HETEROCYCLES, Vol. 60, No. 10, 2003, pp. 2251 - 2258
Received, 7th July, 2003, Accepted, 22nd August, 2003, Published online, 25th August, 2003

PHOTOREACTION OF 9-METHYLBENZ[*c*]ACRIDINE WITH DIPHENYLACETIC ACID IN THE CHIRAL COCRYSTAL

Hideko Koshima,* Ayaka Nakata, Masaki Nagano, and Haitao Yu
Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan

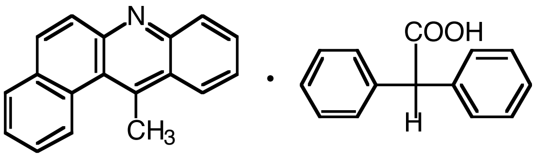
E-mail: koshima@eng.ehime-u.ac.jp

Abstract – Despite 9-methylbenz[*c*]acridine and diphenylacetic acid are achiral molecules, chiral cocrystal was obtained by crystallization from the solution. Irradiation of the enantiomorphous cocrystals caused photodecarboxylation to afford almost racemic photodecarboxylative condensation product as one of the minor products. Reason for the unsuccessful absolute asymmetric photoreaction was discussed based on the molecular arrangement in the lattice.

INTRODUCTION

Absolute asymmetric synthesis by solid-state reaction of chiral crystal spontaneously formed from achiral molecule is a promising methodology for asymmetric synthesis.[1-3] Since our success of absolute asymmetric photodecarboxylative condensation of acridine with diphenylacetic acid in the chiral cocrystal,[4] we would like to design absolute asymmetric synthesis with high reliability. Because spontaneous chiral crystallization cannot be predicted at the present time,[5,6] we have prepared several series of chiral cocrystals by combining two different achiral molecules, based on the working hypothesis that chiral crystallization can occur by freezing two molecules into chiral conformations through hydrogen bonding. These include propeller-type chiral crystal from phenanthridine with diphenylacetic acid[7] and helical-type chiral crystals from tryptamine with various achiral carboxylic acids,[8] phenanthridine with 3-indolepropionic acid,[9] and 2-amino-5-nitropyridine with achiral benzenesulfonic acids.[10] Herein we report a new chiral cocrystal (**1•2**) of 9-methylbenz[*c*]acridine (**1**) with diphenylacetic acid (**2**) and its solid-state photoreaction.

chiral cocrystal **1•2**



1 **2**

RESULTS AND DISCUSSION

The 1:1 chiral cocrystal (**1•2**) was prepared by recrystallization from the solution of **1** and **2** in acetonitrile. Seed crystals of both enantiomorphous crystals of **1•2** were initially obtained by spontaneous crystallization from the slightly supersaturated solutions in several vessels, and were easily discriminated by the measurement of solid-state circular dichroism (CD) spectra as Nujol mulls, giving A or B curve for the crystals in each vessel (Figure 1). Then, the left and right handed crystals could be separately prepared by the seeding on a large scale. The chiral nature was confirmed by X-Ray crystallographic analysis due to the acentric space group *P*1. However, the absolute structure could not be determined because the oxygen atom is not enough heavy to obtain large X-Ray anomalous dispersion using Cu K□ radiation. Figure 2 shows the molecular arrangement in **1•2**. Hydrogen bonding between **1** and **2** is formed with an H•••N distance of 1.46 Å. Diphenylacetic acid molecule has a propeller-like conformation, and 9-methylbenz[c]acridine molecule is not a flat plane but some twisted. The important feature is that only a kind of molecular pair of the absolute configuration presents noncentrosymmetrically in a unit cell (Z = 1) to induce the crystal chirality. Namely, the molecules in themselves are achiral but the molecular shapes are frozen in chiral forms within the lattice.

