

Photoreaction of Cinnamate with Nitrogen Monoxide Catalyzed by Metallosalen Complexes

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(Received January 7, 2002)

Ethyl cinnamate was allowed to react with nitrogen monoxide (NO) by photoirradiation in the presence of metallosalen complexes (**4**), oxygen, and axial ligands for **4** to yield furoxan derivatives (**6**). Oxygen and axial ligands are indispensable for this reaction. Photoirradiation enhanced the yield of **6**. Lowering the reaction temperature increased the yield of **6** up to 55% (at −5 °C).

Nitrogen monoxide (NO) is a gaseous diatomic molecule with a free-radical nature consisting of a nitrogen atom and an oxygen atom.[1] Although NO is expected to be a simple nitrogenating agent for organic compounds, its application to organic synthesis is limited due to a difficulty to control its reactivity. Transition metal complexes have been successfully used to control radical reactions in organic synthesis and polymerization.[2] For example, bis(1,3-diketonato)–transition metal complexes were employed by Yamada et al. as catalysts for nitrogenation using NO.[3]

Salen-transition metal complexes have been extensively developed for organic synthesis, and have continued to be complexes of great interest.[4] We have recently proposed a rational design of helical molecules utilizing the planarity of salen complexes; we synthesized artificial helical polymers from 3,3′-diformylbinaphthol derivatives, diamines, and transition-metal salts, and confirmed their helical structures.[5] We have also disclosed that the chiral space provided by the helical poly(binaphthyl zinc–salen complex)es is effective for the asymmetric addition of diethylzinc to benzaldehyde.[5a] As a part of our program to develop polymeric metallosalen complexes having helical structures, we have investigated the catalysis of the corresponding monomeric metallosalen complexes in organic synthesis. In the course of the study, we found that some metallosalen complexes could catalyze the photoreaction of cinnamates with NO to form furoxan derivatives. Furoxans are known to be useful synthetic precursors for diamines, nitriles, and quinoxaline di-*N*-oxides, and have a wide range of biological activities.[6] Herein, we report on the photoreaction of ethyl cinnamate with NO catalyzed by metallosalen complexes to form furoxan derivatives.

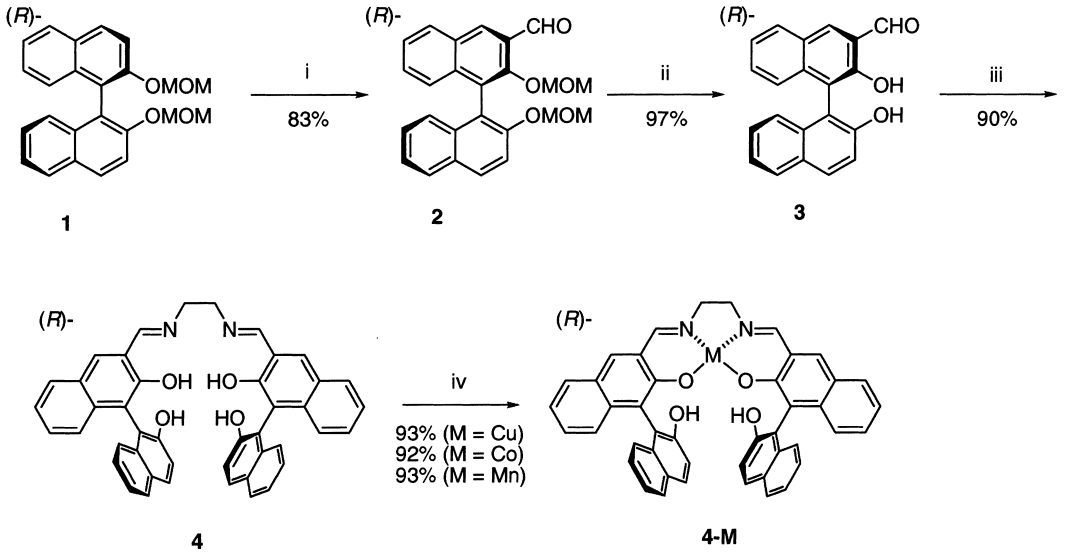
Results and Discussion

Synthesis of Metallosalen Complexes. The synthesis of metallosalen complexes was carried out according to Scheme 1. The treatment of bis(MOM) ether (**1**)[7] with *n*-BuLi and DMF yielded monoformylated bis(MOM) ether (**2**),[8] which was deprotected under acidic conditions to give monoaldehyde (**3**).[8] Condensation between **3** and ethylenediamine afforded the corresponding Schiff base (**4**).[8a] Copper, cobalt, and manganese ions were introduced by treating **4** with the corresponding metal acetate to give metallosalen complexes (**4-M**).

