Diastereoselective Photocyclization of *N*-(*p*-(2,4,6-Triisopropylbenzoyl)benzoyl)-L-phenylalanine Methyl Ester in the Solid State

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Introduction

For the purpose of carrying out photochemical asymmetric induction in the solid state, Scheffer et al. prepared chiral crystals of prochiral organic acids or bases by salt formation with optically active amines or acids, respectively, and the solid-state photochemistry of the resultant crystals led successfully to efficient asymmetric induction in prochiral acids or bases.[1] It sometimes occurs for this acid−base system (two-component crystals[2]) that even in a chiral crystal, the prochiral acid or base component may still exist in both enantiomeric conformations.[3,4] In such a case, the resulting optical activity may be lowered.[3,4] For instance, irradiation of chiral crystalline salts of 2,4,6-triisopropylbenzophenone-4′-carboxylic acid with optically active amines produced the corresponding benzocyclobutenol only in low to medium enantiomeric yields.[4]

In the meantime, we had studied the solid-state photocyclization of several derivatives of 2,4,6-triisopropylbenzophenone bearing a chiral 4′- or 3′-substituent and had achieved a high diastereomer excess for *N*-(*p*-(2,4,6-triisopropylbenzoyl)benzoyl)-L-phenylalanine methyl ester ((*S*)-*p*-**1a**). The results will now be reported. The X-ray analysis of the crystal-to-crystal diastereoselective photocyclization of (S)-p-**1a** into (S,S)-p-**2a** was reported separately.[5]

Results and Discussion

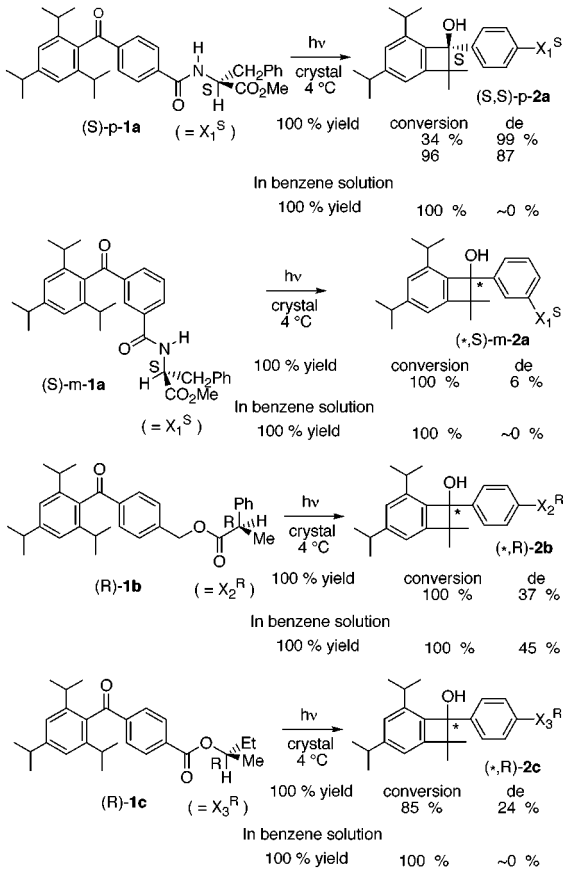
As shown in Table 1 (no. 1−4) and in Scheme 1, solid-state irradiation of (S)-p-**1a**, (S)-m-**1a**, (R)-**1b**, and (R)-**1c** at 4 °C for several hours under nitrogen by using Pyrex-filtered light (>280 nm) afforded the corresponding benzocyclobutenols p-**2a**, m-**2a**, **2b**, and **2c**. Yields were nearly 100% and conversions were more than 85%, judging from NMR and TLC analyses. The diastereomer excess (d.e.) for the benzocyclobutenols was estimated by NMR. Ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] $Yb(hfc)_3$ was used as a shift reagent. The photocyclization of (S)-p-**1a** was highly diastereoselective: 99% and 87% d.e. at 34% and 96% conversion, respectively. These d.e. yields correspond to the (S,S)-p-**2a**/(R,S)-p-**2a** ratios of 99.5/0.5 and 93.5/6.5, respectively (the absolute configuration of (S,S)-p-**2a** was

Table 1. Photolyses of 2,4,6-Triisopropylbenzophenones (TIBP-X) in the Solid State or in Benzene Solution (10^{-2} M)[a]

	TIBP-X		solid		solution	
no.	X	mp, °C	h	conv, %	h	conv, %
1	(S)-p-**1a**	213−214	5	96 (d.e. 87)[b]	5	100 (d.e. ∼0)[b]
2	(S)-m-**1a**	116−118	4	100 (d.e. 6)[b]	4	100 (d.e. ∼0)[b]
3	(R)-**1b**	70	4	100 (d.e. 37)[b]	4	100 (d.e. 45)[b]
4	(R)-**1c**	77−78	5	85 (d.e. 24)[b]	4	100 (d.e. ∼0)[b]
5	p-OMe	111−112	2	100	2	100
6	m-OMe	84−86	2	100	2	100
7	p-t-Bu	120−121	2	100	2	100
8	p-Me	87−87.5	2	100	2	100
9	H	97−99	4	100	2	100
10	p-CO_2Me (**4**)	142−143	10	0[c]	4	100
11	m-CO_2Me	118−120	2	100#	2	100
12	p-CO_2Et	98−101	4	76	4	100
13	p-CO_2H (**5**)	221−223	4	28	5	100
14	p-COCl (**3**)	119−120	10	0[c]	4	21
15	m-COCl (**7**)	127−128	4	35	4	100

