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1. Introduction

Organic crystals have been utilized by organic chemists to identify materials by comparing melting point and mixed melting with known compounds, and to obtain pure materials by recrystallization. Furthermore, many attractive aspects of the crystals have been discovered since the latter half of the 1960's. For example, when organic molecules aggregate and form a crystal, a new property such as the electric conductivity or nonlinear optics characteristic develops by forming a peculiar arrangement style, and these crystals are used as electronic and optical materials. In addition, chemistry using the key information recorded in the molecule in the crystal has been developed. Molecular motion, which was cluttered with a variety of conformations in solution, is considerably controlled in the crystal, and molecules are arranged in a specific conformation depending on the closest-packing and molecular interactions in many cases. Therefore, a different molecular conformation will often be afforded in the crystal and in solution. In some cases, information for chirality recorded in the crystal is particularly interesting. Conglomerate crystals (racemic mixture) afforded from racemic compounds are also chiral crystals, which are used for preferential crystallization for optical resolution of racemate. On the other hand, compounds with unstable axial chirality, even in achiral in solution, may provide an axial chirality in a crystal where the molecular arrangement and molecular conformation are controlled. Using the chiral properties of the crystal, asymmetric synthesis without an external chiral source from achiral substrates has been studied by many research groups. This approach is also broadly recognized as an absolute asymmetric synthesis.

Since the 1970's, the combination of chiral crystallization and the solid-state photoreaction has provided many successful examples of absolute asymmetric synthesis. In these reactions, achiral materials adopted chiral arrangement only by spontaneous crystallization, and optically active products are obtained from the topochemically controlled reaction with high enantiomeric excesses (Figure 1). This method incurs a problem in the crystallization of achiral molecules in chiral space groups, albeit rare and unpredictable. However, in recent years, crystal engineering and the solid-state reaction to a variety of new systems has progressed to such an extent that it can now be regarded as an important branch of organic chemistry. Furthermore, some unique ideas involving solution chemistry utilizing the chiral crystals have also been developed. The achievement of an asymmetric synthesis starting from an achiral reagent and in the absence of any external chiral agent has long been an
intriguing challenge to chemists and is also central to the problem of the origin of optical activity on Earth.

We have designed many molecules suitable for intramolecular photochemical processes, and have reported the asymmetric photochemical reaction in the solid-state. Please refer to the literature because many reviews are provided about this reaction example.\(^5\)

![Diagram](image)

**Fig. 1. Absolute asymmetric synthesis using chiral crystals**

However, this asymmetric synthesis has yet to be recognized as the peculiar example, and there are many issues to be resolved that play a part in synthetic organic chemistry. The greatest problem is the small ratio of substrates forming a chiral crystal, and its inability to adapt to all crystalline organic compounds. Another problem is only applicable to this technique for topochemical reaction. If the crystalline state is broken according to the progress of the reaction, molecular chirality in the crystal would disappear in an instant. Exceptionally, an asymmetric amplification reaction using a chiral crystal surface dialkylzinc developed by Soai yielded product of high optical purity.

Soai *et al.* reported the catalytic asymmetric automultiplication in the addition of the dialkylzinc reagents to pyrimidine aldehydes without decrease in the optical purity of the product. The 1,2-addition in the presence of a small amount of optically active material resulted in enhancement of the ee value in the product formation.\(^6\) The asymmetric reaction was widely spread to the use of chiral crystals as a chiral trigger. The reaction promoted on the surface of the crystal of quartz gave optically active carbonyl addition product in 97% ee. Furthermore, the reaction with chiral crystals of NaClO\(_3\), benzoylglycine, and cocrystals resulted in the formation of product with high ee value.

Håkansson *et al.* reported that two six-coordinate Grignard reagents crystallized as conglomerates and racemized rapidly in solution. Enantiopure Grignard reagents were reacted with butanal to give alcohol in up to 22% ee.\(^7\)

As the first example of asymmetric synthesis using chiral crystals involving solid-gas reaction,\(^8\) some other interesting examples of solid-gas reaction using chiral crystals were reported. Reaction of chiral crystals of chalcone derivative with bromine in connection with rearrangement gave optically active dibromide in 8% ee.\(^9\)

Gerdil *et al.* reported two examples involving the solid-gas reactions of inclusion complexes of tri-o-thymonide with alkene or epoxycyclopentanone. The complex crystallized in a chiral fashion, and the reaction with singlet oxygen or hydrogen chloride gave products up to 22% ee.\(^8\)

The optical purity of the product was not satisfactory even in the reduced conversion rate of the reaction. To solve this problem, we explored a new methodology using molecular...
chirality in crystals as a source of chiral memory in solution (Figure 2). The provisional molecular chirality derived from chiral crystals can be effectively transferred to optically active products with various asymmetric reactions in fluid media. Two requirements must be met for asymmetric synthesis to become possible: chiral crystallization of the starting materials and slow racemization at a controlled temperature.

