Journal of Inclusion Phenomena and Macrocyclic Chemistry (2006) 54: 41–45
DOI 10.1007/s10847-005-3490-9

Enantioselective Oxidation of Sulfides Catalyzed by Chiral Mo^{V} and Cu^{II} Complexes of Catechol-Appended β-Cyclodextrin Derivatives in Water

HIDETAKE SAKURABA* and HIROSHI MAEKAWA
Department of Applied Material and Life Sience, Kanto Gakuin University, 1–50–1 Mutsuurahigashi, 236–8501, Kanazawa-ku, Yokohama, Japan

(Received: 30 June 2004; in final form: 10 March 2005)

Key words: aqueous solution, aromatic sulfide, β-cyclodextrin, catalytic asymmetric oxidation, catechol moiety, hydrogen peroxide, metal complex

Abstract

The two modified β-cyclodextrin (β-CD) derivatives having catechol-type ligand (2,3- and 3,4-dihydroxy groups on the benzoate ring) were synthesized. The chiral catalytic activity of their Mo^{V} and Cu^{II} complexes was examined in the asymmetric oxidation of aromatic sulfides using hydrogen peroxide in water (pH 6.0). The oxidation with the Mo^{V} complexes of two β-CD derivatives were more accelerated than that with the Cu^{II} complexes. The sign of the optical rotation of the sulfoxides obtained in the above two cases showed the opposite configuration in the oxidation of the same sulfide. The difference of the enantioselectivity appeared also between the two complexes of the 2,3- and 3,4-dihydroxybenzoate derivatives with the same metal ion. While the use of the Mo^{V} complexes with the catechol derivatives yielded the sulfoxides with 35–65% ee, the use of the Cu^{II} complexes gave the products with the opposite configuration at 26–52% ee. The chiral induction in the oxidation, observed conversely between the catalysts, was reflected on the chiral conformation of the respective metal catalysts, showed in Induced Circular Dichroism (ICD) spectra. The highest optical yield, 65%, was observed in the oxidation of butyl phenyl sulfide using the catalytic amount (0.1 equiv) of the Mo^{V} complex with mono-6-*O*-(3,4-dihydroxybenzoyl)-β-CD. The reaction gave predominantly the (*S*)-sulfoxide in 95% chemical yield.

Introduction

Cyclodextrins (CDs), bottomless bucket-shaped cyclic oligomers of D-(+)-gulucopyranose, can be act as catalytic smallest size-vessels (0.5–0.9 nm) including both the substrate and the reagent molecules for some useful organic reactions [1–4]. The inclusion phenomenon in CDs enables guest molecules to exhibit different and sometimes new properties from those of free molecules. The utilization of CDs as a chiral host and auxiliary have been also expected to induce asymmetry in a prochiral substrate as a guest molecule interacting with their asymmetric hydrophobic cavities through some reactions [5].

Previously, we achieved high enantioselectivity in the solid-phase oxidation of methyl 1-naphthyl sulfide in its 1:1 (host–guest) crystalline β-CD inclusion complex to give the corresponding (*S*)-sulfoxide with 81% ee [6]. To date this result represents the highest chiral induction in the asymmetric oxidation of sulfides mediated by CDs under both heterogeneous and homogeneous conditions. The asymmetric reaction using a catalytic amount of CD, however, is scarcely reported and the results showed in rather low in the chiral induction [1–3, 5, 8, 9]. Carofiglio *et al.* demonstrated that the oxidation of methyl phenyl sulfide can be improved on this chiral induction up to 60% ee [10]. The oxidation was carried out in the presence of catalytic amounts of a usual ethylenediamine-appended β-CD [2, 3] and molybdenum ion.