[a] Conversions were estimated by NMR and HPLC analyses. Yields of the corresponding benzocyclobutenols were nearly 100% in all cases unless marked by #, where minor amounts of uncharacterized products were formed (<10% by NMR). Many of the data in no. 5−15 were previously reported.[7,8,17] [b] Diastereomer excesses (estimated by NMR) for the corresponding benzocyclobutenols p-**2a**, m-**2a**, **2b**, and **2c** are in parentheses. The d.e. ∼0% means less than 4% of d.e. [c] This unusual photostability in the solid state was ascribed to a narrow reaction cavity.[8,10]

Scheme 1



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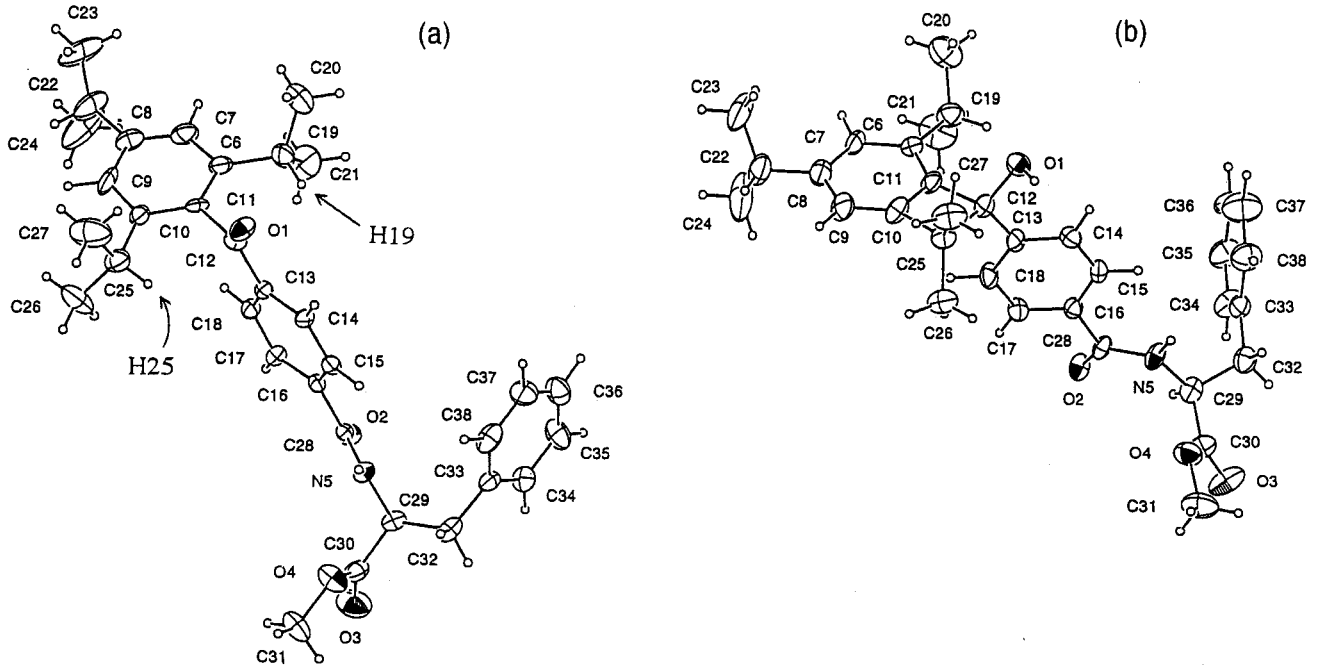

Figure 1. ORTEP drawings of (a) (S)-p-**1a** and (b) (S,S)-p-**2a**.[5]

assigned as described below). When the irradiation of (S)-p-**1a** was performed at >350 nm through a cutoff filter (Ushio UV36 glass filter, $T = 15\%$ at 350 nm), d.e. was 100% even at 100% conversion and the crystal structural regularity was retained throughout the reaction.[5] It is known that tail irradiation is advantageous to induce single-crystal-to-single-crystal transformation.[6] In the case of compounds (S)-m-**1a**, (R)-**1b**, and (R)-**1c**, the diastereoselectivities of the reaction were not good (d.e. 6−37%).

