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ASYMMETRIC AMPLIFICATION AND AUTOCATALYSIS

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12.1. INTRODUCTION

In experimental studies on catalytic asymmetric synthesis, considerable attention has been paid to the interaction between chiral catalysts and the reactants to achieve high enantioselectivity. However, very little attention has been paid to the interaction between the enantiomers of a chiral catalyst when this catalyst is not enantiomerically pure.

Examples of catalytic asymmetric synthesis have been reported in which the enantiomeric purity of the product is much higher than that of the chiral catalyst. A positive nonlinear effect (NLE), that is, asymmetric amplification, is synthetically useful because a chiral catalyst with high ee is not needed to prepare a chiral product with high ee (Scheme 12.1).

In asymmetric autocatalysis, the chiral catalyst **P*** and the product **P*** have the same structure; that is, the chiral product **P*** acts as a chiral catalyst **P*** for its own multiplication. Asymmetric autocatalysis differs from conventional catalytic asymmetric syntheses where the chiral catalyst **C*** and the product **P*** have different structures (Scheme 12.2).

Highly enantioselective asymmetric autocatalysis has recently been reported. In such reactions, a trace amount of chiral molecule automultiplies without the assistance of another chiral molecule. Moreover, asymmetric autocatalysis with an amplification of

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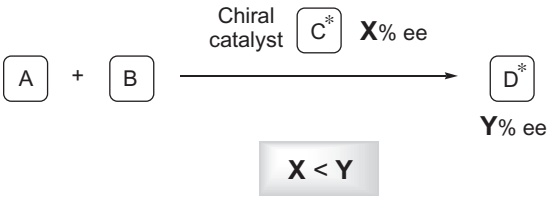
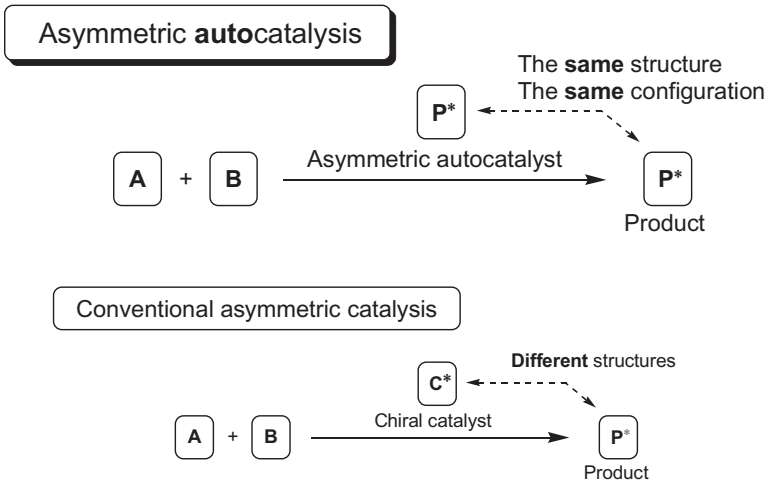


Scheme 12.1. General scheme of positive nonlinear effect in asymmetric synthesis.



Scheme 12.2. Asymmetric autocatalysis and conventional asymmetric synthesis.

ee has been reported, that is, the ee of the initial chiral molecule increases from very low to very high during automultiplication.

This chapter presents an overview of asymmetric amplification [1] and asymmetric autocatalysis [2,3].

12.2. ASYMMETRIC AMPLIFICATION

12.2.1. The History of Asymmetric Amplification

When a chiral catalyst acts as a monomer throughout the reaction in a solution, the relationship between the enantiomeric excess (ee) of the chiral catalyst (or chiral ligand) and the obtained chiral compound should be linear. On the contrary, when a chiral catalyst forms aggregate, such as a dimer and trimer, the relationship possibly deviates from linearity by the diastereomeric recognition and interaction, and the relationship is called NLE. There are positive and negative NLEs; however, the former is more attractive in the synthetic point of view, where a chiral catalyst with lower ee gives a chiral product with higher ee, and it is named as "asymmetric amplification" (Fig. 12.1).

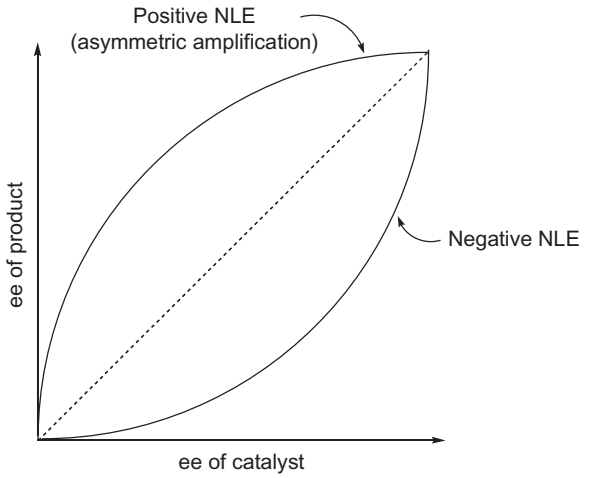
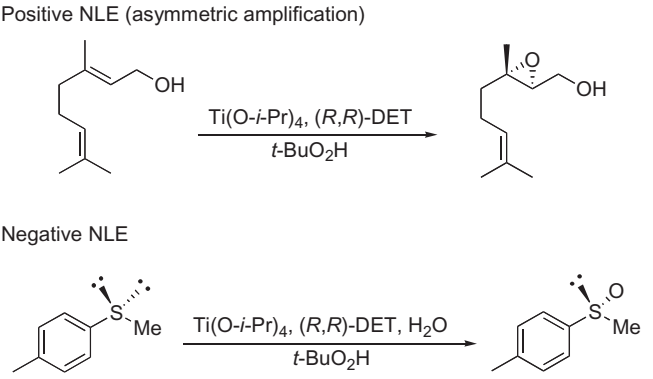


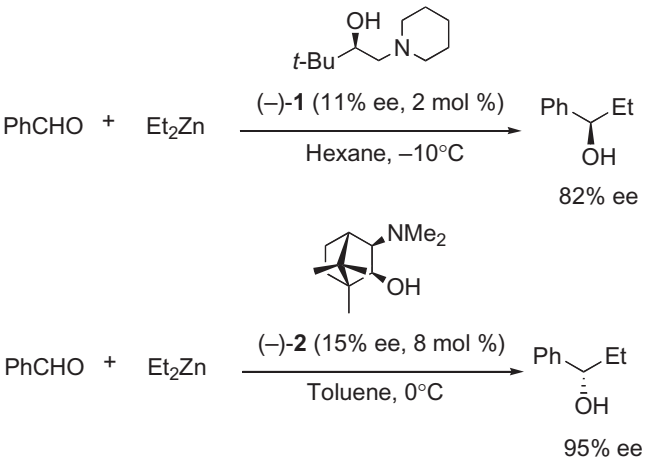
Figure 12.1. Nonlinear relationship between the ee of catalyst and product.



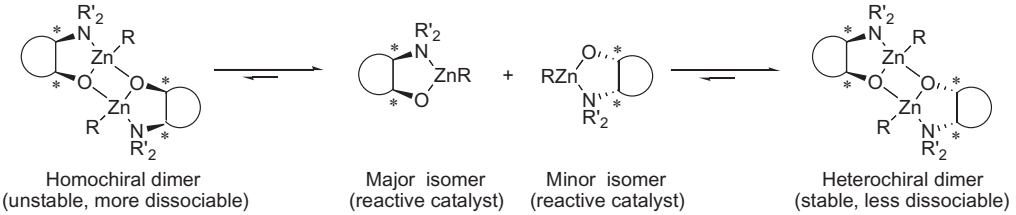
Scheme 12.3.

In 1986, Kagan and others reported the first example of NLE in organic reactions [4] (Scheme 12.3). In Sharpless–Katsuki asymmetric epoxidation, positive NLE, namely asymmetric amplification, was observed. Under the same reaction conditions, negative NLE was ascertained in asymmetric sulfide oxidation. Kagan and others afterward explained these phenomena by computer simulation using mathematical models, where the formation of diastereomeric aggregation of chiral catalyst is very important [5].

The addition reaction of diethylzinc to benzaldehyde was accelerated by an amino alcohol [6], and then chiral amino alcohols were proved to be efficient chiral catalysts for asymmetric alkylation by using dialkylzinc reagents [7]. Oguni reported the positive NLE in alkylation of benzaldehyde using β-amino alcohol **1** with moderate ee as a chiral base catalyst (Scheme 12.4) [8a]. Noyori and others consecutively reported it using their original β-amino alcohol, (2*S*)-3-*exo*-(dimethylamino)isoborneol (DAIB) **2** (Scheme



Scheme 12.4.



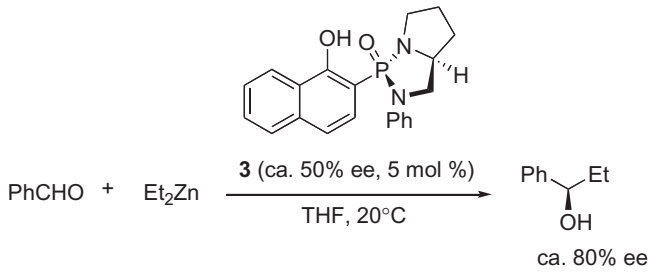
Scheme 12.5.

12.4) [8b]. They further performed the precise mechanistic investigation and presented a model that heterochiral dimer is thermodynamically more stable than homochiral dimer, and that the enantiomerically enriched remaining monomer operates as a catalyst [9] (Scheme 12.5). An ab initio molecular orbital study was also demonstrated in a model reaction between formaldehyde and dimethylzinc using achiral 2-aminoethanol as a catalyst [10].

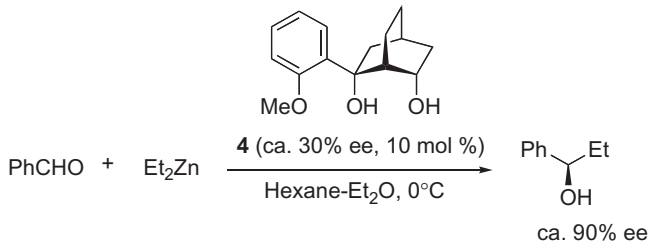
Since the above examples, asymmetric amplification was reported in many reactions using various chiral catalysts. In the following sections, we describe new entries of asymmetric amplifications, which have been published after the second edition of this book [11].

12.2.2. Asymmetric Alkylation, Conjugate Addition, and Cyanation

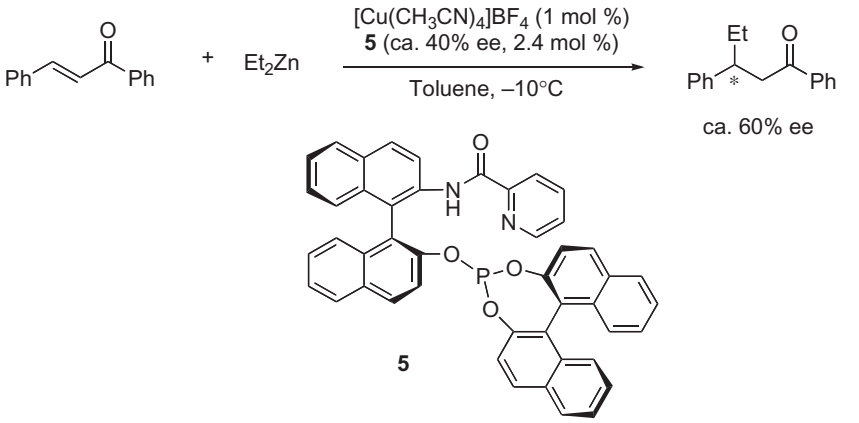
Various β-amino alcohols as chiral base catalysts showed positive NLE in asymmetric 1,2-alkylation of aldehydes. Chiral *o*-hydroxyaryldiazaphosphonamide **3** [12] and 1,3-diol **4**, possessing bicyclo[2.2.2]octane skeleton, with lower ee [13] also gave the chiral secondary alcohol with higher ee in the asymmetric alkylation of benzaldehyde using diethylzinc (Schemes 12.6 and 12.7).



Scheme 12.6.



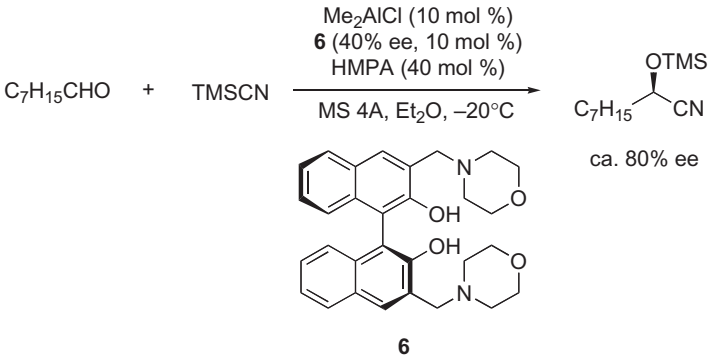
Scheme 12.7.



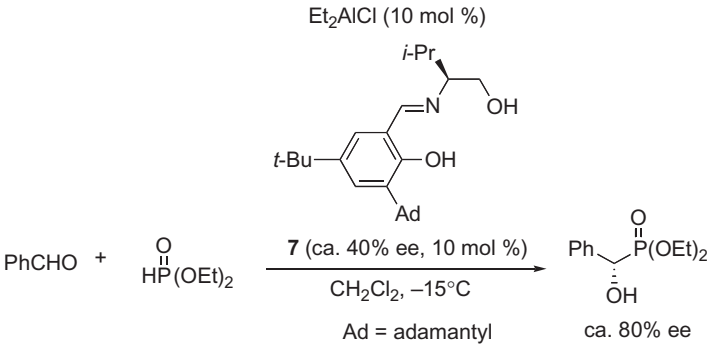
Scheme 12.8.

In the catalytic highly enantioselective conjugate addition of dialkylzinc to enone using Ni catalyst and chiral β-amino alcohol [14], asymmetric amplification has been typically observed [15,16]. Also in the Cu-chiral phosphite ligand **5**, Michael adduct was obtained in the amplified ee (Scheme 12.8) [17]. The observed relationship showed good agreement with Kagan and others' ML_2-type mathematical model [5]; therefore, chiral catalyst should consist of 1:2 complex of copper and ligand.

In the Al-catalyzed asymmetric addition of cyanide to aldehydes, asymmetric amplification was reported; highly enantioselective cyanation was achieved using bifunctionalized BINOL **6** with moderate ee (Scheme 12.9) [18]. Al(III)-tridentate Schiff's base **7** of low ee also induced positive NLE in the enantioselective hydrophosphonylation of benzaldehyde (Scheme 12.10) [19].



Scheme 12.9.

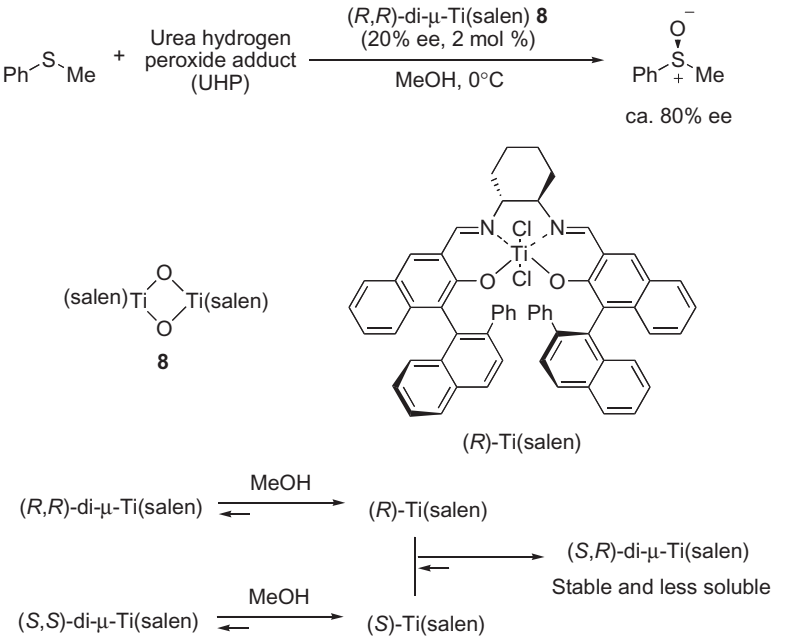


Scheme 12.10.

