Asymmetric Diels−Alder Reaction of Methacrolein with Cyclopentadiene Using Polymer-Supported Catalysts: Design of Highly Enantioselective Polymeric Catalysts

Koichi Kamahori, Koichi Ito, and Shinichi Itsuno*

Department of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441, Japan

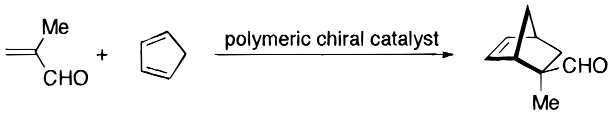
Received March 18, 1996

Introduction

Polymer-supported reagents and catalysts are finding increasing use as new tools in asymmetric synthesis and may also find application in industrial processes. Polymer-supported techniques in asymmetric synthesis offer various advantages over the usual solution reactions, including easy separation, reuse, and nontoxicity of the immobilized species.[1] Since the microenvironment formed in a cross-linked polymer affects the performance of the polymeric catalysts, it should be carefully controlled in order to produce highly effective polymer-supported chiral catalysts. In order to investigate the effect of different microenvironments formed by various cross-linking structures on the catalytic activity of polymeric catalysts, we chose to study the catalytic asymmetric Diels−Alder reaction of methacrolein with cyclopentadiene (Scheme 1).

In the past, numerous efforts have been devoted to the field of enantioselective Diels−Alder reactions,[2] and enantioselectivities greater than 90% have been reported.[3] Although a number of chiral catalysts have been demonstrated for enantioselective Diels−Alder reactions in solution systems, polymer-supported catalysts for the reaction have not been utilized extensively. During our study of polymer-assisted asymmetric synthesis,[4,5] we investigated various polymer-supported chiral catalysts for Diels−Alder reactions and found that polymers possessing chiral oxazaborolidinone units showed satisfactory selectivity and reactivity.[6−8] In this study, several polymer-supported catalysts of chiral oxazaborolidinone having different cross-linking structures were prepared and used for the Diels−Alder reaction of methacrolein with cyclopentadiene. We found that the cross-linking structure greatly affected the performance of the polymeric catalyst. A unique microenvironment generated by oxyethylene cross-linkage in the polymer resulted in enhanced enantioselectivities in the reaction.

Scheme 1



Results and Discussion

The cross-linked polymers possessing chiral *N*-sulfonylamino acid residue **5**, **6**, and **7** were prepared by copolymerization of **1** with styrene and the corresponding cross-linking agents **2**, **3**, and **4**, respectively, in the presence of benzoyl peroxide as radical initiator. Chiral monomer **1** was readily prepared following our reported procedure for 4-vinylbenzenesulfonyl chloride and L-valine.[6] Cross-linking agents **3** and **4**, for forming flexible cross-linkages in the polymer, were prepared as follows. A cross coupling reaction of dibromohexane with 2 equiv of 4-vinylbenzylmagnesium chloride in the presence of Li_2CuCl_4 as catalyst gave cross-linking agent **3** having an octamethylene chain. Cross-linking agent **4** that contains an oxyethylene chain was prepared by treating oligo(ethylene glycol)s with 2 equiv of 4-vinylbenzyl chloride under Williamson conditions. The chain length of these cross-linking agents can be easily controlled as various molecular weights of the starting dibromoalkanes and oligo(ethylene glycol)s are commercially available. Suspension polymerization of the chiral monomers with these flexible chain cross-linkers resulted in insoluble polymers in spherical bead form. They swelled very well in organic solvents, such as benzene, toluene, and tetrahydrofuran, and showed good mechanical stability due to the flexible structure of the cross-linker.[9] Polymer particles with a diameter in the range of 50 to 100 μm were collected and used for the asymmetric transformation. An alternative approach to the synthesis of the chiral polymers involves chemical modification of preformed cross-linked polystyrene. Although the chiral polymer **5** cross-linked with **2** could be prepared by the chemical modification method,[6] the benzyl ether linkage was susceptible to cleavage during the chlorosulfonylation reaction used in the chemical modification process.

