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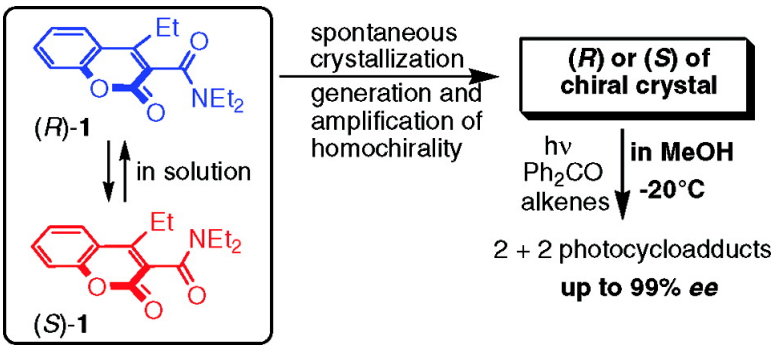

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Photosensitized 2 + 2 Cycloaddition Reaction Using Homochirality Generated by Spontaneous Crystallization

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Mirror symmetry breaking influenced by a chiral crystalline environment can be considered an attractive methodology for obtaining optically active compounds from achiral compounds; this methodology is recognized as the absolute asymmetric synthesis.[1] Many examples of the solid-state photoreaction leading to optically active materials have been successfully demonstrated.[2] Recently, a new methodology using the molecular homochirality in the crystal as a source of homochirality in solution was explored.[3] The chirality can be effectively transferred to optically active products by asymmetric reactions involving a nucleophilic reaction[4] and an intermolecular photochemical reaction.[5] Now we have found that an achiral coumarincarboxamide crystallized in a chiral fashion and the molecular homochirality in the crystal could be transferred by a triplet-sensitized photocycloaddition reaction with almost quantitative enantiomeric yields. This reaction provides the first example of a photosensitized asymmetric reaction using the homochirality generated by spontaneous crystallization.

Achiral *N*,*N*,diethyl-4-coumarin-3-carboxamide **1** was prepared from 4-ethylcoumarincarboxylic acid and diethylamine,[6] and crystallized in a chiral space group, $P2_12_12_1$ (Figure 1). The X-ray single crystallographic analysis of the crystals revealed that the amides **1** tend to have a twisted conformation, of which the amide carbonyl group twists almost orthogonally to the coumarin chromophore. There are two enantiomeric conformations as shown in Figure 1 caused by the C−(C═O) bond rotation in fluid media; however, the chiral crystal is composed of a single enantiomer.

Because the rate of racemization of the amide **1** is slow, a high enantiomeric excess of the bulk crystals could not be obtained by the usual recrystallization from a solvent. Therefore, crystals **1** used for the asymmetric synthesis were prepared by stirred crystallization at high temperature, by which the completely melted sample of **1** at 120 °C (mp: 114 °C) was cooled and solidified by lowering the temperature to 110 °C with stirring.[7] A high level of reproducibility of chiral crystallization was achieved by this method.

To perform the asymmetric synthesis using the homochirality in fluid media, the chemical reaction should occur rather faster than the racemization.[5] Therefore, 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 **1** in THF was too fast at room temperature to determine the rate. On the other hand, when the crystals of **1** 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 and −5 °C, respectively (Table 1). The activation free energy ($\Delta G^{\ddagger}$) was calculated as the temperature dependence of the kinetic constant (5 °C, 4.85×10^{-4}; 0 °C, 1.89×10^{-4}; −5 °C, 7.04×10^{-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

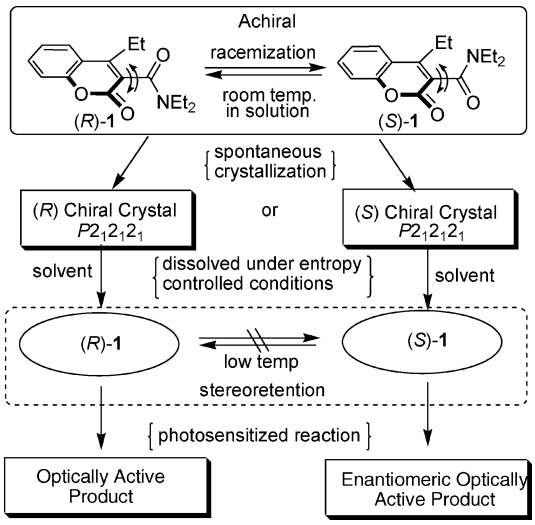

Figure 1. Racemization of **1** caused by the C−(C═O) bond formation and asymmetric synthesis using the homochirality in the crystal.

Table 1. Kinetic Parameters for Racemization of the Coumarincarboxamide **1** in Various Conditions

solvent	temp (°C)	$t_{1/2}$ (min)	$K \times 10^{-4}$ (S^{-1})	$\Delta G^{\ddagger}$(kcal mol^{-1})
THF	−5	82.0	0.704	20.7
	0	30.5	1.89	20.6
	5	11.9	4.85	20.5
MeOH	15	84.8	0.681	22.3
	20	41.0	1.41	22.3
	25	20.2	2.86	22.3
DMF	15	92.7	0.623	22.4
	20	45.5	1.27	22.4
	25	23.6	2.44	22.4

20.2 and 23.6 min of half-life at 25 °C, in MeOH and DMF, respectively. These facts indicate that the racemization of **1** is too fast to resolve in a 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.