On asymmetric synthesis in CD chemistry, the most significant approach is to spot the effective modification of CDs, aiming at a host–guest interactive catalyst which induces a catalytic, not stoichiometric asymmetric reaction. Here we wish to report that the new β-CD derivatives as chiral catechol ligands [11] afford to much higher catalytic activity and enantioselectivity than the native α-, β-, and γ-CDs. Without a guest molecule, the phenyl moiety of the dihydroxybenzoate-connected β-CD, not the ethylenediamine-connected one [2, 3, 10] is embedded shallowly into the β-CD cavity [4] and is therefore induced the new chiral space in the cavity. When a guest substrate is included in the cavity, the molecule and a chelated metal part capping the cavity are closed proximity at each other, expecting to proceed a metalloenzyme mimetic reaction. In addition, the

* Author for correspondence. E-mail: sakuraba@kanto-gakuin.ac.jp

reaction in water without using harmful organic solvents is of current environmental interest (so called green chemistry).

Materials and methods

Materials

α-, β-, and γ-CDs were purchased from Mercian Co. and used without further purification. Butyl phenyl sulfide and methyl 2-naphthyl sulfide were prepared by reaction of the sodium alkyl thiolates with the corresponding aromatic bromides according to the literature [12]. Methyl 1-naphthyl sulfide was prepared by methylation of the lithium thiolate, synthesized from the 1-naphthyl Grignard reagent and sulfur with $LiAlH_4$ [13]. Hydrogen peroxide as a 35% aqueous solution was bought from Kanto Chemical Co. and used as received.

Analytical methods

MALDI-TOFMS spectra were recorded on a SHIMADZU/KOMPACT MALDI III spectrometer. IR spectra were obtained on a JASCO FT/IR-615 spectrophotometer. ^{1}H NMR spectra (400 MHz) were obtained from a VARIAN MERCURY-400 spectrometer in D_2O, DMSO-d_6 and $CDCl_3$ by using 3-(trimethylsilyl)propanesulfonic acid sodium salt (DSS) and $(CH_3)_4Si$ (TMS) as an internal standard. Circular dichroism spectra were obtained from a JASCO J-725 spectropolarimeter in sodium acetate buffer solution of pH 6.0 at 25 °C. Optical rotations were measured in ethanol [6] on a JASCO P-1010GT spectropolarimeter equipped with a 1 dm cell at 25 °C. Optical purity was confirmed by HPLC analysis on a Chiralcel OD-H column (Daicel Ltd.).

Preparation of catechol-appended β-CD derivatives

A solution of mono-6-deoxy-6-(*p*-tolylsulfonyl)-β-CD (2.03 g, 1.56 mmol) in dry *N,N*-dimethylformamide (DMF, 10 cm^3) containing dry KF (139.4 mg, 2.4 mmol) was reacted with 2,3- or 3,4-dibenzyloxybenzoic acid (2,3- or 3,4-DBA-H) (2 mmol) at 90 °C with stirring for 40 h. The reaction mixture was filtrated and evaporated in vacuo at 40 °C to dryness, followed by washing acetone and by recrystallization from a water containing 20% methanol (MeOH), giving a white crystal dibenzyloxybenzoate-appended β-CD in the yields of 34–42%. Deprotection of the dibenzyloxybenzoate-appended β-CD derivatives (0.47–0.70 mmol) was carried out in DMF–MeOH (1:10, *v*/*v*, 50 cm^3) in the presence of Pd–C (400 mg) as a catalyst under hydrogen gas atmosphere at a room temperature with stirring for 4 h. After removing Pd–C, the filtrate was evaporated in vacuo to give a white powder. The powder was chromatographed on ODS-120T column(ϕ 20 × 250 mm, TOSOH Ltd.) with a water containing 20% MeOH as eluent to yield catechol-appended β-CD derivatives in the yields of 30–38%.

