Tetrahedron Letters 49 (2008) 4346–4348

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Single-crystal-to-single-crystal photocyclization of 4-(2,4,6-triisopropylbenzoyl)benzoic acid in the salt crystal with (*S*)-phenylethylamine

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ARTICLE INFO

*Article history:*
Received 2 April 2008
Revised 2 May 2008
Accepted 8 May 2008
Available online 11 May 2008

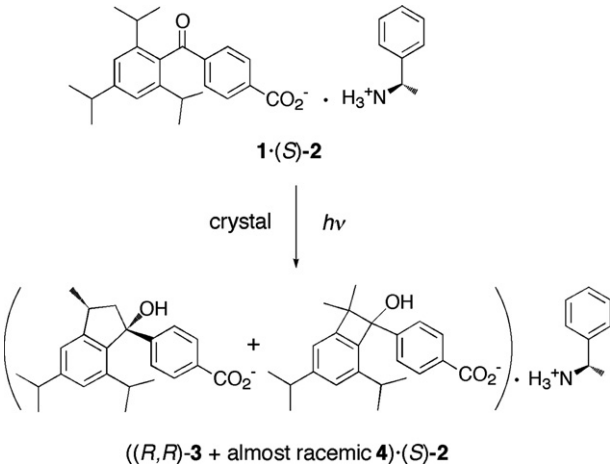
ABSTRACT

Ultraviolet irradiation of a salt crystal of 4-(2,4,6-triisopropylbenzoyl)benzoic acid with (*S*)-phenylethylamine promoted single-crystal-to-single-crystal photocyclization to give an enantiopure (*R*,*R*)-cyclopentenol and almost racemic cyclobutenol. The reaction paths were elucidated by X-ray crystallographic analysis of the crystal before and after irradiation.



Solid-state photoreactions of chiral crystals lead to high enantio- and diastereodifferentiation due to the restricted motion of molecules in the crystal lattice.[1,2] Chiral salt crystals are relatively easily prepared by combining carboxylic acids and amines, one of which is a chiral compound with an ionic chiral handle.[3] Therefore, reactions based on chiral salt crystals provide promising methodologies for asymmetric synthesis. Isopropylbenzophenone derivatives are known to undergo Norrish type II photocyclization in the crystalline state.[4] We have previously reported that the enantioselective photocyclization of carboxylic acid derivatives was achieved in salt crystals with chiral amines and that the reactions proceeded via single-crystal-to-single-crystal transformation.[5,6] Absolute asymmetric induction has been also achieved by utilizing chiral salt crystals spontaneously formed from achiral carboxylic acid derivatives and achiral amines.[7] Here, we report diastereo- and enantiospecific photocyclization in the salt crystal of 4-(2,4,6-triisopropylbenzoyl)benzoic acid **1** with (*S*)-phenylethylamine (*S*)-**2** via single-crystal-to-single-crystal transformation.

The salt crystals of **1**·(*S*)-**2** were prepared by crystallization from the ethanol solution of both components.[8] The pulverized crystals **1**·(*S*)-**2** (200 mg) were placed between two Pyrex glass plates and irradiated with a 400 W high-pressure mercury lamp under argon at 288 K for 48 h. The irradiated mixture was methylated with $CH_2N_2$ and the products were separated by preparative HPLC to give a diastereomeric cyclopentenol **3** and a cyclobutenol **4** in 26% and 21% yield at 89% conversion, respectively (Scheme 1). The low yields are due to the loss in the separation process. The enantiomeric excess was determined by HPLC using a chiral column (Daicel, Chiralpak AD) to be (*R*,*R*)-**3**[9] in 100% ee and (*S*)-**4** in 6% ee; the ratio of (*R*,*R*)-**3**, (*S*)-**4**, and (*R*)-**4** was 55:24:21.




