*Award Accounts*

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# Asymmetric Induction Arising from Enantiomerically Enriched Carbon-13 Isotopomers and Highly Sensitive Chiral Discrimination by Asymmetric Autocatalysis

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Carbon-isotope chirality generated only by the substitution of carbon-13/carbon-12 can be amplified to enantioenriched 5-pyrimidyl alkanol by asymmetric autocatalysis, in which an extremely low enantiomeric excess (ca. 0.00005% ee) can automultiply during three consecutive reactions to >99.5% ee. Chiral carbon-isotopomers can act as a chiral trigger in the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc to induce a small enantioselectivity in the resulting asymmetric autocatalyst, whose enantiomeric excess can be enhanced significantly by the subsequent asymmetric autocatalysis. Asymmetric autocatalysis has the enormous power to recognize the isotope chirality arising from the small difference between carbon ($^{13}C/^{12}C$) and hydrogen (D/H) isotopes. The tiny chiral influence in the hydrogen isotopically chiral amino acids such as glycine can be recognized and amplified by asymmetric autocatalysis. Furthermore, asymmetric autocatalysis can be applied to the highly sensitive chiral discrimination of cryptochiral compounds such as saturated quaternary hydrocarbon and isotactic polystyrene. Circularly polarized light, which is considered a possible candidate for the origin of chirality, acts as the chiral initiator in asymmetric autocatalysis, affording highly enantioenriched products with the absolute configuration correlated to the helicity of CPL. In addition, chiral crystals formed from achiral organic compounds can act as chiral initiators of asymmetric autocatalytic amplification of ee to afford enantioenriched (*S*)- and (*R*)-5-pyrimidyl alkanols corresponding to the solid-state chirality in chiral crystals.

## 1. Introduction

Chirality is one of the most fascinating research topics among the many scientific fields and has been continuously studied to expand its intriguing and important abilities. There are many chiral systems, i.e., systems that cannot be superimposed on their mirror images. Chiral molecules constitute a representative chiral system in chemistry.[1] Starting from the optical resolution of a hemihedral crystal of sodium ammonium tartrate,[2] the theory of tetrahedral carbon centers has now been established.[3,4] Molecules with four different substituents on their tetrahedral carbon atom are typical cases in which molecules have chirality. The fundamental prerequisite for a study on chirality is the availability of a method to discriminate between enantiomeric forms (i.e., chiral discrimination). Thus, the discovery of the rotation of plane-polarized light initiated the study of chiral compounds possessing optical activity.[1] Although significant progress in chiral discrimination has been achieved in the intervening decades,[5] there remains a class of compounds whose chiral discrimination has been very difficult to establish, or has not been possible at all.[6]

We describe herein the highly sensitive chiral discrimination of organic compounds. The extremely small chirality can be amplified to an easily seen experimental outcome by using asymmetric autocatalysis with amplification of enantiomeric excess (ee).[7,8] In the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc (*i*-$Pr_2Zn$), compounds with a tiny chirality induce a slight ee in the isopropylzinc alkoxide of the produced 5-pyrimidyl alkanol. Asymmetric autocatalysis then leads to pyrimidyl alkanol with high ee. The sense of enantiomeric enrichment of the produced 5-pyrimidyl alkanol is controlled by the absolute configurations of the cryptochiral compounds, therefore asymmetric autocatalysis is a powerful method for the recognition and amplification of tiny chirality, which is difficult to discriminate using contemporary methods.

## 2. Asymmetric Autocatalysis with Amplification of Enantiomeric Excess

In reactions including 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 and the

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same absolute configurations (Figure 1). The result is automultiplication of chiral product **P***. Conventional asymmetric catalysis produces a chiral product with a different structure from that of the chiral catalyst. In 1953, Frank proposed a reaction model of asymmetric autocatalysis with amplification of ee in which the chiral product acts as an anticatalyst for the production of the opposite enantiomer without mentioning any chemical structures.[9]

In 1990, Soai et al. reported the first asymmetric autocatalysis of 3-pyridyl alkanol.[10] In the asymmetric addition of *i*-$Pr_2Zn$ to pyridine-3-carbaldehyde, (*S*)-pyridyl alkanol with 86% ee catalyzed the formation of the same *S*-configuration in 35% ee with a yield of 67%. Then, in 1995, a real chemical reaction of asymmetric autocatalysis with amplification of ee was found in the enantioselective addition of *i*-$Pr_2Zn$ to pyrimidine-5-carbaldehyde (**1**) in which the produced 5-pyrimidyl alkanol **2** acted as a highly efficient asymmetric autocatalyst (Table 1).[11] The initial small 2% ee was significantly amplified to a high enantioenrichment (88% ee). When the (*S*)-pyrimidyl alkanol **2** (20 mol %, 2% ee) was employed as an asymmetric autocatalyst, (*S*)-**2** with 10% ee was obtained as a mixture of newly formed product and initial catalyst. Because the structure of the catalyst and product are the same, the reaction proceeded successively by using the product of one reaction as the autocatalyst of the next round of reactions. Starting from compound **2** with 2% ee, the enantioenrichment was enhanced to 88% ee during four rounds of consecutive reactions without the assistance of any other chiral auxiliary.

An investigation of the substituent effect at the pyrimidine ring shows that substrate **4**, having a *tert*-butylethynyl group at the 2-position, possesses a higher asymmetric autocatalytic activity in the addition of *i*-$Pr_2Zn$ to the corresponding pyrimidine-5-carbaldehyde **3**.[12] When 20 mol % of (*S*)-2-(*tert*-butylethynyl)-5-pyrimidyl alkanol **4** with >99.5% ee was employed as an asymmetric autocatalyst, (*S*)-**4** with >99.5% ee was obtained as a mixture of the newly formed and initially added **4** (Figure 2).[12a] The yield of the newly formed **4** was calculated to be >99%. Even after the 10th round, the yield of **4** 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 **4** served as a practically perfect asymmetric autocatalyst.

Furthermore, it was found that compound **4** shows remarkable amplification of ee from as low as approximately 0.00005% ee to near enantiomerically pure (>99.5% ee) product **4** in only three consecutive asymmetric autocatalyses (Figure 3).[12b] The initial round of asymmetric autocatalysis using (*S*)-**4** with ca. 0.00005% ee gave (*S*)-**4** with an amplified 57% ee. The second round of the reaction afforded the product with an ee of 99%. The third and final round of asymmetric autocatalysis gave almost enantiopure (*S*)-**4** with >99.5% ee.

During these three consecutive reactions, the initial slightly excess (*S*)-enantiomer of **4** has automultiplied by a factor of ca. 630000. In contrast, the multiplication factor for the slightly minor (*R*)-**4** was less than 1000 (Figure 4).

In addition to pyrimidyl alkanols **2**[11] and **4**[12] and 3-pyridyl alkanol **5**,[10] it was found that 2-methyl-5-pyrimidyl alkanol **6**,[13a] 3-quinolyl alkanol **7**,[13b,13c] and 5-carbamoyl-3-pyridyl alkanol **8**[13d,13e] are also highly efficient asymmetric autocatalysts with amplification of ee (Figure 5). Derivatization of the terminal groups of 2-ethynyl substituents at the 2-position of the pyrimidine ring expanded the applicable compounds,

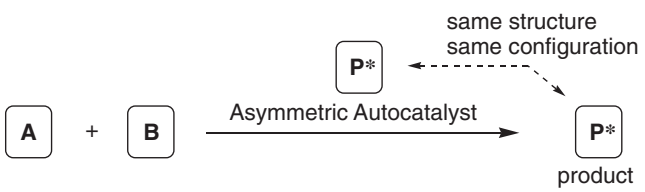
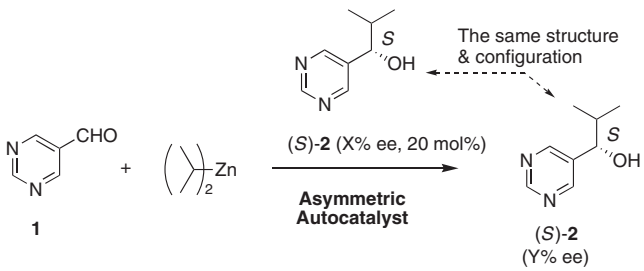



