JOC Article

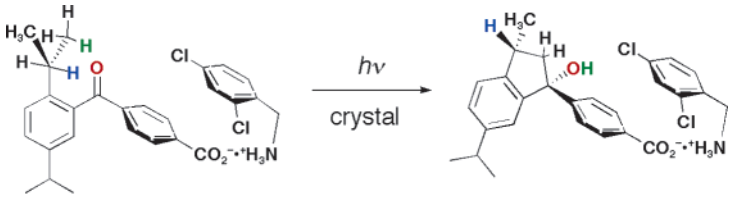
Absolute Asymmetric Photocyclization of Isopropylbenzophenone Derivatives Using a Cocrystal Approach Involving Single-Crystal-to-Single-Crystal Transformation

Hideko Koshima,*,† Hirohisa Kawanishi,† Masaki Nagano,† Haitao Yu,† Motoo Shiro,‡ Takaaki Hosoya,§ Hidehiro Uekusa,§ and Yuji Ohashi§

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan, Rigaku Corporation, Matsubara, 3-9-12, Akishima, Tokyo 196-8666, Japan, and Department of Chemistry and Materials Science, Tokyo Institute of Technology, O-Okayama, Meguro-ku, Tokyo 152-8551, Japan

koshima@eng.ehime-u.ac.jp

Received January 14, 2005



Absolute asymmetric photocyclization of isopropylbenzophenone derivatives was achieved by means of a cocrystal approach. Three chiral salt crystals formed by carboxylic acid derivatives with achiral amines could be prepared by spontaneous crystallization. In the *M*-crystal of 4-(2,5-diisopropylbenzoyl)benzoic acid with 2,4-dichlorobenzylamine, a twofold helical arrangement occurs in a counterclockwise direction to generate the crystal chirality. Conversely, the clockwise helix exists alone in the *P*-crystal. Irradiation of the *M*-crystal at >290 nm caused highly enantioselective Norrish type II cyclization to give the (*R*,*R*)-cyclopentenol, (*R*)-cyclobutenol, and (*R*)-hydrol in a 6:3:1 molar ratio, resulting in successful absolute asymmetric synthesis, while irradiation at around 350 nm afforded the (*R*,*R*)-cyclopentenol as the sole product. The reaction proceeded via single-crystal-to-single-crystal transformation, and therefore the reaction path producing the (*R*,*R*)-cyclopentenol could be traced by X-ray crystallographic analysis before and after irradiation.

Introduction

Absolute asymmetric synthesis by means of solid-state reaction of chiral crystals spontaneously formed from achiral molecules is an attractive and promising methodology for asymmetric synthesis, because it is not necessary to employ any external chiral source like a chiral catalyst. Since the first report of absolute asymmetric [2 + 2] photodimerization of butadiene derivatives in mixed crystals by the Weizmann Institute Group in 1973,[1] around 20 successful examples have been published so far.[2−6] We have also succeeded in carrying out the absolute asymmetric photodecarboxylative condensation of acridine with diphenylacetic acid in their chiral cocrystal.[7] However, absolute asymmetric synthesis has not been extended into a versatile field of synthetic chemistry, because the prediction of chiral crystallization of achiral molecules is not possible at the present time.[8,9]

We have tried to prepare chiral cocrystals composed of two different achiral molecules to discover several

* To whom correspondence should be addressed.
† Ehime University.
‡ Rigaku Corporation.
§ Tokyo Institute Technology.

(1) Elgavi, A.; Green, B. S.; Schmidt, G. M. J. *J. Am. Chem. Soc.* **1973**, *113*, 7311−7312.
(2) Green, B. S.; Lahav, M.; Ravinovich, D. *Acc. Chem. Res.* **1979**, *69*, 191−197.
(3) Sakamoto, M. *Chem. Eur. J.* **1997**, *3*, 684−689.
(4) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *39*, 3418−3438.
(5) Koshima, H. In *Organic Solid-State Reactions*; Toda, F., Ed.; Kluwer Academic Publishers: Dordrecht, 2002; pp 189−268.
(6) Koshima, H. In *Chiral Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Marcel Dekker, Inc.; New York, 2002; pp 485−531.
(7) Koshima, H.; Ding, K.; Chisaka, Y.; Matsuura, T. *J. Am. Chem. Soc.* **1996**, *118*, 12059−12065.
(8) (a) Koshima, H.; Matsuura, T. *J. Synth. Org. Chem.* **1998**, *56*, 268−279. (b) Koshima, H.; Matsuura, T. *J. Synth. Org. Chem.* **1998**, *56*, 466−477.
(9) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley-Interscience: New York, 1981.

10.1021/jo0500784 CCC: $30.25
Published on Web 05/03/2005

TABLE 1. Crystal Data of the Salt Crystals

		P-**1**·**a**	*M*-**1**·**a**	
	2·benzylamine	(before irradiation)	(before irradiation)	(712 h of irradiation)
measured temp (K)	293	93	293	93
formula	$C_{30}H_{37}NO_3$	$C_{27}H_{29}NO_3Cl_2$	$C_{27}H_{29}NO_3Cl_2$	$C_{27}H_{29}NO_3Cl_2$
M_r (g mol^{-1})	459.63	486.44	486.44	486.44
crystal system	triclinic	orthorhombic	orthorhombic	orthorhombic
space group	$P\bar{1}$ (#2)	$P2_12_12_1$ (#19)	$P2_12_12_1$ (#19)	$P2_12_12_1$ (#19)
a (Å)	8.506(1)	6.3071(3)	6.3028(5)	6.275(4)
b (Å)	26.258(5)	12.1522(9)	12.7985(9)	12.617(8)
c (Å)	6.205(2)	32.017(2)	31.838(4)	31.923(19)
α (deg)	95.67(2)	90.0	90.0	90.0
β (deg)	103.93(2)	90.0	90.0	90.0
γ (deg)	88.93(1)	90.0	90.0	90.0
V (Å^3)	1338.6(5)	2454.0(2)	2568.2(4)	2527(3)
Z	2	4	4	4
D (g cm^{-3})	1.140	1.317	1.258	1.278
target	Mo	Cu	Cu	Mo
total reflections	6522	2582	2577	4611
unique reflections	6110	1115	1115	1142
R	0.053	0.0380	0.0898	0.1034
R_w	0.078	0.0452	0.1881	0.3023
Flack parameter		0.05(2)	0.24(5)	

