Crystallization-induced diastereomer transformation of 2-quinolone-4-carboxamide followed by stereoselective intermolecular photocycloaddition reaction†‡§

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2-Quinolone-4-carboxamide derived from (*S*)-proline, which exists as a mixture of two diastereomers before crystallization, converged to a single diastereomer by crystallization (CIDT), and the homochirality was transferred by a intermolecular 2 + 2 photocycloaddition reaction with high optical activity.

Two stereogenic units in one molecule lead to diastereoisomerism, and a valuable method for getting one pure diastereomer is achieved when these units can be epimerized during crystallization.[1] Recently we reported an asymmetric synthesis under homogeneous conditions using a homochiral molecular conformation derived from crystallization-induced diastereomer transformations (CIDT).[2,3] This method was established under two important requirements; one, the diastereomixture should be converged to a single diastereomer by crystallization, and second, the diffusion path back to the diastereomixture must be suppressed under the reaction conditions.[2,4] We have now investigated a wide application of this methodology to diastereoselective reactions and found that the axial chirality of 2-quinolone-4-carboxamide was controlled by the chiral amino acid chromophore by crystallization. Furthermore, the homochiral stereochemistry could be transferred by intermolecular 2 + 2 photochemical cycloaddition reactions with high optical activity.

2-Quinolone-4-carboxamide **1** possessing (*S*)-proline methyl ester as a chiral handle was chosen for our purpose, and it was easily provided from 2-quinolone-4-carboxylic acid[5] and a (*S*)-proline methyl ester. Amide **1** exists as a mixture of two diastereomers in the ratio of a*R* : a*S* = 40 : 60 (diastereomeric excess, de = −20%) before crystallization (Fig. 1). 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 a*R* : a*S* = 95 : 5 (de = 90%). Furthermore, recrystallization of the crystals once from ether easily gave 99% de of amide **1**. Axial chirality was stable for several days at room temperature; however, heating the chloroform solution of (*S*,a*R*)-**1** at 55 °C for 12 h gave exactly the same diastereomixture as before

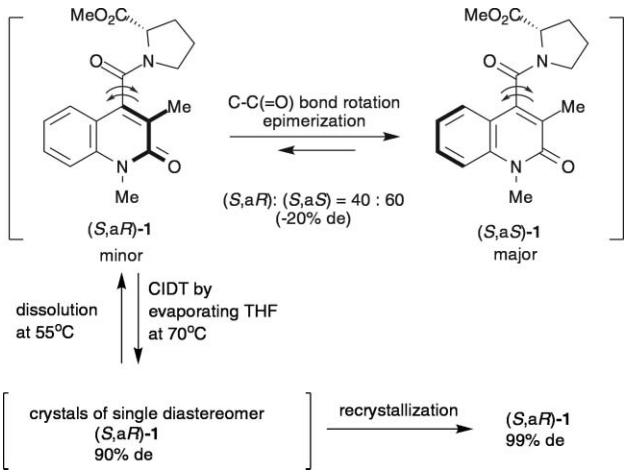

Fig. 1 Epimerization of 2-quinolone-4-carboxamide **1** caused by C–C(=O) bond rotation and crystallization-induced diastereomer transformation (CIDT).

crystallization. Unfortunately, we could not obtain single crystals of **1** suitable for single crystal X-ray crystallographic analysis.

Next, the homochiral crystals were utilized for subsequent diastereoselective reactions. Photochemical reactions of 2-quinolone derivatives have been well-studied, and it has been reported that irradiation in the presence of alkenes gave cyclobutane derivatives.[6,7] Therefore, the diastereoselective 2 + 2 photocycloaddition reaction of amide **1** with alkenes was examined. We tried the photocycloaddition reaction of **1** with a variety of alkenes, such as ethyl vinyl ether, 2-methoxypropene, 2-methylpropene, acrylonitrile, and methacrylonitrile. It was found that the reaction with methacrylonitrile proceeded most effectively, stereo-, and regiospecifically. Therefore, the diastereoselective reaction using methacrylonitrile was examined in detail. First, amide **1** before crystallization was used for the reaction. An argon-purged THF solution containing 0.02 M of amide **1** before crystallization and 0.1 M of methacrylonitrile was irradiated with a high-pressure mercury lamp at 20 °C until most of the starting amide was consumed (2 h). The photochemical reaction occurred effectively, and 2 + 2 cycloadducts were obtained in 100% chemical yields; both diastereomers were *endo* isomers, minor (1*S*,2a*R*,8b*R*)-**2**, major (1*R*,2a*S*,8b*S*)-**2**, and the de value was −25% (Scheme 1 and Table 1, entry 1). 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 **1** before crystallization (−20% de). Both of the absolute configurations

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† The HTML version of this article has been enhanced with colour images.

