

# Asymmetric Intramolecular Cyclobutane Formation via Photochemical Reaction of *N,N*-Diallyl-2-quinolone-3-carboxamide Using a Chiral Crystalline Environment

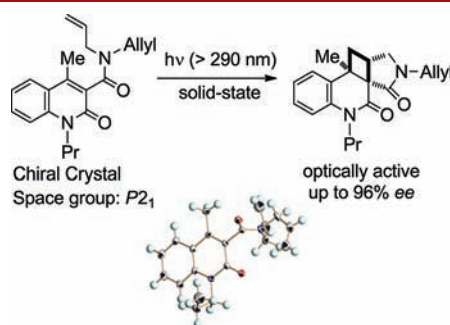
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## ABSTRACT



Crystal structures and photochemical reactions of three *N,N*-diallyl-2-quinolone-3-carboxamides were investigated. One quinolonecarboxamide afforded chiral crystals of a  $P2_1$  crystal system by spontaneous crystallization, and the molecular chirality in the crystal was effectively transferred to cyclobutane in 96% ee by an intramolecular 2 + 2 photocycloaddition reaction in the solid state.

The use of a chiral crystalline environment is an excellent strategy for obtaining optically active compounds from achiral compounds, and this methodology is recognized as the absolute asymmetric synthesis.<sup>1</sup> Recent advances in the use of a variety of solid-state reactions with chiral crystals have progressed to such an extent that this approach

can now be regarded as an important branch of organic chemistry.<sup>2</sup>

Schmidt reported the first asymmetric photochemical reaction using a chiral crystal for a 2 + 2 intermolecular cycloaddition of a mixed crystal of two types of 1,4-diaryl-1,3-dienes.<sup>3</sup> A few enantiomeric intermolecular 2 + 2 cycloaddition reactions in the solid state have also been

(1) (a) Addadi, L.; Lahav, M. In *Origin of Optical Activity in Nature*; Walker, D. C., Ed.; Elsevier: New York, 1979; Chapter 14. (b) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191–197.

(2) (a) Sakamoto, M. In *Chiral Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Marcel Dekker: New York, 2004; Vol. 11, pp 415–461. (b) Scheffer, J. R.; Garcia-Garibay, M.; Nalamasu, O. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York and Basel, 1987; Vol. 8, pp 249–338. (c) Venkatesan, K.; Ramamurthy, V. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; pp 133–184. (d) Vaida, M.; Popovitz-Bio, R.; Leiserowitz, L.; Lahav, M. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; pp 247–302. (e) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203–209. (f) Sakamoto, M. *Chem.—Eur. J.* **1997**, *3*, 684–689. (g) Feringa, B. L.; Van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3419–3438. (h) Sakamoto, M. *J. Photochem. Photobiol. C: Photochem. Rev.* **2006**, *7*, 183–196.

(3) Elgavi, A.; Green, B. S.; Schmidt, G. M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2058–2059.

(4) (a) van Mil, J.; Addadi, L.; Lahav, M.; Leiserowitz, L. *J. Chem. Soc., Chem. Commun.* **1982**, 584–587. (b) Hasegawa, M.; Chung, C. M.; Murro, N.; Maekawa, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5676–5677. (c) Chung, C. M.; Hasegawa, M. *J. Am. Chem. Soc.* **1991**, *113*, 7311–7322.

(5) Suzuki, T.; Fukushima, T.; Yamashita, Y.; Miyashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 2793–2803.

(6) (a) Zhao, D.; Sun, J.; Ding, K. *Chem.—Eur. J.* **2004**, *10*, 5952–5963. (b) Hayashi, M.; Hashimoto, Y.; Takezaki, H.; Watanabe, Y.; Saigo, K. *Tetrahedron: Asymmetry* **1998**, *9*, 1863–1866. (c) Blake, A. J.; Champness, N. R.; Chung, S. S. M.; Li, W. S.; Schroder, M. *Chem. Commun.* **1997**, 1675–1676. (d) Fessler, M.; Eller, S.; Bachmann, C.; Gutmann, R.; Trettenbrein, B.; Kopacka, H.; Mueller, T.; Brueggeller, P. *Dalton Trans.* **2009**, 1383–1395. (e) Haag, D.; Scharf, H.-D. *J. Org. Chem.* **1996**, *61*, 6127–6135.

