SuFEx-Click Approach for the Synthesis of Soluble Polymer-Bound MacMillan Catalysts for the Asymmetric Diels–Alder Reaction

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Abstract: Novel polymeric MacMillan catalysts were prepared from modified chiral imidazolidin-4-one monomers via sulfur(VI) fluoride exchange chemistry. The resulting polysulfates containing chiral imidazolidin-4-one units could be employed as polymeric organocatalysts for the asymmetric Diels–Alder reaction. With the use of these polysulfate catalysts, sufficient catalytic activity and enantioselectivity were obtained, which were similar to those obtained by monomeric catalysts in a homogeneous catalytic reaction. In addition, the polysulfate catalysts could be recovered and reused five times without a considerable loss of activity and selectivity.

Keywords: sulfur(VI) fluoride exchange (SuFEx); asymmetric catalysis; MacMillan catalyst; soluble polymer catalyst; recoverable organocatalyst

1. Introduction

In the past decades, polymer-bound chiral organocatalysts have attracted attention because of their distinctive benefits, such as catalyst reusability and convenient product purification [1–6]. Numerous types of polymer-bound chiral organocatalysts have been designed and synthesized, and they can be classified according to synthetic strategies for the structure of polymer products, that is, main-chain (backbone) and side-chain functionalized polymeric catalysts. Both types of polymeric chiral catalysts have been synthesized and applied to asymmetric catalysis [7].

Among efficient organocatalysts, chiral imidazolidin-4-one (1a), the first-generation MacMillan catalyst, has proven to be a powerful versatile catalyst, operating via the lowest unoccupied molecular orbital (LUMO)-lowering iminium activation [8–15]. Nonetheless, its utilization in asymmetric reactions has some deficiencies such as low turnover frequency and laborious separation. Polymeric immobilization of chiral organocatalysts provides strategic solutions to these drawbacks and is practically applicable for industrial use and flow chemistry [16–19]. There have been many approaches for immobilizing MacMillan imidazolidinone catalysts onto polymers in order to retain selectivity and maintain reusability [20]. Some examples of these include chiral imidazolidin-4-one linked to JandaJel™ [21], poly (ethylene glycol) [22], polymeric imidazolidin-4-one salt [23–27], methacrylate resin [28], poly (methylhydrosiloxane) [29], ionic liquid support [30,31], fluorous tag [32], grafted polystyrene via a Cu(I)-catalyzed click reaction [33], polycrlylate copolymer [34], organic and inorganic silica networks [35,36], multivalent polyglycerol [37], porous organic polymers [38], sulfated chitin [39], and core-corona polymer microspheres [40]. Despite these efforts, polymer-bound MacMillan catalysts commonly show lower yields and enantioselectivities than their homogeneous counterparts. Moreover, reusability issues are still present pending better solutions. This is why the development of efficient and reusable polymer-bound MacMillan catalysts has been continuously attempted. To overcome the drawbacks associated with heterogeneous catalysis, there has been great efforts to utilize soluble polymer-immobilized catalysts [41–47].
In 2014, Sharpless et al. developed a unique metal-free click reaction based on sulfur(VI) fluoride exchange (SuFEx) between an aryl fluorosulfate and an aryl silyl ether [48–52]. Through the click reaction catalyzed by an organic superbase, namely fluoride or bifluoride salt, the newly generated $S^{VI}$-O bonds produce stable linkages between two terminal moieties with comprehensive orthogonality and high efficiency. Like many other click reactions for the production of functional materials, SuFEx click chemistry has been successfully recognized as a reliable method for polymer synthesis [53–57], surface modification [58–62], and post-synthetic modification of macromolecules [63–67]. Linear polysulfate products, prepared by copolymerization in $N$-methyl-2-pyrrolidone (NMP) and $N,N$-dimethylformamide (DMF) as optimal solvents, show a high molecular weight and excellent solubility [49,53,54].

Inspired by the synthetic versatility and good solubility of the linear polysulfates, we envisioned that the solubility of polymeric organocatalysts in NMP or DMF can facilitate homogeneous catalysis, and the catalysts can be recovered by heterogeneous recycling, as is the case with soluble polymer catalysts [68–72]. In this work, we applied SuFEx click chemistry to the synthesis of polysulfate-bound MacMillan catalysts and examined both their catalytic activity and selectivity in the asymmetric Diels–Alder (DA) reaction. Furthermore, soluble polymer-bound organocatalysts can be recovered by separation through precipitation. These polymeric organocatalysts were employed effectively in homogeneous reactions and heterogeneous recycling.

2. Results and Discussion

2.1. Design of Monomeric and Polymeric MacMillan Catalysts

Three different classes of polymeric organocatalysts were designed. Each class is used to provide a specific polymer structure, such as self-supported main-chain polymers (Class I), side-chain functionalized polymers via copolymerization (Class II), and polymers obtained via post-polymerization modification (PPM) (Class III), as shown in Scheme 1. The synthetic design of the phenolic monomers of chiral imidazolidin-4-one is illustrated in Scheme 1b. To synthesize the bisphenol-type and monophenol-type chiral imidazolidin-4-one 2a and 3a, respectively, the phenyl and $N$-methyl groups of the original MacMillan catalyst were modified to accommodate aryl silyl ether or aryl fluorosulfate, the two clickable functionalities for SuFEx chemistry. All SuFEx copolymerization reactions were catalyzed by tetrabutylammonium bifluoride (TBAHF$_2$), which was found to be superior to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in terms of catalytic activity and functional group tolerance [53,54]. The bifluoride salt-mediated polycondensation required low catalyst loading (2.0 mol%) and proceeded almost quantitatively with no side reactions on chiral imidazolidin-4-one units.