**Figure 1.** General description of asymmetric autocatalysis.

**Table 1.** Asymmetric Autocatalysis with Amplification of ee for 5-Pyrimidyl Alkanol **2** in the Reaction between Pyrimidine-5-carbaldehyde (**1**) and Diisopropylzinc




| Entry | Asymmetric autocatalyst **2** | Asymmetric autocatalyst and product **2** | | Product **2** |
|---|---|---|---|---|
| | X/% ee | Yield/% | ee/% | Y/% ee |
| 1 | 2 | 46 | 10 | 16 |
| 2 | 10 | 75 | 57 | 74 |
| 3 | 57 | 80 | 81 | 89 |
| 4 | 81 | 75 | 88 | 90 |
| 5 | 99 | 79 | 88 | 88 |

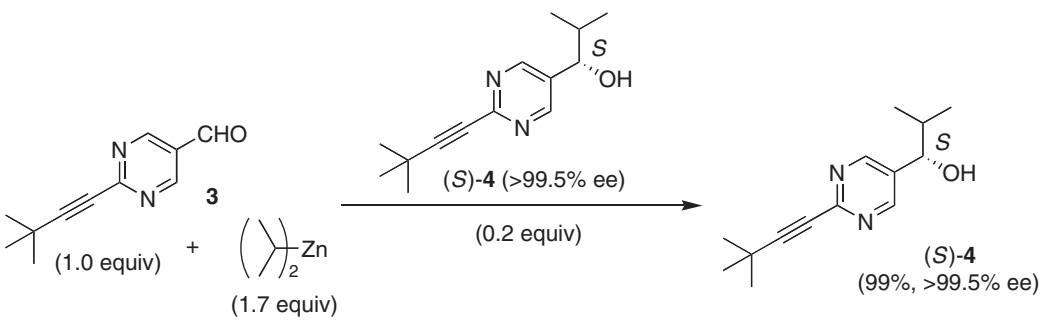



**Figure 2.** Practically perfect asymmetric autocatalysis.

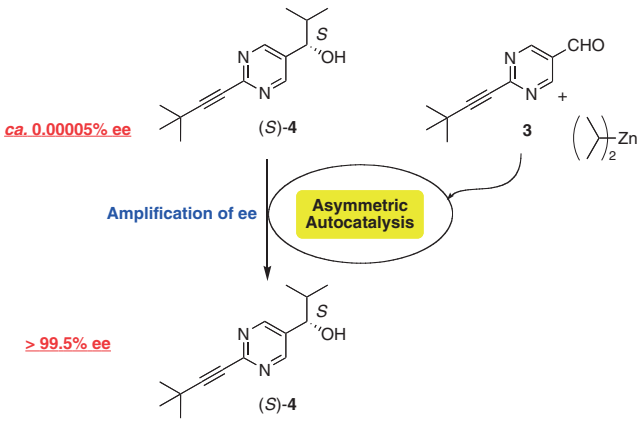



**Figure 3.** Amplification of ee by asymmetric autocatalysis from extremely low (ca. 0.00005% ee) to almost enantiopure (>99.5% ee).

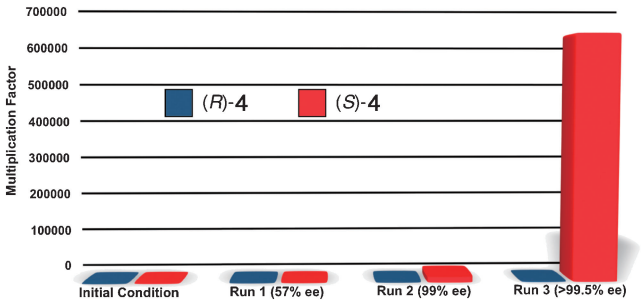



**Figure 4.** The multiplication factor of (*S*)- and (*R*)-5-pyrimidyl alkanol **4** during three consecutive asymmetric autocatalyses. Molar ratios of **4**:**3**:*i*-$Pr_2Zn$ are 0.008:1:2 (run 1) and 0.01:1:2 (run 2 and 3).

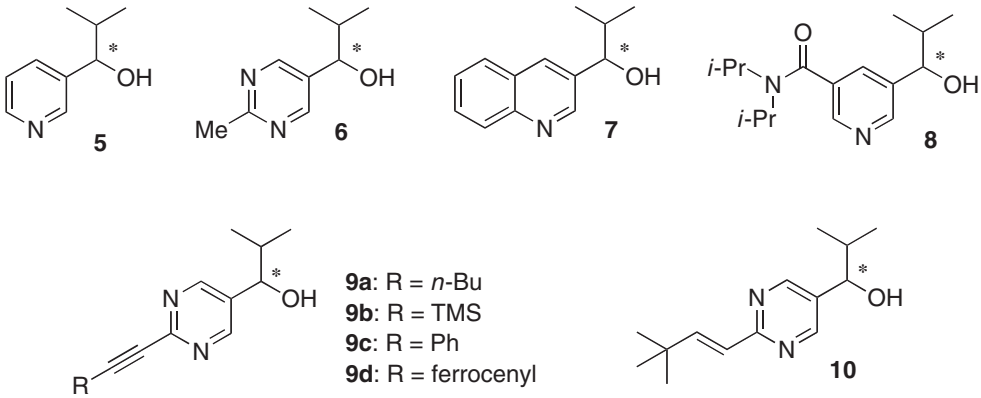



**Figure 5.** The structures of highly efficient asymmetric autocatalysts in the enantioselective *i*-$Pr_2Zn$ addition to the corresponding aldehydes. Molar ratio of **4**:**3**:*i*-$Pr_2Zn$ is 0.2:1:1.2–3.

**9a**–**9d**.[12a] We have reported that the initially employed ferrocene-containing pyrimidyl alkanol **9d** with 8% ee was enhanced to 67% ee by a single round of the addition reaction.[13f] After consecutive reaction cycles, the enantioenrichment was amplified to >99% ee. 5-Pyrimidyl alkanol **10** possessing an alkenyl group at the 2-position also displays a significant amplification of ee.[13g]

A possible mechanistic framework for the asymmetric autocatalysis has been suggested by kinetic experiments using chiral HPLC,[14] a reaction microcalorimeter,[8e,15] NMR,[16] and computational molecular modeling,[17] which showed that the dimer of chiral zinc alkoxide of **4** acts as a reactive species for the production of the next product **4** with the same absolute configuration as the catalyst.

On the other hand, it has been considered that asymmetric autocatalysis should be closely related to spontaneous absolute asymmetric synthesis.[18] We have reported spontaneous absolute asymmetric synthesis in conjunction with asymmetric autocatalysis.[19a,19b] The statistically generated initial small ee could be enhanced to a detectable value of ee by asymmetric autocatalysis to afford enantioenriched (*S*)- and (*R*)-**4**. The distribution of the formation of (*S*)- and (*R*)-enantiomers is stochastic. Thus, these results fulfill for the first time one of the conditions necessary for spontaneous absolute asymmetric synthesis. In the presence of achiral silica gel[19c] and achiral amines[19d] as reaction promoters, an enantiomerically enriched pyrimidyl alkanol **4** with either *S*- or *R*-configurations was obtained stochastically. The spontaneous symmetry breaking in this reaction[20] and its theoretical models have been reported previously.[21]

Mauksch, Tsogoeva, and co-workers reported the asymmetric autocatalytic organocatalysis of compound **11** in the Mannich reaction between N-protected 2-iminoacetate **12** and acetone without amplification of ee (Figure 6).[22a,22b] Water could be used as the solvent in a similar reaction system by using cyclohexanone instead of acetone as the substate.[22c]

## 3. Asymmetric Autocatalysis in the Presence of Chiral Compounds

As mentioned in the preceding section, the significant amplification of enantiomeric purity from a small value can be achieved by asymmetric autocatalysis of pyrimidyl alkanol. Thus, if the enantioenrichment of the initially formed asymmetric autocatalyst could be introduced by a discrete chiral factor, we can expect to obtain pyrimidyl alkanol with a detectable ee by the asymmetric autocatalytic amplification of ee. The sense of the ee should be controlled by the configuration of the originally used external chiral factor. It has been found that various chiral compounds can act as chiral initiators of asymmetric autocatalysis. Chiral alcohols,[23a] amino acids,[23b] epoxides,[23c] and $[Cr(acac)_3]$[23d] can serve as chiral initiators of