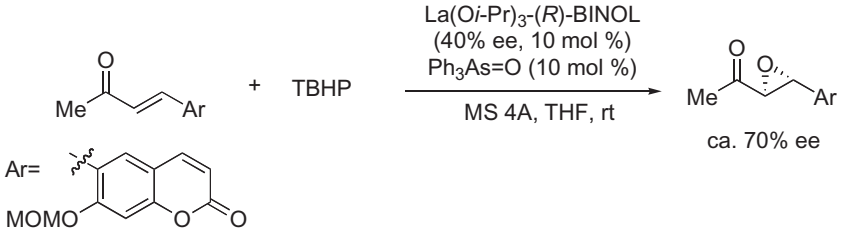
12.2.3. Asymmetric Oxidation

Saito and Katsuki comprehensively studied the highly enantioselective reaction using metal-salen catalyst. They reported asymmetric amplification in the di-μ-oxo Ti(salen) complex **8** catalyzed sulfoxidation (Scheme 12.11). In a methanol solution, di-μ-oxo Ti(salen) was readily dissociated into monomeric species, and it acted as a true catalyst. The racemic complex of (*R*,*S*)-di-μ-oxo Ti(salen) was probably stable and less soluble, and positive NLE was achieved [20].

Shibasaki and others disclosed a chiral La complex-catalyzed epoxidation of enones. The active chiral catalyst was turned out to be 1:1:1 complex generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$, and they concluded that preferential formation of heterochiral



Scheme 12.11.



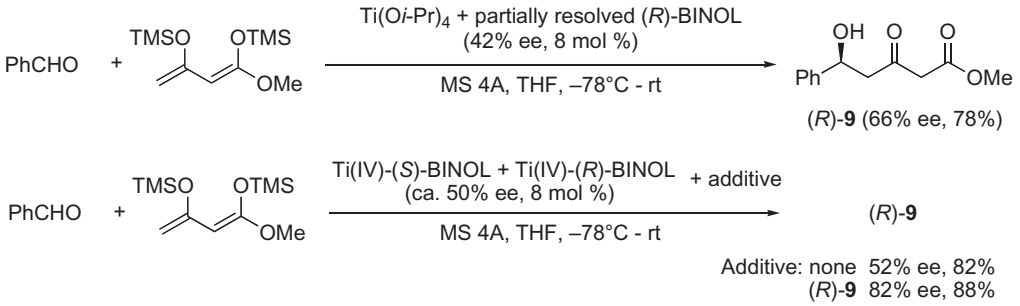
Scheme 12.12.

complex La[(*R*)-binaphthoxide][(*S*)-binaphthoxide]($Ph_3As{=}O)_2$ is the reason for asymmetric amplification after precise mechanistic investigation (Scheme 12.12) [21].

12.2.4. Asymmetric Aldol and Allylation Reactions

Mikami and others reported an ene and Diels–Alder reactions using Ti(IV)-BINOL system [22]. The preparation of chiral catalysts with moderate ee was found to be very important for the induction of asymmetric amplification. Also, in the case of vinylogous aldol reaction of Chan's diene, the mode of preparation made a large difference on the NLE. When the chiral catalyst was prepared from Ti(O-*i*-Pr)$_4$ and (*R*)-BINOL with

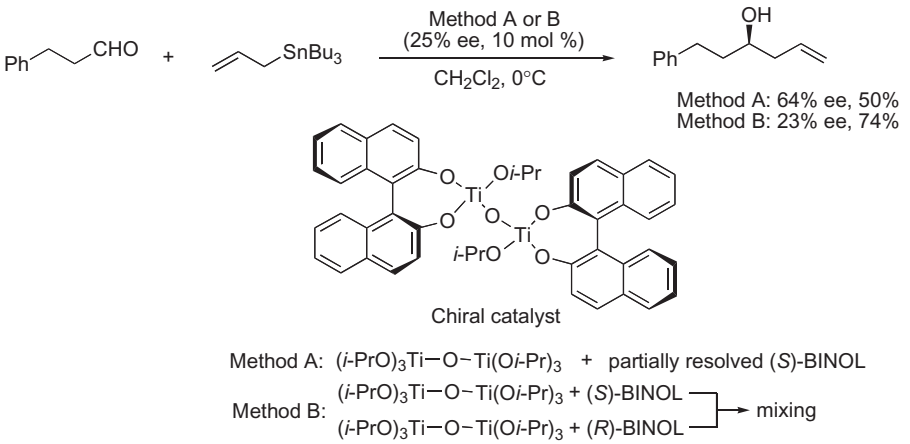
moderate ee, positive deviation from linear relationship between the ee of catalyst and product **9** was ascertained (Scheme 12.13). When it was prepared from Ti(O-*i*-Pr)$_4$-(*R*)-BINOL complex and Ti(O-*i*-Pr)$_4$-(*S*)-BINOL one, however, NLE was not observed. Interestingly, when chiral product **9** was added, autoinductive process occurred and obvious asymmetric amplification was ascertained [23].



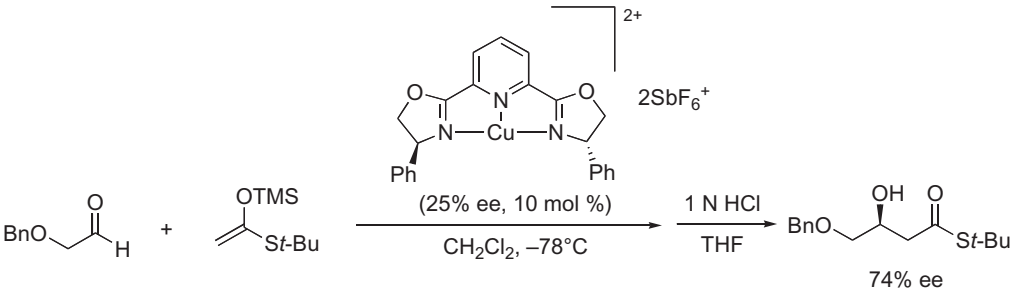
Scheme 12.13.

Maruoka and others developed a μ-oxo-type chiral Lewis acid for the asymmetric allylation of aldehyde, and dinuclear complex was thought to act as an active catalyst (Scheme 12.14) [24]. Actually, when catalyst with moderate ee was prepared from oxo complex and partially resolved (*S*)-BINOL (method A), asymmetric amplification was observed. When it was prepared from oxo complex, (*S*)-BINOL and oxo complex-(*R*)-BINOL (method B), however, NLE was not observed.

Mukaiyama aldol reaction proceeded with positive NLE in the presence of Cu-Ph-pybox catalyst of low ee (Scheme 12.15). Evans and others reported that the formation of 1:2 metal-ligand complex, [Cu((*S*,*S*)-Ph-pybox)((*R*,*R*)-Ph-pybox)]SbF_6, was the reason for the asymmetric amplification (Scheme 12.15) [25].

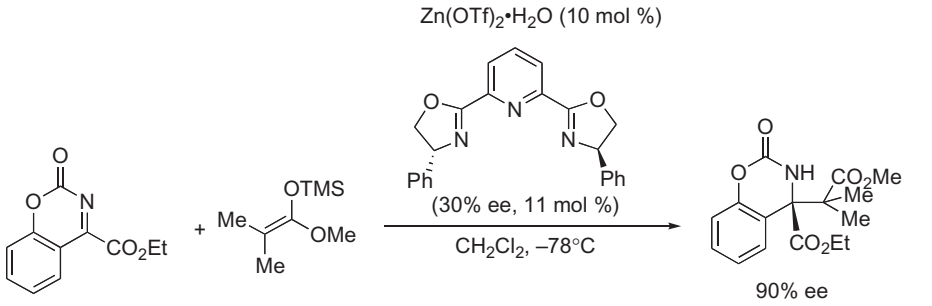


Scheme 12.14.



Scheme 12.15.

Jørgensen and others reported positive NLE in Zn-Ph-pybox complex (ML*)-catalyzed enantioselective alkylation of ketimines for the synthesis of chiral quaternary α-amino acid (Scheme 12.16). They characterized ML* and ML*$_2$ complex, respectively, and found to be ML* as a true catalyst and ML_SL_R as racemic reservoir along with density functional theory (DFT) calculation [26].



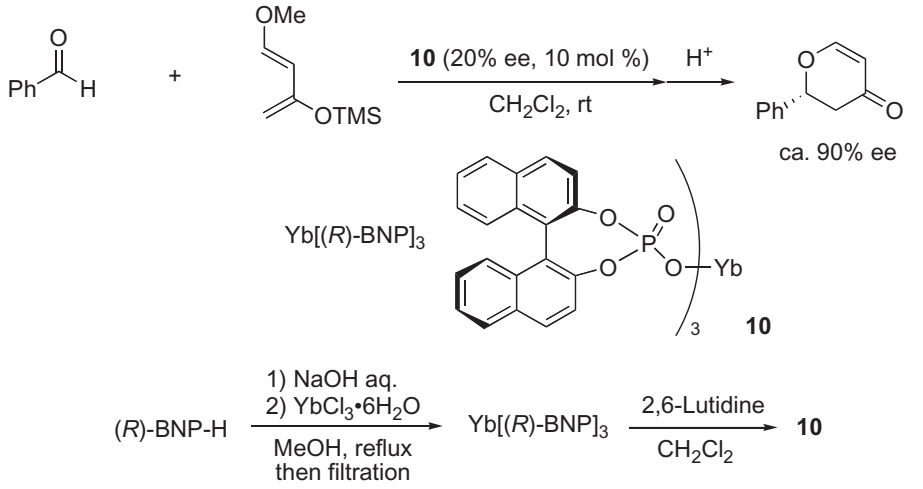
Scheme 12.16.

12.2.5. Asymmetric Hetero-Diels–Alder Reaction

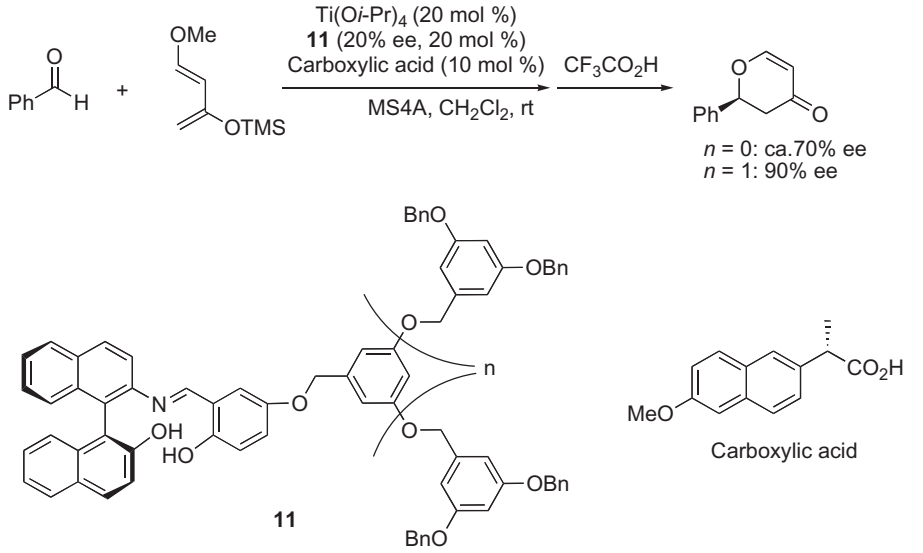
Inanaga and others reported an asymmetric hetero-Diels–Alder reaction of aldehydes and Danishefsky's diene using a chiral Yb catalyst, which was prepared from Yb(III) salt and three equivalents of 1,1′-binaphthyl-2,2′-diyl phosphoric acid (BNP-H) along with the addition of 2,6-lutidine (Scheme 12.17) [27]. This was the first example of NLE in ML_3 system.

Ding and others found positive NLE in asymmetric hetero-Diels–Alder reaction using a chiral tridentate Ti catalyst with carboxylic acid as an additive [28]. More interestingly, higher degree of asymmetric amplification could be achieved by dendron unit-attached tridentate ligand **11** (n = 1) (Scheme 12.18) [29].

Ding and others also developed an asymmetric hetero-Diels–Alder reaction using chiral Zn catalyst, which was prepared from diethylzinc, BINOL derivative **12**, and diimine activator **13**. The positive NLE could be explained by facile dissociation of



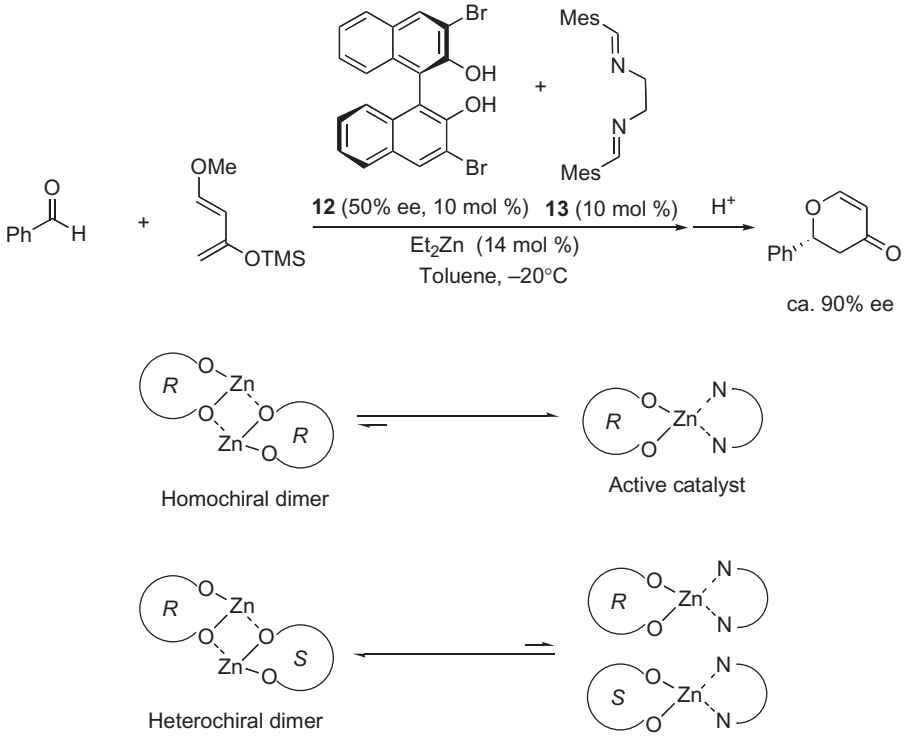
Scheme 12.17.



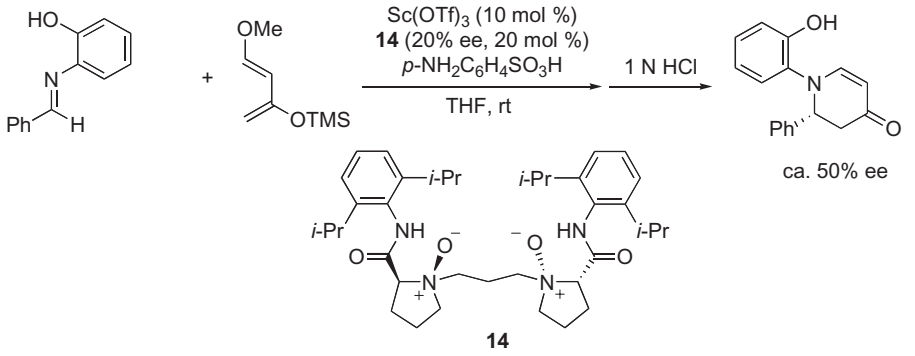
Scheme 12.18.

homochiral dimer to active monomer catalyst, and the formation of less soluble homochiral dimer as racemic reservoir (Scheme 12.19) [30].

In the aza-Diels–Alder reaction using Sc(III)-chiral *N*,*N*′-dioxide **14** complex, positive NLE was observed in the product. ML_2 system was proposed along with ^{1}H-nuclear magnetic resonance (NMR) analyses of the complexes (Scheme 12.20) [31].

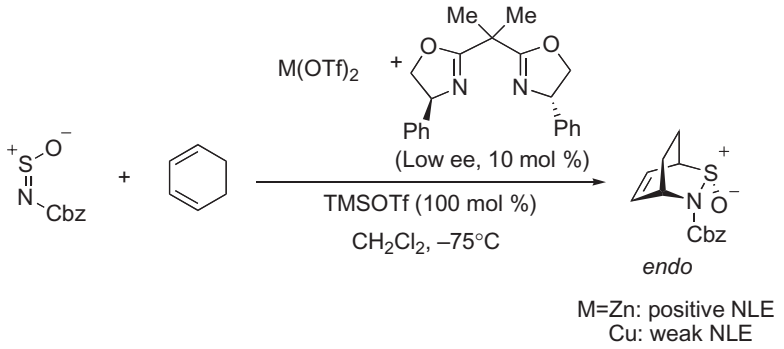


Scheme 12.19.



Scheme 12.20.

