Molecular design of chiral polymeric organocatalysts and their applications in asymmetric catalysis

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DOCTOR OF ENGINEERING

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A b s t r a c t

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(800 words)

Main-chain chiral polymeric organocatalysts have been designed and synthesized from the readily available and inexpensive cinchona alkaloids. Cinchona alkaloids are available in pseudoenantiomeric forms such as quinine, quinidine, cinchonine and cinchonidine. They are among the most privileged chirality inducer in the area of asymmetric catalysis. Due to their diverse chiral skeletons and functionalities several modifications have been done by several groups. The quinuclidine nitrogen of the cinchona alkaloid can easily be quaternized and the OH group also can be modified. The double bond of the cinchona alkaloid also can be hydrogenated and dehydrogenated. Thiol-ene click reaction and Heck coupling reaction also can be carried out at the double bond of cinchonidine. Based on versatile functionalities of cinchona alkaloid, several groups have reported monomeric, dimeric and polymeric organocatalyst containing quaternary ammonium salts.

Cinchona derived quaternary ammonium salts are one of the most popular organocatalysts in the field of asymmetric catalysis especially for the synthesis of unnatural α-amino acids. Although several works have been done with the side-chain chiral polymeric organocatalyst only a limited number of investigations have been carried out for the development and application of main-chain chiral polymeric organocatalyst. Traditionally, the polymer-supported chiral catalysts are prepared by anchoring highly enantioselective monomeric catalysts to flexible and sterically irregular polymer supports. Although a few enantioselective polymer catalysts have been obtained in this manner, a significant reduction of enantioselectivity is often observed after a monomeric catalyst is attached to a polymer support. This indicates that the microenvironment of the polymer is very important for the stereoselectivity of the catalyst. Because of the stereo-irregularity and flexibility of the traditional polymeric chiral catalysts, their catalytic sites do not have well defined microenvironment. It is very difficult to systematically modify the microenvironment of the catalytic sites in these polymers to improve their enantioselectivity. The microenvironment of the catalytic sites in rigid and sterically regular polymers can be systematically modified to produce highly enantioselective polymeric catalysts. The enantioselectivity of a monomeric catalyst can be maintained in a polymer catalyst by the use of a rigid and sterically regular polymer backbone. Compared with the traditional polymer-supported catalysts for which flexible and sterically irregular polymers are used, this new approach can better preserve the catalytic environment of the monomeric catalysts in the polymer as long as the catalytically active species are not aggregates of the monomers. These strategies not only make it possible to obtain easily reusable and highly enantioselective polymeric catalysts for many asymmetric reactions, but also can be further extended to construct polymeric chiral catalysts that are capable of multiple asymmetric catalytic reactions by incorporating different catalytic species in a polymer chain.

Therefore, designing of main-chain chiral polymeric organocatalyst is an important field of research in asymmetric catalysis for obtaining enantiopure compounds. To investigate the effect of main-chain chiral polymeric organocatalyst in asymmetric catalysis, we have designed several types of main-chain chiral polymers using different polymerization methods and applied them in asymmetric benzylation of glycine derivative and asymmetric epoxidation of chalcones.

In this thesis, chapter 1 describes the structural features of cinchona alkaloids and chapter 2 describes the general introduction and background of this thesis work.

Chapter 3 and 4 describe the novel synthesis of main-chain chiral ionic polymer using *ion exchange polymerization* and their application in asymmetric benzylation of glycine derivative. Cinchona derived dimeric quaternary ammonium salts and different types of disulfonate reacted together to give main-chain *ionic polymer*. The synthesized main-chain ionic polymers were employed as novel polymeric organocatalyst in asymmetric benzylation of glycine derivative to give a high enantioselectivities. Furthermore, the polymeric catalyst was recovered and reused.

Chapter 5 describes the synthesis of main-chain chiral polymers by the reaction between cinchona derived dimeric quaternary ammonium salts and aryl diiodide using *Heck coupling polymerization*. To our knowledge, there have been no reports on the application of main-chain chiral polymer synthesized by Heck reaction. In this work, we have employed the main-chain chiral polymers synthesized by *Heck coupling polymerization* as a novel polymeric organocatalyst in asymmetric benzylation of glycine derivative. In this case also quite a high enantioselectivity was obtained and the polymeric catalyst was recovered and reused.

Chapter 6 describes the synthesis of main-chain *ionic polymer* by the reaction of cinchonidine dimers and disulfonates. Cinchodine dimers were modified by iodobenzene at the double bond of cinchonidine using Heck coupling and then the modified cinchonidine dimer utilized in *ion exchnage polymerization* with different types of disulfonates to obtain novel type of main-chain *ionic polymer*. The polymers synthesized were applied in asymmetric benzylation of glycine derivative to give high yields and enantioselectivites.

Chapter 7 describes the synthesis of main-chain chiral polymers using *quternization polymerization* between cinchonidine dimer and dihalide. The cinchonidine dimer was synthesized by Heck coupling of cinchonidine and 4,4'-diaryldiiodide. 2 equivalents of cinchonidine reacted with 1 equivalent of 4,4'-diaryldiiodide to give a novel cinchonidine dimer where two cinchonidine units are connected through the double bond with 4,4'-diaryldiiodide. The polymers were applied in asymmetric benzylation of glycine derivative.

Chapter 8 describes the application of main-chain chiral polymeric organocatalyst in asymmetric epoxidation of chalcones. As the asymmetric epoxidation of chlacones are very sensitive to the catalyst structure, oxidant, solvent, temperature and base. Several types of main-chain chiral polymers have been screened in this work to find a suitable catalyst which gives higher enantioselectivity. Although several works have been done with monomeric dimeric and polymer-supported chiral organoctalyst, there has been almost no report on the application of main-chain chiral polymeric organocatalyst in asymmetric epoxidation of chalcones. In this work, for the first time we have applied main-chiral polymeric organocatlyst in asymmetric epoxidation of chalcones.

Chapter 9 describes the general summary of this thesis work.

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Dedicated to my teachers

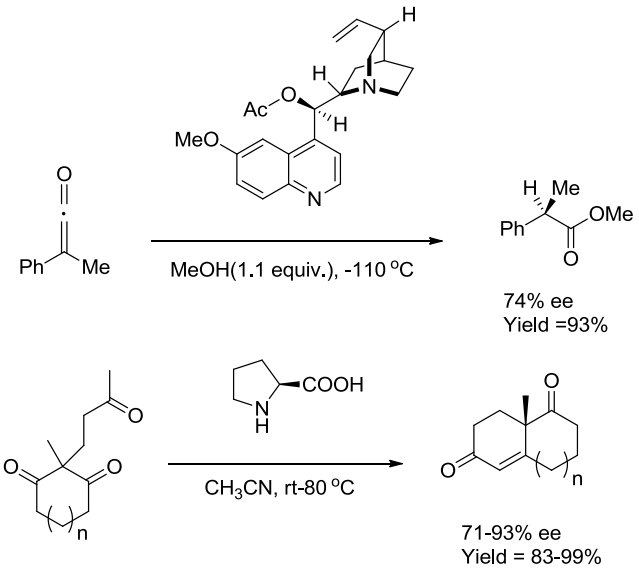
Chapter 1

Introduction

1. Organocatalysis

In the last decade, *organocatalysis*, the use of small chiral organic molecules as catalysts, has proven to be a valuable and attractive tool for the synthesis of enantiomerically enriched molecules. A number of *organocatalysts* and processes, such as one-pot, tandem, cascade or multicomponent reactions, have been reported to date. Furthermore, the many advantages of organocatalysis-robust, non-toxic, affordable, inert atmosphere, easy reaction manipulation, etc.-allow the preparation of bioactive compounds using simple and metal-free procedures, thus avoiding false positives in the biological evaluation.[1a]

In 2000, David W. C. MacMillan coined and defined the term *organocatalysis* as the use of organic molecules with low molecular weight as catalysts in organic reactions. [1b] However, before that time, a large number of publications concerning the use of an organic molecule in a catalytic amount were reported. In 1912, Bredig and Fiske described the addition of HCN to aldehyde in the presence of cinchona alkaloids with low ee's.[2] Later, Pracejus in 1960 described the addition of methanol to ketenes with ee's up to 74% (equation a, Scheme 1).[3,4] One of the milestones in organocatalysis is the intramolecular aldol reaction catalyzed by proline that was developed independently by the pharmaceutical companies Hoffman-La Roche[5] and Schering AG[6] (equation b, Scheme 1). The organocatalysts have two main functions; they can activate the electrophile or the nucleophile (or both in the case of bifunctional catalysis), or they create an asymmetric environment that is responsible for setting the chirality of the product.



Scheme 1 Two pioneering examples of organocatalysis

This reaction, also known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, allows the preparation of intermediates for the synthesis of steroids and other enantiomerically pure molecules. Currently, asymmetric organocatalysis is recognized as an independent synthetic toolbox besides asymmetric metallic catalysis and enzymatic catalysis for the synthesis of chiral organic molecules. Multiple advantages compared with the other two catalytic areas have provoked the rapid growth and acceptance of organocatalysis. In general, organocatalysts are non-toxic and robust compounds, and a large number of them are commercially available and/or easily synthesized. They are usually stable under aerobic conditions, and the reactions do not require extremely dry conditions, and thus, inert-equipment such as vacuum lines or gloveboxes are not necessary. Frequently, the reactions are conducted under mild conditions and in high concentrations avoiding the use of large amounts of solvents and minimizing waste. In addition to these characteristics, organocatalysts are tolerant of numerous functional groups and avoid time-consuming and protecting-group manipulations.

2. Asymmetric catalysis

Asymmetric catalysis is one of the most important strategies for the synthesis of enantiopure compounds (Figure 1). Of the three approaches to asymmetric synthesis, i.e., use of the chiral pool, use of chiral auxiliaries and use of chiral catalysts (Scheme 2), the third method has an edge over the others due to its cost effectiveness and environmental friendliness and, hence, it has acquired conspicuous popularity in recent years. In principle, a single molecule of a chiral catalyst can lead to the production of millions of target molecules. The enormous significance attached to chiral catalysts in asymmetric synthesis led to the award of the Nobel Prize for chemistry in 2001 to William S. Knowles and Ryoji Noyori (for their work on chirally catalyzed hydrogenation reactions) and to Barry K. Sharpless (for his work on chirally catalyzed oxidation reactions).[7] The pioneering work of these three Nobel laureates paved the way for the further development of asymmetric catalysis.

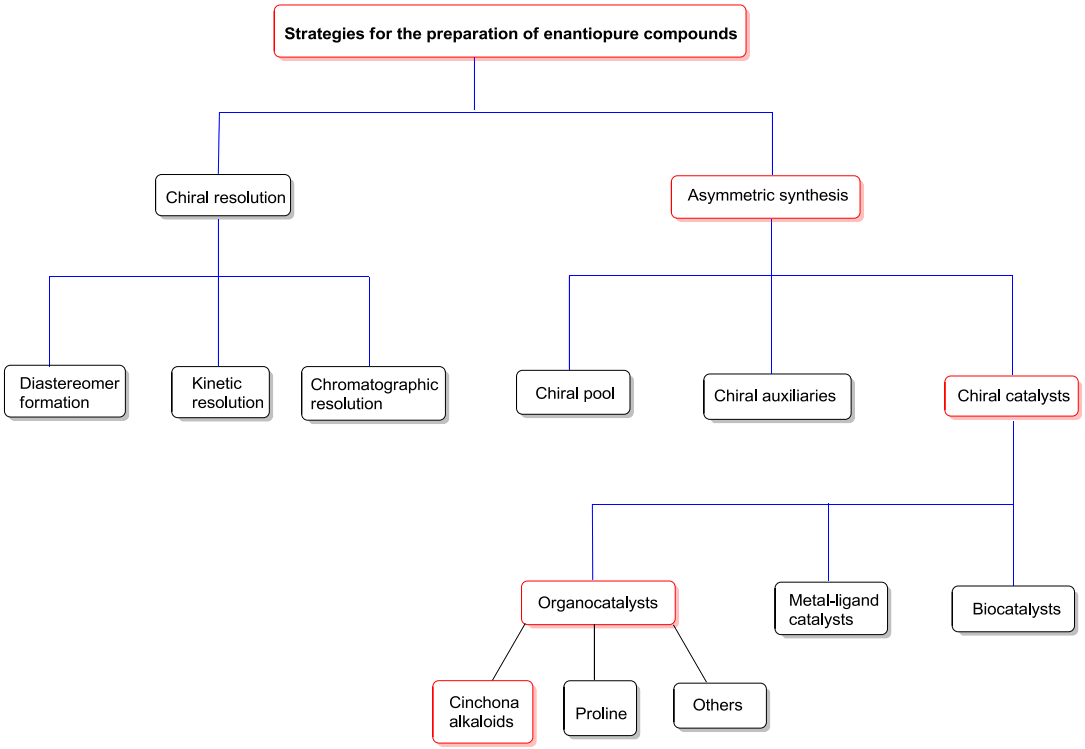
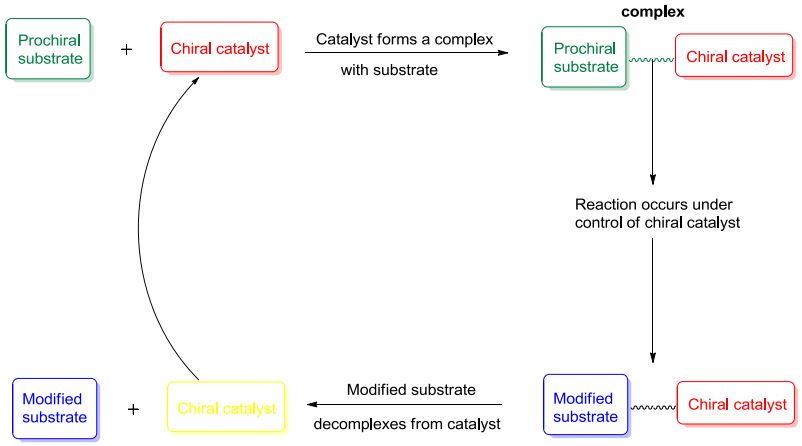


Figure 1 Strategies for the preparation of enantiopure compounds



Scheme 1 Strategies for the prepation of enantiopure compounds

2.1. Asymmetric organocatalysts

The use of metal catalysts or metal–ligand catalysts dominated the research scene up to the end of the last century. A change in perception in recent years, however, has led to a switch in favour of *organocatalysts* or the utilization of small chiral organic molecules as metal-free catalysts, especially in the synthesis of pharmaceuticals because of the 'green' advantage of not contaminating the final product with traces of heavy metals.[8] The neologism

of *organocatalysis* was created and registered as a trademark by David MacMillan,[9] a key researcher in this rapidly expanding field where considerable effort is being directed towards designing a variety of small organic molecules (*organocatalysts*) that can match the levels of stereoselectivity observed in enzymatic reactions. The catalytic efficiency of some of the first successful organic molecule candidates turned out to be more than expected, in that, while enzymes are applicable only to specific reactions, the synthesised *organocatalysts* proved to be effective over a wide range of different reactions and could therefore be described as '*privileged catalysts*'.[10]

2.2. Mechanistic considerations

There are different types of mechanisms displayed by *organocatalysts*:

(i) Some form covalent reactive intermediates

(ii) Some stabilize the transition state in a 'chiral pocket' via weak interactions such as hydrogen bonding and

(iii) Others operate as phase-transfer catalysts (PTCs) by a distinctly different mechanism in which they provide a 'chiral shuttle' for reaction partners located in different phases.

In the second type of catalysis, a reacting molecule, that only has a prochiral centre, is temporarily attached to the catalyst and fixed in an asymmetric environment or 'chiral pocket' or 'chiral space' within the catalyst in such a way that favours one trajectory of the reaction more than the other, thus producing an excess of one enantiomer, because a new chiral centre is enantioselectively introduced into the molecule (Figure 2).[11] The more efficient catalyst would be one that can completely block the other trajectory of reaction. This concept of 'chiral space' has become the basis of rational design and optimization of organocatalysts as opposed to random searching. Random searching has, however, in the past, led to the discovery of several compounds obtained directly from nature that fit the role of 'privileged catalysts'. Among these, the most versatile are proline (an α-amino acid), and the *Cinchona* alkaloids and their derivatives.

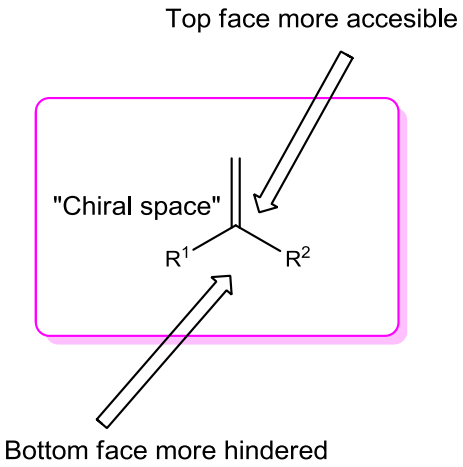


Figure 2 Model illustrating general asymmetric induction at a prochiral centre

3. Structural features of *Cinchona* alkaloids

The naturally occurring *Cinchona* alkaloids are an ideal choice as chiral inducers because they are

(i) Abundantly provided by nature

(ii) Commercially available at relatively moderate prices

(iii) Bench-top stable and recoverable

(iv) Readily modified structurally for diverse catalytic applications and

(v) Readily obtainable in diastereomeric pairs, allowing access to either enantiomeric product.

The basic structure of the *Cinchona* alkaloids consists of two rigid ring moieties (Figure 3), namely an aromatic quinoline ring and an aliphatic quinuclidine ring linked by two carbon–carbon single bonds. They contain five stereocentres, C-(3), C-(4), N-(1), C-(8) and C-(9), but they occur in pairs that differ in configuration only at N-(1) and the two connecting single-bond carbons, C-(8) and C-(9). The absolute configuration at C-(3) and C-(4) is identical in both pairs and is the same in all naturally occurring *Cinchona* alkaloids. The eight major *Cinchona* alkaloids **1**–**8** (Figure 4) are thus related as diastereomeric pairs, but are often referred to as 'pseudoenantiomers'. As an example, the absolute configuration of natural quinine is 1*S*, 3*R*, 4*S*, 8*S*, 9*R* and that of quinidine is 1*S*, 3*R*, 4*S*, 8*R*, 9*S*. They are diastereomers, yet behave like enantiomers, because, when used as chiral catalysts, quinine yields one enantiomer while quinidine yields the opposite enantiomer with equal selectivity.

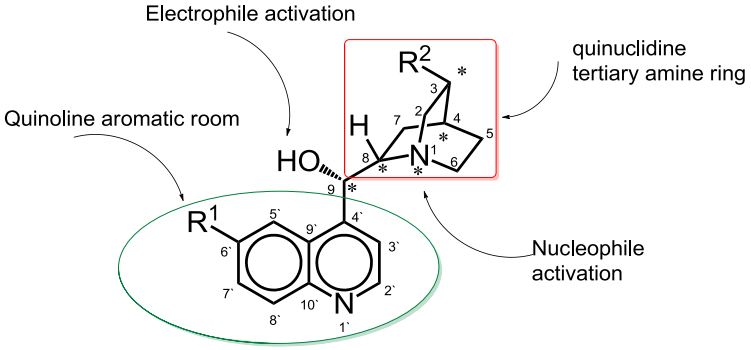


Figure 3 Important structure features of cinchona alkaloids(numbering initially adopted by Rabe[15]

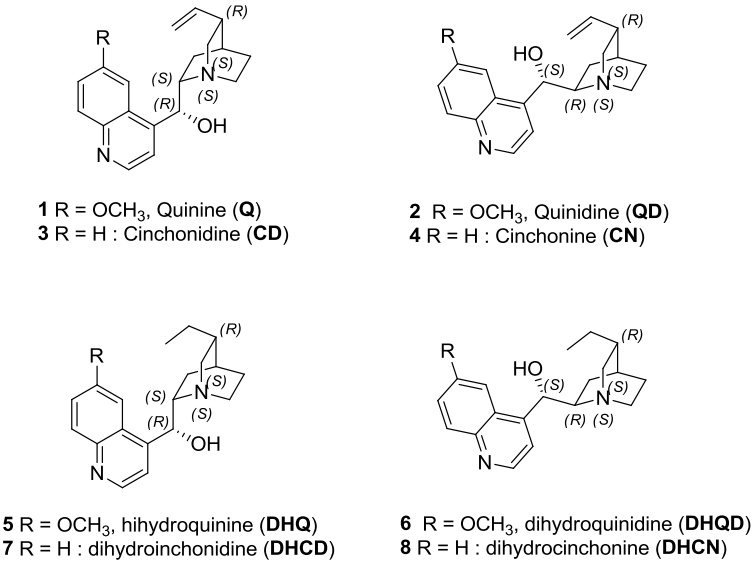


Figure 4 Structures and configurations of the eight major cinchona alkaloids

Recent findings from studies on the structural features responsible for the catalytic performance of the *Cinchona* alkaloids are summarised below.[12]

(i) The relative positions adopted by the bulky quinoline and quinuclidine ring systems possibly generate a rigid enzyme-like pocket or 'chiral pocket' around the substrate that forces enantioselective reactions.

(ii) Free rotation around the linker atoms, C8 and C9, creates a dynamic environment that provides many conformations with different stabilities and abilities to impart enantioselectivity in a given catalytic process. In one example, four low-energy conformations of quinidine (Figure 5) have been identified by Dijkstra and co-workers[13] using NMR studies.

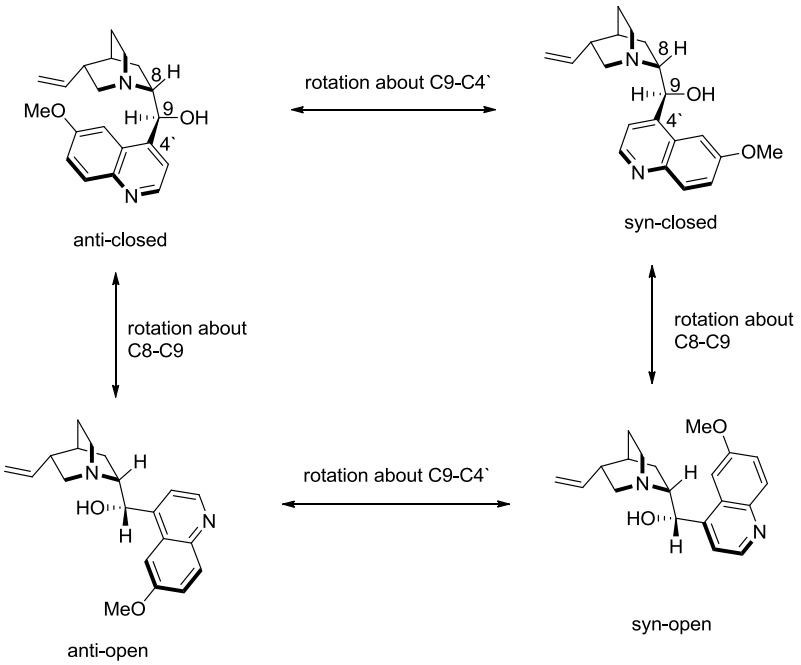


Figure 5 Low-energy conformations of quinidine

(iii) The stabilities of different conformers created around the linker carbons may be influenced by the peripheral groups R^1 and R^2 and, hence, the nature of the chiral promotion may ultimately be influenced by these groups. The *Cinchona* alkaloids have been greatly utilised in the rational design of catalysts for asymmetric synthesis because they are tunable by varying R^1 and R^2 in order to increase or decrease bulkiness, thus controlling steric rigidity and, hence, the stereochemical outcome.

(iv) The quinuclidine tertiary amine nitrogen is nucleophilic and is responsible for the basic character of the *Cinchona* alkaloids as its pK_a value in water is about three times higher than that of the quinoline nitrogen. It can act as an effective ligand for a variety of metal-catalysed processes and also as a reactive centre.

(v) The quinoline aromatic ring is a potential secondary binding site and is the site for adsorption onto solid surfaces in heterogeneous catalysis. This flat aromatic ring has electron-donor abilities that could enable the formation of donor–acceptor complexes with electron-deficient molecules.

(vi) The C-(9) stereocentre makes both diastereomers available, providing access to both enantiomers of a product with almost identical selectivities.

A study of the mechanism of asymmetric catalysis by *Cinchona* alkaloids using computational methods[14] has shown that these alkaloids generally function as bifunctional catalysts. This mode of catalysis simultaneously utilises the quinuclidine nitrogen to activate the nucleophile via general base catalysis and the hydroxyl group at C-(9) to activate the electrophile via hydrogen bond interactions. In other words, the two functional groups provide specific enzyme-like interactions that pre-organise and orient the reactants in an optimum position for reaction and also stabilise the transition-state structure. The highly structured transition state (stabilized by a network of hydrogen bonds) accounts for the enantioselectivity of the reaction. Cucinotta and co-workers showed that, when the C-(9)–OH was substituted by *O*-benzoyl, the stereoselectivity of the reaction dropped drastically, confirming the role of the OH group in the catalysis process.[14] These findings substantiated earlier studies on the conformational behavior of the alkaloids that had been carried out by Dijkstra and co-workers,[13] who found that substituents on C-(9) played a key role in determining the conformation of the *Cinchona* alkaloid in solution, e.g., C9 esters are usually present in the anti-closed form, while methyl ethers prefer an anti-open arrangement (Figure 5).

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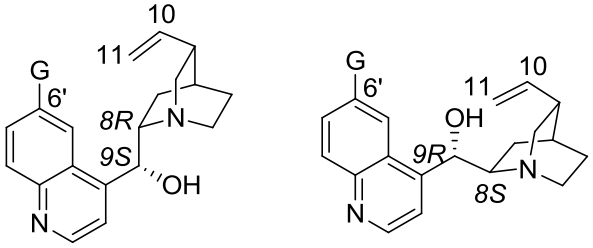
Chapter 2

Cinchona derived quaternary ammonium salts in asymmetric alkylation and asymmetric epoxidation

2.1. Cinchona Alkaloids in Synthesis & Catalysis

Cinchona alkaloids have unique structural nature (figure 1). They have a quite sterically hindered tertiary amine that can be derivatized to provide a variety of quaternary ammonium salts. In addition to the bridgehead tertiary amine, cinchona alkaloids have versatile functional groups such as the 9-hydroxy group, the 6'-methoxy group in quinoline, and the 10,11-vinyl group in the quinuclidine, all of which sometimes play critical roles in chirality-creating steps, either themselves or in chemically modified forms. Owing to these useful functional groups as well as their characteristic structural features, the parent natural alkaloids have frequently been served as valuable sources in the field of catalytic asymmetric organic synthesis, especially as chiral Phase Transfer Catalysis (PTCs). Moreover, the high accessibility in both pseudoenantiomeric forms at low cost is an additional major attraction for their utilization.



Cinchonidine(G=H)
Quinine(G=OMe)

Cinchonine(G=H)
Quinine(G=OMe)

Figure 1 Representative cinchona alkaloids

As mentioned above, quaternary ammonium salts derived from cinchona alkaloids have occupied the central position as efficient PTCs in various organic transformations, especially in the asymmetric α-substitution reaction of carbonyl derivatives. A cinchona alkaloidal

quaternary ammonium salt, which acts as a PTC in various organic reactions, is prepared by a simple and easy chemical transformation of the bridgehead tertiary nitrogen with a variety of active halides, mainly arylmethyl halides. Other moieties of cinchona alkaloids (the 9-hydroxy, the 6′-methoxy, or the 10, 11-vinyl) are occasionally modified for the enhancement of both chemical and optical yields (Figure 2).[1]

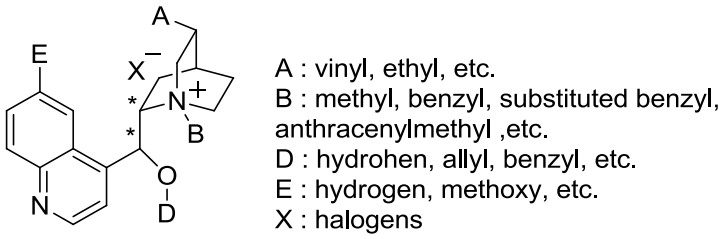
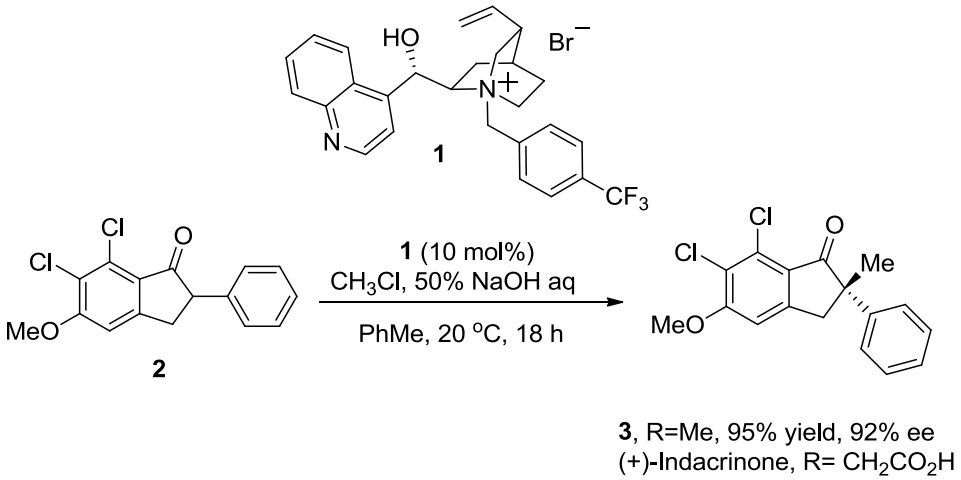


Figure 2 Quaternary ammonium salts derived from cinchona alkaloids

2.2. The pioneer works for Phase-Transfer Catalytic α-substitution

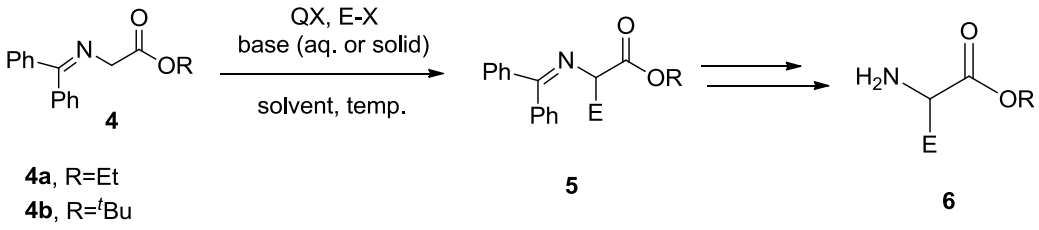
In 1984, the first successful monumental use of cinchona PTC for asymmetric α-substitution of carbonyls was reported by Dolling and coworkers of the Merck research group (Scheme 2.1).[2] In this work, cinchonidium salt **1** was employed in the catalytic asymmetric methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone **2** under phase transfer conditions. The methylated product **3,** which was finally transformed to (+)-indacrinone through three further steps was obtained in 95% conversion with 92% enantiomeric excess (ee). Through the systematic investigation, the group reported the relationship between the chemical/optical yield and the reaction variables (e.g., amount or concentration of each chemical species, halide of methylating reagent, solvent, reaction temperature, and stirring rate etc.).[3] Moreover, the group proposed the way of the PTC **1** may be that in which the quinoline ring, the C9-O bond, and *N*-arylmethyl group lie in one plane. The enolate anion of **2** also has an almost planner structure. Both molecules fit on top of each other, and the electrostatic interaction, hydrogen-bonding, and Π- Π stacking interactions make tight and stable ion pair between the PTC efficiently blocks the rear side of the enolate, the alkylating agent preferentially approaches the ion pair from the front side, giving optically active product **3.**



Scheme 2.1

2.3. Asymmetric alkylation of benzophenone imines of glycine esters using monomeric quaternary ammonium salts

The Merk group's report has undoubtly sparked the development of efficient catalytic organic reaction systems using structurally well-defined chiral organocatalyst. Cinchona alkaloids have taken the lead in this research area, and as a matter of course, a variety of cinchona PTCs have been newly developed and applied to diverse organic transformations. In the early stage of the cinchona PTC history, the structural fine-tuning of catalyst has been mainly focused on the enantioselective alkylation of α-amino acid derivatives (Scheme 2.2).



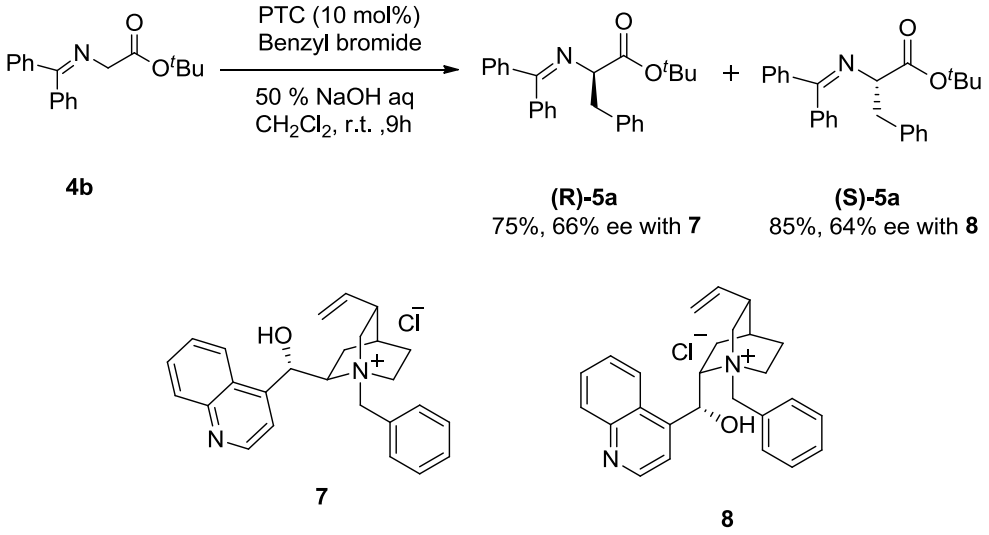
4a, R=Et
4b, R=^{t}Bu

Scheme 2.2

Although there have been lots of examples on the asymmetric phase-transfer catalysis, it is not too much to say that the research on the asymmetric alkylation of benzophenone imines of glycine derivatives esters **4** is the most useful and fruitful one. Most cinchona PTCs, to date, have been developed through this research, and the newly prepared cinchona PTcs have been gradually employed in other various organic catalytic transformations.

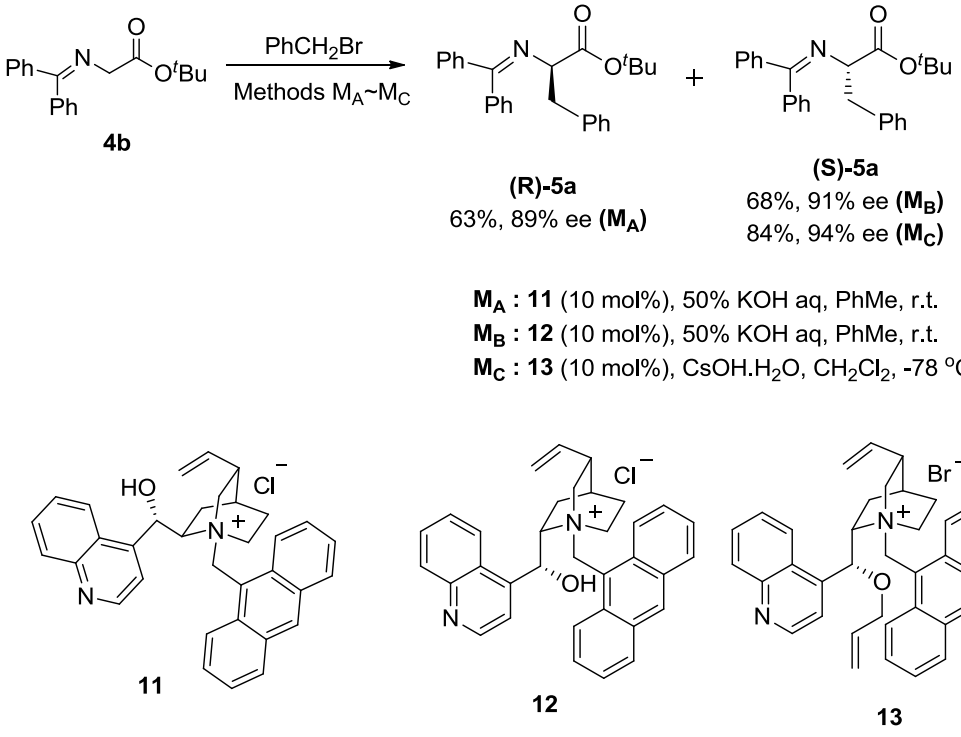
In 1978, O'Donnel and coworkers developed the benzophenone imines of glycine alkyl esters **4** as glycine anion equivalents, which have been found to be perfect to use in the phase-transfer catalysis.[4] An essential feature of this reaction system lies in the selective mono substitution of the starting Schiff base, the O'Donnel substrate **4.** This can be possible because of significant difference in acidity of α-hydrogen between starting substrate **4**. [pk_a(DMSO) 18.7 (R=Et)] and α-monosubstituted product **5 [**pk_a(DMSO) 22.8 (R=Et, E=Me), and 23.2 (R=Et, E=CH_2Ph)][5] This dramatic acidity difference makes it possible for selective formation of only monoalkylated product without concomitant production of undesired dialkylated product or recemization. In 1989, the O'Donnel group first reported the

asymmetric version of this alkylation using cinchona PTC (Scheme 2.3).[6] The asymmetric alkylation of **4b** proceeded smoothly under mild phase transfer conditions using *N*-benzylcinchoninium chloride[7], affording the alkylated product **(R)-5a** in good yield with moderate enantioselectivity, while the opposite enantiomer **(S)-5a** was obtained in similar level of enantioselectivity by using pseudoenantiomerically pure α-alkylated amino acids by a single recrystalization and subsequent deprotection in acidic media.



Scheme: 2.3

Based on the groundbreaking efforts of the O'Donnel group, a great improvement of the enantioselectivity with ee values to the range over 90% ee was reported by the two independent groups, that is, the Corey and the Lygo groups, in 1997 (Scheme 2.4). The key to achieve the dramatic jump in enantioselectivity was the introduction of the bulky 9-anthracenylmethyl moiety to the bridgehead nitrogen of the parent cinchona alkaloids for quaternization. Lygo and coworker prepared the C9-OH PTCs **11, 12** and applied them to the asymmetric phase transfer alkylation of **4b** with a much higher enantioselectivity of approximately 90% ee[8] Corey and coworkers used the prepared O-allyl PTC **13**, and they adopted solid inorganic base system rather than aqueous one to enable the reaction at a low temperature of -78 ^{o}C.[9] Such a low reaction temperature makes the conformation of both the enolate and catalyst more rigid, providing better enantioselectivity. Excellent enantioselectivities and generally high chemical yields were realized in a wide spectrum of electrophiles.



Schme 2.4

On the basis of the results from both the O'Donnel and the Corey groups[6b,9], it can be generalized that a quaternary ammonium salt derived from cinchona alkaloid has an imaginary tetrahedron composed of adjacent four carbons to the bridgehead nitrogen. As shown in Figure 3.

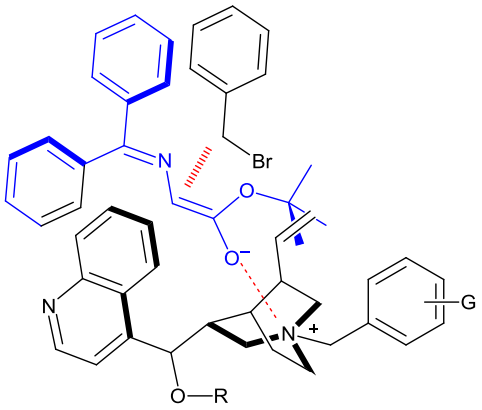
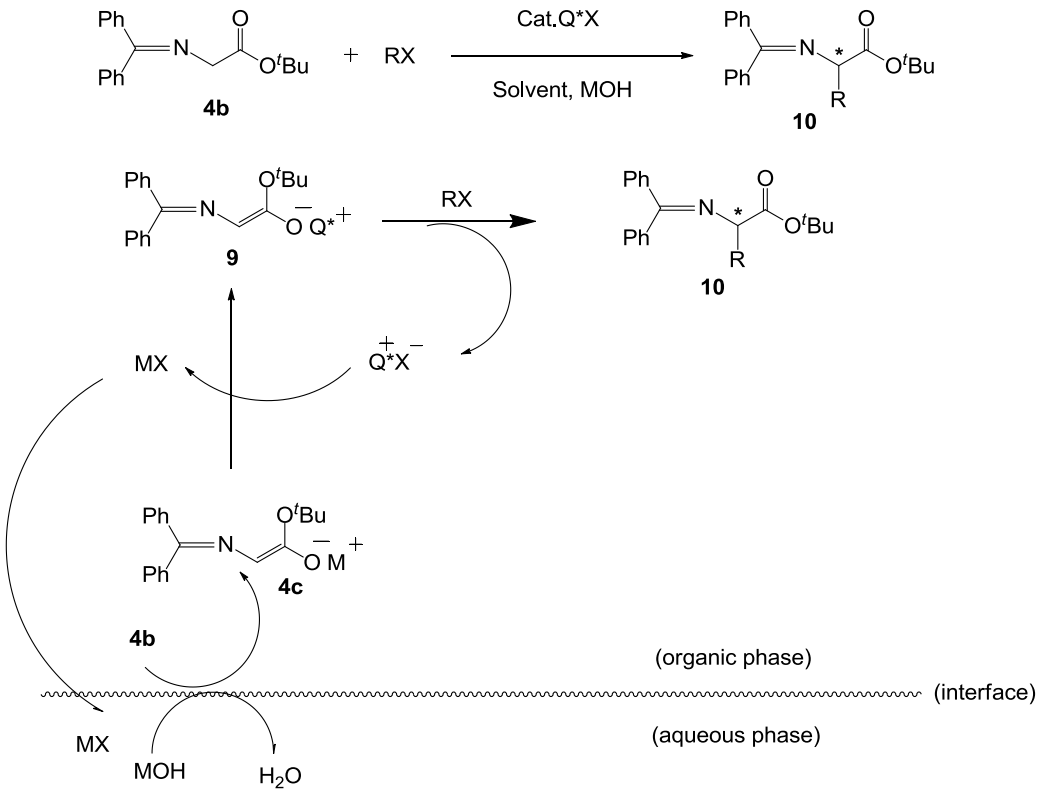


Figure 3 Origin of stereoselectivity of cinchona PTCs

To be an efficient catalyst in this alkylation, the cinchona-derived PTC (cinchonidium PTC model is used for the explanation in this figure) should be designed to provide effective steric screening that can inhibit an approach of the enolate of immine **1** to three faces (F1-F3) of this tetrahedron, while the reminder (F4) should be sufficiently open to allow close contact between the enolate anion and the ammonium cation.[10]

2.4. Mechanism of asymmetric alkylation of benzophenone imines of glycine esters using chiral quaternary ammonium slats

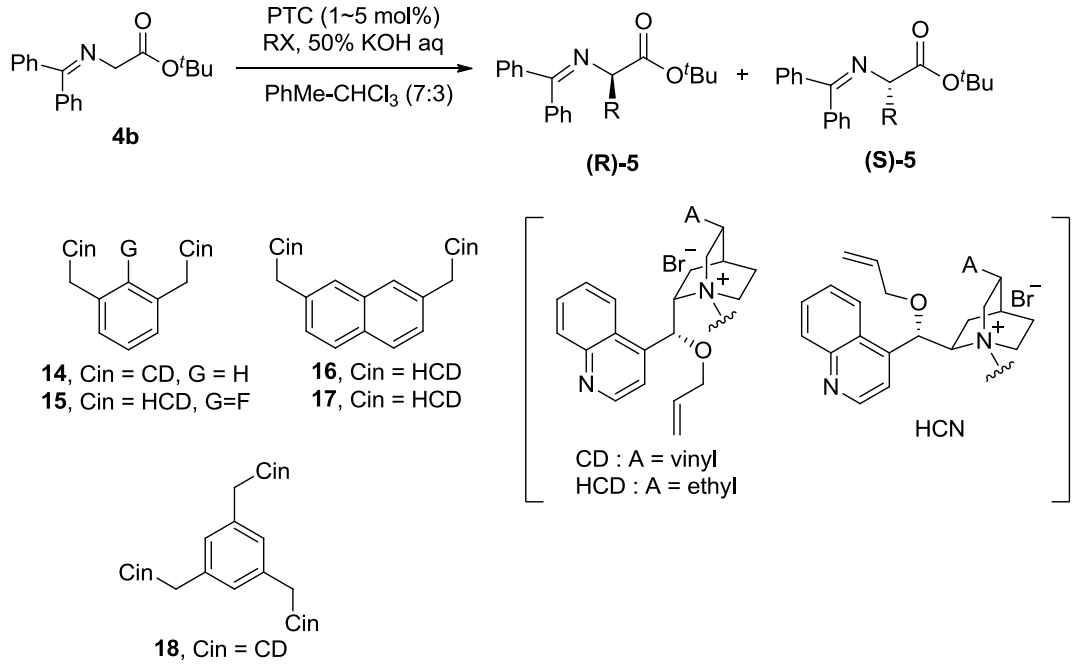
In the first step, glycine Schiff base **4b** reacts with the inorganic base at the interface of two phases to give the metal enolate **4c**, which remains at the interface due to its highly polar character. The metal enolate **3** then exchanges the cation to provide onium enolate **9**. The sufficiently lipophilic **9** then moves into the organic phase to react with alkyl halide. After the reaction, onium halide is regenerated and enters the next catalytic cycle. The key issue to be considered here is the possibility of product racemization and dialkylation. In this example, the basicity of the inorganic base and acidity of the substrate and product, as well as other reaction conditions, are carefully adjusted to circumvent this problem. It should be also noted that control of the E/Z geometry of the enolate is apparently critical to the asymmetric induction, although there is no clear evidence about which isomer is the actual reacting species in this case (Scheme 2.5).[11]



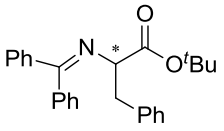
Scheme 2.5 Phase transfer mechanism using chiral quaternary ammonium salt

2.5. Asymmetric alkylation of benzophenone imines of glycine esters using dimeric quaternary ammonium salts

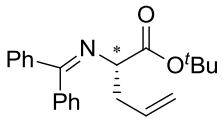
The development of dimeric cinchona alkaloids as very efficient and practical catalysts for asymmetric alkylation of the *N*-protected glycine ester **4b** was reported by park and Jew group.[12] The group devoted attention to the fact that the significant improvement was achieved in sharpless asymmetric dihydroxylation when the dimeric ligands were used. The group applied this advantage of dimerization to design of cinchona derived Phase-transfer catalysts. From the systematic investicgation of Park and Jew group, several highly efficient and practical dimeric and trimeric cinchona PTCs were developed (Scheme 2.6).



