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COMMUNICATION

Design of main-chain polymers of chiral imidazolidinone for asymmetric organocatalysis application†‡

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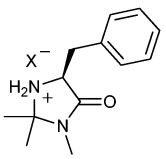
Main-chain polymers of chiral imidazolidinone were successfully synthesized by reaction of chiral imidazolidinone dimers with disulfonic acid. Chiral imidazolidinones were incorporated into the main-chain of the polymer by ionic bonding. These polymers could be used as polymeric chiral organocatalysts for asymmetric Diels–Alder reactions.

Polymer-immobilized chiral organocatalysts have attracted increasing interest in recent decades,[1] since the catalytic activity of proline as a chiral organocatalyst was reported by List and co-workers.[2] Although many kinds of polymer-immobilized chiral organocatalysts have been synthesized with the development of design and practical use of a chiral organocatalyst, most effort was paid to the development of side-chain- or end-functionalized polymeric catalysts and the investigation of main-chain polymers in which the chiral organocatalyst was incorporated into the main-chain of the polymer has been limited. Poly(amino acid)[3] and poly(peptide)[4] systems are examples of main-chain polymers with a chiral organocatalyst and these are successfully used in asymmetric reactions. The regularity of the repeating unit and the rigidity of the main-chain backbone may provide a better defined microenvironment at the catalytic sites and allow systematic modification of their catalytic properties.

Among chiral organocatalysts, chiral imidazolidinone derivatives (**1a**), originally designed and developed as chiral organocatalysts by MacMillan and co-workers, are some of the most efficient organocatalysts[5] (Fig. 1). Chiral imidazolidinone and its salt can be widely applied to catalytic asymmetric reactions such as the Diels–Alder reaction,[6] 1,3-dipolar cycloaddition,[7] Friedel–Crafts alkylation,[8] indole alkylation,[9] α-chlorination of aldehydes,[10] direct aldol reaction,[11] intramolecular Michael reaction,[12] and epoxidation.[13]

Recently, we have found that the complex prepared from a quaternary ammonium salt and a sulfonate is extremely stable in both water and organic solvent.[14] Using this knowledge, novel ionic immobilization of chiral imidazolidinones onto polymers has been developed by the reaction of polymers possessing sulfonic acid and chiral imidazolidinone.[15] Compared with the conventional immobilization by a covalent bond, the methodology of immobilization by ionic interaction has certain advantages because commercially available organocatalysts are directly used for immobilization and the reaction *via* neutralization between a sulfonated polymer and imidazolidinone proceeds under mild conditions without side reactions. The immobilization technique can be categorized as non-covalent immobilization of asymmetric organocatalysts.[16] Some facile immobilizations of imidazolidinones using ionic interaction have also been reported by several groups.[17]



1a: X = Cl
1b: X = OTs

Fig. 1 Chiral imidazolidinones.

In this communication, we applied the ionic bond formation between a chiral imidazolidinone and sulfonic acid to the synthesis of a main-chain polymer of chiral imidazolidinone and employed this as a novel self-supported chiral organocatalyst[18] for asymmetric Diels–Alder reaction.

The synthesis of main-chain polymers of chiral imidazolidinone is illustrated in Scheme 1. To synthesize the chiral imidazolidinone dimers, the phenyl group of **1a** was modified for introducing different linkages. The properties of the linkages, such as hydrophobicity, flexibility, and length, are of significance for the catalytic activity of the chiral imidazolidinone derivative. A chiral imidazolidinone derivative functionalized with a hydroxyl group (**2**) was easily obtained from (*S*)-tyrosine in >97% overall yield.[6,19] The Williamson reaction of two equivalents of **2** with dihalide (**3**) afforded chiral imidazolidinone dimers (**4a–4e**), as shown in Scheme 1.

The synthesis of chiral oxoimidazolidinium sulfonate is generally very simple and quantitative. The reaction between chiral imidazolidinone and sulfonic acid occurs readily to afford the corresponding chiral oxoimidazolidinium sulfonate in quantitative conversion. For example, reaction of **1a** and toluenesulfonic acid occurred immediately to afford chiral oxoimidazolidinium sulfonate **1b**. We then applied the oxoimidazolidinium sulfonate formation reaction to the main-chain polymer synthesis. 2,6-Naphthalenedisulfonic acid (**5**) was chosen as a disulfonic acid for this polymerization. **5** is easily