Like various substituted 2,4,6-triisopropylbenzophenones TIBP-X (no. 5−15 in Table 1),[7,8] the photocyclization of (S)-p-**1a**, (S)-m-**1a**, (R)-**1b**, and (R)-**1c** proceeded quantitatively not only in the solid state but also in solution. Benzene was used as solvent, and the results are also summarized in Scheme 1 and Table 1 (no. 1−4). In contrast to the solid-state irradiation, the observed d.e. was ∼0% except for (R)-**1b**, where the d.e. value in solution (45%) was somewhat higher than that in the solid state (37%). It was found previously[9] that the degree of asymmetric induction due to the influence of a chiral substituent varied with the medium (solid or solution) in which the reaction was carried out and that diastereoselectivity in the solid state might be increased (as exemplified by (S)-p-**1a**, (S)-m-**1a**, and (R)-**1c**) or reduced (as exemplified by (R)-**1b**) compared to that in solution. Generally, however, the former is the case.[2]

The crystal structure of (*S*)-*p*-**1a** was successfully solved (Figure 1a).[5] It belongs to a chiral space group $P2_12_12_1$. The dihedral angle made by the ketone carbonyl plane and the triisopropylphenyl ring deviates considerably from the right angle, that is, 80°. As a consequence, one of two o-i-Pr methine hydrogens (H25) is much nearer to the carbonyl oxygen (H25···O1 = 2.57 Å) than the other (H19) is (H19···O1 = 2.90 Å). This contrasts with many other TIBP-X,[10] where two o-i-Pr methine hydrogens are more or less equidistant from the carbonyl oxygen, that is, $d_1 \sim d_2$ (Table 2).

Table 2. Space Group Distances between Two o-i-Pr Methine Hydrogens and the Carbonyl Oxygen d_1 and d_2, the Dihedral Angle between the Carbonyl Plane and the Triisopropylphenyl Ring θ, and the Calculated Crystal Density D_c for 2,4,6-Triisopropylbenzophenones (TIBP-X)[5,10]

X	space group	d_1, d_2 (Å)	θ (deg)	D_c (g/cm^3)
(S)-p-**1a**	$P2_12_12_1$	2.57, 2.90	80	1.12
p-OMe	$P2_1/c$	2.88, 2.97	82	1.07
m-OMe	$P2_1/n$	2.72, 3.14	79	1.08
p-t-Bu	$P2_1/n$	2.78, 3.06	81	1.03
p-Me	$P2_1/n$	2.91, 3.00	89	1.03
H	$P2_1/n$	2.90, 2.94	86	1.04
p-CO_2Me (**4**)	$P1$	2.95, 2.98	89	1.14
m-CO_2Me	$P2_1/n$	2.78, 2.95	87	1.10
p-CO_2Et	$P1$	2.82, 2.99	87	1.10
p-CO_2H (**5**)	$P1$	2.77, 2.90	84	1.11
p-COCl (**3**)	*Pcab*	2.94, 2.98	86	1.17
m-COCl (**7**)	$P2_1/c$	2.96, 3.07	89	1.16

In the NMR spectrum of p-**2a** that was obtained from the solution photolysis of (S)-p-**1a**, the signal for the ester methyl group was finely split into two peaks of equal intensity (δ 3.735 and 3.741). Upon addition of one mole of Yb(hfc)$_3$, these peaks moved to lower fields and the separation between them increased (δ 4.15 and 4.24). For the solid-state photoproduct p-**2a**, only the former peak (δ 3.735 or 4.15 in the presence of Yb(hfc)$_3$) was clearly observable. Molecular mechanics calculations of (S,S)-p-**2a** and (R,S)-p-**2a** have revealed that the distances between the hydroxy oxygen atom and the ester methyl carbon atom are 8.98 and 8.61 Å, respectively.[11] The

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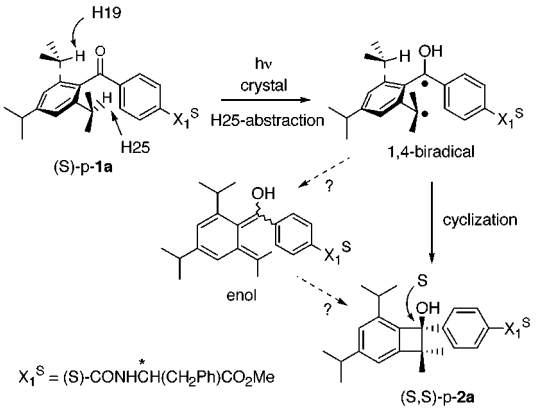
(11) Molecular mechanics calculation was carried out by using CS Chem3D, version 3.2. For brevity, 4-i-Pr was not considered in the calculation.

Scheme 2



hydroxy group can coordinate to the shift reagent. Therefore, induced variation in the chemical shift of the CO_2CH_3 group may be larger for (R,S)-p-**2a**. Based on this premise, the predominant solid-state photoproduct with resonances at δ 3.735 (or at δ 4.15 in the presence of Yb(hfc)$_3$) was assigned to (S,S)-p-**2a** and the solution-state photoproduct was decided to be a 1:1 mixture of (S,S)-p-**2a** and (R,S)-p-**2a**.

