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Asymmetric Synthesis

Asymmetric Synthesis Involving Reversible Photodimerization of a Prochiral Flavonoid Followed by Crystallization

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Abstract: Asymmetric synthesis involving photochemical dimerization of a prochiral flavonoid derivative in solution without any chiral source was achieved. Irradiation of ethyl 6-bromochromonecarboxylate in solution efficiently gave a C_2-chiral *anti*-head-to-head dimer in excellent chemical yield with good quantum efficiency (Φ_{365} = 0.15). X-ray crystallographic analysis revealed that the dimer crystallized as a conglomerate of *C*2 space group. The crystalline dimer precipitated upon irradiation of the monomer in solution, and indirect racemization of the dimer through a reversible photoreaction in solution and selective crystallization simultaneously occurred to give the C_2-chiral dimer in optically active form with up to 80 % *ee*. Optically active photoproducts could be obtained by simply irradiating achiral materials in solution without an external chiral source.

Introduction

Since Havinga discovered the first example of dynamic selective crystallization by using racemic conglomerate crystals,[1] many valuable examples of total optical resolution by deracemization, selectively leading to single-handed molecules, have been reported.[2,3] This concept is closely linked to homochirality of living matter and the origin of life, which is of wide interest in prominent research fields.[4–6]

Asymmetric synthesis from prochiral starting materials by using only crystal chirality under absolutely achiral conditions, that is, absolute asymmetric synthesis,[7] has been investigated by many methods, including solid-state photochemical reactions[8] and asymmetric reactions by using frozen chirality.[9] Recently, elegant examples of asymmetric synthesis have been demonstrated by combining chemical reactions providing asymmetric centers with dynamic selective crystallization, and products with high *ee* values without an external chiral source have been obtained.[10] In such cases, the dynamic crystallization process involves an enolate anion under basic conditions[10,11] and a reversible reaction by thermal racemization.[12] This process has been named the TT-type (thermal reaction and thermal racemization) absolute asymmetric reaction (Figure 1).

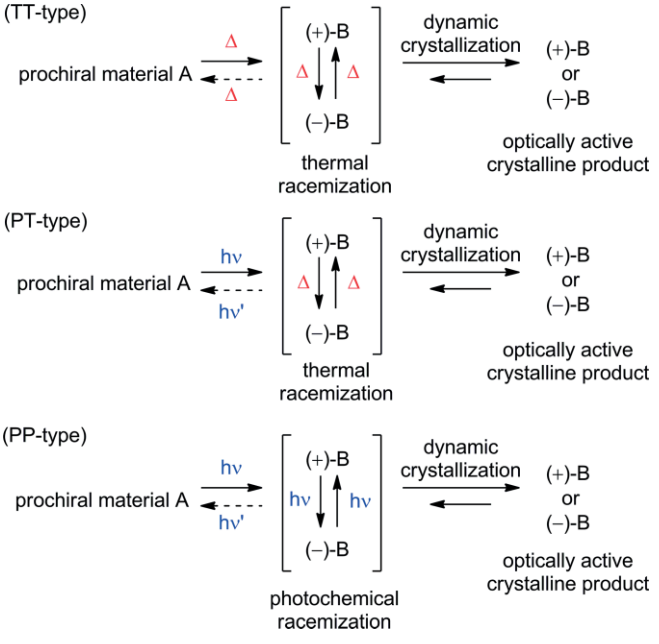

Figure 1. Three types of asymmetric reactions involving dynamic crystallization.

Another example involves the photochemical isomerization reaction of aroylacrylamide followed by intramolecular cyclization and racemization through thermally promoted ring-opening and ring-closing reactions.[13] In this case, a nearly enantiomerically pure product was obtained by irradiating a solution of the prochiral aroylacrylamide with sunlight followed by gradual solidification by evaporation of the solvent outdoors. The reaction was triggered by photoisomerization of the alkenyl group; however, racemization of the cyclization product involved thermal ring-opening and ring-closing reactions. This is called a PT-

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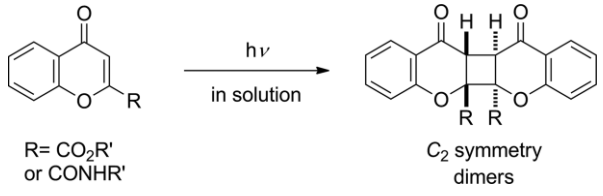
type (photoreaction and thermal racemization) absolute asymmetric reaction. Herein, we focused on developing a new asymmetric synthetic system by simple irradiation of achiral materials in solution, involving a photochemical process both for generating chiral centers and for reversible racemization, a PP-type (photochemical reaction and photochemical racemization) asymmetric reaction.