Reaction of Ethyl Cinnamate with Nitrogen Monoxide in the Presence of Oxygen. The reaction of ethyl *trans*-cinnamate and nitrogen monoxide was investigated (Table 1). Stirring a THF solution of ethyl cinnamate under an NO atmosphere at room temperature without catalyst gave a nitrated product (**5**), as reported by Yamada et al.[9] In this case, no *E*/*Z* selectivity was observed (*E*:*Z* = ca. 50:50, entry 1). In the presence of oxygen, no product was formed from ethyl cinnamate even in the presence of **4-Cu** (entry 2). However, the addition of pyridine as an axial ligand for **4-Cu** yielded a furoxan derivative (**6**)[10] (entry 3). Photoirradiation (150-W Xe lamp) increased the yield of **6**, together with the formation of epoxide (**7**) and ethyl *cis*-cinnamate (**8**) (entry 4). Imidazole and pyridine *N*-oxide (PNO) gave similar results to that for pyridine (entries 5 and 6). Increasing the amount of PNO and oxygen resulted in an increase in the yield of **6** (up to 30%, entries 6–9). In all cases, ethyl cinnamate was completely consumed to yield **5**–**8** and other unidentified products.

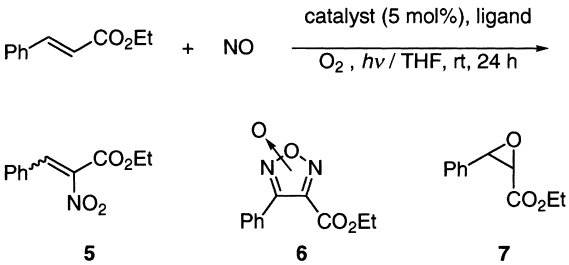
The effect of catalyst on the yield of **6** was investigated, as shown in Table 2. The use of 10 mol% of **4-Cu** hardly changed the yield (entry 2). This suggests that demetallation of the copper complex occurred during the reaction due to the formation of nitrous acid in situ (vide infra). Actually, the obtained reaction mixture was proved to be acidic by a litmus paper test. A further addition of 5 mol% of **4-Cu** to the reaction mixture over a period of 20 h yielded **6** in a higher yield of 42% (entry 3). The use of cobalt and manganese complexes (**4-Co** and **4-Mn**) gave **6** in lower yields (entries 4 and 5). Other copper complexes, such as Cu(salen) (salen = *N*,*N*′-disalicylideneethylenediamine) and $Cu(acac)_2$, resulted in lower yields together with the formation of a considerable amount of **5** (entries 7 and 8).

Solvent effects and temperature were examined, as shown in Table 3. In THF, the yield of **6** was higher at −5 °C than at



Scheme 1. Synthesis of metallosalen complexes **4-M**: (i) *n*-BuLi, DMF/THF, (ii) HCl, *i*-PrOH/CH_2Cl_2, (iii) ethylenediamine/benzene, (iv) $M(OAc)_2/CH_2Cl_2$.

Table 1. Reaction of Ethyl Cinnamate with Nitrogen Monoxide



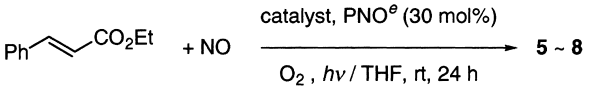
Entry	Catalyst	Ligand (mol%)	O_2 (mol%)	*hv*[a]	Yield/%[b,c]			
					5	**6**	**7**	**8**
1	none	none	none	none	7	0	0	0
2	**4-Cu**	none	100	none	0	0	0	0
3	**4-Cu**	pyidine (5)	100	none	0	4	0	0
4	**4-Cu**	pyidine (5)	150	irrad.	0	10	3	7
5	**4-Cu**	imidazole (5)	150	irrad.	0	8	5	7
6	**4-Cu**	PNO[d] (5)	150	irrad.	0	11	5	5
7	**4-Cu**	PNO (10)	150	irrad.	0	20	4	5
8	**4-Cu**	PNO (30)	150	irrad.	0	19	1	5
9	**4-Cu**	PNO (30)	400	irrad.	0	30	1	4