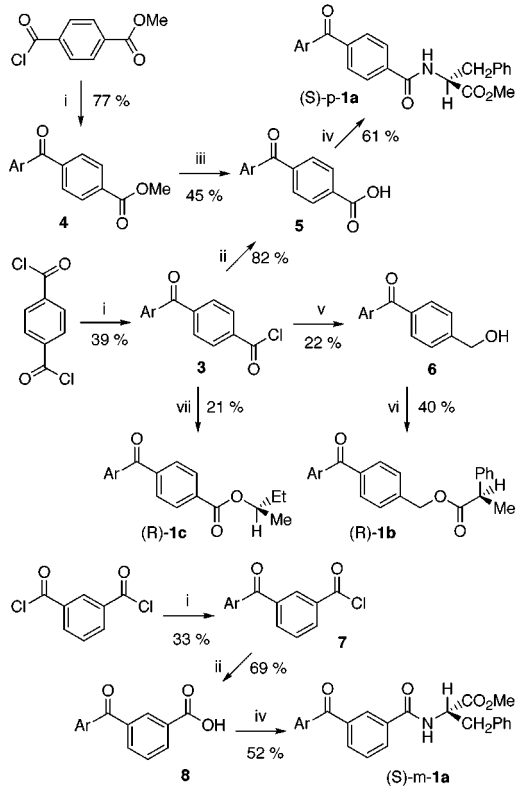
Recrystallization of benzocyclobutenol p-**2a** from various solvents only gave very thin needles, which were unsuitable for the X-ray study. The crystal structure of (S,S)-p-**2a** (Figure 1b) was finally solved by success of its in situ formation through the diastereoselective crystal-to-crystal photocyclization of (S)-p-**1a**, and the orientation of the new stereocenter in the cyclobutenol ring was unambiguously determined to be S.[5] Thus, the absolute configuration of (S,S)-p-**2a**, which had been assigned from the NMR analysis as described above, was proved.

The crystalline molecular structure of (S)-p-**1a** (H25···O1 = 2.57 Å and H19···O1 = 2.90 Å) indicates that both of the o-i-Pr methine hydrogens (H19 and H25) are within the critical limit (3 Å)[12] for hydrogen abstraction by the carbonyl O atom to occur. It is now clear, however, on the basis of the absolute configuration of (S,S)-p-**2a** that the nearer methine hydrogen (H25) was selectively abstracted upon irradiation of (S)-p-**1a** and that the resultant 1,4-biradical collapsed stereospecifically to give the observed product (S,S)-p-**2a** (Scheme 2).[13]

Taking into account the considerable difference between d_1 and d_2, similar stereoselective hydrogen abstraction may occur for TIBP-m-OMe and TIBP-p-t-Bu (Table 2). However, because these crystals are packed in an achiral space group ($P2_1/n$), they are a racemic mixture of chiral rotamers and thus we cannot expect to obtain optically active benzocyclobutenols.

In summary, the solid-state photocyclization reaction (S)-p-**1a** → (S,S)-p-**2a** proceeded quantitatively with ~100% d.e. The nearer o-i-Pr methine hydrogen was selectively abstracted by the carbonyl oxygen, followed by stereospecific cyclization of the resulting biradical leading to (S,S)-p-**2a**.

Scheme 3



Ar = 2,4,6-triisopropylphenyl
All the yields are given as the isolation yield.
(i) 1,3,5-triisopropylbenzene, $AlCl_3$, CS_2. (ii) NaOH, H_2O, Δ. (iii) KOH, MeOH, H_2O. (iv) L-phenylalanine methyl ester hydrochloride, DCC, Et_3N, CH_2Cl_2. (V) $NaBH_4$, dioxane, Δ. (vi) (R)-(-)-2-phenylpropionic acid, DCC, DMAP, CH_2Cl_2. (vii) (R)-(-)-2-butanol, pyridine.

Experimental Section

Materials. The compounds were prepared as outlined in Scheme 3. We had previously prepared *p*- (**3**) and *m*-(2,4,6-triisopropylbenzoyl)benzoyl chloride (**7**)[18] and methyl p-(2,4,6-triisopropylbenzoyl)benzoate (**4**)[19] by the Friedel−Crafts reaction of 1,3,5-triisopropylbenzene with the appropriate acid chlorides. Terephthaloyl chloride and isophthaloyl chloride were commercially available. 4-Methoxycarbonylbenzoyl chloride was prepared according to the published procedure.[20]

***p*-(2,4,6-Triisopropylbenzoyl)benzoic Acid (5).** We had earlier prepared this compound by hydrolysis of **4** with KOH in aqueous methanol. Later, it was prepared by hydrolysis of **3**.

Into a suspension of **3** (7.50 g, 20.2 mmol) in water (80 mL) was added dropwise with stirring an aqueous NaOH (2.4 g, 60

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(13) The X-ray analysis of the crystal-to-crystal transformation of (S)-p-**1a** → (S,S)-p-**2a** has suggested that, in the course of this transformation, the carbonyl carbon and the nearer o-i-Pr methine carbon linearly approached each other with nearly no rotation around the single bonds linking these carbons to the triisopropylphenyl ring.[5] There is a dispute about which is an immediate precursor to benzocyclobutenol, 1,4-biradical (= enol triplet), or enol.[14,15] The present results seem to indicate that it is not necessary to assume enol as an intermediate to benzocyclobutenol. About this point, Zimmerman's theoretical treatments on crystal lattice control of unimolecular rearrangements[16] may provide useful suggestions.

