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Communication

Ionic, Core-Corona Polymer Microsphere-Immobilized MacMillan Catalyst for Asymmetric Diels-Alder Reaction

Md. Wali Ullah and Naoki Haraguchi *

Department of Applied Chemistry and Life Science, Graduate School of Engineering, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi, Aichi 441-8580, Japan; m169402@edu.tut.ac.jp or waliullah@cou.ac.bd

* Correspondence: haraguchi@chem.tut.ac.jp; Tel.: +81-532446812

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Abstract: The improvement of the catalytic activity of a heterogeneous chiral catalyst is one of the most critical issues, as are its recovery and reuse. The design of a heterogeneous chiral catalyst, including the immobilization method and the support polymer, is of significance for the catalytic activity in asymmetric reactions. An ionic, core-corona polymer microsphere-immobilized MacMillan catalyst (ICCC) was successfully synthesized by the neutralization reaction of sulfonic acid functionalized core-corona polymer microsphere (CCM–SO_3H) with a chiral imidazolidinone precursor. We selected the core-corona polymer microsphere as the polymer support for the improvement of catalytic activity and recovery. The MacMillan catalyst was immobilized onto the pendant position of the corona with ionic bonding. ICCC exhibited excellent enantioselectivity up to 92% enantiomeric excess (ee) (*exo*) and >99% ee (*endo*) in the asymmetric Diels-Alder (DA) reaction of (*E*)-cinnamaldehyde and 1,3-cyclopentadiene. ICCC was quantitatively recovered by centrifugation because of the microsphere structure. The recovered ICCC was reused without significant loss of the enantioselectivity.

Keywords: heterogeneous catalyst; polymeric catalyst; organocatalyst; polymer microsphere; ionic bonding; Diels-Alder reaction

1. Introduction

Chiral organocatalysis is one of the most attractive methods for the production of optically active medical and pharmaceutical products due to advantages such as being metal-free, exhibiting higher stability against moisture and oxygen, and facilitating experimental operation [1–3]. Among the chiral organocatalysts, chiral imidazolidinones and their salts, so-called MacMillan catalysts, have been applied to various asymmetric reactions via HOMO or LUMO activation mechanisms, such as the Diels-Alder (DA) reaction [4], 1,3-dipolar cycloaddition [5], Friedel-Crafts alkylation [6], indole alkylation [7], the α-halogenation of aldehydes [8,9], direct aldol reaction [10], intramolecular Michael reaction [11], and the epoxidation [12] of aldehydes. The MacMillan catalysts were also applied for the α-alkylation, α-allylation [13–18], α-benzylation [19], β-arylation [20], and β-alkylation [21] of aldehydes or ketones via the SOMO-activation mechanism [22].

Despite the efficiency of MacMillan organocatalysts in asymmetric reactions, relatively high catalyst loading (generally 5 to 20 mol %) is required to proceed with such asymmetrical reactions at reasonable reaction rates; besides, a burdensome purification method, such as column chromatography, is required to isolate a product and to separate the MacMillan catalyst from a reaction mixture. Therefore, a MacMillan catalyst is generally not reused.

The covalent immobilization of MacMillan catalyst onto a heterogeneous support represents an attractive approach to solving the issues, in regard to its sustainability. Covalently immobilized

MacMillan catalysts have been developed and applied for catalytic, asymmetric reactions [23–38]. However, conventional, polymer-immobilized MacMillan catalysts possess some drawbacks, such as elaborate multistep preparation, and the decrement of catalytic activity due to the modification of the MacMillan catalyst. Therefore, the design of a heterogeneous chiral catalyst, including the immobilization method and the support polymer, is essential for efficient asymmetric reactions.

For the immobilization of method, we developed an ionic immobilization method for chiral organocatalysts, such as MacMillan catalyst and cinchonidinium, via neutralization reaction or ion-exchange reaction with sulfonated polymers [39,40]. The ionic immobilization methodology has been applied for the synthesis of the main chain of chiral polymers, many of which were prepared by intermolecular reactions of chiral organocatalyst dimers with disulfonic acid derivatives [41–46].