Mono-6-*O*-(3,4-dihydroxybenzoyl)-β-CD (**1**) Yield 38%. MALDI-TOFMS: Calcd. for $[M + Na]^+$, *m*/*z* 1294.1, Found: 1293.3. IR (KBr): 1701 cm^{-1} (ester, C = O). ^{1}H NMR (D_2O): β-CD part, δ = 3.51 (t, 7 H, *J* = 9.28 Hz, H-4), 3.58 (dd, 7 H, *J* = 9.28, 2.45 Hz, H-2), 3.67 (dd, 6 H, *J* = 9.28, 3.42 Hz, H-5), 3.72 (d, 6 H, *J* = 9.28 Hz, H-6b), 3.85 (d, 6 H, *J* = 9.28 Hz, H-6a), 3.86 (t, 7 H, *J* = 9.28 Hz, H-3), 4.01 (dd, 1 H, *J* = 9.78, 3.42 Hz, H-5́), 4.34 (s, total OH + HDO), 4.45–4.58 (m, 2 H, H-6á, -6b́), 4.95 (d, 1 H, *J* = 3.42 Hz, H-1́), 4.99 (d, 5 H, *J* = 3.42 Hz, H-1), 5.02 ppm (d, 1 H, *J* = 3.42 Hz, H-1); 3,4-DBA part, δ = 6.89 (d, 1 H, *J* = 7.81 Hz, ArH-5), 7.43 (d, 1 H, J = 7.81 Hz, ArH-6), 7.44 ppm (s, 1 H, ArH-2). ^{13}C NMR (D_2O): β-CD part, δ = 61.0 (C-6), 64.7 (C-6́), 70.5 (C-5́), 72.6 (C-5), 72.8 (C-2), 73.9 (C-3), 81.7 (C-4), 82.6 (C-4́), 102.2 (C-1), 103.0 ppm (C-1́); 3,4-DBA part, δ = 116.2 (Ar-5), 117.7 (Ar-2), 121.9 (Ar-4), 123.7 (Ar-6), 145.1 (Ar-3), 150.9 (Ar-1), 168.1 ppm (ester bond).

Mono-6-*O*-(2,3-dihydroxybenzoyl)-β-CD (**2**) Yield 30%. MALDI-TOFMS: Calcd. for $[M + Na]^+$, *m*/*z* 1294.1, Found: 1293.5. IR (KBr); 1701 cm^{-1} (ester, C = O). ^{1}H NMR (D_2O); β-CD part, δ = 3.37–3.88 (m, 14H, H-4, -2), 3.92–4.15 (m, 25H, H-5, -6a, -6b, -3), 4.19–4.26 (m, 1H, H-5́), 4.64 (s, total OH + HDO), 4.81–4.86 (m, 2H, H-6́), 5.16–5.20 ppm (m, 7H, H-1); 2,3-DBA part, δ = 6.93 (t, 1H, *J* = 7.81 Hz, ArH-5), 7.30 (d, 1H, *J* = 6.84 Hz, ArH-4), 7.42 ppm (d, 1H, *J* = 8.30 Hz, ArH-6).

Asymmetric oxidation of sulfides

The ligand **1** or **2** (6.4 mg, 5 μmol) and the equivalent chloride of molybdenum (Mo^V) or copper (Cu^{II}) were dissolved in 2 cm^3 of 1 M (M = mol dm^{-3}) sodium acetate–HCl buffer solution (pH 6.0). The homogeneous solutions were shaken at a room temperature for 30 min under argon to form their respective chelated complexes. The oxidation was started by introduction of sulfides (50 μmol) and hydrogen peroxide (0.009 cm^3 of 5.6 M aqueous solution, 50 μmol) at 0 °C for 5–20 h under argon atmosphere. After the reaction, the 0.1 M aqueous $Na_2S_2O_3$ (0.5 cm^3, 50 μmol) was added to quench the remaining H_2O_2. The aqueous solution was extracted with CH_2Cl_2 (20 cm^3 × 3). The combined organic layer was washed with aqueous NaCl, dried over Na_2SO_4, and evaporated in vacuo. The extract was chromatographed on Wako C-300 silica gel column with ethyl acetate as eluent to give the optically active sulfoxide as identified by comparison of the ^{1}H NMR and IR spectra with that of the authentically racemic sample. The ee (%) of sulfoxide was confirmed by HPLC analysis on a Chiralcel OD-H column with hexane containing 20% 2-propanol as an eluent.