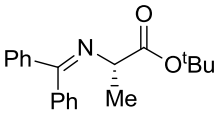
Selected examples



with **14**, -20 °C, 94%, 95% ee (S)
with **15**, -20 °C, 94%, 98% ee (S)
with **16**, 0 °C, 95%, 97% ee (S)
with **16**, -40 °C, 90%, 99% ee (S)
with **17**, -40 °C, 88%, 96% ee (S)
with **18**, -20 °C, 94%, 94% ee (S)



with **14**, -20 °C, 86%, 94% ee
with **15**, -20 °C, 92%, 97% ee
with **16**, -20 °C, 95%, 97% ee
with **18**, -20 °C, 90%, 95% ee



with **14**, -20 °C, 72%, 90% ee
with **16**, 0 °C, 70%, 94% ee
with **18**, -20 °C, 65%, 90% ee

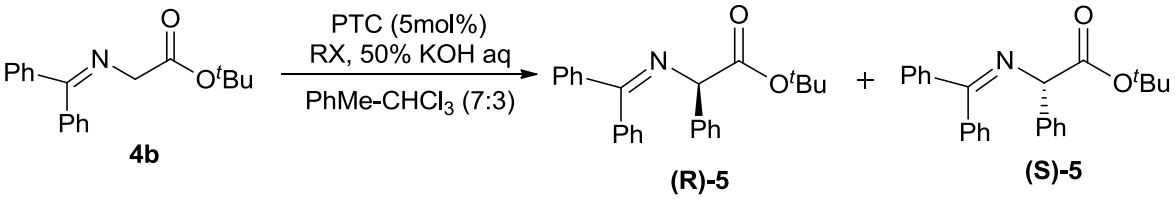
Scheme 2.6

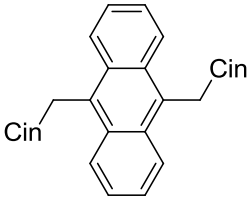
From the systematic investigation of the Park and Jew group, several highly efficient and practical polymeric catalysts with a specific direction of attachment between aromatic linkers (e.g., benzene or naphthalene and each cinchona units were found to be effective in the asymmetric alkylation of **4b.** The phenyl-based polymeric PTCs with the meta-relationship between cinchona units such as **14**, **15**, and **18** showed their high catalytic efficiencies. Furthermore, the 2, 7-dimethylnaphthalene moiety as in **16** and **17** was ultimately found to be the ideal spacer for dimeric cinchona PTC for this asymmetrical alkylation. For example, with 5 mol% of **16**, the benzylation of **4b** was completed within a short reaction time of 30 min at 0 ^{o}C, affording **(S)-5a** in 95% yield with 97% ee. Almost optically pure (>99% ee) **(S)-5a** in was obtained at lower temperature (-40 ^{o}C) with **16**, and moreover, even with a smaller quantity (1 mol %), its high catalytic efficiency in terms of both reactivity and enantioselectivity was well conserved.

Unlike the monomeric catalyst such as **8**, the rotation of phenyl ring in the dimeric catalyst get restricted, especially when two cinchona alkaloid unit can restrict free rotation of both N^{+}-CH_2 (benzylic) bond and CH_2 (benzylic)-C (phenyl) bond, which makes the whole conformation of the dimeric catalyst rigid, providing an efficient blocking of F3 face from an access of enolate to bridgehead nitrogen cation. Stereopair representation of the presumed plausible transition state, consisting of the enolate of **4b** and the PTC **14**. Alkylation of the enolate occurs by attack of the electrofile at Si face of the enolate for steric reasons, leading to the enantiomeric products.

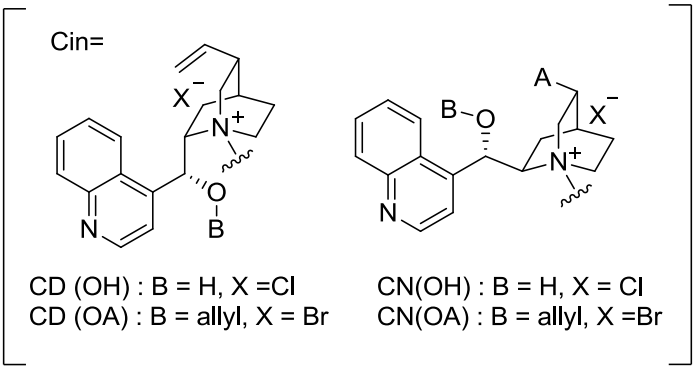
Inspired by the reports by Park and Jew group, further structural variations of dimeric cinchona PTC were performed by several research groups. In 2002, Najera and coworkers prepared dimeric PTCs in which the 9,10-dimethylanthracenyl moiety is incorporated as linker, expecting the advantageous effect shown in monomeric series (Scheme 2.7)[13a] This class of dimeric PTCs gave generally good stereoinduction in the alkylation of **4b** ; however it did not come up to the level of enantioselectivity using the corresponding monomeric PTCs **11-13**. The prepared *O*-allyl derivatives **20** and **22** did not give the better stereoselectivities than the free OH analogues **19** and **21** under the same reaction conditions, which is contrary to the tendency. The group also investigated the counterion effect by exchanging the chloride or bromide anions with the tetraflouroborate (BF_4^-) or hexaflourophosphate (PF_6^-) anions, but

the effect of changing the anion was found to be minimal.[13b] In 2005 and 2006, Siva and coworkers reported several types of new dimeric and trimeric cinchona PTCs and their application to the asymmetric alkylation of **4b**.[14]





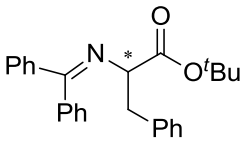
19, Cin = CD (OH)
20, Cin = CD (OA)
21, Cin = CN (OH)
22, Cin = Cn (OA)



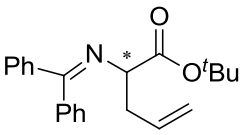
CD (OH) : B = H, X =Cl
CD (OA) : B = allyl, X = Br

CN(OH) : B = H, X = Cl
CN(OA) : B = allyl, X =Br

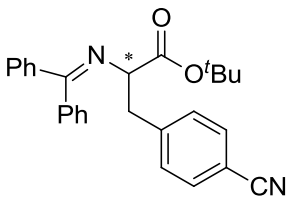
Selected examples



with **19**, 0 °C, 88%, 86% ee (S)
with **20**, 0 °C, 84%, 70% ee (S)
with **21**, 0 °C, 76%, 82% ee (R)
with **22**, 0 °C, 85%, 72% ee (R)



with **20**, 0 °C, 98%, 80% ee
with **22**, 0 °C, 97%, 70% ee



with **19**, -20 °C, 90%, 90% ee (S)
with **21**, -20 °C, 90%, 84% ee (R)

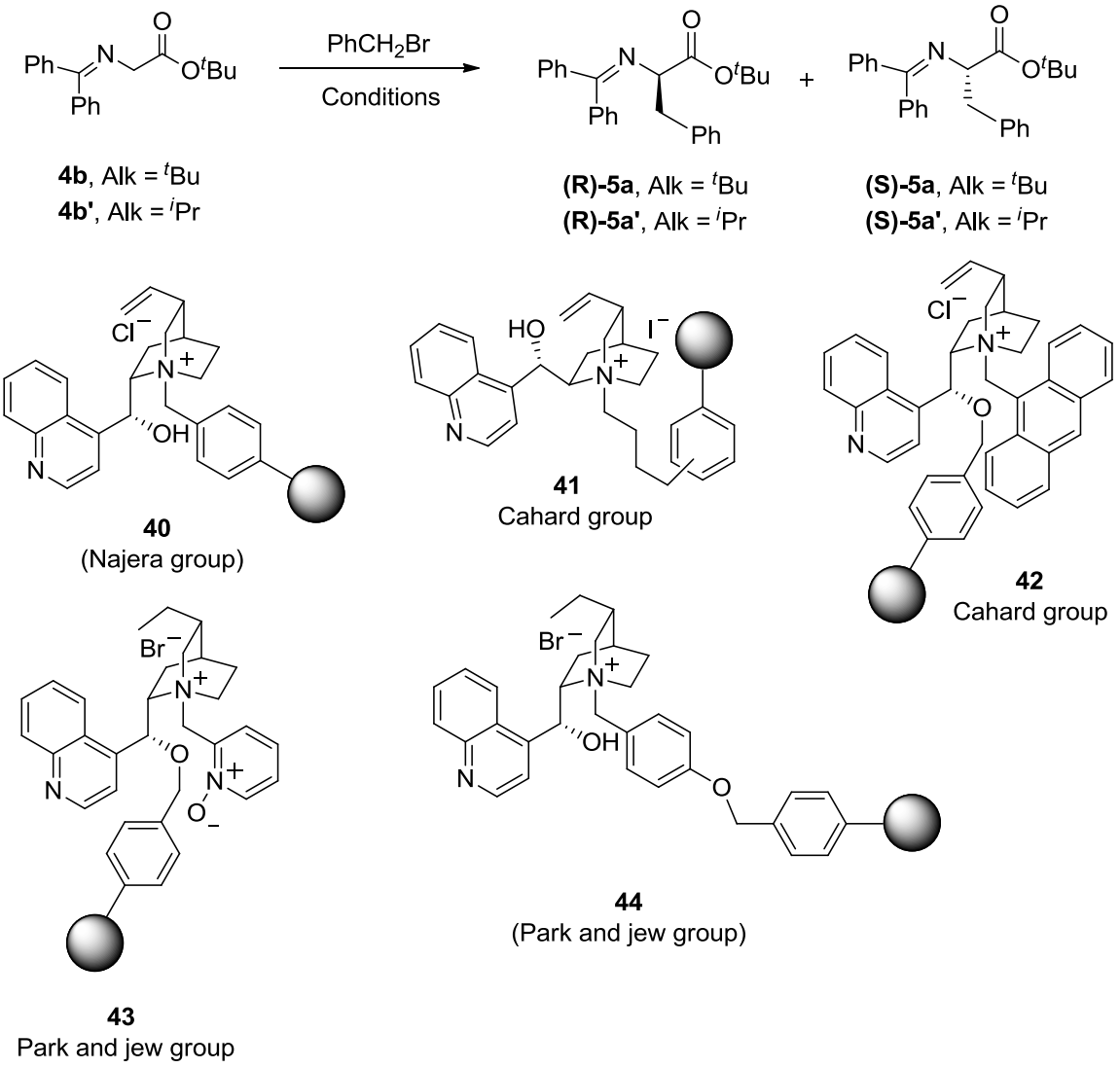
Scheme 2.7

2.6. Asymmetric alkylation of benzophenone imines of glycine esters using polymer-immobilized chiral quaternary ammonium salts that contain covalent-bond

In connection with the development of cinchona PTCs, considerable efforts have been made simultaneously on the preparation of the recyclable polymer-supported cinchona PTCs for the asymmetric alkylation (scheme 2.8). Polymer bound catalysts present advantages such as simplified workup for product purification easy recovery good stability reduced toxicity and potential recycling. In 2000, the Najera group prepared the PTCs supported with Merrifield resin to the bridgehead nitrogen such as **40** and applied them to the asymmetric alkylation.[15] The polymer supported PTCs were found to be more effective in the case of alkylation of isopropyl analogue **(4b')** than that in **4b**. The recovered catalyst showed almost identical chemical and optical yield at its second use in the alkylation.

In 2001, Cahard and coworkers reported two papers on this issue. First, the group designed the similar polymer-supported PTCs such as **41** to the Najera's PTCs **40**, but the group incorporated spacers composed of several methylene units.[16] Interestingly, the same major enantiomer was always obtained irrespective of the nature of the catalyst used, even though cinchonidine are known to behave as pseudoenantiomers. Second the group also reported the modified Lygo-Corey analogue **42** prepared by the attachment of Merrifield resin on the C (9)-OH position.[17] With this PTC, **(S)-5a** was obtained in the enhanced enantioselectivity of 94% ee using $CsOH.H_2O$ at -50 ^oC.

In 2008, Park, Jew, and coworkers reported the Merrifield resin-supported PTCs in which hydrogen bond inducing functional groups are built-in such as **43** and **44**, expecting that the advantageous electronic effect already confirmed in their previous data can also be operative in polymer-supported version.[18] Two types of resin-bound electronically modified PTCs, N-supported PTCs such as **43** and N-supported PTCs such as **44**, were prepared evaluated. Among them, *N*-oxypyridine-based series especially provided the highest stereoselectivity in each series. In addition, the recovered PTC after the first use gave almost similar results in the next several cycles.



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with **40** (10 mol%): 25% NaOH aq, PhMe, 0 °C, 17 h, 90%, 90% ee, **(S)-5a'**
with **41** (10 mol%): 50% KOH aq, PhMe, 0 °C, 15 h, 60%, 81% ee, **(S)-5a**
with **42** (10 mol%): $CsOH\text{-}H_2O$ aq, PhMe, -50 °C, 30 h, 67%, 94% ee, **(S)-5a**
with **43** (20 mol%): 50% KOH aq, PhMe-$CHCl_3$, 0 °C, 10 h, 81%, 95% ee, **(S)-5a**
with **44** (20 mol%): 50% NaOH aq,PhMe-$CHCl_3$, 0 °C, 24 h, 92%, 90% ee, **(S)-5a**

Scheme 2.8

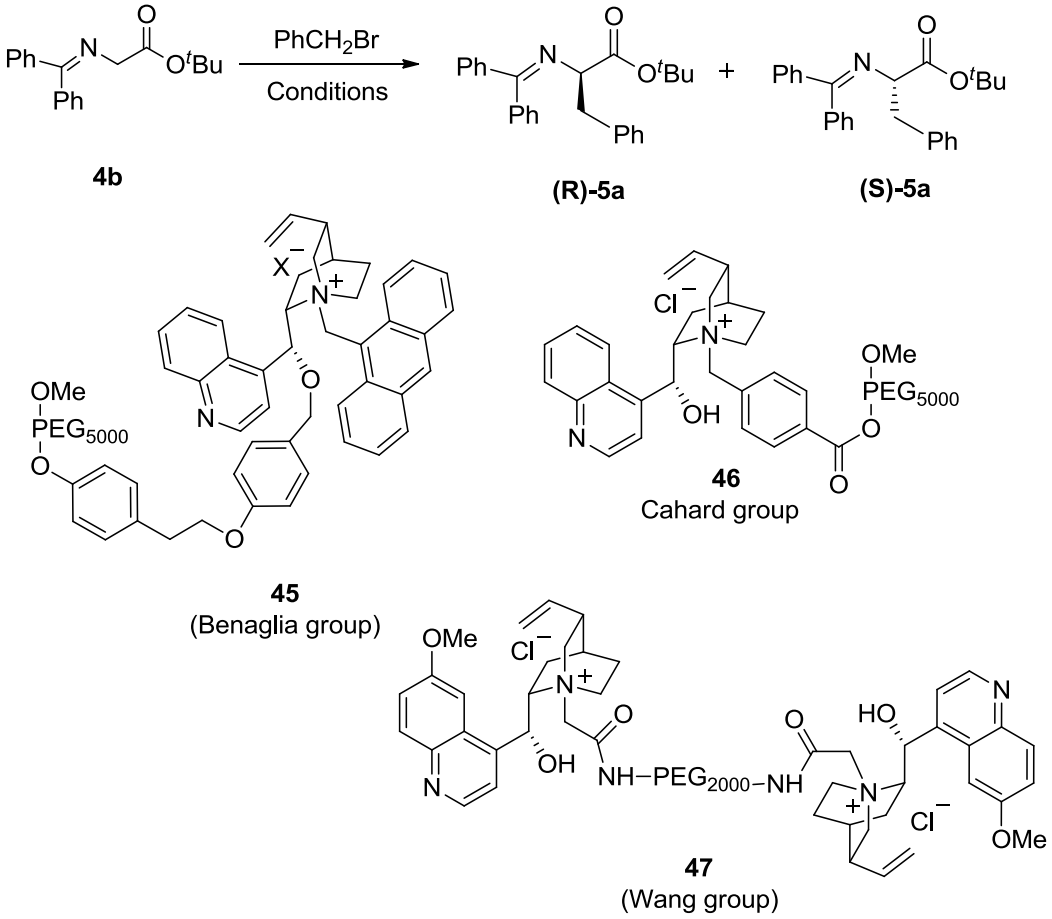
Poly (ethylene glycol) (PEG) supported cinchona PTCs were developed for the asymmetric alkylation by several groups (Scheme 2.9). The advantageous aspect of PEG includes that PEG is inexpensive, readily functionalized and commercially available in different molecular weights. Moreover, it is readily soluble in many organic solvents and insoluble in a few other

solvents, which enable to run a reaction under homogeneous catalytic conditions and to recover the catalyst as if it were bound to an asymmetric matrix.

The first report on the use of PEG-supported cinchona PTC in the alkylation was made by Bengalia and coworker in 2003.[19] The group prepared the PEG-supported derivatives of the Lygo-Corey PTCs by attaching the PEG moiety either on the oxygen at C9 or on the C6′-O of the quinoline ring and evaluated their catalytic efficiencies. The highest enantioselectivity (64%) was achieved with the C9-O supported PTC **45** at low temperature of -78 ^{o}C.

The Cahard group prepared the PEG-bound PTCs such as **46** in which PEG part is connected to the bridgehead nitrogen via benzoyl moity.[20] From the systematic investigation of parameters affecting the reaction, cinchonidium catalyst **46** was found to be the best one for the asymmetric alkylation, and the nonpolar toluene solvent, aqueous potassium hydroxide base and reaction temperature of 0 ^{o}C were determined for optimal reaction conditions. The water soluble PEG-supported dimeric cinchona PTCs such as **47** were developed by Wang and cowokers**.**[21]

The PTCs were prepared by reaction of diacetamido-PEG_{2000} chloride with natural cinchona alkaloids and it was found that they showed better catalytic activity in the asymmetric alkylation of **4b** when he solvent is water rather than organic solvents. The interesting feature of these PTCs is that steady chemical yield along with enantioselectivity is guaranteed even after recovery and recyling several times. What makes this possible is that the acetamido-moity-connected cinchona and PEG might be hardly disintegrated under the mild reaction conditions.

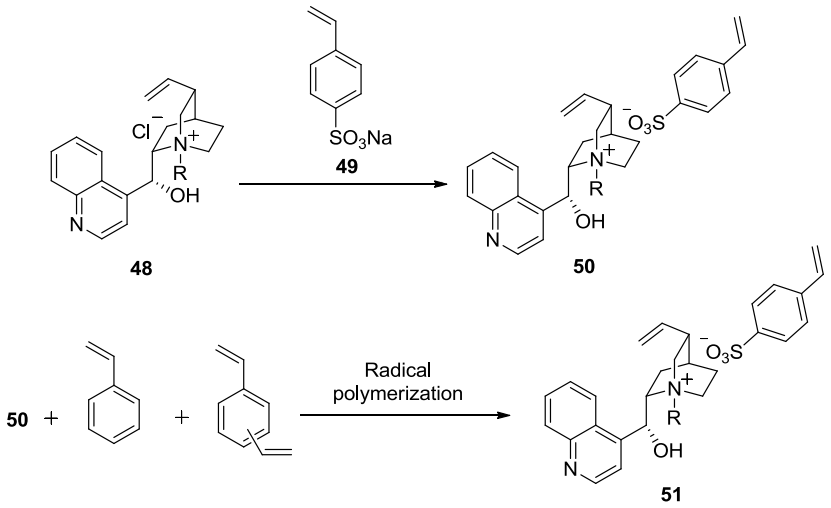


with **45** (10mol%): CsOH-H_2O, CH_2Cl_2, -78 ^oC, 60 h, 75%, 64% ee, **(S)-5a**
with **46** (10mol%): 50% KOH aq, PhMe, 0 ^oC, 15 h, 84%, 81% ee, **(S)-5a**
with **47** (10mol%): 1M KOH aq, r.t., 6 h, 98%, 83% ee, **(S)-5a**

Scheme 2.9

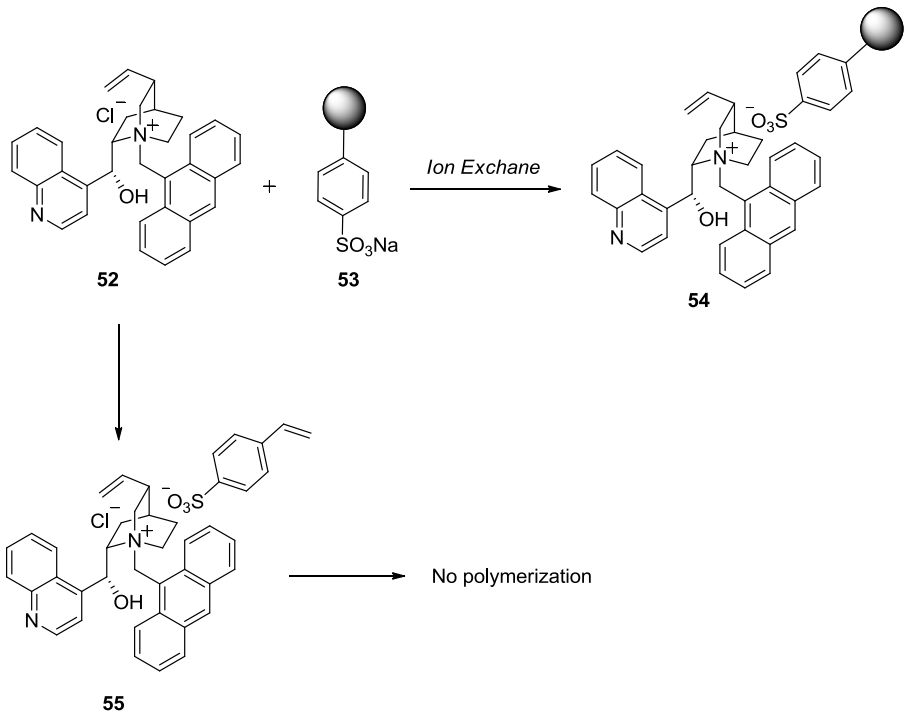
2.7. Asymmetric alkylation of benzophenone imines of glycine esters using polymer-immobilized chiral quaternary ammonium salts that contain ionic-bond

In all the catalysts shown in Scheme 2.8 and Scheme 2.9, the quaternized cinchona alkaloid molecules are covalently bonded to the polymer support, because of which the catalytic performance sometimes degrades.[22a] We have recently developed a novel method by which a quaternized chiral ammonium salt can be noncovalently linked to a polymer support. We chose a quaternary ammonium sulfonate salt since it has a stable structure. The quaternary ammonium salt of cinchonidine **48** was treated with sodium styrene sulfonate **49** to give the quaternary ammonium sulfonate monomer **50** in quantitative yield (Scheme 2.10).



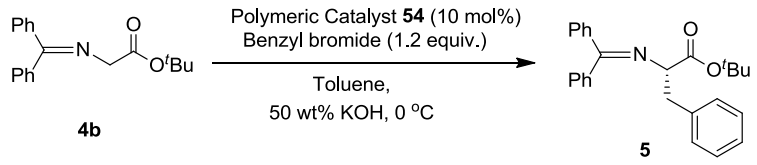
Scheme 2.10

Polymerization of **50** with styrene using divinylbenzene as the crosslinking agent afforded the corresponding polymer **51**, which had a chiral quaternary ammonium salt . In the case of **51**, the chiral catalyst was attached to the polymer support *via* an ionic bond. An alternative method to obtain the polymer -immobilized quaternary ammonium salt involves an ion-exchange reaction between the chiral quaternary ammonium salt and the polymeric sulfonate (Scheme 2.11).



52 53 54 55

Scheme 2.11



4b 5

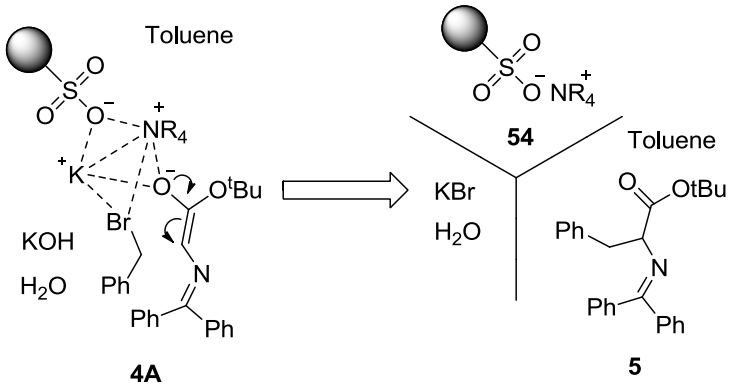
84%, 94% ee

Scheme 2.12

This method is useful for quaternary ammonium salts having a radical-sensitive structure. The styrene sulfonate monomer **55** containing an anthryl moiety did not undergo radical polymerization because of the formation of the stabilized radical. Ion-exchange reaction between **52** and **53** proceeded smoothly to give the corresponding chiral sulfonated polymer **54**. By using the above mentioned two methods, any quaternary ammonium salt can be linked to the polymer support through ionic-bond formation. One of the main advantages of ionically immobilized polymeric chiral quaternary ammonium salts is the simplicity and ease of synthesis. More importantly, the chiral quaternary ammonium salt can be linked to the polymer support without the need for chemical modification of the chiral catalyst . Ionically immobilized catalysts were successfully used in the asymmetric alkylation of **4b** to obtain **5** with high enantioselectivity (Scheme 2.12). When immobilizing a successfully designed catalyst on a polymer support, it is imperative that the original structure of the catalyst is unaltered, so that the catalytic activity is retained even

after immobilization. For example, the Maruoka catalyst , which shows very strong activity in the asymmetric alkylation of glycine derivatives , can be easily immobilized on a polymer support by the ionically immobilized method. The original structure of the Maruoka catalyst is unaltered after immobilization on the polymer , and hence, high catalytic activity and high enantioselectivity are observed.[22b]

When a polystyrene-based crosslinked polymer is used as the support, the reaction proceeds smoothly in a triphase system to afford the chiral product in quantitative yield. The enantioselectivity obtained when using the polymeric catalyst is much higher than that obtained when using the unsupported catalyst . This type of catalyst is considered to work as PTC system, but in the case of a polymeric catalyst, phase transfer seems to be difficult. Although the actual reaction mechanism when using the chiral quaternary ammonium sulfonate has not been clarified, we believe that aggregated ion pairs **4A** are involved in the reaction (Scheme 2.13).



Scheme 2.13 Plausible reaction mechanism with polymeric chiral catalyst

The results obtained for the aforementioned polymer -immobilized catalysts lead us to propose that the polymeric sulfonate plays a major role in the formation of the transition state. Owing to the strong affinity between the sulfonate anions and ammonium cations, the polymeric organocatalyst **54** can be easily recovered. Our ionic-bond formation strategy for polymeric chiral catalyst synthesis can be extended to other catalyst systems as well. One such example is the immobilization of a chiral amine catalyst via the formation of ammonium sulfonate linkages between a polymer and an amine catalyst.[23] the resulting catalyst effectively catalyze the asymmetric aldol reaction.

2.8. Asymmetric alkylation of benzophenone imines of glycine esters using main-chain chiral quaternary ammonium polymer

Traditionally, the polymer-supported chiral catalysts are prepared by anchoring highly enantioselective monomeric catalysts to flexible and sterically irregular polymer supports. Although a few enantioselective polymer catalysts have been obtained in this manner, a significant reduction of enantioselectivity is often observed after a monomeric catalyst is attached to a polymer support. This indicates that the microenvironment of the polymer is very important for the stereoselectivity of the catalyst. Because of the stereo-irregularity and flexibility of the traditional polymeric chiral catalysts, their catalytic sites do not have well defined microenvironment.It is very difficult to systematically modify the microenvironment of the catalytic sites in these polymers to improve their enantioselectivity.[24]

Advantges of main-chain chiral polymeric organocatalyst:

1) The microenvironment of the catalytic sites in rigid and sterically regular polymers can be systematically modified to produce highly enantioselective polymeric catalysts.

2) The enantioselectivity of a monomeric catalyst can be maintained in a polymer catalyst by the use of a rigid and sterically regular polymer backbone.

Compared with the traditional polymer-supported catalysts for which flexible and sterically irregular polymers are used, this new approach can better preserve the catalytic environment of the monomeric catalysts in the polymer as long as the catalytically active species are not aggregates of the monomers. These strategies not only make it possible to obtain easily reusable and highly enantioselective polymeric catalysts for many asymmetric reactions, but also can be further extended to construct polymeric chiral catalysts that are capable of multiple asymmetric catalytic reactions by incorporating different catalytic species in a polymer chain.[24]

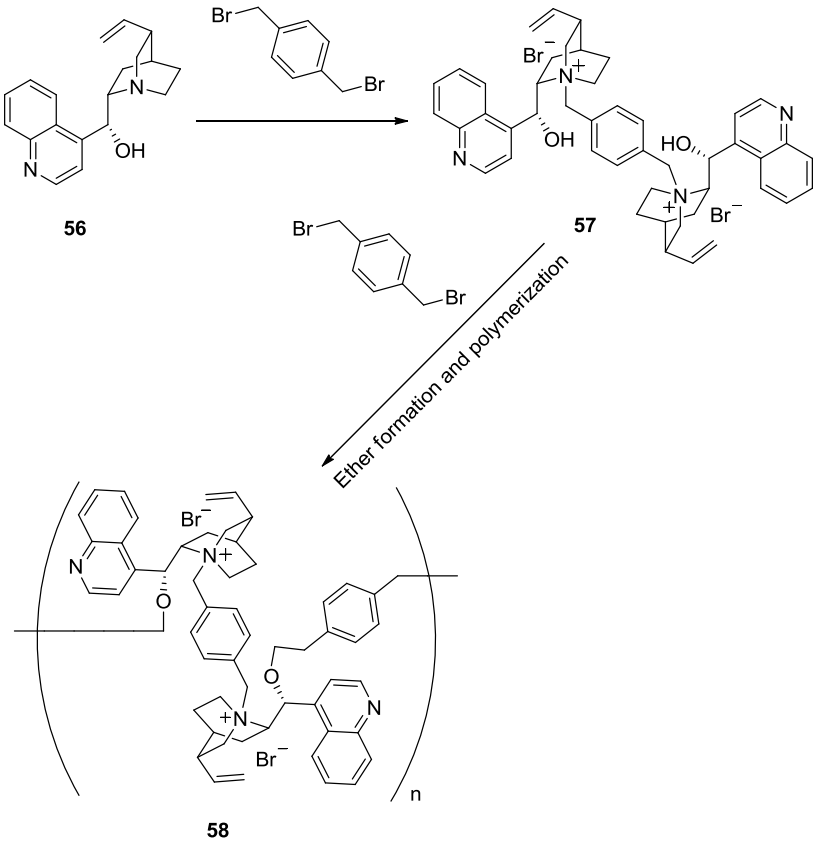
Polymers with main-chain chirality, which are widely used for chiral separation, are being increasingly used for catalytic applications as well. Typical examples of polymers with main-chain chirality used as asymmetric catalysts are chiral 1,1′-binaphthyl polymers,[24] chiral

polythioureas,[25] chiral isotactic polystyrene,[26] poly (amino acid)s,[27] polypeptides,[28] synthetic peptides,[29] helically chiral poly (phenylacetylene)s,[30,31] helically chiral polyquinoxalines,[32] and helically chiral poly (methacrylate)s.[33,34] Some of these polymers have been used as chiral organocatalysts. An important example of such an application is the use of poly((S)-alanine) as a catalyst for the asymmetric epoxidation of chalcone by alkaline hydrogen peroxide.[35] On the basis of this report, many chiral polymers have been synthesized for use as asymmetric organocatalysts.[36] However, main-chain chiral quaternary ammonium salt polymers have not been reported till date. We have developed several polymers containing chiral quaternary ammonium salts in their main chain. These chiral polymers show excellent catalytic activity when used in asymmetric reactions.

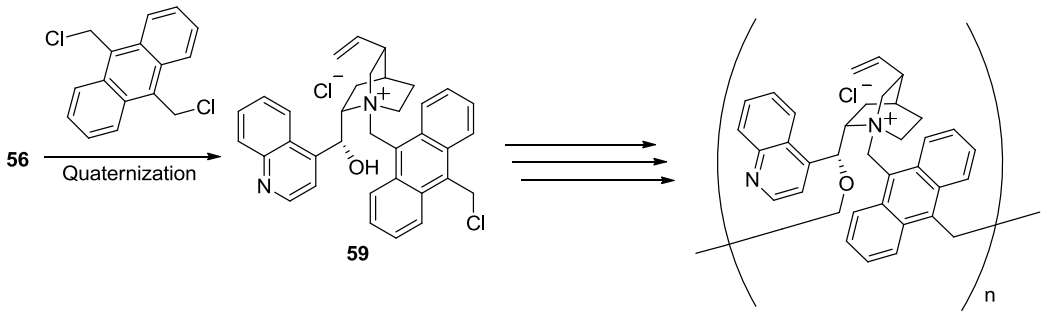
Ammonium polyionenes are ion-containing polymers in which quaternary nitrogen atoms are present in the polymer main-chain of the repeating unit, and not in the pendant position. Various types of ionene polymers have been synthesized from achiral monomers, and these polymers have many potential uses in biomedical applications.

However, till date, optically active ionene polymers have not been synthesized and used as asymmetric organocatalysts. Menschutkin reaction between an optically active tertiary amine and a dihalide readily affords the corresponding dimeric quaternary ammonium salt. Cinchonidine **56** is an optically active tertiary amine having a hydroxyl group. The dimeric quaternary ammonium salt **57** of **56** has two hydroxy groups (Scheme 2.14).

Diol **57** can be polymerized with a dihalide in the presence of NaH to afford chiral polyether **58**, which has a chiral quaternary ammonium moiety in its main chain.[37] When equimolar amounts of dihalide and cinchonidine are allowed to react, a quaternary ammonium salt **59** is formed, as shown in Scheme 2.15. In the presence of NaH, **59** polymerizes by self polycondensation to give the chiral polymer **60**.

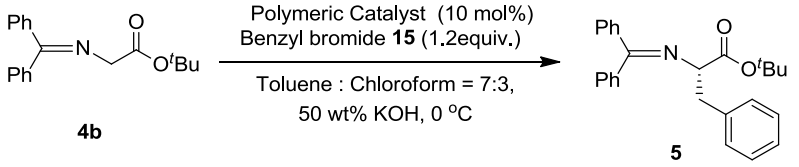


Schme 2.14



Scheme 2.15

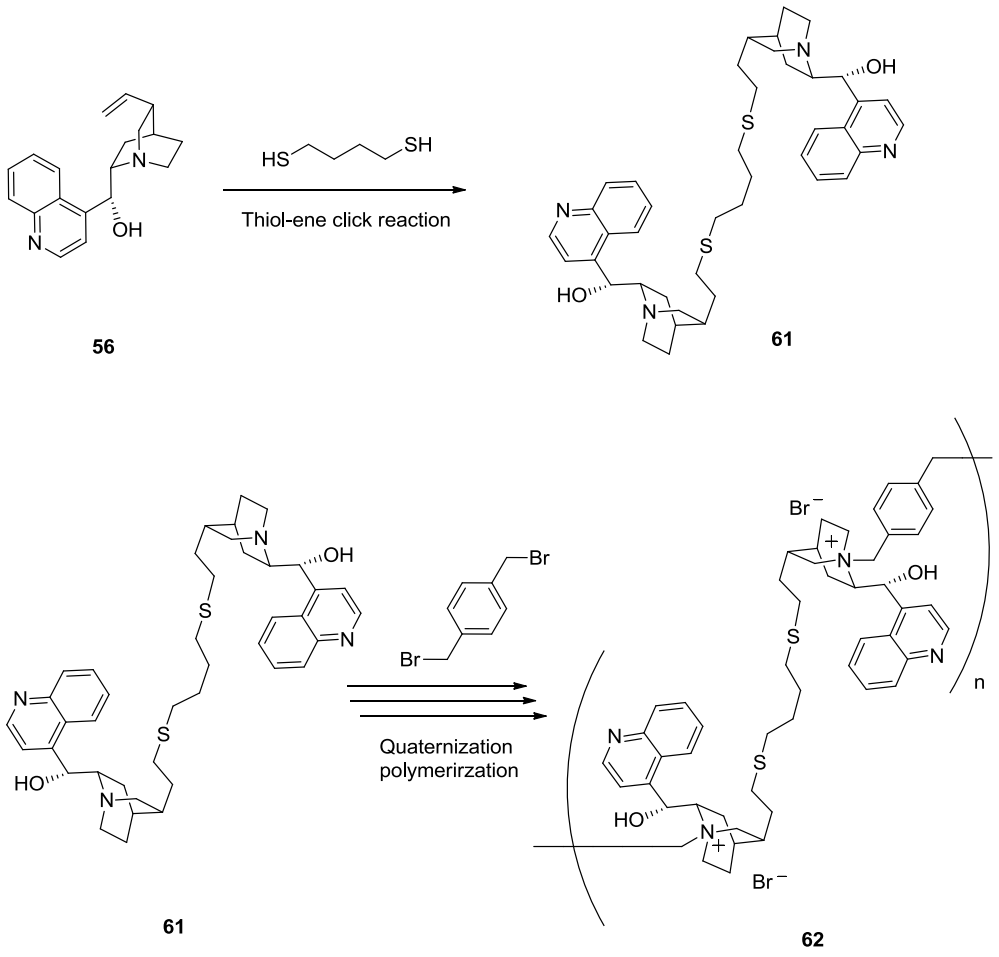
We used these chiral main-chain polymers as catalysts for the asymmetric benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester **4b** (Scheme 2.16). After the asymmetric benzylation, the polymers could be easily recovered by precipitation in hexane and reused for the same reaction without any notable loss of catalytic activity.



Scheme 2.16

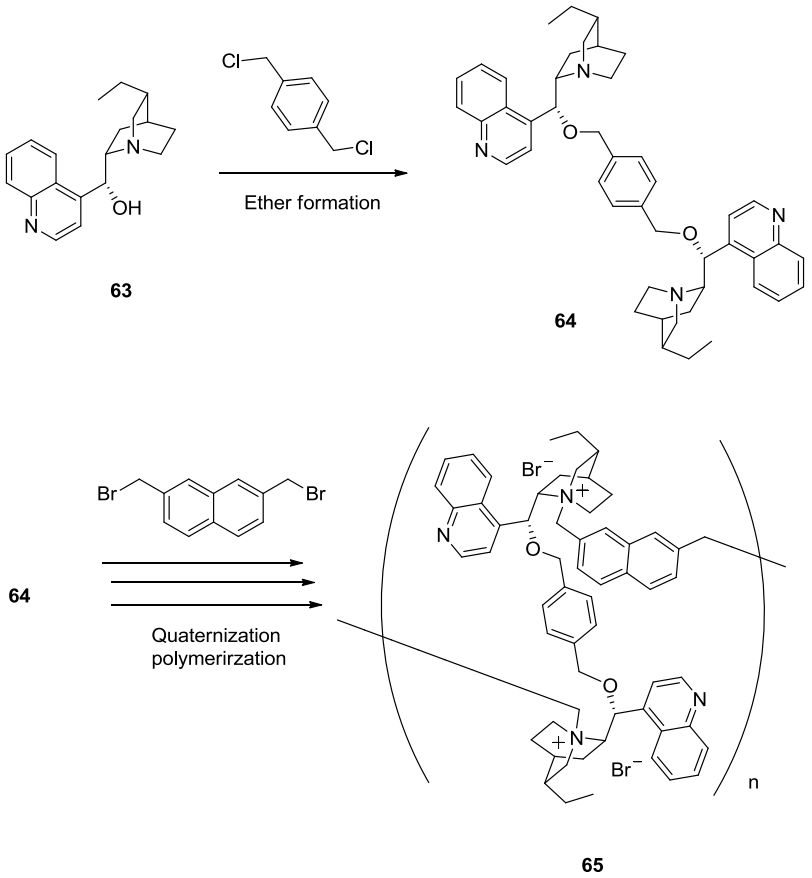
58: 92%, 86% ee
60: 78%, 80% ee

Then we focused our attention to the double of cinchonidine **56**. We utilized the idea of thiol-ene click reaction to modify the double bond of cinchonidine. Dimer **61** can be prepared from 2 equiv. of cinchonidine **56** and a dithiol using thiol-ene click reaction. Repeated quaternization reaction between **61** and a dihalide gives the main-chain chiral polymer **62** (Scheme 2.17).[38]



Scheme 2.17

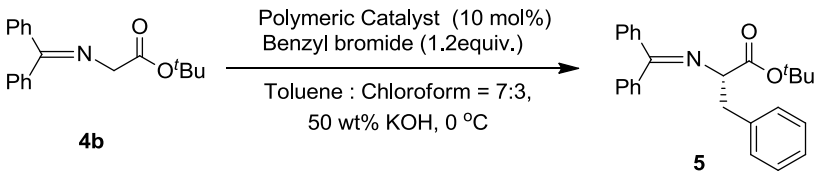
We also prepared main-chain chiral polymer involves the use of the chiral tertiary amine dimer **64**, which can be easily prepared from 2 equiv. of hydrocinchonidine **63** and a dihalide. Repeated quaternization reaction between **64** and a dihalide gives the main-chain chiral polymer **65** (Scheme 2.18).[39]



63 **64** **64** **65**

Scheme 2.18

We employed these main-chain chiral polymers **62** and **65** as novel organocatalysts in asymmetric benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester **4b** (Scheme 2.19). After the asymmetric benzylation, the polymers could be easily recovered and can be reused.



4b **5**

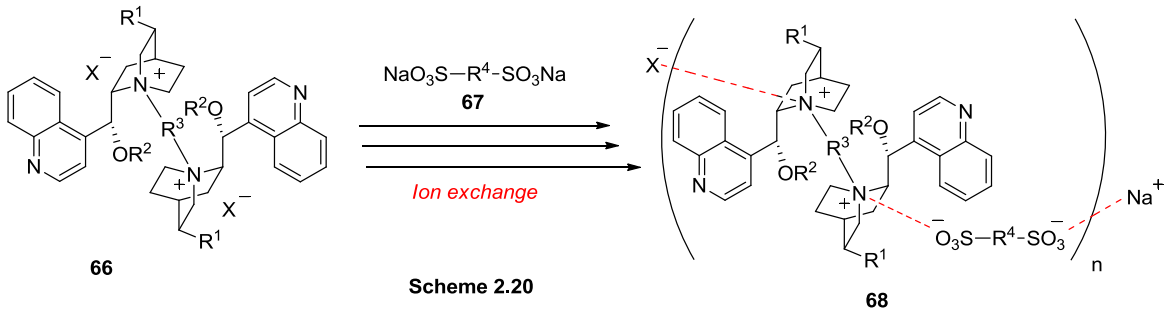
Scheme 2.19

62: 88%, 86% ee
65: 95%, 95% ee

2.9. Main-chain ionic chiral polymers as organocatalysts

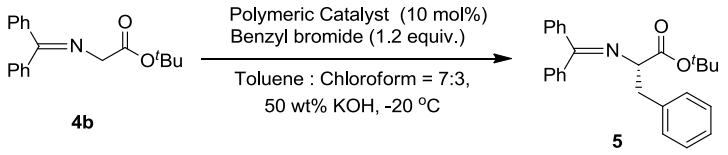
After confirming the high stability of quaternary ammonium sulfonate, as mentioned in Section **2.7**, we attempted to carry out polymeric catalyst synthesis via quaternary ammonium sulfonate formation. As shown in the synthesis of polymer-immobilized quaternary ammonium organocatalysts via ionic-bond formation, the quaternary ammonium halide readily reacts with sodium sulfonate to give a stable quaternary ammonium sulfonate in quantitative yield. Repeated reaction between the dimer of the chiral quaternary ammonium salt and the disulfonate should give the corresponding chiral polymer, in which there is a main-chain ionic bond between the quaternary nitrogen cation and the sulfonate anion.[40] A chiral quaternary ammonium dimer can be easily prepared from an enantiopure tertiary amine and a dihalide.

For example, the dimeric quaternary ammonium salt of cinchonidine **66** is prepared from cinchonidine and a dihalide. Reaction of **66** and disodium sulfonate **67** proceeds smoothly when equimolar amounts of these compounds are allowed to react in water[40a] or in methanol and water[40b] or in methanol[40c] (Scheme 2.20). The precipitated polymer **68** can be easily isolated by filtration. To the best of our knowledge, this is the first example of an optically active polymer with a main-chain ionic bond. The catalytic activity of the ionic polymers **68** is evaluated for the asymmetric benzylation of **4b** (Table 1). The asymmetric reaction proceeds smoothly in the presence of **68** to give **5** with high enantioselectivity. Various structural modifications can be carried out on the chiral quaternary ammonium dimer obtained from cinchonidine derivative.

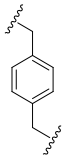
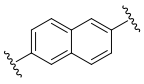
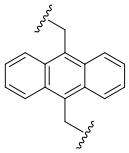
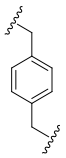
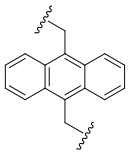
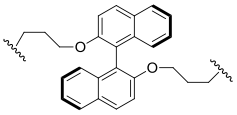


Scheme 2.20

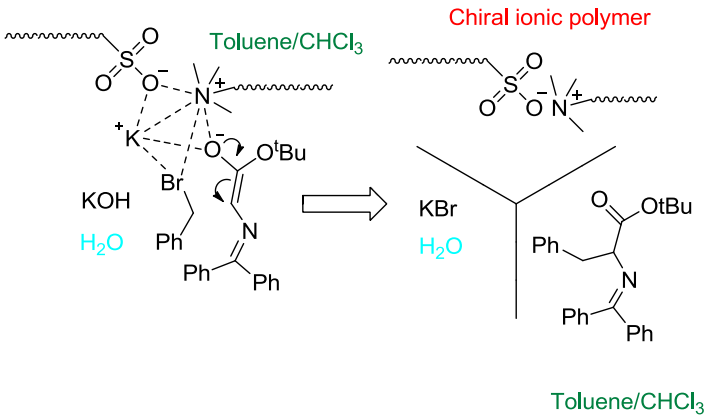
Table 1 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using polymeric catalyst **68**



Scheme 2.21

Entry	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	Ee (%)
1[40a]	Vinyl	Allyl			20	93	94
2[40b]	Ethyl	H			7	98	97
3[40c]	Ethyl	H			6	98	97

Although the reaction mechanism of asymmetric alkylation using chiral ionic polymers is not clear. We believe that aggregated ion pairs are involved in the reaction (Scheme 2.22).



Scheme 2.22 Plausible reaction mechanism with polymeric chiral catalyst

2.10. Design of main-chain chiral polymeric organocatalyst using Heck reaction

2.10.1. Mizoroki-Heck reaction[41]

In the early 1970s, T. Mizoroki and R.F. Heck independently discovered that aryl, benzyl and styryl halides react with olefinic compounds at elevated temperatures in the presence of a hindered amine base and catalytic amount of Pd(0) to form aryl-, benzyl-, and styryl-substituted olefins (Scheme 2.23). Today, the palladium-catalyzed arylation or alkenylation of olefins is referred to as the Heck reaction. Since its discovery, the Heck reaction has become one of the most widely used catalytic carbon-carbon bond forming tools in organic synthesis.

The general features of the reaction are:

1) It is best applied for the preparation of disubstituted olefins from monosubstituted ones.

2) The electronic nature of the substituents on the olefin only has limited influence on the outcome of the reaction; it can be either electron-donating or electron-withdrawing but usually the electron poor olefins give higher yields.