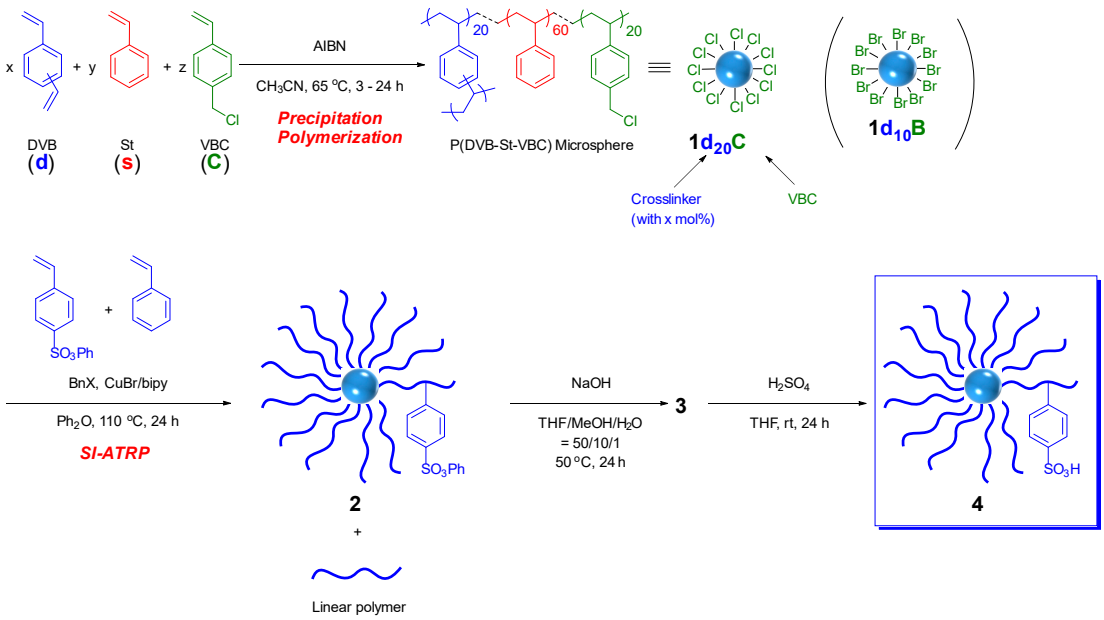
Functionalized polymer microspheres have been widely used as industrial materials in various areas, such as coatings, electronics, biomedical engineering, and organic synthesis [47–49]. Interestingly, some polymer microspheres with achiral or chiral catalysts have been used as heterogeneous catalysts for organic reactions [50–52]. We first synthesized polymer microsphere-immobilized chiral 1,2-diamine ligands with uniform, core-shell, or core-corona structures, and these complexes with ruthenium were used as heterogeneous, polymeric chiral catalysts in the asymmetric transfer hydrogenation (ATH) of ketones [51]. Both the yield and enantiomeric excess (ee) of the product were greatly influenced by the introduction position of the chiral catalyst onto the polymer microsphere and the degree of crosslinking, along with the hydrophobicity of polymer microsphere. Recently, we successfully synthesized core-corona polymer microsphere-supported cinchonidinium salt and applied it as a heterogeneous polymeric catalyst for the asymmetric alkylation reaction of a glycine derivative [52].

In this communication, we describe the synthesis of an ionic, core-corona polymer microsphere-immobilized MacMillan catalyst (ICCC) by the neutralization reaction of the core-corona polymer microsphere having a sulfonic acid moiety (CCM–SO_3H) with the precursor of the MacMillan catalyst. These catalysts were used as heterogeneous polymeric catalysts in a typical asymmetric DA reaction of (*E*)-cinnamaldehyde and 1,3-cyclopentadiene. The catalytic activity of ionic, core-corona polymer microsphere-immobilized MacMillan catalyst was compared with those of a model catalyst, linear-type catalyst, crosslinked gel-type catalyst, polymer microsphere catalyst, and covalently core-corona polymer microsphere-immobilized catalyst in detail.

2. Results and Discussion

2.1. Preparation of Core-Corona Polymer Microsphere Having Sulfonic Acid (CCM–SO_3H)

The preparation of CCM–SO_3H is illustrated in Scheme 1. Benzyl chloride-functionalized polymer microsphere having phenylsulfonate **1** was prepared by the precipitation polymerization of styrene (St), divinylbenzene (DVB), and 4-vinylbenzyl chloride (VBC) [53]. The molar ratio of St/DVB/VBC was set to 60/20/20. The number-averaged diameter (D_n) of the polymer microsphere was 1.14 μm. Because the polydispersity (U) was quite low (1.00), monodispersed polymer microsphere **1d$_{20}$C** was successfully obtained. **1d$_{20}$C** means polymer microsphere synthesized from 20 mol % of divinylbenzene and 4-vinylbenzyl chloride (Scheme 1). The chlorine content measured by the halogen titration method (1.67 mmol g^{-1}) was in good agreement with that calculated (1.68 mmol g^{-1}). In addition to the monodispersed benzyl chloride-functionalized polymer microsphere with 20 mol % DVB, a monodispersed, poorly-crosslinked, benzyl bromide-functionalized polymer microsphere **1d$_{10}$B** was successfully synthesized with a relatively higher yield (37%) by the precipitation polymerization of St, DVB, and a chemically cleavable divinyl crosslinker, followed by a transformation reaction [54]. From the FT-IR spectrum of **1d$_{10}$B**, a new stretching vibration of the C–Br bond was observed at 1227 cm^{-1} (Figure 1). These results indicate that both polymerization and transformation reaction successfully occurred. The D_n of **1d$_{10}$B** was 1.08 μm with narrow size distribution (U = 1.13).



Scheme 1. Synthesis of corona polymer microsphere having a sulfonic acid moiety (CCM–SO_3H) **4**.