Methyl 1-naphthyl sulfoxide: mp. 56–58° (*lit*.[12] 58–65°). IR (KBr): 1049 (S = O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.84 (s, 3H, CH_3), 7.56–7.70 (m, 3H, aromatic (ArH)), 7.91–7.99 (m, 3H, ArH), 8.18 (dd, 1H,

J = 7.25, 1.32 Hz, ArH-8). Anal Calcd. for $C_{11}H_{10}OS$: C, 69.44; H, 5.30. Found: C, 69.36; H, 5.36. The optically pure (*R*)-sulfoxide was prepared in 50% yield by recrystallizations of the product from ethylether–hexane mixture: $[\alpha]^{25}_{D}$ + 459.6° (c 0.1, ethanol) [6].

Results and discussion

The two chiral bidentate ligands of β-CD 3,4- and 2,3-dihydroxybenzoates (**1** and **2**) were synthesized. The chiral catalytic activity of their respective Mo^{V} and Cu^{II} complexes (0.1 equiv) of **1** and **2** was examined on the asymmetric oxidation of aromatic sulfides with H_2O_2 in the pH of 6.0 at 0 °C under argon. Table 1 shows the results that the oxidation of methyl 1-naphthyl sulfide was carried out with the mixture (1:1) of $MoCl_5$ and ligand such as **1**, ethyl 3,4-dihydroxybenzoate (Et-3,4-DBA), α -, β- or γ-CDs. Over-oxidation to achiral sulfone is not observed in this reaction system.

The oxidation rate was remarkably decreased by the absence of either CDs or $MoCl_5$ (entries 1 and 7). The presence of both CDs and $MoCl_5$ in this system shows to accelerate the oxidation 3–9 folds compared with the absence of CDs (entry 1). However, it is quite obvious that the simple inclusion in unmodified CDs (α-, β-, and γ-CDs) or the mixture of Et-3,4-DBA and β-CD (entry 5) is not sufficient to induce appreciable enantioselecton (3–8% ee). In contrast, the reaction for 5 h using the Mo^{V} complex (**1a**) showed most effective catalysis to give the (*R*)-sulfoxide in the optical and chemical yields of 58% and 90%, respectively (entry 6). The enantioselectivity is dependent on the equivalent of **1a** in the oxidation system. There was remarkable change in the optical yields responding to 0, 0.01, 0.05, and 0.1 equivalents of **1a**, changing 0, 24, 43, and 58% ee, respectively. No chiral induction was also observed in the case of **1** alone without transition metal ion on the oxidation process (entry 7). Moreover, the asymmetric catalytic activity of **1a** has been quite lost by the benzyl masking of the phenolic hydroxy groups of **1** to give the racemic sulfoxide in a decreasing yield (entry 8).

Table 1. Asymmetric. oxidation of methyl 1-naphthyl sulfide with hydrogen peroxide catalyzed by Mo(V) complexes of α-, β-, γ-CDs and mono-6-*O*-(3,4-dihydroxhbenzoy1)-β-CD (**1**)[a]

Entry	Catalyst	Time/h	Methyl 1-naphthyl sulfoxide	
			Yield/%[b]	% ee[c] (Config[d])
1	none	20	8	0
2	α-CD	20	21	3 (R)
3	β-CD	20	73	6 (R)
4	γ-CD	20	70	5 (R)
5	β-CD mixture[e]	20	58	8 (R)
6	**1**	5	90	58 (R)
7	**1**[f]	20	29	2 (R)
8	**1**[g]	20	68	0

