# Synthesis of Chiral Polymeric Organocatalysts of Cinchona Alkaloid Derivatives for their Application in Asymmetric Catalysis

（シンコナアルカロイド誘導体を用いるキラル高分子有機触媒の合成と不斉反応への応用）

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# *Abstract*

Chiral organocatalysis is one of the important synthetic tool in asymmetric synthesis owing to their advantages of being cost effective, readily available, non-toxic and environmental friendly. Cinchona alkaloids are some of the most important sources of various kinds of efficient chiral organocatalysts. Each of the cinchona alkaloids, namely, quinine, cinchonidine, quinidine, and cinchonine, contain several functionalities such as secondary alcohol, quinuclidine, and quinoline rings in addition to the vinyl group. These functionalities can be exploited for various chemical modifications. Several different kinds of chiral organocatalysts have been developed and they play a vital role in modern asymmetric catalysis. Cinchona alkaloids and their derivatives are classified as privileged organic chirality inducers, efficiently catalyzing many classes of organic reactions in a highly enantioselective fashion.

As a unique class of bifunctional cinchona organocatalysts, cupreines and cupreidines have also been proved as a powerful chiral catalysts for a wide array of asymmetric transformations. Compared to traditional cinchona catalysts, one of the most noticeable features of cupreines and cupreidines is that they bear a phenolic OH group at the C6' position and a free hydroxyl moiety at C9 position. These could be utilized to tune the steric conformation by further functionalization to achieve higher efficiency in asymmetric reaction. In the aspect of asymmetric organocatalysis for the synthesis of enantiopure organic products in medicinal chemistry, cinchona alkaloids and their derivatives have been well explored. Even though chiral organocatalysts supports green chemistry practices, factors such as unable to be recycled and low catalyst loading are the disadvantages associated with their applications in organic reactions.

On the other hand, chiral polymeric catalysts have received significant attention owing to their easy separation from the reaction mixture and their recyclability. Chiral polymeric organocatalysts as a class of chiral organocatalysis possesses additional advantages of being derived from a metal-free catalyst, hence, providing a clean and safe alternative to conventional methods of asymmetric processes. Not only that they can be applied to a continuous flow system and their practicability, but also, the particular microenvironment they create in a polymer network makes them attractive for utilization in organic reactions especially in stereoselective synthesis.

Even though polymeric organocatalysts in asymmetric synthesis, sometimes exhibit poor reactivity by virtual of their heterogeneity, in some cases, a well-designed polymeric chiral organocatalyst may leads to higher selectivity with sufficient reactivity in asymmetric reactions.

Therefore, in chiral polymeric organocatalysis, polymer design, synthesis and their catalytic use became an important tool for understanding the polymeric catalytic efficiency in asymmetric synthesis for fine chemicals production.

As a privileged class of chirality inducers, cinchona alkaloids have found part in chiral polymeric organocatalysts design. With the advancement made in chiral polymeric organocatalysis, the polymeric catalysts design is an essential tool to understand the efficient catalytic process in asymmetric transformations. As for this reason, in this work, cinchona alkaloids derivatives were used for the design of chiral polymeric organocatalysts. Two types of chiral polymers were synthesized; main-chain chiral polymers and cross-linked chiral polymers of cinchona alkaloids derivatives. Through Mizoroki-Heck coupling reaction catalyzed by Pd, the main-chain chiral polymers of cinchona alkaloids were obtained. The synthetic approaches and the design is explained in Chapter 3 and Chapter 4 of this thesis. In Chapter 3 the main-chain chiral polyesters of cinchona alkaloids are reported, while, in Chapter 4, the main-chain chiral polyurethanes of cinchona alkaloids are reported. Both C6'-OMe and C6'-OH free containing chiral polymeric catalysts of cinchona alkaloids were synthesized.

On the other hand, Pt catalyzed hydrosiylation reaction was employed for synthesis of the cross-linked chiral polymers of cinchona alkaloids derivatives. The design and synthetic approach are explained in Chapter 5. We also tried other alternative approach to synthesize main-chain chiral polymers of cinchona alkaloids that are shortly described in Chapter 6.

The catalytic performance of chiral polymers of cinchona alkaloids were evaluated in asymmetric Michael addition reactions. The asymmetric Michael additions of anthrone to $\beta$-nitrostyrene as well as the addition of $\beta$-ketoester to $\beta$-nitrostyrene were used for the evaluation. Both C6'-OMe and C6'-OH free chiral polymeric catalysts of cinchona alkaloids were used for evaluation. The C6'-OH free chiral polymers have been proved to be effective chiral inducers for the Michael addition reactions reported herein.

During catalytic evaluation, factors such as; the chiral organocatalysts' structural effects (i.e. monomeric, dimeric or polymeric structural effect), reaction conditions (this includes solvent, temperature or catalyst loading effects), substrate scope as well as recyclability test were used to evaluate the catalytic performance of the chiral polymeric catalysts. In general, each chiral polymeric catalyst showed different catalytic effects in asymmetric Michael addition reaction transformations. However, it was found that the chiral polymeric catalysts involves mild reaction conditions, stable and recyclable for the Michael addition transformations while their corresponding lower molecular weight catalysts were not. In some cases, higher catalytic activities and enantioselectivities were achieved with the chiral polymeric catalysts in the enantioselective synthesis for the Michael addition reactions compared to their corresponding lower molecular weight catalysts.

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*Dedicated to my husband.,*

# Chapter 1

# Introduction

## 1.1 Background

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom. Green chemistry has been recognized as a culture and methodology for achieving sustainable development. Green chemistry is a chemistry able to promote innovative technologies that reduce or eliminate the use or generation of hazardous substances. Catalysis (including enzyme catalysis, organometallic catalysis, and organocatalysis, in particular) is identified to be at the heart of greening of chemistry, because this branch of science is found to reduce the environmental impact of chemical processes.[1] Besides producing useful chemicals, implementation of “clean" and “green" chemical technology in industries may help address the problem of environmental degradation. Nowadays organocatalysis is one of the hot research topics in advanced organic chemistry. The term “organocatalysis" described 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. It is a novel synthetic philosophy and mostly an alternative to the prevalent transition metal catalysis. The absence of metal in organocatalyst brings an undeniable advantage considering both the principles of “green chemistry" and the economic point of view.

The interest in this field has been increasing spectacularly due to the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions.[2–5] Although organic molecules have been used since the beginnings of chemistry as catalysts, their application in enantioselective catalysis has emerged as a major concept in organic chemistry todate. Because of both determined scientific interest’s as well technological advances in chemical synthesis methodologies that are also in accordance with green chemistry

practices, it is now widely accepted that, organocatalysis is one of the main branches of enantioselective synthesis.

## 1.2 Importance of organocatalysis

New synthetic methods are most likely to be encountered in the field of biological and organometallic chemistry, however, several review articles has demonstrated the novelty of organocatalysis as a synthetic tool for asymmetric transformations.[1–5] Forexample, D. W. MacMillan explained three crucial factors that contributed to the rapid development of this important tool 'organocatalysis' in the field of enantioselective synthesis for the chemists scientific communities. These factors are grouped as explained below:

i. *Conceptualization of the field of organocatalysis:* The concept describes that, small organocatalysts could be used to solve important problems in chemical synthesis such as industrial chemical wastes management. The term organocatalysis provides a strong identity and helped to unify a fledgling field, as well as attracting the attention of the broader chemical synthesis community.

ii. *The advantages of organocatalytic research:* The chemical synthesis community recognized the fundamental advantages of organocatalysis, namely the ease and low cost of carrying out such reactions in the laboratory and the potential for new lines of academic thought and investigation. Although the impact of metal-based catalysts on chemical synthesis cannot be understated, some (but certainly not all) organometallic systems can be expensive, toxic and/or sensitive to air and moisture. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste.

   *First*, organic molecules are generally insensitive to oxygen and moisture in the atmosphere, so there is no need for special reaction vessels, storage containers and experimental techniques, or for ultra-dry reagents and solvents.

   *Second*, a wide variety of organic reagents, such as amino acids, carbohydrates, hydroxy acids and cinchona alkaloids; are naturally available from biological sources as single enantiomers. There are several examples of organocatalysts, chiral and achiral organocatalysts are readily available, and Fig 1.1 shows the examples of organocatalysts and their advantages focusing on chiral organocatalysts. Simple

organocatalysts are therefore usually cheap, easy to prepare and readily accessible in a range of quantities, suitable for small-scale reactions to industrial-scale reactions.

*Third*, small organic molecules are typically non-toxic and environmentally friendly, increasing the safety of catalysis in both biological research and chemical research across all research settings, including industry and academic institutions. The combination of these factors substantially lowered the entry costs for researchers interested in developing enantioselective catalysts. With no need for inert gases, ultra-dry solvents or even high levels of experimental expertise, it is not surprising that the field quickly became flooded with research groups from around the globe. For any large-scale catalytic process, the most salient considerations are cost and safety. Because organocatalysts are often cheaper than metal-based catalysts, organocatalysts can be used in larger quantities than metal-based ones for the same price. Moreover, it is widely recognized in manufacturing that the removal of toxic catalyst related impurities from the waste stream can often have a larger financial impact. Organocatalysts are typically less toxic than metal-based catalysts, can be tolerated to a large extent in waste streams and are more easily removed from waste streams. With respect to industrial applications, organocatalytic reactions are of great use to medicinal chemists. Medicinal chemists need to find rapid, broadly applicable ways of constructing new candidate drugs for testing, so the most important considerations for a catalyst are its generality, convenience and robustness. Organocatalysts meet all of these operational requirements.

iii. *The advent of generic modes of catalyst activation, induction and reactivity:* A generic activation mode describes a reactive species that can participate in many reaction types with consistently high enantioselectivity. Such reactive species arise from the interaction of a single chiral catalyst with a basic functional group (such as a ketone, aldehyde, alkene or imine) in a highly organized and predictable manner. The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for designing new enantioselective reactions. The small number of activation modes in organocatalysis (and in catalysis in general) is not surprising, when devising a new enantioselective reaction, it is far easier to make use of a known activation mode than to invent a new one (together with a new catalyst). In many ways, this is beneficial to chemists, because it leads to the development of catalysts or catalyst families that are useful for a wide range of

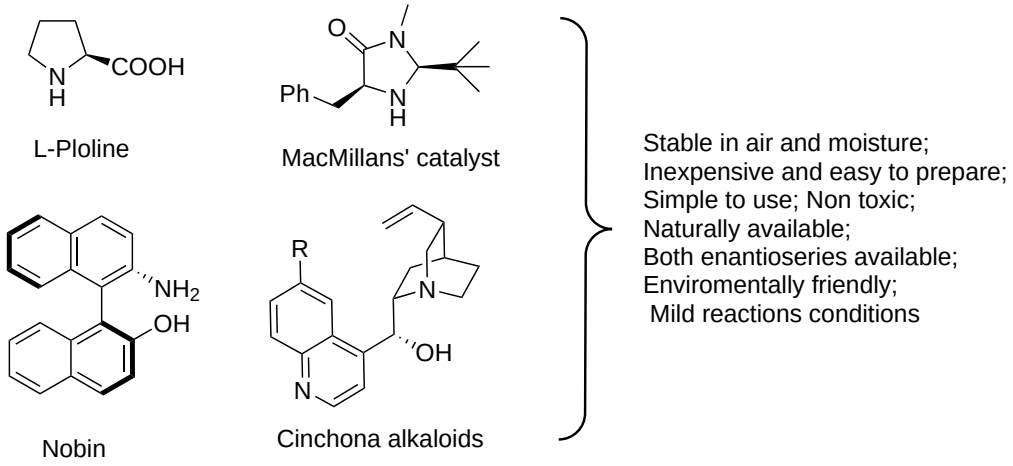



FIGURE 1.1: Few famous examples of organocatalysts and their advantages.[5]

asymmetric reactions. At the same time, it is clear that discovering new activation modes is important for all types of catalysis.

## 1.3 Problem definition

Significant advancement have been made by many scientific researchers to solve existing challenges of recyclability and low catalyst loading associated with lower molecular weight chiral organocatalysts in asymmetric synthesis. With further advances in the understanding of polymers, and with new applications being researched, there is no reason to believe that the revolution of macromolecular sciences will stop any time soon, there are numbers of polymer applications in elastomers, plastics, fibers and as industrial catalyst. Polymeric chiral organocatalysts and reagents have received considerable attention in regard to organic synthesis of optically active compounds.

The use of chiral polymer catalysts has become one of the essential techniques in organic synthesis. Due to the fact that, they can be easily separated from the reaction mixture and reused many times. It is even possible to apply the polymeric catalysts to a continuous flow system. From the point of view of green chemistry, the chiral polymeric organocatalysis method provides a clean and safe alternative to conventional methods of asymmetric processes. Not only the practical aspect of the polymeric catalyst but also the particular micro environment they create in a polymer network, that make them attractive for utilization in organic reactions especially in stereoselective synthesis.

Design of chiral polymers and their catalytic use is now extremely required in organic synthesis of fine chemicals. Most of the work on chiral polymeric catalyst design has

been done on the use of the side chain functionalized polymers including cross-linked polymers. Only a limited number of investigations have been performed to elucidate the use of main-chain functional polymers. Some examples include; polymeric chiral salen ligand, poly(amino acid), poly(tartrate), poly binaphthols, and helical polymers. These main-chain chiral polymers have been successfully applied to a chiral catalyst in various kinds of asymmetric reactions. The rigid and sterically regular polymer catalysts may provide a better-defined microenvironment at the catalytic sites and could allow a systematic modification of their catalytic properties.

There are so many different types of synthetic polymers, including both organic and inorganic polymers. Not only linear polymers but also cross-linked, branched, dendritic polymers are available as support for the chiral catalyst. Each polymer support, would provide a specific microenvironment for the reaction if they can be precisely designed. Despite of the applicability of polymeric organocatalysts, sometimes using polymeric catalyst exhibit poor reactivity by virtual of their heterogeneity.

However, in some cases, a well-designed polymeric chiral catalyst may lead to higher selectivity with sufficient reactivity in asymmetric reactions. These information shows clearly that the design of a polymeric catalyst is very important in oder to understand the efficient catalytic process. Effort has been done in several studies providing the feasibility to address the existing problems.

Recently, some main-chain chiral polymers, including helical polymers and cross-linked chiral polymers have been synthesized and applied in various kinds of asymmetric reactions and they showed good catalytic performances. With these facts, in order to promote green chemistry practices, there is still a need to develop new strategies and methodologies in the class of chiral polymeric organocatalysts for their applications in asymmetric synthesis

## 1.4 Research objectives

The main objective of this research is the design and synthesis of chiral polymeric organocatalysts for their applications in asymmetric synthesis. To start with the design stage that involves the use of cinchona alkaloids derivatives to obtain either main-chain chiral polymers or cross-linked chiral polymers. Then, Mizoroki-Heck coupling reaction and hydrosiylation reaction were used as synthetic methodology to obtain the main-chain chiral polymers and cross-linked chiral polymers respectively and finally, the catalytic

performance of chiral polymeric catalysts were evaluated in asymmetric Michael addition reactions.

## 1.5 Literature review

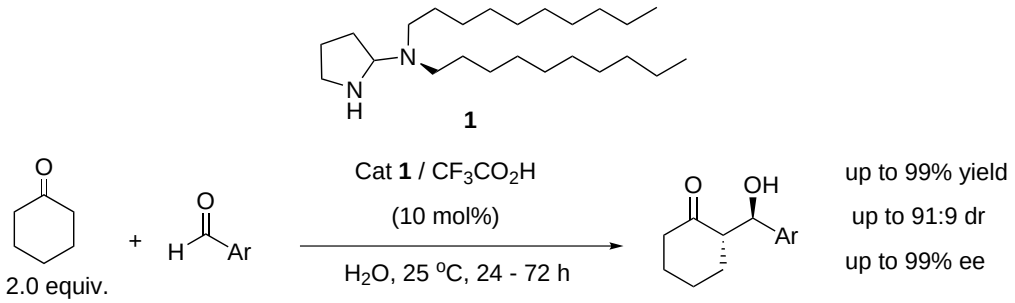
### 1.5.1 Asymmetric catalysis

Asymmetric catalysis constitutes one of the most important subjects in synthetic organic chemistry. Asymmetric synthesis achieving atom economy is a challenge for organic synthesis, and heterogeneous catalysis using metal complexes leads the way. However, the application of such methodologies in chemical industry is rather limited due to the high cost of chiral ligands and noble metals used in such transformations. Moreover, the pharmaceutical entities and food industry products do not tolerate a contamination, of even traces, of any such metals for that matter.

As optically active drugs become increasingly important for the treatment of diseases in patients, still more enantiopure drugs are introduced to the market either as new drugs or as the result of a racemic mixture.[5] An important goal for asymmetric catalysis is to develop new reactions that afford optically active compounds from simple and easily available starting materials and catalysts. The need from chemical industry, especially pharmaceutical, for reliable asymmetric transformations of molecular skeletons is higher than ever. Therefore, asymmetric organocatalysis is in a process of attaining maturity into a very powerful, practical, and broadly applicable methodological approach in the catalytic asymmetric synthesis.

### 1.5.2 Low molecular weight chiral organocatalysts

The development of new chemical transformations for efficient and practical synthesis of complex structures has emerged as the main objective in synthetic organic chemistry. Different enantioselective organocatalysis transformation with low molecular weight catalysts has been reported by chemists researchers,[6–21] these includes C-C bond formation,[11–17] C-O bond formation[18–20] as well as desymmetrization[21] asymmetric transformations. Describing some examples for the commercially available chiral organocatalysts (shown in Fig 1.1) and their derivatives, as successful synthetic tool in asymmetric transformations, gives a clear picture over the precedencies made for organocatalysis applications in asymmetric synthesis.

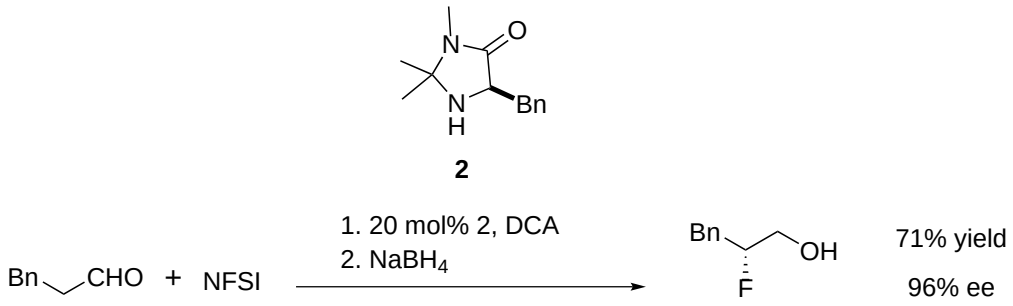



SCHEME 1.1: Example on enantioselective asymmetric aldo reaction with plolinamine derivative as a catalyst.[12]

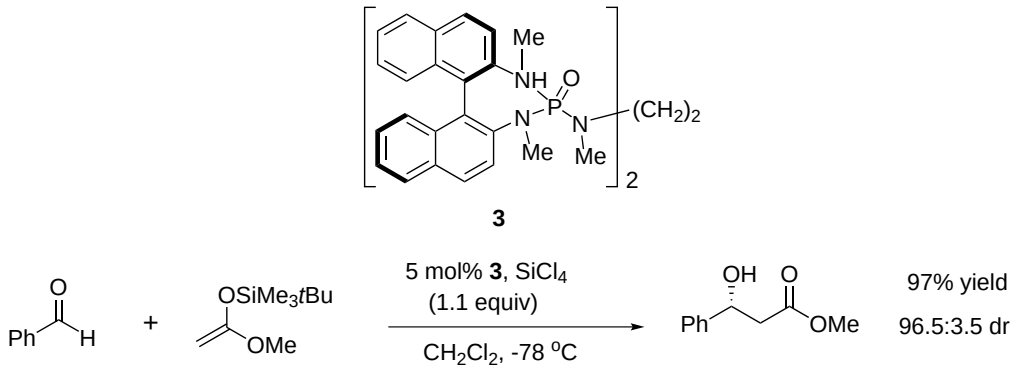
*L-proline:* Among several organocatalysts derived form L-proline as chiral source, pyrrolidine-tertially amine conjugates constitutes a powerful and useful family in asymmetric synthesis.They have been applied in different asymmetric reaction.[11,12] Forexample prolinamide derivatives are readily available through the condensation of proline with amines and they can be utilized in different asymmetric transformation reactions.[3] The Barbas group reported on the effective enantioselective C-C bond formation by prolinamine with lipophilic side chain **1** as a catalyst for the asymmetric aldo reaction.[12] The chiral organocatalyst allowed cyclohexanone to react smoothly with various aldehydes in water to afford the desired aldo products in high yields with excellent diastereo and enantioselectivity (Scheme 1.1).

*MacMillans' catalyst:* The chiral imidazolidin-4-ones as chiral secondary amines had been successfully used in asymmetric synthesis as organocatalysts. They were deployed as chiral auxiliaries for alkylation processes, Michael additions and aldo reactions.[3] The ability to activate both carbonyl compounds by enamine formation as well as $\alpha$, $\beta$-unsaturated carbonyl compounds by intermediate formation of iminium ions makes imidadazolidin-4-ones a valuable class of organocatalysts in both series.[22] As shown in Scheme 1.2, the direct asymmetric fluorination of aldehydes using N-fluorobenzenesulfonamide (NFSI) as a source of electrophilic fluorine depicts the investigations.

*Lewis acid/base catalysts:* The development and application of chiral $C_2$-symmetry organic molecules possessing appropriate Lewis basic/acidic functionalities has made significant contribution in the advancement of asymmetric organocatalysis.[3] Taking an example of Lewis base activation of Lewis acids concepts introduced by Denmark, where its validity and synthetic potential were demonstrated in various bond forming reactions using bis-phosphoramides **3** as catalysts.[23] The aldol asymmetric addition of silyl ketene acetals to aldehydes is well explored by the use of catalyst **3**. The combination of **3**




SCHEME 1.2: Example on asymmetric $\alpha$-fluorination of aldehydes with MacMillans catalyst; DCA (dichloroacetic acid).

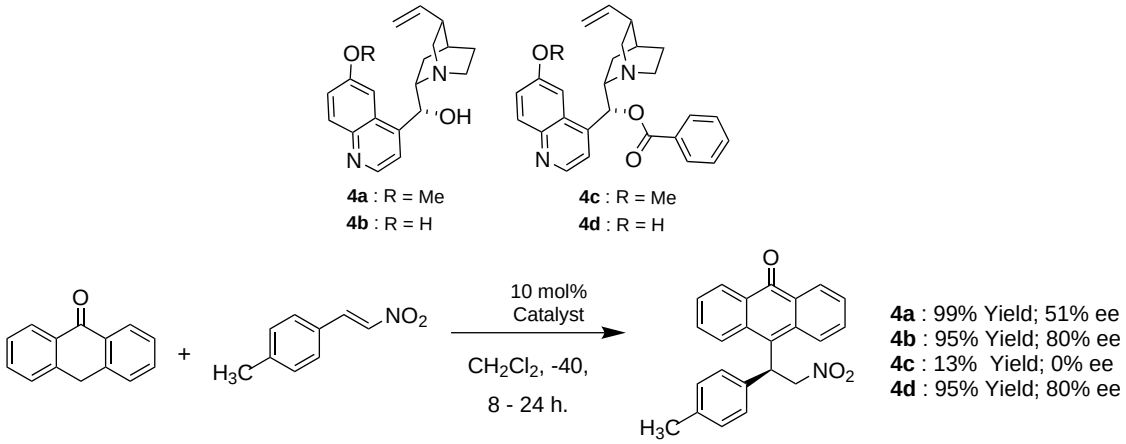



SCHEME 1.3: Asymmetric aldo reaction of silyl ketene acetal with chiral bis-phosphoramides as catalyst.[23]

and a stoichiometric quantity of $SiCl_4$ was very effective for the reactions of methyl acetate-derived silyl ketene acetal with aldehyde (Scheme 1.3).

*Cinchona alkaloids:* These are well known natural products with a fascinating medicinal history. Cinchona alkaloids have long been known as very useful and robust catalysts for many kinds of organic reactions before the explosion of organocatalysis'.[24] Although the first example of asymmetric reaction catalyzed by cinchona alkaloids can be dated back to 1912,[25] only after 1960s, with the development of asymmetric phase transfer catalysts (chiral PTC),[26] and asymmetric dihydroxylation by Sharpless,[27] cinchona organocatalysts have drawn much more attention and have been widely used in a variety of asymmetric reactions.[28] Compared to tradition cinchona catalysts, as a unique class of bifunctional cinchona organocatalysts, cupreines and cupreidines have been proved to be powerful chiral catalysts for a wide array of asymmetric transformations.[29]

Cinchona alkaloids and their derivatives play an important role in asymmetric synthesis as chiral organocatalysts and have been reported as chiral promoters in organic reactions as described in several review articles.[30] Forexample Shi. M and coworkers they have reported on a highly efficient asymmetric Michael addition of anthrone to




SCHEME 1.4: Asymmetric Michael addition of anthrone to 4-methyl-trans $\beta$-styrene with cinchona organocatalysts.[28]

nitroalkenes with cinchona organocatalysts for the first time.[28] Nitroalkenes as reactive Michael acceptors could exclusively produce the corresponding Michael adducts in the presence of bifunctional cinchona organocatalysts. As shown in Scheme 1.4 the importance of the C6'-OH free for the enantioselective synthesis in the asymmetric Michael reaction is observed.

In this thesis too, cinchona alkaloid and their derivatives for their asymmetric catalysis reactions is the main point of interest. Next chapters focuces more on their classifications for asymmetric catalysis.

### 1.5.3 Polymeric chiral organocatalysts

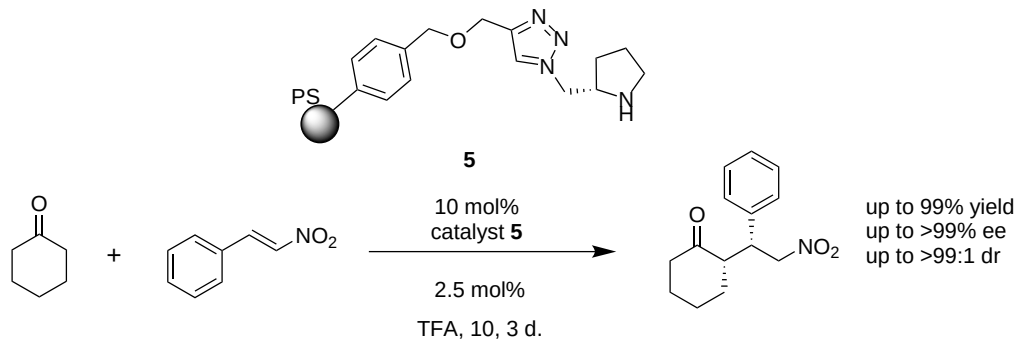
Synthetic chiral polymers includes; polymers possessing side-chain chirality, main-chain chirality, dendritic molecules containing chiral ligands and helical polymers. Polymeric chiral organocatalysts have received considerable attention in regard to organic synthesis of optically active compounds.[31] The use of polymeric catalysts has become one of the essential techniques in organic synthesis, as they can be easily separared from the reaction mixture and reused many times. From the point of view of green chemistry the polymeric chiral organocatalysis method provide a clean and safe alternative to conventional methods of asymmetric processes. It is not only the fact that they can also be applied to a contionous flow system and their practicality but also the particular microenvironment they create in a polymer network makes them attractive for utilization in organic reactions especially in stereoselective synthesis.

It has been reported that, despite of the applicability of polymeric organocatalysts, sometimes using polymeric catalyst exhibit poor reactivity by virtual of their heterogeneity. However, in some cases, a well-designed polymeric chiral catalyst may lead to higher selectivity with sufficient reactivity in asymmetric reactions. These information clearly show that the design of a polymeric catalyst is very important in understanding the efficient catalytic process. There are different types of polymeric catalysts that have been reported by different researchers; based on this thesis the focus is on chiral polymeric catalyst design related to polymer immobilized organocatalysts and main-chain chiral polymer organocatalysts.

### 1.5.4 Polymer-immobilized chiral organocatalyst

Polymer supported chiral organocatalysts have mainly been prepared by two methods; a coupling reaction of a functional polymer with a chiral organocatalysts and copolymerization of a monomer with a chiral organocatalyst.[31–33] Most polymeric support materials used for the chiral catalyst have been cross-linked polystyrene derivatives,mainly because of their easy preparation and introduction of functional groups on the side chain of the polymer. However, there are so many different types of synthetic polymers, including both organic and inorganic polymers. Not only linear polymers but also cross-linked, branched, dendritic polymers are available as support for the chiral catalyst. Various kinds of polymers have been used as support for the chiral catalyst and the suitable polymer network for each reaction have been reported.[31]

With the progress that has been made in organic chemistry, several coupling reaction techniques are available for coupling of a chiral ligand precursor with functionalized polymers. The coupling reaction and functionalization of the chiral organocatalysts should be carefully selected under consideration of the reactivity of the chiral organocatalysts. In the coupling method the quantitative coupling reaction is preferable, and the quantitative characterization of the coupling efficiency is necessary when the coupling reaction is not complete. Because Merrifield-like resin and PEG are the commonly used as a functionalized polymer, the Williamson reaction is mostly employed. The other important bond formation reaction are such as Diels-Alder reaction, Suzuki Miyaura coupling reaction, aldo reaction, Grignard reaction, Mitsunobu reaction and click reaction are available in the coupling reaction.[31]

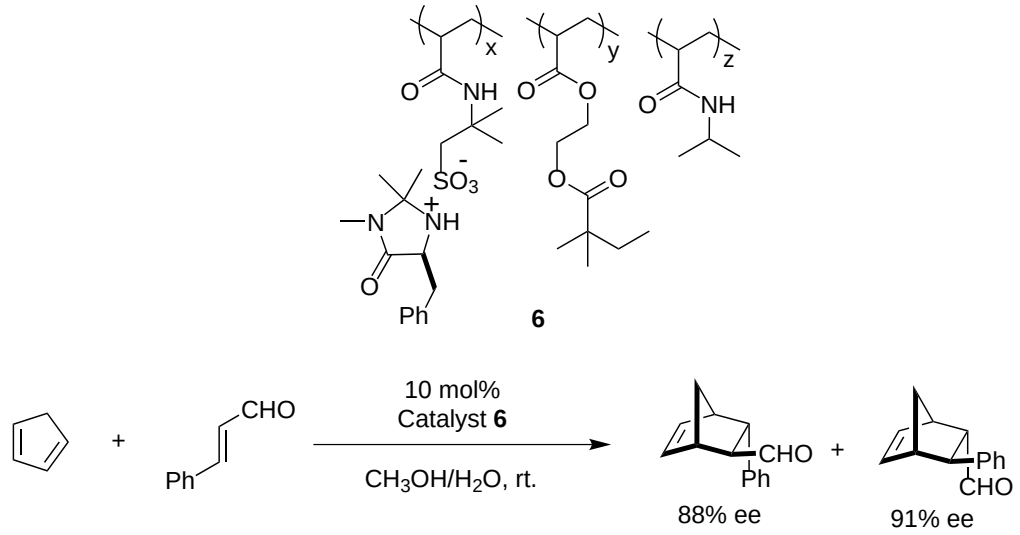



SCHEME 1.5: Enantioselective Michael addition catalyzed by polymer immobilized chiral pyrrolidine **5**.

The degree of cross-linkage of a cross-linked functional polymer and the choice of solvent mainly determine the swelling rate of the cross-linked functional polymer. The rate is of significance in the coupling efficiency of the reaction and accessibility of a substrate to the polymer-support chiral catalyst in the asymmetric reaction. A polymer-support chiral organocatalyst can also be synthesized by polymerization of a functional polymer possessing a chiral ligand, and a variety of monomers can be used according to the style of polymerization. Not only these but also the ion exchange method can be used for the immobilization technique. Cation and anion-exchange resins using a polymer support are commonly employed method in the industrial process. The advantage of using ion exchange method is that further functionalization of a chiral ligand or catalyst is not required for immobilization. A variety of polymerization techniques can be for the preparation of a polymer-supported catalyst. Some examples of polymer supported catalyst are discussed in this chapter based on their application in asymmetric synthesis with their corresponding low molecular weight structure shown in Fig 1.1.

*Polymer immobilized pyrrolidine derivatives:* Pyrrolidine derivatives as shortly explained earlier are among the most efficient motifs as a chiral organocatalysts. They have been used in different asymmetric transformation for an example in Scheme 1.1. Polystyrene-immobilized chiral pyrrolidines containing triazole were prepared by the copper-mediated 1,3-dipolar cycloaddition between the pyrrolidine derivative with azide and polystyrene resins with alkyne. The resulting polystyrene-immobilized chiral pyrrolidine **5** was used in the Michael addition of cyclohexanone to $\beta$-nitrostyrene (Scheme 1.5). An excellent enantioselectivity (>99 % ee) was accomplished and the catalyst could be recovered and reused for ten times without loss of the diastereo- and enantioselectivity.[34]

*Polymer-immobilized MacMillan catalysts:* Like conventional effective chiral catalysts that has been reported, the immobilization of MacMillan's iminium catalyst onto

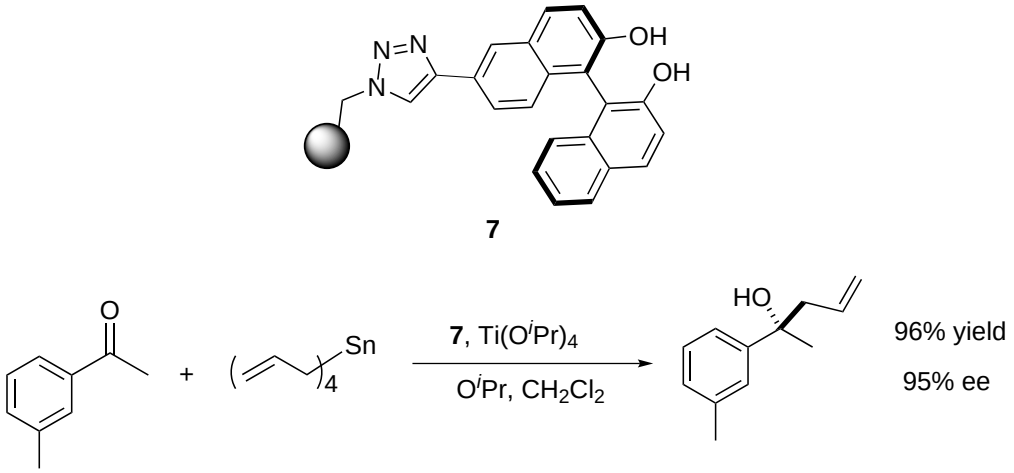



SCHEME 1.6: Polymer-immobilized imidazolidinone sulfonate **6** in the catalytic asymmetric Diels-Alder reaction.[35]

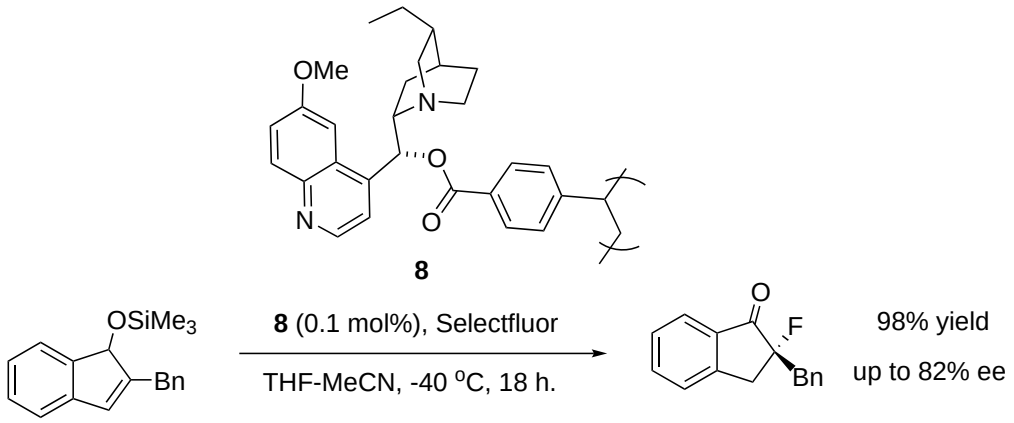
polymeric materials has been developed.[34–36] Several approaches for their immobilization make use of a covalent bond between the polymer support and the catalyst moiety. An alternative method is via ionic bond formation. Imidazolidinones readily form its sulfonates allowing their immobilization through an ionic bond with the ammonium sulfonate structure.[35] The immobilized imidazolidinone sulfonate **6** was successfully used to catalyze the asymmetric Diels-Alder reaction of cyclopentadiene and cinnamaldehyde in Scheme 1.6 to form the Alder products with good enantioselectivities.

*Polymer-immobilized BINOL derivatives catalyst:* BINOL derivatives has also been reported for their applications in polymer immobilized chiral organocatalysts. Forexample, the synthetic and application approaches in different asymmetric reactions was reported by S. Itsunos' review article in polymer-immobilized chiral catalysts.[36] By using a simple, and convenient synthetic route, enantiopure 6ethynylBINOL (BINOL=1,1binaphthol) was synthesized and anchored to an azido methylpolystyrene resin through a coppercatalyzed alkyne-azide cycloaddition (CuAAC) reaction.[37] The polystyrene-immobilized BINOL ligand was converted into its diisopropoxytitanium derivative in situ and used as a heterogeneous catalyst in the asymmetric allylation of ketones with tetraallyl tin as shown in Scheme 1.7. The catalyst showed good activity and excellent enantioselectivity.

*Polymer-immobilized cinchona alkaloid derivatives:* Cinchona alkaloids as the most privileged chirality inducers in the area of asymmetric reactions, they possess some reactive sites that are suitable for the immobilization onto a polymer.[38,39] The vinyl group




SCHEME 1.7: Polystyrene-immobilized BINOL **7** in the catalytic asymmetric allylation of ketones.[37]




SCHEME 1.8: Polymer immobilized cinchona alkaloid **8** in enantioselective $\alpha$-fluorination.[39]

at the C3, hydroxyl group at C9 and hydroxyl group at C6' of the quinoline moiety after demethylation are readily available.[31] For example Cahard and coworkers synthesized linear polystyrene-immobilized cinchona alkaloids **8** and applied it to enantioselective $\alpha$-fluorination (Scheme 1.8). The polymer showed good enantioselectivity and could be reused without loss of enantioselectivities for fourth cycles.[39]

### 1.5.5 Main-chain chiral polymeric organocatalysts

Main-chain chiral polymeric organocatalysts are polymeric catalysts that contain chiral organocatalysts molecules as their repeating units in the main-chain moiety. The primary advantage of polymeric catalysts is their ease of separation from the reaction mixture, that allows very efficient recovery, and reuse of the catalysts in asymmetric synthesis.[40,41] In addition to that, diffusion control as well as long catalytic shelf life are the added

benefit to polymeric organocatalysts. In comparison with polymer-immobilized chiral organocatalysts, main-chain chiral polymers have several important structural advantages for their applications in asymmetric synthesis, these includes;

i. Rigid and defined structure

ii. Constant repeating unit moiety

iii. Possesses high catalyst loading

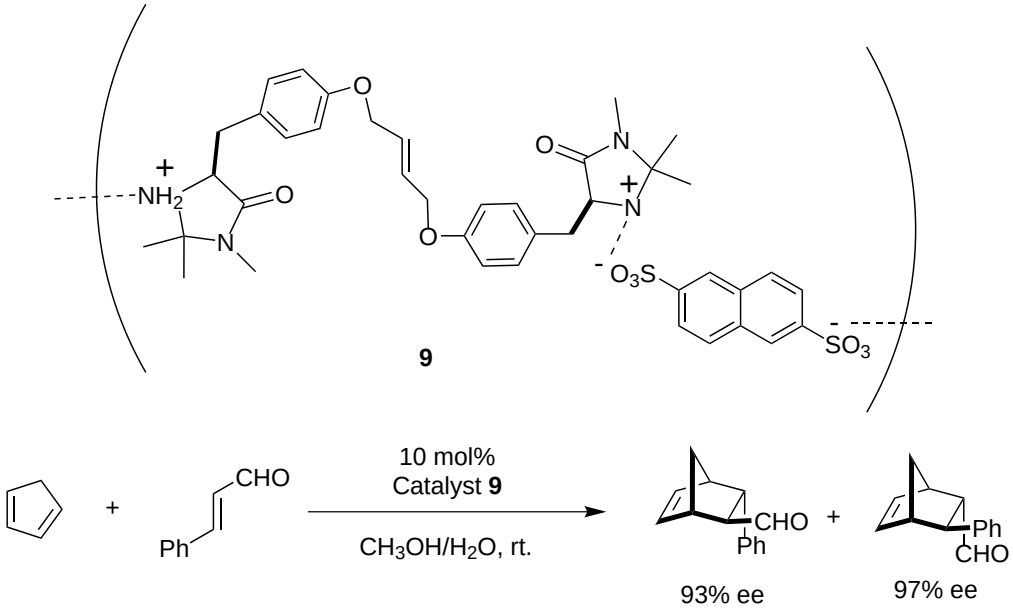
iv. Gives a well-defined micro-environment

Chiral organocatalysts as privileged class of chiral inducers in asymmetric transformation, have been used in the preparation of different main-chain polymeric chiral organocatalysts. Different synthetic methods and approaches have been explored in the preparation of main-chain chiral polymers. Some of the reported methods includes; ionic polymerization,[42] quartinization polymerization,[43–45] Mizorocki-Heck polymerization,[45–51] and ADMET polymerization.[52] The resulted main chiral polymers were used as catalysts in different asymmetric reaction, where in many cases they showed higher enantioselectivity with sufficient catalytic activities.[42–52] Examples on some of the reported main-chain chiral polymeric catalysts are as decribed below;

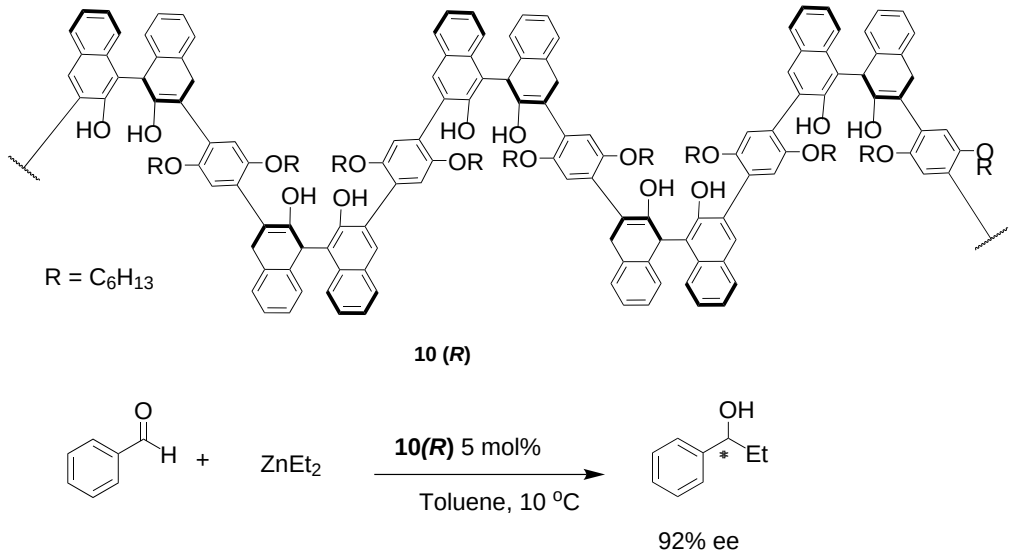
*Main-chain chiral polymeric catalyst of imidazolidinone:* Haraguchi, N and coworkers reported on the synthesis of main-chain chiral polymers of imidazolidinone prepared by reaction of chiral imidazolidinone dimers with disulfonic acid. Chiral imidazolidinones were incorporated into the main-chain of the polymer by ionic bonding.[53] The polymer was used as polymeric chiral organocatalyst for asymmetric Diels-Alder reactions and gave higher enantioselectivities of the corresponding asymmetric product (Scheme 1.9).

*Main-chain chiral polymeric catalyst of BINOL derivatives*: A minor groove polymer of (R)-1,1'-binaphthyls **10** was obtained from the Suzuki coupling reaction with Pd as a catalyst followed by hydrolysis as reported by Pu, L.[54] The polymer was insoluble in common organic solvents. **R(10)** induced excellent enantioselectivity in the reaction of benzaldehyde with diethylzinc (Scheme 1.10). In the presence of 5 mol% catalyst at 0 °C in toluene 92% ee of the asymmetric product was produced. The polymer was easily recovered by precipitation with methanol and the recovered polymer showed the same enantioselectivity as the original polymer.

*Main-chain chiral polymeric catalyst of cinchona alkaloids:* Recently there are several numbers of main-chain chiral polymeric catalysts of cinchona alkaloid mainly synthesized

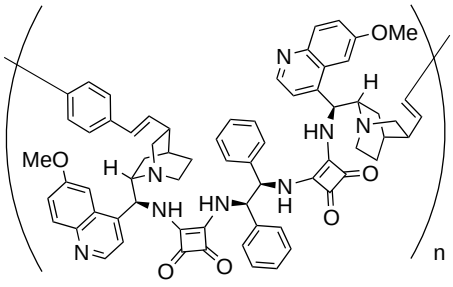



SCHEME 1.9: Main-chain chiral polymer of imidazolidinone sulfonate **9** in the catalytic asymmetric Diels-Alder reaction.[53]

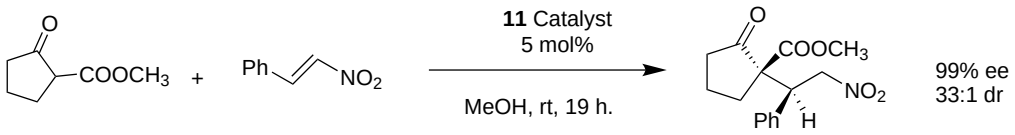



SCHEME 1.10: The asymmetric reaction of aldehydes with diethylzinc in the presence of polybinaphthol **10(R)**.[54]

by Mizorocki-Heck polymerization method.[45–51] As for example, Ullah, M. S and Itsuno. S. have reported on the synthesis of main-chain type cinchona-based squaramides and their application to asymmetric catalysis.[50] Their design involves the use of cinchona squaramide dimer that contains two cinchona squaramide units connected by diamines. The olefinic double bonds in the cinchona squaramide dimer were then used for Mizoroki-Heck (MH) polymerization with aromatic diiodides. The MH polymerization of the cinchona squaramide dimer and aromatic diiodide proceeded well to give the corresponding




**11**




Scheme 1.11: Enantioselective Michael addition of $\beta$-ketoester to nitroolefin in the presence of main-chain cinchona polymeric catalyst **11**.[50]

chiral polymers in good yield. The asymmetric Michael addition of $\beta$-ketoesters to nitroolefins was successfully catalyzed by polymeric cinchona squaramide organocatalysts to obtain the corresponding Michael adducts in good yields with excellent enantio- and diastereoselectivities (Scheme 1.11). The polymeric catalyst was insoluble in commonly used organic solvents, therefore it was easily recovered from the reaction mixture and reused several times without losing its catalytic performance.

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# Chapter 2

# Cinchona alkaloids derivatives in asymmetric catalysis

## 2.1 Introduction

Asymmetric catalysis is the strategy in asymmetric synthetic endeavors, due to the design and development of several natural product-derived chiral molecular frameworks as chiral organocatalysts. The alkaloids of Cinchona species, which were once known for the popular antimalarial drug quinine, have emerged as the most powerful class of compounds in the realm of asymmetric organocatalysis.[1] Apart from natural Cinchona alkaloids, many derivatives, such as those containing hydroxyl groups, amines, ureas, and thiourea functionalities, especially at the C9 position, either alone or in the presence of an additional catalyst that might be a simple achiral compound or metal salt, have been employed in diverse types of enantioselective syntheses by asymmetric catalysis.[1–4] This can be attributed to the naturally occurring of cinchona alkaloids as an ideal choice as chiral inducers in asymmetric catalysis due to the following reasons;

i. Abundantly provided by nature

ii. Commercially available at relatively moderate prices

iii. Readily modified structurally for diverse catalytic applications and

iv. Readily obtainable in diastereomeric pairs, allowing access to either enantiomeric product.

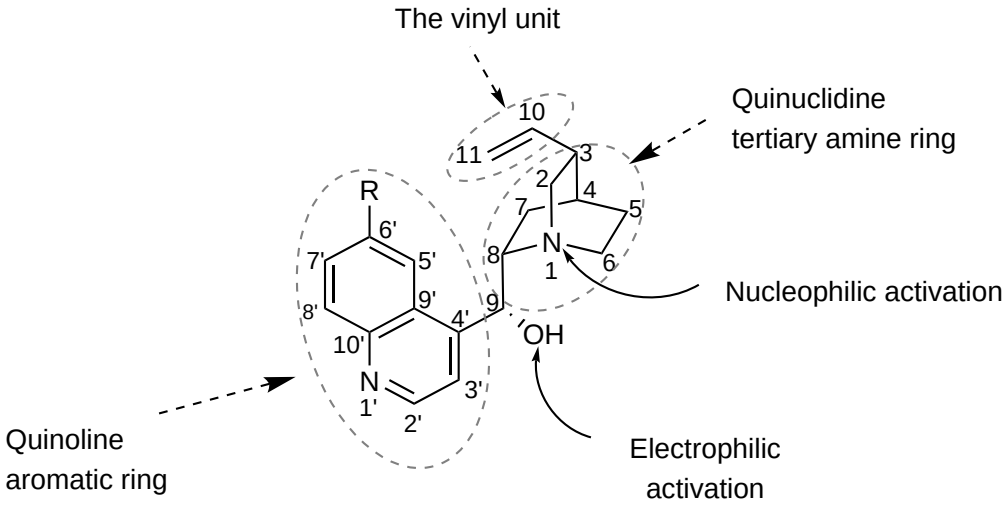


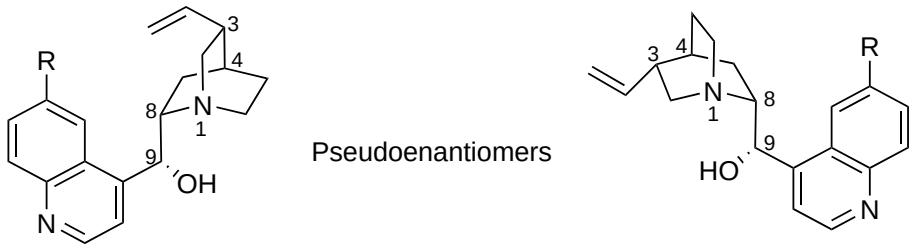

FIGURE 2.1: Important structural features of cinchona alkaloids.

## 2.2 The cinchona alkaloids structure

Alkaloids are classified according to the heterocycle and the taxonomy of the species they were isolated from.The bark of various Cinchona species contains four major alkaloids, namely quinine **QN**, quinidine **QD**, cinchonidine **CD**, and cinchonine **CN**. Their structures contain a central C9-hydroxyl group, vinyl unit as well as quinoline and quinuclidine rings (Fig. 2.1). They contain five stereocentres, C3, C4, N1, C8 and C9, but they occur in pairs that differ in configuration only at N1 and the two connecting single-bond carbons, C8 and C9. The absolute configuration at C3 and C4 is identical in both pairs and is the same in all naturally occurring *Cinchona* alkaloids (Fig. 2.2).

The cinchona alkaloids (Fig. 2.1) are diastereomers, usually referred to as pseudoenantiomers because they offer enantiomeric products when used as catalysts. The structural features of cinchona alkaloids and their derivatives responsible for their catalytic activity in terms of yields, diastereoselectivity and enantioselectivity of the products have been reported.[1–5] The key features responsible for their successful utility in catalysis is that they possess diverse chiral skeletons and are readily tunable for diverse types of reactions (Fig. 2.3).

The presence of the quiniclidine base functionality makes them effective ligands for a variety of metal -catalyzed processes. The metal binding properties of the quinuclidine nitrogen also alow to use cinchona alkaloids as metal surface modifiers. In addition to its ability for metal binding, the quinuclidine nitrogen can be used as a chiral base or chiral nucleophilic catalyst promoting the vast majority of organocatalytic reactions.




R = OMe : Quinine (**QN**)
R = H : Cinchonidine (**CD**)

R = OMe : Quinidine (**QD**)
R = H : Cinchonine (**CN**)

FIGURE 2.2: Cinchona alkaloids structures showing their name and specific stereocenters.[2]

**N1: Quinuclidine nitrogen**

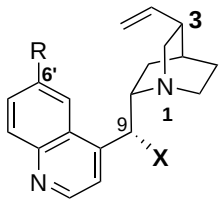
1) Metal binding ability: chiral ligands or chiral modifiers
2) General base: deprotonation
3) Nucleophilic catalyst
4) N-Alkylation: chiral PTC

**C3**

Available for other derivations
eg. Hydrosilylation, Heck reaction,
Thiol-ene click reaction etc

**C6' : R = OH or thiourea**

1) H-Bond donor or acid




**X = OH**

1) H-Bond donor or acid
2) Metal coordination

**X = $NH_2$ or further derivatization**

1) Aminocatalysis (iminium and enamine catalysis
2) H-Bond donors (e.g. ureas, squaramides, amides)

FIGURE 2.3: Common active sites in cinchona alkaloids and their possible derivatives.[4]

The related quaternized ammonium salts of cinchona alkaloids have proved to catalyze numerous reactions under phase transfer conditions, where asymmetric inductions occur through a chiral ion pairing mechanism between the cationic ammonium species and anionic nucleophile.

The C9-hydroxyl group can serve as an acid site or hydrogen bond donor. The derivatization of the OH group into ureas, amides, esters, thioureas and so on, with either retention or inversion of the configuration, provides a more acidic site or hydrogen bond donor.

The C6' methoxy group of quinine and quinidine is readily to be derivatized as an effective H-bond donor. Moreover, the substitution of C9 into the free amino with the inversion of the configuration enables enantioselective aminocatalysis. In general the active sites in cinchona alkaloids and their derivatives act in catalysis not independently but cooperatively, that is, they activate the reacting molecules simultaneously.

## 2.3 Cinchona alkaloids as bifunctional chiral catalysts

The *Cinchona* alkaloids have been greatly utilised in the rational design of catalysts for asymmetric synthesis because they are tunable to either increase or decrease bulkiness, thus controlling steric rigidity and, hence, the stereochemical outcome. Cinchona alkaloids acts as bifunctional catalysts since they present Lewis acidic and basic sites. Both the tertiary amine and hydroxyl moiety are able to activate and orient a nucleophile and an electrophile repectively.[3] Principally cinchona alkaloids and their derivatives can be employed as chiral catalysts in four types of reactions, these involves; C–C bond formation, C-O bond formation, C-Heteroatom bond formation, and miscellaneous reactions such as desymmetrization and hydrogenation.

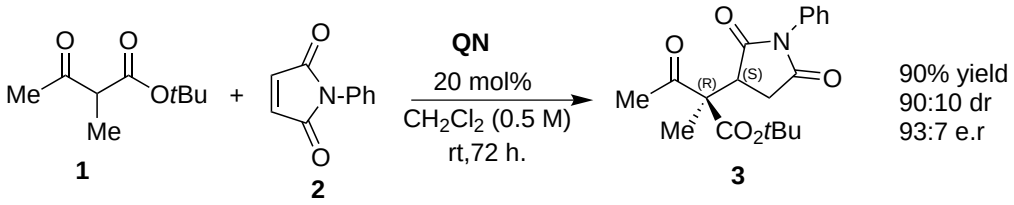
The use of bifunctional chiral catalysis, which are able to simultaneously bind and activate two reacting partners represents an efficient and reliable strategy for the stereoselective preparation of valuable chiral compounds.[6] To understand the general mechanistic study of bifuctionality, Cucinotta C. S. and coworkers explained the general mechanism of bifunctional catalysis with natural cinchona alkaloids in C–C bond formation Michael reaction by computational methods.[7]

In summary, the highly stereoselective one-step construction of such highly conjested product (having two adjacent stereogenic carbon atoms, one of which is quaternary by all carbon substitution) generally depends on the capability of the catalyst to effectively provide a series of specific interactions, generating a highly structured transition state (TS).

With the facts that, kinetic studies have established that the **QN**-catalyzed conjugate addition follows a first-order dependence on the catalyst, the nucleophilic, and the electrophilic, the experimental evidence showed that; (i) the influence of reaction media (either H-bond acceptor or donor solvent) affects the stereoselectivity and (ii) the cooperative mode of catalysis points to an efficient reactivity and selectivity of the cinchona catalyst.

Into consideration of conjugate Michael addition reaction in Scheme 2.1, the observed structure-reactivity and structure-stereoselectivity relationships are consistent with the notion that **QN** acts as an efficient bifunctional catalyst that exploits both the quinuclidine moiety and the OH group to simultaneously activate and orient the Michael donor and the acceptor by means of a network of H-bond interactions.

*Catalytic cycle description on conjugate addition:* The summary of the catalytic cycle




SCHEME 2.1: Quinine catalyzed direct conjugate addition between acyclic *tert*-butyl ketoester **1** and phenyl maleimide **2**.

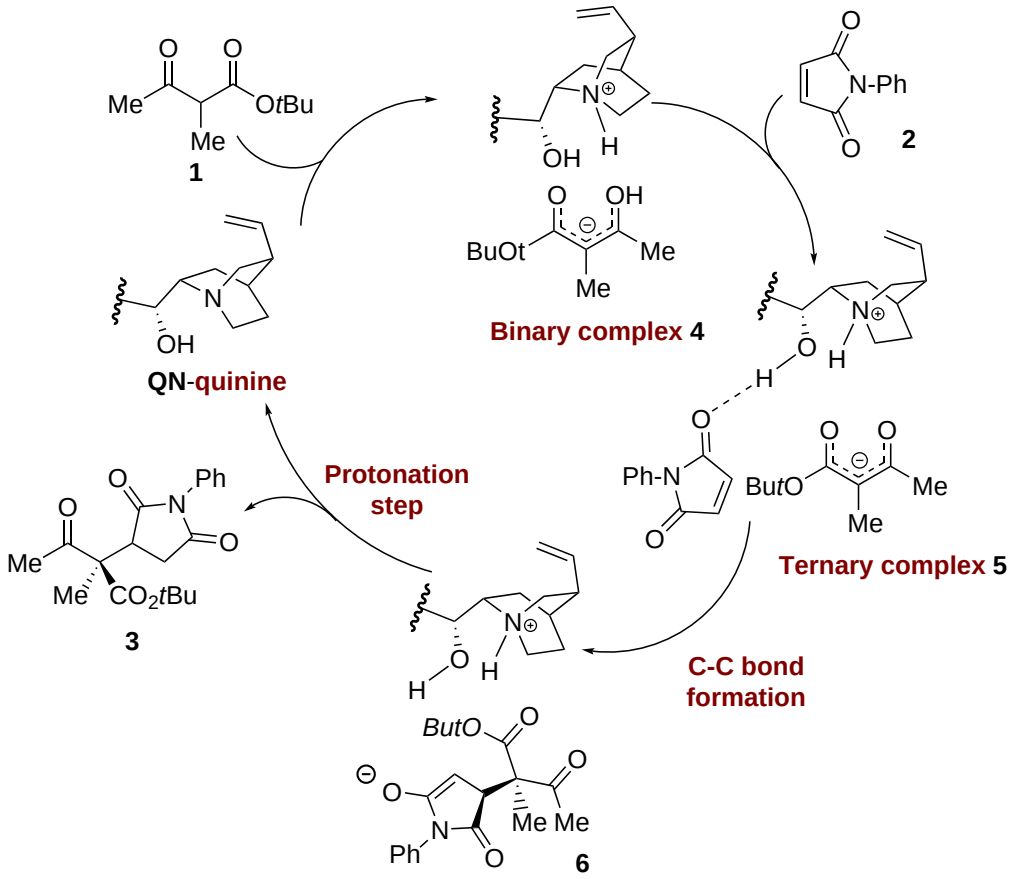



FIGURE 2.4: Cooperative catalysis in the quinine-catalyzed asymmetric conjugate addition.[7]

in the formation of **3** is described in Fig. 2.4, the deprotonation of **1** by the quinuclidine nitrogen, the most basic site in the catalyst, promptly occurs and leads to the formation of a chiral ion pair **4** (Fig. 2.4). The binary complex **4** is the reactive intermediate that can add to N-phenylmaleimide **2** in the rate- and selectivity-determining step, affording an enolate anion intermediate **6**; a subsequent, fast proton-transfer originates the 1,4-adduct **3** and regenerates the active catalyst **QN**. When the electrophilic maleimide **2** approaches this binary complex **4**, a noncovalent ternary complex **5** is likely formed, which can assume several conformations.

## 2.4 Cinchona derivatives as chiral organocatalysts

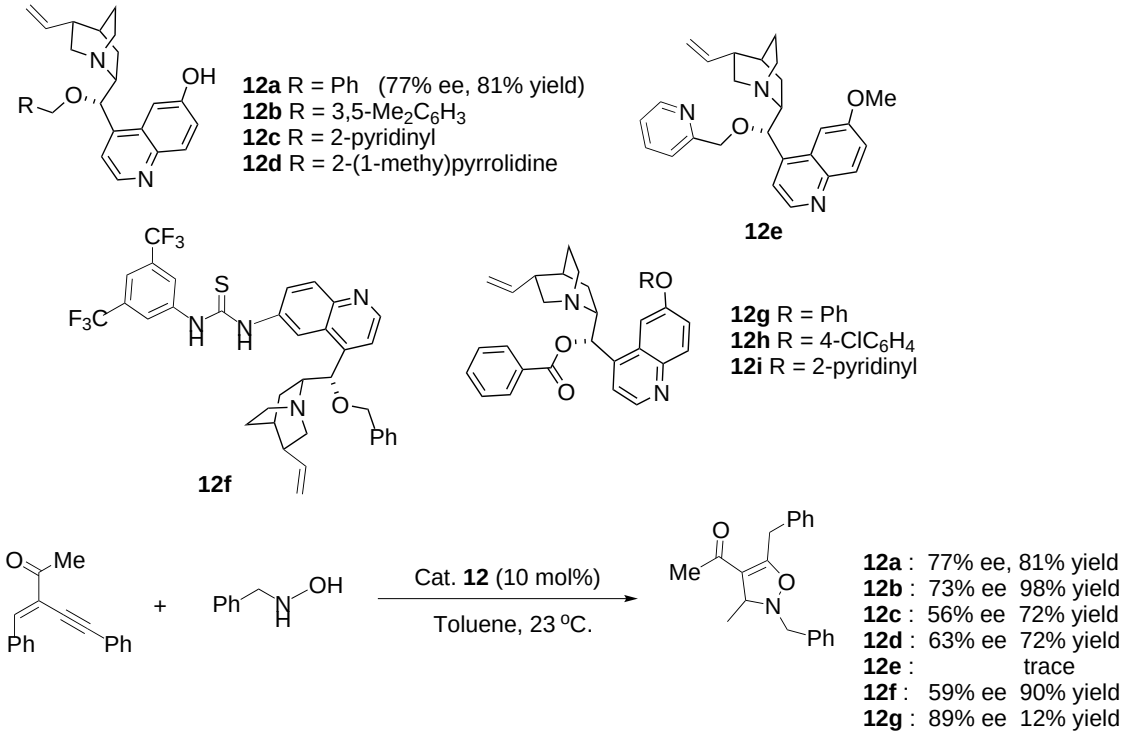
### 2.4.1 Monomeric cinchona derivatives

As a unique class of bifunctional cinchona organocatalysts, cupreines and cupreidines have been proved to be powerful chiral catalysts for a wide array of asymmetric transformations.[1–15] Compared to the traditional cinchona catalysts, one of the most noticeable features of cupreines and cupreidines is that they bear a phenolic OH group at C6' position, and a free hydroxy moiety at C9 position, which can be utilized to tune the steric conformation by further functionalization to achieve higher efficiency in asymmetric reactions.