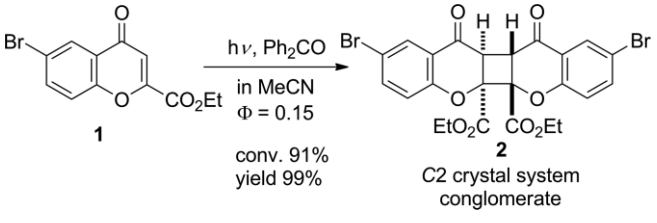
Results and Discussion

To achieve PP-type asymmetric induction, the photochemical dimerization reaction of chromone was selected.[14] Chromone (benzo-γ-pyrone) is the parent of a large number of naturally occurring compounds such as flavonoids and plant pigments and is also found in many pharmaceutical materials.[15] Recently, the photolysis of such chromonecarboxylic acid derivatives in fluid media was explored to give C_2-symmetric *anti*-head-to-head (*anti*-HH) dimers effectively and in excellent chemical yields from the triplet excited state. In this photoreaction, formation of four dimers was possible; however, only the C_2-symmetric *anti*-HH dimers were exclusively produced (Scheme 1).[14]



Scheme 1. Stereoselective and product-selective photochemical dimerization reaction of 2-chromonecarboxylic esters and amides.

If the photodimerization of achiral chromone gives a conglomerate dimer and the reverse reaction occurs photochemically, we can perform the PP-type asymmetric reaction involving dynamic crystallization (Figure 1). We analyzed the crystal structures of several dimers by X-ray structural analysis and HPLC analysis by using a chiral column to determine whether they were conglomerates, and we found that brominated derivative **2** afforded a monoclinic *C*2-racemic conglomerate (Scheme 2). The structure of crystalline dimer **2** was also established to have the *anti*-HH stereochemistry. The absolute structure was determined by X-ray crystallography as the (*S*,*S*,*S*,*S*) configuration for (+)-**2** (Figure 2).[16] We then applied this photodimerization to the proposed absolute asymmetric synthesis involving dynamic crystallization.



Scheme 2. Photochemical dimerization of **1** from the triplet excited state.

Upon irradiation of ethyl 6-bromochromone-2-carboxylate (**1**) in MeCN with a high-pressure mercury lamp under an argon atmosphere, the photodimerization reaction proceeded efficiently, and a single dimer was obtained exclusively (81 % conversion). The quantum yield (Φ) for the dimerization by using a 365 nm line was 0.15 at 0.05 M concentration. The dimerization was also effectively sensitized by benzophenone as a triplet sensitizer. In this case, the photosensitized dimerization reaction reached 91 % conversion and the chemical yield was 99 % (on the basis of consumed monomer).

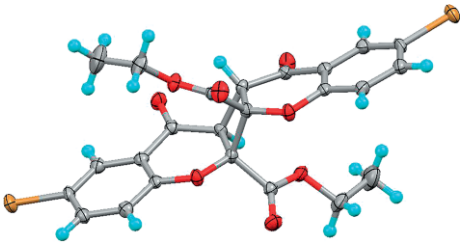


Figure 2. Perspective view of (*S*,*S*,*S*,*S*)-(+)-**2** showing thermal ellipsoids at 50 % probability.

Next, we examined another important requirement, that is, whether racemization of the dimer occurred upon irradiation. Figure 3 shows the UV spectra of monomer **1** (red line) and *anti*-HH photodimer **2** (blue line). The dimer has 2-alkoxyphenone chromophores and absorbs in a longer wavelength region than the monomer. Even under these conditions, the conversion reached 81 % in the photostationary state, because the dimer might also serve as a triplet sensitizer for the dimerization of **1**.

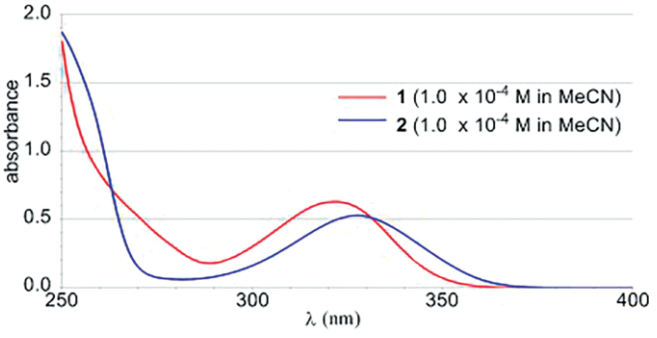


Figure 3. Absorption spectra of monomer **1** (red line) and dimer **2** (blue line) in MeCN, each at a concentration of 1.0×10^{-4} M.