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mmol in 180 mL of water) at 80 °C over a period of 1 h. The mixture was heated under reflux for an additional 50 h. After acidification of the reaction mixture with aqueous HCl to pH 3, the resulting precipitate was collected and recrystallized from hexane to afford 5.9 g (82%) of **5** as pale yellow needles: mp 221−223 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.17 and 7.91 (4 H, AB, J = 8 Hz), 7.06 (2 H, s), 2.93 (1 H, sept, J = 7 Hz), 2.55 (2 H, sept, J = 7 Hz), 1.28 (6 H, d, J = 7 Hz), 1.10 (12 H, broad d, J = 7 Hz); IR (KBr) 3500−2500 (OH), 2970, 1690 (acid C=O), 1675 (ketone C=O), 1280, 1245, 735 cm^{-1}; MS (EI) *m/e* (rel intensity) 352 (44, M^+), 307 (100), 231 (20). Anal. calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.50; H, 7.85.

***N*-(*p*-(2,4,6-Triisopropylbenzoyl)benzoyl)-L-phenylalanine Methyl Ester ((S)-p-1a).** A solution containing L-phenylalanine methyl ester hydrochloride (351 mg, 1.63 mmol) and triethylamine (165 mg, 1.63 mmol) in dry methylene chloride (16 mL) was stirred at room temperature for 30 min. Into this solution was added 571 mg (1.62 mmol) of **5** and subsequently was added dropwise 337 mg (1.63 mmol) of 1,3-dicyclohexylcarbodiimide (DCC) in methylene chloride (8 mL) under cooling with ice/water. The mixture was stirred at 0 °C for 1 h and then for an additional 24 h at room temperature. After the resulting precipitate was filtered off, the filtrate was rotary-evaporated to give the crude desired product. This was purified with column chromatography on silica gel (Wakogel C-200) by using hexane and AcOEt as eluent. Recrystallization from methanol afforded 507 mg (61%) of (S)-p-**1a** as colorless plates: mp 213−214 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.86 and 7.74 (4 H, AB, J = 8.5 Hz), 7.29−7.23 (3 H, m), 7.13−7.08 (2 H, m), 7.05 (2 H, s), 6.56 (1 H, d, J = 8 Hz, NH), 5.06 (1 H, d of t, J = 8 and 6 Hz, C*H*CH_2), 3.76 (3 H, s, CO_2CH_3), 3.27 and 3.23 (2 H, d of AB, J = 6 and 14 Hz, CHC*H*$_2$), 2.92 (1 H, sept, J = 7 Hz), 2.53 (2 H, sept, J = 7 Hz), 1.27 (6 H, d, J = 7 Hz), 1.14 (6 H, broad d, J = 7 Hz), 1.03 (6 H, broad d, J = 7 Hz); IR (KBr) 3280 (NH), 2960, 1740 (ester C=O), 1675 (ketone C=O), 1635 (amide C=O), 1545, 1280, 1245, 1020, 710 cm^{-1}; MS (EI) *m/e* (rel intensity) 513 (8, M^+), 351 (18), 335 (33), 334 (34), 306 (100); HRMS calcd for $C_{33}H_{39}NO_4$ 513.2879, found 513.2859.

***m*-(2,4,6-Triisopropylbenzoyl)benzoic Acid (8).** Similarly to the hydrolysis of **3** to **5**, hydrolysis of 3.7 g (10 mmol) of **7** with NaOH(aq) gave 2.4 g (69%) of **8** as white crystals: mp 185−186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.56 (1 H, t, J = 1.5 Hz), 8.29 (1 H, d of t, J = 8 and 1.5 Hz), 8.05 (1 H, d of t, J = 8 and 1.5 Hz), 7.56 (1 H, t, J = 8 Hz), 7.06 (2 H, s), 2.93 (1 H, sept, J = 7 Hz), 2.56 (2 H, sept, J = 7 Hz), 1.29 (6 H, d, J = 7 Hz), 1.16 (6 H, broad d, J = 7 Hz), 1.04 (6 H, broad d, J = 7 Hz); IR (KBr) 3500−2500 (OH), 2954, 1692 (acid C=O), 1676 (ketone C=O), 1282, 1248, 735 cm^{-1}; MS (EI) *m/e* (rel intensity) 352 (100, M^+), 307 (56), 231 (55).

***N*-(*m*-(2,4,6-Triisopropylbenzoyl)benzoyl)-L-phenylalanine Methyl Ester ((S)-m-1a).** This was prepared by condensation of **8** with L-phenylalanine methyl ester in the same manner as described for the para isomer (S)-p-**1a**. Thus, from 757 mg (2.15 mmol) of **8**, 572 mg (52%) of (S)-m-**1a** was obtained as white plates: mp 116−118 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.25 (1 H, s), 7.93 (1 H, d, J = 8 Hz), 7.84 (1 H, d, J = 8 Hz), 7.48 (1 H, t, J = 8 Hz), 7.3−7.2 (3 H, m), 7.13−7.08 (2 H, m), 7.05 (2 H, s), 6.59 (1 H, d, J = 7 Hz, NH), 5.06 (1 H, d of t, J = 7 and 6 Hz, C*H*CH_2), 3.76 (3 H, s, CO_2CH_3), 3.26 and 3.20 (2 H, d of AB, J = 6 and 14 Hz, CHC*H*$_2$), 2.92 (1 H, sept, J = 7 Hz), 2.54 (2 H, broad sept, J = 7 Hz), 1.27 (6 H, d, J = 7 Hz), 1.15 (6 H, broad d, J = 6 Hz), 1.03 (6 H, broad t, J = 6 Hz); IR (KBr) 3327 (NH), 2961, 1743 (ester C=O), 1670 (ketone C=O), 1649 (amide C=O), 1539, 1250, 731, 701 cm^{-1}; MS (EI) *m/e* (rel intensity) 513 (5, M^+), 351 (13), 335 (33), 334 (35), 306 (100); HRMS calcd for $C_{33}H_{39}NO_4$ 513.2879, found 513.2872.