[a]Reaction conditions: sulfide; 50 μmol, H_2O_2; 50 μmol, ligand; 5 μmol, $MoCl_5$; 5 μmol,reaction temperature; 0 °C, in 2 cm^3 of 1.0 M AcONa–HCl buffer solution (pH 6.0) under argon. **1** is mono(3,4-dihydroxybenzoyl)-β-cyclodextrin.
[b]All yields corresponds to pure products isolated by silica gel chromatography.
[c]Determined by HPLC analysis using Chiralcel OD-H column (Daicel Ltd.).
[d]Configuration of (−)-enantiomer is S, [14].
[e]Mixture (1:1) of β-CD and ethyl 3,4-dihydroxybenzoate.
Without transition metal ion.
[g]Masked two phenolic hydroxy group of **1** with an OBn group.

These results suggest that the neighboring phenolic hydroxy groups of **1** play an important role by coordinating with Mo^{V} for the enantioselective oxidation. Thus, when the sulfide is included in the host ligand during the reaction in water, the guest molecule and the chelated metal part capping the cavity are closed proximity at each other. The coordinate binding of the primary and secondary hydroxy groups of CDs with Mo^{V} may compete with that of phenolic oxygen in the catalytic site, described by Carofiglio *et al.* [10]. However, it was not observed that the reaction was catalyzed enantiomerically by interacting between Mo^{V} and the primary or secondary hydroxy groups of CDs.

Several examples of asymmetric oxidation catalyzed by the Mo^{V} (**1a**, **2a**) and Cu^{II} (**1b**, **2b**) complexes (0.1 equiv) in water are summarized in Table 2. The sulfoxide formations were more accelerated with **1a** and **2a** (2–5 h, 60–99% yields) than with **1b** and **2b** (20 h, 50–89%) except for the low conversions of methyl 2-methyl-1-naphthyl sulfide (20 h, 20–28%). The differential reaction rates are due to stronger coordination of the chelated Mo^{V} than of the Cu^{II} complexes toward the sulfide sulfur atom [15–17]. Since this coordination to substrate is reflected directly in the enantioselection for the oxidation, the asymmetric induction of Mo^{V} complexes (**1a** and **2a**) is higher than that of the Cu^{II} (**1b** and **2b**) complexes.

Although the optical yields in the catalytic oxidation of sulfides were not high (26–65% ee), an interesting result concerning the induced chiralities of products was observed. The reverse chiral induction was appeared between the two metals coordinated by the same β-CD ligand in the combination reaction of **1a** and **1b** or **2a** and **2b** using the same sulfide. The opposite enantioselection was also shown between the two combination reactions of **1a** and **2a** or **1b** and **2b** with the same metal ion. Thus, while the catalytic reactions with **1a** and **2b** yielded the sulfoxides with the same configuration in 35–65% ee, the use of **1b** and **2a** gave the opposite chiral products to the former in 26–55% ee. This indicates that two phenolic hydroxy groups attached at different positions (2,3- and 3,4-) on the phenyl ring of the β-CD ligands induce the opposite chiral environment in or around the cavity of the modified β-CDs.

To explain these reverse enantioselection, the circular dichroism spectra of the β-CD ligand **1** and the respective metal complexes (**1a** and **1b**) were determined in an aqueous buffer solution (pH 6.0) without both H_2O_2 and substrate, as shown in Figure 1. The chiral conformation of the catalyst should be playing an important role to

Table 2. Catalytic oximmetric oxidation of alkyl aryl sulfides with Mo(V) and Cu(II) complexes of **1** or **2**[a]

Sulfide (Ar-S-R)		Time/h	With [Mo^{V}(**1**)], **1a** Sulfoxide		With [Cu^{II}(**1**)], **1b** Sulfoxide		With [Mo^{V}(**2**)], **2a** Sulfoxide		With [Cu^{II}(**2**)], **2b** Sulfoxide	
Ar	R		Yeild/%	% ee (Config.)	Yeild[b]/%	% ee (Config.)	Yeild/%	% ee (Config.)	Yeild[b]/%	% ee (Config.)
Ph	Me	2	99	45 (R)	89	33 (S)	80	40 (S)	80	26 (R)
Ph	Bu	5	95	65 (S)	75	52 (R)	78	55 (R)	70	48 (S)
1-Nap	Me	5	90	58 (R)	52	45 (S)	60	35 (S)	50	33 (R)
2-Me-1-Nap[c]	Me	20	28	44 (R)[d]	23	41 (S)[d]	20	40 (S)[d]	22	30 (R)[d]