Furthermore, irradiation of a low concentration (0.005 M) of dimer **2** in MeCN regenerated monomer **1** quantitatively at 25 % reaction conversion. This is considered the photostationary state under these conditions. Eventually, it was confirmed that the reverse photoreaction proceeded and the achiral monomer was regenerated, which is equivalent to the photoracemization of the primary produced dimer (Figure 4). Upon irradiating **1** in solution, racemic C_2-symmetric dimer **2** was generated at the early stage of the reaction. According to the progress of the photoreaction, the crystalline dimer precipitated, and the process involved selective crystallization. In the mother liquor, the reverse photoreaction occurred, which is not a direct photoracemization, but a process equivalent to racemization involving a reverse reaction. From this reversible photochemical system combined with selective crystallization, we could anticipate obtaining optically active photoproducts by

simple irradiation of an achiral starting material under absolutely achiral conditions.

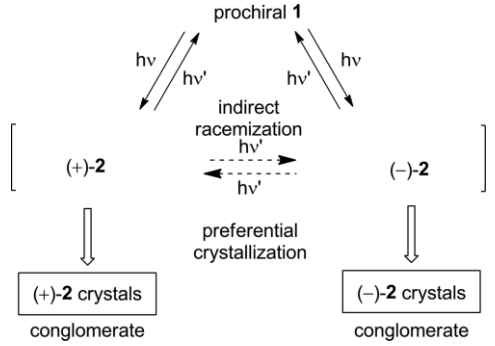


Figure 4. Asymmetric photochemical reaction involving dynamic selective crystallization by racemization by photoreversible reaction (PP-type reaction).

Three procedures were examined for the asymmetric synthesis involving reversible photodimerization followed by crystallization (Table 1). A double glass tube was used for the photoreaction with an artificial light source for methods A and B. An acetonitrile solution of monomer **1** was irradiated with a 365 nm line from a 350 W high-pressure mercury lamp by using a light guide while stirring magnetically. A cooling apparatus was used for the low-temperature experiment.

Table 1. Asymmetric synthesis involving reversible photodimerization followed by crystallization.

Entry	Method	Conc. [M]	Temp [°C]	Seeding	*ee*[a] [%]
1	A	0.04	20	no	0–2
2	A	0.01	20	no	0–29
3	A	0.01	20	yes	32–50[b]
4	B	0.01	–40	no	0–38
5	B	0.01	–40	yes	55–80[b]
6	C	0.02	10–20	no	0–8
7	C	0.02	10–20	yes	15–30[b]

[a] The *ee* value was determined by HPLC by using a CHIRALCEL OD-H column. Crystallization was examined five times each. The major stereoisomer randomly appeared. [b] The product had the same chirality as the seed crystal.

For method A, an acetonitrile solution of **1** was irradiated, and the solvent was gradually evaporated by slow introduction of nitrogen. After all the solvent was evaporated, the remaining solid of dimer **2** was analyzed by HPLC by using a CHIRALCEL OD-H column.

For method B, an acetonitrile solution of **1** was irradiated at –40 °C to promote crystallization of the produced dimer. After irradiation, $CHCl_3$ was added to the reaction mixture to dissolve the crystalline dimer, and the *ee* value of the entire amount of dimer (both in the crystal and the mother liquor) was determined by HPLC analysis.

For method C, an acetonitrile solution of monomer **1** in a vial was irradiated with natural sunlight under open air by gradually evaporating the solvent with stirring magnetically. In all cases, according to the progress of the photodimerization reaction, crystalline dimer **2** precipitated as a colorless powder.

Except for method B, the solvent was removed by evaporation during irradiation, and the solid dimer remained at the bottom of the glass tube. After the reaction, $CHCl_3$ was added to dissolve the precipitate, and the *ee* value of the generated dimer was analyzed by HPLC.

For method A, upon irradiating a 0.04 M acetonitrile solution at 20 °C by evaporating the solvent gradually, the residual crystalline dimer was obtained as nearly a racemate (Table 1, entry 1). A high 0.04 M concentration of the monomer resulted in acceleration of the crystallization and a low *ee* value. Upon decreasing the concentration to 0.01 M to suppress the rate of dimerization against the reverse reaction, the optically active dimer was obtained as expected; however, it had a maximum *ee* value of 29 % (Table 1, entry 2). Seeding of a small amount of dimer crystal was effective in raising the *ee* value to 50 % (Table 1, entry 3). In this case, the product possessed the same handedness of chirality as the seed crystal.