If we can effectively use the chirality of the molecules expressed by spontaneous crystallization, asymmetric synthesis using chiral crystals, which has been restricted to the topochemical solid-state photoreaction, becomes a general synthetic method playing the part of organic synthesis. In this review, a general method of chiral crystallization and a new advanced asymmetric synthesis using the chiral crystals in a non-topochemical process will be described.

Fig. 2. Non-topochemical Asymmetric synthesis using chiral memory derived from the chiral conformation in the crystal.

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2. Generation and amplification of chirality by crystallization

Optically active molecules must crystallize into chiral space groups, but a racemic mixture in solution may either aggregate to form a nonchiral racemic crystal or undergo a spontaneous resolution where the two enantiomers segregate into a conglomerate of enantiopure crystals. Achiral molecules may crystallize into either a nonchiral or a chiral space group. If they crystallize into a chiral space group, the achiral molecules reside in a chiral environment imposed by the lattice. Most achiral molecules are known to adopt interconverting chiral conformations in fluid media, which could lead to a unique conformation upon crystallization. Crystals that have chiral space groups are characterized by being enantiomorphous. They exist in right-handed and left-handed forms that may or may not be visually distinguishable. In spite of impressive work on crystal engineering, predictions on a correlation between crystal symmetry and molecular structures are still hard to make.\(^\text{12}\)

Chiral crystals, like any other asymmetric object, exist in two enantiomorphous equienergetic forms, but careful crystallization of the material can induce the entire ensemble of molecules to aggregate into one crystal, of one-handedness, presumably starting from a single nucleus (Figure 3). However, it is not uncommon to find both enantiomorphs present in a given batch of crystals from the same recrystallization.

For achieving asymmetric synthesis, we should begin with a compound crystallizing in any one of the chiral space groups. Of the 230 distinct space groups, the most commonly occurring are \(P2_1/c\), \(P-1\), \(P2_12_12_1\), \(P2_1\), \(C2/c\), and \(P\bar{b}ca\), the chiral ones being \(P2_12_12_1\), \(P2_1\), \(P_1\) and \(C_2\),\(^\text{13}\)

The asymmetric crystallization of achiral compounds is stimulated by autoseeding with the first crystal formed. Although the chiral sense of the spontaneously formed chiral crystals cannot be predicted, seed crystals of the preferred chirality can be added in a more practical procedure to obtain one enantiomorph of a crystal.

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![Fig. 3. Chiral crystallization with fast enantiomerization](https://www.intechopen.com)

3. Chiral memory effects of molecular conformation

When we start the study for chiral memory and select a molecule with the ability to hold for a certain amount of time the molecular conformation in the crystal lattice, we are focused on

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the molecules with the aromatic amide scaffold; this is because they can be synthesized many derivatives with variety substituents, and show considerable stability for the subsequent reaction. Molecules 1-4, as shown in Figure 4, were designed to consider the development of subsequent asymmetric reactions. Imide 2 has an axial chirality based on the C-N bond; on the contrary, in compounds other than 2, there is C-C bond axial chirality between the aromatic ring and amide groups. The racemization is inhibited to some extent by the steric repulsion between the aromatic ring and substituent on the amide nitrogen atoms of the planar structure. However, depending on the substituents on the aromatic ring and nitrogen atom, the rotational barrier of the N-C(=O) bond, except in special cases, is 20 ~ 24 kcal mol\(^{-1}\), and the bond can rotate slowly even at room temperature.\(^{14}\) In these substrates, when N-C(=O) bond rotation occurs, the racemization spontaneously proceeds depending on the Ar-(C=O) bond rotation; therefore, the maximum free energy of activation for racemization is also controllable. By changing the size and electronic property of the substituents, we can finely tune the energy of racemization of the aromatic amide.

