Synthesis of Cinchona Alkaloids-derived Chiral Squaramide Polymers and Their Application to Asymmetric Catalysis

(シンコナアルカロイドから誘導されたキラルスクアラミド高分子の合成とその不斉触媒反応への応用**)**

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[DOCTOR OF ENGINEERING]

Mohammad Shahid Ullah

モハマド シャヒド ウッラ

TOYOHASHI UNIVERSITY OF TECHNOLOGY

Dedicated to

my better half
'Fatema Tuj Jahura'

and

beloved daughter
'Noor Sabah Binte Shahid'

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Mohammad Shahid Ullah
Department of Environmental and Life Sciences
Toyohashi University of Technology, Japan

Department: Environmental and Life Sciences		ID	**159403**	Supervisor	Professor Dr. Shinichi Itsuno
Applicant's Name	Mohammad Shahid Ullah				

ABSTRACT (Doctor)

Title	Synthesis of Cinchona Alkaloids-derived Chiral Squaramide Polymers and Their Application to Asymmetric Catalysis

[Approx. 800 words]

Cinchona alkaloids-derived squaramide containing chiral main-chain polymers have been successfully synthesized and applied to asymmetric catalysis. Quinine, quinidine, cinchonidine and cinchonine are the common commercially available cinchona alkaloids. These are one of the popular sources for chirality inducers in the field of asymmetric catalysis. Cinchona alkaloids have various functionalities including a quinuclidine tertiary nitrogen, a secondary alcohol, a quinoline ring and a terminal olefin in their structure. The chemical modifications of the functionalities enable us to design new catalysts. Thus, several modifications have been already done by different research groups and synthesis of many monomeric and dimeric organocatalysts having cinchona squaramide moieties have also been reported. The acidic NH of the squaramide can act as a H-bond donor, whereas the tertiary nitrogen of the quinuclidine of cinchona alkaloids may acts as both a H-bond acceptor and a base. Thus the cinchona squaramide can act as a bifunctional H-bonding organocatalyst in the asymmetric transformations.

Cinchona derived squaramides can act as the efficient organocatalysts in different asymmetric transformations. Although several works have been reported with the low-molecular-weight squaramide catalysts derived from cinchona alkaloids, limited number of works have been carried out in the synthesis and application of chiral polymeric organocatalyst on the asymmetric transformation. Cinchona alkaloids containing polystyrene-supported side-chain type polymeric catalysts have been already synthesized and applied on asymmetric reactions. In case of polymer-supported catalysts, flexible and sterically irregular structures are used. On the other hand, the chiral main-chain polymeric organocatalysts contain the rigid and sterically regular structures in their backbone. This approach is more suitable to maintain the catalytic environment of the monomeric catalysts into the polymeric catalysts. The main-chain cinchona squaramide polymers can act as a good organocatalysts in asymmetric reactions due to the creation of a suitable microenvironment by the polymers which is very important for the stereoselectivity of the catalysts. The modification of a microenvironment of polymers is very important and it is possible to control the microenvironment precisely in the chiral main-chain polymeric catalysts. The enantioselectivity of low-molecular-weight monomeric catalysts can be maintained in the corresponding polymeric catalysts due to the formation of rigid and sterically regular backbone in the polymers structure. Cinchona squaramide polymeric catalysts can be prepared by the incorporation of low-molecular-weight dimeric squaramide, using suitable polymerization techniques under optimal reaction conditions.

Therefore, structural design and synthesis of main-chain chiral polymeric organocatalysts are very much attractive field of research in asymmetric synthesis to obtain enantiopure organic compounds. To understand the effect of main-chain chiral polymeric organocatalyst in asymmetric synthesis, we have synthesized several cinchona derived squaramide main-chain polymers using Mizoroki-Heck and ADMET polymerization methods and successfully applied in the enantioselective Michael addition reactions.

In this thesis, chapter **1** presents the general introduction which includes the structural features of cinchona alkaloids, chiral organocatalysts, polymeric organocatalysts and the background of this thesis work. This chapter also includes the general reviews about low-molecular-weight cinchona alkaloids squaramide catalyzed different asymmetric reactions, including Michael addition reaction, Friedel-Crafts reaction, Strecker reaction, and Mannich reaction.

Chapter **2** presents the synthesis of novel chiral squaramide polymers by the reaction of cinchona derived-squaramide and various aromatic diiodo compounds using Mizoroki-Heck polymerization. The Mizoroki-Heck reactions between the double bonds of the cinchona-based squaramide and aromatic diiodides proceeded smoothly to give cinchona squaramide chiral polymers. The asymmetric Michael addition of β-ketoesters to nitroolefins was successfully catalyzed by the squaramide polymers to give the corresponding Michael adducts in good yields and excellent enantioselectivities of up to 97% ee. As the polymeric catalysts were insoluble in commonly used organic solvents, these were recovered and reused without any loss of catalytic activity.

Chapter **3** describes the synthesis of novel chiral polymers of diamine connected cinchona squaramides using Mizoroki-Heck polymerization as highly efficient catalysts in the asymmetric Michael addition reaction. We designed novel cinchona squaramide dimers that contain two cinchona squaramide units connected by diamines. The olefinic double bonds in this dimer were used for Mizoroki–Heck polymerization with aromatic diiodides to give the corresponding chiral polymers in good yields. We have surveyed the effect of the chiral polymer structure on the catalytic activity and enantioselectivity of the asymmetric reaction. The novel squaramides and also polymers were applied in asymmetric Michael addition of β-ketoesters to nitroolefins to obtain the adducts in good yields with excellent stereoselectivities. In this case the polymeric catalysts were recovered and reused for several times.

Chapter **4** describes the synthesis of cinchona alkaloid-derived novel chiral squaramide polymers by acyclic diene metathesis (ADMET) polymerization and their application to asymmetric catalysis. The first synthesis of high molecular weight cinchona alkaloid-derived chiral squaramide polymers by ADMET polymerization is reported, using the Hoveyda-Grubbs 2nd generation catalysts (HG_2). We have synthesized novel chiral polymeric catalysts containing cinchona squaramide moieties in the main chain of the polymer by ADMET reaction. The ADMET polymerization reactions between the cinchona alkaloid-derived squaramide diene and HG_2 catalyst afforded the chiral polymers. The chiral polymers were also used as catalysts in asymmetric Michael addition reactions to give the products in good yields with excellent stereoselectivities. They were easily recovered from the reaction mixture and reused several times.

Chapter **5** presents the general summary of this whole thesis works.