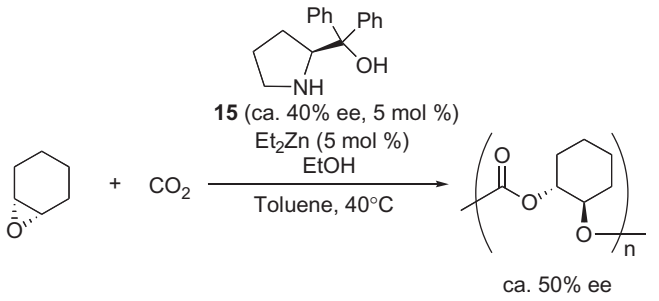
Gautun and others reported the hetero-Diels–Alder reaction of *N*-sulfinyl dienophile using metal triflate-bis(oxazoline) catalyst. $Zn(OTf)_2$ showed obvious positive NLE; on the contrary, $Cu(OTf)_2$ did a nearly linear relationship between the ee of ligand and the bicyclic product (Scheme 12.21) [32].



Scheme 12.21.

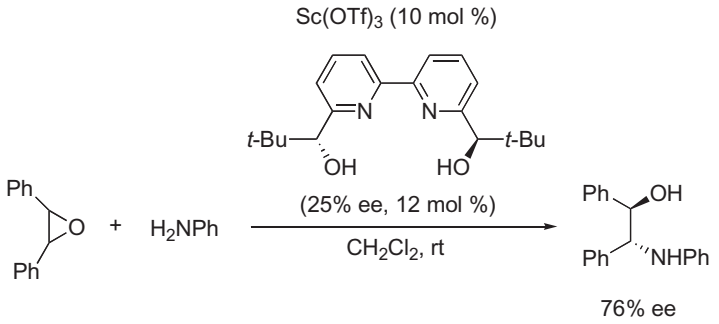
12.2.6. Asymmetric Ring Opening of *meso*-Epoxide

Nozaki and others reported an asymmetric alternating copolymerization of cyclohexene oxide and carbon dioxide. The catalyst was prepared from diphenyl prolinol **15** of 40% ee and diethylzinc, and the ee of diol was determined to be ca. 50% ee after the hydrolysis of the obtained polymer (Scheme 12.22) [33]. This is the first example of nonlinear phenomenon in the asymmetric synthesis of chiral polymers with main-chain chirality.



Scheme 12.22.

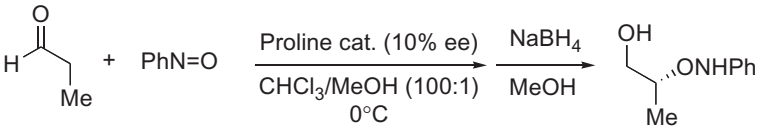
Mai and Schneider showed positive NLE in the enantioselective aminolysis of *cis*-stilbene oxide. Sc(III)-chiral pyridine complex catalyzed the reaction (Scheme 12.23) [34].



Scheme 12.23.

12.2.7. Amplified Enantiomeric Excess in Solution

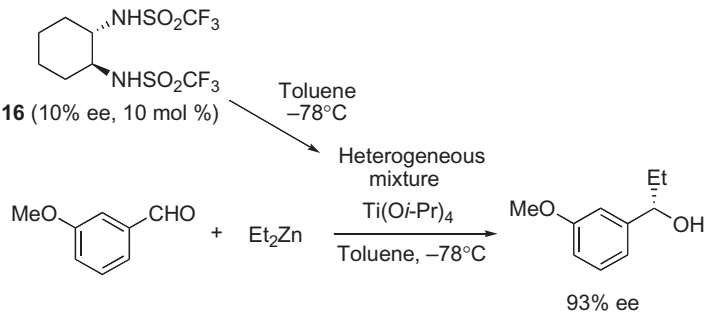
Recently, organocatalysts attract great attention in organic synthesis. Proline and its derivatives in particular have been found to be efficient chiral catalysts in various reactions. Hayashi and others reported large positive NLE in enantioselective α-aminoxylation of propanal using proline catalyst: when a proline solution was prepared from solid proline (10% ee), and was used after filtration, product with 96% ee was obtained (Scheme 12.24) [35]. After careful investigation, ee of proline in $CHCl_3$ solution was found to be excellent (99% ee) when 10% ee proline was employed. As solubility of racemic and chiral proline was very different, this phenomenon is explained by the dissolution–precipitation mechanism. This result means the enrichment of an enantiomer in a solid/solution system. On the other hand, when the reaction was examined without filtration, only a slight asymmetric amplification was observed. Along with the reaction proceeds, the generated product act as a polar solvent, and insoluble D- and L-proline solids are dissolved in the reaction solution, which suppress the great asymmetric amplification. Blackmond and others reported a detailed investigation on the phenomenon of asymmetric amplification of amino acid in solid/solution system [36].



A solution of proline was used after filtration: 96% ee, 93%
Without filtration: 19% ee, 90%

Scheme 12.24.

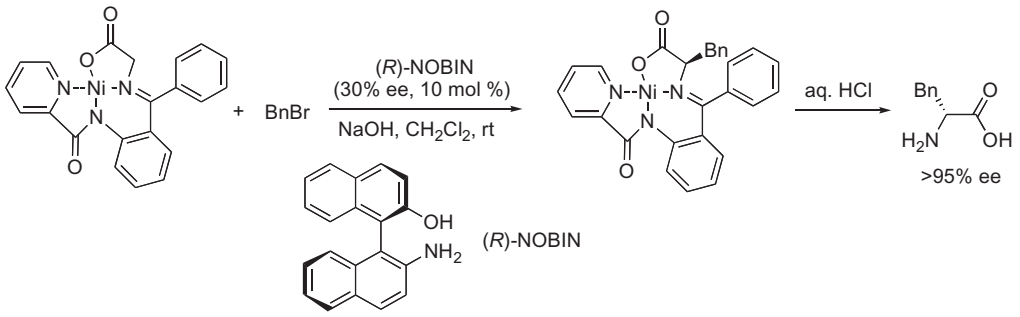
Kagan and others achieved the asymmetric amplification of chiral ligand in solid/solution system without filtration. When a toluene solution of bistriflamide **16** (10% ee) was cooled at –78°C and the obtained heterogeneous mixture was used for the Ti-catalyzed asymmetric alkylation of aldehyde using diethylzinc, the secondary alcohol of 93% ee was obtained (Scheme 12.25) [37].



Scheme 12.25.

12.2.8. Miscellaneous Cycloadditions

Belokon and others developed the enantioselective alkylation of achiral Ni(II) complex of glycine-derived Schiff's base for the synthesis of α-amino acid. The benzylation was catalyzed by 2-hydroxy-2′-amino-1,1′-binaphthyl (NOBIN) of 30% ee under the basic conditions, and chiral phenylalanine of more than 95% ee was obtained after acid treatment (Scheme 12.26) [38].



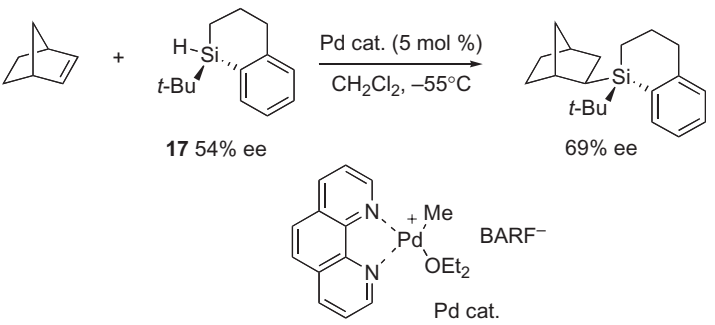
Scheme 12.26.

Oestreich and Rendler reported a reagent-controlled Pd-catalyzed reaction of norbornene with chiral hydrosilane **17** of 54% ee to give hydrosilylated product in 69% ee (Scheme 12.27) [39]. This is an unusual example of chiral transfer from silicon to carbon along with NLE.

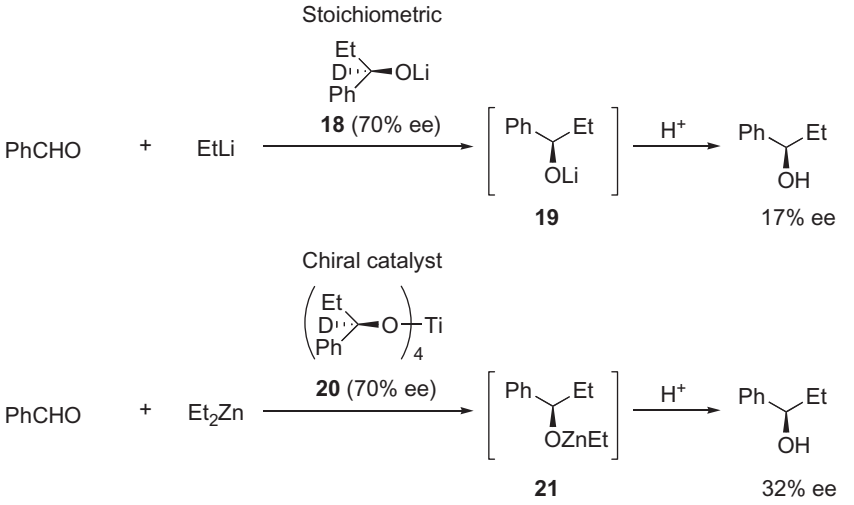
12.3. ASYMMETRIC AUTOCATALYSIS

12.3.1. Background

In 1953, Frank proposed a reaction mechanism, without showing any chemical structure for the molecules, in which a chiral product acts as a chiral catalyst for its own production (asymmetric autocatalysis) and prohibits the formation of its antipode [40]. In such



Scheme 12.27.



Scheme 12.28.

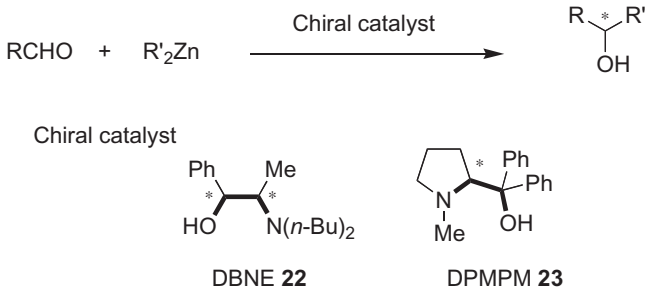
a reaction, if it exists, the enantiomeric purity of the product would increase as the reaction progresses. Since then, asymmetric autocatalysis has attracted considerable attention [41].

Seebach and others recognized the importance of the effect of mixed aggregates of products (lithium enolates) on enantioselectivity [42]. Alberts and Wynberg reported an asymmetric autoinduction (Scheme 12.28) in which ethyllithium adds to benzaldehyde to give *in situ* lithium alkoxide of chiral 1-phenyl-1-propanol **19** with 17% ee in the presence of a stoichiometric amount of lithium alkoxide of 1-phenyl-1-propanol-d_1 **18** with the same configuration [43]. They also described an enantioselective addition (32% ee) of diethylzinc to benzaldehyde using titanium (IV) tetraalkoxide of chiral 1-phenyl-1-propanol-l-d_1 **20**. In this reaction, the structures of the chiral catalyst **20** and the product **21** (zinc alkoxide before quenching the reaction) are different [43,44]. Danda and others reported an asymmetric autoinductive cyanohydrin-forming reaction using

2,5-diketopiperazine as a chiral catalyst; the presence of a chiral product enhances the enantioselectivity of the chiral catalyst [45].

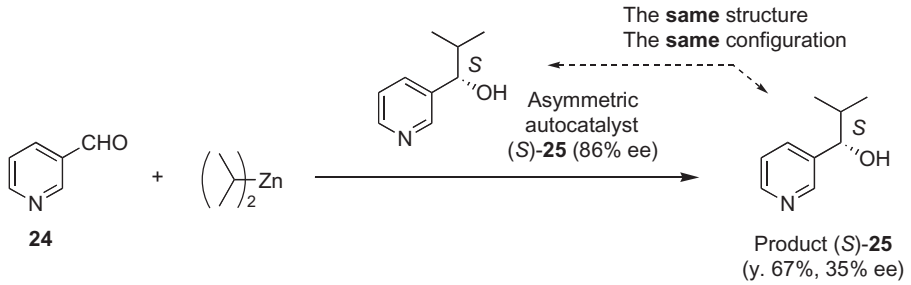
12.3.2. Discovery of Asymmetric Autocatalysis

We have developed the addition of dialkylzincs to aldehydes using β-amino alcohols as the chiral ligand to afford *sec*-alcohols [7b]. The coordination of nitrogen and oxygen atoms to the zinc atom of dialkylzinc accelerates the nucleophilic attack of alkyl group to a suitable electrophile. The formation of the complex between dialkylzinc and amino alcohol enables the C–C bond-forming reaction [6]. Using appropriate chiral amino alcohols as a chiral ligand, asymmetric catalysis is available, especially *N*,*N*-dibutylnorephedrine (DBNE **22**) [46–48] and diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM **23**) [49,50] are well-established chiral catalysts to afford chiral products in high yields and high enantiomeric excesses (Scheme 12.29).



Scheme 12.29. Chiral amino alcohol-catalyzed asymmetric dialkylzinc addition to aldehydes.

During our continuing study on the enantioselective addition of dialkylzincs to nitrogen-containing aldehydes, we found in 1990, for the first time, that chiral 3-pyridyl alkanol **25** acts as an asymmetric autocatalyst in the addition of diisopropylzinc (*i*-Pr_2Zn) to pyridine-3-carbaldehyde **24** (Scheme 12.30) [51]. In the enantioselective addition of *i*-Pr_2Zn to 3-pyridinecarbaldehyde **24**, (*S*)-3-pyridyl alkanol **25** with 86% ee acts as an



Scheme 12.30. Asymmetric autocatalysis of chiral pyridyl alcohol.

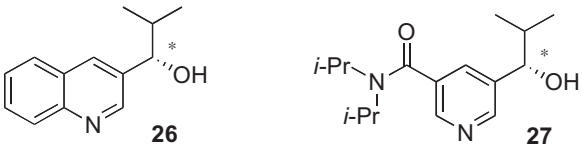
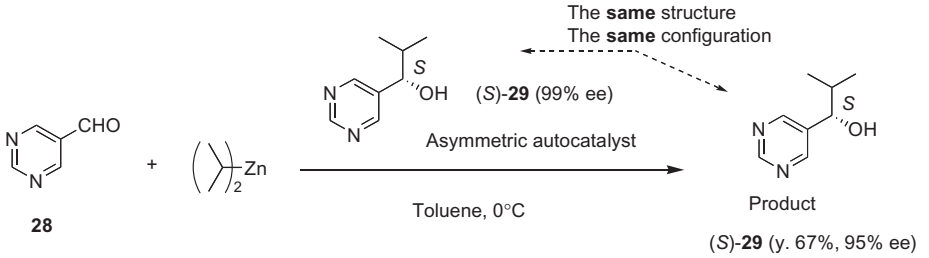


Figure 12.2. Asymmetric autocatalysts containing quinoline and carbamoylpyridine ring for the reaction of *i*-Pr_2Zn and the corresponding aldehydes.

asymmetric autocatalyst to afford the same compound **25** with 35% ee. In this reaction, the resulting product **25** forms the amino alcohol moiety, and it acts as the chiral catalyst for the next *i*-Pr_2Zn addition, that is, catalyzes its own production. This is the first experimental observation that realizes asymmetric autocatalysis.

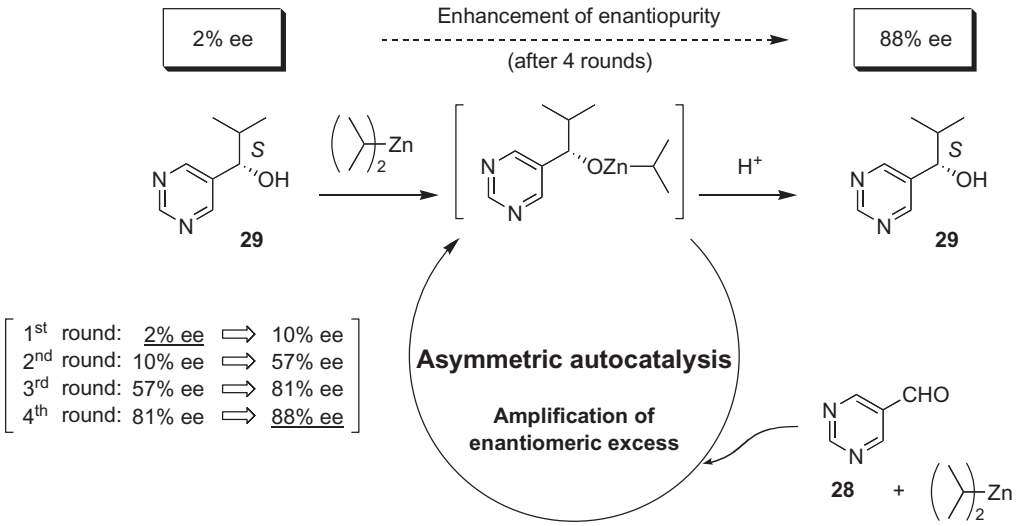
After searching various nitrogen-containing compounds, we found that the zinc alkoxide of 2-methyl-1-(3-quinolyl)propan-1-ol **26** catalyzes the enantioselective formation of itself with the same configuration in the reaction between quinoline-3-carbaldehyde and *i*-Pr_2Zn to afford the product **26** in high ee (up to 94% ee) [52]. In addition, 5-carbamoyl-3-pyridyl alkanol **27** can act as the efficient autocatalyst to catalyze its own production in highly enantioselective manner (up to 86% ee) (Fig. 12.2) [53].