Azumaya et al. also reported an example of retention of the molecular chirality when the chiral crystal of 1,2-bis(N-benzoyl-N-methylamino)benzene 5 was dissolved in cold CDCl\(_3\.\)\(^{15}\) The BIPHOS ligand 6 crystallizes as a conglomerate, and a single crystal in CH\(_2\)Cl\(_2\) at -78°C reacts with [PdCl\(_2\)(CH\(_3\)CN)\(_2\)] to give the enantiomerically pure complex [PdCl\(_2\)(biphos)]. Tissot et al. reported an example of catalytic asymmetric synthesis where the enantiomerically pure complex was used in the catalytic asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with the anion of dimethyl malonate to give product in 93% yield and with 80% ee.\(^{16}\)

![Fig. 4. Achiral molecules with chiral memory effect](image)

**4. Asymmetric reactions using chiral memory derived from chiral crystals**

**4.1 Asymmetric nucleophilic addition to carbonyl group using chiral crystals of 2-benzoylbenzamides**

When 2-benzoyl benzamides 1a-d with various sizes of substituents on the nitrogen atom were synthesized and the crystal structure was analyzed by X-ray crystallographic analysis,
it was revealed that three substrates 1a-c afforded chiral crystals (Figure 5).\(^7\) As mentioned, achiral materials generally yield chiral crystals in about 10%; however, the designed molecules with the polarity and their round shapes crystallized in the chiral space group in very high proportion.\(^8\) In these substrates, the two carbonyl groups are unable to form a planar conformation, but formed a twisted up and down structure, and chiral crystals were obtained by forming crystals of either enantiomer. If the substrate had a relatively fast rate of racemization, the same enantiomeric crystals were obtained in the flask by the usual recrystallization from a solution. It is easy to obtain large quantities of the desired enantiomer crystals by adding seed crystals of one enantiomer during crystallization.

![Diagram](figure5.png)

Fig. 5. Achiral 2-benzoylbenzamides studied for chiral crystallization and asymmetric synthesis.

When the chiral crystals were dissolved in a solvent at room temperature, the molecular chirality disappeared in an instant. How long chiral molecular conformation is retained after the crystals were dissolved in a cold solvent? There are several techniques to measure the rate of racemization, and it can be obtained from the decay of optical rotation or CD spectra by longer life to some extent. However, these substrates have very fast rates of racemization, and the Cotton effect was not observed by the CD spectra immediately after dissolving the crystals in a solvent of -80°C by using a cryostat apparatus. Therefore, the rate of racemization for 1b was determined using VT-NMR techniques. Methylene protons of the diethyl group on the nitrogen atom of 1b are observed at the two different positions of anti and syn at room temperature; however, the protons in the diastereomeric relationship will be observed as four peaks at low temperatures. Activation free energy of racemization was calculated from the chemical shift, the coalescence temperature was 10.3 kcal mol\(^{-1}\) in toluene at -60°C, and the half-life could be reached in 2.2 \times 10^3 sec. The half-life is very short; however, asymmetric synthesis of a sufficiently high stereoselectivity was expected to be achieved by selecting a stereospecific reaction faster than racemization.

Nucleophilic addition reactions to the carbonyl group were examined. When the chiral crystals of 1 were added to a cooled toluene solution containing butyllithium, the adduct 7 was obtained in high yield. Optical purity of the product was determined after induction to phthalide 8 by treatment with acetic acid (Table 1). The product from 1a showed optical activity of 17% ee because of the significantly faster rate of racemization of 1a having small steric hindrance of dimethyl groups on the nitrogen atom. On the other hand, when using the chiral crystals of 1b and 1c, the product could be obtained with optical purity of more than 80% ee. As a matter of course, when using the crystals of racemic 1d, 7d and 8d were obtained as racemates. Whereas compound 1 showed short-lived chiral memory, it was enough to react with butyllithium. These results prepared unprecedented asymmetric
synthesis involving nucleophilic reaction of carbonyl groups using chiral memory with C-C axial chirality.

![Diagram of asymmetric reaction]

Table 1. Reaction using the crystal of 2-benzoylbenzamides with n-BuLi

| amide | R¹ | R² | space group | yield (%) of 8 | ee (%) of 8 |
|-------|----|----|-------------|---------------|------------|
| 1a    | Me | Me | P2₁2₁2₁     | 82            | 17         |
| 1b    | Et | Et | P2₁2₁2₁     | 82            | 82         |
| 1c    | Et | Bn | P2₁2₁2₁     | 83            | 80         |
| 1d    | Bn | Bn | Pbc a       | 87            | 0          |