3) The reaction conditions tolerate a wide range of functional groups on the olefin component: esters, ethers, carboxylic acids, nitriles, phenols, dienes, etc., are all well-suited for the coupling, but allylic alcohols tend to rearrange.

4) The reaction rate is strongly influenced by the degree of substitution of the olefin and usually the more substituted olefin undergoes a slower Heck reaction.

5) Unsymmetrical olefins (e.g., terminal alkenes) predominantly undergo substitution at the least substituted olefinic carbon.

6) The nature of the X group on the aryl or vinyl component is very important and the reaction rates change in the following order: I > Br ~ OTf >> Cl.

7) The R^1 group in most cases is aryl, heteroaryl, alkenyl, benzyl, and rarely alkyl (provided that the alkyl group possesses no hydrogen atoms in the β-position), and these groups can be either electron-donating or electron-withdrawing.

8) The active palladium catalyst is generated in situ from suitable precatalysts (e.g., $Pd(OAc)_2$, $Pd(PPh_3)_4$) and the reaction is usually conducted in the presence of monodentate or bidentate phosphine ligands and a base.

9) The reaction is not sensitive to water, and the solvents need not be thoroughly deoxygenated.

10) The Heck reaction is stereospecific as the migratory insertion of the palladium complex into the olefin and the β-hydride elimination both proceed with syn stereochemistry.

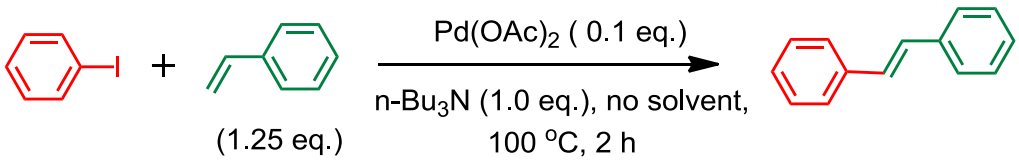
There are a couple of drawbacks of the Heck reaction:

1) The substrates can not have hydrogen atoms on their β-carbons, because their corresponding organopalladium derivatives tend to undergo rapid β-hydride elimination to give olefins.

2) Aryl chlorides are not always good substrates because they react very slowly.

Several modifications were introduced during the past decade.

1) Asymmetric versions
2) Generation of quaternary stereocenters in the *intramolecular Heck reaction*
3) Using water as the solvent with water-soluble catalysts
4) Heterogeneous palladium on carbon catalysis.

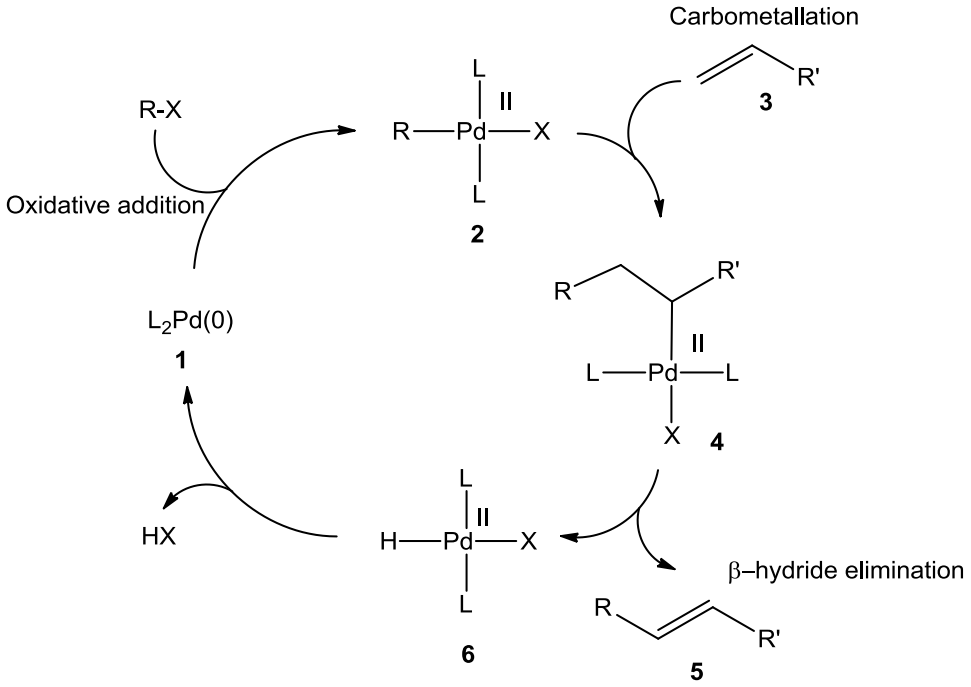


R. F. Heck et al. *J. Org. Chem.* **1972,** *37*, 2320-2322.

Scheme 2.23 Mizoroki-Heck reaction

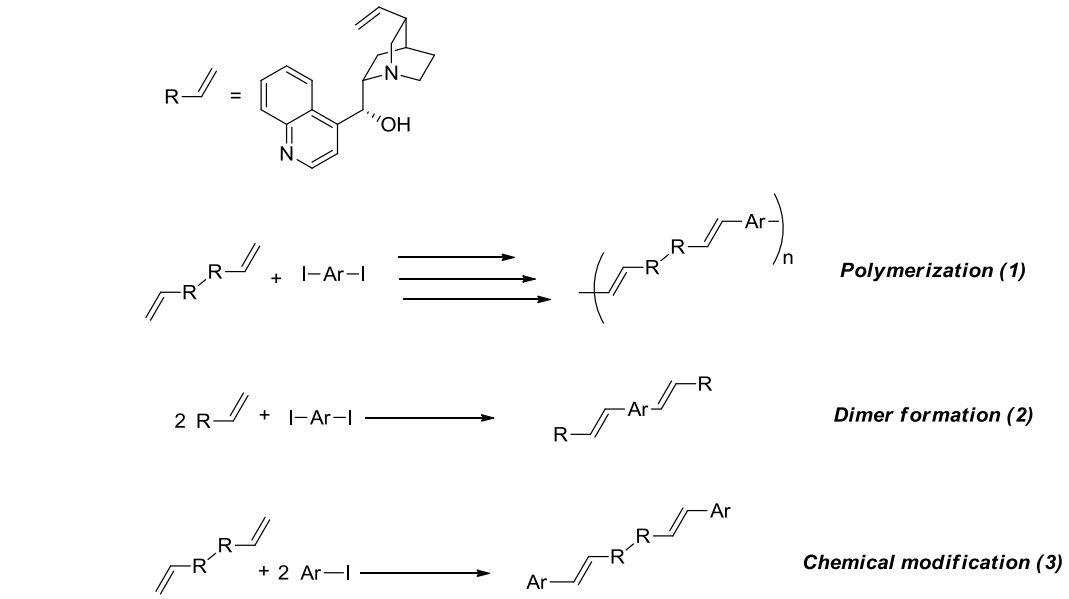
Mechanism:

The mechanism of the Heck reaction is not fully understood and the exact mechanistic pathway appears to vary subtly with changing reaction conditions. Scheme 2.24 shows a simplified sequence of events beginning with the generation of the active Pd (0) catalyst. The rate-determining step is the *oxidative addition* of Pd (0) into the C-X bond. To account for various experimental observations, refined and more detailed catalytic cycles passing through anionic, cationic or neutral active species have been proposed.

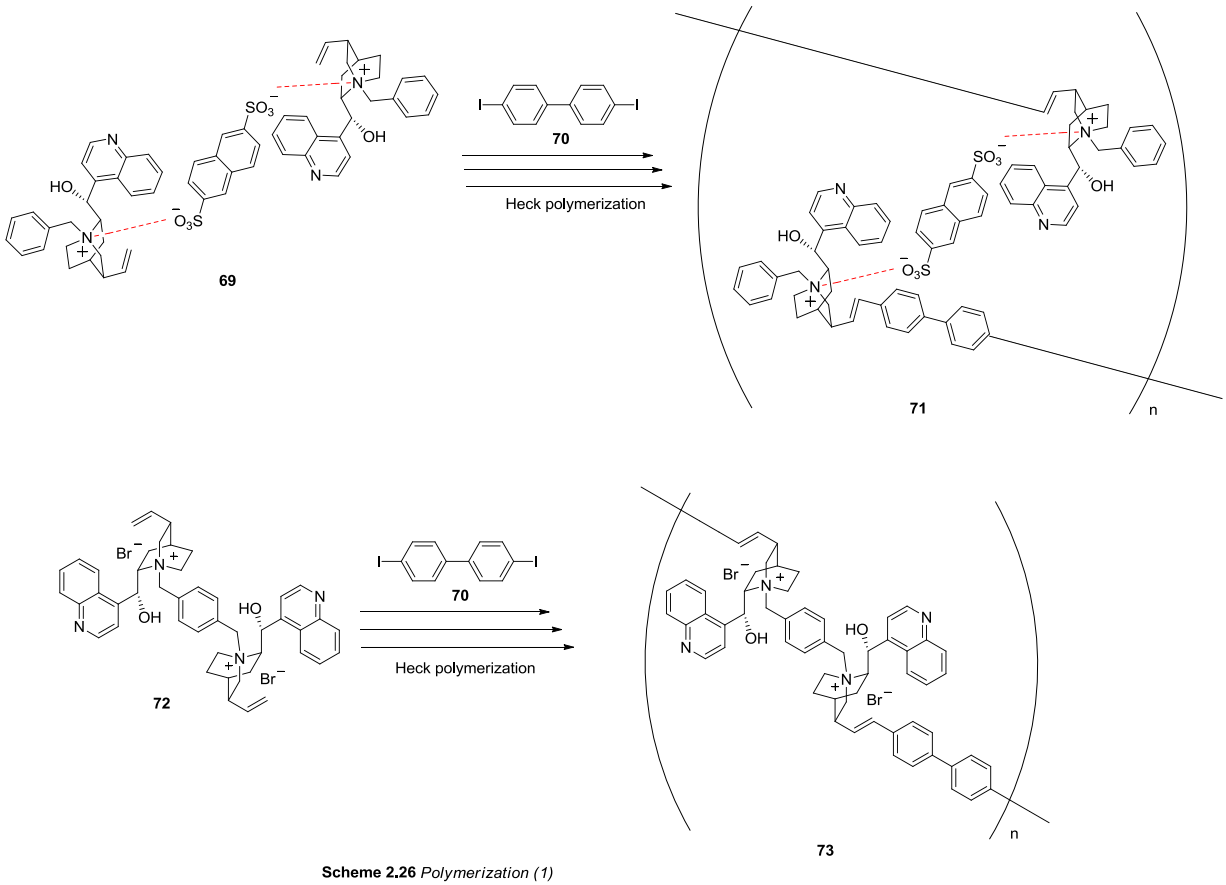


Scheme 2.24 Mechanism of Mizoroki-Heck reaction

Over the last few years, limited number of works have been done with the main-chain chiral polymers using Heck coupling reaction and their applications.[42-45] The chiral polymers synthesized by Heck coupling was used as biosensor. To our knowledge, none of the main-chain polymers synthesized by Heck coupling have been used as organaocatalyst. We have found that the double bond of the cinchonidine can be modified by Heck coupling reaction. Then we have used Heck coupling reaction for the synthesis of cinchonidine derived main-chain polymeric organocatalyst, for the synthesis of cinchonidine dimer and for the chemical modification of cinchonidine (Scheme 2.25).[46]



Scheme 2.25

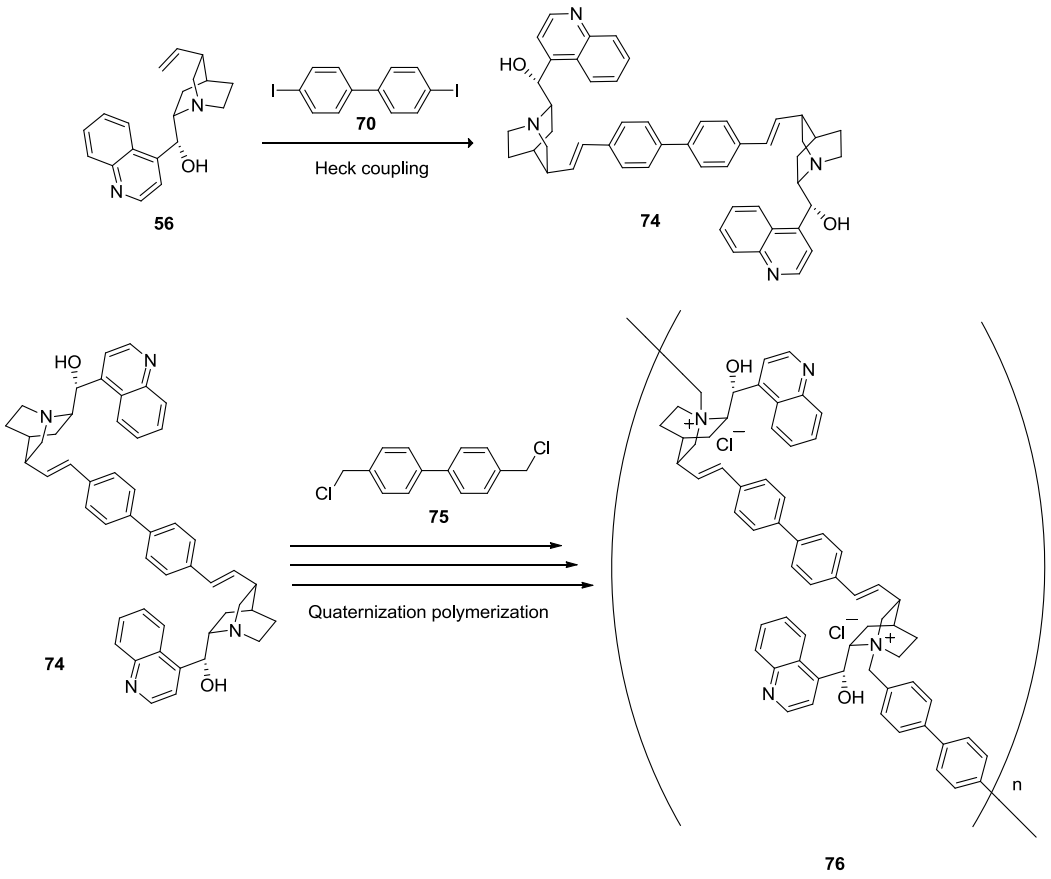


Scheme 2.26 *Polymerization (1)*

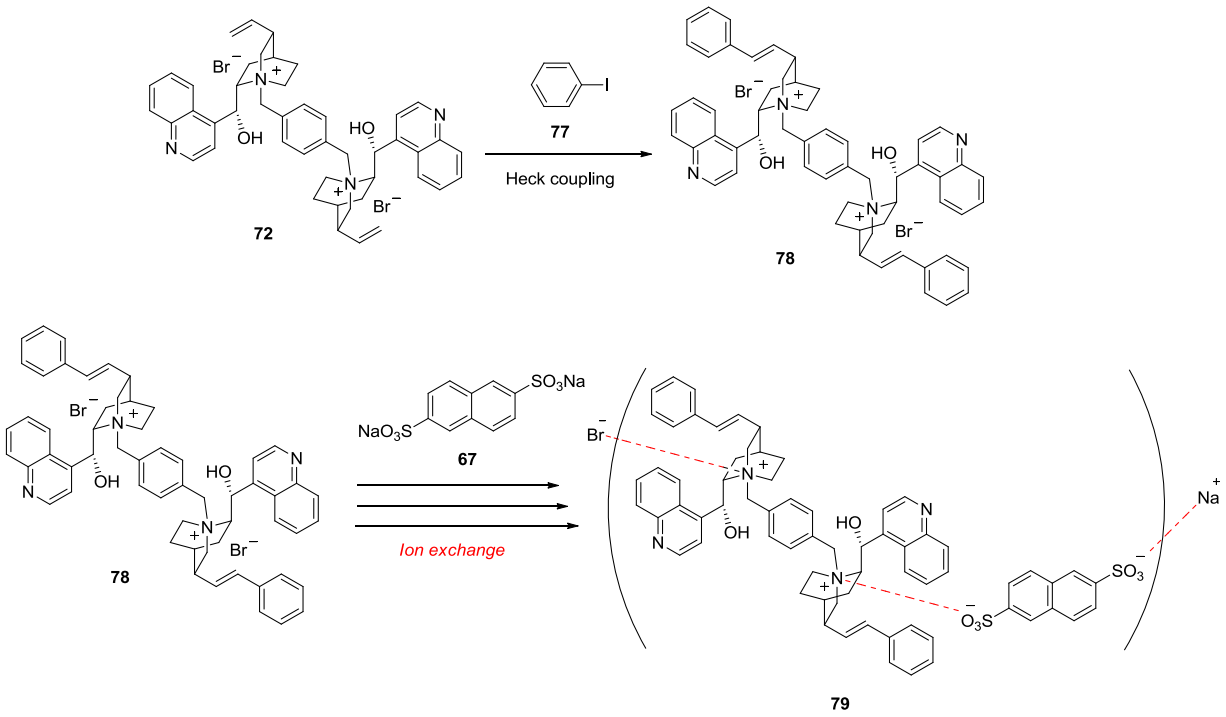
Ionic dimer **69** can easily be prepared by *ion exchange* reaction between cinchonidium salt and disulfonate. When equimolar amount of **69** and **70** reacts together by Heck reaction, main-chain chiral polymer **71** is obtained. Another polymer **73** also can be obtained in a similar manner by Heck reaction from cinchonidium dimer **72** and aryldiiodide **70** (Scheme 2.26).[46]

Cinchonidine dimer **74** can easily be prepared using Heck coupling reaction between **56** and **70**. When equimolar amount of **74** and **75** reacts together, subsequent quaternization between **74** and dilhalide **75** gives the main-chain chiral polymer **76** (Scheme 2.27).[46]

Other types of dimer **78** also can be obtained by Heck coupling reaction between cinchonidium dimer **72** and iodobenzene **77.** *Ion exchange* polymerization between dimer **78** and disulfonate **67** gives the chiral ionic polymer **79** (Scheme 2.28).[46]

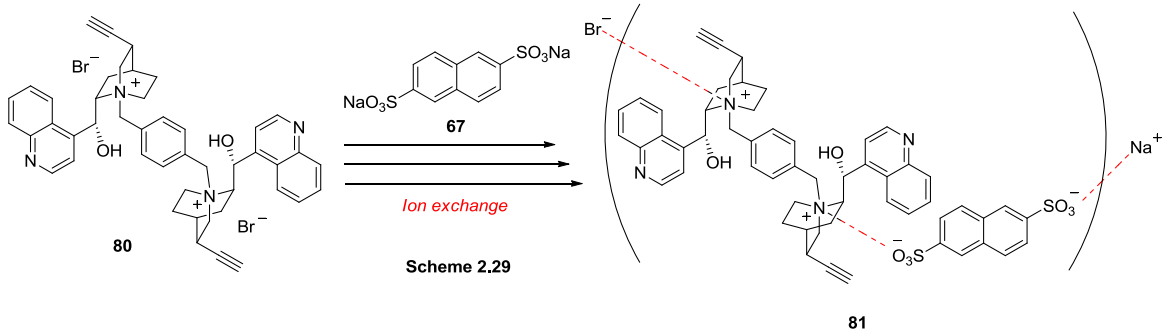


Scheme 2.27 *Dimer formation by Heck coupling (2) and quternization polymerization*



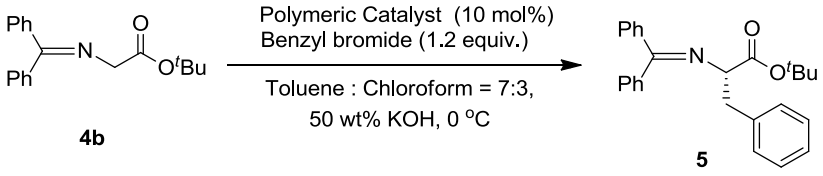
Scheme 2.28 *Chemical modification (3) and ion exchangePolymerization*

We have also utilized the 10, 11 dehydrocinchonidine for the synthesis of dimer **80.** Then by *ion exchange* polymerization we obtained main-chain chiral polymers **81** (Scheme 2.29).[47]



Scheme 2.29

Main-chain chiral polymers obtained from Scheme 2.26~Scheme 2.29 was applied in asymmetric benzylation of glycine derivative **4b** and quite a high yield and enantioselectivity was obtained (Scheme 2.30).



4b **5**

Scheme 2.30

with **71**: 69%, 65% ee
with **73:** 83%, 91% ee
with **76**: 84%, 72% ee
with **79**: 78%, 90% ee
with **81**: 94%, 83% ee

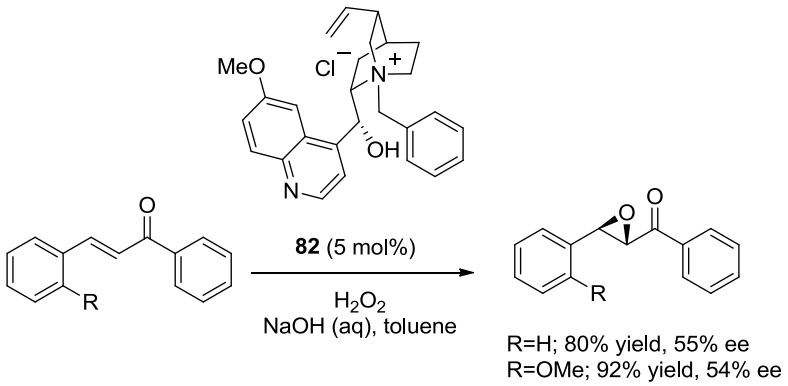
2.11. Cinchona-Based Organocatalysts for Asymmetric Oxidations

2.11.1. Introduction

The asymmetric oxidation of SP^2 carbons are most important approaches controlling the absolute configuration of asymmetric SP^3 can be achieved through facial selectivity. Although transition metal-metal based reactions have been well established for these oxidations and reductions, the sensitivity of the reaction conditions toward moisture and oxygen, as well as toxic metal contamination in the product, restrict their large-scale application. Thus, at present, there is much interest in chiral organocatalysts, as they tend to be less toxic and more environmental friendly than traditional metal-based catalysts.[48] They are usually robust and thus tolerate moisture and oxygen, so that they usually do not demand any special reaction conditions.

Two complementary methodologies have been developed for the asymmetric epoxidation of electron-poor olefins, where either cinchona based phase transfer catalysts (PTCs) or 9-amino-9-(deoxy)-epi-cinchona alkaloids are used as organocatalyst. Mechanistically, in these two methodologies, the reaction proceeds via a chiral ion pairing mechanism and iminium catalysis, respectively. The catalytic asymmetric epoxidation of electron-deficient olefins has been regarded as one of the most representative asymmetric PTC reactions.

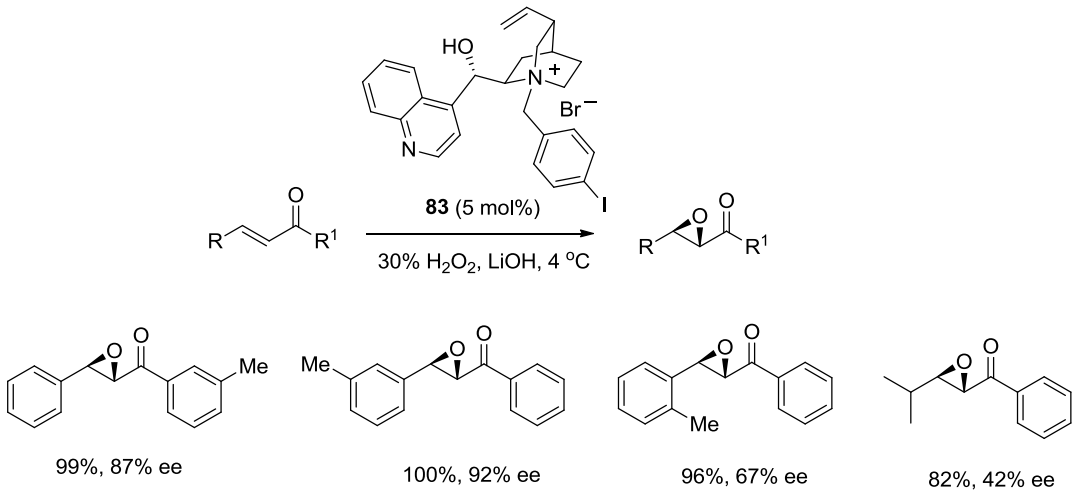
However, one drawback associated with this process is the substrate limitation. High enantioselectivites can be achieved only with acylic enones. With most cyclic enones, cinchona based chiral PTCs gave only poor to moderate enantioselectivities. The inherent difficulties in the enantioselective epoxidation of cyclic enones using PTCs have quite recently, been overcome by adopting the iminium catalysis approach, in which 9-amino-epi-cinchona alkaloids are employed as catalysts. Using this approach, most β-substituted cyclic enones afford the corresponding epoxides with excellent ee values. Here again, iminium catalysis using 9-amino-epi-cinchona alakaloids has proven to be quite successful.



Scheme 2.31

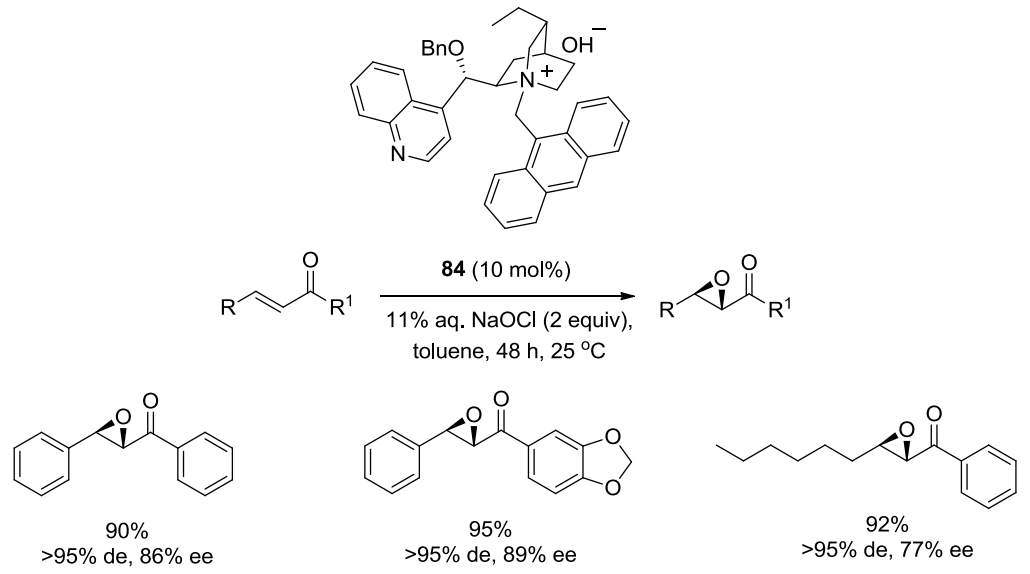
The asymmetric epoxidation of electron-deficient olefins using stoichiometric oxidant (e.g., hydrogen peroxide, an alkyl hydroperoxide or sodium hypochlorite) has been regarded as one of the most representative asymmetric PTC reactions. The pioneering studies by Wynberg during the 1970s established that cinchona based chiral PTCs can be used to effect this reaction. However, only low to moderate enantioselectivities (up to 55% ee) were obtained in the epoxidation of trans-chalcone derivatives with basic hydrogen peroxide using *N*-benzylquinium chloride **82** as a phase transfer catalyst (Scheme 2.31)[49] interestingly, the absolute configuration of the product highly depended on the type of oxidant used. For example, the opposite absolute configuration of the products was obtained on switching from bleach (NaOCl) to H_2O_2.[50]

An improvement of the enantioselectivity (ee values of more than 90%) was reported independtly by the Arai, Lygo, corey, and park-Jew groups. Aria and coworkers observed that a dramatic jump in the ee values could be achieved simply by introducing the iodo group at the para position on the phenyl ring of the *N*-benzyl moiety of the wyneberg type PTC **82.** Using 5 mol% of the *N*-4-iodobenzyl derivative **83** as a catalyst along with aqueous H_2O_2 as an oxidant, the epoxidation of trans-chalcones proceeded smoothly under biphasic conditions (aqueous LiOH, *n*-Bu_2O, 4 ^oC) to afford the corresponding epoxides in quantitative yields with much higher ee values (up to 92% ee) than obtained using Wyneberg's catalyst **82** (Scheme 2.32).[51]



Scheme 2.32

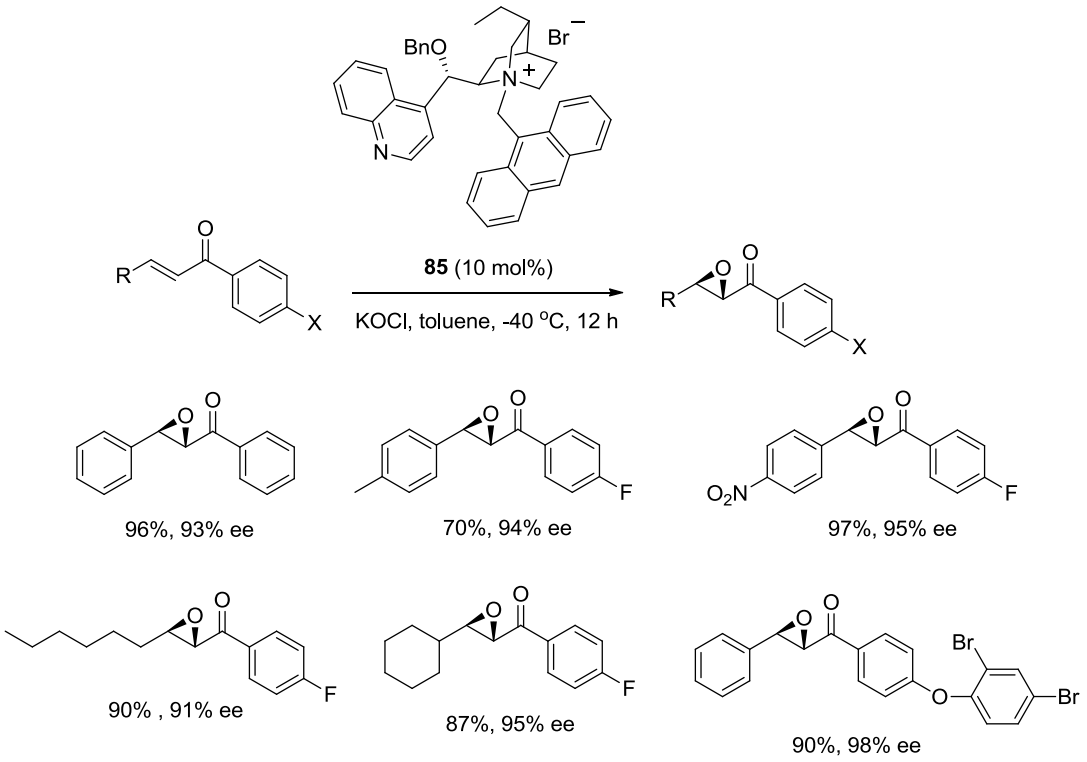
The Lygo and Corey groups independently reported that the cinchona-based PTCs **84** and **85** bearing an *N*-anthracenylmethyl function exhibited significantly increased enantioselectivity. Using *O*-benzylated *N*-anthracenylmethyl dihydro-cinchonidium hydroxide **84** (10 mol%) as a catalyst with aqueous sodium hypochlorite as an oxidant, acylic enones can be smoothly oxidized to the corresponding epoxidation in excellent yields with high enantioselectivity values (76-89%) (Scheme 2.33).[52]



Scheme 2.33

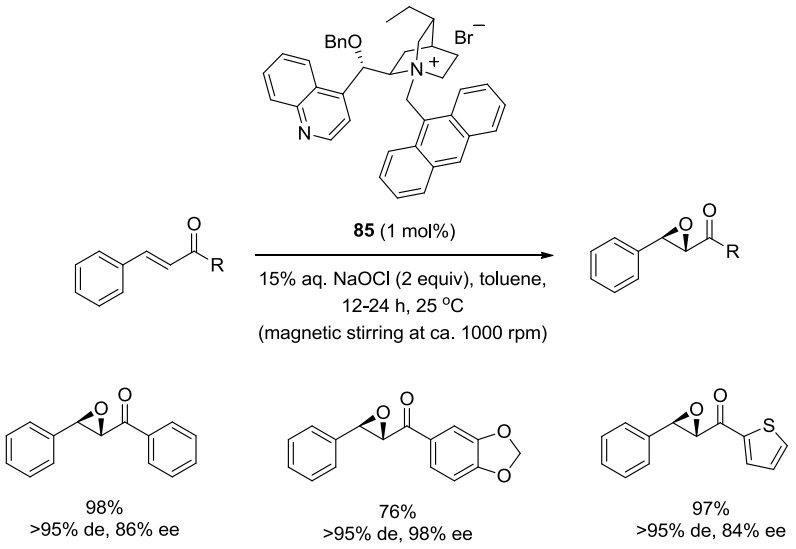
A further improvement was achieved by replacing the hydroxide anion of **84** with the bromide anion. The reaction of various α,β-enones with aquous KOCl as an oxidant were

found to take place quite efficiently in the presence of 10 mol% of catalyst **85** in toluene at -40 ^{o}C. Very high enantioselectivities (ranging from 91 to 98.5% ee) of the epoxide products were obtained along with excellent yields (70~96%) in most cases. (Scheme 2.34).[53] To explain the observed sense of the stereoselectivity and rate acceleration effect of **85,** Corey proposed a plausible transition-state structure that allows for the charge-accelerated, face-selective conjugate addition of the ion-paired hypochlorite.



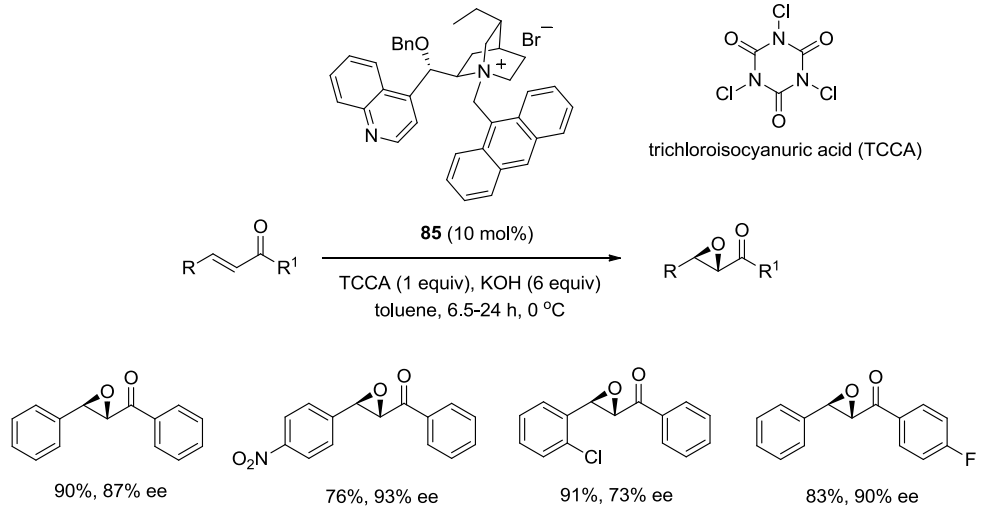
Scheme 2.34

Another optimization study by Lygo's group revealed that only 1 mol% of catalyst **85** is sufficient to give almost the same results (Scheme 2.35)[54] Under asymmetric PTC conditions using **85** as a catalyst, Lygo also reported that allyl alcohols with aromatic and aliphatic side chains could be converted directly to epoxyketones with moderate to good ee values.[55]



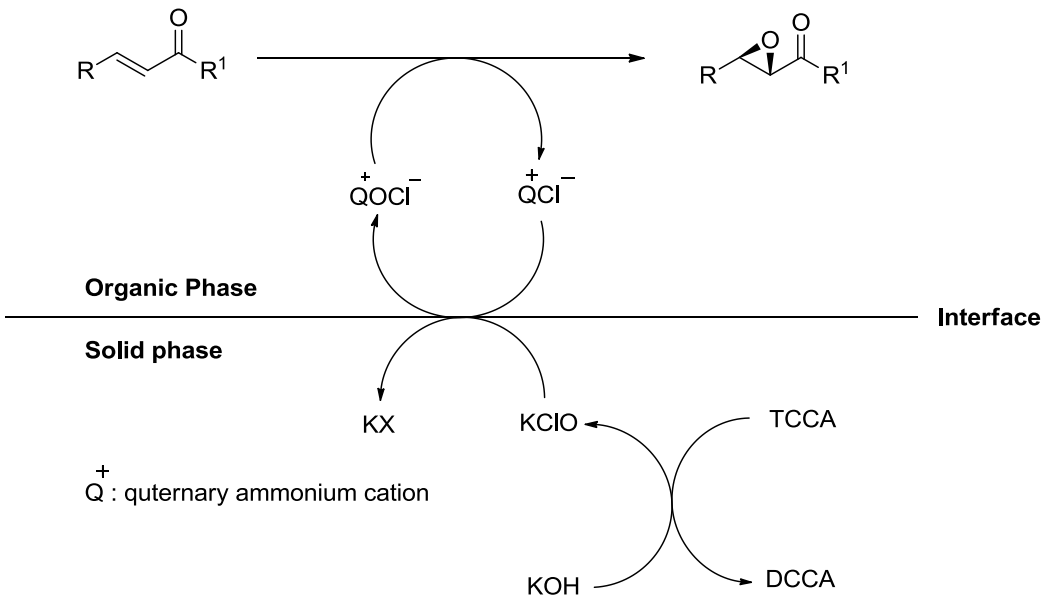
Scheme 2.35

Later on, Liang and coworkers successfully employed trichloroisocyanuric acid (TCCA) as a new type of stoichiometric oxidant for the asymmetric epoxidation of acyclic enones in the presence of 10 mol% of catalyst **85** (Scheme 2.36).[56]



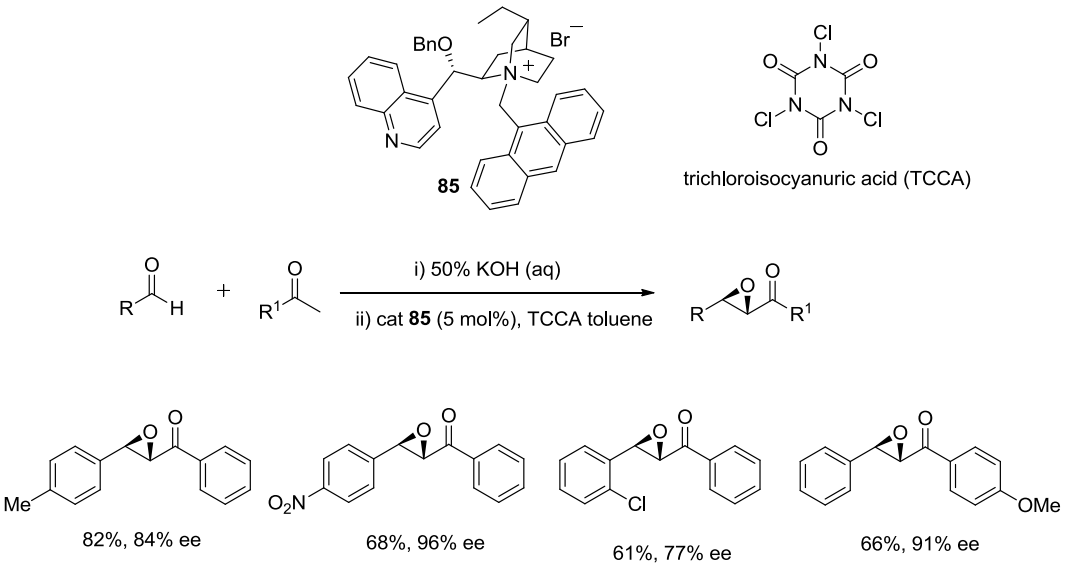
Scheme 2.36

The desired epoxy ketones were obtained in good yields (69~93%) with high enantiselectivities (73~93% ee) under nonaqueous solid-liquid conditions.[56b] In this reaction TCCA reacts with an inorganic base (KOH) to form a hypochlorite salt, which is transferred to the organic phase by the phase-transfer catalyst and oxidizes the enones to the corresponding epoxy ketones (Scheme 2.37).



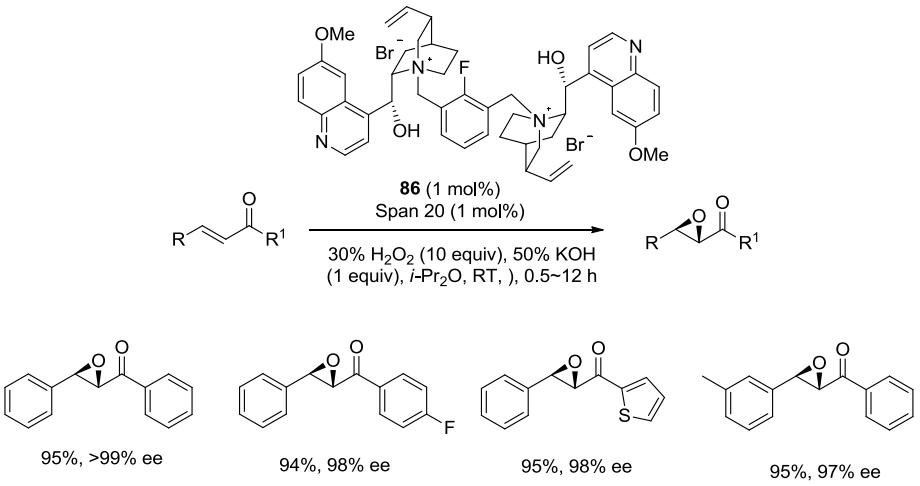
Scheme 2.37

Later, Liang and coworkers successfully extended their protocol to a tandem Claisen-Schmidt condensation-epoxidation sequence, providing a one pot entry to enantioenriched α,β-epoxy ketones (Scheme 2.38).[57]



Scheme 2.38

Quite recently, one of the most efficient phase-transfer-catalyzed epoxidation methods for chalcone-type enones was developed by the Park-Jew group.[58] A series of meta-dimeric cinchona PTCs with modified phenyl linkers were prepared. Among this series, the 2-fluoro substitute's catalyst **86,** exhibited unprecedented activity and enantioselectivity for the epoxidation of various trans-chalcones in the presence of surfactant such as Triton X-100, Tween 20, or Span 20. Using just 1 mol% of the dimeric alkaloid catalyst **86,** 1 mol% of span 20, 30% aqueous H_2O_2 and 50% KOH in diisopropyl ether, the corresponding epoxided were obtained in nearly quantitative yields and excellent enantioselectivities (97% to 99% ee) at room temperature (Scheme 2.39).



Scheme 2.39

A plausible transition-state model was proposed by the authors in which the chalcone located between two cinchona units in the catalyst **86,** and the β-phenyl moiety of the chalcone has a π-π stacking interaction with one of the quinolone moieties in **86**. The carbonyl oxygen atom is placed as close to one of the ammonium cations as permitted by Vander Waals forces. The other ammonium cation is ion paied with the hydrogen peroxide ion through hydrogen bonding with the oxygen of the 6′-OMe group in the quinolone moiety. As a consequence, the hydrogen peroxide anion can only approach the β-carbon of the chalcone from above in the 1,4-addition to afford the αS, βR-stereoisomer (Figure 4).

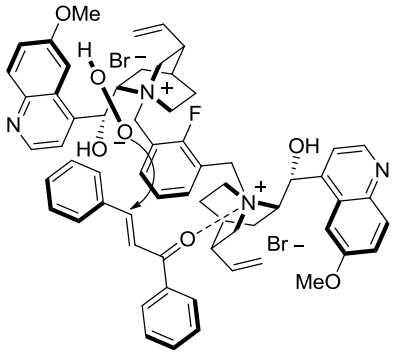


Figure 4 Plausable transition state for theb asymmetric epoxidation catalyzed by **86**

Wang and coworkers reported the asymmetric epoxidation of chalcone derivatives using polyethylene glycol (PEG) supported cinchona-based dimeric PTCs and *tert*-buyl hydroperoxide as an oxidant. However, only low to moderate ee values 33-86% ee were obtained.[59]

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Chapter 3

Molecular design of chiral quaternary ammonium polymers for asymmetric catalysis applications

3. 1. Introduction

In asymmetric synthesis, chiral organocatalysts have received a considerable amount of attention in recent years as chiral organocatalysts meet the green chemistry requirements. One of the important chiral organocatalysts is optically active quaternary ammonium salt, which can be utilized in various kinds of asymmetric transformations. The development of the asymmetric quaternary ammonium catalyst was triggered by the pioneering studies of the Merck research group in 1984. They reported the α-substitution of phenylindanone derivative in the presence of cinchonine derived chiral quaternary ammonium salt. The α-alkylated product was obtained in excellent yield with high enantiomeric excess.[1,2] Inspired by the Merck results, O'Donnel group first reported the asymmetric alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester using cinchona derived quaternary ammonium catalysts.[3–5] Based on O'Donnel's results, Lygo[6,7] and Corey et al.[8–10] independently developed highly effective catalysts for the same reaction, which were derived from cinchonidine. Furthermore, Park and Jew developed new catalysts consisting of dimeric and trimeric quaternary ammonium salts derived from cinchonidine.[11–15] They designed appropriately positioned catalytic active sites on the catalyst molecule.

Although highly efficient quaternary ammonium organocatalysts have been developed, we sometimes encounter problems in their separation from the reaction mixture mainly due to their amphiphilic properties. In comparison with transition metal catalysts, a relatively large amount of the organocatalyst is required to complete the reaction. Separation of the quaternary ammonium organocatalyst is an important process in the reaction. In order to overcome the separation issue, a number of polymer-immobilized quaternary ammonium catalysts have been prepared.[16] The first report on the asymmetric alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester using crosslinked polystyrene-immobilized cinchona-derived quaternaryammonium salts was made by Hodge et al.[17] Improvement in the catalytic activity of the same polymeric catalyst was achieved by Najera et al.[18–21] Polymer-immobilized cinchona alkaloid salts with spacers were used in the same reaction.[22–

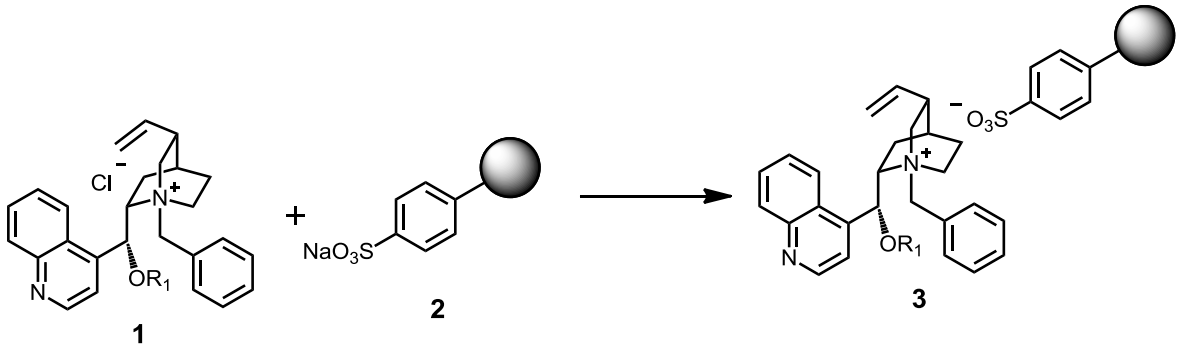
[24] Some other examples of immobilized cinchona ammonium salts have been developed.[25–27] In 2008 we proposed a new methodology of immobilization of quaternary ammonium salts in a polymer-support.[28] Our method involves a stable ionic bond between the polymer support and catalyst. Chiral quaternary ammonium salt organocatalyst was attached to polymeric sulfonate through ammonium sulfonate linkage, which is stable enough to immobilize the organocatalyst in the polymer-support.