performed with other types of dienes<sup>4</sup> and a charge transfer complex.<sup>5</sup>

Optically active cyclobutane analogues are greatly desirable in chiral ligands for catalytic asymmetric synthesis,<sup>6</sup> natural products,<sup>7</sup> and pharmaceuticals.<sup>8</sup> Photochemical 2 + 2 photocycloaddition is a powerful tool for C–C bond formation and is often used for construction of the important cyclobutane structure.<sup>9</sup> We investigated a new asymmetric synthesis of cyclobutanes via absolute asymmetric synthesis using an intramolecular 2 + 2 photochemical reaction in a chiral crystalline environment. Chiral molecular arrangements in the crystal lattices are required for intermolecular photochemical cycloaddition reactions.<sup>3,4,10</sup> In contrast, the intramolecular photochemical reaction is more easily controlled because the molecular conformation can be designed such that reacting sites are closely placed together. Despite this, there is no precedent for an asymmetric intramolecular photochemical cyclobutane formation using chiral crystals.

Molecules with an *N,N*-diallylamide chromophore are well-known to undergo intramolecular 2 + 2 photocycloaddition leading to polycyclic cyclobutanes.<sup>11</sup> Thus, we synthesized three *N,N*-diallyl-4-methyl-2-quinolone-3-carboxamides **1a–c** and analyzed their crystal structures (Scheme 1). Recrystallization of these amides from a chloroform–hexane solution afforded colorless prisms in all cases. All crystals were subjected to X-ray crystallographic analysis to elucidate the crystal chirality, molecular conformation, and architecture (Figures S1–S3).<sup>12–14</sup> X-ray analysis showed that the crystals of **1c** adopted the monoclinic chiral space group *P2*<sub>1</sub>, and the constituent molecules were frozen as homochiral and helical conformations in the crystal lattice. Crystals of **1a** and **1b** were in the racemic space groups of *Pbca* and *P2*<sub>1</sub>/*c*, respectively, and each single crystal was composed of both enantiomeric molecules.

Photolysis was conducted on solid powder samples sandwiched between Pyrex glasses on the inside of polyethylene bags fixed outside of an immersion well apparatus and cooled during irradiation in a water bath (15 °C).

(7) (a) Lajiness, J. P.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 13936–13940. (b) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539–1602. (c) Sagawa, T.; Takaishi, Y.; Fujimoto, Y.; Duque, C.; Osorio, C.; Ramos, F.; Garzon, C.; Sato, M.; Okamoto, M.; Oshikawa, T.; Ahmed, S. U. *J. Nat. Prod.* **2005**, *68*, 502–505. (d) Takahashi, M.; Ichikawa, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 57–59.

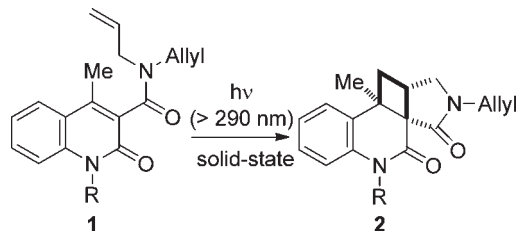
(8) (a) Ortuno, R. M.; Moglion, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237–259. (b) Hury, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768. (c) Bell, E. A.; Qureshi, M. Y.; Pryce, R. J.; Janzen, D. H.; Lemke, P.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 1409–1412. (d) Avotins, F. *Russ. Chem. Rev.* **1993**, *62*, 897. (e) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181. (f) Avenoza, A.; Busto, J. H.; Canal, N.; Corzana, F.; Peregrina, J. M.; Fernandez, M. P.; Rodriguez, F. *J. Org. Chem.* **2010**, *75*, 545–552.

(9) (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485–1537. (b) Ruff, E. L.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1483.