![Scheme 1](image_url)

**Scheme 1.** (a) Three classes of polymeric MacMillan catalysts based on SuFEx-click polymerization. (b) Core structure modification.
2.2. Synthesis of Class I Polymeric MacMillan Catalysts

For the construction of Class I polymeric catalysts, a chiral imidazolidin-4-one derivative functionalized with aryl bis (silyl ether) 2b was obtained from commercially available N-(tert-butoxycarbonyl)-L-tyrosine (N-Boc-L-tyrosine). In addition, several types of aryl bis (fluorosulfate) linkers 4a–g were prepared (Table 1). The synthetic details of aryl silyl ether-type (2b) and aryl bis (fluorosulfate)-type monomers (4a–g) are described in the Supplementary Materials. The SuFEx-click polymerization of aryl bis (silyl ether) 2b with aryl bis (fluorosulfate) monomer 4a–g afforded the corresponding chiral imidazolidin-4-one polysulfates 5a–f in good yields, with the MacMillan catalyst monomer embedded as a repeating unit in the backbone (main-chain) of the synthetic polymers. The presence of both the MacMillan catalyst and the linker unit was confirmed by the NMR spectra of the polysulfate products. The molecular weight and polydispersity index (PDI) of the polymer products were measured by gel permeation chromatography (GPC) in tetrahydrofuran (THF) or DMF. The chiral polysulfates 5a–f were synthesized in high yields (91–97%), with moderate number-average molecular weights (Mn over 9 kDa) and good molecular weight distribution (PDI below 2), and exhibited good solubility in NMP and DMF (Table 1, entries 1–6). Only a trace amount of 5g was obtained from bis (sulfonyl fluorides) monomer 4g, presumably due to the formation of methanol-soluble low-molecular-weight products (entry 7).

To obtain a high-load polymeric organocatalyst 5h, which has no linker units embedded on the polymer backbone, we prepared three additional monomers, namely an aryl bis (fluorosulfate) monomer bearing chiral imidazolidin-4-one 2c, 2d with two functional groups in a single molecule, and its N-Boc-tyrosine precursor 2e. Product 5h was obtained via three distinct methods: cross-condensation and both late-stage and early-stage polymerization (entries 8–10). First, monomer 2b underwent cross-condensation with 2c under the same reaction conditions, giving 5h a lower yield and molecular weight than the polymer products bearing linker units 5a–f. To obtain a higher molecular-weight polymer 5h, we devised two alternative approaches for homo-condensation polymerization. One method involved late-stage polymerization in the final step using MacMillan catalyst monomer 2d, while the other involved early-stage polymerization. N-Boc-tyrosine monomer 2e underwent polymerization first, followed by two-step PPM and Boc removal from the resulting product, and N,N-ketal formation proceeded sequentially. The polymer product 5h obtained from monomer 2d possessing two functionalities by late-stage polymerization was readily soluble in NMP and DMF, reaching a higher molecular weight (Mn: 17.7 kDa) (entry 9) compared to that of 5h prepared by other synthetic approaches. We assumed that the low-molecular-weight products by early-stage polymerization were formed because of the low reaction temperature, which was needed to avoid decomposition of the N-Boc group of monomer 2e (entry 10).

2.3. Synthesis of Class II Polymeric MacMillan Catalysts

Next, for the construction of side-chain functionalized polymeric organocatalysts, we adopted a drastically different approach. The construction of two new types (Class II and III) of polymers were devised. Of these two types, the former (Class II) is equipped with a bisphenol-type polysulfate backbone produced by copolymerization of organocatalyst-attached monomers, while the latter (Class III) is composed of a polystyrene backbone functionalized by PPM. From commercially available 1,1,1-tris (4-hydroxyphenyl)ethane, we obtained bisphenol-type monomers 6a–d attached to a MacMillan catalyst unit. The synthetic details of aryl bis (silyl ether) 6b, aryl bis (fluorosulfate) 6c, and bifunctional monomer 6d are described in the Supplementary Materials. Under the same copolymerization conditions as used in the construction of the self-supported polymer 5, the SuFEx-click polymerization between aryl bis (silyl ether) monomer 6b and linker unit monomer 4a–g gave bisphenol-type polysulfates 7a–g in high yields (88–98%). The structures of 7a–g were confirmed by NMR spectra of the products and they showed lower molecular weights (Mn over 4.4 kDa) and broader molecular weight distribution than those of polymer 5 (PDI...
over 1.8), although they exhibited decent solubility in NMP and DMF, as expected (Table 2, entries 1–7).

Table 1. Synthesis of Class I polymeric MacMillan catalysts.