Then, we discovered that chiral 2-methyl-1-(5-pyrimidyl)propan-1-ol **29** serves as a highly enantioselective asymmetric autocatalyst for the addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **28** (Scheme 12.31) [54]. In this compound, the formyl group is connected to the symmetric pyrimidine ring instead of the pyridine ring. When highly enantioenriched (*S*)-pyrimidyl alkanol **29** with 99% ee was employed as an asymmetric autocatalyst, (*S*)-**29** with 95% ee composed of both the newly formed and the initially used **8** was obtained. The yield of the newly formed **29** was calculated to be 67%, and the enantiomeric excess was 93% ee.



Scheme 12.31. Highly enantioselective asymmetric autocatalysis of pyrimidyl alkanol in the enantioselective *i*-Pr_2Zn addition.

The result of such a high enantioselectivity in asymmetric autocatalytic reaction encouraged us to investigate the enantioselective alkylation utilizing the asymmetric autocatalyst with low ee of 2%. In this pyrimidine system, we found for the first time asymmetric autocatalysis with amplification of enantiomeric excess, that is, the initial small enantioenrichment (2% ee) was significantly enhanced to the high



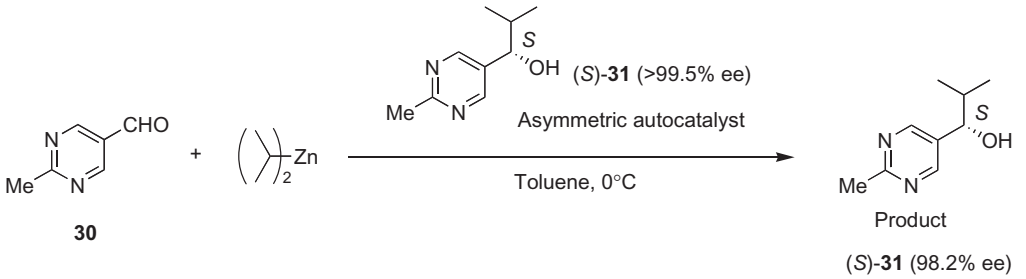
Scheme 12.32. Asymmetric autocatalysis with significant amplification of chirality from low (2%) to high (88%) ee.

enantioenrichment of 88% ee (Scheme 12.32) [55]. When the (*S*)-pyrimidyl alkanol **29** (20 mol %, 2% ee) was employed as an asymmetric autocatalyst, (*S*)-**29** with 10% ee was obtained in 46% yield as a mixture of newly formed product and initial catalyst. The reaction was performed successively by serving the chiral product of one reaction as the autocatalyst of the next round of reaction, observing further enhancement of enantiomeric excess to reach 88% ee after four rounds of the reaction. The overall process was the asymmetric autocatalysis of (*S*)-**29** starting from a low ee of 2% with significant amplification of chirality to 88% ee, without aid of any other chiral auxiliaries, along with the increase in the amount. This chemical process is the first example of realization of asymmetric autocatalysis with amplification of chirality [55].

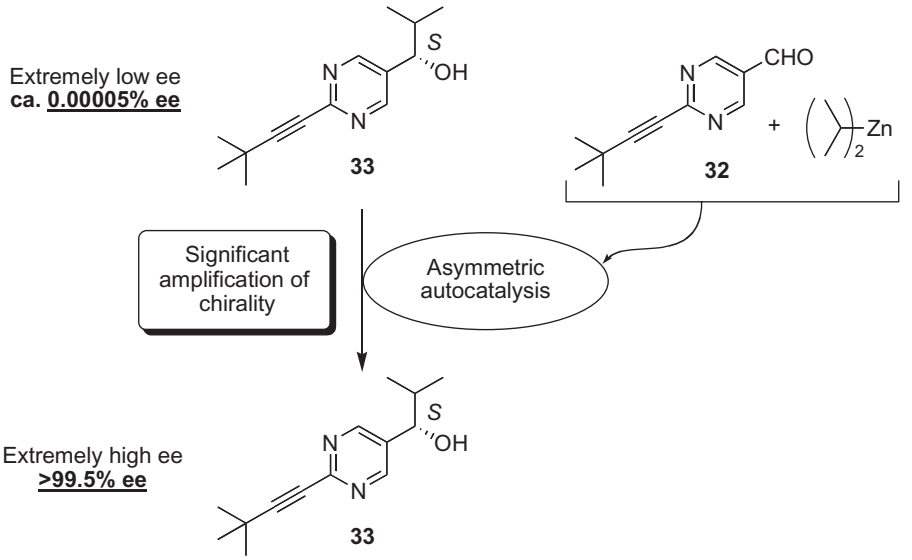
12.3.3. Practically Perfect Asymmetric Autocatalysis

The asymmetric autocatalysis in the addition reaction of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde was examined using (*S*)-2-methyl-1-(5-pyrimidyl)-1-propanol **31** with high ee (Scheme 12.33). The treatment of the corresponding 2-methylpyrimidine-5-carbaldehyde **30** with *i*-Pr_2Zn in the presence of autocatalyst **31** with >99.5% ee resulted to a highly efficient asymmetric automultiplication to afford the product (*S*)-**31** with 98.2% ee [54]. In addition, the result of the experiment using (*S*)-**31** with 0.28% ee as autocatalyst has demonstrated the ability of asymmetric autoamplification in this pyrimidine autocatalytic system. That is to say, the enhancement of the enantioenrichment of 0.28% ee occurred to reach 87% ee by one-pot asymmetric autocatalysis [56].

This asymmetric autocatalytic process is a very powerful method for amplifying the tiny imbalance of enantiomer to high enantioenrichment. When a pyrimidyl alkanol with low ee was used as an asymmetric autocatalyst, the ee of the product was higher than



Scheme 12.33. Highly enantioselective asymmetric autocatalysis of chiral pyrimidyl alkanol.



Scheme 12.34. Autocatalytic amplification of chirality from ca. 0.00005% ee to >99.5% ee.

that of the original catalyst. One of the advantages of asymmetric autocatalysis with amplification of ee over non-autocatalytic amplification of ee is that the product of one round is used as the asymmetric autocatalyst for the following round. Thus, extremely low enantioenrichment of pyrimidyl alkanol could be amplified to very high enantioenrichment by the consecutive asymmetric autocatalysis.

We found efficient amplification of chirality by using (*S*)-2-(*tert*-butylethynyl)-5-pyrimidyl alkanol **33** [57] from as low as ca 0.00005% ee to an almost enantiomerically pure (>99.5% ee) product **33** in only three consecutive asymmetric autocatalyses (Scheme 12.34) [58]. The first round of asymmetric autocatalysis using (*S*)-**33** with ca. 0.00005% ee in the *i*-Pr_2Zn addition to 2-alkynylpyrimidyne-5-carbaldehyde **32** gave (*S*)-**33** in 96% yield with an enhanced ee of 57%. The second round of asymmetric autocatalysis using the autocatalyst of 57% ee produced (*S*)-**33** with 99% ee, and the ee of (*S*)-**33** finally reached >99.5% ee in the third round of asymmetric autocatalysis.

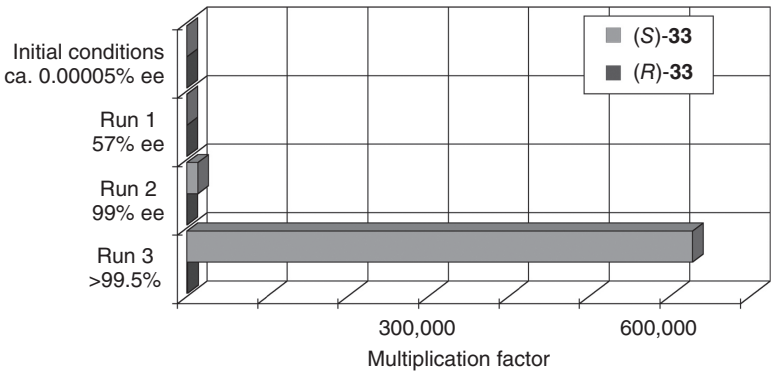
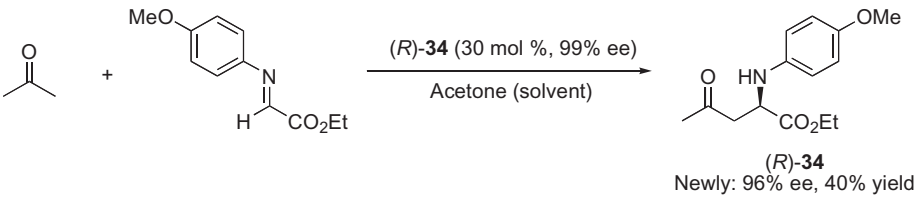


Figure 12.3. The increase in the amount of (*S*)- and (*R*)-pyrimidyl alkanol **33** during consecutive asymmetric autocatalyses with significant amplification of ee.

During these three consecutive asymmetric autocatalyses, the initial slightly major (*S*)-enantiomer of **33** automultiplied by a factor of ca. 630,000, whereas the initially slightly minor (*R*)-enantiomer of **33** automultiplied by less than 1000 (Fig. 12.3). The tiny enantiomeric imbalance of ca. 0.00005% ee corresponds to only a few molecules of difference in the number of enantiomeric **33** in an almost racemic mixture of ca. 5,000,000 molecules of (*S*)-**33** and ca. 5,000,000 molecules of (*R*)-**33** [58].

Recently, Mauksch, Tsogoeva, and coworkers reported asymmetric autocatalysis of **34** without positive NLE in the organocatalytic Mannich reaction (Scheme 12.35) [59–61].



Scheme 12.35. Asymmetric autocatalytic Mannich reaction.

12.3.4. Model and Mechanism of the Asymmetric Autocatalysis of Pyrimidyl Alkanol

Kinetic analysis of asymmetric autocatalysis was performed to study the reaction mechanism of asymmetric autocatalysis. The relationship between the reaction time and the yields of the product was investigated [62]. The *i*-Pr_2Zn addition to pyrimidine-5-carbaldehyde **32** was performed in the presence of enantiomerically pure autocatalyst, the reaction being monitored by high performance liquid chromatography (HPLC) using naphthalene as an internal standard. The plots shown in Figure 12.4a constitute S-shaped

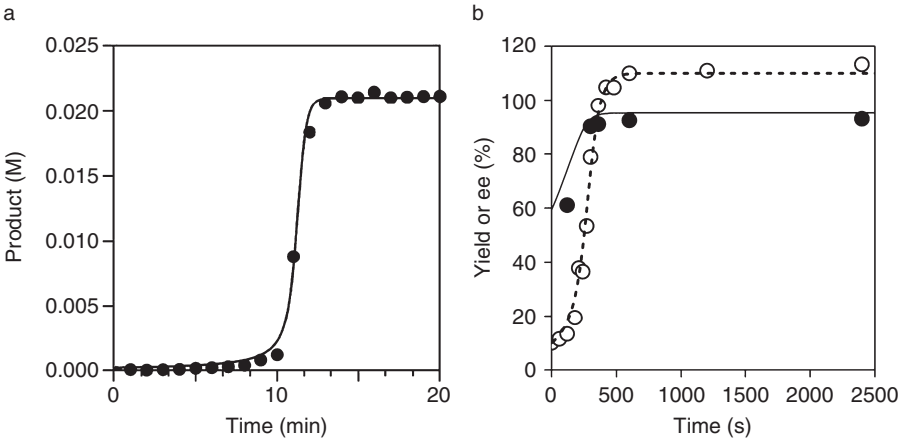


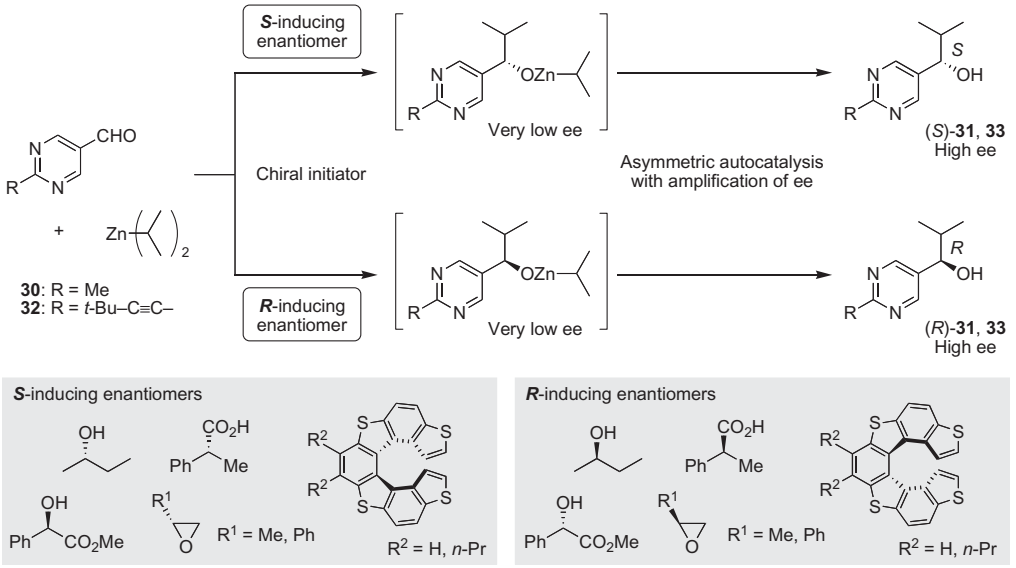
Figure 12.4. Relationship between time versus concentration, yield, and ee in asymmetric autocatalysis of pyrimidyl alkanol **33**. (a) Enantiopure (>99.5% ee) asymmetric autocatalyst was used. Experimental concentration of alkanol (filled circle), simulation (solid line) [62]. (b) Asymmetric autocatalyst with 59% ee was used. Experimental yield (open circle), experimental ee (filled circle) [63].

curves that are characteristic of an autocatalytic reaction. The relationship between time, yield, and enantiomeric excess was also measured in the asymmetric autocatalysis with amplification of ee using high to low ee of pyrimidyl alkanol as the catalyst (Fig. 12.4b) [63]. Portions of the reaction mixture were quenched periodically and analyzed by HPLC fitted with a chiral stationary phase. When pyrimidyl alkanols with high to good ee are used as the asymmetric autocatalyst, the observed values of yield and ee were well matched to our simulated kinetic model, that is, first order in *i*-Pr_2Zn and pyrimidine-5-carbaldehyde, and the second order in pyrimidyl alkanol. However, the analysis using a pyrimidyl alkanol with low (20%) ee exhibited higher ee than the predicted value of ee based on the above model. Therefore, we considered the possibility of the presence of an inhibition process other than our simulated kinetic model. The inhibition process, that is, the major enantiomer inhibits the production of the minor enantiomer, might enable the high magnitude of amplification of ee in asymmetric autocatalysis.

The model and the mechanism of the reaction have also been studied by other groups. Blackmond, Brown, and coworkers showed second-order kinetics for zinc alkoxide of pyrimidyl alkanol by studying the kinetics using a microcalorimeter [64,65]. Brown, Gridnev, and coworkers performed the structural study for the catalyst of asymmetric autocatalysis by using NMR spectroscopy and DFT calculations [66–70]. Micheau, Buhse, and coworkers proposed the kinetic model for the asymmetric autocatalytic reaction to analyze the generation and amplification of ee [71–73]. Pályi, Caglioti, and coworkers suggested the empirical formula, which enables the quantitative calculation of ee in the asymmetric autocatalysis [74,75]. Lente reported the stochastic kinetic model of asymmetric autocatalysis [76], and Saito and Hyuga reported the theoretical model for the autocatalytic amplification in a closed system [77,78].