This was confirmed by M. Shi with cowokers in their development of a highly efficient asymmetric Michael addition of anthrone to nitroalkenes with cinchona organocatalysts.[8] Quinine derivatives were used for the modifications of the effective organocatalysts. As shown in Scheme 1.4, both the free phenolic OH group at C6' position and the steric bulkiness and structure at C9 position in *O*-benzoylcupreine **4d** are crucial in the asymmetric Michael addition of anthrone to nitroalkenes catalyzed by cinchona alkaloid. O-benzoylcupreine gave the corresponding adducts in higher ee than those of catalysts without free phenolic OH group at C6' position or with rigid conformation at C9 position.

In this reaction, anthrone functions as a nucleophile rather than an active diene, exclusively affording the corresponding Michael addition products in up to 99% ee.[8] The dual organocatalysis have been applied successfully in different other reactions like Baylis-Hillman reaction, conjugate addition, electrophilic amination and nitroaldol reactions.[9] with other many examples in their applications including W. Li and coworkers who also reported on the multifuctionality of O-benzoylcupreidine **12g** derived from quinidine **QD** as chiral catalyst in asymmetric construction of 2,3-dihydroisoxazoles.[10]

The stereocontrolled Michael addition of $\alpha$, $\beta$-disubstituted system was reported several functionalized C6'-C9 quinidine derivatives were investigated and their catalytic performances based on their structural transformation have been analysed. The results have been summarized in Scheme 2.2, and they implied that the maltifunctionality constisting of an ester group, the basic heterocycle and hydroxyl group was crucial for catalytic activity and enantioselectivity.

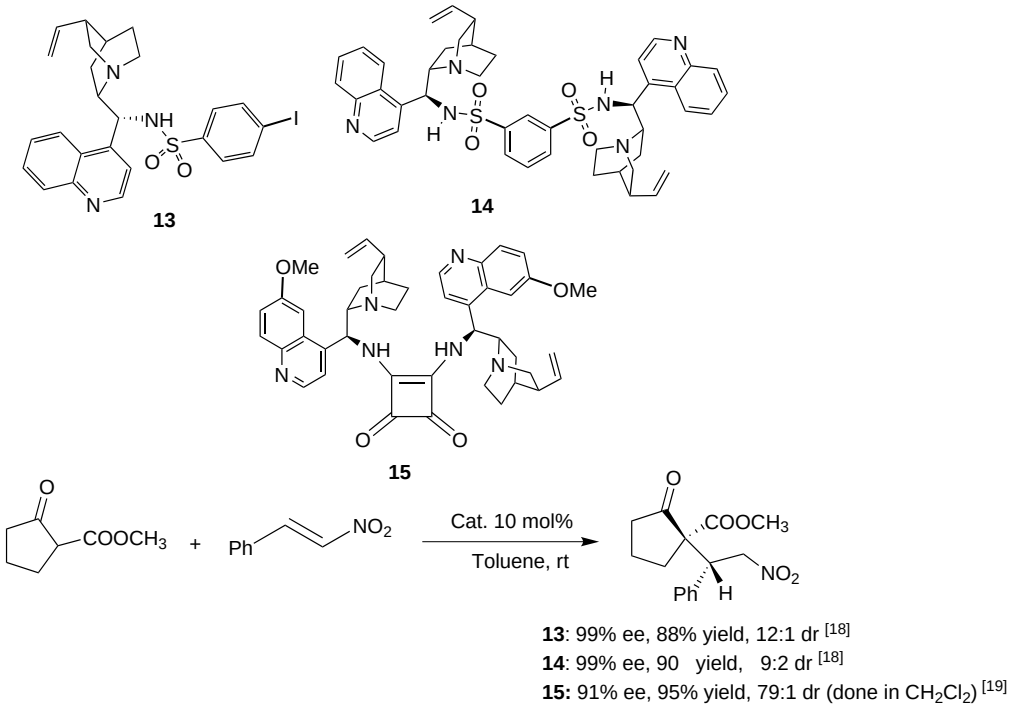



SCHEME 2.2: Asymmetric construction of 2,3-dihydroisoxazoles with monomeric cinchona derived organocatalysts.[9]

## 2.4.2 Dimeric cinchona alkaloids derivatives

Dimeric cinchona alkaloids are not isolated from any species but are products of designed partial chemical synthesis, the synthetic dimers found most use in the field of asymmetric synthesis.[11,15] Various synthetic routes exploit reactivity of the alkaloids at the N1, C3, C6' and C9. This availability of reactive sites, in combination with a plethora of linker molecules, contributes to the diversity of the products obtained. The transition from a monomeric to dimeric alkaloid molecule results in accumulation of functional groups confined within a limited space. Modifications of Cinchona alkaloids at the central 9-OH group and at the quinuclidine N1 atom led to the most effective dimeric catalysts and biologically active compounds.

*Dimers connected at the C9-position:* The C9-OH group offers an attractive site for modification (i.e. etherification and esterification reactions). Alternatively, the hydroxyl group can be replaced with a few other groups (e.g., $NH_2$) and subsequently used for dimerization. Starting with the work reported by Itsuno and coworkers, the C9-amino derivatives of cinchonidine **13**, **14** that were prepared by Mitsunobu-type azide formation, followed by Staudinger reduction.[15,16] These cinchona sulfonamide derivatives have been enantioselective effective for the asymmetric desymmetrization of cyclic anhydride[15]



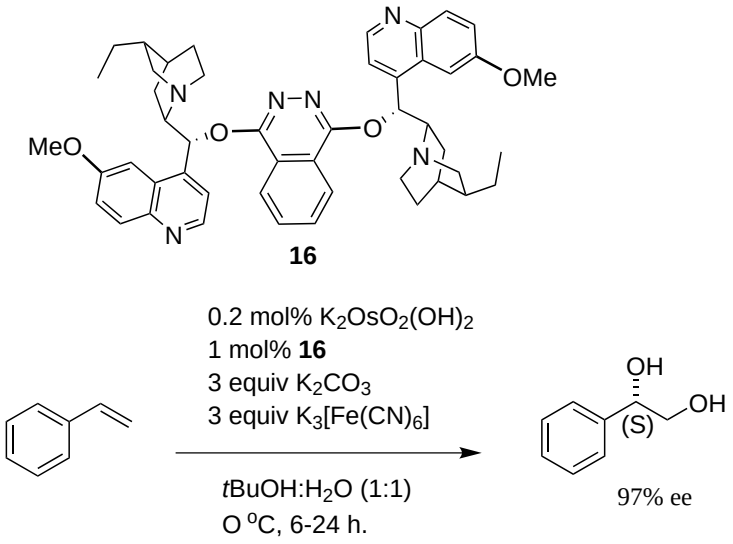

SCHEME 2.3: Asymmetric Michael addition of $\beta$-ketoester and $\beta$-nitrostyrene catalyzed by C9-amino derivatives of cinchona alkaloids.

as well as Michael addition of $\beta$- ketoester to $\beta$-nitrostyrene.[16] Scheme 2.3 shows the comparison between monomeric **13** and dimeric **14** cinchona sulfonamide derivatives catalysts in enantioselective synthesis of Michael addition $\beta$- ketoester to $\beta$-nitrostyrene.

In addition, C9 cinchona squaramide dimer **15** have been reported to be an effective chiral organocatalysts for the same asymmetric Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene.[17] The acidic NH of squaramide acts as H-bond donor and quinuclidine N1 acts as H-bond acceptor in the asymmetric Michael reaction (Scheme 2.3).

Synthesis of C9-dimeric alkaloid alkyl ethers involves the Williamson etherification of an alkali metal alkaloid salt and the respective alkyl dihalide. They have also been applied in different asymmetric reactions.[15] An example of C9-ether cinchona alkaloid dimer **16** have been presented for its use as catalyst in sharpless asymmetric dihydroxylation and enantioselectivity of 97% ee was achieved (Scheme 2.4).[15–19]

On the other hand, the C9 dimeric esters of cinchona alkaloid have also been involved in the asymmetric catalysis applications. The esters of dicarboxylic acids are most often used in the preparation of acid dichlorides. The transformation of alkaloid C9-ester dimer involves the use of a base (usually trimethylamine and sometimes with a catalytic amount of dimethylaminopyridine) and acids dichlorides. The dimers could also be obtained in a one-pot reaction, where by the starting diacids can be transformed to the corresponding

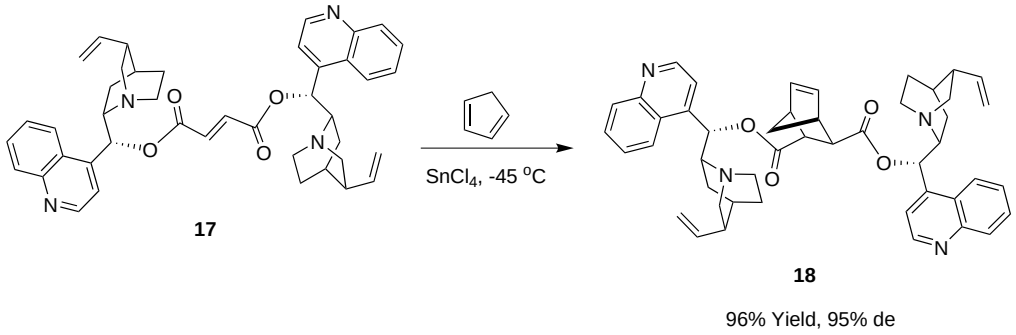



Scheme 2.4: Example of C9-cinchona ether derivative in asymmetric dihydroxylation of olefin.[15]

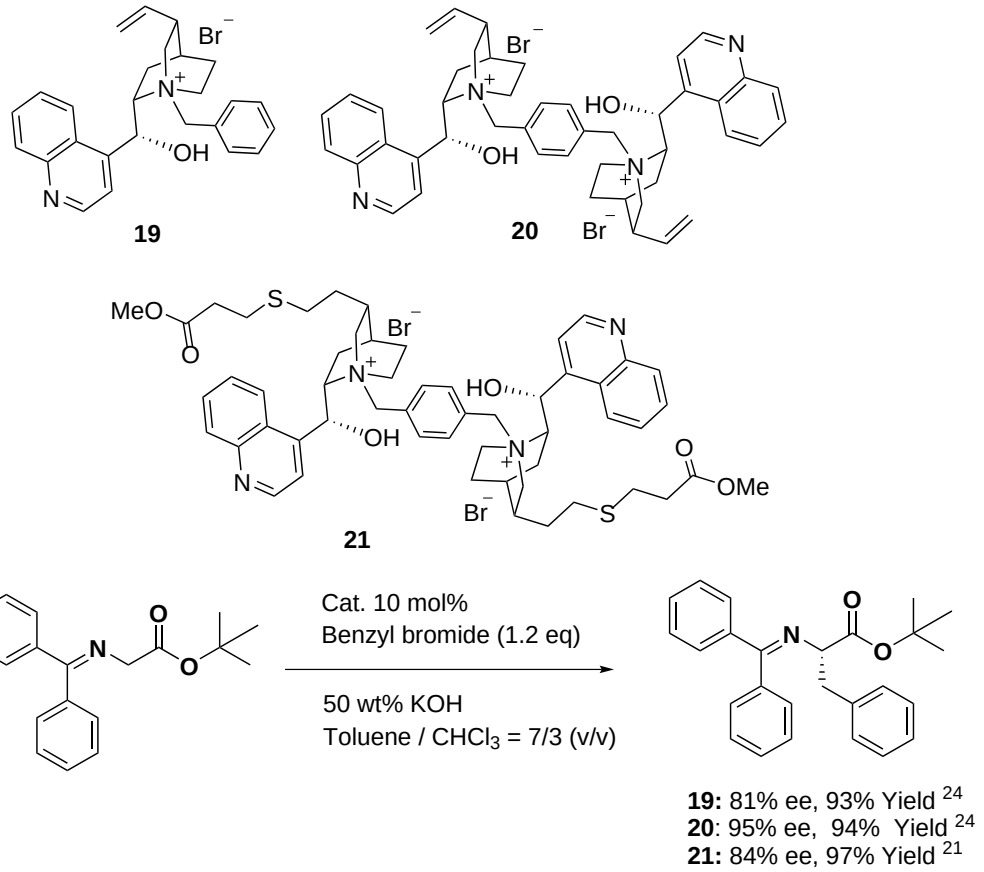
dichlorides with thionyl or oxalyl chloride and subsequently coupled with the alkaloids.[15] A few number of C9-cinchona ester dimers have been utilized in asymmetric reactions, the cinchona alkaloids could be used as chiral auxiliaries for the diels-alder reaction. Forexample Suzuki H. and coworkers have reported on the catalytic activity of dimeric ester **17** prepared from the reaction of cinchonidine and fumaroyl dichloride.[20] The reactivity of the activated double bond was further exploited in a Diels-Alder reaction with cyclopentadiene and isoprene. Consequently, a bicyclic dicarboxylic acid esters **18** was obtained with good diastereoselectivity of 95% de (Scheme 2.5).

Furthermore, N1-quartenary ammonium salts of cinchona alkaloids have been applied in different asymmetric reactions. Among them alkylations reactions are explored, asymmetric benzylation glycine tert-butyl ester have been reported to efficiently be catalyzed by quartenary ammonium salts of cinchona alkaloids in PTC reaction.[20–23] PTC is a catalyst which facilitates the migration of a reactant in a heterogeneous system from one phase into another phase where reaction can take place. Ionic reactants are often soluble in an aqueous phase but are insoluble in an organic phase unless the phase transfer catalyst is present.

In scheme 2.6 cinchona alkaloid ammonium salt catalysts **19**, **20**, **21** were evaluated in the alkylation reaction. The catalyst **20** showed enhancement in catalytic efficiency by the dimerization effect in comparison to monomeric catalyst **19** in the benzylation of glycine ester.




SCHEME 2.5: Example of C9-cinchona ester derivative in diastereoselective Diels-Alder reaction.[15,19]




SCHEME 2.6: N1-chiral quarternary ammonium salts in asymmetric benzylation of glycine ester.

### 2.4.3 Polymeric cinchona alkaloids derivatives

Cinchona alkaloids partly introduced in Chapter 1, offers a unique platform for new reactions and methodologies in chiral catalyst design including their application as polymer-immobilized catalysts as demonstrated in Scheme 1.8 and main-chain type polymers as

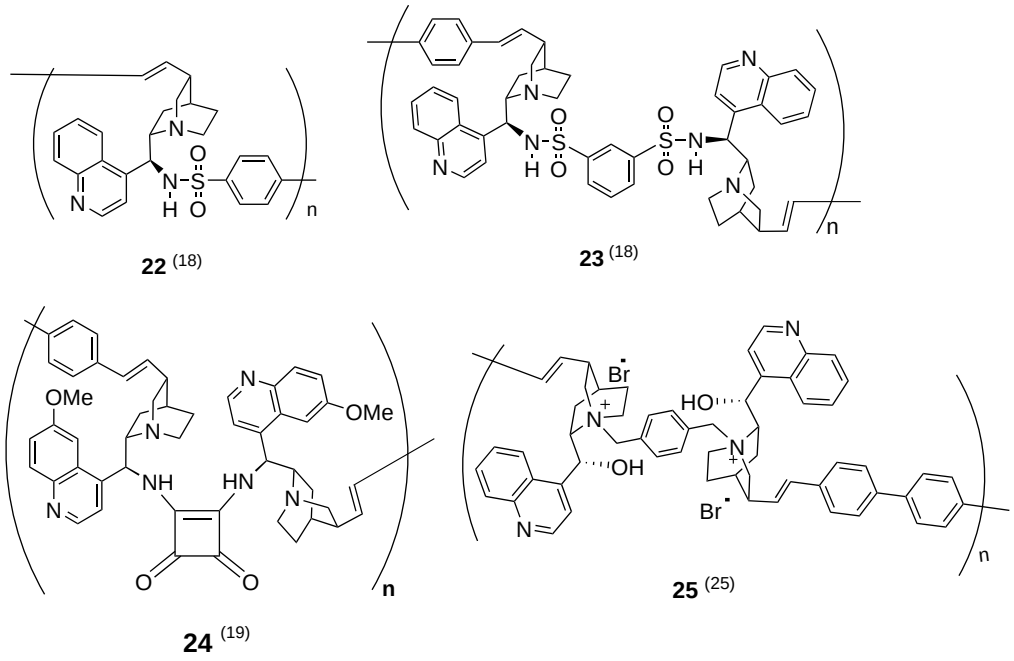
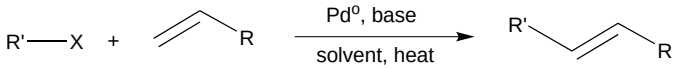



FIGURE 2.5: Main-chain type chiral polymers of cinchona alkaloid derivatives prepared by Mizoroki-Heck reaction.

per example shown in Scheme 1.11. Chiral polymeric catalysts including cinchona alkaloids polymeric catalyst in general has the advantage of easy separation from the reaction mixture and their recyclability. There are numbers of polymeric chiral catalyst derived from cinchona alkaloid that have been prepared through different methods such as MH polymerization method.[16–18,21,24–29] Fig. 2.5 shows the examples of non-ionic and ionic main-chain chiral polymers of cinchona alkaloids prepared by MH polymerization. These polymers were successfully applied for enantioselective synthesis in the asymmetric reactions.

Polymeric catalysts **22**, **23** and **24** in were used in the asymmetric Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene in Scheme 2.3 for their catalytic performance evaluations. They both showed good enantioselectivities with sufficient catalytic activities. The enantioselectivities of 97% ee ,90% ee, 97% ee and diastereoselectivity ratios of 5:1 dr, 6:1 dr, 28:1 dr and isolated yields of 58%, 98%, 71% were achieved with the polymeric catalysts **22**, **23** and **24** respectively in the formation of Michael adduct in Scheme 2.3. The chiral polymeric catalyst **25** were used in asymmetric alkylation reaction in Scheme 2.6. The polymer showed higher enantioselectivity of 94% ee and catalytic activity of 99% yield in the enantioselective benzylation of glycine ester. Comparative catalytic activity and enantioselectivity was observed with polymeric catalyst **25** to dimeric catalyst **20**.




SCHEME 2.7: General scheme for Mizoroki-Heck coupling reaction.

## 2.5 General introduction on synthesis methods

We have employed existing polymerization approaches for the polymerization of cinchona alkaloids derivatives. Mizorock-Heck and hydrosiylation reactions were used to prepare main-chain type chiral polymers of cinchona alkaloid and cross-linked gel-type chiral polymers of cinchona alkaloid, respectively. In Chapters 3 and 4, the MH polymerization method was used as the key synthetic method for polymerization, while in Chapter 5; the hydrosilylation reaction was the key synthetic method of polymerization. The synthesized polymers were then used as chiral catalysts in the asymmetric Michael addition reactions for their catalytic performances evaluation.

### 2.5.1 The Mizoroki-Heck reaction

The Mizoroki-Heck reaction, commonly known as the Heck reaction, is the palladium-catalysed addition of aryl, vinyl, or substituted vinyl groups to organic halides or triflates. The cross coupling reaction occurs between an aryl/alkenyl halide and a terminal olefin in the presence of a Pd(0) catalyst to produce a substituted olefin. In the early 1970s, Mizoroki T. and Heck R.F. 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.[30] Since its discovery, the Heck reaction has become one of the most widely used catalytic carbon-carbon bond forming tools in organic synthesis.

*The reaction mechanism:* The general mechanism involves the oxidative addition of the halide, migratory insertion (or carbometallation) of the olefin, and $\beta$-hydride elimination to form the product. The palladium(0) catalyst is then regenerated using a base in the reductive elimination step. Even though the mechanism of the Heck reaction is not fully understood and the exact mechanistic pathway appears to vary subtly with changing reaction conditions, Fig. 2.6 shows a simplified proposed sequence of events beginning with the generation of the active Pd(0) catalyst in correspondence to Scheme 2.7. The general characteristics features of the Heck reaction are;

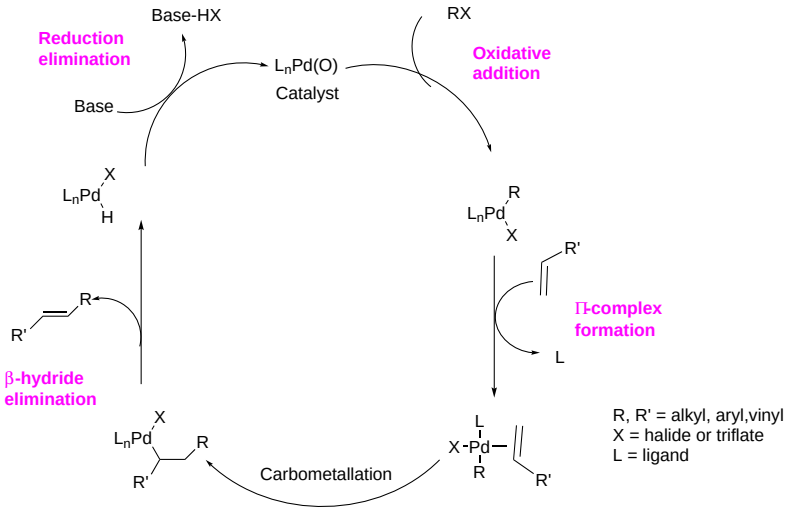



FIGURE 2.6: General mechanism of Mizoroki-Heck coupling reaction.[30]

i. It is the best reaction applied for the preparation of disubstituted olefins from mono-substituted ones.

ii. The reaction is highly functional group selective and high yielding.

iii. 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.

iv. 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.

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

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

vii. 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.

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

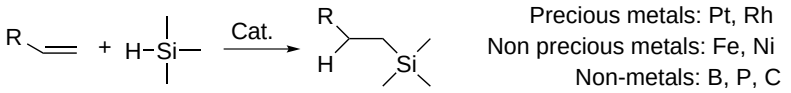
ix. Both migratory insertion and $\beta$-hydride elimination occur in *syn*-orientation to the palladium. This is important to understand the stereochemistry of the Heck reaction (especially in the cases involving the synthesis of fused ring systems).

Todate, Mizoroki-Heck reaction conditions have been optimized from lower molecular weights C–C bond forming reactions to a repetitive C–C bond forming reactions in polymerization technique. Being known as Mizoroki-Heck polymerization method', it has been successfully applied in the synthesis of several main-chain type polymers especially of cinchona alkaloids derivatives.[17,18,24,26–29] an example is described in Chapter 1 (Scheme 1.11). Generally, these polymers consist of cinchona alkaloid moiety in their main-chain as the repeating units. Another example was reported by Itsuno, S. and coworkers on the synthesis of cinchona alkaloid sulfonamide polymers **22**, **23**, in Fig. 2.5 through MH-polymerization technique. Their design involves the use of one component and two component polycondensation approaches. The cinchonidine-derived sulfonamide monomer **13** possessing both the olefinic double bond and aromatic iodide under the presence of Pd catalyst resulted into main-chain structure of cinchonidine sulfonamide polymer **22**, they called this as '*self-polycondensation technique*'.

On the other hand, they used cinchonidine sulfonamide dimer **14** with the two olefin double bonds and the aromatic diiodide (1,4-diiodobenzene) in the presence of Pd catalyst to obtain main-chain sulfonamide polymer **23**, they called this technique as '*two-component polycondensation*'.[17]

### 2.5.2 The hydrosiylation reaction

The hydrosilylation reaction, which enables the addition of silicon hydrides across C–C multiple bonds, is an efficient method for the formation of organosilicon compounds and represents one of the most important reactions in silicon chemistry.[31] The process is widely applied in industry to produce silane coupling agents and silicone polymers such as oils, rubbers and resins. The hydrosilylation reactions can also produce various organosilicon reagents, which are used in fine chemical synthesis for stereospecific oxidation, cross-coupling reactions,etc. There are three classes of catalysis that could be employed in hydrosiylation reaction, these includes; precious metals, non-precious metals and non-metals catalysis (Scheme 2.8)




SCHEME 2.8: General catalysis classification of hydrosilylation reaction.

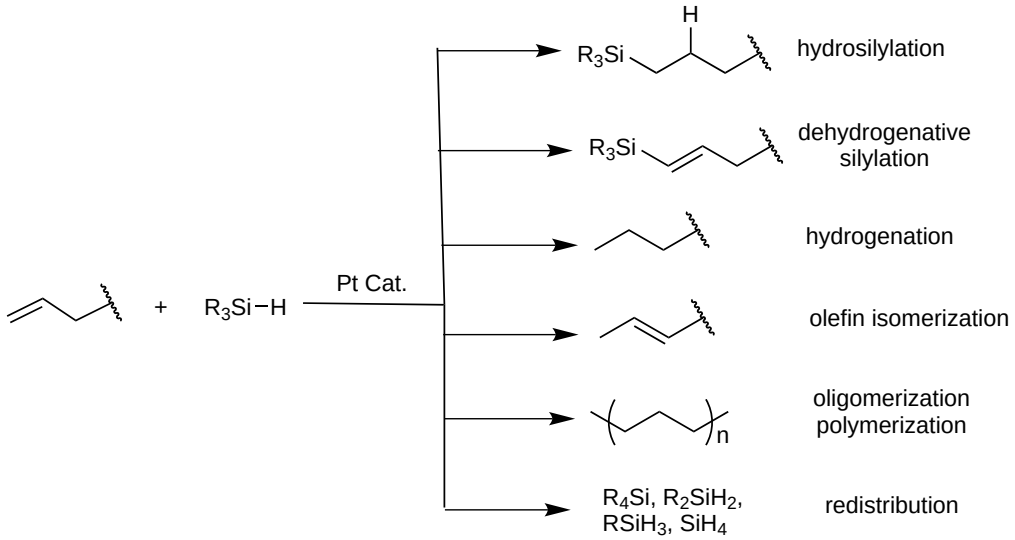



FIGURE 2.7: Possible reactions of olefin with hydrosilane in the presence of a Pt catalyst.

The first hydrosilylation reaction was reported in 1947 by Sommer in which trichlorosilane and 1-octene reacted in the presence of peroxide in a free-radical mechanism although the reaction selectivity was quite low. In the late 1950s, hexachloroplatinic acid $[H_2PtCl_6].H_2O$ was revealed to be a very effective homogeneous transition metal catalyst (Speier's catalyst), in which the selectivity was improved to a large extent. In 1973, Karstedt developed the platinum(0) complex containing vinyl-siloxane ligands (Karstedt's catalyst which exhibits extremely improved activity and selectivity as well as high solubility in polysiloxane compositions).

In spite of the high utility of the platinum-catalysed hydrosilylation reaction of olefins, the reaction process is often accompanied by side reactions mentioned in Fig. 2.7, these side reactions usually lead to significant yield losses of the desired product. Therefore, development of a well-designed catalytic system with higher selectivity and activity. General factors that influence the reactivity of hydrosiylation reaction involves; substrate, silane, transition metal catalyst, ligand, etc.

*The general reaction mechanism:* A well-known mechanism of metal catalyzed hydrosilylation is the Chalk-Harrod mechanism shown in Fig. 2.8. It proceeds through oxidative addition of the Si-H to the metal center and then alkene insertion to the metal hydride. Reductive elimination of Si-C then occurs and gives the final product and return

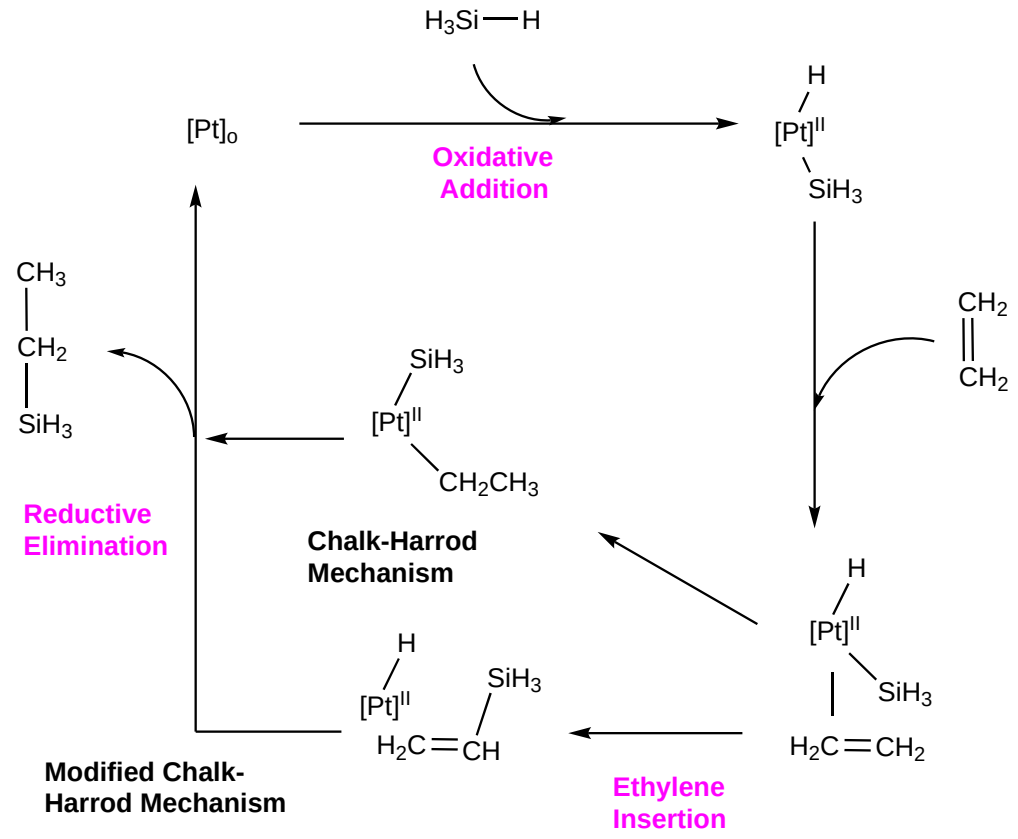



FIGURE 2.8: Hydrosilylation reaction mechanism for platinum catalysis as adopted by Chalk-Harrod.[32]

the metal to the original oxidation state.

Todate, Platinum or Rhodium catalyzed silicone-carbon bond formation in polycarbosilanes preparation have been known as a versatile synthetic method. However, over the reported polysiloxanes scaffolds for macromolecular reagent development, cinchona based polysiloxanes have not been prepared except for DeClue M. S. and Siegel J. S. who reported on the polysiloxane-bound ligand accelerated catalysis in a modular approach to heterogeneous and homogeneous macromolecular asymmetric dihydroxylation ligands.[33] They have demonstrated the feasibility of cinchona alkaloid derivatives to be immobilized in silicone oil scaffolds under Pt catalysis. We have also employed this approach for the preparation of cross-linked chiral polysiloxanes of cinchona alkaloid derivatives (Chapter 5).

### 2.5.3 Enantioselective synthesis

Enantioselective synthesis is the key process in modern chemistry and is particularly important in the field of pharmaceuticals, as the different enantiomers or diastereomers

of a molecule often have different biological activity. As explained in Section 2.3 of this chapter, cinchona alkaloids and their derivatives have been known as privileged class of chirality inducers. They have been applied over a several numbers of asymmetric reactions as catalysts. Amongst them, are C–C bond forming reactions such as; Alkylation, Aldo, Darzens, Michael addition, Diels-Alder, etc.[34] Focusing on Michael reaction or addition as the nucleophilic addition of a carbanion or another nucleophile to an $\alpha$, $\beta$-unsaturated carbonyl compound.

This type of Michael reaction belongs to the larger class of conjugate additions, and it is one of the most useful methods for the mild formation of C–C bonds. In addition, it has high functional groups tolerance and it is a widely applied reaction in synthetic polymerizations methods under favorable reactions rates.

Simply, the Michael addition involves the addition of a nucleophile, also called a Michael donor,' to an activated electrophilic olefin, the Michael acceptor', resulting in a Michael adduct'. The Michael adduct obtained can be chiral or achiral depending on the nature of the catalyst being used for the activation of the reacting substrates.

In this work, enantioselective synthesis is our focus point of interest. We have prepared chiral organocatalysts derived from cinchona alkaloids and use them as catalysts in the Michael addition reactions. There are many types of Michael additions reactions reported in literatures, however, considering the C–C bond forming Michael addition, an example of base catalyzed addition of ethyl acetoacetate to methy acryrate was demonstrate by Mather B. D. and coworkers and the general mechanism is as shown in Fig. 2.9. The acetoacetate is first deprotonated by the base, providing an enolate anion (Michael donor) in equilibrium. The enolate anion then reacts in a 1,4-conjugate addition to the olefin of the acrylate (Michael acceptor). The carbonyl of the acrylate stabilizes the resulting anion until proton transfer occurs, regenerating the base. The overall driving force for the conjugate addition is the enthalpic change that accompanies replacement of a $\pi$-bond with a $\delta$-bond. Thus, there is the preference for 1,4-addition over 1,2-addition.[35] General factors that can affects the Michael reaction mechanism involves; (i) Type of base catalyst (ii) Reacting substrates and (iii) Reaction solvent

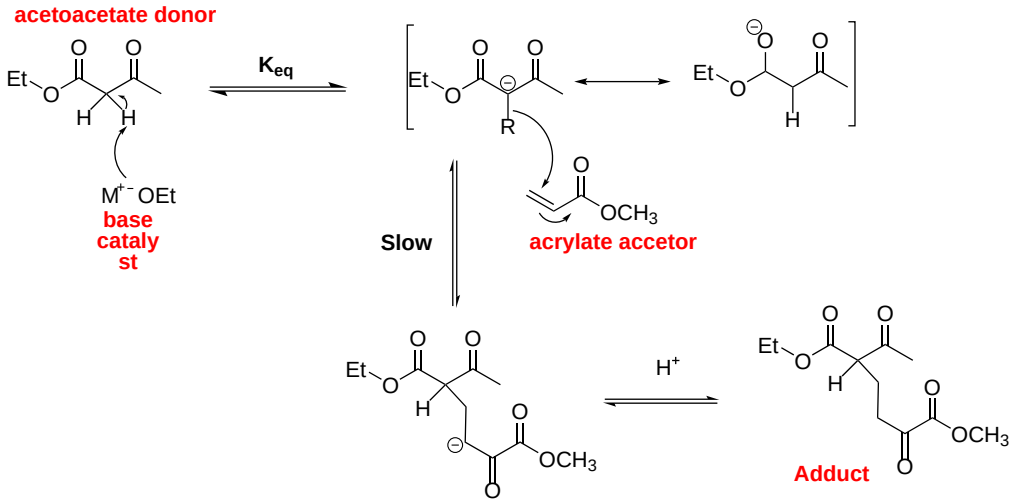



FIGURE 2.9: General mechanism for a base catalyzed Michael addition reaction.[36]

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# Chapter 3

# Synthesis of chiral polyesters of cinchona alkaloids for the enantioselective catalysis in the Michael addition of anthrone to nitroalkenes

Chiral polyesters of cinchona alkoloid derivatives were synthesized by means of repetitive Mizoroki-Heck (MH) coupling reaction. Under MH reaction condition, 4-iodobenzoylquinine and 4-iodobenzoylcuprein were easily polymerized by self polycondensation manner to give the corresponding chiral polyesters. Combination of cinchona ester dimer and aromatic diiodide were also polymerized by using repetitive MH reaction to give the chiral polyesters in two component polycondensation manner. The cinchona-based chiral polyesters prepared by MH polymerization were successfully used as polymeric organocatalysts in asymmetric Michael addition reaction. The chiral polyesters bearing free OH at the C6' position of the quinoline rings showed high catalytic activities and good enantioselectivities (up to 92 %) in the Michael addition of anthrone to nitroalkenes. The polymeric catalysts were stable enough to be recycled and reused for several times.

## 3.1 Introduction

Cinchona alkaloid has been recognized as one of the most important source for the various kinds of efficient chiral organocatalysts.[1,2] Each of cinchona alkaloids; quinine, cinchonidine, quinidine and, cinchonine contains several functionalities such as secondary alcohol, quinuclidine, and quinoline rings as well as vinyl group. These functionalities

can be exploited for various chemical modifications.[1–3] Various kinds of chiral organocatalysts have been developed and they have played a vital role in modern asymmetric catalysis.[3] Cinchona alkaloids and their derivatives are classified as privileged organic chirality inducers, efficiently catalyzing many classes of organic reactions in a highly enantioselective fashion.[4,5]

Cinchona alkaloids modified at C9-OH group,[1–9] quinuclidine nitrogen,[10–17] as well as C6' methoxy group[18–26] are among the most reported effective enantioselective catalysts. With the advancement in chemical synthesis methodologies, which promotes green chemistry practices, cinchona alkaloids offer a unique platform for new reactions and methodologies in chiral catalyst design including polymer-immobilized catalysts.[27–35] Recently, chiral polymeric catalysts have received much attention mainly due to their easy separation from the reaction mixture and their recycle uses.[5,6,31] Cinchona alkaloid derivatives have been attached to a variety of synthetic polymers,[28–30,32–34] which were used as chiral modifiers and chiral ligands in metal complex catalysts[36–38] and polymeric organocatalysts.[6,35,39–42]

While many heterogeneous reactions using polymeric catalysts suppress reactivity due to their heterogeneity, in some cases, well-designed polymeric chiral catalysts give higher selectivity with sufficient reactivity in asymmetric reactions.[43] Cinchona alkaloid C9 ester derivatives bearing free OH at their C6' position of the quinoline have been explored and successfully applied in many enantioselective reactions.[2,18–26,44]

Nevertheless, chiral polyesters having cinchona-based C6'-OH derivative as a repeating unit in their main-chain have not been reported yet. Design of such polymer synthesis is the most important issue to obtain efficient chiral polymer catalysts. Our design on chiral polyester synthesis involves the use of C3 olefinic double bond of the cinchona alkaloid. Mizoroki-Heck (MH) coupling reaction of aryl iodide represents one of the most effective palladium-catalyzed carbon-carbon bond forming processes.[43] Through the MH polymerization, we have previously synthesized several kinds of chiral polymers except for chiral polyesters.[33,35,39,40]

In this chapter we prepared chiral polyesters from cinchona alkaloid by means of MH polymerization. Repetitive MH reaction of iodophenyl ester of cinchona alkaloid may give the chiral polyesters. Another possible method to obtain similar chiral polyesters from cinchona alkaloid involves repetitive MH reaction between cinchona alkaloid ester dimers and diiodides. Herein, through MH polymerization, quinine was chosen as a starting cinchona alkaloid to synthesize main-chain type chiral polyesters bearing free

OH at the C6' position of the quinoline. The chiral polymers were obtained in good yield. The chiral polyesters were subsequently used as catalysts in asymmetric Michael addition of anthrone to nitroalkenes. Details on the synthesis of the chiral polyesters and their catalytic performance evaluations are discussed in this article.

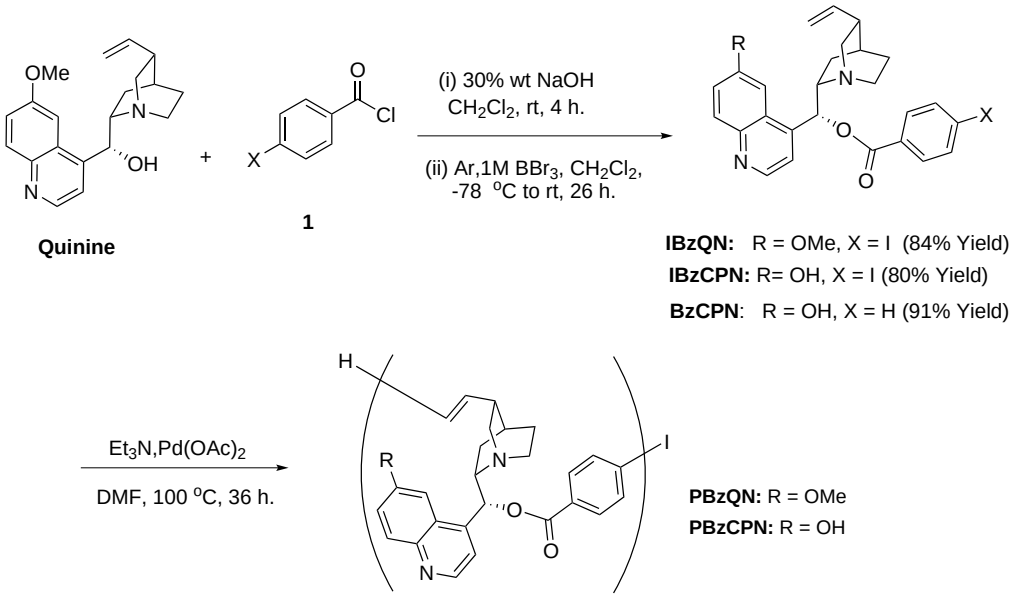
## 3.2 Results and Discussion

The quinine-based chiral polyesters bearing free OH at the C6' position of the quinoline ring were designed and synthesized. We prepared two different types of chiral polyesters. The first type was prepared by the one-component self-polycondensation method shown in Scheme 3.1. The Mizoroki-Heck (MH) reaction occurred between the olefinic double bond and the aromatic iodide. This reaction took place repeatedly on the monomer containing both olefinic double bond and aromatic iodide in its molecule.

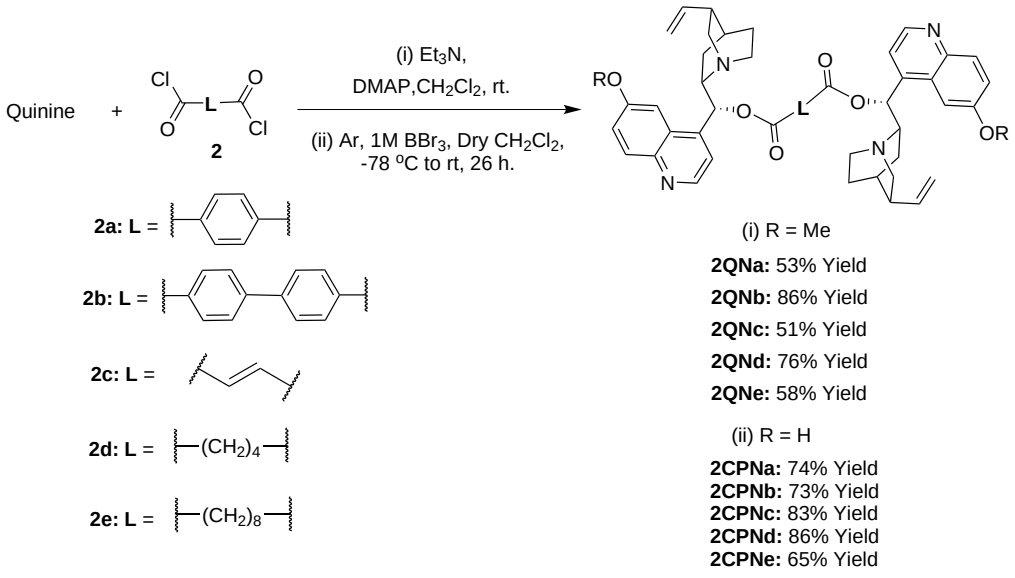
The second type of polyesters were prepared by the two-component polycondensation method. MH polycondensation between the cinchona ester dimers **2** (Scheme 3.2) and aromatic diiodide **3** yielded chiral polyesters as shown in Scheme 3.3. In order to confirm the importance of the C6'-OH group in the polymeric catalysts, we prepared polyesters with the C6'-OH groups **PCPN** and compared their catalytic performance with that of the C6'-OMe polyesters **PQN**. In case of polyesters prepared by two-component polycondensation, various kinds of ester linkers were introduced into the quinine ester dimer.

### 3.2.1 Preparation of quinine based chiral polyesters by one-component self-polycondensation

A monomer containing both olefinic double bond and aromatic iodide moieties can be polymerized through one-component self-polycondensation style polymerization. We prepared quinine derived ester monomers **IBZQN**, **IBzCPN** having iodophenyl group by esterification of quinine with 4-iodobenzoyl chloride (Scheme 3.1).[45,46] The monomer **IBZQN** was then subjected to boron tribromide in $CH_2Cl_2$ to give **IBzCPN** monomer having C6'-OH functionality. In the presence of Pd(OAc)2, repetitive MH reaction smoothly occurred on **IBZQN** and **IBzCPN** monomers in DMF to give the chiral polyesters **PBzQN** and **PBzCPN** respectively.[33,39,40] As shown in Table 3.1 (entries 1,2), one-component




SCHEME 3.1: Synthetic route for the preparation of main-chain chiral polyesters of cinchona alkaloid by one-component MH polymerization.

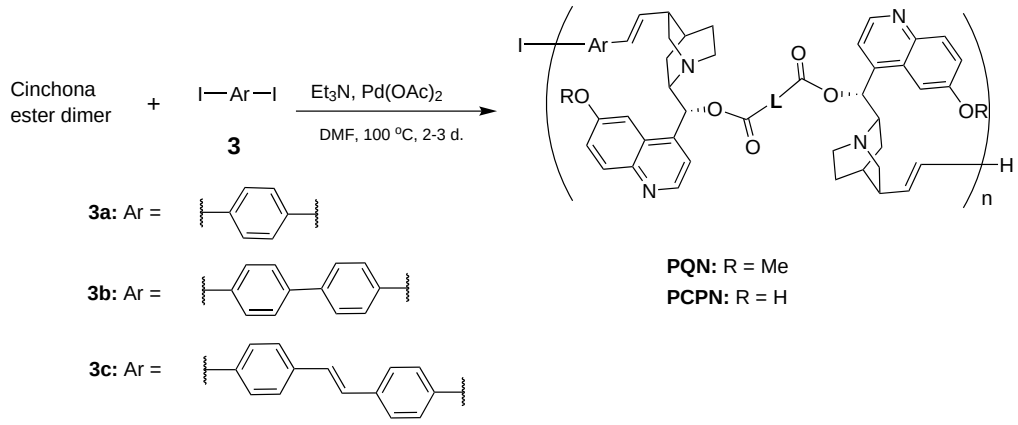



SCHEME 3.2: Preparation of quinine-derived ester dimers.

self-polycondensation smoothly occurred to give the corresponding polyesters having over 7000 molecular weight in good yield.

### 3.2.2 Preparation of quinine based chiral polyesters by two-component polycondensation

MH polymerization between quinine derived ester dimers **2QNa**, **2CPNa–2CPNe** and aromatic diiodides is another method to obtain cinchona based chiral polyesters. We first



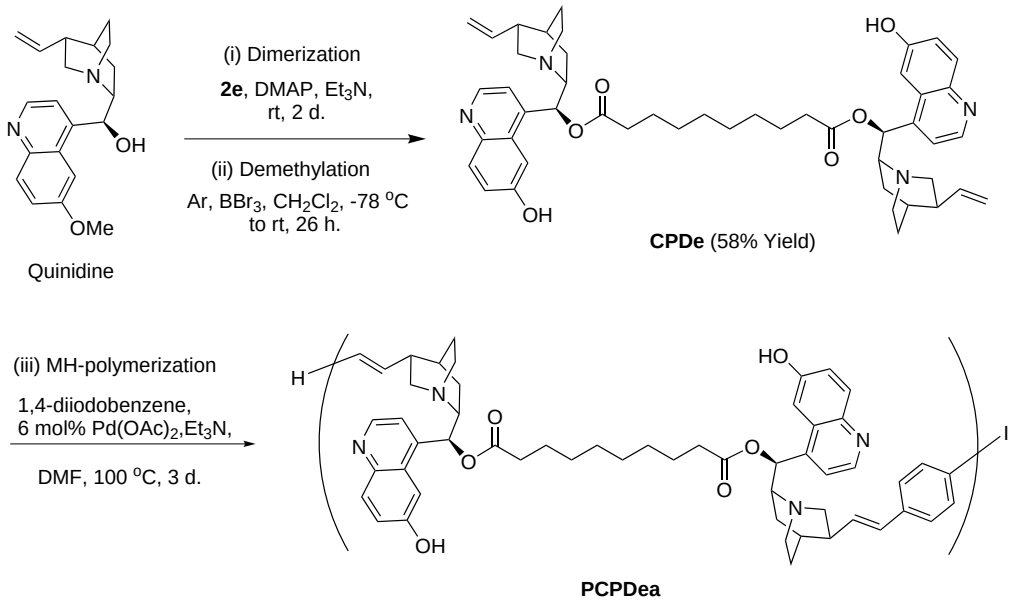

SCHEME 3.3: Preparation of main-chain cinchona based chiral polyesters **PQN** and **PCPN** by MH polymerization.

TABLE 3.1: Synthesis of chiral polyesters by MH coupling reaction[a].

| Entry | Dimeric compound | Diiodides (Ar) | Chiral Polyester | Time (h) | Yield (%) | $M_n^b$ | $M_w^b$ | $M_w/M_n$ |
|---|---|---|---|---|---|---|---|---|
| 1[c] | - | - | **PBzQN** | 36 | 93 | 7,400 | 11,400 | 1.5 |
| 2 | - | - | **PBzCPN** | 36 | 97 | 9,300 | 12,300 | 1.3 |
| 3[c] | **2QNa** | **3a** | **PQNaa** | 48 | 98 | 6,800 | 8,800 | 1.2 |
| 4 | **2CPNa** | **3a** | **PCPNaa** | 72 | 81 | 5,000 | 5,100 | 1.1 |
| 5 | **2CPNd** | **3a** | **PCPNda** | 72 | 74 | 5,400 | 6,000 | 1.1 |
| 6 | **2CPNb** | **3a** | **PCPNba** | 72 | 77 | 5,000 | 5,500 | 1.1 |
| 7 | **2CPNe** | **3a** | **PCPNea** | 72 | 98 | 7,000 | 8,100 | 1.2 |
| 8 | **2CPNc** | **3a** | **PCPNca** | 72 | 82 | 7,000 | 8,900 | 1.3 |
| 9 | **2CPNd** | **3c** | **PCPNdc** | 72 | 72 | -[d] | -[d] | -[d] |
| 10 | **2CPNe** | **3b** | **PCPNeb** | 72 | 98 | 9,700 | 22,300 | 2.3 |
| 11 | **2CPNe** | **3c** | **PCPNec** | 72 | 85 | -[d] | -[d] | -[d] |
| 12 | **2CPNa** | **3c** | **PCPNac** | 48 | 86 | 3,000 | 4,400 | 1.2 |
| 13[e] | **CPDe** | **3a** | **PCPDea** | 72 | 70 | 7,500 | 14,600 | 2 |

[a]Polymerized in dry DMF at 100 °C. [b]Determined by SEC (polystyrene standard) using DMF as an eluent at a flow rate of 0.1 mL $min^{-1}$ and 40 °C. [c]C6'-OMe chiral polyesters . [d]SEC measurements were failed due to their poor solubility in DMF. [e]Chiral polyester derived from quinidine linked by decanedioyl chloride **1e**.

prepared cinchona ester dimers 2QNa–2QNe as illustrated in Scheme 3.2. These dimers were prepared by using two equivalents of quinine with dicarboxylic acid dichlorides **1** based on the reported procedures.[47,48] We used various kinds of dicarboxylic acid dichlorides **1a–1e** in order to evaluate the effect of the linker structure on the catalytic performances of the chiral polyester organocatalysts **PQN**, **PCPN**. These cinchona ester dimers were then treated with boron tribromide in $CH_2Cl_2$ to give C6'-OH derivatives **2CPNa–2CPNe** in good yields. We also prepared another ester dimer **CPDe** having

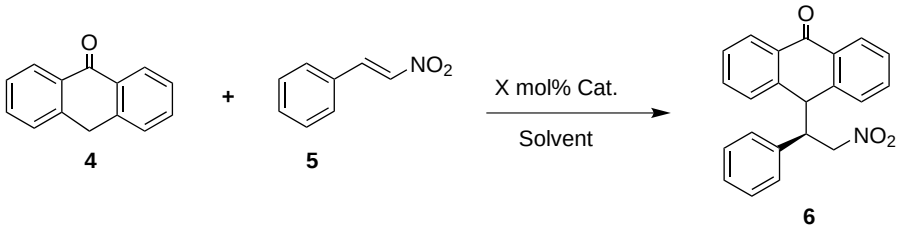



SCHEME 3.4: Synthetic route of chiral polyester **PCPDea** derived from quinidine.

C6'-OH from quinidine, which is pseudoenantiomer of quinine. The chemical structure of the dimer is presented in Scheme 3.4.

These cinchona ester dimers contain two olefinic double bonds in their molecule, which makes them possible to be polymerized with aromatic diiodides by two-component polycondensation process under MH reaction conditions. Cinchona ester dimer **2QNa** was allowed to react with 1,4-diiodobenzene **3a** in the presence of Pd catalyst in DMF. The MH polymerization smoothly occurred to give the polyester **PQN** in 98 % yield (Table 3.1, entry 3). Number average molecular weight of **PQN** was 6,800. The polymerization of C6'-OH dimers **2CPNa–2CPNe** were also proceeded under MH polymerization conditions to yield the corresponding polymers **PCPNa–PCPNe** in good yields (Scheme 3.3).

MH polymerization is relatively tolerant to functional groups including phenolic hydroxyl group of C6'-OH. Various combinations of cinchona ester dimers **2CPNa–2CPNe**, and aromatic diiodides **3** were chosen to prepare the corresponding chiral polyesters (Scheme 3.3). The MH polymerization results of two-component polycondensation system are summarized in Table 3.1 (entries 3-13). In all cases, the chiral polyesters **PCPN** were successfully obtained in high yields (from 70 % to 98 %). These polymers were all insoluble in commonly used organic solvents such as ether, ethylacetate, acetonitrile, toluene and THF. Most of them are soluble in polar aprotic solvents including DMF and DMSO. Due to the poor solubility of the chiral polyesters **PCPNdc** and **PCPNec**, attempts




SCHEME 3.5: Asymmetric Michael addition of anthrone **4** to $\beta$-nitrostyrene **5** in the presence of chiral organocatalysts.

of SEC measurement of these polymers were failed (Table 3.1, entries 9, 11).

### 3.2.3 Asymmetric Michael addition of anthrone and $\beta$-nitrostyrene with monomeric and dimeric cinchona derived ester catalysts

Shi et al. reported the asymmetric Michael addition of anthrone and $\beta$-nitrostyrene in the presence of O-benzoyl cuprein **BzCPN** as a catalyst to give the Michael adduct in 94 % yield with 96 % ee at −40 °C (Table 3.2, entry 1).[45] We examined the catalytic capability of the ester monomers **IBZQN**, **IBzCPN** and dimers **2QNa**, **2CPNa–2CPNe** and **CPDe** in the same asymmetric transformation of anthrone and $\beta$-nitrostyrene (Scheme 3.5). The results of the asymmetric reaction are summarized in Table 3.2. Although **IBZQN** having OMe at the C6' position gave very low enantioselectivity in the Michael reaction (entry 2), C6'-OH derivative **IBzCPN** showed almost the same capability as **BzCPN**.

In case of the dimeric catalysts, similar catalytic performances were observed. C6'-OMe dimer **2QNa** gave the product in low enantioselectivity (entry 4) while C6'-OH dimers **2CPNa–2CPNe** showed high level of enantioselectivities in all cases (entries 5–9). In the cases of **2CPNb** and **2CPNd** they both gave 98 % ee in the same reaction. When dimer **2CPNd** and monomer **IBzCPN** were used as catalyst at −50 °C, the achieved enantioselectivity of **10** was lower as compared to when the reaction was done at −40 °C (entries, 11, 12 vs entries 3, 8 respectively). Dimer **CPDe** was prepared from quinidine, which is pseudoenantiomer of quinine. When this dimer was used as a catalyst in the same reaction, chiral product having opposite enantiomer compared to those obtained by using quinine-derived catalysts was predominantly obtained (entry 10).

TABLE 3.2: Monomeric and dimeric effect of cinchona derived ester catalysts in the Michael addition of anthrone to $\beta$-nitrostyrene[a].

| Entry | Chiral Cat. | (T) °C | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | **BzCPN** | −40 | 12 | 94 | 96 |
| 2[e] | **IBzQN** | rt | 24 | 58 | 9 |
| 3 | **IBzCPN** | −40 | 16 | 89 | 94 |
| 4[e] | **2QNa** | rt | 24 | 80 | 11 |
| 5 | **2CPNa** | −40 | 24 | 75 | 94 |
| 6 | **2CPNb** | −40 | 24 | 69 | 98 |
| 7 | **2CPNc** | −40 | 24 | 81 | 94 |
| 8 | **2CPNd** | −40 | 24 | 79 | 98 |
| 9 | **2CPNe** | −40 | 24 | 69 | 90 |
| 10[f] | **CPDe** | rt | 24 | 97 | 90 |
| 11 | **2CPNd** | 50 | 3 | 92 | 90 |
| 12 | **IBzCPN** | 50 | 3 | 95 | 86 |

[a]Entries 2–9; Reactions were done by anthrone **4** (0.48 mmol), $\beta$-nitrostyrene **5** (0.40 mmol) with 10 mol % of quinine derived catalysts in $CH_2Cl_2$ (3.0 mL) while, entries 11–12; 15 mol % of the catalyst was used for the formation of **6** with (*R*) configuration.[45] [b]Isolated yield of the product. [c]The enantiomeric excess (ee) values determined by HPLC-Chiralcel AS-H with Hexane/IPA = 5/1 as eluent at a flow rate of 0.7 mL/min. [d]Reference data with 5 mol% catalyst loading of **BzCPN** at −40 °C as reported in literature.[45] [e]C6' OMe group quinine derived ester dimer. [f]Reaction done by anthrone **4** (0.24 mmol), $\beta$-nitrostyrene **4** (0.20 mmol) with 15 mol % of C6'-OH cupreidine ester dimer **CPDe** as a catalyst in $CH_2Cl_2$ (2.0 mL) in the formation of **6** with (*S*) configuration.

### 3.2.4 Asymmetric Michael addition of anthrone and $\beta$-nitrostyrene with chiral polyester catalysts

In order to evaluate the catalytic performance of the chiral polyesters **PBzQN**, **PBzCPN**, **PQN** and, **PCPN** derived from quinine, we used the polymers as organocatalysts in asymmetric Michael addition reaction (Scheme 3.5). We first used the chiral polyester **PBzQN** as a polymeric organocatalyst prepared by one-component self-polycondensation. Although the insoluble polymeric catalyst gave heterogeneous condition, asymmetric Michael addition of anthrone **4** and $\beta$-nitrostyrene **5** smoothly occurred to give the corresponding Michael adduct **6** in 61 % yield with 33 % ee (Table 3.3, entry 1).

In case of **PBzCPN** having C6'-OH as a catalyst, higher enantioselectivity (88 % ee) was obtained as expected from the results obtained with low molecular weight catalysts. Next, a series of chiral polyesters **PQN**, **PCPN** prepared by two-component

TABLE 3.3: Cinchona based chiral polyester catalysts screening for the formation of **6** in the Michael addition of anthrone to $\beta$-nitrostyrene[a].

| Entry | Chiral Cat. | (T) °C | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | **PBzQN** | rt | 36 | 61 | 33 |
| 2 | **PBzCPN** | −40 | 48 | 75 | 88 |
| 3[d] | **PQNaa** | rt | 40 | 62 | 11 |
| 4 | **PCPNaa** | −40 | 84 | 50 | 79 |
| 5 | **PCPNda** | −40 | 72 | 61 | 80 |
| 6 | **PCPNba** | −40 | 72 | 52 | 90 |
| 7 | **PCPNba** | rt | 24 | 73 | 79 |
| 8 | **PCPNea** | −40 | 48 | 73 | 88 |
| 9 | **PCPNea** | rt | 40 | 84 | 90 |
| 10 | **PCPNca** | −40 | 48 | 67 | 71 |
| 11 | **PCPNdc** | −40 | 72 | 51 | 92 |
| 12 | **PCPNdc** | rt | 20 | 85 | 86 |
| 13 | **PCPNeb** | rt | 40 | 85 | 88 |
| 14 | **PCPNec** | rt | 40 | 85 | 84 |
| 15 | **PCPNac** | rt | 48 | 63 | 70 |
| 16[d] | **PCPDea** | rt | 48 | 78 | 82 |

[a]Reactions were done with anthrone **4** (0.48 mmol or 0.24 mmol), nitroalkene **5** (0.40 mmol or 0.20 mmol) and with 10 mol % or 15 mol % polymeric catalyst loading in $CH_2Cl_2$ (3 mL or 2.0 mL) under the specified reaction temperature and time for the formation of **6** with

(*R*)

configuration.[45] [b]Isolated yield of the product. [c]The enantiomeric excess (ee) values determined by HPLC -Chiralcel AS-H with Hexane/IPA = 5/1 as eluent at a flow rate of 0.7 mL/min. [d]C6' OMe group chiral polymeric catalyst was used in the formation of **6**((*R*)). [e]C6'-OH quinidine derived polymeric catalyst was used in the formation of **6** with

(*R*)

configuration.

MH-polycondensation was used as catalysts for the same reaction; the results were summarized in Table 3.3.

The polyester **PQNaa** containing C6'-OMe catalyzed the asymmetric reaction to give **6** with 11 % ee (entry 3). When the chiral polyesters **PCPN** containing C6'-OH were used as catalysts, the asymmetric Michael reaction occurred under heterogeneous condition to give **6** with much higher enantioselectivities (from 70 % ee–92 % ee, entries 4–16). Compared with the results obtained by using the corresponding dimeric catalysts 2CPN, somewhat lower enantioselectivites were obtained with the polymeric catalysts.

