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Novel polymer-supported organocatalyst via ion exchange reaction: facile immobilization of chiral imidazolidin-4-one and its application to Diels–Alder reaction

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ABSTRACT

The polymer-supported organocatalyst was prepared by ion exchange reaction of MacMillan iminium catalyst with polymer-supported sulfonic acids. Resulting polymeric organocatalyst was effective for Diels–Alder reaction of 1,3-cyclopentadiene and *trans*-cinnamaldehyde in CH_3OH/H_2O, affording good enantioselectivity and reusability.

In addition to the metal and enzyme catalysis processes, organocatalysis has been recognized to possess high potential catalytic activity in asymmetric reaction. Unlike the conventional metal catalyst, organocatalyst has advantages in catalytic asymmetric reaction especially in the synthesis of medicines, agrichemicals, and pharmaceuticals because of metal-free catalyst which can avoid metal contamination of the product.

Among a variety of organocatalysts, one of the efficient organocatalysts which are designed at present is the chiral immidazolidin-4-one derivative **1** developed by D. W. C. MacMillan and coworkers.[1] The imminium salt can be widely applied to catalytic asymmetric reactions such as Diels–Alder reaction,[2] 1,3-dipolar cycloaddition,[3] Friedel-Crafts alkylation,[4] indole alkylation,[5] α-chlorination of aldehydes,[6] direct aldol condensation,[7] and epoxidation.[8]

From the viewpoint of reaction efficiency, polymer-immobilized organocatalysts which have been used for asymmetric reactions are of considerable interest in organic synthesis. Unfortunately, higher loading of organocatalyst than that of metal catalyst is necessary because of the catalytic activity. In addition, organocatalysis possesses difficulty in the separation and reuse as well as metal catalyst. The immobilization of organocatalysts would provide one of the solutions to the above.[9]

As well as conventional effective chiral catalysts that have been reported, the immobilization of MacMillan's iminium catalyst onto polymeric or inorganic materials has been developed by several groups. The first example was reported by Benagila and Cozzi in 2002. They prepared poly(ethylene glycol)-supported chiral imidazolidin-4-one and the salt was used for asymmetric Diels–Alder cycloaddition[10] and 1,3-dipolar cycloaddition.[11] Pihko et al. used JandaJel for the polymer-support and **1** was immobilized from *N*-position of amide moiety.[12] Ying and coworkers immobilized **1** onto siliceous and polymer-coated mesocellular forms and the resulting polymer-supported organocatalyst was used for asymmetric Friedel–Crafts alkylation and Diels–Alder reaction.[13]

To date, most immobilization of MacMillan's iminium catalyst onto crosslinked-polymer or inorganics was commonly achieved by covalent bond to support polymer. However, these immobilized catalysts have some disadvantages, including multistep preparations and loss of catalytic activity due to the modifications required to immobilized catalyst. All the above-mentioned examples involve a covalent bond between the polymer and the chiral quaternary ammonium salt. We have recently found that quaternary ammonium sulfonate is quite stable and that the polymers possessing sulfonate groups can immobilize quaternary ammonium cations through ionic bonding. We have recently developed two methods of the ionic immobilization: the first involves the polymerization of a chiral quaternary ammonium sulfonate monomer, and the second is the immobilization of a chiral quaternary ammonium salt onto a sulfonated polymer through an ion exchange reaction. These polymeric chiral quaternary ammonium salts were successfully used as polymeric organocatalysts in the asymmetric alkylation of a glycine derivative.[14] This is the first example of the immobilization of quaternary ammonium salt through an ionic interaction. The similar strategy for the immobilization of asymmetric organocatalyst was reported by Luo and Cheng.[15] They used 1% divinylbenzene cross-linked polystyrene/sulfonic acid as a polymeric support to immobilize chiral 1,2-diamine by ionic interaction. The polymeric chiral ammonium salts could be used for asymmetric direct aldol reaction.

Recently, the immobilization of organocatalyst into cray or ionic liquid has also been reported. The synthesis of layered double hydroxide-supported L-proline,[16] ionic liquid-supported L-proline,[17] and motrmorinite-supported MacMillan's iminium catalyst[18] via ion exchange has been reported and these catalysts were applied for asymmetric reaction.