(Entries 1–8) Synthesis of polysulfate catalysts 5a–h from monomer 2b and linker units 4 (Cross-condensation)

(Entry 9) Alternative synthesis of 5h from monomer 2d (Late-stage polymerization with homo-condensation)

(Entry 10) Alternative synthesis of 5h by sequential PPM of poly-2e (Early-stage polymerization with homo-condensation)

| Entry | Reactant | Product | Yield (%) | Mw (Da) | Mn (Da) | PDI |
|-------|----------|---------|-----------|---------|---------|-----|
| 1     | 2b + 4a  | 5a      | 96        | 38.8 k  | 22.9 k  | 1.70|
| 2     | 2b + 4b  | 5b      | 97        | 37.4 k  | 22.7 k  | 1.64|
| 3     | 2b + 4c  | 5c      | 92        | 21.2 k  | 11.1 k  | 1.91|
| 4     | 2b + 4d  | 5d      | 96        | 35.0 k  | 22.1 k  | 1.58|
| 5     | 2b + 4e  | 5e      | 91        | 15.6 k  | 9.1 k   | 1.72|
| 6     | 2b + 4f  | 5f      | 94        | 30.8 k  | 17.8 k  | 1.73|
| 7     | 2b + 4g  | 5g      | trace     | n.d.    | n.d.    | n.d.|
| 8     | 2b + 2c  | 5h      | 91        | 7.1 k   | 4.4 k   | 1.64|
| 9     | 2d + 2e  | 5h      | 95        | 31.6 k  | 17.7 k  | 1.78|
| 10    | 2e       | 5h      | 92        | 8.0 k   | 4.9 k   | 1.63|

* Reaction conditions (entries 1–8): a mixture of monomers 2b (0.30 mmol), 4 or 2e (0.30 mmol), and TBAHF₂ (2.0 mol%) was stirred in 0.60 mL NMP at 120 °C for 8 h and analyzed by GPC. * Isolated yield by precipitation with MeOH. * Overall yield from 2e after three steps.
Table 2. Synthesis of Class II polymeric MacMillan catalysts a.

| Entry | Reactant | Product | Yield (%) b | M_w (Da) | M_n (Da) | PDI |
|-------|----------|---------|-------------|----------|----------|-----|
| 1     | 6b + 4a  | 7a      | 93          | 12.2 k   | 6.3 k    | 1.94 |
| 2     | 6b + 4b  | 7b      | 93          | 7.2 k    | 4.5 k    | 1.56 |
| 3     | 6b + 4c  | 7c      | 95          | 8.5 k    | 4.4 k    | 1.95 |
| 4     | 6b + 4d  | 7d      | 98          | 36.6 k   | 8.8 k    | 4.16 |
| 5     | 6b + 4e  | 7e      | 95          | 10.2 k   | 5.6 k    | 1.83 |
| 6     | 6b + 4f  | 7f      | 96          | 31.9 k   | 7.2 k    | 4.41 |
| 7     | 6b + 4g  | 7g      | 88          | 9.0 k    | 6.0 k    | 1.51 |
| 8     | 6b + 6c  | 7h      | 90          | 9.9 k    | 4.5 k    | 2.18 |
| 9     | 6d       | 7h      | n.r.        | n.d.     | n.d.     | n.d. |
| 10    | 2b + 6c  | 8       | 97          | 156 k    | 22.3 k   | 7.00 |

a Reaction conditions: a mixture of monomers 2b or 6b (0.20 mmol), 4 or 6c (0.20 mmol), and TBAHF<sub>2</sub> (2.0 mol%) was stirred in 0.40 mL of NMP at 120 °C for 8 h and analyzed by GPC. b Isolated yield by precipitation with MeOH.

To obtain a high-load polymeric organocatalyst 7h with no linker units on the main-chain, we prepared two additional monomers bearing chiral imidazolidin-4-one, aryl bis (fluorosulfate) 6c, and bifunctional monomer 6d. We achieved the synthesis of the anticipated polymer product from the cross-condensation of monomers 6b and 6c with acceptable properties (Table 2, entry 8). However, from homo-condensation polymerization of monomer 6d, no polymer products precipitated with the addition of MeOH, despite the complete disappearance of monomer 6d. This unexpected result was different from that of the self-supported polymer 5h, where the highest M<sub>n</sub> was achieved from the reaction of the monomer of two functionalities of 2c (entry 9). Additionally, we synthesized copolymer 8, combining two species, namely self-supported MacMillan catalyst unit 2b and side-chain functionalized bisphenol-type monomer 6c, in an alternating sequence. The cross-condensation of monomers 2b and 6c produced the anticipated copolymer 8, which revealed very poor solubility in common organic solvents including DMF, NMP, chloroform, and THF probably due to strong intramolecular hydrogen-bonding, which inevitably increases the rigidity of the polymer backbone (entry 10) [73].

2.4. Synthesis of Class III Polymeric MacMillan Catalysts

As the SuFEx-click reactions have been efficiently employed in the post-synthetic modification of macromolecules [58–67], we implemented the PPM method for the func-
tionalization of the phenolic polymers. Due to the high selectivity and conversion of phenolic hydroxy groups to aryl fluorosulfates from the reaction with sulfuryl fluoride gas, we envisioned that commercially available plastic powder, poly(4-hydroxy styrene) 9a, could be utilized for the straightforward SuFEx-mediated construction of organocatalysts. Polymer 9a has been extensively exploited as an organic transistor and photoresist material in the device industry [74,75]. For the construction of Class III polymers based on the PPM technique, we devised two synthetic pathways starting from poly (4-hydroxy styrene): first, the combination of silyl ether-modified polymer 9b with fluorosulfate-derivatized monomer 3c (Table 3, entry 1), and second, the reaction of fluorosulfate-modified polymer 9c with silyl ether-derivatized monomer 3b (entry 2). The synthetic details for the preparation of modified polymers 9b–c and their clickable monomers 3b–c are described in the Supplementary Materials. The SuFEx-click reaction of polymer 9 with its compatible monomer 3 was catalyzed with 5.0 mol% of TBAHF2 in NMP. The resulting polymer 10, verified by NMR, indicated the complete conversion of the clickable fluorosulfate or silyl ether groups in the polymer intermediates 9b–c. Both two-step post-polymerization modification pathways for SuFEx-mediated covalent attachment of the MacMillan catalyst unit 3 proceeded quantitatively to produce polymer 10 with high efficiency. Polymer 10a generated from entry 1 exhibited a higher molecular weight than 10b from entry 2. Polymers 10a and 10b exhibited low solubility in DMF and NMP.

