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Two-Step Asymmetric Reaction Using the Frozen Chirality Generated by Spontaneous Crystallization

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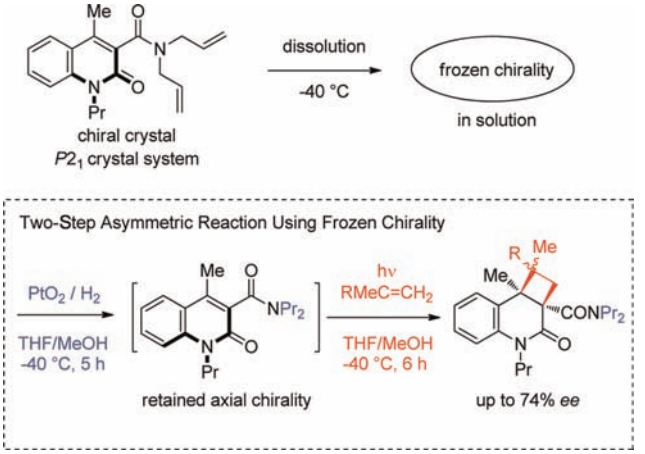
ABSTRACT



***N,N*-Diallyl-4-methyl-1-propyl-2-quinolone-3-carboxamide afforded chiral crystals of a $P2_1$ crystal system by spontaneous crystallization. The molecular chirality in the crystal was retained after the crystals were dissolved in a solvent at a low temperature, and the frozen molecular chirality was effectively transferred to the products by a two-step reaction involving hydrogenation and intermolecular photocycloaddition reactions.**

Mirror symmetry breaking without an external chiral source is an attractive methodology for obtaining optically active compounds from achiral compounds. This methodology is recognized as the absolute asymmetric synthesis.[1] Two main approaches of this methodology are exemplified by (a) photoreaction with circularly polarized light[2] and (b) the use of the chirality in chiral crystals of achiral or racemic materials.[3] Nevertheless, few examples of absolute asymmetric synthesis have been discovered so far, such as the elegant solid-state photoreaction of chiral crystals leading to optically active materials, which has been demonstrated in good reproducibility.[4] Recently, a new methodology using the molecular chirality in a crystal as a source of chirality in a solution was explored. The chirality can be effectively transferred to optically active products

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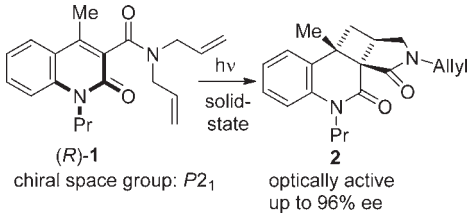
by asymmetric reactions involving a nucleophilic reaction,[5] an intermolecular photochemical reaction,[6] kinetic resolution of racemic amines,[7] and an electrophilic reaction.[8] This concept has high potential for the widespread use of asymmetric synthesis using chiral crystals.[9]

This methodology has now been extensively applied to an one-pot reaction involving a multistep asymmetric reaction. One-pot reactions are an attractive methodology in organic chemistry, since separation and purification processes can be skipped. Much effort has been devoted to the development of these types of reactions as a new strategy to form objective building blocks. Thus, this method has become a powerful tool for organic synthesis, especially in the total synthesis of natural products.[10]

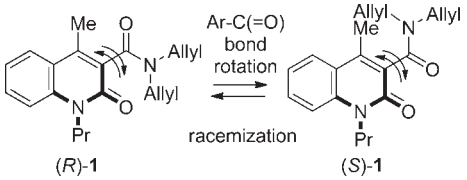
We recently reported that achiral *N,N*-diallyl-2-quinolone-3-carboxamide **1** crystallized in a chiral fashion by spontaneous crystallization, and subsequent solid-state photolysis gave the optically active polycyclic product via an intramolecular [2 + 2] cycloaddition reaction (Scheme 1).[11] We have now discovered that the chirality in the crystal was retained after the chiral crystals were dissolved in a cooled solvent, and the chirality was effectively transferred by intramolecular photochemical cycloaddition reaction. Furthermore, the chirality was used in a two-step asymmetric reaction involving hydrogenation and intermolecular [2 + 2] photocycloaddition reaction. This reaction provides a fine example of a two-step asymmetric reaction using the chirality generated by spontaneous crystallization.