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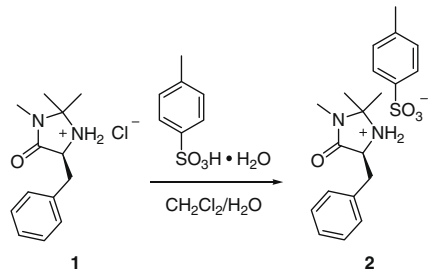


Scheme 1. MacMillan catalyst and ion exchange reaction.

The methodology of immobilization by ionic interaction has certain advantages since commercially available organocatalysts are directly used for immobilization and the reaction via ion exchange between sulfonated polymer and quaternary ammonium salt proceeded under mild condition without any side reaction. In addition, the catalytic activity of supported organocatalyst is expected as same as that of the original one.

We herein present a new strategy for polymer-supported chiral imidazolidin-4-one via ion exchange reaction.

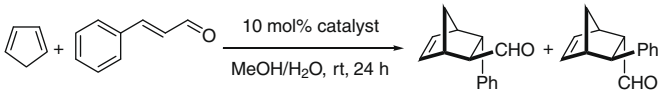
We have firstly prepared chiral imidazolidine-4-one derivative with *p*-toluenesulfonate (**2**) from the ion exchange reaction of imidazolidine-4-one hydrochloride (**1**) with *p*-toluenesulfonic acid monohydrate (Scheme 1). Three equivalents of *p*-toluenesulfonic acid monohydrate were treated with **1** in water, and subsequent extraction with dichloromethane gave **2** in quantitative yield (99%). Trace (8%) reaction was observed when *p*-toluenesulfonic acid sodium salt was used instead of *p*-toluenesulfonic acid monohydrate.

The sulfonated polymers (**P-3a**, **P-3b**, and **P-3c**) for polymer support were prepared by copolymerization of 4-vinylbenzene sulfonic acid sodium salt, styrene, and divinylbenzene under radical condition, followed by treatment with 2*N* HCl (Scheme 2). Ion exchange reaction of **P-3** with **1** proceeded in CH_2Cl_2/H_2O at room temperature for 24 h without side reaction to give the polymer-supported MacMillan's catalyst **P-4**.

The degree of ion exchange reaction, which was estimated by FT-IR and elemental analysis, was quantitative. As a result, we could immobilize MacMillan's catalyst onto support polymer via ion exchange reaction. This methodology is effective especially in the case that the further functionalization of catalyst is difficult or the corresponding chiral monomers interfere with polymerization.

The catalytic activity of the non-supported chiral organocatalyst **1** and **2** was preliminarily examined. The Diels–Alder reaction of 1,3-cyclopentadiene (**5**) and *trans*-cinnamaldehyde (**6**) was performed in methanol/H_2O (95/5, *v*/*v*) mixed solvent at room temperature for 24 h. The result is shown in Table 1. Desired chiral

Table 1
Diels–Alder reaction of 1,3-cyclopentadiene and *trans*-cinnamaldehyde[a]



5 **6** **7** (*exo*) **8** (*endo*)

Catalyst	Conv.[b] (%)	**7**:**8**[b]	ee (*exo*)[c] (%)	ee (*endo*)[c] (%)
1	>99	55:45	93	93
2	>99	55:45	88	92
P-4a	>99	55:45	84	83

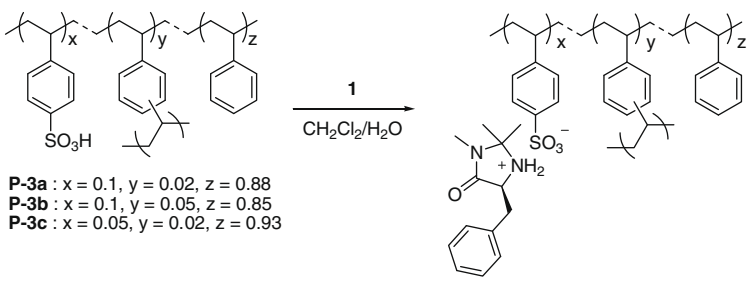
[a] 3 equiv of **5** was used.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR with (*R*,*R*)-TsDPEN (see Supplementary data).

adducts **7** and **8** catalyzed by the original catalyst **1** were obtained quantitatively and the ee values of *exo* and *endo* isomers were 93% and 93%, respectively. Imidazolidinone derivative with toluene sulfonate anion (**2**) was also found to be effective for the reaction.