series of chiral cocrystals; these include the cocrystals of aza aromatic compounds with diphenylacetic acid,[10] aza aromatic compounds with 3-indolepropionic acid,[11] tryptamine with carboxylic acids,[12] and aminonitropyridine with benzenesulfonic acid.[13] We found that the cocrystal approach was efficient for the preparation of new chiral crystals. However, their asymmetric reactions failed, possibly for reasons such as an unsuitable molecular arrangement for enantioselective reaction[10,11] or lack of photoreactivity.[12,13] In the present work, isopropylbenzophenone derivatives were used as the component molecules for the preparation and photoreaction of chiral cocrystals with achiral amines, because the compounds are well known to undergo Norrish type II photocyclization both in solution and in the solid state.[14] Using the ionic chiral auxiliary method,[15] solid-state photoreaction of the carboxylic acid derivatives in the chiral salt crystals with optically pure amines afforded the optically active cyclobutenol.[16] Recently, we have achieved the enantiospecific single-crystal-to-single-crystal photocyclization of 4-(2,5-diisopropylbenzoyl)benzoic acid in its salt crystals with optically pure 1-phenylethylamine.[17] Herein, we report absolute asymmetric single-crystal-to-single-crystal photocyclization using the cocrystal approach.

Results and Discussion

Preparation of Chiral Salt Crystals. We used 4-(2,5-diisopropylbenzoyl)benzoic acid **1** and 4-(2,4,6-diisopropylbenzoyl)benzoic acid **2** as the carboxylic acid derivatives of isopropylbenzophenone. To find new chiral salt crystals, first we prepared a number of salt crystals of **1** and **2** combined with more than 30 achiral amines such as anilines, naphthylamines, benzylamines, phenylethylamines, aliphatic amines, and cyclic amines by recrystallization of their solutions. The Nujol mulls of the powdered crystals obtained were submitted to measure the solid-state circular dichromism (CD) spectra. Unfortunately, we could not observe any significant CD spectra for these all the crystals and inferred that no chiral crystals were obtained. Next, we carried out the X-ray crystallographic analysis of the salt crystal of **2** with benzylamine and confirmed its achiral nature from the space group $P\bar{1}$ (Table 1). However, as shown in Figure 1, we found an important difference in the molecular packing arrangements between the achiral crystal of **2** with benzylamine and the chiral crystal (space group $P2_12_12_1$) of **1** with (*S*)-phenylethylamine.[17] In the unit cell of the achiral crystal (Figure 1a), a symmetrical pair is formed between two molecules of **2** and two molecules of benzylamine through $NH_3^+\cdots{}^-O_2C$ quaternary ammonium salt bridges (1.75, 1.83, and 1.89 Å). On the other hand, in the chiral crystal (Figure 1b), a twofold helical arrangement occurs between the molecules of **1** and (*S*)-phenylethylamine through similar $NH_3^+\cdots{}^-O_2C$ quaternary ammonium salt bridges (1.78, 1.87, and 1.89 Å). The crystal chirality is induced by the helical structure in a counterclockwise direction.

Here, we came across the idea that if hindered benzylamine derivatives substituted with bulky groups or atoms are combined with **1** or **2** in the salt crystals, the

(10) (a) Koshima, H.; Nakagawa, T.; Matsuura, T.; Miyamoto, H.; Toda, F. *J. Org. Chem.* **1997**, *62*, 6322−6325. (b) Koshima, H.; Nakata, A.; Ngano, M.; Yu, H. *Heterocycles* **2003**, *60*, 2251−2258.

(11) (a) Koshima, H.; Hayashi, E.; Matsuura, T.; Tanaka, K.; Toda, F. *Tetrahedron Lett.* **1997**, *38*, 5009−5012. (b) Koshima, H.; Hayashi, E.; Matsuura, T. *Supramol. Chem.* **1999**, *11*, 57−66.

(12) (a) Koshima H.; Khan, S. I.; Garcia-Garibay, M. A. *Tetrahedron: Asymmetry* **1998**, *9*, 1851−1854. (b) Koshima. H.; Honke, S. *J. Org. Chem.* **1999**, *64*, 790−793. (c) Koshima, H.; Honke, S.; Fujita, J. *J. Org. Chem.* **1999**, *64*, 3916−3921.

(13) (a) Koshima, H.; Hamada, M.; Yagi, I.; Uosaki, K. *Cryst. Growth Des.* **2001**, *1,* 467−471. (b) Koshima, H.; Miyamoto, H.; Yagi, I.; Uosaki, K. *Cryst. Growth Des.* **2004**, *4*, 807−811.

(14) (a) Ito, Y.; Nishimura, H.; Umehara, Y.; Yamada, Y.; Tone, M.; Matsuura, T. *J. Am. Chem. Soc.* **1983**, *105*, 1590−1597. (b) Ito, Y.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 3087−3090.

(15) (a) Gudmundsdottir, A. D.; Scheffer, J. R. *Tetrahedron Lett.* **1990**, *31*, 6807−6810. (b) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203−209.

(16) (a) Koshima, H.; Maeda, A.; Matsuura, T.; Hirotsu, K.; Okada, K.; Mizutani, H., Ito, Y.; Fu, T. Y.; Scheffer, J. R.; Trotter, J. *Tetrahedron: Asymmetry* **1994**, *5*, 1415−1418. (b) Hirotsu, K.; Okada, K.; Mizutani, H.; Koshima, H.; Matsuura, T. *Mol. Cryst. Liq. Cryst.* **1996**, *277*, 99−106.

(17) Koshima, H.; Matsushige, D.; Miyauchi, M. *CrystEngComm* **2001**, *33*, 1−3.