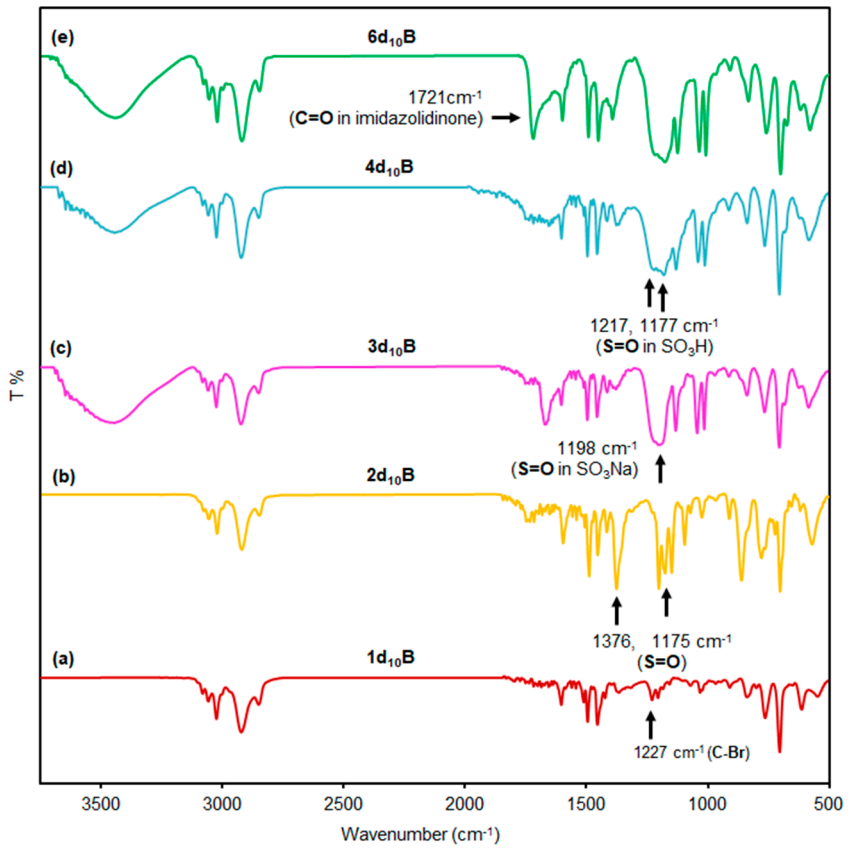


Figure 1. FT-IR spectra. (**a**) **1d$_{10}$B**, (**b**) **2d$_{10}$B**, (**c**) **3d$_{10}$B**, (**d**) **4d$_{10}$B**, and (**e**) **6d$_{10}$B**.

The core-corona polymer microsphere functionalized with phenylsulfonate (CCM-SO_3Ph) **2** was synthesized by the surface-initiated atom transfer radical polymerization (SI-ATRP) of styrene (70 mol %) and phenyl *p*-styrenesulfonate (S) (30 mol %) by using **1d$_{20}$C** or **1d$_{10}$B** as a macroinitiator [55]. In the polymerization, benzyl chloride (BnCl) was simultaneously added as a sacrificial initiator. By the SEC analysis of the resultant free polymer initiated with BnCl, both M_n and M_w/M_n of the grafted polymers

onto the surface of **1** were estimated. In FT-IR of **2**, two characteristic absorption peaks at 1376 and 1175 cm^{-1} were observed for the stretching vibration of the S = O bond of phenylsulfonate (Figure 1). The M_n of the corona was successfully controlled by changing the M/I, and the M_w/M_n values were relatively low (<1.3). The M_w/M_n was increased with the increase of the M/I. We found that the SI-ATRP with low M/I proceeded in a controlled manner, and a well-defined CCM-SO_3Ph was obtained. Compared with D_n (**1**), D_n (**2**) was increased when the grafted polymers were formed only by the initiators on the surface. D_n (**2**) became higher when increasing M/I from 50 to 200. The polydispersity (U) was low enough (<1.3).

The CCM–SO_3H **4** was prepared by the deprotection of phenylsulfonate moiety of **2**, followed by treatment with H_2SO_4. For example, **4d$_{10}$C** represents the CCM–SO_3H synthesized from **1d$_{10}$C** and SI-ATRP of styrene and *p*-styrenesulfonate with M/I = 50, and **4d$_{10}$B-200** represents that from **1d$_{10}$B** with M/I = 200. The deprotection reaction was conducted with NaOH aqueous solution in a 50/10/1 THF/CH_3OH/H_2O mixed solvent at 50 °C for 24 h. The characterization is summarized in Table 1. The yield was quantitative (93%–97%), and the sulfur content was in the range between 1.0 and 1.6 mmol g^{-1}. The absorption peaks at 1376 cm^{-1} disappeared after the deprotection of phenylsulfonate moiety of **2** from the FT-IR spectra of **3** and **4** (Figure 1). Sulfur contents determined by the titration method were close to those calculated. As a result, CCM–SO_3H was successfully prepared by the precipitation polymerization, SI-ATRP, and the regeneration of the sulfonic acid.

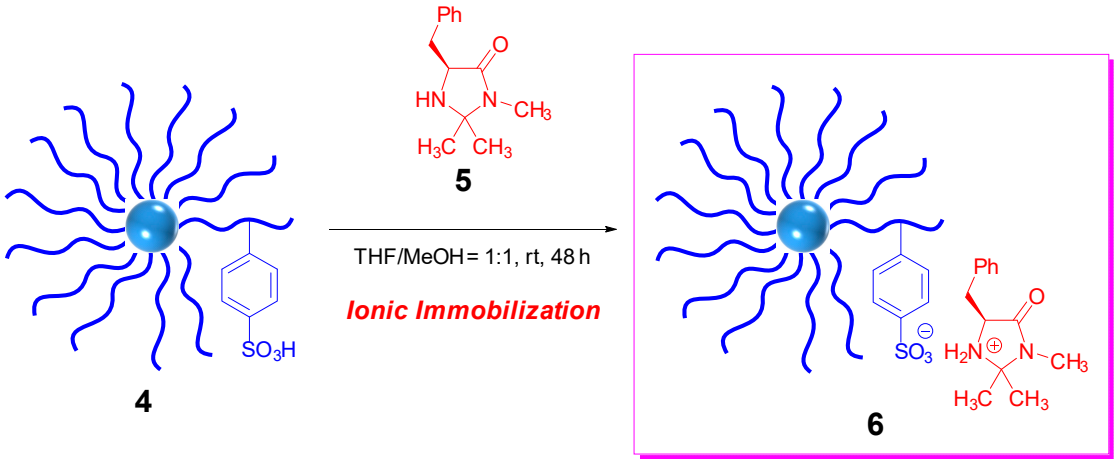
Table 1. Characterization of CCM–SO_3H **4**.