4-Hydroxymethyl-2′,4′,6′-triisopropylbenzophenone (6). A solution containing 5.50 g (14.8 mmol) of **3** and 4.80 g (127 mmol) of $NaBH_4$ in dioxane (50 mL) was heated with stirring at 90−100 °C for 5 days. The reaction mixture was poured onto water and was extracted with ether. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was separated with column chromatography on silica gel (Wakogel C-200, hexane/AcOEt), followed by recrystallization with hexane/benzene (trace), to give 1.1 g (22%) of **6** as white needles: mp 85−86 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (2 H, d, J = 8 Hz), 7.42 (2 H, d, J = 8 Hz), 7.04 (2 H, s), 4.76 (2 H, s), 2.92 (1 H, sept, J = 7 Hz), 2.59 (2 H, sept, J = 7 Hz), 1.27 (6 H, d, J = 7 Hz), 1.14 (6 H, d, J = 7 Hz), 1.03 (6 H, d, J = 7 Hz); IR (KBr) 3500 (OH), 2960, 1650 (ketone C=O), 1605, 1460, 1285, 1260, 950 cm^{-1}; MS (EI) *m/e* (rel intensity) 338 (16, M^+), 320 (79), 307 (100), 231 (9); HRMS calcd for $C_{23}H_{30}O_2$ 338.2246, found 338.2231.

***p*-(2,4,6-Triisopropylbenzoyl)benzyl (*R*)-2-Phenylpropionate ((R)-1b).** Into a solution containing 210 mg (1.40 mmol) of (*R*)-(−)-2-phenylpropionic acid and 16 mg (0.13 mmol) of 4-(dimethylamino)pyridine in dry CH_2Cl_2 (5 mL) was added 288 mg (1.40 mmol) of DCC in dry CH_2Cl_2 (2 mL), then 450 mg (1.33 mmol) of **6** in dry CH_2Cl_2 (3 mL). The solution was stirred at room temperature for 60 h. The reaction mixture was filtered, and the filtrate was washed successively with water, 5% aqueous AcOH, and water. After drying over $MgSO_4$, the solvent was removed by rotary-evaporation and the residue was separated by preparative TLC (Merck Kieselgel 60 F_{254}, 5:1 hexane/AcOEt). Recrystallization from hexane afforded 250 mg (40%) of (R)-**1b** as white crystals: mp 70 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.75 (2 H, d, J = 8.5 Hz), 7.33−7.19 (7 H, m), 7.04 (2 H, s), 5.15 (2 H, s), 3.78 (1 H, q, J = 7 Hz), 2.92 (1 H, sept, J = 7 Hz), 2.56 (2 H, sept, J = 7 Hz), 1.51 (3 H, d, J = 7 Hz), 1.27 (6 H, d, J = 7 Hz), 1.14 (6 H, d, J = 7 Hz), 1.02 (6 H, d, J = 7 Hz); IR (KBr) 2952, 1726 (ester C=O), 1666 (ketone C=O), 1607, 1454, 1285, 1254, 1229, 1153, 1065, 760, 726, 698 cm^{-1}; MS (EI) *m/e* (rel intensity) 470 (0.4, M^+), 320 (100), 305 (11). Anal. calcd for $C_{32}H_{38}O_3$: C, 81.66; H, 8.14. Found: C, 81.40; H, 8.38.

***(R)-s*-Butyl *p*-(2,4,6-Triisopropylbenzoyl)benzoate ((R)-1c).** A solution containing 435 mg (1.17 mmol) of **3** and 200 mg (2.70 mmol) of (R)-(−)-2-butanol in dry pyridine (15 mL) was kept at room temperature for 24 h with stirring. After the reaction, the reaction mixture was evaporated under reduced pressure and the residue was separated by preparative TLC (Merck Kieselgel 60 F_{254}, $CHCl_3$) to afford 99 mg (21%) of (R)-**1c** as a yellow oil, which crystallized on standing in a refrigerator as pale yellow needles: mp 77−78 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.10 and 7.88 (4 H, AB, J = 8.5 Hz), 7.06 (2 H, s), 5.09 (1 H, sext, J = 6 Hz), 2.92 (1 H, sept, J = 7 Hz), 2.56 (2 H, sept, J = 7 Hz), 1.71 and 1.66 (2 H, quint of AB, J = 7 and 14 Hz, CH_2), 1.31 (3 H, d, J = 6 Hz), 1.27 (6 H, d, J = 7 Hz), 1.14 (6 H, broad d, J = 6 Hz), 1.03 (6 H, broad d, J = 6 Hz), 0.94 (3 H, t, J = 7 Hz); IR (KBr) 2960, 1720 (ester C=O), 1670 (ketone C=O), 1280, 1100, 730 cm^{-1}; MS (EI) *m/e* (rel intensity) 408 (22, M^+), 351 (67), 307 (100); HRMS calcd for $C_{27}H_{36}O_3$ 408.2664, found 408.2672.