The chiral polymers obtained by suspension polymerization were used for the asymmetric Diels−Alder reaction of methacrolein with cyclopentadiene; results are summarized in Table 1. Treatment of the chiral polymers **5**, **6**, and **7** with equimolar amount of borane-methyl sulfide at 0 °C generated hydrogen to form the polymeric catalysts **8**, **9**, and **10**, respectively. While no cycloadduct was detected without catalyst, smooth reaction occurred even at −78 °C in the presence of the polymeric catalyst to afford highly *exo* selective cycloadduct in excellent yield. It should be noted that no compounds derived from

---

[1] Reviews on polymer-supported reagents and catalysts: (a) Itsuno, S. In *Macromolecules 1992*; Kahovec, J., Ed.; VSP: Utrecht, 1993; p 413. (b) Itsuno, S. In *Polymeric Materials Encyclopedia; Synthesis, Properties and Applications*; Salamone, J. C., Ed.; CRC Press: Boca Raton, FL, 1996; Vol. 10, p 8078. (c) Sherrington D. C.; Hodge, P., Eds. *Syntheses and Separations Using Functional Polymers*; Wiley: Chichester, 1988. (d) Blossey, E. C.; Ford, W. T. in *Comprehensive Polymer Science*; Allen, G. Ed.; Pergamon Press: Oxford, 1989; Vol. 6, 81.

[2] Reviews on asymmetric Diels−Alder reactions: (a) Paquette, L. A. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3B. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleminng, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 315. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92,* 1007.

[3] (a) Motoyama, Y.; Terada, M.; Mikami, K. *Synlett* **1995**, 967 and references therein. (b) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412. (c) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (d) Maruoka, K.; Murase, N.; Yamamoyo, H. *J. Org. Chem.* **1993**, *58,* 2938.

[4] Itsuno, S.; Ito, K. In *Trends in Organic Chemistry*; Menon, J., Ed.; Council of Scientific Research Integration, Research Trends: Trivandrum, 1991; Vol. 1, p 199.

[5] Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. J. *J. Org. Chem.* **1990**, *55,* 304.

[6] Kamahori, K.; Tada, S.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2547.

[7] Itsuno, S.; Watanabe, K.; Koizumi, T.; Ito, K. *React. Polym.* **1995**, *24,* 219.

[8] Itsuno, S.; Kamahori, K. Watanabe, K.; Koizumi, T.; Ito, K. *Tetrahedron: Asymmetry* **1994**, *5*, 523.

[9] No destruction was observed after 1 week stirring at 200 rpm using a magnetic stirring bar, while polymers cross-linked with divinylbenzene (**2**) began to lose their spherical shape after 4 days of stirring.