a) 150-W Xe lamp with Pyrex filter. b) Determined by GC. c) In all case, ethyl cinnamate was consumed completely to yield **5**–**8** and other unidentified products. d) pyridine *N*-oxide.

room temperature, although the reaction at −5 °C yielded 13% of **5** to reduce the selectivity of **6** (entry 2). The lowered selectivity is attributed to the higher solubility of NO (or N_2O_3) gas to THF at lower temperatures. 1,2-Dichloroethane (1,2-DCE) gave **6** in 40% yield at room temperature (entry 3). The formation of **5**, however, dominated over that of **6** at −5 °C (entry 4). The use of pyridine as a solvent resulted in a low yield of **6** (entry 5).

The reaction mechanisms for the formation of the furoxan derivative (**6**), epoxide (**7**), and *cis*-cinnamate (**8**) are proposed as shown in Scheme 2. Nitrogen monoxide is known to react with oxygen to form dinitrogen trioxide, which should be the actual NO source (Eq. 1).[1] The reaction starts from the coordination of cinnamate to the metal complex (M(**4**)L) to form complex **A**. The coordination is promoted by photoirradiation. The activated olefin moiety of **A** nucleophilically attacks at dinitrogen trioxide to form mononitroso complex **B**, which was deprotonated to form the carbene complex **C**. Complex **C** further attacks nucleophilically at dinitrogen trioxide to form dinitroso complex **D**, which undergoes β-elimination to give the furoxan derivative (**6**). The formation of ethyl *cis*-cinnamate **8** is attributable to the *E*/*Z* isomerization of complex **A**. The metal complex (M(**4**)L) is oxidized to the corresponding oxo complex (O=M(**4**)L), which acts as an epoxidation agent

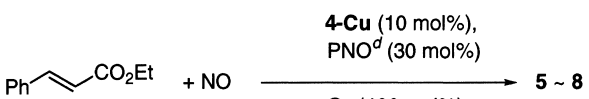
Table 2. Effect of Catalyst



Entry	Catalyst (mol%)	Yield/%[c),d)]			
		5	**6**	**7**	**8**
1	**4-Cu** (5)	0	30	1	4
2	**4-Cu** (10)	0	33	1	3
3	**4-Cu** (5 + 5)[a)]	0	42	2	2
4	**4-Co** (5 + 5)[a)]	0	27	0	2
5	**4-Mn** (5 + 5)[a)]	0	31	0	1
6	Cu(salen)[b)] (5)	47	25	0	0
7	$Cu(salen)_2$ (5)	20	2	0	0

a) Addition of further 5 mol% of the catalyst over the period of 20 h to the reaction mixture which originally contained 5 mol% of the catalyst. b) salen = *N*,*N*′-disalicylideneethylenediamine. c) Determinied by GC. d) In all case, ethyl cinnamate was consumed completely to yield **5**–**8** and other unidentified products. e) pyridine *N*-oxide.

Table 3. Effects of Solvent and Temperature



Entry	Solvent	Temp/°C	Yield/%[b),c)]			
			5	**6**	**7**	**8**
1	THF	rt	0	42	2	2
2	THF	−5 °C	13	55	0	0
3	1,2-DCE[a)]	rt	0	40	1	2
4	1,2-DCE[a)]	−5 °C	42	35	0	0
5	pyridine	rt	0	25	0	1

a) 1,2-dichloroethane. b) Determined by GC. c) In all case, ethyl cinnamate was consumed completely to yield **5**–**8** and other unidentified products. d) pyridine *N*-oxide.

for the olefin to give the corresponding epoxide **7**.