[a]See the footnote in Table 1. 2 is mono-6-*O*-(2,3-dihydroxybenzoyl)-β-CD.
[b]All reaction proceeded for 20 h.
[c]1-Nap = 1-Naphthyl. 2-Me-1-Nap = 2-Methyl-1-naphthyl.
[d]Configuration of (+)-enantiomer is R, [18].

introduce the chirality involved in the enantioselective reaction. The two induced circular dichroism (ICD) spectra of **1a** ((λ_{ext} 232 nm ($\Delta\epsilon$ + 0.88), 259 (0.0), 260 (−0.05), 296 (−0.16), 313 (0.0), 331 (+0.22)) and **1b** (λ_{ext} 237 nm ($\Delta\epsilon$ − 0.88), 264 (0.0), 275 (+0.10), 311 (+0.56)) were not conformed each other and to that of **1** (λ_{ext} 260 nm ($\Delta\epsilon$ − 0.71), 295 (−0.54), 311 (+0.10)). These spectral data indicate the formation of the two different chelated metal complexes between **1** and the respective metal ion. Both sign and intensity of the two ICD spectra of **1a** and **1b** were reverse each other among 200 and 350 nm. This shows that the conformation of two catalysts was asymmetrically fixed in opposite configuration. Thus, the opposite enantioselectivity observed in the oxidation was presumably occurred in this chiral environment induced by the metal complex of the β-CD ligand. Furthermore, the ICD spectrum of **2a** (λ_{ext} 244 nm ($\Delta\epsilon$ − 1.54), 259 (0.0), 266 (+0.45), 272 (0.0), 290 (−0.50), 330 (−0.15)) was also observed contrary to that of **1a**, resulting in the opposite chiral induction between the two catalyses. Thus, it is assumed that there is a distinctive difference of the transition state between the combination reactions of **1a** and **1b** or **2a** and **2b** or **1a** and **2a** or **1b** and 2b, respectively.