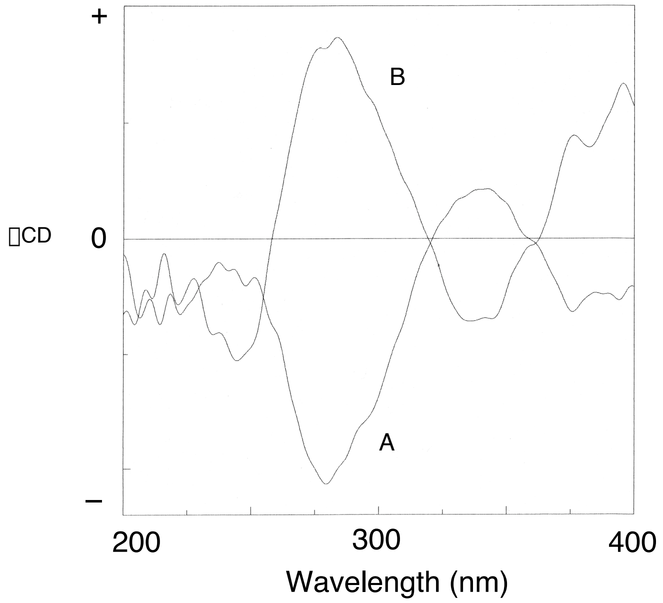


Figure 1. Solid-state CD spectra of the enantiomorphous cocrystals of **1•2**

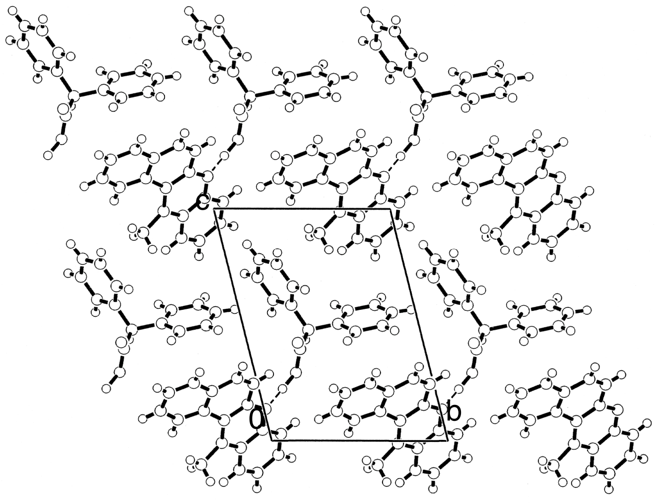
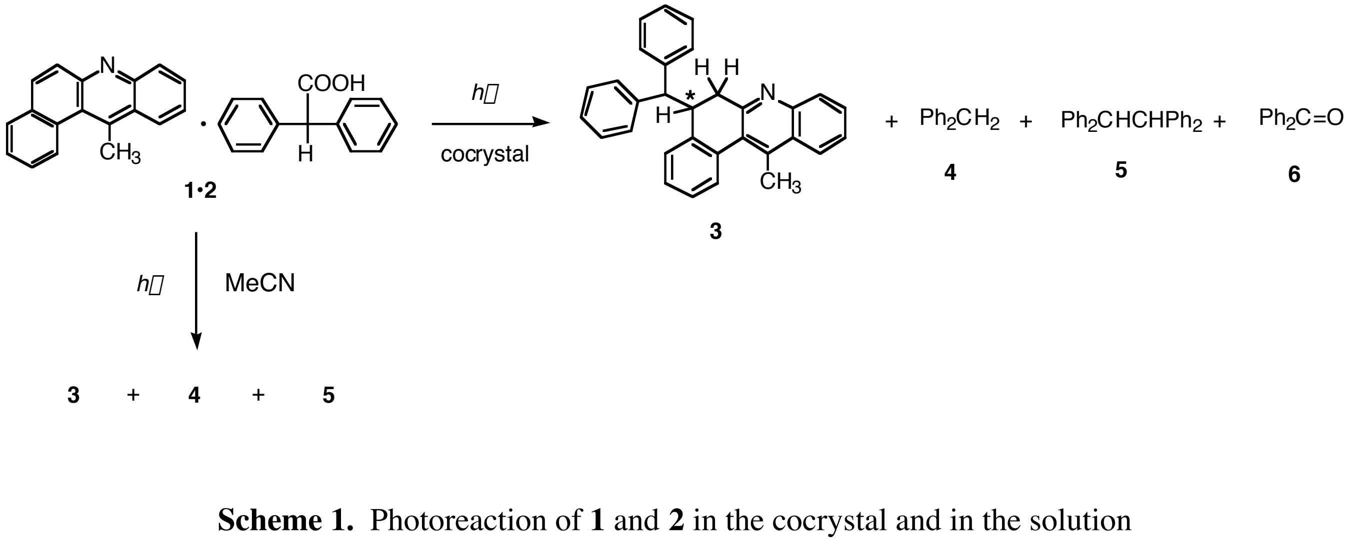


Figure 2. Molecular arrangement in the cocrystal (**1•2**)

The cocrystals of **1•2** prepared by seeding (curve A in Figure 1) were pulverized and irradiated to cause mainly photodecarboxylation, giving four products (Scheme 1). Decarboxylative condensation product (**3**) having a chiral center carbon was obtained in 13% yield. Decarboxylated compounds diphenylmethane (**4**) as a main product and the dimer tetraphenylethane (**5**) were produced in 34% and 3% yields, respectively. Dehydration product benzophenone (**6**) was also obtained in 13% yield.