(10) (a) Hasegawa, M. *Chem. Rev.* **1983**, *83*, 507–518. (b) Schlutz, A. G.; Taveras, A. G.; Taylor, R. E.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8725–8727. (c) Toda, F.; Miyamoto, H.; Kikuchi, S. *J. Chem. Soc., Chem. Commun.* **1995**, 621–622.

(11) (a) Sakamoto, M.; Kato, M.; Oda, E.; Kobaru, S.; Mino, T.; Fujita, T. *Tetrahedron* **2006**, *62*, 3028–3032. (b) Aoyama, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1851–1854.

**Scheme 1.** Space Group of Quinolones **1a–c** and Expected Intramolecular Photochemical Cycloaddition Reaction Leading to Polycyclic Heterocycles **2a–c**



**1a** : R = Me, Space group: *Pbca*

**1b** : R = Et, Space group: *P2*<sub>1</sub>/*c*

**1c** : R = Pr, Space group: *P2*<sub>1</sub>

Sandwiched glasses incorporated into Pyrex tubes were used for the solid-state photolysis at –45 °C with a methanol bath using an immersion cooler.

Photolysis of powdered **1a** at 15 °C for 1 h gave a 74% yield of cyclobutane **2a** (Table 1, entry 1). Solid-state 2 + 2 photocycloaddition reactions of **1b** and **1c** also proceeded, leading to **2b** and **2c** in 62% and 56% yields, respectively (entries 3 and 5). In all cases, polymeric materials were produced as byproducts, and all cyclobutanes were obtained as single stereoisomers. Furthermore, when **1a** and **1b** were irradiated at –40 °C, the solid-state photoreaction had a low conversion rate, although the corresponding cyclobutanes were obtained in good yields, and the generation of polymeric materials was relatively suppressed (entries 2 and 4).

The structure of **2** including the stereochemistry was deduced on the basis of its spectral data. When cyclobutane **2c** was reduced to **3c** by hydrogen in the presence of platinum oxide, the structure could be unequivocally established by X-ray crystallographic analysis (Scheme S1, Figure S4).<sup>15</sup>

**Table 1.** Photochemical Reaction of Quinolonecarboxamides **1a–c**

entry	amide <b>1</b>	temp (°C)	conv (%)	yield of <b>2</b>	
				(%) <sup>a</sup>	ee of <b>2</b> (%) <sup>c</sup>
1	<b>1a</b>	15	99	74 <sup>b</sup>	0
2	<b>1a</b>	–40	43	86	0
3	<b>1b</b>	15	95	62 <sup>b</sup>	0
4	<b>1b</b>	–40	38	76	0
5	<b>1c</b>	15	35	56 <sup>b</sup>	90 <sup>d</sup>
6	<b>1c</b>	15	59	43 <sup>b</sup>	88 <sup>d</sup>
7	<b>1c</b>	–40	48	92	96 <sup>d</sup>
8	<b>1c</b>	–40	67	92	95 <sup>d</sup>

<sup>a</sup> Chemical yields were determined on the basis of consumed amides **1a–c**. <sup>b</sup> Polymeric materials were also produced as byproduct. <sup>c</sup> Ee's were determined by HPLC using CHIRALCEL AD-H column. <sup>d</sup> Irradiation of crystals with opposite chirality gave the cyclobutane (*ent-2c*) with corresponding stereochemistry with the same ee value.

(12) Crystal data of **1a** (recrystallized from a mixture of CHCl<sub>3</sub> and hexane); C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>, *M*<sub>r</sub> = 296.36, orthorhombic space group *Pbca*, *a* = 7.8220(5) Å, *b* = 14.5983(8) Å, *c* = 27.4838(16) Å, *V* = 3138.3(3) Å<sup>3</sup>, *Z* = 8, ρ = 1.254 Mg/m<sup>3</sup>, in the final least-squares refinement cycles

The space groups of the crystals **1a–b** were racemic in both cases (Scheme 1) and afforded the racemic cyclobutanes **2a–b** (Table 1, entries 1–4). Therefore, we focused on the achiral amide **1c** crystallized in the chiral crystal space group,  $P2_1$ . Despite having two possible enantiomeric conformations arising from C—(C=O) bond rotation in fluid media, the chiral crystal was composed of a single enantiomer. This allowed the performance of the asymmetric intramolecular 2 + 2 photocycloaddition in the solid state.