4.2 Asymmetric reactions using chiral memory derived from asymmetric imides

We reported the asymmetric reaction using chiral memory owing to the C-N axial chirality derived from the chiral crystal of acyclic imide (Figure 6). The imide nitrogen atom has a planar structure, similar to the sp²-hybridized amide nitrogen atom, and can form multiple structures of EE, EZ, ZE, and ZZ. In imide 2, the tetrahydronaphthyl group (TENAP) on the nitrogen atom exhibited almost perpendicular conformation to the plane of the imide. Depending on the direction of the TENAP group, each conformation enters an enantiomeric relationship. Racemization rate of the substrate could be determined by measuring the decay of the CD spectra using a cryostat apparatus by dissolved chiral crystals in a cold solvent. Activation free energy of racemization of this imide was 18.4 kcal mol⁻¹ in THF at -20°C, which indicates that the chiral molecular conformation could be retained long enough after the chiral crystals were dissolved in a solvent. We tried the reaction of butyllithium with chiral molecules using this chiral memory. The reaction site is the benzoyl group of the side of the imide plane, and was reacted at -80°C; 9 and 10 were obtained as optically active forms of 83% and 81% ee, respectively. Furthermore, when provisional chiral molecule was irradiated in THF at -60°C, optically active oxetanes 11 and 12 were isolated.

4.3 Development of chiral crystallization and asymmetric reactions using the chiral crystal of naphthamides

To perform this asymmetric synthesis, 2-alkoxy-1-naphthamides 3 were chosen because the bond rotation between the naphthalene ring and the amide carbonyl corresponds to enantiomerization of 3, and the rate is considerably affected by the substituent of both the naphthalene ring and the amide group (Figure 7). Naphthamides with a bulky group such as the N,N-diisopropyl amide group have stable axial chirality, which is utilized in many
asymmetric synthesis. \(^{21}\) Therefore, achiral naphthamides possessing a relatively compact-size amide group derived from pyrrolidine and piperidine, \(3a\) and \(3b\), were prepared for our purpose. The X-ray single crystallographic analyses of the crystals revealed that both amides tend to have almost the same molecular conformation; remarkably, each carbonyl group twists almost orthogonally to the naphthalene plane.

![Diagrams and structures](https://www.intechopen.com)

Fig. 6. Chiral crystallization of achiral acyclic imide and asymmetric synthesis using the chiral memory

Fortunately, both \(3a\) and \(3b\) crystallized in a chiral space group, \(P\bar{2}_1\bar{2}_1\), and the constituent molecules adopted a chiral and helical conformation in the crystal lattice. The rate of racemization of \(3\) after dissolving the chiral crystals in a solvent was measured based on the changes in the CD spectra. The activation free energy (\(\Delta G^\neq\)) was calculated from the temperature dependence of the kinetic constant between 5 and 15°C as 21.2 ± 0.2 kcal mol\(^{-1}\) in THF. These facts indicate that the racemization of \(3b\) is too fast to be resolved in the usual manner. The lifetime can be lengthened by lowering the temperature so that the racemization is sufficiently slow and the reaction can be used to accomplish asymmetric synthesis.

The crystals of naphthamide \(3\) used for the asymmetric reaction were prepared by stirred crystallization from the melt. \(^{22}\) The samples were completely melted at 120°C, which greatly exceeds their melting points (mp of \(3b\): 110-112°C), cooled and solidified by lowering the temperature by stirring to 100°C. High reproducibility of both the chiral crystallization and asymmetric reaction was achieved by this method; however, the direction of the optical rotation of the photoproduct was inconsistent and appeared randomly. Of course, the
desired crystals of 3 could be selectively prepared in large quantities by the addition of a corresponding seed crystal during the crystallization process.

![Racemization of 2-alkoxy-1-naphthamides by Ar-(C=O) bond rotation](image)

We examined the asymmetric reaction using the provisional molecular chirality of naphthamide 3b (Figure 8). After chiral crystals of 3b were dissolved in a toluene solution containing diene (0.10 M) at -20°C, the solution was irradiated at the same temperature. Cyclobutane 13 was obtained in an optically active form of 76% ee at a 10% conversion of 3b. Furthermore, with the increase of the conversion of 3b, the ee value of 13 decreased rapidly. The rate of racemization of 3 at -20°C is very slow, and chirality was retained during irradiation. Why did the ee values decrease during the progress of the reaction? The amide directly racemized on irradiation via the twisted intramolecular charge transfer (TICT) mechanism from the singlet excited state.