Encouraged by these results, the asymmetric Diels–Alder reaction of 1,3-cyclopentadiene (**5**) and *trans*-cinnamaldehyde (**6**) catalyzed by **P-4a** was carried out in methanol/water mixed solvent at room temperature. The cycloaddition proceeded quantitatively within 24 h without side reaction. The ratio of *exo*/*endo*, **7**/**8,** is as same as those of **1** and **2**. Even though the enantioselectivity of **7** and **8** was slightly lower than that of **2** probably because of the hydrophobicity, the polymeric organocatalyst **P-4a** could be used for asymmetric Diels–Alder reaction.

The solvent effect was also briefly examined with the use of **P-4a** as a representative catalyst (Table 2). Generally, degree of swelling of a support polymer has a significant influence on the catalytic activity of corresponding polymer-supported catalyst. **P-4a** was well swollen in CH_2Cl_2 and CH_3CN, but not in H_2O. Interestingly, the conversion was moderate in CH_2Cl_2 and CH_3CN but was quantitative in neat water. In biphasic system, CH_3OH/H_2O (95/5, *v*/*v*) mixed solvent gave the desired adducts quantitatively with higher enantioselectivity. These results clearly indicated that the presence of H_2O in Diels–Alder reaction enhanced the reactivity.[19]

Table 3 shows the results of Diels–Alder reaction using some polymer-supported MacMillan's imminium catalysts at room temperature for 24 h. We found that 5 mol% crosslinked polymer-supported catalyst **P-4b** gave lower conversion compared with **P-4a** (2 mol% crosslinked polymer-supported catalyst) and lower catalyst contents of polymer-supported catalyst also decreased the conversion. **P-9** and **P-10** were synthesized by ion exchange reaction of **1** with the corresponding sulfonated polymers (Fig. 1). Even the reactivity of **P-9** was moderate, the enantioselectivity was higher. Interestingly, hydrophilic polymer-supported catalyst

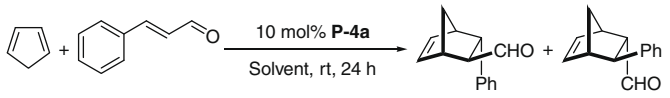


P-3a : x = 0.1, y = 0.02, z = 0.88
P-3b : x = 0.1, y = 0.05, z = 0.85
P-3c : x = 0.05, y = 0.02, z = 0.93

P-4a : x = 0.1, y = 0.02, z = 0.88
P-4b : x = 0.1, y = 0.05, z = 0.85
P-4c : x = 0.05, y = 0.02, z = 0.93

Scheme 2. Preparation of polymer-supported MacMillan catalysts.

Table 2
Diels–Alder reaction of 1,3-cyclopentadiene and *trans*-cinnamaldehyde catalyzed by **P-4a** in various solvent[a]

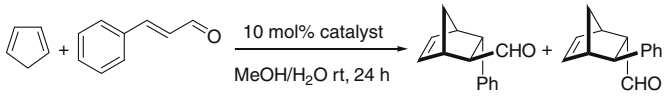


5 6 7 (*exo*) 8 (*endo*)

Solvent	Conv. (%)[b]	**7**:**8**[b]	ee (*exo*)[c] (%)	ee (*endo*)[c] (%)
CH_2Cl_2	44	57:43	67	nd
CH_3CN	67	58:42	73	72
H_2O	95	55:45	81	83
CH_3CN/H_2O	94	52:48	80	81
$MeOH/H_2O$	>99	55:45	84	83
THF/H_2O	10	52:48	nd	nd

[a] 3 equiv of **5** was used.
[b] Determined by ^1H NMR.
[c] Determined by ^1H NMR with (*R*,*R*)-TsDPEN (see Supplementary data).

Table 3
Diels–Alder reaction of 1,3-cyclopentadiene and *trans*-cinnamaldehyde catalyzed by polymer-supported chiral imidazolidin-4-one and its reusability[a]



5 6 7 (*exo*) 8 (*endo*)

Catalyst	Cycle	Conv.[b] (%)	**7**:**8**[b]	ee (*exo*)[c] (%)	ee (*endo*)[c] (%)
P-4a	1	>99	55:45	84	83
P-4a	2	99	55:45	85	87
P-4b	1	30	53:47	80	82
P-4c	1	80	55:45	85	84
P-9	1	68	56:44	91	88
P-10[d]	1	67	58:42	84	90
P-10	1	>99	56:44	88	91
P-10	2	97	57:43	88	86

[a] 3 equiv of **5** was used.
[b] Determined by ^1H NMR.
[c] Determined by ^1H NMR with (*R*,*R*)-TsDPEN (see Supplementary data).
[d] For 7 h.