Entry	4	D_n (Core) (μm) [a]	Corona		D_n (Core-Corona) (μm) [a]	U (4) [a]	S Content (mmol g^{-1}) [c]
			M_n [b]	M_w/M_n [b]			
1	**4d$_{20}$C**	1.14	7630	1.18	1.34	1.00	1.00
2	**4d$_{10}$B**	1.08	11,000	1.32	1.40	1.23	1.61
3	**4d$_{10}$B-200**	1.08	30,400	1.57	1.95	1.20	1.48

[a] Measured from SEM image. [b] Determined by SEC (polystyrene standards). [c] Determined by titration method.

2.2. Synthesis of Core-Corona Polymer, Microsphere-Immobilized Macmillan Catalyst (ICCC)

The ionic, core-corona polymer, microsphere-immobilized MacMillan catalyst (ICCC) **6** was synthesized by the neutralization reaction of the CCM–SO_3H **4** with MacMillan catalyst precursor **5** (Scheme 2). For example, **6d$_{20}$C** was synthesized from **4d$_{20}$C** and **5**. These results were summarized in Table 2. The degree of catalyst immobilization measured by the recovered catalyst was more than 60%. No side reaction was observed at all. The degree was slightly increased when low-crosslinked polymer microsphere **4d$_{10}$B** was used instead of that with 20 mol % of crosslinking **4d$_{20}$C**. The significant improvement was observed when the reaction was conducted in CH_2Cl_2/CH_3OH mixed solvent (entry 7 versus 8) Interestingly, the degree by the core-corona polymer microsphere with longer corona (**6d$_{10}$B-200**) was higher, possibly because the graft polymer chain was an extended chain rather than a random coil due to the higher M_n of the corona. The catalyst contents in **6** determined from the mass of the recovered catalyst were in the range of 0.53–1.1 mmol g^{-1}. The characteristic strong absorption peak at 1721 cm^{-1} for C = O in the imidazolidinone moiety was observed from the FT-IR of **6** (Figure 1). The SEM images of ICCC are shown in Figure 2. Since the deprotection of phenylsulfonate of **2**, the acidification of the sodium sulfonate of **3**, and the ionic immobilization between **4** and **5** did not affect the particle diameter, the D_n (**6**) was unchanged. For example, the D_n values of **3d$_{10}$B**, **4d$_{10}$B**, and **6d$_{10}$B** were 1.90, 1.92, and 1.91 μm, respectively. The nitrogen content measured in **6d$_{10}$B** was comparable to that calculated. From these results, MacMillan catalyst precursor **5** was successfully immobilized onto the pendant position of CCM with ionic bonding by the neutralization reaction to afford ICCC **6**.



Scheme 2. Synthesis of ionic, core-corona polymer microsphere-immobilized MacMillan catalyst (ICCC) **6** by neutralization reaction.

Table 2. Characterization of ICCC **6**.

Entry	6	Solvent	Degree of Immobilization (%)	Catalyst Content (mmol g^{-1})
1	**6d$_{20}$C**	1/1 THF/CH_3OH	61	0.533
2	**6d$_{10}$B**	1/1 THF/CH_3OH	67	0.581
3	**6d$_{10}$B**	1/1 CH_2Cl_2/CH_3OH	86	1.06
4	**6d$_{10}$B-200**	1/1 CH_2Cl_2/CH_3OH	98	1.10

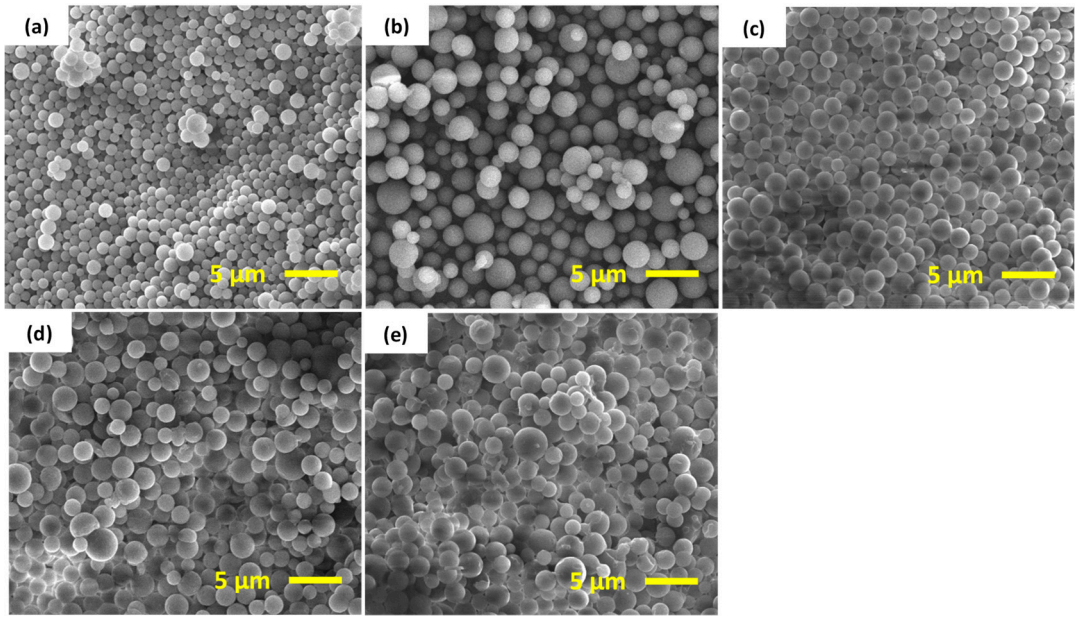
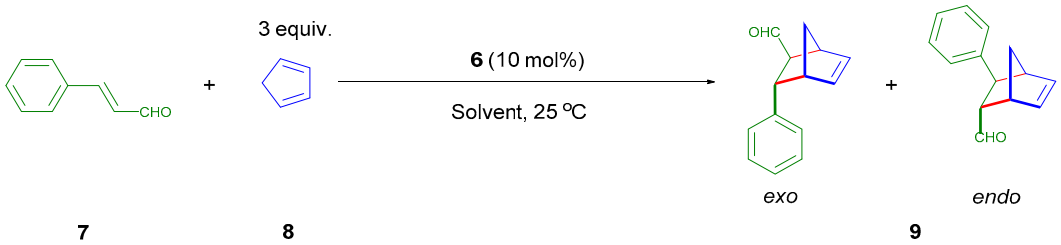