Highly stable ionic linkage of the quaternary ammonium sulfonate made us aware of the main-chain chiral polymers containing the ionic bond between the repeating units. Reaction of bisquaternary ammonium halide and disodiumsulfonate yielded the polymeric compound containing quaternary ammonium sulfonate linkages in their main-chain.[29] In asymmetric organocatalysis, only a limited number of investigations to elucidate the use of main-chain functionalized chiral polymers have been performed.[30–32] In this article, we report the details of the synthesis of novel chiral polymers with ionic linkages between the repeating units. The catalytic activity of the chiral polymers in the asymmetric alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester was also discussed.

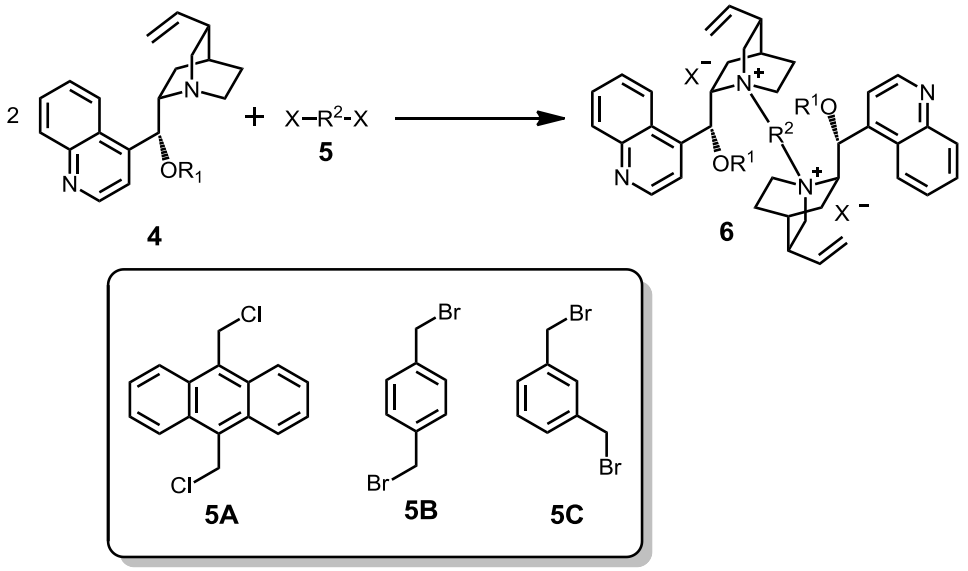
3. 2. Results and discussion

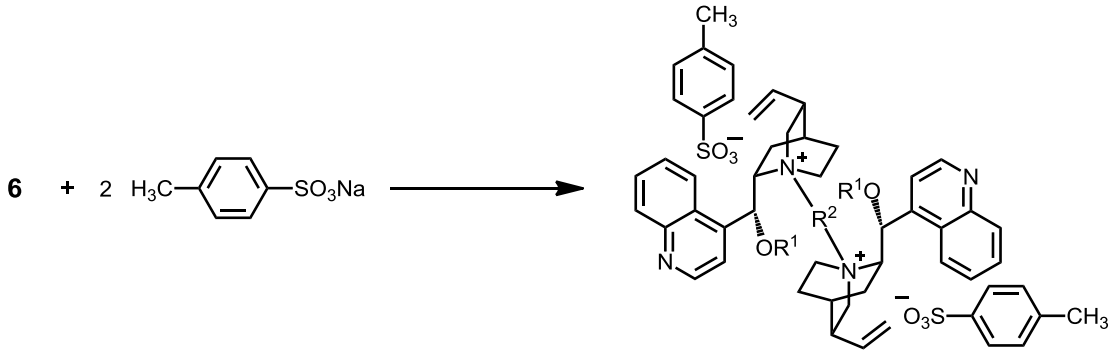
The reaction between quaternary ammonium salt and sulfonate smoothly occurred to give the quaternary ammonium sulfonate. For example, polymer-supported cinchonidium sulfonate **3** was easily prepared from the reaction of crosslinked polymer **2** possessing SO_3Na pendant groups with cinchonidine quaternary ammonium salt **1** as shown in Scheme 1. Ionically immobilized quaternary ammonium salt was stable enough to be used as a catalyst for asymmetric reaction.[28] In order to apply this quaternary ammonium sulfonate formation reaction to polymer synthesis, we prepared dimeric quaternary ammonium halide of cinchonidine **6**. As a model reaction of polymerization, we examined ion exchange reaction between **6** and sodium toluene- 4-sulfonate **7** (Scheme 2). The reaction easily occurred to give the corresponding bissulfonate **8** in quantitative conversion. If disulfonate is used instead of the sulfonate **7**, we realized that the stable ionic bond formation reaction can be utilized for the novel type of polymer synthesis. Ion-exchange reaction between bis (quaternary ammonium halide) and disulfonate may give quaternary ammonium sulfonate polymer, which contains ionic bonds between each repeating units. To the best of our knowledge, this

is a new polymerization method (ion-exchange polymerization) for producing a chiral polymer main-chain structure, which we term "ionic polymer". The ion-exchange polymerization requires no catalyst and proceeds simply at room temperature, which may provide a various kinds of ionic polymers including chiral polymers. Since the chiral quaternary ammonium salts act as organocatalyst in various kinds of asymmetric transformation, the generated chiral ionic polymers should be used as catalyst for the asymmetric reactions.



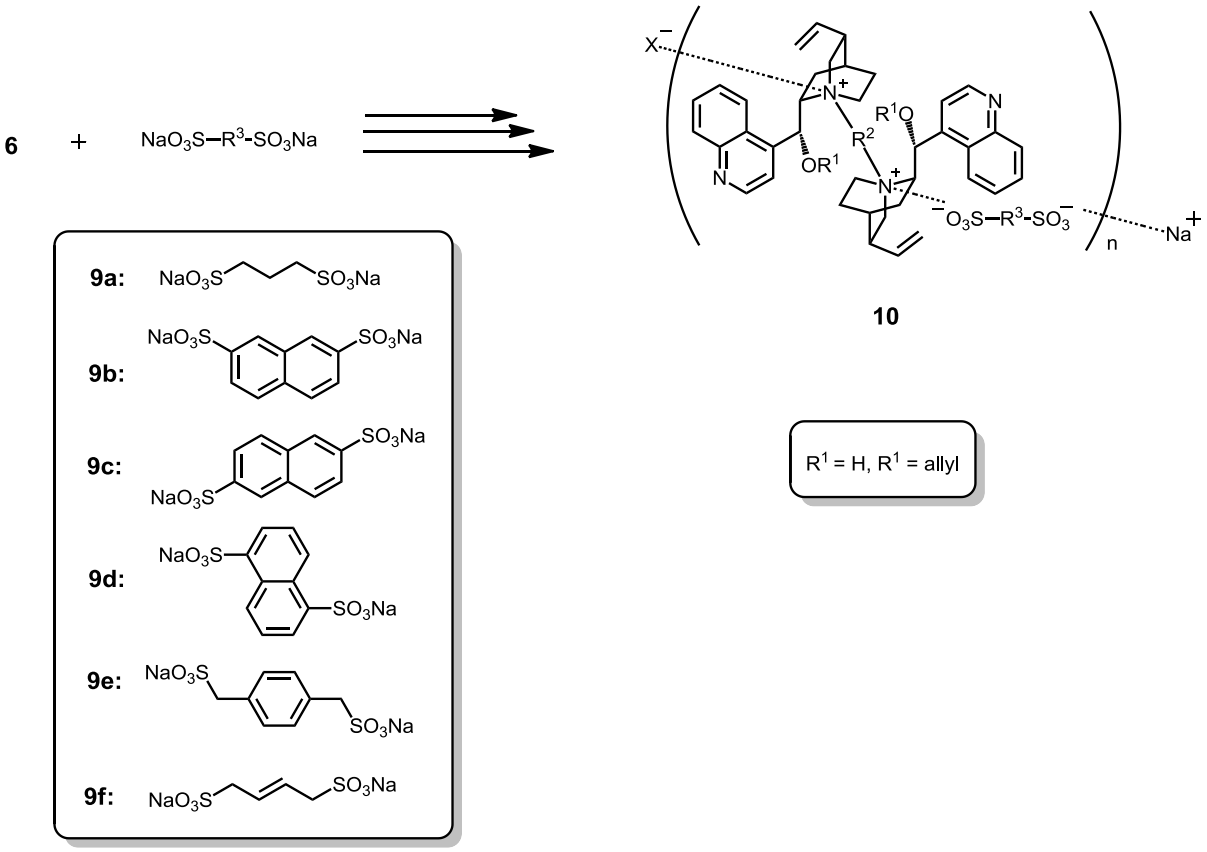
Scheme 1 Syntheis of ionicallyimmobilized cinchonidium salt





Scheme 2 Syntheis of cinchonidium sulfonate dimer

In our preliminary experiments we found that the reaction between dimeric quaternary ammonium salt **6** and 2,6- naphthalene disulfonate **9c** smoothly occurred to give the corresponding chiral polymer **10** in high chemical yield (Scheme 3).[29] As illustrated in Scheme 3, the repeated ion exchange reaction occurred to give the ionic bond between the monomers. This is the first example of the chiral ionic polymer synthesis by ion-exchange polymerization. In this study, we have synthesized various kinds of dimeric quaternary ammonium salt **6** from cinchonidine **4** and dihalides **5**. Various kinds of disulfonates **9** were used to form chiral ionic polymers **10** (Scheme 3).



Scheme 3 Synthesis of cinchonidine derived chiral ionic polymer

The effects of the structure variation of the chiral polymers on the catalytic activity in the asymmetric alkylation reaction have been investigated. The procedure of ion-exchange polymerization is very simple. A solution of the chiral ammonium dimer **6** in organic solvent was treated with the equimolar amount of disulfonate **9** in water to afford the precipitation of the ionic chiral polymer **10**. Disulfonates **9e** and **9f** were synthesized from the corresponding chlorides, while the other disulfonates are all commercially available. Secondary OH group of cinchonidine can be easily modified by ether formation. Since the *o*-allylated cinchonidine derivatives as chiral organocatalyst gave higher catalytic activities in some asymmetric reactions,[8] we synthesized O-allylated compounds (R^1 = allyl). The 10,11-vinyl group of cinchonidine can also be chemically modified. As a simple example, we modified the vinyl group by hydrogenation to give 10, 11-dihydrocinchonidine **11**. The corresponding quaternary ammonium salt dimers **12** derived from **11** were also prepared and polymerized with disulfonates **9** to give **13** (Scheme 4). All the chiral ionic polymers obtained from the ion-exchange polymerization showed low solubility in common organic solvents except for dimethyl sulfoxide. Intrinsic viscosity [η] of the dimethyl sulfoxide solution of the polymers measured in dimethyl sulfoxide at 40 ^{o}C was in the range of 0.1 to 0.2. The successful application of cinchona-based quaternary ammonium salts as a chiral organocatalyst in asymmetric methylation of phenylindanone by Merck research group[1] initiated the further development of the related organocatalysts. Park et al.[11] first reported that chiral quaternary ammonium dimers derived from cinchona alkaloid gave higher enantioselectivity compared to the corresponding monomeric salts in the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **14** (Scheme 5).

We synthesized several chiral quaternary ammonium salt dimers **6**, **12** and **8**, which were applied to the same asymmetric reaction. Results of the asymmetric benzylation using these dimeric catalysts are summarized in Table 1. In case of OH free dimeric catalysts, anthryl linker A showed higher enantioselectivities in comparison with xylyl linkers B or C (entries 1 and 2, 3, entries 4 and 5, 6, entries 13 and 14, 15, respectively). The dimeric catalysts **8** having sulfonate counter anion showed the catalytic activity similar to 6. The asymmetric benzylation with *O*-allylated catalysts (entries 7–12) showed the opposite tendency of the catalytic activity in the same reaction. *O*-allylated catalyst having 1,3-xylyl type linker C gave the highest ee (entries 9 and 12).

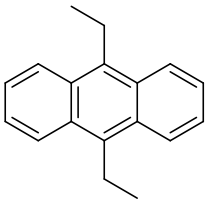
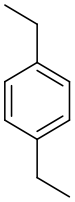
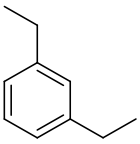
Table 1 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[cd] (%)
1[e]	**6AH**	6	88	86
2[f]	**6BH**	12	91	80
3[g]	**6CH**	4	90	84
4	**12AH**	4	95	95
5	**12BH**	4	89	89
6	**12CH**	4	76	71
7[e]	**6AAllyl**	1	84	70
8[h]	**6BAllyl**	4	92	80
9[h]	**6CAllyl**	2	91	90
12[g]	**12CAllyl**	4	94	93
13	**8AH**	8	86	89
14	**8BH**	8	93	78
15	**8CH**	7	86	65

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 °C. [b]Determined by ^{1}H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref. 20. [f]See ref. 29. [g]See ref. 15. [h]See ref. 11.

Cinchonidine derived ionic polymers **10** were then used as chiral catalysts for the asymmetric benzylation reaction. Since these polymers are not soluble in both the aqueous phase and organic phase, the polymers are suspended between the two phases. In all cases, the asymmetric benzylation of glycine tertbutyl ester **14** smoothly occurred under reaction conditions similar to those for the dimeric catalyst. For example, the ionic polymer catalyst **10AaH** prepared from cinchonidinium dimer **6AH** and disodium 1,3-propanedisulfonate **9a** was used in the asymmetric benzylation reaction to give the corresponding chiral product **15** in 86% yield with 87% ee (Table 2, entry 1). The catalytic activity of the polymeric catalyst **10AaH** is similar to that of the corresponding dimer catalyst **6AH**. The structure of disulfonate influenced on the catalytic activity of the ionic polymer catalyst. In a series of **10AH** catalysts (entries 1–8), trans-butenyldisulfonate gave the highest ee (entry 8). By using **10AeH**, the recyclability of the polymeric catalyst was examined. The polymeric catalyst was easily separated from the reaction mixture due to its insolubility. When the recovered catalyst was used for the same reaction, the polymeric catalyst showed the same catalytic activity as that obtained from the original catalyst. When *O*-allylated catalysts 1**0AAllyl** (entries 9–13) were used, lowering of the ee values in the asymmetric benzylation was observed.

Table 2 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using cinchonidine derived ionic polymer **10**[a]

Entry	R^2	Catalyst	Time (h)	Yield[b] (%)	ee[cd] (%)
1		**10AaH**	16	86	87
2		**10AbH**	22	55	74
3		**10AcH**	48	83	87d
4		**10AdH**	16	86	87
5		**10AeH**	12	87	88
6f		**10AeH**	14	88	88
7g		**10AeH**	14	89	88
8		**10AfH**	5	92	92
9		**10AaAllyl**	5	88	69
10		**10AbAllyl**	5	85	75
11		**10AcAllyl**	5	77	63
12		**10AdAllyl**	5	82	87
13		**10AeAllyl**	4	93	82
14		**10BaH**	7	94	88
15		**10BbH**	12	91	80
16		**10BcH**	15	92	82e
17		**10BdH**	8	86	85
18		**10BeH**	12	91	89
19		**10BfH**	6	94	88
20		**10BaAllyl**	5	91	86
21		**10BbAllyl**	5	88	85
22		**10BcAllyl**	20	90	91[e]
23		**10BdAllyl**	5	95	85
24		**10BeAllyl**	5	92	91
25		**10BfAllyl**	16	96	85
26		**10CaH**	12	55	61
27		**10CbH**	12	73	66
28		**10CcH**	12	75	60[e,h]
29		**10CdH**	15	76	63
30		**10CeH**	18	67	68
31		**10CfH**	16	84	69
32		**10CaAllyl**	5	88	91
33		**10CbAllyl**	6	90	92
34		**10CcAllyl**	15	86	92[e]
35		**10CdAllyl**	4.5	83	91
36		**10CeAllyl**	4.5	92	94
37		**10CfAllyl**	4	95	92

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 °C. [b]Determined by ^1H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref. 29. [f]The polymeric catalyst **10AeH** used in entry 6 was reused. [g]The polymeric catalyst **10AeH** used in entry 7 was reused. [h]At room temp.

In the series of 10BH catalysts, enantioselectivities similar to those from **10AH** catalysts were obtained (entries 14–19). The selectivity did not decrease with the *O*-allylated catalysts **10BAllyl** (entries 20–25). Enantioselectivities obtained by using the polymeric catalyst **10B**

are always higher than those obtained from the corresponding dimeric catalysts described in Table 1. Polymeric catalysts **10CH** containing meta-substituted linker gave the lower enantioselectivity in the same reaction (entries 26–31). However, interestingly, *O*-allylated catalysts **10CAllyl** showed high level of enantioselectivities in all cases (entries 32–37). This tendency was also found in the corresponding dimer catalyst series **6CH** and **6CAllyl** (Table 1). In case of *O*-allylated polymeric catalysts **10CAllyl**, slightly higher enantioselectivity compared with the corresponding dimeric catalysts **6CAllyl** was obtained. All the polymeric catalysts used were stable and no degradation of the polymers was detected during the reaction. We recovered the polymeric catalyst by simple filtration. Before and after the reaction, the intrinsic viscosity values [η] and NMR spectra of the polymeric catalyst did not change.

Table 3 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using hydrocinchonidine derived ionic polymers **13**[a]

Entry	Catalyst	Temp. ^{o}C	Time (h)	Yield[b] (%)	ee[cd] (%)
1	**13AeH**	0	4.5	88	86
2	**13AeH**	-20	7	91	80
3	**13AeH**	-40	30	90	84
4	**13AfH**	0	4	95	95
5	**13BeH**	0	4.5	89	89
6	**13BfH**	0	4	76	71
7	**13CeH**	0	4.5	84	70
8	**13CfH**	0	4	92	80
13	**13CeAllyl**	0	4.5	91	90
14	**13Cfllyl**	0	4	94	93

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 ^{o}C. [b]Determined by ^{1}H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration.

Chiral ionic polymers **13** prepared from 10,11-dihydrocinchonidine **11** were then used as a catalyst for the same asymmetric reaction. Polymeric catalyst **13AeH** showed an excellent catalytic activity with 95% ee (Table 3, entry 1). When the reaction temperature was lowered to −20 °C, higher enantioselectivity (97% ee) was obtained (entry 2). The reaction still occurred even at −40 °C to give the product in high conversion with high enantioselectivity (entry 3). *O*-allylated polymeric catalysts **13CAllyl** showed excellent catalytic activity with higher enantioselectivities in comparison with OH free catalysts **13CH**.

3. 3. Conclusions

We have prepared chiral ionic polymers from cinchonidine quaternary ammonium dimer and disulfonate. Repeated ion exchange reaction occurred smoothly to give the corresponding chiral ionic polymer (**10**, **13**). The synthesis of the chiral ionic polymer is simple and quantitative. The chiral ionic polymers showed excellent performance as catalyst in the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **14** to give phenylalanine derivative **15**. A high level of enantioselectivities up to 97% ee was obtained in this reaction with the chiral polymeric catalysts. Most of the enantioselectivities obtained with the polymeric catalyst are superior to those from the corresponding low-molecular-weight catalyst. Since the ionic polymers were insoluble in water and most of the usual organic solvent, their separation from the reaction mixture is easy and could be reused several times without loss of catalytic activity. During the reaction, the ionic polymers are stable and no change in the polymer structure was observed. The polymers used in the asymmetric reaction were quantitatively recovered as original.Various kinds of main-chain chiral polymers can be prepared by this novel strategy. This method will be applicable to the preparation of many other different chiral organocatalysts having ionic structure.

3. 4. Experimental

General

All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd, or Tokyo Chemical Industry Co., Ltd at the highest available purity and used as is unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). Column chromatography was performed with a silicagel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. 1H (300 MHz) spectra were measured on a Varian Mercury 300 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. GC analyses were performed with a Shimadzu Capillary Gas Chromatograph 14B equipped with a capillary column (SPERCO β-DEX 325, 30 m × 0.25 mm). HPLC analyses were performed with a JASCO HPLC system comprising a three-line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCEL OD or AD, Daicel); hexane–2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10 cm thermostated microcell. Intrinsic viscosity [η] of each soluble sample was determined by viscosimetry, using a Ubbelohde viscometer at 40 °C in dimethyl sulfoxide (DMSO) solvent.

Synthesis of 8AH

A mixture of cinchonidine dimer **6AH** (0.5 mmol, 0.43 g) in methanol (40 mL) and sodium *p*-toluene sulfonate (1.5 mmol, 0.2913 g) in water (10 mL) was stirred for 3 hours. Methanol was evaporated and the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the product was dried under vacuum to give a yellow solid **8AH** in 85% yield. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.14 (d, J = 9.0 Hz, 2H), 9.07–9.05 (m, 2H), 8.87 (d, J = 9.0 Hz, 2H), 8.62–8.56 (m, 2H), 8.17 (dd, J = 1.8, 1.8, 2H), 7.97–7.80 (m, 12H), 7.31–7.27 (m, 4H), 7.23 (d, J = 3.6 Hz, 2H), 7.09 (s, 2H), 7.04–7.01 (m, 4H), 6.60 (d, J = 13.2 Hz, 2H), 5.98 (d, J = 11.4, 2H), 5.76–5.60 (m, 2H), 5.06–4.90 (m, 4H), 4.61–4.44 (m, 4H), 3.93 (d, J = 11.1, 2H), 3.30–3.22 (m, 4H), 3.02–2.89 (m, 2H), 2.25–2.16 (m, 8H), 1.94–1.84 (m, 2H), 1.68–1.51 (m, 2H), 1.38–1.30 (m, 2H). ^{13}C NMR (d^6 -DMSO, 75 MHz) δ 150.3, 147.8, 145.69, 145.17,

138.4, 137.9, 123.05, 123.00, 129.83, 129.58, 128.1, 127.3, 126.5, 125.90, 125.29, 124.59, 124.48, 120.4, 116.35, 68.0, 65.2, 60.9, 54.6, 51.7, 36.7, 25.3, 24.2, 21.55, 20.8 ppm. $[\alpha]_D^{25} = -329.10\ (c\ 1.0, \mathrm{DMSO})$. IR (KBr) ν 3230, 2949, 1941, 1660, 1590, 1509, 1453, 1180, 1120, 1032, 1009. mp: 205–207 ^{o}C. Anal. Calcd for $C_{68}H_{70}N_4O_8S_2$: C, 71.93; H, 6.21; N, 4.93. Found: C, 71.75; H, 6.17; N, 4.89.

Synthesis of 8BH

A mixture of cinchonidine dimer **6BH** (0.5 mmol, 0.42 g) in methanol (35 mL) and sodium *p*-toluene sulfonate (1.5 mmol, 0.2913 g) in water (10 mL) was stirred for 2 hours. The methanol was evaporated and the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the product was dried under vacuum to give a yellow solid **8BH** in 88% yield. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.00 (d, J = 4.5 Hz, 2H), 8.29 (d, J = 8.10 Hz, 2H), 8.13 (d, J = 8.10 Hz, 2H), 7.95–7.74 (m, 12H), 7.45 (d, J = 7.8, 3H), 7.09 (dd, J = 0.6, 0.3, 3H), 6.78 (d, J = 4.2, 2H), 6.59 (s, 2H), 5.76–5.65 (m, 2H), 5.20–5.13 (m, 4H), 5.05–4.96 (m, 4H), 4.28 (s, 2H), 3.96–3.90 (m, 2H), 3.75 (d, J = 13.5, 2H), 3.50–3.42 (m, 3H), 2.73 (s, 3H), 2.27 (s, 5H), 2.20–2.02 (m, 7H), 1.87 (s, 2H), 1.36–1.28 (m, 2H). ^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 147.7, 145.4, 138.30, 138.29, 137.9, 134.2, 129.92, 129.80, 129.54, 128.2, 127.3, 125.5, 124.3, 123.6, 120.2, 116.3, 67.8, 64.3, 62.2, 59.3, 50.7, 36.7, 26.0, 24.1, 21.1, 20.8 ppm. $[\alpha]_D^{25} = -125.16\ (c\ 1.0, \mathrm{DMSO})$. IR (KBr) ν 3207, 2952, 1942, 1656, 1589, 1509, 1461, 1217, 1172, 1120, 1032, 1009, 818, 777, 681, 567. mp: 221–223 ^{o}C. Anal. Calcd for $C_{60}H_{66}N_4O_8S_2$: C, 69.61; H, 6.43; N, 5.41. Found: C, 69.53; H, 6.40; N, 5.38.

Synthesis of 8CH

A mixture of cinchonidine dimer **6CH** (0.5 mmol, 0.42 g) in methanol (30 mL) and sodium *p*-toluene sulfonate (1.5 mmol, 0.2913 g) in water (10 mL) was stirred for 2 hours. Methanol was evaporated and the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the product was dried under vacuum to give a yellow solid **8CH** in 90% yield. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.98 (d, J = 3.90 Hz, 2H), 8.28–8.22 (m, 3H), 8.11 (d, J = 8.40 Hz, 2H), 7.87–7.81 (m, 6H), 7.74–7.69 (m, 3H), 7.47 (d, J = 7.5 Hz, 4H), 7.08 (d, J = 7.2 Hz, 4H), 7.00 (s, 2H), 6.61 (s, 2H), 5.73–5.62 (m, 2H), 5.29 (d, J = 11.7 Hz, 2H), 5.17 (s, 1H), 5.11–5.05 (m, 3H), 4.94 (d, J = 10.2 Hz, 2H), 4.33 (s, 2H), 3.96–3.90 (m, 2H), 3.74 (d, J = 10.2 Hz, 2H), 2.66 (s, 2H), 2.26 (s, 5H), 2.11–2.05 (m, 3H), 1.99 (s, 2H), 1.75 (s, 2H), 1.33–1.26 (m,

2H), 1.13 (d, J = 12.3 Hz, 4H), 0.94 (d, J = 6.6 Hz, 2H). ^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.6, 145.37, 145.04, 139.69, 139.25, 138.10, 138.07, 135.1, 129.89, 129.43, 128.6, 128.19, 127.3, 125.5, 124.3, 123.5, 120.1, 116.3, 67.9, 64.3, 59.2, 50.6, 46.2, 36.8, 25.9, 24.3, 20.8, 18.9 ppm. $[\alpha]_D^{25} = -127.43$ (c 1.0, DMSO). IR (KBr) ν 3247, 2512, 1920, 1640, 1590, 1570, 1509, 1460, 1208, 1118, 1032, 1009, 814, 777, 755, 683, 565. mp: 213–215 ^{o}C. Anal. Calcd for $C_{60}H_{66}N_4O_8S_2$: C, 69.61; H, 6.43; N, 5.41. Found: C, 69.55; H, 6.38; N, 5.35.

Synthesis of 12AH

A mixture of (-)-10,11-dihydrocinchonidine (3.0 g, 10.2 mmol) with 9,10-bis (chloromethyl) anthracene (1.38 g, 5 mmol) in a mixture of 30 mL (Ethanol:DMF:$CHCl_3$/5:6:2) was stirred at 100 ^{o}C for 6 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was diluted with methanol (25 mL) and then added dropwise to ether (300 mL) with stirring. The solid precipitated was filtered, washed with ether (200 mL). The crude solid was reprecipitated from methanol–ether to afford 3.82 g (88% yield) of product. $[\alpha]_D^{25} = -229.53$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.04–8.90 (m, 4H), 8.71–8.66 (m, 2H), 8.17–8.04 (m, 2H), 7.95–7.75 (m, 8H), 7.69–7.53 (m, 4H), 7.01 (brs, 1H), 6.58–5.41 (m, 3H), 4.69–4.38 (m, 2H), 4.00–3.41 (m, 3H), 3.20–3.11 (m, 2H), 2.20–1.93 (m, 4H), 1.75 (s, 4H), 1.52–1.37 (m, 5H), 1.31–1.02 (m, 8H), 0.75–0.70 (m, 3H), 0.55–0.519 (m, 5H). ^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.1, 147.70, 147.66, 147.14, 146.0, 132.8, 129.66, 129.23, 126.9, 124.67, 124.14, 120.5, 118.8, 65.7, 59.5, 54.9, 42.6, 34.6, 25.61, 25.47, 24.3, 22.5, 17.2, 11.3 ppm. IR (KBr) ν 3170, 2957, 2560, 1662, 1590, 1509, 1457, 1385, 781, 758. mp: 181–183 ^{o}C. Anal. Calcd for $C_{54}H_{60}N_4O_2Cl_2$: C, 74.72; H, 6.97; N, 6.45. Found: C, 74.68; H, 6.83; N, 6.35.

Synthesis of 12BH

The procedure described for **12AH** was followed using (-)-10,11-dihydrocinchonidine (3.0 g, 10.2 mmol) and α,α′- dibromo *p*-xylene (1.32 g, 5 mmol), which gave **12BH** (4.12 g, 96% yield). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.00 (d, J = 4.2 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.95 (s, 1H), 7.89 (s, 1H), 7.84 (d, J = 5.1 Hz, 2H), 7.78–7.73 (m, 1H), 6.74 (d, J = 4.5 Hz, 1H), 6.58 (d, J = 3.6 Hz, 1H), 5.28 (d, J = 12 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 4.28 (s, 1H), 3.98–3.93 (m, 1H), 3.71–3.63 (m, 1H), 3.52 (d, J = 9.9, 1H), 3.43 (d, J = 5.1, 1H), 2.14–2.07 (m, 1H), 1.99–1.83 (m, 4H), 1.35–1.28 (m, 1H), 1.24–1.05 (m, 2H), 0.71–0.66 (m, 3H). ^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.15, 147.6, 145.3, 134.0,

129.81, 129.77, 129.35, 127.3, 124.3, 123.8, 120.1, 67.6, 64.0, 61.93, 61.59, 50.5, 35.8, 25.6, 24.6, 23.6, 20.8, 11.3 ppm. $[\alpha]_D^{25} = -95.49$ (c 1.0, DMSO). IR (KBr) ν 3154, 2954, 1938, 1666, 1591, 1507, 1458, 1404, 1388, 1120, 1093, 1056, 855, 780, 758. mp: 227–229 ^{o}C. Anal. Calcd for $C_{46}H_{56}N_4O_2Br_2$: C, 64.49; H, 6.59; N, 6.54. Found: C, 64.55; H, 6.51; N, 6.38.

Synthesis of 12CH

The procedure described for **12AH** was followed using (-)-10,11-dihydrocinchonidine (3.0 g, 10.2 mmol) and α,α′- dibromo *m*-xylene (1.32 g, 5 mmol), which gave **12CH** (4.2 g, 98% yield). ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ 9.00 (d, J = 4.4 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.95–7. 76 (m, 5H), 6.77 (s, 1H), 6.61 (s, 1H), 5.33 (d, J = 11.2 Hz, 1H), 5.13 (d, J = 11.2 Hz, 1H), 4.33 (s, 1H), 3.99 (s, 1H), 3.53–3.31 (m, 2H), 2.10–1.75 (m, 6H), 1.30–1.13 (m, 3H), 0.66 (d, J = 7.2 Hz, 3H). ^{13}C NMR (d^{6}-DMSO, 125 MHz) δ 149.9, 147.3, 145.0, 138.7, 134.8, 129.54, 129.16, 128.3, 127.1, 124.1, 123.6, 120.0, 67.3, 63.9, 61.91, 61.01, 50.2, 35.6, 30.5, 24.5, 23.9, 20.6, 11.0 ppm. $[\alpha]_D^{25} = -132.18$ (c 1.0, DMSO). IR (KBr) ν 3434, 3200, 2958, 2875, 2113, 1933, 1664, 1590, 1509, 1458, 1387, 1116, 1062, 803, 778, 754. mp: 224–226 ^{o}C. Anal. Calcd for $C_{46}H_{56}N_4O_2Br_2$: C, 64.49; H, 6.59; N, 6.54. Found: C, 64.32; H, 6.55; N, 6.42.

Synthesis of disulfonate 9e

A mixture of α,α′-dibromo *p*-xylene (10 mmol, 2.64 g) in DMSO (30 mL) and Na_2SO_3 (22 mmol, 2.77 g) in H_2O (20 mL) was stirred at 100 ^{o}C for 12 hours. After completion of the reaction, the reaction mixture was filtered and filtrate was collected. The amount of solvent in the filtrate was reduced to 15 mL by pump. The concentrated solution was added into ethanol (250 mL) with stirring. The white precipitate obtained was filtered, washed with methanol, hexane and dried under vacuum to give **9e** in 98% yield. ^{1}H NMR (D_2O, 300 MHz) δ = 7.44 (s, 2H), 4.21 (s, 2H). ^{13}C NMR (D_2O, 75 MHz) δ 131.6, 56.6. IR (KBr) ν 3468, 2978, 1629, 1516.74, 1425, 1148, 1057, 969, 852, 743, 633, 533. Anal. Calcd for $C_8H_8Na_2O_6S_2$: C, 30.97; H, 2.60. Found: C, 31.05; H, 2.58.

Synthesis of disulfonate 9f

A mixture of trans-1,4-dibromo-2-butene (10 mmol 2.1390 g) in DMF (15 mL) and Na_2SO_3 (22 mmol, 2.77 g) in H_2O (15 mL) were stirred at 100 ^oC for 11 h. After cooling the reaction mixture to room temperature, H_2O (30 mL) and ethanol (20 mL) were added successively to the reaction mixture. The excess Na_2SO_3 precipitated was filtered out and the filtrate was collected, washed with CH_2Cl_2 (3 × 20 mL) to remove the unreacted trans-1,4-dibromo-2-butene. The volume of the reaction mixture was reduced by rotary evaporator and dried under vacuum to obtain the crude product. The crude product was recrystallized in ethanol-H_2O (6 : 4) mixture to give **9f** in 96% yield as a white solid. ^1H NMR (D_2O, 300 MHz) δ = 5.89–5.85 (m, 1H), 3.70–3.68 (m, 2H). ^{13}C NMR (D_2O, 75 MHz) δ 127.2, 54.7. IR (KBr) ν 3478, 1677, 1622, 1410, 1187, 1049, 628, 615, 597, 536. Anal. Calcd for $C_4H_6Na_2O_6S_2$: C, 18.46; H, 2.32. Found: C, 18.52; H, 2.38.

General procedure for catalytic enantioselective benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester (14) using chiral polymeric catalyst 10AeH

Chiral polymeric catalyst **10AeH** (100 mg) and *N*-diphenylmethylidene glycine *tert*-butyl ester (14: 0.53 g, 1.78 mmol) were added to a mixed solvent of toluene (7 mL) and chloroform (3 mL). 50 wt% aqueous KOH solution (2.5 mL) was added to the above mixture. Benzyl bromide (0.37 g, 2.14 mmol) was then added dropwise at 0 ^oC to the mixture. The reaction mixture was stirred vigorously for 12 h. Saturated sodium chloride solution (10 mL) was then added, and the mixture was subsequently filtered to recover **10AeH**, which was washed with water and dichloromethane several times. The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether– hexane = 1 : 10 as eluent) gave (S)-*tert*-butyl *N*-(diphenylmethylidene) phenylalaninate (15) (0.60 g, 1.55 mmol, 87% yield). The enantiomeric excess (88% ee) was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane–2-propanol = 100 : 1, flow rate = 0.3 mL min^{-1}, retention time: R enantiomer = 27.6 min, S enantiomer = 47.9 min). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[3]

Recycling experiment of the polymeric catalyst 10AeH

Recovered **10AeH** was dried in vacuo at room temperature. Benzyl bromide (0.33 g, 1.93 mmol) was added dropwise at 0 ^{o}C to a mixture of **14** (0.47 g, 1.6 mmol), chiral polymeric catalyst **10AeH** (90 mg) in toluene (7 mL) and chloroform (3 mL), and 50 wt% aqueous KOH solution (2.5 mL). The reaction mixture was stirred vigorously for 14 h. Saturated sodium chloride solution (10 mL) was then added, and the mixture was subsequently filtered to recover **10AeH**, which was washed with water and dichloromethane several times. The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether–hexane = 1 : 10 as eluent) gave (S)-*tert*-butyl *N*-(diphenylmethylene) phenylalaninate (15) (0.54 g, 1.41 mmol, 88% yield, 88% ee).

Preparation of ionic polymer 10H

A solution of cinchona derived dimeric quaternary ammonium salt **6AH~6CH** (1 mmol,) in 10 mL CH_3OH and a solution of disulfonic acid-disodium salt **9** (1 mmol) in 8 mL water were mixed together and stirred vigorously at room temperature for 24 hours. Then it was filtered and washed with water and hexane to obtain the resulting ionic polymer **10H**. The yield of the products was 75~90%. The intrinsic viscosity [η] of the polymers in DMSO at 40 ^{o}C were in the range of 0.10~0.20.

Ionic polymer 10AaH

^{13}C NMR (d^{6}-DMSO, 75 MHz) δ 150.8, 147.9, 146.3, 144.5, 138.77, 138.75, 133.46, 133.43, 130.53, 130.09, 128.2, 125.1, 124.5, 121.0, 117.4, 68.3, 65.9, 61.6, 54.7, 52.37, 50.02, 37.9, 25.83, 35.25, 21.4 ppm. IR (KBr) υ 3232, 2944, 1662, 1509, 1453, 1029, 777, 754. From the chlorine analysis of **10AaH**, the molecular weight was estimated as follows. Molecular weight of the repeating unit of polymer **10AaH** ($C_{57}H_{62}N_4O_8S_2$) is 995.27. The molecular weight of the polymer for the compositional formula $(C_{57}H_{62}N_4O_8S_2)_nClNa$ can be calculated as 995.27 n × 35.45 + 22.99. Cl content in the polymer is found to be 0.46. From the following equation, 100 × (35.45) ÷ (1079.35 × n + 35.45 + 22.99) = 0.46, n is calculated to be 10.1. Then the molecular weight of the polymer is estimated to be 10100. Anal. Calcd for $(C_{57}H_{62}N_4O_8S_2)_{10.1}ClNa$: C, 68.38; H, 6.24; N, 5.60, Cl, 0.35. Found: C, 67.75; H, 5.95; N, 5.45; Cl, 0.35.

Ionic polymer 10AbH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.5, 146.2, 145.8, 138.72, 138.04, 133.05, 133.01, 132.6, 131.3, 129.6, 127.3, 126.96, 126.34, 124.68, 124.57, 124.43, 120.54, 120.51, 120.48, 116.3, 67.7, 65.7, 62.8, 55.4, 42.17, 42.16, 37.1, 26.8, 17.63 ppm. IR (KBr) υ 3407, 1637, 1590, 1508, 1191, 1102, 1025, 780, 697. From the chlorine analysis of 10AbH, the molecular weight was estimated to be 7600. Anal. Calcd for $(C_{64}H_{62}N_4O_8S_2)_{7.0}ClNa$: C, 70.68; H, 5.75; N, 5.15, Cl, 0.46. Found: C, 70.25; H, 5.55; N, 5.05; Cl, 0.46.

Ionic polymer 10AdH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.6, 146.1, 143.7, 138.6, 133.06, 132.99, 129.60, 129.51, 129.06, 127.3, 126.97, 126.96, 126.33, 126.03, 124.62, 124.42, 124.00, 123.9, 120.4, 116.3, 67.8, 65.0, 60.5, 54.4, 42.16, 40.4, 37.1, 25.4, 21.6 ppm. IR (KBr) υ 3388, 1638, 1590, 1508, 1235, 1208, 1161, 1049, 1029, 780, 760, 611. $[\alpha]_D^{25} = -213.48$ (c 1.0, DMSO). From the chlorine analysis of 10AdH, the molecular weight was estimated to be 8900. Anal. Calcd for $(C_{64}H_{62}N_4O_8S_2)_{8.2}ClNa$: C, 70.75; H, 5.75; N, 5.15, Cl, 0.40. Found: C, 68.76; H, 5.25; N, 5.02; Cl, 0.40.

Ionic polymer 10AfH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.4, 147.7, 145.8, 138.57, 138.02, 133.1, 129.85, 129.61, 127.17, 127.10, 126.63, 126.31, 125.8, 124.57, 124.25, 120.4, 116.6, 67.9, 65.0, 60.7, 55.4, 54.5, 51.4, 37.2, 25.4, 24.63, 216 ppm. $[\alpha]_D^{25} = -326.38$ (c 1.0, DMSO). IR (KBr) υ 3232, 2952, 1654, 1590, 1509, 1453, 1186, 1029, 779, 618. From the chlorine analysis of **10AfH**, the molecular weight was estimated to be 8400. Anal. Calcd for $(C_{58}H_{62}N_4O_8S_2)_{8.3}ClNa$: C, 68.68; H, 6.16; N, 5.52, Cl, 0.42. Found: C, 68.50; H, 6.08; N, 5.20; Cl, 0.42.

Ionic polymer 10BaH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.6, 145.4, 138.3, 134.1, 129.88, 129.79, 129.50, 127.4, 124.3, 123.7, 120.1, 116.2, 67.7, 64.2, 62.1, 59.1, 50.77, 50.54, 36.7, 26.0, 24.1, 21.41, 21.18 ppm. $[\alpha]_D^{25} = -8.75$ (c 1.0, DMSO). IR (KBr) υ 3151, 2948, 1934, 1849, 1721, 1665, 1590, 1507, 1455, 1389, 1159, 1094, 1029, 923, 855, 779, 758. From the bromine analysis of **10BaH**, the molecular weight was estimated to be 9800. Anal. Calcd for $(C_{49}H_{58}N_4O_8S_2)_{10.8}BrNa$: C, 65.06; H, 6.46; N, 6.19, Br, 0.82. Found: C, 64.76; H, 6.58; N, 5.97; Br, 0.82.

Ionic polymer 10BbH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.1, 147.4, 145.30, 145.27, 138.1, 134.1, 133.0, 131.1, 129.73, 129.64, 129. 27, 127.79, 127.46, 125.0, 124.59, 124.13, 123.41, 120.0, 116.3, 67.5, 64.5, 62.2, 59.3, 50.7, 36.7, 25.9, 24.2, 21.3, ppm. $[\alpha]_D^{25} = -11.48$ (c 1.0, DMSO). IR (KBr) υ 3260, 2121, 1639, 1590, 1509, 1462, 1317, 1218, 1103, 1026, 945, 855, 777, 758, 700. From the bromine analysis of **10BbH**, the molecular weight was estimated to be 9100. Anal. Calcd for $(C_{56}H_{58}N_4O_8S_2)_{9.2}BrNa$: C, 67.91; H, 5.90; N, 5.66, Br, 0.88. Found: C, 64.93; H, 6.04; N, 5.36; Br, 0.88.

Ionic polymer 10BdH

Due to the low solubility NMR spectra were not recorded. IR (KBr) υ 3208, 3083, 3029, 3007, 2955, 2878, 1929, 1714, 1640, 1589, 1508, 1464, 1321, 1237, 1216, 1127, 1059, 1031, 778, 765, 612. From the bromine analysis of **10BdH**, the molecular weight was estimated to be 12000. Anal. Calcd for $(C_{56}H_{58}N_4O_8S_2)_{12.1}BrNa$: C, 68.10; H, 5.92; N, 5.67, Br, 0.67. Found: C, 67.62; H, 6.02; N, 5.33; Br, 0.67.

Ionic polymer 10BeH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 147.6, 145.5, 138.4, 134.1, 133.0, 129.89, 129.73, 129.62, 129.55, 127. 42, 124.39, 123.8, 120.1, 116.3, 67.7, 64.2, 62.1, 59.2, 57.4, 50.4, 36.7, 26.0, 24.1, 21.1, ppm. $[\alpha]_D^{25} = -8.55$ (c 1.0, DMSO). IR (KBr) υ 3228, 1639, 1589, 1509, 1461, 1218, 1178, 1130, 1935, 1021, 777, 605. From the bromine analysis of **10BeH**, the molecular weight was estimated to be 7300. Anal. Calcd for $(C_{54}H_{60}N_4O_8S_2)_{7.5}BrNa$: C, 66.80; H, 6.23; N, 5.77, Br, 1.10. Found: C, 66.54; H, 5.88; N, 5.45; Br, 1.10.

Ionic polymer 10BfH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.6, 145.3, 138.3, 134.1, 129.88, 129.79, 129.48, 127.32, 126.42, 124. 3, 123.8, 123.8, 120.1, 116.2, 67.5, 64.2, 62.87, 62.04, 59.1, 50.6, 36.3, 25.9, 24.1, 21.2 ppm. IR (KBr) υ 3223, 1642, 1589, 1572, 1509, 1461, 1124, 1061, 1034, 929, 823, 777, 755. From the bromine analysis of **10BfH**, the molecular weight was estimated to be 9000. Anal. Calcd for $(C_{50}H_{58}N_4O_8S_2)_{9.8}BrNa$: C, 65.44; H, 6.37; N, 6.11, Br, 0.89. Found: C, 63.23; H, 6.27; N, 5.85; Br, 0.89.

Ionic polymer 10CaH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 147.6, 145.4, 139.0, 138.2, 135.4, 129.875, 129.58, 129.57, 128.7, 127. 5, 124.4, 123.8, 120.24, 116.4, 67.7, 64.3, 62.3, 50.7, 50.54, 36.8, 25.9, 24.28, 24.25, 21.43, 21.23 ppm. $[\alpha]_D^{25} = -189.89$ (c 1.0, DMSO). IR (KBr) υ 3428, 3215, 2955, 1935, 1866, 1639, 1591, 1507, 1459, 1163, 1117, 1064, 1029, 931, 778, 762. From the bromine analysis of **10CaH**, the molecular weight was estimated to be 9900. Anal. Calcd for $(C_{49}H_{58}N_4O_8S_2)_{11.0}BrNa$: C, 65.07; H, 6.46; N, 6.19, Br, 0.80. Found: C, 64.78; H, 6.65; N, 5.95; Br, 0.80.

Ionic polymer 10CbH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.4, 147.6, 145.42, 145.37, 139.1, 138.1, 135.3, 132.9, 131.26, 129.93, 129. 91, 129.61, 128.7, 127.56, 127.49, 124.80, 124.59, 124.40, 123.6, 120.2 116.4, 67.8, 64.5, 62.5, 59.4, 50.8, 36.9, 25.9, 24.3, 21.2 ppm. IR (KBr) υ 3390, 2951, 1639, 1590, 1509, 1461, 1217, 1102, 1026, 777, 699, 574. $[\alpha]_D^{25} = -161.04$ (c 1.0, DMSO). From the bromine analysis of **10CbH**, the molecular weight was estimated to be 12600. Anal. Calcd for $(C_{56}H_{58}N_4O_8S_2)_{12.8}BrNa$: C, 68.13; H, 5.92; N, 5.67, Br, 0.63. Found: C, 68.02; H, 6.05; N, 5.56; Br, 0.63.