**Scheme 1.**

Photoirradiation of the single crystals of **1**·(*S*)-**2** maintained the initial transparency, confirming the single-crystal-to-single-crystal reaction. Finally, a piece of single crystal (0.38 × 0.31 × 0.31 mm) of **1**·(*S*)-**2** was submitted to X-ray crystallographic analysis at 293 K, and the absolute structure was determined on the basis of the *S* configuration of the phenylethylamine molecule **2**.[10,11] The ORTEP drawing of a salt bond pair arranged in the reactant **1**·(*S*)-**2** is given (Fig. 1).

Next, the single crystal was irradiated successively at >290 nm with a high-pressure mercury lamp through Pyrex under argon at 288 K, and the cell constant was measured periodically at 293 K. The reaction proceeded slowly and was completed after irradiation for 240 h. The sizes of the unit cells changed, increasing

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doi:10.1016/j.tetlet.2008.05.041

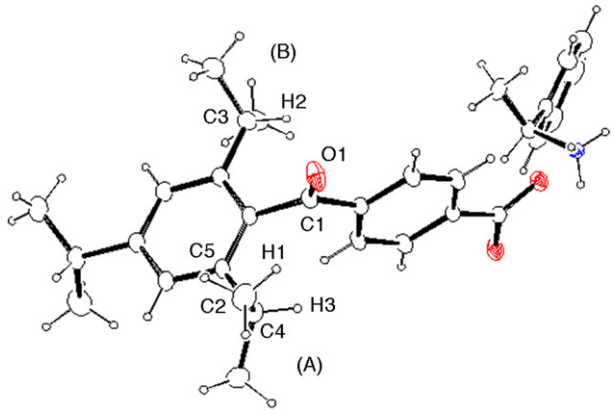



**Figure 1.** ORTEP drawing of the reactant crystal of **1**·(*S*)-**2** at the 15% probability level. Please note that the methyl H1, methine H2, and H3 atoms are projected toward carbonyl O1 oxygen atom for abstraction to yield the corresponding cyclopentenol and cyclobutenol products **3** and racemic **4**, respectively.

(+3.02%) along the *a*-axis, decreasing (−3.29%) along the *b*-axis, and increasing (+0.37%) along the *c*-axis, resulting overall in no change (0.0%) in total cell volume.

However, the structure analysis of the product crystal after irradiation was not successful, probably due to the deterioration of the crystal during prolonged irradiation. The crystal structure could be solved by the data collected at 93 K as the disordered structure of the cyclopentenol (*R*,*R*)-**3** and the enantiomeric (*S*)-**4** and (*R*)-**4** in 57:29:14 occupancy (Fig. 2a).[10,11] The ORTEP drawings of (*R*,*R*)-**3** and (*S*)-**4** are shown separately (Fig. 2b and c, respectively).

After the X-ray structure analysis was completed, the irradiated single crystal was treated with $CH_2N_2$ and analyzed by HPLC using a chiral column (Daicel, Chiralpak AD) to give (*R*,*R*)-**3**, (*S*)-**4**, and (*R*)-**4** in 55:24:21; (*R*,*R*)-**3** in 100% ee; and (*S*)-**4** in 6% ee, which were consistent with results obtained by the preparative scale photoreaction of the powdered crystals mentioned above, and fairly consistent with the 57:29:14 occupancy obtained by X-ray crystallographic analysis.