Scheme 1. Absolute Asymmetric Cyclobutane Formation in a Chiral Crystalline Environment



To perform the asymmetric synthesis using the chirality of **1** in fluid media, subsequent reactions should proceed much faster than the racemization process. The rate of racemization was determined on the basis of the changes of the optical rotation, immediately after chiral crystals were dissolved in a solvent, and the activation free energies and half-lives were calculated (Table 1 and Table S1, Supporting Information). The half-lives of racemization in toluene were 590, 170, and 65 s at temperatures of 20, 30, and 40 °C, respectively. The half-life for racemization of **1** increased as the temperature was lowered in THF or MeOH. In comparison with the rate of racemization in toluene, the rate was considerably suppressed in the polar protic solvent MeOH, because of the increase in zwitterionic character of the amide group and the intermolecular hydrogen bonding with the protic solvent. The half-life of **1** in THF at 0 °C was estimated on the basis of the Arrhenius equation to be about 5 h. These results indicate that the racemization can be controlled by lowering the temperature and by the selection of the solvent, and that the chiral conformation adopted in the crystal is retained long enough for application to subsequent asymmetric synthesis as a frozen molecular chirality.

Table 1. Kinetic Parameters for Racemization of Quinolonamide **1** by Ar−C(=O) Bond Rotation



solvent	$t_{1/2}$[a] (s)	$\Delta G^{\ddagger a,c}$	$\Delta H^{\ddagger a,b,c}$	$\Delta S^{\ddagger a,d}$
toluene	5.90×10^2	21.5	19.5	−6.7
THF	9.00×10^2	21.7	23.2	5.0
MeOH	3.68×10^4	23.9	22.2	−5.6

[a] Values at 20 °C. [b] Eyring parameter E values were 20.1, 23.8, and 21.0 kcal mol^{-1} in toluene, THF, and MeOH, respectively. [c] kcal mol^{-1}. [d] cal mol^{-1} K^{-1}.

Before the asymmetric reaction of amide **1**, the photochemical reaction in a solution was examined using the provisional molecular chirality derived from chiral crystals (Scheme 2). When the powdered crystals of **1** (0.01 mol L^{-1}) were dissolved in cooled THF (0 °C) and irradiated through a Pyrex filter for 3 h, optically active adducts **2** and an unexpected spiro compound **3**, which was not produced in the solid-state reaction,[10] were obtained in 57 and 21% yields with 55 and 59% ee, respectively (Table 2, entry 1). The structure of **3** was unequivocally established by X-ray crystallographic analysis. The mechanism for the formation of **3** was reasonably explained in terms of the biradical intermediate followed by a 1,5-hydrogen shift.

When the reaction temperature was decreased to −40 °C, better ee values were obtained (73% ee for **2** and 76% ee for **3**) (entry 2). Next, irradiation in a mixed solvent of THF and MeOH (1:1) was used, increasing the ee values dramatically. In consideration of solubility of **1** at the low

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(8) Most recentry, electrophilic reaction using frozen chirality was reported.Mai, T. T.; Branca, M.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Angew. Chem. Int. Ed.* 2012, DOI: 10.1002/anie. 201200950.

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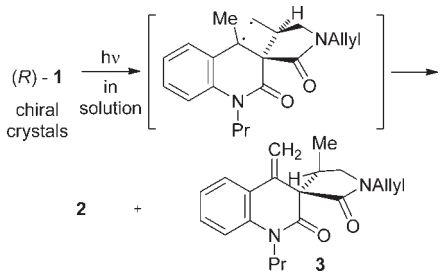
(11) Yagishita, F.; Sakamoto, M.; Mino, T.; Fujita, T. *Org. Lett.* **2011**, *13*, 6168–6171.