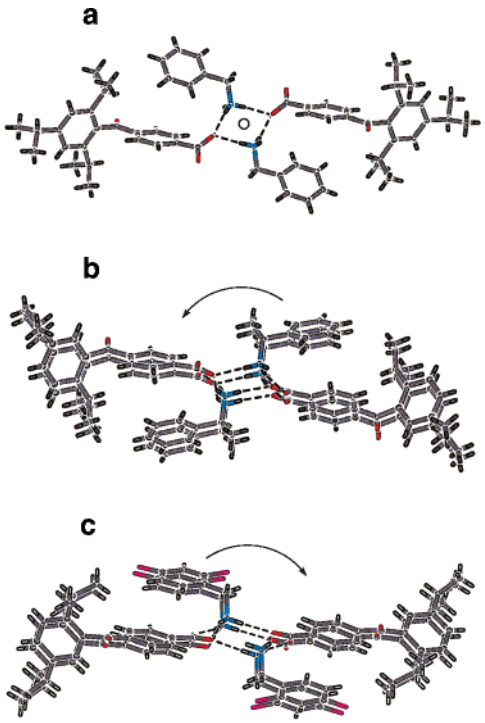
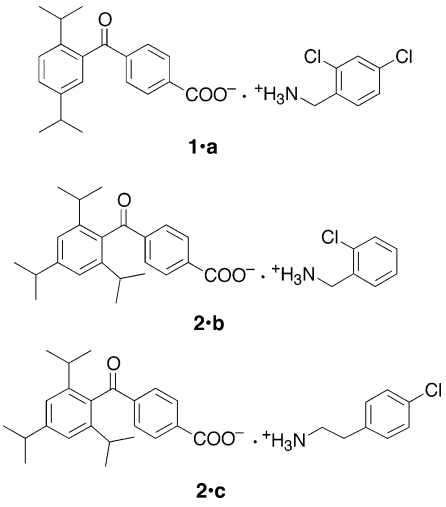


FIGURE 1. (a) Symmetrical molecular pair formed in the achiral salt crystal of **2** with benzylamine, (b) twofold helical arrangement in the chiral salt crystal of **1** with (*S*)-phenylethylamine, and (c) twofold helical arrangement in the chiral salt crystal *P*-**1**·**a**.

CHART 1. Chiral Salt Crystals



symmetrical pair (Figure 1a) may be distorted, and a helical arrangement similar to that in Figure 1b may be formed. We prepared another 20 salt crystals of **1** or **2** with eight substituted benzylamines (2,4-dichlorobenzylamine **a**, 3,4-dichlorobenzylamine, *o*-chlorobenzylamine **b**, *m*-chlorobenzylamine, *p*-chlorobenzylamine, *o*-bromobenzylamine, *o*-methylbenzylamine, and *p*-methylbenzylamine,), 1-(2′-chlorophenyl)ethylamine, and 1-(4′-chlorophenyl)ethylamine **c**, and thereby discovered three chiral salt crystals, **1**·**a**, **2**·**b**, and **2**·**c** (Chart 1). The statistical probability for achieving chiral crystallization of achiral compounds was found to be 8.0% by our recent survey of 190 000 compounds compiled in the Cambridge Structural Database (CSD).[18] The 15% probability (3 out of 20) obtained here is 2 times higher than the statistical probability 8.0%. Hence, we believe that it is important for the preparation of chiral crystals from achiral molecules in increased probability to learn and utilize the information obtained from the molecular arrangements of both achiral and chiral crystals of analogous compounds (Figures 1a and 1b).

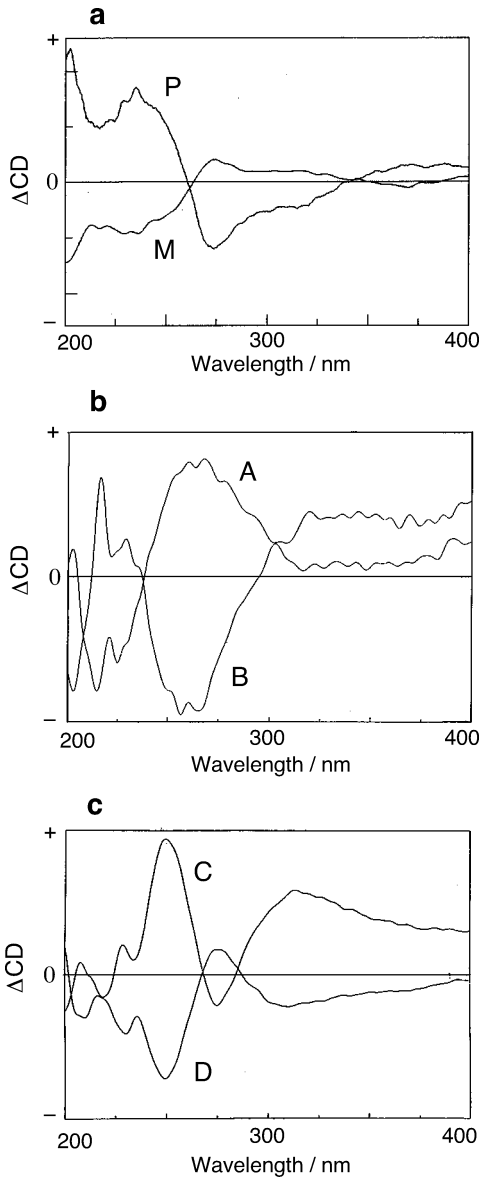
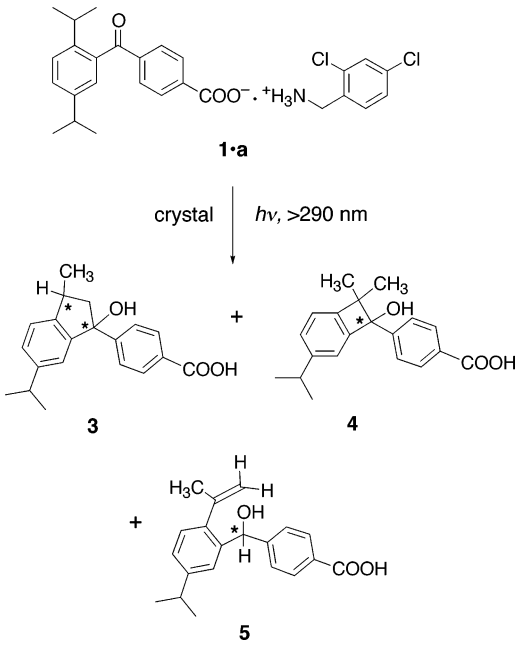


FIGURE 2. Solid-state CD spectra of the salt crystals (a) **1**·**a**, (b) **2**·**b**, and (c) **2**·**c**. The CD curves P and M correspond to *P*- and *M*-**1**·**a**, respectively.