This reaction was applied to ethyl crotonate as an aliphatic conjugated ester to investigate the potential utility of this reaction as a synthetic method for furoxan derivatives. The photoirradiation of a mixture of ethyl crotonate, **4**-Cu (10 mol%), PNO (30 mol%), and O_2 (400 mol%) in THF under an NO atmosphere afforded the corresponding furoxan derivative (**9**)[10,11] in 39% yield (Scheme 3). This result suggests that this protocol would be useful for preparing other furoxan derivatives.

In summary, the reaction of ethyl cinnamate with NO catalyzed by Cu-salen complex (**4-Cu**) was investigated in this work. The oxygen molecule and axial ligands for the complex are necessary for the furoxan formation. Photoirradiation enhances the yield of furoxan derivative (**6**). The use of other metallosalen complexes, such as Cu(salen), resulted in a decrease in the yield of **6**. In the reaction at −5 °C, the highest yield of **6** was 55%. The application of this procedure to ethyl crotonate afforded the corresponding furoxan derivative (**9**).

Experimental

General: Melting points were measured on a Yanagimoto micro melting-point apparatus and were uncorrected. IR spectra were recorded on a JASCO FT-IR model 230 spectrometer. ^{1}H and ^{13}C NMR measurements were performed on JEOL JNM-GX-270 and JNM-L-400 spectrometers in $CDCl_3$ with tetramethylsilane as an internal reference. FAB-MS measurements were performed on a Finnigan TSQ-70 instrument. Gas chromatographic analyses were performed on a Shimadzu model GC 14A with a flame-ionization detector and a capillary column CBP20-M25-025. Photoirradiation was performed on an L5662-04 apparatus (Hamamatsu, Co. Ltd.) with a 150-W xenon lamp.

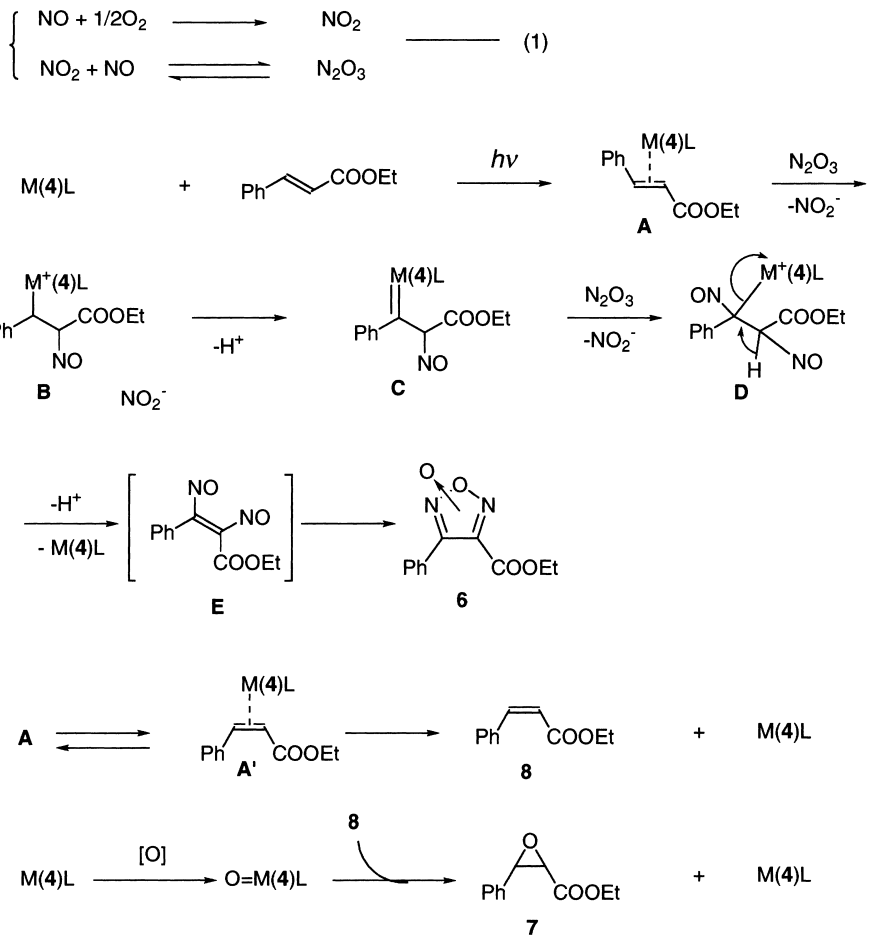
Preparation of Metallosalen Complexes: (*R*)-2,2′-Bis-(methoxymethoxy)-1,1′-binaphthyl (**1**) was prepared from (*R*)-1,1′-bi(2-naphthol) (> 99.9% ee, Kankyo Kagaku Co. Ltd.) according to the procedure reported by Katsuki et al.[7]