Solution Photolyses. A 10-mL solution containing 10^{-2} M chiral 2,4,6-triisopropylbenzophenone (S)-p-**1a**, (S)-m-**1a**, (R)-**1b**, or (R)-**1c** in benzene was placed in a Pyrex tube and was irradiated at 10 °C with a 400-W high-pressure mercury lamp under bubbling of N_2 for 4 or 5 h. The corresponding 4,6-diisopropyl-2,2-dimethyl-1-(4′- or 3′-substituted phenyl)-1,2-dihydrobenzocyclobuten-1-ols p-**2a**, m-**2a**, **2b**, and **2c** were produced almost quantitatively (NMR and TLC). They were isolated by preparative TLC (Merck Kieselgel 60 F_{254}, hexane/AcOEt, $CHCl_3$/ether or $CHCl_3$/acetone).

Solid-State Photolyses. The crystals of a chiral 2,4,6-triisopropylbenzophenone (S)-p-**1a**, (S)-m-**1a**, (R)-**1b**, or (R)-**1c** (50−100 mg) were lightly crushed and spread between two Pyrex plates, and then irradiated with a 400-W high-pressure mercury lamp for several hours under a nitrogen stream. During the irradiation, the photolysis vessel was cooled from the outside by circulation of cold water (4 °C). The benzocyclobutenol was produced almost quantitatively in each case (NMR and TLC) and was isolated by preparative TLC.

Diastereomer ratios of benzocyclobutenols p-**2a**, m-**2a**, **2b**, and **2c** were determined by ^{1}H NMR. Ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] Yb(hfc)$_3$ was used as a shift reagent. Specific rotations were measured by a Perkin-Elmer 243 polarimeter. For instance, for p-**2a** obtained by the solution photolysis, $[\alpha]^{20}_D$ = +44.5 (c 0.76, CH_2Cl_2) and for p-**2a** obtained by the solid-state photolysis, $[\alpha]^{20}_D$ = −23.8 (c 0.61, CH_2Cl_2). The diastereomers (S,S)- and (R,S)-p-**2a** could not be separated by chiral HPLC (Chiralcel OD, OJ, and OB columns).

Benzocyclobutenol p-**2a** obtained from the solid-state photolysis of (S)-p-**1a**: mp 187−188 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (2 H, d, J = 8.6 Hz), 7.30 (2 H, d, J = 8.3 Hz), 7.26−7.09 (5 H, m), 7.05 (1 H, d, J = 1 Hz), 6.88 (1 H, d, J = 1 Hz), 6.58

(1 H, d, J = 8 Hz, NH), 5.07 (1 H, d of t, J = 8 and 6 Hz, C*H*CH_2), 3.74 (3 H, s, CO_2CH_3), 3.25 and 3.20 (2 H, d of AB, J = 6 and 14 Hz, CHC*H*$_2$), 2.90 (1 H, sept, J = 7 Hz), 2.82 (1 H, sept, J = 7 Hz), 2.69 (1 H, s, OH), 1.43 (3 H, s), 1.26 (6 H, d, J = 7 Hz), 1.18 (3 H, d, J = 7 Hz), 1.13 (3 H, d, J = 7 Hz), 0.77 (3 H, s); IR (KBr) 3560 (OH), 3380 (NH), 2960, 1735 (ester C═O), 1650 (amide C═O), 1532, 1247, 1038, 760, 705 cm^{-1}; MS (EI) *m*/*e* (rel intensity) 513 (12, M^+), 351 (15), 335 (31), 334 (28), 306 (100); HRMS calcd for $C_{33}H_{39}NO_4$ 513.2879, found 513.2863. The ratio of the two diastereomers (S,S)/(R,S) was estimated by NMR as 94/6, after addition of Yb(hfc)$_3$. Recrystallization of p-**2a** from EtOH, aqMeOH, i-PrOH, benzene/hexane, aqAcOH, etc. only afforded fibrous needles, which were unsuitable for the X-ray analysis.

For p-**2a** that was obtained from the solution photolysis of (S)-p-**1a**, a slight difference in the chemical shift of the CO_2CH_3 group could be observed: the (S,S)-isomer at δ 3.735 and the (R,S)-isomer at δ 3.741. Their peak intensities were comparable, that is, the diastereomer ratio (S,S)/(R,S) is roughly 1. After addition of Yb(hfc)$_3$, the $\Delta\delta$ of the CO_2CH_3 group between the two diastereomers was expanded and (S,S)/(R,S) was estimated to be 52/48.