Table 3. Synthesis of Class III polymeric MacMillan catalysts.

| Entry | Reactant | Product | M_n (Da) | M_w (Da) | PDI |
|-------|----------|---------|----------|----------|-----|
| 1     | 9b + 3c  | 10a     | 33.6 k   | 21.7 k   | 1.55|
| 2     | 9c + 3b  | 10b     | 25.7 k   | 19.2 k   | 1.34|

*Reaction conditions: a mixture of polymer 9b–c (1.5 mmol), compatible monomer 3b–c (3.0 mmol), and TBAHF2 (5.0 mol%) was stirred in 0.40 mL of NMP at 120 °C for 12 h and analyzed by GPC.

2.5. Optimization of Reaction Conditions for the Asymmetric Diels–Alder Reaction

With the various polymeric chiral imidazolidin-4-ones in hand, we evaluated the catalytic activities by means of an asymmetric DA reaction between (E)-cinnamaldehyde and cyclopentadiene. To optimize the reaction conditions, polymeric catalyst 7a was chosen because of its simple structure and scalable preparation, and several common solvents and acid co-catalysts were screened (Table 4). Both monomeric and polymeric MacMillan catalysts showed improved catalytic performance in organic solvent-H2O mixed media [26,76]. First, we examined various solvents such as H2O, MeOH-H2O (95:5), toluene-H2O (95:5), dichloromethane (DCM)-H2O (95:5), acetonitrile (ACN)-H2O (95:5), THF-H2O (95:5), and DMF-H2O (95:5). Except for H2O and MeOH-H2O (95:5 (v/v)), all the reaction conditions we examined could dissolve polysulfate catalyst 7a for homogeneous catalysis. When the catalyst was not completely soluble in the reaction media, no or low yields and moderate enantioselectivities were observed (Table 4, entries 1 and 2, respectively). In contrast to heterogeneous catalysis, homogeneous reactions with solvents such as DCM, ACN, THF, and DMF led to improved yields and good enantioselectivities (92–93% ee) for both endo and exo DA products. There was almost no diastereoselectivity between the endo and exo DA products, as was the case for many other asymmetric DA reactions.
employing recoverable MacMillan catalysts \cite{7,20}. When 10 mol\% of polysulfate catalyst 7a was used instead of 20 mol\%, the yield dropped even when the reaction time was prolonged (entry 13). When the reaction was performed at 0 °C, the enantioselectivity increased to 94% ee, while the reaction took a much longer time (48 h) to give an acceptable yield (80\%) (entry 14). When various acid co-catalysts such as trifluoroacetic acid (TFA), p-toluenesulfonic acid (p-TsOH), HCl, HClO4, methanesulfonic acid (MsOH), and HBF4 were examined, the yields and both the diastereomeric and enantioselectivities of the asymmetric reactions remain almost similar (entries 8–12). Thus, we chose DMF:H2O (95:5 (v/v)) with 20 mol\% of the polymeric MacMillan catalyst and 22 mol\% of the TFA co-catalyst at room temperature as the optimized DA reaction conditions (entry 7).

Table 4. Optimization of reaction conditions for the asymmetric Diels–Alder reaction \textsuperscript{a}.

| Entry | Solvent | Acid | Time (h) | Yield (%) | 11 \textsuperscript{c} exo/endo | exo ee (%) | \textsuperscript{d} endo ee (%) |
|------|---------|------|----------|-----------|----------------|-----------|----------------|
| 1    | H2O     | TFA  | 24       | trace     | n.d.          | n.d.      | n.d.          |
| 2    | MeOH:H2O (95:5) | TFA  | 24       | 57        | 46/53         | 63        | 59            |
| 3    | Toluene:H2O (95:5) | TFA  | 24       | 46        | 57/43         | 73        | 64            |
| 4    | DCM:H2O (95:5) | TFA  | 24       | 69        | 53/47         | 80        | 79            |
| 5    | ACN:H2O (95:5) | TFA  | 24       | 79        | 60/40         | 89        | 91            |
| 6    | THF:H2O (95:5) | TFA  | 24       | 88        | 54/46         | 91        | 94            |
| 7    | DCM:H2O (95:5) | TFA  | 24       | 92        | 51/49         | 92        | 93            |
| 8    | DMF:H2O (95:5) | p-TsOH | 24     | 85        | 55/45         | 91        | 91            |
| 9    | DMF:H2O (95:5) | HCl   | 24       | 92        | 56/44         | 90        | 89            |
| 10   | DMF:H2O (95:5) | HClO4 | 24       | 82        | 52/48         | 89        | 88            |
| 11   | DMF:H2O (95:5) | MsOH  | 24       | 84        | 53/47         | 88        | 91            |
| 12   | DMF:H2O (95:5) | HBF4  | 24       | 79        | 56/44         | 91        | 89            |
| 13   | DMF:H2O (95:5) | TFA  | 24       | 62        | 53/47         | 92        | 92            |
| 14   | DMF:H2O (95:5) | TFA  | 48       | 80        | 51/49         | 94        | 94            |

\textsuperscript{a} Reaction conditions: 0.050 mmol (49 mg, 20 mol\%) of the polysulfate catalyst 7a, 0.055 mmol (22 mol\%) of the acid co-catalyst, 0.25 mmol (31 \mu L, 1 equiv) of (E)-cinnamaldehyde, and 1.25 mmol (0.11 mL, 5 equiv) of cyclopentadiene at room temperature in 0.50 mL of solvent. \textsuperscript{b} Yield of isolated product. \textsuperscript{c} Determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{d} Determined by HPLC with a chiral OJ-H column after converting the products to the corresponding alcohol. \textsuperscript{e} The reaction was performed with 10 mol\% of polysulfate catalyst 7a and 11 mol\% of TFA. \textsuperscript{f} The reaction was performed at 0 °C.