Among the screened polymeric organocatalysts, C6'-OH chiral polyesters, **PCPNba**,

TABLE 3.4: Effect of solvent in the Michael addition of anthrone to $\beta$-nitrostyrene in the formation of **6** with **PCPNea** as a catalyst[a].

| Entry | Solvent | Time (h) | Yield[c] (%) | ee[d] (%) |
|---|---|---|---|---|
| 1 | EtOH | 96 | 48 | 82 |
| 2 | Acetone | 70 | 44 | 80 |
| 3 | EtOAc | 96 | 29 | 84 |
| 4 | $Et_2O$ | 96 | 51 | 90 |
| 5 | $CH_2Cl_2$ | 48 | 73 | 88 |
| 6 | Toluene | 96 | 34 | 16 |
| 7 | Hexane | 70 | 25 | 86 |
| 8 | $CH_3CN$ | 72 | 51 | 88 |
| 9 | THF | 96 | 67 | 90 |

[a]All reactions were carried out with anthrone **4** (0.48 mmol), $\beta$-nitrostyrene **5** (0.40 mmol) and 10 mol % catalyst loading at −40 °C for the specified time in the formation of **6** with (*R*) configuration. [b]Conversion percentage calculated by $^1$H NMR. [c]Isolated yield of the product. [d]The enantiomeric excess (ee) values determined by HPLC-Chiralcel AS-H with Hexane/IPA = 5/1 as eluent at a flow rate of 0.7 mL/min.

**PCPNea**, **PCPNdc**, and **PCPNeb** showed good enantioselectivities (88 % ee–92 % ee, entries 6, 8, 9, 11, and 13) with good yields. Due to the heterogeneity of the polymeric catalysts, longer reaction time was required for some cases (entries 4–6, 11). Among the evaluated chiral polyesters shown in Table 3.3, the linearly spaced chiral polyesters **PCPNea**, **PCPNdc**, **PCPNeb** and, **PCPNec** showed good performance in terms of their catalytic activity and enantioselectivitiy in the formation of Michael product **6** when the reaction was done at room temperature (entries 9, 12–14). In addition, **PCPDea** prepared from quinidine dimer **CPDe** (Scheme 3.4) showed good enantioselectivity with chiral product having opposite enantiomer (Table 3.3, entry 16).

We then surveyed the effect of solvent on the catalytic performance of chiral polyester by using **PCPNea**. The results of asymmetric Michael reaction with **PCPNea** were summarized in Table 3.4. The chiral polyesters are tolerant to various kinds of solvents. For all selected solvents except for toluene, the enantioselectivities achieved in the formation of **6** were above 80 % ee. In toluene as a reaction media, only poor enantioselectivity (16 % ee) was obtained (Table 3.4, entry 6).

We next examined the temperature effect on the catalytic activity of the polymeric catalyst **PCPNea** in the asymmetric Michael reaction. Interestingly, enantioselectivities obtained showed no significant changes between −40 °C to 50 °C as shown in Table 3.5. Higher temperature required relatively shorter reaction time to complete the reaction

TABLE 3.5: Reaction condition optimizations for the Michael addition of anthrone to $\beta$-nitrostyrene in the formation of **6** with **PCPNea** as a catalyst[a].

| Entry | Catalyst mol % | T °C | Time (h) | Yield[b] (%) | ee[c](%) |
|---|---|---|---|---|---|
| 1 | 10 | −40 | 48 | 68 | 88 |
| 2 | 20 | −40 | 48 | 79 | 88 |
| 3 | 20 | −20 | 48 | 69 | 86 |
| 4 | 5 | RT | 24 | 55 | 84 |
| 5 | 10 | RT | 24 | 68 | 84 |
| 6 | 15 | RT | 24 | 88 | 90 |
| 7 | 20 | RT | 24 | 97 | 86 |
| 8 | 15 | 50 | 12 | 87 | 88 |

[a]All reactions were carried out with anthrone **4** (0.24 mml), $\beta$-nitrostyrene **5** (0.20 mmol) in $CH_2Cl_2$ (2.0 mL) under specified reaction conditions in the formation of **6** with (*R*) configuration. [b]Isolated yield of the product. [c]The enantiomeric excess values determined by HPLC (Chiralcel AS-H with Hexane/IPA = 5/1 as eluent at a flow rate of 0.7 mL $min^{-1}$.

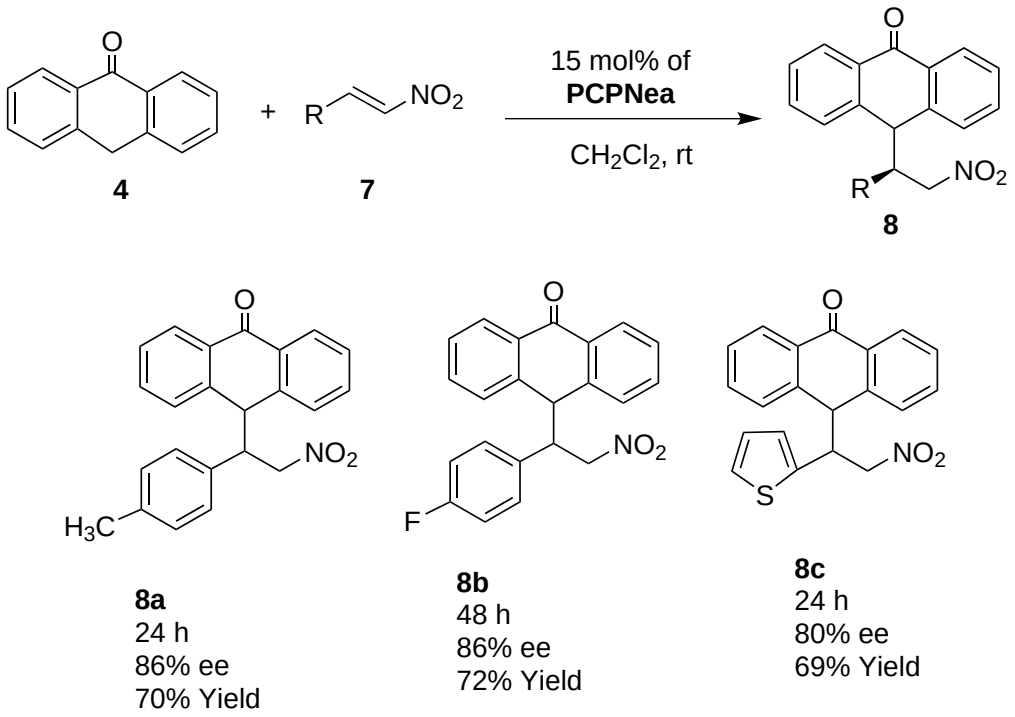
(entry, 8). The catalyst loading from 5 mol % to 20 mol % also caused no significant effect on the enantioselectivity (entries, 4–7).

### 3.2.5 Substrate scope evaluation

With the use of the optimized reaction conditions, the performance of the chiral polyester **PCPNea** was evaluated by changing the Michael acceptor substituents **7** in the asymmetric Michael reaction presented in Scheme 3.6. The aryl nitroalkene derivatives bearing electron withdrawing or electron donating substituents on the benzene ring, showed higher enantioselectivities and good catalytic activity in the formation of the corresponding Michael adducts **8a** and **8b**. In addition, the thiophene derived nitroalkene also showed good enantioselectivity as well as catalytic activity when it was used as an acceptor in the Michael reaction for the formation of **8c**. The structural configuration of these Michael products were not determined.

### 3.2.6 Recyclability evaluation of chiral polyesters

With the fact that all synthesized chiral polyesters were insoluble in varieties of common solvents. Recovery of the polymeric catalyst after completion of the reaction was possible. To confirm the recyclability of the polyester catalyst, **PCPNdb** was used as a catalyst (Scheme 3.5). In order to compare the stability of the catalyst, the reaction was




SCHEME 3.6: Substrate scope of asymmetric Michael addition of **4** to nitro alkene derivatives **7** with **PCPNea** as a catalyst.

performed at room temperature as well as under reflux condition in dichloromethane. Under reflux condition, **PCPNdb** performed well to complete the asymmetric Michael reaction within 5h. After completion of the reaction in each cycle, the catalyst was separated by centrifugation and reused in the next cycle. The results on the enantioselectivity and catalytic activity of **PCPNdb** are summarized in Table 3.6. The catalyst showed no loss on its enantioselective or activity property in both reaction conditions and it could be used up to three cycles.

TABLE 3.6: Recyclability evaluation with **PCPNeb** as a catalyst in the formation of **6**[a].

| Entry | Cycle no. | Reaction Temperature | | | |
|---|---|---|---|---|---|
| | | rt | | 50 (°C) | |
| | | Yield[b] (%) | ee[c] (%) | Yield[b] (%) | ee[c] (%) |
| 1 | Initial | 85 | 88 | 80 | 88 |
| 2 | First | 80 | 86 | 82 | 90 |
| 3 | Second | 79 | 84 | 85 | 86 |
| 4 | Third | 80 | 84 | 75 | 85 |

[a]All reactions were carried out with **4** (0.72 mmol), **5** (0.60 mmol) and 15 mol % catalyst loading for 24 h at room temperature and 5 h at 50 oC in $CH_2Cl_2$ for the formation of **6** with (*R*) configuration.[45] [b]Isolated yield of **6**. [c]Determined by HPLC (chiralcel AS-H with Hexane/IPA = 5/1 as eluent at a flow rate of 0.7 mL $min^{-1}$.

## 3.3 Conclusion

Main-chain cinchona based chiral polyesters bearing free OH at the C6' position of the quinoline, were successfully synthesized by MH polymerization method with good isolated yields. The chiral polyesters were used as catalysts in the enantioselective Michael addition of anthrone to nitroalkenes. The chiral polyesters showed higher catalytic activities and good enantioselectivities (up to 92 % ee) when used as organocatalysts in the Michael reaction. The catalytic activities of the polymeric catalysts were also affected by the type of linker used in the preparation of the chiral polyesters. It was found that the linearly spaced cinchona polymeric catalysts were catalytically effective compared to aromatic linked chiral polyesters in the formation of Michael product **6**. The linearly spaced chiral polyesters **PCPNea** and **PCPNeb** showed good stability when subjected under either reflux or relatively low reaction temperature, without affecting its enantioselective and catalytic activity property.

On the other hand, low molecular weight catalyst showed somewhat lower enantioselectivity when subjected under reflux condition as compared to lower reaction temperature. The chiral polyesters were easily recovered from the reaction mixture and could be used up to three times without loss in the catalytic activity and enantioselectivity. The notable features in the evaluation of the main-chain cinchona based chiral polyester as catalysts for the Michael addition of anthrone to nitro alkenes were; high catalytic activity and enantioselectivity, recyclability and stability.

## 3.4 Experimental Part

### 3.4.1 General methods and materials

All solvents and reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., and Tokyo Chemical Industry Co., Ltd. at the highest available purity and were used as received, unless otherwise stated. Analytical thin-layer chromatography (TLC) was conducted using pre-coated silica gel plates (Merck TLC silica gel, 60F254) for monitoring the reaction progress. Column chromatography was performed using silica gel columns (Wakogel C-200, 100–200 mesh). Melting points (mp) were recorded with a Yanaco micro melting apparatus and the average values of the analyzed samples were recorded. Optical rotation was determined using a JASCO DIP-149 digital polarimeter and 10 cm-long thermostated microcell. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in $CDCl_3$ or $DMSO-d_6$ at room temperature operating at 400 MHz ($^1H$) and 100 MHz ($^{13}C\{^1H\}$). Tetramethylsilane (TMS) was used as an internal standard for $^1H$ NMR and $^{13}C$ NMR in $CDCl_3$. Chemical shifts and J values are reported in parts per million (ppm) and hertz (Hz), respectively. The IR spectra were recorded on a JEOL JIR-7000 FTIR spectrometer by using KBr pellets and the wavenumbers are reported in $cm^{-1}$. HRMS (ESI) spectra were recorded using a Bruker micro OTOF II HRMS instrument. High-performance liquid chromatography (HPLC) was performed with a JASCO HPLC system composed of a DG-980-50 three-line degasser, the Intelligent HPLC pump (PU 2080), and a UV/Vis detector (UV-2075). The instrument was equipped with a chiral column (Chiralpak AS-H, Daicel) and hexane/2-propanol were used as the eluent at a flow rate of 0.7 mL $min^{-1}$ at room temperature. Size exclusion chromatography (SEC) was performed using a Tosoh instrument with either HLC 8020 UV (254 nm) or refractive index detection. Two polystyrene gel columns of bead size 10 mm were used and dimethylformamide (DMF) was used as the carrier solvent with a flow rate of 1.0 mL/min at 40 °C. A calibration curve was obtained to determine the number-average molecular weight ($M_n$) and molecular weight distribution ($M_w/M_n$) in comparison with polystyrene standards.

### 3.4.2 Synthesis of cinchona ester monomer IBzQN

A typical synthetic procedure as reported in literature was employed.[40] To a stirred solution of quinine (1.00 g, 3.086 mmol) in anhydrous $CH_2Cl_2$ (20 mL), 4-iodobenzoyl

chloride (0.93 g, 3.500 mmol) and a 30% w/w NaOH aqueous solution (4.3 mL) were added sequentially at room temperature. The mixture was stirred vigorously for 4 h, as reaction completion was confirmed by TLC (EtOAc:$Et_3N$ = 50:1). Subsequently, $H_2O$ (15 mL) and $CH_2Cl_2$ (10 mL) were added simultaneously to the reaction mixture. The two layers were separated and the aqueous layer was extracted by $CH_2Cl_2$. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography with EtOAc:$Et_3N$ = 50:1 as an eluent mixture to afford **IBzQN** as white solid (1.44 g, 84% yield); mp: 198.0 °C–199.7 °C; $[\alpha]_D^{30}$ = +166.17 (c 1.0, DMF); $^1$H NMR ($CDCl_3$, TMS, 400 MHz,) $\delta_H$ = 1.50–1.60 (m, 2H), 1.70–1.80 (m, 2H), 2.10–2.18 (m, 1H), 2.31 (br, 1H), 2.59 (m, 4H), 2.50–2.54 (m, 1H), 2.91–2.97 (m, 1H), 3.25 (br, 1H), 3.59–3.63 (m, 1H), 4.05 (2, 3H), 5.08–5.15 (t, 2H), 6.04–6.13 (m, 1H), 6.6 (d, J = 8.86 Hz, 1H), 7.51–7.55 (dd, J = 2.75, 1H), 7.65–7.70 (m, 2H), 7.8 (m, 2H), 7.90 (d, J = 1.83 Hz, 1H), 8.00–8.10 (m, 3H), 8.6–8.7 (d, J = 4.58 Hz, 1H). $^{13}$C NMR ($CDCl_3$, TMS = 77.16, 400 MHz) $\delta_C$ = 8.1, 24.3, 27.7, 28.0, 39.7, 42.6, 42.8, 55.7, 56.8, 59.5, 74.8, 101.5, 114.7, 118.7, 122.0, 127.0, 129.3, 131.1, 132.0, 138.1, 141.7, 143.5, 144.9, 147.5, 158.1, 165.2. IR (KBr) $\nu_{max}$ [cm$^{-1}$]: 3057 (C–$H_{arom}$), 1721 (C=O), 1459 (C=Carom), 1261 (C–O). HRMS (ESI) $m/z$ for $C_{27}H_{27}IN_2O_3$ [$M^+H^+$] calcd. 555.1139, found 555.1066.

### 3.4.3 Synthesis of cinchona ester dimer 2QNb

A slightly modified synthetic procedure for the dimeric compounds with aromatic dicarboxylic linkers was employed.[42] To a solution of quinine (3.00 g, 9.259 mmol) in 25 mL of anhydrous $CH_2Cl_2$ at 0 °C, 4.3 mL of $Et_3N$ was added and the mixture was stirred for 10 min. Next, powdered 4,4'-biphenyl dicarbonyl chloride **2b** was added portion wise and the solution was stirred for 1 h at 0 °C. The mixture was cooled to room temperature and stirred for 5 h. Upon reaction completion, water (25 mL) was added and the organic layer was separated from the aqueous layer, washed with $NH_4Cl$ aqueous solution, extracted by $CH_2Cl_2$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc:EtOH:$Et_3N$ = 7:3:0.5 as the eluent to afford **2QNb** as a white solid (4.00 g, 51% yield); mp: 218.6 °C–220.2 °C; $[\alpha]_D^{31}$ = +222.63 (c 1.0, DMF); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 1.02–1.07 (m), 1.14–1.19 (m), 1.68–1.83 (m), 1.97–1.98 (br, s), 2.47–2.51 (m), 2.82–2.89 (m), 3.88–3.89 (br, s), 3.92–3.96 (m), 4.91–4.97 (m), 4.98–4.99 (m), 5.04–5.07 (m), 5.74 (br, s), 5.95

(br, s), 5.97–5.99 (d, J = 2.44 Hz), 6.00 (br, s), 6.01–6.03 (d, J = 2.44 Hz), 6.54–6.58 (d, J = 8.54 Hz), 7.36–7.39, (dd, J = 2.75 Hz), 7.41–7.45 (dd, J = 2.75 Hz), 7.49–7.50 (d, J = 3.97 Hz), 7.58–7.62 (dd, J = 4.58), 8.14–8.17 (d, J = 8.24), 8.66–8.67 (d, J = 4.58 Hz), 8.66–8.70 (d, J = 4.58). $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta_C$ = 11.7, 11.8, 22.1, 24.5, 27.9, 28.0, 28.1, 28.2, 40.0, 40.2, 42.9, 43.4, 46.5, 55.9, 56.0, 57.0, 57.2, 59.7, 60.3, 72.2, 74.9, 77.2, 77.3, 77.6, 77.8, 101.5, 101.7, 114.7, 114.8, 118.9, 121.8, 122.2, 126.98, 127.2, 127.8, 129.7, 130.6, 132.1, 142.0, 143.9, 145.0, 145.0, 147.7, 147.8, 147.9, 158.3, 165.5. IR (KBr) $\nu_{max}$ [cm$^{-1}$]: 3073 (C–$H_{arom}$), 1720 (C=O), 1508 (C=$C_{arom}$), 1264 (C–O). HRMS (ESI) $m/z$ for $C_{54}H_{54}N_4O_6$ [$M^+H^+$] calcd. 855.4116, found 855.4106.

### 3.4.4 Synthesis of cinchona ester dimer 2QNe

The typical literature procedure for the synthesis of dimers with linear spacers was slightly modified.[42] To a solution of quinine (2.00 g, 6.173 mmol) in 20 mL of anhydrous $CH_2Cl_2$, 0.5 equivalents of decanedioyl chloride **2e** and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added sequentially. After 2 d of vigorous stirring, 2 mL of triethylamine was added to the mixture. After further 2 h of stirring, the solvent was removed in vacuo and the residue was further dried in a vacuum oven at 40 °C for 1 d without further purification. **2QNe** was obtained as a solid orange (3.95 g, 76% yield); mp: 67.2 °C–68.5 °C. $[\alpha]_D^{31}$ = –10.75 (c 1.0, DMF); $^1$H NMR ($CDCl_3$, TMS, 400 MHz) $\delta_H$ = 0.81–0.84 (m), 1.1–1.29 (m), 1.49–1.56 (m), 1.49–1.56 (m), 1.68–1.74 (m), 1.81–1.84 (m), 2.17–2.36 (m), 2.87–2.91 (m), 3.00–3.10 (m), 3.30–3.40 (m), 3.94 (s), 4.96–5.01 (m), 5.73–5.85 (m), 6.48–6.50 (d, J = 6.71 Hz), 7.22–7.43 (m), 7.98–8.00 (d, J = 9.16 Hz), 8.66–8.71 (d, J = 4.58 Hz). $^{13}$C NMR ($CDCl_3$, TMS = 77.16, 400 MHz) $\delta_C$ = 0.2, 9.4, 12.2, 24.3, 24.9, 27.7, 27.8, 29.1, 29.3, 29.4, 34.5, 35.7, 37.3, 39.3, 39.7, 42.5, 42.6, 45.6, 55.6, 55.9, 56.0, 56.6, 58.2, 58.9, 59.1, 73.6, 73.7, 77.5, 77.6, 101.6, 106.7, 114.8, 118.8, 119.0, 122.1, 127.1, 131.8, 141.7, 143.9, 144.8, 147.5, 158.2, 172.8, 172.9, 178.4. IR (KBr) $\nu_{max}$ [cm$^{-1}$]: 3074 (C–$H_{arom}$), 1740 (C=O), 1508 (C=$C_{arom}$), 1228 (C–O). HRMS (ESI) $m/z$ for $C_{50}H_{62}N_4O_6$ [$M^+H^+$] calcd. 815.4742, found 815.4717.

### 3.4.5 Synthesis of C6'-OH free cinchona ester derivatives

As reported from literatures, the preparation of C6' OH-free compounds procedure was slightly modified.[40,48] A representative procedure for **2CPNe** is described: Under argon atmosphere, **2QNe** (1.80 g, 2.209 mmol) was dissolved in dry $CH_2Cl_2$ (25 mL) and

stirred at −78 °C for 15 min. Next, 35 mL of 1 M boron tribromide solution in $CH_2Cl_2$ was added slowly over 10 min and the mixture was stirred vigorously for 2 h. It was then cooled to room temperature and allowed to stir for 24 h. Subsequently, water (20 mL) and 10% w/w NaOH aq. solution (40 mL) were added carefully and simultaneously to the reaction mixture. The solution pH was adjusted to ≈ 12. The organic phase was separated and the aqueous phase was neutralized by 2 N HCl aq. solution to pH ≈ 8. The aqueous phase was extracted several times using $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain **2CPNe** as an orange solid (1.40 g, 86% yield); mp 183.2 °C–184.3 °C. $[\alpha]_D^{31}$ = –17.18 (c 1.0, DMF); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.76–0.79 (m), 1.15–1.90 (m), 1.40–1.50 (m), 2.32–2.44 (m), 4.97–5.20 (m), 5.83–5.92 (m), 6.23–6.35 (m), 7.30–7.50 (m), 7.87–7.97 (m), 8.60–8.62 (d, J = 4.27 Hz), 10.10 (br, s).$^{13}$C NMR (DMSO-d6, 100 MHz) $\delta_C$ = 7.8, 9.0, 24.3, 24.6, 24.8, 26.3, 27.1, 27.2, 27.3, 28.6, 28.8, 33.9, 34.0, 38.9, 42.6, 46.1, 49.5, 55.3, 55.3, 58.8, 105.1, 119.0, 122.1, 131.7, 143.6, 146.9, 156.2, 172.5. IR (KBr) $\nu_{max}$ [$cm^{-1}$]; 3356 (O–H), 3072 (C–$H_{arom}$), 1726 (C=O), 1618 (C=$C_{arom}$), 1241 (C–O). HRMS (ESI) $m/z$ for $C_{48}H_{58}IN_4O_6$ [$M^+H^+$] calcd. 788.4465, found 788.4456. Other C6'-OH free cinchona ester derivatives were synthesized and characterized in the same way.

**IBzCPN** was obtained as orange solid product (1.80 g, 80% yield). m.p found 196.5 °C–200.1 °C. $[\alpha]_D^{30}$ = +84.73 (c 1.0, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 1.60-1.66 (m, 2H), 2.45–2.47 (m, 5H), 2.78–2.85 (m, 1H), 3.40–3.50 (m, 1H), 4.92–5.00 (m, 2H), 5.86–5.96 (m, 1H), 6.35–6.38 (d, J = 7.93 Hz), 6.50 (br,s, 1H), 7.20–7.30 (m, 1H), 7.45–7.46 (d, J = 4.58 Hz, 1H), 7.49–7.50 (d, J = 2.14 Hz, 1H), 7.74–7.79 (m, 3H), 7.83–7.85 (m, 1H), 8.54–8.58 (m, 2H), 10.03 (br,s 1H). $^{13}$C NMR (DMSO-d6, 100 MHz) $\delta_C$ = 24.41, 24.44, 26.86, 26.98, 38.58, 38.79, 39.85, 41.37, 55.69, 58.96, 74.89, 102.24, 104.18, 114.08, 121.37, 126.57, 128.32, 130.69, 131.03, 131.25, 137.64, 141.95, 142.93, 146.33,155.42, 164.44. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3446 (OH), 2940 ($CH_{arom}$), 1723 (C=O), 1585 (C=$C_{arom}$), 1098 (C−O). HRMS (ESI) calc'd $m/z$ for $C_{27}H_{27}IN_2O_3$ [$M^+H^+$] requires 541.0943, found 541.0984.

**2CPNa** was obtained as orange solid product (0.55 g, 74% Yield). m.p found 230.73 °C–234.5 °C. $[\alpha]_D^{29}$ = +16.37 (c 0.61, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.74-0.8 (m), 1.15–1.21 (m), 1.35 (s), 1.55–1.73 (m), 1.99 (s), 4.00–4.06 (q), 4.93–5.07 (m), 5.21–5.33 (br, s), 5.74–5.89 (m), 6.42–6.50 (d, J = 7.02 Hz), 7.25–7.35 (m), 7.44–7.55 (m), 7.83–7.91 (m), 8.09–8.33 (m), 8.60–8.64 (d, J = 4.27 Hz), 10.07–10.24 (br,s). $^1$3C

NMR (DMSO-$d_6$, 400 MHz) $\delta_C$ = 14.61, 21.29, 27.72, 27.81, 42.62, 60.28, 60.37, 60.49, 105.44, 115.14, 119.28, 119.42, 121.77, 127.47, 130.41, 131.68, 131.90, 142.80, 143.68, 147.14, 155.93. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3356 (OH), 2941 ($CH_{arom}$), 1726 (C=O), 1509 (C=$C_{arom}$), 1099 (C−O). HRMS (ESI) calcd $m/z$ for $C_{46}H_{46}IN_4O_6$ [$M^+H^+$]: 751.3490, found: Not determined, **2CPNa** was insoluble in either acetonitrile, isopropanol or ultrapure water used for analysis.

**2CPNb** was obtained as yellowish solid product (0.88 g, 83% Yield). m.p found 256.3 °C–258.2 °C. $[\alpha]_D^{31}$ = +173.35 (c 1.0, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$= 0.76-0.80 (m), 1.40–2.02 (m), 2.22–2.32 (br,s), 3.13 (s), 4.95–5.09 (m), 5.87–5.96 (m), 6.42–6.54 (br,s), 7.30–7.37 (m), 7.50–7.56 (m), 7.82–7.91 (m), 8.01–8.04 (d, J = 8.24 Hz), 8.15–8.17 (d, J = 7.93 Hz), 8.59–8.60 (d, J = 4.27 Hz), 10.12 (s). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) failed due to poor solubility of **2CPNb** in DMSO-$d_6$. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3421 (OH), 2940 ($CH_{arom}$), 1720 (C=O), 1512(C=$C_{arom}$), 1264(C−O). HRMS (ESI) calcd $m/z$ for $C_{52}H_{50}IN_4O_6$ [$M^+H^+$] requires 826.3730, found: Not determined due to poor solubility of **2CPNb** in either acetonitrile, isopropanol or ultrapure water used for analysis.

**2CPNc** was obtained as brown solid (1.40 g, 86% Yield). m.p no decomposition of the product was seen up to 390 °C. $[\alpha]_D^{29}$ = +5.61 (c 0.67, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$= 0.90–0.94 (m), 1.03–1.05 (ss), 1.39–1.50 (m), 1.60–1.80 (m), 2.2 (br, s), 2.37–2.5 (m), 2.80–2.88 (m), 2.90–3.10 (m), 4.91–5.01 (m), 5.02–5.03 (br, s), 5.08–5.14 (m), 5.58–5.57 (d, J = 4.58 Hz), 5.80–5.97 (m), 6.24–6.29 (m), 6.6 (br, s), 6.90–6.93 (m), 7.25–7.33 (m), 7.40–7.45 (m), 7.83–7.89 (m), 8.58–8.60 (m), 10.10 (br, s). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta_C$ 10, 14, 21, 22, 26,31, 42, 47, 56, 60, 61, 71, 92, 97, 107, 114, 120, 131, 136, 139, 142, 143, 147, 165, 170, 173. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3357 (OH), 3023 ($CH_{arom}$), 1731 (C=O), 1486 (C=$C_{arom}$), 1131(C−O). HRMS (ESI) calcd $m/z$ for $C_{42}H_{44}IN_4O_6$ [$M^+H^+$] requires 700.3261, found: measurement failed due to poor solubility of **2CPNc** was in either acetonitrile, isopropanol or ultrapure.

**2CPNd** was obtained as orange solid product (1.10 g, 73% Yield). m.p found 197.96 °C–200.5 °C. $[\alpha]_D^{28}$= –19.61 (c 1.0, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$= 0.76-0.81 (m), 1.15 –1.20 (m), 1.39–1.7 (m), 1.78 (br, s), 2.13–2.18 (m), 2.3 (br, s), 3.05–3.15 (m), 4.28–4.38 (m), 4.90–5.07 (m), 5.71 (br, s), 5.81–5.92 (m), 6.2–6.34 (m), 6.5 (s), 7.33–7.72 (m), 7.86–7.91 (m), 8.59–8.61 (d, J = 4.27 Hz), 10.00 (br, s). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta_C$= 7.93, 9.11, 12.15, 24.09, 25.50, 27.45, 33.69, 39.58, 39.79, 40.41, 55.42, 55.75, 58.10, 58.86, 69.24, 73.17, 73.34, 98.59, 105.05, 105.28, 118.88,

119.19, 121.93, 122.23, 127.17, 131.80, 141.76, 142.41, 143.68, 147.08, 156.33, 172.50. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3421 (OH), 2940 ($CH_{arom}$), 1741 (C=O), 1469 ($C{=}C_{arom}$), 1231 (C−O). HRMS (ESI) calcd $m/z$ for $C_{44}H_{50}IN_4O_6$ $[M^+H^+]$ requires 731.3730, found 731.3803.

**Dimer CPD** was obtained as orange solid (1.21 g, 50% Yield). m.p found 198.5 °C–203.6 °C. $[\alpha]_D^{31}$ = +166.17 (c 1.0, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$= 0.86–0.90 (m), 1.08–1.20 (m), 1.40–1.60 (m), 1.78–1.82 (m), 2.30–2.40 (m), 3.05–3.11 (q), 5.06–5.23 (m), 5.89 (br), 5.98–6.07 (m), 6.34–6.40 (m), 6.5 (br), 7.32–7.46 (m), 7.53–7.58 (m), 7.85–7.92 (m), 8.60–8.68 (dd, J = 4.27 Hz), 10.1 (br, s). $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta_C$ = 9.11, 24.82, 28.80, 28.94, 31.20, 34.15, 48.59, 49.54, 55.44, 59.10, 59.67, 73.47, 79.21, 89.32, 92.039, 105.05, 106.64, 119.04, 122.07, 127.29, 131.81, 143.56, 143.71, 147.06, 147.20, 156.26, 156.36, 156.46, 172.55, 206.98. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3421 (OH), 2932 ($CH_{arom}$), 1747 (C=O), 1509 ($C{=}C_{arom}$), 1131(C−O). HRMS (ESI) calcd $m/z$ for $C_{48}H_{58}IN_4O_6$ $[M^+H^+]$ requires 788.4463, found 788.4429.

### 3.4.6 Synthesis of chiral polyester PBzCPN

The typical procedure of self-polycondensation via the MH reaction has been described in the literature.[31] In this method, **IBzQN** (0.20 g, 0.369 mmol), 3 mol% of $Pd(OAc)_2$ (7.62 mg), and $Et_3N$ (0.07 mL) were stirred in 2 mL of dry DMF at 100 °C for 72 h. After the completion of the reaction, the mixture was allowed to cool down to room temperature, and then precipitated into distilled water (200 mL). The mixture was stirred for 24 h at room temperature. Subsequently, the precipitate was filtered and sequentially washed with water, ethyl acetate, hexane, and diethyl ether, followed by drying in a vacuum oven at 40 °C to afford a brown powder of **PBzCPN** (0.15 g, 98% yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3447 (O–H), 2936 ($C{=}H_{arom}$), 1716 (C=O), 1618 ($C{=}C_{arom}$), 1267 (C−O). $M_n$ (SEC) = 9,300, $M_w/M_n$ =1.33.

### 3.4.7 Synthesis of chiral polyester PCPNea

A typical representative procedure for the two component polycondensation by MH coupling reaction is described:[36–38] **2CPNe** (0.39 g, 0.500 mmol) and 1, 4-diiodobenzene **3a** (0.17 g, 0.500 mmol) were stirred together in 2 mL of dry DMF at 100 °C for 72 h in the presence of 6 mol% of $Pd(OAc)_2$ (15 mg) and $Et_3N$ (0.07 mL). Subsequently, the mixture was allowed to cool to room temperature, then precipitated into distilled water (200 mL)

with stirring. The mixture was stirred for 24 h at room temperature. The precipitate was filtered and sequentially washed by water, ethyl acetate, hexane, and diethyl ether, and then dried in a vacuum oven at 40 °C to afford a brown powder of **PCPNea** (0.43 g, 98% yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3447 (O–H), 2928 (C=$H_{arom}$), 1747 (C=O), 1465 (C=$C_{arom}$), 1231 (C–O). $M_n$ (SEC) = 7,000; $M_w/M_n$ = 1.2.

**PQNaa** was obtained as a brown solid 0.75 g (98% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3131 ($CH_{arom}$), 1724 (C=O), 1508 (C=$C_{arom}$), 1263(C−O). $M_n$ (SEC) = 6,800; $M_w/M_n$= 1.2. $[\alpha]_D^{25}$ = +54.98 (c 0.4, DMF).

**PCPNaa** was obtained as brown solid 0.35 g (81% yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3447 (OH), 2931 ($CH_{arom}$), 1747 (C=O), 1730 (C=$C_{arom}$), 1240 (C−O). $M_n$ (SEC) = 5,001; $M_w/M_n$ = 1.1. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNaa** in either DMF or DMSO used for analysis.

**PCPNba** was obtained as solid brown 0.35 g (77% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3447 (OH), 3034 ($CH_{arom}$), 1722 (C=O), 1505 (C=$C_{arom}$), 1261(C−O). $M_n$ (SEC) = 5,000; $M_w/M_n$ = 1.1. $[\alpha]_D^{25}$: Measurement failed due to instability of **PCPNba** in either DMF or DMSO used for analysis.

**PCPNca** was obtained as solid brown product 0.43 g (98% yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3566 (OH), 3026 ($CH_{arom}$), 1699 (C=O), 1619 (C=$C_{arom}$), 1230 (C−O). $M_n$ (SEC) = 7,048; $M_w/M_n$ = 1.3. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNca** in either DMF or DMSO used during analysis.

**PCPNda** was obtained as brown solid 0.30 g (74% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3446(OH), 2942($CH_{arom}$), 1747 (C=O), 1469(C=$C_{arom}$), 1233(C−O). $M_n$ (SEC) = 5,426; $M_w/M_n$ = 1.1. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNda** in either DMF or DMSO used for analysis.

**PCPNdc** was obtained as solid brown 0.14 g (72% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3393 (OH), 2931 ($CH_{arom}$), 1744 (C=O), 1509 (C=$C_{arom}$), 1231(C−O). $M_n$ (SEC) = Measurements failed due to poor solubility of **PCPNdc** in DMF. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNdc** in either DMF or DMSO used during analysis.

**PCPNeb** was obtained as solid brown 0.22 g (98% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3420 (OH), 3025 ($CH_{arom}$), 1747 (C=O), 1509 (C=$C_{arom}$), 1230(C−O). $M_n$ (SEC) = 9,700; $M_w/M_n$ = 2.3. $[\alpha]_D^{25}$: Measurement failed due to instability of **PCPNeb** in either DMF or DMSO used for analysis.

**PCPNec** was obtained as solid brown 0.17 g (85% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3446 (OH), 3023 ($CH_{arom}$), 1747 (C=O), 1505 (C=$C_{arom}$), 1231(C−O). SEC measurement

failed due to poor solubility of **PCPNec** in DMF. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNec** in either DMF or DMSO used for analysis.

**PCPNac** was obtained as solid brown 0.13 g (86% Yield). IR (KBr) $\nu_{max}$ $cm^{-1}$: 3022 ($CH_{arom}$), 1716 (C=O), 1508 (C=$C_{arom}$), 1241(C−O). $M_n$ (SEC) = 3,000; $M_w/M_n$ = 1.2. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNac** in either DMF or DMSO used for analysis.

**PCPDea** was obtained as brown solid product 0.18 g (70% Yield) IR (KBr) $\nu_{max}$ $cm^{-1}$: 3446 (OH), 1748 (C=O), 1509(C=$C_{arom}$), 1230(C−O). $M_n$ (SEC) = 7,500; $M_w/M_n$ = 2.0. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPDea** in either DMF or DMSO during analysis.

### 3.4.8 Asymmetric catalysis in the Michael addition reaction with cinchona ester derivatives

A representative procedure for the Michael addition of anthrone to nitroalkenes (Table 3.3 entry 9) using chiral polymeric catalyst **PCPNea** is described:[48] Trans-$\beta$-nitrostyrene **5** (0.03 g, 0.200 mmol) and 15 mol% (0.033 g) of **PCPNea** were dissolved in $CH_2Cl_2$ (2.0 mL) and stirred for 10 min at room temperature. Next, anthrone **4** (0.047 g, 0.24 mmol) was added and the mixture was stirred for 40 h. Subsequently, the reaction mixture was filtered and washed thoroughly with $CH_2Cl_2$. The filtered solution was then concentrated in vacuo. The residue was purified via column chromatography using hexane/EtOAc = 5/1 as the eluent and **6** was obtained as a white solid (0.07 g, 84% yield). HPLC analysis (Chiralcel AS-H column with hexane/isopropanol = 5/1, v/v, at a flow rate of 0.7 mL $min^{-1}$) of **6** was conducted at room temperature and ee was determined to be 90%, $t_{major}$ = 18.78 min, $t_{minor}$ = 21.28 min. Thus, in the same way, except for recyclability evaluation, all synthesized cinchona-derived chiral organocatalysts were used as catalysts for enantioselective synthesis in the Michael addition of anthrone to nitroalkenes. The same procedure was followed in the synthesis of all other Michael products 8 and their characterization was done according to literature.[48]

During recyclability evaluation, at the end of each reaction the catalyst was separated from the reaction mixture by centrifugation method. The solution was taken by pipette and concentrated for purification by column chromatography. The catalyst was re-used in the next circle without any further purification. Racemic products were prepared by

treating the corresponding substrates with either trimethylamine or **IBzQN** as catalysts at room temperature.

Michael product **8c** was obtained as white solid (69% Yield). m.p found 174.3 °C–176.1 °C. $^{1}$H NMR ($CDCl_3$, TMS, 400 MHz) $\delta_H$= 4.35–4.44 (m) 1H, 4.51–4.55 (m) 1H, 4.56–4.59 (m) 1H, 4.78–4.86 (m) 1H, 5.81 (d, J = 3.66) 1H, 6.68–6.71 (m) 1H, 7.05–7.07 (dd, J = 1.22, 0.92) 1H, 7.49–7.55 (m) 2H, 7.60–7.65 (dd, J = 1.22, 1.53) 2H, 7.66–7.69 (dd, J=1.22, 1.53) 1H, 8.00–8.14 (dd, dd, J= 1.22) 2H. $^{13}$C NMR ($CDCl_3$, TMS, 100 MHz $\delta_C$= 46.30, 48.06, 48.66 125.94, 126.35, 127.24, 127.53, 128.07, 128.14, 128.44, 128.61, 132.29, 132.65, 133.15, 133.50, 133.89, 134.99, 138.94, 141.77, 183.52. Chiralcel AS-H, hexane/*i*PrOH = 5/1, 0.7 mL min$^{-1}$, 254 nm, $t_{major}$ = 19.34 min, $t_{minor}$ = 21.35 min (80% ee)

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# Chapter 4

# Synthesis of chiral polyurethanes of cinchona alkaloids for the enantioselective synthesis in asymmetric catalysis

Chiral polyurethanes of cinchona alkaloid were synthesized via repetitive Mizoroki-Heck (MH) coupling reaction. The Pd-catalyzed polycondensation of the cinchona urethane dimers and aromatic diiodides afforded the chiral polyurethanes in good yields (up to 85 % yield). The cinchona-based chiral polyurethane organocatalysts were successfully applied in the asymmetric Michael addition reactions. The polymeric catalysts showed higher catalytic activities (up to 97 % yield) and enantioselectivities (up to 97 % ee) in the Michael addition reactions in comparison to their corresponding lower molecular weight catalysts. Futher more, the polymeric catalysts could be easily recycled and reused several times without loosing their catalytic performance.

## 4.1 Introduction

Chiral organocatalysts including cinchona alkaloid derivatives have been recognized as powerful synthetic tool for the synthesis of chiral organic molecules due to their multiple advantages such as their stability to moisture and oxygen, easy structure tuning and treatment, and environmentally benignness.[1] Chemically modified cinchona alkaloids[2] have produced various chiral organocatalysts suitable for different kinds of asymmetric transformations.[3] Cinchona alkaloids contain various functionalities that are proven to play important role in asymmetric catalysis,[1–7] including continuous flow asymmetric

catalysis.[8] The hydroxyl group at C9 position of the cinchona alkaloid could further be utilized to tune their catalytic activity by its modifications.[1] Many of effective enantioselective organocatalysts have been derived from the chemical modification of C9 position. These include C9-ethers,[7] C9-esters,[9,10] C9-squaramides,[9–17] C9-thiourea,[18] C9-urea,[19] and C9-sulfonamide derivatives.[20–22]

Despite their diverse applications in asymmetric catalysis, C9-urethane cinchona alkaloid derivatives have never been applied as chiral organocatalysts in asymmetric reactions. Polyurethanes are reported to have versatile processing methods and mechanical properties.[23] Their wide range of properties makes them indispensable materials.[24] For example, urethane derivatives of bisphenol A-glycidyl methacrylate have been reported as resin based dental materials with excellent properties,[25] and biodegradable polyurethanes have been applied in tissue regeneration materials.[26]

However, there is scarce information on the synthesis and applications of chiral polyurethane materials. In this respect, cinchona-based chiral polyurethanes have been rarely reported. For example, Hubel et al. reported metal complexes of cinchona urethane derivatives for in vitro tests,[27] while Lee et al. reported the synthesis of side-chain cinchona-based chiral poly(methacrylate)s and their applications to chiral stationary phase for high performance liquid chromatography (HPLC).[28] However, their application as organocatalysts in asymmetric reactions has never been reported.

Cinchona alkaloids and their derivatives have been used in several synthetic chiral polymeric organocatalysts and applied in different asymmetric reactions.[2,3,29,30] However, by virtue of their heterogeneity, polymeric catalysts exhibit poor reactivity.[6] Nevertheless, in some cases a well-designed polymeric chiral catalyst may lead to higher selectivity with sufficient reactivity in asymmetric reactions.[6] We have previously utilized the palladium-catalyzed Mizorocki-Heck (MH) coupling reaction of aryl iodides as an effective carbon-carbon bond forming process in the preparation of a number of chiral cinchona polymeric catalysts.[2,3,29,30]

These polymeric catalysts were successfully applied in different asymmetric reactions. As a result of the special features of polyurethanes, in this chapter, we have reported the first preparation of chiral polyurethanes of cinchona alkaloids by MH polymerization and discuss their catalytic performance in asymmetric Michael reactions.

## 4.2 Results and discussion

### 4.2.1 Preparation of cinchona urethane monomer

The non-catalyzed reaction between the C9-OH of cinchona alkaloids and aromatic isocyanates was reported by Hubel et al.[27] Similarly, we prepared cinchona urethane monomer **1QN** by refluxing a mixture of quinine and phenyl isocyanate **1** in chloroform. Following the slightly modified literature procedures,[9,30,31] subsequently the monomer **1QN** was treated with 1M $BBr_3$ solution to afford cinchona urethane monomer **1CPN** having C6'-OH (Scheme 4.1). In case of cinchona alkaloid ester derivatives, the importance of the free OH at the C6' position of the quinoline ring as catalysts for the enantioselective Michael addition has been reported.[9,30]

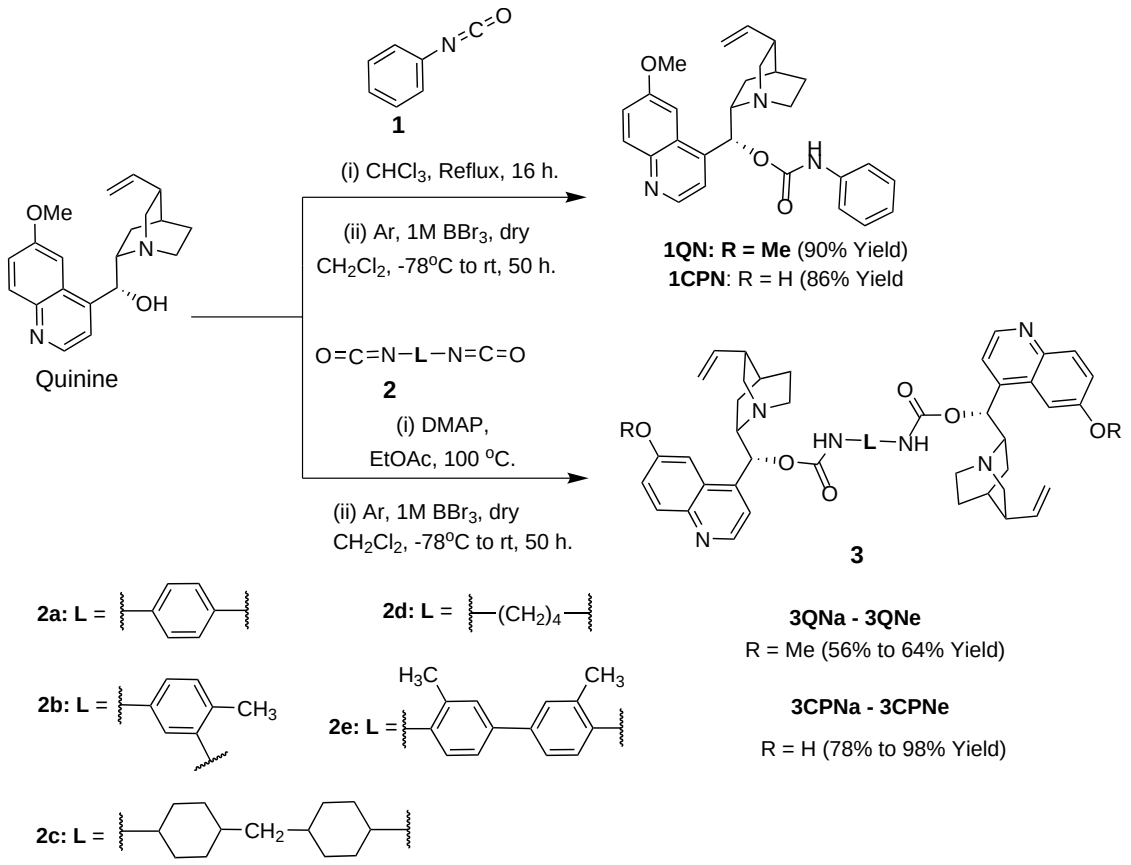
In order to study the effect of urethane structure in the Michael addition reaction, cinchona urethane monomer **1CPN** was used in the Michael addition of anthrone to $\beta$-nitrostyrene in Scheme 4.3. The monomeric model catalyst **1CPN** showed good catalytic activity (95 % yield) and enantioselectivity (80 % ee). Thus, based on these results, we prepared additional cinchona urethanes dimers **3**.

### 4.2.2 Preparation of cinchona urethane dimers

Attempts to optimize the conditions for the non-catalyzed reaction of diisocyanates derivatives with the C9-OH group of cinchona alkaloids failed. The catalyzed isocyanate-hydroxyl reaction has also been reported.[32,33] Thus, the reaction between two equivalent of quinine and diisocyanate derivatives **2** as catalyzed by dimethylaminopyridine (DMAP) refluxing in ethyl acetate, successfully afforded cinchona urethane dimers **3QN** in good yields (Scheme 4.2). Different diisocyanate derivatives **2a**–**2e** were chosen for the preparation of different cinchona urethane dimers **3QNa**–**3QNe**. Furthermore, demethylation of the dimers **3QN** was also possible. The C6'-OH free cinchona urethane dimers **3CPN** were obtained in good yields (Scheme 4.1).

### 4.2.3 Preparation of cinchona-based chiral polyurethanes by MH-polymerization

The repetitive MH coupling reaction between cupreine urethane dimers **3CPN** and aromatic diiodides **4** afforded the corresponding chiral polyurethanes **PCPN**, that contain



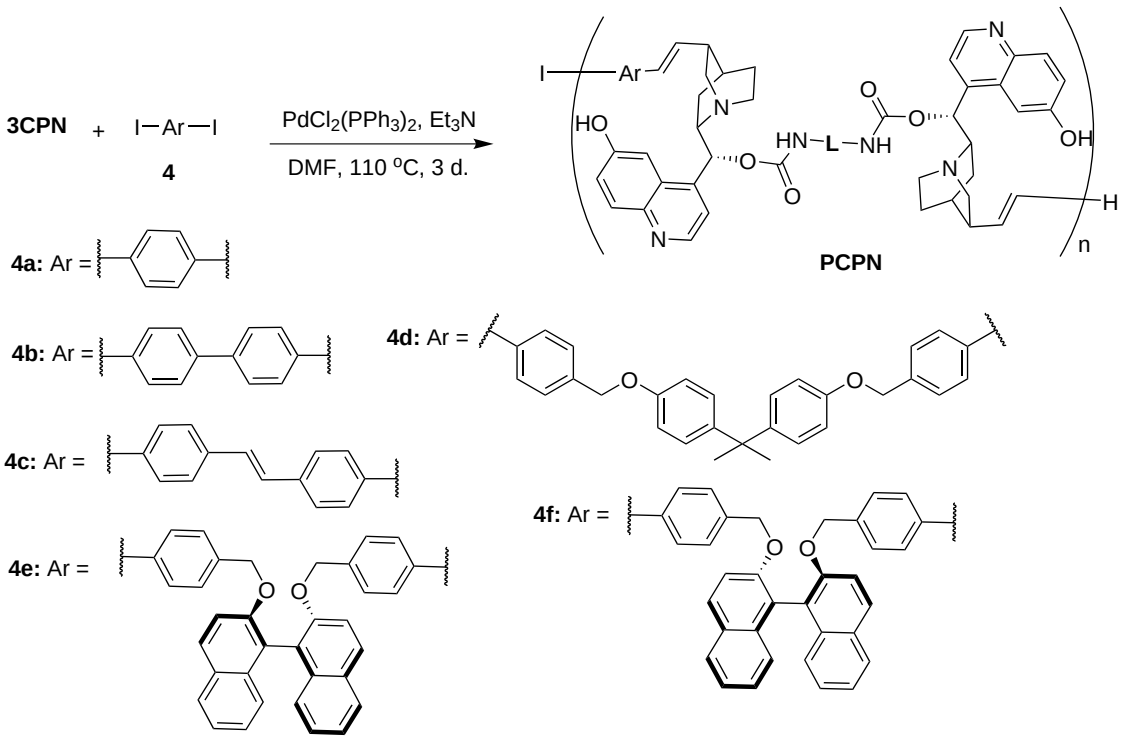

SCHEME 4.1: Synthetic route for cinchona-based urethane monomers **1QN**, **1CPN** and dimers **3CPN**.

cupreine-urethane derivatives in their main chain (Scheme 4.2). The chiral polymers were obtained in good yields (from 58 % to 85 %) with number average molecular weight over 8500. Various combinations of the cupreine urethane dimers **3CPNa–3CPNe** and aromatic diiodides **4a–4f** were chosen to prepare the corresponding chiral polyurethanes **PCPN**. In order to study the structural effect of the diiodides on the chiral polymeric structure formation, the new chiral ether containing aromatic diiodides **4d–4f** were synthesized following literature procedure.[34] The summary of the results on polymer formation and their SEC analysis are shown in Table 1.

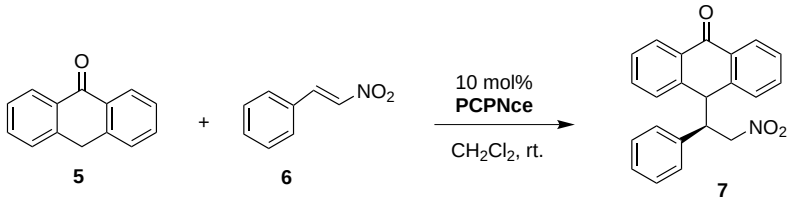
## 4.2.4 Asymmetric catalysis with cinchona urethane derivatives in Michael addition reactions

### 4.2.4.1 Lower molecular weight chiral catalysts

The cinchona urethanes derivatives were then applied as catalysts in the asymmetric Michael reaction for the formation of Michael product **7** (Scheme 4.3). Dimeric cinchona




Scheme 4.2: Synthesis of main-chain cinchona based chiral polyurethanes **PCPN** by MH polymerization.




Scheme 4.3: Asymmetric Michael addition of anthrone **5** to nitroalkenes **6** catalyzed by cinchona based urethane derivatives for the formation of **7**.

urethane catalysts **3CPNa**–**3CPNe** showed high catalytic activities (90 %–95 % yield) and good enantioselectivities (82 % ee–86 % ee) with a shorter reaction time than the reaction with monomeric catalyst **1CPN**. The results have been summarized in Table 2.

#### 4.2.4.2 Chiral polyurethanes derivatives in catalyst screening

The chiral polyurethanes **PCPN** were then evaluated as catalysts in the asymmetric Michael reaction in Scheme 4.3 for the formation of Michael product **7**. The results have been summarized in Table 3.4. The catalytic activities and enantioselectivities decreased when polymeric catalysts obtained from aromatic diiodides **4a**–**4c** were used irrespective of the diisocyanates from which they were derived (entries 1–9). Good

TABLE 4.1: Synthesis of chiral polyurethanes via Mizoroki-Heck coupling reaction[a].

| Entry | Dimeric compound | Diiodides (Ar) | Chiral Polyurethane | Yield (%) | $M_n^b$ | $M_w^b$ | $M_w/M_n$ |
|---|---|---|---|---|---|---|---|
| 1 | **3CPNa** | a | **PCPNaa** | 67 | 7,100 | 14,400 | 2.03 |
| 2 | **2CPNb** | a | **PCPNba** | 83 | 11,200 | 19,100 | 1.71 |
| 3 | **3CPNc** | **a** | **PCPNca** | 66 | 11,800 | 22,500 | 1.91 |
| 4 | **3CPNd** | **a** | **PCPNda** | 75 | 8,900 | 10,000 | 1.12 |
| 5 | **3CPNe** | **a** | **PCPNea** | 83 | 7,000 | 13,000 | 1.86 |
| 6 | **3CPNc** | **b** | **PCPNcb** | 68 | 12,200 | 17,400 | 1.43 |
| 7 | **3CPNd** | **c** | **PCPNdc** | 58 | 12,700 | 20,200 | 1.59 |
| 8 | **3CPNb** | **c** | **PCPNbc** | 67 | 9,500 | 15,000 | 1.58 |
| 9 | **3CPNa** | **b** | **PCPNab** | 66 | 8,800 | 12,000 | 1.36 |
| 10 | **3CPNc** | **d** | **PCPNcd** | 75 | 14,500 | 27,500 | 1.89 |
| 11 | **3CPNd** | **d** | **PCPNdd** | 80 | 8,000 | 8,500 | 1.06 |
| 12 | **3CPNe** | **d** | **PCPNed** | 85 | 9,200 | 10,000 | 1.08 |
| 13 | **3CPNc** | **e** | **PCPNce** | 79 | 9,200 | 9,900 | 1.08 |
| 14 | **3CPNc** | **f** | **PCPNcf** | 69 | 8,800 | 9,600 | 1.08 |
| 15 | **3CPNe** | **f** | **PCPNef** | 75 | 8,800 | 9,700 | 1.1 |
| 17 | **3CPNa** | **f** | **PCPNaf** | 78 | 9,000 | 9,700 | 1.07 |
| 18[d] | **3QNa** | **a** | **PQNaa** | 85 | 10,000 | 14,900 | 1.49 |

[a]Polymerized in DMF at 110 °C for 3 days. [b]Determined by SEC (polystyrene standard) using DMF as an eluent at a flow rate of 0.5 mL $min^{-1}$ and 40 °C. [c]Chiral polyurethane with OMe group at the C6' position of the quinoline ring.

TABLE 4.2: Monomeric and dimeric effect of chiral urethane derivatives as catalysts in the formation of **7**[a].

| Entry | Chiral Catalyst | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **1CPN** | 20 | 95 | 80 |
| 2 | **3CPNa** | 12 | 90 | 84 |
| 3 | **3CPNb** | 16 | 95 | 82 |
| 4 | **3CPNc** | 12 | 95 | 86 |
| 5 | **3CPNd** | 12 | 94 | 84 |
| 6 | **3CPNe** | 12 | 92 | 86 |

[a]Reactions were conducted by using **5** (0.24 mmol) and **6** (0.20 mmol) as substrates with 15 mol% of the quinine-derived urethane catalysts in $CH_2Cl_2$ (2.0 mL) for a specified time at room temperature to obtain **7**(*R*). [b]Isolated yield of the product. [c]Determined HPLC-Chiralcel AS-H column with hexane/isopropanol = 5/1 as eluent at a flow rate of 0.7 mL $min^{-1}$.

catalytic performances were observed in some cases when chiral polyurethanes **PCPN(d–f)** with flexible ether derived diiodides **4d**–**4f** were used as catalysts (entries 10, 12–15).

TABLE 4.3: Chiral polyurethanes **PCPN** catalysts screening in the Michael addition of anthrone to $\beta$-nitrostyrene[a].

| Entry | Chiral polymeric catalyst | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **PCPNaa** | 36 | 85 | 62 |
| 2 | **PCPNba** | 48 | 61 | 57 |
| 3 | **PCPNca** | 40 | 85 | 66 |
| 4 | **PCPNda** | 48 | 69 | 66 |
| 5 | **PCPNea** | 48 | 83 | 62 |
| 6 | **PCPNab** | 40 | 73 | 68 |
| 7 | **PCPNbc** | 40 | 85 | 70 |
| 8 | **PCPNcb** | 48 | 73 | 57 |
| 9 | **PCPNdb** | 48 | 49 | 44 |
| 10 | **PCPNcd** | 24 | 92 | 84 |
| 11 | **PCPNdd** | 48 | 73 | 75 |
| 12 | **PCPNce** | 16 | 97 | 84 |
| 13 | **PCPNcf** | 16 | 97 | 82 |
| 14 | **PCPNef** | 18 | 95 | 80 |
| 15 | **PCPNef** | 18 | 92 | 84 |
| 16 | **PCPNaf** | 24 | 85 | 70 |

[a]All reactions were conducted with anthrone 5 (0.24 mmol) and b-nitrostyrene **6** (0.20 mmol) as substrates with 10 mol% of catalysts in $CH_2Cl_2$ (2.0 mL) under the specified time at room temperature to give **7**(*R*). [b]Isolated yield of product. [c]Determined by HPLC (Chiralcel AS-H column with hexane/isopropyl alcohol = 5/1 as eluent at a flow rate of 0.7 mL $min^{-1}$).

#### 4.2.4.3 Solvent screening with chiral polyurethane as catalyst

We then surveyed the effect of the reaction media for the enantioselective synthesis of Michael product **7** with the chiral polymeric catalyst **PCPNce** (Scheme 4.3). Different kinds of solvents were chosen, polar and non-polar in nature. The result have been summarised in Table 4. When diethylether was used for reaction higher catalytic activity (95 % isolated yield) with poor enantioselectivity (36 % ee) was achieved in the formation of Michael product **7**. Among the screened solvents, highe enantioselectivity of 84 % ee with higher catalytic activity (95 % isolated yield) was obtained when dichloromethane was used as reaction media with **PCPNce** as catalyst (entries 8).

#### 4.2.4.4 Reaction conditions optimization with chiral polyurethane as catalyst

Determination of the suitable reaction conditions for the efficiency catalysis of chiral polyurethanes as catalysts for the enantioselective synthesis of Michael product **7** (Scheme

TABLE 4.4: Solvent screening with **PCPNce** as catalyst in the formation of **7**[a].

| Entry | Solvent | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | THF | 14 | 95 | 78 |
| 2 | $CH_3CN$ | 20 | 88 | 74 |
| 3 | EtOAc | 20 | 96 | 72 |
| 4 | Toluene | 36 | 55 | 58 |
| 5 | Hexane | 36 | 62 | 74 |
| 6 | EtOH | 20 | 88 | 74 |
| 7 | $CH_2Cl_2$ | 20 | 95 | 36 |
| 8 | DCM | 16 | 95 | 84 |
| 9 | Acetone | 20 | 90 | 76 |

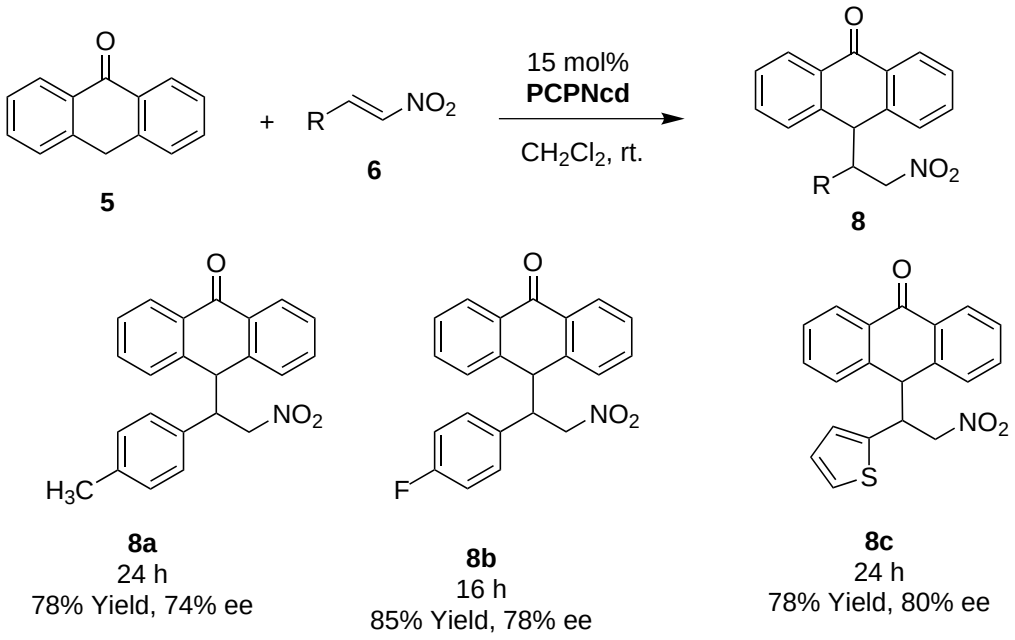
[a]All reaction was done with anthrone **5** (0.24 mmol), nitrostyrene 6 (0.20 mmol) and 10 mol% of **PCPNce** at room temperature to give **7**(*R*). [b]Isolated yield of the product. [c]Determined by using the HPLC -Chiralcel AS-H column with hexane/isopropyl alcohol = 5/1 as eluent at a flow rate of 0.7 mL $min^{-1}$.