(*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl-3-carbaldehyde (2):[8] To a THF solution (32 mL) of bis(MOM ether) (**1**) (3.00 g, 8.01 mmol) was added dropwise a hexane solution of *n*-BuLi (1.6 M, 5.0 mL, 8.0 mmol) at room temperature. The resulting greenish yellow solution was stirred for additional 25 min. To this mixture was added DMF (586 mg, 8.01 mmol), and the solution was stirred at room temperature for 1 h. Then, sat. aq NH_4Cl was added to the mixture. The mixture was extracted with benzene. The extract was washed successively with sat. aq $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified with silica-gel chromatography (benzene:ether = 20:1) to give the corresponding monoaldehyde (**2**) as a white crystal (2.67 g, 83%). Mp 133.5–134.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H, CHO), 8.56 (s, 1H, ArH), 8.10–7.85 (m, 3H, ArH), 7.65–7.10 (m, 7H, ArH), 5.10 (ABq, J_1 = 33 Hz, J_2 = 7 Hz, 2H, OCH_2OCH_3), 4.69 (ABq, J_1 = 33 Hz, J_2 = 7 Hz, 2H, OCH_2OCH_3), 3.16 (s, 3H, OCH_3), 2.99 (s, 3H, OCH_3).

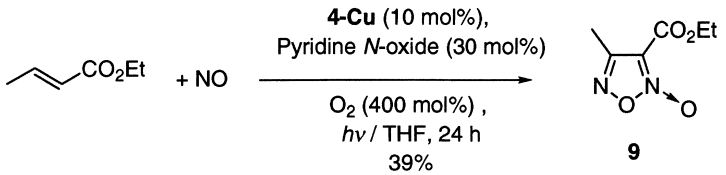
(*R*)-2,2′-Dihydroxy-1,1′-binaphthyl-3-carbaldehyde (3):[8] To a dichloromethane solution (50 mL) of bis(MOM ether) (**2**) was added a mixture of conc. HCl (20 mL) and *i*-PrOH (80 mL). The mixture was stirred at room temperature for one day, and then extracted with chloroform. The extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated to give the dihydroxy compound (**3**) as a yellow solid (8.4 g, 97%). Mp 213–220 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.62 (s, 1H, CHO), 10.21 (s, 1H, OH), 8.39 (s, 1H, ArH), 8.00–7.85 (m, 4H, ArH), 7.45–7.05 (m, 6H, ArH), 4.91 (s, 2H, OH).

(*R*,*R*)-BINOL-Schiff Base (4):[8a] A benzene solution (30 mL) of monoaldehyde (**3**) (10.0 g, 23.2 mmol) and ethylenediamine (775 μL, 11.6 mmol) was refluxed overnight while removing water with a Dean–Stark apparatus. The solution was evaporated to dryness. The residue was recrystallized from CH_2Cl_2/hexane to give the title compound (**4**) (6.81 g, 90%). Mp 198–201 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 13.27 (s, 2H, OH), 8.61 (s, 2H, ArCH=N), 7.95–7.82 (m, 10H, ArH), 7.35–7.06 (m, 12H, ArH), 5.06 (s, 2H, OH), 3.97 (ABq, J_1 = 9.7 Hz, J_2 = 2.7 Hz, 4H, CH_2N). IR (KBr) 3413 ($\nu_{O\text{-}H}$), 1633 ($\nu_{C=N}$) cm^{-1}.