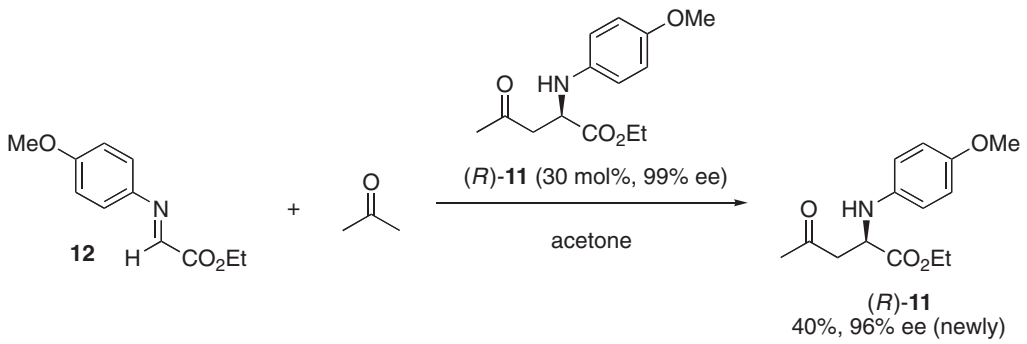



**Figure 6.** Asymmetric autocatalysis in the organocatalytic Mannich reaction.

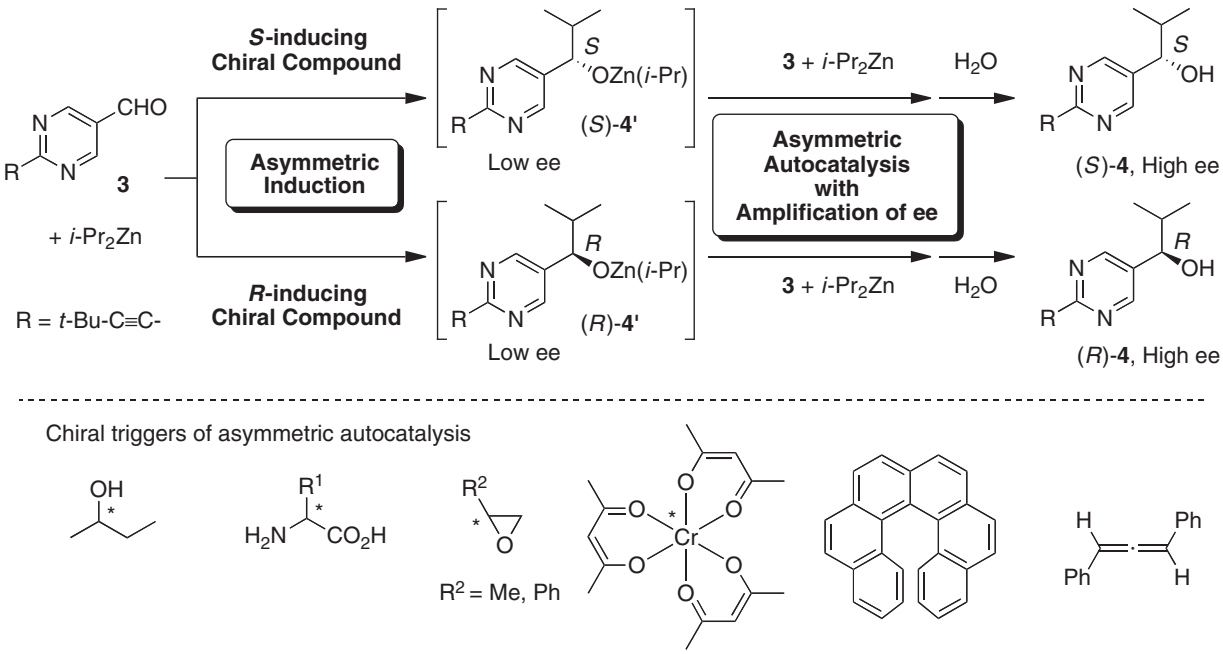



**Figure 7.** Asymmetric autocatalysis initiated by chiral compounds. For example, the molar ratio of $[Cr(acac)_3]$:aldehyde **3**:*i*-$Pr_2Zn$ was 0.005:1.325:2.675. Aldehyde **3** and *i*-$Pr_2Zn$ were added in four separate portions.

asymmetric autocatalysis to give alkanol **4** in high ee with the corresponding absolute configurations (Figure 7). In addition, chiral hydrocarbons such as helicenes[23e] and allenes[23f] can initiate asymmetric autocatalysis with amplification of ee.

Chiral compounds even without catalytic activity can serve as chiral initiators of asymmetric autocatalysis to induce enantiomeric imbalance in isopropylzinc alkoxide **4′** of pyrimidyl alkanol **4**. The initial small ee can be amplified dramatically in conjunction with asymmetric autocatalysis. Thus, it is considered that asymmetric autocatalysis can be utilized as a highly sensitive chiral sensor for tiny chirality. Even if the ee is very low and can induce only a slight bias in ee, asymmetric autocatalysis would greatly enhance the amount and ee to achieve an easily analyzable outcome. Therefore, chiral discrimination of a tiny imbalance of chirality by using asymmetric autocatalysis would be a boon.

## 4. Discrimination of Cryptochirality in Saturated Quaternary and Tertiary Hydrocarbons

Chiral discrimination of saturated quaternary hydrocarbons has been very difficult because the difference between the four substituents on the asymmetric carbon atom is very small. 5-Ethyl-5-propylundecane (**13**), that is, (*n*-butyl)ethyl(*n*-hexyl)-(*n*-propyl)methane (**13**) bearing the same four methylene ($CH_2$) groups adjacent to the quaternary asymmetric carbon center is a representative example (Figure 8). The difference in the number of carbon atoms in the four alkyl substituents is only one or two. Wynberg reported that the enantiomer of alkane **13** exhibits practically no optical rotation ($|\alpha| < 0.001$) between 280 and 580 nm.[24a] The enantiomer **13** is a chiral, but optically inactive, compound. Mislow called such hidden chirality "cryptochirality" and referred to the corresponding measurement as the "operational null."[6]

The enantiomers of saturated quaternary alkane **13** were prepared as shown in Figure 8. Racemic acetylthiophene **14** derived from 3-hexanone was resolved using HPLC with a chiral stationary phase into (*R*)- and (*S*)-enantiomers **14** with >99.5% ee.[25] The absolute configurations of **13** were determined from X-ray single-crystal analysis of 2,4-dinitrophenylhydrazone derived from (*R*)-**14**. Subsequent deoxygenative reduction, desulfurization, and hydrogenation gave the cryptochiral saturated quaternary hydrocarbons (*R*)- and (*S*)-**13**.

