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Absolute Asymmetric Phthalide Synthesis via the Solid-State Photoreaction of *N*,*N*-Disubstituted 2-Benzoylbenzamides Involving a Radical Pair Intermediate

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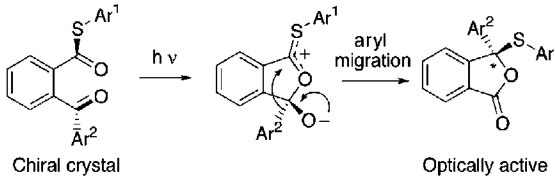
Asymmetric generation influenced by a chiral crystalline environment can be considered as an attractive methodology to obtain optically active compounds from achiral compounds; this methodology is recognized as the "absolute" asymmetric synthesis.[1−9] Recently, we reported an example involving the solid-state photoreaction of *S*-aryl 2-aroylbenzothioate **1**, which formed chiral crystals, leading to optically active 3-phenyl-3-(phenylthio)phthalide **2** (Scheme 1).[10,11] According to the absolute-to-absolute correlation study of the X-ray crystal structures before and after the photoreaction, the product formation can be rationalized by an unusual pathway involving aryl migration. We studied the X-ray structural analysis and the solid-state photoreaction of the amide derivatives, *N*,*N*-disubstituted 2-benzoylbenzamides, to explore the generality and utilization of the pathway for the asymmetric synthesis.

Benzoylbenzamides **3a**−**c** were conveniently prepared by a condensation reaction from commercially available amines and the corresponding 2-benzoylbenzoic acids using DCC and DMAP.[11] Recrystallization of these amides from the chloroform−hexane solution afforded colorless prisms in all cases. All crystals were subjected to X-ray crystallographic analysis to obtain details of the molecular conformation and the architecture in the crystals.

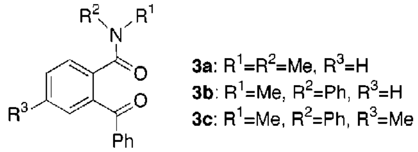
Table 1 shows the crystal data of amides **3a**−**c**. For all prochiral amides **3a**−**c**, the constituent molecules adopted orthorhombic chiral space group $P2_12_12_1$ and were frozen in a chiral and helical conformation in the crystal lattice. A spontaneous optical resolution occurred during the crystallization process, in which the molecules were associated and fixed in a chiral fashion. Generally, the selection of either enantiomorphic form of molecular configuration is equally probable. Once enantiomorphic crystals are formed, a large amount of chiral crystals with the same optical rotation can be selectively prepared through recrystallization by seeding the desired crystals.

Scheme 1



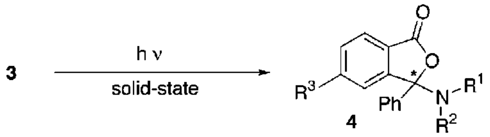
1 **2**

Table 1. Crystal Data for *N*,*N*-Dialkyl-2-benzoylbenzamides **3a**−**c**



entry	**3a**	**3b**	**3c**
formula	$C_{16}H_{15}NO_2$	$C_{21}H_{17}NO_2$	$C_{22}H_{19}NO_2$
mol weight	253.30	315.37	329.39
crystal system	orthorhombic	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	4	4
a/Å	10.420(2)	11.453(6)	19.106(5)
b/Å	17.208(4)	18.572(5)	8.019(2)
c/Å	7.519(2)	8.107(2)	11.986(3)
V/Å^3	1348.3(6)	1724.5(8)	1836.3(9)
ρ_{calc}/g cm^{-3}	1.246	1.213	1.19
μ(CuKα)/cm^{-1}	6.614	6.217	6.036
F(000)	536	664	696
crystal size/ mm	0.40 × 0.30 × 0.30	0.30 × 0.10 × 0.10	0.30 × 0.20 × 0.20
used reflctns	1156	837	613
R	0.032	0.044	0.044
R_w	0.035	0.044	0.045