TABLE 4.5: Reaction condition optimization using chiral polyurethane **PCPNce** for the formation of Michael product **7**[a].

| Entry | Catalyst (mol%) | Solvent | Temp. (°C) | Time (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 15 | THF | −40 | 72 | 55 | 78 |
| 2 | 15 | $CH_3CN$ | −40 | 72 | 55 | 64 |
| 3 | 15 | $CH_2Cl_2$ | −40 | 60 | 89 | 86 |
| 4 | 15 | $CH_2Cl_2$ | −20 | 48 | 90 | 84 |
| 5 | 15 | $CH_2Cl_2$ | 0 | 48 | 85 | 80 |
| 6 | 15 | $CH_2Cl_2$ | rt | 16 | 96 | 84 |
| 7 | 10 | $CH_2Cl_2$ | rt | 16 | 97 | 84 |
| 8 | 5 | $CH_2Cl_2$ | rt | 24 | 68 | 82 |

[a]All reactions were carried out with **5** (0.24 mmol), **6** (0.20 mmol) under the specified reaction conditions for the formation of **7** (*R*). [b]Isolated yield. [c]Determined by HPLC (Chiralcel AS-H column with hexane/isopropanol = 5/1 as eluent at a flow rate of 0.7 mL $min^{-1}$).

4.3) was conducted. The chiral polyurethane **PCPNce** was used in the evaluation. The results have been summarized in Table 5. The temperature effect was only seen on the catalytic activity of **PCPNce**, while there was insignificant effect on the enantioselectivities (entries 3–6). Lowering the catalyst loading to 5 mol % at room temperature showed the decrease in the isolated yield of Michael product **7** to 68 % respectively (entry 8). Thus, the optimal reaction conditions using **PCPNce** as catalyst for the Michael reaction in Scheme 4.3 were 10 mol % catalyst loading in dichloromethane at room temperature.




SCHEME 4.4: Enantioselective synthesis of **8** with chiral polyurethanes of cinchona alkaloids.

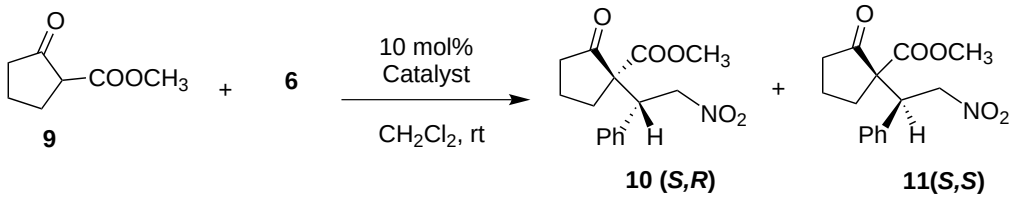
#### 4.2.4.5 Substrate scope study with cinchona chiral polyurethane as a catalyst

With the optimized reaction conditions in hand, the substrate scope was investigated with **PCPNcd** as catalyst in the formation of Michael products derivatives **8** (Scheme 4.4). The summary of the results are shown in Scheme 4.4. Both electron withdrawing and donating substituted Michael acceptors **6** showed good catalytic activities and enantioselectivities with chiral polyurethane **PCPNcd** as a catalyst.

We then extended the substrate scope by changing the Michael donor substituent to $\beta$-ketoester **9** (Scheme 4.5). Both low molecular weight and polymeric cinchona urethane catalysts, bearing C6'-OMe or C6'-OH were used in the enantioselective Michael addition of $\beta$-ketoester **9** to $\beta$-nitrostyrene **6**. The results on asymmetric catalysis have been presented in Table 6. Chiral polyurethane **PCPNcd** efficiently catalyzed the reaction to give the major and minor diastereomers with 96 % ee and 97 % ee respectively with diastereomeric ratio of 5:1 dr(entry 5). These results showed again the existence of phenolic OH (C6'-OH) of the cinchona-urethane derived catalyst played an important role for the enantioselective synthesis of Michael products.

#### 4.2.4.6 Recyclability test with cinchona chiral polyurethane as catalyst

The ability of the catalyst to be recycled and re-used in the enantioselective synthesis of the Michael addition of anthrone **5** to $\beta$-nitrostyrene **6** for the formation of **7** (Scheme3)




SCHEME 4.5: Enantioselective Michael addition of $\beta$-ketoester **9** to $\beta$-nitrostyrene **6** catalyzed by cinchona-urethane derivatives.

TABLE 4.6: Enantioselective Michael addition of $\beta$-ketoester **9** to nitrostyrene **6** with cinchona-urethane derivatives.

| Entry | Chiral Catalyst | Time (h) | Yield (%)[b] | ee (%)[c] | dr[c] |
|---|---|---|---|---|---|
| 1[d] | **3QNc** | 12 | 72 | 23/41 | 7:01 |
| 2[e] | **3CPNc** | 36 | 62 | 85/55 | 5:01 |
| 3[f] | **PQNaa** | 36 | 56 | 04/18 | 3:01 |
| 4 | **PCPNca** | 24 | 62 | 93/95 | 4:01 |
| 5 | **PCPNcd** | 24 | 75 | 96/97 | 5:01 |

[a]All reaction were performed with $\beta$-ketoester **9** (0.50 mmol), $\beta$-nitrostyrene **6** (0.55 mmol) in $CH_2Cl_2$ (2.5 mL) at room temperature for the formation of **10** and **11** as major and minor diastereomers, respectively.[3,29,35,36] [b]Isolated yield of the product. [c]Determined by HPLC (Chiralcel OD-H column with hexane/isopropanol = 4/1 as eluent at a flow rate of 1 mL/min). [d]C6'-OMe and [e]C6'-OH urethane dimers were used as catalysts. [f]C6'-OMe containing chiral polymeric catalyst.

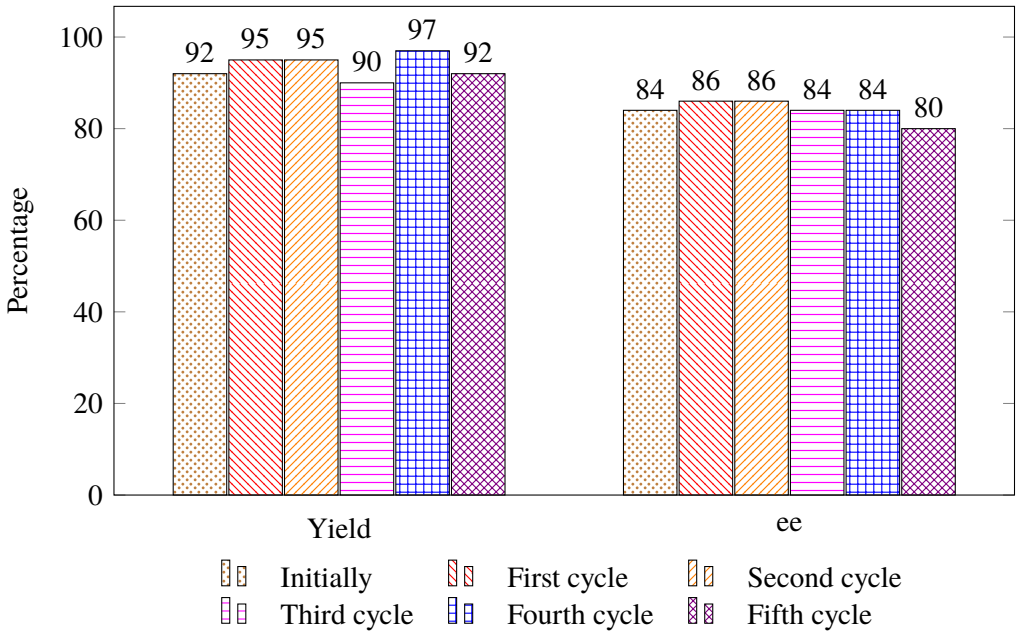



FIGURE 4.1: The recyclability test results for the enantioselective Michael addition reaction (Scheme 3.3).

was perfomed. The chiral polyurethane **PCPNcd** was used as a catalyst in the recyclability. Owing to its insolubility in the reaction solvent, the polymeric catalyst was easily recovered from the reaction mixture by centrifugation. The catalyst could be recycled and reused up to five cycles without losing its catalytic performance. The recyclability test results have been summarized in Fig. 4.1.

## 4.3 Conclusion

We have successfully synthesized main-chain cinchona-based chiral polyurethanes by MH polymerization method. Both C6'-OMe containing and C6'-OH free chiral polyurethane were synthesized through MH-polymerization technique. The catalytic performance of the chiral polyurethanes were done in asymmetric Michael addition reactions. These chiral polymers successfully catalyzed the asymmetric Michael additions of anthrone to nitroalkenes as well as $\beta$-ketoester to $\beta$-nitrostyrene. The C6'-OH free chiral polyurethanes showed high level of catalytic activities and enantioselectivities (up to 97 % ee) in the Michael addition reactions. Moreover, the chiral polymers were recyclable and could be reused for several times without losing their catalytic performances.

## 4.4 Experimental section

### 4.4.1 General methods and materials

All solvents and reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry (TCI) Co., Ltd. at the highest available purity and were used as received, unless otherwise stated. Reactions progress were monitored by analytical thin-layer chromatography (TLC) using pre-coated silica gel plates (Merk TLC silica gel, 60F254). Column chromatography was performed using silica gel column (Wakogel C–200, 100–200 mesh). Melting points (MP) were recorded by using Yanaco micro melting apparatus and the values were taken as averages of the analyzed samples. Optical rotation was recorded with JASCO DIP-149 digital polarimeter by using 10 cm thermostated microcell. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in $CDCl_3$ or DMSO-$d_6$ at room temperature operating at 400 MHz ($^1$H) and 100 MHz ($^{13}$C{1H}). Tetramethylsilane (TMS) was used as an internal standard for $^1$H NMR and $^{13}$C NMR in $CDCl_3$. Chemical shifts are reported in parts per million

(ppm), and the J values were recorded in hertz (Hz). The IR spectral were recorded on a JEOL JIR-7000 FTIR spectrometer by using KBr pellets, wave numbers are reported in $cm^{-1}$. A Bruker micro OTOF II HRMS instrument recorded HRMS (ESI or APCI) spectral. Size exclusion chromatography (SEC) was performed using a Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection, two polystyrene gel columns of bead size 10 mm were used and dimethylfornamide (DMF) was used as the carrier solvent at a flow rate of 1.0 mL/min at 40 °C. A calibration curve was obtained to determine the number-average molecular weight ($M_n$) and molecular weight distribution ($M_w/M_n$) values with polystyrene standards. Highly-performance liquid chromatography (HPLC) was performed with a JASCO HPLC system composed of a DG-980-50 three-line degasser, intelligence HPLC pump (PU 2080), and UV/VIS detector (UV-2075), equipped with a chiral column (Chiralpak AS-H, Daicel) with hexane/2-propanol as an eluent at a flow rate of 0.7 mL $min^{-1}$ at room temperature or Chiralcel OD-H column with hexane/isopropanol = 4/1 as eluent at a flow rate of 1 mL/min.

## 4.4.2 Synthesis of cinchona-based urethane derivatives

### 4.4.2.1 C6'-OMe cinchona urethane derivatives

Representative procedure for the synthesis of C6'-OMe dimers as modified from literatureis described;[32,33] 2 equiv. of quinine were dissolved in 20 mL of EtOAc, then diisocyanate compound and a catalytic amount of 4-dimethylaminopyridine (DMAP) was added and the mixture were refluxed at 100 °C for 24 h. The solvent was removed in *vacuo* and the residue was purified by column chromatography (EtOH: EtOAc = 3:7) to obtain the product of C6'-OMe urethane dimers.

**3QNa** was obtained as white solid product (1.80 g, 80% Yield). m.p found 162.2 °C to 164.2 °C. $[\alpha]_D^{25}$ = +47.57 (c 1.0, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 0.75–0.91 (m), 1.40–1.95 (m), 2.20–2.30 (br, s), 2.35–2.42 (br, s), 2.56–2.61 (q), 2.74–2.85 (m), 2.98–3.20 (m), 3.30–3.40 (m), 3.80–3.92 (m), 4.92–5.02 (m), 5.61–5.70 (m), 5.77–5.88 (m), 6.48–6.50 (d, J = 7.32 Hz), 7.10–7.35 (m), 7.46 (br, s), 7.52–5.54 (d, J = 4.58 Hz), 9.88–7.90 (d, J = 9.16 Hz), 7.88–7.99 (m), 8.63–8.67 (q). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 0.66, 11.70, 25.04, 27.14, 28.11, 28.19, 28.37, 39.66, 40.29, 43.09, 44.11, 46.77, 56.34, 56.82, 59.77, 60.69, 70.65, 101.55, 102.20, 115.20, 116.03, 119.25, 119.54, 122.45, 126.90, 132.10, 132.26, 140.93, 142.35, 144.48, 144.72, 148.01, 158.60, 158.65.

IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3500 (N-$H_{amide}$), 2930 ($CH_{arom}$), 1720 (C=$C_{arom}$), 1620 (C=O). HRMS (ESI) calc'd $m/z$ for $C_{48}H_{52}N_6O_6$ [$M^+H^+$] requires 809.3948, found 809.3079.

**3QNb** was obtained as white solid product (1.60 g, 64% Yield). m.p found 183.4 °C to 184.5 °C. $[\alpha]_D^{25}$ = +67.29 (c 1.0, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 0.80–0.9 (m), 1.19 - 1.27 (m), 1.40–2.04 (m), 2.10 - 2.40 (m), 2.50–2.70 (m), 2.99–3.20 (m), 3.30–3.50 8 (m), 3.90–4.40 (3 H), 4.90–5.10 (m), 5.79–5.9 (m), 6.40–6.50 (d, J = 6.71 Hz), 7.03–7.06 (m), 7.30–7.50 (m), 8.00–8.05 (m), 8.20–8.25 (d, J = 6.41 Hz), 8.70–8.80 (dd, J = 4.58, 4.27 Hz), 10.50–10.60 (m). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 0.67, 8.31, 17.66, 24.93, 28.15, 28.45, 39.70, 40.39, 43.14, 55.96, 56.36, 57.20, 59.88, 87.76, 91.02, 102.11, 102.81, 107.25, 115.17, 119.55, 122.45, 127.81, 131.54, 132.36, 136.72, 139.95, 140.99, 142.44, 145.33, 148.14, 150.35, 154.91, 158.61. IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3560 (N-$H_{amide}$), 2930 ($CH_{arom}$), 1720 (C=$C_{arom}$), 1620 (C=O). HRMS (ESI) calc'd $m/z$ for $C_{49}H_{54}IN_6O_6$ [$M^+H^+$] requires 823.4138, found 823.4070.

**3QNc** was obtained as white solid product (1.60 g, 59% Yield). m.p found 97.5 °C to 99.7 °C. $[\alpha]_D^{25}$ = +35.18 (c 1.0, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 0.72–1.20 (m), 1.33–2.00 (m), 2.10–2.30 (m), 2.50–2.61 (m), 2.80–3.10 (m), 3.23–3.41 (m), 3.81–4.07 (m), 4.83–5.00 (m), 5.43–5.49 (m), 5.63–5.83 (m), 6.32–6.43 (m), 7.25–7.32 (m), 7.38–7.48 (m), 7.90–7.97 (dd, J = 3.05, 2.75 Hz), 8.08–8.14 (m), 8.62–8.68 (m). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 0.65, 1.66, 14.83, 22.59, 24.95, 28.17, 28.40, 28.54, 39.66, 40.40, 48.08, 51.34, 56.32, 57.70, 59.88, 60.67, 72.71, 73.66, 101.97, 102.14, 107.19, 114.98, 115.09, 119.17, 122.43, 127.38, 132.22, 142.47, 142.65, 148.28, 148.06, 148.28, 150.17, 154.86, 155.54, 158.29, 158.44, 158.51. IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3500 (N-$H_{amide}$), 2920 ($CH_{arom}$), 1710 (C=$C_{arom}$), 1600 (C=O). HRMS (ESI) calc'd $m/z$ for $C_{55}H_{70}IN_6O_6$ [$M^+H^+$] requires 911.5357, found 911.5357.

**3QNd** was obtained as white solid product (1.42 g, 56% Yield). m.p found 95.5 °C to 96.8 °C. $[\alpha]_D^{25}$ = +6.29 (c 1.0, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 0.76–0.80 (t), 1.10–1.20 (m), 1.29–1.50 (m), 1.60–1.82 (m), 1.9 (s), 2.14–2.25 (m), 2.50–2.60 (m), 2.93–3.08 (m), 3.20–3.30 (m), 3.80–3.90 (m), 4.01–4.10 (m), 4.90–5.00 (m), 5.18–5.23 (m), 5.43–5.45 (d, J = 4.27 Hz), 5.65–5.82 (m), 6.30–6.42 (m), 7.15–7.21 (m), 7.36–7.45 (m), 7.90–7.95 (d, J = 9.16 Hz), 8.10–8.14 (m), 8.60–8.70 (d, J = 4.27). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 9.32, 12.11, 24.20, 24.85, 27.69, 29.1, 29.03, 34.45, 39.59, 42.45, 45.53, 55.77, 56.47, 59.03, 73.48, 101.49, 114.71, 118.86, 121.99, 127.05, 131.76, 141.59, 143.78, 144.75, 147.38, 158.04, 172.82, 178.4. IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3230 (N-$H_{amide}$), 2930 ($CH_{arom}$), 1620 (C=O), 1500 (C=$C_{arom}$). HRMS (ESI) calc'd

$m/z$ for $C_{48}H_{60}IN_6O_6$ [$M^+H^+$] requires 817.4574, found 817.4608.

3QNe was obtained as white solid product (1.79 g, 63% Yield). m.p found 102.1 °C–106.1 °C. $[\alpha]_D^{25}$ = +48.93 (c 1.0, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 1.00–1.05 (t), 1.50–2.05 (m), 2.27 (s), 2.50–2.54 (q), 2.60–2.73 (m), 3.02–3.20 (m), 3.36–3.50 (m), 3.87–4.00 (m), 4.90–5.10 (m), 5.54–5.57 (d, J = 4.58 Hz), 5.70–5.95 (m), 6.46–6.50 (m), 6.53–6.58 (d, J = 7.93 Hz), 6.64 (br,s), 7.29–7.39 (m), 7.42–7.44 (d, J = 3.66 Hz), 7.48–7.55 (m), 8.00 (s), 8.18–8.22 (m), 8.72–8.79 (dd, J = 4.58 Hz). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 0.72, 18.58, 25.27, 28.21, 28.49, 31.67, 39.75, 40.44, 43.12, 56.38, 57.18, 57.76, 59.80, 60.74, 115.25, 119.20, 119.71, 122.28, 129.57, 132.46, 135.29, 142.51, 144.35, 145.52, 148.20, 150.40, 154.93, 158.68, 207.80. IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3500 (N-$H_{amide}$), 2930 ($CH_{arom}$), 1700 (C=O), 1620 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{56}H_{60}N_6O_6$ [$M^+H^+$] requires 913.4608, found 913.5678

#### 4.4.2.2 C6'-OH cinchona urethane derivatives

Representative experimental procedure for the synthesis of C6'OH cinchona urethane compounds as modified from literatures is described;[9,30,31] under argon atmosphere, a representative amount of C6'-OMe quinine-derived urethane compound was dissolved in dry $CH_2Cl_2$ and cooled to −78 °C. Then, 40 mmol equiv. of 1M boron tribromide solution in $CH_2Cl_2$ was added and the mixture was stirred for 2 h. The mixture was then transferred to room temperature and allowed to stir for 2 d. To the reaction mixture, NaOH 10% w/w solution and pure water was carefully added simultaneously to adjust the solution mixture to around 12 pH and the organic phase was separated. The aqueous phase was then neutralized with 2N HCl to around 8 pH. The observed precipitates were filtered, washed by $H_2O$ followed by $CH_2Cl_2$ and dried to obtain the corresponding C6'-OH quinine-derived urethane compound. No further purification was done. The summary on their characterization for the compounds in Scheme 1 are as follows; **1CPN** was obtained as yellow solid product (0.69 g, 86% Yield). m.p found 235.8 °C–236.6 °C. $[\alpha]_D^{25}$ = +84.73 (c 0.8, DMSO). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 1.40–2.00 (m, 1H), 2.10–2.40 (m, 2H), 5.00–5.20 (dd, J = 17.09, 10.38 Hz, 2H), 5.70–5.90 (m, 1H), 6.70–6.80 (m, 1H), 7.00–7.10 (m, 1H), 7.20–7.30 (t, 2H), 7.40–7.80 (m, 4H), 7.98–8.01 (d, J = 9.16 Hz, 1H), 10.31–10.35 (m, 2H). $\delta_C$ = 24.9, 26.9, 41.3, 55.6, 57.7, 58.9, 102.2, 104.1, 114.0, 115.1, 118.5, 118.6, 120.8, 121.3, 124.5, 125.5, 128.2, 130.6, 131.0, 131.2, 137.6, 141.5, 142.1, 142.6, 146.2, 155.3, 154.4. IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3550 (N-$H_{amide}$),

3500 (OH), 2950 ($CH_{arom}$), 1720 (C=O), 1520 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{26}H_{27}N_3O_3$ [$M^+H^+$] requires 429.2052, found 429.5210.

**3CPNa** was obtained as off white solid product (0.50 g, 78% Yield). m.p found 285.5 °C–288.5 °C. $[\alpha]_D^{25}$ = +5.93 (c 0.8, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.70–0.90 (m), 1.00–1.30 (m), 1.40–1.98 (m), 2.70–3.15 (m), 2.70–3.15 (m), 4.90–5.10 (m), 5.79–5.93 (m), 6.20–6.34 (m), 7.20–7.56 (m), 7.84–7.92 (d , J = 9.16 Hz), 8.60–8.67 (m), 9.75–9.87 (br, s), 10.10–10.20 (m). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3560 (N-$H_{amide}$), 3500 (OH), 2940 ($CH_{arom}$), 1720 (C=O), 1510 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{46}H_{48}N_6O_6$ [$M^+H^+$] requires 781.3669, found: not determined due insolubility of **3CPNa** in either acetonitrile, isopropyl alcohol or ultra-pure water used for analysis.

**3CPNb** was obtained as off white solid product (0.50 g, 86% Yield). m.p found 328.4 °C–330.6 °C. $[\alpha]_D^{25}$ = +31.32 (c 0.8, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.70–2.32 (m), 2.73–3.20 (m), 4.96–5.2 (m), 5.80–5.92 (m), 6.26 (br, s), 6.5 (br, s), 7.00–7.18 (m), 7.30–7.60 (dd, J = 7.32, 14.65 Hz), 7.82–7.98 (m), 8.60–8.70 (m), 9.11 (br, s), 9.86 (br, s), 10.11–10.30 (m). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3420 (OH), 2940 ($CH_{arom}$), 1710 (C=O), 1510 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{47}H_{50}N_6O_6$ [$M^+H^+$] requires 795.3829, found: not determined due insolubility of **3CPNb** in either acetonitrile, isopropyl alcohol or ultra-pure water used for analysis.

**3CPNc** was obtained as off white solid product (0.50 g, 100% Yield). m.p found 264.4 °C–268.3 °C. $[\alpha]_D^{25}$ = −22.25 (c 0.8, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.79–2.02 (m), 2.60–2.73 (m), 2.88–3.20 (m), 4.90–5.10 (m), 5.80–5.93 (m), 6.20–6.43 (br, s), 6.53 (s), 7.30–7.60 (m), 7.87–7.96 (d, J = 8.85 Hz), 8.60–8.70 (br, s), 10.00–10.20 (br, s). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3420 (OH), 2920 ($CH_{arom}$), 1630 (C=O), 1510 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{53}H_{66}N_6O_6$ [$M^+H^+$] requires 882.5044, found: not determined due insolubility of **3CPNc** in either acetonitrile, isopropyl alcohol or ultra-pure water used for analysis.

**3CPNd** was obtained as off white solid product (0.57 g, 98% Yield). m.p found 264.4 °C–268.3 °C. $[\alpha]_D^{25}$ = −22.27 (c 0.8, DMF). 1H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.70–0.84 (m), 1.15–2.25 (m), 2.66–3.20 (m), 3.85–4.00 (m), 4.93–5.13 (m), 5.78–5.90 (d, J = 7.32 Hz), 6.30–6.60 (m), 6.80 (s), 6.92–6.94 (d, J = 7.32 Hz), 7.50–7.80 (m), 7.88–7.90 (d, J = 8.85 Hz), 8.19–8.21 (d, J = 7.63 Hz), 10.02 (br, s), 10.20–10.50 (m). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3350 (OH), 2930 ($CH_{arom}$), 1610 (C=O), 1510 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{46}H_{56}N_6O_6$ [$M^+H^+$] requires 789.42.95, found: not determined due insolubility of 3 CPNd in either acetonitrile, isopropyl alcohol or ultra-pure water used

for analysis.

**3CPNe** was obtained as off white solid product (0.35 g, 85% Yield). m.p found 264.4 °C–268.3 °C. $[\alpha]_D^{25}$ = +43.43 (c 0.8, DMF). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta_H$ = 0.70–0.80 (m), 1.20–2.00 (m), 2.10–2.40 (m), 2.63–3.15 (m), 4.90–5.10 (m), 5.81–5.90 (m), 6.30–6.41 (m), 6.54 (s), 7.29–7.60 (m), 7.87–7.90 (d, J = 9.16 Hz), 8.63–8.71 (d, J = 4.27 Hz), 9.20–9.40 (br, s), 9.60–9.68 (br,s), 10.10–10.30 (m). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3420 (OH), 2940 ($CH_{arom}$), 1610 (C=O), 1510 (C=$C_{arom}$). HRMS (ESI) calc'd $m/z$ for $C_{54}H_{56}N_6O_6$ [$M^+H^+$] requires 885.4295, found: not determined due insolubility of **3CPNe** in either acetonitrile, isopropyl alcohol or ultra-pure water used for analysis.

### 4.4.3 Synthesis of aryl diiodide derivatives

Experimental procedure as modified from literature is described;[34] To the mixture of 2, 2-bis-4-hydroxyphenylpropane (0.750 mmol, 0.171 g) and 4-iodobenzyl bromide (1.500 mmol, 0.444 g) dissolved in dry DMF (10 mL), there was added $K_2CO_3$ (3.000 mmol, 0.621 g) and stirred at room temperature for 24 h. After reaction completion, 50 mL of water was added to the mixture and extracted by $CH_2Cl_2$ (200 mL). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The crude mixture was purified by column chromatography (DCM:Hex = 4:2) to obtain a white sponge product of ether containing diiodide **4**.

Compound '**4**' was obtained as white sponge product (0.50 g, 53% Yield). m.p found 152.6 °C–153.3 °C. $[\alpha]_D^{25}$ = +0.36 (c 0.8, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 1.63 (s, 6H), 4.97 (s, 4H), 6.83–6.86 (d, J = 8.24 Hz), 7.12–7.18 (q, 8H). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 0.64, 31.65, 42.36, 69.90, 94.03, 114.76, 128.43, 129.92, 137.55, 138.28, 144.19, 157.00. HRMS (APCI) calc'd $m/z$ for $C_{29}H_{26}I_2O_2$ [$M^+H^+$] requires 660.0022, found 660.0022.

Compound '**4e**' was obtained as white solid product (0.53 g, 49% Yield). m.p found 62.0 °C–63.3 °C. $[\alpha]_D^{25}$ = −19.95 (c 0.8, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 4.86 (s, 4H), 6.52–6.55 (d, J = 8.24 Hz, 4H), 7.07–7.17 (m, 4H), 7.25–7.31 (m, 8H), 7.79–7.89 (dd, J = 7.93, 9.16 Hz, 4H). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 71.02, 93.32, 116.27, 121.26, 124.36, 125.89, 126.90, 128.37, 129.11, 129.84, 129.95, 134.51, 137.59, 154.16. HRMS (APCI) calc'd $m/z$ for $C_{34}H_{24}I_2O_2$ [$M^+H^+$] requires 718.9899, found 718.9866.

Compound '**4f**' was obtained as white solid product (0.53 g, 49% Yield). m.p found 73.5 °C–74.1 °C. $[\alpha]_D^{25}$ = +15.70 (c 0.8, DMF). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta_H$ = 4.94

(s, 4H), 6.60–6.65 (d, J = 8.54 Hz, 4H), 7.15–7.25 (m, 4H), 7.33–7.39 (m, 8H), 7.87–7.96 (dd, J = 7.93, 8.85 Hz, 4H). $^{13}$CNMR ($CDCl_3$, TMS, 100 MHz) $\delta_C$ = 71.02, 93.32, 116.27, 121.26, 124.36, 125.89, 126.90, 128.37, 129.11, 129.84, 129.95, 134.51, 137.59, 154.16. HRMS (APCI) calc'd $m/z$ for 34 $H_{24}I_2O_2$ [$M^+H^+$] requires 718.9899, found 718.9866.

### 4.4.4 Synthesis of main-chain cinchona chiral polyurethanes

A typical representative procedure for two component polycondensation of **PCPNcd** by MH coupling reaction is described: **3CPNc** (0.400 mmol, 0.38g,) and diiodide **d** (0.400 mmol, 0.25g) in the presence of 6 mol% PdCl2(PPh3)2 and Et3N (0.400 mmol, 0.056 mL) was stirred in 2 mL DMF at 110 °C for 72 h. The mixture was let to cool down to room temperature, then precipitated into 200 mL of methanol. The mixture was stirred overnight at room temperature. Followed by decantation,the solvent was removed and the precipitates was washed by centrifugation sequentially with methanol, hexane and diethyl ether. The precipitate was dried in vacuum oven at 40 °C to afford brown solid product of **PCPNcd** (0.41 g, 79% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3400 (OH), 2926 ($CH_{arom}$), 1723 (C=O), 1509 (C=$C_{arom}$), $M_n$ (SEC) = 14,500; $M_w/M_n$= 1.89. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNcd** in either DMF or DMSO used for analysis.

Chiral polymer **PCPNaa** was obtained as brown solid (0.19, 67% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3402 (OH), 2925 ($CH_{arom}$), 1729 (C=O), 1510 (C=$C_{arom}$), $M_n$ (SEC) = 7100; $M_w/M_n$= 2.03. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNaa** in either DMF or DMSO used for analysis.

Chiral polymer **PCPNba** was obtained as brown solid (0.24 g, 83% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3419 (OH), 2929 ($CH_{arom}$), 1702 (C=O), 1509 (C=$C_{arom}$), $M_n$ (SEC) = 11,200; $M_w/M_n$= 1.71. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNba** in either DMF or DMSO used for analysis.

Chiral polymer **PCNca** was obtained as brown solid (0.21 g, 66% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3400 (OH), 2900 ($CH_{arom}$), 1700 (C=O), 1500 (C=$C_{arom}$), $M_n$ (SEC) = 11,800; $M_w/M_n$= 1.91. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNca** in either DMF or DMSO used for analysis.

Chiral polymer **PCPNda** was obtained as brown solid (0.22 g, 75% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3400 (OH), 2900 ($CH_{arom}$), 1721 (C=O), 1511 (C=$C_{arom}$), $M_n$ (SEC) = 8,900; $M_w/M_n$= 1.12. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNda** in either DMF or DMSO used for analysis. Chiral polymer **PCPNea** was obtained as brown solid

(0.22 g, 83% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3421 (OH), 2900 ($CH_{arom}$), 1730 (C=O), 1510 ($C{=}C_{arom}$), $M_n$ (SEC) = 7,000; $M_w/M_n$= 1.86. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNea** in either DMF or DMSO used for analysis.

Chiral polymer **PCPNcb** was obtained as brown solid (0.30 g, 68% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3420 (OH), 2920 ($CH_{arom}$), 1720 (C=O), 1510 ($C{=}C_{arom}$), $M_n$ (SEC) = 8,800; $M_w/M_n$= 1.08. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNcf** in either DMF or DMSO used for analysis.

Chiral polymer **PCPNcf** was obtained as brown solid (0.29 g, 69% Yield). IR (KBr) $\nu_{max}$ [$cm^{-1}$]: 3421 (OH), 2900 ($CH_{arom}$), 1723 (C=O), 1510 ($C{=}C_{arom}$), $M_n$ (SEC) = 8,800; $M_w/M_n$= 1.08. $[\alpha]_D^{25}$: Measurements failed due to instability of **PCPNcf** in either DMF or DMSO used for analysis.

### 4.4.5 Enantioselective synthesis for the Michael reaction with chiral urethanes derivatives

#### 4.4.5.1 Asymmetric Michael addition of anthrone to nitroalkenes

A representative procedure for the asymmetric reaction in Table 2, entry 10 is described: In a 10 mL flask, $\beta$-nitrostyrene **6** (30 mg, 0.200 mmol) was dissolved in $CH_2Cl_2$ (2.0 mL) and stirred at room temperature, then 10 mol% of chiral polyurethane **PCPNcd** catalyst was suspended to the solution and stirred for 10 min. Anthrone **5** (47 mg, 0.24 mmol) was added to the mixture and stirred for 24 h. The reaction mixture was filtered and the precipitates were thoroughly washed with $CH_2Cl_2$. The filtrate was then concentrated in *vacuo*. The residue was purified by silica gel column chromatography using hexane/EtOAc = 5/1 as eluent and **7** was obtained as a white solid (80 mg, 92%). HPLC analysis (Chiralcel AS-H column with hexane/2-propanol = 5/1, v/v, at a flow rate of 0.7 mL $min^{-1}$) for **7** showed the enantioselectivity of 84%.

#### 4.4.5.2 Asymmetric Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene

A representative procedure for the asymmetric reaction in Table 2, entry 10 is described: In a 10 mL flask, $\beta$-nitrostyrene **6** (82 mg, 0.55 mmol) was dissolved in $CH_2Cl_2$ (2.5 mL), then 10-mol% catalyst was suspended into solution. The mixture was then stirred for 10 min at room temperature. Methyl 2-oxocyclopentanecarboxylate **9** (63 $\mu$L, 0.50 mmol) was added to the mixture and stirred for 24 h. The reaction mixture was then filtered and the catalyst was separated. The filtrate was then concentrated in *vacuo* and

the residue was purified by silica gel column chromatography with hexane/EtOAc=6/1 as eluent to afford 8 as a white solid (0.12 g, 75% yield). HPLC analysis (Chiralcel OD-H column with hexane/2-propanol=4/1 at a flow rate of 1.0 mL/min) showed two diastereomers **10** and **11** (5:1 dr). The enantioselectivities were 96% ee and 97% ee respectively.

#### 4.4.5.3 Asymmetric Michael addition of anthrone to $\beta$-nitrostyrene for recyclability test

The macro scale for asymmetric Michael addition reaction (Scheme 3) was performed for recyclability test. In a 20 mL flask, $\beta$-nitrostyrene **6** (60 mg, 0.400 mmol) was dissolved in $CH_2Cl_2$ (4.0 mL) and stirred at room temperature, then 10 mol% of chiral polyurethane **PCPNcd** catalyst was suspended to the solution and stirred for 10 min. Anthrone **5** (94 mg, 0.48 mmol) was added to the mixture and stirred for a specified time as confirmed by TLC. The reaction mixture was then centrifuged and the solution was separated, concentrated in *vacuo*. The residue was purified by silica gel column chromatography using hexane/EtOAc = 5/1 as eluent and **7** was obtained as a white solid and was analysed by HPLC (Chiralcel AS-H column with hexane/2-propanol = 5/1, v/v, at a flow rate of $0.7\,mL\,min^{-1}$). The catalyst was then used for the next cycle without any purification. The same amount of reacting substrates **6** and **5** was added for every new cycle for the asymmetric reaction.

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# Chapter 5

# Synthesis of cross-linked chiral polysiloxanes of cinchona alkaloid derivatives for their applications in asymmetric catalysis

In this chapter, cross-linked chiral polysiloxanes containing cinchona alkaloid derivatives were synthesized from poly(methylhydrosiloxane) by hydrosilylation reaction. The C3-vinyl group of cinchona alkaloid derivatives were easily hydrosilylated with Si-H functional groups of poly(methylhydrosiloxane) by using Pt catalyst. The Pt catalysis of Si-H groups in poly(methylhydrosiloxane) and cinchona alkaloid dimers afforded the cross-linked structure of chiral polysiloxanes. Hydrolysis of Si-H bonds with Pt catalyst during reaction resulted in a formation of extra cross-linkages of chiral polysiloxanes. Mixed solvent (toluene and DMF) system was employed for a successful immobilization of C6'-OH free cinchona alkaloid derivatives into poly(methylhydrosiloxane). Both cinchona alkaloid C9-ester and C9-urethane derivatives were incorporated into poly(methylhydrosiloxane) through Si-C bond. The resulted cross-linked chiral polysiloxanes were insoluble in common organic solvents. Their catalytic performance was evaluated in asymmetric Michael addition reactions. The C6'-OH free chiral polysiloxanes of cinchona alkaloid showed higher enantioselectivities (up to 99% ee) with sufficient catalytic activities in the Michael addition reactions. The chiral polysiloxanes were easily recovered by filtration or centrifugation method and could be reused for several times without losing their catalytic performance.

## 5.1 Introduction

Readily available and inexpensive cinchona alkaloids with pseudoenantiomeric forms, such as quinine and quinidine or cinchonine and cinchonidine, and their derivatives are among the most privileged chirality inducers in the area of asymmetric catalysis.[1–4] Despite their stability to moisture and oxygen and being environmentally friendly, cinchona alkaloids possesses various functionalities that are available for chemical modifications.[5–14]

Furthermore, they offer a unique platform for new reactions and methodologies in chiral polymeric catalysts design. They have been used in various synthetic chiral polymeric organocatalysts, such as main-chain chiral polymers,[15–21] polymer-supported chiral catalysts,[4,22–36] as well as cross-linked chiral polymers.[37,38] Their catalytic performance have been evaluated in different asymmetric reactions.[4,15–36] Despite of their recyclability advantage, in some cases polymeric catalyst exhibit poor reactivity by virtue of their heterogeneity.[20] On the other hand, well-designed polymeric catalyst may lead to higher selectivity with sufficient reactivity.[4]

Immobilized polymers of cinchona alkaloids at the C3 vinyl group,[4,22–26] C9 hydroxyl group,[27–33,39] N1 quinuclidine nitrogen[34,35] as well as C6' position of the quinoline ring[36] have been reported for their application in asymmetric synthesis. With the exploration of alternative anchoring strategies, chiral derivatives, and support materials, a large number of insoluble polymer-bound catalysts and ligands are known for the attainment of high catalytic activity and enantioselectivity. The polyfunctional nature of alkaloids, gives a large array for the preparation of immobilized insoluble as well as soluble polymeric bound catalysts.[36] Alkaloids have been successfully coupled to commercially available resins. In their preparation, insoluble polymers have been reported to exhibit lower catalyst loading, as a result of decrease in reactivity.

Linear polysiloxanes are widely used as fluids, surfactants, release agents and lubricants. They are often available as viscous oils or gums soluble in many solvent. Polysiloxanes possess good thermal, oxidative, chemical and biological stability and are available with silane (Si–H) functionality. Due to their physiochemical properties, they have been known for their applicability in functional materials as well as support materials for chiral organocatalysts. Among a variety of available soluble supports, polymethylhydrosiloxane (PMHS) has many positive features. It is a commercially available and inexpensive polymer and can be readily functionalized. Despite the availability and favorable chemical characteristics of PMHS, it is relatively developed as a catalyst support.

The immobilization of alkaloid derivatives onto polysiloxanes have been achieved via catalyzed hydrosilylation reaction. Even though the use of organosilicon polymers in asymmetric organocatalysis is rarely, organosilicon polymers have been known for their applicability in functional materials due to their physicochemical properties.[40–43]

Hydrosilylation reaction as a widely used reaction in chemical industries, have been used for the preparation of several organosilicon compounds.[33] Platinum or Rhodium catalyzed silicone-carbon bond formation in polycarbosilanes preparation have been known as a versatile synthetic method.[39–43]

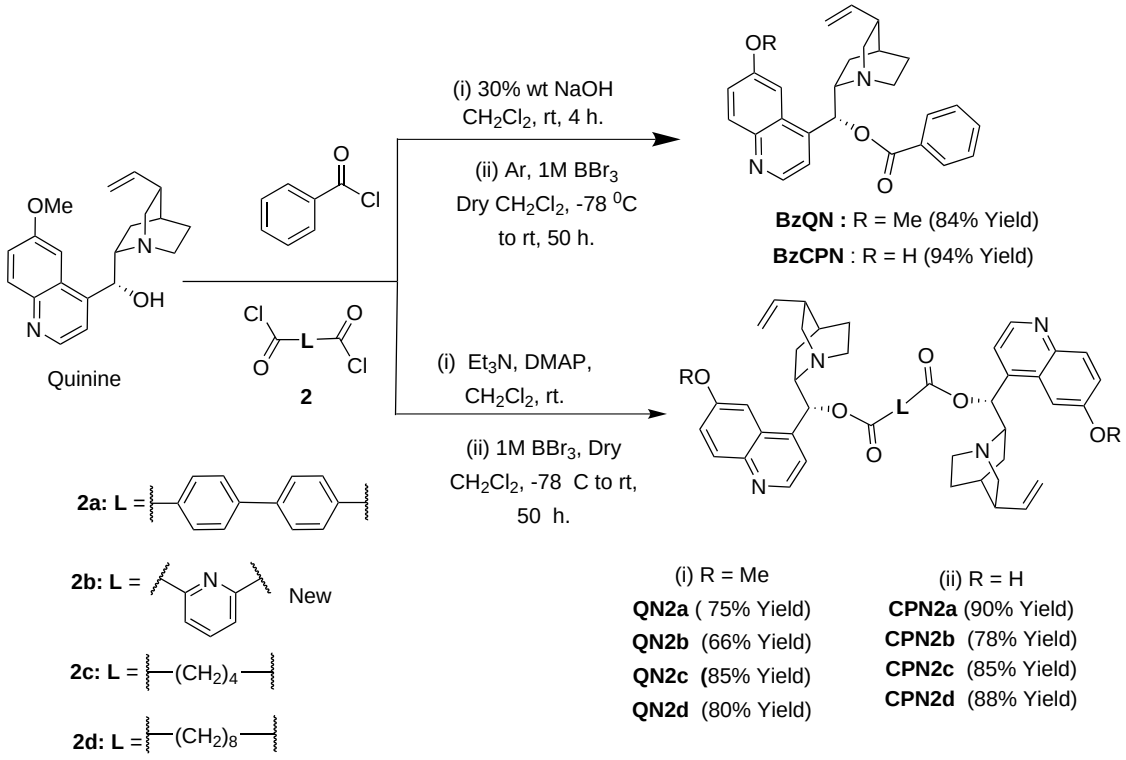
In the class of bifunctional organocatalysts; cupreine, cupreidine and their C9-derivatives are among the most prevalent effective enantioselective catalysts. However, they have not been grafted into PHMS, except for silica gel as support material.[24] Over the reported polysiloxanes scaffolds for macromolecular catalyst development, C6-OMe containing cinchona derivatives have been grafted into PMHS. Both soluble and insoluble cinchona polymers derived from PHMS have been prepared by Pt catalyzed hydrosilylation reaction. For example, DeClue M. S. and Siegel J. S. have reported on polysiloxane-bound ligand of cinchona alkaloid for asymmetric dihydroxylation.[39] They have optimized the C3 as well as C9 position of the cinchona alkaloid derivatives for grafting onto polysiloxane by using dichlorodi(cyclopentadienyl)platinum (II) ($Cl_2$Ptdcp) as a catalyst. Their attempt to utilize the vinyl group of quinidine itself without modification failed.

In this chapter, crosslinked chiral polysiloxanes of C6-OH free alkaloid derivatives were synthesized via Pt catalyzed hydrosilylation reaction. The C3-vinyl group of cinchona alkaloid derivatives were hydrosilylated by Si-H functionalities of PMHS **KF-99**. Monomeric and dimeric cinchona alkaloid derivatives were used for the preparation of crosslinked gel type chiral polysiloxanes. Their synthetic methodologies and catalytic performance evaluation in asymmetric Michael addition reactions are discussed.

## 5.2 Results and discussion

### 5.2.1 Preparation of cinchona ester derivatives

Ester derivatives of cinchona alkaloids were easily prepared following experimental procedures presented in chapter three except the dimer **CPN2b** that was prepared from pyridine derivative. The C6'-OMe ester dimers **QN2a – QN2d** were prepared by using two equivalents of quinine and dicarboxylic dichlorides compounds **2a – 2d** in

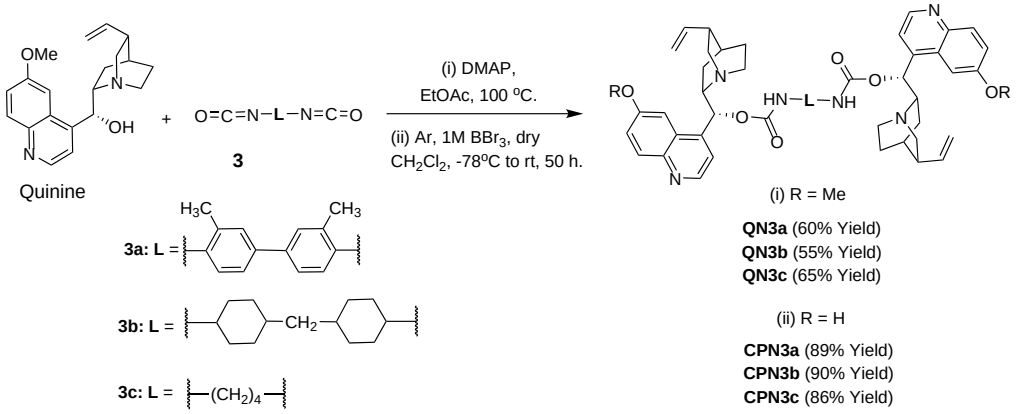



SCHEME 5.1: Synthetic route for the preparation of cinchona ester derivatives.

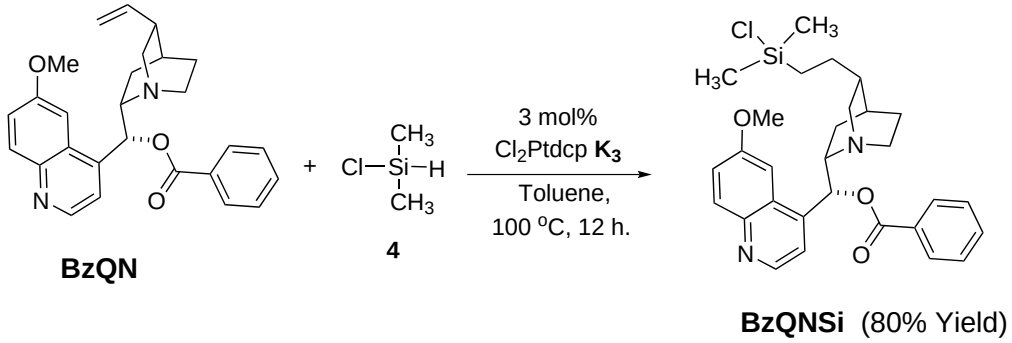
dichloromethane with a catalytic amount of DMAP at room temperature. The dimers were obtained in good yields (Scheme 5.1). Subsequently ester cinchona derivatives were subjected to demethylation condition by using 1M $BBr_3$ solution to obtain corresponding C6'-OH free cinchona derivatives **CPN2a–CPN2d**.

### 5.2.2 Preparation of cinchona urethane derivatives

Cinchona urethane derivatives used for the hydrosiylation reaction were also prepared as per experimental procedures presented in chapter four. By refluxing the mixture of quinine, 0.5 equivalent of diisocyanate derivatives **3** and DMAP as a catalyst in EtOAC, the C6'-OMe cinchona urethane dimers **QN3a – QN3c** were obtained in good yield. Subjecting them to demethylation conditions C6'-OH free cinchona urethane dimers **CPNa – CPNc** were obtained in good yield too. The summary on their isolated yield is as shown in Scheme 5.2.



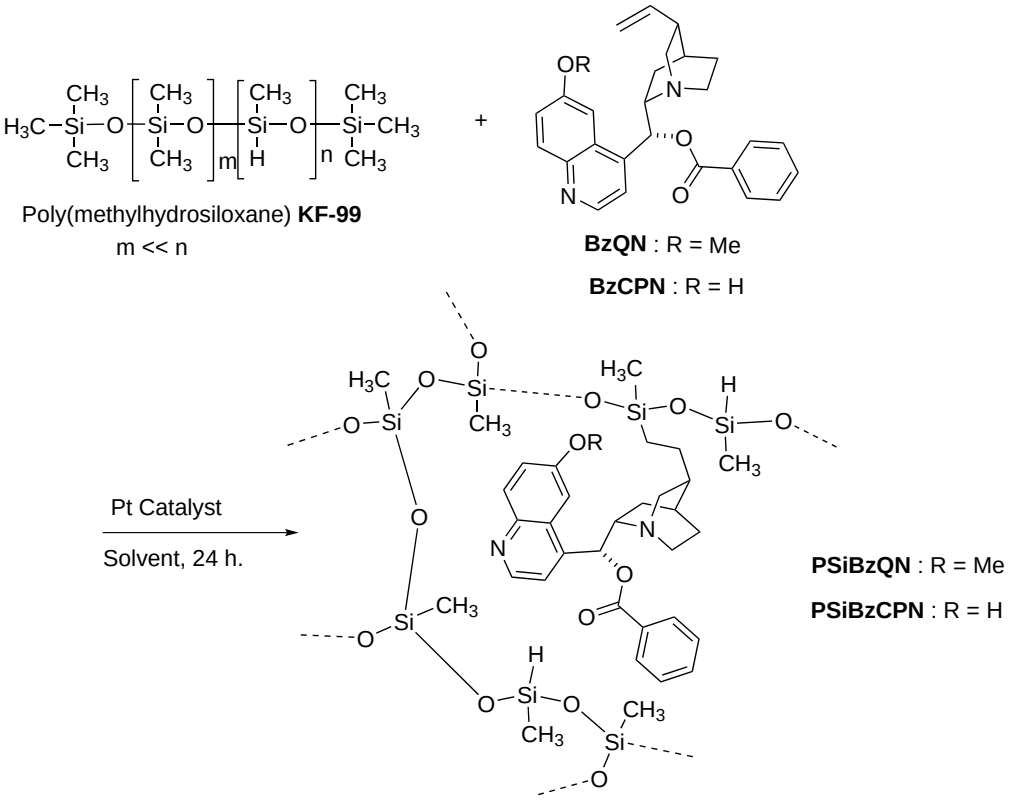

SCHEME 5.2: Synthesis of cinchona urethane dimers by using diisocyanate derivatives **3**




SCHEME 5.3: Hydrosiylation reaction between **BzQN** and chlorodimethylsilane **4**.

### 5.2.3 Synthesis of cross-linked chiral polysiloxanes of cinchona derivatives

Poly(methyl hydrosiloxane) contains Si-H bonds as functional groups in their main chains. The industrially prepared poly(methyl hydrosiloxane) **KF-99** used in this study is miscible with solvents like acetone, hexane, dichloromethane, chloroform, ethyl acetate, ether as well as tetrahydrofuran and immiscible with high polor solvents such as dimethylfornamide and dimethy sulfoxide. With the use of the C3 vinyl unit of cinchona alkaloid derivatives, the hydrosiylation reaction between Si-H functional groups present in poly(methyl hydrosiloxane) and cinchona derivative is feasible. To demonstrate the feasibility of hydrosilylation reaction process with cinchona alkaloid derivatives, low molecular weight compounds were hydrosilylated by using Pt catalyst. The cinchona ester monomer **BzQN** and chlorodimethylsilane **4** with $Cl_2$Ptdcp $\mathbf{K}_3$ as a catalyst were allowed to react in toluene to successfully form **BzQNSi** in good yield (Scheme 5.3). Following this result, other cinchona derived compounds were then hydrosiylated into poly(methyl hydrosiloxane) chains by using Pt as catalyst.




SCHEME 5.4: Synthesis of cross-linked gel-type chiral polysiloxanes of cinchona alkaloids.

#### 5.2.3.1 Synthesis of cross-linked chiral polysiloxane of cinchona monomer

With the same reaction conditions, the immobilization of **BzQN** into PMHS **KF-99** was accomplished to form chiral polysiloxane **PSiBzQN**, the resulted structure is as predicted in Scheme 5.4. The disappearance of olefin signals from $^1$H-NMR with existence of carbonyl group (1735 $cm^{-1}$) and diminished Si-H bond (2200 $cm^{-1}$) from a convenient window in IR spectrum verified the successfully immobilization of **BzQN** into PMHS **KF-99**. Attempt to immobilize **BzCPN** under the same reaction conditions failed because **BzCPN** was not soluble in toluene. **BzCPN** could be easily solubilized in DMF but **KF-99** is not miscible with DMF. However, after several trials with different solvent mixture and Pt catalysts, **BzCPN** were successfully immobilized onto PMHS **KF-99** to form chiral polysiloxane **PSiBzCPN** (Scheme 5.4) by using Toluene/DMF,v/v solvent mixture system as selected during optimization of reaction conditions studies. The results have been summarized in Table 5.1.

Different reaction solvent mixture achieved the hydrosiylated polysiloxane of cinchona alkaloid monomer with a good isolated yield (up to 100 % yield).The transformation phase of poly(methyl hydrosiloxane) into gel under heating condition with Pt catalyst was also

TABLE 5.1: Reaction conditions optimization using **BzCPN** for immobilization into PMHS**KF-99** by hydrosiylation reaction[a].

| Entry | **KF-99** (mmol of Si-H) | **BzCPN** (mmol) | Pt Catalyst (mol%) | Solvent | T (°C) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1[c] | 0.25 g (4.20) | 0.10 g (0.24) | $\mathbf{K}_3$ (3) | Toluene | 100 | 100 |
| 2 | 0.25 g (4.20) | 0 | $\mathbf{K}_1$ (5) | Toluene | 100 | 76 |
| 3 | 0.13 g (2.10) | 0.10 g (0.24) | $\mathbf{K}_1$ (5) | Toluene/DMF | 100 | 96 |
| 4 | 0.13 g (2.10) | 0.10 g (0.24) | $\mathbf{K}_2$ (3) | Toluene/DMF | 100 | 86 |
| 5 | 0.13 g (2.10) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | Toluene/DMF | 100 | 100 |
| 6 | 0.25 g (4.20) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | Toluene/DMF | 100 | 100 |
| 7 | 0.25 g (4.20) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | Toluene/DMSO | 100 | 81 |
| 8 | 0.50 g (8.40) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | Toluene/DMF | 100 | 83 |
| 9 | 0.25 g (4.20) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | THF | 100 | 71 |
| 10 | 0.25 g (4.20) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | DMF | 100 | 68 |
| 11 | 0.25 g (4.20) | 0.10 g (0.24) | $\mathbf{K}_3$ (5) | Toluene/DMF | 60 | 88 |

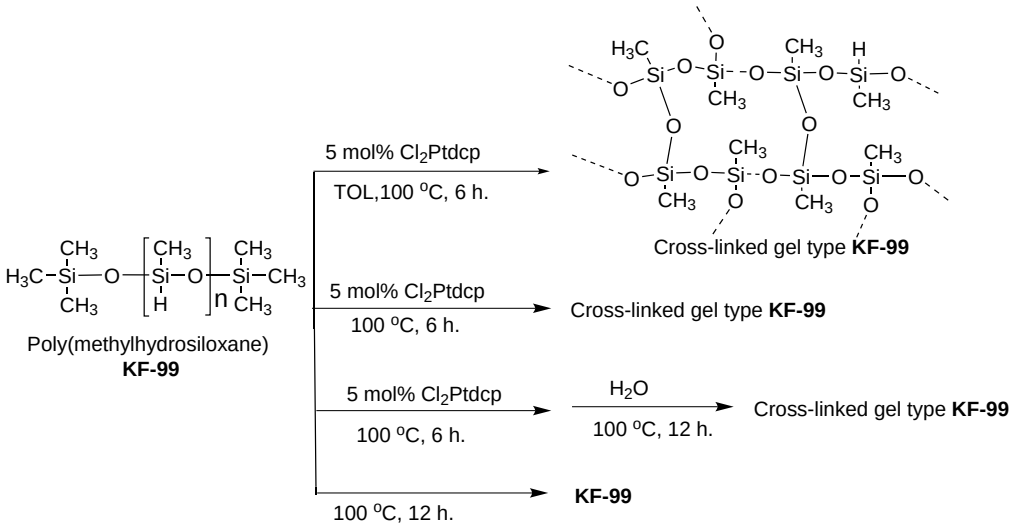
[a]All reactions were carried out with Pt catalyst in a solvent (4/1,v/v) except entries 3 5 (3/1, v/v) at a specific temperature for 24 h. [b]Calculated as weight ratio between isolated polymer to total weight of reacting substrates. [c]Chiral polysiloxane immobilized with cinchona monomer **BzQN**. $\mathbf{K}_1$ = Karstedt's catalyst, $\mathbf{K}_2$ = Speiers' catalyst (Hydrogen hexachloroplatinate (IV) hexahydrate), $\mathbf{K}_3$ = Dichloro di(cyclopentadienyl) platnum II ($Cl_2$Ptdcp

seen. As shown in entry 2 it was possible to recover the polymeric material after reaction. In general, the grafting of **BzCPN** monomer into PMHS**KF-99** was affected with the starting amount of reacting substrates, Pt catalyst type as well as reaction solvent mixture.

We noted that both hydrosilyation and hydrolysis reaction of the poly(methyl hydrosiloxane) occurred simultaneously in the presence of Pt catalyst (as confirmed with the reaction done in entry 2). This may be taken as a reason for a cross-linkage formation of the immobilized chiral polysiloxanes as a result of low catalyst loading. This phenomenon is described in Scheme 5.5, where by, the predicted cross-linked structure of chiral polysiloxanes shown in Scheme 5.4 can be proved. The physical appearance of the gellated poly(methyl hydrosiloxane) **KF-99** is shown in Fig. 5.1. The structure confirmation by IR spectrum for the chiral polysiloxane **PSiBzCPN** is as shown in Fig. 5.2

#### 5.2.3.2 Synthesis of cross-linked chiral polysiloxane of dimeric cinchona derivatives

With the precedents established for poly(methyl hydrosiloxane)s' **KF-99** ability to function as scaffold for C6'-OH free cinchona alkaloid monomer immobilization, it




SCHEME 5.5: Cross-linkage investigations of poly(methyl hydrosiloxane) **KF-99** with Pt catalysis.

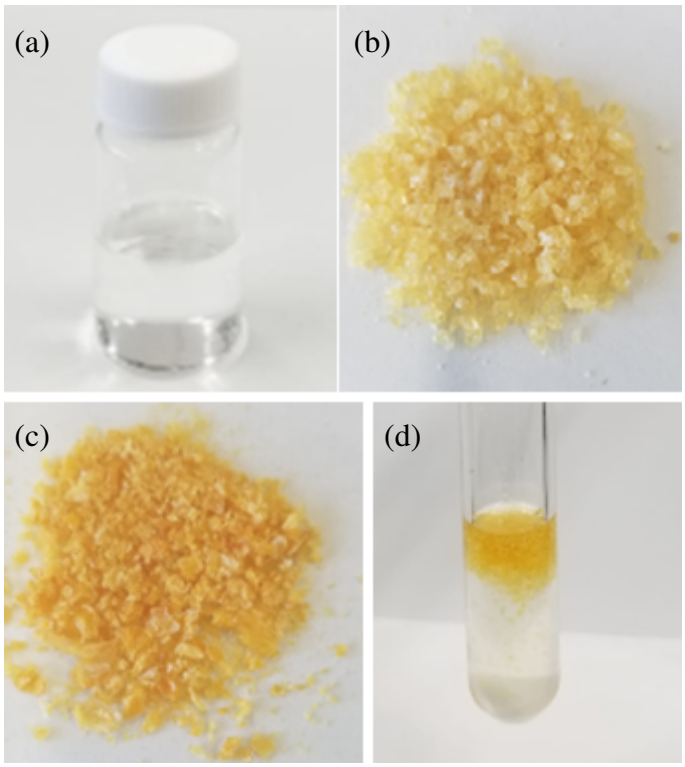



FIGURE 5.1: Physical states of (a) poly(methylhydrosiloxane) **KF-99**, (b) cross-linked gellated PMHS **KF-99**, (c) cross-linked chiral polysiloxane **PSiBzCPN** and (d) suspended chiral polysiloxane **PSiBzCPN** in $CH_2Cl_2$.

became a priority to improve its scope to the use of C6'-OH free dimeric cinchona derivatives. Cinchona alkaloid dimers were used as cross-linking agent into PMHS **KF-99** by hydrosiylation reaction. The dimeric cinchona derivatives each possessing two vinyl units at the C3 position in their molecule, thus made them possible for the hydrosiylation

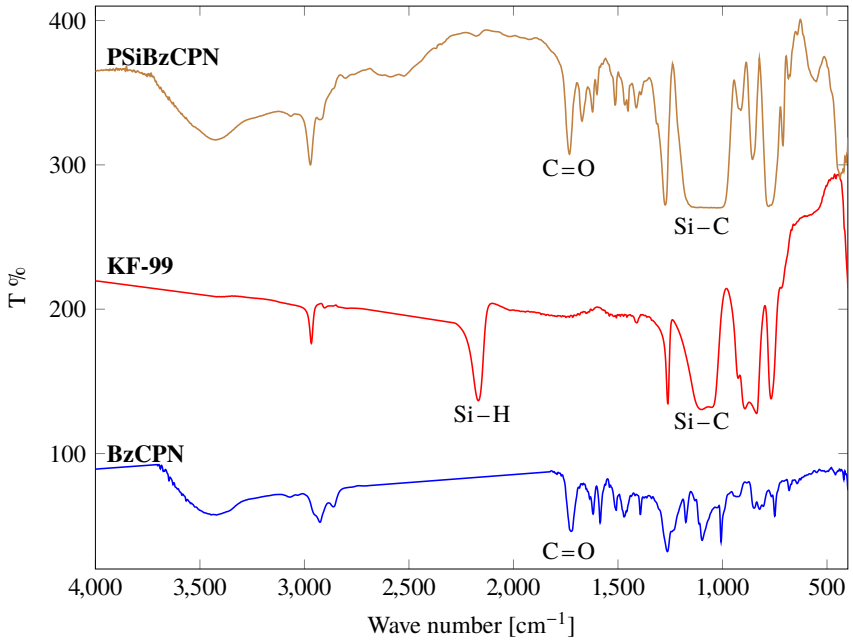



FIGURE 5.2: Structure confirmation of chiral polysiloxane **PSiBzCPN** by IR spectrum comparison with the reacting substrates.

into poly(methyl hydrosiloxane) by Pt catalysis.