12.3.5. Asymmetric Autocatalysis in the Presence of Chiral Organic Compound

As described in the preceding section, asymmetric autocatalysis is capable of amplifying the ee of initially added asymmetric autocatalyst. Low ee (ca. 0.00005%) of the initial pyrimidyl alkanol is amplified to almost enantiomerically pure (>99.5% ee) during consecutive asymmetric autocatalysis [58]. It was also found that not only the asymmetric autocatalyst itself but also other chiral organic compounds can act as a chiral trigger for asymmetric autocatalysis, that is, a slight asymmetry induced by the chiral organic compound is amplified by asymmetric autocatalysis to reach high enantioenrichment (Scheme 12.36) [79]. When pyrimidine-5-carbaldehyde is alkylated by *i*-Pr_2Zn in the presence of a chiral organic compound, tiny enantiomeric excess should be induced in the initially formed product. The subsequent addition of *i*-Pr_2Zn and pyrimidine-5-carbaldehyde to the reaction mixture leads to an asymmetric autocatalysis, and a highly enantiomerically enriched pyrimidyl alkanol is obtained. Therefore, the absolute configuration of the product alkanol with high ee is correlated to that of the chiral initiator that was originally used.



Scheme 12.36. Asymmetric autocatalysis initiated by chiral organic compounds.

As shown in Scheme 12.36, various chiral organic compounds can act as chiral initiators of asymmetric autocatalysis. 2-Methylpyrimidine-5-carbaldehyde **30** was subjected to the addition of *i*-Pr_2Zn in the presence of chiral butan-2-ol, methyl mandelate, and carboxylic acid [79]. When the chiral alcohol, (*S*)-butan-2-ol with ca. 0.1% ee was used as a chiral initiator of asymmetric autocatalysis, (*S*)-pyrimidyl alkanol **31** with 73% ee was obtained. In contrast, (*R*)-butan-2-ol with 0.1% ee induced the production of (*R*)-**31** with 76% ee. In the same manner, methyl mandelate (ca. 0.05% ee) and a chiral carboxylic acid (ca. 0.1% ee) can act as chiral initiators of asymmetric autocatalysis; therefore, the

S- and *R*-enantiomers of methyl mandelate and carboxylic acid induce the formation of (*R*)- and (*S*)-alkanol **31**, respectively. Chiral propylene oxide (2% ee) and styrene oxide (2% ee) also induce the imbalance of ee in initially forming zinc alkoxide of the pyrimidyl alkanol in the addition reaction of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **32** [80]. Further consecutive reactions enable the amplification of ee to produce the highly enantiomerically enriched pyrimidyl alkanol **33** (up to 96% ee) with the corresponding absolute configuration to that of the chiral epoxide. *P*- and *M*-tetrathia-[7]-helicenes with helical chirality can serve as chiral initiators of asymmetric autocatalysis to produce the enantiomerically enhanced chiral alkanol **33** with a good correlation between absolute configurations [81].

The chirality in the organic compound (even though with small ee) can be converted into almost enantiomerically pure pyrimidyl alkanol by asymmetric autocatalysis with amplification of chirality.

12.4. EXPERIMENTAL APPROACHES TO UNDERSTAND THE ORIGINS OF BIOLOGICAL HOMOCHIRALITY

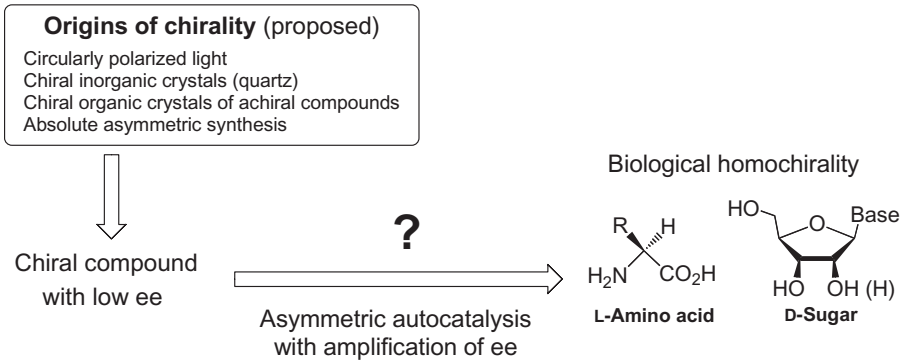
12.4.1. Introduction

Many of the biocompounds such as L-amino acids and D-sugars are chiral. Although they have left- and right-handed mirror image forms, biology uses essentially only one enantiomer, with only a few exceptions. One of the greatest puzzles in science is the question of biological homochirality, that is, why life on Earth is based on L-amino acids and D-sugars, and not based on their mirror image molecules [82]. The homochirality of biomolecules might have been established before the origin of life, and the chiral homogeneity of biomolecules is considered to be closely related to the origin and evolution of life. How and when biomolecules achieved high enantioenrichment is an attractive issue requiring significant analysis. To date, several mechanisms have been proposed for elucidating the origins of the chirality of organic compounds, including circularly polarized light (CPL) [83–86], chiral inorganic crystals [87,88] such as quartz, chiral organic crystals composed of achiral organic molecules [89–94], spontaneous absolute asymmetric synthesis [71,95], parity-violating energy difference (PVED) [96,97], and so on. Although the initial enantiomeric imbalance can be introduced via these proposed mechanisms, a suitable amplification process for chirality is required to reach single-handedness 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 (Scheme 12.37), so an experiment on the effect of proposed chiral factors as the origin or trigger of biological homochirality can be performed using this autocatalytic reaction. In this section, we describe enantioselective synthesis, in combination with asymmetric autocatalysis, triggered by CPL, quartz, and chiral organic crystals formed from achiral compounds, including a spontaneous absolute asymmetric synthesis.

12.4.2. CPL

Right (*r*)- and left (*l*)-handed CPL have long been proposed as one of the origins of chirality of organic compounds [83–86]. The occurrence of strong *l*- or *r*-CPL in nature has been observed in a star formation region of the Orion constellation [98]. However, because of the very small anisotropy (*g*) factors of organic compounds, only low enan-



Scheme 12.37. Proposed origins of chirality and the pathway to the biological homogeneity.

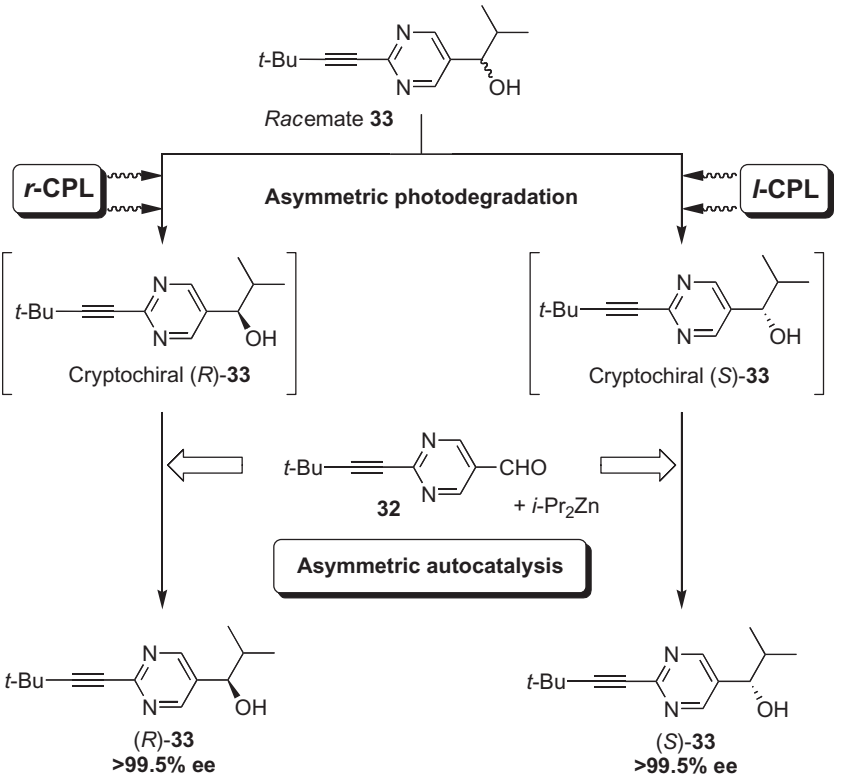
tioenrichments of organic compounds have been induced by the irradiation with CPL. For example, asymmetric photodecomposition of *rac*-leucine by *r*-CPL (213 nm) produces L-leucine with only 2% ee [99]. Hexahelicene with less than 2% ee is formed by asymmetric photosynthesis using CPL [100]. Irradiation of racemic alkylidenecyclohexanone with CPL induces a small enantiomeric imbalance (<2% ee) [101]. These low enantiomeric enrichments induced by CPL have not been correlated with the homochirality of organic compounds. We considered that chiral organic compounds with low ee induced by CPL could act as a chiral trigger in the asymmetric autocatalysis to afford highly enantioenriched pyrimidyl alkanol with an absolute configuration corresponding to that of the handedness of the CPL.

Indeed, in the presence of L-leucine with only 2% ee as a chiral initiator, the reaction of 2-methylpyrimidine-5-carbaldehyde **30** with *i*-Pr_2Zn produced (*R*)-pyrimidyl alkanol **31** with an enhanced ee of 21% [79,102,103]. In contrast, when D-leucine with 2% ee was used as a chiral initiator, (*S*)-**31** with an increased ee of 26% was obtained. As described in the preceding section, the ee of the obtained pyrimidyl alkanol can be amplified significantly by consecutive asymmetric autocatalysis to achieve homochirality. When 2-(*tert*-butylethynyl)pyrimidine-5-carbaldehyde **32**, instead of the 2-methylpyrimidine derivative **30**, was subjected to the autocatalytic reaction in the presence of chiral leucine with extremely low ee, highly enantioenriched pyrimidyl alkanol **33** with the absolute configuration corresponding to that of chiral leucine was also obtained. But it should be noted that the resulting alkanol **33** showed the opposite enantioselectivity to that of alkanol **31** with high enantioenrichment.

Next, we found that (*P*)-hexahelicene with 0.13% ee, which is lower than that induced by CPL [100,104], also acts as a chiral initiator for asymmetric autocatalysis. Thus, the chirality of CPL has been correlated with that of alkanol **33** with high ee by using hexahelicene as the chiral source of asymmetric autocatalysis. And then, we performed the irradiation of CPL to the *rac*-alkylidenecyclohexanones, and the resulting compounds were subjected to the asymmetric autocatalysis as the chiral trigger. As a result, enantioenriched (*S*)- and (*R*)-pyrimidyl alkanols with the absolute configurations correlated to the chirality of CPL were obtained. The alkylidenecyclohexanone acted as the practical mediator between the CPL and highly enantiomeric organic compound in conjunction with asymmetric autocatalysis. Thus, low enantioenrichments in compounds induced

by CPL have been correlated to an organic compound with very high enantioenrichments by asymmetric autocatalysis.

Further investigation is the direct correlation between CPL and enantioenriched organic compound (Scheme 12.38). Thus, we performed the irradiation of CPL to the asymmetric autocatalyst. (*R*)- and (*S*)-pyrimidyl alkanols **33** exhibit positive and negative Cotton effects in circular dichroism (CD) spectra at 313 nm, respectively [105]. We thought that the direct irradiation of racemic alkanol **33** by left-handed (*l*) CPL would induce the asymmetric photodegradation of (*R*)-pyrimidyl alkanol **33** and leave the slightly enantioenriched (*S*)-**33**. Even when the enantioenrichment of the remaining (*S*)-pyrimidyl alkanol **33** is extremely low, as described in the preceding section, the compound serves as an asymmetric autocatalyst in the subsequent asymmetric autocatalysis with amplification of chirality to produce itself with high enantioenrichment. Indeed, direct irradiation of racemic **33** by left-handed CPL and the subsequent asymmetric autocatalysis produces highly enantioenriched (*S*)-alkanol **33** with >99.5% ee (Scheme 12.38). On the other hand, irradiation with right-handed (*r*) CPL, instead of *l*-CPL, formed (*R*)-**33** with >99.5% ee. The process provides direct correlation of the handedness of CPL with that of the organic compound with high enantiomeric excess [105].

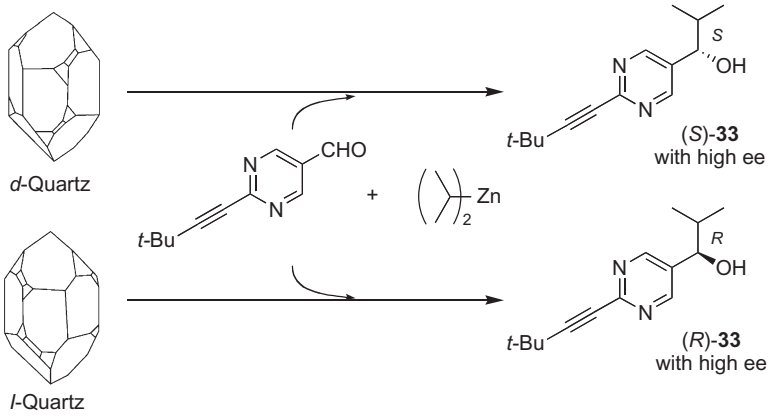


Scheme 12.38. Short pathway to obtain a near enantiopure compound by CPL irradiation followed by asymmetric autocatalysis.

12.4.3. Enantiomorphous Inorganic Crystal-Induced Asymmetric Autocatalysis

Chiral crystals provide an environment for the discrimination of chiral molecules, so their possible roles in the origin of biological homochirality have been discussed for a long time [87]. In the Earth's crust, there are a wide variety of chiral minerals, such as chiral oxides and silicates, which serve as accessible chiral surfaces in the prebiotic evolution of chiral organic molecules. However, no apparent asymmetric induction using chiral minerals has been observed. Only a very small asymmetric induction has been reported in an adsorption of chiral compounds on quartz [106].

The possible interaction between the chiral surface of minerals and the organic molecules remains obscure, so we performed an asymmetric autocatalysis triggered by quartz. When pyrimidine-5-carbaldehyde **32** was treated with *i*-Pr_2Zn in the presence of *d*-quartz powder, (*S*)-pyrimidyl alkanol **33** with 97% ee was obtained in a yield of 95% (Scheme 12.39) [107]. In contrast, in the presence of *l*-quartz, (*R*)-**33** with 97% ee was obtained in a yield of 97%. These reproducible results clearly show that the absolute configurations of the pyrimidyl alkanol formed were regulated by the chirality of quartz. A small enantiomeric imbalance of the initially formed pyrimidyl alkanol zinc alkoxide induced by quartz was amplified significantly by the subsequent consecutive asymmetric autocatalysis to produce pyrimidyl alkanol with very high ee.



Scheme 12.39. Asymmetric autocatalysis utilizing inorganic crystals as an initial source of chirality.

The achiral inorganic ionic sodium chlorate ($NaClO_3$) and sodium bromate ($NaBrO_3$), both of which crystallize in enantiomorphs belonging to the cubic space group $P2_13$, also act as the origin of chirality of asymmetric autocatalysis to provide the enantioenriched alkanol [108]. The reaction of *i*-Pr_2Zn to aldehyde **30** and **32** in the presence of *d*-$NaClO_3$ crystal affords (*S*)-pyrimidyl alkanols **31** and **33**, respectively. On the other hand, (*R*)-alkanol **31** and **33** are formed in the presence of *l*-$NaClO_3$ crystal. It should be noted that *d*-$NaBrO_3$ has the opposite absolute configuration of the crystal structure to that of *d*-$NaClO_3$. In other words, *d*-$NaBrO_3$ and *l*-$NaClO_3$ have the same absolute configuration of the crystal structure. Thus, *d*-$NaBrO_3$ crystal affords (*R*)-alkanol **33**, while *l*-$NaBrO_3$ crystal affords (*S*)-**33**.

12.4.4. Chiral Crystals of Achiral Organic Compounds

Some achiral organic compounds form chiral crystals, with each crystal exhibiting one of the two possible enantiomorphs [89–94]. These chiral crystals composed of an achiral organic compound may serve as an efficient chiral seed in a prebiotic world; therefore, a study of asymmetric autocatalysis using these chiral organic crystals is an interesting subject.

Cytosine **34**, a constituent of DNA and RNA, is a base of cytidine and deoxycytidine, and is an essentially flat achiral molecule. It is conceivable that cytosine **34** was formed under prebiotic conditions [109] and already existed before the RNA world emerged. Thus, the investigation of the enantioselective reaction utilizing the crystal chirality of achiral cytosine is an important experimental approach to understanding of the origin of biological homochirality (Fig. 12.5).