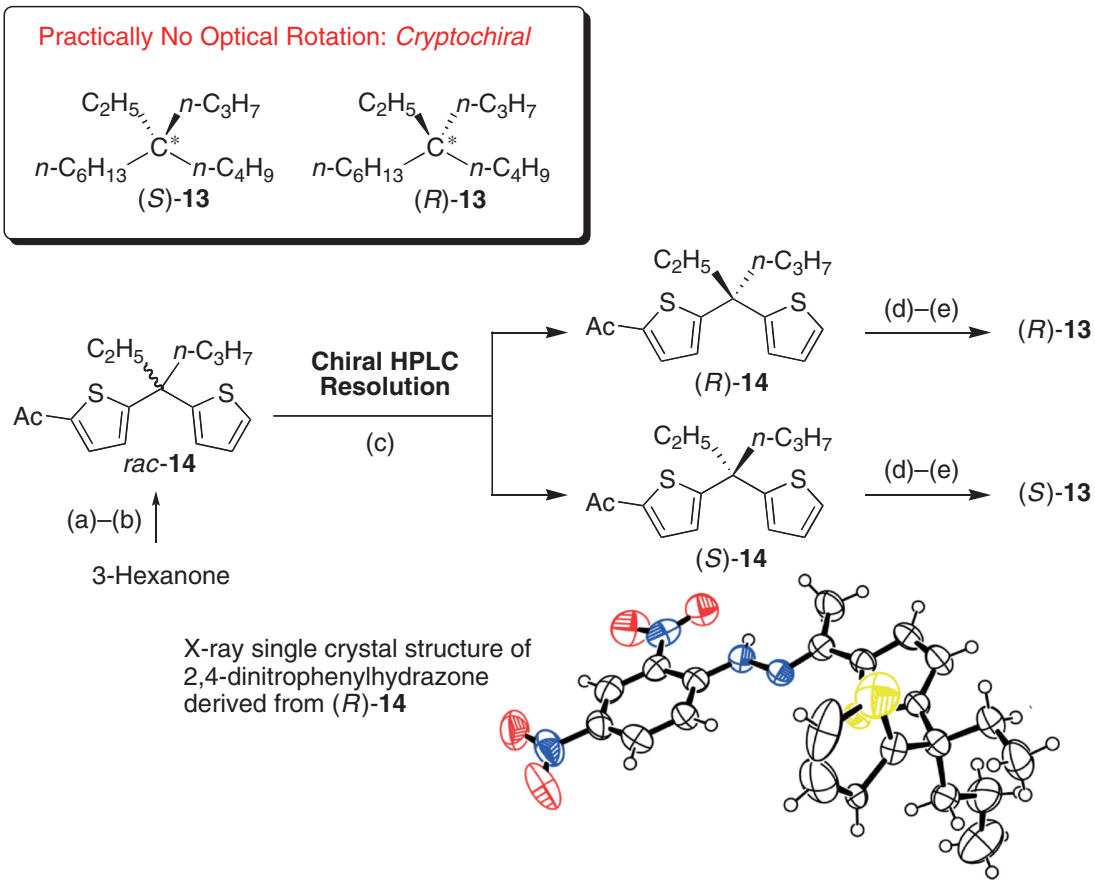



**Figure 8.** Cryptochiral saturated quaternary hydrocarbon with undetectable optical rotatory power. (a) Thiophene, $H_2SO_4$; (b) $Ac_2O$, $HClO_4$; (c) Column: Daicel chiralpak AD-H; shorter retention time: (*R*)-**14**, longer retention time: (*S*)-**14**; (d) $N_2H_4$, KOH (93%); (e) $Ni_2B$, MeOH/THF then Raney Ni (W7) (66%).

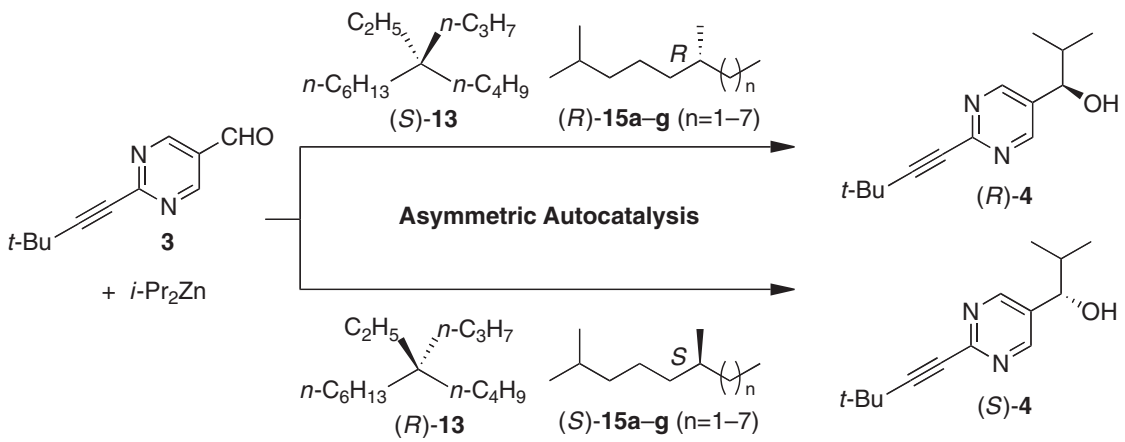



**Figure 9.** Asymmetric autocatalysis in the presence of cryptochiral saturated hydrocarbons.

It was found that the cryptochirality of the saturated quaternary hydrocarbon **13** was successfully discriminated by the asymmetric autocatalysis with amplification of ee (Figure 9).[25] That is, when asymmetric addition of *i*-$Pr_2Zn$ to pyrimidine-5-carbaldehyde **3** in the presence of chiral saturated quaternary hydrocarbon (*S*)-**13**, (*R*)-pyrimidyl alkanol **4** in high ee was formed after the amplification of ee by asymmetric autocatalysis. In contrast, asymmetric autocatalysis in the presence of (*R*)-**13** gave (*S*)-alkanol **4**. In addition, chiral saturated tertiary alkanes **15a**–**15g** could be successfully used as the chiral initiators of asymmetric autocatalysis (Figure 9). Asymmetric autocatalysis in the presence of (*S*)- and (*R*)-*tert*-alkanes **15** gave (*S*)- and (*R*)-alkanol **4** with high ee, respectively.

It is thought that the CH–$\pi$ interactions between the CH group of chiral hydrocarbon **13** and the $\pi$-electrons of the pyrimidine-5-carbaldehyde **3** should be involved in the present chiral induction. The subsequent attack of *i*-$Pr_2Zn$ on aldehyde

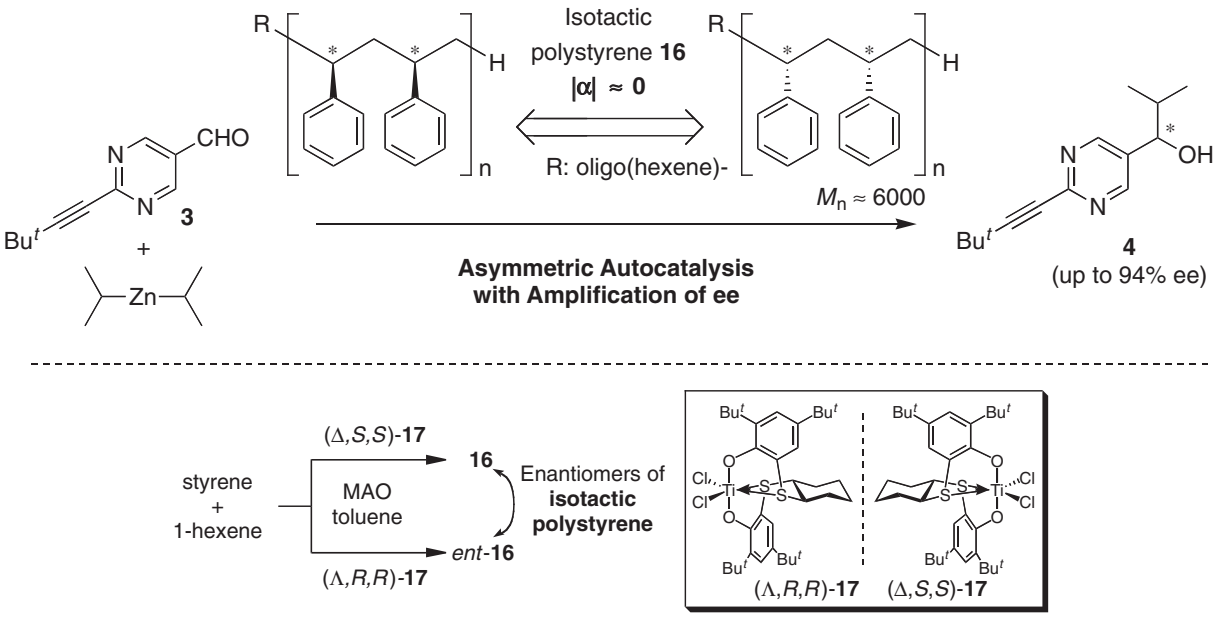



**Figure 10.** Asymmetric autocatalysis initiated with cryptochiral polystyrene **16** and the asymmetric synthesis of enantiomers of polystyrene **16**.

**3** would occur from one preferential enantioface to form pyrimidyl alkanol **4** (as isopropylzinc alkoxide **4′**) with an absolute configuration corresponding to the chirality of **13**. Once a tiny enantioenrichment is formed in the asymmetric autocatalyst, the chirality will amplify during further asymmetric autocatalytic amplification.

Asymmetric autocatalysis is a significant method for discriminating the cryptochirality of saturated quaternary hydrocarbons. The hidden cryptochirality of a nonfunctionalized saturated quaternary asymmetric carbon center can be transmitted to a visible chirality using asymmetric autocatalysis. Recently, discrimination and determination of the absolute configuration of 4-ethyl-4-methyloctane, which shows a small specific rotation,[24b] have been reported by using vibrational circular dichroism (VCD).[26]

## 5. Cryptochiral Isotactic Polystyrene Induces Asymmetric Autocatalysis

Cryptochirality can be observed in isotactic poly(α-olefins), such as polypropylenes and polystyrenes. Neglecting the chain ends, poly(α-olefins) have $C_s$ symmetry and therefore possess a pseudomirror plane. Because of the recent development of single-site catalysts for the synthesis of stereoregular and enantiomerically pure poly(α-olefins), it is now possible to correlate the chiroptical properties of isotactic poly(α-olefins) to their chain length. Okuda et al. reported the synthesis of enantioenriched isotactic polystyrene **16**, and the dependence of the specific optical rotation on the molecular weight of the isotactic polystyrenes has been demonstrated (Figure 10).[27] Thus, it was found that high-molecular-weight enantioenriched polystyrene **16** ($M_n > 5000$) possesses no detectable optical rotation, that is, cryptochiral.