Cinchona ester dimers **CPN2** (Scheme 5.1) and cinchona urethane dimers **CPN3** (Scheme 5.2) were used for the preparation of cross-linked chiral polysiloxanes **PSiCPN** (Scheme 5.6). Two solvent mixture system was used as reaction media for hydrosiylation process. The reaction conditions optimization on the cross-linking process of poly(methyl hydrosiloxane) with dimeric cinchona derivatives was done by using dimer **CPN2a**, the same factors as reported in the case of monomeric cinchona derivatives for the formation of cross-linked chiral polysiloxane were observed. The results have been summarized in Table 5.2. The amount of starting reacting substrate, solvent and Pt catalyst type were observed to affect the cross-linking of cinchona dimer **CPN2a** into PMHS**KF-99**. The isolated chiral polymers were free from reacting substrates due to miscibility of poly(methyl hydrosiloxane) in hexane (that was used as precipitating solvent) as well as solubility of the cinchona dimers in methanol (that was used for washing the polymers). The chiral polysiloxanes **PSiCPN** were isolated in good yield (up to 100 % yield) with maximum catalyst loading of 0.56 millmole per gram of isolated polymer. The results have been summarized in Table 5.3. The chiral polymers were literally insoluble in most common solvents and slightly soluble in high polar solvent like DMSO. Their insolubility made characterization by $^{1}$H-NMR or Size Exclusion Chromatography (SEC) impossible. The characterization of chiral polysiloxanes was done by IR spectrum

TABLE 5.2: Reaction conditions optimization using **CPN2a** for immobilization into PMHS **KF-99** by hydrosiylation reaction[a].

| Entry | **KF-99** (mmol of Si-H) | **CPN2a** (mmol) | Pt Catalyst (mol%) | Solvent | T (°C) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 0.30 g (5.00) | 0.24 | $\mathbf{K}_1$ (5) | Toluene/DMF | 100 | 100 |
| 2 | 0.30 g (5.00) | 0.24 | $\mathbf{K}_1$ (3) | Toluene/DMF | 100 | 63 |
| 3 | 0.30 g (5.00) | 0.24 | $\mathbf{K}_1$ (1) | Toluene/DMF | 100 | 50 |
| 4 | 0.30 g (5.00) | 0.24 | $\mathbf{K}_1$ (5) | Toluene/DMF | 60 | 48 |
| 5 | 0.30 g (5.00) | 0.24 | $\mathbf{K}_1$ (5) | Toluene/DMF | 80 | 64 |
| 6 | 0.50 g (8.40) | 0.24 | $\mathbf{K}_1$ (5) | Toluene/DMF | 100 | 46 |
| 7 | 0.20 g (3.36) | 0.24 | $\mathbf{K}_1$ (5) | Toluene/DMF | 100 | 76 |
| 8 | 0.10 g (1.68) | 0.24 | $\mathbf{K}_1$ (5) | Toluene/DMF | 100 | 100 |
| 9 | 0.25 g (4.20) | 0.24 | $\mathbf{K}_2$ (5) | Toluene/DMF | 100 | 90 |
| 10 | 0.25 g (4.20) | 0.24 | $\mathbf{K}_2$ (5) | DMF | 100 | 50 |
| 11 | 0.25 g (4.20) | 0.24 | $\mathbf{K}_3$ (5) | Toluene/DMF | 100 | 100 |
| 12 | 0.25 g (4.20) | 0.12 | $\mathbf{K}_3$ (5) | Toluene/DMF | 100 | 100 |
| 13 | 0.25 g (4.20) | 0.12 | $\mathbf{K}_3$ (5) | Toluene/DMSO | 100 | 60 |
| 14 | 0.25 g (4.20) | 0.12 | $\mathbf{K}_3$ (5) | DMF/Pyridine | 100 | 72 |
| 15 | 0.25 g (4.20) | 0.12 | $\mathbf{K}_3$ (5) | DMF/p-Xylene | 100 | 80 |

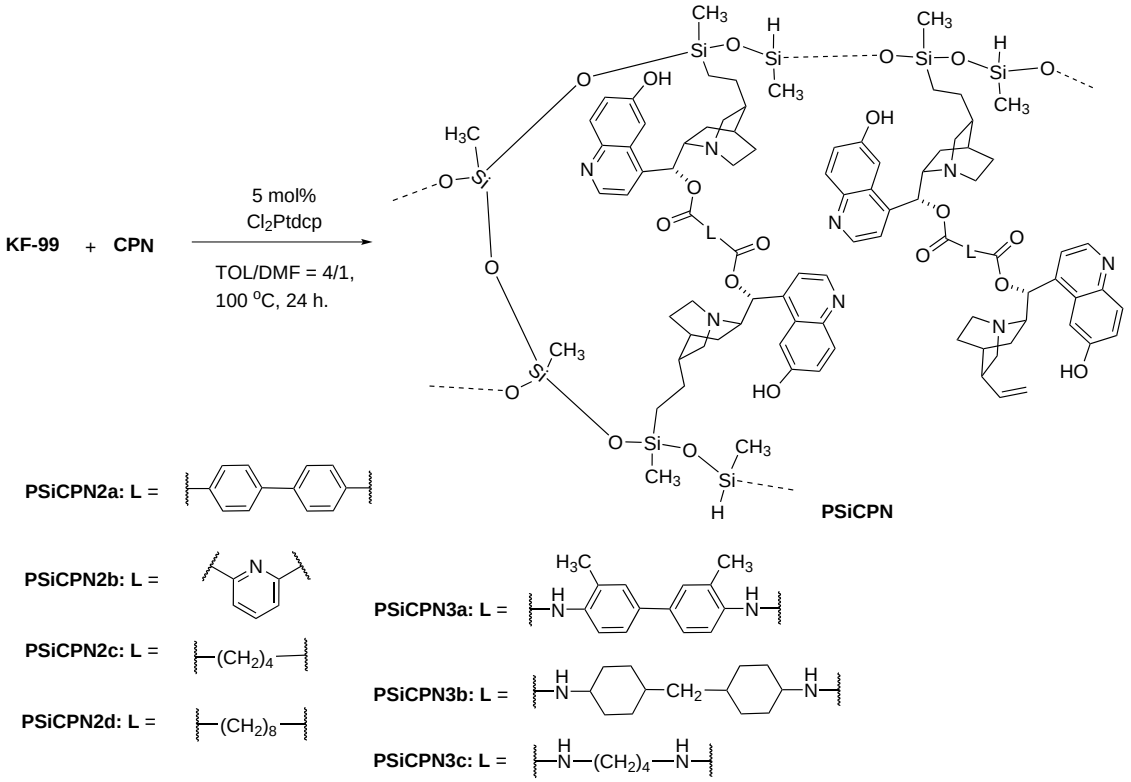
[a]All reactions were carried out with Pt catalyst(K) in a solvent (5 mL). [b]Calculated as weight ratio of the isolated polymer. $\mathbf{K}_1$ = Karstedt's catalyst, $\mathbf{K}_2$ = Speiers' catalyst (Hydrogen hexachloroplatinate(IV) hexahydrate), $\mathbf{K}_3$ = Dichloro di(cyclopentadienyl) platnum (II).

TABLE 5.3: Synthesis of cross-linked chiral polysiloxanes of cinchona alkaloids derivatives.

| Entry | Cinchona Dimer | Chiral Polysiloxanes | [b]Isolated Yield (wt%) |
|---|---|---|---|
| 1 | **CPN2a** | **PSiCPN2a** | 100 |
| 2 | **CPN2b** | **PSiCPN2b** | 100 |
| 3 | **CPN2c** | **PSiCPN2c** | 75 |
| 4 | **CPN2d** | **PSiCPN2d** | 90 |
| 5 | **CPN3a** | **PSiCPN3a** | 88 |
| 6 | **CPN3b** | **PSiCPN3b** | 85 |
| 7 | **CPN3c** | **PSiCPN3c** | 100 |

[a]All reactions were carried out with 5 mol% $Cl_2$Ptdcp $\mathbf{K}_3$ in a mixture of solvent (Toluene/DMF = 4/1, v/v mL) at 100 °C for 24 h. [b]Calculated as weight ratio of isolated polymer to total weight of reacting substrates.

analysis. Representation in Fig. 5.2 shows the IR spectrum of chiral polysiloxane **PSiCPN2a** in comparison to their reacting substrates functional groups.




SCHEME 5.6: Synthesis of cross-linked chiral polysiloxanes **PSiCPN** of cinchona alkaloid derivatives by hydrosiylation reaction.

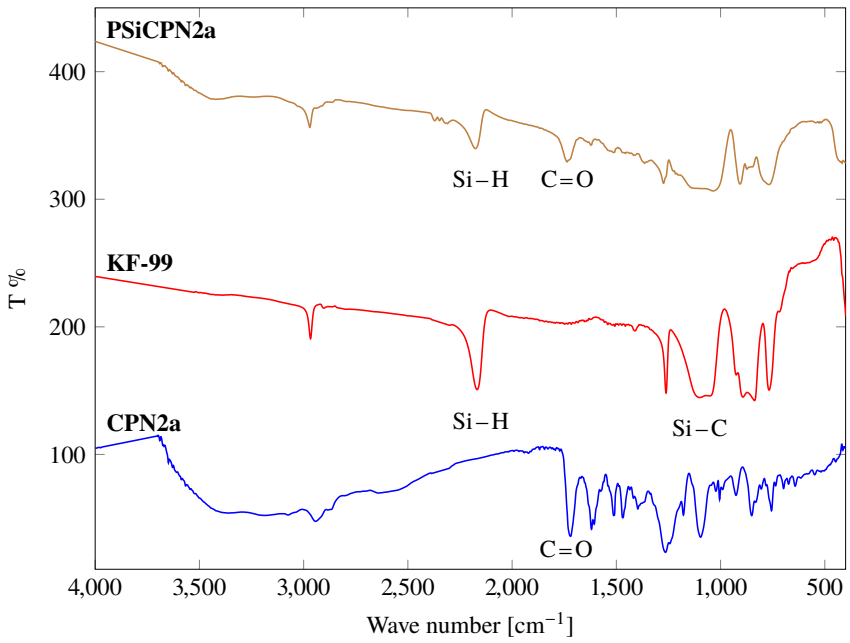



FIGURE 5.3: Structure confirmation of chiral polysiloxane **PSiCPN2a** by IR spectrum comparison.

### 5.2.4 Asymmetric catalysis with cross-linked chiral polysiloxanes of cinchona alkaloid

The presence of C6-OH free in chiral polymeric or lower molecular weight catalyst of cinchona alkaloids derivatives as mentioned in chapter 3 and 4, plays an important role in the asymmetric Michael addition reaction of anthrone to nitroalkenes as well as the addition of $\beta$-ketoester to $\beta$-nitrostyrene. The catalytic performance of the cross-linked chiral polysiloxanes of cinchona alkaloids derivatives were also evaluated in the same asymmetric reactions.

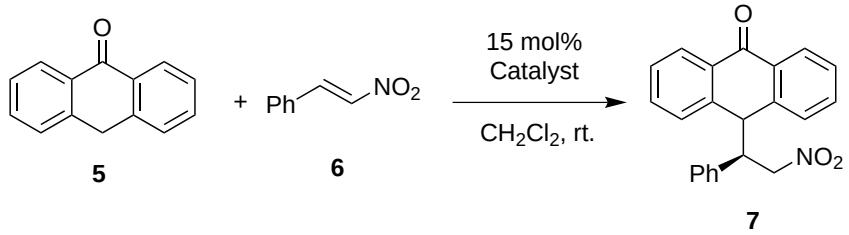
#### 5.2.4.1 Asymmetric Michael addition of anthrone and $\beta$-nitrostyrene

The catalytic performance of C6'-OH free cross-linked chiral polysiloxanes of cinchona derivatives were also examined in the Michael addition reaction (Scheme 5.7). The chiral polysiloxanes **PSiBzQN**, **PSiBzCPN**, **PSiCPN**, were used as catalysts for the formation of Michael product **7**. Despite of the insolubility of the chiral polysiloxanes in the reaction solvent, the heterogeneous system efficiently catalyzed the asymmetric Michael addition of anthrone **5** to $\beta$-nitrostyrene **6** for the formation of **7**. The results on their evaluation have been summarized in Table 5.4. The C6'-OMe chiral polysiloxane **PSiBzQN** showed poor enantioselectivity of 13 % ee (entry 1) compared to the corresponding C6'-OH free chiral polymer **PSiBzCPN** that achieved 84 % ee (entry 2).

In general, cinchona ester chiral polysiloxanes showed higher enantioselectivities (entries 2 – 6) when compared with cinchona urethane chiral polysiloxanes (entries 7 – 9). All the chiral polymers gave nearly the same catalytic activities but relatively lower compared to their corresponding lower molecular weight catalysts shown in Table 5.5. Lower enantioselectivities achieved by chiral polysiloxanes in comparison to their lower molecular weight catalysts could be attributed by the polymeric structure as well as heterogeneous nature of the catalysts in reaction mixture (Table 5.4 vs Table 5.5). The polymeric catalyst **PSiCPN2a** showed the highest enantioselectivity of 86 % ee in the formation of Michael product **7**.

#### 5.2.4.2 Asymmetric Michael addition of $\beta$-ketoester and $\beta$-nitrostyrene

We then evaluated the effect of Michael donor substrate in the enantioselective synthesis with cinchona ester chiral polysiloxanes. Michael donor $\beta$-ketoester **8** was used in the asymmetric reaction as presented in Scheme 5.8. Chiral polysiloxanes **PSiBzCPN**,




SCHEME 5.7: Enantioselective synthesis of Michael product **7** with chiral polysiloxanes of cinchona alkaloid derivatives.

TABLE 5.4: Polymeric effect on enantioselective synthesis of **7** with chiral polysiloxane[a].

| Entry | Chiral Polysiloxane | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **PSiBzQN** | 36 | 85 | 11 |
| 2 | **PSiBzCPN** | 48 | 90 | 84 |
| 3 | **PSiCPN2a** | 36 | 80 | 86 |
| 4 | **PSiCPN2b** | 48 | 88 | 79 |
| 5 | **PSiCPN2c** | 48 | 85 | 82 |
| 6 | **PSiCPN2d** | 48 | 75 | 84 |
| 7 | **PSiCPN3a** | 48 | 80 | 62 |
| 8 | **PSiCPN3b** | 48 | 85 | 74 |
| 9 | **PSiCPN3c** | 48 | 75 | 57 |

[a]All reactions were conducted with anthrone **5** (0.24 mmol) and $\beta$-nitrostyrene **6** (0.20 mmol) as substrates with 15 mol% of catalysts in $CH_2Cl_2$ (2.0 mL) under the specified time at room temperature to give **7**(R).[13] [b]Isolated yield of product. [c]Determined by HPLC (Chiralcel AS-H column with hexane/isopropyl alcohol = 5/1 as eluent at a flow rate of 0.7 mL/min.

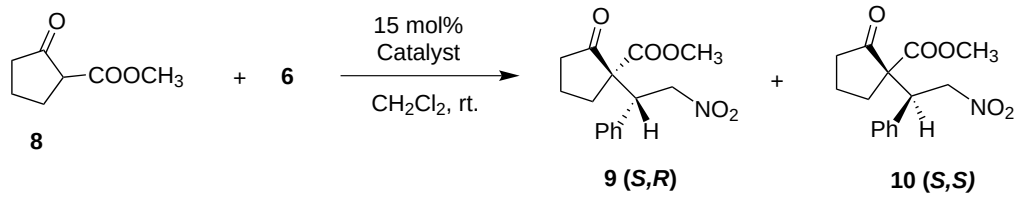
**PSiCPN2a** and **PSiCPN2d** were used as catalysts in the enantioselective synthesis of Michael products **9** and **10** as major and minor diastereomer respectively. The results have been summarized in Table 5.6. The C6'-OMe containing chiral polysiloxanes showed high enatioselectivity of the major diastereomer (84 % ee) and very poor enantioselectivity in case of minor diastereomer (37 % ee) with moderate diastereomeric (entry 1). The opposite was seen in case C6'-OH free chiral polysiloxanes, the polymeric catalysts showed higher enantioselectivities and diastereoselectivities for both diastereomer.

Either the monomeric or the dimeric cinchona immobilized chiral polysiloxanes showed good catalytic performances in the enantioselective synthesis of Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene. In general, cinchona ester chiral polysiloxanes catalysts showed higher diastereoselectivies in comparison to their corresponding lower molecular weight catalysts (Table 5.6 vs Table 5.7). The chiral polymeric catalyst **PSiCPN2a**

TABLE 5.5: Effect of low molecular weight chiral organocatalysts in the formation of **7**[a].

| Entry | Chiral catalyst | Time (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **BzQN** | 12 | 84 | 9 |
| 2 | **BzCPN** | 12 | 94 | 96 |
| 3 | **CPN2a** | 24 | 80 | 98 |
| 4 | **CPN2b** | 24 | 75 | 84 |
| 5 | **CPN2c** | 24 | 79 | 98 |
| 6 | **CPN2d** | 24 | 88 | 90 |
| 7 | **CPN3a** | 12 | 95 | 86 |
| 8 | **CPN3b** | 12 | 94 | 84 |
| 9 | **CPN3c** | 12 | 92 | 86 |

[a]All reaction was done with anthrone **5** (0.24 mmol), nitrostyrene **6** (0.20 mmol) and 15 mol% of catalyst at room temperature to give **7**(*R*). [b]Isolated yield of the product. [c]Determined by using the HPLC–Chiralcel AS-H column with hexane/isopropyl alcohol = 5/1 as eluent at a flow rate of 0.7 mL/min.




SCHEME 5.8: Enantioselective Michael addition of $\beta$-ketoester **8** and $\beta$-nitrostyrene **6** by cinchona ester chiral polysiloxanes.

TABLE 5.6: Asymmetric Michael addition of $\beta$-ketoestor and $\beta$-nitrostyrene catalyzed by chiral polysiloxanes[a].

| Entry | Chiral Polysiloxane | Time (h) | Yield[b] (%) | $ee^{c}_{\mathbf{9}}$ (%) | $ee^{c}_{\mathbf{10}}$ (%) | dr[b] |
|---|---|---|---|---|---|---|
| 1[d] | **PSiBzQN** | 48 | 60 | 84 | 37 | 3.4:1 |
| 2 | **PSiBzCPN** | 48 | 79 | 98 | 96 | 2.5:1 |
| 3 | **PSiCPN2a** | 60 | 75 | 98 | 92 | 4.8:1 |
| 4 | **PSiCPN2d** | 60 | 65 | 99 | 88 | 4.5:1 |

[a]All reaction were performed with $\beta$-ketoester **8** (0.50 mmol), $\beta$-nitrostyrene **6** (0.60 mmol) in $CH_2Cl_2$ (2.5 mL) at room temperature for the formation of **9** and **10** as major and minor diastereomers respectively.[21] [b]Isolated yield of the product. [c]Determined by HPLC (Chiralcel OD-H column with hexane/isopropanol = 4/1 as eluent at a flow rate of 1 mL $min^{-1}$). [d]Chiral polysiloxanes with C6'-OMe.

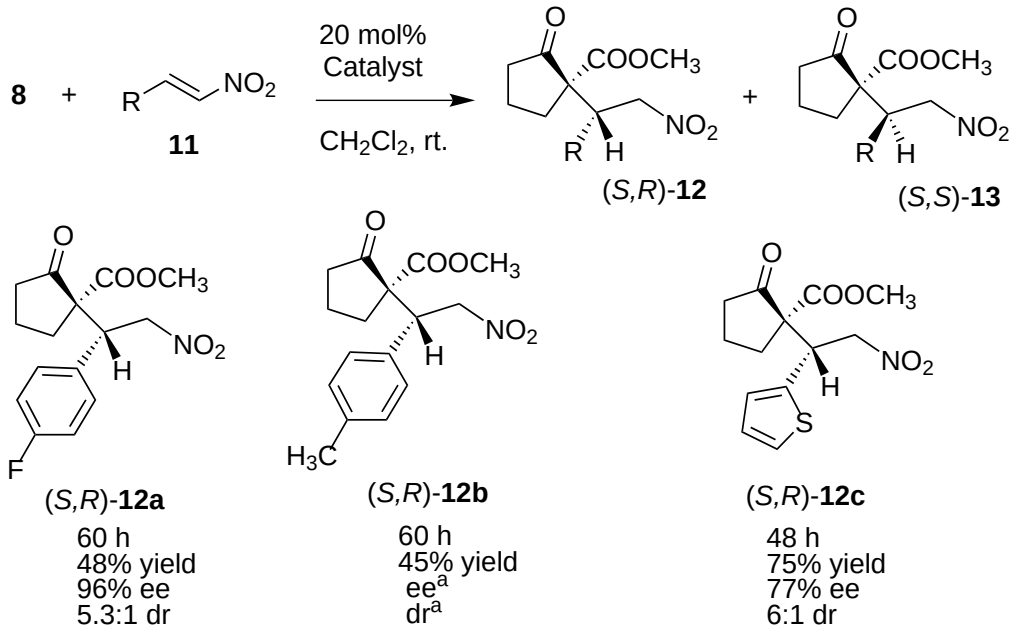
achieved 98 % ee and 92 % ee of **9(*S,R*)** and **10(*S,S*)** respectively with a highest diastereomeric ratio of 4.8:1 dr (Table 5.6, entry 3).

With these finding, further substrate scope evaluation was done by using different nitroalkene derivatives **11**. The results have been summarized in Scheme 5.9. The

TABLE 5.7: Asymmetric Michael addition of $\beta$-ketoestor and $\beta$-nitrostyrene catalyzed by low molecular weight cinchona derivatives[a].

| Entry | Chiral | Yield[b] (%) | $ee^{b}_{\mathbf{9}}$ (%) | $ee^{c}_{\mathbf{10}}$ (%) | dr[c] |
|---|---|---|---|---|---|
| 1 | **BzQN** | 80 | 71 | 20 | 1:3.4 |
| 2 | **BzCPN** | 75 | 95 | 93 | 3.4:1 |
| 3 | **CPN2a** | 83 | 93 | 91 | 5.6:1 |
| 4 | **CPN2d** | 85 | 98 | 88 | 4.5:1 |

[a]All reaction were performed with $\beta$-ketoester **8** (0.50 mmol), $\beta$-nitrostyrene **6** (0.55 mmol) and 15 mol% catalyst in $CH_2Cl_2$ (2.5 mL) at room temperature for 24 h.[21] [b]Isolated yield of the product. [c]Determined by HPLC (Chiralcel OD-H column with hexane/isopropanol = 4/1 as eluent at a flow rate of 1 mL $min^{-1}$).




SCHEME 5.9: Enantioselective Michael addition of $\beta$-ketoester **8** and nitroalkenes **11** with cinchona ester cross-linked chiral polysiloxanes.[a]Stereoselectivity was not determined due to peak separation problem.

Michael donor with electron donating group gave higher enantioselectivity of 96 %ee with diastereomeric ratio of 5.3:1 for the Michael products **12**, **13** with **PSiCPN2d** as a catalyst.

*Reaction conditions optimization*: Chiral polymer **PSiCPN2a** was used for reaction conditions evaluation in the formation of Michael products **9(*S,R*)** and **10(*S,S*)** in Scheme 5.8. The results have been summarized in Table 5.8. Higher enantioselectivities of both diastereomers were obtained when the reactions was done at room temperature in different reaction solvent. The highest enantioselectivities of 98 % ee and 96 % ee with diastereomeric ratio of 2.5:1 dr for the formation of major **9(*S,R*)** and minor **10(*S,S*)** diastereomers,

TABLE 5.8: Reaction conditions optimization with cinchona ester chiral polysiloxane **PSiCPN2a**[a].

| Entry | Solvent | T (°C | Time (h) | Yield[b] (%) | $ee^{c}_{\mathbf{9}}$ (%) | $ee^{c}_{\mathbf{10}}$ (%) | dr[c] |
|---|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | 48 | 85 | 98 | 96 | 2.5:1 |
| 2[d] | $CH_2Cl_2$ | rt | 48 | 70 | 98 | 92 | 5.4:1 |
| 3 | $CH_2Cl_2$ | −40 | 72 | 50 | nd[e] | nd[e] | nd[e] |
| 4 | $CH_2Cl_2$ | 50 | 12 | 75 | 99 | 77 | 4.2:1 |
| 5 | MeOH | rt | 48 | 55 | 98 | 79 | 5.2:1 |
| 6 | $Et_2O$ | rt | 48 | 74 | 99 | 88 | 2.9:1 |
| 7 | Hexane | rt | 48 | 60 | 96 | 82 | 3.4:1 |
| 8 | $CH_3CN$ | rt | 48 | 80 | 96 | 85 | 4.3:1 |
| 9 | EtOAc | rt | 48 | 65 | 99 | 87 | 3.4:1 |
| 10 | THF | rt | 48 | 48 | 99 | 91 | 5:1 |

[a]All reaction were performed with $\beta$-ketoester **8** (1.00 mmol), $\beta$-nitrostyrene **6** (1.10 mmol) and 20 mol% of chiral catalyst in $CH_2Cl_2$ (5.0 mL) at a specified temperature.[15–21] [b]Isolated yield of the product. [c]Determined by HPLC (Chiralcel OD-H column with hexane/isopropanol = 4/1 as eluent at a flow rate of 1 mL $min^{-1}$). [d]Carried out with 15 mol% of catalyst. [e]Not determined due to peak separation problem.

respectively were obtained with **PSiCPN2a** as catalyst in $CH_2Cl_2$ (entry 1). In addition, other solvents like MeOH, hexane, $Et_2O$ and THF gave higher enantioselectivities of major diastereomer and slightly lower enantioselectivities of minor diastereomer with good diastereoselectivities were obtained with chiral polymeric catalyst **PSiCPN2a**.

*Recyclability*: The insolubility of chiral polysiloxane **PSiCPN2a** in reaction solvent made its isolation from the reaction mixture very easy. At the end of reaction in each cycle, the reaction mixture was centrifuged and the catalyst was separated. The catalyst was used in the next cycle without any further purification. The recovered catalyst could be used for several times without losing its catalytic performance. The results on recyclability test for the enantioselective synthesis of Michael product **9**have been summarized in Table 5.9. Higher enantioselectivities and diastereoselectivities with sufficient catalytic activities were observed in all cycles. Both minor and major diastereomers showed constantly higher enantioselectivities.

TABLE 5.9: Recyclability test with cinchona ester chiral polysiloxanes[a].

| Entry | Run | Yield$^{b}_{\mathbf{7}}$ (%) | ee$^{c}_{\mathbf{9}}$ (%) | ee$^{c}_{\mathbf{10}}$ (%) | dr$^{c}$ |
|---|---|---|---|---|---|
| 1 | Fresh | 88 | 98 | 96 | 2.5:1 |
| 2 | Cycle 1 | 80 | 99 | 90 | 4.5:1 |
| 3 | Cycle 2 | 85 | 98 | 88 | 3.4:1 |
| 4 | Cycle 3 | 79 | 96 | 82 | 3.4:1 |
| 5 | Cycle 4 | 84 | 99 | 88 | 3.9:1 |
| 6 | Cycle 5 | 78 | 97 | 79 | 3.7:1 |

[a]All reaction were performed with $\beta$-ketoester **8** (1.00 mmol), $\beta$-nitrostyrene **6** (1.20 mmol) and 20 mol% of chiral catalyst in $CH_2Cl_2$ (5.0 mL) at room temperature for 2 days.[15–21] [b]Isolated yield of the product. [c]Determined by HPLC (Chiralcel OD-H column with hexane/isopropanol = 4/1 as eluent at a flow rate of 1 mL min$^{-1}$).

## 5.3 Conclusion

Cross-linked gel type chiral polysiloxanes of cinchona alkaloid were successfully synthesized by hydrosilylation reaction. The immobilization of C3-vinyl group of the cinchona alkaloid derivatives into poly(methylhydrosiloxane) **KF-99** as catalyzed by Pt, resulted in a successful formation of substituted Si-C bond. The C6'-OMe and C6'-OH free cinchona alkaloid derivatives were used for the immobilization into poly(methylhydrosiloxane). The hydrosiylation and hydrolysis reactions in the presence of Pt catalyst resulted into a cross-linked gel type structures of chiral polysiloxanes of cinchona derivatives. The chiral polymers were insoluble in most common organic solvents. The catalytic performance of the cross-linked gel type chiral polysiloxanes of cinchona alkaloid derivatives were evaluated in asymmetric Michael addition reactions. The asymmetric Michael addition of anthrone to $\beta$-nitrostyrene as well as the addition of $\beta$-ketoester to $\beta$-nitrostyrene were used for the catalytic performance evaluations. The C6'-OH free cross-linked gel type chiral polysiloxanes of cinchona alkaloid derivatives showed high level of enantioselectivities with sufficiency catalytic activities in the Michael addition reactions.

## 5.4 Experimental part

### 5.4.1 General methods and materials

All solvents and reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry (TCI) Co., Ltd. at the highest available purity and were used as received, unless otherwise stated. poly(methyl hydrosiloxane) **KF-99** was used as received from Shin-Etsu Chemical Co. Ltd. Reactions progress were monitored by analytical thin-layer chromatography (TLC) using pre-coated silica gel plates (Merk TLC silica gel, 60F254). Column chromatography was performed using silica gel column (Wakogel C-200, 100 – 200 mesh). NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in $CDCl_3$ or DMSO-d6 at room temperature operating at 400 MHz ($^1$H) and 100 MHz ($^{13}$C{$^1$H}). Tetramethylsilane (TMS) was used as an internal standard for 1H NMR and $^{13}$C NMR in $CDCl_3$. Chemical shifts are reported in parts per million (ppm), and the J values were recorded in hertz (Hz). The IR spectral were recorded on a JEOL JIR-7000 FTIR spectrometer by using KBr pellets, wave numbers are reported in $cm^{-1}$. Highly-performance liquid chromatography (HPLC) was performed with a JASCO HPLC system composed of a DG-980-50 three-line degasser, intelligence HPLC pump (PU 2080), and UV/VIS detector (UV-2075), equipped with a chiral column (Chiralpak AS-H) with hexane/2-propanol as an eluent at a flow rate of 0.7 mL/min at room temperature or (Chiralpak OD-H) with hexane/2-propanol as an eluent at a flow rate of 1 mL $min^{-1}$ at 25 °C.

### 5.4.2 General experimental procedures

#### 5.4.2.1 Synthesis of CPN2b

Procedure as modified from literature is explained: Thionyl chloride (30 mL) was added to pyridine 2, 6 dicarboxylic acid (1.00g, 5.988 mmol) and refluxed at 80 °C under argon atmosphere for 3 h until clear yellow solution was obtained. The excess thionly chloride was removed under reduced pressure. The product was dried in vacuum oven at 40 °C for 3 hour and the white precipitate of 2,6-pyridinedicarbonyl dichloride was obtained (99 % yield). No purification was done. Then, into a solution of quinine (1.00 g, 3.086 mmol) in dry $CH_2Cl_2$ (15 mL) at 0 °C, 2 mL of triethylamine was added to the solution and stirred. 2,6-pyridinedicarboxylic dichloride (0.38 g, 1.543 mmol) was added

portion wise and stirred for 1 hour at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was poured into 10 mL water, the organic layer was separated, and washed with saturated NaCl solution and water. The organic solution was dried over $MgSO_4$ and evaporated in vacuo followed by purification by flash chromatography on silica gel (EtOAc/EtOH/$Et_3N$ = 7/3/0.5) to obtain solid white product of **QN2b** (66 % yield).

Under argon atmosphere, **QN2b** was dissolved in dry $CH_2Cl_2$ and cooled to −78 °C. Then, 40-mmol equiv. of 1M boron tribromide solution in $CH_2Cl_2$ was added slowly over 10 minutes and the mixture was stirred for 2 h. The mixture was then transferred to room temperature and allowed to stir further for 2 days. To the reaction mixture, NaOH 10 % w/w solution and pure water was carefully added simultaneously to adjust the solution mixture to around 12 pH and the organic phase was separated. The aqueous phase was then neutralized with 2N HCl to around 8 pH. The precipitate was seen. The observed precipitates were filtered, washed by $H_2O$ followed by $CH_2Cl_2$ and dried to obtain **CPN2b** (78 % yield).

#### 5.4.2.2 Asymmetric Michael addition of anthrone to $\beta$-nitrostyrene

A representative procedure is described: (Table 5.4, entry 3) In a 10 mL flask, $\beta$-nitrostyrene **6** (30 mg, 0.200 mmol) were dissolved in $CH_2Cl_2$ (2.0 mL) and 15 mol% of chiral polysiloxane **PSiCPN2a** (calculated based on catalyst loading in the polymer in mmol/g) were dispersed and stirred for 10 min at room temperature. Anthrone **5** (47 mg, 0.24 mmol) was added to the mixture and stirred for 36 h. The reaction mixture was centrifuged and the catalyst was separated from the mixture. The solution was then concentrated in *vacuo*. The residue was purified by silica gel column chromatography using hexane/EtOAc = 5/1 as eluent and Michael product **7** was obtained as a white solid (69 mg, 92%). HPLC analysis (Chiralcel AS-H column with hexane/2-propanol = 5/1, v/v, at a flow rate of 0.7 mL/min) for **7** showed the enantioselectivity of 86% ee.

#### 5.4.2.3 Asymmetric Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene

A representative procedure is described: (Table 5.6, entry 3) In a 10 mL flask, *beta*-nitrostyrene **6** (82 mg, 0.55 mmol) was dissolved in $CH_2Cl_2$ (2.5 mL) and 15 mol% catalyst **PSiCPN2a** (calculated based on catalyst loading in the polymer in mmol/g) was dispersed into a solution and stirred for 10 minutes at room temperature. Methyl 2-oxocyclopentanecarboxylate **8** (63 $\mu$L, 0.50 mmol) was added to the mixture and stirred

for 24 h. The reaction mixture was centrifuged and the catalyst was separated. The filtrate was then concentrated in vacuo and the residue was purified by silica gel column chromatography with hexane/EtOAc = 6/1 as eluent to afford the Michael products **9** and **10** as a white solid (0.12 g, 75% yield). HPLC analysis (Chiralcel OD-H column with hexane/2-propanol = 4/1 at a flow rate of 1.0 mL/min) showed the diastereomeric ratio of **9** and **10** (4.8:1 dr) and enantioselectivities of 98% ee and 92% ee, respectively.

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# Chapter 6

# General Conclusion

## 6.1 Introduction

Chiral polymeric catalysts have received significant attention owing to their easy separation from the reaction mixture and their recyclability. Chiral polymeric organocatalysts as a class of chiral organocatalysis possesses additional advantages of being derived from a metal-free catalyst hence providing a clean and safe alternative to conventional methods of asymmetric processes. Not only that they can be applied to a contionous flow system and their practicality but also the particular microenvironment they create in a polymer network makes them attractive for utilization in organic reactions especially in stereoselective synthesis.

Even though polymeric organocatalysts in asymmetric synthesis, sometimes exhibit poor reactivity by virtual of their heterogeneity. However, a well-designed polymeric chiral organocatalyst leads to higher selectivity with sufficient reactivity in asymmetric reactions.

Because, chemically modified cinchona alkaloids have produced various chiral organocatalysts suitable for different kinds of asymmetric transformations. As a privileged class of chirality inducers, cinchona alkaloids have found part in chiral polymeric organocatalysts design. In the progress of addressing the early stated challenges of using polymeric organocatalysts in asymmetric synthesis. The polymeric catalyst design is an essential tool to understand the efficient catalytic process in asymmetric transformations. For this reason, cinchona alkaloid derivatives were used for the design of chiral polymeric organocatalysts in this work. We have reported mainly two types of chiral polymers designed from cinchona alkaloids derivatives, these are; main-chain type chiral polymeric organocatalysts and cross-linked chiral organocatalysts. The catalytic performance evaluation of these chiral polymers were done in asymmetric Michael addition reactions.

## 6.2 The main-chain chiral polymers of cinchona alkaloids by MH-polymerization

Mizoroki-Heck coupling reaction was used for the preparation of main-chain chiral polymers of cinchona alkaloids derivatives in chapter 3 and 4. We have reported on the design and synthesis of main-chain chiral polymers of cinchona alkaloids as catalysts for their application in asymmetric reactions. Our design of chiral polymers involves the use of C3 olefinic double bond of the cinchona alkaloid derivatives through Mizoroki-Heck (MH) coupling reaction of aryl diiodides and we called the approach as two components polycondensation'. Another approach was one-component polycondensation' where by the cinchona monomer with the C3 olefin double bond and aromatic diiodide in its molecule was used for polymerization via MH-reaction. The C9-cinchona esters and C9-cinchona urethanes derivatives have been used for the preparation of main-chain chiral polymeric organocatalysts. We named the polymers as, chiral polyesters when C9-cinchona ester derivatives were used during polymerization and chiral polyurethanes when C9-cinchona urethane derivatives were used during polymerization. Some of the observed characteristic features of the main-chain chiral polymers includes;

i. The linearly 1D geometrical properties

ii. The synthetic method was spontaneously one-step reaction

iii. The best method of the purification after polymerization was by precipitation

iv. Their reaction could be easily scaled-up

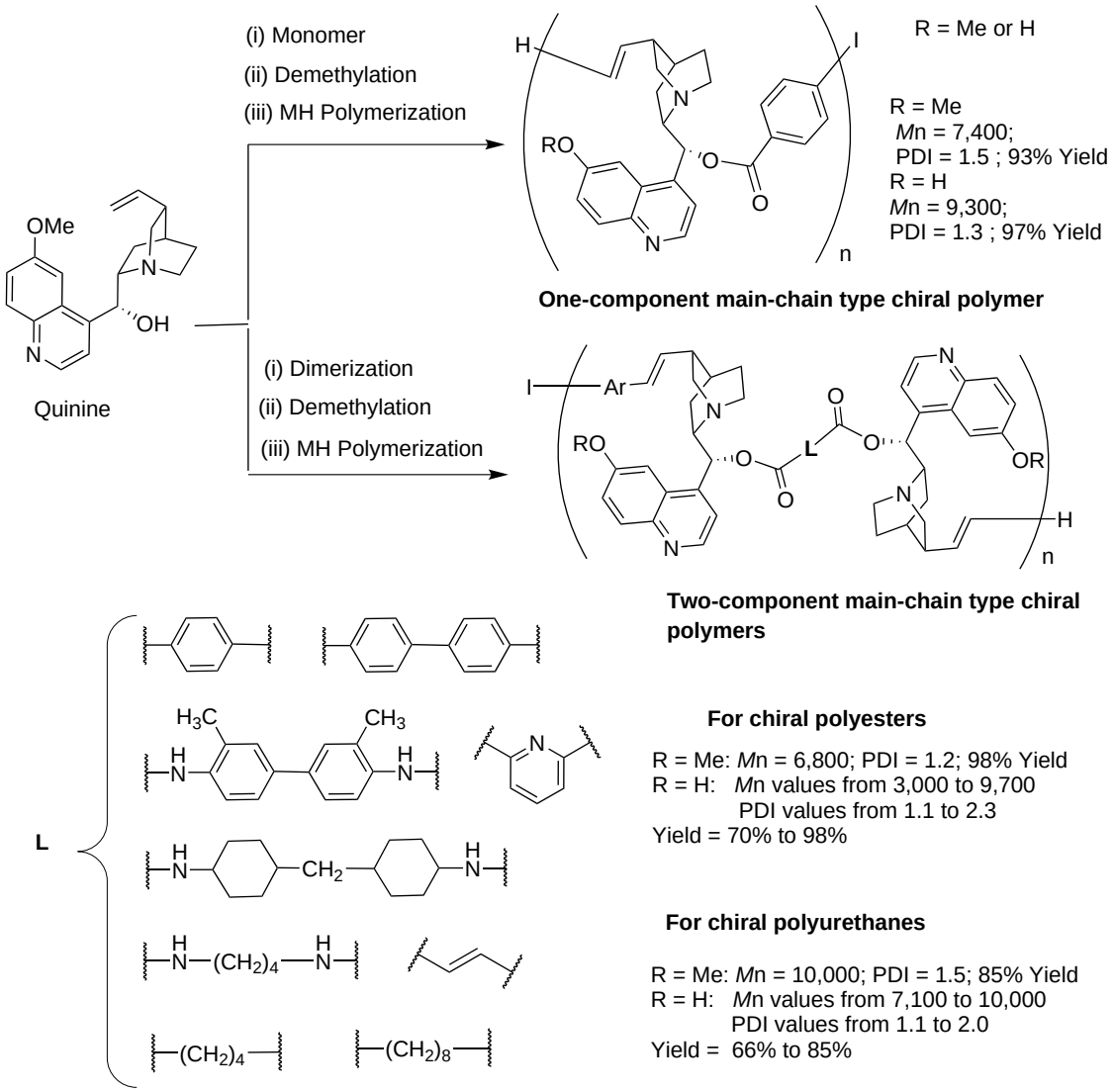
v. They possess variable molecular weights and PDI values of more than 1.1

vi. The entanglement between the reacting molecules was controlled by their structural properties

vii. The solubility of the polymers were low due their high viscosities

viii. The functional groups are available at the two terminal ends of the polymer

In the preparation of main-chain chiral polymers, quinine was used as a starting material in the preparation of monomeric or dimeric cinchona alkaloid derivatives. Different kinds of either ester or urethane derivatives were prepared. The cinchona derivatives

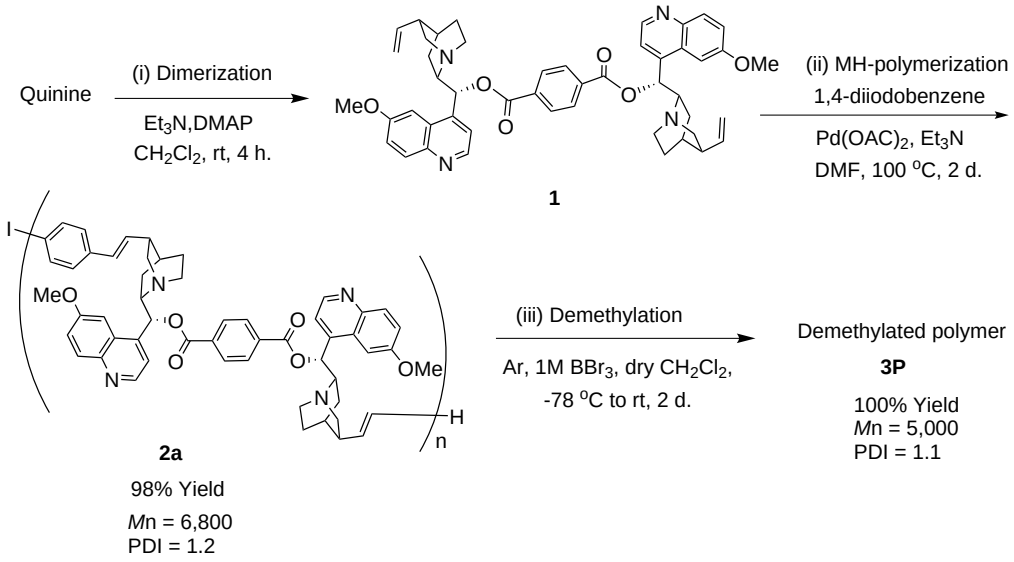



SCHEME 6.1: Synthetic route of main-chain chiral polymeric organocatalysts.

were then used for polymerization by MH- coupling reaction. The cinchona monomers possessing aromatic iodide and olefinic double bond were used for one-component main-chain type chiral polymer preparation, while the dimeric cinchona alkaloids containing two olefinic double bonds in their molecules were polymerized with aromatic diiodides compounds by MH-coupling reaction to obtain main-chain chiral polymeric structures. The terminal ends of the chiral polymers possesses the iodine and hydrogen as their functional groups ( Scheme 6.1). General characterization methods for the main-chain chiral polymers in this work involves;

i. Proton-NMR analysis

ii. Size exclusion (SEC) measurements analysis




SCHEME 6.2: Functionalization of the main-chain chiral polymer by demethylation reaction.

iii. Specific rotation measurements

iv. FT-IR spectrum analysis

The summary on the synthetic route for the main-chain chiral polymers of cinchona alkaloids derivatives is as shown in Scheme 6.1. The chiral polymers were all obtained in good yields with high average number molecular weights and good polydispersity indexes. In general, the synthesis sequence of main-chain chiral polymers of cinchona alkaloids in this work involves mono or di-merization, demethylation and finally polymerization. Another way of obtaining C6'-OH free chiral polymer is by demethylation after polymerization. However, this approach gives partial demethylation of the functional group, Scheme 6.2 describes the synthetic approach for chiral polymer **3P**.

### 6.2.1 Synthesis of main-chain chiral polyurethanes by diisocyanates-diols reaction

Despite of the synthetic route for chiral polyurethanes described in Scheme 6.1, another possible way to obtain main-chain chiral polyurethanes is by using diisocyanates-diols reaction. In this reaction, the MH-coupling reaction was used for the preparation of diol-dimer **5** derived from quinine, then the C9-OH of the dimer were allowed to reacts alternatively with 4,4'-diisocyanato-3,3'-dimethylbiphenyl **6** under reflux condition to form the main-chain chiral polymer **7P**. The chiral polymer was then subjected under 1M

$BBr_3$ to obtain a demethylated polymer **8P**. The synthetic route is as shown in Scheme 6.3.

### 6.2.2 The catalytic performance of main-chain chiral polymers of cinchona alkaloids

The main-chain chiral polymers as presented in chapter 3 and 4 were then evaluated in the Michael addition reactions for their catalytic performance. Asymmetric Michael addition of anthrone to $\beta$-nitrostyrene as well as the addition of $\beta$-ketoester to $\beta$-nitrostyrenes were used for catalytic performance evaulations. The following were the parameters used for their evaluation in asymmetric synthesis;

i. The effect of C6'-substituent group

ii. Monomeric, dimeric as well as polymeric structure effects

iii. Primary and secondary linker structure effects

iv. Solvent effect

v. Reaction conditions effect i.e. temperature, catalyst loading

vi. Reacting substrates effect

vii. Recyclability and stability evaluation

Each of the evaluated parameters showed different catalytic effect in the enantioselective synthesis of Michael products with chiral polymeric organocatalysts of cinchona alkaloids derivatives.

*The C6'-functional group of cinchona alkaloids derivatives*: With either the esters' or urethanes' cinchona alkaloid organocatalysts in the enantioselective synthesis of the Michael products, the C6'-OH free catalysts showed higher enantioselectivities compared to the C6'-OMe containing catalysts. The cinchona ester derivatives organocatalysts in Fig. 6.1 and the cinchona urethane derivatives organocatalysts in Fig. 6.2 are examples of the catalysts used for the enantioselective synthesis in Michael additions reactions in Scheme 6.3 and Scheme 6.4. The structure of the catalyst as well as the existence of C6'-OH have been the major factors for the effective enantiosective synthesis of Michael adduct **11**. The whole phenomenon is as summarized in Scheme 6.4. The chiral polymeric catalyst **3P**, where the C6'-OH free were obtained after polymerization

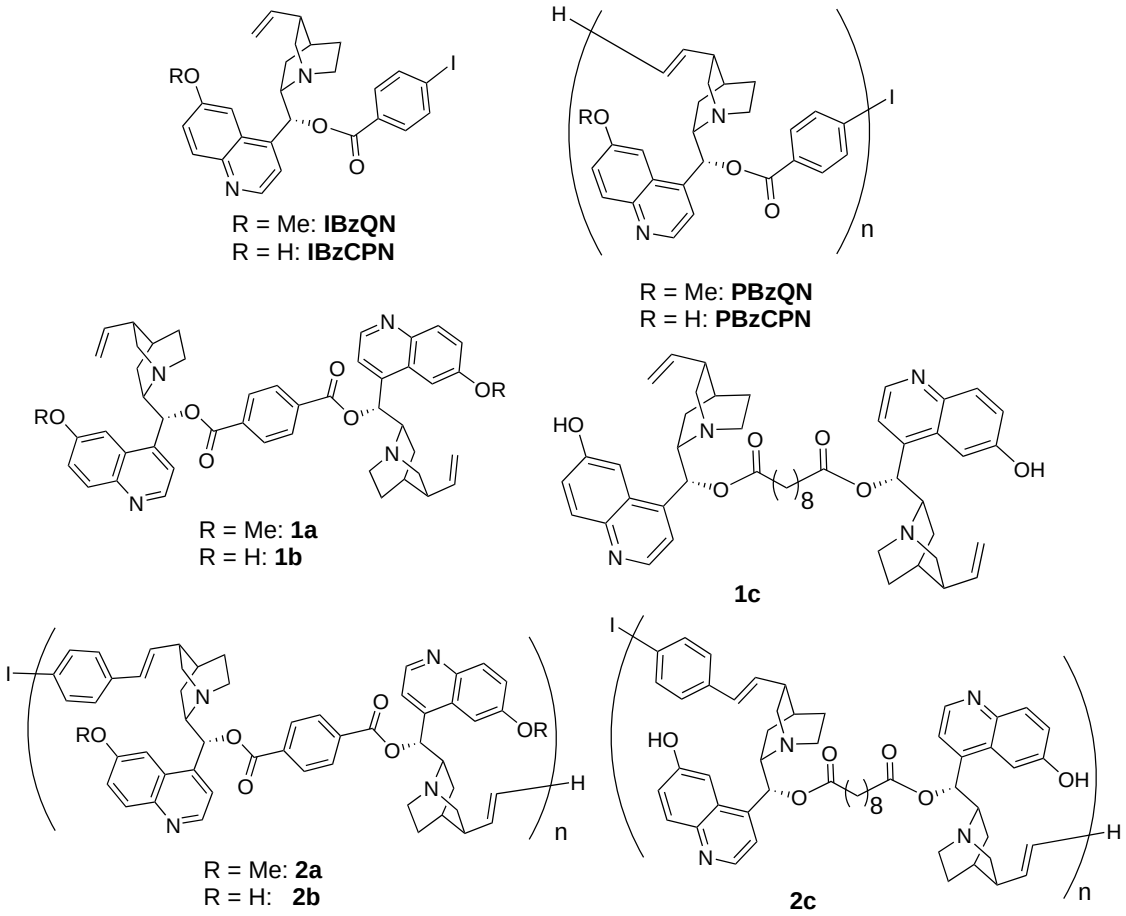



FIGURE 6.1: Ester derivatives of cinchona alkaloids organocatalysts.

showed poor enatioselectivities of 55% ee in comparison to chiral polymer **2b** of the same structure but different synthetic approach that achieved 79% ee in the formation of Michael product **11**.

The same scenario was observed when the chiral organocatalysts were used in the asymmetric Michael addition of $\beta$-ketoester **12** to nitrostyrene **10** in Scheme 6.5. The C6'-OH catalysts **1e**, **2f** showed higher enantioselectivities compared to C6'-OMe containing catalyst **1f**.

*Recyclability and stability*: The main-chain chiral polymers reported in this work has shown stability with no temperature dependence when evaluated in the enantioselective synthesis of Michael product **11**. Forexample the main-chain chiral polyester **PCPNdb** in chapter 3 showed stability in the achieved enantioselectivities of Michael product **11** when the reaction was done at either moderate or vigorous reactions conditions during recyclability test. However, when corresponding lower molecular weight catalyst was placed under the same reaction conditions, the enantioselectivity of the Michael product dropped from 94% ee to 86% ee.

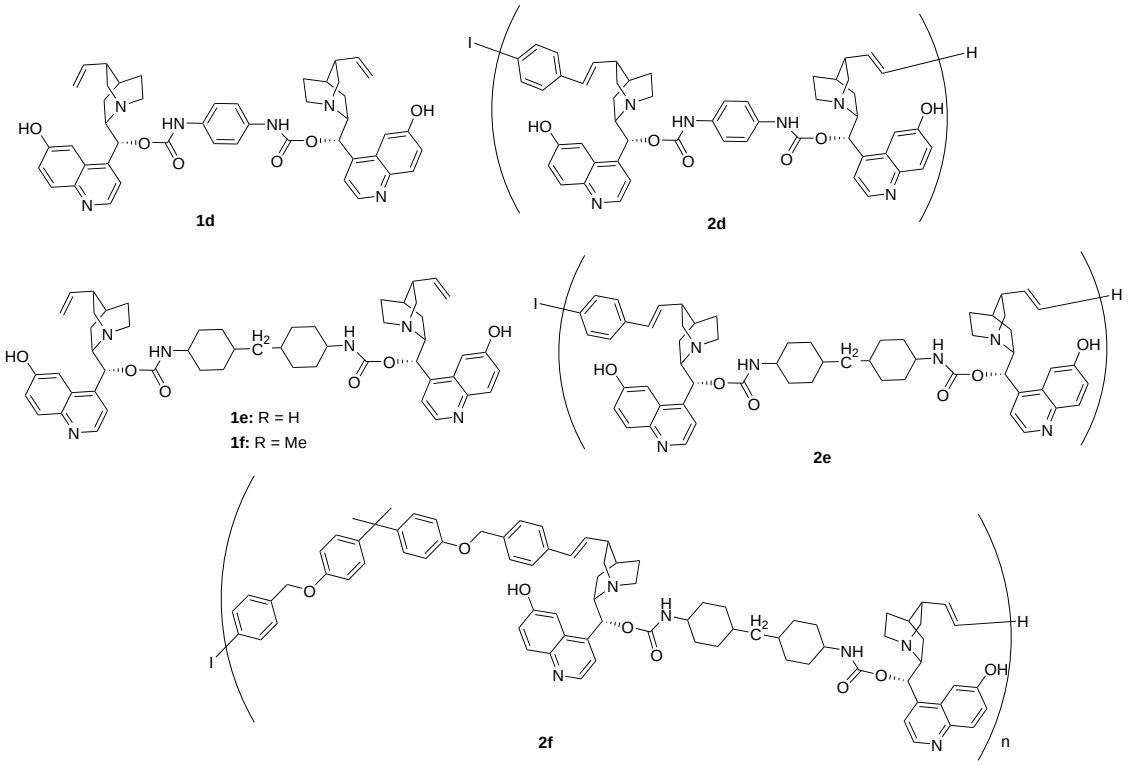
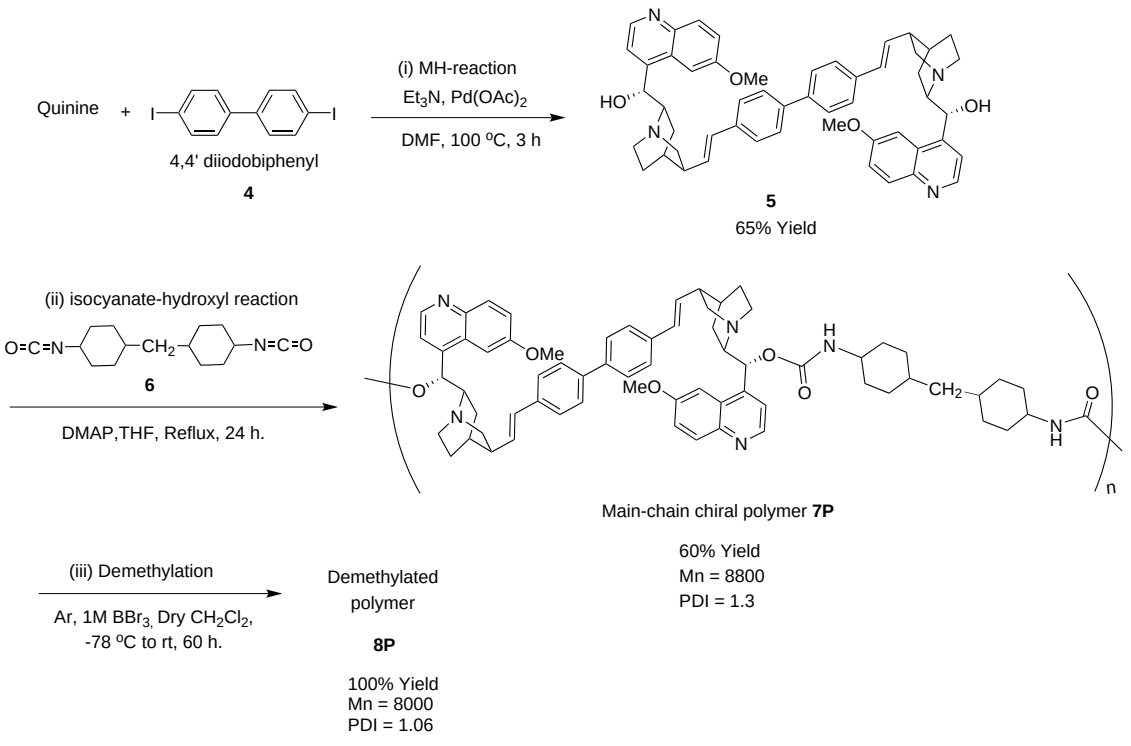
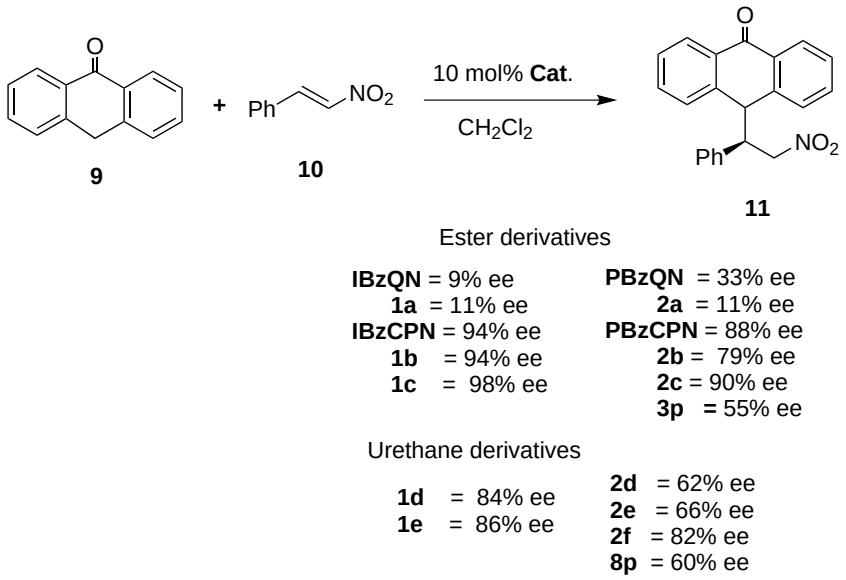



FIGURE 6.2: Urethane derivatives of cinchona alkaloids organocatalysts.




SCHEME 6.3: Synthesis of main-chain chiral polymer by diisocyanates-diols reaction.

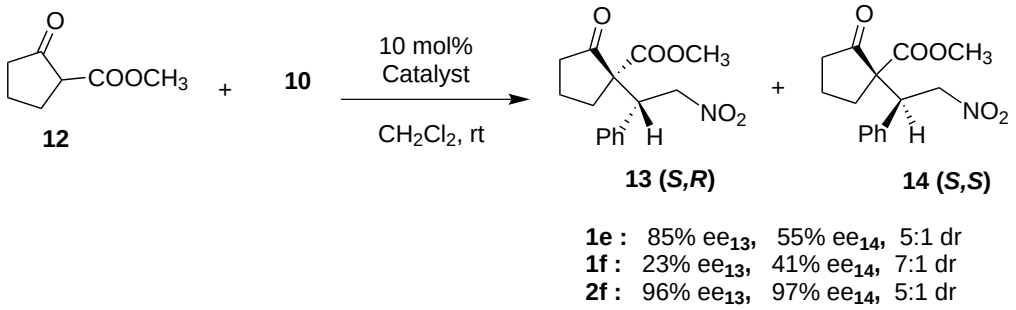
*Linking structure effect*: In the enantioselective synthesis with main-chain chiral polymeric catalysts, both, the primary linker structures (used in the dimeric compound's




SCHEME 6.4: Cinchona derivatives organocatalysts in the enantioselective synthesis of **11**.

preparation) as well as secondary linker structures (diiodides compopunds used for polymerization) were observed to affect the enantioselective synthesis of Michael product **11** in Scheme 6.4. This phenomenon was observed when chiral polyesters or chiral polyurethanes organocatalysts were used in the asymmetric Michael addition reactions. Forexample, the chiral polyesters **2b** and **2c** in Fig. 6.1 showed an enantioselectivities of 79% ee and 90% ee respectively in the formation of **11** (Scheme 6.4). Same like with chiral polyurethanes organocatalysts **2e** and **2f**, an enantioselectivities of 66% ee and 82% ee was obtained in the formation of Michael product **11**. More examples on their relation can be seen in Chapter 4. It was found that, the flexible linker in the polymeric structure reduces the entanglement between the reacting molecules, hence more flexible chiral polymers **2c** and **2f** were obtained, and the proper microenvironment for the enantioselective synthesis of **11** was created. In addition, the maltifunctionality of the C9-substituents, the basic heterocycles and a hydroxyl group of the polymeric catalysts were observed to be crucial factors for catalytic activities and enantioselectivities in the Michael addition reactions.

*Polymeric structure effect*: In comparison to their corresponding lower molecular weight catalysts, in some cases, it was found that, the same or higher enantioselectivities and catalytic activities were observed when chiral polymeric organocatalysts were used for the enantioselective synthesis in asymmetric Michael reactions. Forexample, the dimeric catalyst **1e** and polymeric catalyst **2f** in Fig. 6.2 for the enantioselective synthesis of Michael products **13 (S,R)** and **14 (S,S)** in Scheme 6.5. Enantioselectivities of 85% ee




SCHEME 6.5: Asymmetric Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene.

and 55% ee respectively and diastereomeric ratio of 5:1 dr was obtained when **1e** was used as catalyst, while higher enantioselectivies of 96% ee and 97% ee with diastereomeric ratio of 5:1 dr was obtained when polymeric catalyst **2f** was used. However, it was not the case for the asymmetric Michael reaction in Scheme 6.4 when catalyst **1e** and **2f** was used. Therefore the chemistry between the polymeric structure and the type of reacting substrates could be assumed as the major contributing factors for the effective enantioselective synthesis with polymeric organocatalysis.