On the other hand, solution photolysis of **1** and **2** in acetonitrile afforded racemic **3** as a main product in 53% yield and **4** and **5** in 2% and 12% yields, showing different photoreactivity and product selectivity from the solid-state photoreaction. The molecular structure of **3** was confirmed by X-Ray crystallographic analysis using a single crystal of 1:1 inclusion complex of racemic **3** with MeOH (Figure 3).



Scheme 1. Photoreaction of **1** and **2** in the cocrystal and in the solution

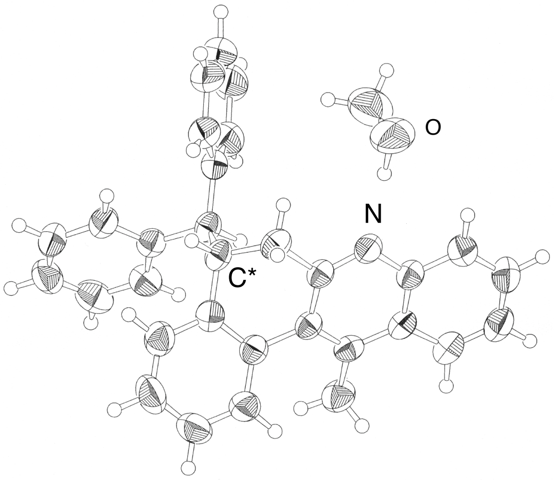


Figure 3. Molecular structure of the product (**3**•MeOH)

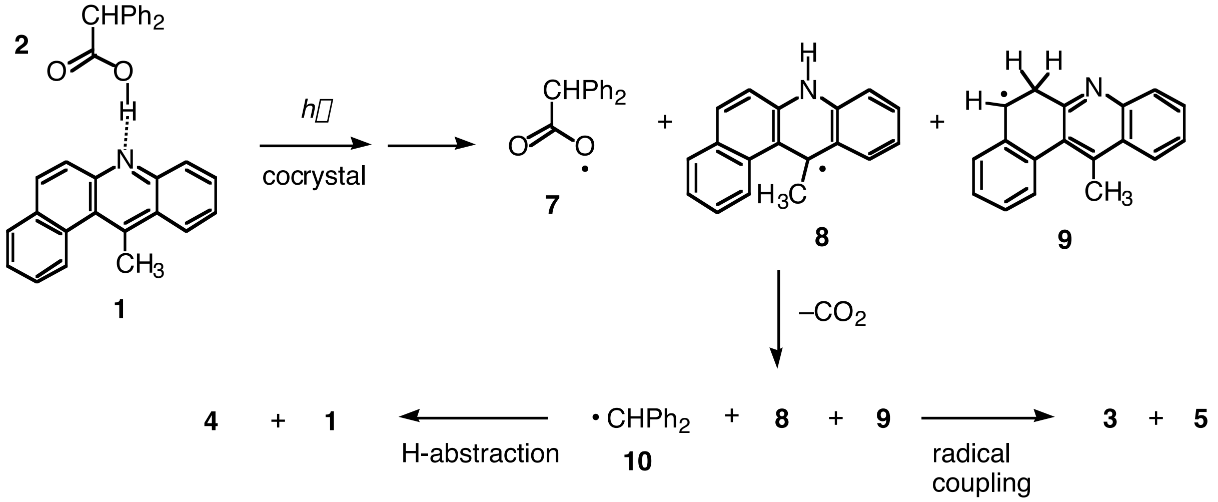
In order to know whether absolute asymmetric synthesis was achieved or not, the condensation product (**3**) obtained by the solid-state photoreaction was submitted to HPLC analysis using a chiral column. However, the enantiomeric excess could not be accurately determined due to the smallness. Hence, enantiomorphous single crystals (2–3 mg) (A and B in Figure 1) were irradiated piece by piece followed by HPLC determination. The results are summarized in Table 1. Irradiation of crystal A at room temperature with a high-pressure mercury lamp and a superhigh-pressure mercury lamp gave both plus and minus signals of low ees (Entries 1-3), showing not significant. In the case of crystal B, similar results were obtained (Entries 6-8). Even upon irradiation under cooling at –20 ~ –30 °C, the enantiomeric excesses did not increase (Entries 4, 5 and 9). So we concluded that absolute asymmetric synthesis was not achieved by the solid-state photoreaction of this chiral cocrystal.