2.6. Asymmetric Diels–Alder Reaction with Class I–III Organocatalysts

With the optimized homogeneous reaction conditions, polymeric MacMillan catalysts 5, 7, and 10 were investigated in asymmetric DA reactions. With the first two classes of polymeric MacMillan catalysts 5a–f and 7a–g, interestingly, their catalytic activities and enantioselectivities were comparably satisfactory, despite differences in their backbone structures. DA reactions using 5a–f and 7a–g all proceeded in good yields (86–93\%) and enantioselectivities of the desired product 11 (88–93\% ee for exo and endo DA products) (Table 5, entries 4–9 and 13–19, respectively). Comparing the yields and enantioselectivities of the DA product 11 with those of monomeric catalysts 2a, 3a, and 6a as references (entries 1–3), we conclude that the catalytic effectiveness of the polysulfate MacMillan catalysts was comparable to that of the monomeric organocatalysts, except for the slightly lower enantioselectivities. However, the enantioselectivities of the DA reactions employing high-load polysulfate organocatalysts with no linker units embedded, that is, 5h and 7h, were lower than those of catalysts with linker units such as 5a–f and 7a–g (84–86\% ee for exo and 82–88% ee for endo, entries 10–12 and 20). In the case of the reaction with polymeric catalyst 10 obtained by the SulFEx-mediated PPM method with compact immobilization density on a polyphenolic support, the catalytic activity was lower, giving 64\% and 69\%
yields, and product enantioselectivities dropped to 61% and 66% ee for exo and 67% and 69% ee for endo (entries 21 and 22). This is presumably due to the sterically crowded catalytic sites and the partial insolubility of the catalysts. It was observed that the catalytic performance was not directly correlated with the molecular weight (M<sub>n</sub>) but was more strongly affected by the microenvironment of the catalytic site on the polymer. These findings are in accordance with a previous report by Gutmann et al. [36,77].

Table 5. Asymmetric Diels–Alder reaction with monomeric 2a, 3a, and 6a, and polymeric organocatalysts Class I–III.

| Entry | Catalyst | Calculated Catalysts' Loading (mmol/g) | Yield (%) | 11<sup>c</sup> | exo ee (%) | endo ee (%) |
|-------|----------|----------------------------------------|-----------|--------------|------------|------------|
|       |          | Monomeric organocatalysts               |           |              |            |            |
| 1     | 2a       | 3.06                                   | 95        | 56/44        | 95         | 92         |
| 2     | 3a       | 3.62                                   | 96        | 56/44        | 97         | 96         |
| 3     | 6a       | 1.55                                   | 96        | 49/51        | 97         | 97         |
|       |          | Class I                                |           |              |            |            |
| 4     | 5a       | 1.53                                   | 90        | 53/47        | 90         | 89         |
| 5     | 5b       | 1.47                                   | 91        | 54/46        | 89         | 90         |
| 6     | 5c       | 1.50                                   | 86        | 56/44        | 87         | 87         |
| 7     | 5d       | 1.39                                   | 89        | 48/53        | 91         | 92         |
| 8     | 5e       | 1.64                                   | 87        | 57/43        | 89         | 88         |
| 9     | 5f       | 1.57                                   | 91        | 52/48        | 92         | 92         |
| 10    | 5h<sup>e</sup> | 2.57                              | 79        | 55/45        | 86         | 86         |
| 11    | 5h<sup>f</sup> | 2.57                              | 73        | 56/44        | 85         | 86         |
| 12    | 5h<sup>g</sup> | 2.57                              | 78        | 54/46        | 84         | 88         |
|       |          | Class II                               |           |              |            |            |
| 13    | 7a       | 1.03                                   | 92        | 51/49        | 92         | 93         |
| 14    | 7b       | 1.00                                   | 93        | 54/46        | 92         | 92         |
| 15    | 7c       | 1.02                                   | 89        | 51/49        | 90         | 91         |
| 16    | 7d       | 0.96                                   | 92        | 53/47        | 89         | 92         |
| 17    | 7e       | 1.08                                   | 88        | 60/40        | 89         | 90         |
| 18    | 7f       | 1.05                                   | 90        | 54/46        | 91         | 91         |
| 19    | 7g       | 1.08                                   | 88        | 53/47        | 93         | 93         |
| 20    | 7h       | 1.41                                   | 93        | 50/50        | 86         | 85         |
|       |          | Class III                              |           |              |            |            |
| 21    | 10a      | 2.18                                   | 64        | 52/48        | 61         | 67         |
| 22    | 10b      | 2.18                                   | 69        | 51/49        | 66         | 69         |

<sup>a</sup> Reaction conditions: 0.050 mmol of organocatalyst (20 mol%), 0.085 mmol of TFA (22 mol%), 0.25 mmol of (E)-cinnamaldehyde, and 1.25 mmol of cyclopentadiene at r.t. in 0.50 mL of DMF:H<sub>2</sub>O (95:5) for 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> Determined by HPLC with the OJ-H column after reduction to the corresponding alcohol. <sup>d</sup> Monomer mass yield of isolated product. <sup>e</sup> 5h from Table 1, entry 8. <sup>f</sup> 5h from Table 1, entry 9. <sup>g</sup> 5h from Table 1, entry 10.