At first, we discovered that achiral cytosine **34**, when crystallized from methanol with stirring without adding any seed crystal, affords powder-like crystals that exhibit either plus or minus Cotton effect in solid-state CD spectra [110] at ca. 310 nm. The stochastic behavior of the formation of [CD(+)310]- and [CD(–)310]-crystals of cytosine **34** was observed.

Next, the chiral crystals that are spontaneously formed with stirring are used as chiral triggers for asymmetric autocatalysis (Scheme 12.40) [110]. When pyrimidine-5-carbaldehyde **32** and *i*-Pr_2Zn reacted in the presence of a [CD(+)310]-crystal of cytosine **34**, enantioenriched (*R*)-pyrimidyl alkanol **33** was obtained after the subsequent autocatalytic amplification of ee. On the other hand, spontaneously obtained [CD(–)310]-cytosine crystal induced the production of enantioenriched (*S*)-alkanol **33**. These results clearly exhibit the correlation between the chirality of the crystal of cytosine and the absolute configuration of the resulting alkanol.

This sequence of reactions represents one of the chemical processes in which the scenario for the evolution of chirality from the achiral nucleobase cytosine was achieved in real chemical reactions. The sequential process of asymmetric induction in the organic product with an asymmetric carbon atom and the amplification of chirality through

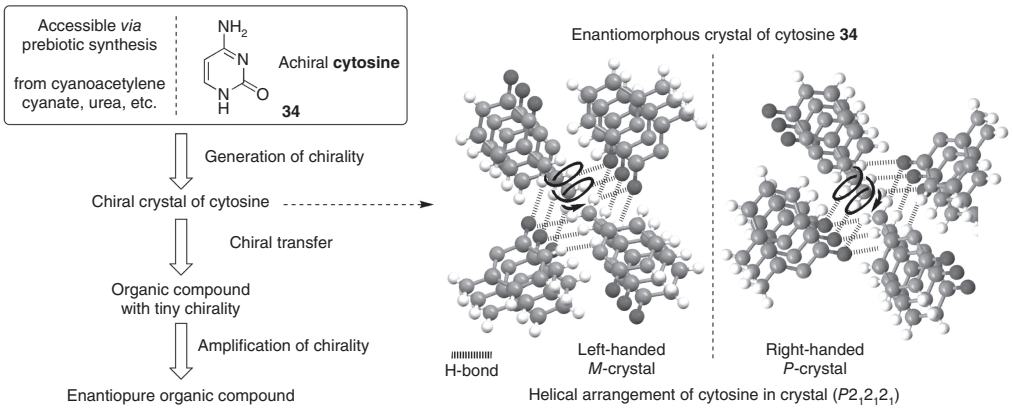
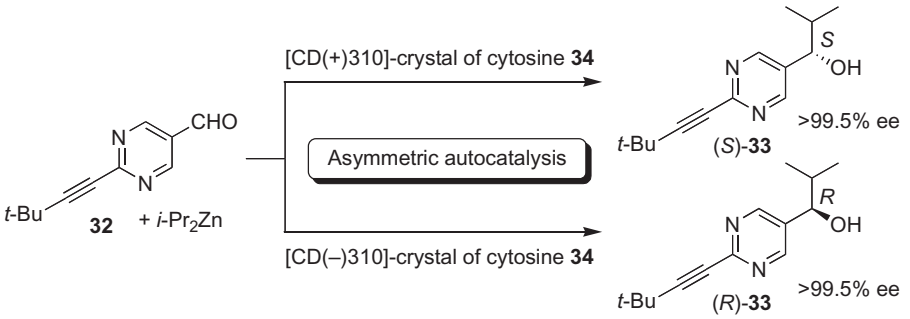


Figure 12.5. Proposed scenario for the evolution of chirality in nature using achiral cytosine as an origin of chirality.



Scheme 12.40. Highly enantioselective asymmetric autocatalysis using chiral crystal of cytosine.

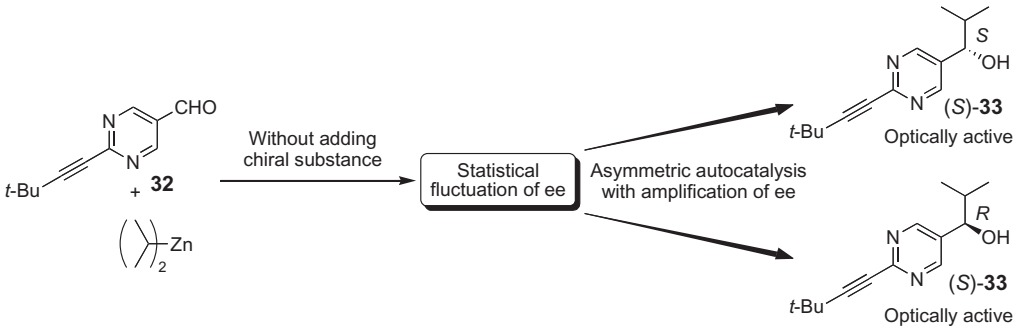
asymmetric autocatalysis indicate the possibility that cytosine is the origin of biological homochirality.

In addition, cocrystals of achiral tryptamine and *p*-chlorobenzoic acid, which belongs to a chiral space group ($P2_12_12_1$) and have both clockwise (*P*) and counterclockwise (*M*) helicities in its crystal state, can act as a chiral source of asymmetric autocatalysis to afford enantioenriched pyrimidyl alkanol whose absolute configuration was controlled by the chirality of the cocrystal [111]. The enantiomorphous crystals composed of achiral hippuric acid, that is, naturally occurring *N*-benzoylglycine, have been used successfully as chiral inducers in asymmetric autocatalysis [112].

12.4.5. Spontaneous Absolute Asymmetric Autocatalysis in Conjunction with Asymmetric Autocatalysis

Spontaneous absolute asymmetric synthesis, that is, the formation of enantioenriched compound without the intervention of any chiral factors, has been proposed as one of the origins of biological homochirality in nature [71,95]. It has been well accepted that, without the intervention of any chiral factor, the probability of the formation of *R* and *S* product is fifty-fifty (50:50); racemate is formed. However, according to the theory of statistics, the numbers of *R* and *S* enantiomers are not exactly the same, that is, there is almost always the fluctuation in numbers of enantiomers [95,113]. We thought that, when a reaction system involves asymmetric autocatalysis with amplification of ee, the initial small fluctuation of ee in racemic mixtures that arises from the reaction of achiral reactants can produce an enantiomerically enriched product. We anticipated that when *i*-Pr_2Zn was treated with pyrimidine-5-carbaldehydes *without* adding any chiral substance, extremely slight enantioenrichment would be induced statistically in the initially formed zinc alkoxide of the alkanol, and that the subsequent amplification of chirality by asymmetric autocatalysis would produce the pyrimidyl alkanol with detectable enantioenrichment (Scheme 12.41).

The reaction of pyrimidine-5-carbaldehyde **28** and 2-methylpyrimidine-5-carbaldehyde **30** with *i*-Pr_2Zn without adding a chiral substance produced enantioenriched (*S*)- or (*R*)-pyrimidyl alkanol **29** and 2-methylpyrimidyl alkanol **31**, respectively [114]. When 2-alkynylpyrimidine-5-carbaldehyde **32** reacted with *i*-Pr_2Zn in a mixed solvent of ether and toluene, the subsequent one-pot asymmetric autocatalysis with amplification of ee gave enantiomerically enriched pyrimidyl alkanol **33** whose ee was well above the detec-



Scheme 12.41. Spontaneous absolute asymmetric synthesis of pyrimidyl alkanol **33** without the addition of a chiral substance.

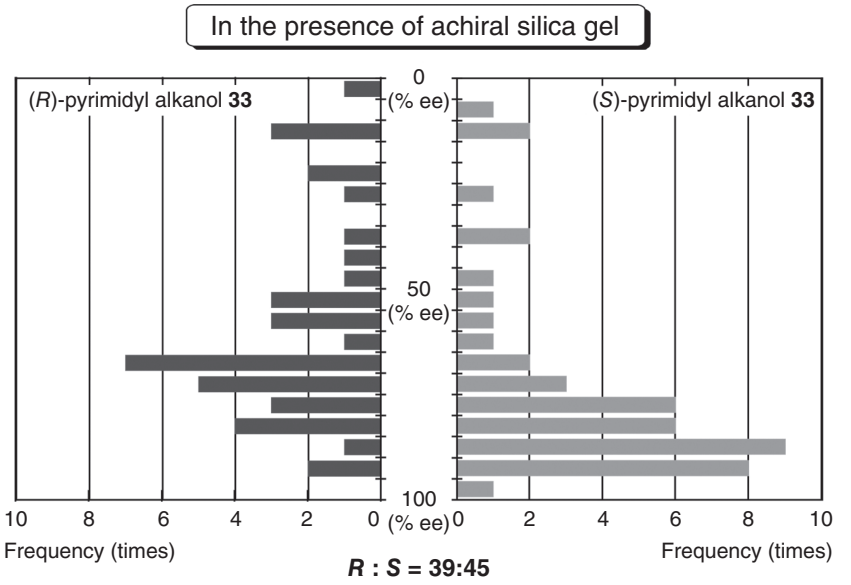


Figure 12.6. Histogram of the absolute configuration and the enantiomeric excess of pyrimidyl alkanol **33** formed by spontaneous absolute asymmetric synthesis in the presence of achiral silica gel.

tion level [115]. The absolute configurations of the pyrimidyl alkanol **33** exhibit an approximate stochastic distribution of *S* and *R* enantiomers (formation of *S* 19 times and *R* 18 times).

In addition, we performed the asymmetric autocatalysis in the presence of an achiral silica gel in toluene under achiral conditions; the enantioenriched pyrimidyl alkanol **33** is generated from the reaction between 2-alkynylpyrimidine-5-carbaldehyde **32** and *i*-Pr_2Zn in conjunction with the subsequent asymmetric autocatalysis (Fig. 12.6) [116]. The

reaction of pyrimidine-5-carbaldehyde **32** with *i*-Pr_2Zn in the presence of achiral silica gel in toluene, followed by a one-pot asymmetric autocatalysis with amplification of ee gave the enantioenriched (*S*)- and (*R*)-5-pyrimidyl alkanol **33** with ee above the detection level. In order to examine the distribution of the absolute configuration of the predominantly formed enantiomers in each experiment, 84 experiments were run under the same reaction conditions. In all cases, enantioenriched 5-pyrimidyl alkanols with either *S* or *R* configurations were formed. The absolute configurations of the resulting **33** exhibited an approximate stochastic distribution, that is, the formation of the *S* form occurred 45 times and the formation of the *R* form occurred 39 times (Fig. 12.6).

We have demonstrated the stochastic formation of (*S*)- and (*R*)-5-pyrimidyl alkanol **33** from pyrimidine-5-carbaldehyde **32** and *i*-Pr_2Zn without the intervention of a chiral auxiliary. Even in the reactions performed in toluene alone, stochastic behavior of the formation of (*S*)- and (*R*)-**33** was observed in the presence of achiral silica gel. We believe that the approximate stochastic behavior in the formation of alkanols fulfills one of the conditions necessary for chiral symmetry breaking by spontaneous absolute asymmetric synthesis.

12.5. CHIRAL DISCRIMINATION BY ASYMMETRIC AUTOCATALYSIS WITH AMPLIFICATION OF EE

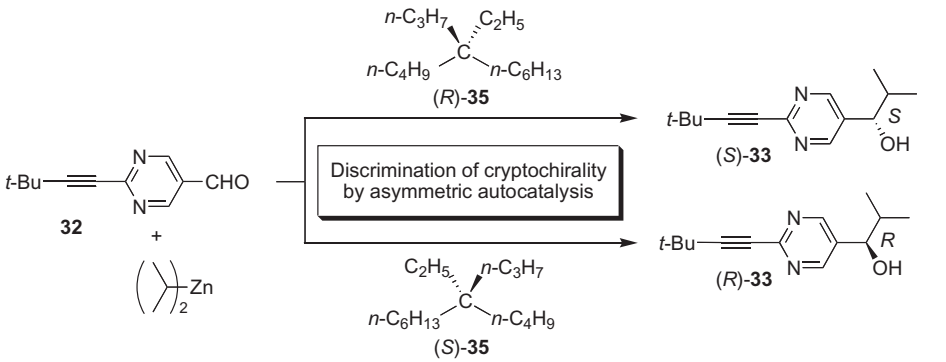
12.5.1. Introduction

Chirality plays a major role in many aspects of modern science. The fundamental prerequisite of a study on chirality is the availability of a method to discriminate between enantiomeric forms. Significant progress in chiral discrimination has been achieved in recent decades; however, there remains a class of compounds whose chiral discrimination has been very difficult to establish, or has not been possible at all. The compound is a chiral, but to all intents an optically inactive compound. Mislow called such hidden chirality "cryptochirality" [95,117]. Herein, we demonstrate that the asymmetric autocatalysis has enormous power to recognize the hidden cryptochirality.

12.5.2. Discrimination of Cryptochirality in a Saturated Quaternary Hydrocarbon by Asymmetric Autocatalysis

Chiral saturated hydrocarbons form a class of compounds whose chiral discrimination has often been very difficult [118]. Unlike other functionalized compounds, chiral saturated hydrocarbons do not bear heteroatoms, π-electrons, or chromophores; therefore, the difference between the four substituents on the asymmetric carbon atom is very small. An example of a compound whose chiral discrimination poses the utmost difficulty is a saturated quaternary hydrocarbon bearing similar substituents on the asymmetric carbon atom, with a representative example being 5-ethyl-5-propylundecane, that is, (*n*-butyl)ethyl(*n*-hexyl)(*n*-propyl)methane **35** [119]. The enantiomer of this hydrocarbon exhibits the optical rotation ($|\alpha| < 0.001$) below the detection level between 280 and 580 nm.

We found that the chirality of the saturated quaternary hydrocarbon was successfully discriminated using asymmetric autocatalysis [120]. The asymmetric autocatalysis initiated by the chiral (*R*)-quaternary hydrocarbon using pyrimidine-5-carbaldehyde **32** and *i*-Pr_2Zn produced (*S*)-pyrimidyl alkanol **33** with 97% ee and 93% yield. In contrast,



Scheme 12.42. Chiral discrimination of cryptochiral quaternary hydrocarbon.

asymmetric autocatalysis in the presence of the (*S*)-quaternary hydrocarbon **35** produced (*R*)-alkanol **33** with 94% ee in 91% yield (Scheme 12.42). These stereochemical correlations were found to be reproducible. The present chiral discrimination may involve the CH–π interactions between the CH group of the chiral hydrocarbon and the π-electrons of the pyrimidine-5-carbaldehyde **32**.

In addition, various chiral hydrocarbons with such as saturated tertiary hydrocarbons [120], 1,1′-binaphthyls [121], helicenes [122], olefins [123], allenes [124], and [2.2]paracyclophanes [125] also serve as chiral initiators in this asymmetric autocatalysis.

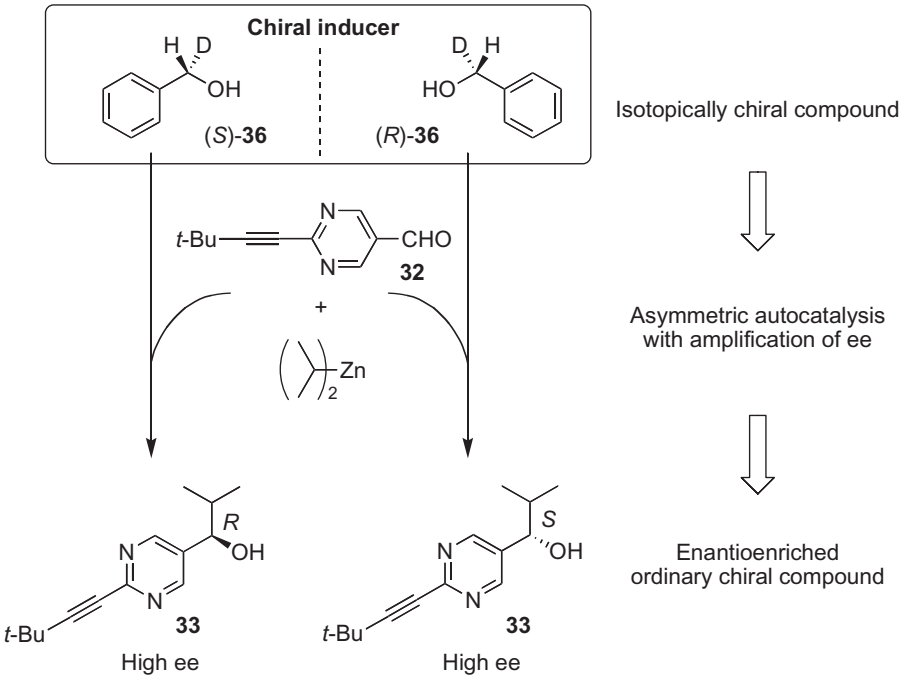
12.5.3. Recognition of Chirality Generated by the Isotope Substitution

Isotopically chiral compounds form unique category of chiral compounds, which are not superimposable with its mirror image due to the substitution of isotopes. The chirality of hydrogen isotope enantiomers is mainly due to the very small difference between the lengths of carbon–deuterium and carbon–hydrogen bonds [126]. Thus, unlike other enantiomers whose chirality results from the difference in the number of protons in the atomic nucleus, these isotopic enantiomers are considered to show only very small differences in asymmetric reactions and recognition [127].