Benzocyclobutenol m-**2a** obtained from the solid-state or solution photolysis of (S)-m-**1a**: mp 62−64 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.74 (0.5 H, s) and 7.71 (0.5 H, s), 7.65−7.56 (1 H, m), 7.42−7.30 (2 H, m), 7.30−7.21 (3 H, m), 7.16−7.09 (2 H, m), 7.07 (1 H, s), 6.90 (1 H, s), 6.59 (0.5 H, d, J = 7 Hz, NH) and 6.53 (0.5 H, d, J = 7 Hz, NH), 5.07 (0.5 H, q, J = 6 Hz, C*H*CH_2) and 5.05 (0.5 H, q, J = 6 Hz, C*H*CH_2), 3.74 (3 H, s, CO_2CH_3), 3.26 and 3.20 (2 H, d of AB, J = 6 and 14 Hz, CHC*H*$_2$), 2.93 (0.5 H, sept, J = 7 Hz) and 2.925 (0.5 H, sept, J = 7 Hz), 2.84 (0.5 H, sept, J = 7 Hz) and 2.83 (0.5 H, sept, J = 7 Hz), 2.585 (0.5 H, s, OH) and 2.58 (0.5 H, s, OH), 1.46 (1.5 H, s) and 1.455 (1.5 H, s), 1.285 (ca. 2 H, d, J = 7 Hz) and 1.28 (ca. 4 H, d, J = 7 Hz), 1.20 (1.5 H, d, J = 7 Hz), 1.195 (1.5 H, d, J = 7 Hz), 1.16 (1.5 H, d, J = 7 Hz) and 1.15 (1.5 H, d, J = 7 Hz), 0.80 (3 H, s); IR (KBr) 3440, 2960, 1735 (ester C═O), 1650 (amide C═O), 1520, 1360, 1215, 750, 700 cm^{-1}; MS (EI) *m*/*e* (rel intensity) 513 (11, M^+), 335 (17), 306 (100); HRMS calcd for $C_{33}H_{39}NO_4$ 513.2879, found 513.2868. Chemical shift nonequivalence in ^{1}H NMR was observed for many protons of the two diastereomers (S,S)- and (R,S)-m-**2a**. The ratios of the peak intensities of the diastereomers were about 1. After addition of Yb(hfc)$_3$, the diastereomer ratios were estimated to be 53/47 (solid) and 50/50 (solution) on the basis of the relative intensity of the CO_2CH_3 peaks.

For p- and m-**2a**, the OH proton peak in ^{1}H NMR disappeared on deuteration with D_2O. The NH proton was deuterated by adding simultaneously D_2O and Et_3N.

Benzocyclobutenol **2b** obtained from the solid-state or solution photolysis of (R)-**1b**: mp 97−99 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32−7.13 (9 H, m), 7.06 (1 H, s), 6.88 (1 H, s), 5.10 and 5.08 (2 H, AB, J = 13 Hz, CH_2), 3.77 (1 H, q, J = 7 Hz), 2.91 (1 H, sept, J = 7 Hz), 2.86 (1 H, sept, J = 7 Hz), 2.52 (1 H, broad s), 1.50 (3 H, d, J = 7 Hz), 1.43 (3 H, s), 1.27 (6 H, d, J = 7 Hz), 1.21 (3 H, d, J = 7 Hz), 1.15 (3 H, d, J = 7 Hz), 0.78 (3 H, s); IR (KBr) 3580 (OH), 2960, 1730 (ester C═O), 1450, 1195, 1160, 1035, 795, 730, 700 cm^{-1}; MS (EI) *m*/*e* (rel intensity) 468 (18, $M^+ - 2$), 320 (100), 306 (34), 305 (33); HRMS for $M^+ - 2$ calcd for $C_{32}H_{36}O_3$ 468.2664, found 468.2649. After addition of Yb(hfc)$_3$, the methylene signal in ^{1}H NMR separated and the ratio of the two diastereomers (S,R)- and (R,R)-**2b** could be estimated as 68/32 (solid) and 72/28 (solution).

Benzocyclobutenol **2c** obtained from the solid-state or solution photolysis of (R)-**1c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.97 (2 H, d, J = 8.5 Hz), 7.32 (2 H, d, J = 8.5 Hz), 7.06 (1 H, s), 6.89 (1 H, s), 5.07 (1 H, sext, J = 6 Hz), 2.91 (1 H, sept, J = 7 Hz), 2.84 (1 H, sept, J = 7 Hz), 2.64 (1 H, broad s), 1.71 and 1.66 (2 H, quint of AB, J = 7 and 14 Hz, CH_2), 1.44 (3 H, s), 1.31 (3 H, d, J = 6 Hz, C*H*$_3$CHCH$_2$), 1.27 (6 H, d, J = 7 Hz), 1.19 (3 H, d, J = 7 Hz), 1.14 (3 H, d, J = 7 Hz), 0.95 (3 H, t, J = 7 Hz, C*H*$_3$CH$_2$), 0.80 (3 H, s); IR (KBr) 3500 (OH), 2960, 1705 (ester C═O), 1285, 1110, 760 cm^{-1}.

In ^{1}H NMR, the two s-Bu methyl groups at δ 1.31 and 0.95 were slightly split: $\Delta\delta$ 0.006 ppm for C*H*$_3$CH and $\Delta\delta$ 0.009 ppm for C*H*$_3$CH$_2$. From the relative intensity of the split peaks, the ratios of the two diastereomers (S,R)- and (R,R)-**2c** were estimated as 62/38 (solid) and 52/48 (solution).

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Supporting Information Available: ^{1}H NMR spectra of compounds (S)-p-**1a**, (S)-m-**1a**, (R)-**1b**, (R)-**1c**, p-**2a**, m-**2a**, **2b**, **2c**, **5**, **6**, and **8** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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