![Photochemical cycloaddition of naphthamide 3b with 2,5-dimethylhexa-2,4-diene](image)

We also reported the 4+4 cycloaddition of excited 9-cyanonaphthalene with the ground state of 3, leading to an optically active 4+4 adduct with high enantioselectivity (Table 2). Chiral crystals of 3b was dissolved in a cooled THF solution of -20°C including 9-CNAN, and the solution was irradiated with an ultra-high pressure mercury lamp for 30 min. Only one cycloadduct 14 was obtained in 100% chemical yield, and the adduct showed optical activity of 95% ee. When we used a mixed solvent of MeOH and THF, almost the same ee value (94% ee) was obtained. Even at 20°C, we were able to obtain 29% ee of the adduct from the reaction in THF, in which the enantiomerization occurs competitively with the photocycloaddition. The rate of enantiomerization in alcoholic solvent is more suppressed than in THF, and the half-life is still 62.6 min. at 20°C. Surprisingly, we could obtain 88% ee of the product at 20°C.

For the stereochemistry of the reaction pathway, the (S)-proline derivatives were synthesized. The comparison of the absolute structure of the starting naphthamide and the adduct was studied, and it can be estimated that 9-CNNAp approaches from the vacant site of the carbonyl group to avoid the bulky substituents on the nitrogen atom (Figure 9).
Fig. 9. Reaction course of the photocycloaddition of chiral conformation of \((S)-3b\) with excited state of 9-CNAN

### Table 2. Asymmetric photochemical cycloaddition reaction of 3b with 9-cyanoanthracene using the provisional axial chirality

| entry | solvent          | temp (deg) | conc (mol L\(^{-1}\)) | conv of 3b (%) | ee of 14 (%) |
|-------|------------------|------------|------------------------|----------------|--------------|
| 1     | THF              | -20        | 0.05                   | 52             | 95           |
| 2     | THF              | 20         | 0.05                   | 45             | 29           |
| 3     | MeOH/THF         | -20        | 0.025                  | 54             | 94           |
| 4     | MeOH/THF         | 20         | 0.025                  | 40             | 88           |

4.4 Chiral lock of the provisional chiral memory of naphthamides

Next, we examined how to lock the bond rotation affecting racemization of the amides 3.\(^{25}\)

The racemization should be suppressed by substitution of the methoxy group at the 2-position of the naphthalene ring with the more bulky group.

A THF solution containing 3.0 eq. of \(-t\)-BuLi was cooled to -80°C and was followed by the addition of chiral crystals of 3a. After reaction for 1 h at the same temperature, the reaction mixture was treated in the usual manner. Analysis of the reaction product showed the formation of 2-\(t\)-butyl derivatives 15a in a 97% yield and in an optically active form of 85% \(ee\). When the chiral crystal of 3b was used for the \(S_NAr\) reaction, nearly similar results were
obtained. When the crystals of (+)-3a or 3b were used for the SNAr reaction, (+)-15a,b were obtained. Both amides 15a and 15b have stable axial chirality and did not racemize at room temperature for several months.

![Chemical structure](image)

Fig. 10. Asymmetric SNAr reaction of 3 with t-butyllithium using the provisional axial chirality

### 4.5 Kinetic resolution of racemic amines using provisional molecular chirality

We found that the kinetic resolution of racemic piperidines alkylated at the 2- or 3-position was performed using the provisional enantiomeric conformation of naphthamide 3a derived from chiral crystals. Chiral crystals of naphthamide 3a were added to a THF solution of racemic lithium amides prepared by the reaction of substituted piperidines with n-BuLi at -80°C; the reaction mixture was stirred for 5 hours at -20°C because the substitution reaction did not proceed below -20°C.

When a 2.0 equimolar amount of 2-methylpiperidine was used, 30% of naphthamide 3a was consumed, and 30% of 16a was isolated. The reaction conversion was low; however, the reaction was very clean, and 70% of unreacted naphthamide was recovered. Fortunately, 16a was obtained as the optically active form in 94% ee. Based on an increase of the amount of lithium amide to 5 eq., all naphthamide 3a was consumed and converted to 16a quantitatively with 81% ee. These results indicate that the 2.0 equimolar amounts of lithium amide form a stable intermediacy complex with naphthamide 3a, and an extra amount of piperidine must be necessary to obtain product 16 in good yield. The intermediacy enantiomeric complex reacts preferentially with one enantiomer of the racemic peridine.