A high enantiomeric excess and a large amount of crystals of **1c** must be prepared to perform the asymmetric reaction. Unfortunately, such crystals could not be obtained by the usual recrystallization method from a solvent because of the comparatively slow racemization due to the rotation of the C—C(=O) bond. Therefore, crystallization from the melt was performed to obtain chiral crystals of **1c** to be used for the asymmetric synthesis. After the solid sample of **1c** was completely melted at 110 °C (mp: 97 °C), it was gradually cooled to 80 °C with stirring and was solidified. High optical purity was achieved by this procedure.<sup>16</sup> Generally, the selection of either enantiomeric form of a molecular configuration is equally probable. Once enantiomeric crystals are formed in a typical crystallization, a large amount of chiral crystals with the same optical rotation can be selectively prepared through recrystallization by seeding the desired crystals.

When powdered crystals of (+)-**1c** were irradiated at room temperature,<sup>17</sup> the cyclobutane-type adduct (–)-**2c** was obtained in 56% yield at 35% conversion. Product **2c** showed an enantiomeric excess of 90% (entry 5). Increasing the reaction conversion to 59% resulted in a decrease in both the chemical yield and ee value (entry 6). In this case, polymerized material was also produced as a byproduct in the early stage of the reaction, and its formation increased along with the increase of the reaction conversion.

on  $F^2$ , the model converged at  $R_1 = 0.0372$ ,  $wR_2 = 0.0912$ , and GOF = 0.984 for 2790 reflections CCDC830789.

(13) Crystal data of **1b** (recrystallized from a mixture of  $\text{CHCl}_3$  and hexane);  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ ,  $M_r = 310.39$ , monoclinic space group  $P2_1/c$ ,  $a = 16.127(2)$  Å,  $b = 9.1351(14)$  Å,  $c = 12.0699(17)$  Å,  $\beta = 102.693(2)^\circ$ ,  $V = 1734.7(4)$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho = 1.188$  Mg/m<sup>3</sup>, in the final least-squares refinement cycles on  $F^2$ , the model converged at  $R_1 = 0.0491$ ,  $wR_2 = 0.1166$ , and GOF = 0.927 for 1756 reflections CCDC830790.

(14) Crystal data of **1c** (recrystallized from a mixture of  $\text{CHCl}_3$  and hexane);  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$ ,  $M_r = 326.43$ , monoclinic space group  $P2_1$ ,  $a = 8.8137(15)$  Å,  $b = 7.6421(13)$  Å,  $c = 13.261(2)$  Å,  $\beta = 93.732(2)^\circ$ ,  $V = 891.3(3)$  Å<sup>3</sup>,  $Z = 2$ ,  $\rho = 1.209$  Mg/m<sup>3</sup>, in the final least-squares refinement cycles on  $F^2$ , the model converged at  $R_1 = 0.0333$ ,  $wR_2 = 0.0896$ , and GOF = 1.026 for 3517 reflections CCDC830788.

(15) Crystal data of **3c** (recrystallized from a mixture of  $\text{CHCl}_3$  and hexane);  $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2$ ,  $M_r = 326.43$ , monoclinic space group  $P2_1/c$ ,  $a = 15.726(5)$  Å,  $b = 9.432(3)$  Å,  $c = 12.590(4)$  Å,  $\beta = 103.660(4)^\circ$ ,  $V = 1814.7(10)$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho = 1.195$  Mg/m<sup>3</sup>, in the final least-squares refinement cycles on  $F^2$ , the model converged at  $R_1 = 0.0392$ ,  $wR_2 = 0.1062$ , and GOF = 1.053 for 3210 reflections CCDC830791.