Ionic polymer 10CdH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.5, 145.5, 143.3, 139.0, 138.1, 135.2, 129.75, 129.63, 129.55, 129. 20, 128.6, 127.51, 127.48, 124.37, 124.11, 123.61, 123.59, 120.2, 116.4, 67.8, 64.4, 62.5, 59.3, 50.8, 36.8, 25.9, 24.6, 21.1, ppm. $[\alpha]_D^{25} = -159.37$ (c 1.0, DMSO). IR (KBr) υ 3233, 2951, 1638, 1590, 1509, 1460, 1239, 1185, 1030, 797, 777, 763, 610, 563, 523. From the bromine analysis of **10CdH**, the molecular weight was estimated to be 11600. Anal. Calcd for $(C_{56}H_{58}N_4O_8S_2)$ 11.7BrNa: C, 68.08; H, 5.92; N, 5.67, Br, 0.69. Found: C, 67.72; H, 5.85; N, 5.38; Br, 0.69.

Ionic polymer 10CeH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 147.6, 145.4, 139.2, 138.2, 135.3, 132.9, 129.87, 129.57, 129.44, 128.6, 127.5, 124.4, 123.80, 123.78, 120.2, 116.3, 67.7, 64.4, 62.3, 59.3, 57.3, 50.7, 36.8, 25.9, 24.3, 21.1, ppm. $[\alpha]_D^{25} = -176.90$ (c 1.0, DMSO). IR (KBr) υ 3209, 1702, 1639, 1590, 1509, 1460, 1421, 1215, 1168, 1130, 1035, 1021, 801, 776, 755, 633, 607, 552, 521. From the bromine analysis of **10CeH**, the molecular weight was estimated to be

12500. Anal. Calcd for $(C_{54}H_{60}N_4O_8S_2)_{13}BrNa$: C, 67.02; H, 6.27; N, 5.81, Br, 0.64. Found: C, 66.25; H, 6.27; N, 5.79; Br, 0.64.

Ionic polymer 10CfH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 147.6, 145.4, 139.2, 138.1, 135.2, 129.87, 129.52, 129.45, 128.6, 127.4, 126.8, 124.4, 123.7, 120.2, 116.4, 67.8, 64.2, 62.2, 59.2, 55.3, 50.6, 36.9, 25.9, 24.2, 21.1 ppm. $[\alpha]_D^{25} = -181.55$ (c 1.0, DMSO). IR (KBr) υ 3210, 1639, 1590, 1509, 1459, 1210, 1030, 801, 777, 758. From the bromine analysis of **10CfH**, the molecular weight was estimated to be 11500. Anal. Calcd for $(C_{50}H_{58}N_4O_8S_2)_{12.6}BrNa$: C, 65.61; H, 6.39; N, 6.12, Br, 0.69. Found: C, 65.32; H, 6.18; N, 5.99; Br, 0.69.

Synthesis of ionic polymer 10Allyl

A solution of cinchona derived dimeric quaternary ammonium salt **6AAllyl~6CAllyl** (1 mmol) in 10 mL CH_3OH and a solution of disulfonic acid-disodium salt **9** (1 mmol) in 8 mL water were mixed together and stirred vigorously at room temperature for 24 hours. After completion of reaction the volume of solvent was reduced by rota evaporator and then 10 mL DCM and 5 mL water was added to the reaction mixture. Then it was extracted with DCM (3X20 mL) and the amount of DCM was reduced by rotavaporator and recrystallized in methanol-ether system to get the ionic polymer **10Allyl**. The yield of the products was 70~90%. The intrinsic viscosity [η] of the polymers in DMSO at 40 ^{o}C were in the range (0.10~0.20).

Ionic polymer 10AaAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.0, 141.3, 140.9, 138.4, 137.8, 134.1, 132.94, 129.7, 127.4, 126.2, 125.3, 124.4, 124.4, 123.5, 119.7, 117.5, 116.7, 72.1, 69.2, 65.9, 62.4, 60.1, 52.4, 50.8, 37.3, 36.8, 26.2, 24.6, 21.4 ppm. IR (KBr) υ 3449.06, 3074.94, 2948.63, 1642.09, 1588.09, 1508.06, 1459.85, 1240.00, 1222.65, 1192.76, 1068.37, 1042.34, 774.28, 758.85. From the chlorine analysis of **10AaAllyl**, the molecular weight was estimated to be 12400. Anal. Calcd for $(C_{63}H_{70}N_4O_8S_2)_{11.5}ClNa$: C, 70.03; H, 6.53; N, 5.19, Cl, 0.29. Found: C, 68.89; H, 6.02; N, 4.93; Cl, 0.2

Ionic polymer 10AbAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 148.17, 147.99, 145.3, 141.27, 141.04, 138.3, 137.8, 134.1, 133.1, 132.8, 132.3, 130.6, 129.7, 127.3, 126.9, 125.4, 124.23, 124.15, 119.7, 117.2,

116.3, 71.9, 69.2, 67.4, 62.5, 54.6, 51.6, 37.2, 24.58, 24.20, 21.9 ppm. $[\alpha]_D^{25} = -201.53$ (c 1.0, DMSO). IR (KBr) υ 3400, 3074, 2946, 1643, 1589, 1598, 1457, 1192, 1100, 1025, 775, 758, 696. From the chlorine analysis of **10AbAllyl**, the molecular weight was estimated to be 10000. Anal. Calcd for $(C_{70}H_{70}N_4O_8S_2)_{8.6}ClNa$: C, 72.09; H, 6.05; N, 4.80, Cl, 0.35. Found: C, 71.02; H, 6.12; N, 4.56; Cl, 0.35.

Ionic polymer 10AdAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 148.15, 147.99, 141.3, 140.9, 138.4, 137.8, 136.8, 134.11, 134.07, 133.3, 132.9, 129.8, 127.4, 126.2, 125.29, 125.06, 124.4, 123.6, 119.7, 117.5, 116.7, 69.3, 66.0, 62.4, 60.1, 59.2, 46.3, 37.2, 26.1, 24.4, 21.8 ppm. IR (KBr) υ 3420, 3077, 2943, 1644, 1589, 1508, 1457, 1238, 1202, 1030, 996, 929, 796, 761, 610. From the chlorine analysis of **10AdAllyl**, the molecular weight was estimated to be 10700. Anal. Calcd for $(C_{70}H_{70}N_4O_8S_2)_{9.2}ClNa$: C, 72.12; H, 6.05; N, 4.81, Cl, 0.33. Found: C, 71.50; H, 6.16; N, 4.44; Cl, 0.33.

Ionic polymer 10AeAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.4, 148.2, 140.9, 138.4, 134.2, 133.33, 133.07, 133.00, 129.96, 129.85, 129.35, 127.46, 127.15, 126.5, 125.74, 125.38, 124.4, 120.2, 117.0, 70.7, 69.4, 67.5, 60.7, 58.6, 57.3, 54.6, 36.9, 25.4, 24.3, 21.9 ppm. IR (KBr) υ 3400, 3075, 2950, 1643, 1588, 1509, 1453, 1215, 1180, 1131, 1068, 1034, 920, 776, 758, 605. $[\alpha]_D^{25} = -319.19$ (c 1.0, DMSO). From the chlorine analysis of **10AeAllyl**, the molecular weight was estimated to be 11800. Anal. Calcd for $(C_{68}H_{72}N_4O_8S_2)_{10.3}ClNa$: C, 71.45; H, 6.35; N, 4.90, Cl, 0.30. Found: C, 70.59; H, 6.26; N, 4.54; Cl, 0.30.

Ionic polymer 10AfAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 148.16, 147.99, 141.3, 140.9, 138.4, 137.8, 134.1, 133.3, 132.9, 129.7, 127.3, 126.2, 125.3, 124.4, 123.5, 119.7, 116.7, 69.3, 67.4, 65.9, 62.4, 60.0, 59.2, 46.3, 37.2, 26.1, 24.4, 21.8 ppm. IR (KBr) υ 3380, 3074, 2935, 1717, 1644, 1588, 1508, 1452, 1068, 1029, 995, 920, 775, 757. From the chlorine analysis of **10AfAllyl**, the molecular weight was estimated to be 8900. Anal. Calcd for $(C_{64}H_{70}N_4O_8S_2)_{8.1}ClNa$: C, 70.23; H, 6.45; N, 5.12, Cl, 0.40. Found: C, 69.56; H, 6.55; N, 4.87; Cl, 0.40.

Ionic polymer 10BaAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.4, 148.1, 141.5, 137.9, 134.35, 134.18, 129.9, 127.6, 126.2, 125.2, 123.6, 119.8, 117.93, 117.80, 116.8, 72.2, 69.4, 67.7, 66.1, 62.6, 60.3, 52.5, 50.7, 37.3, 26.2, 24.7, 20.7 ppm. $[\alpha]_D^{25} = -81.51$ (c 1.0, DMSO). IR (KBr) υ 3401, 3073, 2944, 2119, 1642, 1569, 1508, 1459, 1185, 1068, 1029, 758. From the bromine analysis of **10BaAllyl**, the molecular weight was estimated to be 11600. Anal. Calcd for $(C_{55}H_{66}N_4O_8S_2)_{11.8}BrNa$: C, 67.13; H, 6.76; N, 5.69, Br, 0.69. Found: C, 66.31; H, 6.81; N, 5.34; Br, 0.69.

Ionic polymer 10BbAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.0, 1451.9, 141.3, 137.8, 134.33, 134.23, 134.09, 132.6, 131.3, 129.97, 129.71, 127.35, 127.24, 126.1, 125.1, 124.60, 124.53, 119.7, 117.6, 116.7, 72.1, 69.3, 66.0, 62.5, 59.0, 52.4, 37.2, 26.1, 24.6, 20.6 ppm. $[\alpha]_D^{25} = -49.38$ (c 1.0, DMSO). IR (KBr) υ 3418, 3072, 2941, 2119, 1941, 1643, 1589, 1508, 1460, 1196, 1101, 1026, 758, 696. From the bromine analysis of **10BbAllyl**, the molecular weight was estimated to be 11600. Anal. Calcd for $(C_{62}H_{66}N_4O_8S_2)_{10.9}BrNa$: C, 69.67; H, 6.22; N, 5.24, Br, 0.69. Found: C, 68.05; H, 6.11; N, 5.10; Br, 0.69.

Ionic polymer 10BdAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.03, 148.02, 143.8, 141.3, 137.8, 134.1, 129.97, 129.74, 129.63, 129.16, 129.71, 127.4, 126.1, 125.1, 124.2, 123.95, 123.48, 119.7, 117.7, 116.7, 72.1, 69.4, 67.6, 62.6, 59.1, 51.0, 37.3, 26.0, 24.6, 20.6 ppm. $[\alpha]_D^{25} = -68.24$ (c 1.0, DMSO). IR (KBr) υ 3412, 3073, 2937, 2119, 1942, 1844, 1641, 1589, 1508, 1460, 1238, 1202, 1030, 760, 610. From the bromine analysis of **10BdAllyl**, the molecular weight was estimated to be 13600. Anal. Calcd for $(C_{62}H_{66}N_4O_8S_2)_{12.7}BrNa$: C, 69.76; H, 6.23; N, 5.25, Br, 0.59. Found: C, 68.85; H, 6.33; N, 5.16; Br, 0.59.

Ionic polymer 10BeAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.0, 141.30, 141.29, 140.6, 137.9, 134.2, 133.2, 129.6, 127.2, 126.2, 129.71, 125.04, 125.01, 119.7, 117.5, 116.56, 116.06, 72.1, 69.3, 66.0, 63.3, 62.4, 58.9, 52.2, 37.2, 28.9, 26.2, 20.9 ppm. $[\alpha]_D^{25} = -67.27$ (c 1.0, DMSO). IR (KBr) υ 3402, 3071, 2943, 2119, 1942, 1641, 1589, 1509, 1460, 1215, 1185, 1132, 1035, 1022.09, 758, 607. From the bromine analysis of **10BeAllyl**, the molecular weight was estimated to be

12600. Anal. Calcd for $(C_{60}H_{68}N_4O_8S_2)_{12.0}BrNa$: C, 68.90; H, 6.55; N, 5.36, Br, 0.64. Found: C, 67.36; H, 6.45; N, 5.14; Br, 0.64.

Ionic polymer 10BfAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.0, 141.30, 137.87, 137.86, 134.15, 134.07, 129.7, 127.54, 127.31, 126.21, 125.0, 123.0, 119.7, 116.2, 72.0, 69.2, 67.6, 65.8, 62.4, 58.8, 50.7, 37.2, 26.1, 24.4, 20.9 ppm. $[\alpha]_D^{25} = -63.97\ (c\ 1.0, \mathrm{DMSO})$. IR (KBr) υ 3389, 3071, 2940, 2118, 1642, 1588, 1508, 1459, 1422, 1068, 997, 925, 774, 757. From the bromine analysis of **10BfAllyl**, the molecular weight was estimated to be 11400. Anal. Calcd for $(C_{56}H_{68}N_4O_8S_2)_{11.4}BrNa$: C, 67.37; H, 6.87; N, 5.61, Br, 0.70. Found: C, 66.71; H, 6.63; N, 5.35; Br, 0.70.

Ionic polymer 10CaAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.1, 148.0, 141.39, 141.31, 138.74, 138.00, 134.55, 134.11, 128.50, 128.47, 125.09, 125.07, 120.7, 119.86, 119.58, 117.70, 117.16, 71.9, 67.7, 63.0, 59.8, 50.98, 50.67, 36.7, 31.1, 26.3, 25.7, 24.8, 22.0 ppm. $[\alpha]_D^{25} = -105.84\ (c\ 1.0, \mathrm{DMSO})$. IR (KBr) υ 3403, 3073, 2950, 1933, 1641, 1589, 1508, 1459, 1167, 1068, 1030, 999, 926, 806, 775, 757. From the bromine analysis of **10CaAllyl**, the molecular weight was estimated to be 11500. Anal. Calcd for $(C_{55}H_{66}N_4O_8S_2)_{11.7}BrNa$: C, 67.13; H, 6.76; N, 5.69, Br, 0.69. Found: C, 66.04; H, 6.63; N, 5.45; Br, 0.69.

Ionic polymer 10CbAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.45, 150.16, 148.0, 145.76, 145.74, 141.40, 141.38, 137.8, 134.1, 132.7, 131.25, 131.23, 128.52, 128.51, 127.52, 127.06, 126.99, 125.11, 125.09, 124.7, 123.4, 119.9, 116.6, 71.9, 67.9, 63.3, 59.2, 51.35, 51.03, 36.7, 26.3, 25.7, 21.2 ppm. $[\alpha]_D^{25} = -104.95\ (c\ 1.0, \mathrm{DMSO})$. IR (KBr) υ 3413, 3073, 2950, 1642, 1589, 1508, 1460, 1197, 1102, 1068, 697. From the bromine analysis of **10CbAllyl**, the molecular weight was estimated to be 12900. Anal. Calcd for $(C_{62}H_{66}N_4O_8S_2)_{12.1}BrNa$: C, 69.74; H, 6.23; N, 5.25, Br, 0.62. Found: C, 69.03; H, 6.81; N, 5.13; Br, 0.62.

Ionic polymer 10CdAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.0, 143.7, 141.3, 138.9, 137.8, 135.4, 134.2,129.95, 129.70, 129.57, 129.09, 128.4, 127.6, 125.05, 125.03, 124.1, 123.83, 123.57, 119.6, 117.6, 116.6, 72.0, 69.3, 68.0, 63.1, 59.0, 50.9, 36.8, 26.0, 24.2, 20.8 ppm. $[\alpha]_D^{25} = -10294$ (c 1.0, DMSO). IR (KBr) υ 3412, 3074, 2946, 1943, 1640, 1589, 1508, 1459, 1238, 1202, 1030, 796, 760, 610. From the bromine analysis of **10CdAllyl**, the molecular weight was estimated to be 11300. Anal. Calcd for $(C_{62}H_{66}N_4O_8S_2)_{10.6}BrNa$: C, 69.66; H, 6.22; N, 5.25; Br, 0.71. Found: C, 68.73; H, 6.38; N, 5.09; Br, 0.71.

Ionic polymer 10CeAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.47, 150.17, 148.06, 148.04, 141.4, 138.1, 134.50, 134.16, 133.1, 129.6, 128.5, 127.92, 127.09, 128.4, 127.6, 125.1, 124.2, 123.6, 119.7, 117.8, 116.6, 71.9, 68.1, 63.1, 59.0, 57.4, 50.9, 36.8, 26.3, 25.8, 24.3, 21.3 ppm. $[\alpha]_D^{25} = -128.61$ (c 1.0, DMSO). IR (KBr) υ 3411, 3073, 2947, 1641, 1589, 1509, 1459, 1213, 1186, 1133, 1068, 1035, 1022, 928, 776, 757, 607. From the bromine analysis of **10CeAllyl**, the molecular weight was estimated to be 11500. Anal. Calcd for $(C_{60}H_{68}N_4O_8S_2)_{11.0}BrNa$: C, 68.85; H, 6.55; N, 5.35; Br, 0.69. Found: C, 68.19; H, 6.49; N, 5.16; Br, 0.69.

Ionic polymer 10CfAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 148.0, 141.3, 137.9, 135.5, 134.31, 134.28, 129.93, 129.90, 129.69, 129.50, 128.4, 127.6, 125.0, 123.8, 119.6, 117.7, 116.5, 72.0, 69.4, 67.8, 62.95, 62.84, 58.8, 50.9, 36.7, 26.0, 24.2, 20.9 ppm. $[\alpha]_D^{25} = -119.44$ (c 1.0, DMSO). IR (KBr) υ 3392, 3071, 2943, 1640, 1589, 1508, 1458, 1068, 997, 923, 805.13, 775, 756. From the bromine analysis of **10CfAllyl**, the molecular weight was estimated to be 9800. Anal. Calcd for $(C_{56}H_{68}N_4O_8S_2)_{9.8}BrNa$: C, 67.27; H, 6.86; N, 5.60; Br, 0.81. Found: C, 66.81; H, 6.78; N, 5.72; Br, 0.81

Synthesis of ionic polymers derived from dihydrocinchonidine 13H, 13Allyl

A solution of 10,11-dihydrocinchonidine derived dimeric quaternary ammonium salt **12AH~12CH**, **12AAllyl~12CAllyl** (1 mmol,) in 10 mL CH_3OH and a solution of disulfonic acid-disodium salt **9** (1 mmol) in 8 mL water were mixed together and stirred vigorously at room temperature for 24 hours. After completion of reaction the volume of solvent was reduced by rota evaporator and then 10 mL DCM and 5 mL water was added to the reaction

mixture. Then it was extracted with DCM (3X20 mL) and the amount of DCM was reduced by rotavaporator and recrystalized in methanol-ether system to get the ionic polymer **12H**, **12Allyl.** The yield of the products was 70~90%. The intrinsic viscosity [η] of the polymers in DMSO at 40 ^{o}C were in the range (0.10~0.20).

Ionic polymer 13AeH

^{13}C NMR (d^{6}-DMSO, 75 MHz) δ 150.4, 147.8, 146.0, 133.1, 129.89, 129.64, 127.59, 127.17, 125.87, 125.21, 124.82, 124.43, 123.90, 120.68, 119.26, 67.7, 65.5, 60.1, 57.4, 56.1, 51.6, 35.6, 26.2, 25.9, 24.5, 11.77, 11.57 ppm. $[\alpha]_D^{25} = -209.59$ (c 1.0, DMSO). IR (KBr) υ 3389, 2958, 2875, 1661, 1590, 1509, 1457, 1214, 1180, 1129, 1034, 1021, 781, 758, 606. From the chlorine analysis of **13AeH**, the molecular weight was estimated to be 8500. Anal. Calcd for $(C_{62}H_{68}N_4O_8S_2)_{11.0}$BrNa: C, 68.85; H, 6.55; N, 5.35; Br, 0.69. Found: C, 68.19; H, 6.49; N, 5.16; Br, 0.69.

Ionic polymer 13AfH

^{13}C NMR (d^{6}-DMSO, 75 MHz) δ 150.3, 147.7, 145.9, 133.0, 129.83, 129.55, 127.23, 127.04, 126.9, 124.66, 124.45, 124.35, 120.5, 118.9, 67.4, 65.1, 62.8, 59.5, 55.3, 42.8, 35.86, 35.21, 25.70, 25.45, 24.2, 11.4 ppm. $[\alpha]_D^{25} = -237.45$ (c 1.0, DMSO). IR (KBr) υ 3219, 2957, 1661, 1590, 1509, 1457, 1186, 1123, 1030, 780, 618. From the chlorine analysis of **13AfH**, the molecular weight was estimated to be 9000. Anal. Calcd for $(C_{58}H_{66}N_4O_8S_2)_{8.8}$BrNa: C, 68.44; H, 6.53; N, 5.50; Cl;, 0.40. Found: C, 68.22; H, 6.35; N, 5.40; Br, 0.40.

Ionic polymer 13BeH

^{13}C NMR (d^{6}-DMSO, 75 MHz) δ 150.6, 148.6, 144.3, 134.7, 131.9, 130.41, 130.20, 129.1, 128.7, 127.3, 125.28, 125.05, 121.2, 68.1, 64.9, 62.54, 62.35, 57.8, 51.1, 35.6, 26.3,, 25.3, 24.2, 21.4, 12.0 ppm. $[\alpha]_D^{25} = -109.86$ (c 1.0, DMSO). IR (KBr) υ 3202, 2959, 2091, 1636, 1599, 1544, 1509, 1460, 1219, 1168, 1129, 1035, 857, 778, 606. From the bromine analysis of **13BeH**, the molecular weight was estimated to be 8800. Anal. Calcd for $(C_{54}H_{64}N_4O_8S_2)_{9.0}$ BrNa: C, 66.68; H, 6.63; N, 5.76; Br, 0.91. Found: C, 67.12; H, 6.68; N, 5.59; Br, 0.91.

Ionic polymer 13BfH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.3, 149.1, 147.6, 145.4, 134.1, 129.84, 129.51, 127.4, 126.9, 124.4, 123.8, 120.2, 67.6, 64.2, 62.8, 61.7, 55.4, 50.6, 35.0, 25.7, 24.7, 23.6, 20.8, 11.5 ppm. $[\alpha]_D^{25} = -94.71$ (c 1.0, DMSO). IR (KBr) υ 3234, 2958, 1654, 1590, 1509, 1460, 1207, 1125, 1056, 1032, 778. From the bromine analysis of **13BfH**, the molecular weight was estimated to be 6600. Anal. Calcd for $(C_{50}H_{62}N_4O_8S_2)_{7.1}BrNa$: C, 64.88; H, 6.75; N, 6.05; Br, 1.22. Found: C, 64.32; H, 6.40; N, 5.95; Br, 1.22.

Ionic polymer 13CeH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 148.94, 147.98, 145.3, 139.1, 135.13, 135.11, 130.6, 129.4, 128.66, 128.06, 126.4, 124.56, 124.12, 124.16, 120.5, 67.6, 64.3, 62.2, 61.4, 50.51, 50.49, 35.2, 25.7, 24.90, 24.17, 20.9, 11.3 ppm. $[\alpha]_D^{25} = -121.57$ (c 1.0, DMSO). IR (KBr) υ 3203, 2959, 2875, 1651, 1590, 1509, 1458, 1217, 1036, 777, 755. From the bromine analysis of **13CeH**, the molecular weight was estimated to be 11700. Anal. Calcd for $(C_{50}H_{62}N_4O_8S_2)_{12.7}BrNa$: C, 65.33; H, 6.80; N, 6.09; Br, 0.68. Found: C, 64.96; H, 6.85; N, 5.95; Br, 0.68.

Ionic polymer 13CfH

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 147.6, 145.4, 139.1, 135.1, 129.86, 129.46, 128.7, 127.4, 126.8, 124.4, 123.76, 123.74, 120.3, 67.6, 64.2, 62.3, 61.4, 50.5, 50.49, 35.2, 25.7, 24.88, 24.21, 20.8, 11.3 ppm. $[\alpha]_D^{25} = -136.56$ (c 1.0, DMSO). IR (KBr) υ 3208, 2957, 1651, 1590, 1509, 1458, 1187, 1166, 1119, 1030, 803, 778, 755. From the bromine analysis of **13CfH**, the molecular weight was estimated to be 8800. Anal. Calcd for $(C_{50}H_{62}N_4O_8S_2)_{9.9}BrNa$: C, 65.16; H, 6.78; N, 6.08; Br;, 0.88. Found: C, 64.56; H, 6.70; N, 5.97; Br, 0.88.

Ionic polymer 13CeAllyl

^{13}C NMR (d^6-DMSO, 75 MHz) δ 150.2, 148.0, 141.4, 135.4, 134.3, 129.92, 129.66, 129.64, 129.53, 129.45, 128.5, 127.6, 125.1, 123.8, 119.69, 119.67, 117.5, 72.0, 69.2, 67.8, 63.1, 60.9, 50.8, 34.9, 25.4, 24.83, 24.41, 20.6 , 14.8, 11.1 ppm. $[\alpha]_D^{25} = -81.21$ (c 1.0, DMSO). IR (KBr) υ 3395, 2957, 2874, 1645, 1589, 1508, 1458, 1213, 1128, 1069, 1033, 756. From the bromine analysis of **13CeAllyl**, the molecular weight was estimated to be 12000. Anal. Calcd for $(C_{60}H_{72}N_4O_8S_2)_{11.4}BrNa$: C, 68.61; H, 6.91; N, 5.33; Br, 0.67. Found: C, 67.98; H, 6.88; N, 5.26; Br, 0.67.

Ionic polymer 13CfAllyl

^{13}C NMR (d^{6}-DMSO, 75 MHz) δ 150.3, 148.0, 141.4, 139.3, 135.4, 134.4, 129.89, 129.70, 129.45, 128.48, 127.6, 126.8, 125.1, 124.0, 119.7, 117.6, 72.0, 69.3, 67.7, 63.1, 60.95, 55.4, 50.8, 34.9, 25.4, 24.88, 24.45, 20.8 , 11.1 ppm. $[\alpha]_D^{25} = -90.23$ (c 1.0, DMSO). IR (KBr) υ 3410, 2957, 2874, 1645, 1589, 1508, 1458, 1189, 1125, 1069, 1030, 757. From the bromine analysis of **13CfAllyl**, the molecular weight was estimated to be 8800. Anal. Calcd for $(C_{56}H_{70}N4O_8S_2)_{8.8}BrNa$: C, 67.06; H, 7.03; N, 5.59; Br, 0.91. Found: C, 66.68; H, 7.18; N, 5.35; Br, 0.91.

Characterization for compound 15 synthesized using polymeric catalyst

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59~7.57 (m, 2H), 7.35~7.23 (m, 6H), 7.20~7.12 (m, 3H), 7.06~7.04 (m, 2H), 6.60 (d, *J* = 6 Hz, 2H), 4.14~4.10 (m, 1H), 3.26~3.14 (m, 2H), 1.43 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.92, 170.39, 139.6, 138.4, 136.4, 130.19, 130.00, 128.80, 128.30, 128.17, 128.14, 128.03, 127.7, 126.3, 81.2, 68.0, 39.7, 28.1 ppm.

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Chapter 4

Synthesis of Chiral Ionic Polymers Containing Quaternary Ammonium Sulfonate Structure and their Catalytic Activity in Asymmetric Alkylation

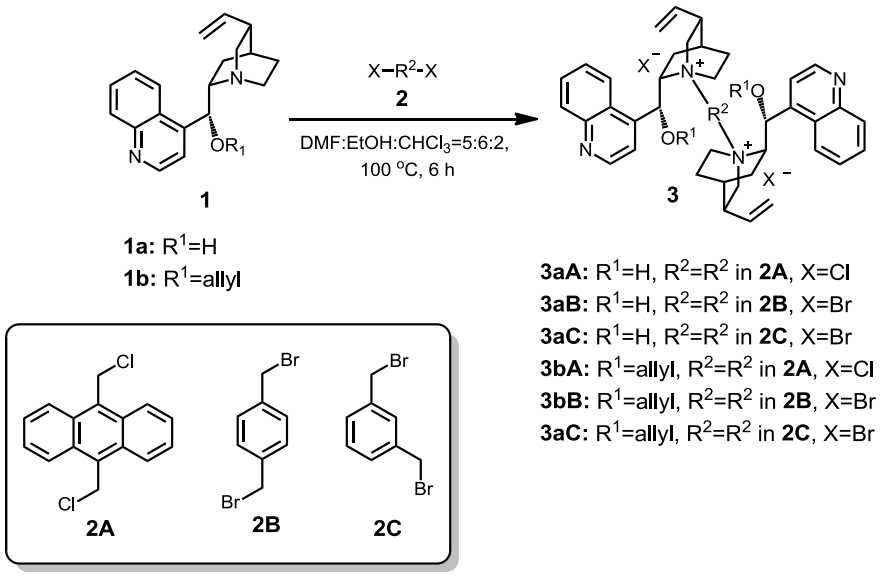
4. 1. Introduction

Chiral quaternary ammonium salts have been recognized as efficient organocatalyst in various asymmetric transformations under mild reaction condition.[1] Recently, extremely high catalytic activities have been reported in some cases.[2] However, compared with the transition metal based catalysts, large amount of organocatalyst molecule is generally required to complete the reaction. Moreover, due to the amphiphilicity of the quaternary ammonium salt, the catalyst separation might be difficult in some cases. When the chiral quaternary ammonium catalyst is incorporated into polymer, such a separation issue would be clearly solved. Insoluble polymeric catalyst can be easily separated from the reaction mixture by simple filtration. Several examples of polymer-immobilized chiral quaternary ammonium salt have been developed and used as catalyst for asymmetric synthesis.[3] In these examples of the polymeric catalysts, the catalyst was immobilized on the side-chain of the support polymer. We have designed a main-chain polymeric catalyst which incorporated the chiral quaternary ammonium catalyst into its main-chain.We synthesized chiral quaternary ammonium dimer and disodium disulfonate. Ion exchange reaction between these two molecules resulted in ionic bond formation to generate insoluble polymer, which we term “chiral ionic polymer”. Since the chiral ionic polymers contain quaternary ammonium structure in their repeating units, the polymers should have catalytic activity in some asymmetric transformations. In order to evaluate the catalytic activity of the chiral ionic polymers, we chose the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester.[4] We synthesized chiral ionic polymers based on various combinations of chiral quaternary ammonium dimers and disodium disulfonates. These chiral ionic polymers were applied to asymmetric organocatalysis. Catalytic activity and enantioselectivity of the chiral ionic polymer have been investigated in this paper.

4. 2. Results and discussion

Since the reaction between quaternary ammonium halide and disodium sulfonate smoothly occur to give the quaternary ammonium sulfonate,[5] we have used the ion exchange reaction for the chiral ionic polymer synthesis. Chiral quaternary ammonium dimers **3** were easily prepared from cinchonidine derivatives **1** and dihalide **2** according to Park and Jew's procedure (Scheme I).[6] 10,11- Dihydrocinchonidine derived chiral quaternary ammonium dimers **5** were also prepared by the same method (Scheme II).

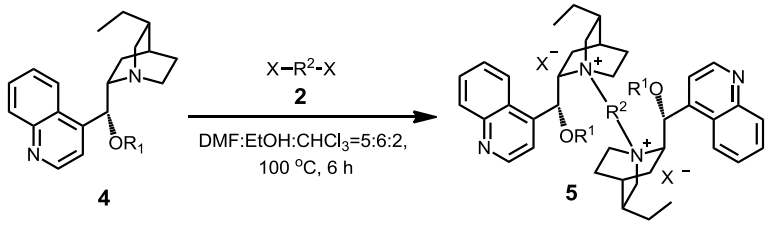
Scheme I Chiral quaternary ammonium dimer **3** prepared from cinchonidine



1a: R^1=H
1b: R^1=allyl

3aA: R^1=H, R^2=R^2 in **2A**, X=Cl
3aB: R^1=H, R^2=R^2 in **2B**, X=Br
3aC: R^1=H, R^2=R^2 in **2C**, X=Br
3bA: R^1=allyl, R^2=R^2 in **2A**, X=Cl
3bB: R^1=allyl, R^2=R^2 in **2B**, X=Br
3aC: R^1=allyl, R^2=R^2 in **2C**, X=Br

Scheme II Chiral quaternary ammonium dimer **5** prepared from 10,11-dihydrocinchonidine



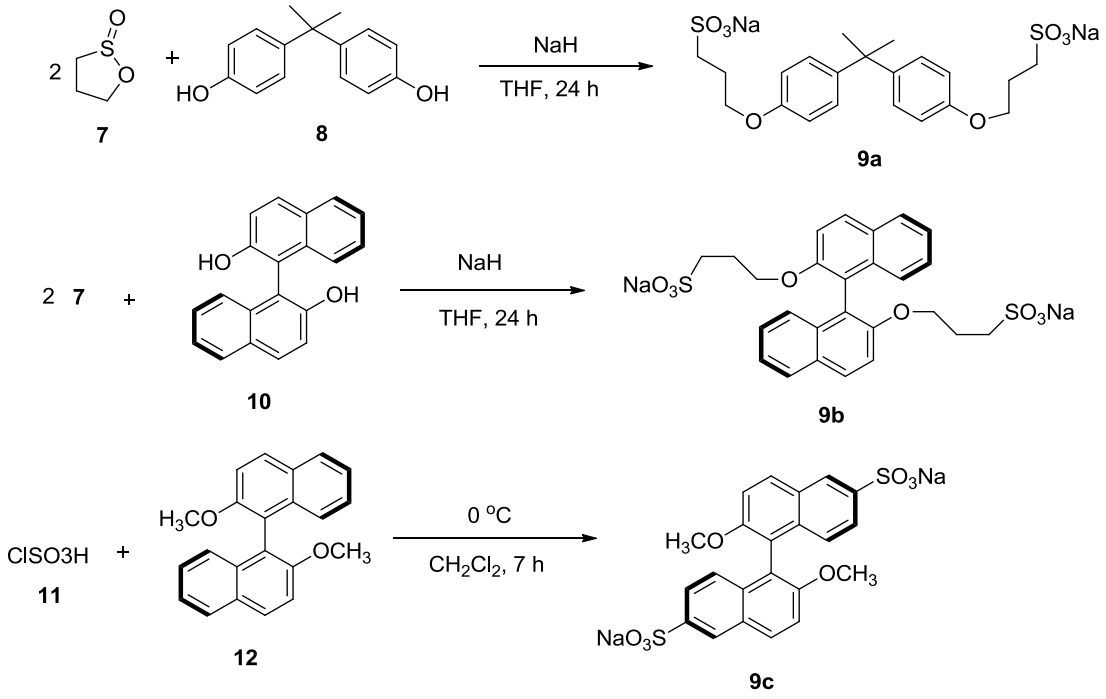
4a: R^1=H
4b: R^1=allyl

5aA: R^1=H, R^2=R^2 in **2A**, X=Cl
5aB: R^1=H, R^2=R^2 in **2B**, X=Br
5aC: R^1=H, R^2=R^2 in **2C**, X=Br
5bC: R^1=allyl, R^2=R^2 in **2C**, X=Br

Another component of the chiral ionic polymer is disodium disulfonate.We have prepared 3 different disodium disulfonates **9** as shown in Scheme III. Since it has been reported that alkoxides are sufficiently reactive to open 1,3- propanesultone ring to form alkyl sulfonate,[7] this reaction was used to form disulfonates (**9a**, **9b**). Dialkoxide preparedfrom 4,4'-(1-

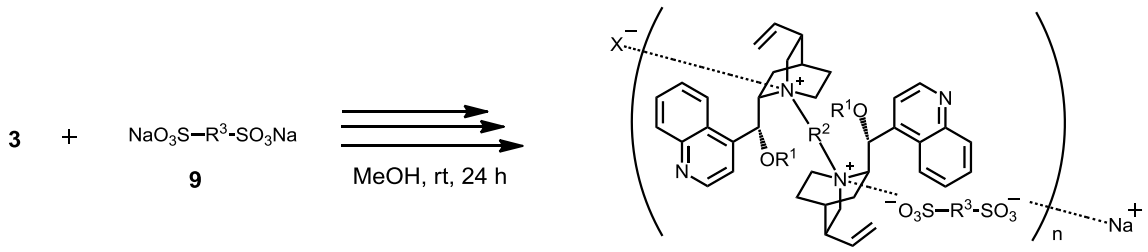
methylethylidene)-bisphenol **8** (bisphenol-A) easily reacted with 1,3 propanesultone **7** to give the corresponding disodium disulfonate **9a**. Optically active disodium disulfonate **9b** was prepared by the same method using (*S*)-1,1'-bi-2-naphthol **10** and the sultone **7**. Optically active aromatic disodium disulfonate **9c** was also prepared by sulfonation of (*S*)-1,1'-bi-2-naphthol derivative **12**.[8]

Scheme III Preparation of disulfonate **9**



Since we have succeeded in the novel polymerization between chiral quaternary ammonium dimer and disodium naphthalene disulfonate,[9] we applied this polymerization method to the combinations of chiral quaternary ammonium dimers (**3**, **5**) and the disodium disulfonates (**9**) including chiral disulfonate.

Scheme IV Polymerization of cinchonidine derived quaternary ammonium dimer **3** and disulfonate **9**

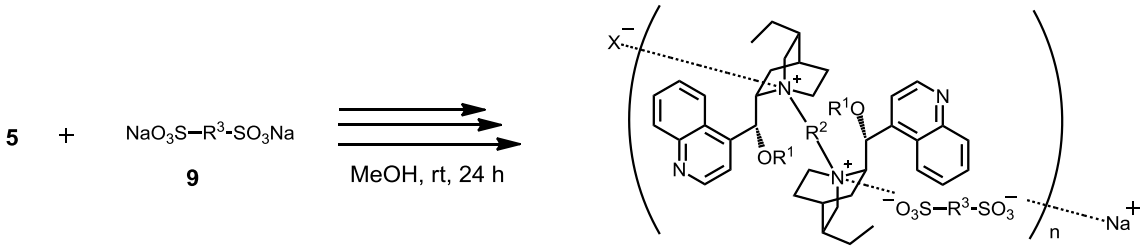


13

13aAa: R^1=H, R^2=R^2 in **2A**, R^3=R^3 in **9a**
13aAb: R^1=H, R^2=R^2 in **2A**, R^3=R^3 in **9b**
13aAc: R^1=H, R^2=R^2 in **2A**, R^3=R^3 in **9c**
13aBa: R^1=H, R^2=R^2 in **2B**, R^3=R^3 in **9a**
13aBb: R^1=H, R^2=R^2 in **2B**, R^3=R^3 in **9b**
13aBc: R^1=H, R^2=R^2 in **2B**, R^3=R^3 in **9c**
13aCa: R^1=H, R^2=R^2 in **2C**, R^3=R^3 in **9a**
13aCb: R^1=H, R^2=R^2 in **2C**, R^3=R^3 in **9b**
13aCc: R^1=H, R^2=R^2 in **2C**, R^3=R^3 in **9c**

13bAa: R^1=allyl, R^2=R^2 in **2A**, R^3=R^3 in **9a**
13bAb: R^1=allyl, R^2=R^2 in **2A**, R^3=R^3 in **9b**
13bAc: R^1=allyl, R^2=R^2 in **2A**, R^3=R^3 in **9c**
13bBa: R^1=allyl, R^2=R^2 in **2B**, R^3=R^3 in **9a**
13bBb: R^1=allyl, R^2=R^2 in **2B**, R^3=R^3 in **9b**
13bBc: R^1=allyl, R^2=R^2 in **2B**, R^3=R^3 in **9c**
13bCa: R^1=allyl, R^2=R^2 in **2C**, R^3=R^3 in **9a**
13bCb: R^1=allyl, R^2=R^2 in **2C**, R^3=R^3 in **9b**
13bCc: R^1=allyl, R^2=R^2 in **2C**, R^3=R^3 in **9c**

Scheme V Polymerization of 10,11-dihydrocinchonidine derived quaternary ammonium dimer **5** and disulfonate **9**



14

14aAa: R^1=H, R^2=R^2 in **2A**, R^3=R^3 in **9a**
14aAb: R^1=H, R^2=R^2 in **2A**, R^3=R^3 in **9b**
14aAc: R^1=H, R^2=R^2 in **2A**, R^3=R^3 in **9c**
14aBa: R^1=H, R^2=R^2 in **2B**, R^3=R^3 in **9a**
14aBb: R^1=H, R^2=R^2 in **2B**, R^3=R^3 in **9b**
14aBc: R^1=H, R^2=R^2 in **2B**, R^3=R^3 in **9c**
14aCa: R^1=H, R^2=R^2 in **2C**, R^3=R^3 in **9a**
14aCb: R^1=H, R^2=R^2 in **2C**, R^3=R^3 in **9b**
14aCc: R^1=H, R^2=R^2 in **2C**, R^3=R^3 in **9c**
14bCa: R^1=allyl, R^2=R^2 in **2A**, R^3=R^3 in **9a**
14bCb: R^1=allyl, R^2=R^2 in **2B**, R^3=R^3 in **9b**
14bCc: R^1=allyl, R^2=R^2 in **2C**, R^3=R^3 in **9c**

We confirmed that the polymerization was successfully applied to the selected combinations of quaternary ammonium dimers and disulfonates. The polymerization with ion exchange reaction between two components generated chiral main-chain ionic polymers. We prepared chiral ionic polymers **13** by repetitive ion exchange polymerization between quaternary ammonium dimers **3** and disodium disulfonate **9** as shown in Scheme IV. From the equimolar amount of **3** and **9** without any initiators and additives at room temperature, the corresponding chiral ionic polymers **13** were obtained in high yield. Scheme V shows the same polymerization with 10,11 dihydrocinchonidine derived dimer **5** to give the chiral ionic polymers **14**. In all cases polymeric products were precipitated in the reaction media, which could be easily isolated by filtration.

Due to the simplicity of the ion exchange polymerization, various kinds of chiral ionic polymers can be easily prepared by this method. The chiral ionic polymers **13** and **14** containing quaternary ammonium salt structure in their repeating units should have a catalytic activity of chiral organocatalyst. In order to investigate the catalytic activity of the chiral ionic polymers, we chose the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **15** to chiral amino acid derivative **16** as a typical asymmetric transformation using chiral quaternary ammonium salt.[10] We have tested the asymmetric benzylation reaction with the chiral ionic polymers **13** and **14** (Scheme VI).

Scheme VI Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **15**

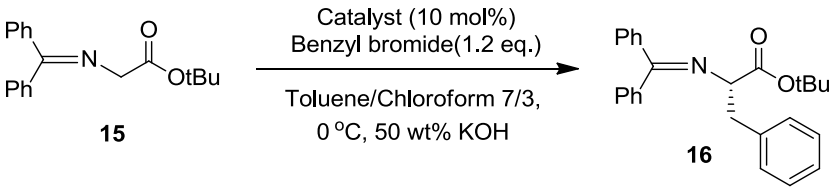


Table 2 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using cinchonidine derived ionic polymeric catalyst **13**[a]

Entry	Catalyst	Time (h)	Yield (%)	ee[a] (%)
1	**13aAa**	24	72	86
2	**13aAb**	10	81	92
3	**13aAc**	24	58	30
4	**13aBa**	24	64	89
5	**13aBb**	24	78	87
6	**13aBc**	24	92	87
7	**13aCa**	24	90	88
8[b]	**13aCa**	24	88	88
9	**13aCb**	4	81	81
10	**13aCc**	24	81	74
11	**13bAa**	4	92	88
12	**13bAb**	4	81	86
13	**13bAc**	4	89	86
14	**13bBa**	24	45	89
15	**13bBb**	4	89	90
16	**13bBc**	24	34	85
17	**13bCa**	24	78	92
18	**13bCb**	4	90	92
19	**13bCc**	4	83	90

[a]The enantimeric excess (ee%) of the product was determined by HPLC (Chiralcel OD-H) measurement.
[b]Polymeric catalyst **13aCa** used in entry 7 was reused.

Results of the asymmetric reaction were summarized in Table 1 and 2. First we used cinchonidine derived ionic polymers **13** as a chiral catalyst for the asymmetric benzylation reaction. The substrate molecule **15** in organic solvent was allowed to react with benzyl bromide in the presence of the polymeric chiral catalyst **13** and aqueous potassium hydroxide. In all cases, the asymmetric reaction smoothly took place with the polymeric catalyst in the two phase system. For example, chiral ionic polymer **13aAa** catalyzed the benzylation to give the corresponding chiral (*S*)-phenylalanine derivative **16** in 72% yield with 86% ee (Table 1, entry 1). The structure combination of R^1, R^2, and disulfonate in the polymeric catalyst influences on the enantioselectivity. When anthracenyl was introduced as R^2, free OH polymer catalysts (entries 1, 2, 3) showed higher enantioselectivity compared with the *O*-allylated polymeric ones (entries 10, 11, 12).

In case of 1, 3-disubstituted benzene ring as R^2, *O*-allylated polymeric catalysts gave higher enantioselectivities (entries 7, 8, 9 and 16, 17, 18). The similar tendency was observed in polymers containing 1,4-disubstituted benzene ring as R^2. Since the polymeric catalyst was

not soluble in both phases, the catalyst can be easily separated from the reaction mixture by filtration when the reaction was completed. Recovered polymeric catalyst was reused without loss of the catalytic activity (entry 8).

Table 2 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using cinchonidine derived ionic polymeric catalyst **13**[a]

Entry	Catalyst	Time (h)	Yield (%)	ee[a] (%)
1	**14aAa**	4	85	94
2	**14aAb**	4	91	95
3[b]	**14aAb**	6	98	97
4	**14aAc**	4	84	89
5	**14aBa**	4	71	89
6	**14aBb**	4	94	88
7	**14aBc**	4	85	88
8	**14aCa**	4	68	71
9	**14aCb**	4	87	78
10	**14aCc**	4	77	73
11	**14bCa**	4	90	91
12	**14bCb**	4	94	93
13	**14bCc**	4	93	90

[a]The enantimeric excess (ee%) of the product was determined by HPLC (Chiralcel OD-H) measurement.
[b]Polymeric catalyst **13aCa** used in entry 7 was reused.

Another chiral ionic polymers **14** derived from 10,11- dihydrocinchonidine **4** also showed high catalytic activity in the same asymmetric reaction as shown in Table 2. The use of 10,11-dihydrocinchonidine based ionic polymers containing free OH groups and 9,10-disubstituted anthracene structure afforded somewhat higher enantioselectivities (Table 2, entries 1-3). The reaction still occurred even at -20 °C to give the same product with higher enantioselectivity (97% ee) by using the polymeric catalyst **14aAb** (entry 3). In the case of 1,3-disubstituted benzene ring as R^2, the more noticeable decrease in enantioselectivities were observed (entries 8-10). *O*-allylated polymers **14bC** afforded high catalytic activity (entries 11-13) as in the cases of cinchonidine based polymers **13bC**.

4. 3. Conclusion

Under mild reaction condition with a simple reaction procedure, chiral main-chain polymers (**13**, **14**) were prepared. Repeated ion exchange reaction of chiral quaternary ammonium dimers (**3**, **5**) and disodium disulfonates (**9**) smoothly occurred to give the corresponding chiral ionic polymers (**13**, **14**) in high yield. These chiral ionic polymers showed excellent catalytic activity in the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **15** to give (*S*) phenylalanine derivative **16**. High level of enantioselectivities up to 97% ee were obtained in this reaction with the chiral polymeric catalysts. Various kinds of main-chain chiral polymers can be prepared by the ion exchange polymerization. This polymerization enable us to prepare a number of different kinds of chiral ionic polymers which show catalytic activity in asymmetric transformations.