When *i*-$Pr_2Zn$ addition to pyrimidine-5-carbaldehyde **3** was performed in the presence of polystyrene **16** ($M_n$ = ca. 6000), synthesized using (Δ,*S*,*S*)-**17** as a polymerization catalyst, pyrimidyl alkanol **4** with *S*-configuration was obtained. On the other hand, the enantiomer of isotactic polystyrene **16** (*ent*-**16**) prepared using (Λ,*R*,*R*)-**17** as chiral initiator afforded (*R*)-alkanol **4**.[28]

The cryptochirality caused by a small difference between the end groups of the polystyrene chains may control the *Si*- or *Re*-enantioface selection of *i*-$Pr_2Zn$ addition to pyrimidine-5-carbaldehyde **3** to afford the asymmetric autocatalyst with a minute enantiomeric imbalance. Because of the following amplification of ee by asymmetric autocatalysis, the enantiomeric purity of pyrimidyl alkanol **4** was greatly increased during the reaction. We can therefore distinguish the enantiomeric form of cryptochiral polystyrene **16** by determining the absolute configuration of the resulting alkanol **4**.

## 6. Asymmetric Autocatalysis Initiated by Chiral Compounds Because of Hydrogen Isotope (D/H) Substitution

Chiral compounds arising only from the replacement of hydrogen (H) by deuterium (D) are important in the fields of stereochemistry and biochemistry.[1b,29] A very small difference has been reported between the lengths of the C–D and C–H bonds, that is, the time-averaged C–D bond length (0.1099 nm) is shorter than the C–H bond by only 0.0004 nm.[30] Chiral recognition of these isotopic enantiomers is more difficult than for other enantiomers. The enantioselectivities that have been reported in asymmetric synthesis[31a] and kinetic resolution[31b] induced by hydrogen-isotope enantiomers have been extremely low. Previously, Green et al. reported that the cooperation–amplification effect could control the macromolecular helical sense of polyisocyanates to show a large value of optical rotation by using deuterium-substituted chiral monomer (Figure 11).[31c]

Glycine and α-methylalanine are achiral amino acids. However, deuteration of one of the hydrogens of the methylene

group of glycine and one methyl group of α-methylalanine makes these compounds chiral because of the hydrogen-isotope substitution, glycine-α-*d* **18**[32a] and α-methyl-$d_3$-alanine **19**[32b] (Figure 12).

We used the isotopically chiral glycine-α-*d* **18** and α-methyl-$d_3$-alanine **19** as chiral initiators in the enantioselective addition of *i*-$Pr_2Zn$ to pyrimidine-5-carbaldehyde **3** to afford, in combination with asymmetric autocatalysis, pyrimidyl alkanol **4** with significantly high ee (Figure 12).[33] The absolute configuration of the corresponding alkanol **4** was controlled efficiently by the chirality resulting from hydrogen-isotope substitution. When the *i*-$Pr_2Zn$ addition to aldehyde **3** was performed in the presence of (*S*)-**18**, (*S*)-5-pyrimidyl alkanol **4** was obtained in high ee. On the other hand, in the presence of (*R*)-**18** instead of (*S*)-**18**, (*R*)-**4** was formed. These results clearly show the correlation between the isotope chirality of the glycine-α-*d* **18** and the absolute configuration of the resulting alkanol **4**. In addition, (*R*)- and (*S*)-α-methyl-$d_3$-alanine **19** acted as the chiral trigger of asymmetric autocatalysis. Thus, (*R*)-**19** induces the formation of (*S*)-**4**, and (*S*)-**19** promoted the production of (*R*)-**4**.

This is the first example of a highly enantioselective reaction induced by chirality resulting from deuterium substitution of amino acids. Furthermore, glycine and α-methylalanine were identified in meteorites as a deuterium-enriched form.[34a] Thus, regarding the extraterrestrial origin of biological homochirality, the present results should increase the implications of chiral amino acids arising from isotope substitution in achiral meteoritic amino acids.[34b]

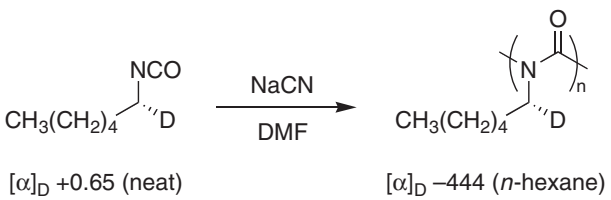



**Figure 11.** Synthesis of polyisocyanate from chiral monomer because of deuterium substitution and the change in optical activity.

## 7. Carbon Isotope Chirality Triggers Asymmetric Autocatalysis

Many apparently achiral organic molecules on Earth may be chiral because of the random substitution of the naturally abundant carbon isotopes in an enantiotopic moiety (Figure 13). However, carbon-isotope chirality is experimentally difficult to discriminate because the chirality originates from the very small difference between the carbon isotopes ($^{13}C/^{12}C$). It has been a question whether isotopically substituted carbon chiral compounds can induce chirality in some reactions. To address this problem, we performed asymmetric autocatalysis triggered by a chiral compound arising solely from carbon-isotope ($^{13}C/^{12}C$) substitution. It was found that the chiral carbon isotopomer can control the enantioselectivity in an asymmetric reaction.[35]

At first, carbon isotopically chiral methyl-$^{13}$C-methylphenylmethanol (**20**) was prepared as shown in Figure 14. To restrict chiral effects to the influence of the carbon-isotope chirality, both enantiomers of **20** were prepared from the same chiral ligand **21**[36] via direct asymmetric dimethylzinc addition to acetophenone (route I). (*R*)-Alcohol **20** was synthesized using $^{13}$C-labeled acetophenone and unlabeled dimethylzinc. In contrast, (*S*)-**20** was prepared from $^{13}$C-labeled dimethylzinc and unlabeled acetophenone. In route II, the stereogenic center of **20** was introduced by asymmetric epoxidation[37] of the $^{13}$C-labeled allyl alcohol, followed by reduction of the tosylate and the epoxide.