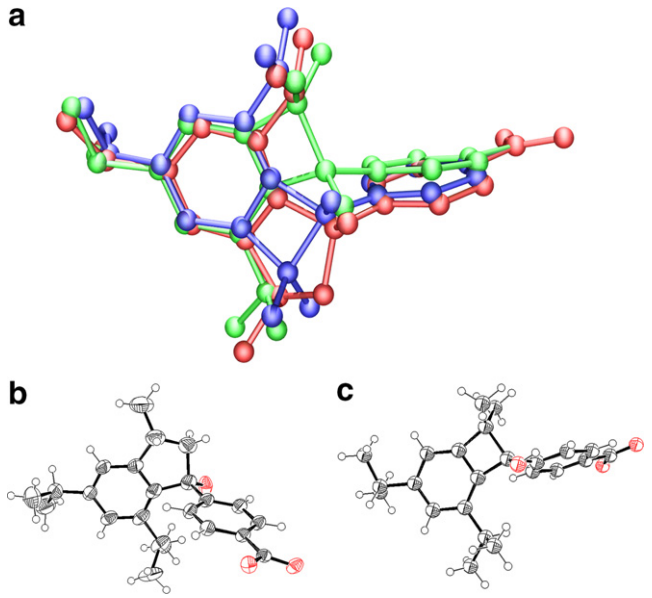



**Figure 2.** (a) Coexistence of the products (red) (*R*,*R*)-**3**, (green) (*S*)-**4**, and (blue) (*R*)-**4**; hydrogen atoms are omitted for clarity. ORTEP drawings of (b) (*R*,*R*)-**3**, and (c) (*S*)-**4**, at the 25% probability level.

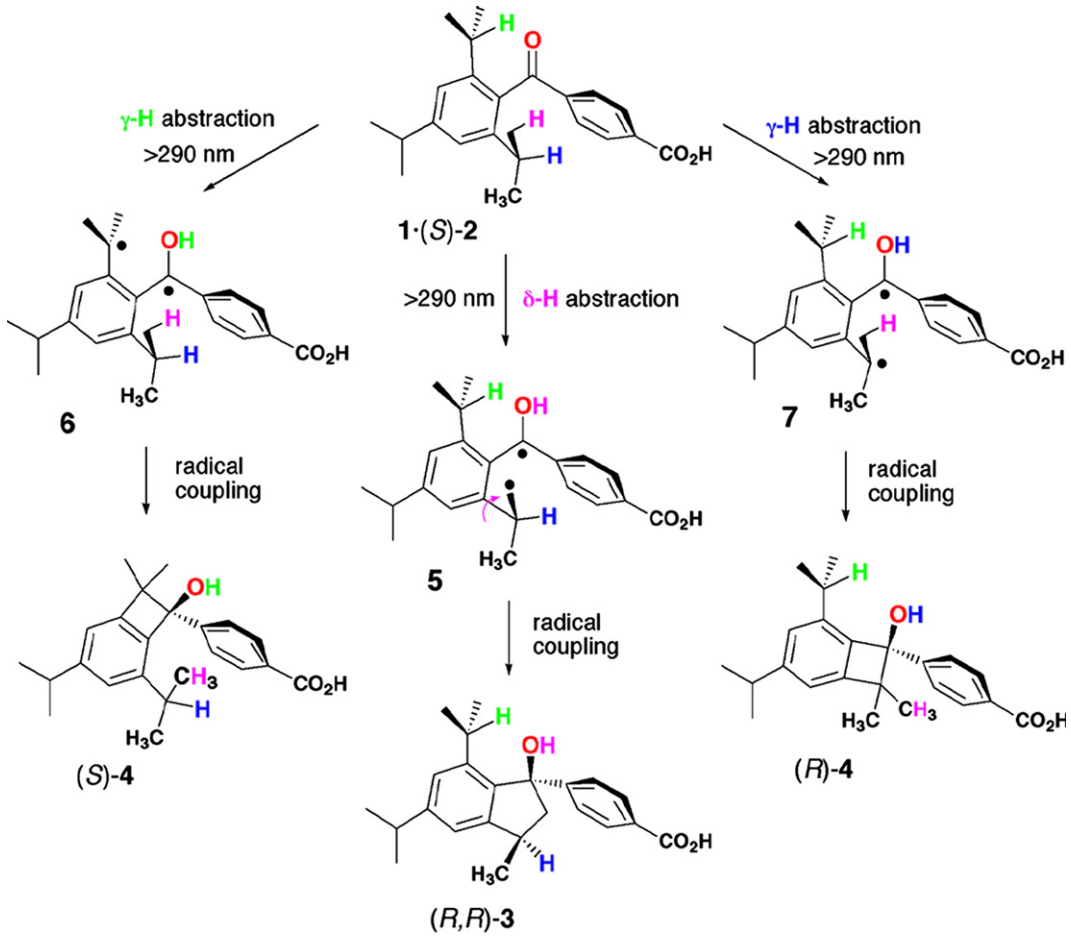
Scheme 2 shows the possible reaction mechanism. The reaction paths should be discussed on the bases of the crystal structure (Fig. 1). Irradiation of the crystal at >290 nm with a high-pressure mercury lamp through Pyrex glass causes n–$\pi^*$ excitation of the carbonyl group of the molecule **1**. The O1 atom of the excited carbonyl group should abstract the methyl H1 δ-hydrogen atom of the *o*-isopropyl group A in the highest priority due to the shortest O1–H1 distance (2.64 Å) and the favorable C1=O1–H1 angle (99.3°) to give the ketyl radical ·C1 and the methyl radical ·C2.[12] This corresponds to the biradical **5** in Scheme 2. Other methyl hydrogen atoms cannot be abstracted by the O1 atom due to the long distances (3.9–5.4 Å). As the C4–C5 bond of the *o*-isopropyl group A rotates in the clockwise direction, the ·C1 and ·C2 radicals gradually approach each other and finally couple to form the new C1–C2 bond, giving cyclopentenol (*R*,*R*)-**3**.