4. 4. Experimental

General

All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). Column chromatography was performed with a silica-gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. ^{1}H (300 MHz) spectra were measured on a Varian Mercury 300 spectrometer. Elemental analyses were performed at the Microanalysis Center of Kyoto University. GC analyses were performed with a Shimadzu Capillary Gas Chromatograph 14B equipped with a capillary column (SPERCO β-DEX 325, 30 m × 0.25 mm). HPLC analyses were performed with a JASCO HPLC system comprising a three line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCELOD or AD, Daicel); hexane/2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell. Intrinsic viscosity [η] of each soluble sample was determined by viscometry, using a Ubbelohde viscometer at 40 ^{o}C in dimethyl sulfoxide (DMSO) solvent.

Preparation of disodium disulfonate

Synthesis of 9a

To a stirred solution of bisphenol-A (4.38 mmol, 1 g) in THF (10 mL), NaH (17.6 mmol, 0.42 g) was added and stirred at room temperature under Ar atmosphere. After 30 minutes, 1,3 Propanesultone (13.2 mmol, 1.62 g) was added to the reaction mixture and stirred for 2 h. Then the reaction mixture was refluxed for 24 h under Ar atmosphere. The reaction mixture was transferred to a centrifuge tube and centrifuged to give the white precipitate. The THF layer was removed. This process was repeated three times. The residue was dried and the white solid obtained was washed with methanol and dried under vacuum to afford **9a** in 80% yield. ^{1}H NMR (D_2O, 300MHz) δ 7.30 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 8.7, 2H), 8.87 (d, J = 9.0 Hz, 2H), 4.22~4.18 (m, 2H), 3.15~3.10 (m, 2H), 2.29~2.20 (m, 2H), 1.69 (s, 3H). Anal. Calc. for $C_{21}H_{26}Na_2O_6S_2$: C, 48.83; H, 5.07. Found: C, 48.78; H, 5.10.

Synthesis of 9b

To a solution of 1,1′-bi-2-naphthol (1.75 mmol, 0.50 g) in (5 mL) THF, NaH (3.50 mmol, 0.43 g) was added and stirred at room temperature under Ar atmosphere. After 30 minutes, 1,3 propanesultone (5.24 mmol, 0.64 g) was added to the reaction mixture and stirred for 2 h. Then the reaction mixture was refluxed for 24 h under Ar atmosphere, during which time a white product was precipitated out from the solution. The product was collected by filtration and washed with ethanol to give a white solid. The crude product was further purified byrecrystallization from EtOH:MeOH (1:1) to afford **9b** in 93% yield. ^{1}H NMR (D_2O, 300MHz) δ 8.12 (dd, *J* = 2.1, 1.5 Hz, 1H), 8.01 (d, *J* = 8.4, 1H), 7.61 (dd, *J* = 2.1, 2.4 Hz, 1H), 7.18~7.07 (m, 2H), 4.22~4.03 (m, 2H), 2.31~2.25 (m, 2H), 1.92~1.83 (m, 2H). Anal. Calc. for $C_{26}H_{24}Na_2O_8S_2$: C, 54.35; H, 4.21. Found: C, 54.21; H, 4.14.

Synthesis of 9c

To a solution of dimethoxybinaphthyl **12** (0.64 mmol, 0.20 g) in dichloromethane (4.0 mL), chlorosulfonic acid (1.53 mmol, 0.18 g, 0.1 mL) was slowly added at 0 ^{o}C. The reaction mixture was then stirred at 0 ^{o}C for 7 h and aqueous solution of NaOH (0.5 N, 20.0mL) was added to the reaction mixture. The light yellow colored solution obtained was concentrated in vacuo to give a solid. EtOH (6 mL) was then added to the solid and filtered. The solid was washed with EtOH and dried under reduced pressure to give **9c** in 85% yield. ^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.18 (d, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 9.00 Hz), 7.61 (d, *J* = 9.30 Hz, 1H), 7.44 (dd, *J* = 1.80, 1.50 Hz, 1H), 6.87 (d, *J* = 8.70, 1H), 3.71 (s, 3H). Anal. Calc. for $C_{22}H_{16}Na_2O_8S_2$: C, 50.96; H, 3.11. Found: C, 50.68; H, 3.06.

General procedure for the synthesis of ionic polymer 13

A solution of dimeric quaternary ammonium salt **3** (0.5mmol) and disodium disulfonate **9** (0.5mmol) inmethanol (5 mL) was stirred vigorously at room temperature for 24 h. The solvent was then evaporated to give a suspension of the ionic polymer. The precipitate was collected by filtration and washed with water and hexane to give the ionic polymer **13**. The yield of the ionic polymer was in the range of 75~90%. The intrinsic viscosity [η] of the ionic polymers in DMSO at 40 ^{o}C was in the range of 0.10~0.20.

Synthesis of 13aAa

80% yield. $[\alpha]_D^{25} = -3.11$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.1~8.6 (m, Ar-H), 8.2~7.9 (m, Ar-H), 7.3~6.7 (m, Ar-H), 6.0 (m), 5.7 (m), 5.0 (m), 4.5 (m), 3.9 (m), 3.3 (m), 3.0 (m), 2.2 (m), 1.9 (m), 1.6 (m).

Synthesis of 13aAb

82% yield. $[\alpha]_D^{25} = -2.66$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.1~9.0 (m, Ar-H), 8.9~8.8 (m, Ar-H), 8.7~8.5 (m, Ar-H), 8.14~ 8.12 (m, Ar-H), 7.9~7.8 (m, Ar-H), 7.44~7.42 (m, Ar-H), 7.4 (m), 7.3~7.2 (m, Ar-H), 7.14~7.11 (m, Ar-H), 7.0 (m, Ar-H), 6.84~6.82 (m, Ar-H), 6.6~6.5 (m), 5.96~5.92 (m), 5.7~5.6 (m), 5.1~4.9 (m), 4.6~4.4 (m), 4.0~3.9 (m), 3.3 (m), 3.0 (m), 2.11~2.07 (m), 2.0~1.9 (m), 1.6~1.3 (m).

Synthesis of 13aAc

88% yield. $[\alpha]_D^{25} = +1.25$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.2~ 8.6b (m, Ar-H), 8.3~7.3 (m, Ar-H), 6.9~6.8 (m, Ar-H), 6.0~5.9 (m), 5.3~4.5 (m), 3.0~2.7 (m), 2.4~1.0 (m).

Synthesis of 13aBa

85% yield. $[\alpha]_D^{25} = +1.67$ (c 1.0, DMSO). ^{1}HNMR (d^6-DMSO, 400 MHz) δ 9.05~8.98 (m, Ar-H), 8.36~8.34 (m, Ar-H), 8.14~8.10 (m, Ar-H), 7.9~7.7 (m, Ar-H), 7.9~7.8 (m, Ar-H), 7.0~6.6 (m, Ar-H), 5.7~5.6 (m), 5.3~5.1 (m), 4.94~4.92 (m), 4.26 (m), 3.9~3.6 (m), 3.5~3.4 (m), 2.9~2.6 (m), 2.59~2.55 (m), 2.12~1.96 (m), 1.5 (m), 1.25 (m).

Synthesis of 13aBb

88% yield. $[\alpha]_D^{25} = +1.59$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3~7.8 (m, Ar-H), 7.5~7.2 (m, Ar-H), 6.8~6.6 (m, Ar-H), 5.67 (m), 5.2~4.9 (m), 4.3~3.4 (m), 2.8 (m), 2.2~1.7 (m), 1.27 (m).

Synthesis of 13aBc

90% yield. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0~8.8 (m, Ar-H), 8.6~8.5 (m, Ar-H), 8.3~7.6 (m, Ar-H), 7.5~7.1 (m, Ar-H), 6.9~6.6 (m, Ar-H), 6.2 (m), 5.7~5.6 (m), 5.3~4.9 (m), 4.5~3.9 (m), 3.7~3.4 (m), 2.9~2.6 (m), 2.1~1.9 (m), 1.7~0.7 (m).

Synthesis of 13aCa

92% yield. $[\alpha]_D^{25} = +119.25\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3 (m, Ar-H), 8.1 (m, Ar-H), 7.9~7.8 (m, Ar- H), 7.0~7.6 (m, Ar-H), 5.7 (m), 5.2~4.9 (m), 4.5~3.8 (m), 3.5~3.4 (m), 2.9~2.7 (m). 2.54 (m), 2.1~2.0 (m), 1.5 (m), 1.3 (m).

Synthesis of 13aCb

90% yield. $[\alpha]_D^{25} = +144.64\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3~8.1 (m, Ar-H), 7.9~7.7 (m, Ar-H), 7.4~7.2 (m, Ar-H), 6.9~6.6 (m), 5.7 (m), 5.3~4.9 (m), 4.5~3.8 (m), 3.5~3.4 (m), 2.7 (m), 2.2~1.7 (m), 1.3~1.2 (m).

Synthesis of 13aCc

88% yield. $[\alpha]_D^{25} = +157.27\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0~ 8.98 (m, Ar-H), 8.36~8.33 (m, Ar-H), 8.2~8.0 (m, Ar-H), 7.95~7.83 (m, Ar-H), 7.8~7.7 (m, Ar-H), 7.61~7.58 (m, Ar-H), 7.45~7.42 (m, Ar-H), 6.93~6.84 (m, Ar-H), 6.6 (m), 5.7~5.6 (m). 5.3~5.2 (m), 4.95~4.92 (m), 4.32 (m), 3.99~ 3.94 (m), 3.83~3.80 (m), 3.7 (m), 3.6~3.5 (m), 3.37 (m), 2.74 (m), 2.54 (m), 2.1~1.9 (m), 1.8 (m).

Synthesis of 13bAa

85% yield. $[\alpha]_D^{25} = +2.51\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.2~9.0 (m, Ar-H), 8.7~8.5 (m, Ar-H), 8.2~8.1 (m, Ar-H), 8.0~7.8 (m, Ar-H), 7.1~7.0 (m, Ar-H), 6.8~6.5 (m), 6.35~6.30 (m), 5.96~5.92 (m), 5.8~5.6 (m), 5.49~5.46 (m), 5.03~4.96 (m), 4.6~2.58 (m), 4.26~4.22 (m), 4.0 ~3.7 (m), 3.5~3.4 (m), 2.8~2.7 (m), 2.4~2.3 (m), 2.0~1.8 (m), 1.5~1.4 (m).

Synthesis of 13bAb

80% yield. $[\alpha]_D^{25} = +2.19\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.3~9.0 (m, Ar-H), 8.6 (m, Ar-H), 8.2~7.5 (m, Ar-H), 7.3~6.9 (m, Ar-H), 6.6~6.02 (m), 5.9~5.5 (m), 5.0~4.0 (m), 3.7~3.4 (m), 2.1~1.0 (m).

Synthesis of 13bAc

85% yield. $[\alpha]_D^{25} = +2.25\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.2~9.0 (m, Ar-H),8.6~8.5 (m, Ar-H), 8.2~8.0 (m, Ar-H), 7.9~7.7 (m, Ar-H), 7.6~7.5 (m, Ar-H), 7.34~7.32

(m, Ar-H), 7.0 (m, Ar-H), 6.8 (m), 6.6~6.2 (m), 6.0~5.6 (m), 5.5~5.4 (m), 5.0~4.9 (m), 4.6~4.2 (m), 3.9~3.5 (m), 3.4~3.3 (m), 2.6 (m), 2.2~1.7 (m), 1.6~1.2 (m).

Synthesis of 13bBc

90% yield. $[\alpha]_D^{25} = +6.93\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0~8.8 (m, Ar-H), 8.5 (m, Ar-H), 8.2~8.0 (m, Ar-H), 7.7~7.9 (m, Ar-H), 6.88~6.86 (m, Ar-H), 6.2~5.6 (m), 5.3~4.9 (m), 4.0~3.2 (m), 2.3~1.4 (m).

Synthesis of 13bCa

85% yield. $[\alpha]_D^{25} = -108.34\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.03~ 9.01 (m, Ar-H), 8.3~8.1 (m, Ar-H), 7.9~7.7 (m, Ar-H), 7.0~6.6 (m, Ar-H), 6.46 (m), 6.2~6.1 (m), 5.7~5.6 (m), 5.5~4.9 (m), 4.4~3.6 (m), 3.5~3.3 (m), 2.67~2.54 (m), 2.3~ 1.8 (m), 1.5~1.4 (m).

Synthesis of 13bCb

85% yield. $[\alpha]_D^{25} = +136.70\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3~8.1 (m, Ar-H), 7.9~7.7 (m, Ar-H), 7.5~6.9 (m, Ar-H), 6.45 (m), 6.1 (m), 5.7 (m), 5.5~4.9 (m), 4.4~3.7 (m), 3.5~3.1 (m), 2.7 (m), 2.3~2.0 (m), 1.8 ~1.5 (m).

Synthesis of 13bCc

88% yield. $[\alpha]_D^{25} = +112.02\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.2~7.2 (m, Ar-H), 6.8 (m, Ar-H), 6.45 (m), 6.1 (m), 5.7 (m), 5.5~4.9 (m), 4.4 (m), 3.7 (m), 2.7 (m), 3.5~3.3 (m), 2.3~2.0 (m), 2.6 (m), 2.3 (m), 2.1~1.5 (m).

Synthesis of 14aAa

85% yield. $[\alpha]_D^{25} = +136.81\ (c\ 1.0, \mathrm{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.2~ 9.0 (m, Ar-H), 8.9~8.6 (m, Ar-H), 8.3~8.1 (m, Ar-H), 8.0~ 7.7 (m, Ar-H), 7.05~6.95 (m, Ar-H), 6.8~6.5 (m), 6.0~5.2 (m), 5.7 (m), 4.6~4.5 (m), 4.2~3.8 (m), 3.7~3.4 (m), 3.0~ 2.7 (m), 2.3~1.5 (m), 0.8~0.6 (m).

Synthesis of 14aAb

85% yield. $[\alpha]_D^{25} = +204.60(c\ 1.0, \text{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.1~8.4 (m, Ar-H), 8.2~7.7 (m, Ar-H), 7.5~7.1 (m, Ar-H), 6.9~6.6 (m), 6.0~5.5 (m), 4.5~3.9 (m), 2.9~2.7 (m), 2.0~1.2 (m), 0.7~0.6 (m).

Synthesis of 14aAc

85% yield. $[\alpha]_D^{25} = +106.02\ (c\ 1.0, \text{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.2~ 8.5 (m, Ar-H), 8.3~7.5 (m, Ar-H), 7.4~7.1 (m, Ar-H), 6.9~ 6.5 (m), 6.0~5.2 (m), 4.8~4.1 (m), 3.8~3.1 (m), 2.9~2.7 (m), 2.3~1.1 (m), 0.8~0.5 (m).

Synthesis of 14aBa

88% yield. $[\alpha]_D^{25} = +85.86\ (c\ 1.0, \text{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 8.9 (m, Ar-H), 8.3~7.6 (m, Ar-H), 7.0~6.9 (m, Ar-H), 6.7~6.6 (m), 5.3~5.0 (m), 4.3~3.2 (m), 2.6 (m), 2.1~1.1 (m), 0.7 (m).

Synthesis of 14aBb

85% yield. $[\alpha]_D^{25} = +91.73\ (c\ 1.0, \text{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 8.9 (m, Ar-H), 8.3~7.7 (m, Ar-H), 7.5~7.1 (m, Ar-H), 6.9~6.6 (m), 5.2~4.9 (m), 4.3 (m), 4.1~3.9 (m), 3.4~3.2 (m), 2.2~1.7 (m), 1.4~1.1 (m), 0.7 (m).

Synthesis of 14aBc

85% yield. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.5~7.1 (m, Ar-H), 6.9~ 6.6 (m), 5.3~4.9 (m), 4.3 (m), 3.7 (m), 3.4~3.0 (m), 2.1~1.8 (m), 1.3~0.7 (m).

Synthesis of 14aCa

85% yield. $[\alpha]_D^{25} = +102.01\ (c\ 1.0, \text{DMSO})$. $[\alpha]^{25}$ = 102.01 (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.6~7.5 (m, Ar-H), 7.1~6.9 (m, Ar-H), 6.8~6.6 (m), 4.4~3.0 (m), 2.1~1.1 (m), 0.7 (m).

Synthesis of 14aCb

85% yield. $[\alpha]_D^{25} = +129.26\ (c\ 1.0, \text{DMSO})$. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3~7.7 (m, Ar-H), 7.4~7.1 (m, Ar-H), 6.8~6.6 (m), 5.3~4.9 (m), 4.3~3.9 (m), 3.4~3.2 (m), 2.2~1.7 (m), 1.3~0.7 (m).

Synthesis of 14aCc

88% yield**.** $[\alpha]_D^{25} = +110.52$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.5~8.0 (m, Ar-H), 7.9~7.2 (m, Ar-H), 6.9~6.6 (m), 5.3~4.9 (m), 4.3 (m), 3.9~3.0 (m), 2.1~1.2 (m), 0.7 (m).

Synthesis of 14bCa

80% yield. $[\alpha]_D^{25} = -77.00$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3~7.7 (m, Ar-H), 7.0~6.9 (m, Ar-H), 6.7~6.4 (m), 6.2~6.1 (m), 5.5~5.0 (m), 4.4~3.2 (m), 2.57~2.53 (m), 2.3~1.7 (m), 1.6~1.1 (m), 0.7 (m).

Synthesis of 14bCb

85% yield. $[\alpha]_D^{25} = -89.36$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0 (m, Ar-H), 8.3~8.1 (m, Ar-H), 7.9~7.7 (m, Ar-H), 7.5~7.1 (m, Ar-H), 6.9~6.4 (m), 5.5~4.9 (m), 4.4~4.0 (m), 3.5~3.3 (m), 2.3~1.9 (m), 1.8~1.2 (m), 0.7 (m).

Synthesis of 14bCc

85% yield. $[\alpha]_D^{25} = -41.29$ (c 1.0, DMSO). ^{1}H NMR (d^6-DMSO, 400 MHz) δ 9.0~8.9 (m, Ar-H), 8.1~7.2 (m, Ar-H), 6.9~6.8 (m), 6.5~6.4 (m), 6.2~6.1 (m), 5.9~5.7 (m), 5.5~5.4 (m), 5.3~4.9 (m), 4.4~ 4.3 (m), 4.0~3.9 (m), 3.7~3.6 (m), 3.6~3.2 (m), 2.3~1.1 (m), 0.8~0.6 (m).

General Procedure for Catalytic Enantioselective Benzylation of *N*-Diphenylmethylidene Glycine *tert*- Butyl Ester (15) Using Chiral Polymeric Catalyst 13

Chiral polymeric catalyst **13** (100 mg) and *N*-diphenylmethylidene glycine *tert*-butyl ester (**15**: 0.53 g, 1.78 mmol) were added into a mixed solvent of toluene (7 mL) and chloroform (3 mL).11 50 wt% aqueous KOH solution (2.5 mL) was added to the above mixture. Benzyl bromide (0.37 g, 2.14 mmol) was then added dropwise at 0 ^{o}C to the mixture. The reaction mixture was stirred vigorously at 0 °C for several hours. Saturated sodium chloride solution (10 mL) was then added, and the mixture was subsequently filtered to recover **13**, which was washed with water and dichloromethane several times. The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:10 as eluent) gave (*S*)-*tert*-butyl *N*- (diphenylmethylidene) phenylalaninate (**16**). The enantiomeric excess was determined by

HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol = 100:1, flow rate = 0.3 mL/min, retention time: *R* enantiomer = 27.6 min, *S* enantiomer = 47.9 min). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[4]

4. 5. References

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(11) Jew and Park reported that the mixed solvent system provided high performance of the cinchonidinium salt catalysts in the asymmetric alkylation.[6]

Chapter 5

Synthesis of main-chain chiral quaternary ammonium polymers using Heck coupling and their applications in asymmetric catalysis

5. 1. Introduction

Cinchona alkaloids with pseudoenantiomeric forms such as quinine and quinidine or cinchonine and cinchonidine are one of the most important chirality inducers in the area of asymmetric catalysis.[1] The quinuclidine nitrogen of the cinchona alkaloid can easily be quaternized and the OH group also can be modified.[2-4] The double bond of the cinchona alkaloid also can be hydrogenated[5] and dehydrogenated.[6] Thiol-ene click reaction[7] and Heck coupling[8] reaction also can be carried out at the double bond of cinchonidine. Based on versatile functionalities of cinchona alkaloid several groups have reported monomeric,[2-4] dimeric[9-13] and polymeric organocatalyst[14-21] containing quaternary ammonium salts. Although several works have been done with the side-chain chiral polymeric organocatalyst only a limited number of investigations have been carried out for the development and application of main-chain chiral polymeric organocatalyst. The rigid and sterically regular structure of main-chain chiral polymers may have better defined microenvironment at the catalytic sites and have allowed systematic modification of their catalytic properties. We have recently developed main-chain chiral polymeric organocatalysts using different polymerization techniques[22-28] such as ion exchange polymerization, neutralization polymerization, quaternization polymerization, etherification polymerization. Most of the main-chain chiral polymers showed higher enantioselectivities than those obtained by using the corresponding monomeric catalysts when employed in asymmetric benzylation of glycine derivative.

Mizoroki-Heck coupling is one of the most efficient C-C bond formation reactions.[29] We have found that the double bond of the cinchonidine can be modified using Heck coupling reaction and we synthesized cinchonidine derived model compound **Heck-QCD** scheme 1. Over the last few years, limited number of works has been done with the main-chain chiral polymers using Heck coupling reactions and their applications.[30-33] The chiral polymers synthesized by Heck coupling was used as biosensor. To our knowledge, none of the main-

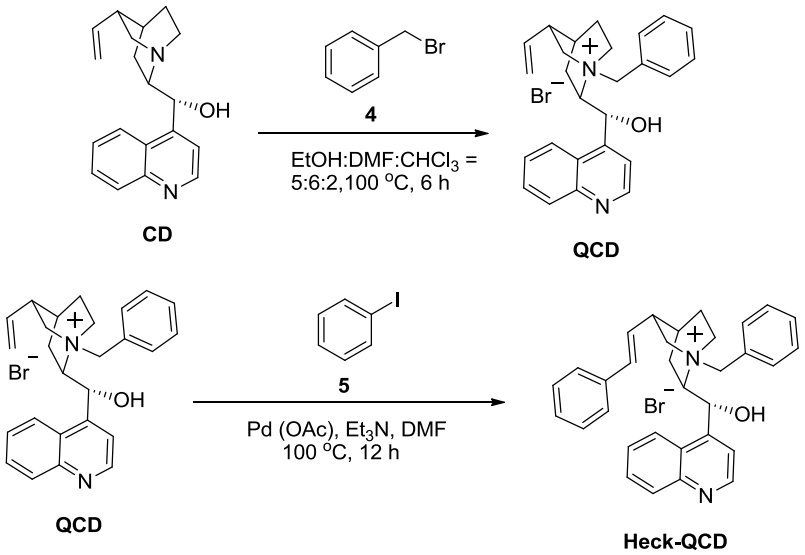
chain polymers synthesized by Heck coupling have been used as organocatalyst. Here we report a new kind of main-chain chiral polymers synthesized by Heck coupling using cinchona alkaloid and successfully employed as polymeric organocatalysts in asymmetric benzylation of glycine derivative.

5. 2. Results and discussion

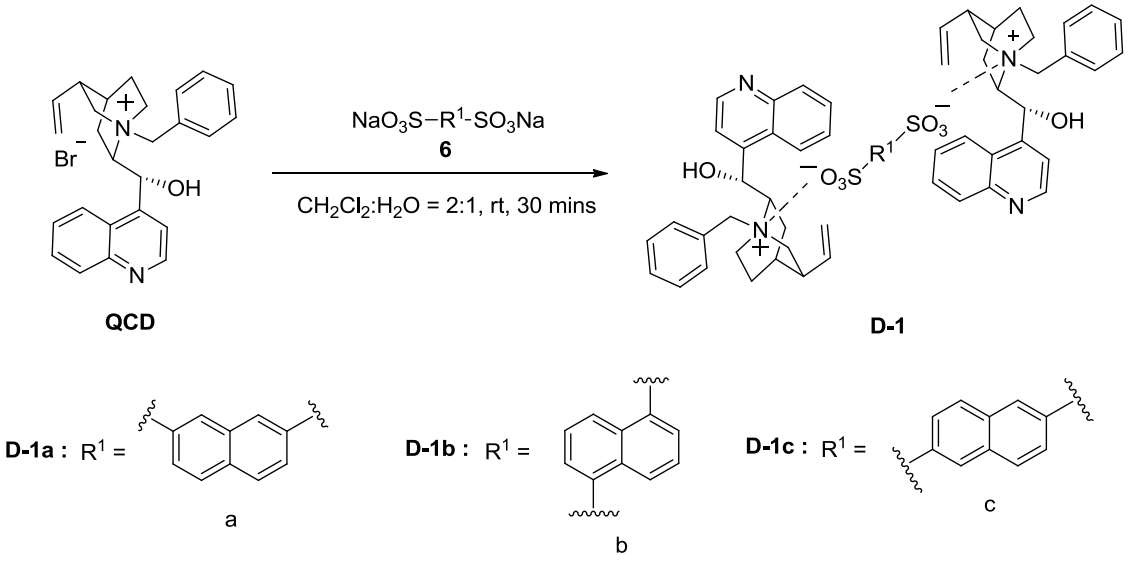
5. 2. 1. Synthesis of chiral main-chain polymers

Main-chain chiral polymers **PI** and **P-1** have been synthesized by the reaction between cinchona derived dimeric quaternary ammonium salts and diaryl halides. For the synthesis of main-chain polymers **PI,** we started with the quaternization of cinchonidine **CD** to obtain the product **QCD** Scheme 1. Ion exchange reaction between **QCD** and different types of disulfonates **6** gives the ionic dimer **D-1** Scheme 2. The ion exchange reaction takes place very fast (within 30 mins) in CH_2Cl_2 and water. Then the dimer **D-1** was used for polymerization reaction with 4, 4 diiodobiphenyl **7** using Mizoroki-Heck reaction scheme 3. The reaction takes place quatitatively and high yield was obtained. The number average molecular weight of the polymers varies from 7000-14000.

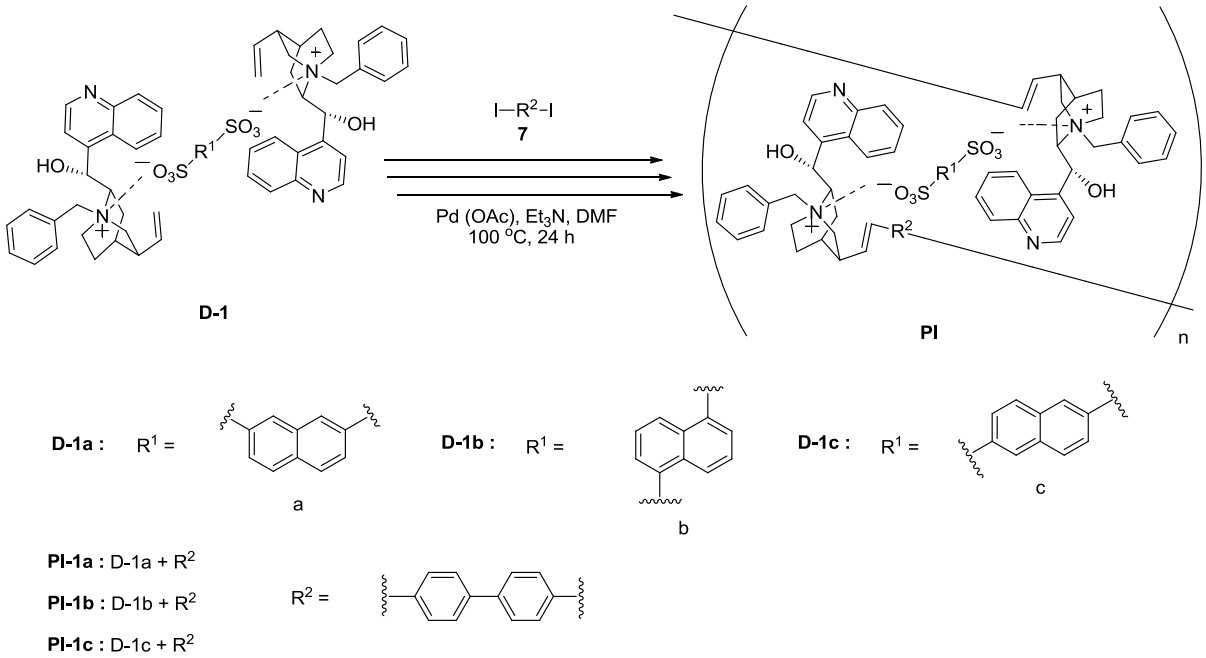
Scheme 1. Synthesis of Heck-QCD from cinchonidine



Scheme 2. Synthesis of dimer **D-1** from **QCD**



Scheme 3. Synthesis of polymer PI from dimer D-1



Other kind of main-chain chiral polymers **P-1** were synthesized from cinchona derived dimeric quaternary ammonium salts **1**and 4, 4' diiodobiphenyl **7** using Mizoroki-Heck coupling reaction Scheme 4. We also synthesized model dimeric compound **Heck-1b** Scheme 4. The dimerization of cinchonidine was carried out by the reaction between cinchonidine **CD** and different types of dihalides[9,10] using mixed solvent system of EtOH/DMF/$CHCl_3$= 5/6/2

at 100 ^{o}C Scheme 4. Then we polymerized the dimer **1** with **7** using Heck coupling. In this case also, the polymerization reaction is quantitative and high yield of the polymers were obtained. In polymerization we used DMF as a solvent and $Pd(OAc)_2$ as catalyst. We also optimized the polymerization condition changing the palladium catalyst, solvent and temperature. The optimization data are summarized in Table 1. When temperature was reduced to 80 ^{o}C Table 1 entry 5, molecular weight drastically decreased. When the palladium catalyst was changed to $PdCl_2$, the molecular weight also decreased. When THF was used as solvent the polymerization did not take place entry 7. Using DMSO as solvent also low molecular weight polymer was obtained entry 8. So, best condition for the synthesis of cinchona derived main-chain chiral polymer using Heck coupling is shown in entry 4.

Scheme 4. Synthesis of main-chain polymer using Heck coupling reaction

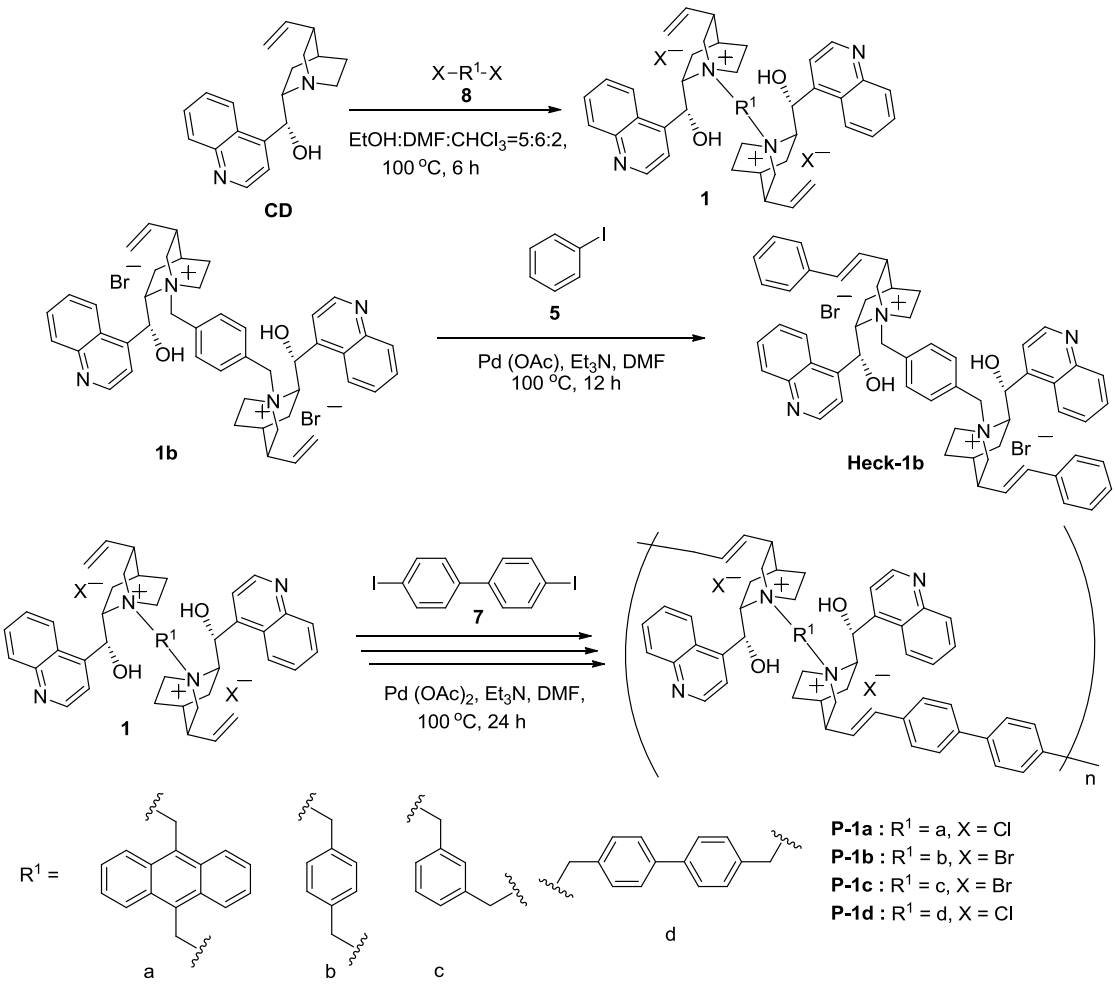


Table 1 Optimization of Polymerization conditions using Heck coupling

Entry	Solvent	Temp. (^{o}C)	Polymer	Catalyst	Time (h)	Yield (%)	M_n[a]	(M_w/M_n)[a]
1	DMF	100	**P-1a**	$Pd(OAc)_2$	24	71	14000	1.71
2	DMF	100	**P-1b**	$Pd(OAc)_2$	24	85	29000	1.66
3	DMF	100	**P-1c**	$Pd(OAc)_2$	24	80	24000	1.58
4	DMF	100	**P-1d**	$Pd(OAc)_2$	24	76	37000	1.43
5	DMF	80	**P-1d**	$Pd(OAc)_2$	48	75	5600	1.11
6	DMF	100	**P-1d**	$PdCl_2$	24	70	6600	1.11
7	THF	75	**P-1d**	$Pd(OAc)_2$	24	-	-	-
8	DMSO	95	**P-1d**	$Pd(OAc)_2$	24	72	6500	1.10

[a]Determined by GPC using DMF as a solvent at a flow rate of 1.0 mL/min at 40 ^{o}C

As cinchona derived quaternary ammonium salts are one of the most useful organocatalyst in the field of asymmetric synthesis, we assumed that the ionic dimer **D-1** also should have some catalytic activity in asymmetric reactions. We applied this dimeric and polymeric catalyst in asymmetric benzylation of glycine derivative **2** to obtain the product **3** scheme 5. The result obtained with ionic dimer **D-1** and main-chain chiral polymers PI in the asymmetric benzylation of glycine derivative are summarized in Table 2. Among the three ionic dimers, **D-1b** shows high yield and enantioselectivity entry 2. When we employed the polymers **PI** as a novel polymeric organocatalyst in asymmetric benzylation of glycine derivative it showed good yield and enantioselectivity Table 2 entry (4~6).

Scheme 5. Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester

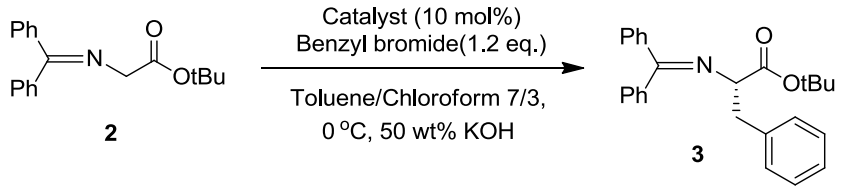


Table 2 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric catalyst[a] **D-1**[a] and polymeric catalyst **PI-1**[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[cd] (%)
1	**D-1a**	4	88	78
2	**D-1b**	4	91	79
3	**D-1c**	4	90	76
4	**PI-1a**	5	95	70
5	**PI-1b**	5	89	66
6	**PI-1c**	5	76	65

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 ^oC. [b]Determined by ^1H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration.

In 1989 O'Donnel[2] et al. first reported the asymmetric alkylation of glycine derivative using cinchona derived quaternary salts and in 2001 Perk and Jew[7] et al. synthesized cinchona derived dimeric quaternary ammonium salts and successfully applied in asymmetric alkylation of glycine derivative. The results of the asymmetric benzylation of glycine derive using monomeric, dimeric and polymeric catalysts are shown in Table 3.

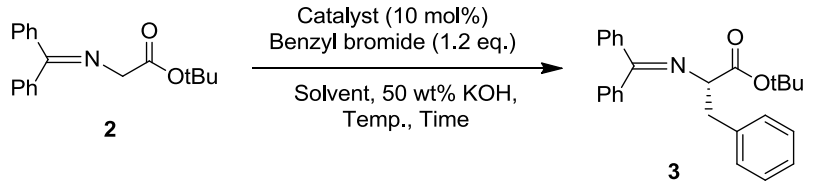
The monomeric catalyst **QCD** gives 71% enantioselectivity in asymmetric benzylation reactions. The modified quaternized cinchonidine **Heck-QCD** gives same enantioselectivity as **QCD**. Entry 3~6 shows the results of the asymmetric benzylation of glycine derivative using dimeric catalyst. When the double bond of the catalyst **1b** modified by Heck coupling using iodobenzene (**Heck-1b**) it shows higher enantioselectivity than **1b**. As the monomeric and dimeric quaternary ammonium salts are an efficient catalyst for the asymmetric alkylation, the polymeric organocatalyst synthesized from dimeric catalyst should also show some catalytic activity in asymmetric alkylation. When we applied the polymeric organocatayst **P-1** in asymmetric benzylation of glycine derivative good to excellent yield and enantioselectivity was obtained Table 3 entry 8~11. Among them **P-1b** showed excellent yield and enantioselectivity compare to other polymeric organocatalyst and 91% enantioselectivity was obtained at 0 ^oC when Toluene and chloroform was used at a ratio of 7:3. The polymeric catalyst also can be reused from the reaction mixture. Catalyst **P-1d** was recovered from entry 11 was reused in entry 12 with slightly decrease in enantioselectivity.

Table 3 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using monomeric, dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[cd] (%)
1	**QCD**	5	91	71
2	**Heck-QCD**	5	86	71
3[e]	**1a**	6	88	86
4[f]	**1b**	12	91	80
5[g]	**1c**	4	90	84
6	**1d**	4	89	83
7	**Heck-1b**	5	85	88
8	**P-1a**	6	55	64
9	**P-1b**	8	83	91
10	**P-1c**	4	69	67
11	**P-1d**	5	83	82
12[h]	**P-1d**	6	81	79

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 °C. [b]Determined by ^{1}H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref. 13. [f]See ref. 22. [g]See ref. 10. [h]Catalyst recovered from entry 11 was reused.

Table 4 Optimization of asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using and polymeric catalyst **P-1b**[a]



Entry	Solvent	Time (h)	Temp. (°C)	Yield[b] (%)	ee[cd] (%)
1	Toluene	10	0	84	72
2	Toluene:$CHCl_3$=7:3	8	0	83	91
3	Toluene:$CHCl_3$=7:3	24	-20	99	94
4	Toluene:$CHCl_3$=7:3	72	-40	58	93
5	Toluene:$CHCl_3$=5:5	6	0	99	93
6	Toluene:$CHCl_3$=5:5	24	-20	93	95
7	Toluene:$CHCl_3$=3:7	6	0	84	92
8	$CHCl_3$	6	0	80	90

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 °C. [b]Determined by ^{1}H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration.

Then we tried to optimize the reaction condition by changing solvent ratio and temperature Table 4. Using toluene only as a solvent enantioselectivity decreased to 72% entry 1. When the temperature was reduced to -20 ^{o}C 94% ee was obtained entry 3. Further lowering the temperature to -40 ^{o}C enantioselectivity decreases to 93% and rate of reaction is also very slow and after 72 hours 91% yield was obtained entry 4. When the Toluene/$CHCl_3$ ratio was changed from 7:3 to 5:5 the enantioselectivity increased from 91% to 93% entry 5. We also tried with the lower temperature from 0 ^{o}C to -20 ^{o}C and again enantioselectivity increased from 93% to 95% entry 6. When the solvent ratio was change to Toluene/$CHCl_3$ = 3/7 92% enantioselectivity was obtained entry 7. 90% enantioselectivity was obtained when only $CHCl_3$ was used entry 7. So, we can say the reaction is little sensitive to the solvent and temperature.

5. 3. Conclusion

We have prepared some main-chain chiral polymeric organacatalyst using Mizoroki-Heck coupling in the polymerization reaction. The reaction occurred smoothly and quantitatively to give the corresponding polymeric organocatalyst **PI** and **P-1** from the dimer **D-1** and **1** respectively. Some of the polymeric organocatalyst showed excellent yield and enantioselectivity in asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **2** to give the phenyl alanine derivative **3**. A high level of enantioselectivity up to 95% ee was obtained with newly developed main-chain chiral polymeric organocatalyst.

5. 4. Experimental

General

All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. DMF was distilled from calcium hydride before use. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). Column chromatography was performed with a silica-gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. ^{1}H (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were measured on Mercury 300 or Jeol ECS 400 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. HPLC analyses were performed with a JASCO HPLC system comprising a three-line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCEL ODH); hexane/2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell. Size exclusion chromatography (SEC) was obtained with Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 ^{o}C. Two polystyrene gel columns of bead size 10 µm were used. A calibration curve was made to determine number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards.

General procedure for catalytic enantioselective benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester (2 using chiral polymeric catalyst P-1b

Chiral polymeric catalyst **P-1b** (10 mol %) and N-diphenylmethylidene glycine *tert*-butyl ester **2** (0.53 g, 1.78 mmol) were added to a mixed solvent of toluene (7 mL) and chloroform (3 mL). 50 wt% aqueous KOH solution (2.5 mL) was added to the above mixture. Benzyl bromide (0.37 g, 2.14 mmol) was then added drop wise at 0 °C to the mixture. The reaction mixture was stirred vigorously for 8 h. Saturated sodium chloride solution (10 mL) was then added and the organic phase was extracted with ethyl acetate and concentrated in vacuo to give the crude product as colorless oil. Purification of the residual oil by column chromatography on silica gel (ether–hexane = 1:10 as eluent) gave (S)-*tert*-butyl *N*-

(diphenylmethylidene) phenylalanine. The enantiomeric excess (91% ee) was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane–2-propanol = 100:1, flow rate = 0.3 mL min^{-1}, retention time: R enantiomer = 27.6 min, S enantiomer = 47.9 min). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[2]

Synthesis of QCD from CD

A mixture of (-) cinchonidine **CD** (1.47 g, 5.0 mmol) with benzyl bromide (0.89 g, 5.2 mmol) was stirred in a mixture of 20 mL (Ethanol: DMF: $CHCl_3$ / 5:6:2) at 100 ^oC for 6 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was added drop wise to ether (300 mL) with stirring. The solid precipitated was filtered, washed with ether (100 mL) and hexane to afford 2.25 g (88 % yield) of product. ^1H NMR (d^6-DMSO, 300 MHz) δ 8.98 (d, J = 4.5 Hz, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.4 1H), 7.87~7.80 (m, 2H), 7.77~7.73 (m, 3H), 7.58~7.56 (m, 3H), 6.67 (d, J = 4.5 Hz, 1H), 6.56 (d, J = 3.6 Hz, 1H), 5.73~5.62 (m, 1H), 5.21~5.13 (m, 2H), 5.05 (d, J = 12.3 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 4.32~4.25 (m, 1H), 3.97~3.91 (m, 1H), 3.78 (d, J = 12.3 Hz, 1H), 3.26~3.18 (m, 2H), 2.69 (s, 1H), 2.15~1.99 (m, 3H), 1.85~1.77 (m, 1H), 1.32~1.24 (m, 1H). ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.05, 147.39, 145.48, 138.04, 133.82, 130.09, 129.63, 129.51, 128.89, 127.99, 127.38, 124.28, 123.87, 120.14, 116.38, 67.49, 63.96, 62.44, 59.11, 50.55, 36.77, 25.88, 24.19, 21.02. IR (KBr) υ 3295, 3090, 2921, 2189, 1967, 1663, 1608, 1587, 1509, 1457, 1343, 1213, 1127, 939, 799, 760. $[\alpha]_D^{25} = -123.40$ (c 1.0, DMSO).

Synthesis of H-QCD:

A mixture of **QCD** (0.93 g, 2.0 mmol) with iodobenzene (0.45 g, 2.2 mmol) in presence of 3 mol% Pd $(OAc)_2$ (0.06 mmol 0.01 g) and Et_3N (0.2 mL, 2.0 mmol) was stirred in 10 mL dry DMF at 100 ^oC for 12 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (300 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 1.01 g (87 % yield) of the product. ^1H NMR (d^6-DMSO, 400 MHz) δ 8.99 (d, J = 4.0 Hz, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.81 (d, J =12.2 Hz, 1H), 7.58 (s, 3H), 7.25~7.14 (m, 4H), 6.72~6.50 (m, 2H), 6.23~6.06 (m, 1H), 5.41~4.96 (m, 2H), 4.29~3.84 (m, 2H), 3.45~3.39 (m, 1H), 3.12~3.10 (m, 2H), 2.96~2.91 (m, 2H), 2.08 (d, J= 13.2, 2H),

1.86~1.46 (m, 1H), 1.20~1.16 (m, 5H). ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.59, 147.96, 146.07, 136.97, 134.34, 131.36, 130.68, 130.40, 130.21, 130.00, 129.48, 128.92, 128.47, 127.95, 127.92, 126.60, 124.89, 124.38, 120.61, 68.36, 64.60, 63.31, 60.37, 51.29, 37.21, 27.01, 24.84, 21.55. IR (KBr) υ 3231.15, 2942.84, 1590.02, 1508.06, 1387.53, 1233.25, 1159.97, 1031.73, 757.89, 701.00. $[\alpha]_D^{25} = +94.70$ (c 1.0, DMSO). mp: 144-146.

Synthesis of Heck-1b

A mixture of cinchonidine dimer **1b** (0.85 g, 1.0 mmol) with iodobenzene (0.45 g, 2.2 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^{o}C for 12 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.88 g (88 % yield) of the product. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 8.99 (d, J = 4.4 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.13~8.09 (m, 1H), 8.01~7.93 (m, 1H), 7.84~7.78 (m, 3H), 7.32~7.15 (m, 4H), 7.04~6.20 (m, 3H), 5.39~4.93 (m, 3H), 4.39~3.61 (m, 2H), 3.40 (s, 4H), 3.22~2.91 (m, 1H), 2.29~1.80 (m, 4H), 1.49~1.43 (m, 1H), 1.21~1.16 (m, 1H) .^{13}C NMR (d6-DMSO, 100 MHz) δ 150.25, 147.65, 145.40, 145.04, 136.49, 134.18, 130.77, 129.91, 129.44, 128.45, 128.36, 127.35, 126.09, 124.42, 124.22, 123.83, 120.13, 68.61, 68.11, 64.18, 62.38, 59.83, 36.74, 26.55, 24.11, 21.39. IR (KBr) υ 3227, 2944, 1652, 1590, 1509, 1455, 1233, 1161, 953. $[\alpha]_D^{25} = +50.78$ (c 1.0, DMSO). mp: 216-218.