[Table of contents]

❖ Chapter 1: Introduction

[List of abbreviations]

aq	aqueous
ac	acetyl
s	singlet
br	broad
d	doublet
m	multiplet
Calcd	calculated
DMF	*N*,*N*-dimethylformamide
ee	enantiomeric excess
dr	diastereomeric ratio
Equiv.	equivalent
Et	ethyl
Et_3N	triethylamine
$Pd(OAc)_2$	palladium acetate
EtOAc	ethyl acetate
MeOH	methanol
g	gram
h	hour
HPLC	high performance liquid chromatography
^{i}Pr	isopropyl
IR	infrared
M	molar
MHz	megahertz
mL	milliliter
mmol	millimole
MP	melting point
NMR	nuclear magnetic resonance
ppm	parts per million
Ph	phenyl
R_f	retention factor
rt	room temperature
^{t}Bu	tertiary butyl
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time
U.V	ultra violet

[Notations]

α	alpha
β	beta
%	percentage
J	coupling constant
δ	chemical shift
°C	degrees Celsius
$[\alpha]_D$	specific rotation

Chapter 1

INTRODUCTION

1.1 Cinchona alkaloids

Cinchona alkaloids are isolated from the bark of several species of cinchona trees. Cinchona is a genus of flowering plants in the family of Rubiaceae. The naturally occurring cinchona alkaloids are important chiral sources because of numerously available in nature, commercially available at reasonable prices, stable, and easily possible to modify structurally for various catalytic application purposes. These are popular as chiral sources for efficient catalysts, due to their various functional groups, including-

- a quinuclidine group
- a secondary alcohol
- a quinoline ring, and a vinylic unit.

All cinchona alkaloids contain many stereocenters, C-(3), C-(4), C-(8), C-(9) and N-(1). The absolute configuration of C-(3) and C-(4) is identical in the all naturally occurring cinchona alkaloids, but they occur in pair and configuration differ only at position N-(1), C-(8) and C-(9).

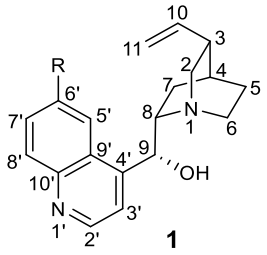

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Figure 1: Structural feature of cinchona alkaloid with numbering that adopted by Rabe.[1]

There are eight major cinchona alkaloids, **2–5** (Figure **2**) those are related to diastereomeric pairs, but are often referred to as 'pseudoenantiomers'. For example, both quinine and quinidine, cinchonine and cinchonidine are diastereoisomers and also pseudoenantiomeric pairs to each other. Each pair differs in the stereochemistry at C-8 and C-9 position in the cinchona alkaloid structure.

In chemistry, the important application of cinchona alkaloids is to apply on many enantioselective transformations to accelerate the reactions in both homogeneous and heterogeneous catalytic systems. In 1912, the first asymmetric reaction reported by Bredig and Fiske by using a cinchona base as a catalyst.[2] They reported that the addition reaction of HCN and benzaldehyde is occurred by the pseudoenantiomeric alkaloids, quinine and quinidine, and the resulting products are optically active. After the reporting of several pioneer works, the popularity of cinchona derivatives in asymmetric catalysis has increased remarkably. Nowadays, cinchona alkaloids and their derivatives are classified as the most prominent organic chirality inducers.

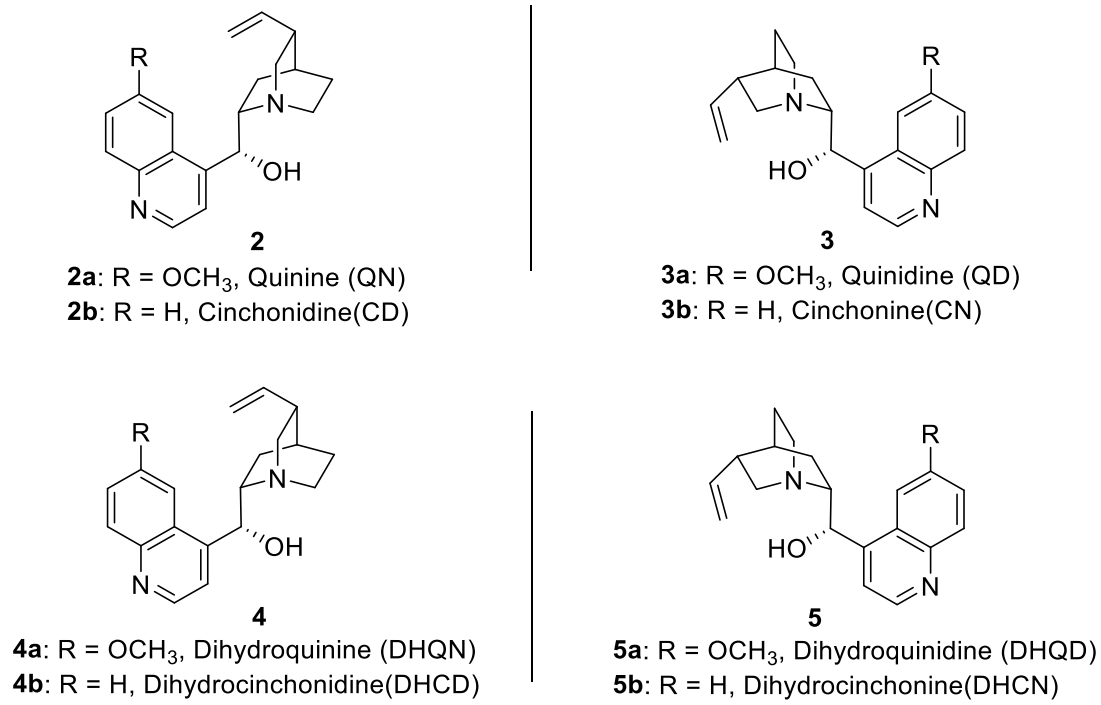


Figure 2. Structures of major cinchona alkaloids.

There are many active sites in all cinchona alkaloids such as (1) Tertiary amine nitrogen of quinuclidine group: this has metal binding ability and the presence of the quinuclidine base functionality makes them effective ligand for a variety of metal-catalyzed reactions; acts as a general base for deprotonation process; use as chiral nucleophilic catalyst promoting the many of organocatalytic reactions and chiral PTC properties (*N*-alkylation property). For example, the quaternizatied ammonium salts of cinchona alkaloids could be used to catalyze asymmetric reactions under phase-transfer conditions, where asymmetric induction occurs through a chiral ion pairing mechanism between the cationic ammonium species and the anionic nucleophile.[3]

(2) The secondary 9-hydroxy group of the cinchona alkaloids or the various derivatives (urea, squaramide, amide, and so on) of the OH group can serve as strong hydrogen bond donor [4] or a more powerful acidic site.

(3) The 6'-methoxy group of quinine and quinidine can also be easily modified to the free OH group or thiourea moiety, which can also serve as an effective H-bond donor in the asymmetric reaction.

(4) The planar aromatic ring in quinoline aromatic part of cinchona alkaloids has electron-donor capability and in many cases, the catalysis is also supported by a π–π interaction with the aromatic quinoline ring or by its steric hindrance.

The chiral induction and discrimination processes could be understood by the conformational investigation of the cinchona alkaloids using computational and spectroscopic methods. Dijkstra et al. first identify that the C8–C9 and C4'–C9 bonds are the most important in determining the overall

conformations of cinchona alkaloids by investigating the conformational behavior using NMR spectroscopy and molecular mechanics in 1989.[5] The function of cinchona alkaloids in asymmetric reactions is dual functionality and this was proved by mechanistic studies of asymmetric catalysis by cinchona alkaloids using computational method.[6] The bifunctional mode of catalysis simultaneously implies the quinuclidine nitrogen to activate the nucleophile using general base catalysis and the hydroxyl group at C-(9) to activate the electrophile via hydrogen bond interactions.