2.7. Substrate Scope of Asymmetric Diels–Alder Reaction with Chiral Polysulfate Organocatalyst 7a

Next, to explore the versatility of the polysulfate MacMillan catalyst, we extended the scope of the asymmetric DA reaction between several α,β-unsaturated aldehyde substrates such as dienophiles, cyclopentadiene, and diphenylisobenzofuran. Under the same reaction conditions employing polymeric MacMillan catalyst 7a, these aldehyde substrates were converted to the respective products in good yields (76–97%) and enantioselectivities (52–95% ee for exo and 82–95% ee for endo) (Table 6). In the case of 1,3-diphenylisobenzofuran as a diene, high exo-selectivity was observed with 85% ee for the exo-product.
Table 7. Substrate scope of the asymmetric Diels–Alder reaction with chiral polysulfate organocatalyst 7a.

| Entry | Diene | R | Time (h) | Yield (%) | 11' exo/endo | exo ee (%) | endo ee (%) |
|-------|-------|---|----------|-----------|-------------|-----------|------------|
| 1     | Cyclopentadiene | p-F-C₆H₄ | 20 | 97 | 51/49 | 93 | 93 |
| 2     | Cyclopentadiene | p-Cl-C₆H₄ | 20 | 95 | 54/46 | 91 | 95 |
| 3     | Cyclopentadiene | p-Br-C₆H₄ | 24 | 96 | 51/49 | 90 | 92 |
| 4     | Cyclopentadiene | p-NO₂-C₆H₄ | 18 | 90 | 53/47 | 95 | 94 |
| 5     | Cyclopentadiene | o-NO₂-C₆H₄ | 18 | 93 | 42/58 | 52 | 82 |
| 6     | Cyclopentadiene | Me | 24 | 76 | 53/47 | 64 | 81 |
| 7     | 1,3-Diphenylisobenzofuran | Me | 16 | 85 | 90/10 | 84 | n.d. |

* Reaction conditions: 0.10 mmol of the polysulfate catalyst 7a (20 mol%), 0.11 mmol of TFA (22 mol%), 0.50 mmol of dienophile, and 2.5 mmol of diene at r.t. in 1.0 mL of DMF:H₂O (95:5), r.t., time.

2.8. Comparisons of Soluble Polymeric MacMillan Catalysts for the Asymmetric Diels–Alder Reaction

We compared the results of soluble polymeric MacMillan catalysts 7a with those of other reported soluble and reusable MacMillan catalysts for asymmetric DA reactions (Table 7). The results indicate that polymeric MacMillan catalysts generally show lower turnover numbers (TON) than that of the monomer catalyst. Notably, the enantioselectivities observed from the reactions employing catalyst 7a were among the highest of those obtained from the reactions using polymeric organocatalysts (entry 5). In addition, reactions using polymeric catalyst 7a showed acceptable TON when compared with those of other reported polymeric catalysts.

Table 7. Comparisons of various soluble polymeric MacMillan catalysts for asymmetric Diels–Alder reaction between (E)-cinnamaldehyde and cyclopentadiene.

| Entry | Immobilization Strategy | Catalysts' Loading (mol%) | Time (h) | Temperature (°C) | Yield (%) | TON | exo endo | exo ee (%) | endo ee (%) |
|-------|-------------------------|---------------------------|----------|-----------------|-----------|-----|---------|------------|------------|
| 1     | PEG₅₀₀₀ monomethyl ether | 10 | 40 | 24 | 67 | 6.7 | 6/94 | 86 | 92 |
| 2     | Poly(methyl hydrosiloxane) (PMHS) | 10 | 40 | 0 | 65 | 6.5 | 55/45 | 92 | 93 |
| 3     | Polycrystalline copolymer | 5 | 24 | r.t. | 92 | 18.4 | 1/1.2 | 68 | 79 |
| 4     | Chiral organosilica polymer (ChiOSP) | 20 | 36 | r.t. | 94 | 4.7 | 1.1/1 | 90 | 86 |
| 5     | Linear polysulfate 7a | 20 | 24 | r.t. | 92 | 4.6 | 51/49 | 92 | 93 |

* DA reaction between acrolein and 1,3-cyclohexadiene.

2.9. Recycling Test of Polysulfate Organocatalysts in Asymmetric Diels–Alder Reaction

Confirming that homogeneous catalytic reactions using polymeric organocatalysts were efficacious, we further studied the recyclability of the catalysts. The copolymer catalysts 5b and 7a were selected for the repetitive asymmetric DA reaction, providing product 11. After each reaction cycle in DMF:H₂O, the used catalyst was recovered by simple precipitation with the addition of diethyl ether, followed by decantation of the supernatant containing the aldehyde product, and washing and drying of the precipitated polymer. After drying, the recovered polymeric organocatalyst was used directly in the next catalytic cycle. The visual overview of the recycling procedures is depicted in the Supplementary Materials.