We diminished the amount of piperidines using such additives as diisopropylamine, TMEDA, and HMPA by displacing the complex ligand. When 3.0 eq. of LDA was added to the 2.0 eq. of the piperidine lithium amide, the substitution reaction occurred in a 100% conversion, and 3a was isolated almost quantitatively in 73% ee. The addition of 1.0 eq. of TMEDA was also effective, and 80% of product was obtained with 80% ee. When 3.0 eq. of HMPA was used for the additives, all naphthamide was consumed, and 16a was obtained in 90% with 69% ee.

When racemic 2-ethylpiperidine was reacted with the provisional chiral conformation of 3a, similar results were obtained as the reaction with 2-methylpiperidine. However, when racemic 3-methylpiperidine was used as a nucleophile, the substitution reaction occurred quantitatively; however, the ee value resulted in 17%. The methyl group at the 3-position of the piperidine ring was insufficient to control the stereoselectivity because of the distance between the reacting nitrogen atom and the substituent. On the contrary, the substituent at the 2-positions worked sufficiently as strong chiral flags to control the stereoselectivity.
4.6 Photosensitized 2+2 cycloaddition reaction using chiral memory

Achiral \( N,N,4\)-triethylcoumarin-3-carboxamide 4 crystallized in a chiral space group, \( P2_12_12_1 \) (Figure 12).\(^{20}\) The X-ray single crystallographic analysis of the crystals revealed that the amides 12 tend to have a twisted conformation, of which the amide carbonyl group twists almost orthogonally to the coumarin chromophore. There are two enantionic conformations as shown in Figure 12 caused by the C-(C=O) bond rotation in fluid media; however, the chiral crystal is composed of a single enantiomer.

The rate of racemization was measured according to the changes in the CD spectra using a cryostat apparatus, and the activation free energy and the half-life were calculated. The racemization of 4 in THF was too fast at room temperature to determine the rate. On the other hand, when the crystals of 4 were dissolved in THF at 5°C, the half-life of racemization was 11.9 min. The half-life increased as the temperature was lowered, and \( t_{1/2} \) was 30.5 and 82.0 min at the temperatures of 0°C and -5°C, respectively. The activation free energy (\( \Delta G^\ddagger \)) was calculated as the temperature dependence of the kinetic constant (5°C: 4.85 \times 10^{-4}, 0°C: 1.89 \times 10^{-4}, -5°C: 7.04 \times 10^{-5}) to be 20.5-20.7 kcal mol\(^{-1}\). In the case of the racemization in MeOH or DMF, the rate showed a considerably low activation free energy of 22.3-22.4 kcal mol\(^{-1}\), and exhibited 20.2 and 23.6 min of half-life at 25°C, in MeOH and DMF, respectively. These facts indicate that the racemization of 4 is too fast to resolve in the usual manner; however, it can be controlled by lowering the temperature and with the selection of the solvent, and the lifetime becomes long enough for utilization in asymmetric synthesis.

Fig. 12. Racemization of coumarinecarboxamide 4 owing to the rotation of the Ar-(C=O) bond
When powdered crystals of 4 (0.02 mol L\(^{-1}\)) were dissolved in a cooled MeOH solution (-20°C) containing ethyl vinyl ether (0.1 mol L\(^{-1}\)) and irradiated at -20°C with a 365 nm line, optically active adducts 17 were obtained as would be expected. However, the ee values were affected by the conversion. High ee values of products (82% ee of endo-17 and 86% ee of exo-17) were obtained by suppressing the conversion of 18%; however, the ee value decreased as the conversion increased. We measured the changes of the CD spectral of an MeOH solution of 4 using a cryostat apparatus by irradiating at -20°C, and it was confirmed that racemization of the starting amide 4 in the singlet-excited state had occurred. Therefore, we examined the triplet-sensitized photocycloaddition of 4 using benzophenone (BP) as a triplet sensitizer to avoid photoracemization from the singlet-excited state. When powdered crystals of 4 were dissolved to a cooled MeOH solution (-20°C) containing ethyl vinyl ether and benzophenone (0.01 mol L\(^{-1}\)) and were irradiated at -20°C for 3 h, high optical yields of adducts, 94% ee of both endo- and exo-17, were obtained. The use of 0.02 mol L\(^{-1}\) of benzophenone resulted in 100% conversion and a 98% chemical yield of adducts; furthermore, surprisingly high ee values of products, 96% ee of endo-17 and exo-17, were obtained. Finally, 98% ee of endo-17 and 97% ee of exo-17 were isolated by increasing the concentration of benzophenone to 0.1 mol/L.

