structure. However, carbon isotope chirality is experimentally difficult to discriminate because the chirality originates from the very small difference between the carbon isotopes ($^{13}C/^{12}C$). Thus, it has been a question whether isotopically substituted carbon chiral compounds can induce chirality in asymmetric reactions. Therefore, we performed the asymmetric autocatalysis triggered by an isotopically substituted carbon chiral compound. When *i*-Pr_2Zn addition to pyrimidine-5-carbaldehyde **21** was performed in the presence of the chiral *tert*-alcohol, (*R*)-dimethylphenylmethanol (**44**) resulting from ^{13}C substitution in the methyl group, (*S*)-pyrimidyl alkanol **22** was obtained with high ee [113] (Fig. 16). In contrast, (*S*)-**44** with carbon isotope chirality triggers the formation of (*R*)-**22** and the following autocatalytic amplification of ee affords the enantiomerically enriched product. This is the first example of demonstrating clearly the control of enantioselectivity by an isotopically substituted carbon chiral compound. Chiral alcohols **45** and **46** resulting from ^{13}C substitution can also act as chiral triggers of asymmetric autocatalysis to afford pyrimidyl alkanols **22** with high ee that have the corresponding absolute configurations as those of the isotopically substituted carbon chirality of **45** and **46** [113]. Asymmetric autocatalytic amplification of 5-pyrimidyl alkanol **22** during the reaction of *i*-Pr_2Zn and pyrimidine-5-carbaldehyde **21** has the enormous power to amplify the minute enantiomeric imbalance induced by carbon isotope enantiomers, which has enabled detection of the minute control of enantioselectivity by isotopically substituted carbon chiral compounds as a detectable ee of the asymmetric autocatalyst [114].

On the other hand, meteorites contain achiral amino acids such as glycine and α-methylalanine that have been identified as deuterium-enriched forms [115]. Organic compounds with slight ee such as L-amino acids have also been detected in meteorites, and these compounds have been proposed as candidates for the extraterrestrial origin of biological homochirality on Earth [116]. However, another approach to the origin of chirality is the analysis

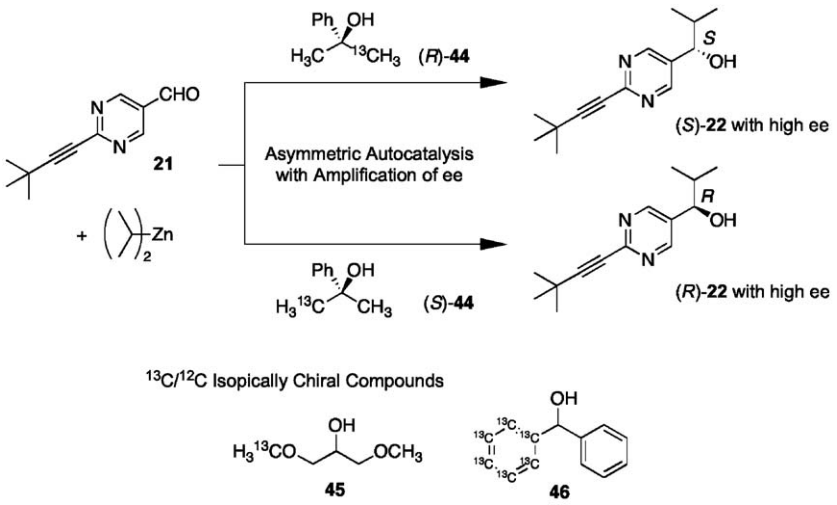

Fig. 16. Asymmetric autocatalysis triggered by a chiral compound by carbon isotope substitution.

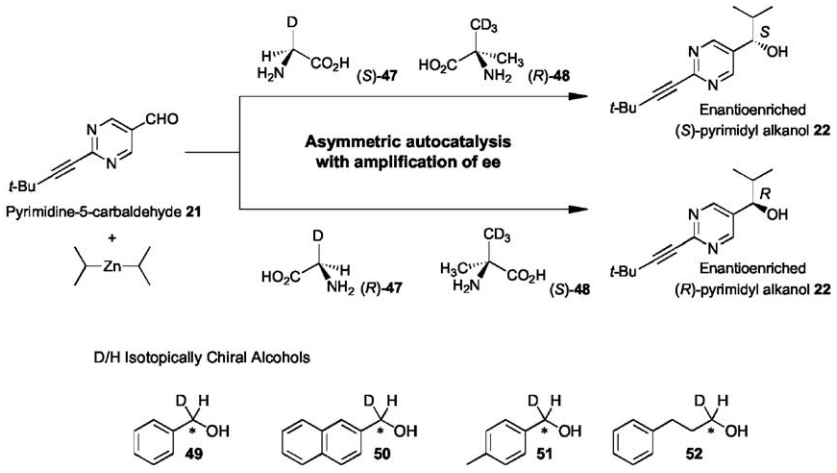

Fig. 17. Asymmetric autocatalysis triggered by a chiral compound by hydrogen isotope substitution.