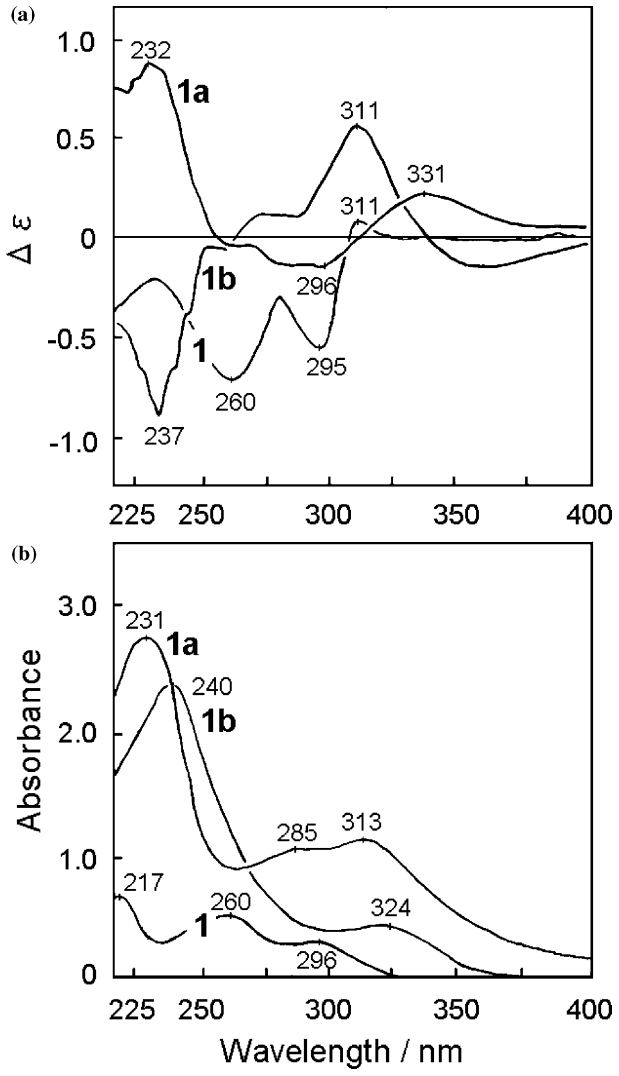

Figure 1. Circular dichroism (a) and UV absorption (b) spectra of **1**, **1a** and **1b** in 1.0 M AcONa–HCl buffer solution (pH 6.0) at 25 °C. Concentration: [ligand **1**] = [metal chloride] = 1.0×10^{-4} M.

The highest optical yield, 65%, was observed by the catalytic oxidation in the combination of butyl phenyl sulfide and **1a**, giving the corresponding (*S*)-sulfoxide in a chemical yield of 95%. The precise chiral induction mechanism has not been clearly yet. However, the selective use of the catalysts, giving the inverted products even though moderate optical yields, will add a new aspect to asymmetric reactions using CDs in water.

Acknowledgements

The financial support of this work by the Scientific Promotional Foundation of Tokyo Ohka Kougyo Co., Ltd. is gratefully acknowledged.

References

1. Cramer F., W. Dietsche, (1959). Chem. Ber. 92: 1739.
2. M.L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer Verlag, Berlin (1978).
3. F. Toda and A. Ueno (eds.), *Cyclodextrin*, Sangyo Tosho, Tokyo (1995).
4. H. Sakuraba , M. Horii, and T. Takezutsumi: (2000). Nippon Kagaku Kaishi 685; Chem. Abstr. 134, 30601z (2001).

5. K. Takahashi and K. Hattori: *J. Incl. Phenom. Mol. Recogn. Chem.* **17**, 1 (1994).
6. H. Sakuraba, K. Natori, and Y. Tanaka: *J. Org. Chem.* **56**, 4124 (1991).
7. H. Sakuraba and S. Ushiki: *Tetrahedron Lett.* **31**, 5349 (1990).
8. S. Banfi and S. Colonna: *Synthetic Commun.* **13**, 1049 (1983).
9. Y. Inoue, F. Dong, K. Yamamoto, L. H. Tong, H. Tsuneishi, T. Hakushi, and A. Tai: *J. Am. Chem. Soc.* **117**, 11033 (1995).
10. M. Bonchio, T. Carofiglio, F. D. Furia, and R. Fornasier.: *J. Org. Chem.* **60**, 5986 (1995).
11. S. J. Rodgers, C. Y. Ng, and K. N. Raymond: *J. Am. Chem. Soc.* **107**, 4094 (1985).
12. V. N. Ipatieff, H. Pines, and B. S. Friedman: *J. Am. Chem. Soc.* **60**, 2731 (1938).
13. W. Czarnik: *J. Org. Chem.* **49**, 924 (1984).
14. J. Jacobus and K. Mislow: *J. Am. Chem. Soc.* **89**, 5228 (1967).
15. B. Spivack, Z. Pori, and E. I. Steifel: *Inorg. Nucl. Chem. Lett.* **11**, 501 (1975).
16. A. Beheshti, W. Clegg, and M. Hosai Sadr: *Polyhedron* **20**, 179 (2001).
17. S. Lu, Y. Ke, J. Li, and Y. Zhang: *Cryst. Res. Technol.* **37**, 1153 (2002).
18. D. Casarini, E. Foresti, F. Gasparrini, L. Lunazzi, D. Mac-ciantelli, D. Misti, and C. Villani: *J.Org. Chem.* **58**, 5674 (1993).