Table 2. Solid-State Photoreaction of **3** under Various Conditions



entry	amide	condition[a] of the solid	temp (°C)	conv (%)	yield (%) of **4**	ee (%) of **4**[b]
1	**3a**	powder	15	recovered	0	
2	**3b**	powder	15	100	>99	80
3	**3b**	powder	0	100	>99	83
4	**3b**	powder	−50	47	>99	87
5	**3b**	crystal	0	56	>99	86
6	**3b**	crystal	−50	46	>99	97
7	**3c**	powder	15	100	>99	42
8	**3c**	powder	−50	25	>99	87

[a] Powder was prepared by grinding the crystals. [b] ee value was determined by HPLC using Chiral Cell OJ column.

All of the solid-state photolyses were done under an atmosphere of deoxygenated and dried argon. Solid samples placed in the bottom of the test tube were cooled in a cooling apparatus and were irradiated by Pyrex-filtered light transmitted by using a flexible light guide from a 250-W ultra-high-pressure mercury lamp. When the powdered **3a** was irradiated at 15 °C, the solid remained unchanged for 10 h; however, it gradually changed to amorphous on prolonged irradiation. At this point, no isolable photoproduct was obtained, and the unchanged starting amide was verified by IR and NMR spectroscopy (Table 2, entry 1). On the other hand, photolysis of powdered **3b** at 15 °C for 2 h gave a quantitative amount of 3-(*N*-methylanilino)-3-phenylphthalide **4b**,

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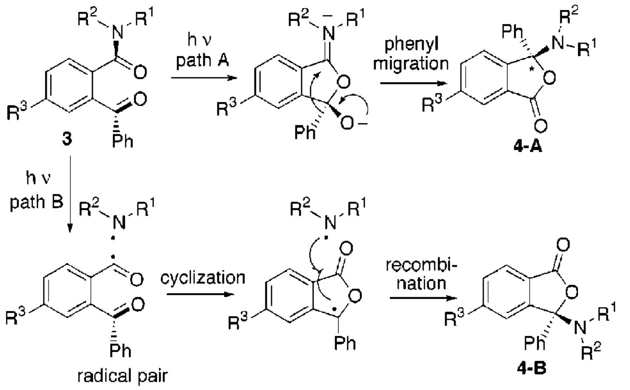
Scheme 2

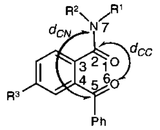


the structure of which was determined on the basis of spectral data. As expected, the asymmetric induction in **4b** was confirmed by observation of its optical rotation, the $[\alpha]^{20}_{D}$ value of which was 21° (c =1.0 in $CHCl_3$) (Table 2, entry 2). The ee value was determined by HPLC using a chiral cell OJ column (Daicel Chemical Ind.). As a result of the suppression of the reaction conversion yield and by decreasing the reaction temperature to −50 °C, the enantiomeric purity rose to 87% ee (entries 3 and 4). Furthermore, irradiation of single crystals of **3b** gave 97% ee of **4b** when the reaction conversion reached 46% (entries 5 and 6).

In regard to the mechanism of the solid-state photoreactions, there are two possible pathways from the starting amides to phthalides (Scheme 2). Path A involves phenyl migration, the same as in the mechanism of thioester derivatives **1** as shown in Scheme 1. The other path, B, is initiated by homolytic cleavage of the C(=O)−N bond to generate a radical pair intermediate. The radical mechanism has been confirmed in the photo-Fries rearrangement of aromatic amides.[12] To answer the question of the reaction mechanism involved, regiochemical correlation was examined using a methyl probe (R^3 = Me) on the central aryl ring in the starting material. The findings based on the methyl probe between the starting material and the final product provide straightforward proof for the determination of the pathway since the position of this substituent in the product can represent the reaction course as shown in Scheme 2. Different regiochemical isomers, **4-A** or **4-B**, should be obtained from each reaction pathway.