## 6.3 The Cross-linked chiral polysiloxanes of cinchona alkaloids

Crosslinked chiral polysiloxanes containing cinchona alkaloid derivatives were synthesized from poly(methylhydrosiloxane) by hydrosilylation reaction. The C3-vinyl group of cinchona alkaloid derivatives were easily hydrosilylated with Si-H functional groups of poly(methylhydrosiloxane) by using Pt catalyst. The Pt catalysis of Si-H groups in poly(methylhydrosiloxane) and cinchona alkaloid dimers afforded the cross-linked structure of chiral polysiloxanes. Hydrolysis of Si-H bonds with Pt catalyst during reaction resulted in a formation of extra cross-linkages of chiral polysiloxanes. Mixed solvent (toluene and DMF) system was employed for a successful immobilization of C6-OH free cinchona alkaloid derivatives into poly(methylhydrosiloxane). Both cinchona alkaloid C9-ester and C9-urethane derivatives were incorporated into poly(methylhydrosiloxane) through Si-C bond. The resulted crosslinked chiral polysiloxanes were insoluble in common organic solvents. Fig. 6.3 shows some examples of chiral polysiloxanes derived from cinchona alkaloids.

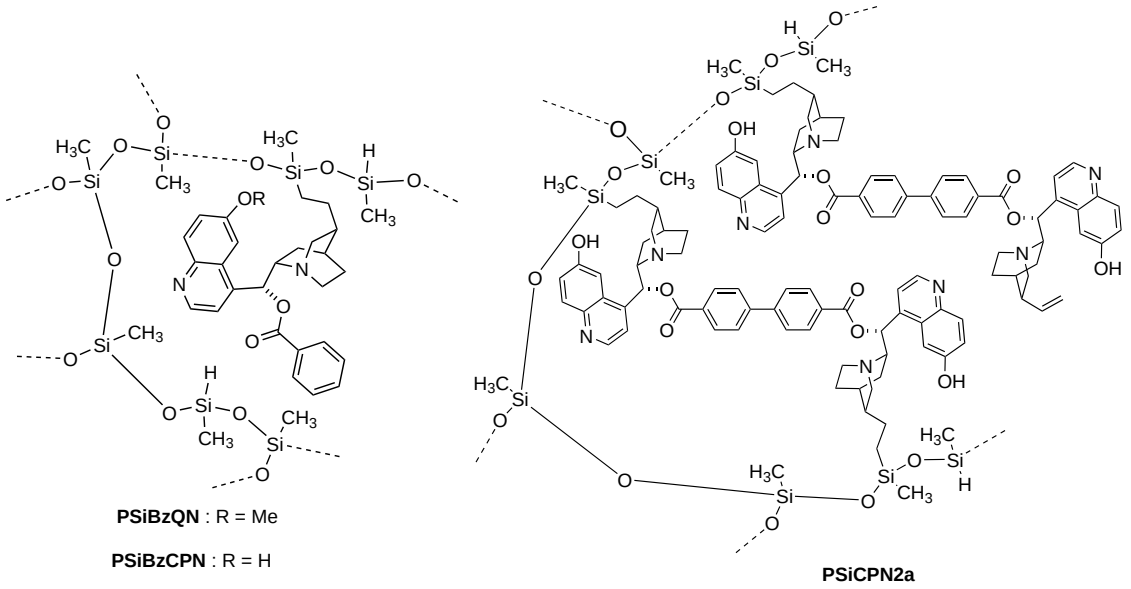



FIGURE 6.3: Examples of cross-linked gel-type chiral polysiloxanes of cinchona alkaloids.

### 6.3.1 The catalytic performance of the cross-linked chiral polysiloxanes

The catalytic performance of the cross-linked chiral polysiloxanes of cinchona alkaloid derivatives were evaluated in asymmetric Michael addition reactions. The asymmetric Michael addition of anthrone to $\beta$-nitrostyrene (Scheme 6.4) as well as the addition of $\beta$-ketoester to $\beta$-nitrostyrene (Scheme 6.5) were used for their evaluations. The same parameters as for main-chain chiral polymers were used for evaluation. The C6'-OH free chiral polysiloxanes of cinchona alkaloid showed higher enantioselectivities with sufficient catalytic activities in the Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene for the formation of **13** and **14**. The chiral polysiloxanes were recyclable and could be re-used for several times without losing their catalytic performance.

The comparison on their catalytic performance for the chiral polymeric organocatalysts of cinchona alkaloids was done by using the Michael addition reactions in Scheme 6.4 and 5. The main-chain chiral polymeric catalysts and cross-linked gel-type polymeric catalysts of C6'-OH free cinchona alkaloids derivatives were used for the comparative analysis. The results are as summarized in Table 6.1 and Table 6.2. It has been found that each and every polymer structure has its own special characteristic features in creating the proper microenvironment for the enantioselective synthesis of asymmetric product.

TABLE 6.1: Asymmetric Michael addition of anthrone to $\beta$-nitrostyrene with chiral polymeric catalysts of cinchona alkaloids[a].

| Entry | Polymeric catalyst | Time (h) | Yield[b] (%) | $ee^{c}_{\mathbf{11}}$ (%) |
|---|---|---|---|---|
| **1** | **PBzCPN** | 24 | 75 | 88 |
| 2 | **2f** | 24 | 92 | 84 |
| 3 | **PSiBzCPN** | 48 | 90 | 84 |
| 4 | **PSiCPN2a** | 36 | 80 | 86 |

[a]Reactions were conducted with **9** (0.24 mmol), **10** (0.20 mmol) and 15 mol% catalysts in $CH_2Cl_2$ (2.0 mL) at room temperature. [b]Isolated yield of the product. [c]Determined by HPLC-Chiralcel AS-H column

TABLE 6.2: Asymmetric Michael addition of $\beta$-ketoester to $\beta$-nitrostyrene with chiral polymeric catalysts of cinchona alkaloids[a]

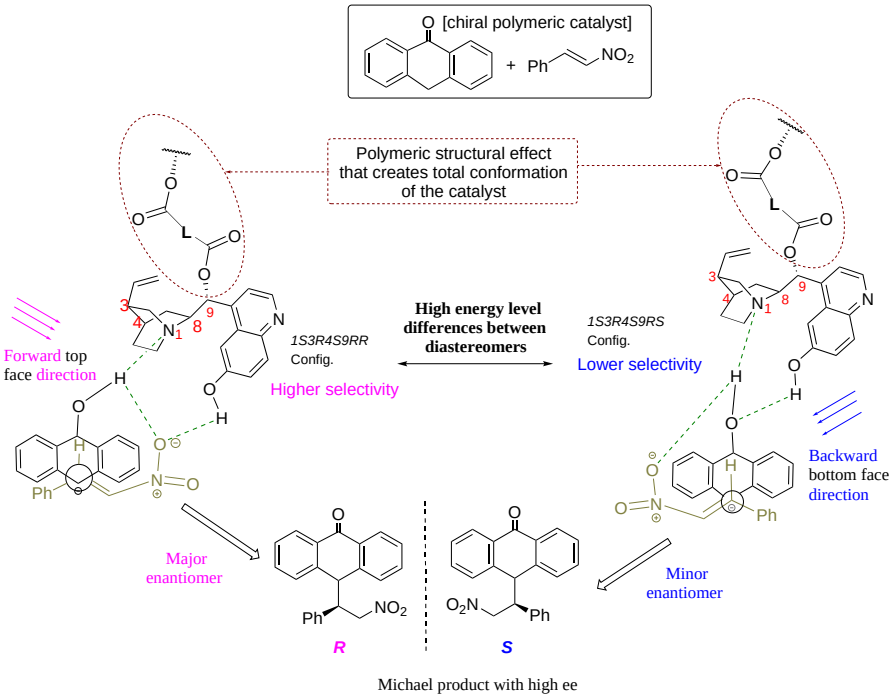
| Entry | Polymeric catalyst | Time (h) | Yield[b] (%) | $ee^{c}_{\mathbf{13}}$ (%) | $ee^{c}_{\mathbf{14}}$ (%) | dr[c] |
|---|---|---|---|---|---|---|
| **1** | **PBzCPN** | 36 | 80 | 97 | 96 | 2.4:1 |
| 2 | **2f** | 24 | 75 | 96 | 97 | 4.7:1 |
| 3 | **PSiBzCPN** | 48 | 79 | 98 | 96 | 2.5:1 |
| 4 | **PSiCPN2a** | 60 | 65 | 98 | 92 | 5:01 |

[a]All reaction were performed with $\beta$-ketoester **12** (0.50 mmol), $\beta$-nitrostyrene **10** (0.55 mmol) and 15 mol% catalyst in $CH_2Cl_2$ (2.5 mL) at room temperature.[b]Isolated yield of the product. [c]Determined by chiralcel OD-H column

## 6.4 General catalytic mechanism

The results obtained from the evaluation of chiral polymeric organocatalysts prepared in this work implies that the multifunctionality of the polymeric catalyst consisting of the C9- substituents, the basic heterocycles (quinuclidine and quinolone rings) and the hydroxyl group are crucial for catalytic activities and enantioselectivities of the asymmetric Michael addition reactions presented in Scheme 6.4 and Scheme 6.5.

The general catalytic mechanism in the case of Michael addition presented in Scheme 6.4. Anthrone, the Michael donor is deprotonated by the basic side of the cinchona polymeric catalyst (N1) to form the carbanion as a strong nucleophile. The $\beta$-nitrostyrene acts as a strong electrophile self-stabilised by delocalisation of $\pi$-electron. As assisted by the presence of quinoline ring as well as the hydroxyl group,in the transition state, nucleophilic substitution between the carbanion and the delocalised -electron of the Michael acceptor results into new C-C bond formation and finally the Michael product

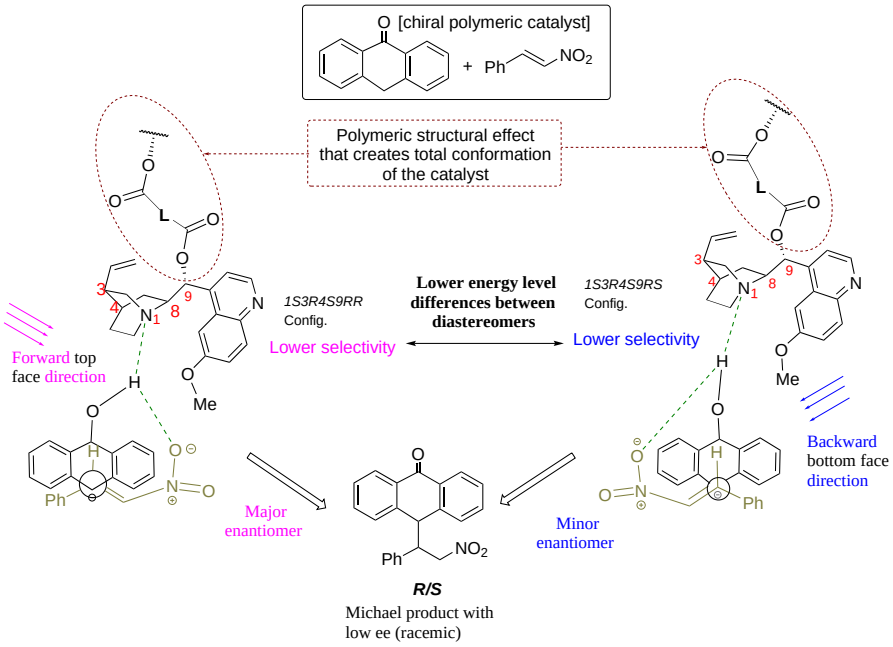



SCHEME 6.6: Proposed transition state of asymmetric Michael addition of anthrone **9** to $\beta$-nitrostyrene **10** with C6'-OH free cinchona ester derivatives as catalyst.

is then protonated generating the active catalyst. When the polymeric catalyst with C6'-OMe group was used for the same reaction, in the rate-selectivity determining step, the H-bonding effect responsible for stabilizing the Michael acceptor substrate is absent, as a result of lower selectivity. Scheme 6.6 shows the proposed transition state of asymmetric Michael addition of anthrone **9** to $\beta$-nitrostyrene **10** with C6'-OH cinchona derivative as a catalyst. While Scheme 6.7 shows the proposed transition state of asymmetric Michael addition of anthrone **9** to $\beta$-nitrostyrene **10** with C6'-OMe cinchona derivative as a catalyst

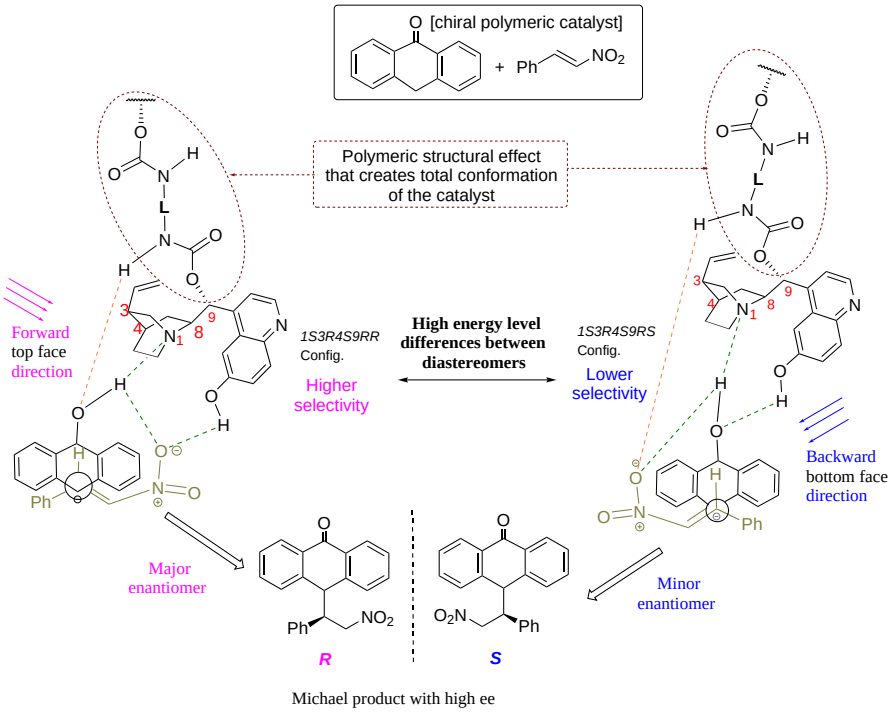
The same scenario could be applicable for another Michael addition reaction in Scheme 6.5. However, the difference in catalytic and enantioselectivity when $\beta$-ketoester is used as Michael donor is due to the presence of two carbonyl groups that could be easily protonated by the strong basic side of the catalyst to form a nucleophilic complex. When an electrophilic Michael acceptor approaches the nucleophilic complex gives the possible orientation for giving out the major or minor diastereomers of the Micheal products depending on the substrate attack orientation state.

On the other hand, possible transition states for the asymmetric Michael addition reaction of anthrone **9** to $\beta$-nitrostyrene **10** in the formation of **11** ( Scheme 6.6) with C6'-OH cinchona urethane derivative as a catalyst can be presented as shown in Scheme




SCHEME 6.7: Proposed transition state of asymmetric Michael addition of anthrone **9** to $\beta$-nitrostyrene **10** with C6'-OMe cinchona ester derivatives as catalyst.

6.8. The extra hydrogen bond (compared to ester derivatives of cinchona alkaloid) with other catalytic sites present in urethane structure of cinchona derivatives, participates in the transition states of the reacting substrates to give higher enantioselective synthesis of Michael product **11**.




SCHEME 6.8: Proposed transition state of asymmetric Michael addition of anthrone **9** to $\beta$-nitrostyrene **10** with C6'-OH free cinchona urethane derivatives as catalyst.

## 6.5 Conclusion

In this work, chiral polymeric organocatalysts of cinchona alkaloids were successfully synthesized via Pd catalyzed Mizoroki-Heck coupling reaction and Pt catalysed hydrosiylation reaction methods. The summary of each work on chiral polymeric catalysts of cinchona alkaloids are as explained below;

i. Chiral polyesters of cinchona alkaloid derivatives were synthesized via repetitive Mizoroki-Heck (MH) coupling reaction. Under MH conditions, 4-iodobenzoylquinine and 4-iodobenzoylcupreine were easily polymerized via self polycondensation to afford the corresponding chiral polyesters. The MH reaction conditions were also applied to the two-component polycondensation of cinchona ester dimer and aromatic diiodide to obtain the chiral polyesters. These cinchona-based chiral polyesters were successfully applied as polymeric organocatalysts in the asymmetric Michael addition reaction. The chiral polyesters bearing free OH groups at the C6' position of the quinoline rings showed high catalytic activities (up to 97% isolated yield) and good enantioselectivities (up to 92% ee) in the Michael addition of anthrone to nitroalkenes. Furthermore, these polymeric catalysts were stable and could be recycled and reused several times.

ii. Chiral polyurethanes of cinchona alkaloid were synthesized via repetitive Mizoroki-Heck (MH) coupling reaction. The Pd-catalyzed polycondensation of cinchona urethane dimers and aromatic diiodides afforded the chiral polyurethanes. The chiral polyurethane bearing free OH group at the C6' position of the quinoline ring in the cinchona alkaloid unit showed high catalytic activities and excellent enantioselectivities (up to 97% ee) in the Michael addition reactions.

iii. Cross-linked chiral polysiloxanes of cinchona alkaloids were synthesized from industrially prepared poly(methyl hydrosiloxane) by hydrosilylation reaction. The Pt catalysis of the poly(methyl hydrosiloxane)s' Si-H functional groups and cinchona alkaloid derivatives afforded the cross-linked structure of chiral polysiloxanes. Their catalytic performance were evaluated in asymmetric Michael addition reactions. The C6'-OH free chiral polysiloxanes of cinchona alkaloid showed higher enantioselectivities (up to 99% ee) with sufficiency catalytic activities in the Michael addition reactions. The chiral polysiloxanes were easily recovered by centrifugation method and could be reused for several times without losing their catalytic performance.

In general, The chiral polymeric organocatalysts of cinchona alkaloids presented in this work have shown the practicability of chiral polymeric organocatalysts in asymmetric synthesis and could be used for fine chemicals production. Because the chiral polymeric catalysts were easily prepared (only in three reaction steps) and they were easily applied for the enantioselective synthesis in Michael addition reactions introduced in this work. The following features have been observed;

i. The catalytic effficiency of each polymer depends on the polymeric catalyst structure design

ii. The solubility of the chiral polymeric catalyst was attributed with the design criteria of the polymer

iii. The chiral polymers showed high enantioselectivities with sufficiency catalytic activities when used as catalysts in Michael addition reactions.

iv. Even under vigorous reaction conditions, the chiral polymeric catalysts showed no deterioration on catalytic perfomances

v. The chiral polymeric catalysts were effective under wide range of common organic solvents used for asymmetric synthesis

vi. The chiral polymeric catalysts involves mild reaction conditions, that is they are effective at room temperature

vii. The free OH at the quinoline ring of the chiral polymeric catalyst was the key factor for the higher enantioselectivities in the asymmetric transformations.

viii. The chiral polymers were recyclable and could be used for several times without loosing their catalytic perfomances.

With the advancements made in chiral polymeric organocatalysis in asymmetric synthesis, chiral polymeric catalysts of cinchona alkaloids synthesized in this work can be applied in other organic reactions for asymmetric transformations rather than Michael addition reactions reported in this work. Also the chiral polymers could be used in continous flow chemistry for the sustainability of green chemistry practices in asymmetric synthesis.

# Appendix A

# List of Publications

## A.1 Journal papers

J.1. Yuta Endo, Shohei Takata, **Bahati Thom Kumpuga** and Shinichi Itsuno, "Synthesis of cinchona alkaloid sulfonamide polymers as enantioselective catalysts for the Michael addition reaction of Ketoester and Nitrostyrenes. *ChemistrySelect* **2017**, 1, 1–6.

J.2. **Bahati Thom Kumpuga** and Shinichi Itsuno, "Synthesis of chiral polyesters of cinchona alkaloid catalysts for enantioselective Michael addition reaction. *Journal of Catalysis* **2018**, 361, 398–406.

J.3. **Bahati Thom Kumpuga** and Shinichi Itsuno, "Synthesis of chiral polyurethanes of cinchona alkaloids for the enantioselective synthesis in asymmetric catalysis. *Catalysis Communications* **2019**, 118, 5–9.

J.4. **Bahati Thom Kumpuga** and Shinichi Itsuno, "Synthesis of cross-linked chiral polysiloxanes of cinchona alkaloids for their enantioselective synthesis in asymmetric catalysis. *Asian Journal of Organic Chemistry* **2019**, 8, 251–256.

## A.2 Conference presentations

C.1. **Bahati Thom Kumpuga**, Naoki Haraguchi and Shinichi Itsuno. *"Synthesis of chiral polyesters derived from cinchona alkaloids for their sustainable application in asymmetric reactions."* 47th Annual meeting of Union of Chemistry-Related Societies in Chubu Area, Toyohashi, Japan, **2016**.

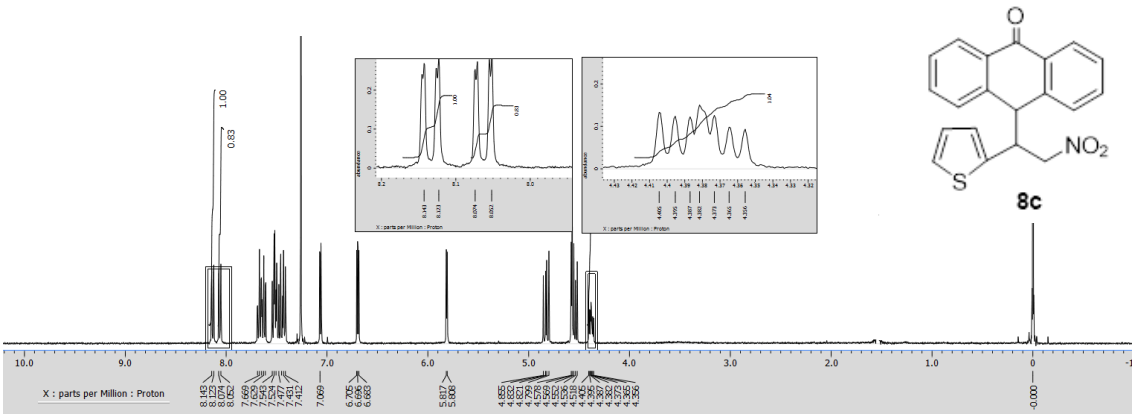
C.2. **Bahati Thom Kumpuga**, Naoki Haraguchi and Shinichi Itsuno, *"Synthesis of chiral polyesters derived from cinchona alkaloids for their sustainable application in asymmetric reactions.* The 29th International Symposium on Chirality (ISCD-2017), Waseda University Conference Center, Tokyo-Japan, **2017**.

C.3. **Bahati Thom Kumpuga**, Naoki Haraguchi and Shinichi Itsuno,*"Synthesis of chiral polyesters of cinchona alkaloid catalysts for their application in asymmetric reactions.* The 67th SPSJ Annual Meeting, Nagoya-Japan, **2018**.

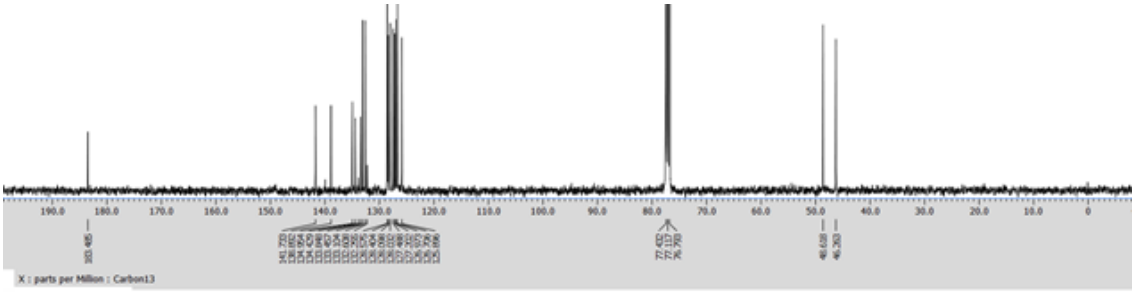
# Appendix B

# Supporting document for Chapter 3

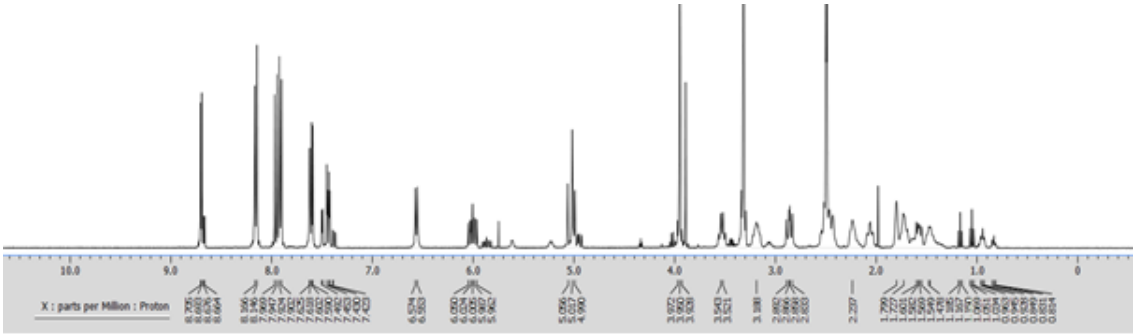
## B.1 $^{1}H$ and $^{13}C$ NMR data for cinchona ester derivatives



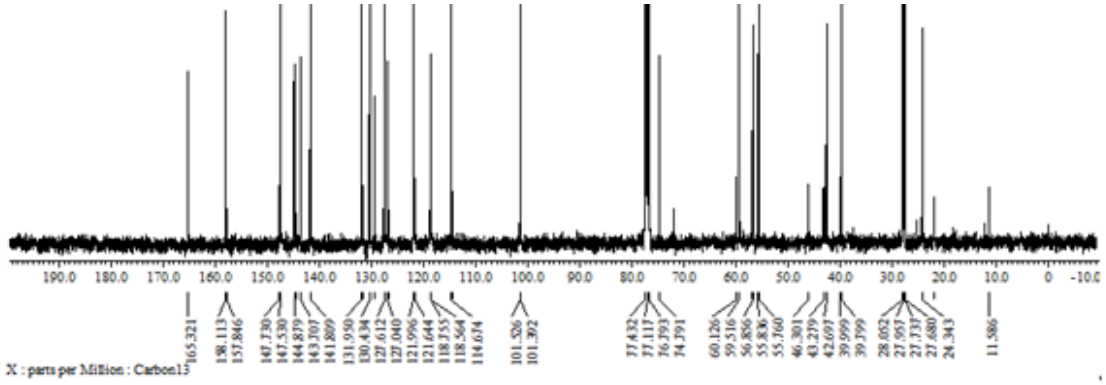

$^{1}H$ NMR of **8c** in $CDCl_3$



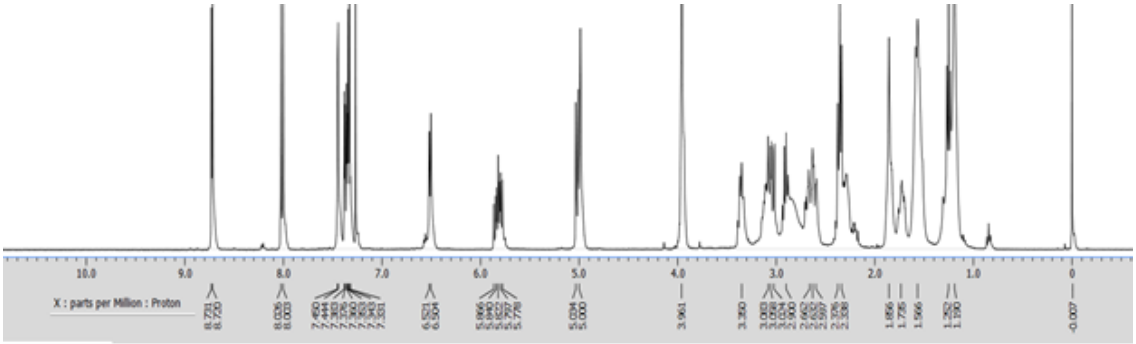

$^{13}C$ NMR of **8c** in $CDCl_3$



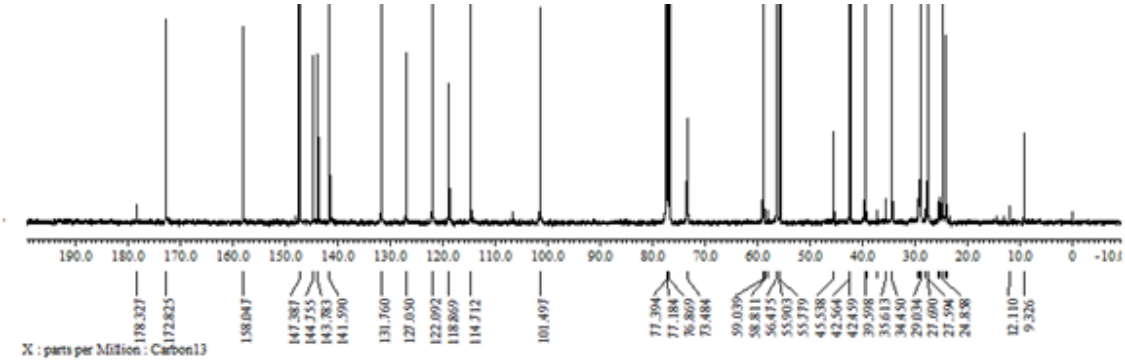

$^{1}$H NMR for **2QNb** in DMSO-$d_6$



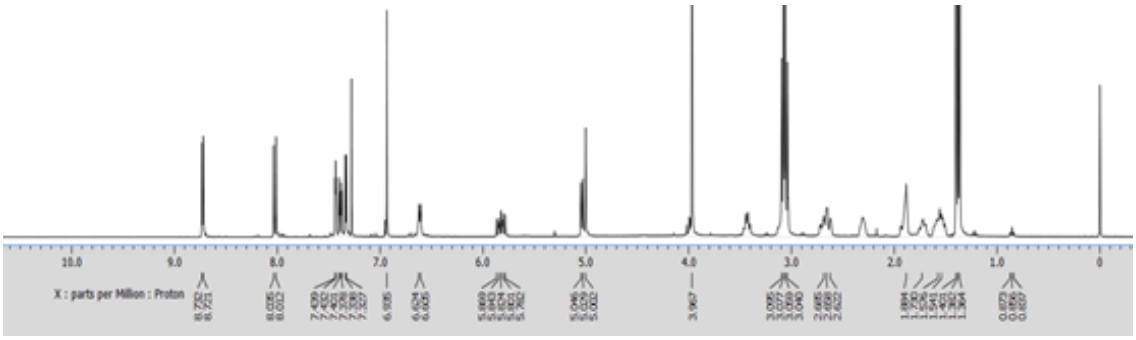

$^{13}$C NMR for **2QNb** in $CDCl_3$



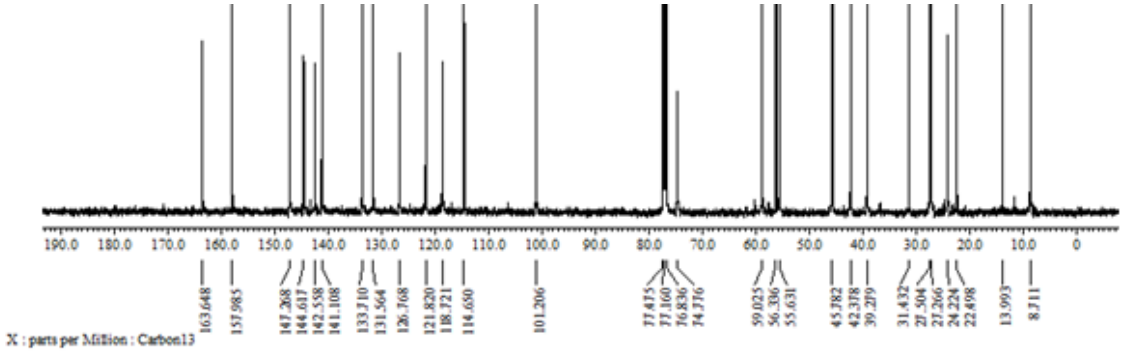

$^{1}$H NMR for **2QNe** in $CDCl_3$



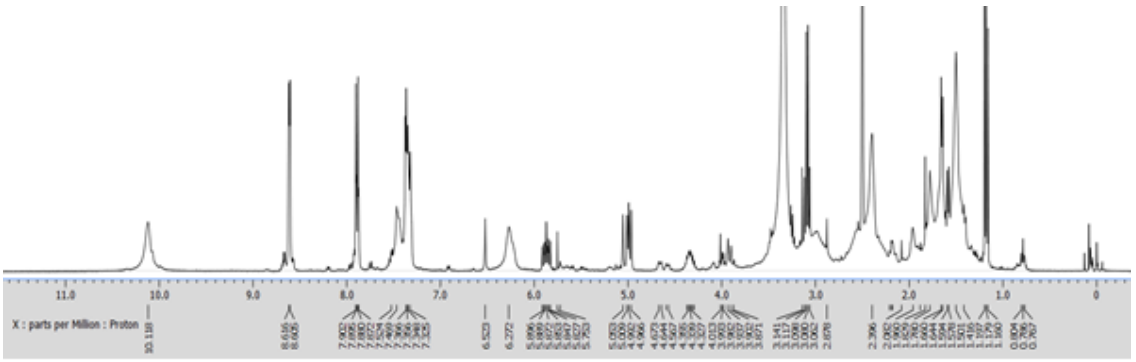

$^{13}$C NMR for **2QNe** in $CDCl_3$



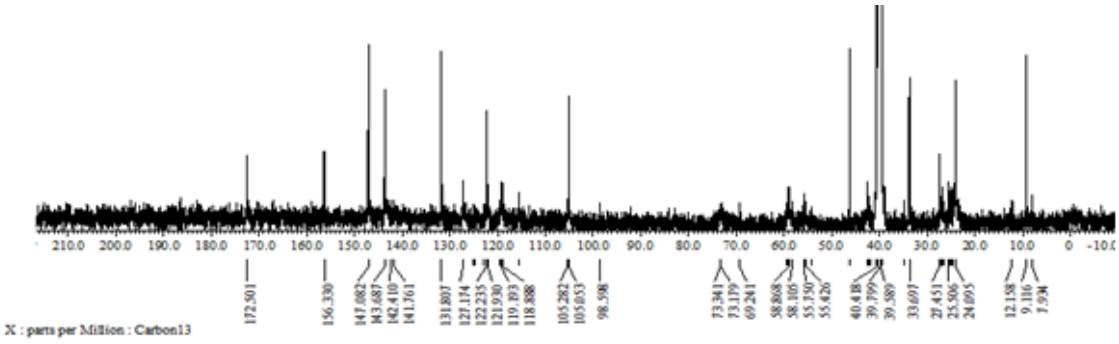
$^{1}$H NMR for **2QNc** in $CDCl_3$



$^{13}$C NMR for **2QNc** in $CDCl_3$



$^{1}$H NMR for **2CPNd** in DMSO-$d_6$



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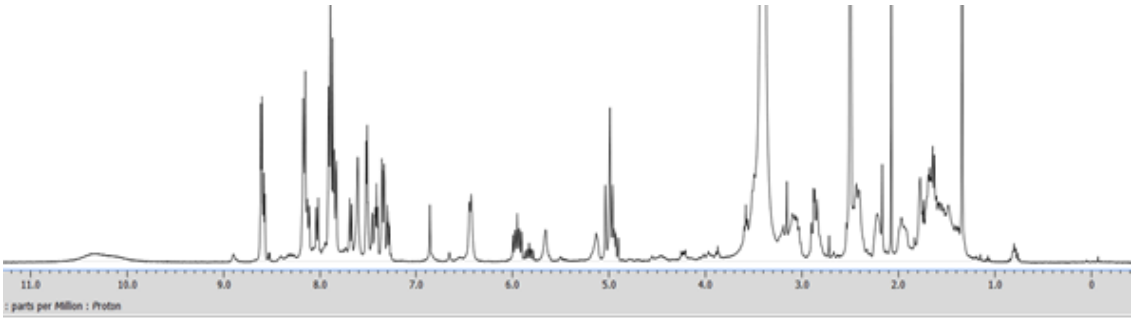
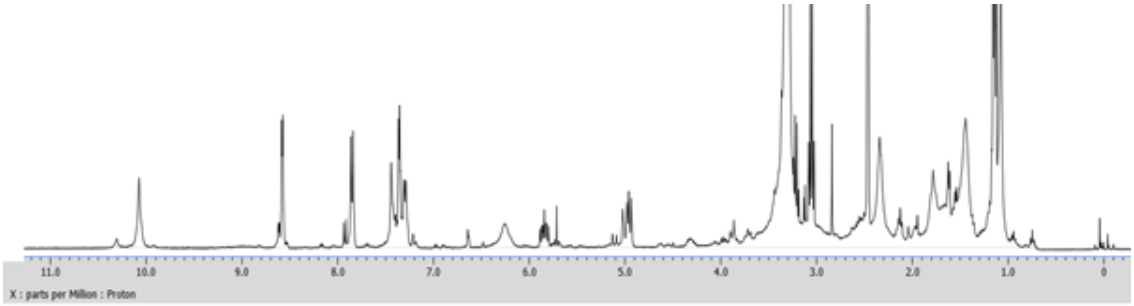
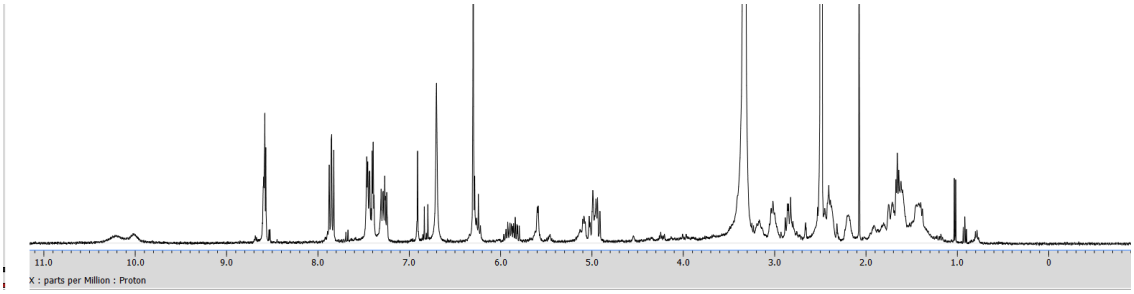


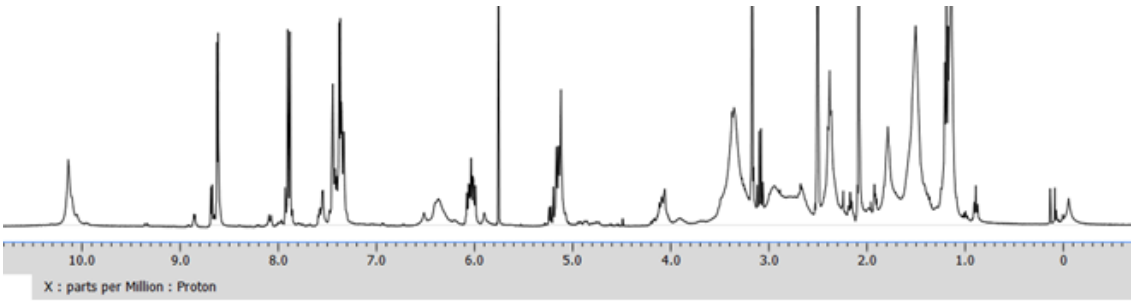

$^{1}$H NMR for **2CPNb** in DMSO-$d_6$



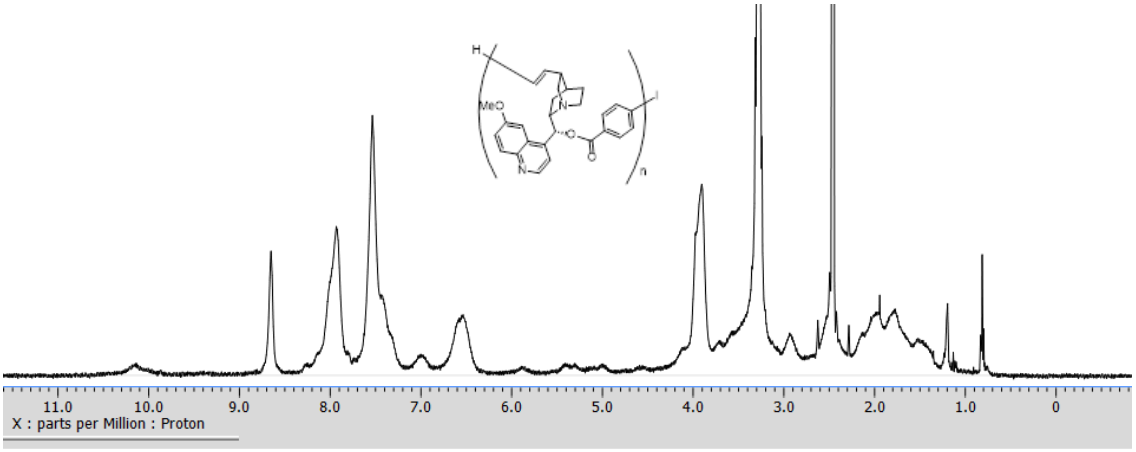

$^{1}$H NMR for **2CPNe** in DMSO-$d_6$



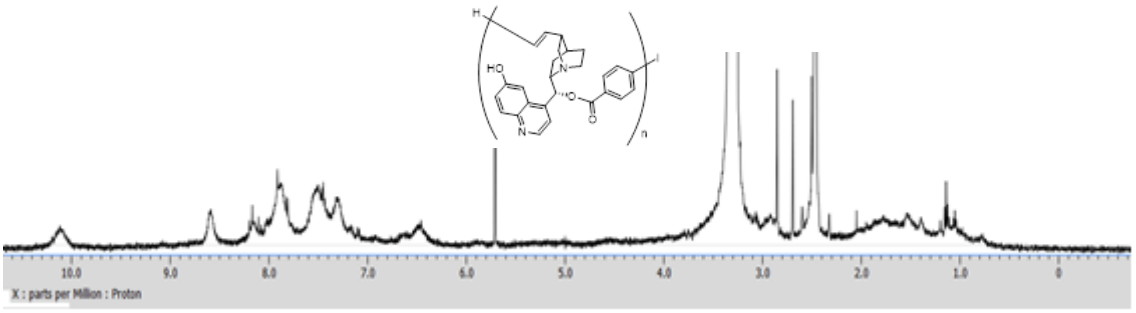

$^{1}$H NMR for **2CPNc** in DMSO-$d_6$




$^{1}$H NMR in $CDCl_3$ for **CPDe**




$^{1}$H NMR for **PBzQN** in DMSO-$d_6$

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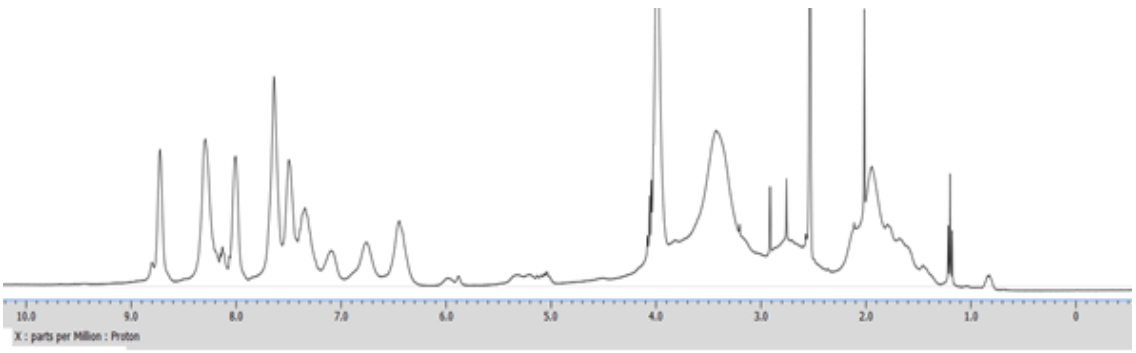


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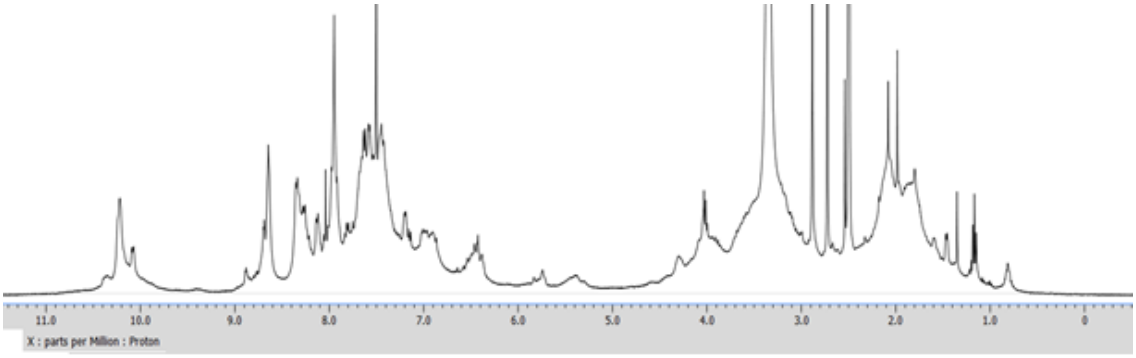
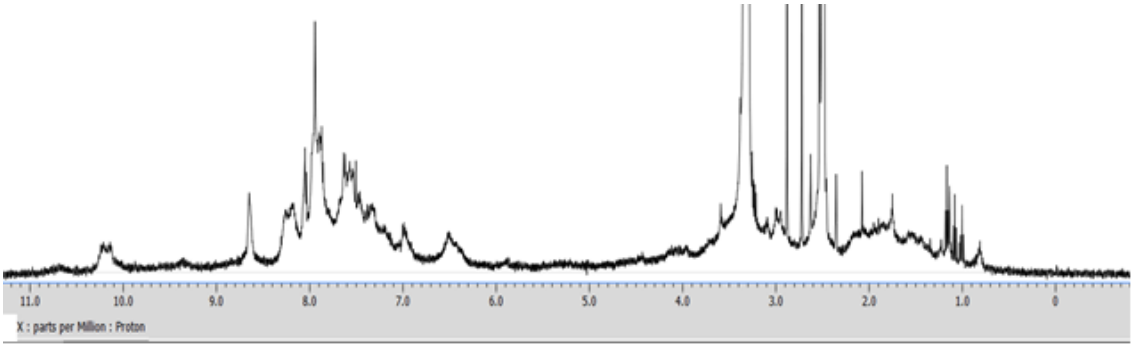



$^{1}$H NMR for **PCPNaa** in DMSO-$d_6$

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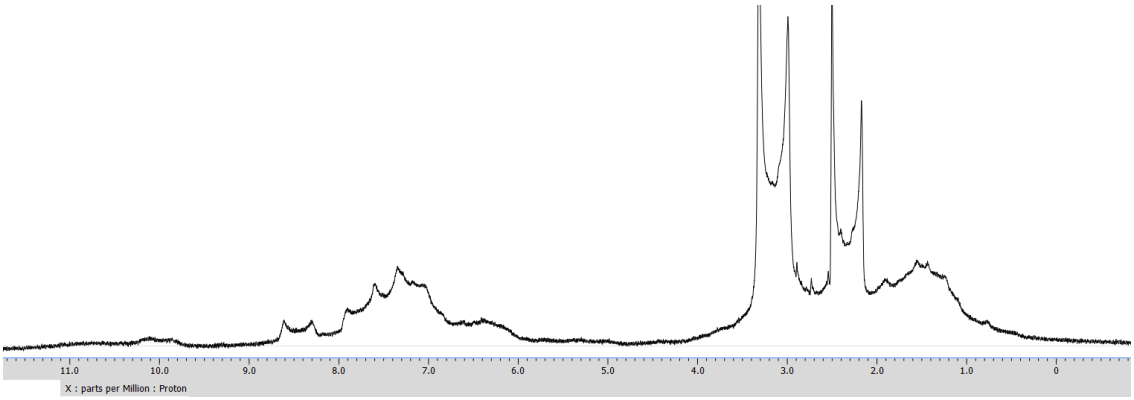
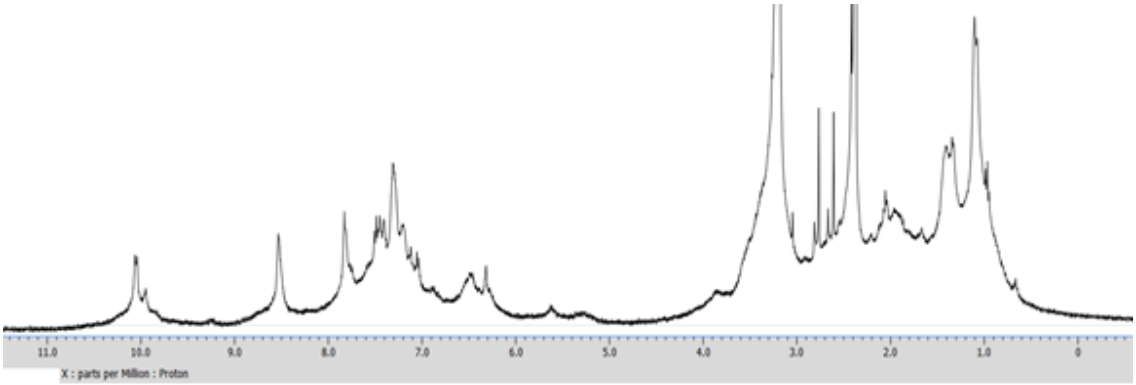



$^{1}$H NMR for **PCPNda** in DMSO-$d_6$

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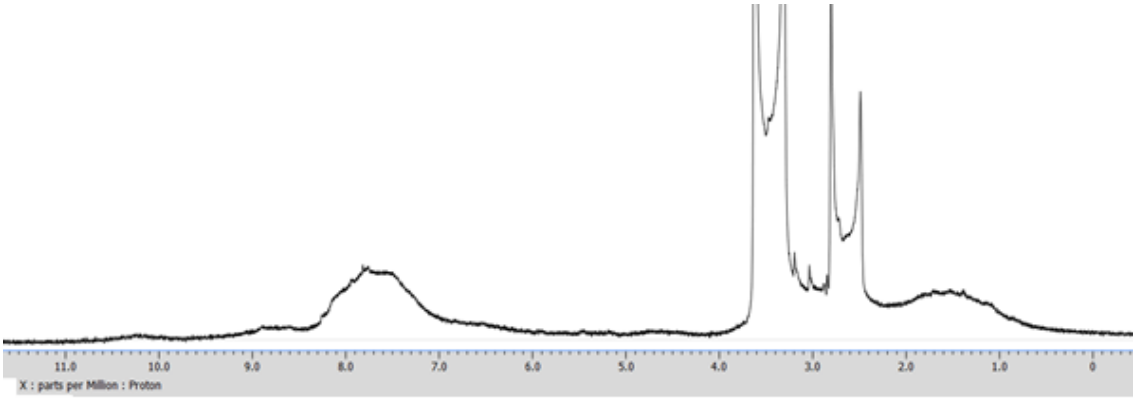


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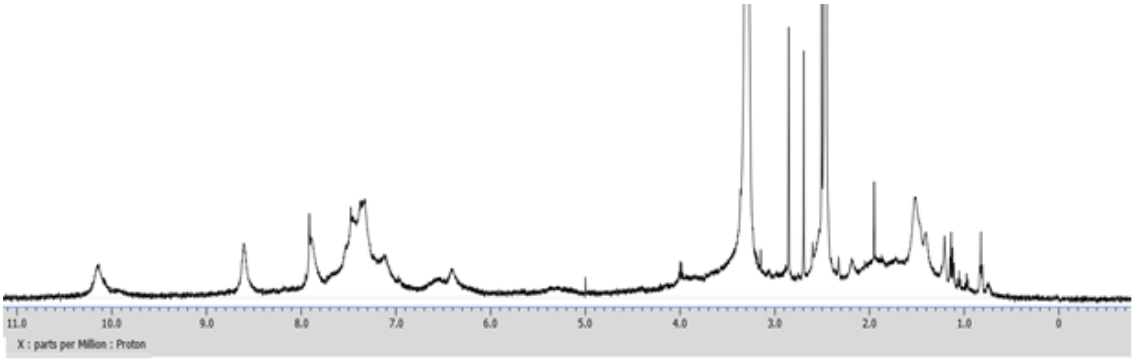


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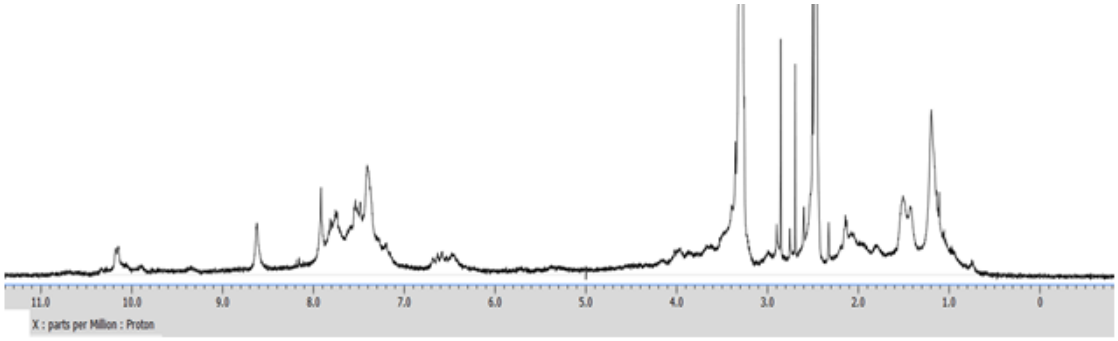


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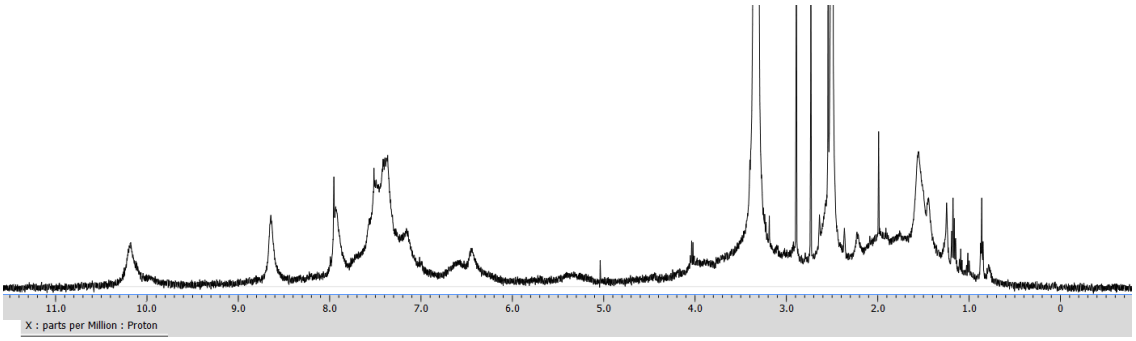


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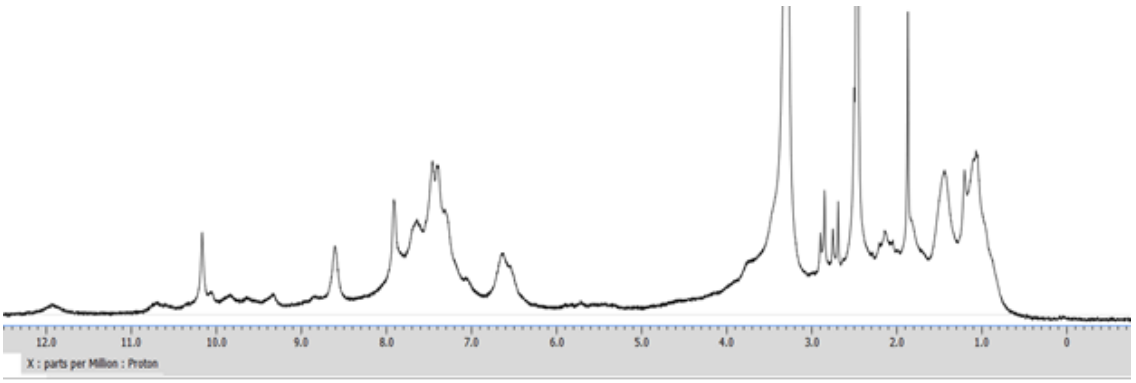
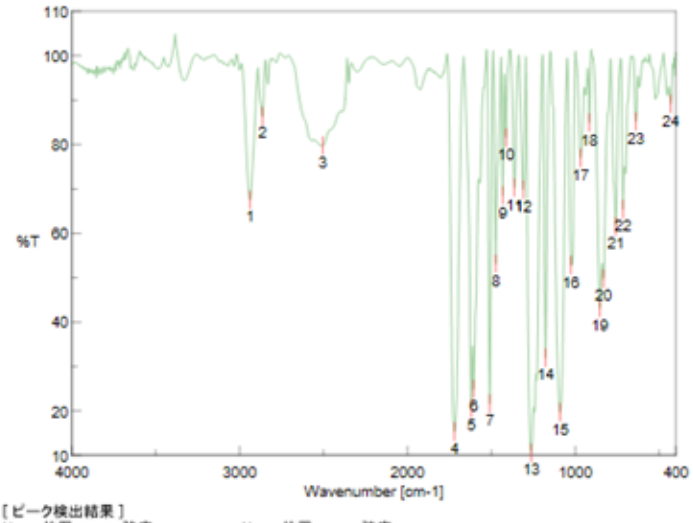



$^{1}$H NMR for **PCPDea** in DMSO-$d_6$

## B.2 FT/IR spectrum for chiral polyesters




[ピーク検出結果]

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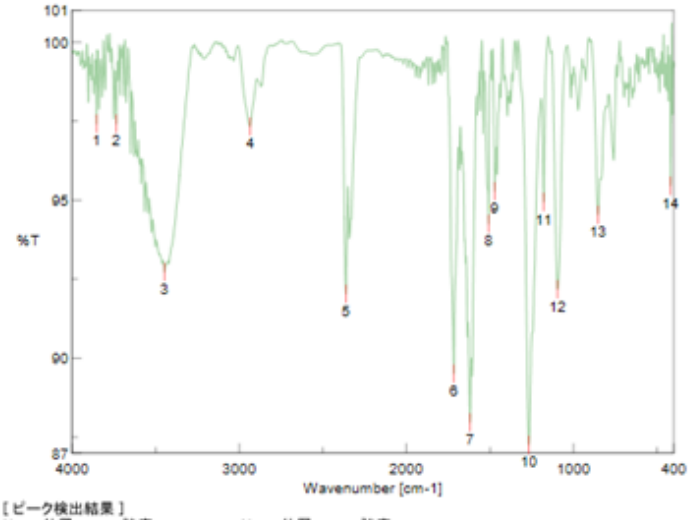
| 3 | 2505.08 | 79.7192 | 4 | 1719.23 | 15.3773 |
| 5 | 1619.91 | 20.5055 | 6 | 1605.45 | 24.8858 |
| 7 | 1509.03 | 21.6277 | 8 | 1473.35 | 53.1577 |
| 9 | 1431.89 | 68.5195 | 10 | 1412.6 | 81.5638 |
| 11 | 1362.46 | 70.304 | 12 | 1309.43 | 69.8265 |
| 13 | 1263.15 | 10.5664 | 14 | 1177.33 | 31.9824 |
| 15 | 1090.55 | 19.71 | 16 | 1025.94 | 52.8236 |
| 17 | 968.09 | 76.9838 | 18 | 916.022 | 84.9161 |
| 19 | 853.347 | 43.207 | 20 | 831.169 | 49.7938 |
| 21 | 757.888 | 61.5611 | 22 | 715.461 | 65.4284 |
| 23 | 638.323 | 85.1865 | 24 | 431.012 | 89.1831 |

FT/IR **PBzQN**




[ピーク検出結果]

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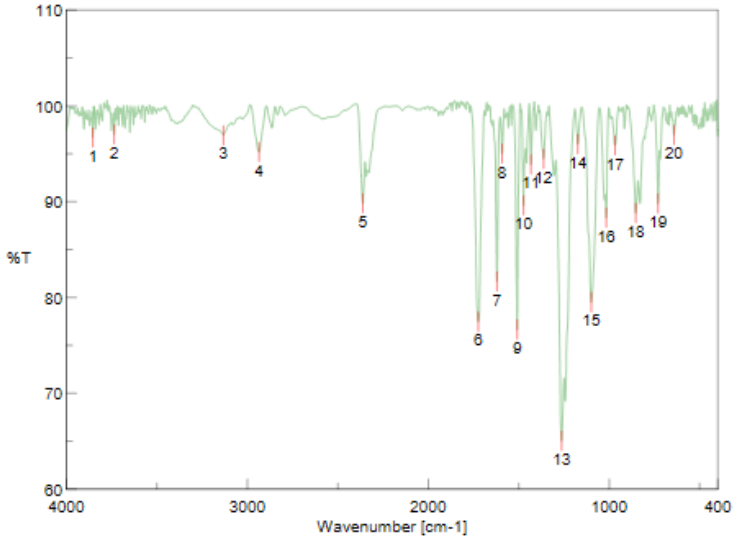
| 3 | 3447.13 | 92.7245 | 4 | 2936.09 | 97.3297 |
| 5 | 2361.41 | 92.0317 | 6 | 1716.34 | 89.5083 |
| 7 | 1618.95 | 87.9608 | 8 | 1508.06 | 94.2493 |
| 9 | 1471.42 | 95.2794 | 10 | 1267 | 87.2573 |
| 11 | 1178.29 | 94.9406 | 12 | 1095.37 | 92.1757 |
| 13 | 853.347 | 94.5339 | 14 | 419.442 | 95.4516 |

FT/IR for **PBzCPN**

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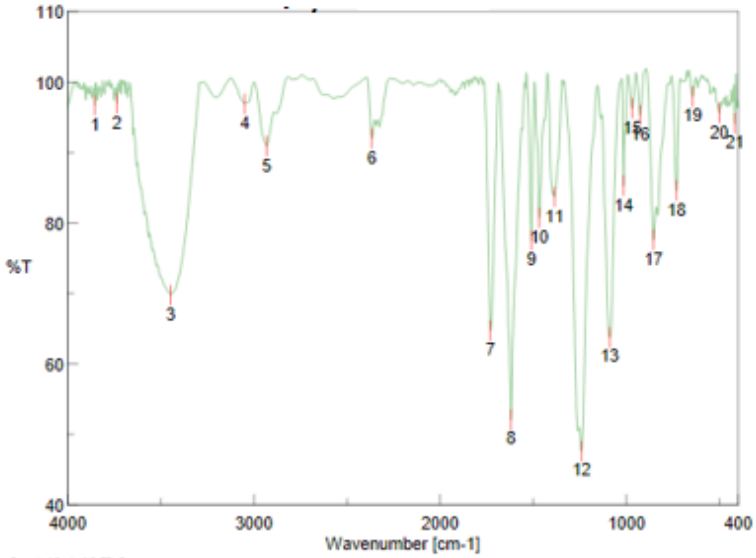
| 3 | 3131.83 | 96.9194 | 4 | 2936.09 | 95.1905 |
| 5 | 2361.41 | 89.8234 | 6 | 1724.05 | 77.4738 |
| 7 | 1620.88 | 81.6938 | 8 | 1591.95 | 95.0237 |
| 9 | 1508.06 | 76.6475 | 10 | 1473.35 | 89.6223 |
| 11 | 1432.85 | 93.8842 | 12 | 1362.46 | 94.4721 |
| 13 | 1263.15 | 65.0347 | 14 | 1173.47 | 96.001 |
| 15 | 1099.23 | 79.4985 | 16 | 1016.3 | 88.346 |
| 17 | 968.09 | 95.8771 | 18 | 853.347 | 88.8206 |