1.2 Chiral organocatalyst and organocatalysis

In organic synthesis, organocatalysts are very much attractive due to the absence of metal-based catalysis. Thus making a significant contribution to 'green chemistry'. Chiral organocatalysts play an important role for the synthesis of enantiomerically enriched organic molecules. These have many advantages such as inexpensive, readily available, non-toxic, inertness towards moisture and oxygen, environmentally benign, having atom economy and can be easily used to prepare various bioactive compounds using simple and convenient operation. MacMillan's catalyst, *L*-proline, cinchona alkaloids, these are commonly used known chiral organocatalysts that have been widely used in different types of asymmetric reactions.

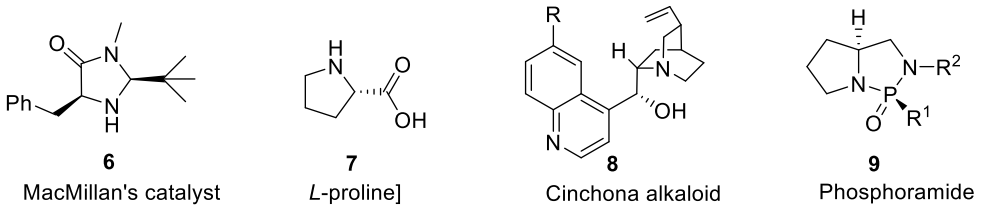
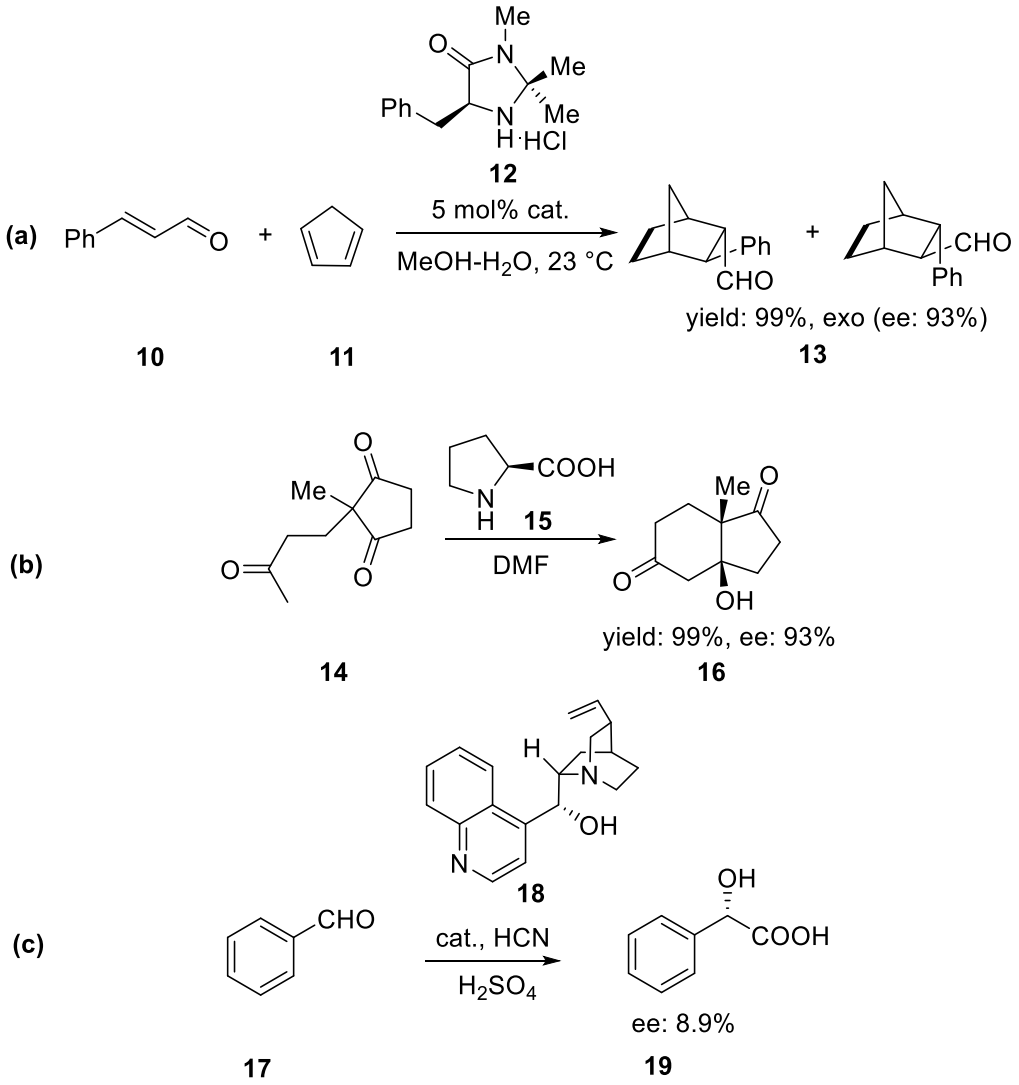


Figure 3. Examples of chiral organocatalyst.

The imidazolidinone ring containing compounds are suitable catalysts for many asymmetric reactions such as enantioselective Michael addition reaction, Diels-Alder reaction, Friedel-Crafts alkylation, and epoxidation. The first successful, highly enantioselective Diels-Alder reaction was conducted by D. W. C MacMillan in 2000.[7] (Scheme **1a**).

One important application of *L*-proline chiral organocatalyst is the intramolecular aldol reaction (Scheme **1b**). The achiral triketone converts to a chiral ketol in 93% of *ee* using only 3 mol% of proline as a catalyst. This is the first example of proline-catalyzed asymmetric aldol reaction.[8] In 1912, Bredig and Fiske demonstrated the asymmetric addition reaction of HCN to aldehyde using (–)-cinchonidine as an organocatalyst with very low *ee* value (Scheme **1c**).[2] The chiral organocatalysts can activate the electrophile or nucleophile and also both of these in case of bifunctional catalysts. They create an asymmetric environment which is responsible for the creation of a new chiral center in the new asymmetric products. Nowadays, asymmetric organocatalysis is very much useful synthetic pathway to



Scheme 1. Examples of organocatalytic reaction.

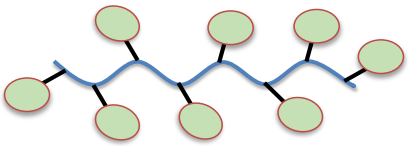
prepare highly enantioenriched organic compounds compared to other two asymmetric techniques, metallic catalysis and enzymatic catalysis. Moreover, a large number of organocatalysts are commercially available or easily synthesized and these are stable under extreme conditions, do not need dry or inert condition/environment. Beside these, organocatalysts are various functional groups tolerant catalysts and the organocatalysis reactions are conducted under mild reaction condition due to the presence of many favorable sites.