The asymmetric cycloaddition using the homochirality in the crystal was also performed by the use of 2-methoxypropene. In this case, only endo-17 was obtained in an almost quantitative yield, and asymmetric synthesis with high ee, up to 99%, was performed.

This reaction provided the first example of photosensitized intermolecular cycloaddition with high enantiomeric excess using the homochirality in the crystal generated by spontaneous crystallization.

Table 3. Asymmetric photosensitized cycloaddition reaction of 4 with alkenes using the provisional axial chirality

| Alkene | conv. of 4 (%) | yield of 17 (%) | endo-17 : exo-17 | ee of 17 (%) |
|--------|----------------|----------------|------------------|-------------|
| OEt    | 96             | 99             | 3 : 1            | 98          |
| Me     | 74             | 98             | 100 : 0          | 99          |

Reaction conditions: 4 (0.02 mol/L), alkene (0.2 mol/L), BP (0.1 mol/L)

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5. Diastereoselective reaction using memory effect of molecular chirality controlled by crystallization

Asymmetric chiral transfer techniques using chiral memory derived from chiral crystals can be applied to diastereoselective reaction (Figures 13, 14). We used the aromatic amides 18-20 with an optically active proline group as the chiral source to give the chiral memory capabilities. Four diastereomers are possible in these compounds owing to the rotational isomer of C(=O)-N and C-(C=O) bonds. When we used diastereomeric mixture in asymmetric reactions, we obtained the mixture of products reflecting the ratio of starting diastereomers, and high stereoselective reaction could not be achieved. However, when diastereomixture of amides were crystallized, epimerization owing to the bond rotation was promoted, and the mixture automatically converged to a single diastereomer by Crystallization-Induced Diastereomer Transformation (CIDT) (Figure 13).

5.1 Diastereoselective reaction using memory effect of naphthamides

In the NMR spectrum of naphthamide 18, several peak pairs were observed derived from diastereomixtures, which suggested that this amide existed as a mixture of diastereomers in the solution. After evaporating the solution to solidify the amide, NMR spectrum measured immediately after dissolving the solid to CDCl₃ showed only peaks derived from single diastereomers. This fact indicated that diastereomixture crystallized by converging to single crystalline diastereomer by simple solidification (Figure 15). Conformation in the crystal was determined as (S,aR)-18-A by single crystal X-ray crystallographic analysis. Moreover, this chiral molecular conformation in solution was also retained at low temperature for long enough time to be used as a chiral memory.

Fig. 13. Asymmetric synthesis using chiral memory derived from CIDT
Diastereoselective photocycloaddition reaction with 9-CNAN was examined. Irradiation of amides 18a-b before solidification in the presence of 9-CNAN gave adducts 21a and 21b with the de values of 63% and 53%, respectively. On the other hand, when the crystals of amides obtained by CIDT were dissolved in THF at -20°C, 96% de of adduct 21a and 100% de of 21b were obtained. The molecular conformation of 18 was retained in a cold solution after dissolving the crystals, and could act as a chiral molecular memory; 9-CNNAAP approached selectively from the less hindered site of carbonyl group of naphthamide.

Fig. 14. Aromatic amides with chiral memory effect derived from CIDT

![Diagram showing the reaction pathway and conformational changes](image)

Fig. 15. CIDT of naphthamide with proline group

5.2 Diastereoselective reaction using memory effect of coumarin-carboxamides

We found that coumarin carboxamide 19 also existed as a mixture of diastereomers in solution, and could be converged to (S,aR)-conformer by solidification. When the crystals of 19 were dissolved in MeOH at -20°C and irradiated in the presence of electron-rich alkenes, perfectly stereo-controlled 1:1 photoadduct 22 was obtained in 100% de (Figures 16, 17).
Table 4. Diastereoselective photocycloaddition using chiral memory derived from CIDT

| Amide 18-A | Solidification conv. of 18 (%) | Yield of 21 (%) | De of 21 (%) |
|------------|--------------------------------|-----------------|--------------|
| 18a (R = Me) before | 77 | >99 | 63 |
| 18b (R = Et) before | 70 | >99 | 53 |
| 18a (R = Me) after | 62 | >99 | 96 |
| 18b (R = Et) after | 70 | >99 | 100 |

Fig. 16. Epimerization of coumarinecarboxamide with chiral handle

Fig. 17. Stereoselective photocycloaddition using chiral memory derived from CIDT