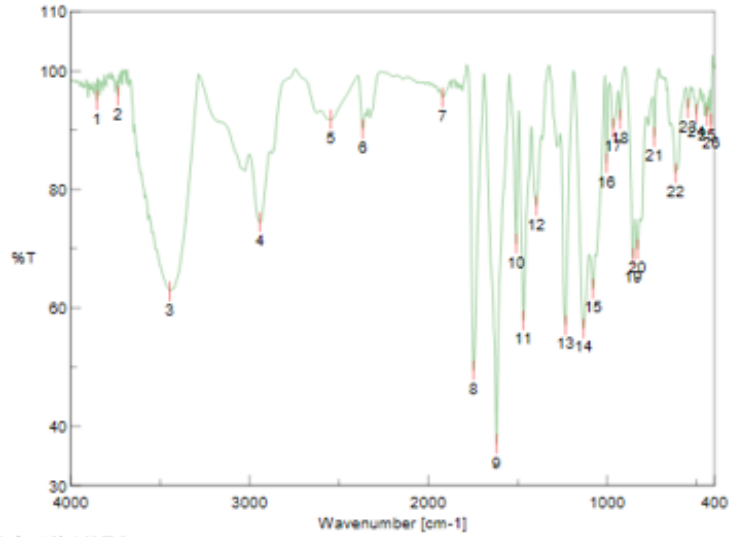
FT/IR for **PQNaa**




［ピーク検出結果］

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3854.04 | 96.741 | 2 | 3736.4 | 96.9686 |
| 3 | 3447.13 | 69.7493 | 4 | 3049.87 | 96.9106 |
| 5 | 2931.27 | 90.9174 | 6 | 2366.23 | 91.9871 |
| 7 | 1730.8 | 64.717 | 8 | 1618.95 | 52.0945 |
| 9 | 1509.03 | 77.503 | 10 | 1467.56 | 80.7448 |
| 11 | 1386.57 | 83.7173 | 12 | 1240.97 | 47.6054 |
| 13 | 1089.58 | 63.7483 | 14 | 1015.34 | 85.2761 |
| 15 | 969.055 | 96.2939 | 16 | 925.664 | 95.3098 |
| 17 | 854.311 | 77.6185 | 18 | 730.889 | 84.6148 |

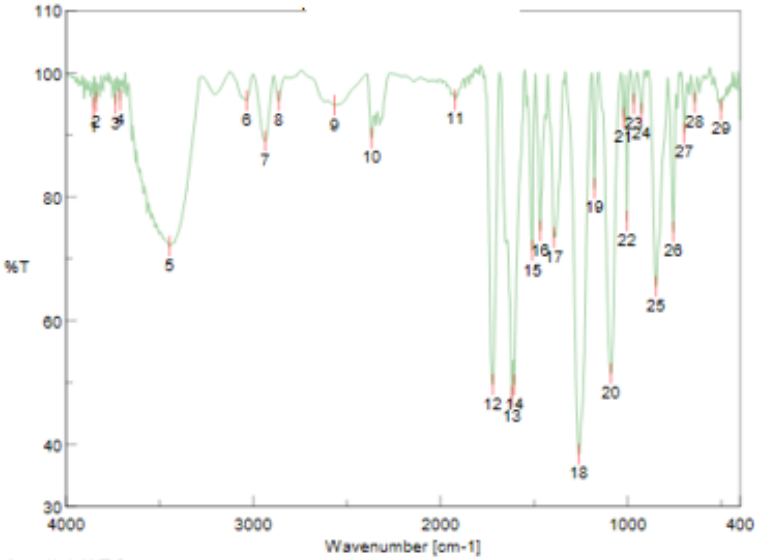
FT/IR for **PCPNaa**




[ピーク検出結果]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3854.04 | 95.0157 | 2 | 3735.44 | 95.7644 |
| 3 | 3446.17 | 62.7774 | 4 | 2942.84 | 74.4453 |
| 5 | 2544.61 | 91.7875 | 6 | 2367.19 | 90.1042 |
| 7 | 1920.75 | 95.5154 | 8 | 1747.19 | 49.4403 |
| 9 | 1618.95 | 37.0005 | 10 | 1509.03 | 70.8128 |
| 11 | 1469.49 | 57.8372 | 12 | 1397.17 | 77.1869 |
| 13 | 1233.25 | 57.0093 | 14 | 1132.97 | 56.4736 |
| 15 | 1078.98 | 63.155 | 16 | 1003.77 | 84.4056 |
| 17 | 967.126 | 90.3068 | 18 | 928.557 | 91.7945 |

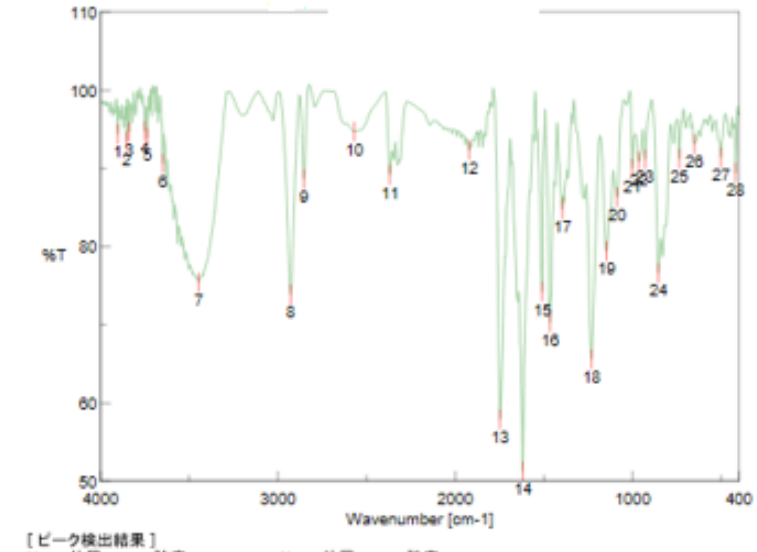
FT/IR for **PCPNda**




[ピーク検出結果]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3854.04 | 94.349 | 2 | 3839.58 | 95.3459 |
| 3 | 3735.44 | 95.0027 | 4 | 3711.33 | 95.6245 |
| 5 | 3447.13 | 71.9681 | 6 | 3034.44 | 95.5374 |
| 7 | 2937.06 | 88.9279 | 8 | 2863.77 | 95.5199 |
| 9 | 2566.79 | 94.7808 | 10 | 2368.16 | 89.4578 |
| 11 | 1921.72 | 95.6797 | 12 | 1722.12 | 49.6654 |
| 13 | 1618.95 | 47.6852 | 14 | 1606.41 | 49.6342 |
| 15 | 1509.03 | 71.3148 | 16 | 1467.56 | 74.5226 |
| 17 | 1395.25 | 73.4008 | 18 | 1261.22 | 38.4188 |
| 19 | 1178.29 | 81.3622 | 20 | 1090.55 | 51.4237 |

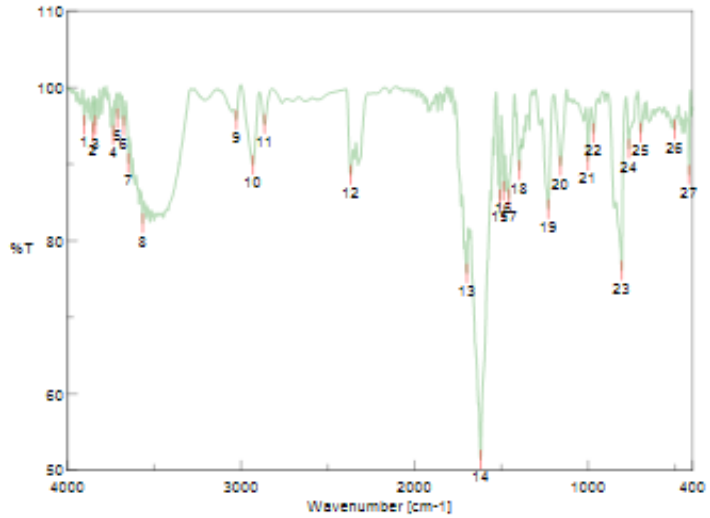
FT/IR for **PCPNba**




［ピーク検出結果］

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3903.22 | 94.3687 | 2 | 3854.04 | 93.4656 |
| 3 | 3839.58 | 94.6927 | 4 | 3750.87 | 94.7907 |
| 5 | 3735.44 | 93.9077 | 6 | 3648.66 | 90.6112 |
| 7 | 3447.13 | 75.4313 | 8 | 2928.38 | 73.9071 |
| 9 | 2853.17 | 88.6217 | 10 | 2568.72 | 94.696 |
| 11 | 2368.16 | 89.1765 | 12 | 1921.72 | 92.3456 |
| 13 | 1747.19 | 57.897 | 14 | 1618.95 | 51.2773 |
| 15 | 1509.03 | 74.2223 | 16 | 1465.63 | 70.326 |
| 17 | 1396.21 | 84.7683 | 18 | 1231.33 | 65.6292 |
| 19 | 1147.44 | 79.4254 | 20 | 1086.69 | 86.3282 |

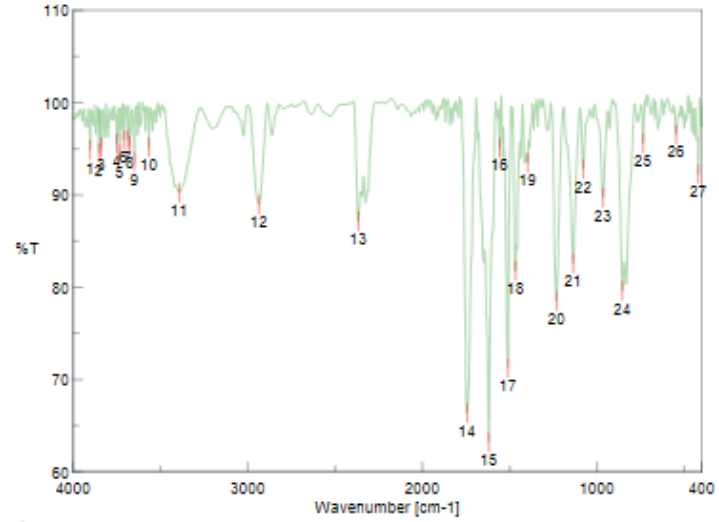
FT/IR for **PCPNea**




［ピーク検出結果］

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3903.22 | 95.1088 | 2 | 3854.04 | 94.1574 |
| 3 | 3839.58 | 95.0607 | 4 | 3735.44 | 93.8048 |
| 5 | 3711.33 | 95.9834 | 6 | 3676.62 | 95.0116 |
| 7 | 3648.66 | 90.1061 | 8 | 3566.7 | 82.2672 |
| 9 | 3026.73 | 95.7849 | 10 | 2932.23 | 89.9021 |
| 11 | 2864.74 | 95.2232 | 12 | 2368.16 | 88.559 |
| 13 | 1698.98 | 75.7252 | 14 | 1619.91 | 51.4035 |
| 15 | 1508.06 | 85.4039 | 16 | 1487.81 | 86.463 |
| 17 | 1456.96 | 85.4724 | 18 | 1397.17 | 89.1896 |
| 19 | 1230.36 | 84.097 | 20 | 1159.97 | 89.7472 |
| 21 | 1001.84 | 90.3976 | 22 | 969.055 | 94.066 |

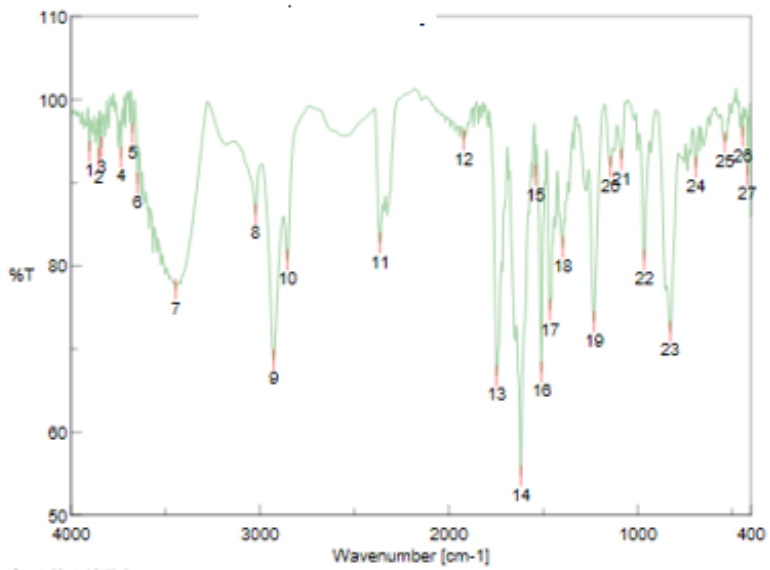
FT/IR for **PCPNca**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3903.22 | 94.8346 | 2 | 3854.04 | 94.5121 |
| 3 | 3839.58 | 95.119 | 4 | 3750.87 | 95.5333 |
| 5 | 3735.44 | 94.3919 | 6 | 3711.33 | 95.954 |
| 7 | 3690.12 | 95.9761 | 8 | 3675.66 | 95.339 |
| 9 | 3648.66 | 93.5802 | 10 | 3566.7 | 95.1253 |
| 11 | 3393.14 | 90.2467 | 12 | 2936.09 | 88.9572 |
| 13 | 2367.19 | 87.1305 | 14 | 1744.3 | 66.3643 |
| 15 | 1619.91 | 63.1944 | 16 | 1558.2 | 95.0796 |
| 17 | 1509.03 | 71.2234 | 18 | 1466.6 | 81.7373 |
| 19 | 1397.17 | 93.4485 | 20 | 1231.33 | 78.4763 |
| 21 | 1136.83 | 82.5672 | 22 | 1078.01 | 92.7827 |

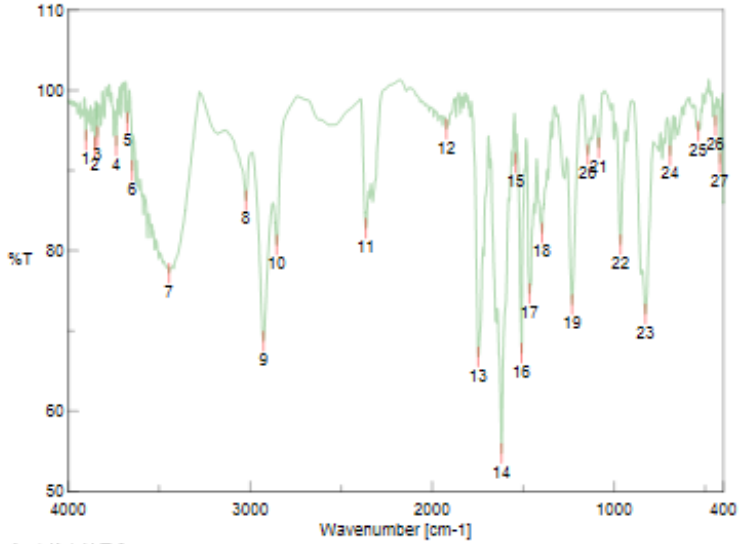
FT/IR for **PCPNdc**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3903.22 | 93.7256 | 2 | 3854.04 | 92.925 |
| 3 | 3839.58 | 94.2011 | 4 | 3735.44 | 93.0581 |
| 5 | 3675.66 | 95.9542 | 6 | 3648.66 | 89.9693 |
| 7 | 3446.17 | 77.1901 | 8 | 3023.84 | 86.2204 |
| 9 | 2927.41 | 68.7155 | 10 | 2854.13 | 80.6778 |
| 11 | 2364.3 | 82.7552 | 12 | 1921.72 | 95.1419 |
| 13 | 1747.19 | 66.7577 | 14 | 1618.95 | 54.7422 |
| 15 | 1540.85 | 90.8847 | 16 | 1509.03 | 67.2468 |
| 17 | 1465.63 | 74.6608 | 18 | 1397.17 | 82.1756 |
| 19 | 1231.33 | 73.2786 | 20 | 1144.55 | 91.9338 |

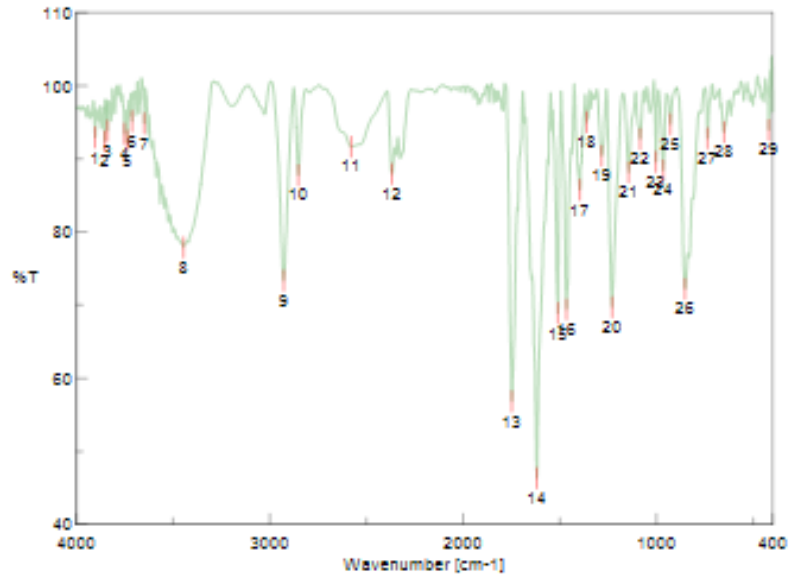
FT/IR for **PCPNeb**




［ピーク検出結果］

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3903.22 | 93.7256 | 2 | 3854.04 | 92.925 |
| 3 | 3839.58 | 94.2011 | 4 | 3735.44 | 93.0581 |
| 5 | 3675.66 | 95.9542 | 6 | 3648.66 | 89.9693 |
| 7 | 3446.17 | 77.1901 | 8 | 3023.84 | 86.2204 |
| 9 | 2927.41 | 68.7155 | 10 | 2854.13 | 80.6778 |
| 11 | 2364.3 | 82.7552 | 12 | 1921.72 | 95.1419 |
| 13 | 1747.19 | 66.7577 | 14 | 1618.95 | 54.7422 |
| 15 | 1540.85 | 90.8847 | 16 | 1509.03 | 67.2468 |
| 17 | 1465.63 | 74.6608 | 18 | 1397.17 | 82.1756 |
| 19 | 1231.33 | 73.2786 | 20 | 1144.55 | 91.9338 |
| 21 | 1085.73 | 92.7921 | 22 | 966.162 | 80.736 |

FT/IR for **PCPNec**

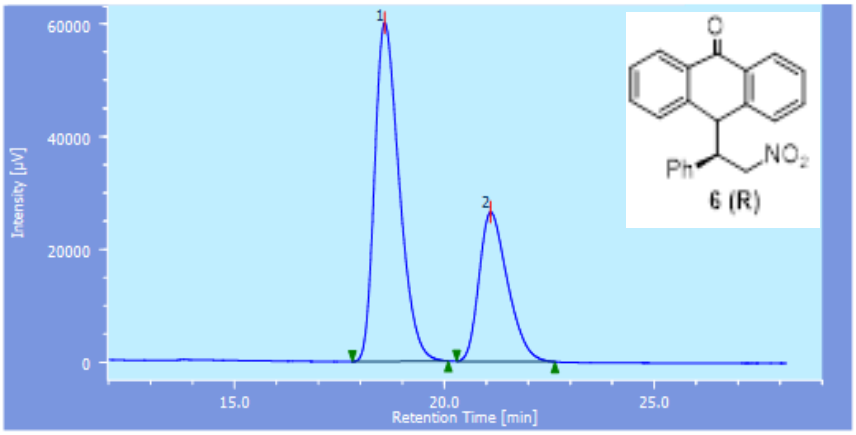



［ピーク検出結果］

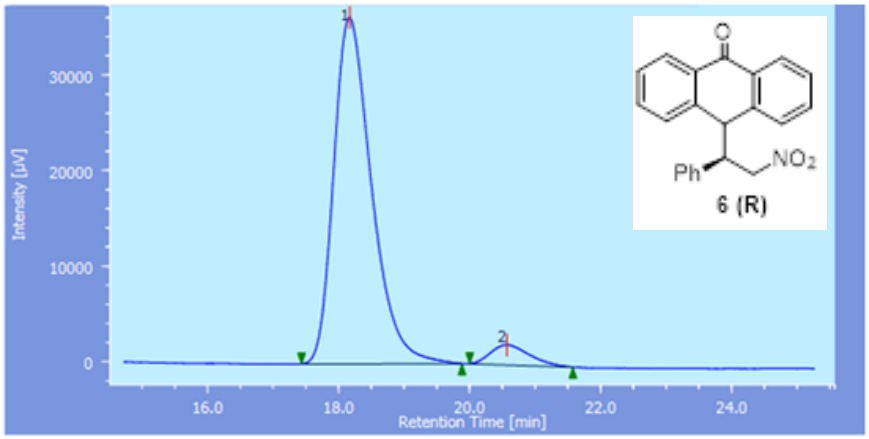
| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3903.22 | 92.9246 | 2 | 3854.04 | 92.3731 |
| 3 | 3839.58 | 93.8176 | 4 | 3750.87 | 93.4365 |
| 5 | 3735.44 | 92.4648 | 6 | 3711.33 | 95.1262 |
| 7 | 3648.66 | 94.8389 | 8 | 3446.17 | 77.8741 |
| 9 | 2928.38 | 73.312 | 10 | 2852.2 | 87.7225 |
| 11 | 2578.36 | 91.6333 | 12 | 2368.16 | 87.9051 |
| 13 | 1748.16 | 56.8247 | 14 | 1618.95 | 46.3127 |
| 15 | 1509.03 | 68.876 | 16 | 1465.63 | 69.3953 |
| 17 | 1397.17 | 85.763 | 18 | 1361.5 | 95.0141 |
| 19 | 1283.39 | 90.413 | 20 | 1230.36 | 69.6768 |

FT/IR for **PCPDea**

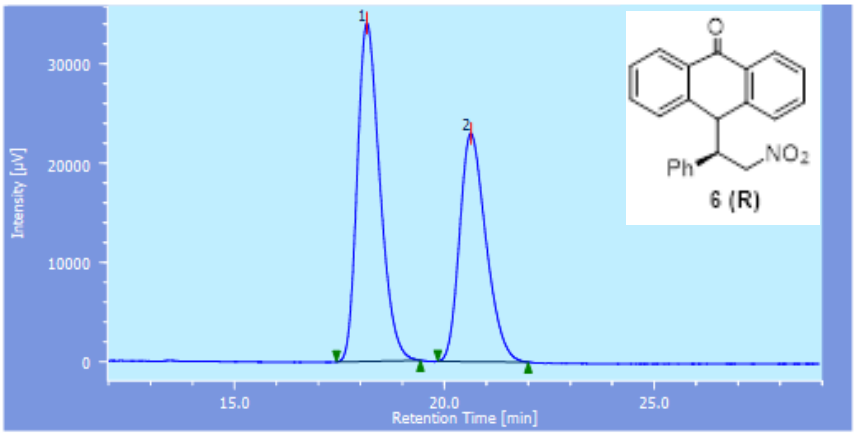
## B.3 Chromatogram data for Michael products



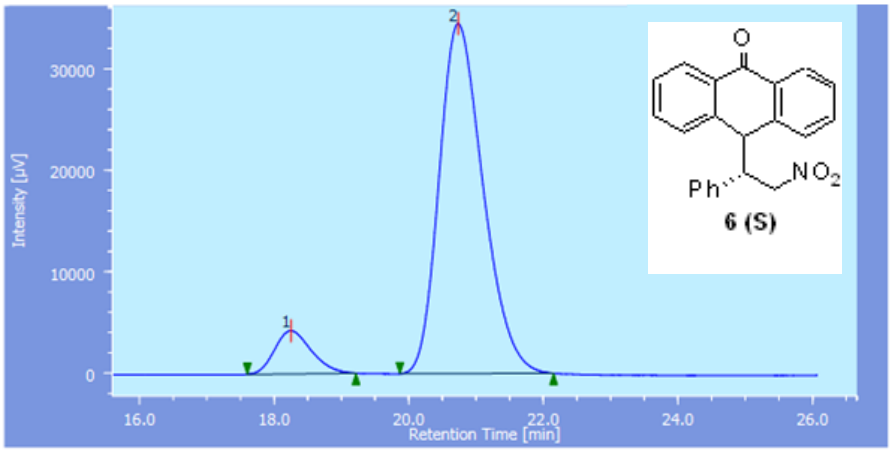

With **PBzQN** as catalyst



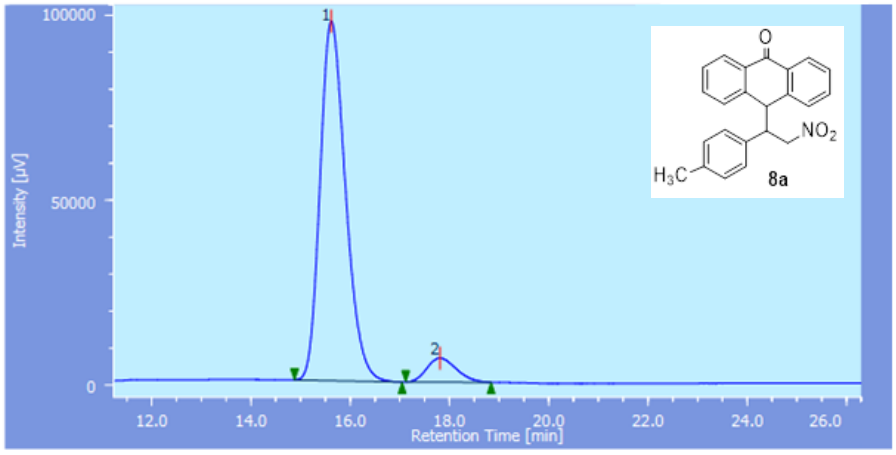

With **PCPNea** as catalyst



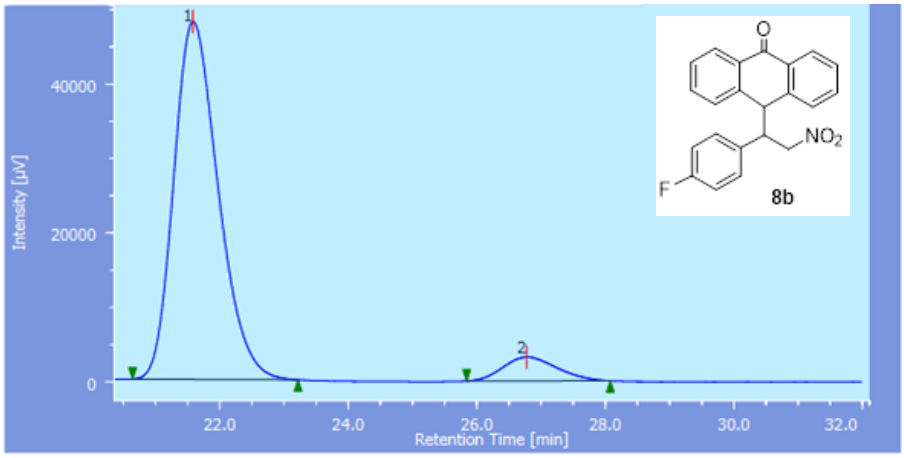

With **PQNaa** as catalyst (11% ee)



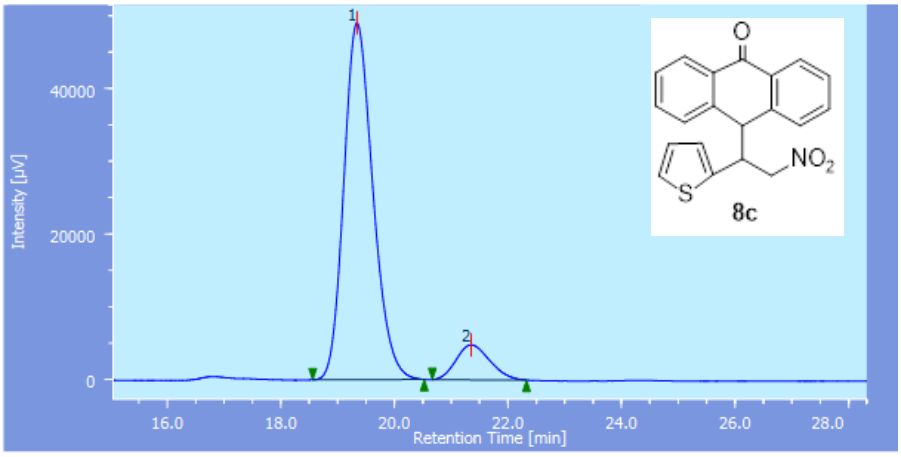

With **PCPDea** as catalyst




With **PCPNea** as a catalyst




With **PCPNea** as a catalyst

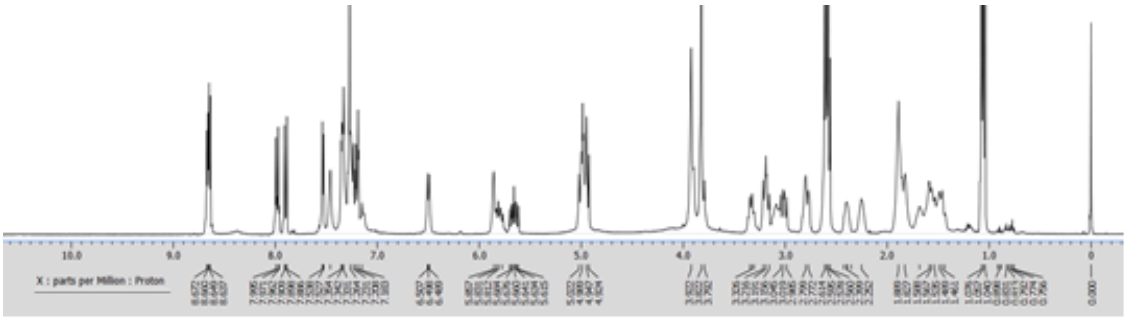



With **PCPNea** as a catalyst

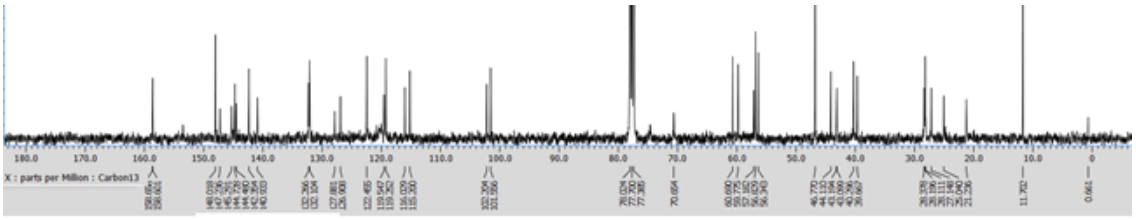
# Appendix C

# Supporting document for Chapter 4

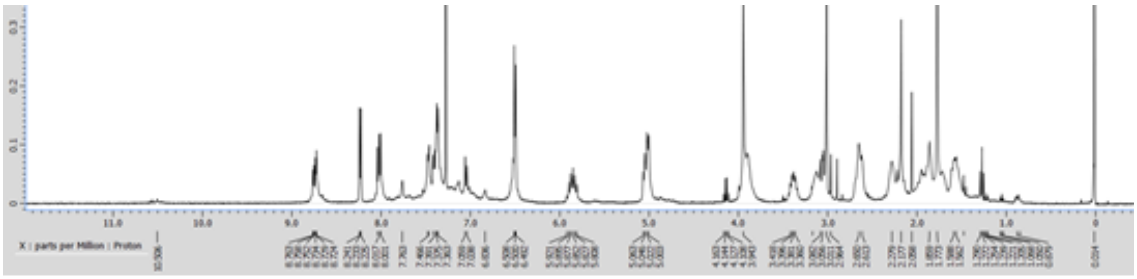
## C.1 $^{1}$H and $^{13}$C NMR for urethane derivatives of cinchona alkaloid



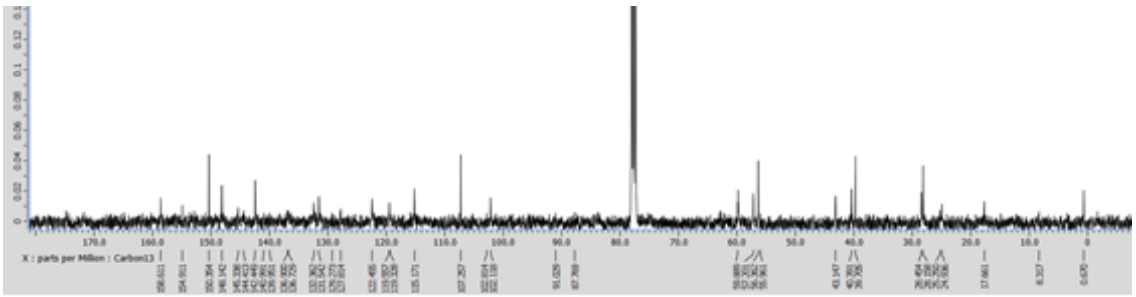

$^{1}$H NMR for **3QNa** in $CDCl_3$



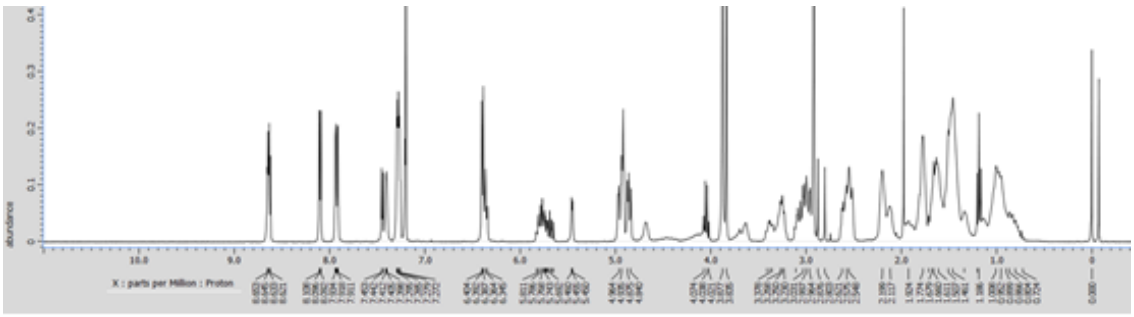

$^{13}$C NMR for **3QNa** in $CDCl_3$



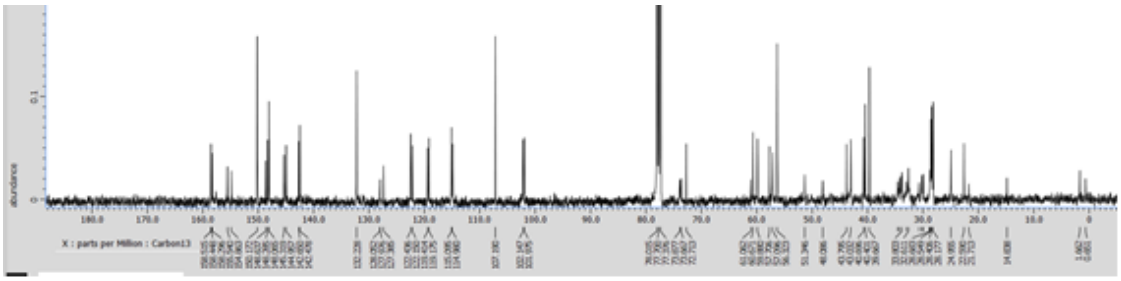
$^{1}$H NMR for **3QNb** in $CDCl_3$



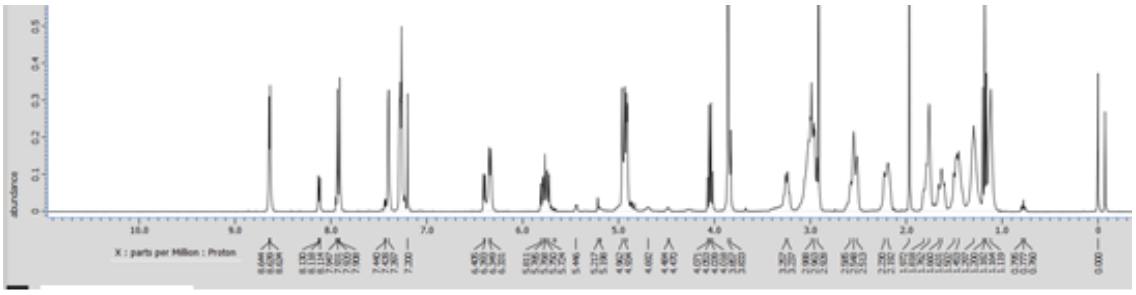
$^{13}$C NMR for **3QNb** in $CDCl_3$



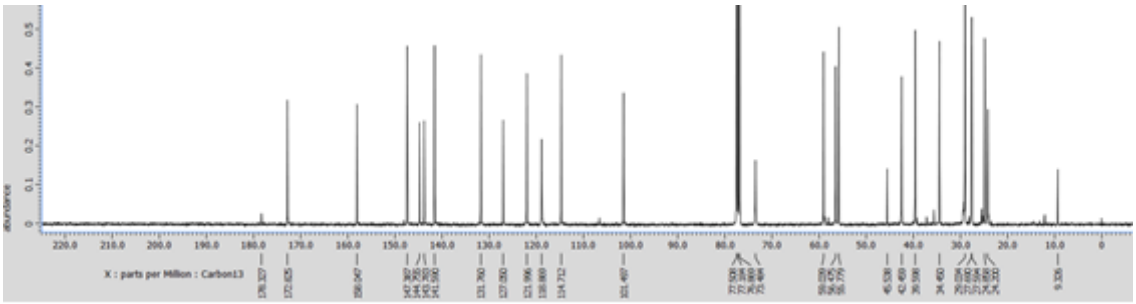
$^{1}$H NMR for **3QNc** in $CDCl_3$



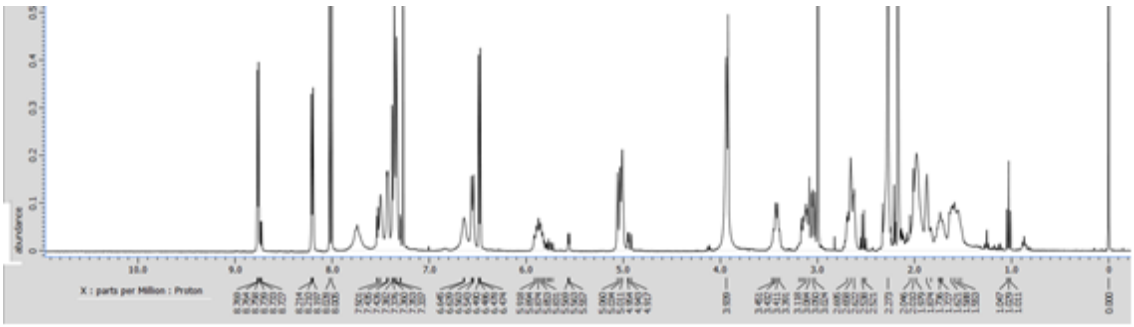
$^{13}$C NMR for **3QNc** in $CDCl_3$



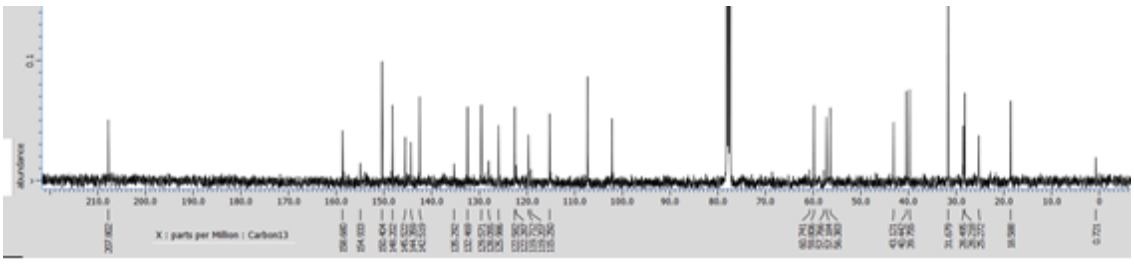
$^{1}$H NMR for **3QNd** in $CDCl_3$



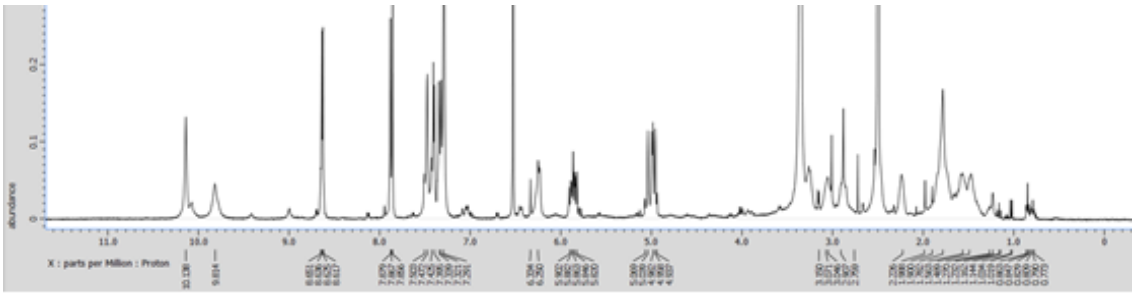
$^{13}$C NMR for **3QNd** in $CDCl_3$



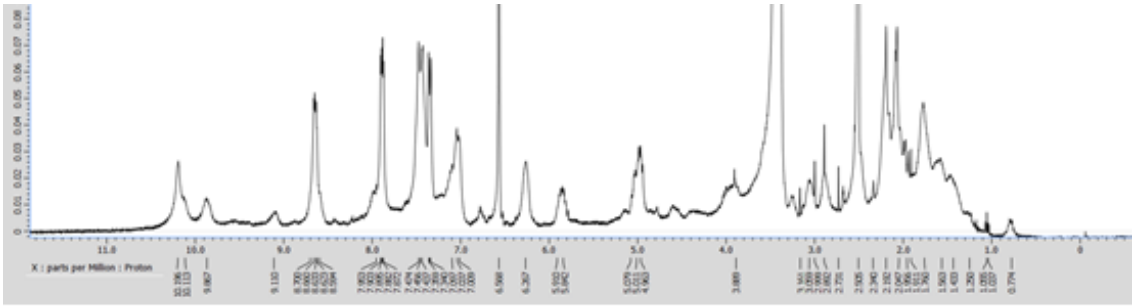
$^{1}$H NMR for **3QNe** in $CDCl_3$



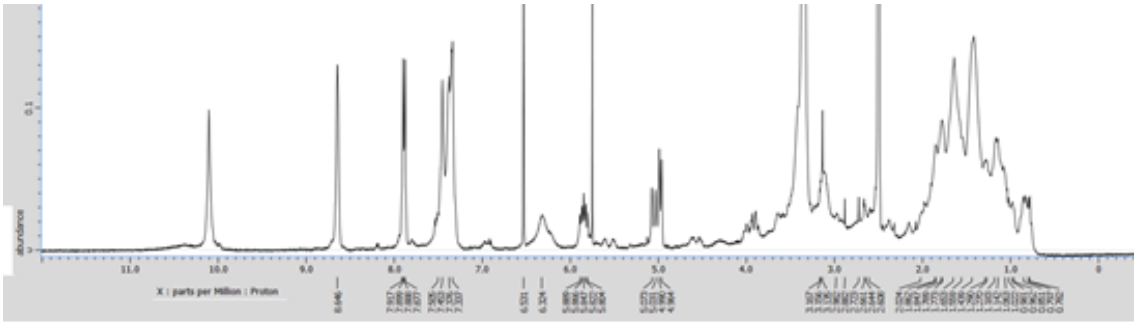
$^{13}$C NMR for **3QNe** in $CDCl_3$



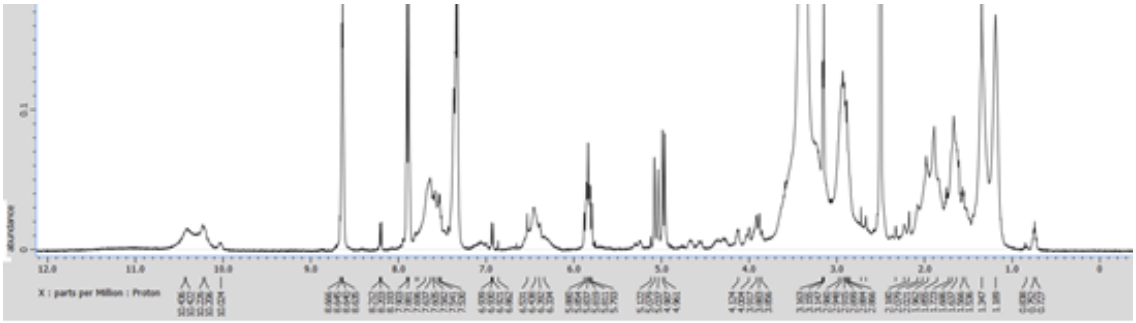
$^{1}$H NMR for **3CPNa** in DMSO-$d_6$



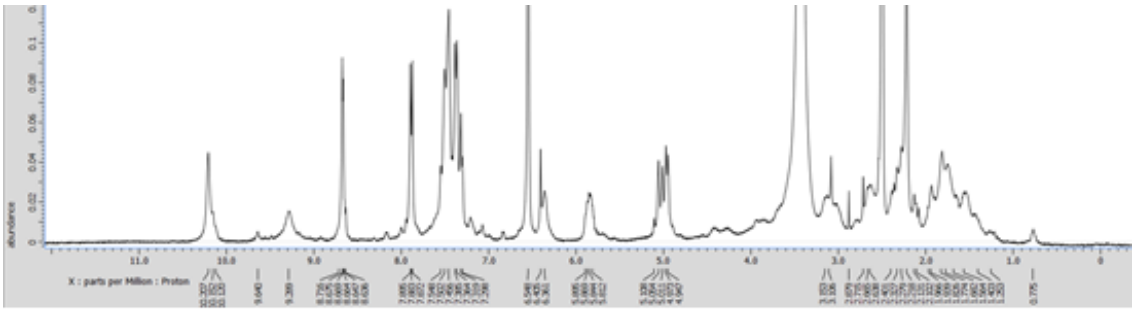
$^{1}$H NMR for **3CPNb** in DMSO-$d_6$



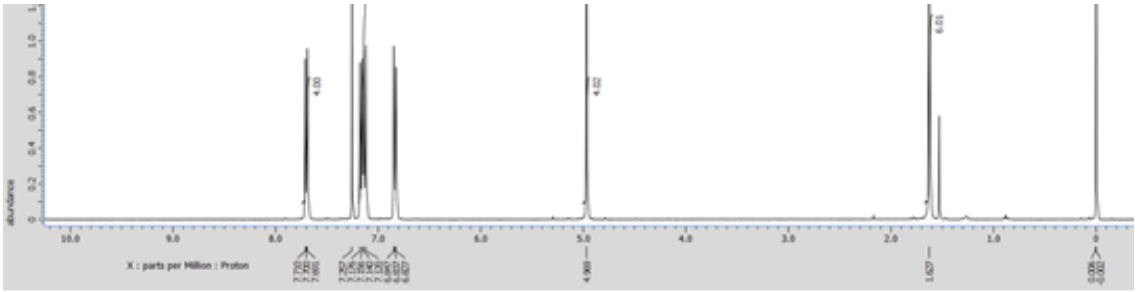
$^{1}$H NMR for **3CPNc** in DMSO-$d_6$



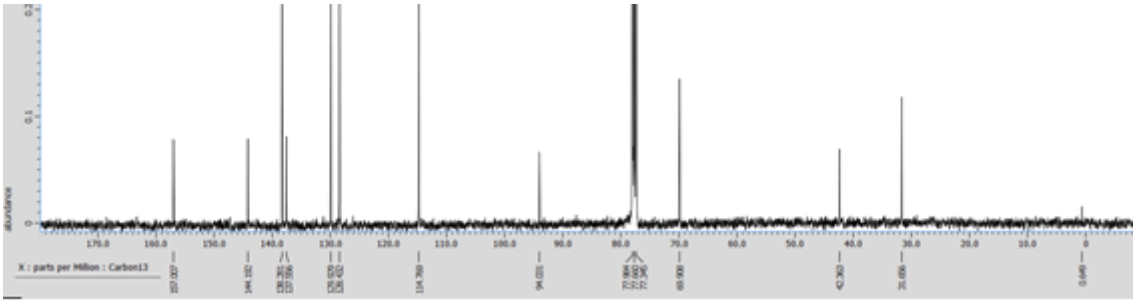
$^{1}$H NMR for **3CPNd** in DMSO-$d_6$S



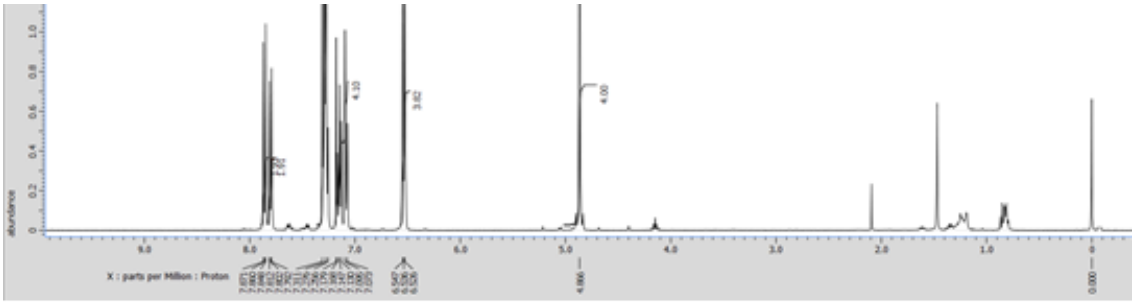
$^{1}$H NMR for **3CPNe** in DMSO-$d_6$



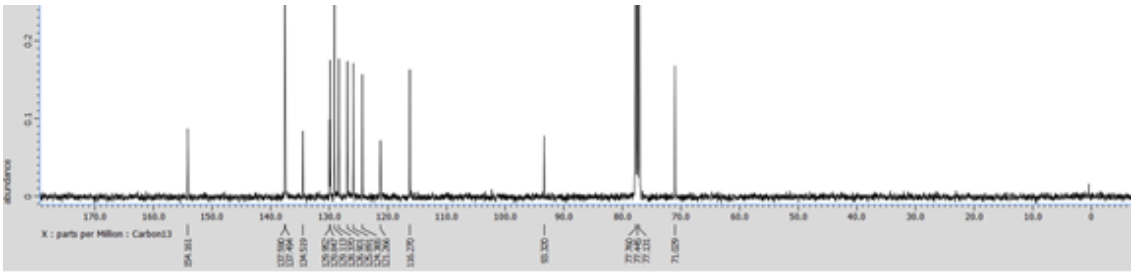
$^{1}$H NMR for aromatic diiodide **d** in $CDCl_3$



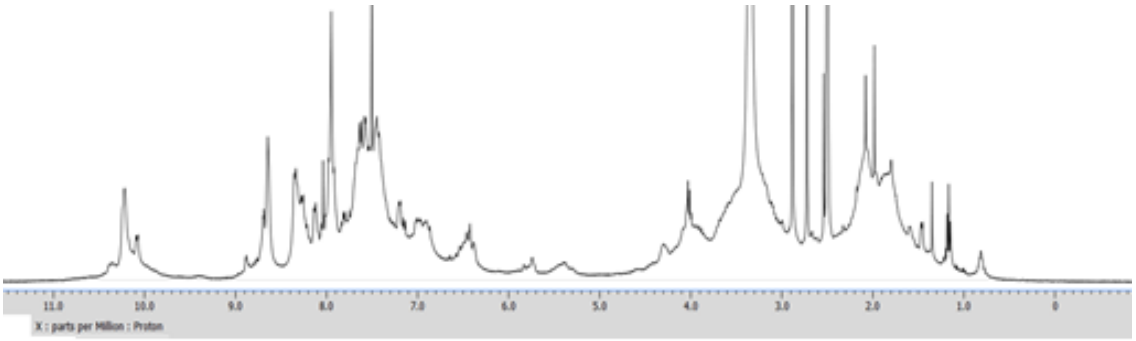
$^{13}$C NMR for aromatic diiodide **d** in $CDCl_3$



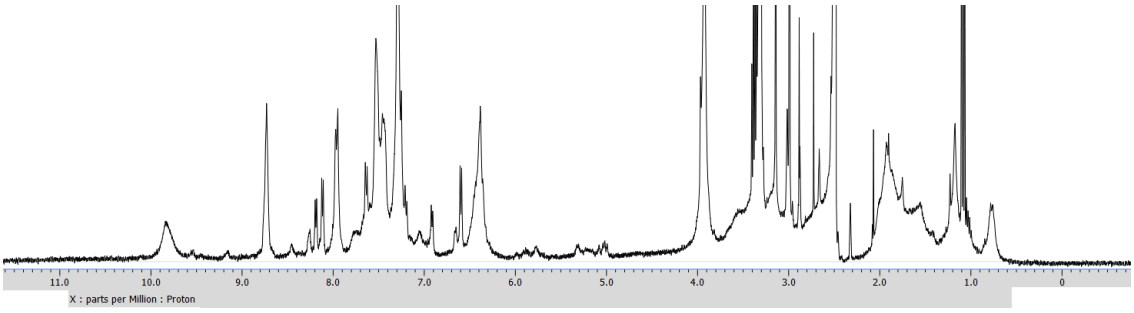
$^{1}$H NMR for aromatic diiodide **e** in $CDCl_3$