Synthesis of D-1a

A mixture of **QCD** (1.21 g, 2.60 mmol) with 2, 7-naphthalene disodium disulfonate (0.42g, 1.25 mmol) was stirred in a mixture of 20 mL (CH_2Cl_2) and 10 mL (H_2O) at room temperature for 30 minutes. After completion of reaction, the reaction mixture was filtered through a glass filter and washed with CH_2Cl_2, water and hexane. The solid obtained was dried under vacuum at 40 ^{o}C. The yield of the product was calculated 1.20 g (91 %). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.98 (d, J = 4.5 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.11 (s, 2H), 7.86~7.82 (m, 3H), 7.77~7.69 (m, 4H), 7.56 (s, 3H), 6.79 (d, 1H), 6.57 (s, 1H), 5.76~5.61 (m, 1H), 5.16~5.10 (m, 2H), 4.99~4.92 (m, 2H), 4.24 (s, 1H), 3.94~3.88 (m, 1H), 3.71 (d, J = 11.1 Hz, 1H), 3.32~3.20 (m, 2H), 2.68 (s, 1H), 2.15~1.98 (m, 3H), 1.84~1.76 (m, 1H), 1.32~1.24 (m, 1H). ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.23, 147.63, 145.88, 145.40,

138.15, 133.79, 132.59, 131.29, 130.17, 129.89, 129.53, 129.00, 127.93, 127.27, 124.56, 124.39, 123.63, 120.11, 116.39, 67.63, 64.20, 62.91, 59.18, 50.64, 36.85, 25.91, 24.24, 20.90. IR (KBr) υ 3208, 3005, 2848, 1935, 1845, 1640, 1590, 1509, 1498, 1458, 1422, 1267, 1061, 779, 698. $[\alpha]_D^{25} = -121.69\ (c\ 1.0, \mathrm{DMSO})$. mp: 230-232 ^{o}C.

Synthesis of D-1b

A mixture of **QCD** (1.21 g, 2.60 mmol) with 1, 5-naphthalene disodium disulfonate (0.42g, 1.25 mmol) was stirred in a mixture of 20 mL (CH_2Cl_2) and 10 mL (H_2O) at room temperature for 30 minutes. After completion of reaction, the reaction mixture was filtered through a glass filter and washed with CH_2Cl_2, water and hexane. The solid obtained was dried under vacuum at 40 ^{o}C. The yield of the product was calculated 1.21 g (92 %). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.98 (d, J = 3.9 Hz, 1H), 8.87 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.1 1H), 8.11 (d, J = 8.1, 1H), 7.93 (d, J = 6.6, 1H), 7.87~7.81 (m, 2H), 7.77~7.72 (m, 1H), 7.66 (s, 2H), 7.55 (s, 3H), 7.39~7.34 (m, 1H), 6.79 (d, J = 3.6 Hz, 1H), 6.57 (s, 1H), 5.76~5.60 (m, 1H), 5.16~5.10 (m, 2H), 4.98~4.92 (m, 2H), 4.27~4.20 (m, 1H), 3.94~3.89 (m, 1H), 3.70 (d, J = 5.1 Hz, 1H), 3.39~3.17 (m, 2H), 2.68 (s, 1H), 2.16~1.98 (m, 3H), 1.84~1.76 (m, 1H), 1.33~1.24 (m, 1H). ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.24, 147.64, 145.39, 143.75, 138.14, 133.77, 130.17, 129.90, 129.57, 129.53, 127.91, 127.29, 124.35, 124.11, 123.96, 123.62, 120.11, 116.40, 67.65, 64.19, 62.94, 59.19, 50.63, 36.86, 25.91, 24.23, 20.88. IR (KBr) υ 3446, 3196, 2960, 1933, 1845, 1636, 1589, 1508, 1497, 1421, 1217, 1028, 764, 607. $[\alpha]_D^{25} = -123.78\ (c\ 1.0, \mathrm{DMSO})$. mp: 247~249 ^{o}C.

Synthesis of D-1c

A mixture of **QCD** (1.21 g, 2.60 mmol) with 2, 6-naphthalene disodium disulfonate (0.42g, 1.25 mmol) was stirred in a mixture of 20 mL (CH_2Cl_2) and 10 mL (H_2O) at room temperature for 30 minutes. After completion of reaction, the reaction mixture was filtered through a glass filter and washed with CH_2Cl_2, water and hexane. The solid obtained was dried under vacuum at 40 ^{o}C. The yield of the product was calculated 1.25 g (95 %). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.96 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 8.11 (s, 2H), 7.85~7.82 (m, 3H), 7.76~7.68 (m, 4H), 7.55 (s, 3H), 6.80 (d, J = 1.2 Hz, 1H), 6.57 (s, 1H), 5.71~5.60 (m, 1H), 5.15~5.10 (m, 2H), 4.99~4.92 (m, 2H), 4.26~4.21 (m, 1H), 3.93~3.89 (m, 1H), 3.70 (d, J = 12.0 Hz, 1H), 3.28~3.22 (m, 2H), 2.68 (s, 1H), 2.16~1.98 (m, 3H), 1.84~1.77 (m, 1H), 1.31~1.24 (m, 1H). ^{13}C NMR (d^6-DMSO, 100 MHz) δ 149.79, 146.85,

146.30, 145.87, 138.15, 133.80, 131.95, 130.18, 129.90, 129.23, 129.00, 128.92, 128.13, 127.93, 127.52, 124.30, 123.86, 123.75, 120.18, 116.40, 67.54, 64.23, 62.88, 59.21, 50.63, 36.85, 25.91, 24.13, 20.79. IR (KBr) υ 3217, 1700, 1637, 1591, 1570.74, 1509.03, 1421.28, 1387.53, 1195.65, 1024.98, 780.06. $[\alpha]_D^{25} = -86.85$ (c 1.0, DMSO).

Synthesis of main-chain chiral polymers PI-1a from ionic dimer D-1a using Heck reaction

A mixture of ionic dimer **D-1a** (0.53 g, 0.5 mmol) with 4,4'-diiodo biphenyl (0.20 g, 0.5 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.07 mL, 0.5 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper added drop wise to water (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate, CH_3OH, and hexane to afford 0.42 g (70 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.21, 147.64, 145.87, 145.45, 138.31, 137.70, 135.63, 133.82, 132.61, 131.29, 130.46, 130.21, 129.88, 129.47, 129.03, 128.62, 127.93, 127.29, 126.71, 126.46, 126.35, 124.57, 123.69, 120.11, 68.02, 64.19, 63.12, 59.97, 50.85, 36.85, 26.52, 24.38, 20.98. IR (KBr) υ 3230, 2947, 1918, 1699, 1654, 1590, 1508, 1456, 1316, 1216, 1180, 1101, 1025, 699. $[\alpha]_D^{25} = -134.73$ (c 1.0, DMSO). M_n (SEC) =7,000. M_w/M_n=1.71.

Synthesis of main-chain chiral polymers PI-1b from ionic dimer D-1b using Heck reaction

A mixture of ionic dimer **D-1b** (0.53 g, 0.5 mmol) with 4,4'-diiodo biphenyl (0.20 g, 0.5 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.07 mL, 0.5 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to water (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate, CH_3OH, and hexane to afford 0.50 g (80 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.21, 147.64, 145.50, 143.67, 138.31, 135.65, 133.81, 130.46, 130.20, 129.88, 129.57, 129.16, 129.04, 127.91, 127.41, 126.71, 126.44, 124.44, 124.19, 124.03, 123.73, 120.12, 68.03, 64.20, 63.10, 59.96, 50.84, 36.84, 26.61, 24.37, 20.98. IR (KBr) υ 3233, 3027, 2947, 1654, 1590, 1508,

1456, 1387, 1216, 1029, 796, 703. $[\alpha]_D^{25} = -148.58$ (c 1.0, DMSO). M_n (SEC) =7,000. M_w/M_n =1.43.

Synthesis of main-chain chiral polymers PI-1c from ionic dimer D-1c using Heck reaction

A mixture of ionic dimer **D-1c** (0.53 g, 0.5 mmol) with 4,4'-diiodo biphenyl (0.20 g, 0.5 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.07 mL, 0.5 mmol) was stirred in 18 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to water (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate, CH_3OH, and hexane to afford 0.55 g (89 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.21, 147.65, 145.81, 145.45, 138.30, 135.63, 133.82, 131.97, 130.44, 130.20, 129.88, 129.46, 129.02,128.18, 127.93, 127.38, 126.71, 126.44, 126.34, 124.44, 124.29, 123.90, 123.71, 120.11, 67.98, 64.19, 63.05, 59.94, 50.84, 36.83, 26.57, 24.38, 20.97. IR (KBr) υ 3391, 2951, 1636, 1590, 1508, 1496, 1456, 1326, 1216, 1086, 1026, 904, 760. $[\alpha]_D^{25} = -115.35$ (c 1.0, DMSO). M_n (SEC) =15,000. M_w/M_n =1.33.

Synthesis of main-chain chiral polymer P-1a from cinchonidine dimer 1a using Heck reaction

A mixture of cinchonidine dimer **1a** (0.86 g, 1.0 mmol) with 4, 4'-diiodo biphenyl (0.41 g, 1.0 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to water (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.7 g (71 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.34, 147.74, 146.70, 138.24, 135.92, 130.53, 129.93, 129.44, 127.14, 127.10, 127.06, 127.01, 126.88,126.77, 126.53, 126.41, 124.71, 123.56, 119.11, 66.22, 59.86, 53.86, 43.02, 37.79, 36.73, 27.31, 27.26, 23.85, 18.10. IR (KBr) υ 3309, 3023, 2943, 1733, 1698, 1653, 1591, 1508, 1456, 1375, 1024, 807, 754. $[\alpha]_D^{25} = +58.73$ (c 1.0, DMSO). M_n (SEC) =14,000. M_w/M_n =1.71.

Synthesis of main-chain chiral polymer P-1b from cinchonidine dimer 1b using Heck reaction

A mixture of cinchonidine dimer **1b (**0.85 g, 1.0 mmol) with 4, 4'-diiodo biphenyl (0.41 g, 1.0 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.85 g (85 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.24, 147.60, 145.43, 145.05, 137.66, 134.20, 129.87, 129.53, 128.59, 128.07, 127.38, 126.78, 126.44, 124.42, 124.21, 123.84, 120.12, 67.92, 64.18, 62.85, 59.77, 50.48, 36.56, 26.52, 24.13, 20.99. IR (KBr) υ 3231, 2945, 1655, 1590, 1509, 1457, 1422, 1386, 1233, 112, 1061, 998, 812, 757. $[\alpha]_D^{25} = +50.73\ (c\ 1.0, \mathrm{DMSO})$. M_n (SEC) =29,000. M_w/M_n =1.66.

Synthesis of main-chain chiral polymer P-1c from cinchonidine dimer 1c using Heck reaction

A mixture of cinchonidine dimer **1c** (0.85 g, 1.0 mmol) with 4, 4'-diiodo biphenyl (0.41 g, 1.0 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to methanol (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate, CH_3OH and hexane to afford 0.8 g (80 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.23, 147.65, 145.30, 138.99, 138.25, 137.68, 135.36, 129.95, 129.52, 128.75, 128.61, 127.42, 126.71, 126.46, 126.38, 124.32, 123.74, 120.16, 68.12, 64.30, 62.62, 59.77, 50.80, 36.76, 26.54, 24.26, 21.08. IR (KBr) υ 3227, 2945, 1919, 1698, 1590, 1508, 1456, 1386, 1234, 1120, 1000, 954, 800, 774. $[\alpha]_D^{25} = +28.67\ (c\ 1.0, \mathrm{DMSO})$. M_n (SEC) =24,000. M_w/M_n =1.58.

Synthesis of main-chain chiral polymer P-1d from cinchonidine dimer 1d using Heck reaction

A mixture of cinchonidine dimer **1d** (0.84 g, 1.0 mmol) with 4, 4'-diiodo biphenyl (0.41 g, 1.0 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 20 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.75 g (76 % yield) of the product. ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.26, 147.64, 145.46, 140.58, 137.69, 134.47, 130.51, 130.39, 129.48, 129.53, 129.49, 128.61, 127.31, 127.15, 126.76, 126.46, 124.37, 123.78, 120.16, 68.11, 64.11, 62.56, 59.81, 50.95, 36.91, 26.63, 23.97, 21.08. IR (KBr) υ 3224, 2943, 1654, 1591, 1508, 1457, 1387, 1211, 1119, 1000, 952, 811, 774. $[\alpha]_D^{25} = +42.86\ (c\ 1.0, \mathrm{DMSO})$. M_n (SEC) =37,000. M_w/M_n =1.43.

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Chapter 6

Synthesis of main-chain chiral ionic polymers from Heck modified cinchonidine dimer and their applications in asymmetric catalysis

6. 1. Introduction

Cinchona derived quaternary ammonium salts are one of the most widely used organocatalyst in the field of asymmetric synthesis. Several modifications of cinchona alkaloid have been done for the appropriate design of organocatalyst. Several groups have reported monomeric,[1-3] dimeric[4-8] and polymeric organocatalyst[9-16] containing quaternary ammonium salts of cinchona alkaloid. Although several works have been done with the side-chain chiral polymeric organocatalyst only a limited number of investigations have been carried out for the development and application of main-chain chiral polymeric organocatalyst. The rigid and sterically regular structure of main-chain chiral polymers may have better defined microenvironment at the catalytic sites and have allowed systematic modification of their catalytic properties. We have recently reported some main-chain chiral polymeric organocatalysts using different polymerization techniques[17-23] such as ion exchange polymerization, neutralization polymerization, quaternization polymerization, etherification polymerization. Most of the main-chain chiral polymers showed higher enantioselectivities than those obtained by using the corresponding monomeric catalysts when employed in asymmetric benzylation of glycine derivative. Mizoroki-Heck coupling is one of the most efficient C-C bond formation reactions.[24]

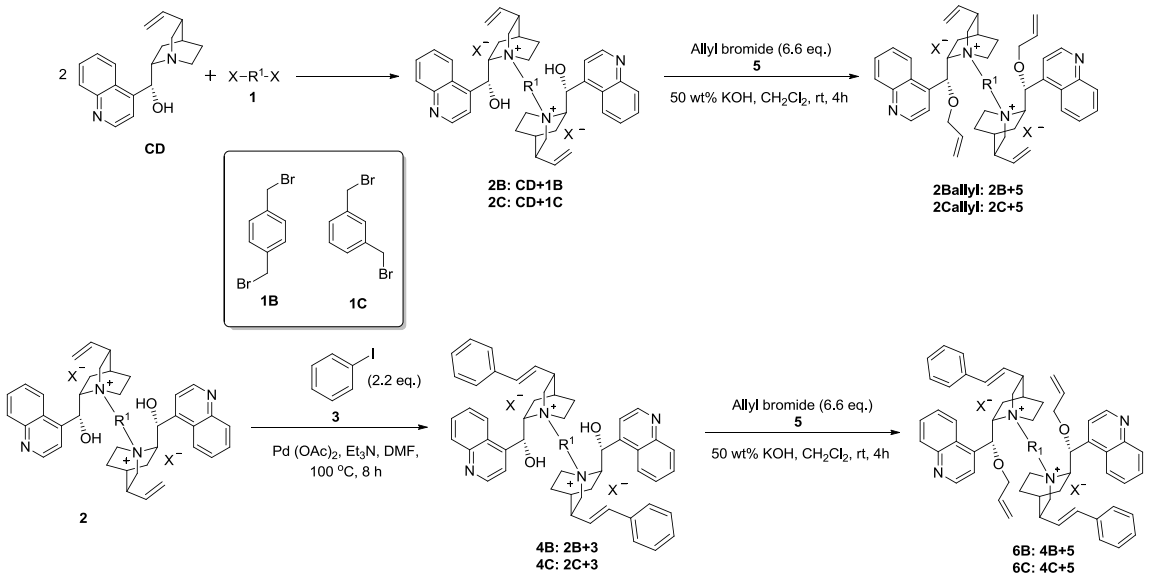
Heck coupling reaction has not widely been used for the modification of double bond of cinchonidine. Only one group has reported the utilization of Heck coupling for the modification of the double bond of cinchonidine.[25] We have also found that the double bond of the cinchonidine can be modified using Heck coupling reaction and we synthesized cinchonidine derived dimer **4** scheme 1. We utilized the ion exchange polymerization technique[17-20] for the synthesis of main-chain chiral polymer **P-4** and **P-6**.

6. 2. Results and discussion

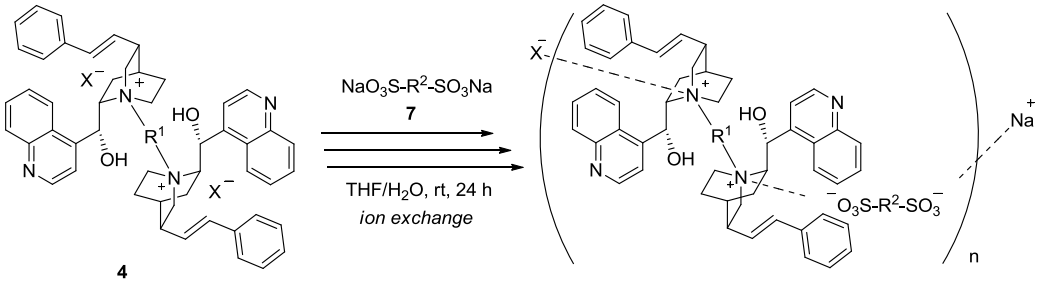
6. 2. 1. Synthesis of main-chain chiral polymers

Main-chain chiral polymeric organocatalyst **P-4** and **P-6** have been synthesized using ion exchange polymerization Scheme 3.[17-20] First of all, we synthesized cinchonidium dimer **2B** and **2C** using two different spacers **1B** and **1C** Scheme 1.[4] As the dimeric catalyst **2** contains double bond in cinchonidine moiety, we modified the double bond by Heck coupling using iodobenzene **3** and obtained dimer **4**. Allylation of dimer **4** at OH group gives the dimer **6.**[4] Ion exchange polymerization of dimer **4** with disulfonate **7** gives polymer **P-4.** Reaction occurred smoothly in THF-H_2O system to give the polymer **P-4**. Using the same ion exchange polymerization ionic polymer **P-6** synthesized from **6** and disulfonate **7** Scheme 2.

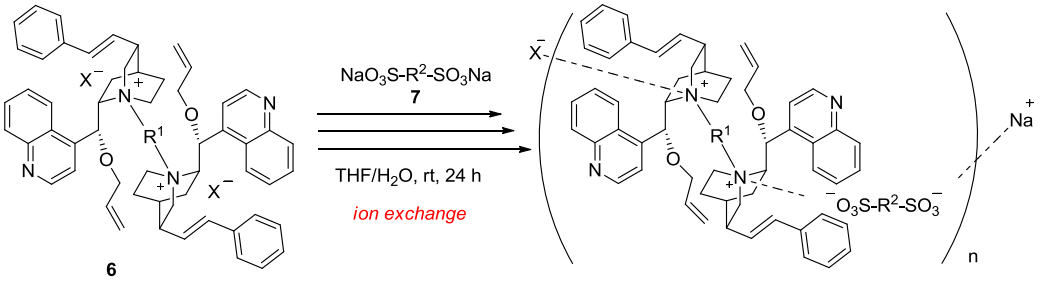
Schme 1 Synthesis of dimer **4** and **6**



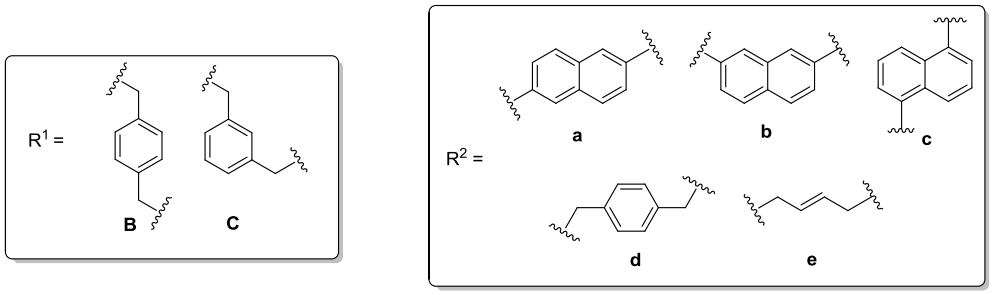
Scheme 2 Synthesis of ionic polymer **P-4** and **P-6**



P-4Ba: 4B+a, **P-4Bb:** 4B+b, **P-4Bc:** 4B+c, **P-4Bd:** 4B+d, **P-4Be:** 4B+e
P-4Ca: 4C+a, **P-4Cb:** 4B+b, **P-4Cc:** 4C+c, **P-4Cd:** 4B+d, **P-4Ce:** 4C+e



P-6Ba: 4B+a, **P-6Bb:** 4B+b, **P-6Bc:** 4B+c, **P-6Bd:** 4B+d, **P-6Be:** 4B+e
P-6Ca: 4C+a, **P-6Cb:** 4B+b, **P-6Cc:** 4C+c, **P-6Cd:** 4B+d, **P-6Ce:** 4C+e



6. 2. 2. Applications of main-chain chiral polymers in asymmetric benzylation of glycine derivative

As the dimeric catalyst **2** synthesized by Park and Jew[4] had catalytic activity in asymmetric benzylation of glycine derivative the dimer **4** and **6**, polymer **P-4** and **P-6** synthesized from dimer **2** should show some catalytic activity in asymmetric benzylation of glycine derivative. When the dimeric and polymeric catalysts were applied in asymmetric benzylation of glycine derivative **8** Scheme 3, quite a high yield and enantioselectivity was obtained.

Scheme 3 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester

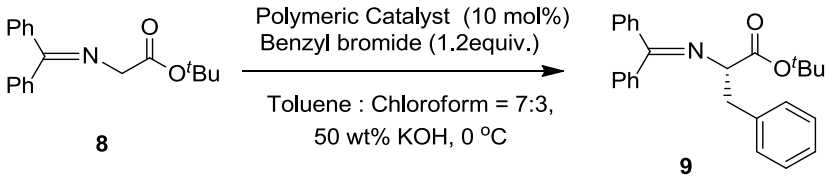


Table 1 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c,d] (%)
1[e]	**2B**	12	91	80
2	**4B**	5	85	88
3	**P-4Ba**	8	78	90
4[f]	**P-4Ba**	14	87	93
5[g]	**P-4Ba**	48	33	93
6	**P-4Bb**	6	91	91
7[h]	**P-4Bb**	4	84	84
8	**P-4Bc**	6	80	84
9[f]	**P-4Bc**	12	87	92
10	**P-4Bd**	4	90	90
11	**P-4Be**	5	91	91

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 °C. [b]Determined by ^{1}H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref. 17. [f]Carried out at -20 °C. [g]Carried out at -40 °C. [h]Reused from entry 6.

The synthesized main-chain chiral ionic polymers **P-4B (a~e)** which contain *p*-xylene moiety were applied in asymmetric benzylation of glycine derivative Table 1. The Heck modified dimer **4B** showed improved enantioselectivity Table 1 entry 2 compare to the dimeric catalyst **1B**. Using polymeric catalyst **P-4Ba** 90% ee was obtained entry 3. Lowering the temperature to -20 °C enantioselectivity increased entry 4. Further lowering the temperature to -40 °C, 93% enantioselectivity was obtained. The catalyst was reused in entry 7 from entry 6 and slightly decrease in enantioselectivity was observed. In case of catalyst **4Bc**, lowering the temperature to -20 °C enantioselectivity was increased from 84% to 92% entry 8 and entry 9. In case of catalyst **P-4Bd** and **P-4Be** also high level of enantioselectivity was obtained entry 10 and entry 11.

Table 2 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c,d] (%)
1[e]	**2Ballyl**	4	92	80
2	**6B**	3	56	79
3	**P-6Ba**	4	71	85
4	**P-6Bb**	5	81	81
5	**P-6Bc**	5	95	86
6	**P-6Bd**	5	94	90
7	**P-6Be**	5	96	85

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 ^oC. [b]Determined by ^1H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref.4.

When polymeric catalyst containing *p*-xylene moiety **P-6B (a~e)** was employed in asymmetric benzylation of glycine derivative high enantioselectivity was obtained Table 2. Heck modified dimer **6B** showed quite a good enantioselectivity entry 2. Among the five polymeric catalysts, **P-6Bd** showed highest enantioselectivity entry 6.

Table 3 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c,d] (%)
1[e]	**2C**	4	90	84
2	**4C**	7	79	81
3	**P-4Ca**	12	89	84
4	**P-4Cb**	5	80	74
5	**P-4Cc**	4	77	77
6	**P-4Cd**	12	83	82
7	**P-4Ce**	12	72	80

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 ^oC. [b]Determined by ^1H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref. 5.

Main-chain chiral polymeric organocatalyst containing *m*-xylene moiety **P-4C (a~e)** also showed good enantioselectivity when applied in asymmetric benzylation of glycine derivative Table 3. **P-4Ca** showed highest enantioselectivity compare to other polymeric catalyst entry 3.

Table 4 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c,d] (%)
1[e]	**2Callyl**	2	91	90
2	**6C**	5	83	88
3	**P-6Ca**	5	96	90
4	**P-6Cb**	5	95	90
5	**P-6Cc**	5	94	90
6	**P-6Cd**	5	97	88
7	**P-6Ce**	5	96	90

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 ^oC. [b]Determined by ^1H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration. [e]See ref. 4.

Polymeric catalyst **P-6C (a~e)** containing *m*-xylene moiety also employed in asymmetric benzylation of glycine derivative Table 4. Heck modified dimeric catalyst showed 88% enantioselectivity entry 2. Almost all the polymeric catalyst showed excellent enantioselectivity entry 3~entry **7** when applied in asymmetric benzylation of glycine derivative.

6. 3. Conclusion

In this work, we have designed a novel type of main-chain chiral ionic polymers of cinchona alkaloids where cinchona alkaloid double bond was modified by Heck coupling. These chiral ionic polymers showed excellent catalytic activity in the asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **8** to give (*S*) phenylalanine derivative **9**. High level of enantioselectivity up to 93% was obtained in this reaction with the chiral polymeric catalysts. Using this method, it is possible to design number of chiral main-chain polymeric organocatalyst.

6. 4. Experimental

General

All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. DMF was distilled from calcium hydride before use. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). Column chromatography was performed with a silica-gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. ^{1}H (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were measured on Mercury 300 or Jeol ECS 400 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. HPLC analyses were performed with a JASCO HPLC system comprising a three-line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCEL ODH); hexane/2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell. Size exclusion chromatography (SEC) was obtained with Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 ^{o}C. Two polystyrene gel columns of bead size 10 μm were used. A calibration curve was made to determine number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards.

General procedure for catalytic enantioselective benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester using chiral polymeric catalyst P-4Ba

Chiral polymeric catalyst **P-4ba** (10 mol %) and *N*-diphenylmethylidene glycine *tert*-butyl ester **6** (0.53 g, 1.78 mmol) were added to a mixed solvent of toluene (7 mL) and chloroform (3 mL). 50 wt% aqueous KOH solution (2.5 mL) was added to the above mixture. Benzyl bromide (0.37 g, 2.14 mmol) was then added drop wise at 0 °C to the mixture. The reaction mixture was stirred vigorously for 8 h. Saturated sodium chloride solution (10 mL) was then added and the organic phase was extracted with ethyl acetate and concentrated in vacuo to give the crude product as colorless oil. Purification of the residual oil by column chromatography on silica gel (ether–hexane = 1:10 as eluent) gave (S)-*tert*-butyl *N*-

(diphenylmethylidene) phenylalanine. The enantiomeric excess (91% ee) was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane-2-propanol = 100:1, flow rate = 0.3 mL min^{-1}, retention time: R enantiomer = 27.6 min, S enantiomer = 47.9 min). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[1]

Synthesis of 4B

A mixture of cinchonidine dimer **2B** (0.85 g, 1.0 mmol) with iodobenzene (0.45 g, 2.2 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 12 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.88 g (88 % yield) of the product. ^1H NMR (d^6-DMSO, 400 MHz) δ 8.99 (d, J = 4.4 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.13~8.09 (m, 1H), 8.01~7.93 (m, 1H), 7.84~7.78 (m, 3H), 7.32~7.15 (m, 4H), 7.04~6.20 (m, 3H), 5.39~4.93 (m, 3H), 4.39~3.61 (m, 2H), 3.40 (s, 4H), 3.22~2.91 (m, 1H), 2.29~1.80 (m, 4H), 1.49~1.43 (m, 1H), 1.21~1.16 (m, 1H) .^{13}C NMR (d6-DMSO, 100 MHz) d 150.25, 147.65, 145.40, 145.04, 136.49, 134.18, 130.77, 129.91, 129.44, 128.45, 128.36, 127.35, 126.09, 124.42, 124.22, 123.83, 120.13, 68.61, 68.11, 64.18, 62.38, 59.83, 36.74, 26.55, 24.11, 21.39. IR (KBr) υ 3227, 2944, 1652, 1590, 1509, 1455, 1233, 1161, 953. $[\alpha]_D^{25} = +50.78\ (c\ 1.0, \mathrm{DMSO})$. mp=216~218.

Synthesis of 6B

To a suspension of **4B** (1.77 g, 1.76 mmol) in dichloromethane (5 mL) was added allyl bromide (1 mL, 11.56 mmol) and 50% aqueous KOH (2 mL, 17.6 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, during which time all of solids dissolved. The mixture was diluted with water (5 mL) and was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was reprecipitated from dichloromethane-hexane to yield 1.55 g (81% yield) of desired product as a light yellow solid. ^1H NMR (d^6-DMSO, 400 MHz) δ 9.02 (d, J = 26.0 Hz, 1H), 8.37~8.07 (m, 2H), 7.93~7.70 (m, 5H), 7.44~7.02 (m, 4H), 6.51~6.43 (m, 1H), 6.25~5.99 (m, 2H), 5.80~5.59 (m, 2H), 5.51~5.15 (m, 3H), 5.08~4.85 (m, 1H), 4.58~4.22 (m, 1H), 4.07~3.90 (m, 5H), 3.25~3.19 (m, 1H), 2.21~2.05 (m, 1H), 1.80~1.39 (m, 1H), 1.26~1.19 (m, 3H). ^{13}C NMR (d6-

DMSO, 100 MHz) d 150.15, 147.11, 141.29, 136.41, 135.06, 134.01, 129.88, 129.59, 128.35, 127.65, 127.00, 126.02, 125.52, 125.32, 129.63, 117.63, 116.56, 72.01, 70.61, 69.51, 62.21, 59.25, 52.83, 52.15, 26.61, 24.46, 20.59, 7.28. IR (KBr) υ 3339, 2932, 1644, 1590, 1507, 1492, 1450, 1357, 1235, 1164, 1068, 993, 926, 856. $[\alpha]_D^{25} = +0.83\ (c\ 0.1, \mathrm{DMSO})$. mp=150~152.

Synthesis of 4c

A mixture of cinchonidine dimer **2C** (0.85 g, 1.0 mmol) with iodobenzene (0.45 g, 2.2 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 12 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.92 g (92 % yield) of the product. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 8.98 (d, J = 19.2 Hz, 1H), 8.37~8.21 (m, 1H), 7.95~7.73 (m, 4H), 7.32~6.99 (m, 4H), 6.72~6.49 (m, 2H), 5.38~4.84 (m, 3H), 4.45~4.28 (m, 1H), 4.08~3.94 (m, 1H), 3.80~3.65 (m, 1H), 3.11~3.09 (m, 1H), 2.95~2.89 (m, 2H), 2.33~1.68 (m, 3H), 1.55~1.38 (m, 1H), 1.20~1.15 (m, 4H) . ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.09, 147.52, 145.31, 145.03, 138.84, 136.45, 135.34, 135.15, 130.74, 129.91, 129.76, 129.40, 128.37, 127.37, 126.05, 124.34, 124.19, 123.79, 120.09, 67.89, 64.24, 62.43, 59.81, 50.66, 36.58, 26.59, 24.09, 21.18. IR (KBr) υ 3238, 2945, 1654, 1590, 1509, 1491, 1450, 1386, 1233, 1162, 1061, 955, 860. $[\alpha]_D^{25} = +14.80\ (c\ 0.1, \mathrm{DMSO})$. mp=206~208.

Synthesis of 6C

To a suspension of **4c** (1.77 g, 1.76 mmol) in dichloromethane (5 mL) was added allyl bromide (1 mL, 11.56 mmol) and 50% aqueous KOH (2 mL, 17.6 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, during which time all of solids dissolved. The mixture was diluted with water (5 mL) and was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was reprecipitated from dichloromethane-hexane to yield 1.65 g (86% yield) of desired product as a light yellow solid. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 8.99 (d, J = 3.6 Hz, 1H), 8.31~7.91 (m, 2H), 7.85~7.64 (m, 3H), 7.45~7.13 (m, 7H), 6.48~6.34 (m, 1H), 6.28~5.99 (m, 1H), 5.76~5.53 (m, 2H), 5.51~5.36 (m,

1H), 5.26~4.81 (m, 7H), 4.06~3.83 (m, 4H), 2.33~2.23 (m, 2H), 2.08~1.99 (m, 1H), 1.87~1.54 (m, 1H), 1.23~1.14 (m, 1H), 0.83~0.77 (m, 1H) . ^{13}C NMR (d^6-DMSO, 100 MHz) d 150.21, 147.99, 147.79, 141.32, 140.75, 136.38, 134.20, 130.96, 129.90, 129.60, 128.54, 128.37, 127.63, 127.39, 127.04, 126.05, 125.51, 125.05, 119.64, 117.59, 109.51, 71.95, 69.31, 68.26, 64.61, 59.25, 52.83, 36.51, 26.48, 24.22, 20.91. IR (KBr) υ 3395, 2931, 1645, 1590, 1507, 1491, 1450, 1360, 1235, 1164, 1067, 993. $[\alpha]_D^{25} = +0.45\ (c\ 0.1, \mathrm{DMSO})$. mp =140~142.

Preparation of ionic polymer P-4B (1a~1e), P-4C (1a~1e), P-6B (1a-1e) and P-6C (1a~1e)

A solution of cinchona derived dimeric quaternary ammonium salt **4B/4C/6B/6C** (1 mmol) in 10 mL THF and a solution of disulfonic acid-disodium salt **5** (1 mmol) in 8 mL water were mixed together and stirred vigorously at room temperature for 24 hours. Then the solvent was removed washed with water and hexane to obtain the resulting ionic polymer **P-4B (1a~1e), P-4C (1a~1e), P-6B (1a-1e) and P-6C (1a~1e)**. The yield of the products was 75~90%.

Synthesis of P-4Ba

IR (KBr) υ 3219, 2946, 1698, 1653, 1590, 1509, 1490, 1456, 1387, 1318, 1217, 1163, 1061, 1026, 953. M_n (SEC) =5900. M_w/M_n=1.17.

Synthesis of P-4Bb

IR (KBr) υ 3398, 2949, 1654, 1591, 1509, 1491, 1458, 1388, 1218, 1184, 1103, 1063, 946. M_n (SEC) =5100. M_w/M_n=1.08.

Synthesis of P-4Bc

IR (KBr) υ 3229, 1654, 1590, 1509, 1491, 1457, 1387, 1321, 1216, 1061, 1029, 953. M_n (SEC) =6300. M_w/M_n=1.17.

Synthesis of P-4Bd

IR (KBr) υ 3225, 2945, 1653, 1590, 1572, 1509, 1491, 1456, 1422, 1387, 1318, 1217, 1164., 1061, 1035, 973. M_n (SEC) =6200. M_w/M_n=1.17.

Synthesis of P-4Be

IR (KBr) υ 3231, 2946, 1654, 1590, 1572, 1509, 1491, 1456, 1422, 1387, 1319, 1216, 1162, 1061, 1030, 954. M_n (SEC) =6200. M_w/M_n=1.17.

Synthesis of P-5Ba

IR (KBr) υ 3420, 2936, 1645, 1588, 1507, 1491, 1422, 1353, 1267, 1195, 1067, 993, 923. M_n (SEC) =5500. M_w/M_n=1.07.

Synthesis of P-5Bb:

IR (KBr) υ 3421, 2938, 1942, 1684, 1645, 1588, 1507, 1451, 1422, 1385, 1203, 1134, 1066, 994. M_n (SEC) =5300. M_w/M_n=1.02.

Synthesis of P-5Bc

IR (KBr) υ 3420, 2937, 1942, 1645, 1588, 1507, 1493, 1453, 1422, 1385, 1237, 1188, 1095, 1066, 994, 924. M_n (SEC) =5500. M_w/M_n=1.05.

Synthesis of P-5Bd

IR (KBr) υ 3407, 2933, 1943, 1685, 1646, 1589, 1508, 1491, 1456, 1422, 1384, 1351, 1213, 1184, 1094, 994, 935. M_n (SEC) =5600. M_w/M_n=1.08.

Synthesis of P-5Be

IR (KBr) υ 3420, 2937, 1684, 1645, 1588, 1507, 1492, 1421, 1352, 1210, 1132, 1066, 993, 924. M_n (SEC) =5500. M_w/M_n=1.07.

Synthesis of P-4Ca

IR (KBr) υ 3392, 3054, 1653, 1592, 1508, 1455, 1387, 1267, 1086, 1026, 904. M_n (SEC) =4900. M_w/M_n=1.01.

Synthesis of P-4Cb

IR (KBr) υ 3397, 3054, 1592, 1508, 1455, 1317, 1102, 1025, 946. M_n (SEC) =5400. M_w/M_n=1.07.

Synthesis of P-4Cc

IR (KBr) υ 3394, 3023, 1700, 1654, 1592, 1508, 1456, 1387, 1209, 1160, 1029, 857. M_n (SEC) =5000. M_w/M_n=1.03.

Synthesis of P-4Cd

IR (KBr) υ 3237, 2946, 1653, 1590, 1508, 1456, 1387, 1213, 1129, 1035, 956. M_n (SEC) =5300. M_w/M_n=1.02.

Synthesis of P-4Ce

IR (KBr) υ 3230, 2947, 1653, 1590, 1508, 1490, 1455, 1387, 1320, 1209, 1122, 1061, 1030, 957. M_n (SEC) =4900. M_w/M_n=1.02.

Synthesis of P-5Ca

IR (KBr) υ 3418, 2937, 1708, 1646, 1589, 1507, 1490, 1361, 1220, 1068, 1028, 994. M_n (SEC) =5700. M_w/M_n=1.07.

Synthesis of P-5Bb

IR (KBr) υ 3431, 2935, 1645, 1590, 1507, 1490, 1361, 1267, 1101, 1026, 993. M_n (SEC) =5200. M_w/M_n=1.05.

Synthesis of P-5Bc

IR (KBr) υ 3421, 2937, 1942, 1645, 1589, 1507, 1491, 1361, 1238, 1066, 1030, 994. M_n (SEC) =5600. M_w/M_n=1.15.

Synthesis of P-5Bd

IR (KBr) υ 3396, 2931, 1645, 1588, 1507, 1491, 1384, 1210, 1066, 1032, 993. M_n (SEC) =5700. M_w/M_n=1.06.

Synthesis of P-5Be

IR (KBr) υ 3397, 2932, 1943, 1646, 1588, 1507, 1491, 1353, 1209, 1066, 1028, 993. M_n (SEC) =5700. M_w/M_n=1.05.

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Chapter 7

Design of quaternary ammonium polymers from cinchonidine dimer synthesized by Heck coupling and their applications in asymmetric catalysis

7. 1. Introduction

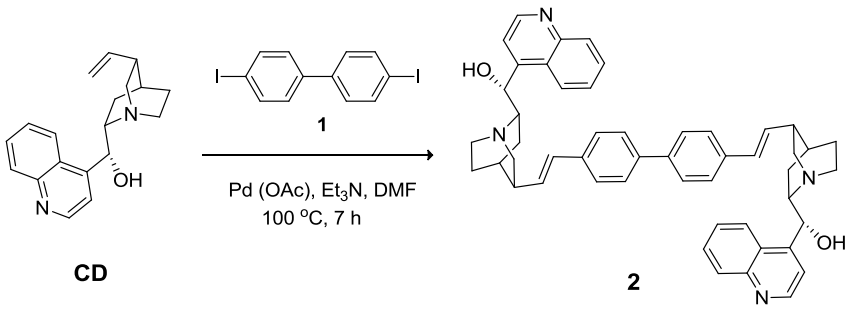
The development of chiral polymer catalysts with rigid and sterically regular structure may have a better defined microenvironment at the catalytic sites and have allowed systematic modification of their catalytic properties. For that purpose, we have demonstrated some chiral main-chain polymers as catalyst for asymmetric reaction.[3-9] Among the reports two described the synthesis of main-chain chiral polymers where repetitive quaternization reaction (Menshutkin reaction) between cinchona alkaloid dimer and dihalide.[7] We have examined the catalytic activity of the chiral polymeric catalyst in asymmetric alkylation reaction. We have found that the double bond of cinchonidine can be modified using Heck coupling reaction. [10, Chap. 5] We utilized the double bond of cinchonidine for the synthesis of cinchonidine dimer **2** using Heck coupling. Quaternization of dimer **2** gives the polymer **QP-2.**

7. 2. Results and discussion

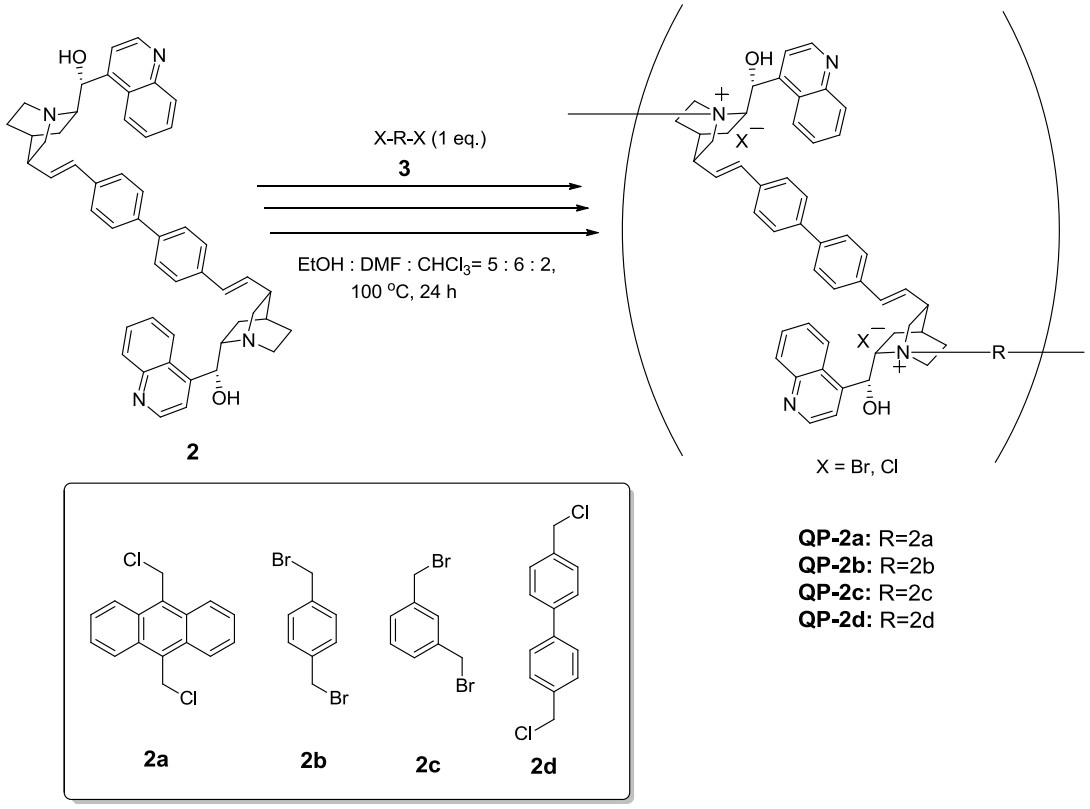
7. 2. 1 Synthesis of cinchonidine dimer and main-chain chiral polymers

Utilizing the double bond of cinchonidine dimer **2** was synthesized. Heck coupling reaction between cinchonidine **CD** and 4, 4'-diiodobiphenyl gives the dimer **2** Scheme 1. When equimolar amounts of dimer **2** and dihallide **3** are allowed to react together repeated quaternization reaction between **2** and **3** gives the main-chain chiral polymer **QP-2** Scheme 2. The quaternization polymerization occurred smoothly in mixed solvent system to give the polymer **QP-2**. The number average molecular weight of the polymers vary from 4600~5200.

Scheme 1 Synthesis of cinchonidine dimer



Scheme 2 Synthesis of main-chain chiral quaternary ammonium polymers



7. 2. 2. Applications of main-chain chiral polymers in asymmetric benzylation of glycine derivative

As the low molecular weight quaternary ammonium salts[1] and dimeric quaternary ammonium salts[2] have catalytic activity in asymmetric benzylation of glycine derivative **4**. So, main-chain polymer **QP-2** prepared from cinchonidine should show some catalytic activity. When polymeric main-chain polymeric organocatalyst **QP-2** was applied in

asymmetric benzylation of glycine derivative Scheme 3 good enantioselectivity was obtained which are summarized in Table 1.

Scheme 3 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester

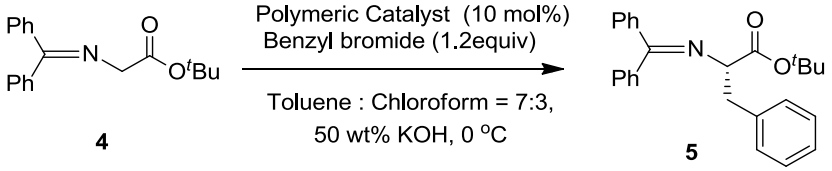


Table 1 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[cd] (%)
1	**QP-2a**	6	82	49
2	**QP-2b**	5	82	68
3	**QP-2c**	5	77	54
4	**QP-2d**	6	84	72

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 °C. [b]Determined by ^{1}H NMR. [c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration.

Main-chain polymer containing anthracenyl moiety **QP-2a** gave only 49% enantioselectivity Table 1 entry 1. **QP-2b** containing *p*-xylene moiety gave 68% enantioselectivity entry 2. In case of *m*-xylene moiety containing main-chain polymer **QP-2c** gave 54% enantioselectivity entry 3. Polymer **QP-2d** containing biphenyl moiety gave highest 72% enantioselectivity compare to other polymeric catalyst Table 1 entry 4.

7. 3. Conclusion

In this work, we have synthesized a novel type of cinchonidine dimer **2** using Heck coupling reaction. Dimer **2** has been polymerized using quaternization polymerization to obtain the polymer **QP-2**. The polymers were employed as the polymeric organocatalyst in asymmetric benzylation glycine derivative **4** to obtain the phenylalanine derivative **5**.