Furthermore, both the O1–H2 (2.94 Å) and O1–H3 (3.00 Å) distances are short; the angles of C1=O1–H2 (52.0°) and C1=O1–H3 (56.9°) are similar. The angles are defined as the degree to which the abstracted H2 and H3 γ-hydrogen atoms lie outside the mean plane of the carbonyl group. The angles themselves are also similar and are 51.3° and 55.1°, respectively. Therefore, the O1 atom of the excited carbonyl group has the other possibility of abstraction from both the methine H2 and H3 γ-hydrogen atoms of two *o*-isopropyl groups B and A to produce the ketyl radical and the corresponding methine radicals (**6** and **7** in Scheme 2). The radicals then approach each other and finally couple to confer the enantiomeric cyclobutenols (*S*)-**4** and (*R*)-**4**, respectively. The enantiomeric excess was only 6% ee in slight excess of (*S*)-**4**, reflecting the slightly shorter O1–H2 distance (2.94 Å) compared with the O1–H3 (3.00 Å).

Finally, we would like to discuss briefly why the compound **3** was not produced nearly exclusively despite that the O1–H1 distance (2.64 Å) to make **3** is considerably shorter than the corresponding distances (2.94 and 3.00 Å) required for the production of **4**. One of the reasons is that the major product **3** can be formed via a seven-membered transition state of the Norrish type II reaction, which is unusual in ketone photochemistry, in contrast to the normal six-membered transition state to give the minor product **4**.[12] Very few examples of the seven-membered transition state have been reported in the photolysis of the phenyl ketones.[13] Second, the methyl radical (**5** in Scheme 2) formed from the methyl group is energetically less favorable than the methine radicals (**6** and **7**) from the methine groups. These two factors most probably lead to the formation of not only **3** but also **4**. We have previously obtained the cyclopentenol as a major product and the cyclobutenol as a minor product by the absolute asymmetric photocyclization of 4-(2,5-diisopropylbenzoyl)benzoic acid in the salt crystal with 2,4-dichlorobenzylamine via single-crystal-to-single-crystal transformation.[7]

Such a photocyclization, however, did not greatly change the molecular conformation. The ionic bridge between the carboxylate anion of **1** and the ammonium cation of (*S*)-**2** forms a twofold helical chain in the reactant crystal. The helical salt bridges remain after the reaction. The strong salt bonding is believed to fix the molecules and promote the complete reaction without destroying the crystal; that is, it leads to single-crystal-to-single-crystal transformation.

In the case of the single-crystal-to-single-crystal photocyclization in the salt crystal of **1** with L-prolinol, the low optical purity of (*R*)-**4** (30% ee) was due to the pseudo mirror image-related arrangement of the bonzophenone moiety in the asymmetric unit.[5] The enantiospecific single-crystal-to-single-crystal photocyclization in the salt crystal of 4-(2,5-diisopropylbenzoyl)benzoic acid with (*S*)-**2** was due to enantiomeric γ-hydrogen abstraction from the *o*-isopropyl group by the carbonyl oxygen atom of the excited benzophenone unit.[6] Thus, the enantioselectivity of the crystalline state reaction is controlled by the crystal structure.