1.3 Polymeric organocatalyst

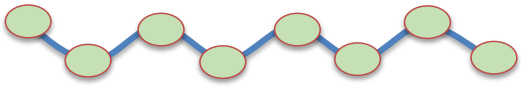
Currently, polymeric chiral organocatalyst is very much attractive tool for the synthesis of different chiral building blocks. Since low-molecular-weight chiral organocatalysts have many advantages in the case of enantioselective synthesis those have some drawbacks also. Incorporation of a chiral organocatalysts (quaternary ammonium salt, cinchona squaramides, cinchona sulfonamides etc.) into a

polymer allows for the preparation of a polymeric chiral organocatalyst that can be used in various asymmetric reactions in organic synthesis. There are three types of polymeric chiral organocatalysts:

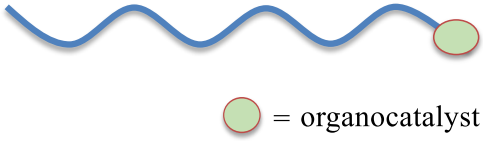
- Side-chain type polymeric catalyst



- Main-chain type polymeric catalyst



- Chain-end type polymeric catalyst

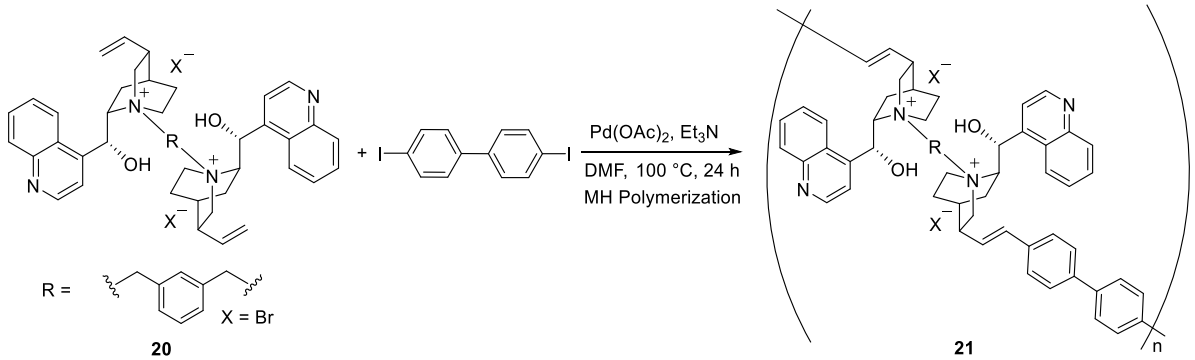


There are many main-chain chiral polymers that have been synthesized from cinchona-based low-molecular-weight organocatalysts or others and successfully applied in different asymmetric transformations. These have some advantages over the other two polymeric catalysts, such as-

- Rigid and sterically regular structure
- Constant repeating unit
- Enhancement of enantioselectivity (ee)

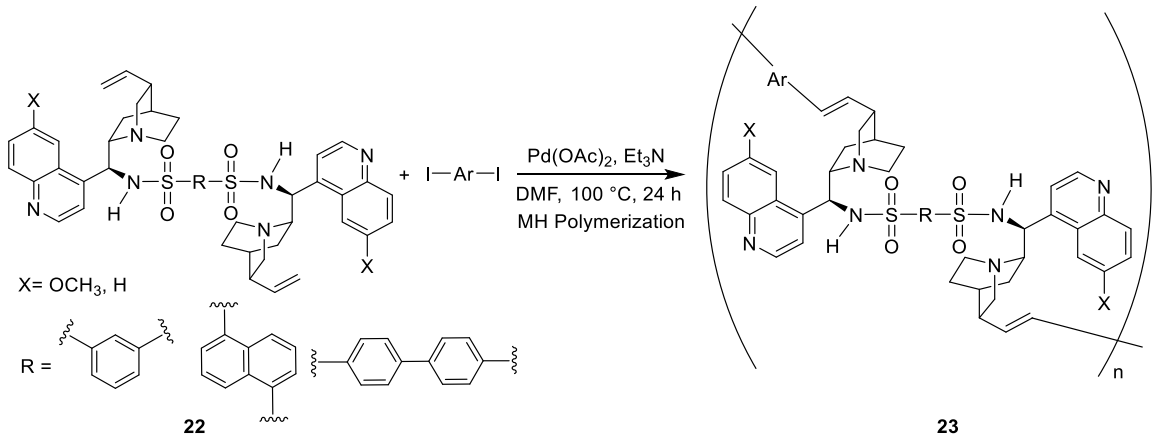
Some reported examples of main-chain type chiral polymers from cinchona alkaloids are discussed in here.

1 Main-chain type polymer of cinchonidium dimer with diiodo compound under Mizoroki-Heck reaction conditions.[9]



The asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester was successfully occurred with this above cinchonidine-based polymeric catalyst **21** and high levels of enantioselectivity (up to 95% *ee*) was obtained.

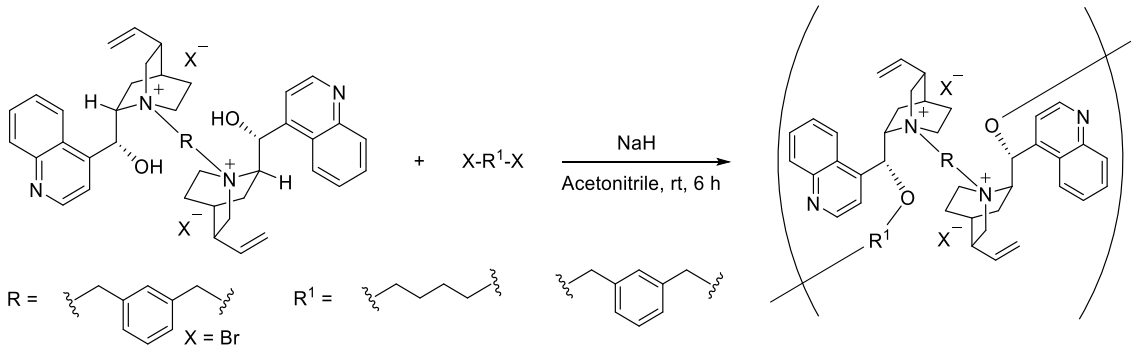
2 Main-chain type cinchona alkaloid sulfonamide polymers with aromatic diiodo compounds under MH reaction condition.[10]



22 **23**

This is the first synthesis of a chiral polymeric catalysts containing a cinchona-based sulfonamide structure in their main chain that was successfully synthesized by Mizoroki–Heck polymerization. The chiral polymers showed high levels of enantioselectivity in the enantioselective desymmetrization of cyclic anhydrides.