Table 1. Solid-state photoreaction of the chiral single cocrystal (**1**•**2**)

Entry	Crystal[a]	Irradiation		Conversion (%)		Yield based on consumed **2** (%)				Ee[d] (%)
		(°C)	(min)	**1**	**2**	**3**	**4**	**5**	**6**	**3**
1	A	18[b]	2.5	18	91	5	71	0.1	9	(+) 1
2	A	18[b]	5	34	92	4	53	0.1	11	(+) 2
3	A	15[c]	10	19	62	2	39	0.5	6	(–) 4
4	A	–21[c]	30	13	38	2	61	0.3	4	(–) 4
5	A	–33[c]	30	2	34	2	47	0	2	(–) 4
6	B	18[b]	2.5	18	91	4	61	1	8	(+) 3
7	B	18[b]	5	34	92	4	59	0.4	10	(+) 6
8	B	15[c]	10	19	67	1	61	0.3	7	(–) 4
9	B	–32[c]	30	8	37	2	38	1	0	(+) 3

[a] Single crystals corresponding to the CD curves A and B in Figure 1. [b] Irradiation with a 400 W high-pressure Hg lamp. [c] Irradiation with a 500 W superhigh-pressure Hg lamp. [d] Signals of ees were termed (+) for the first peak of HPLC, (–) for the second peak.

The reason for unsuccessful absolute asymmetric photodecarboxylative condensation can be discussed based on the molecular arrangement in the crystal lattice as follows (Scheme 2). Irradiation of **1•2** can cause electron transfer from **2** to **1** followed by proton transfer to afford a carboxylate radical (**7**) and hydrobenz[*c*]acridine radicals (**8**) and (**9**).[4,11] Then decarboxylation of the carboxylate radical produces a •$CHPh_2$ diphenylmethyl radical (**10**). Next radical coupling between the •$CHPh_2$ radical (**10**) and the hydrobenz[*c*]acridine radical (**9**) forms **3**. Four directions for the radical coupling are possible in the crystal (Figure 4). Absolute configuration of **3** obtained by •C1---•C2 coupling with the shortest distance (4.42 Å) is opposite to those by couplings between •C1 and the other three •C3, •C4 and •C5 radicals with the longer distances (6.49, 6.44 and 6.50 Å), to lead to almost racemic mixture of (+)- and (–)-**3**.



Scheme 2. Possible reaction mechanism

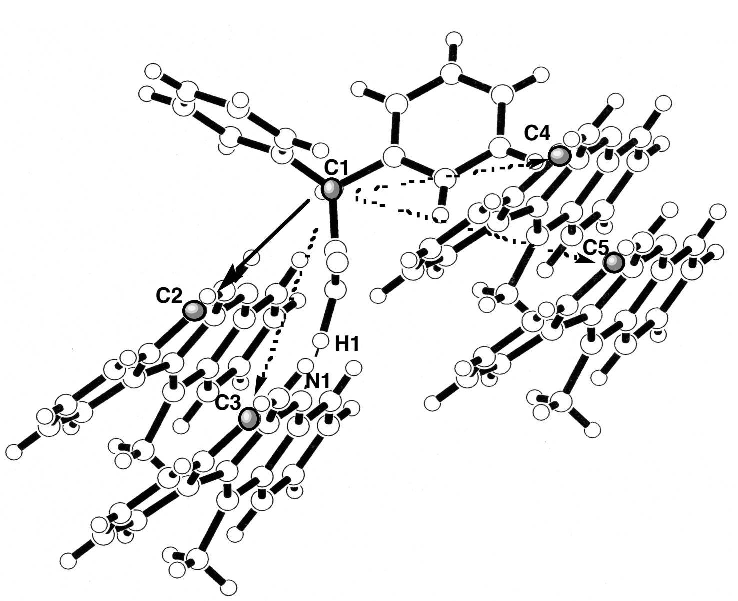


Figure 4. Possible reaction path in the cocrystal (**1•2**)

In addition, the formation of diphenylmethane (**4**) is caused by hydrogen abstraction by the •$CHPh_2$ radical (**10**) from the hydrobenz[*c*]acridine radical (**8**) because the •C1---H1 distance (3.50 Å) is short enough to abstract the hydrogen H1.[11] The regeneration of **1** is the reason for the lower conversion of **1** than that of **2** (Table 1). In conclusion, solid state photoreactivity is controlled by the crystal structure.