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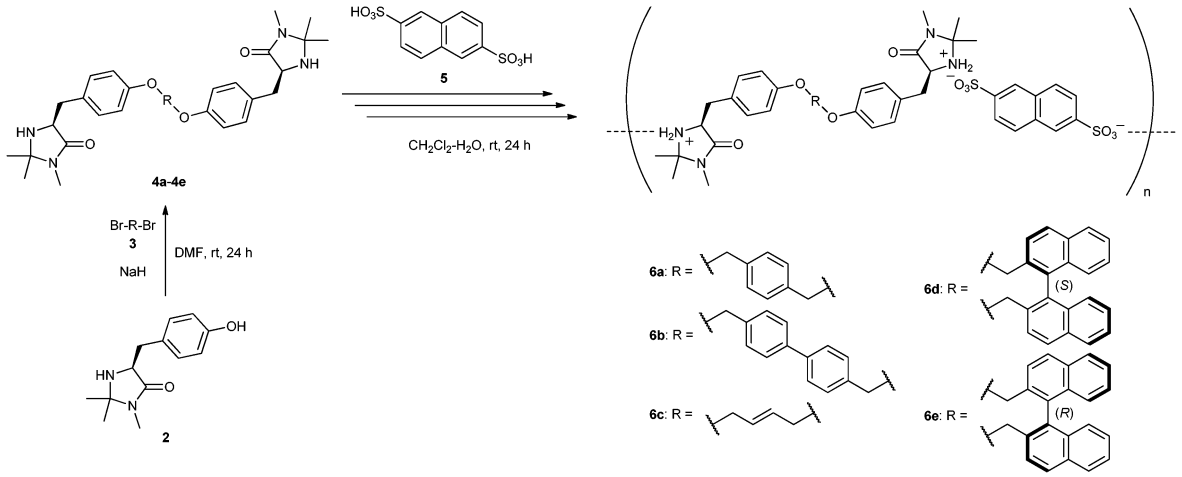


Scheme 1 Synthesis of main-chain polymers of chiral imidazolidinone.

soluble in water, while **4a–4e** are soluble in organic solvents, such as CH_2Cl_2, methanol, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). The polymerization of **4a–4e** and **5** was carried out by adding a CH_2Cl_2 solution of **4a–4e** to an aqueous solution of **5** at room temperature (Scheme 1).

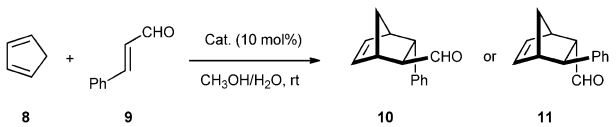
A white precipitate was obtained as soon as the CH_2Cl_2 solution of **4a–4e** was added, which indicates that the polymerization is relatively fast. Interestingly, only a slight reaction was observed when the corresponding disulfonic acid disodium salt was used instead of **5**. After 24 h, the precipitated product was thoroughly washed with dichloromethane and water to remove unreacted **4a–4e** and **5**, respectively. The yield was sufficiently high (88–99%) and the solid obtained was insoluble both in water and some organic solvents, such as CH_2Cl_2 and methanol, but was soluble in DMF or DMSO.

The ^{1}H and ^{13}C NMR spectra of the product contained both the oxoimidazolidinium and naphthalenedisulfonate moieties. The number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) of the product measured by gel permeation chromatography (GPC) are summarized in Table 1. The M_n values ranged from 19 to 93 kg mol^{-1} and the M_w/M_n values were greater than 2. The degree of polymerization calculated from M_n and the molecular weight of the repeating unit was greater than 20. These results clearly indicated that these polymerizations proceeded *via* polyaddition to afford main-chain polymers containing chiral imidazolidinone moieties **6a–6e**. We first used the original chiral imidazolidinone (**1a**) as a chiral organocatalyst for the asymmetric Diels–Alder reaction of 1,3-cyclopentadiene (**8**) and *trans*-cinnamaldehyde (**9**) as a preliminary experiment (Scheme 2).

Table 1 Characterization of the main-chain polymers of chiral imidazolidinone

Entry	Polymer	Yield (%)	M_n[a] (kg mol^{-1})	M_w[a] (kg mol^{-1})	M_w/M_n[a]	DP[b]
1	**6a**	96	58.9	193	3.28	62
2	**6b**	99	18.6	42.5	2.28	20
3	**6c**	88	26.2	89.1	3.40	30
4	**6d**	>99	92.5	240	2.59	87
5	**6e**	79	24.7	56.6	2.29	23

[a] Measured by GPC. [b] DP (degree of polymerization) = $M_{n(polymer)}/M_{n(4+5)}$.



Scheme 2 Asymmetric Diels–Alder reaction.

Desired chiral adducts **10** and **11** were obtained quantitatively and the ee values of **10** (*exo* isomer) and **11** (*endo* isomer) were 93% and 93%, respectively (entry 1 in Table 2).[6] The chiral imidazolidinone derivative with a toluene sulfonate anion (**1b**) was also found to be effective for the reaction (entry 2). We next used the chiral imidazolidinone dimers (**7a–7e**) (Fig. 2) which were quantitatively obtained by the reaction of **4a–4e** with HCl in 1,4-dioxane for the asymmetric Diels–Alder reaction. **7a–7e** were completely soluble in methanol and water mixed solvent. Chiral imidazolidinones with an achiral linker (**7a–7c**) showed similar diastereoselectivity and enantioselectivity to **1a** (entries 3–5). Interestingly, the enantioselectivity of chiral imidazolidinone with a chiral linker (**7d**) decreased possibly because of the mismatch of configuration between imidazolidinone and linker (entry 6). As expected, higher enantioselectivity was observed when the linker with the opposite configuration (**7e**) was employed (entry 7). Not only these chiral imidazolidinone hydrochloric acid salts but the chiral imidazolidinone with toluenesulfonate (**7c′**) were also effective for the reaction (entry 8). The results indicate that the catalytic activity of these chiral imidazolidinone dimers is similar to that of the original chiral imidazolidinone catalyst.