S0022-3263(96)00518-X CCC: $12.00

Scheme 2

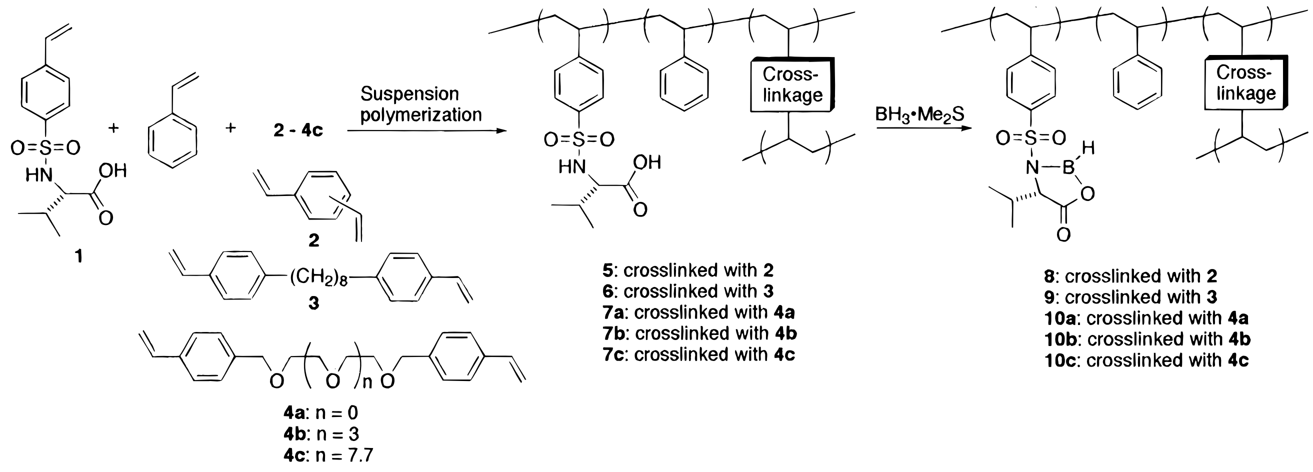


Table 1. Enantioselective Diels–Alder Reaction of Methacrolein with Cyclopentadiene Using a Polymeric Catalyst[a]

run	polymeric catalyst	yield,[b] %	reactn temp, °C	cycloadduct **11** *endo*:*exo*[c]	cycloadduct **11** %ee (config)[d]
1	**8**	87	−78	1:99	65 (*R*)
2	**9**	86	−78	8:92	84 (*R*)
3	**10a**	85	−78	5:95	77 (*R*)
4	**10b**	96	0	10:90	23 (*R*)
5	**10b**	95	−30	7:93	71 (*R*)
6	**10b**	93	−78	1:99	92 (*R*)
7	**10c**	88	−78	4:96	95 (*R*)

[a] See Experimental Section for a representative procedure. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] The enantiopurity of the *exo* isomer was determined by GC.

chiral Lewis acid were detected in the product solution. This indicates that the reaction is catalyzed by the solid catalyst. When the polymeric catalyst **8** was used as a chiral catalyst for the reaction, *exo* adduct was predominantly formed with 65% ee (Table 1, run 1). Interestingly, the use of the polymeric catalyst **9** having the same catalyst structure with flexible alkylene chain cross-linkage gave a higher enantioselectivity of 84% ee (run 2) for the same reaction. This is comparable to the selectivity obtained from using the unsupported catalyst in solution as reported by Helmchen (86% ee).[10,11] Polymeric catalysts **10** cross-linked with oligo(oxyethylene) chain also gave high selectivities in this reaction. The polymeric catalyst with a longer oxyethylene chain cross-linkage gave enantioselectivities as high as 95% ee, results that are superior to those obtained from using the free catalyst in solution. Although a clear explanation is not available for these results at the moment, there are very few reports of polymeric chiral catalysts that exhibit higher enantioselectivity than that obtained from their low molecular weight counterparts. As pointed out by Helmchen, donor additives such as THF might help to dissociate the aggregated structure of the catalyst and cause a decrease in the selectivity of the reaction.[10] Ether oxygens of the oligo(oxyethylene) cross-linkage may act as donor additives in this reaction. All of the Diels–Alder reactions predominantly gave the adduct having the *R* configuration. The effect of temperature on enantioselectivity is as expected, with better results being obtained at −78 °C than at −30 °C or 0 °C.

Due to their insolubility, the cross-linked polymer-supported catalysts were easily recovered and reused many times. On the other hand, substrates and chiral products remain in the solvent. It is not necessary to regenerate the polymeric catalyst after reaction is complete, if the product can be separated. Thus, one of the most attractive methods for doing asymmetric synthesis using insoluble catalysts may be to use a flow system in which the chiral product can be produced continuously. If the prochiral substrates can be converted into a chiral adduct during their passage through a column filled with the insoluble catalyst, a continuous flow system for an asymmetric Diels–Alder reaction can be realized. Polymer **7b** was chosen to test this method. Since no reaction occurs between methacrolein and cyclopentadiene without catalyst, dichlomethane solution of these two substrates was added slowly to a column containing the insoluble polymer **7b** pretreated with borane–methyl sulfide as shown in Figure 1. Column temperature was maintained at −30 °C by using a cooling jacket. A solution of the chiral product was eluted continuously from the column. Using a continuous flow system containing 5.7 mmol of the polymeric catalyst, a total of 138 mmol of (*R*)-adduct with 71% ee was obtained, which is comparable to the selectivity obtained from the batch system (Table 1, run 5). The continuous flow system is advantageous as it eliminates the need for stirring, which may cause destruction of the polymeric catalyst during repeated reactions.[12]