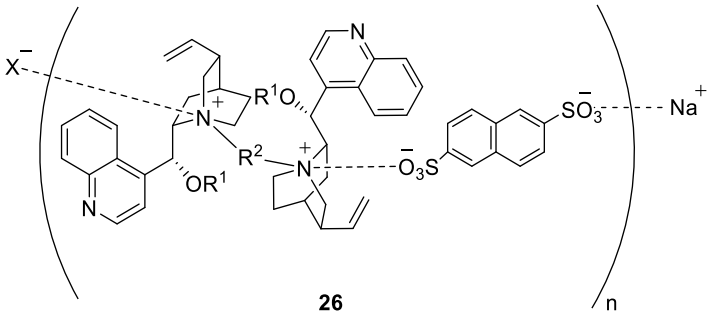
3 Main-chain chiral quaternary ammonium polymers using etherification polymerization.[11]



24 **25**

The chiral polymers containing quaternary ammonium salt structure in their main chain have been successfully prepared by simple polycondensation reaction under *Williamson ether* synthesis conditions. The polymers were used as organocatalyst for the asymmetric alkylation of *N*-diphenylmethylidene glycine *tert*-butyl ester.

4 Main-chain ionic optically active quaternary ammonium sulfonate polymers using ion-exchange polymerization.[12]



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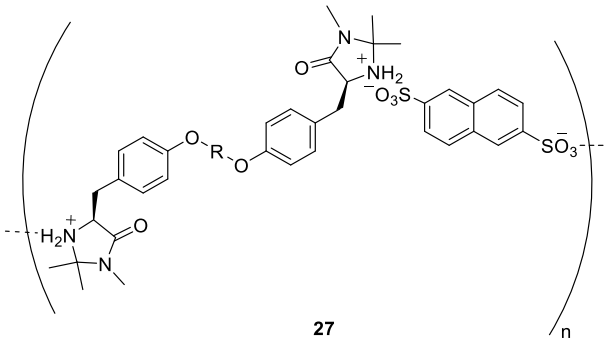
Chiral bis(quaternary ammonium salt) containing the cinchonidine unit react with disodium 2,6-naphthalenedisulfonate gave a chiral polymer, **26** which contains ionic bonds in its main chain by applying ion-exchange reaction. The chiral ionic polymers were also applied as a catalyst in the asymmetric benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester to prepare (*S*)-phenylalanine derivatives with excellent catalytic activities.

5 Design of main-chain polymers of chiral imidazolidinone for asymmetric organocatalysis application.[13]



27

In this polymerization, chiral imidazolidinones were incorporated into the main-chain of the polymer by ionic bonding. This type of polymers were successfully synthesized by the reaction of chiral imidazolidinone dimers with disulfonic acid. The asymmetric Diels–Alder reaction was successfully catalyzed by this polymeric chiral organocatalyst, **27**.

1.4 Squaric acid and squaramide

Squaric acid is a dibasic organic acid. The conjugate base of squaric acid is hydrogensquarate anion $C_4HO_4^-$; and the conjugate base of hydrogensquarate anion is the divalent squarate anion $C_4O_4^{2-}$. Actually the structure of squaric acid is not perfectly square, as the carbon–carbon bond lengths are not quite equal. The acidity of the first proton in squaric acid is more than the second proton which is attributable to resonance stabilization of the anion.[14] The negative charges are equally distributed in

between two oxygen atoms and the dianion of squaric acid is completely symmetrical although the squaric acid is not symmetrical. In dianion, all C–C bonds are equal length and also all C–O bonds are identical.

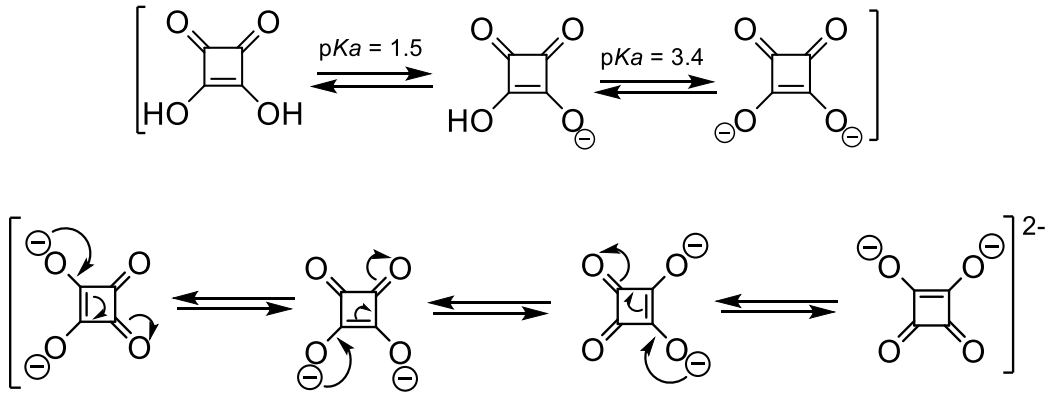


Figure 4. Squaric acid dianion resonance forms.

Squaramides are four-membered ring system derived from squaric acid that have two H-bond acceptor sites and two H-bond donor sites and the ability to form up to four hydrogen bonds. It is possible to synthesize different types of squaramides from squaric acid. Cinchona alkaloid-derived squaramides

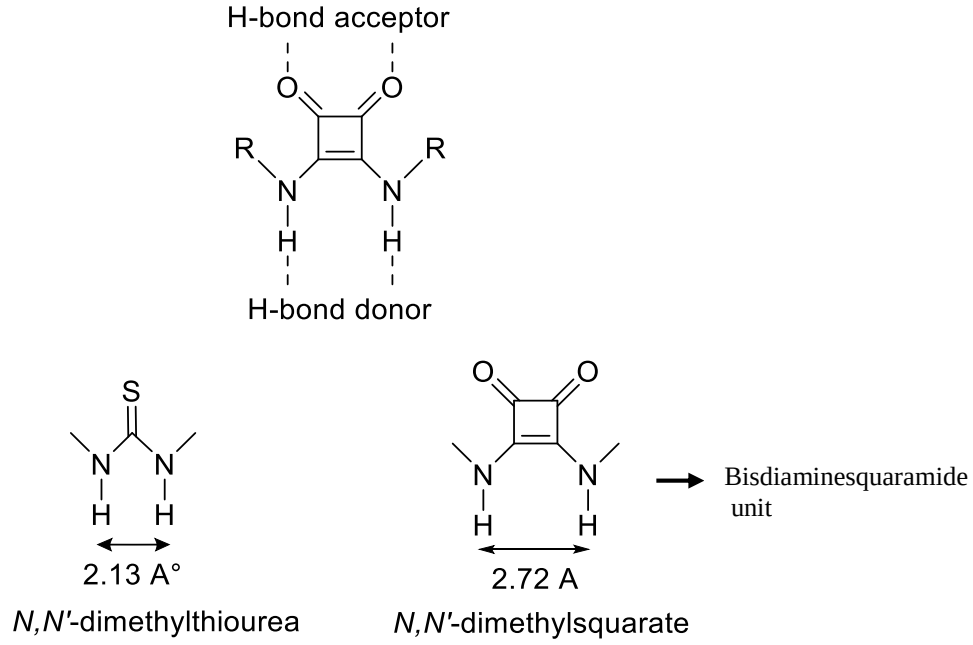


Figure 5. The calculated H–H bond distances in *N,N'*-dimethlythiourea and *N,N'*-dimethlysquaramide.

are one of them that are used in various asymmetric transformations. The distance between two donor hydrogens in bisdiaminesquaramides is higher than the distance of two hydrogens in thioureas and it is estimated to be 33% larger than in thioureas.[15] The bisdiaminesquaramide unit can play the major role in the case of dual activation hydrogen bonding catalysis.[16] The p*Ka* range of squaramide is 8.37-16.46