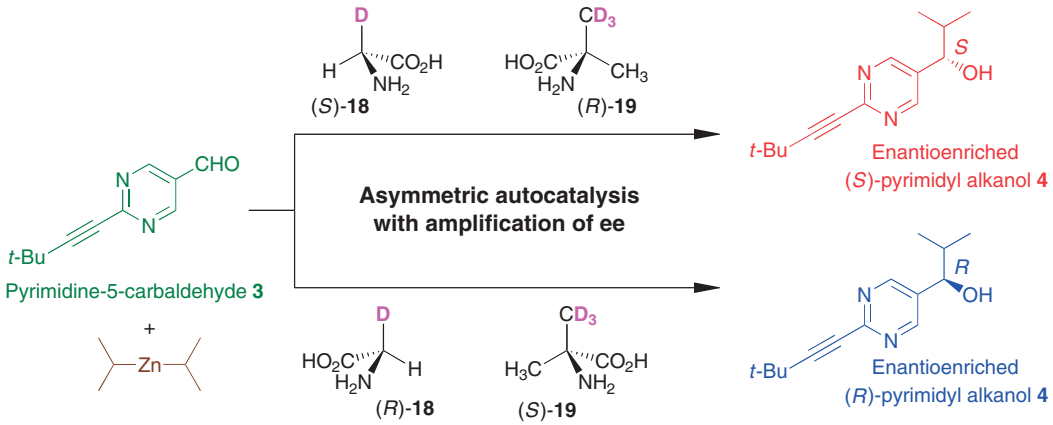



**Figure 12.** Asymmetric autocatalysis triggered by chiral amino acids arising only from deuterium substitution.

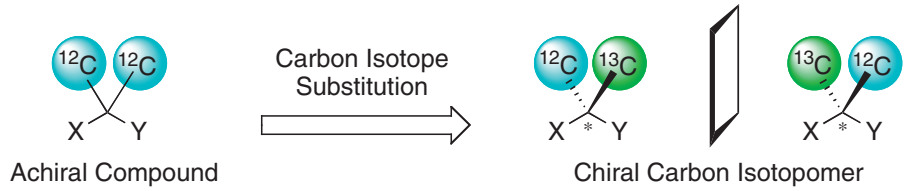



**Figure 13.** Generation of the carbon-isotope ($^{13}C/^{12}C$) chirality.

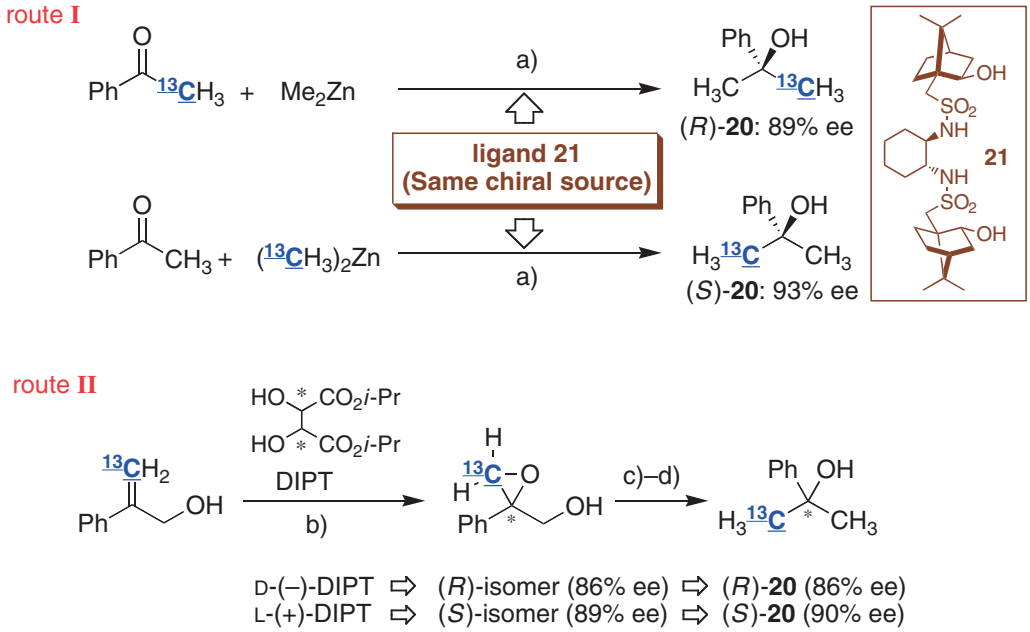



**Figure 14.** Synthesis of carbon isotopomer **20**: a) [Ti(O*i*-Pr)$_4$], **21**, toluene or $Et_2O$; b) D- or L-DIPT, [Ti(O*i*-Pr)$_4$], TBHP, $CH_2Cl_2$; c) $Ts_2O$, DMAP, pyr.; d) LAH, $Et_2O$.

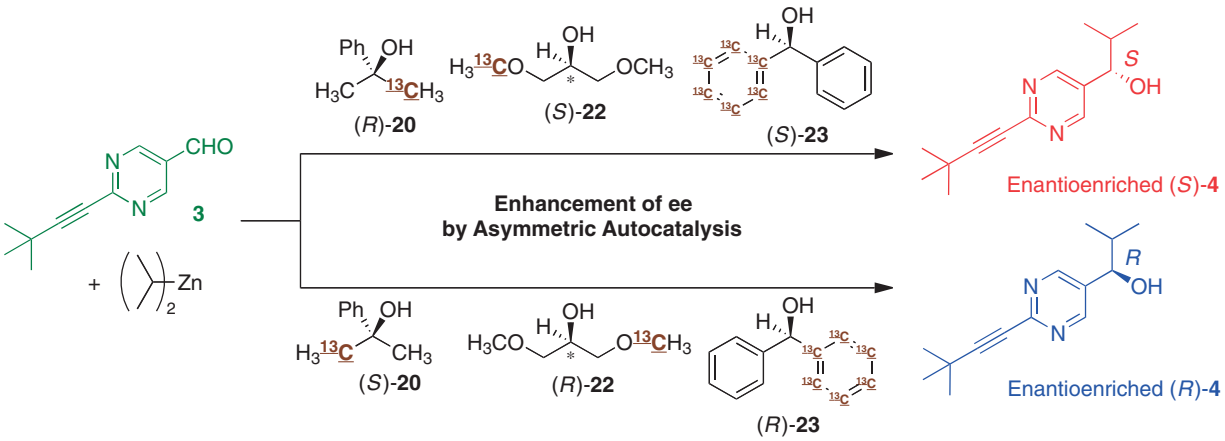



**Figure 15.** Asymmetric autocatalysis triggered by chiral compounds arising from carbon-13 substitution.

When *i*-Pr$_2$Zn addition to pyrimidine-5-carbaldehyde **3** was performed in the presence of (*R*)-dimethylphenylmethanol (**20**) arising from $^{13}C$ substitution of the methyl group, (*S*)-pyrimidyl alkanol **4** was obtained with high ee (Figure 15). In contrast, (*S*)-**20** afforded (*R*)-**4**. Chiral alcohols **22** and **23** resulting from $^{13}C$ substitution can also act as chiral triggers of asymmetric autocatalysis to afford pyrimidyl alkanols **4** with high ee that have the corresponding absolute configurations of the isotopically substituted carbon chirality of **22** and **23**.

We have shown the first examples of the chiral effect, that is, asymmetric induction by carbon-isotopically chiral compounds. The neglected carbon-isotope chirality of many organic compounds on Earth—a characteristic that has largely eluded discrimination using contemporary methods—can thus be discriminated by asymmetric autocatalysis, which is a highly sensitive reaction for recognizing and amplifying the extremely small chiral influence between $^{12}C$ and $^{13}C$.

## 8. Asymmetric Autocatalysis Triggered by Circularly Polarized Light

Right (*r*)- and left (*l*)-handed circularly polarized light (CPL) are chiral physical forces that have long been considered as one of the origins of chirality of organic compounds.[38] However, only low enantioenrichments have been induced by irradiation with CPL. For example, asymmetric photodecomposition of *rac*-leucine by *r*-CPL (213 nm) produces L-leucine with only 2% ee.[39a] Hexahelicene with less than 2% ee is formed by asymmetric photosynthesis using CPL.[39b] Irradiation of racemic alkylidenecyclohexanone with CPL induces a small enantiomeric imbalance (<2% ee) in asymmetric photoequilibrium.[39c] These low enantiomeric enrichments induced by CPL have not been correlated with the homochirality of bioorganic compounds. Therefore, we speculated that chiral organic compounds with high ee could be obtained from CPL by the combination with asymmetric autocatalysis with amplification of ee.

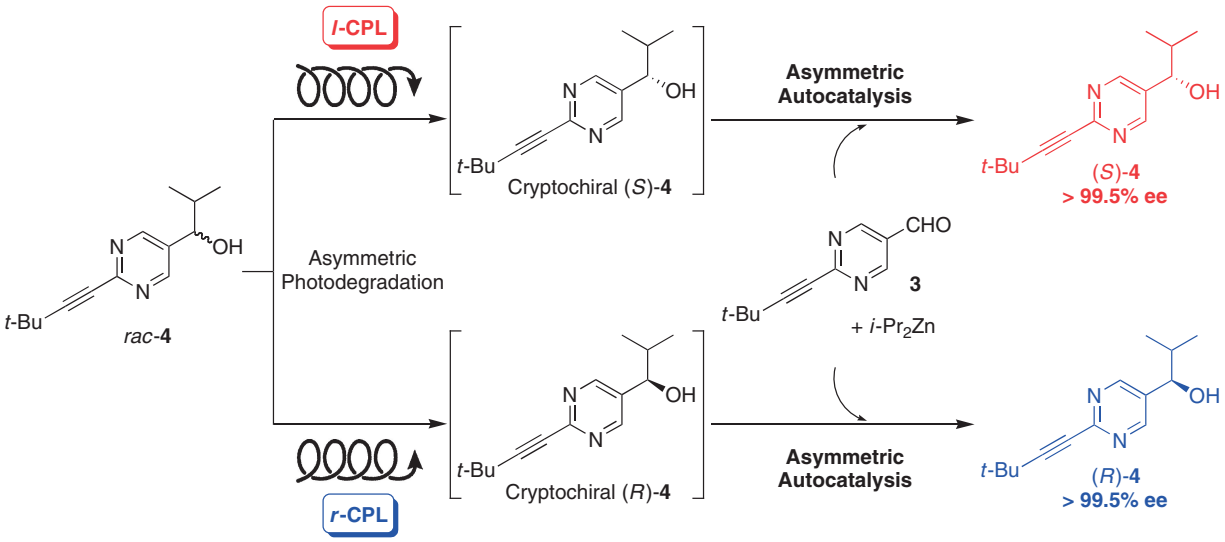



**Figure 16.** Short pathway to obtain a near enantiopure compound by CPL irradiation followed by asymmetric autocatalysis.