Figure 2. SEM images. (**a**) **1d$_{10}$B**, (**b**) **2d$_{10}$B**, (**c**) **3d$_{10}$B**, (**d**) **4d$_{10}$B**, and (**e**) **6d$_{10}$B**.

2.3. The Effect of Solvent in an Asymmetric DA Reaction Catalyzed by ICCC 6

The asymmetric DA reaction of (*E*)-cinnamaldehyde **7** and 1,3-cyclopentadiene **8** catalyzed by ICCC **6** was carried out as a benchmark reaction (Scheme 3). The optimization of the reaction solvent was firstly investigated (Table 3). The reaction solvent in the asymmetric reaction using MacMillan catalyst significantly affected the catalytic reactivity, and did when using a homogeneous catalyst as well [40,45,56]. The reaction was performed with 10 mol % of catalyst **6** in a solvent at 25 °C for the comparison of the catalytic performance of **6** with those previously reported. The reaction time was determined by the consumption of **7** by TLC. Both the yield and enantiomeric excess (ee) were

increased by increasing the polarity of the reaction solvent (entries 1–4). The catalyst **6d$_{10}$B** showed low reactivity with slightly low enantioselectivity (82% ee (*exo*)) when a highly polar solvent, such as H_2O, was used as the solvent, which was probably due to poor dispersity of the polymer microsphere and the hydrophobic polymer chains (entry 4 versus 5). When dry MeOH was used, enantioselectivity was decreased (entry 4 versus 6), which indicated that a trace of H_2O in the solvent assisted with increasing the ee value. There has been a report that the presence of H_2O in the DA reaction catalyzed by the MacMillan catalyst enhances reactivity [56]. With the addition of H_2O (in 95/5 THF/H_2O or 95/5 CH_3CN/H_2O), both reactivity and enantioselectivity were improved (entry 1 versus 7 and entry 3 versus 8). When a 95/5 MeOH/H_2O mixed solvent was used, the catalyst showed excellent reactivity and enantioselectivity (92% ee (*exo*), >99% ee (*endo*)) (entry 9). When the amount of H_2O in the mixed solvent was increased to 25 vol%, the yield and ee were decreased due to the decrease of dispersity of the catalyst (entry 11). From these results, 95/5 MeOH/H_2O mixed solvent was accepted as the optimized reaction solvent for the asymmetric DA reaction.



Scheme 3. Asymmetric Diels-Alder (DA) reaction catalyzed by ICCC **6**.

Table 3. Asymmetric DA reaction catalyzed by ICCC **6** [a].

Entry	Solvent	Time (h)	9			
			Yield (%) [b]	*Exo*/*Endo* [b]	ee (*Exo*) (%) [c]	ee (*Endo*) (%) [c]
1	THF	60	18	51/49	57	67
2	CH_2Cl_2	60	25	50/50	61	68
3	CH_3CN	60	29	52/48	66	74
4	MeOH	38	91	56/44	88	>99
5	H_2O	60	97	52/48	82	>99
6	Dry MeOH	38	92	44/56	85	94
7	95/5 THF/H_2O	60	87	52/48	85	97
8	95/5 CHCN/H_2O	60	96	53/47	81	92
9	95/5 MeOH/H_2O	38	99	54/46	92	>99
10	85/15 MeOH/H_2O	50	99	56/44	91	99
11	75/25 MeOH/H_2O	62	99	50/50	89	98

[a] Reactions were conducted with **7** and **8** (3 equiv.) at 25 °C using **6d$_{10}$B** (10 mol %). [b] By 1H NMR spectroscopy. [c] By GC analysis (CHIRALDEX β-PH).

2.4. Comparison of the Catalytic Activeity of a Model and Polymeric Macmillan Catalyst in an Asymmetric DA Reaction

The catalytic activity of **6** was compared with that of the corresponding MacMillan catalyst and another polymeric MacMillan catalyst in the same reaction (Table 4 and Figure 3). The original MacMillan catalyst **5Cl** exhibited excellent reactivity with 93% ee (*exo*) and 93% ee (*endo*) (entry 1). The enantioselectivity of MacMillan catalyst with *p*-toluenesulfonate **5OTs** was somewhat lower (entry 2). The linear-type polymeric catalyst in which MacMillan catalyst is immobilized at the pendant **10** (Figures S7–S9) exhibited high enantioselectivity comparable to the low molecular weight counterpart (entry 3). By contrast, the enantioselectivity of the gel-type polymeric catalyst **11** was decreased, possibly due to the steric hindrance or the conformational restriction by polymer network (entry 4). Even though the reactivity was somewhat low, the polymer microsphere-immobilized MacMillan catalyst **12d$_{20}$C** exhibited high enantioselectivity (entry 5). The ICCC **6d$_{20}$C** exhibited