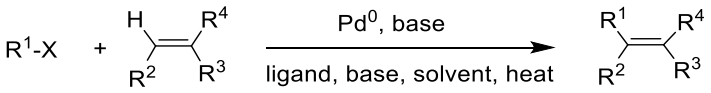
whereas in case of thiourea it is 8.5-21.1. The NH of squaramide is more acidic than the NH of thiourea and both can act as the bifunctional hydrogen-bonding catalysts.[17]

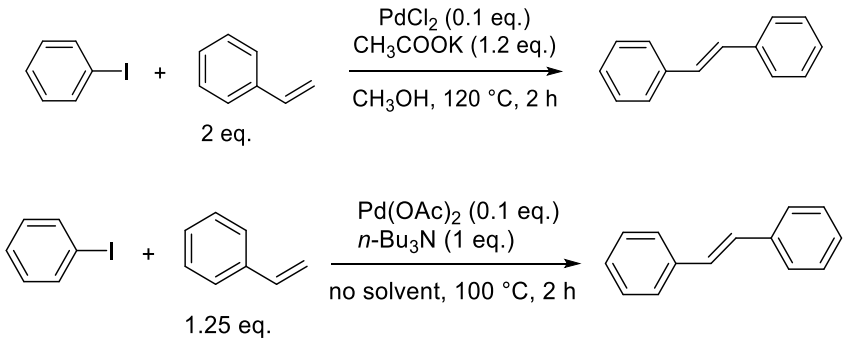
1.5 Enantioselective synthesis

Enantioselective synthesis is a special type of chemical synthesis in which one or more new elements of chirality are formed in a new substrate molecule and which produces the enantiomeric or diastereoisomeric products in an unequal amounts. This is a very important technique in modern chemistry, basically in the field of pharmaceuticals, as the different enantiomers or diastereomers of a molecule have different biological activities and also for the advantages of 'green chemistry' as the final product does not contain any heavy metals.[18] Asymmetric catalysis is one kind of catalysis process in which a chiral catalyst accelerates the formation of a chiral compound under suitable reaction conditions. The importance of asymmetric synthesis is very much commendable. For the application of chiral catalysts in asymmetric synthesis, the Nobel Prize for chemistry in 2001 was awarded to William S. Knowles and Ryoji Noyori (for their work on chirally catalyzed hydrogenation reactions)[19] and to Barry K. Sharpless (for his work on chirally catalyzed oxidation reactions).[20] After the pioneer works on chirally catalyzed hydrogenation and oxidation reactions, now the way of further scope for asymmetric synthesis is very much easy to do. In asymmetric catalysis, at first the chiral catalysts form a complex with achiral substrates. Then the reaction proceeds under the control of chiral catalysts to modify achiral substrate to chiral substrate. Finally, chiral catalyst and chiral substrate are separated to give desire chiral compound.

1.6 Mizoroki-Heck polymerization

In 1971, Tsutomu Mizoroki describes the coupling reaction between iodobenzene and styrene to form stilbene in CH_3OH at 120 °C temperature (autoclave) with CH_3COOK as a base and $PdCl_2$ as a catalyst.[21] Basically, this work was an extension of earlier work by Fujiwara (1967) on the Pd(II)-mediated coupling of arenes (Ar–H) and alkenes[22] and earlier work by Heck (1969) on the coupling of arylmercuric halides (ArHgCl) with alkenes using a stoichiometric amount of a palladium(II)species.[23] After one year, in 1972, Richard F. Heck modified the Mizoroki reaction conditions and he did the same reaction without any solvent at 100 °C temperature with *n*-Bu_3N amine as a base and $Pd(OAc)_2$ as a catalyst.[24] After that, now this palladium-catalyzed coupling reaction is referred to as the Mizoroki-Heck reaction. This coupling reaction is one of the most efficient C–C bond formation reactions of olefinic compounds with aromatic halides to form various compounds and also polymers.





Scheme 2. General scheme of Mizoroki-Heck coupling reaction.

Now, Mizoroki-Heck coupling reaction is one of the most widely used catalytic reaction to form new C–C bonds in organic synthesis. The conditions of MH reaction can be applied on the olefin compounds with a wide range of functional groups: esters, ethers, carboxylic acids, nitriles, phenols, dienes, etc. There is no significant effect of the electronic nature of the substituents of olefin on the formation of product as the substituent may be either electron-donating or electron-withdrawing. But the reaction rate is influenced by the degree of substitution of the olefin, usually in case of more substituted olefin, the slower reaction rate is observed. The rate of reaction is greatly affected by the nature of halide group on the aryl or vinyl compound and the rate changes according to this order: I > Br > OTf >> Cl. The R^1 group may be the aryl, vinyl (alkenyl), benzyl, alkyl (no β hydrogen); R^2, R^3, R^4 = alkyl, aryl, alkenyl; ligand: trialkylphosphines, triarylphosphines, chiral phosphines; base: 2°, 3° amine, KOAc, NaOAc, $NaHCO_3$. In this reaction, the active palladium catalyst (Pd^0) is generated in *situ* from suitable precatalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_4$ and the reaction is usually conducted in the presence of monodentate or bidentate phosphine ligands and a base. Usually, this reaction is not sensitive to water, so solvents need not to be dried or de-oxygenated and this is also a stereospecific reaction. Though it is a very good reaction to form new C–C bond, this has some drawbacks such as the substrates cannot have hydrogen atoms on their β-carbons, because there is a possibility to undergo rapid β-hydride elimination to give olefins and aryl chlorides are not always good substrates due to the lower reaction rate.

❖ Mechanism of Mizoroki-Heck reaction:

The exact mechanistic pathway of Heck reaction is not fully fixed, it may to vary with the change of reaction conditions. The mechanism proposed by Heck when the precursor is $Pd(OAc)_2$ associated with monophosphine ligands, L is described in here.

This mechanism was proposed by Dieck and Heck for reactions catalyzed by $Pd(OAc)_2$ associated with monophosphine ligands in 1974.[25] After the formation of a Pd(0) catalyst from the precursor $Pd(OAc)_2$ by a reduction process, the following steps of the catalytic cycle were proposed:

(a) The oxidative addition of the aryl halide to a Pd(0) complex is the first step of this catalytic cycle. This step is supported by oxidative addition of aryl halides to $Pd^0(PPh_3)_4$.