Both enantiomeric crystals were obtained by spontaneous crystallization from methanol solutions. The solid-state CD spectra as Nujol mulls are shown in Figure 2. The CD curves of both the enantiomorphous crystals of **1**·**a**, **2**·**b**, and **2**·**c** are good mirror images. A single crystal of **1**·**a** was cut into two pieces. One of these was subjected to solid-state CD spectroscopy (curve P in Figure 2a). The other was submitted to X-ray crystallographic analysis with Cu Kα radiation at 93 K. The crystal belongs to

(18) Matsuura, T.; Koshima, H. *J. Photochem. Photobiol. C: Photochem. Rev.* **2005**, *6*, 7−24.

SCHEME 1



chiral space group $P2_12_12_1$, and the absolute structure was determined to be the *P*-form with a high degree of certainty from the Flack parameter[19] $\chi = 0.05(2)$ (Table 1). Thereafter, the absolute structures of **1·a** could be determined from the CD spectra. In the crystal *P*-**1·a**, a similar clockwise twofold helical arrangement occurs between the two components through $NH_3^+\cdots{}^-O_2C$ quaternary ammonium salt bridges (1.79, 1.80, and 1.85 Å) (Figure 1c). Unfortunately, X-ray crystallographic analysis of **2·b** and **2·c** could not be carried out due to the low quality of the single crystals.

Solid-State Photoreaction. Both the enantiomorphous crystals of **1·a**, **2·b**, and **2·c** for the solid-state photoreaction were prepared by seeding on a large scale and differentiated by measuring their solid-state CD spectra (Figure 2). The crystals of *P*-**1·a** were pulverized and irradiated at >290 nm on a preparative scale with a high-pressure mercury lamp through Pyrex under argon at 293 K. The irradiated mixture was methylated with CH_2N_2 and separated by preparative HPLC to afford three chiral products cyclopentenol **3**, cyclobutenol **4**, and hydrol **5** in 19, 11, and 3% chemical yield, respectively, at 98% conversion (Scheme 1). The enantiomeric excesses of **3**−**5** were determined by HPLC using a chiral column to be 82, 86, and 76% ee, respectively. The absolute configuration of the major enantiomer of **4** is already known to be the (*S*)-form from the single-crystal-to-single-crystal reaction of the salt crystal of **1** with (*S*)-phenylethylamine, which we previously reported.[17] As explained in the following X-ray structure study, the absolute configuration of the cyclopentenol **3** was determined to be the (*S*,*S*)-form. The minor hydrol product is most probably (*S*)-**5** by analogy with (*S*,*S*)-**3** and (*S*)-**4**.

Next, the dependence of chemical yields and enantiomeric excesses on the irradiation time was examined by using the crystals (5 mg) on an analytical scale. Treatment of the irradiated mixtures with CH_2N_2 and direct determination by HPLC using a chiral column gave the results listed in Table 2. Photoreaction of *P*-**1·a** afforded cyclopentenol (*S*,*S*)-**3** as a major product, and the chemical yield increased from 18 to 56% with extending the irradiation time from 45 to 180 min (entries 1−3). The optical yields of **3** were high and almost constant (86−87% ee) over the wide conversion range of **1** (28−91%). Cyclobutenol (*S*)-**4** with almost constant enantiomeric excesses of 80−82% was also obtained in 7−27% chemical yields. Further, (*S*)-**5** was obtained as a minor product in 79−85% ee. The molar ratio in the chemical yields of **3**:**4**:**5** was approximately 6:3:1. Irradiation of the oppositely handed crystals of *M*-**1·a** also afforded the oppositely handed products of (*R*,*R*)-**3**, (*R*)-**4**, and (*R*)-**5** in almost constant and high optical yields (entries 4−6). The almost constant magnitudes of enantiomeric excesses suggested that the reactions might be proceeding without change in the crystal structures before and after irradiation, i.e., single-crystal-to-single-crystal reaction.

On the other hand, irradiation of the enantiomorphous crystals of **2·b** (CD curve A in Figure 1b) gave the well-known cyclobutenol (*R*)-**6** as the sole product in low enantiomeric excesses (Scheme 2 and entries 7−9 in Table 2). The *R* configuration of the major enantiomer was confirmed by the X-ray crystallographic analysis of the single-crystal-to-single-crystal reaction of the salt crystal of **2** with L-prolinol.[16] Solid-state photoreaction of the enantiomorphous crystals of **2·c** (CD curve C in Figure 1c) produced almost racemic mixtures of cyclobutenol **6** as the sole product (entries 10−12 in Table 2).