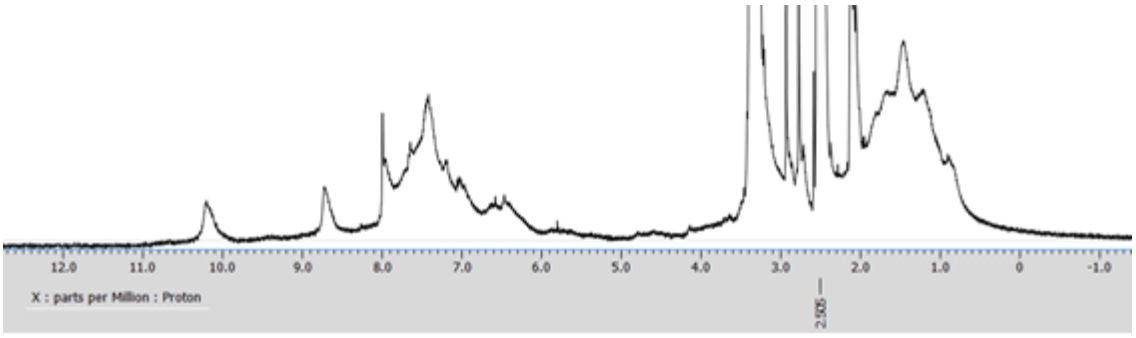

$^{13}$C NMR for aromatic diiodide **e** in $CDCl_3$



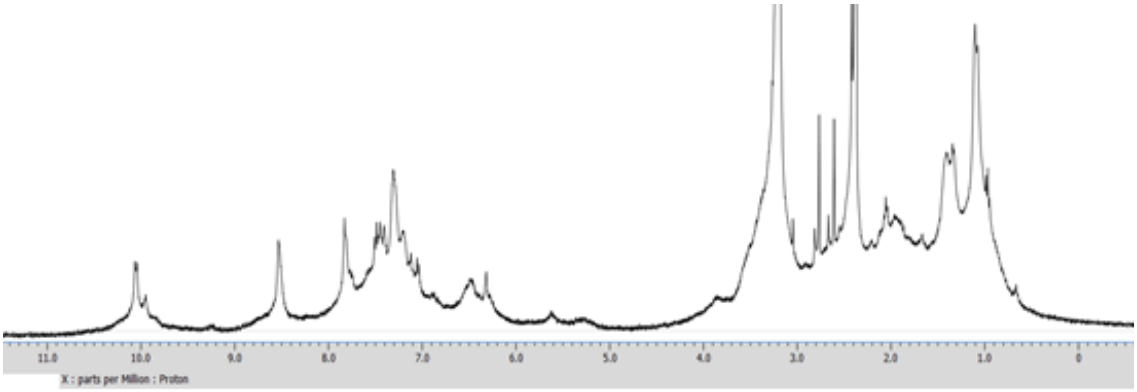

$^{1}$H NMR for **PCPNaa** in DMSO-$d_6$



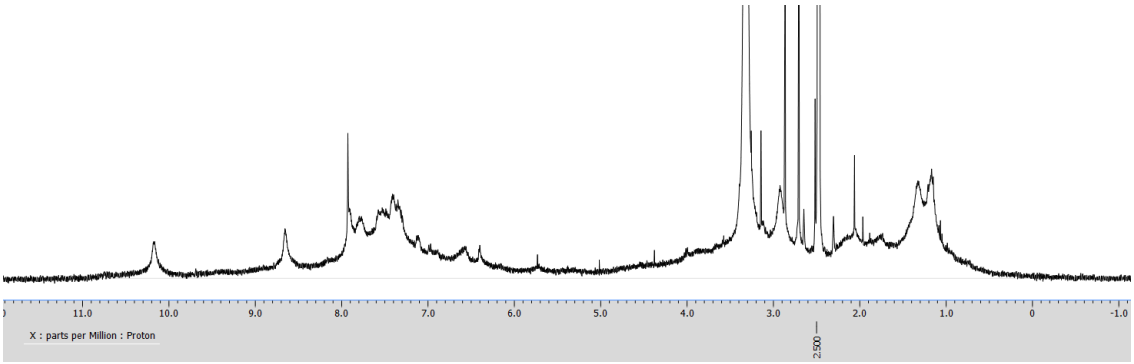

$^{1}$H NMR for **PCPNba** in DMSO-$d_6$



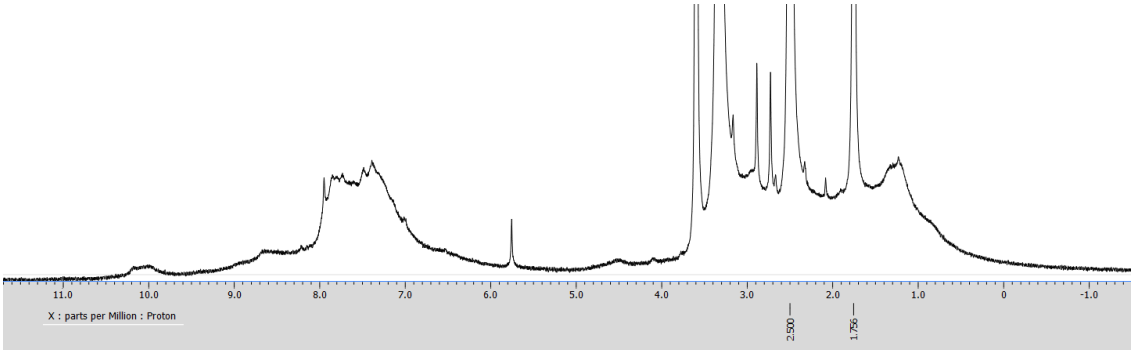

$^{1}$H NMR for **PCPNca** in DMSO-$d_6$



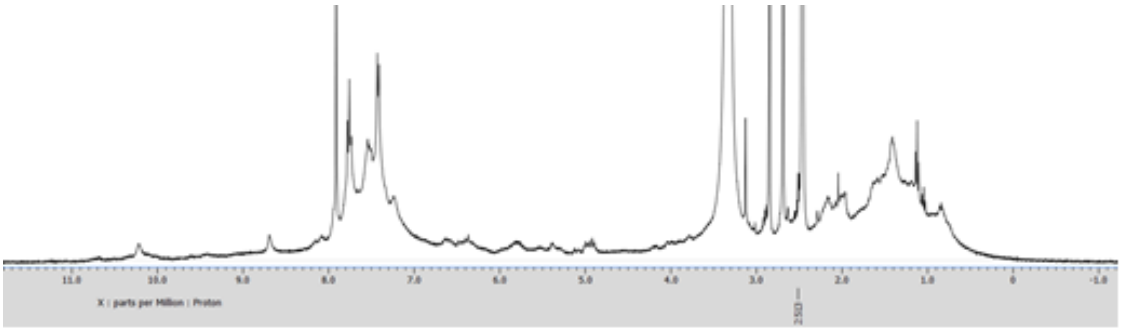

$^{1}$H NMR for **PCPNda** in DMSO-$d_6$



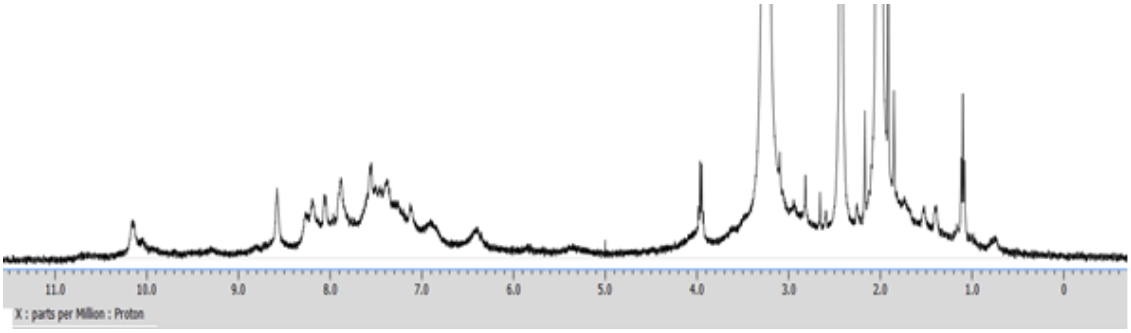

$^{1}$H NMR for **PCPNea** in DMSO-$d_6$



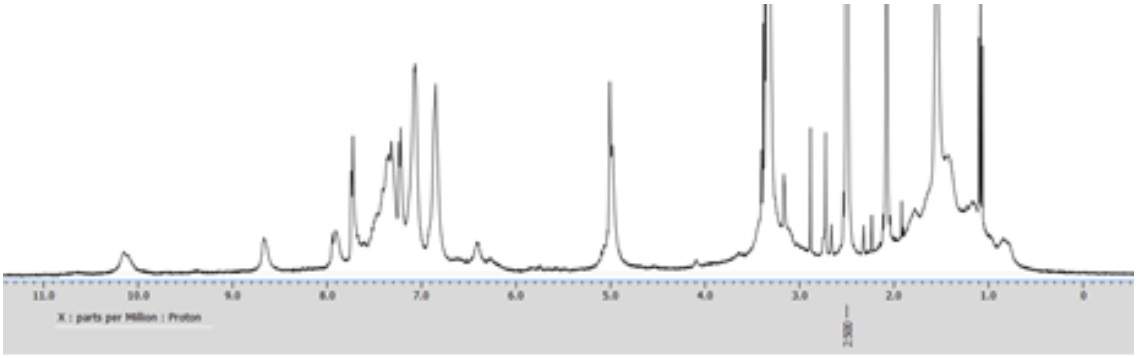

$^{1}$H NMR for **PCPNcb** in DMSO-$d_6$



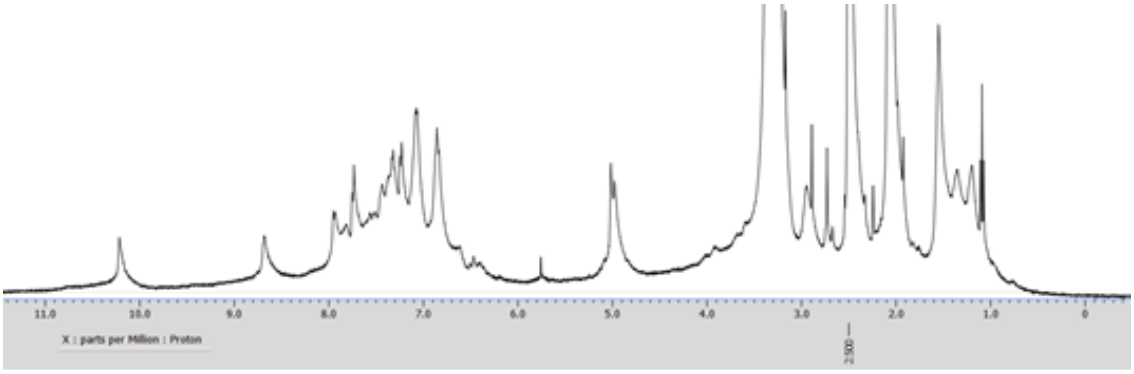

$^{1}$H NMR for **PCPNdc** in DMSO-$d_6$



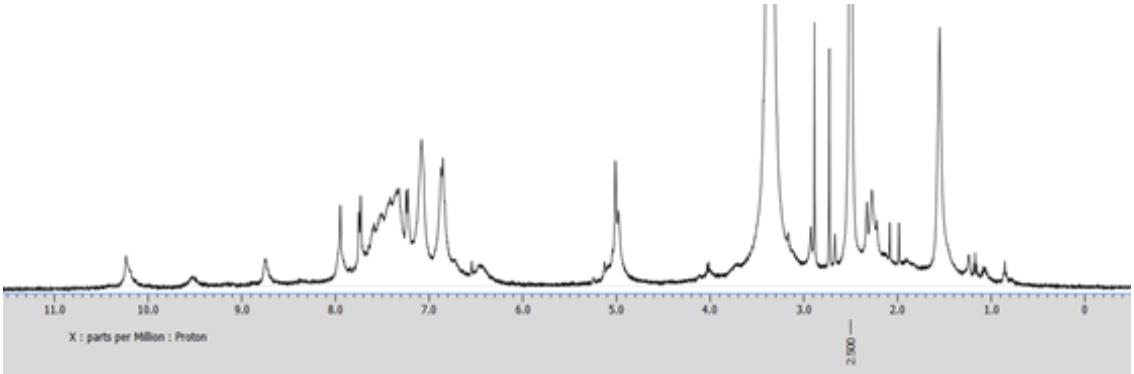

$^{1}$H NMR for **PCPNab** in DMSO-$d_6$



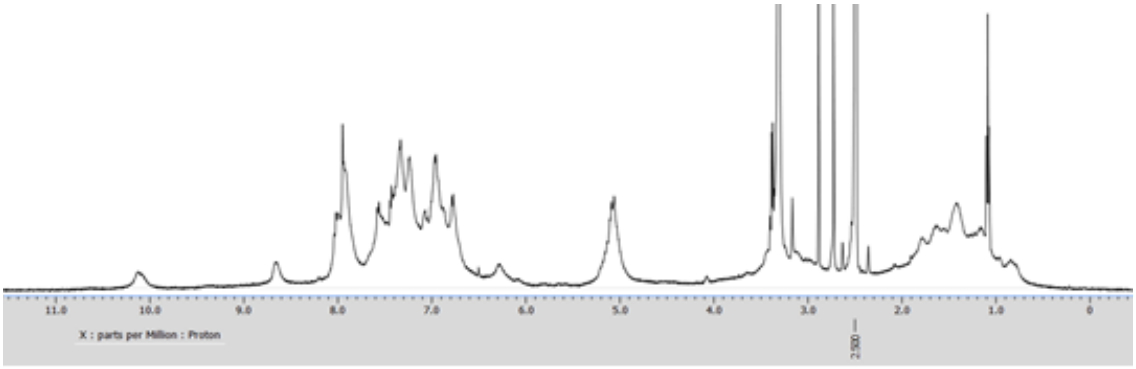

$^{1}$H NMR for **PCPNcd** in DMSO-$d_6$



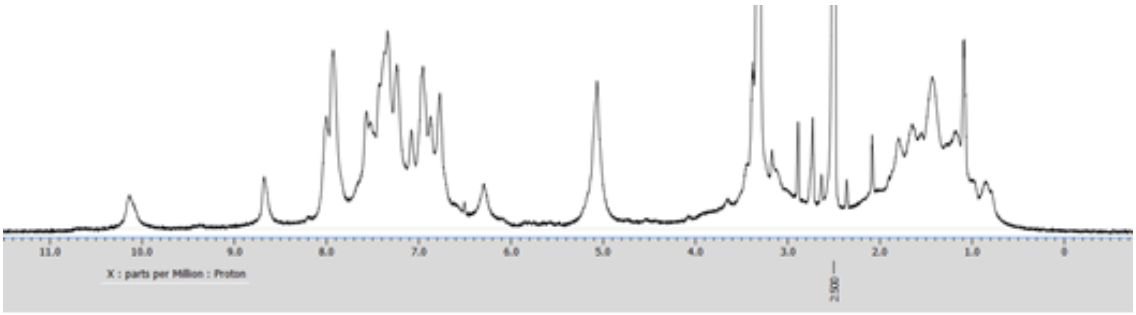

$^{1}$H NMR for **PCPNdd** in DMSO-$d_6$



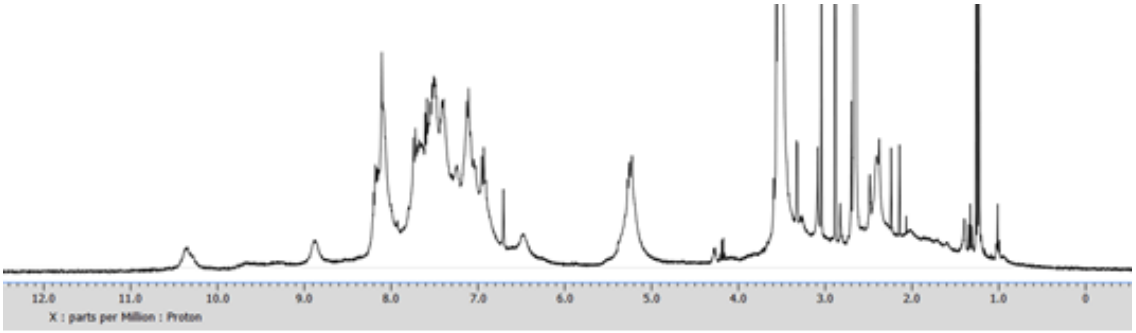

$^{1}$H NMR for **PCPNed** in DMSO-$d_6$



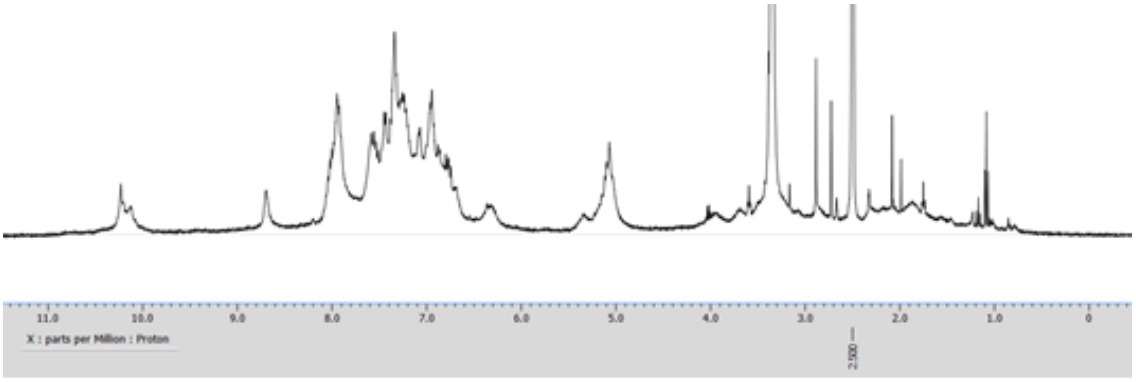

$^{1}$H NMR for **PCPNce** in DMSO-$d_6$



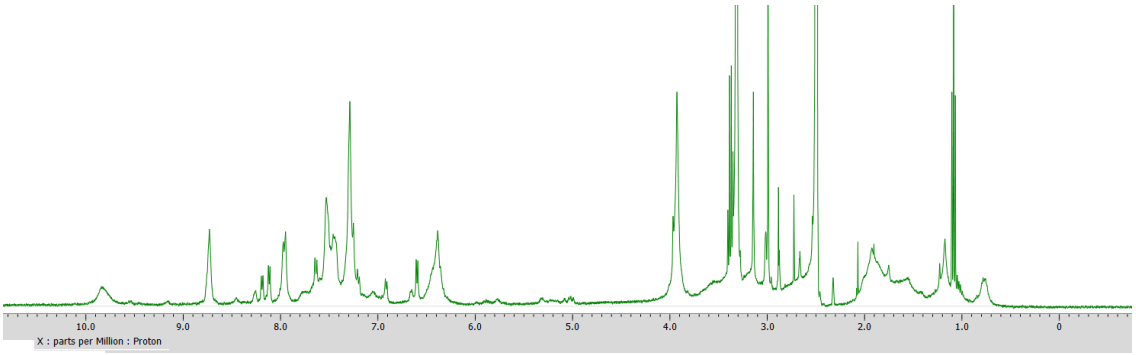

$^{1}$H NMR for **PCPNcf** in DMSO-$d_6$




$^{1}$H NMR for **PCPNef** in DMSO-$d_6$

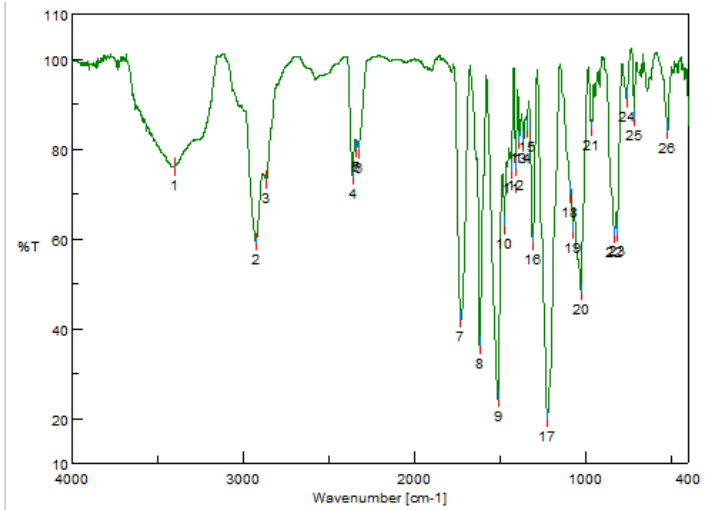



$^{1}$H NMR for **PCPNaf** in DMSO-$d_6$




$^{1}$H NMR for **PQNaa** in DMSO-$d_6$

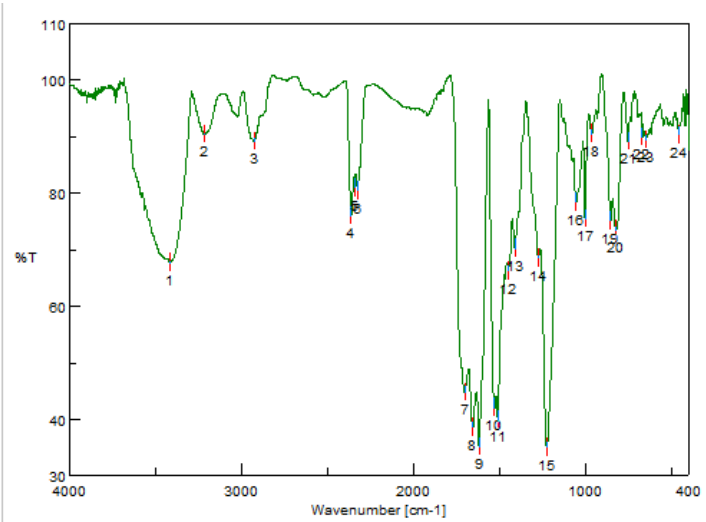
## C.2 FT/IR for chiral polyurethanes of cinchona alkaloids




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3402.78 | 75.9109 | 2 | 2926.45 | 59.1672 |
| 3 | 2865.7 | 73.109 | 4 | 2360.44 | 73.9011 |
| 5 | 2343.09 | 80.0267 | 6 | 2326.7 | 79.6586 |
| 7 | 1729.83 | 42.0656 | 8 | 1618.95 | 36.254 |
| 9 | 1510.95 | 24.3393 | 10 | 1474.31 | 62.3307 |
| 11 | 1433.82 | 75.1042 | 12 | 1407.78 | 75.8493 |
| 13 | 1388.5 | 81.77 | 14 | 1362.46 | 81.8402 |
| 15 | 1341.25 | 84.3453 | 16 | 1309.43 | 59.1942 |
| 17 | 1223.61 | 19.987 | 18 | 1086.69 | 69.8617 |
| 19 | 1073.19 | 61.7973 | 20 | 1026.91 | 48.0537 |
| 21 | 965.198 | 84.5899 | 22 | 832.133 | 60.8291 |

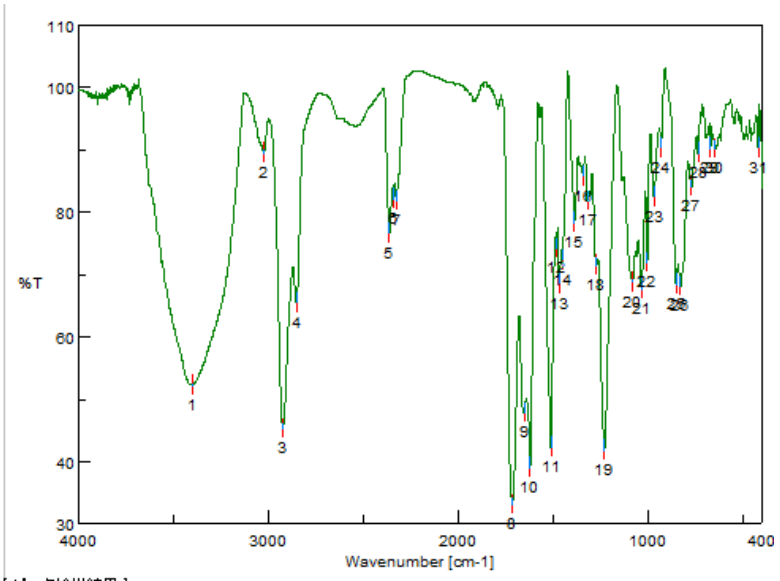
IR spectrum for **PCPNaa**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3419.17 | 67.6953 | 2 | 3218.61 | 90.446 |
| 3 | 2929.34 | 89.1425 | 4 | 2364.3 | 76.0854 |
| 5 | 2343.09 | 80.9888 | 6 | 2326.7 | 80.4847 |
| 7 | 1702.84 | 44.7787 | 8 | 1656.55 | 38.5992 |
| 9 | 1618.95 | 35.1475 | 10 | 1529.27 | 42.0367 |
| 11 | 1509.03 | 39.9387 | 12 | 1448.28 | 66.2482 |
| 13 | 1410.67 | 70.2467 | 14 | 1274.72 | 68.547 |
| 15 | 1225.54 | 35.0811 | 16 | 1055.84 | 78.3841 |
| 17 | 1002.8 | 75.4786 | 18 | 964.233 | 90.5005 |
| 19 | 853.347 | 75.126 | 20 | 823.455 | 73.498 |
| 21 | 752.102 | 89.205 | 22 | 669.178 | 89.9426 |
| 23 | 647.965 | 89.4187 | 24 | 457.047 | 90.2937 |

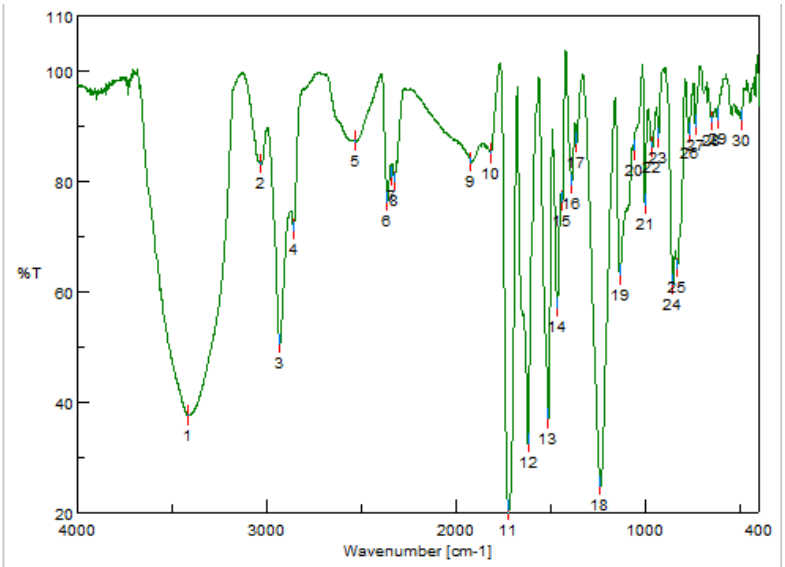
IR spectrum for **PCPNba**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3402.78 | 52.2226 | 2 | 3025.76 | 89.5583 |
| 3 | 2925.48 | 45.2348 | 4 | 2854.13 | 65.4943 |
| 5 | 2364.3 | 76.6552 | 6 | 2343.09 | 82.123 |
| 7 | 2326.7 | 81.81 | 8 | 1715.37 | 33.0681 |
| 9 | 1653.66 | 47.7452 | 10 | 1619.91 | 39.0093 |
| 11 | 1510.95 | 42.28 | 12 | 1482.99 | 74.1625 |
| 13 | 1467.56 | 68.567 | 14 | 1449.24 | 72.3001 |
| 15 | 1386.57 | 78.3429 | 16 | 1340.28 | 85.7735 |
| 17 | 1318.11 | 81.7956 | 18 | 1270.86 | 71.4771 |
| 19 | 1229.4 | 41.7818 | 20 | 1081.87 | 68.7344 |
| 21 | 1033.66 | 67.6548 | 22 | 1003.77 | 71.8719 |

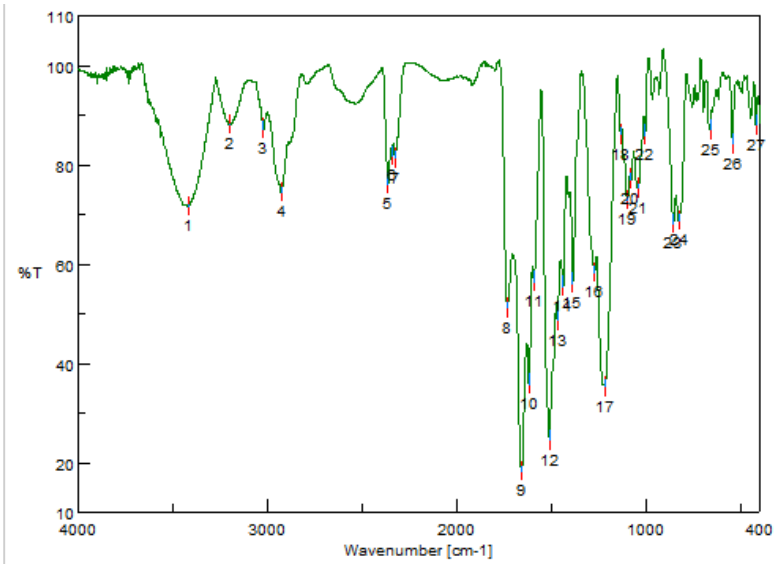
IR spectrum for **PCPNca**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3413.39 | 37.6377 | 2 | 3033.48 | 83.0921 |
| 3 | 2931.27 | 50.5685 | 4 | 2858.95 | 71.2768 |
| 5 | 2530.15 | 87.2367 | 6 | 2364.3 | 76.3156 |
| 7 | 2343.09 | 80.8424 | 8 | 2326.7 | 80.014 |
| 9 | 1920.75 | 83.4593 | 10 | 1812.76 | 85.0114 |
| 11 | 1721.16 | 20.5003 | 12 | 1618.95 | 32.5424 |
| 13 | 1511.92 | 37.0633 | 14 | 1465.53 | 57.1138 |
| 15 | 1438.64 | 76.381 | 16 | 1387.53 | 79.3768 |
| 17 | 1362.46 | 86.9882 | 18 | 1238.08 | 24.9101 |
| 19 | 1132.97 | 63.075 | 20 | 1060.56 | 85.61 |

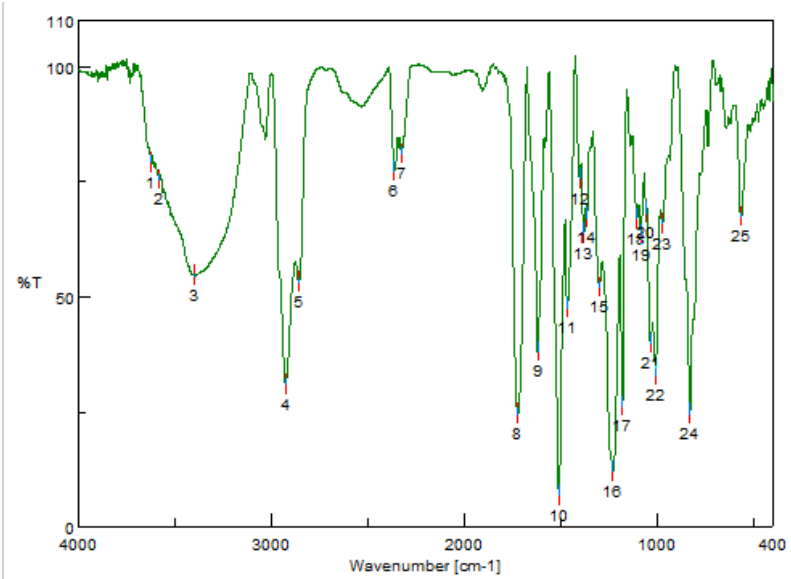
FT-IR for **PCPNda**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3421.1 | 71.538 | 2 | 3199.33 | 88.1373 |
| 3 | 3022.87 | 87.2349 | 4 | 2927.41 | 74.4157 |
| 5 | 2363.34 | 76.1635 | 6 | 2343.09 | 81.6964 |
| 7 | 2326.7 | 81.2975 | 8 | 1732.73 | 51.1796 |
| 9 | 1658.48 | 18.3477 | 10 | 1618.95 | 35.8734 |
| 11 | 1591.95 | 56.4728 | 12 | 1509.03 | 24.5035 |
| 13 | 1467.56 | 48.6368 | 14 | 1437.67 | 55.5695 |
| 15 | 1386.57 | 56.1738 | 16 | 1272.79 | 58.3188 |
| 17 | 1216.86 | 35.3353 | 18 | 1133.94 | 86.0876 |
| 19 | 1098.26 | 72.8185 | 20 | 1078.01 | 77.066 |
| 21 | 1041.37 | 75.3035 | 22 | 1004.73 | 85.9446 |

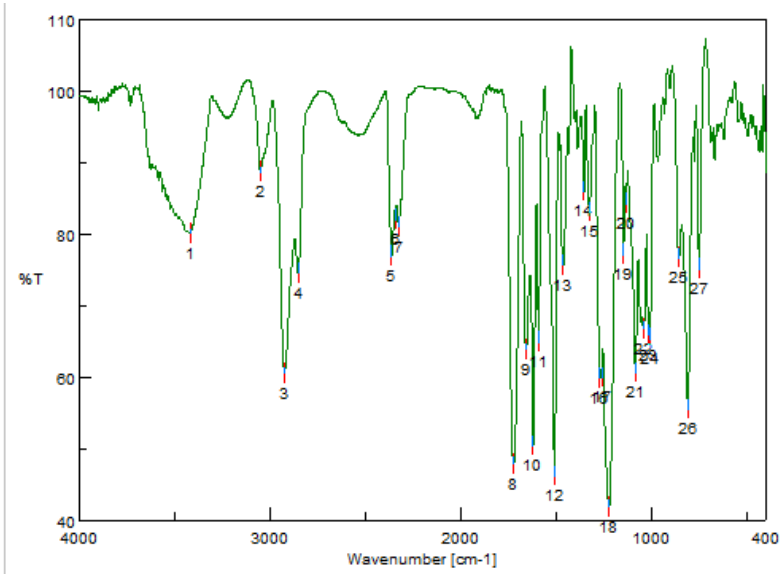
IR spectrum for **PCPNea**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3626.48 | 79.1525 | 2 | 3585.98 | 75.4285 |
| 3 | 3401.82 | 54.571 | 4 | 2926.45 | 30.9592 |
| 5 | 2857.99 | 53.2119 | 6 | 2364.3 | 77.2999 |
| 7 | 2326.7 | 81.0554 | 8 | 1723.09 | 24.5749 |
| 9 | 1618.95 | 38.058 | 10 | 1509.03 | 6.93172 |
| 11 | 1465.63 | 47.5055 | 12 | 1402 | 75.6056 |
| 13 | 1380.78 | 63.7985 | 14 | 1362.46 | 67.1738 |
| 15 | 1298.82 | 52.0664 | 16 | 1228.43 | 12.1724 |
| 17 | 1180.22 | 26.1908 | 18 | 1104.05 | 66.9038 |
| 19 | 1083.8 | 63.3979 | 20 | 1067.76 | 68.2819 |

IR spectrum for **PCPNcd**

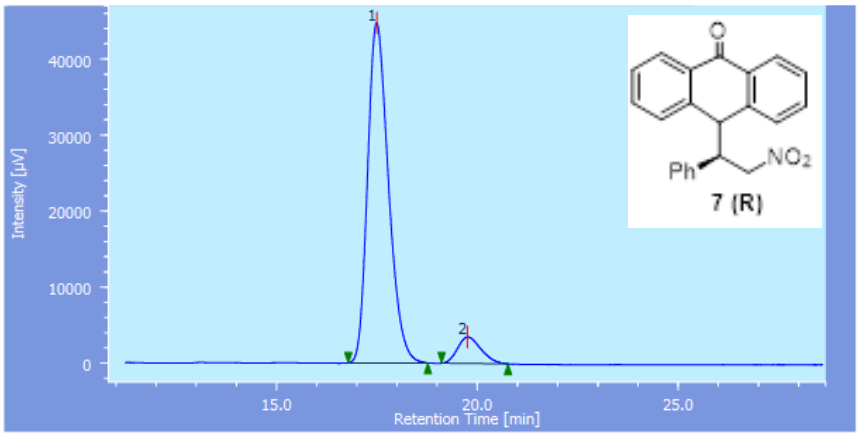



[ ピーク検出結果 ]

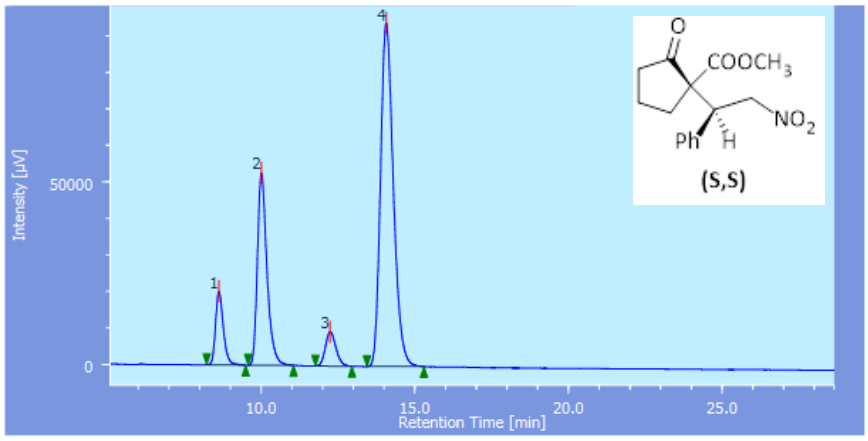
| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3421.1 | 80.1393 | 2 | 3051.8 | 88.7447 |
| 3 | 2925.48 | 60.5805 | 4 | 2854.13 | 74.6187 |
| 5 | 2364.3 | 76.9771 | 6 | 2343.09 | 82.1057 |
| 7 | 2326.7 | 81.0091 | 8 | 1723.09 | 47.9652 |
| 9 | 1656.55 | 63.8977 | 10 | 1619.91 | 50.4921 |
| 11 | 1590.99 | 64.9634 | 12 | 1508.06 | 46.2256 |
| 13 | 1462.74 | 75.7014 | 14 | 1353.78 | 85.9849 |
| 15 | 1324.86 | 83.1154 | 16 | 1270.86 | 59.9848 |
| 17 | 1261.22 | 60.0379 | 18 | 1221.58 | 41.9909 |
| 19 | 1146.47 | 77.1852 | 20 | 1132.01 | 84.2902 |
| 21 | 1083.8 | 60.6594 | 22 | 1040.41 | 66.821 |
| 23 | 1016.3 | 65.9078 | 24 | 1006.56 | 65.4079 |

IR spectrum for **PCPNcf**

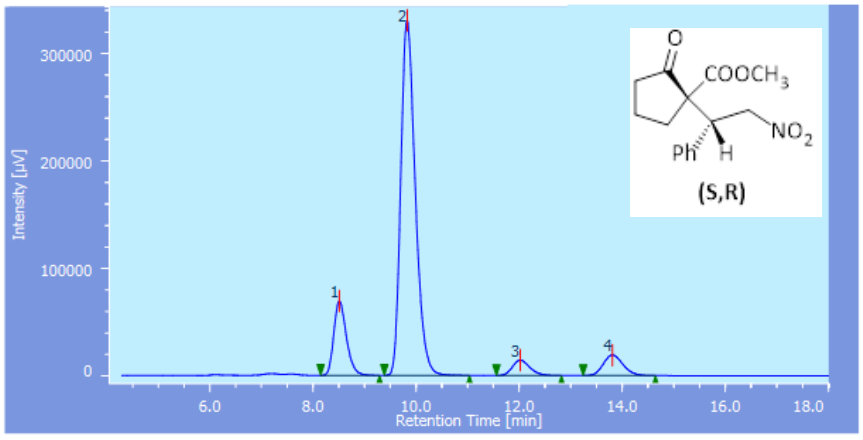
## C.3 Chromatogram data for Michael products



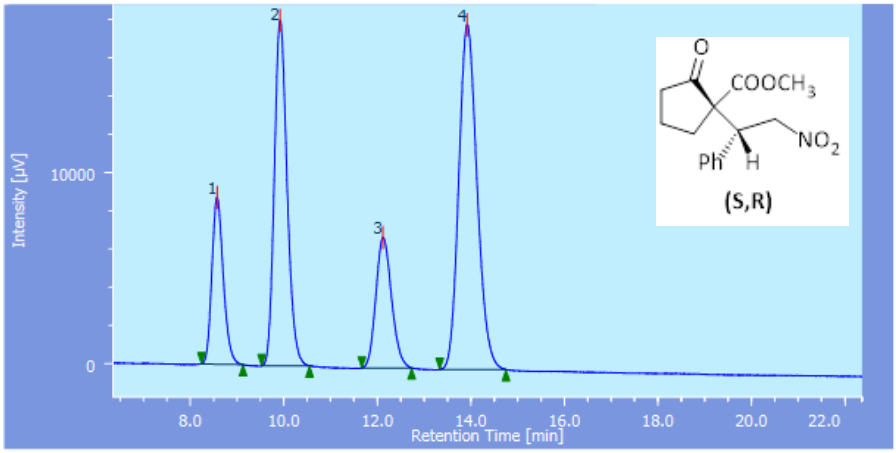

With **PCPNce** as catalyst



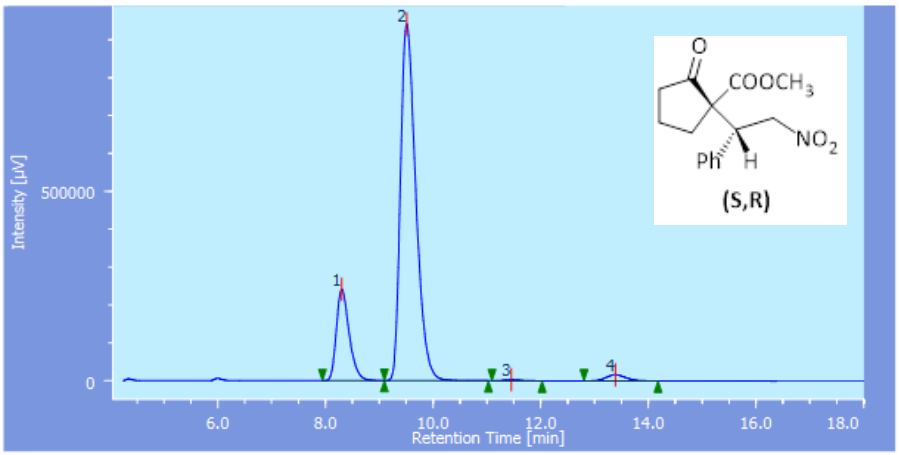

With **3QNc** as catalyst




With **3CPNc** as catalyst




With **PQNaa** as catalyst

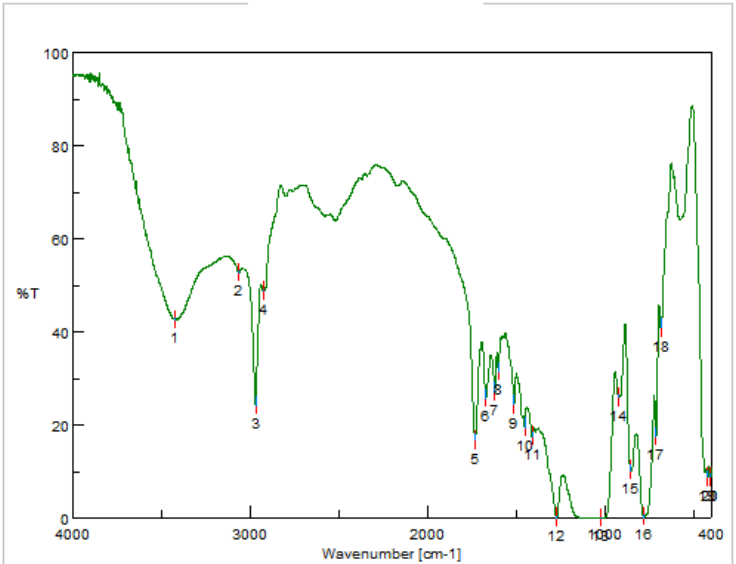



With **PQNcd** as catalyst

# Appendix D

# Supporting document for Chapter 5

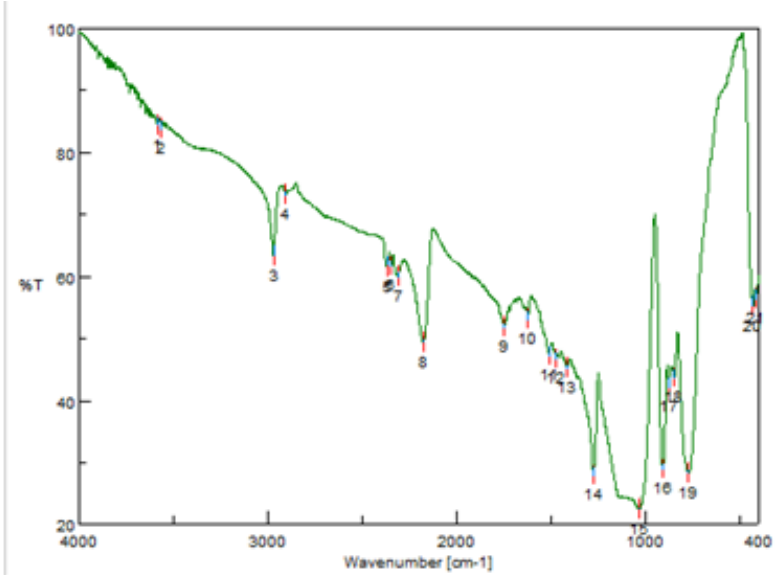
## D.1 FT/IR spectrum for cross-linked chiral polysiloxanes of cinchona derivatives




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3423.99 | 42.5232 | 2 | 3065.3 | 52.6904 |
| 3 | 2971.77 | 24.1727 | 4 | 2921.63 | 48.8115 |
| 5 | 1731.76 | 16.7633 | 6 | 1671.98 | 25.6804 |
| 7 | 1621.84 | 27.1505 | 8 | 1600.63 | 31.4381 |
| 9 | 1512.88 | 24.4102 | 10 | 1452.14 | 19.489 |
| 11 | 1410.67 | 17.5928 | 12 | 1273.75 | 0.278712 |
| 13 | 1025.94 | 0.0417249 | 14 | 922.771 | 25.8905 |
| 15 | 853.347 | 10.2748 | 16 | 778.136 | 0.319379 |
| 17 | 711.604 | 17.4624 | 18 | 685.57 | 40.9185 |
| 19 | 419.442 | 8.87478 | 20 | 408.835 | 8.78624 |

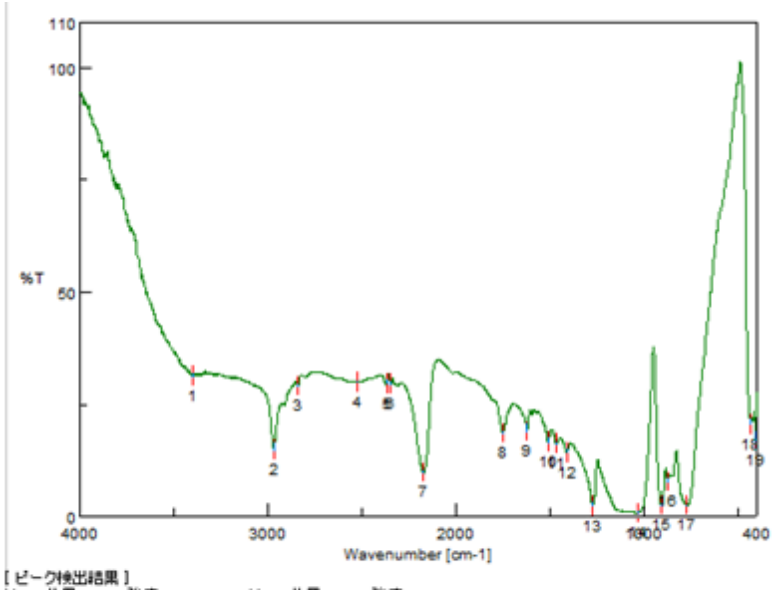
IR spectrum for **PSiBzCPN**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3586.95 | 84.3874 | 2 | 3566.7 | 83.7926 |
| 3 | 2971.77 | 63.3027 | 4 | 2908.13 | 73.1552 |
| 5 | 2371.05 | 61.5657 | 6 | 2349.84 | 61.6608 |
| 7 | 2310.3 | 59.965 | 8 | 2177.24 | 49.4193 |
| 9 | 1749.12 | 51.8754 | 10 | 1622.8 | 53.1393 |
| 11 | 1508.06 | 47.1662 | 12 | 1472.38 | 46.7023 |
| 13 | 1417.42 | 45.2115 | 14 | 1274.72 | 27.8685 |
| 15 | 1033.66 | 22.5385 | 16 | 906.379 | 28.3623 |
| 17 | 873.596 | 42.1565 | 18 | 845.633 | 43.6138 |
| 19 | 771.387 | 28.3399 | 20 | 427.155 | 55.2109 |
| 21 | 416.549 | 56.4654 | | | |

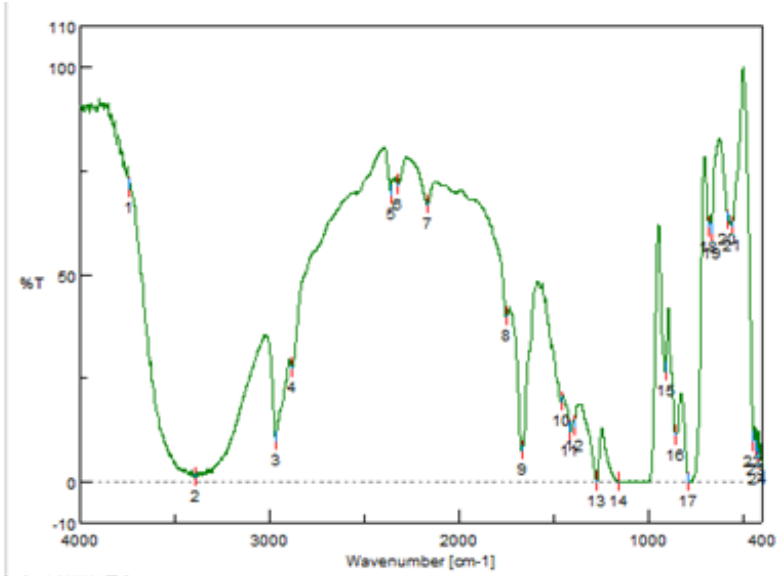
IR spectrum for **PSiCPN2b**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3397.96 | 31.2056 | 2 | 2968.87 | 14.8218 |
| 3 | 2841.6 | 28.974 | 4 | 2524.36 | 29.9078 |
| 5 | 2371.05 | 29.4604 | 6 | 2349.84 | 29.4548 |
| 7 | 2173.38 | 9.88807 | 8 | 1750.08 | 18.5666 |
| 9 | 1622.8 | 18.9481 | 10 | 1508.06 | 16.5882 |
| 11 | 1467.56 | 16.2128 | 12 | 1411.64 | 14.2554 |
| 13 | 1273.75 | 2.42511 | 14 | 1092.69 | 0.8425 |
| 15 | 907.344 | 2.53336 | 16 | 873.596 | 7.76621 |
| 17 | 775.244 | 2.55806 | 18 | 430.048 | 20.459 |
| 19 | 406.907 | 16.8641 | | | |

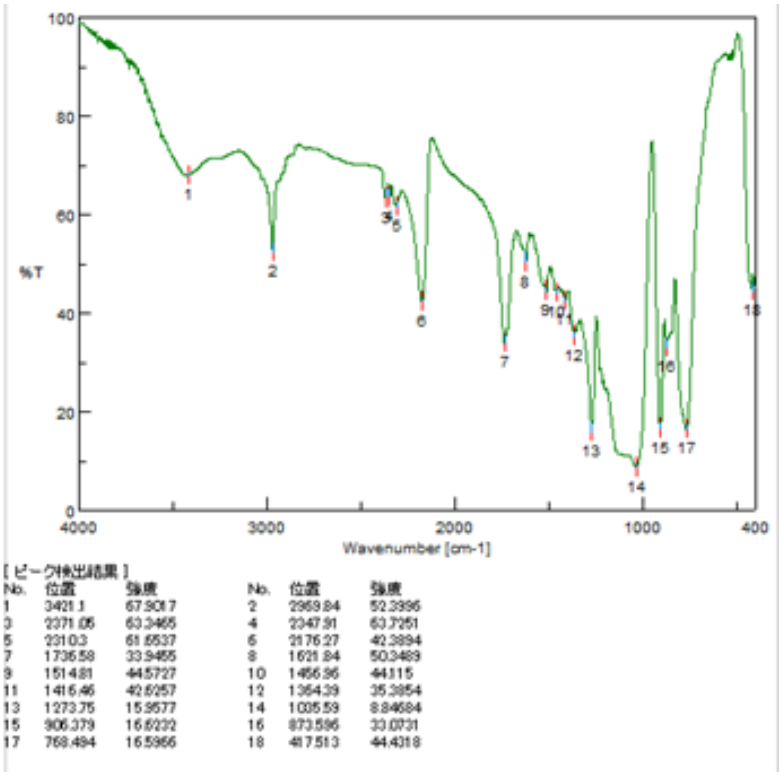
IR spectrum for **PSiCPN2c**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3742.19 | 70.9000 | 2 | 3389.28 | 1.02841 |
| 3 | 2967.91 | 9.81099 | 4 | 2883.06 | 27.5375 |
| 5 | 2359.48 | 69.1588 | 6 | 2325.73 | 71.635 |
| 7 | 2167.6 | 66.9531 | 8 | 1752.01 | 39.9659 |
| 9 | 1670.06 | 7.5276 | 10 | 1461.78 | 19.4504 |
| 11 | 1413.57 | 12.2219 | 12 | 1390.42 | 13.449 |
| 13 | 1272.79 | 0.0811213 | 14 | 1161.9 | -1.20027E-007 |
| 15 | 910.236 | 26.5407 | 16 | 856.239 | 11.2403 |
| 17 | 786.815 | -1.14521E-007 | 18 | 680.749 | 61.4828 |
| 19 | 666.285 | 59.8977 | 20 | 580.469 | 63.1134 |
| 21 | 557.327 | 61.6216 | 22 | 445.476 | 9.70319 |
| 23 | 431.977 | 7.65985 | 24 | 420.406 | 5.58413 |

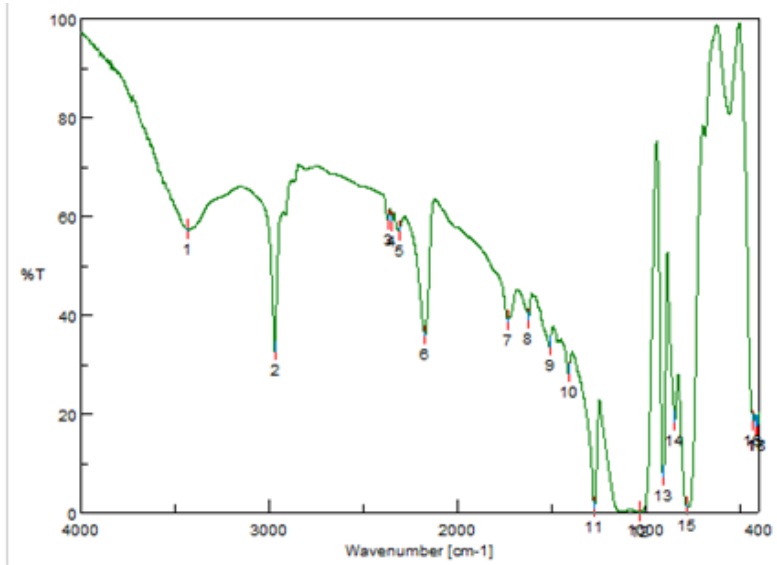
IR spectrum for **PSiCPN2d**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3421.1 | 67.9017 | 2 | 2959.84 | 52.3396 |
| 3 | 2371.05 | 63.3465 | 4 | 2347.91 | 63.7251 |
| 5 | 2310.3 | 61.6537 | 6 | 2176.27 | 42.3894 |
| 7 | 1736.58 | 33.9455 | 8 | 1621.84 | 50.3489 |
| 9 | 1514.81 | 44.5727 | 10 | 1456.96 | 44.115 |
| 11 | 1416.46 | 42.6257 | 12 | 1364.39 | 35.3854 |
| 13 | 1273.75 | 15.9577 | 14 | 1035.59 | 8.84684 |
| 15 | 906.379 | 16.6232 | 16 | 873.596 | 33.0731 |
| 17 | 768.494 | 16.5966 | 18 | 417.513 | 44.4318 |

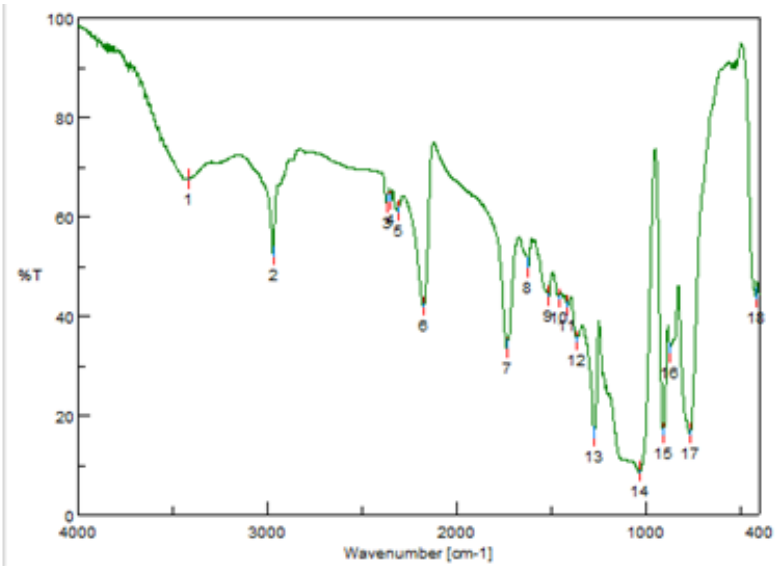
IR spectrum for **PSiCPN3a**




[ ピーク検出結果 ]

| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3431.71 | 57.2235 | 2 | 2971.77 | 32.6804 |
| 3 | 2370.09 | 59.1777 | 4 | 2348.87 | 58.9778 |
| 5 | 2310.3 | 57.0342 | 6 | 2174.35 | 35.9553 |
| 7 | 1731.76 | 38.8553 | 8 | 1622.8 | 39.1816 |
| 9 | 1509.03 | 33.6542 | 10 | 1411.64 | 28.396 |
| 11 | 1273.75 | 1.14497 | 12 | 1028.84 | 0.171852 |
| 13 | 907.344 | 7.44133 | 14 | 845.633 | 18.529 |
| 15 | 781.029 | 1.31628 | 16 | 427.155 | 18.7007 |
| 17 | 416.549 | 17.6607 | 18 | 404.014 | 17.7122 |

IR spectrum for **PSiCPN3b**

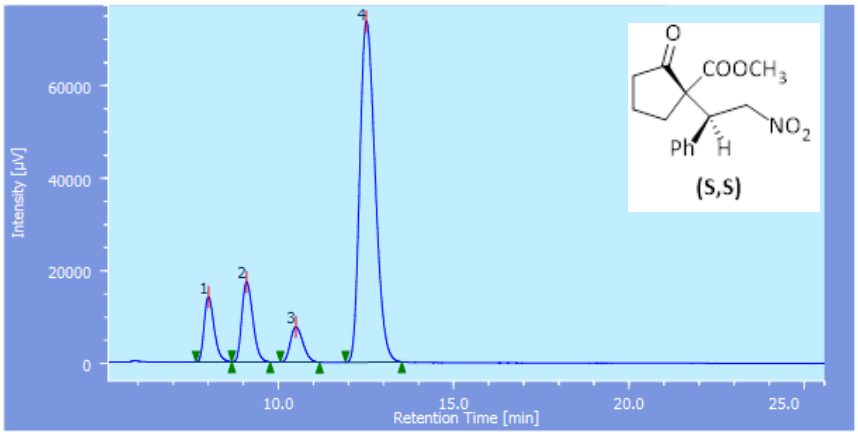



[ ピーク検出結果 ]

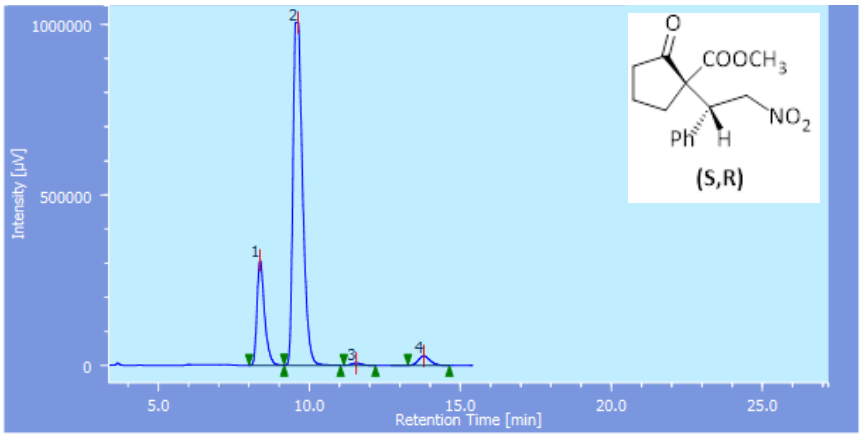
| No. | 位置 | 強度 | No. | 位置 | 強度 |
|---|---|---|---|---|---|
| 1 | 3421.1 | 67.4925 | 2 | 2969.84 | 52.0248 |
| 3 | 2371.05 | 62.7815 | 4 | 2347.91 | 63.1519 |
| 5 | 2310.3 | 61.0914 | 6 | 2176.27 | 41.9835 |
| 7 | 1736.58 | 33.5639 | 8 | 1621.84 | 49.7585 |
| 9 | 1514.81 | 44.029 | 10 | 1456.96 | 43.5653 |
| 11 | 1416.46 | 42.0866 | 12 | 1364.39 | 34.9291 |
| 13 | 1273.75 | 15.7449 | 14 | 1035.59 | 8.7178 |
| 15 | 906.379 | 16.3685 | 16 | 873.596 | 32.56 |
| 17 | 768.494 | 16.3284 | 18 | 417.513 | 43.6071 |

IR spectrum for **PSiCPN3c**

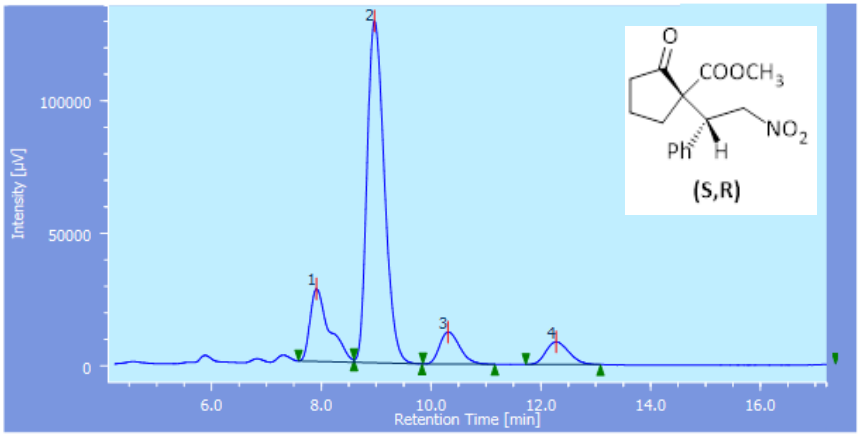
## D.2 Chromatogram data for Michael products



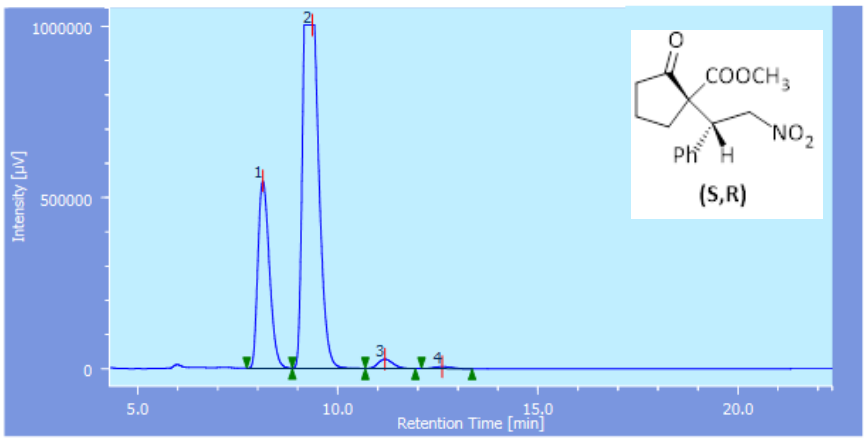

With **BzQN** as catalyst



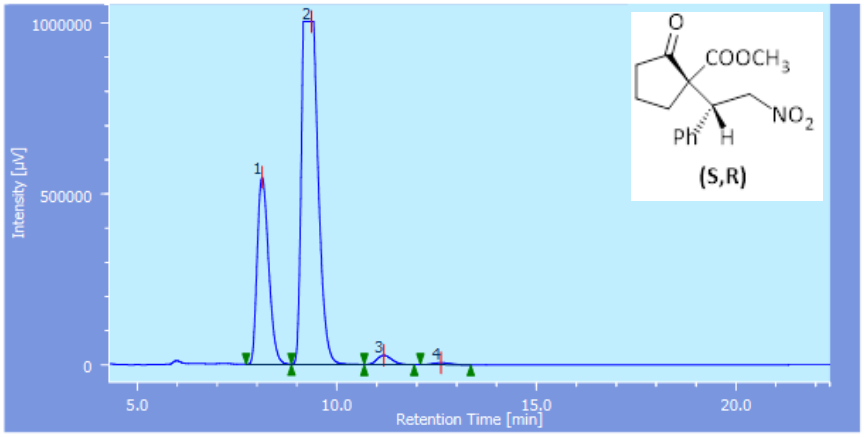

With **BzCPN** as catalyst



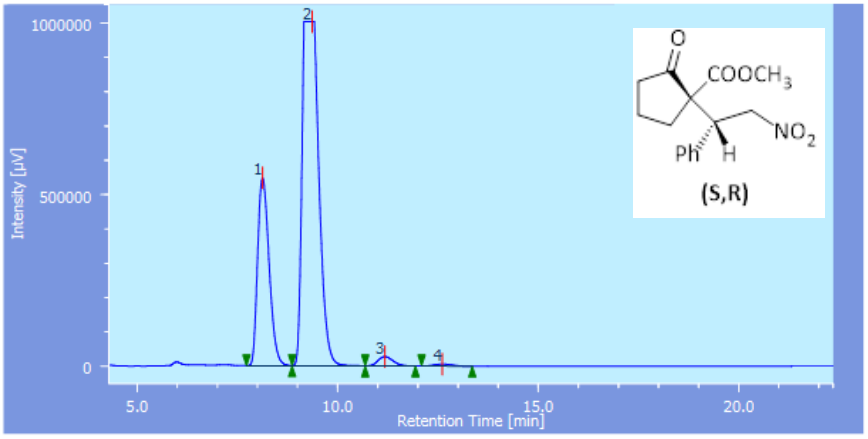

With **PSiBzQN** as catalyst




With **PSiBzCPN** as catalyst



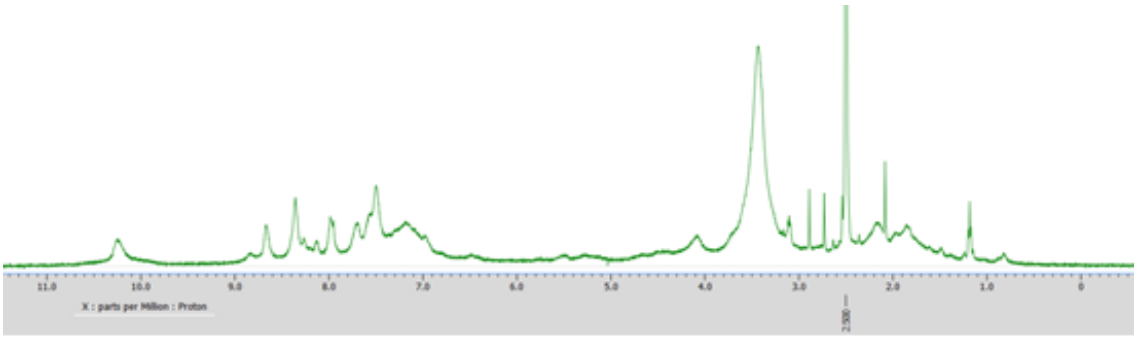

With **CPN2d** as catalyst



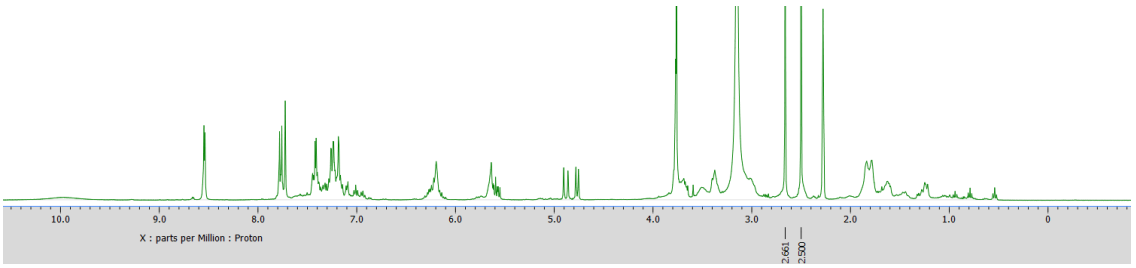

With **PSiCPN2d** as catalyst

# Appendix E

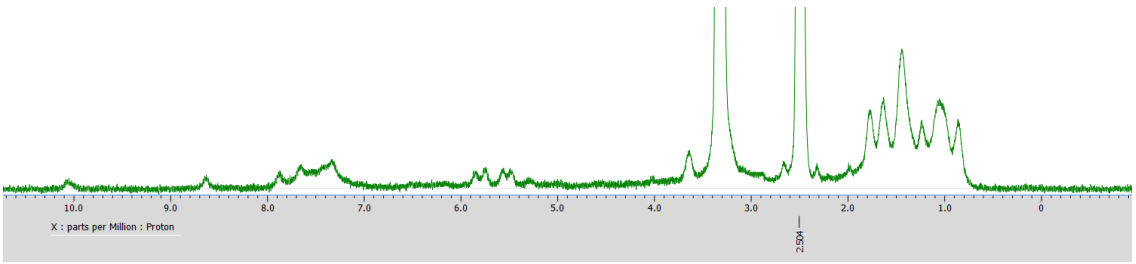
# Supporting document for Chapter 6




**3P**




**5**




**8P**