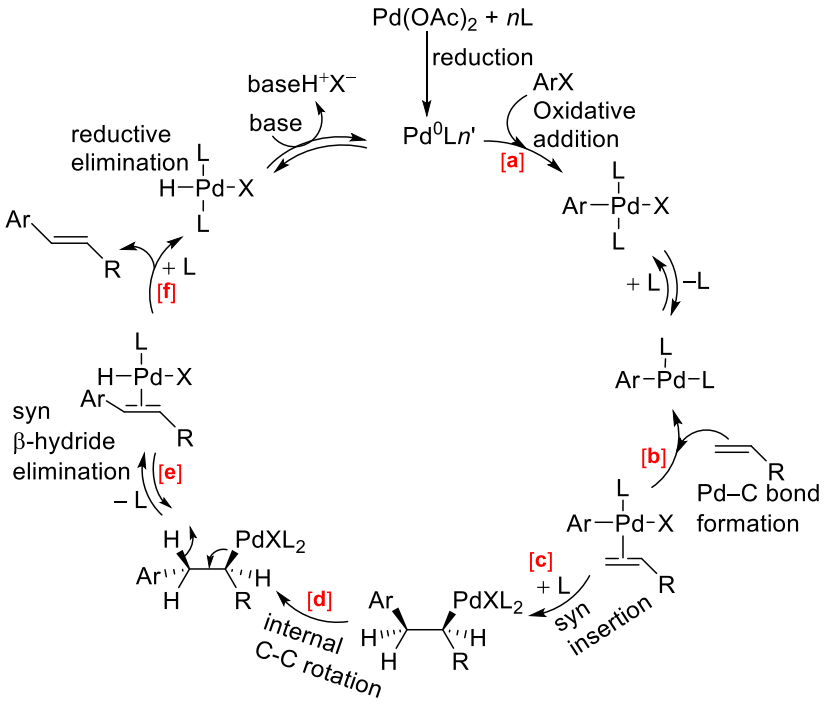


Figure 6. Mechanism of Mizoroki-Heck reaction.

(b) The first step gives a σ-aryl-palladium(II) halide ($ArPdXL_2$), which first coordinates to the alkene after the dissociation of one phosphine. This reaction is referred to as *organopalladation*, which is the origin of the regioselectivity of Mizoroki-Heck reaction.

(c) Then undergoes a *syn* insertion of the alkene, leading to a σ-alkyl-palladium(II) halide. The phosphine dissociation is necessary due to the negative effect on the rate of the reaction of *trans*-$ArPdXL_2$ and alkene.

(d) The internal C–C bond rotation on the σ-alkyl-palladium(II) halide bring an SP^3-bonded β-hydrogen in a *syn* position relative to the palladium atom.

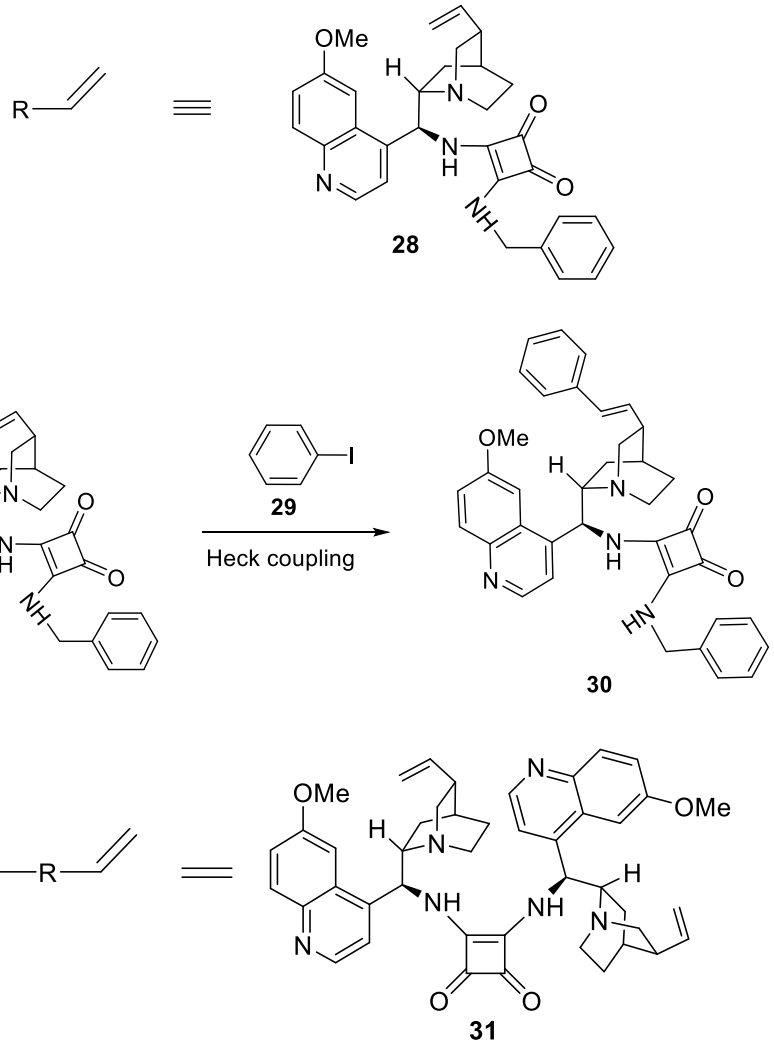
(e) Then a *syn* β-hydride elimination gives a hydridopalladium(II) halide associated with the arylated alkene.

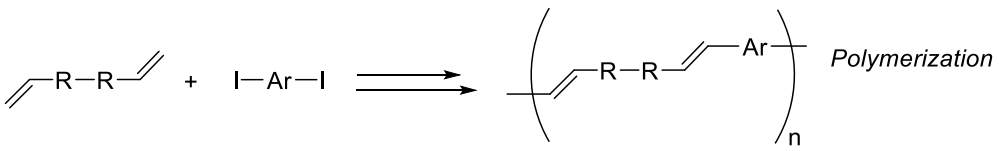
(f) Finally, after the dissociation from arylated alkene, the hydridopalladium(II) halide undergoes a reversible *reductive elimination* to generate the active Pd(0) complex. The base shifts this equilibrium towards the Pd(0) catalyst by quenching the hydrogen halide.

Mizoroki–Heck (MH) coupling reaction of olefinic double bonds with aromatic iodides is one of the easiest way to form new C–C bond in organic synthesis. Some achiral polymers have been synthesized using the MH reaction,[26] and polymerization of BINOL like materials is also reported[27] but there have