EXPERIMENTAL

General Procedure

^{1}H-NMR spectra were measured on a JEOL JNM-GSX270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Melting points (mp) were not corrected. Elemental analysis was carried out with a Yanaco CHN Corder MT-5. The solvents for gelation experiments were of analytical grade. All the solvents and reagents were commercially available and used as received.

Preparation of cocrystal (1•2)

9-Methylbenz[*c*]acridine (**1**) was synthesized by the reaction of 1-naphthylphenylamine and acetic acid in the presence of zinc chloride under microwave irradiation for several minutes.[12] Chiral cocrystal (**1•2**) was prepared by slow evaporation of 1:1 solution of **1** and diphenylacetic acid **2** in MeCN at rt. Both enantiomorphous crystals could be prepared by the seeding.

1•2. yellow prisms; mp 137-139 °C; IR (KBr) 1705, 1962, 2461, 3432 cm^{-1}.

Preparative photoreaction of 1 with 2 in MeCN

A solution of **1** (622 mg, 2.56 mmol) and **2** (542 mg, 2.56 mmol) in MeCN (100 mL) was internally irradiated with a 100 W high-pressure mercury lamp through Pyrex for 2 h under argon bubbling at rt. After the irradiation, the reaction mixture was submitted to silica gel column chromatography (toluene-ethyl acetate, 5:1) to give **3** (866 mg), **4** (16 mg) and **5** (164 mg) in 53, 2 and 12% yields, respectively, at 78% conversion of **1**. The IR and ^{1}H NMR spectral signals of **4** and **5** were in accordance to those of the authentic samples.

3. yellow prisms, mp 140-146 °C (from MeCN); IR (KBr) no NH band; ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.58 (t, J = 6.8 Hz, 2H), 6.96-7.26 (m, 12H), 6.81 (d, 7.0 Hz, 1H), 3.81-3.88 (m, 1H), 3.69 (d, J = 11.6 Hz, 1H), 3.28 (dd, J = 16.0, 4.1 Hz, 1H), 3.18 (dd, J = 13.0, 3.0 Hz, 1H), 3.02 (s, 3H). Anal. Calcd for $C_{31}H_{25}N$: C 92.42, H 4.83, N 2.55. found: C 92.42, H 4.83, 2.55.

Preparative solid-state photoreaction of chiral crystal (1•2)

Enantiomorphous crystals of **1•2** (1.5 g) prepared by seeding was pulverized, and 100-mg powders were separately placed between two Pyrex plates and irradiated with a 400 W high-pressure mercury lamp for 4 h under argon at rt. The irradiated mixture was treated with CH_2N_2 and submitted to silica gel column chromatography (toluene-ethyl acetate, 5:1) to give **3** (144 mg), **4** (191 mg), **5** (28 mg) and **6** (79 mg) in 13, 34, 3 and 13% yields, respectively, at 53% conversion of **1**. The IR and ^1H NMR spectral signals of **6** were in accordance to those of the authentic samples.

HPLC study of solid-state photoreaction

One single crystal (2–3 mg) was pulverized, placed between two Pyrex plates and irradiated with a 400 W high-pressure or 500 W superhigh-pressure mercury lamp under argon at appropriate temperatures and times. The irradiated sample was methylated with CH_2N_2 and submitted to HPLC analysis using chiral column (Daicel Chiralpak AD). The results are shown in Table 1.

X-Ray structure analysis

Two crystals of **1•2** and **3**•MeOH were submitted to X-Ray crystallographic analysis. Data were collected on a Rigaku RAXIS RAPID imaging plate diffractometer with Cu Kα radiation to a maximum 2θ of 136.5°. A total of 30 x 5.00° oscillation images was collected, each being exposed for 15.0 min. The reflection data were corrected for Lorentz-polarization effects and secondary extinction. The structures were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were not refined. The final cycle of full-matrix least-squares refinement was based on all reflections ($2\theta < 136.5°$) and variable parameters and converged with unweighted and weighted agreement factors of: $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ for $I > 2.0\sigma(I)$ and $R_w = \{\Sigma w(F_o{}^2-F_c{}^2)^2/\Sigma w(F_o{}^2)^2\}^{1/2}$. All calculations were performed by using a teXsan crystallographic software, Molecular Structure Corporation.