(16) (a) Viedma, C. *Phys. Rev. Lett.* **2005**, *94*, 065504. (b) Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science* **1971**, *174*, 1018–1020. (c) Sakamoto, M.; Utsumi, N.; Ando, M.; Saeki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishio, T.; Kashima, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4360–4363. (d) Sakamoto, M.; Yagishita, F.; Ando, M.; Sasahara, Y.; Kamataki, N.; Ohta, M.; Mino, T.; Kasashima, Y.; Fujita, T. *Org. Biomol. Chem.* **2010**, *8*, 5418–5422.

(17) Optical rotatory of the chiral crystals of **1c** was measured by polarimeter immediately after dissolving crystals to  $\text{CHCl}_3$ .

We also examined the photoreaction at low temperature. When the chiral crystal of (+)-**1c** was irradiated at –40 °C, an effective enantioselective reaction was achieved, and the photoadduct **2c** was obtained in 92% yield and 96% ee at 48% reaction conversion (entry 7). Furthermore, even when increasing the reaction conversion to 67%, the enantiospecific intramolecular 2 + 2 photocycloaddition reaction was performed with 95% ee (entry 8), where the formation of polymerized materials could fortunately be avoided.

**Table 2.** Molecular Conformation of **1a–c**

	torsion angle <sup>a</sup>	$d_1$ (Å) for C <sub>2</sub> –C <sub>4</sub>	$d_2$ (Å) for C <sub>1</sub> –C <sub>5</sub>
<b>1a</b>	72.7	3.42	4.88
<b>1b</b>	86.9	3.89	5.86
<b>1c</b>	74.3	3.72	4.12

<sup>a</sup>Torsion angle for C<sub>1</sub>–C<sub>2</sub>–C<sub>3</sub>–O<sub>1</sub>.



**Figure 1.** Geometry of **1**.

X-ray crystallographic analysis revealed the molecular conformations of all amides **1** and showed that they adopted an almost perpendicular conformation of the quinolone ring against the amide plane, which was twisted from 72.7° to 86.9° (Table 2, Figures 1, S1–S3). The torsion of the amide group brings one alkenyl group, C<sub>4</sub>–C<sub>5</sub>, close to the C<sub>1</sub>–C<sub>2</sub> double bond of the quinoline chromophore. For **1a**, the distance between C<sub>2</sub> and C<sub>4</sub> ( $d_1$ ) is quite short at 3.42 Å, and the distance  $d_2$  between C<sub>1</sub> and C<sub>5</sub> is 4.88 Å, considerably longer than  $d_1$ , which is caused by the conformation of the diallyl chromophore. The C<sub>4</sub>–C<sub>5</sub> alkenyl double bond is located vertically to the quinolone ring. Amide **1b** adopts a similar conformation to **1a**, and the  $d_1$  distance for each reacting carbon atom is sufficiently short for effective bond formation, while the other site ( $d_2$ ) is located far away. In the case of **1c**, both  $d_1$  and  $d_2$  are short enough for the photocycloaddition reaction.

The reactivity predicted from the geometrical conformation in the crystalline lattice is clearly consistent with the results from low temperature photolysis. Solid-state photochemical reactivity for 2 + 2 cyclobutane formation has been extensively studied,<sup>3,4</sup> and bond formation is possible when the distance is within 4.2 Å, which is the well-known value according to Schmidt's rule.<sup>18</sup> Only **1c**

satisfies these conditions and shows high reactivity even at low temperature, whereas **1a** and **1b** were ineffective in low temperature photolysis.<sup>19</sup>

In conclusion, the solid-state photoreaction of *N*, *N*-diallyl-2-quinolone-3-carboxamides involving intramolecular 2 + 2 photocyclization to polycyclic cyclobutanes, in which one of the quinolones promoted absolute asymmetric conversion with good enantioselectivity, was discovered. This

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(18) (a) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996–2000. (b) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647–678. (c) Cohen, M. D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 386–393.

(19) Keating, A. E.; Garcia-Garibay, M. A. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1998; Vol. 2, pp 195–248.

reaction provides the first example of an absolute asymmetric reaction via the intramolecular 2 + 2 photocycloaddition reaction in a chiral crystalline environment.

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**Supporting Information Available.** Experimental procedures, synthesis of **1a–c**, crystallographic data, all cif files and spectral data are included in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.