X-ray Structure Study. The single crystals of **1·a** were still transparent after the irradiation, confirming that the reaction proceeded via the single-crystal-to-single-crystal transformation. Hence, we tried to trace the reaction process by X-ray crystallographic analysis. A single crystal of **1·a** was cut into two pieces, and its absolute structure was determined to be the *M*-form by measurement of the solid-state CD spectrum (curve M in Figure 2a) using the first half. The second half was submitted to X-ray crystallographic analysis with Cu Kα radiation at 293 K, and the absolute structure was independently confirmed to be the *M*-form from the Flack parameter $\chi = 0.24(5)$. Next, the single crystal of *M*-**1·a** was irradiated successively at around 350 nm with a superhigh-pressure mercury lamp through a UV transparent filter under argon at 293 K, and the cell constant was measured periodically at 293 K. The wavelength of around 350 nm used is the absorption edge of the molecule **1** and corresponds to the forbidden $n\pi^*$ transition band, because it has been reported that slow conversion by the excitation of the absorption edge keeps the crystal from deteriorating due to the irradiation.[20] The reaction proceeded very slowly and was not complete even after prolonged irradiation for 712 h (almost 1 month). The unit cell volume gradually increased from the initial 2568.3 Å^3 before irradiation to 2578.0 (a 0.37% increase), 2607.8 (a 1.54% increase), 2616.4 (a 1.87% increase), 2618.0 (a 1.94% increase), and 2616.0 Å^3 (a 1.86% increase) after irradiation for 144, 385, 540, 670, and 712 h, respectively. The length of axis *b* also increased gradually from 12.799 Å to 13.005 (a 1.61% increase),

(19) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876−881.

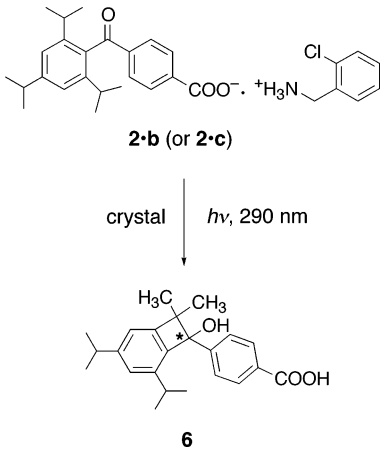
(20) Enkelmann, V.; Wegner, G.; Novak, K.; Wagener, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 10390−10391.

TABLE 2. Solid-State Photoreaction of Chiral Salt Crystals

entry	crystal	irradiation time (min)	conversion (%)	3		4		5		6	
				yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)
1	*P*-**1·a**	45	28	18	(*S*,*S*) 86	7	(*S*) 80	2	(*S*) 79		
2	*P*-**1·a**	90	81	46	(*S*,*S*) 87	23	(*S*) 82	7	(*S*) 85		
3	*P*-**1·a**	180	91	56	(*S*,*S*) 86	27	(*S*) 80	8	(*S*) 83		
4	*M*-**1·a**	45	28	17	(*R*,*R*) 80	7	(*R*) 78	4	(*R*) 80		
5	*M*-**1·a**	90	75	43	(*R*,*R*) 83	21	(*R*) 84	8	(*R*) 83		
6	*M*-**1·a**	180	85	52	(*R*,*R*) 86	25	(*R*) 85	7	(*R*) 81		
7	**2·b**[a]	1	34							27	(*R*) 10
8	**2·b**[a]	10	99							88	(*R*) 4
9	**2·b**[a]	60	100							93	(*R*) 2
10	**2·c**[b]	1	12							7	<1[c]
11	**2·c**[b]	10	68							57	<1[c]
12	**2·c**[b]	60	98							94	<1[c]

[a] Enantiomorphous crystals corresponding to CD curve A in Figure 1b. [b] Enantiomorphous crystals corresponding to CD curve C in Figure 1c. [c] Almost racemic.

SCHEME 2



13.073 (a 2.14% increase), 13.163 (a 3.64% increase), 13.135 (a 3.36% increase), and 13.146 Å (a 2.71% increase) along with the extension of irradiation times, but the lengths of axes *a* and *b* were not greatly altered.

Figure 3a shows the ORTEP drawing of a salt bond pair arranged in the reactant *M*-**1·a** before irradiation measured at 293 K. The thermal vibrations of the atoms were large. In particular, the high anisotropic atomic factors of the diisopropylbenzene moiety suggested the possibility of some disorder. The γ-hydrogen of the *o*-isopropyl group could be solved in front (H10A) or behind (H10B) the carbonyl oxygen O1 with 50:50 occupancy, but the two γ-methyl groups could not be separated into four methyl groups. The carbon atoms of the phenyl ring and the *p*-isopropyl group could not be separated into a disordered structure either.

Under cooling at 93 K, the cell constant of the *M*-**1·a** changed slightly from $a = 6.3028$ (5), $b = 12.7985(9)$, $c = 31.838(4)$ Å, $V = 2568.2(4)$ Å^3 at 293 K to $a = 6.3071(3)$, $b = 12.1522(9)$, $c = 32.017(2)$ Å, $V = 2454.0(2)$ Å^3 (Table 1). The thermal vibrations of atoms decreased considerably, and the disordered structure of the diisopropylbenzene moiety disappeared (Figure 3b). The conformation of the *o*-isopropyl group changed: the γ-hydrogen H10 was only positioned behind the carbonyl oxygen O1. The rear position of the γ-hydrogen is different from the front position found in the salt crystal of **1** with (*S*)-phenylethylamine.[17]

The X-ray measurement of *M*-**1·a** after the irradiation for 712 h was first carried out at 293 K, but the structure analysis was not successful probably due to the deterioration of the crystal during the prolonged irradiation. The crystal structure could be solved by the data collected at 93 K as the disordered structure of the cyclopentenol **3** and the remaining reactant **1** in 53:47 occupancy (Figure 3c). Figures 3d and 3e depict separately the molecular pairs of the cyclopentenol **3** and the remaining reactant **1** with **a**, respectively. The newly produced atoms of the cyclopentenol ring are numbered in green. The newly produced hydroxyl oxygen O1′ (red), cyclopentenol carbon C12′ (green), and C13′ (green) atoms of (*R*,*R*)-**3** (Figure 3c,d) and the initial O1 (red), C11 (black), C12(black), and C13 (black) atoms of **1** (Figure 3c,e) were refined by the isotropic temperature factors. The atomic thermal vibrations after irradiation are considerably large even at 93 K (Figure 3c−e) in comparison with those before irradiation (Figure 3b). This suggests that not only the atomic positions directly related to the reaction but also the other atomic positions were altered to a small extent before and after the reaction. However, the structures due to the reactant and the cyclopentenol could not be separated, except for the atoms that underwent bonding changes during the reactions (O1′, C12′, C13′), maybe due to the low data quality ($R = 0.103$).