higher reactivity and enantioselectivity than **12d$_{20}$C** (entry 6 versus entry 5). The enantioselectivity was comparable to the corresponding model and linear-type polymeric catalysts. The improvement of the yield was observed when low-crosslinked ICCC **6d$_{10}$B** was used due to the increase of the accessibility of substrates to the catalytic site (entry 7 versus entry 6) (Figures S19 and S20). The effect of corona length on the catalytic performance was also examined. Both the yield and enantiomeric excess were decreased when **6d$_{10}$B-200** was used (entry 8). This result indicated that the increase of steric hindrance near the catalytic site significantly affected the catalytic performance. We also surveyed the effect of the immobilization method. The covalently core-corona polymer nanosphere-immobilized MacMillan catalyst **13** developed by Z. Fu group afforded *endo*-enriched **9** in 95/5 CH_3CN/H_2O, and the catalytic activity was lower than that of **6d$_{10}$B** (entry 9) [38]. These results clearly indicated that the combination of the core-corona structure and ionic immobilization was critical to increasing the catalytic activity. The asymmetric reaction between (*E*)-2-methoxycinnamaldehyde and **8** afforded the Diels-Alder adducts **14** (Figures S13–S15) with 99% yields with 91% ee (*exo*) and 88% ee (*endo*) (Figure 4, Figures S21 and S22). The stability of ionic bonding between phenylsulfonate and chiral imidazolidinonium was also checked. We carefully checked the reaction mixture after the reaction, and no leaching of MacMillan catalyst was observed by TLC and elemental analysis. Finally, the core-corona catalyst used in entry 7 was easily and quantitatively recovered by centrifugation and could be reused twice with maintaining the catalytic performance (entry 10 and 11).

Table 4. Catalyst comparison in the asymmetric DA reaction [a].

Entry	Catalyst	Time (h)	9			
			Yield (%) [b]	*Exo*/*Endo* [b]	ee (*Exo*) (%) [c]	ee (*Endo*) (%) [c]
1	**5Cl**	8	99	57/43	93	93
2	**5OTs**	24	94	55/45	88	92
3	**10**	36	89	60/40	94	96
4	**11**	24	99	55/45	84	83
5	**12d$_{20}$C**	44	97	55/45	90	>99
6	**6d$_{20}$C**	36	94	54/46	92	>99
7	**6d$_{10}$B**	38	99 (97) [d]	54/46	92	>99
8	**6d$_{10}$B-200**	60	64	51/49	91	95
9 [e]	**13**	21	78	36/64	92	88
10 [f]	**6d$_{10}$B**	40	99	54/46	92	>99
11 [g]	**6d$_{10}$B**	43	99	55/45	91	>99

[a] Reactions were conducted with **7** and **8** (3 equiv.) in 95/5 CH_3OH/H_2O at 25 °C using 10 mol % of catalyst. [b] By 1H NMR spectroscopy. [c] By GC analysis (CHIRALDEX β-PH). [d] By isolated yield. [e] In 95/5 CH_3CN/H_2O. [f] Recovered catalyst in entry 7 was used. [g] Recovered catalyst in entry 10 was used.

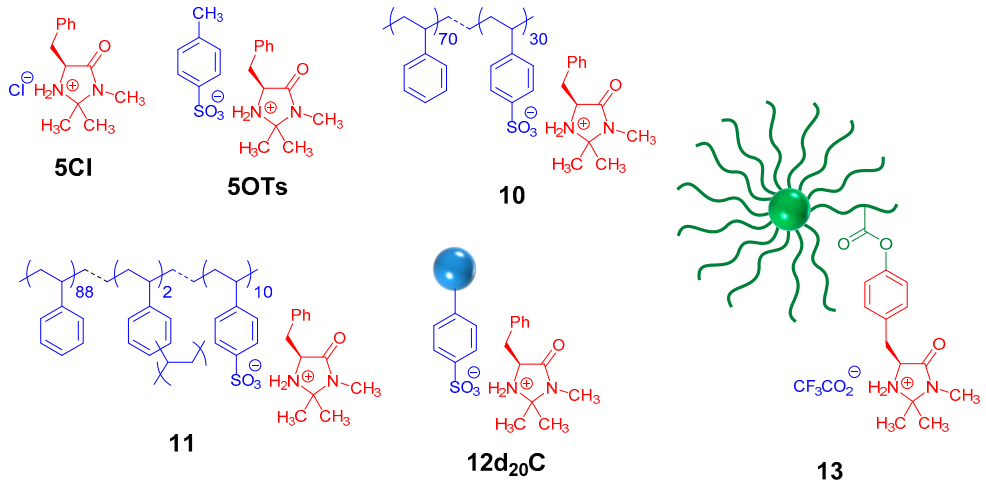


Figure 3. Model and polymeric MacMillan catalysts.

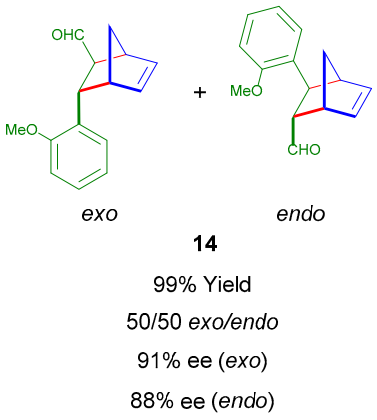


Figure 4. DA adducts **14** from (*E*)-2-methoxycinnamaldehyde and **8** catalyzed by ICCC **6**.