7. 4. Experimental

General

All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. DMF was distilled from calcium hydride before use. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). Column chromatography was performed with a silica-gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. ^{1}H (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were measured on Mercury 300 or Jeol ECS 400 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. HPLC analyses were performed with a JASCO HPLC system comprising a three-line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCEL ODH); hexane/2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell. Size exclusion chromatography (SEC) was obtained with Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 ^{o}C. Two polystyrene gel columns of bead size 10 µm were used. A calibration curve was made to determine number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards.

General procedure for catalytic enantioselective benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester using chiral polymeric catalyst QP-2d

Chiral polymeric catalyst **QP-2d** (10 mol %) and *N*-diphenylmethylidene glycine *tert*-butyl ester **4** (0.53 g, 1.78 mmol) were added to a mixed solvent of toluene (7 mL) and chloroform (3 mL). 50 wt% aqueous KOH solution (2.5 mL) was added to the above mixture. Benzyl bromide (0.37 g, 2.14 mmol) was then added drop wise at 0 °C to the mixture. The reaction mixture was stirred vigorously for 8 h. Saturated sodium chloride solution (10 mL) was then added and the organic phase was extracted with ethyl acetate and concentrated in vacuo to give the crude product as colorless oil. Purification of the residual oil by column chromatography on silica gel (ether–hexane = 1:10 as eluent) gave (S)-*tert*-butyl *N*-(diphenylmethylidene) phenylalanine. The enantiomeric excess (91% ee) was determined by

HPLC analysis (Daicel Chiralcel OD-H, hexane-2-propanol = 100:1, flow rate = 0.3 mL min^{-1}, retention time: R enantiomer = 27.6 min, S enantiomer = 47.9 min). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[1]

Synthesis of dimer 2

A mixture of cinchonidine **CD** (0.59 g, 2.0 mmol) with 4, 4'-diiodo biphenyl **1** (0.41 g, 1.0 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 12 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate and hexane to afford 0.65 g (88 % yield) of the product. ^1H NMR (d^6-DMSO, 300 MHz) δ 8.93 (s,1H), 8.33 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 6.9, 1H), 7.75~7.66 (m, 3H), 7.60~7.52 (m, 1H), 7.39 (d, J = 6.9 Hz, 1H), 7.25~7.18 (m, 1H), 6.51~6.30 (m, 2H), 5.84 (s, 1H), 3.90~3.54 (m, 3H), 3.20~3.15 (m, 2H), 2.83~2.72 (m, 1H), 2.03~1.91 (m, 2H), 1.81~1.71 (m, 2H), 1.55~1.44 (m, 1H), 1.23~0.75 (m, 1H) . ^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.22, 147.86, 138.17, 136.16, 129.85, 129.09, 128.76, 128.41, 126.99, 126.67, 126.51, 126.37, 125.50, 123.86, 119.17, 68.73, 60.49, 55.36, 42.35, 38.10, 32.24, 27.64, 26.97. IR (KBr) υ 3315, 2931, 2639, 1653, 1590, 1509, 1456, 1422, 1386, 1237, 1175, 1093, 952, 853. $[\alpha]_D^{25} = +0.32\ (c\ 1.0, \mathrm{DMSO})$. mp=188~190.

General procedure for the synthesis of QP-2 polymers

A mixture of cinchonidine dimer **2** (1 mmol) and dihallide **3** (1 mmol) in a mixed solvent EtOH:DMF:$CHCl_3$=5:6:2 (10 mL) were mixed together stirred at 100 ^oC for 24 h. After completion of the reaction, the reaction mixture was added drop wise to ether (400 mL) with stirring. The solid precipitated was filtered, washed with water ether and Hexane dried under vacuum oven to obtain the polymeric product **QP-2**.

Synthesis of polymer QP-2a

IR (KBr) υ 3356, 2936, 2766, 1635, 1590, 1509, 1458, 1422, 1314, 1236, 1175, 1021, 952. M_n (SEC) =5200. M_w/M_n=1.03.

Synthesis of polymer QP-2b

IR (KBr) υ 3371, 2943, 2761, 1700, 1590, 1509, 1457, 1423, 1236, 1090, 952. M_n (SEC) =5100. M_w/M_n=1.01.

Synthesis of polymer QP-2c

IR (KBr) υ 3370, 2942, 1698, 1590, 1508, 1456, 1236, 1090, 1002. M_n (SEC) =4600. M_w/M_n=1.01.

Synthesis of polymer QP-2d

IR (KBr) υ 3372, 2931, 1698, 1651, 1615, 1496, 1456, 1395, 1236, 1087, 1003, 952. M_n (SEC) =4500. M_w/M_n=1.01.

7. 5. References

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Chapter 8

Asymmetric epoxidation of *trans*-chalcone using different types of main-chain chiral organocatalyst

8. 1. Introduction

Optically active epoxides have become one of the fields of interest since Sharpless et al. first reported the asymmetric epoxidation of allylic alcohol in 1980.[1] After that many methods have been developed for the epoxidation of both un functionalized olefins and electron-deficient enones.[2] Among the methods chiral phase transfer catalysis is one of the widely used method applied to the asymmetric epoxidation of electron-deficient olefins and is probably the most simple and easy. Enantioselective epoxidation of electron deficient olefins under PTC conditions catalyzed by quaternized cinchona alkaloids pioneered by Wynberg et al.[3] Later Lygo[4] and Corey[5] improved the method. Dimeric cinchona derived catalysts with surfactants was reported by Park and Jew[6] and very high enantioselectivity was obtained with shorter reaction time. Non-Cinchona-derived species, such as spiro ammonium salts was reported by Maruoka et al.[7] polyamino acids by Juliá et al.[8] lanthanoid-binaphthol complexes,[9] and chiral crown ethers derived from D-glucose, D-galactose, and D mannitol[10] have also been used in this kind of asymmetric epoxidation. Moreover, polymer-supported cinchona derived phase transfer catalyst was reported by Wang et al.[11] in asymmetric epoxidation of chalcones. Although several works have done with the monomeric, dimeric and polymer-supported cinchona derived quaternary ammonium salts, there is almost no report on the application of main-chain chiral polymeric organocatalyst in the asymmetric epoxidation of chalcones.

Herein, we have utilized some main-chain chiral polymers synthesized in our previous work [12, chap.5] and some newly synthesized main-chain chiral polymeric organocatalyst in asymmetric epoxidation of *trans*-chalcone.

8. 2. Results and discussion

8. 2. 1. Synthesis of main-chain chiral polymers

We have employed some main-chain chiral polymers (Figure 1 and Figure 2) synthesized in our previous work.[12, chapter 5] We also synthesized some main-chain chiral ionic polymers (Scheme 1) by the reaction between different types of cinchona derived dimer **2c** and different types of disulfonates **3.** Another kind of main-chain chiral polymer was synthesized (Scheme 2) from dimer **QN-2c** and 4, 4′-diiodobiphenyl using Heck coupling reaction to obtain the polymeric catalyst **PQN-2c**.

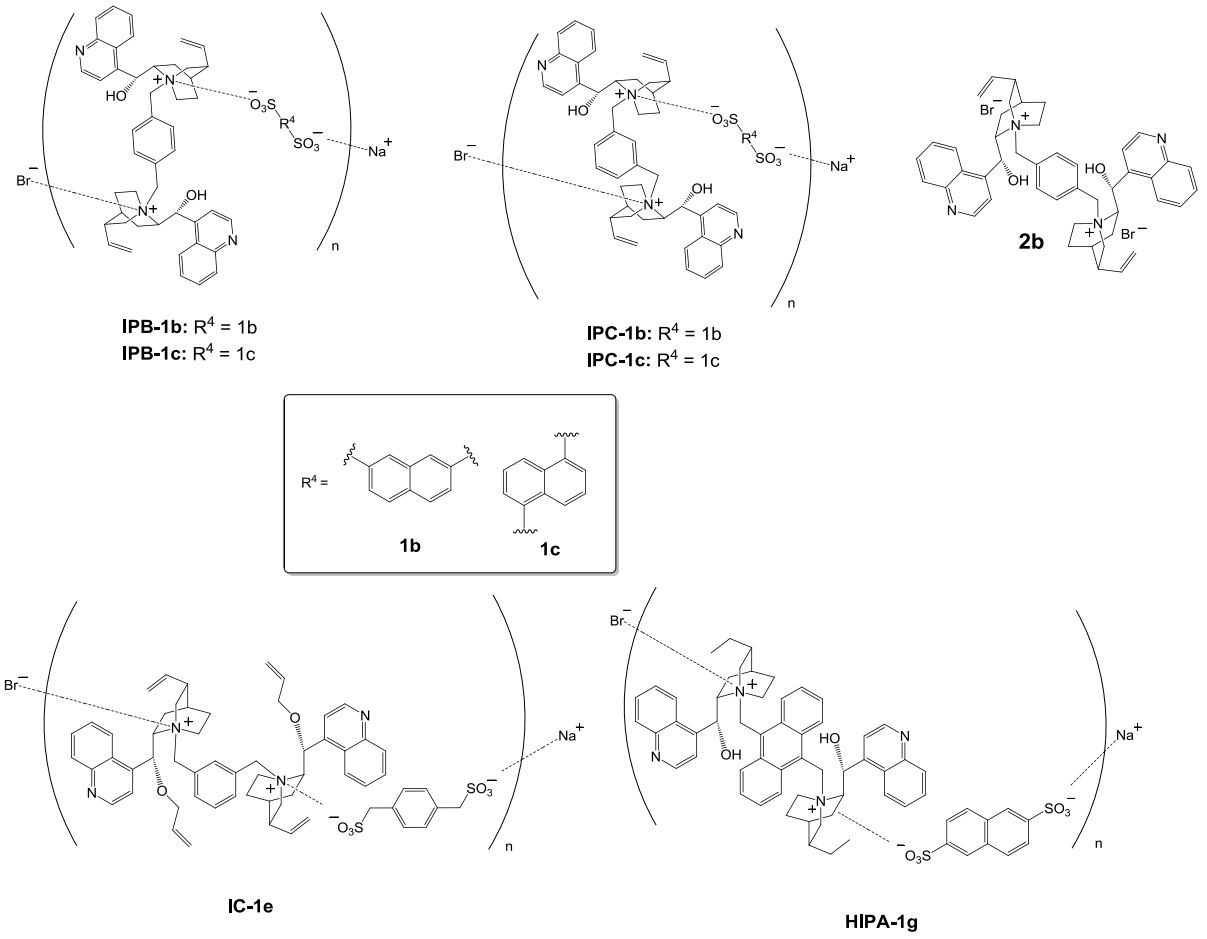


Figure 1 Main-chain chiral ionic polymer[ref]

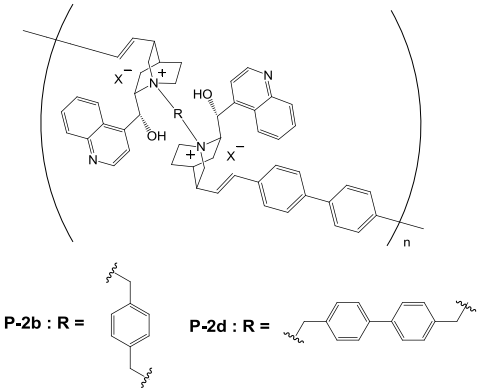
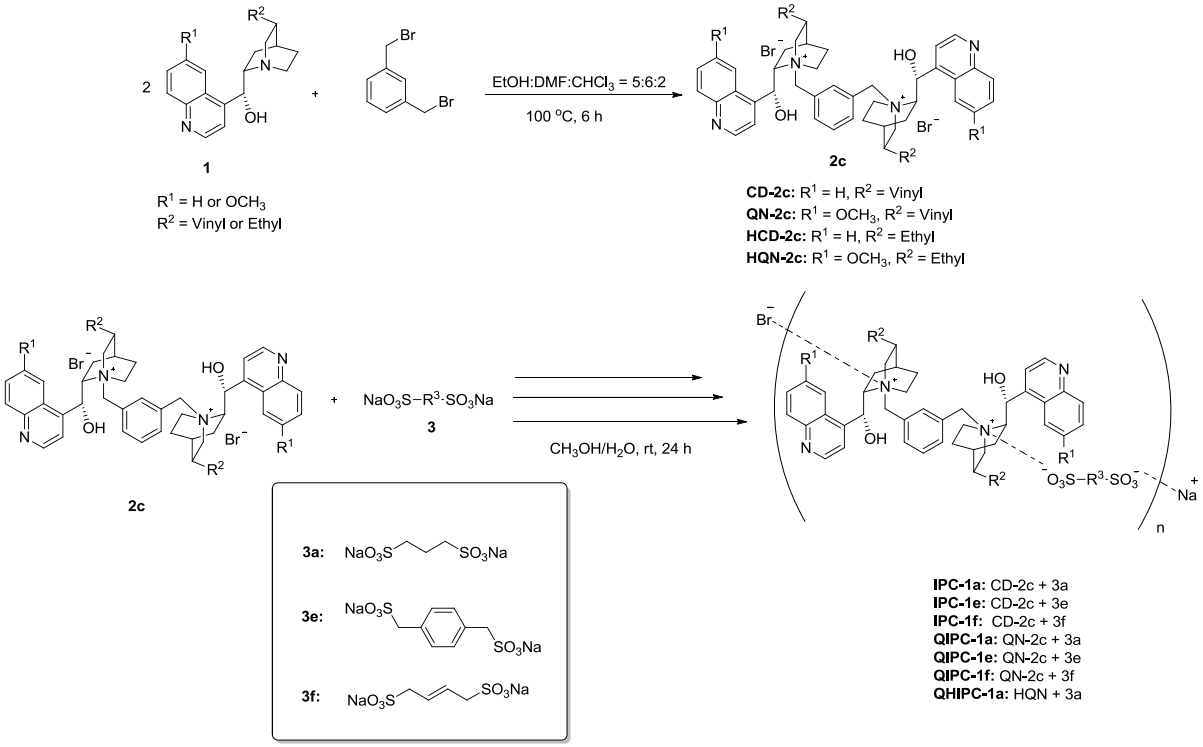
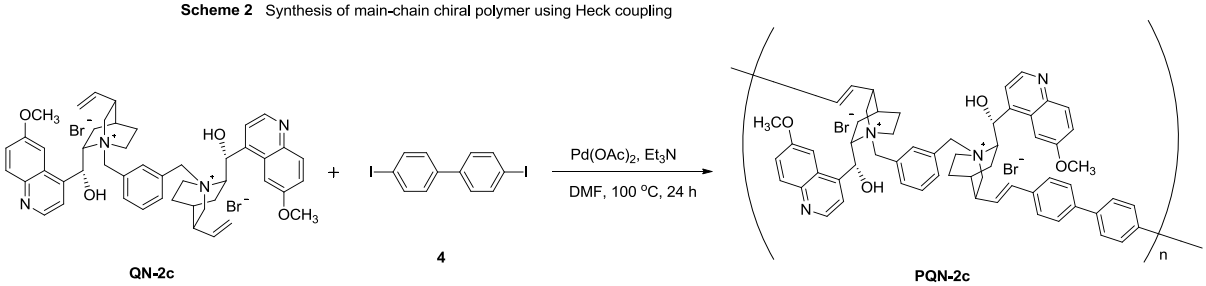


Figure 2 Main-chain chiral polymer[ref]

Scheme 1 Synthesis of main-chain ionic polymer



Scheme 2 Synthesis of main-chain chiral polymer using Heck coupling

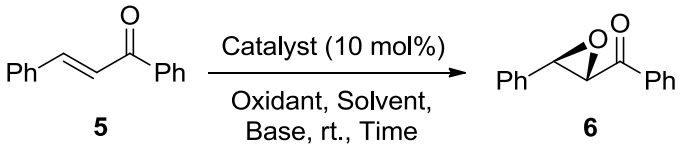


8. 2. 2. Application of main-chain chiral polymers

As cinchona derived quaternary ammonium salts have catalytic activity in asymmetric epoxidation of chalcones the polymers containing cinchonidium unit synthesized from cinchona alkaloid should show some catalytic activity in asymmetric epoxidation of chalcones. Several groups have reported the asymmetric epoxidation using cinchona derived quaternary ammonium salts using several types of oxidants, solvents, bases to obtain chiral epoxides. The reaction is very sensitive towards the catalyst structure, oxidant, solvent and base. Although number of works has been done using low molecular weight catalyst in asymmetric epoxidation of chalcones, not a single work has been reported for the asymmetric epoxidation of chalcones using main-chain chiral polymeric organocatalyst. So, it was quite challenging to obtain an optimized condition for the asymmetric epoxidation of chalcones using main-chain chiral polymeric oraganocatalyst.

We arbitrarily started with the optimization of the reaction with different dimeric and polymeric catalysts, oxidants, solvents and bases Table 1. But unfortunately, most of the cases racemic product was obtained.

Table 1. Optimization of asymmetric epoxidation of chalcone **1**



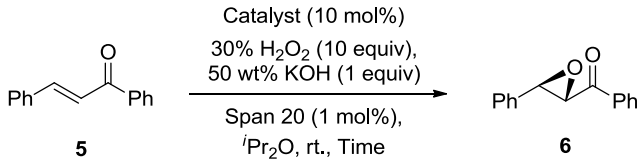
5 **6**

Entry	Catalyst	Oxidant	Solvent	Base	Time (h)	Conv. (%)[a]	Ee (%)[b]
1	**2b**	NaOCl	Toluene	------	24	0	ND
2	**2b**	^{t}BuOOH	DCM	1 M KOH	120	95	53
3	**IPB-1c**	H_2O_2	Toluene	LiOH	48	48	Racemic
4	**IPB-1c**	H_2O_2	Bu_2O	LiOH	48	60	Racemic
5	**IPB-1e**	NaOCl	Toluene	------	72	0	ND
6	**IPC-1b**	H_2O_2	Bu_2O	$LiOH.H_2O$	48	50	6
7[c]	**IPC-1b**	H_2O_2	Bu_2O	$LiOH.H_2O$	96	60	5
8	**IPC-1c**	NaOCl	Toluene	------	72	0	ND
9	**IC-1e**	NaOCl	Toluene	------	72	0	ND
10[d]	**P-1d**	H_2O_2	Toluene	LiOH	168	65	3
11[c]	**P-1d**	^{t}BuOOH	DCM	1 M KOH	192	100	Racemic

[a]Determined by ^{1}H NMR. [b]Determined by HPLC (Chiralcel OD-H column). [b](αS, βR) major product. [c]Carried out at 0 ^{o}C. [d]Opposite configuration was obtained.

Then we turned our attention to the addition of surfactant to the reaction mixture. Park and Jew reported asymmetric epoxidation of choalcones using surfactant surprisingly the rate of reaction increased and high enantioselectivity was obtained.[6] We also tried to apply the main-chain chiral ionic polymer in asymmetric epoxidation of chalcones in presence of 1 mol% of span 20, diisopropyl ether as solvent and 30% H_2O_2 as an oxidant Table 2.

Table 2. Asymmetric epoxidation of chalcone with the addition of surfactant



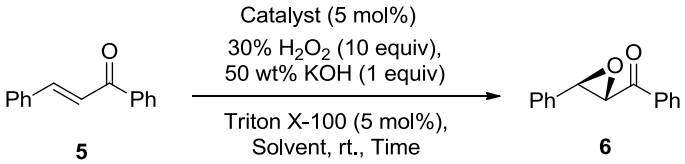
Entry	Catalyst	Time (h)	Conv. (%)[a]	Ee (%)[b]
1[d]	**IPB-1a**	24	68	3
2	**IPB-1b**	24	52	8
3	**IPB-1c**	24	88	Racemic
4[d]	**IPB-1e**	24	59	2
5	**IPB-1f**	24	100	Racemic
6	**IPC-1a**	24	100	26
7	**IPC-1b**	24	99	Racemic
8	**IPC-1c**	24	100	Racemic
9	**IPC-1e**	24	89	33
10	**QIPC-1a**	8	99	18
11	**QIPC-1e**	8	100	14
10[d]	**HIPA-1g**	24	61	4
11	**P-1b**	48	0	ND
12	**P-1d**	48	0	ND

[a]Determined by ^{1}H NMR. [b]Determined by HPLC (Chiralcel OD-H column). [b](αS, βR) major product.
[d]Opposite configuration was obtained.

In this case, we noticed that that polymer containing *p*-xylene moiety employed in asymmetric epoxidation of chalcones did not show good catalytic activity and sometime racemic products were obtained Table 2 entry (1~5). Main-chain polymer containing m-xylene moiety showed some catalytic activity entry (6~9). But using the polymeric catalyst **IPC-1b** and **IPC-1c** racemic product was obtained entry 7 and entry 8. From these results one thing can be assumed that rigid structure of the polymers **IPC-1b** and **IPC-1c** is responsible for obtaining the racemic product. On the other hand, **IPC-1a** and **IPC-1e** polymers have little flexible structure gave 26% and 33% enantioselectivity entry 6 and entry 9. When

quinine derivative flexible polymers were applied in asymmetric epoxidation 18% and 14% enantioselectivity were obtained entry 10 and entry 11. When hydrocinchonidine derivative polymer containing anthracenyl moiety gave only 4% ee with opposite enantiselctivty entry 10. The reaction did not take place with main-chain chiral polymers **P-1b** and **P-1d** entry 12 and entry 12.

Table 3. Asymmetric epoxidation of chalcone



5 **6**

Entry	Catalyst	Solvent	Time (h)	Conv. (%)[a]	Ee (%)[b]
1	**IPC-1a**	$^{i}Pr_2O$	16	100	38
2	**IPC-1e**	$^{i}Pr_2O$	16	100	51
3	**IPC-1f**	$^{i}Pr_2O$	16	100	33
4	**QIPC-1a**	$^{i}Pr_2O$	15	100	63
5	**QIPC-1e**	$^{i}Pr_2O$	15	100	36
6	**QIPC-1a**	Bu_2O	3	100	84
7	**QIPC-1e**	Bu_2O	6	100	52
8	**QIPC-1f**	Bu_2O	16	100	69
9[c]	**QIPC-1a**	Bu_2O	16	42	71
10[c]	**QIPC-1e**	Bu_2O	16	53	53
11[e]	**QIPC-1a**	Bu_2O	16	100	6
12[e]	**QIPC-1e**	Bu_2O	16	100	5
13	**QIPC-1a**	CPME	16	24	16
14	**QIPC-1a**	1, 4dioxane	3	100	Racemic
15[f]	**QIPC-1a**	Bu_2O	5	100	71
16	**QHIPC-1a**	Bu_2O	12	100	17
17	**HQN-2c**	Bu_2O	12	100	33
18	**QN-2c**	Bu_2O	12	100	65
19	**HCD-2c**	Bu_2O	5	87	Racemic
20	**PQN-1c**	Bu_2O	12	100	Racemic
21[g]	**QIPC-1a**	Bu_2O	12	100	Racemic

[a]Determined by ^{1}H NMR. [b]Determined by HPLC (Chiralcel OD-H column). [b](αS, βR) major product. [c]Carried out at 0 °C. [d]Opposite configuration was obtained. [e]2.5 mol% catalyst was used. [f]3 equiv. of KOH was used. [g]30 equiv. of 30% H_2O_2 was used.

Then we chose flexible type polymer for further optimization Table 3. We used 5 mol% catalyst and 5 mol% of Triton-X 100 as surfactant.

After changing the surfactant from Span 20 to Triton-X 100 the enantioselectivity increased. Cinchonidine derived polymers gave up to 51% enantioselectivity entry 1~entry 3. Quinine derivative polymers gave up to 63% enantioselectivity entry 4 and entry 5. The enantioselectivity was increased when the solvent was changed from $^{i}Pr_2O$ to Bu_2O entry 6~entry 7 and up to 84% enantioselectivity was obtained. When the temperature was reduced to 0 ^{o}C from room temperature the enantioselectivity decreased to 71% in case of **QIPC-1a** entry 9. Enantioselectivity almost remain same in case of **QIPC-1e** when temperature was reduced to 0 ^{o}C entry 10. Reducing the catalyst loading to 2.5 mol% leads towards the very low enantioselectivity of the product entry 11 and entry 12.

Changing the solvent to cyclopentyl methyl ether (CPME) only 16% enantioselectivity was obtained entry 13. Using 1, 4 dioxane racemic products were obtained entry 14. When the amount of KOH was being increased to 3 equivalents the enantioselectivity decreased to 71% ee entry 15. Hydroquinine derivative polymer **QHIPC-1a** gave only 17% enantioselectivity entry 16 whereas hydroquinone derivative dimer **HQN-2c** gave 33% ee entry 17. Using quinine derivative dimer **QN-2c** gave 65% ee entry 18. Hydrocinchonidine derivative dimer did not give optically active product entry 19. Main-chain chiral polymer **PQN-1c** gave racemic product entry 20. When the amount of H_2O_2 was increased to 30 equivalents using **QIPC-1a** surprisingly racemic product was obtained.

8. 3. Conclusion

Asymmetric epoxidation of *trans*-chalcone has been carried out using main-chain chiral polymeric organocatlyst. Several types of main-chain chiral polymers have been utilized to get a suitable structure. The reaction is sensitive to the catalyst structure, oxidant, solvent, temperature and base. After screening all the polymeric catalyst and optimization of the reaction up to 84% enantioselectivity was obtained in asymmetric epoxidation of chalcones. Asymmetric epoxidation of other chalcone derivatives are underway.

8. 4. Experimental

General

All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. DMF was distilled from calcium hydride before use. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). Column chromatography was performed with a silica-gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. ^{1}H (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were measured on Mercury 300 or Jeol ECS 400 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. HPLC analyses were performed with a JASCO HPLC system comprising a three-line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCEL ODH); hexane/2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell. Size exclusion chromatography (SEC) was obtained with Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 ^{o}C. Two polystyrene gel columns of bead size 10 μm were used. A calibration curve was made to determine number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards.

General procedure for asymmetric epoxidation of chalcone

Aqueous hydrogen peroxide (30 %, 0.27 mL; 2.4 mmol) and 50 % aqueous KOH (0.027 mL, 0.24 mmol) were added to a mixture of chalcone **5** (50 mg, 0.24 mmol), catalyst QIPC-1a 5 mol% and Triton-X 100 (5 mol%) in Bu_2O (0.8 mL), and the reaction mixture was stirred vigorously at room temperature until the starting material had been consumed. The resulting suspension was diluted with ether (10 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to get the desired product 6 as a white solid. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD, hexanes/ethanol=90:10, flow rate=1.0 mL min^{-1}, 23 °C, λ=254 nm; retention times: 16.6 min (minor), 24.0 min (major). The absolute configuration was determined by comparison of the HPLC retention time with reported data.[4]

HQN-2c

A mixture of (-)-10, 11-dihydroquinine (1.20 g, 3.7 mmol) with α,α′-dibromo-*m*-xylene (0.48 g, 1.8 mmol) in DMF was stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was added drop wise to ether (300 mL) with constant stirring. The solid precipitated was filtered, washed with ether (200 mL) to afford 1.60 g (96% yield) of product. ^{1}H NMR (d^{6}-DMSO, 400 MHz, DMSO–d^{6}): δ 8.83 (d, *J* = 4.4 Hz, 2H), 8.07~ 8.02 (m, 3H), 7.87~7.72 (m, 5H), 7.50 (d, *J* = 9.2 Hz, 2H), 7.41 (s, 2H), 6.65 (d, *J* = 12.8 Hz, 2H), 5.56 (d, *J* = 12.2 Hz, 2H), 4.70 (d, *J* = 12.0 Hz, 2H), 4.31~4.26 (m, 2H), 4.05 (s, 6H), 3.89~3.85 (m, 2H), 3.56~3.48 (m, 4H), 2.25–2.23(m, 2H), 2.11 (d, *J* = 6.4 Hz, 2H), 1.96 (s, 2H), 1.88–1.84 (m, 2H), 1.74 (s, 2H), 1.51–1.45 (m, 2H), 1.30–1.15 (m, 4H), 0.74–0.71 (m, 8H), ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ 157.44, 147.26, 143.86, 143.54, 138.65, 134.88, 131.28, 129.44, 128.49, 125.26, 121.40, 120.25, 101.83, 68.21, 63.62, 62.81, 61.01, 55.57, 50.60, 34.72, 25.44, 24.63, 24.26, 20.17, 11.09 ppm. IR (KBr) υ 3221, 2957, 2875, 1925, 1619, 1590, 1509, 1458, 1431, 1384, 1359, 1240, 1173, 1082, 1057, 948, 858. $[\alpha]_D^{25} = -1.66$ (c 1.0, DMSO). mp=210~212.

Preparation of main-chain ionic polymer

A solution of cinchona derived dimeric quaternary ammonium salt **2c** (1 mmol,) in 10 mL CH_3OH and a solution of disulfonic acid-disodium salt **3** (1 mmol) in 8 mL water were mixed together and stirred vigorously at room temperature for 24 hours. Then it was filtered and washed with water and hexane to obtain the resulting ionic polymer. The yield of the products was 80~90%.

Preparation of QIPC-1a

^{13}C NMR (d^{6}-DMSO, 100 MHz) δ 157.48, 147.46, 143.94, 143.70, 138.73, 138.12, 135.18, 131.46, 129.65, 128.63, 125.44, 121.55, 120.37, 116.52, 101.99, 68.48, 63.65, 62.85, 59.07, 55.69, 50.70, 50.56, 36.98, 26.05, 24.15, 21.35, 20.47 ppm. IR (KBr) υ 3225, 2945, 1619, 1590, 1508, 1456, 1360, 1257, 1172, 1061, 913, 858. $[\alpha]_D^{25} = -1.90$ (c 1.0, DMSO). M_n (SEC) =5100. M_w/M_n=1.09.

Preparation of QIPC-1e

^{13}C NMR (d^{6} -DMSO, 100 MHz) δ 158.01, 147.99, 144.49, 144.26, 139.29, 138.67, 135.68, 133.39, 131.99, 130.10, 129.94, 129.09, 126.02, 122.04, 120.88, 117.00, 102.57, 68.94,

64.23, 63.31, 59.60, 57.69, 56.23, 51.16, 37.45, 26.61, 24.66, 21.03 ppm. IR (KBr) υ 3221, 2945, 1619, 1590, 1509, 1457, 1361, 1259, 1174, 1061, 913, 857. $[\alpha]_D^{25} = -1.92\ (c\ 1.0, \mathrm{DMSO})$. M_n (SEC) =5700. M_w/M_n=1.11.

Preparation of QIPC-1f

^{13}C NMR (d^6 -DMSO, 100 MHz) δ 157.49, 147.37, 143.92, 143.59, 138.70, 138.12, 135.15, 131.37, 129.62, 128.59, 125.43, 121.60, 120.36, 116.48, 102.01, 68.40, 63.67, 62.82, 59.09, 55.74, 50.68, 36.96, 26.02, 24.12, 20.5 ppm. IR (KBr) υ 3219.58, 2941.88, 1619.91, 1590.02, 1508.06, 1456.96, 1361.50, 1259.29, 1173.47, 1059.69, 922.22, 858.17. $[\alpha]_D^{25} = -1.73\ (c\ 1.0, \mathrm{DMSO})$. M_n (SEC) =6600. M_w/M_n=1.17.

Preparation of QHIPC-1a

^{13}C NMR (d^6 -DMSO, 100 MHz) δ 157.45, 147.42, 143.99, 143.70, 138.83, 135.05, 131.42, 129.56, 128.69, 125.45, 121.55, 120.42, 101.57, 68.42, 63.61, 62.79, 61.15, 55.67, 50.57, 34.95, 25.45, 24.75, 24.38, 21.33, 20.27, 11.19 ppm. IR (KBr) υ 3218, 2956, 1703, 1619, 1590, 1509, 1458, 1360, 1324, 1240, 1172, 1082, 1028, 911, 858.17. $[\alpha]_D^{25} = -1.86\ (c\ 1.0, \mathrm{DMSO})$. M_n (SEC) =4900. M_w/M_n=1.03.

Preparation of main-chain polymer PQN-1c

A mixture of cinchonidine dimer **QN-1c** (0.92 g, 1.0 mmol) with 4,4'-diiodo biphenyl (0.41 g, 1.0 mmol) in presence of 3 mol% Pd $(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 ^oC for 24 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature the reaction mixture was filtered by filter paper added drop wise to water (400 mL) with stirring. The solid precipitated was filtered, washed with water, ether, ethyl acetate, CH_3OH, and hexane to obtain 75 % yield of the product. ^{13}C NMR (d^6 -DMSO, 100 MHz) δ 157.49, 147.40, 143.53, 138.27, 137.61, 135.40, 131.34, 130.59, 129.89, 128.90, 128.54, 128.37, 126.70, 126.35, 125.48, 121.53, 120.31, 102.10, 68.72, 63.84, 63.11, 59.60, 55.76, 50.99, 26.57, 24.10, 20.61 ppm. IR (KBr) υ 3392, 2942, 1654, 1919, 1509, 1457, 1430, 1361, 1240, 1226, 1172, 1060, 954, 826. $[\alpha]_D^{25} = +22.90\ (c\ 0.1, \mathrm{DMSO})$. M_n (SEC) =5300. M_w/M_n=1.08.

8. 5. References

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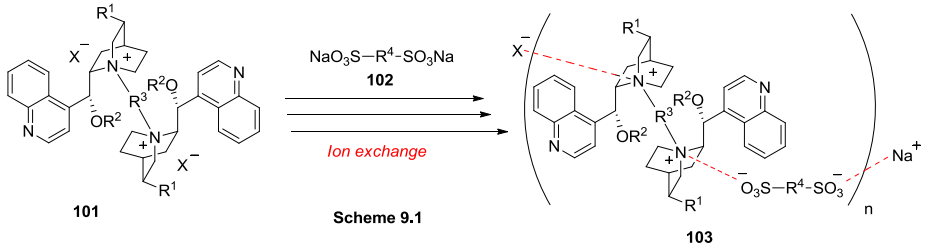
Chapter 9

Summary

In my PhD work, I have designed and synthesized different types of main-chain chiral polymeric organocatalysts containing cinchonidium unit in the main-chain using different polymerization techniques. These polymeric organocatalysts were applied in asymmetric catalysis.

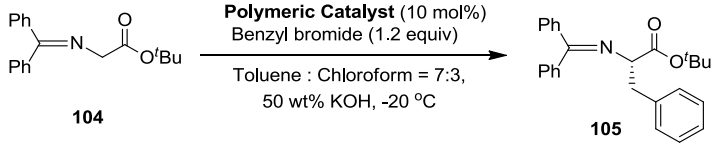
9.1. Main-chain chiral ionic polymer in asymmetric catalysis

Chapter 3 and 4 describe the design of main-chain chiral polymeric organocatalyst (Scheme 9.1) and their application in asymmetric benzylation of glycine derivative (Scheme 9.2).

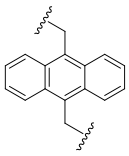
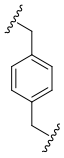
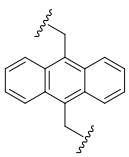
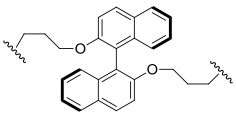


Scheme 9.1

Table 1 Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using polymeric catalyst **103**



Scheme 9.2

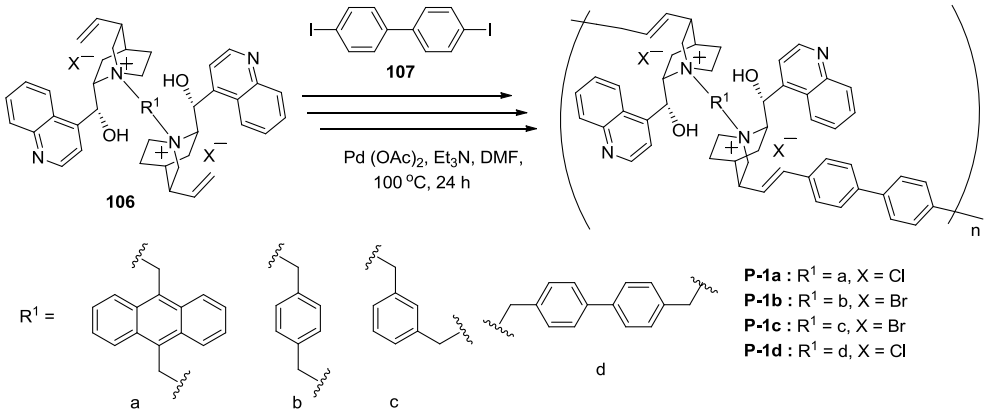
Entry	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	Ee (%)
1	Ethyl	H			7	98	97
2	Ethyl	H			6	98	97

Main- chain chiral ionic polymers of type **103** were synthesized by the reaction between different types of cinchona derived dimer **101** and different types of disulfonate **102** by ion exchange polymerization. When these polymeric organocatalysts were applied in asymmetric benzylation of glycine derivative and quite a high levels of enantioselectivity up to 97% were obtained Table 1.

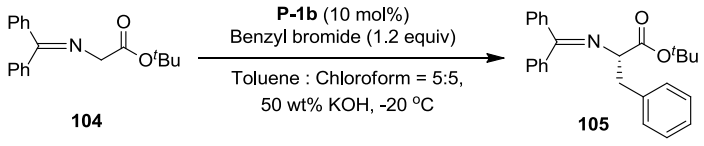
9.2. Main-chain chiral polymer synthesis using Heck coupling and their asymmetric catalysis application

In chapter 5 I have designed and synthesized main-chain chiral polymeric organocatalyst using Heck coupling. Mizoroki-Heck coupling is one of the most efficient C-C bond formation reactions. There are some reports on the synthesis of main-chain chiral polymers using Heck coupling but to our knowledge, none of the main-chain polymers synthesized by Heck coupling have been used as organocatalyst. We have found that the double bond of the cinchonidine can be modified using Heck coupling and synthesized some main-chain chiral polymers using Heck coupling and employed them as a novel polymeric organocatalyst in asymmetric benzylation of glycine derivative. Scheme 9.3 shows the synthesis of main-chain chiral polymeric organocatlyst **P-1** by the reaction between cinchona derived dimer **106** and diiodide **107**.

Scheme 9.3 Synthesis of main-chain polymer using Heck coupling reaction



When the main-chain polymeric organocatalyst **P-1** was employed in asymmetric benzylation of glycine derivative **104** (Scheme 9.4) and using polymeric catalyst **P-1b** 95% enantioselectivity was obtained.



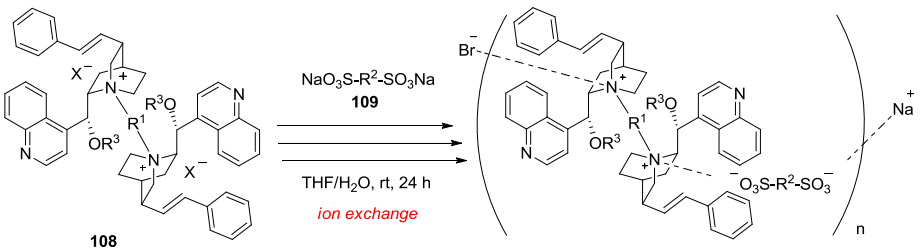
Scheme 9.4

93% yield, 95% ee

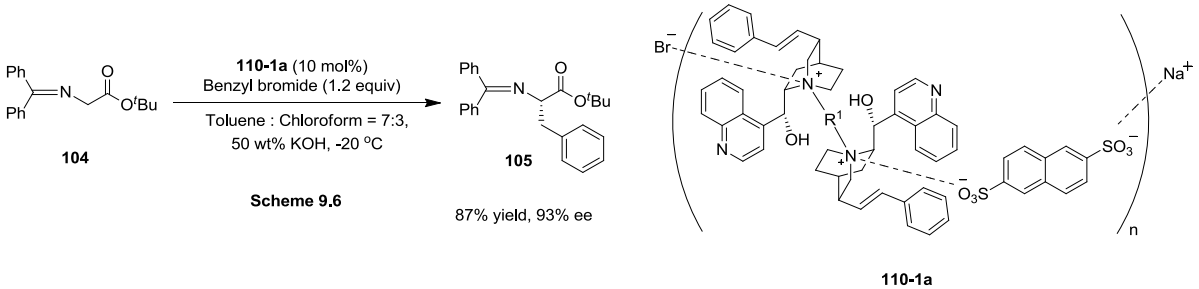
9.3. Synthesis of main-chain chiral ionic polymers from Heck modified cinchonidine dimer and their applications in asymmetric catalysis

In chapter 6 we have synthesized main-chain chiral polymer using ion exchange polymerization. Heck coupling reaction has not widely been used for the modification of double bond of cinchonidine. Using Heck coupling reaction we have synthesized cinchonidine dimer **108**. Then we utilized the ion exchange polymerization technique for the synthesis of main-chain chiral polymer **110** cinchonidine dimer **108** and disulfonate **109** (Scheme 9.5).

Scheme 9.5 Synthesis of ionic polymer **110**



When these polymeric organocatalysts were applied in asymmetric bezylation of glycine derivative up to 93% enantioselectivity was obtained (Scheme 9.6).



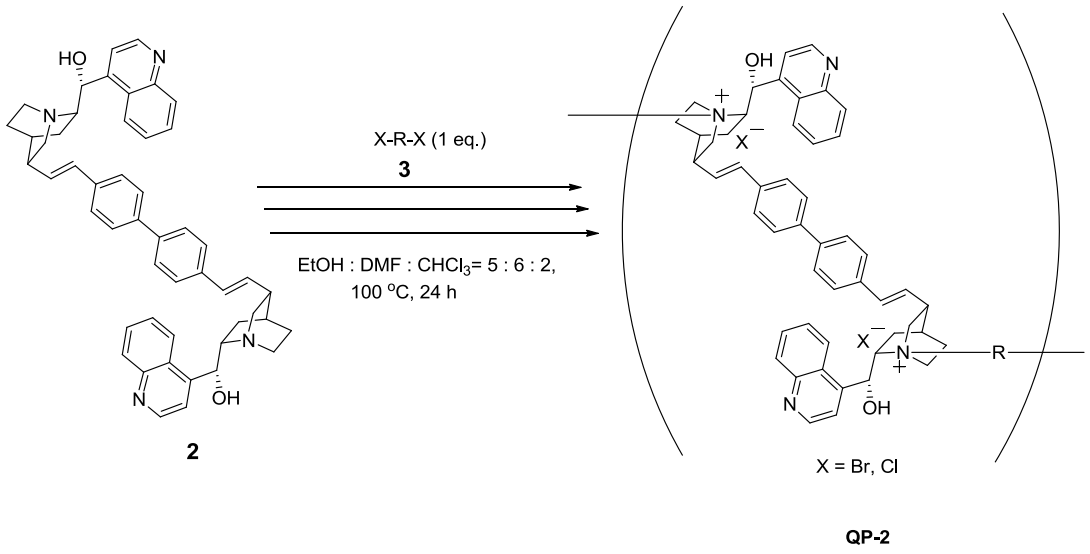
Scheme 9.6

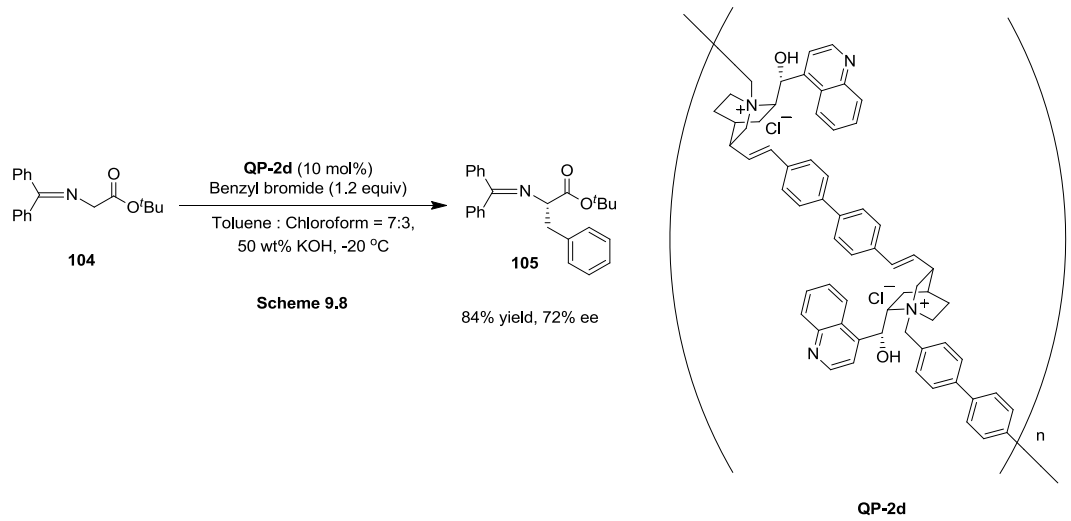
87% yield, 93% ee

9. 4. Main-chain chiral polymer synthesis using quaternization polymerization of cinchonidine and their asymmetric catalysis application

In chapter 7 I have synthesized a novel type of cinchonidine dimer **2** using Heck coupling reaction. Dimer **2** has been used in quaternization polymerization to obtain the main-chain polymer **QP-2** (Scheme 9.7). These polymers were employed as the polymeric organocatalyst in asymmetric benzylation glycine derivative **4** to obtain the phenylalanine derivative **5** and up to 72% enantioselectivity was obtained (Scheme 9.8).

Scheme 9.7 Synthesis of main-chain chiral quaternary ammonium polymers

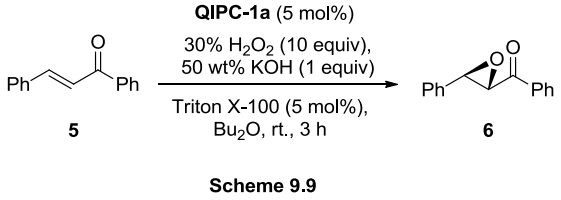




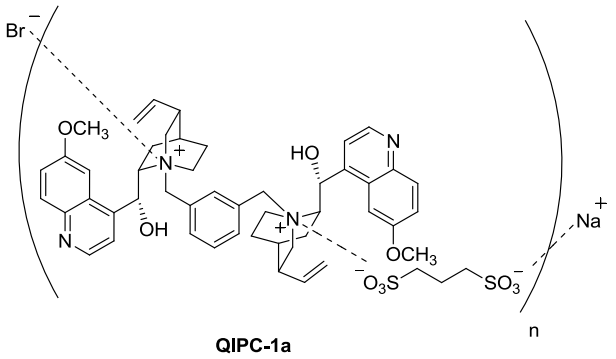
Scheme 9.8

9. 5. Main-chain chiral polymer in asymmetric epoxidation of chalcones

In chapter 8, different types of main-chain chiral polymeric organocatalysts have been employed in asymmetric epoxidation of chalcones. Several types of oxidants were screened and H_2O_2 was found to be the best oxidant in presence of surfactant Triton X-100 and Bu_2O as solvent. Main-chain chiral polymers with flexible structure showed higher enantioselectivity. Most of the cases main-chain chiral polymers with rigid structure gave racemic mixture.



Scheme 9.9



QIPC-1a

After screening several types of main-chain polymeric organocatalyst **QIPC-1a** gave the highest enantioselectivity 84% in asymmetric epoxidation of chalcone **5** (Scheme 9.9).