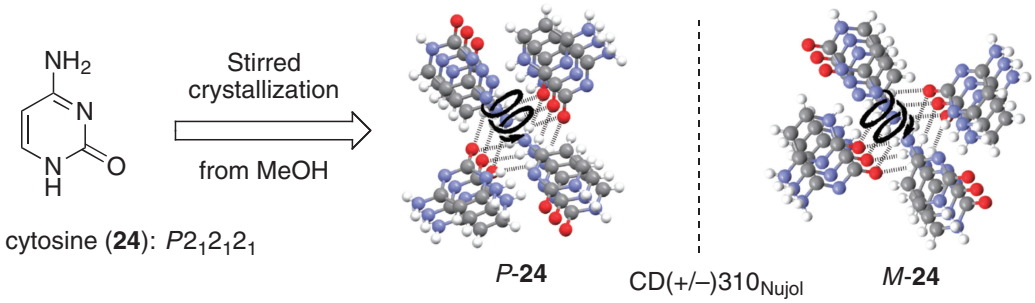



**Figure 17.** Generation of crystal chirality of cytosine (**24**) by stirred crystallization.

(*R*)- and (*S*)-Pyrimidyl alkanols **4**, asymmetric autocatalysts, exhibit positive and negative Cotton effects in circular dichroism (CD) spectra at 313 nm, respectively.[40] Thus, the direct irradiation of *l*-CPL (313 nm) to racemic alkanol **4** would induce the asymmetric photodegradation of (*R*)-pyrimidyl alkanol **4** and leave the slightly enantioenriched (*S*)-**4**. Indeed, direct irradiation of racemic **4** by *l*-CPL (313 nm) and the subsequent asymmetric autocatalysis produces highly enantioenriched (*S*)-alkanol **4** with >99.5% ee (Figure 16). On the other hand, irradiation with *r*-CPL (313 nm) instead of *l*-CPL, formed (*R*)-**4** with >99.5% ee after the asymmetric autocatalysis. The initial chirality induced by the direct irradiation of CPL to the racemic **4** was significantly amplified to high ee by the asymmetric autocatalysis with amplification of chirality. The process provides direct correlation of the handedness of CPL with that of the organic compound with high ee.[40]

These results are a demonstration of the enantioselective synthesis of near enantiopure compounds by asymmetric photodecomposition of racemic 5-pyrimidyl alkanol **4** by CPL followed by asymmetric autocatalysis. This is the first example of asymmetric autocatalysis triggered directly by a chiral physical factor.

## 9. Asymmetric Autocatalysis Initiated by Chiral Crystal Composed of Achiral Organic Compounds

There are achiral organic compounds that crystallize in chiral form, with each crystal exhibiting one of the two possible enantiomorphs.[41] There are 65 chiral space groups out of the 230 possible space groups. It is worth noting that based upon a survey of ca. 29000 crystal-structure determinations, among the five most common space groups of organic crystalline compounds, ca. 18% of the crystals belonged to two chiral space groups ($P2_12_12_1$ and $P2_1$).[41d] Chiral crystallization of achiral compounds including inorganic compounds such as quartz[42] are among the important phenomena for the origin of chirality of biologically related compounds.

Stereospecific reactions using chiral crystals of achiral compounds by using themselves as reactants have been reported.[41] In contrast, we paid attention to a highly enantioselective reaction using chiral crystals as a chiral initiator (or catalyst); therefore, a study of asymmetric autocatalysis using these chiral organic crystals as the source of chirality is an interesting subject.

First of all, we focused on cytosine (**24**), which is a base of cytidine and deoxycytidine, and is an essentially flat achiral molecule. It is conceivable that cytosine was formed under prebiotic conditions[43] and already existed before the RNA world emerged. In the single-crystal structure of **24** (space group: $P2_12_12_1$),[44] the hydrogen bond between the carbonyl and primary amino group of neighboring molecules forms a left- or right-handed helical arrangement, so that crystal chirality is generated (Figure 17). We discovered that achiral cytosine (**24**), when crystallized from methanol with stirring[45] without adding any seed crystal, affords powder-like crystals

that exhibit either a plus or minus Cotton effect in solid-state CD spectra at ca. 310 nm using Nujol mulls.[46] The stochastic behavior of the formation of [CD(+)310$_{Nujol}$]- and [CD(−)310$_{Nujol}$]-**24** was observed.

Next, the chiral crystals that were spontaneously formed with stirring were used as chiral triggers for asymmetric autocatalysis (Figure 18).[46] When pyrimidine-5-carbaldehyde **3** and *i*-Pr$_2$Zn reacted in the presence of [CD(+)310$_{Nujol}$]-**24**, enantioenriched (*R*)-pyrimidyl alkanol **4** was obtained after the subsequent autocatalytic amplification of ee. On the other hand, [CD(−)310$_{Nujol}$]-**24** gave (*S*)-**4**. These results clearly exhibit the correlation between the chirality of the crystal of cytosine and the absolute configuration of the resulting alkanol **4**. Thus, crystal chirality of cytosine is responsible for the asymmetric addition of *i*-Pr$_2$Zn to pyrimidine-5-carbaldehyde **3**, and the subsequent autocatalytic reaction amplified the ee of **4**.

In addition, we have examined the asymmetric autocatalysis induced by other chiral organic crystals, that is, cocrystals of 3-indolylpropionic acid and phenanthridine **25**,[47a] hippuric acid (**26**),[47b] tetraphenylethylene (**27**),[47c] and benzil (**28**).[47c] Cocrystal **25** belongs to the chiral space group $P2_1$ (Figure 19).[48a] Hippuric acid (**26**) is an achiral naturally occurring amino acid derivative, which belongs to the chiral space group $P2_12_12_1$ and has both clockwise (*P*) and counterclockwise (*M*) helicities in its crystal state.[48b] It is possible to discriminate between the enantiomorphs of the obtained single crystals by using solid-state CD spectroscopic analysis with Nujol mulls. We found that chiral crystals of the achiral hydrocarbon tetraphenylethylene (**27**) (space group: $P2_1$)[48c] afforded right- and left-