5.3 Diastereoselective reaction using memory effect of quinolonecarboxamides

2-Quinolone-4-carboxamide 20 possessing (S)-proline methyl ester as a chiral handle was chosen for the purpose. Amide 20 exists as a mixture of two diastereomers in the ratio of aR:aS = 40:60 (diastereomeric excess, de = -20%) before crystallization (Figure 18). When the mixture was crystallized from a THF solution by evaporating solvent at 70°C, the minor
isomer was easier to crystallize than the major isomer, and they converged to almost a single
diastereomer in a ratio of aR:aS = 95:5 (de = 90%). Furthermore, recrystallization of the
crystals once from ether easily gave 99% de of amide 20. Axial chirality was stable for several
days at room temperature; however, heating the chloroform solution of (S,aR)-20 at 55°C for
12 hrs gave the exact same diastereomixture as before crystallization.

Next, the homochiral crystals were utilized for subsequent diastereoselective reactions.
Diastereoselective 2+2 photocycloaddition reaction of amide 20 with methacrylonitrile was
examined. The reaction with methacrylonitrile proceeded effectively, stereo-, and
regiospecifically. The amide 20 before crystallization was irradiated in the presence of
methacrylonitrile with a high-pressure mercury lamp at 20°C until most of the starting amide
was consumed (2 hrs). The photochemical reaction occurred effectively, and 2 + 2
cycloadducts were obtained in 100% chemical yields; both diastereomers were endo isomers,
minor (1S,2aR,8bR)-23, major (1R,2aS,8bS)-23, and the de value was -25%. Since epimerization
was not observed at 20°C, it seems that the de value of the photoproducts should be attributed
to the ratio of the diastereomers of the amide 20 before crystallization (-20% de).

Fig. 18. Epimerization of quinolonecarboxamide with chiral handle and stereoselective
photoaddition using chiral memory.

Furthermore, we examined a photocycloaddition reaction using the homochiral molecular
conformation converged by CIDT. The crystals were expected to be composed of a single
diastereomer of (S,aR)-conformation, and the epimerization in the solution caused by the
bond rotation between the quinolone and the carbonyl group was restricted at room
temperature. In other words, conformation in the crystals may be retained as frozen after
dissolving them in the solvent at room temperature, and molecular homochirality can be
effectively transferred to the products. The THF solution of \((S,aR)\)-20 containing methacrylonitrile was irradiated with a high-pressure mercury lamp for 2 hrs until the starting amide was consumed. When the reaction was performed at 20°C, two 2 + 2 adducts, major \((1S,2aR,8bR)\)-23 and minor \((1R,2aS,8bS)\)-23 were obtained in 99% yield. As expected, epimerization was strongly controlled at this temperature, and a high de of 89% was achieved. Even at low temperature, the reaction proceeded effectively, and after decreasing the temperature, the de values improved; the best de of 98% was obtained in the reaction at -80°C. The axial chirality evoked by crystallization directed the course of the approach of the reacting molecules, and a fully controlled diastereoselective intermolecular photocycloaddition reaction was performed.

6. Prospects for new asymmetric reaction using crystal

New aspects of chemistry are deployed by effectively utilizing the unique nature of crystals. In this chapter, a new approach to asymmetric chemistry using chiral crystals found in our research groups is introduced. We succeeded in transferring the chirality expressed by chiral crystallization of achiral substrate to products in a variety of reactions in homogeneous systems. Stereoselective reaction using chiral crystals was limited to the topochemical solid-state photoreaction, and the reactions expanded in a homogeneous system were able to achieve the highly stereoselective asymmetric reaction. Some readers may think that chiral molecules possessing memory effects introduced in this chapter are like acrobats using a very narrow energy band. Figure 19 shows an energy diagram for racemization of chiral molecules that express chirality by spontaneous crystallization or by Crystallization-Induced Enantiomer Transformation (CIET). We can effectively use molecules with

![Fig. 19. Energy diagram for racemization of axially chiral and achiral materials available for asymmetric synthesis via spontaneous chiral crystallization](www.intechopen.com)
activation free energy of racemization from 10 to 30 kcal mol\(^{-1}\) for chiral memory. It is not an unusual technique, but a rather typical approach that can be widely utilized in asymmetric reactions. We have found many more applications to this method using chiral memory; we will present them in future work. In addition, this method could be applied to the diastereoselective reaction using chiral memory derived from CIDT. These findings suggest that the molecular information in the crystal can be widely applied to a variety of chemistry, in addition to organic asymmetric reaction.

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