(*R*,*R*)-Cu^{II}-BINOL-Salen Complex (4-Cu): To a CH_2Cl_2 solution (20 mL) of **4** (1.31 g, 2.00 mmol) was added $Cu(OAc)_2 \cdot H_2O$ (400 mg, 4.00 mmol). The mixture was refluxed for 3 h and then filtered off. The filtrate was poured into hexane and the precipitate was collected by suction filtration. The crude product was purified by reprecipitation from THF/pentane to give the title compound (**4-Cu**) as a dark-brown powder (93%). Mp > 300 °C.



Scheme 2. A possible reaction mechanism for the formation of furoxan **6**–**8**.



Scheme 3. Reaction of ethyl crotonate with nitrogen monoxide.

FT-IR (KBr) 1614 ($\nu_{C=N}$) cm^{-1}. FAB-MS (matrix: mNBA) *m*/*z* 714 [(M + H)$^+$]. Found: C, 72.3; H, 4.5; N, 3.9%. Calcd for $C_{44}H_{30}N_2O_4 \cdot H_2O$: C, 72.2; H, 4.4; N, 3.8%.

(*R*,*R*)-Co^{II}-BINOL-Salen Complex (4-Co): The title compound (**4-Co**) was prepared from an equimolar amount of **4** and $Co(OAc)_2 \cdot 4H_2O$ in a similar manner to that for **4-Cu** (dark-green powder, 92%). Mp $>$ 300 °C. FT-IR (KBr) 1616 ($\nu_{C=N}$) cm^{-1}. FAB-MS (matrix: mNBA) *m*/*z* 710 [(M + H)$^+$].

(*R*,*R*)-Mn^{III}-BINOL-Salen Complex (4-Mn): The title compound (**4-Mn**) was prepared from an equimolar amount of **4** and $Mn(OAc)_2 \cdot 4H_2O$ in a similar manner to that for **4-Cu** (black powder, 93%). Mp $>$ 300 °C. FT-IR (KBr) 1612 ($\nu_{C=N}$) cm^{-1}. FAB-MS (matrix: mNBA) *m*/*z* 705 [M$^+$].

A Typical Procedure for the Reaction of Ethyl Cinnamate with Nitrogen Monoxide: A THF solution (3 mL) of ethyl cinnamate (176 mg, 1.0 mmol), **4-Cu** (34 mg, 50 μmol), pyridine *N*-oxide (29 mg, 0.30 mmol), and hexadecane (10 mg) was put into a 30-mL three-necked flask (Pyrex) with a gas syringe (used as a pressure equalizer), a stopcock, and a light guide cap under an Ar atmosphere. An Ar atmosphere was substituted for nitrogen monoxide gas (1 atm). To the flask was introduced gaseous oxygen (90 mL, 4.0 mmol). The mixture was irradiated with a 150-W xenon lamp for 24 h. The reaction progress was monitored by GC using hexadecane as an internal standard. The reaction mixture was poured into hexane and filtered off. The residue was purified by SiO_2 chromatography.

3 (or 4-)-Ethoxycarbonyl-4- (or 3-) phenyl-1,2,5-oxadiazole 2-Oxide (6):[10] Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.98–7.43 (m, 5H, ArH), 4.38 (q, J = 7.3 Hz, 2H, CH_2CH_3), 1.26 (t, J = 7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 156.3, 155.9, 133.0, 131.0, 129.2, 128.5, 108.2, 63.0, 13.9. FT-IR (film) 2986, 1738 ($\nu_{C=O}$), 1606 ($\nu_{C=N=O}$), 1479 (ν_{NO_2}), 1455 (ν_{NO_2}), 1328, 1203 cm^{-1}. EI-MS (70 eV) *m*/*z* 234 ([M]$^+$, 9.2), 204 ([M $-$ NO]$^+$, 18.0), 174 ([M $-$ 2NO]$^+$, 19.0).

3-Ethoxycarbonyl-4-methyl-1,2,5-oxadiazole 2-Oxide (9):[10,11] yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.30 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.48 (s, 3H, CH_3), 1.33 (t, J = 7.2 Hz, 3H, OCH_2CH_3).

This work was financially supported by Sumitomo Foundation, Nissan Science Foundation, and Mitsubishi-Yukakagaku Chemistry Foundation, which are greatly acknowledged. We are grateful to Professor F. Sanada of Kyoto University for the elemental analysis.

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