1•2. $C_{32}H_{25}NO_2$, M_w = 455.56, yellow prism crystal (0.23 x 0.19 x 0.14 mm^3), triclinic, space group $P1$ with a = 5.683(1), b = 9.110(2), c = 12.111(2) Å, α = 101.443(6)°, β = 98.399(6)°, γ = 103.08(1)°, V = 586.5(2) Å^3, Z = 1, ρ_{calc} = 1.290 g cm^{-3}, F(000) = 240.00, μ = 6.27 cm^{-1}. A total of 6528 reflections were measured, 1990 independent. Final R = 0.061, R_w = 0.144, GOF = 1.89 for 318 parameters.

3•MeOH: $C_{32}H_{29}NO$, M_w = 443.59, yellow prism crystal (0.73 x 0.55 x 0.25 mm^3), orthorhombic, space group Pbca with a = 18.995(1), b = 12.2607(6), c =21.294(1) Å, V =4959.3(4) Å^3, Z = 8, ρ_{calc} = 1.188 g cm^{-3}, F(000) = 1888.00, μ = 5.45 cm^{-1}. A total of 42752 reflections were measured, 15738 independent. Final R = 0.0730, R_w = 0.228, GOF = 1.65 for 308 parameters.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in Aid for scientific research from the Ministry of Education, Sports, Culture, Science and Technology, Japan (No. 14340220) and Kurata Memorial Hitachi Science and Technology Foundation in Japan.

REFERENCES

1. H. Koshima, 'Organic Solid State Reactions,' ed. by F. Toda, Kluwer Academic publishers, Dordrecht, 2002, pp. 189-268.
2. B. L. Feringa and R. A. van Delden, *Angew. Chem., Int. Ed.,* 1999, **39**, 3418.
3. M. Sakamoto, *Chem. Euro. J.,* 1997, **3**, 684.
4. H. Koshima, K. Ding, Y. Chisaka, and T. Matsuura, *J. Am. Chem. Soc.,* 1996, **118**, 12059.
5. J. Jacques, A. Collet, and S. H. Wilen, 'Enantiomers, Racemates, and Resolutions,' Wiley-Interscience, New York, 1981.
6. a) H. Koshima and T. Matsuura, *J. Synth. Org. Chem.,* 1998, **56**, 268 (Japanese). b) H. Koshima and T. Matsuura, *J. Synth. Org. Chem.,* 1998, **56**, 466 (Japanese).
7. H. Koshima, T. Nakagawa, T. Matsuura, H. Miyamoto, and F. Toda, *J. Org. Chem.,* 1997, **62**, 6322.
8. a) H. Koshima, S. I. Khan, and M. A. Garcia-Garibay, *Tetrahedron: Asymmetry,* 1998, **9**, 1851. b) H. Koshima and S. Honke, *J. Org. Chem.,* 1999, **64**, 790. c) H. Koshima, S. Honke, and J. Fujita, *J. Org. Chem.,* 1999, **64**, 3916. c) H. Koshima, S. Honke, and M. Miyauchi, *Enantiomer,* 2000, **5**, 125. d) H. Koshima, M. Miyauchi, and M. Shiro, *Supramol. Chem.,* 2001, **13**, 137.
9. a) H. Koshima, E. Hayashi, T. Matsuura, K. Tanaka, F. Toda, M. Kato, and M. Kiguchi, *Tetrahedron Lett.,* 1997, **38**, 5009. b) H. Koshima, E. Hayashi, and T. Matsuura, *Supramol. Chem.,* 1999, **11**, 57.
10. H. Koshima, M. Hamada, I. Yagi, and K. Uosaki, *Cryst. Growth Des.,* 2001, **1**, 467.
11. a) H. Koshima, K. Ding, and T. Matsuura, *J. Chem. Soc., Chem. Commun.,* 1994, 2053. b) H. Koshima, K. Ding, Y. Chisaka, T. Matsuura, I. Miyahara and K. Hirotsu, *J. Am. Chem. Soc.*, 1997, **119**, 10317.
12. H. Koshima and K. Kutsunai, *Heterocycles,* 2002, **57**, 1299.