3. Materials and Methods

3.1. General Methods

All solvents and reagents were purchased from Tokyo Chemical Industry Co., Ltd., Wako Pure Chemical Industries, Ltd., or Sigma-Aldrich at the highest available purity and used as is unless noted otherwise. Styrene, divinylbenzene, and 4-vinylbenzylchloride were washed with NaOH, and distilled from CaH_2. 1,3-Cyclopentadine was obtained by the pyrolysis of dicyclopentadiene at 200 °C. Reactions were monitored by TLC using precoated silica gel aluminum plates (Merck 5554, 60F254, Merck & Co., Inc.). Column chromatography was performed with a silica gel (Wakogel C-200, 100–200 mesh, Wako Pure Chemical Industries, Ltd.) as a stationary phase. NMR spectra were recorded on JEOL JNM-ECS 400SS spectrometers (JEOL Ltd.) in $CDCl_3$ or DMSO-d_6 at 25 °C operating at 400 MHz (1H) and 100 MHz (^{13}C). IR spectra were recorded with a JEOL JIR-7000 FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Size exclusion chromatography (SEC) was obtained with Tosoh instrument with HLC 8020 UV (254 nm) detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 °C. Two polystyrene gel columns of bead size 10 μm (Shodex KF-806L, Showa Denko K. K.) were used. GC measurements were performed using a Shimadzu Capillary Gas Chromatograph GC-2014 equipped with a capillary column (Astec CHIRALDEX β-PH, 30 m × 0.25 mm). HPLC analyses were performed with a JASCO HPLC system composed of 3-line degasser DG-980-50, HPLC pump PU-2080, column oven CO-2065, equipped with a chiral column (CHIRALCEL OJ-H, Daicel) using hexane/2-propanol as eluent. A UV detector JASCO UV-2075 was used for the peak detection.

3.2. General Procedure for the Preparation of CCM–SO_3H

To a glass vial (6 mL) with a magnetic stirring bar, CuBr (34 mg, 0.24 mmol), benzyl chloride-functionalized polymer microsphere (0.120 g, 0.200 mmol) and Ph_2O (2 mL) were added. After the purging with Ar for 5 min, 2,2′-bipyridine (0.114 g, 0.730 mmol) was added to the mixture, and additional Ar purging for 5 min was performed. Next, styrene (0.872 g, 8.37 mmol, 70 mol %), *p*-phenyl styrenesulfonate (0.944 g, 3.63 mmol, 30 mol %), and benzyl chloride (5.6 mg, 0.044 mmol) were added to the mixture. The polymerization was conducted at 110 °C for 24 h. The solid was separated from the reaction mixture by centrifugation and washed with THF, methanol-glacial acetic acid mixed solvent (95/5, v/v), and Et_2O three times. The white solid was dried at 40 °C under vacuum for 12 h.

To a round-bottom flask (25 mL) with a magnetic stirring bar, CCM-SO_3Ph (0.334 g, 0.477 mmol of phenylsulfonate moiety), NaOH (0.059 g, 1.4 mmol), and 50/10/1 THF/MeOH/H_2O mixed solvent (9.6 mL) were added. The mixture was stirred at 50 °C for 24 h. The solid was isolated by centrifugation

and washed with CH_3OH, H_2O, and acetone three times. The white solid was dried at 40 °C under vacuum for 12 h.

To a round-bottom flask (50 mL) with a magnetic stirring bar, CCM-SO_3Na (0.284 g, 0.440 mmol of the sodium sulfonate moiety) and THF (15 mL) were added. H_2SO_4 (0.47 mL, 8.8 mmol) was slowly added to the mixture at room temperature. The reaction was stirred at room temperature for 24 h. The solid was isolated by centrifugation and washed with H_2O, CH_3OH, and acetone three times. The white solid was dried at 40 °C under vacuum for 12 h.

3.3. General Procedure for the Preparation of ICCC

To a Schlenk tube with a magnetic stirring bar, CCM–SO_3H (0.144 g, 0.118 mmol of sulfonic acid moiety) in THF (1.2 mL) and MacMillan catalyst precursor (54 mg, 0.25 mmol) in CH_3OH (1.2 mL) were added at room temperature. The reaction mixture was vigorously stirred at room temperature for 48 h. The solid was separated from the mixture by centrifugation. After washing with CH_3OH and acetone, the white solid was dried at 40 °C under vacuum for 12 h.

3.4. General Procedure for the Asymmetric DA Reaction

To a Schlenk tube equipped with a magnetic stirring bar, ionic, core-corona polymer microsphere-immobilized catalyst (0.050 mmol of catalyst), (*E*)-cinnamaldehyde (66 mg, 0.50 mmol), and CH_3OH/H_2O (95/5, v/v) mixed solvent (0.25 mL) were added. Afterwards, 1,3-cyclopentadiene (99 mg, 1.5 mmol) was added at room temperature, and the reaction mixture was stirred at 25 °C for 36 h. The catalyst was then isolated by centrifugation and washed with Et_2O three times. The solution of products was concentrated by rotary evaporator until the solution was 1 mL. For the deprotection of acetal, 2/2/1 CH_2Cl_2/H_2O/trifluoroacetic acid was then added to the solution and stirred at room temperature for 2 h. That was followed by adding saturated $NaHCO_3$ aqueous solution. After the extraction with Et_2O, the collected organic layer was washed with saturated NaCl and dried with anhydrous $MgSO_4$. The removal of $MgSO_4$ by filtration and the concentration by rotary evaporator and vacuum gave the crude. The leaching of MacMillan catalyst was checked by TLC and the elemental analysis for nitrogen content. The crude was purified by silica gel column chromatography (with 1/19 ethyl acetate/hexane) to give the Diels-Alder adducts as colorless liquids. The yield and *exo*/*endo* ratio were determined using 1H NMR spectrum through comparison of the 1H signals of aldehydes. The enantiomeric excess (ee) for *exo* and *endo* isomers was determined using GC through a comparison of the peak area ratio of isomers (Astec CHIRALDEX β-PH; injection temperature of 180 °C; detection temperature of 180 °C; the column temperature was increased from 150 °C to 180 °C with 1 °C/min; retention times: 35.1 min (*exo*(2*R*)), 35.7 min (*exo*(2*S*)), 36.6 min (*endo*(2*R*)), and 37.1 min (*endo*(2*S*))).