In summary, we have prepared new chiral polymeric catalysts useful in promoting asymmetric Diels–Alder reactions. Polymeric catalysts having oxyethylene cross-linkages exhibit better performance in promoting enantioselective Diels–Alder reactions than their nonpolymeric counterparts. They also have the advantage that they can be recycled or used in a continuous flow system.

Experimental Section

Unless otherwise noted, all reactions were performed in oven-dried glassware, under an atmosphere of nitrogen. Cyclopentadiene was obtained by thermal decomposition of dicyclopentadiene. All other commercial chemicals were used without

---

(10) Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron: Asymmetry* **1991**, *2*, 639.

(11) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197.

(12) Destruction of the polymeric beads by vigorous stirring results in the formation of fine powder of the polymers, which drastically hinders their handling in filtration and reduces their ability to be recycled repeatedly.

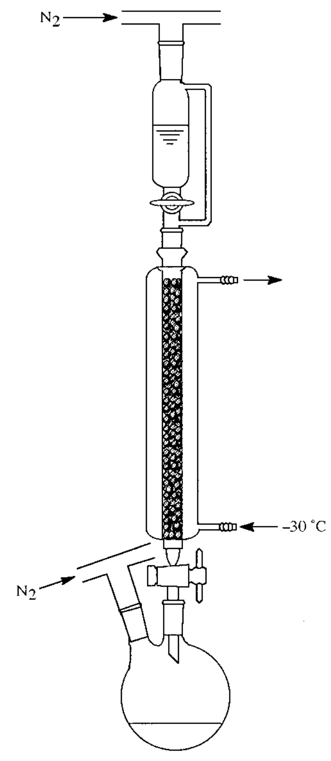


Figure 1.

purification. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 270 and 67.8 MHz, respectively, with tetramethylsilane as the internal standard. Solid state ^{11}B NMR spectra were obtained at 128.3 MHz, and ^{11}B chemical shifts were reported in δ (ppm) relative to $BF_3{\cdot}OEt_2$. Infrared spectra were obtained in KBr; only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were obtained using Yanaco MT-3 CHN CORDER. Melting points are uncorrected. Optical purity was determined by Shimadzu Capillary Gas Chromatograph 14A with a chiral capillary column (Astec Chiraldex G-TA, 20 m or 30 m). Precoated silica gel plates (Merck 5554, 60 F_{254}) were used for thin layer chromatography. Silica gel (Wakogel C-200) was used for column chromatography. Optical rotations were taken on a JASCO DIP-140 digital polarimeter using a 10 cm thermostated microcell. Capacities of the polymers determined by microanalysis and titrimetry are expressed in millimoles of functional groups per gram of dry resin (mmol/g) or as degree of functionalization (DF). For example, DF = 0.10 if 10% of the styrene units are functionalized. 4-Vinylbenzyl chloride was a gift from the Seimi Chemical Co.