When the crystal of **3c** was irradiated at 15 °C for 1 h, a single regioisomer of **4c** was obtained quantitatively (Table 2, entry 7). Direct establishment of the regiochemistry was not performed; however, the structure could be determined as **4c-B** on the basis of the fact that 3-hydroxy-6-methyl-3-phenylphthalide was obtained by hydrolysis of **4c** with aqueous potassium hydroxide.[13] As is apparent from the regiochemical correlation, reaction pathway B was indispensable for the rationalization of the product formation since path A would lead to another regioisomer, **4c-A** (Scheme 2). Apparently, the reaction of **3b** also involves the same reaction mechanism as **3c**; however, the pathway could not be definitively proved.

Table 3. Geometrical Parameters for the Reaction Pathway



	torsional angle (deg)		distance	
amide	C=O$_{amide}$[a]	C=O$_{benzoyl}$[b]	d_{CC}[c]	d_{CN}[d]
3a	66	38	2.80	3.77
3b	63	26	2.74	3.87
3c	65	31	2.74	3.88

[a] C=O$_{amide}$ is defined as the torsional angle for C4−C3−C2−O1. [b] C=O$_{benzoyl}$ is defined as the torsional angle for C3−C4−C5−O6. [c] d_{CC} is the distance between C2 and O6. [d] d_{CN} is the distance between C5 and N7.

X-ray structural analysis indicates that the crystal of **3c** is also chiral, in the space group $P2_12_12_1$ (Table 1). When powdered **3c** was irradiated at 15 °C until the conversion reached 100%, the photoproduct **4c-B** showed an optical activity of 42% ee (Table 2, entry 7). Furthermore, a higher ee value for **4c-B** (87% ee) was obtained by the reaction at −50 °C (entry 8).

It has been generally argued that solid-state reactions proceed with minimum atomic or molecular movement.[14−16] Therefore, the reactivities are mainly influenced by atomic arrangement represented by distances and angles between the reaction centers. The twist around the C−C bonds defined by benzoyl and amide against the central phenyl ring may be the most important factor for the formation of the helical and chiral structures. The X-ray structural studies revealed that all amides **3a−c** tend to have almost the same molecular conformation (Table 3). Remarkably, the amide carbonyl is inclined to strongly twist against the central phenyl ring (63−66°), and the twisted angle formed by the benzoyl carbonyl is small (26−38°). Table 3 also lists interatomic distances responsible for the photochemical events via radical cyclization. The d_{CC} value is the distance between the amide carbonyl carbon and the benzoyl oxygen atoms, which are placed close to each other, and is much less than the sum of van der Waals radii (3.22 Å), ranging from 2.74 to 2.80 Å. Although the d_{CN} value, defined as the distance between the benzoyl carbon and amino nitrogen atoms, was slightly longer (3.77−3.88 Å) than the sum of van der Waals radii (3.25 Å), the subsequent recombination of the amino radical with the phthalide radical might occur since some conformational changes enhanced by initial cyclization would allow the reaction centers to be located close to each other. These atomic arrangements in the crystal lattices satisfy the effective radical cyclization followed by recombination between the phthalide and amino radical pair. Although all amides offered almost the same molecular conformation, *N*,*N*-dimethyl derivative **3a** was inert toward the photocylization. It is generally understood that the cleavage of the C(=O)−N bond of aliphatic amides is an unfavorable process owing to the difference in stabilities of the amino radicals.[17,18]

In conclusion, the solid-state photoreaction of *N*,*N*-disubstituted 2-benzoylbenzamides promoted intramolecular cyclization to phthalides via a radical pair intermediate, in which the "absolute" asymmetric conversion into the prochiral starting materials in the chiral crystalline environment was performed with good enantioselectivity.

Supporting Information Available: X-ray structural information on **3a−c** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) When the photoproduct **4c** was hydrolyzed with aqueous potassium hydroxide, 3-hydroxy-6-methyl-3-phenylphthalide was isolated. This material was also obtained by the same treatment of **3c** or 4-methyl-2-benzoylbenzoic acid.

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