of the hydrogen isotopic chirality in meteoritic achiral molecules. Therefore, we performed asymmetric autocatalysis initiated with the meteoritic achiral amino acids, glycine and α-methylalanine with hydrogen (D/H) isotope chirality. When the *i*-Pr_2Zn addition was performed in the presence of the (*S*)-glycine-α-*d* (**47**) with an ee of 93%, the (*S*)-5-pyrimidyl alkanol **22** was obtained in a 94% yield with an ee of 96% [117]. On the other hand, (*R*)-**22** with an ee of 95% was obtained in the presence of (*R*)-**47**. Next, the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **21** using (*R*)- and (*S*)-α-methyl-d_3-alanine (**48**) was performed. In the presence of (*R*)-**48**, (*S*)-**22** was induced, and the reaction of aldehyde **21** and *i*-Pr_2Zn in the presence of (*S*)-**48** always gave (*R*)-alkanol **22** with a high ee of 96–99%. Thus, the asymmetric autocatalysis can serve as a highly sensitive method for recognizing isotope chirality in meteoritic amino acids. In addition, we have reported the highly enantioselective synthesis utilizing chiral primary alcohol **49**–**52** with deuterium substitution in conjunction with asymmetric autocatalysis [118] (Fig. 17).

7. Summary

This review provides examples of the pathways by which enantiomeric enrichment was amplified to high ee values. Association of the enantiomers of chiral compounds enables the formation of homochiral and heterochiral aggregates, which show different physical properties. These diastereomeric interactions between the enantiomers promote self-disproportionation of enantiomers, thus it is possible for a compound to amplify the ee of itself under achiral conditions such as distillation, sublimation and column chromatography using achiral silica gel. Fluorine-containing compounds possess a strong differential effect between the energy of homochiral and heterochiral aggregates. Thus, fluorine-containing chiral compounds show large amplification effects without another chiral auxiliary.

Asymmetric amplification can be observed in enantioselective catalysis. The key feature in the asymmetric catalysis possessing amplification of ee is the formation of a diastereomeric species. The preferential formation of heterochiral aggregates of catalyst enantiomers and the higher catalytic activity of homochiral species would help asymmetric amplification in enantioselective catalyses. Amino acid-catalyzed asymmetric reactions with amplification of ee are strongly correlated to the origin of chirality.

The amplification of ee in asymmetric autocatalytic systems is considered as one of the models for the chemical origin and evolution of homochirality. We found that 5-pyrimidyl alkanols are highly enantioselective asymmetric autocatalysts for the addition of *i*-Pr_2Zn to the corresponding pyrimidine-5-carbaldehyde. In particular, 2-alkynyl-5-pyrimidyl alkanol **22** is an

extremely efficient asymmetric autocatalyst with over 99.5% enantioselectivity. Moreover, asymmetric autocatalysis with amplification of ee from extremely low ee (*ca.* 0.00005%) to more than 99.5% ee was realized using pyrimidyl alkanol **22** as the asymmetric autocatalyst. In addition, 3-quinolyl alkanol and 5-carbamoyl-3-pyridyl alkanol can also act as highly enantioselective asymmetric autocatalysts in the reaction of the corresponding aldehyde and *i*-Pr_2Zn.

Asymmetric autocatalysis is closely related to the origin of the homochirality of organic compounds. The proposed origins of chirality such as CPL, inorganic crystals, quartz, chiral organic crystals of achiral compounds and statistical fluctuation of ee can serve as the origin of chirality of asymmetric autocatalysis with amplification of ee. Thus, we have linked the proposed origins of chirality with almost enantiomerically pure organic compound *via* the amplification of ee by asymmetric autocatalysis.

Using asymmetric autocatalysis, we revealed for the first time, the remarkable phenomenon that isotopically substituted carbon chiral compounds can induce enantioselectivity in the asymmetric reaction, namely, enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **21**. The discrimination of chirality because of deuterium substitution is also accessible by the highly sensitive asymmetric autocatalysis.

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