**Scheme 2.** Possible reaction mechanisms in the crystal **1**·(*S*)-**2**.

In conclusion, we achieved single-crystal-to-single-crystal photocyclization of the salt crystal of the triisopropylbenzophenone derivative.

## Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Asahi Glass Foundation, and Ehime University COE incubation program.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.041.

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8. Salt crystal of **1**·(*S*)-**2**; colorless needles; mp 183–185 °C; IR (KBr): $\nu$ 3314, 1668 $cm^{-1}$.
9. Methyl ester of (*R*,*R*)-**3**: white powder; mp 56.7–57.0 °C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.94 (d, $J$ = 4.8 Hz, 2H), 7.31 (d, $J$ = 4.8 Hz, 2H), 7.05 (s, 1H), 6.98 (s, 1H), 3.90 (s, 3H), 3.01–3.12 (m, 1H), 2.92–3.00 (m, 2H), 2.68 (dd, $J$ = 14.6, 8.5 Hz, 1H), 2.04 (dd, $J$ = 14.6, 9.5 Hz, 1H), 1.38 (d, $J$ = 7.7 Hz, 3H), 1.30 (d, $J$ = 7.7 Hz, 3H), 1.29 (d, $J$ = 7.7 Hz, 3H), 1.17 (d, $J$ = 7.7 Hz, 3H), 0.75 (d, $J$ = 7.5 Hz, 3H); IR (KBr): $\nu$ 3552, 1715 $cm^{-1}$; HRMS calcd for $C_{24}H_{30}O_3$ $(M)^+$ 366.2195, found 366.2197.
10. CrystalStructure, Ver. 3.7, Rigaku Corporation, Tokyo, 2005.
11. X-ray diffractions were collected on a Rigaku RAXIS-RAPID imaging plate two-dimensional area detector using graphite-monochromatized Mo-K$\alpha$ radiation. All crystallographic calculations were performed using CrystalStructure crystallographic software of the Rigaku/MSC and Rigaku Corporation.[10] The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were not refined. Hydrogen atoms attached to carbon atoms were located in the calculated positions. The absolute structures for **1**·(*S*)-**2** before and after irradiation were determined by reference to the known configuration of the chiral amine molecule (*S*)-**2**. Crystal data for **1**·(*S*)-**2**: $C_{23}H_{27}O_3{\cdot}C_8H_{12}N$; fw = 473.65, orthorhombic, $P2_12_12_1$, colorless block measuring 0.38 × 0.31 × 0.31 mm, $T$ = 293 K, $a$ = 6.2434(14), $b$ = 13.787(3), $c$ = 32.470(8) Å, $V$ = 2795.0(12) $Å^3$, $Z$ = 4, $D_c$ = 1.123 mg $mm^{-3}$, $\mu$ = 0.071 $mm^{-1}$, $T_{max}$ = 0.978, $T_{min}$ = 0.798, GOF = 1.063, $R$ = 0.0653, $wR_2$ = 0.1891. CCDC-683361. Crystal data for **1**·(*S*)-**2** after irradiation: $C_{23}H_{27}O_3{\cdot}C_8H_{12}N$; fw = 473.65, orthorhombic, $P2_12_12_1$, colorless block measuring 0.38 × 0.31 × 0.31 mm, $T$ = 93 K, $a$ = 6.3355(17), $b$ = 13.129(4), $c$ = 32.62(1) Å, $V$ = 2713.3(14) $Å^3$, $Z$ = 4, $D_c$ = 1.159 mg $mm^{-3}$, $\mu$ = 0.073 $mm^{-1}$, $T_{max}$ = 0.978, $T_{min}$ = 0.983, GOF = 1.048, $R$ = 0.0753, $wR_2$ = 0.2117. CCDC-683363.
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