As shown in Table 8, the recovered polymers 5b and 7a could be reused for the iterative reactions. In the case of the reactions with catalyst 5b, the yields and enantioselectivities of the recycle reaction were maintained up to the fourth reuse of the catalyst and then decreased to a noticeable degree at the fifth (Table 8, entries 1–5). In the case of the reactions employing catalyst 7a, the yields and enantioselectivities were maintained until the sixth
recycle (entries 6–11). No obvious structural change or loss of the MacMillan catalyst unit in the polymer was detected by Fourier-transform infrared spectroscopy (FT-IR) and $^{13}$C NMR after the fourth and fifth cycles. Presumably, the results could be triggered not only by catalyst loss during the recovery process but also by partial and gradual hydrolytic degradation of the N,N-ketal of the imidazolidin-4-one moiety, which may induce a gradual decline in the catalytic activity and enantioselectivity.

Table 8. Recycle use of polysulfate organocatalysts 5b and 7a in the asymmetric Diels–Alder reaction.

| Entry | Catalyst | Cycle | Time (h) | Yield (%) $^b$ | 11 $^c$ | exo ee (%) $^d$ | endo ee (%) $^d$ |
|-------|----------|-------|----------|---------------|---------|----------------|----------------|
| 1 $^a$ | 5b       | Fresh | 24       | 91            | 54/46   | 89             | 90             |
| 2     | 5b       | 1st   | 24       | 92            | 53/47   | 89             | 90             |
| 3     | 5b       | 2nd   | 24       | 87            | 54/44   | 89             | 89             |
| 4     | 5b       | 3rd   | 36       | 86            | 55/44   | 87             | 87             |
| 5     | 5b       | 4th   | 36       | 77            | 54/46   | 81             | 81             |
| 6 $^a$ | 7a       | Fresh | 24       | 92            | 51/49   | 92             | 93             |
| 7     | 7a       | 1st   | 24       | 92            | 52/48   | 92             | 92             |
| 8     | 7a       | 2nd   | 24       | 88            | 52/48   | 89             | 90             |
| 9     | 7a       | 3rd   | 24       | 83            | 52/48   | 88             | 89             |
| 10    | 7a       | 4th   | 30       | 85            | 51/49   | 87             | 88             |
| 11    | 7a       | 5th   | 36       | 80            | 51/49   | 86             | 86             |

$^a$ Reaction conditions: 0.10 mmol of the polysulfate catalyst (20 mol%), 0.11 mmol of TFA (22 mol%), 0.50 mmol of (E)-cinnamaldehyde, and 2.5 mmol of cyclopentadiene at r.t. in 1.0 mL of DMF:H$_2$O (95:5, v/v). $^b$ Yield of isolated product. $^c$ Determined by $^1$H NMR spectroscopy. $^d$ Determined by HPLC with the OJ-H column after reduction to the corresponding alcohol.

3. Materials and Methods

3.1. General Remarks

All solvents and reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA), Alfa Aesar (Tewksbury, MA, USA), Tokyo Chemical Industry Co. (Tokyo, Japan), and Samchun Chemicals (Seoul, Korea), and were used without further purification unless otherwise noted. Sulfuryl fluoride gas (purity 99%) was purchased from SynQuest Laboratories (Alachua, FL, USA) and used as received. Tetrabutylammonium bifluoride (TBAHF$_2$) was prepared in a large scale according to the method described in the literature [78]. Reactions were monitored by thin layer chromatography (TLC), which was performed using silica gel 60 F$_{254}$ coated on an aluminum sheet (E. Merck, Art. 5554). Chromatograms were visualized using an UV lamp and/or stained with 2% ninhydrin/ethanol solution and KMnO$_4$ solution. Column chromatography was performed on silica gel (Merck. 7734 or 9385 Kiesel gel 60) and the eluent is mentioned in each procedure. The $^1$H, $^{13}$C, and $^{19}$F NMR spectra were measured with the Agilent 400-MR DD2 Magnetic Resonance System ($^1$H, 400 MHz; $^{13}$C, 100 MHz; $^{19}$F, 376 MHz) (Santa Clara, CA, USA). Chemical shifts were measured as part per million (δ values) using tetramethysilane as an internal standard at the probe temperature in CDCl$_3$, DMF-d$_7$, and acetone-d$_6$. Coupling constants are provided in Hz with the following spectral pattern designations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; and br, broad. Gas chromatography–mass spectrometry (GC–MS) analyses were performed using the Agilent Technologies 7820A series with an HP-5 capillary column and an Agilent 5977E network mass-selective detector (MSD). High-performance liquid chromatography (HPLC) analysis was carried out on a Hewlett-Packard 1100 system, composed of an autosampler, quaternary pump, photodiode array detector (DAD), and Agilent ChemStation software. UV detection was monitored at 254 nm using a Chiralcel OJ-H or Chiralpak AD-H column (25 cm). Liquid
chromatography–mass spectrometry (LC–MS) was performed on the Agilent 6100 Series LC/MSD with LC (Agilent 1200 infinity) and Agilent 6120 quadrupole LC/MS (electrospray ionization, ESI). The separation was carried out on a C18 Shiseido Capcell pak column (5 μm, 4.6 mm i.d. × 25 cm) with 0.1% trifluoroacetic acid in water (A) and acetonitrile (B) as the mobile phase at a flow rate of 1 mL/min at ambient temperature. High-resolution mass spectrometry (HRMS) data were obtained from the Organic Chemistry Research Center at Sogang University with a Bruker compact™ spectrometer. Gel permeation chromatography (GPC) for polymer molecular weight analysis was carried out with a Thermo Dionex HPLC, Ultimate 3000 RI System (quaternary pump, refractive index detector, and UV detector) and Shodex GPC GF-806L or KD-806M column eluted with tetrahydrofuran or N,N-dimethylformamide (GPC grade, Honeywell Burdick & Jackson, Charlotte, NC, USA). Samples were diluted in 0.10–0.20 wt% with THF or DMF and filtered with a 0.20 μm polytetrafluoroethylene (PTFE) membrane filter before injection into the GPC. Optical rotation was obtained at 589 nm using a JASCO P-1030 automatic polarimeter. Fourier transform infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum Two spectrophotometer (Waltham, MA, USA) for solid and liquid samples, at νmax cm−1.