We tried the intermolecular 2 + 2 photocycloaddition reaction of the temporary chiral amide with alkenes. Before the asymmetric reaction, the photochemical cycloaddition reaction of **1** with ethyl vinyl ether at 20 °C was examined because the cycloaddition reaction of coumarincarboxamide derivatives has not been reported. MeOH was used as a solvent to control the bond rotation corresponding to the racemization of **1**. An argon-purged MeOH solution prepared by dissolving a solid of coumarincarboxamide **1** (0.02 mol/L) and ethyl vinyl ether (0.1 mol/L) at room temperature was irradiated for 3 h at 20 °C. The addition reaction proceeded

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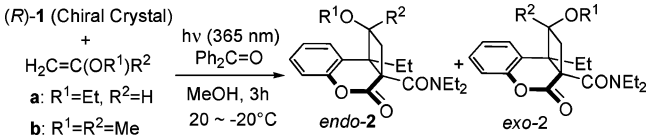
Table 2. Asymmetric Photochemical Reaction of Coumarincarboxamide **1** with Alkenes Using Homochirality in the Crystal



entry	alkene	BP[f] (mol L^{-1})	temp (°C)	conv of **1** (%)	yield of **2** (%)	ratio of *endo*-**2**/ *exo*-**2**	ee (%) of *endo*-**2**[g]	ee (%) of *exo*-**2**[g]
1[a]	a	0	20	100	99	2:1	0	0
2[b,c]	a	0	−20	18	95	3:1	82	86
3[b]	a	0	−20	100	95	3:1	51	52
4[b,d]	a	0.01	−20	80	99	3:1	94	94
5[b,d]	a	0.02	−20	100	98	3:1	96	96
6[b,d]	a	0.1	−20	100	99	3:1	98	97
7[b,d]	b	0.02	−20	74	98	1:0	99	
8[b,d,e]	b	0.1	−20	90	97	1:0	97	

[a] A MeOH solution containing coumarinecarboxamide**1** before crystallization (0.02 mol/L) and 0.1 mol/L of ethyl vinyl ether was irradiated for 3 h at 20 °C. [b] Powdered crystals of **1** (0.02 mol/L) was added to a cooled MeOH solution (−20 °C) containing 0.1 mol/L of ethyl vinyl ether or 2-methoxypropene and benzophenone (0∼0.1 mol/L), and the solution was irradiated at the same temperature under argon atmosphere. [c] Irradiated for 0.5 h. [d] Benzophenone (BP) was added as a triplet sensitizer. [e] Irradiated for 6 h. [f] Absorption coefficients of the amide **1** and BP at 365 nm in the MeOH were 20 and 60 mol^{-1} cm^{-1} dm^3, respectively. [g] The ee value was determined by HPLC using a CHIRALCEL AD-H column.

effectively and two cyclobutane-type adducts were isolated in the ratio of *endo*-**2a**/*exo*-**2a** = 2:1 (Table 2, entry 1). As a matter of course, the racemization took place after dissolving crystals at room temperature; therefore, racemic cyclobutanes **2a** were isolated. The structure of the minor *exo*-isomer was unequivocally determined by X-ray single-crystal structural analysis, whereas the major *endo*-**2a** did not give available single crystals.

Next, the proposed asymmetric reaction using the homochirality derived from spontaneous crystallization of achiral coumarincarboxamide **1** was tried.

When powdered crystals of **1** (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 **2a** were obtained as would be expected (entries 2, 3). However, the ee values were affected by the conversion. High ee values of products (82% ee of *endo*-**2a** and 86% ee of *exo*-**2a**) were obtained by suppressing the conversion of 18% (entry 2); however, the ee value decreased as the conversion increased. After 100% consumption of starting amide **1**, lower ee values of **2** were obtained (entry 3). We measured the changes of the CD spectral of an MeOH solution of **1** using a cryostat apparatus by irradiating at −20 °C, and it was confirmed that racemization of the starting amide **1** in the singlet-excited-state had occurred. Therefore, we tried the triplet-sensitized photocycloaddition of **1** using benzophenone (BP) as a triplet sensitizer to avoid photoracemization from the singlet-excited state. When powdered crystals of **1** 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*-**2a,** were obtained (entry 4). 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*-**2a** and *exo*-**2a**, were obtained (entry 5). Finally, 98% ee of *endo*-**2a** and 97% ee of *exo*-**2a** were isolated by increasing the concentration of benzophenone to 0.1 mol/L (entry 6).

The use of crystals generated by spontaneous crystallization in the photocycloaddition reaction can lead to isolation of either of the enantiomers of the cycloadduct. Of course, the desired crystals of **1** could be selectively prepared in large quantities by the addition of a corresponding seed crystal during the crystallization process.

The asymmetric cycloaddition using the homochirality in the crystal was also performed by the use of 2-methoxypropene (entries 7, 8). In this case, only *endo*-**2b** was obtained in an almost quantitative yield, and asymmetric synthesis with high ee, up to 99%, was performed (entry 7). The structure was also unequivocally established by X-ray crystallographic analysis.

In conclusion, we have demonstrated the first example of photosensitized intermolecular cycloaddition with high enantiomeric excess using the homochirality in the crystal generated by spontaneous crystallization.

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Supporting Information Available: Experimental procedures, crystal data of **1**, *exo*-**2a**, *endo*-**2b**. This material is available free charge via the Internet at http://pubs.acs.org.

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