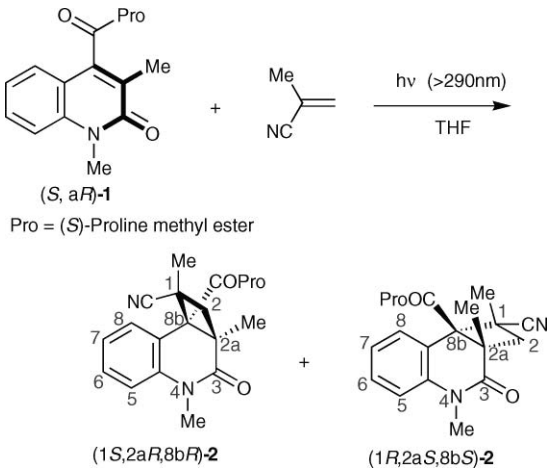
‡ CCDC reference numbers 667898 [(1*S*,2a*R*,8b*R*)-**2**] and 667899 [(1*R*,2a*S*,8b*S*)-**2**]. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b719761f

§ Electronic supplementary information (ESI) available: Experimental data and crystal data for **2**. See DOI: 10.1039/b719761f

Table 1 Photocycloaddition reaction of quinolonecarboxamide **1** in the presence of methacrylonitrile

Entry	Temp/°C	Yield of **2** (%)	Ratio of (1*S*,2a*R*,8b*R*)-**2** : (1*R*,2a*S*,8b*S*)-**2**[c]	De (%) of **2**[d]
1[a]	20	100	45 : 65	−25
2[b]	20	99	94.5 : 5.5	89
3[b]	−40	93	98 : 2	96
4[b]	−80	90	99 : 1	98

[a] The amide **1** before crystallization was used. [b] The amide **1** (99% de) obtained by crystallization was used. [c] De value was determined on the basis of the ^{1}H NMR spectral data. [d] De (%) of (1*S*,2a*R*,8*b*)-**2**.



Scheme 1 Photochemical reaction of quinolonecarboxamide **1** with methacrylonitrile.

were determined by X-ray crystallographic analysis on the basis of the configuration of the (*S*)-proline group.[8,9]

Furthermore, we tried a photocycloaddition reaction using the homochiral molecular conformation converged by CIDT. The crystals were expected to be composed of a single diastereomer of (*S*,a*R*)-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*,a*R*)-**1** (0.02 mol l^{-1}) containing methacrylonitrile (0.10 mol l^{-1}) was irradiated with a high-pressure mercury lamp for 2 h until the starting amide was consumed. When the reaction was performed at 20 °C (Table 1, entry 2), two 2 + 2 adducts, (1*S*,2a*R*,8b*R*)-**2** and (1*R*,2a*S*,8b*S*)-**2**, 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 (entries 2–4), and the best de of 98% was obtained in the reaction at −80 °C (entry 4).

Absolute conformation of amide **1** could not be determined directly by X-ray crystallographic analysis because **1** did not afford appropriate single crystals; therefore, conformation was expected from the absolute configuration of photoproducts **2**. In our previous study on 4 + 4 photocycloaddition of a naphthamide possessing a proline group, the reactant avoided the bulky proline group and approached from the side of the oxygen atom of the amide carbonyl group.[2] In the reaction of **1**, we expect that methacrylonitrile approaches the excited quinolonecarboxamide **1** from the side of the oxygen atom of the amide carbonyl in the same manner shown in Fig. 2. From these facts, it is acceptable that the conformation in the crystals of **1** obtained by CIDT was the (*S*,a*R*) conformation.

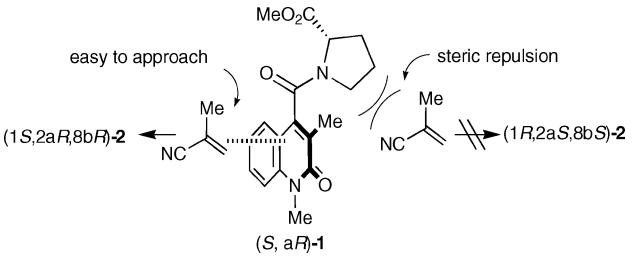


Fig. 2 Reaction course of quinolonecarboxamide **1** toward methacrylonitrile leading to (1*S*,2a*R*,8b*R*)-**2**.

In conclusion, quinolonecarboxamides **1** derived from (*S*)-proline methyl ester, which exist as a mixture of two diastereomers in solution, converged to a single diastereomer by CIDT. After the crystals were dissolved in the solvent, homochiral conformation was retained long enough for the subsequent photochemical reaction. The axial chirality invoked by crystallization directed the course of the approach of the reacting molecules, and a fully controlled diastereoselective intermolecular photocycloaddition reaction was performed. This reaction provides a fine example of a highly controlled stereoselective 2 + 2 photoreaction using a process of the CIDT method.[10]

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9 Crystal data for (1*R*,2a*S*,8b*S*)-**2**, (recrystallized from $CHCl_3$–hexane): Orthorhombic, space group $P2_12_12_1$, a = 8.0817(10) Å, b = 14.5195(18) Å, c = 17.141(2) Å, V = 2011.4(4) Å^3, Z = 4, ρ = 1.306 Mg m^{-3}; in the final least-square refinement cycles on F^2, the model converged to R_1 = 0.0330, wR_2 = 0.0809 for 4309 reflections, CCDC 667899.
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