3.2. Synthesis of Class I Polymeric MacMillan Catalysts

Bis (tert-butyldimethylsilyl ether) 2b (0.30 mmol) and bis (fluorosulfate) or bis (fluorosulfonate) 4a–4h or 2c (0.30 mmol) was added to a dried vial with stirring bar. The tube was purged with Ar gas and then charged with anhydrous NMP (0.60 mL) and TBAHF2 (2.0 mol%). The mixture was heated to 120 °C with stirring for 8 h under an inert atmosphere. The solution was added slowly by pipette into a flask containing MeOH (25 mL) with vigorous stirring to precipitate the desired polysulfates 5a–5f and 5h. The precipitate was then isolated by filtration, washed with MeOH (20 mL), and dried under high vacuum at 50 °C to obtain a yellow to yellowish-brown powder.

3.3. Synthesis of Class II Polymeric MacMillan Catalysts

Bis (tert-butyldimethylsilyl ether) 6b or 2b (0.20 mmol) and bis (fluorosulfate) or bis (fluorosulfonate) 4a–4g, 6c (0.20 mmol) was added to a dried vial with stirring bar. The tube was purged with argon gas and then charged with anhydrous NMP (0.40 mL) and TBAHF2 (2.0 mol%). The mixture was heated to 120 °C with stirring for 8 h under an inert atmosphere. The solution was added slowly by pipette into a flask containing methanol (30 mL) with vigorous stirring to precipitate the desired polysulfonate 7a–7h and 8. The precipitate was then isolated by filtration, washed with methanol (20 mL), and dried under high vacuum at 50 °C, to obtain a yellow to yellowish-brown powder.

3.4. Synthesis of Class III Polymeric MacMillan Catalysts

TBAHF2 (5.0 mol%) was added to a stirred solution of modified polymer 9b or 9c (1.5 mmol), aryl fluorosulfate 3c, or aryl silyl ether organocatalyst monomer 3b (3.0 mmol) in NMP (4.0 mL). The reaction mixture was stirred at 120 °C for 12 h. The residue was precipitated in MeOH to give the desired product of 10a or 10b as a yellowish powder.

3.5. General Procedure for the Asymmetric Diels–Alder Reaction and Recycling

Trifluoroacetic acid (8.4 µL, 0.11 mmol, 22 mol%) was added to a stirred solution of the polymer catalyst (0.10 mmol, 20 mol%) in DMF:H2O (95:5 (v/v), 1.0 mL) and the mixture was stirred for 10 min at room temperature. Cinnamaldehydes (0.50 mmol) and cyclopentadiene (0.21 mL, 2.50 mmol) were added sequentially. The mixture was vigorously stirred at room temperature and monitored by TLC. When the reaction was complete, diethyl ether (5.0 mL) was added to the stirred mixture to precipitate the polymer catalyst and the organic solution was separated by decantation. After evaporation of the decanted solution using a vacuum pump, the residue was purified by flash column chromatography (hexane/ethyl acetate as an eluent) to give the aldehyde product. The precipitated polymer was washed with diethyl ether (5.0 mL), dried under high vacuum.
at 40 °C, and subsequently reused. The ratio of exo and endo isomers was determined by 1H NMR spectroscopy. The products were reduced to the corresponding alcohols with sodium borohydride and enantiomeric excess was determined by HPLC using a Daicel CHIRALCEL® OJ-H, CHIRALPAK® AD-H, CHIRALPAK® IA, or CHIRALCEL® OD-H column.

4. Conclusions

In conclusion, by employing robust and versatile SuFEx-mediated polymerization, we developed three novel types of polymeric MacMillan catalysts with main or side-chains that are functionalized via linear copolymerization or PPM. These polymeric catalysts could be effectively applied to the asymmetric DA reaction under homogeneous reaction conditions. Out of the three class polymeric catalysts, Class I and II exhibited similar catalytic activities and enantioselectivities, while Class II catalysts performed comparatively more satisfactorily for their better precipitation capability, which enabled them to be recycled. As expected, the polymeric organocatalysts could be reused at least five times by heterogeneous separation without losing their structural integrity as a chiral organocatalyst. We point out that the SuFEx-mediated copolymerization strategy can be a powerful bottom-up technique for immobilizing various chiral secondary amine organocatalysts.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11091044/s1, Figure S1: Process diagram for the asymmetric Diels–Alder reaction and solid-liquid biphasic separation, in which an excess of the poor solvent (5.0 mL of diethyl ether) is added to precipitate the soluble polysulfate-bound MacMillan catalyst; Figure S2: (a) FT-IR spectra of polymer catalyst 5b as the fresh catalyst (below) and the recovered polymer catalyst (above) after fifth-time catalytic reactions, and (b) FT-IR spectra of polymer catalyst 7a as the fresh catalyst (below) and the recovered polymer catalyst (above) after sixth-time catalytic reactions; Figure S3: 13C NMR spectra of polymer catalyst 5b as the fresh catalyst (below) and the recovered polymer catalyst (above) after fifth-time catalytic reactions; and Figure S4: 13C NMR spectra of polymer catalyst 7a as the fresh catalyst (below) and the recovered polymer catalyst (above) after sixth-time catalytic reactions.

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