Scheme 2. Photochemical Reaction in Fluid Media



temperature a mixed solvent of THF and MeOH was used. The photoreaction in a 1:1 volume ratio of THF-MeOH solvent at −40 °C gave very high ee values of the products (96% ee for both **2** and **3**) (entry 4). The high inductivity of optical activity in a protic solvent is due to a decrease in the rate of racemization.

Table 2. Intramolecular Photochemical Cycloaddition Reaction in Fluid Media[a]

entry	solvent	temp (°C)	conv (%)	yield[b] [ee][c] of **2** (%)	yield[b] [ee][c] of **3** (%)
1	THF	0	91	57 [55]	21 [59]
2	THF	−40	88	59 [73]	20 [76]
3	THF/MeOH[d]	0	96	64 [84]	14 [83]
4	THF/MeOH[d]	−40	85	63 [96]	13 [96]

[a] Irradiation conditions: A 0.01 M solution prepared by dissolving ground chiral crystal of **1** to a cooled solvent was irradiated for 3 h with a Pyrex filtered light from a 350 W superhigh pressure mercury lamp with a light guide. [b] Isolated yields. [c] ee values were determined by HPLC using CHIRALPAK AD-H. [d] A mixed solvent composed of a 1:1 volume ratio of THF and MeOH.

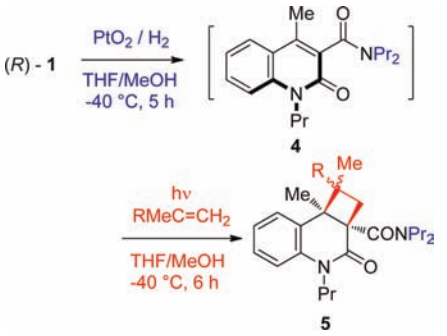
Next, we attempted the intermolecular asymmetric photochemical reaction with alkenes using provisional molecular chirality. However, irradiation of **1** in the presence of alkenes did not give intermolecular reaction products because the intramolecular reaction occurred preferentially. We then examined the two-step asymmetric reaction combined with the catalytic reduction and intermolecular asymmetric photocycloaddition reaction with alkenes.

The powdered chiral crystals of **1** were dissolved in a THF−MeOH solution containing a catalytic amount of PtO_2 at −40 °C, and the mixture was stirred under hydrogen atmosphere for 5 h to reduce the allyl groups. Fortunately, hydrogenation resulted in the formation of **4** by reduction of only the allyl moiety, while the alkenyl group incorporated in the quinolone ring remained intact. After the alkenes were added, the reaction mixture was bubbled with Ar for 20 min, and the solution was irradiated for 6 h with Pyrex filtered light from a super high pressure mercury lamp with a light guide. Two kinds of alkenes were examined for the photochemical cycloaddition reaction: methacrylonitrile as an electron-deficient alkene and 2-methoxypropene as an electron-rich alkene.

As expected, the molecular chirality derived from the chiral crystals was retained through both hydrogenation and photochemical reactions, and intermolecular [2 + 2] cycloadducts **5a**,**b** were obtained in optically active form. The structure of photoproducts **5** was unequivocally confirmed by X-ray structural analyses.

When methacrylonitrile was used, the [2 + 2] adducts were obtained as a mixture of *endo* and *exo* stereoisomers (Table 3, entry 1). In this case, hydrogenated amide **4** was also isolated in 42% yield, because of its low photochemical reactivity. Both cycloadducts showed optical activity of 74 and 70% ee, respectively. In the case of 2-methoxypropene, the photoreaction proceeded more effectively, entirely consuming hydrogenated amide **4** and providing only the *endo* adduct in 60% yield and 71% ee (entry 2).