To promote crystallization in method B, the reaction temperature was decreased to –40 °C instead of evaporating the solvent. If a concentration of 0.01 M was used, decreasing the temperature to –40 °C accelerated the crystallization and gave better results. We obtained the optically active product without seeding with up to 38 % *ee* (Table 1, entry 4). Finally, irradiation of **1** involving dynamic crystallization by seeding a tiny piece of single crystal controlled the handedness of chirality to achieve a higher *ee* value of up to 80 % (Table 1, entry 5).

Both monomer **1** and dimer **2** absorb longer wavelengths in the UV region, and dimerization by method C proceeded by the use of natural sunlight. An acetonitrile solution of **1** was irradiated with natural sunlight at 10–20 °C on the roof of the chemistry building of Chiba University on a sunny day. The solution was continuously stirred until all of the solvent had evaporated, which took 6 h. The remaining colorless solid was analyzed by HPLC. With no seeding, crystallization was promoted spontaneously, and a low *ee* or a racemic dimer was obtained (0–8 % *ee*; Table 1, entry 6). On the other hand, by seeding a small amount of powdered crystal during irradiation, we obtained the dimer with 15–30 % *ee* possessing the same chirality as the seed crystal (Table 1, entry 7).

We obtained optically active materials simply by irradiating prochiral materials in solution under absolutely achiral conditions. This reaction is an example of absolute asymmetric synthesis by using the properties of crystal chirality. Generation of chirality and spontaneous breaking of symmetry are closely linked to homochirality of living matter and the origin of life, which is of wide interest in prominent research fields.

Conclusions

We achieved an asymmetric photodimerization reaction by irradiating prochiral materials in solution with a reversible photoreaction and selective crystallization. Three important requirements are needed to achieve this asymmetric photoreaction: (1) the structure of the product must be chiral; (2) the dimer must crystallize as a conglomerate; (3) racemization of the dimer must occur effectively by a reverse photoreaction. This reaction provides not only the first example of asymmetric synthesis by combining a reversible photochemical reaction with crystallization but also introduces the useful asymmetric synthesis of a pharmaceutically important flavonoid derivative.

Acknowledgments

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Keywords: Asymmetric amplification · Photochemistry · Dimerization · Crystallization · Reversible reactions

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[16] Single crystal X-ray structure analysis of (*S*,*S*,*S*,*S*)-(+)-**2**. Colorless prismatic ($0.20 \times 0.10 \times 0.05$ mm^3), monoclinic space group *C*2, a = 11.6061(6) Å, b = 10.3303(5) Å, c = 9.9374(5) Å, β = 108.8720(10)°, V = 1127.39(10) Å^3, Z = 2, λ (Cu-K_α) = 1.54 Å, ϱ = 1.750 g cm^{-3}, μ = 5.003 mm^{-1}, 3092 reflections measured (T = 173 K, 4.702° < θ < 68.173°), number of independent data collected: 5877, number of independent data used for refinement: 2027 in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0218, wR_2 = 0.0559 [$I > 2\sigma(I)$], R_1 = 0.0218, wR_2 = 0.0560 (all data), and GOF = 1.081, H-atom parameters constrained. Flack parameter = 0.075(6) for (*S*,*S*,*S*,*S*) configuration. CCDC 1576823 [for (*S*,*S*,*S*,*S*)-(+)-**2**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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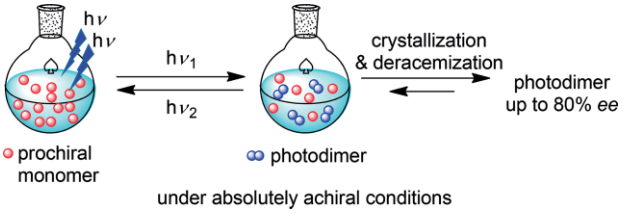
Asymmetric Synthesis Involving Reversible Photodimerization of a Prochiral Flavonoid Followed by Crystallization



Asymmetric photodimerization is achieved by irradiating a prochiral flavonoid derivative in solution under absolutely achiral conditions. The crystalline dimer precipitates upon irradiation of the monomer in solution, and indirect racemization of the dimer through a reversible photoreaction in solution and selective crystallization occur simultaneously to give the C_2-chiral dimer.

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