Preparation of Cross-linking Agent 3. A solution of 1,6-dibromohexane (4.88 g, 20 mmol) and 8 mL of Li_2CuCl_4 (0.1 M in THF) in dry THF (60 mL) was stirred at 0 °C, and an ether solution of 4-vinylbenzylmagnesium chloride prepared from 4-vinylbenzyl chloride (12.2 g, 80 mmol) and magnesium (2.14 g, 88 mmol) was added dropwise. The solution was stirred overnight at room temperature and then quenched with methanol and water. The solvent was removed *in vacuo*, and the product was extracted into ether. The ether solution was further washed with water and then dried over Na_2SO_4 and concentrated. The product obtained was purified by column chromatography on silica gel with hexane as an eluent to give 5.8 g (90%) of **3** as a white solid: mp 42−44 °C; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.30 (d, 4H, $J = 8.3$ Hz), 7.12 (d, 4H, $J = 8.3$ Hz), 6.70 (dd, 2H, $J = 10.7, 17.6$ Hz), 5.70 (d, 2H, $J = 17.6$ Hz), 5.18 (d, 2H, $J = 10.7$ Hz), 2.58 (t, 4H, $J = 6.7$ Hz), 1.50−1.70 (m, 4H), 1.20−1.40 (m, 8H). Anal. Calcd for $C_{24}H_{30}$: C, 90.50; H, 9.49. Found: C, 90.43; H, 9.36.

Preparation of Cross-linking Agent 4a. To a suspension of sodium hydride (NaH 60 wt % in oil, 6.0 g, 150 mmol) in DMF (120 mL) was added a DMF (30 mL) solution of ethylene glycol (3.7 g, 60 mmol) at 0 °C. After 2 h of stirring at room temperature, a solution of 4-vinylbenzyl chloride (22 g, 144 mmol) in DMF (50 mL) was added dropwise to the above mixture. The resulting mixture was stirred for 24 h at room temperature. The mixture was then poured into water and extracted with ethyl acetate (2 × 200 mL). Combined organic layers were washed with water (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, chloroform) afforded **4a** (15.3 g, 86%) as a pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.33 (d, 4H, $J = 8.3$ Hz), 7.25 (d, 4H, $J = 8.3$ Hz), 6.65 (dd, 2H, $J = 17.5, 10.7$ Hz), 5.69 (d, 2H, $J = 17.5$ Hz), 5.17 (d, 2H, $J = 10.7$ Hz), 4.50 (s, 4H), 3.59 (s, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.5, 136.4, 136.1, 127.4, 125.7, 113.2, 72.4, 69.1. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.54; H, 7.56.

Preparation of Cross-linking Agent 4b. The reaction was carried out as described above for **4a** starting from tetraethylene glycol (11.7 g, 60 mmol) to give after column chromatography (silica gel, chloroform) 16 g of pure **4b** (63%) as a pale yellow oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.33 (d, 4H, $J = 8.3$ Hz), 7.25 (d, 4H, $J = 8.3$ Hz), 6.65 (dd, 2H, $J = 17.5, 10.7$ Hz), 5.69 (d, 2H, $J = 17.5$ Hz), 5.17 (d, 2H, $J = 10.7$ Hz), 4.50 (s, 4H), 3.59 (br, 16H). IR (KBr) 1630, 1100 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.18; H, 8.05.

Preparation of Cross-linking Agent 4c. The reaction was carried out as described above for **4a** starting from poly(ethylene glycol) 400 (average molecular weight; ca. 400, 24 g, 60 mmol) to give after column chromatography (silica gel, chloroform) 21.2 g of pure **4c** (56%) as a pale yellow oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.33 (d, 4H, $J = 8.3$ Hz), 7.25 (d, 4H, $J = 8.3$ Hz), 6.65 (dd, 2H, $J = 17.5, 10.7$ Hz), 5.69 (d, 2H, $J = 17.5$ Hz), 5.17 (d, 2H, $J = 10.7$ Hz), 4.50 (s, 4H), 3.59 (br, 30.8H). Anal. Calcd for $C_{35.4}H_{52.8}O_{9.7}$: C, 67.10; H, 8.40. Found: C, 67.19; H, 8.47.