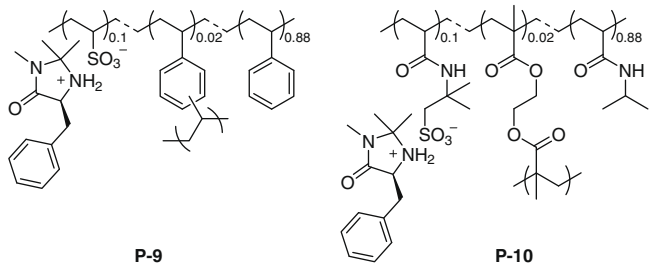


Figure 1. Hydrophilic polymer-supported MacMillan catalysts.

P-10 afforded quantitative conversion and higher enantioselectivity. 67% conversion was obtained even after 7 h by using **P-10**. These results indicated that the hydrophobicity-hydrophilicity balance of polymer-supported catalyst as well as the degree of cross-linkage and catalyst contents was important for the design of polymer-supported chiral catalyst.

After the reaction, the polymeric catalyst was easily separated and quantitatively recovered with the use of a glass filter. No elimination of the iminium catalyst moiety was observed in solution.

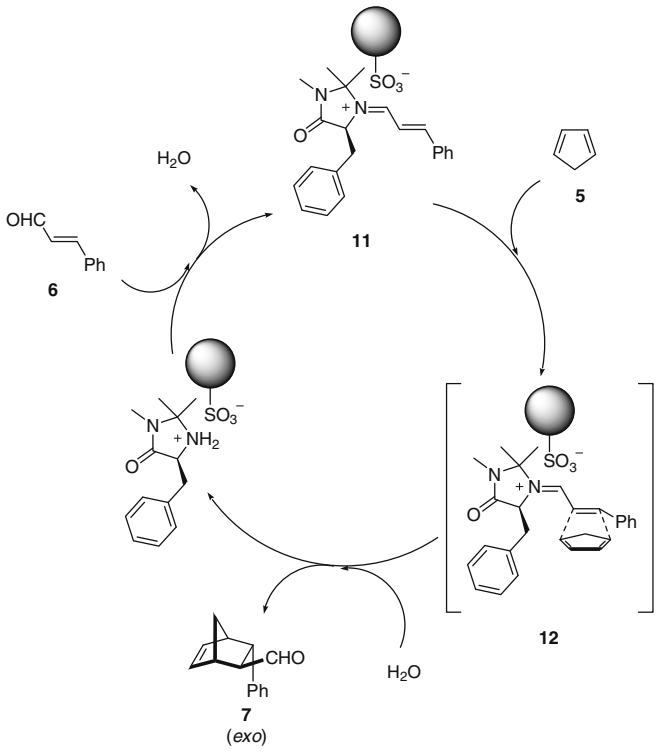


Figure 2. Plausible reaction mechanism.

The ^1H NMR of polymer-supported iminium catalyst was unchanged after the reaction. The recovered polymeric catalysts, **P-4a** and **P-10** were successfully used again for the same reaction. This showed the stability of polymeric catalyst and ionic interaction between the sulfonated anion and iminium cation.

Plausible reaction mechanism is illustrated in Figure 2. The reaction mechanism was essentially similar to that of the original MacMillan's catalyst. An activated imminium species **11** prepared from polymer-supported MacMillan's catalyst and *trans*-cinnamaldehyde can enantiomerically intercept 1,3-cyclopentadiene to form the transition state **12**. Addition of water provide the adduct **7** (or **8**) and polymer-supported MacMillan's catalyst is recovered. In the course of the reaction cycle, polymeric sulfonate must be closely located by the iminium or ammonium cation owing to the strong affinity.

In conclusion, we have shown a facile and efficient immobilization of the chiral imidazolidin-4-one salt through ionic bonds between sulfonate groups of polymer-support and iminium catalyst. In principle, any type of chiral quaternary ammonium organocatalyst can be easily immobilized by using this methodology. The Diels–Alder reaction proceeded smoothly and the diastereomeric products were obtained by using this type of polymeric catalyst. The polymeric catalyst can be reused without the need for regeneration of the catalyst.

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Supplementary data

Supplementary data (synthetic procedure and characterization data of **2**, **P-4**, **P-9**, and **P-10**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.088.

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