9: ^{1}H NMR (400 MHz, $CDCl_3$, δ = 7.26 ($CHCl_3$)): δ = 9.92 (d, *J* = 2.1 Hz, 1H), 9.60 (d, *J* = 2.1 Hz, 1H), 7.31–7.16 (m, 10H), 6.42 (dd, *J* = 5.8, 2.4 Hz, 1H), 6.34 (dd, *J* = 5.5, 1.8 Hz, 1H), 6.17 (dd, *J* = 5.5, 2.8 Hz, 1H), 6.07 (dd, *J* = 5.5, 2.4 Hz, 1H), 3.73 (dd, *J* = 4.9, 1.5 Hz, 1H), 3.34–3.33 (m, 1H), 3.24–3.22 (m, 2H), 3.14–3.13 (m, 1H), 3.10 (d, *J* = 1.22 Hz, 1H), 3.08 (d, *J* = 1.22, 1H), 3.00–2.97 (m, 1H), 2.61–2.59 (m, 1H), 1.82–1.80 (m, 1H), 1.64–1.60 (m, 2H), 1.57–1.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ = 77.1 ($CDCl_3$)): δ = 203.5, 202.8, 143.5, 142.6, 139.2, 136.5, 136.3, 133.8, 128.6, 128.1, 127.9, 127.3, 126.3, 126.2, 60.8, 59.4, 48.4, 48.4, 47.6, 47.1, 45.6, 45.5, 45.4, 45.2.

4. Conclusions

The core-corona polymer microsphere with sulfonic acid (CCM–SO_3H) **4** was prepared by the surface-initiated ATRP (SI-ATRP) of styrene and phenyl *p*-styrenesulfonate with monodispersed benzyl halide-functionalized polymer microsphere **1** prepared via precipitation polymerization as a macroinitiator, followed by the regeneration of sulfonic acid. The ionic, core-corona polymer microsphere-immobilized chiral MacMillan catalyst (ICCC) **6** was successfully synthesized by the neutralization reaction between the CCM–SO_3H **4** and MacMillan catalyst precursor **5**. The solvent effect and the structural effect of the catalyst was evaluated in the asymmetric Diels-Alder (DA) reaction

of (*E*)-cinnamaldehyde and 1,3-cyclopentadiene. We found that the increase of steric hindrance near the catalytic site by longer corona significantly decreased both the reactivity and enantioselectivity. The catalyst **6d$_{10}$B** gave the DA adducts with 99% yields and excellent ee values (92% ee for the *exo* isomer and >99% ee for the *endo* isomer). The catalytic activity of the ionic, core-corona polymer microsphere catalyst was comparable to that of the linear-type polymeric catalyst. We conclude that the design of polymeric chiral organocatalyst, including the immobilization method and the support polymer, is of significance for improving the catalytic activity. The effect of the monomer and the diameter of **6** are under investigation.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/11/960/s1: Synthesis and characterization of **10** and **12d$_{20}$C**. Figure S1: SEM image of **12d$_{20}$C**, Figure S2: FT-IR spectra of **M-S**, **M-SNa**, **M-SH**, and **12d$_{20}$C**, Figure S3: ^{1}H NMR of **sS$_{30}$** in $CDCl_3$, Figure S4: ^{13}C NMR of **sS$_{30}$** in $CDCl_3$, Figure S5: ^{1}H NMR of **sSNa$_{30}$** in $CDCl_3$, Figure S6: ^{13}C NMR of **sSNa$_{30}$** in $CDCl_3$, Figure S7: ^{1}H NMR of **10** in DMSO-d_6, Figure S8: ^{13}C NMR of **10** in DMSO-d_6, Figure S9: FT-IR spectra of **sS$_{30}$**, **sSNa$_{30}$**, **sSH$_{30}$** and **10**, Procedure for check of MacMillan catalyst leaching, Procedure for asymmetric Diels-Alder reaction of (*E*)-2-methoxycinnamaldehyde with 1,3-cyclopentadiene, Figure S10: ^{1}H NMR of crude **9** in $CDCl_3$, Figure S11: ^{1}H NMR of **9** after purification in $CDCl_3$, Figure S12: ^{13}C NMR of **9** after purification in $CDCl_3$, Figure S13: ^{1}H NMR of crude **14** in $CDCl_3$, Figure S14: ^{1}H NMR of **14** after purification in $CDCl_3$, Figure S15: ^{13}C NMR of **14** after purification in $CDCl_3$, Figure S16: ^{1}H NMR of **14** after reduction in $CDCl_3$, Figure S17: ^{13}C NMR of **14** after reduction in $CDCl_3$, Figure S18: GC chromatogram of racemic **9**. (a) Full chromatogram. (b) Expanded chromatogram, Figure S19: GC chromatogram of crude **9** (entry 7 in Table 4). (a) Full chromatogram. (b) Expanded chromatogram, Figure S20: GC chromatogram of **9** after purification (entry 7 in Table 4). (a) Full chromatogram. (b) Expanded chromatogram, Figure S21: HPLC chromatogram of crude **14** after reduction, Figure S22: HPLC chromatogram of **14** after reduction.

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