Polymer-Supported *N*-Sulfonylamino Acid 6. **6** was obtained by a copolymerization method using the conditions reported for **5**.[6] Suspension copolymerization of **1** (1.42 g, 5 mmol), styrene (4.17 g, 40 mmol), and **3** (1.59 g, 5 mmol) gave 6.4 g (89%) of **6**. Both sulfur and nitrogen analysis indicated a loading of chiral amino acid corresponding 0.77 mmol/g (DF = 0.1). IR (KBr) 3280, 2913, 1724, 1601, 1460, 1156, 1091 cm^{-1}.

Polymer-Supported *N*-Sulfonylamino Acid 7a. Suspension copolymerization of **1** (1.42 g, 5 mmol), styrene (4.17 g, 40 mmol), and **4a** (1.47 g, 5 mmol) gave 6.83 g (93%) of polymer **7a**. Both sulfur and nitrogen analysis indicated a loading of chiral amino acid corresponding 0.77 mmol/g (DF = 0.1). IR (KBr) 3280, 2913, 1724, 1601, 1487, 1156, 1091 cm^{-1}.

Asymmetric Diels−Alder Reaction with Polymeric Catalyst. A typical experimental procedure is as follows: the chiral polymeric catalyst **10a** was generated *in situ* by stirring borane−methyl sulfide complex (1.0 M solution in dichloromethane, 1.5 mmol) and **7a** (1.5 mmol) suspended in 30 mL of dichloromethane for 4 h at room temperature. Generation of hydrogen ceased during this period. IR spectra of **10a** displayed characteristic absorption at 2260 cm^{-1}, attributed to the B−H stretching vibration. The solid state ^{11}B NMR spectrum of **10a** showed a broad singlet peak at 6.4 ppm. Methacrolein (0.83 mL, 10 mmol) and cyclopentadiene (1.2 mL, 12 mmol) were then added successively to the above suspension at −78 °C. The reaction mixture was stirred for 2 h at this temperature and then quenched with aqueous sodium hydrogen carbonate. After removal of the chiral polymer by filtration, the filtrate was extracted with CH_2Cl_2 (2 × 200 mL) and the extract was washed with water (2 × 200 mL). The organic solution was dried ($MgSO_4$) and concentrated on a rotary evaporator to give 1.16 g (85%) of the cycloadduct. The *endo* adduct was removed by column chromatography (24:1 hexane/ethyl acetate) to give a pure *exo* adduct **11** as a colorless solid. The optical yield was determined to be 77% ee by GLC analysis after conversion to the chiral acetal with (2*R*,4*R*)-(−)-2,4-pentanediol.[13,14] The specific rotation of the *exo* adduct was $[\alpha]_D$ −18.03 (*c* 5.94, ethanol). The optical yield (77% ee) was also calculated by the observed specific rotation and the known maximum rotation of the cycloadduct, $[\alpha]_{D\max}$ 23.3 (ethanol).[15]

Asymmetric Diels−Alder Reaction in a Continuous Flow System. A glass column (7 mm × 500 mm) covered by a

---

[13] Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1483.

[14] Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

[15] Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

cooling jacket (27 mm × 500 mm) was filled with the chiral polymer **7b** (8.83 g, 5.7 mmol). Borane−methyl sulfide (5.7 mmol, 1 M solution in dichloromethane) was added from the dropping funnel fixed on the top of the column as shown in Figure 1. Cooled methanol (−30 °C) was supplied to the cooling jacket from a cooling bath. A solution of methacrolein (0.44 M) and cyclopentadiene (0.66 M) in dichloromethane was added dropwise slowly (10 mL/h) from the dropping funnel. After 60 mL of the substrates were added to the column, the usual workup of the solution obtained in the receiver flask afforded 3.4 g (25.0 mmol) of cycloadduct with 71% ee. Another 60 mL addition of substrates gave the same product (3.5 g) with 71% ee. A total amount of 18.8 g (138 mmol) of the adduct was obtained in 71% ee.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research in Priority Areas (No. 08246227, 07214217) from the ministry of Education, Science, Sports and Culture, Japan.

JO960518E