We investigated highly enantioselective asymmetric autocatalysis of a chiral compound induced by the isotopic enantiomer of a primary alcohol-α-*d* (Scheme 12.43) [128]. The correlation between the absolute configurations of the obtained pyrimidyl alkanol and the isotopic chiral compound is reproducible; thus, the small isotope chirality can be recognized by asymmetric autocatalysis.

When aldehyde **32** was reacted with *i*-Pr_2Zn in the presence of chiral (*S*)-benzyl alcohol-α-*d* **36**, (*R*)-alkanol **33** with 96% ee was obtained with a yield of 95%. On the other hand, in the presence of (*R*)-deuterated alcohol (>95% ee), (*S*)-**33** with 95% ee was obtained in 98% yield. Thus, (*S*)- and (*R*)-benzyl alcohol-α-*d* **36** acted as chiral inducers to give (*R*)- and (*S*)-pyrimidyl alkanols **33** with high ee after consecutive asymmetric autocatalysis, respectively.

Furthermore, chiral tolyl methanol-α-*d*, 2,2-naphthyl methanol-α-d and 3-phenylpropanol-α-*d* acted as a chiral initiator in the enantioselective addition of *i*-Pr_2Zn to aldehyde **32**, and pyrimidyl alkanol (*R*)-**33** with high ee was synthesized,



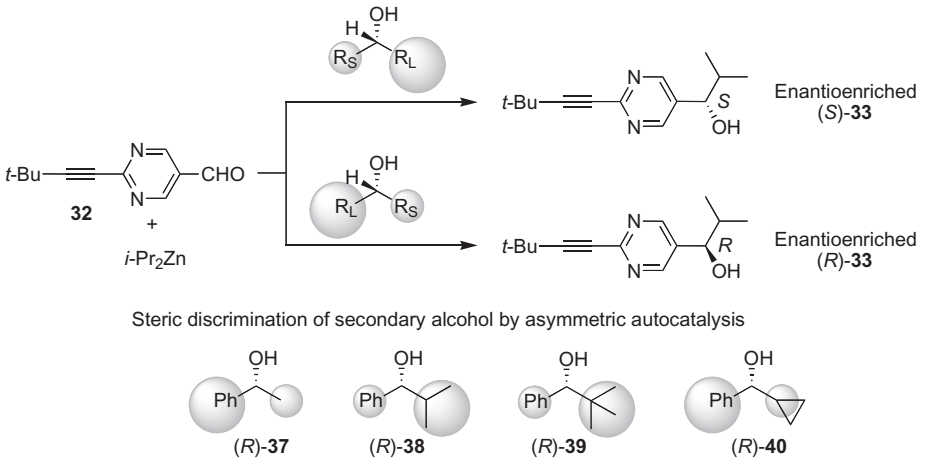
Scheme 12.43. Enantioselective addition of *i*-Pr_2Zn to aldehyde **32** using chiral α-deuterated alcohols as chiral inducers.

respectively [128]. Thus asymmetric autocatalysis is an efficient method to discriminate hydrogen isotope chirality.

12.5.4. Steric Discrimination of Chiral Secondary Alcohol by Asymmetric Autocatalysis

When the isopropylation of pyrimidine-5-carbaldehyde **32** was examined in the presence of (*S*)-2-butanol with ca. 0.1% ee, (*S*)-pyrimidyl alkanol **33** with 83% ee was obtained [79]. (*R*)-2-butanol induced the formation of opposite (*R*)-enantiomer. In the present enantioselective reaction, the steric influence of the substituents ($R_L > R_S$) of a chiral secondary alcohol is discriminated by the asymmetric autocatalysis. Thus, the bulkiness of various substituents in the secondary alcohols was determined in comparison with the phenyl group, based on the correlation of the absolute configurations of *sec*-alcohol as the chiral initiator and the obtained pyrimidyl alkanol **33**.

Chiral secondary alcohols, that is, alkyl-substituted benzyl alcohols with ca. 10% ee were submitted to the asymmetric autocatalysis as the chiral initiator (Scheme 12.44) [129]. When the alkylation was examined in the presence of (*S*)-methyl phenyl carbinol **37**, (*S*)-pyrimidyl alkanol **33** was obtained in high ee and yield and vice versa. The correlation ((*S*)-secondary alcohol induces (*S*)-**33**) is the same as 2-butanol. On the contrary, in the case of isopropyl phenyl carbinol **38**, the correlation was opposite: (*S*)-secondary



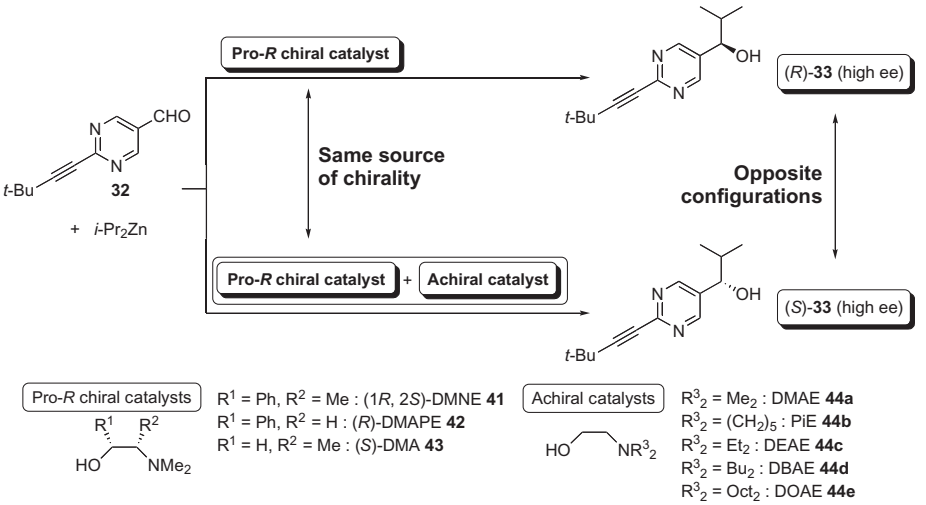
Scheme 12.44. The concept of steric discrimination in the enantioselective alkylation of **32** using chiral secondary alcohols as chiral initiators.

alcohol **38** induces (*R*)-**33**. When the isopropyl group was replaced by a more bulky *tert*-butyl group, that is, *tert*-butyl phenyl carbinol **39** was subjected to the asymmetric autocatalysis, the correlation was the same as the result of **38**. On the other hand, when alcohol **40** with the cyclopropyl group instead of isopropyl substitution was used, the correlation was opposite, which means that the correlation was the same as the case of methyl phenyl carbinol **37**, that is, the cyclopropyl group was recognized as the smaller substituent than the phenyl group. We also investigated the unsaturated group-substituted benzyl alcohols such as phenyl isopropenyl carbinol, phenyl vinyl carbinol, and β-branched alkyl-substituted benzyl alcohols as chiral initiator of asymmetric autocatalysis.

12.5.5. Reversal Phenomena of Enantioselectivity in Asymmetric Autocatalysis Initiated by Mixed Catalytic System of Chiral and Achiral β-Amino Alcohols

The use of achiral additives in asymmetric organometallic catalysis was shown to be a promising approach for the optimization of the enantioselectivity of chiral catalysts [130]. However, the achiral additives sometimes reverse the enantioselectivity of a chiral catalyst.

We discovered an unexpected reversal of the enantiofacial selectivity of chiral β-amino alcohol catalysts by a smaller amount of achiral β-amino alcohol catalysts in dialkylzinc addition to aldehyde (Scheme 12.45) [131]. The addition of *i*-Pr_2Zn to aldehyde **32** using a catalytic amount of chiral (1*R*,2*S*)- or (1*S*,2*R*)-*N*,*N*-dimethylnorephedrine (DMNE **41**, >99.5% ee) alone afforded (*R*)- or (*S*)-alkanol **33** with high ee, respectively. On the other hand, when the same reaction was catalyzed by a mixture of chiral (1*R*,2*S*)-DMNE **41** (0.5 mol %) and achiral *N*,*N*-dibutylaminoethanol (DBAE **44d**, 19.5 mol %), alkanol **33** was obtained with the opposite *S* configuration to that of expected from chiral catalyst. And the subsequent asymmetric autocatalysis with significant asymmetric amplification affords a highly enantiomerically enriched product. The reversal of the sense of enantioselectivity was also observed by using the chiral catalyst



Scheme 12.45.

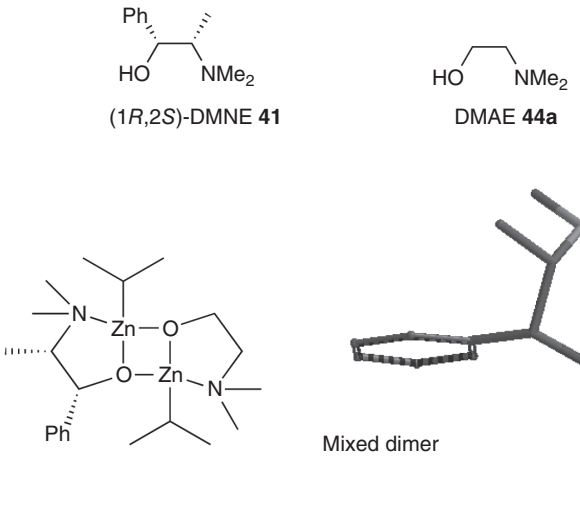


Figure 12.7. Calculated structure of mixed dimer resulting from the aggregation of isopropylzinc alkoxides of (1*R*,2*S*)-DMNE **41** and DMAE **44a**.

with (1*S*,2*R*)-DMNE, and achiral DBAE, (*R*)-**33** being obtained. Thus, the enantiofacial selectivity of the chiral catalyst was reversed by the achiral catalyst **44d**.

Kinetic studies of this reaction with various loadings of catalyst and *ab initio* molecular orbital calculations indicate that the reversal of the sense of enantioselectivity is due to the preferential formation of a catalytically active chiral heterodinuclear aggregate derived from zinc alkoxides of chiral and achiral ligands (Fig. 12.7) [132]. In these reac-

tions, the chiral catalyst and achiral ligand possesses the same functionalities and similar catalytic activities in the addition of dialkylzinc. Thus, these observation may bring some new insights to the mechanism of the β-amino alcohol catalyzed addition of dialkylzincs to aldehydes, because only monomeric species have been proposed to be catalytically active in the dialkylzinc addition to aldehydes catalyzed by β-amino alcohols [133,134].

12.6. SUMMARY

As described, there have been examples of positive NLE in catalytic asymmetric synthesis. NLE is very important not only for obtaining chiral products with higher ees using chiral catalysts with lower ees but also for elucidating the structure and mechanism of asymmetric catalysis.

As to asymmetric autocatalysis, we found that chiral 5-pyrimidyl alkanol, 3-quinolyl alkanol and 5-carbamoyl-3-pyridyl alkanol are highly enantioselective asymmetric autocatalysts for the addition of *i*-Pr_2Zn to the corresponding aldehydes, respectively. Among these, 2-alkynyl-5-pyrimidyl alkanol is a highly efficient asymmetric autocatalyst with more than 99.5% enantioselectivity. Moreover, asymmetric autocatalysis with amplification of ee from extremely low ee to more than 99.5% ee was realized for the first time by consecutive asymmetric autocatalysis without the need for any other chiral auxiliary. Kinetic analysis of pyrimidyl alkanol suggested that the reaction is second order in the zinc monoalkoxide of the pyrimidyl alkanol.

Chiral organic compounds with low ee, when exposed to CPL serve as chiral triggers for asymmetric autocatalysis. The overall process correlates, for the first time, the chirality of CPL with an organic compound with very high ee. Chirality of the CPL was directly correlated with the chirality of the pyrimidyl alkanol with high ee by asymmetric photodegradation of racemic pyrimidyl alkanol in combination with asymmetric autocatalysis. Chiral inorganic crystals, such as quartz and sodium chlorate, act as chiral triggers and regulate the sense of the asymmetric autocatalysis. The process correlates, for the first time, the chirality of inorganic crystals with an organic compound with very high ee.

Chiral organic crystals composed of achiral compounds such as cytosine act as the initial source of chirality of asymmetric autocatalysis to produce the highly enantiomerically pure product. In this reaction, chiral organic crystals are utilized as a chiral inducer, not as a reactant. Therefore, these results are the realization of the process, in which the crystal chirality of achiral organic compounds induces asymmetry in another organic compound and its chirality was amplified to produce a large amount of an enantiomerically pure organic compound, pyrimidyl alkanol, in conjunction with asymmetric autocatalysis.

Spontaneous absolute asymmetric synthesis was described in the formation of enantiomerically enriched pyrimidyl alkanol from the reaction of pyrimidine-5-carbaldehyde and *i*-Pr_2Zn without adding a chiral substance in combination with asymmetric autocatalysis. The approximate stochastic distribution of the absolute configurations of pyrimidyl alkanols strongly suggests that the reaction is a spontaneous absolute asymmetric synthesis.

It was shown that the asymmetric autocatalysis of chiral pyrimidyl alkanol is the only possible method to discriminate cryptochiral quaternary saturated hydrocarbons, whose chirality is not capable of determination by any conventional methods. The discrimination of chirality due to deuterium substitution is also accessible by the highly sensitive

asymmetric autocatalysis. It is possible to discriminate the bulkiness of various substituents in the secondary alcohols by the comparison of the absolute configurations of *sec*-alcohol used as chiral initiator and the obtained pyrimidyl alkanol. In addition, we observed an unexpected reversal of the enantiofacial selectivity of chiral β-amino alcohol catalysts by a smaller amount of achiral β-amino alcohol catalysts in the asymmetric autocatalysis.

As described, asymmetric autocatalysis is closely related to the origin of the homochirality of organic compounds.

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REFERENCES

1. Reviews: (a) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901. (b) Brown, J. M.; Davies, S. G. *Nature* **1989**, *342*, 631. (c) Kagan, H. B.; Girard, C.; Guillaneux, D.; Rainford, D.; Samuel, O.; Zhang, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *50*, 345. (d) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron Asymmetry* **1997**, *8*, 2997. (e) Soai, K. (Ed.). *Amplification of Chirality*. Berlin Heidelberg: Springer-Verlag, 2008; Vol. 284.
2. Reviews and accounts by our group: (a) Soai, K.; Shibata, T. In *Advances in Biochirality* (Eds. Pályi, G.; Zucchi, C.; Caglioti, L.). Oxford: Elsevier, 1999; Chapter 11, p. 125. (b) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382. (c) Soai, K. *Enantiomer* **1999**, *4*, 591. (d) Soai, K.; Shibata, T. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55*, 994. (e) Soai, K.; Shibata, T. In *Catalytic Asymmetric Synthesis*, 2nd Ed. (Ed. Ojima, I.). New York: Wiley-VCH, 2000; Chapter 9, p. 699. (f) Soai, K.; Shibata, T.; Sato, I. *Nippon Kagaku Kaishi* **2001**, 141. (g) Soai, K.; Sato, I.; Shibata, T. *Chem. Rec.* **2001**, *1*, 321. (h) Soai, K.; Sato, I. *Chirality* **2002**, *14*, 548. (i) Soai, K. In *Fundamentals of Life* (Eds. Pályi, G.; Zucchi, C.; Caglioti, L.). Paris: Elsevier, 2002; p. 427. (j) Soai, K.; Sato, I.; Shibata, T. *Yuki Gosei Kagaku Kyokaishi* **2002**, *60*, 668. (k) Soai, K.; Sato, I. *Viva Orig.* **2002**, *30*, 186. (l) Soai, K.; Sato, I.; Shibata, T. In *Methodologies in Asymmetric Catalysis* (Ed. Malhotra, S. V.). Washington, DC: American Chemical Society, 2004; p. 85. (m) Soai, K. *Yuki Gosei Kagaku Kyokaishi* **2004**, *62*, 673. (n) Soai, K.; Shibata, T.; Sato, I. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1063. (o) Soai, K.; Kawasaki, T. *Chirality* **2006**, *18*, 469. (p) Soai, K.; Kawasaki, T. *Shokubai (Catalysts & Catalysis)* **2006**, *48*, 346. (q) Soai, K.; Kawasaki, T. *Top. Curr. Chem.* **2008**, *284*, 1. (r) Soai, K.; Kawasaki, T. In *Asymmetric Synthesis—The Essentials* (Eds. Christmann, M.; Bräse, S.). Weinheim: Wiley-VCH, 2007; p. 212. (s) Soai, K.; Kawasaki, T. In *New Frontiers in Asymmetric Catalysis* (Eds. Mikami, K.; Lautens, M.). Hoboken, NJ: Wiley-Interscience, 2007; Chapter 9, p. 259. (t) Soai, K.; Kawasaki, T. *Fine Chem.* **2008**, *37*, 5. (u) Soai, K.; Kawasaki, T. In *Recent Developments in Physical Chemistry* (Eds. Diaz-Herrera, E.; Juaristi, E.). Melville, NY: American Institute of Physics, 2008; p. 68.
3. Reviews by other groups: (a) Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1657. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Commun.* **2000**, 887. (c) Buschmann, H.; Thede, R.; Heller, D. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 4033. (d) Todd, M. H. *Chem. Soc. Rev.* **2002**, *31*, 211. (e) Podlech, J.; Gehring, T. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 5776. (f) Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369. (g) Caglioti, L.; Zucchi, C.; Pályi, G. *Chimica Oggi* **2005**, *23*, 38. (h) Stankiewicz, J.; Eckardt, L. H. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 342.
4. Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.

5. Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.
6. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
7. Reviews, see: (a) Soai, K.; Sato, I.; Kawasaki, T. In *The Chemistry of Organozinc Compounds* (Eds. Rappoprt, Z.; Marek, I.). Chichester, UK: John Wiley & Sons, 2006; Chapter 12, p. 555. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis* (Eds. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.). New York: Springer, 1999; Chapter 26.1, pp. 911–923. (d) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49. (e) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
8. (a) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.
9. Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R.; Zhai, Z.; Suga, H. *J. Phys. Chem.* **1994**, *98*, 12776.
10. Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327.
11. Ojima, I. (Ed.). *Catalytic Asymmetric Synthesis*, 2nd Ed. New York: Wiley-VCH, 2000.
12. Legrand, O.; Brunel, J.-M.; Buono, G. *Tetrahedron Lett.* **2000**, *41*, 2105.
13. Sarvary, I.; Wan, Y.; Frejd, T. *J. Chem. Soc. Perkin Trans. 1* **2002**, 645.
14. Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc. Chem. Commun.* **1989**, 516.
15. Bolm, C. *Tetrahedron Asymmetry* **1991**, *2*, 701.
16. deVries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479.
17. Hu, Y.; Liang, X.; Zheng, Z.; Hu, X. *Tetrahedron Asymmetry* **2003**, *14*, 2771.
18. Qin, Y.-C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381.
19. Zhou, X.; Liu, X.; Yang, X.; Shang, D.; Xin, J.; Feng, X. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 392.
20. Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 8333.
21. Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.
22. (a) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (b) Mai, E.; Schneider, C. *Chem. Eur. J.* **2007**, *13*, 2729.
23. Villano, R.; De Rosa, M.; Salerno, C.; Soriente, A.; Scettri, A. *Tetrahedron Asymmetry* **2002**, *13*, 1949.
24. (a) Hanawa, H.; Hashimoto, T.; Maruoka K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (b) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem. Eur. J.* **2003**, *9*, 4405.
25. Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.
26. Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 6145.
27. Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49.
28. (a) Yuan, Y.; Long, J.; Sun, J.; Ding, K. *Chem. Eur. J.* **2002**, *8*, 5033. (b) Yuan, Y.; Li, X.; Sun, J.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 14866.
29. Ji, B.; Yuan, Y.; Ding, K.; Meng, J. *Chem. Eur. J.* **2003**, *9*, 5989.
30. Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465.
31. Shang, D.; Xin, J.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. *J. Org. Chem.* **2008**, *73*, 630.
32. Endeshaw, M. M.; Bayer, A.; Hansen, L. K.; Gautun, O. R. *Eur. J. Org. Chem.* **2006**, 5249.
33. Nakano, K.; Hiyama, T.; Nozaki, K. *Chem. Commun.* **2005**, 1871.
34. Mai, E.; Schneider, C. *Chem. Eur. J.* **2007**, *13*, 2729.
35. Hayashi, Y.; Matsuzawa, M.; Yamaguchi, J.; Yonehara, S.; Matsumoto, Y.; Shoji, M.; Hashizume, D.; Koshino, H. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 4593.
36. Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H., Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.
37. Satyanarayana, T.; Ferber, B.; Kagan, H. B. *Org. Lett.* **2007**, *9*, 251.

38. Belokon, Y. N.; Bespalova, N. B.; Churkina, T. D.; Cisarova, I.; Ezernitskaya, M. G; Harutyunyan, S. R.; Hrdina, R.; Kagan, H. B.; Kocovsky, P.; Kochetkov, K. A; Larionov, O. V; Lyssenko, K. A; North, M.; Polasek, M.; Peregudov, A. S; Prisyazhnyuk, V. V; Vyskocil, S. *J. Am. Chem. Soc.* **2003**, *125*, 12860.
39. Oestreich, M.; Rendler, S. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 1661.
40. Frank, F. C. *Biochim. Biophys. Acta* 1953, *11*, 459.
41. (a) Calvin, M. *Chemical Evolution*. London: Clarendon Press, 1969. (b) Wynberg, H. *J. Macromol. Sci. Chem. A* **1989**, *26*, 1033.
42. Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.
43. Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265.
44. For other asymmetric autoinductive reactions: (a) Soai, K.; Inoue, Y.; Takahashi, T.; Shibata, T. *Tetrahedron* **1996**, *52*, 13355. (b) Shibata, T.; Takahashi, T.; Konishi, T.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2458.
45. Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740.
46. Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc. Chem. Commun.* **1987**, 1690.
47. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.
48. Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908.
49. Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc. Chem. Commun.* **1987**, 467.
50. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
51. Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc. Chem. Commun.* **1990**, 982.
52. Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *Chem. Commun.* **1996**, 751.
53. Shibata, T.; Morioka, H.; Tanji, S.; Hayase, T.; Kodaka, Y.; Soai, K. *Tetrahedron Lett.* **1996**, *37*, 8783.
54. Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471.
55. Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767.
56. Shibata, T.; Hayase, T.; Yamamoto, J.; Soai, K. *Tetrahedron Asymmetry* **1997**, *8*, 1717.
57. Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 659.
58. Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 315.
59. Mauksch, M.; Tsogoeva, S. B.; Martynova, I. M.; Wei, S. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 393.
60. Mauksch, M.; Tsogoeva, S. B.; Wei, S.; Martynova, I. M. *Chirality* **2007**, *19*, 816.
61. Amedjkouh, M.; Brandberg, M. *Chem. Commun.* **2008**, 3043.
62. Sato, I.; Omiya, D.; Tsukiyama, K.; Ogi, Y.; Soai, K. *Tetrahedron Asymmetry* **2001**, *12*, 1965.
63. Sato, I.; Omiya, D.; Igarashi, H.; Kato, K.; Ogi, Y.; Tsukiyama, K.; Soai, K. *Tetrahedron Asymmetry* **2003**, *14*, 975.
64. Blackmond, D. G.; McMillan, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 10103.
65. Blackmond, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5732.
66. Gridnev, I. D.; Serafimov, J. M.; Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4884.
67. Gridnev, I. D.; Serafimov, J. M.; Quiney, H.; Brown, J. M. *Org. Biomol. Chem.* **2003**, *1*, 3811.
68. Klankermayer, J.; Gridnev, I. D.; Brown, J. M. *Chem. Commun.* **2007**, 3151.
69. Gridnev, I. D. *Chem. Lett.* **2006**, *35*, 148.
70. Brown, J. C.; Gridnev, I.; Klankermayer, J. *Top. Curr. Chem.* **2008**, *284*, 35.
71. Islas, J. S.; Lavabre, D.; Grevy, J. M.; Lamoneda, R. H.; Cabrera, H. R.; Micheau, J. C.; Buhse, T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 13743.
72. (a) Buhse, T. *Tetrahedron Asymmetry* **2003**, *14*, 1055. (b) Buhse, T. *J. Mex. Chem. Soc.* **2005**, *49*, 328.
73. Lavabre, D.; Micheau, J.-C.; Islas, J. R.; Buhse, T. *Top. Curr. Chem.* **2008**, *284*, 67.
74. Micskei, K.; Pota, G.; Caglioti, L.; Pályi, G. *J. Phys. Chem. A* **2006**, *110*, 5982.
75. Micskei, K.; Rábai, G.; Gál, E.; Caglioti, L.; Pályi, G. *J. Phys. Chem. B* **2008**, *112*, 9196.

76. Lente, G. *J. Phys Chem. A* **2005**, *109*, 11058.
77. Saito, Y.; Hyuga, H. *J. Phys. Soc. Jpn.* **2004**, *73*, 33.
78. Saito, Y.; Hyuga, H. *Top. Curr. Chem.* **2008**, *284*, 97.
79. Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K. *J. Am. Chem. Soc.* **1998**, *120*, 12157.
80. Kawasaki, T.; Shimizu, M.; Suzuki, K.; Sato, I.; Soai, K. *Tetrahedron Asymmetry* **2004**, *15*, 3699.
81. Kawasaki, T.; Suzuki, K.; Licandro, E.; Bossi, A.; Maiorana, S.; Soai, K. *Tetrahedron Asymmetry* **2006**, *17*, 2050.
82. Maddox, J. *What Remains to be Discovered: Mapping the Secrets of the Universe, the Origins of Life, and the Future of the Human Race*. New York: Free Press, 1998.
83. Kuhn, W.; Knopf, E. Z. *Phys. Chem. B* **1930**, *7*, 292.
84. Inoue, Y. *Chem. Rev.* **1992**, *92*, 741.
85. Bonner, W. A.; Rubenstein, E. *Biosystems* **1987**, *20*, 99.
86. Feringa, B. L.; van Delden, R. A. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3418.
87. Hazen, R. M. In *Progress in Biological Chirality* (Eds. Palyi, G.; Zucchi, C.). Oxford: Elsevier, 2004; Chapter 9, p. 137.
88. Hazen, R. M.; Sholl, D. S. *Nat. Mater.* **2003**, *2*, 367.
89. Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1972**, *12*, 191.
90. Matsuura, T.; Koshima, H. *J. Photochem. Photobiol. C Photochem. Rev.* **2005**, *6*, 7.
91. Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
92. Sakamoto, M. *Chem. Eur. J.* **1997**, *3*, 684.
93. Hasegawa, M. *Chem. Rev.* **1983**, *83*, 507.
94. Claborn, K.; Isborn, C.; Kaminsky, W.; Kahr, B. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 5706.
95. Mislow, K. *Collect. Czech. Chem. Commun.* **2003**, *68*, 849.
96. Mason, S. F.; Tranter, G. E. *Mol. Phys.* **1984**, *53*, 1091.
97. (a) Lente, G. *Phys. Chem. Chem. Phys.* **2007**, *9*, 6134. (b) Davankov, V. A. *Chirality* **2006**, *18*, 459.
98. Bailey, J.; Chrysostomou, A.; Hough, J. H.; Gledhill, T. M.; McCall, A.; Clark, S.; Menard, F.; Tamura, M. *Science* **1998**, *281*, 672.
99. Nishino, H.; Kosaka, A.; Hembury, G. A.; Aoki, F.; Miyauchi, K.; Shitomi, H.; Onuki, H.; Inoue, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11618.
100. Kagan, H.; Moradpour, A.; Nicoud, J. F.; Balavoine, G.; Tsoucaris, G. *J. Am. Chem. Soc.* **1971**, *93*, 2353.
101. Suarez, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1995**, *117*, 6732.
102. Soai, K.; Sato, I. *Enantiomer* **2001**, *6*, 189.
103. Sato, I.; Ohgo, Y.; Igarashi, H.; Nishiyama, D.; Kawasaki, T.; Soai, K. *J. Organomet. Chem.* **2007**, *692*, 1783.
104. Bernstein, W. J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* **1972**, *94*, 494.
105. Kawasaki, T.; Sato, M.; Ishiguro, S.; Saito, T.; Morishita, Y.; Sato, I.; Nishino, H.; Inoue, Y.; Soai, K. *J. Am. Chem. Soc.* **2005**, *127*, 3274.
106. Bonner, W. A.; Kavasmaneck, P. R.; Martin, F. S.; Flores, J. J. *Science* **1974**, *186*, 143.
107. Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. *J. Am. Chem. Soc.* **1999**, *121*, 11235.
108. (a) Sato, I.; Kadowaki, K.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1510. (b) Sato, I.; Kadowaki, K.; Ohgo, Y.; Soai, K. *J. Mol. Catal. A Chem.* **2004**, *216*, 209.
109. Robertson, M. P.; Miller, L. *Nature* **1995**, *375*, 772.
110. Kawasaki, T.; Suzuki, K.; Hakoda, Y.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 496.
111. Kawasaki, T.; Jo, K.; Igarashi, H.; Sato, I.; Nagano, M.; Koshima, H.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 2774.

112. Kawasaki, T.; Suzuki, K.; Hatase, K.; Otsuka, M.; Koshima, H.; Soai, K. *Chem. Commun.* **2006**, 1869.
113. Mills, W. H. *Chem. Ind.* **1932**, *51*, 750.
114. Soai, K.; Shibata, T.; Kowata, Y. Japan Kokai Tokkyo Koho (Patent), 9268179, **1997**.
115. Soai, K.; Sato, I.; Shibata, T.; Komiya, S.; Hayashi, M.; Matsueda, Y.; Imamura, H.; Hayase, T.; Morioka, H.; Tabira, H.; Yamamoto, J.; Kowata, Y. *Tetrahedron Asymmetry* **2003**, *14*, 185.
116. Kawasaki, T.; Suzuki, K.; Shimizu, M.; Ishikawa, K.; Soai, K. *Chirality* **2006**, *18*, 479.
117. Mislow, K.; Bickart, P. *Isr. J. Chem.* **1976–1977**, *15*, 1.
118. Eliel, E. L.; Wilen, S. W. In *Stereochemistry of Organic Compounds* (Ed. Eliel, E. L.; Wilen, S. W.). New York: Wiley, 1994; Chapter 4, pp. 71–99.
119. Wynberg, H.; Hekkert, G. L.; Houbiers, J. P. M.; Bosch, H. W. *J. Am. Chem. Soc.* **1965**, *87*, 2635.
120. Kawasaki, T.; Tanaka, H.; Tsutsumi, T.; Kasahara, T.; Sato, I.; Soai, K. *J. Am. Chem. Soc.* **2006**, *128*, 6032.
121. Sato, I.; Osanai, S.; Kadowaki, K.; Sugiyama, T.; Shibata, T.; Soai, K. *Chem. Lett.* **2002**, 168.
122. Sato, I.; Yamashima, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1096.
123. Sato, I.; Sugie, R.; Matsueda, Y.; Furumura, Y.; Soai, K. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4490.
124. Sato, I.; Matsueda, Y.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Soai, K. *Helv. Chim. Acta* **2002**, *85*, 3383.
125. (a) Sato, I.; Ahno, A.; Aoyama, Y.; Kasahara, T.; Soai, K. *Org. Biomol. Chem.* **2003**, *1*, 244. (b) Tanji, S.; Ohno, A.; Sato, I.; Soai, K. *Org. Lett.* **2001**, *3*, 287.
126. Bartell, L. S.; Roth, E. A.; Hollowell, C. D.; Kuchitsu, K.; Young, J. E., Jr. *J. Chem. Phys.* **1965**, *42*, 2683.
127. Barabas, B.; Caglioti, L.; Micskei, K.; Zucchi, C.; Pályi, G. *Orig. Life Evol. Biosph.* **2008**, *38*, 317.
128. Sato, I.; Omiya, D.; Saito, T.; Soai, K. *J. Am. Chem. Soc.* **2000**, *122*, 11739.
129. Shibata, T.; Iwahashi, K.; Kawasaki, T.; Soai, K. *Tetrahedron Asymmetry* **2007**, *18*, 1759.
130. Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1570.
131. Lutz, F.; Igarashi, T.; Kawasaki, T.; Soai, K. *J. Am. Chem. Soc.* **2005**, *127*, 12206.
132. Lutz, F.; Igarashi, T.; Kinoshita, T.; Asahina, M.; Tsukiyama, K.; Kawasaki, T.; Soai, K. *J. Am. Chem. Soc.* **2008**, *130*, 2956.
133. Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832.
134. (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464.