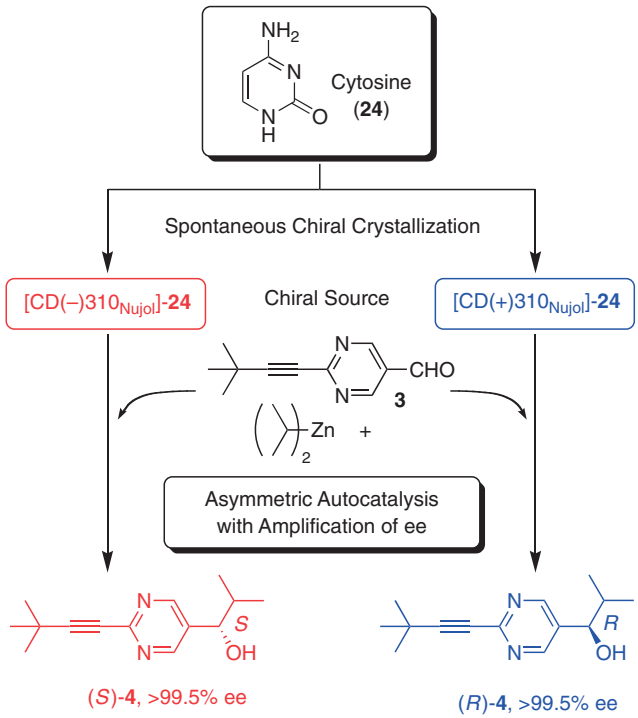



**Figure 18.** Asymmetric autocatalysis initiated with spontaneously generated chiral crystals of cytosine.

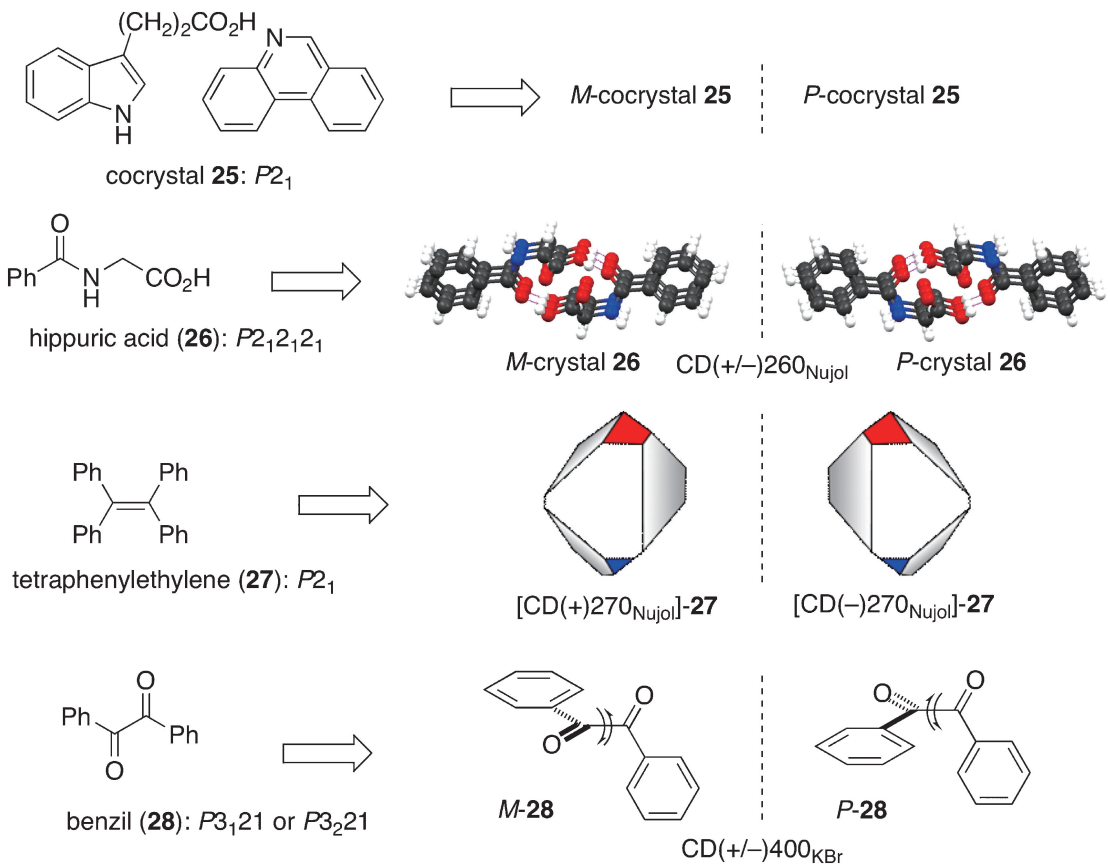



**Figure 19.** Enantiomorphs of achiral organic compounds **25**–**28**.

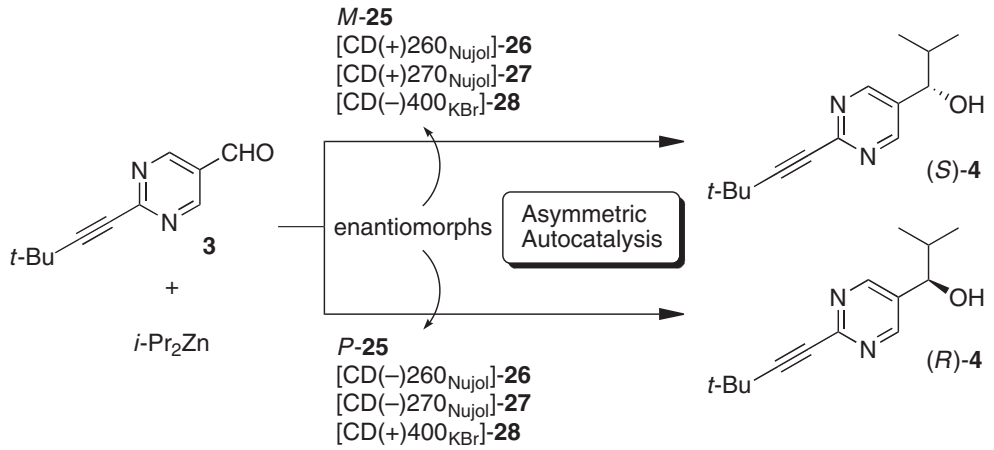



**Figure 20.** Asymmetric autocatalysis in the presence of enantiomorphous crystals of achiral organic compounds.

handed hemihedral crystals.[47c] Therefore, the enantiomorphs of **27** can be distinguished by eye from the single-crystal shapes. Benzil (**28**), often called "organic quartz," has the same space group ($P3_121$ or $P3_221$) as quartz.[48d] The two benzoyl groups in the molecule are torsionally arranged to point in the same *P* or *M* direction, so that crystalline chirality is generated.

These enantiomorphous crystals composed of achiral organic compounds **25**–**28**, have been used successfully as chiral inducers in asymmetric autocatalysis to give enantioenriched pyrimidyl alkanol **4** with the absolute configurations corresponding to the crystal chiralities of **25**–**28** (Figure 20).[47] The enantioselectivity observed in these asymmetric reactions may be explained as follows: the chiral crystals form a chiral reaction field, which mediates the enantioface-selection in the addition reaction of *i*-$Pr_2Zn$ to pyrimidine-5-carbaldehyde **3**, so that a small ee was induced in the initially forming autocatalyst **4** (as isopropylzinc alkoxide **4′**). Then, subsequent asymmetric autocatalysis afforded alkanol **4** (as isopropylzinc alkoxide **4′**) in a high ee and with the absolute configuration corresponding to the chirality of the submitted crystals. We assume the possibility of asymmetric interactions between the crystals and pyrimidine-5-carbaldehyde **3** and/or initially formed isopropylzinc alkoxide of alkanol **4**. The coordination of *i*-$Pr_2Zn$ with the crystal may form zinc species. These chiral influences would induce the initial asymmetry in the autocatalyst.

We have demonstrated that chiral crystals of achiral organic compounds were responsible for the enantioselective addition of *i*-$Pr_2Zn$ to pyrimidine-5-carbaldehyde **3** to give enantioenriched pyrimidyl alkanol **4** in conjunction with asymmetric autocatalysis. The crystal chirality of the achiral compound disappears by dissolution or melting; thus, the initial reaction to form asymmetric autocatalyst occurred under heterogeneous conditions. In addition to chiral crystals of achiral organic compounds, chiral inorganic crystals such as quartz,[42b] sodium chlorate,[49a] and sodium bromate[49b] can act as a chiral seed for asymmetric autocatalysis. We have recently reported the enantioselective formation of a chiral crystal of cytosine by the dehydration of crystal water from the enantiotopic faces.[50]

## 10. Summary

As described, 2-alkynyl-5-pyrimidyl alkanol is a highly enantioselective asymmetric autocatalyst with greater than 99.5% enantioselectivity for the addition of *i*-$Pr_2Zn$ to the corresponding pyrimidine-5-carbaldehydes. We have demonstrated that the asymmetric autocatalysis of pyrimidyl alkanol is an efficient method to discriminate the cryptochirality in saturated quaternary hydrocarbons and isotactic polystyrene, whose chirality is not capable of determination by any conventional methods. Amino acids that are chiral because of hydrogen-isotope substitution such as glycine-$\alpha$-*d* and $\alpha$-methyl-$d_3$-alanine can induce asymmetric autocatalysis with amplification of ee. The discrimination of chirality because of deuterium substitution is also possible by the highly sensitive asymmetric autocatalysis. The absolute configuration of the resulting pyrimidyl alkanol was related to the hydrogen-isotope chirality. In addition, carbon-isotope chirality can induce asymmetry in the enantioselective addition of *i*-$Pr_2Zn$ to pyrimidine-5-carbaldehyde to afford enantiomerically enriched pyrimidyl alkanol. Thus, chiral carbon isotopomers can act as chiral triggers of asymmetric autocatalysis, which can recognize and amplify the tiny chirality generated from the difference between carbon-13 and carbon-12. This is the first example of a chiral compound resulting from carbon-isotope ($^{13}C/^{12}C$) substitution controlling the enantioselectivity of an asymmetric reaction.

The chirality of CPL was directly correlated with the chirality of the pyrimidyl alkanol with high ee by asymmetric photodegradation of a racemic pyrimidyl alkanol in combination with asymmetric autocatalysis. 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 a process in which the crystal chirality of achiral organic compounds induces asymmetry in discrete organic compounds and the chirality was amplified to produce a large amount of an enantiomerically pure organic compound, pyrimidyl alkanol, in conjunction with asymmetric autocatalysis. Thus, asymmetric autocatalysis of pyrimidyl alkanol in the reaction of *i*-$Pr_2Zn$ and pyrimidine-5-carbaldehyde can be utilized as a highly sensitive chiral sensor to discriminate small chiral effects.

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