The absolute structure of the irradiated crystal could not be directly confirmed by the Flack parameter due to the measurement with Mo Kα radiation and the low data quality (Table 1). However, the absolute configuration of the cyclopentenol **3** was determined to be (*R*,*R*)-**3** from the coincidence of the absolute structures between the remaining reactant *M*-**1·a** (Figure 3e) and the starting *M*-**1·a** (Figure 3b), both of the X-ray measurements being carried out at 93 K. The other products, the cyclobutenol **4** and the hydrol **5**, were not found in the crystal structure (Figure 3c). This indicates that the product selectivity was different from the irradiation of the powder samples at >290 nm, which afforded not only **3** but also **4** and **5** (Scheme 1 and entries 1−6 in Table 2).

After the X-ray structure analysis was completed, the irradiated single crystal was dissolved in methanol, treated with CH_2N_2, and submitted to HPLC analysis using a C_{18} column to give the cyclopentenol **3** as the sole product and the remaining reactant **1** in an approximate 70:30 molar ratio. The cyclobutenol **4** and the hydrol **5** were not detected by the HPLC analysis, coincident with the result obtained from the X-ray structure analysis. We

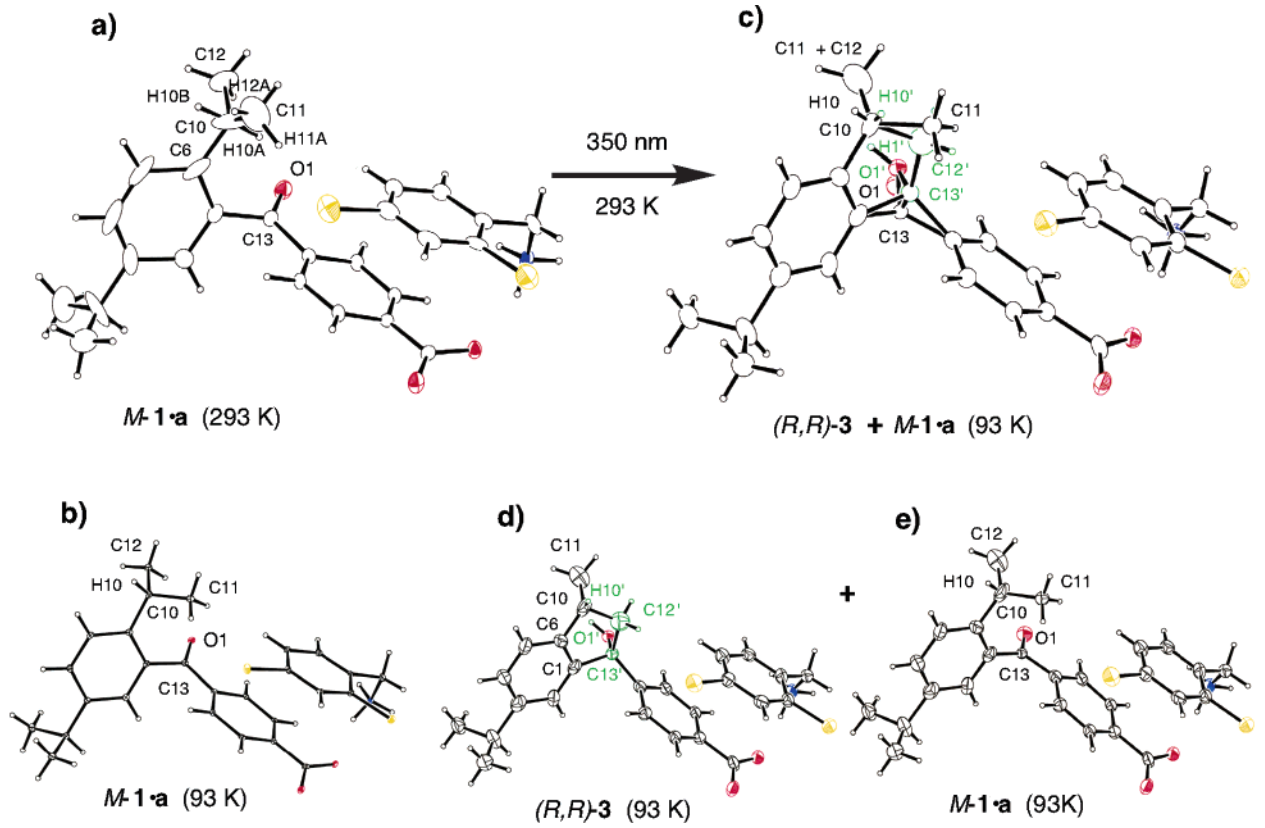
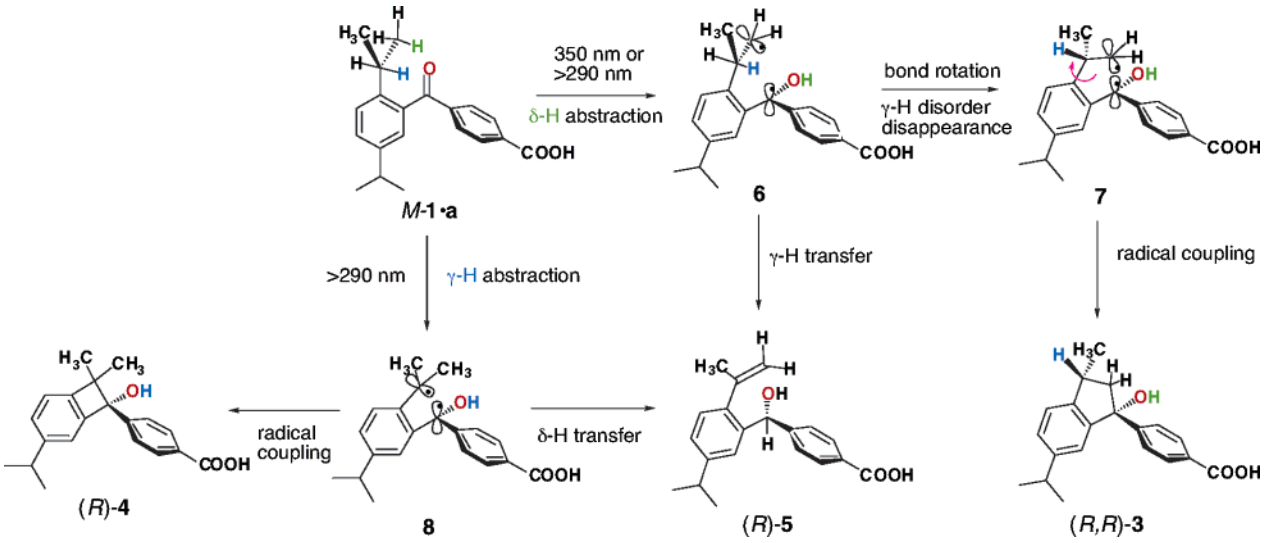