Table 3. Two-Step Asymmetric Reaction Involving Hydrogenation and Intermolecular Photocycloaddition Reactions[a]



entry	alkene	yield[b] [ee][c] of *endo* **5** (%)	yield[b] [ee][c] of *exo* **5** (%)
1[d]	**a**: R = CN	28 [74]	22 [70]
2	**b**: R = OMe	60 [71]	0 [−]

[a] Irradiation conditions: A 0.01 M solution prepared by dissolving ground chiral crystal of **1** to a cooled solvent was hydrogenated by H_2 with PtO_2 for 5 h; 10 equiv of alkenes was added to the reaction mixture, which was then bubbled with Ar for 20 min and irradiated for 6 h with a 350 W superhigh pressure mercury lamp with a light guide. [b] Isolated yields. [c] ee values were determined by HPLC using CHIRALPAK AD-H. [d] Hydrogenated **4** was isolated in 42% yield.

The mechanism for chirality transfer via a two-step reaction is shown in Figure 1. The axial chirality owing to the torsion between the quinolone chromophore was retained in the hydrogenation of the allyl groups at −40 °C. It seems that the intermediate *N*,*N*-dipropylquinolonamide **4** has almost the same $\Delta G^{\ddagger}$ value for racemization as the starting *N*,*N*-diallylquinolonamide **1**. Alkenes approached the quinolone ring from the side of the carbonyl oxygen of the amide group in the subsequent photoreaction, because

(12) Asymmetric photoreaction of quinolones using a chiral template was reported; see: (a) Müller, C.; Bauer, A.; Maturi, M. M.; Cuquerella, M. C.; Miranda, M. A.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 16689–16697. (b) Austin, K. A. B.; Herdtweck, E.; Bach, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8416–8419.

(13) Asymmetric photoreaction using atropisomerism of amides was reported; see: (a) Jesuraj, J. L.; Sivaguru, J. *Chem. Commun.* **2010**, *46*, 4791–4793. (b) Ayitou, A. J.; Jesuraj, J. L.; Barooah, N.; Ugrinov, A.; Sivaguru, J. *J. Am. Chem. Soc.* **2009**, *131*, 11314–11315.

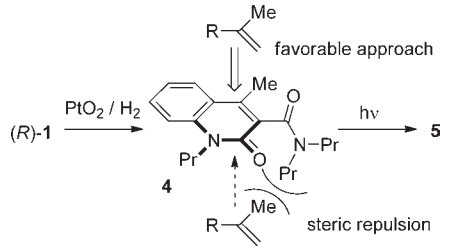


Figure 1. Reaction course of the photocycloaddition of intermolecular photocycloaddition.

the other side was blocked by the bulky substituent on the nitrogen atom. Finally, enantioselective addition of alkenes was performed.[12,13] To prove this hypothesis, the absolute configuration of both the starting quinolonecarboxamide **1** and the products has to be determined; however, it is under investigation. Furthermore, we also tried the reation with arizing the concentration of alkenes (20 equiv) to obtain better ee values; however, it gave almost same results. The optical purity of the products is lower than the expected value from the rate of racemization at −40 °C. The major reason depends on partial racemization in the hydrogenation step and in the excited state of **4**, and photochemical racemization of axially chiral arene amides was also observed.[5b,c]

In this paper, we applied the chirality generated by spontaneous crystallization to a one-pot synthesis involving a two-step asymmetric reaction in fluid media. The axial chirality of *N,N*-diallyl-4-methyl-1-propyl-3-quinolonecarboxamide in the crystals was retained after dissolution in a cold solvent as a result of slow atropisomerism. This reaction provides a fine example of absolute asymmetric synthesis involving a two-step reaction using chiral crystals of achiral materials without any other external chiral source.

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Supporting Information Available. Detailed experimental procedures, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.