Table 2 Asymmetric Diels–Alder reaction using monomeric and dimeric chiral imidazolidinones

Entry	Catalyst	Time (h)	Conv. (%)	**10**/**11**[a] (*exo*/*endo*)	ee (**10**)[b] (%)	ee (**11**)[b] (%)
1	**1a**	7	>99	55/45	93	93
2	**1b**	7	>99	55/45	92	88
3	**7a**	4	>99	55/45	92	94
4	**7b**	4	98	56/44	92	92
5	**7c**	4	95	56/44	91	92
6	**7d**	10	>99	57/43	80	73
7	**7e**	10	>99	59/41	91	93
8	**7c′**	24	90	57/43	89	94

[a] Determined by ^{1}H NMR. [b] Determined by GC (Astec CHIRALDEX B-PH column).

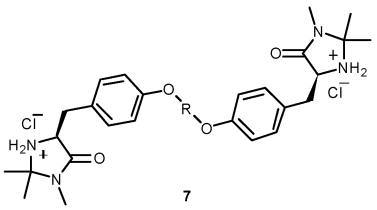


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Fig. 2 Chiral imidazolidinone dimers.

Table 3 Asymmetric Diels–Alder reactions using main-chain polymers of chiral imidazolidinone

Entry	Catalyst	Time (h)	Conv. (%)	**10**/**11**[a] (*exo*/*endo*)	ee (**10**)[b] (%)	ee (**11**)[b] (%)
1	**6a**	24	>99	57/43	90	81
2	**6b**	9	97	58/42	91	97
3	**6c**	8	95	55/45	93	97
4	**6d**	24	>99	58/42	92	81
5	**6e**	24	>99	55/45	90	89
6[c]	**6c**	24	73	56/44	94	99
7[d]	**6c**	24	92	55/45	91	95
8[e]	**6c**	48	95	57/43	92	94
9[f]	**6c**	72	83	59/41	91	95

[a] Determined by ^{1}H NMR. [b] Determined by GC (Astec CHIRALDEX B-PH column). [c] At 0 °C. [d] **6c** used in entry 3 was reused. [e] **6c** used in entry 7 was reused. [f] **6c** used in entry 8 was reused.

Encouraged by these results, these main-chain polymers of chiral imidazolidinone (**6a–6e**) were used as organocatalysts in the asymmetric Diels–Alder reaction under similar conditions in order to investigate their catalytic activity (Table 3). **6a–6e** were not soluble but were suspended in methanol and water mixed solvent, and the cycloaddition proceeded quantitatively within 24 h without side reactions. After the asymmetric Diels–Alder reaction was complete, chiral adducts **10** and **11** were easily obtained by washing the mixture with CH_2Cl_2. No destruction of the complex of imidazolidinone and sulfonic acid was detected by ^{1}H NMR and GPC. In most cases, the ratio of **10/11** (*exo*/*endo*) was similar to that using **1**. When **6a** was used as a chiral organocatalyst, the reaction occurred smoothly to afford **10** in 90% ee and **11** in 81% ee (entry 1). The enantioselectivity of **11** was increased to 97% when **6b** and **6c** were used (entries 2 and 3). In the presence of **6c**, the same reaction occurred with 95% yield, and 93% ee for **10** and 97% ee for **11** (entry 3). The enantioselectivity of polymeric organocatalyst **6c** was obviously higher than that of the model catalyst **7c**. When **6d** was employed instead of **7d**, enhancement of the enantioselectivity was observed (entry 4). In contrast, **6e** showed a lower enantioselectivity than **7e** (entry 5). Lowering the reaction temperature enhanced the enantioselectivity of **6c** (entry 6). Since these polymeric chiral catalysts were not soluble in the mixed solvent used in the reaction, these polymers could be easily separated from the reaction mixture. The recovered polymer **6c** could be reused for the same reaction with similar enantiomeric excesses, while in slowly decreasing conversions (entries 7–9). The M_n and M_w/M_n values of reused **6c** by GPC changed slightly after the reuse. The change might be caused by partial hydrolytic degradation, which may give rise to the decrease of conversion. This will probably be suppressed by using more hydrophobic (or bulkier) substituents or linkers.

In conclusion, we have designed a novel type of main-chain chiral polymer that comprises an ionic complex of a chiral imidazolidinone and sulfonic acid. The main-chain polymers of chiral imidazolidinone were successfully used as polymeric chiral organocatalysts for the asymmetric Diels–Alder reaction of *trans*-cinnamaldehyde and 1,3-cyclopentadiene. The effect of disulfonic acid on the catalytic performance is under investigation.

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