FIGURE 3. *M*-**1**·**a** before irradiation measured (a) at 293 K and (b) at 93 K. (c) Coexistence of the product (*R*,*R*)-**3** and the remaining *M*-**1**·**a** after irradiation measured at 93 K, and the separate representation of (d) the product (*R*,*R*)-**3** and (e) the remaining *M*-**1**·**a**. ORTEP drawings are shown at the 10% probability level.

SCHEME 3. Possible Reaction Mechanisms in Crystal *M*-1·a



further checked the dependence of the product selectivity on the irradiation wavelength. Irradiation of the single crystals of *M*-**1**·**a** at >290 nm gave three products, **3**−**5**, the reaction proceeding considerably faster than irradiation at around 350 nm. In contrast, irradiation of the powder crystals of *M*-**1**·**a** at around 350 nm gave **3** as the sole product, showing higher product selectivity than the irradiation at >290 nm.

Scheme 3 shows the possible reaction mechanisms occurring in *M*-**1**·**a**. The reaction paths must be discussed on the basis of the crystal structure measured at 293 K (Figure 3a), because the crystal was irradiated at 293 K. Irradiation at around 350 nm causes the $n\pi^*$ excitation of the carbonyl O1 oxygen atom of the molecule **1**. As seen in Figure 3a, the O1 atom in excited **1** can abstract enantiomerically the methyl H12A δ-hydrogen atom of the *o*-isopropyl group due to the short O1- - -H12A distance (2.73 Å)[21] to give the (*R*)-ketyl radical •C13 and the methyl radical •C12. This corresponds to the biradical **6** in Scheme 3. In contrast, the δ-H11A hydrogen cannot

be abstracted by the excited O1 because of the long O1- - -H11A distance (3.70 Å) (Figure 3a). Next, the C6−C10 bond of the *o*-isopropyl group of **6** rotates in the clockwise direction; the •C13 and •C12 radicals gradually approach each other from the initial C12- - -C13 distance (3.71 Å), and the disordered γ-H10B hydrogen disappears to give the radical conformation **7**. Finally, radical coupling between the •C13 and the •C12 radicals occurs to form the new C12′−C13′ bond and give the cyclopentenol (*R*,*R*)-**3**. The C11 and C12 methyl groups in the product (*R*,*R*)-**3** and the reactant **1**, respectively, should be disordered but cannot be separately resolved (Figure 3c−e). In (*R*,*R*)-**3**, the O1′-H1′ hydroxyl group and the disordered (C11 + C12) methyl group are positioned downward. Conversely, H10′ and the benzoic acid moiety are positioned upward. The cyclopentenol ring is not a flat plane, but the C12′ carbon atom is positioned slightly upward, because the C1═C6 double bond (1.39 Å) is shorter than the other single bonds of C12′−C13′ (1.58 Å), C10−C12′ (1.53 Å), C1−C13′ (1.51 Å), and C6−C10 (1.50 Å).

Finally, we would like to discuss briefly the dependence of the product selectivity on wavelength. Irradiation at >290 nm can more effectively cause the $n\pi^*$ excitation of the carbonyl O1 oxygen than irradiation at around 350 nm. The $n\pi^*$ excited oxygen can abstract the closest γ-H10A (2.38 Å) in preference to the δ-H12A (2.73 Å) to give the •C10 tertiary radical and the •C13 ketyl radical. The $\pi\pi^*$ transition state is excited by the irradiation at >290 nm, but the $\pi\pi^*$ excitation state is inefficient for hydrogen abstraction. Next, the two unpaired electrons present in **8** (Scheme 3) approach each other from the initial C10- - -C13 distance (3.02 Å) without racemization, affording the cyclobutenol (*R*)-**4** in high enantioselectivity. The formation of the hydrol (*R*)-**5** by the irradiation of *M*-**1·a** at >290 nm can be caused by the δ-hydrogen transfer of the radical species **8** (Scheme 3).[22] The hydrol (*R*)-**5** in the irradiation with >290 nm light may also be formed by hydrogen transfer from C10 to the ketyl radical center C13 in the diradical **6**. However, the reason for the almost complete lack of formation of (*R*)-**4** and (*R*)-**5** in the irradiation at around 350 nm cannot be explained at the present time. Further study is necessary to elucidate the dependence of the product selectivity on wavelength.

Conclusion

Absolute asymmetric photocylization of the isopropylbenzophenone derivatives was achieved by using the chiral salt crystals obtained from achiral amines. Irradiation of the *M*-crystal of 4-(2,5-diisopropylbenzoyl)benzoic acid with 2,4-dichlorobenzylamine caused highly enantioselective Norrish type II cyclization to give the (*R*,*R*)-cyclopentenol as a major product. The reaction proceeded via single-crystal-to-single-crystal transformation, and therefore the reaction path was confirmed by the X-ray crystallographic analysis before and after irradiation.

Experimental Section

All melting points are uncorrected. ^{1}H NMR (300 MHz) spectra were measured with tetramethylsilane as an internal standard. IR spectra were recorded as films. Mass spectra were obtained using EI. The solvents were of analytical grade.

Preparation of Salt Crystals. Both enantiomorphous salt crystals *P*-**1·a** and *M*-**1·a** were prepared by spontaneous crystallization from a solution of 4-(2,5-diisopropylbenzoyl)-benzoic acid **1** with 2,4-dichlorobenzylamine **a** in methanol and then by seeding. Other crystals **2·b** and **2·c** were prepared similarly. Crystal *P*-**1·a**: colorless crystal; mp 175−179 °C; IR (KBr) 3450, 2650, 1660, 1640 cm^{-1}. Crystal *M*-**1·a**: colorless crystal; mp 175−179 °C; IR (KBr) 3450, 2650, 1660, 1640 cm^{-1}. Crystal **2·b**: colorless crystal; mp 198−200 °C; IR (KBr) 3440, 1670, 1630 cm^{-1}. Crystal **2·c**: colorless crystal; mp 196−199 °C; IR (KBr) 3450, 1660, 1620 cm^{-1}.

Photoreaction of Salt Crystals of 1·a. Pulverized crystals of *P*-**1·a** (2.0 g) were placed between two Pyrex plates and irradiated with a 400 W high-pressure mercury lamp under argon at 20 °C. The irradiated mixture was methylated with CH_2N_2 and separated by preparative HPLC using a C_{18} column and methanol/water to afford the three methyl esters of **3**−**5**. For the photoreaction on an analytical scale, enantiomorphous crystals of *P*-**1·a** (5 mg) were irradiated, methylated, and determined by HPLC using a chiral column (Chiralpak AD) and hexane/2-propanol with monitoring at 254 nm.

Methyl Ester of Cyclopentenol (3): colorless oil, not solidified; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.35 (d, J = 7.0 Hz, 3H), 1.97 (dd, J = 13.5, 8.8 Hz, 1H), 2.67 (dd, J = 13.5, 6.6 Hz, 1H), 2.82 (septet, J = 7.0 Hz, 1H), 3.51 (sextet, J = 7.0 Hz, 1H), 3.93 (s, 3H), 6.77 (s, 1H), 7.23 (d, J = 9.2 Hz, 2H), 7.55 (dt, J = 8.6, 1.8 Hz, 2H), 8.02 (dt, J = 8.4, 1.8 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.2, 24.1, 34.0, 36.2, 52.1, 54.5, 76.6, 77.0, 77.4, 84.4, 121.7, 123.5, 126.2, 127.3, 128.6, 129.3, 146.7, 147.3, 148.4, 151.6, 167.1; IR (KBr) 3445, 1703 cm^{-1}; MS (*m*/*z*) 325 (M^+). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.78; H, 7.49.

Methyl Ester of Cyclobutenol (4): colorless powder, mp 103.8−106.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.27 (d, J = 7.0 Hz, 6H), 1.49 (s, 3H), 2.95 (septet, J = 7.0 Hz, 1H), 3.16 (s, 1H), 3.87 (s, 3H), 7.11 (dd, J = 7.5, 0.9 Hz, 1H), 7.23 (d, J = 3.2 Hz, 2H), 7.36 (dt, J = 8.4, 1.8 Hz, 2H), 7.97 (dt, J = 8.4, 1.8 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.9, 24.3, 24.4, 24.9, 34.8, 55.5, 76.6, 77.0, 77.4, 85.6, 120.6, 121.4, 127.0, 128.1, 128.6, 129.9, 144.8, 148.5, 149.4, 150.3, 171.6; IR (KBr) 3448, 1718 cm^{-1}; MS (*m*/*z*) 325 (M^+). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.54; H, 7.32.

Methyl Ester of Hydrol (5): colorless powder, mp 95.5−97.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 2.00 (s, 3H), 2.20 (s, 1H), 2.80 (septet, J = 7.0 Hz, 1H), 3.90 (s, 3H), 4.86 (d, J = 1.1 Hz, 1H), 5.23 (s, J = 1.7 Hz, 1H), 6.14 (d, J = 3.3 Hz, 1H), 7.07−7.18 (m, 3H), 7.42 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.9, 25.8, 33.9, 52.1, 76.6, 77.0, 77.4, 116.0, 125.5, 125.7, 126.7, 128.2, 128.9, 129.3, 129.6, 139.4, 140.7, 144.8, 148.2, 149.2, 167.0; IR (KBr) 3511, 1706 cm^{-1}; MS (*m*/*z*) 325 (M^+). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.56; H, 7.31.

X-ray Crystallographic Analysis. X-ray diffraction data were collected on a Rigaku RAPID imaging plate two-dimensional area detector using graphite-monochromatized Cu Kα or Mo Kα radiation. All crystallographic calculations were performed by using the teXsan crystallographic software package of the Molecular Structure Corporation.[23] The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were not refined. Hydrogen atoms attached to carbon atoms were placed in the calculated positions.

(21) Scheffer, J. F. In *Organic Solid State Chemistry;* Desiraju, G. R., Ed.; Elsevier: New York, 1987; pp 1−45.

(22) Braga, D.; Chen, S.; Filson, H.; Maini, L.; Netherton, M. R.; Patrick, B. O.; Scheffer, J. R.; Scott, C.; Xia, W. *J. Am. Chem. Soc.* **2004**, *126*, 3511−3520.

(23) *TeXsan, X-ray Structure Analysis Package*; Molecular Structure Corporation: The Woodlands, TX, 1985.

The absolute configuration was determined from the Flack parameter.[19] The crystal data are summarized in Table 1.

Acknowledgment. This research was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Sports, Culture, Science and Technology (MEXT) and Kurata Memorial Hitachi Science and Technology.

Supporting Information Available: X-ray crystallographic data (CIF) of the four salt crystals, **2**·benzylamine, *P*-**1**·**a**, and *M*-**1**·**a** before irradiation and after irradiation. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0500784