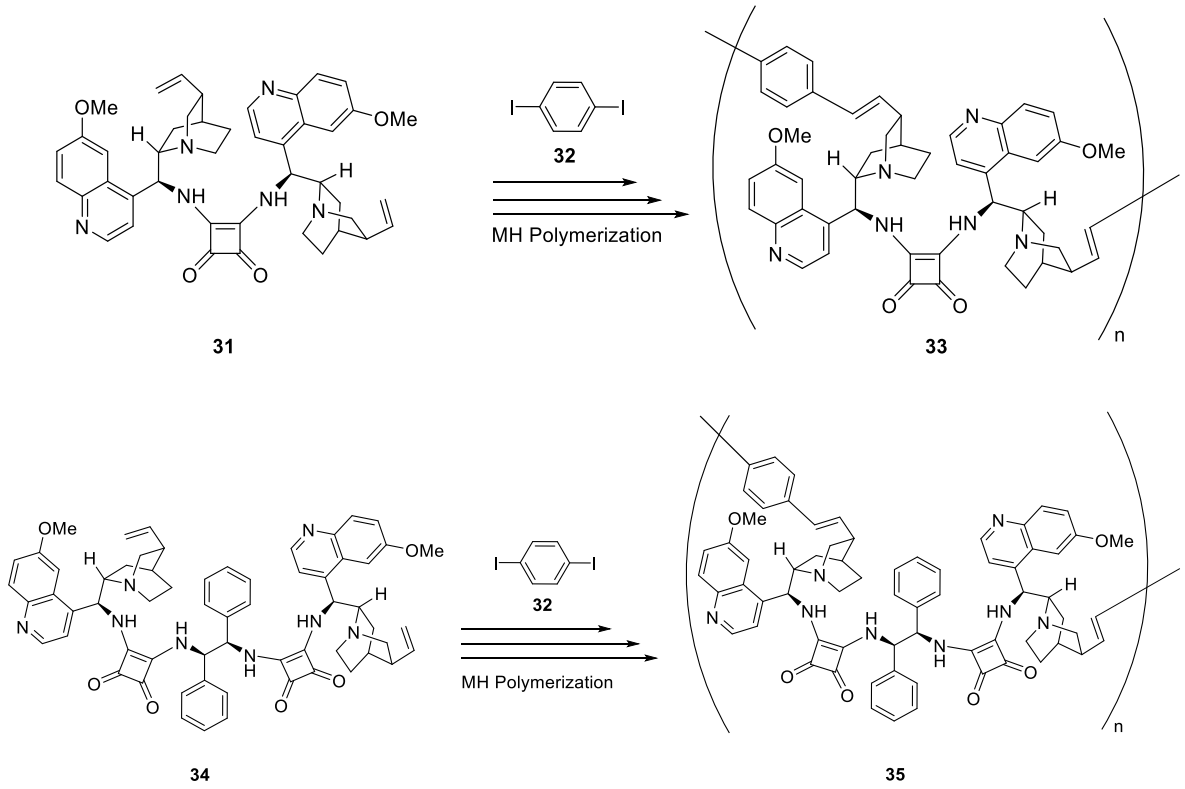
been no examples of chiral polymer synthesis using this method except for our research group reported works.[28-33] To our knowledge, no one uses the chiral main-chain polymers synthesized by MH reaction as an organocatalysts in asymmetric reaction. It has been proved that the double bond of cinchona alkaloids can be modified by Heck coupling reaction. Then we have used Heck coupling reaction for the synthesis of novel chiral cinchona alkaloid derived squaramide having main-chain polymers from the cinchona squaramide dimers.

Compound **30** is formed from the compound **28** and diiodide **29** using Heck coupling reaction. The squaramide **31** can easily be prepared by the reaction of dimethylsquarate and 9-amino derivative of quinine at room temperature. When equimolar amount of **31** and **32** reacts to each other under Heck coupling reaction conditions, main-chain chiral squaramide polymer **33** is obtained with quantitative yields.[30] Another polymer **35** also can be obtained in a same manner by Mizoroki-Heck coupling reaction from another modified cinchona alkaloid-derived squaramide **34** and diiodo compound **32** (scheme **5**).[32]



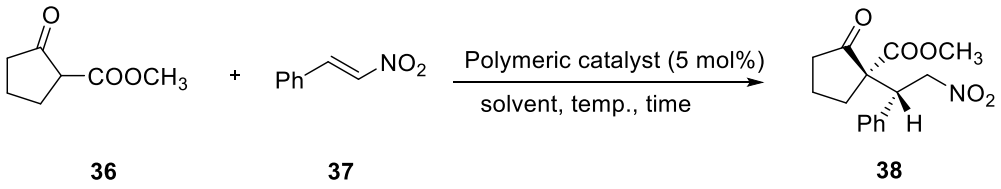


Scheme 4. Polymerization by Mizoroki-Heck coupling reaction.



Scheme 5. Polymerization of cinchona derived squaramide.

The cinchona alkaloid-derived squaramides and main-chain chiral squaramide polymers from scheme **4** and **5** were successfully applied in enantioselective Michael addition of methyl 2-oxocyclopentanecarboxylate **36** to *trans*-β-nitrostyrene **37**.

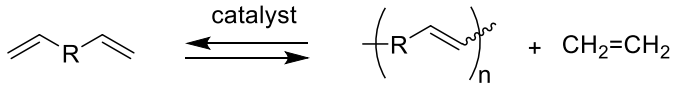


Scheme 6. Enantioselective Michael addition reaction.

1.7 ADMET polymerization

The term ‘olefin metathesis’ was coined by Calderon in 1967 and refers to a reaction in which the carbon atoms between a pair of double bonds are interchanged. The acyclic diene metathesis (ADMET)

reaction is a special type of olefin metathesis that could be utilized to make high molecular weight polymers. The ADMET reaction has been the primary focus of research in the Wagener group.[34, 35] The first successful ADMET polymerization was reported by the Wagener group in 1991.[36] There are many requirements for the ADMET reaction including steric and electronic factors, functional groups tolerated by available catalysts, catalyst selection and also the necessary length and structural characteristics of the diene monomer.



Scheme 7: General scheme of ADMET polymerization.

The ADMET polymer have some significant characteristics, such as-

- Defect free or analytically pure (no termination conjugation)
- High stereo-regularity (all *trans* olefinic double bonds)
- Well defined polymer chain ends and high molecular weight polymers

The molecular weight attainable depends on many factors, such as

- The efficiency of stirring and condensate removal
- Purity and dryness of reagents
- Catalyst efficiency and lifetime
- Monomer-catalyst compatibility
- The physical properties of the monomer and polymer

The general conditions for ADMET are like most other polycondensation reactions. The reaction is usually carried out in bulk monomer, where the monomer acts as both reactant and solvent. Cyclization is a common phenomenon in polycondensation chemistry but it can be substantially avoided in ADMET reactions by using α, ω-dienes with a chain length of ten atoms or more. If the dienes are any shorter, they may form thermodynamically stable five-, six-, and seven-membered rings in preference to polymer. Another general reaction condition for ADMET polymerization is the use of reduced pressure to remove the condensate. This is important in bulk ADMET polymerizations, where the viscosity of the growing polymer can impede stirring and the diffusion of the condensate, limiting the ultimate molecular weight of the polymer. By increasing the reaction temperature, the viscosity can usually be lowered and higher molecular weights may be obtainable.

ADMET reaction times are often on the order of days, so catalyst decomposition can become an issue, particularly when solvents and elevated temperatures are used. The monomers and solvents used in ADMET reactions should be of high purity to avoid possible side reactions and premature catalyst decomposition. An alternative is the use of an argon or nitrogen flow to drive off the ethylene condensate. The reaction is considered complete when the evolution of ethylene (bubbling) is no longer

observed and/or the mixture can no longer be stirred. The importance of a good magnetic stir bar and a powerful magnetic stirrer cannot be overstressed. As the viscosity (molecular weight) of the polymer increases the percent conversion becomes increasingly limited by the diffusion of reactive end-groups. Once the reaction has reached this stage, it is cooled to room temperature and the catalyst is quenched by adding a terminating agent, such as ethyl vinyl ether, diethyl ether, benzaldehyde, or by exposure to air.

The resulting ADMET polymer typically has a number average molecular weight in the range of 20,000 to 70,000 grams per mole and a polydispersity index of 2. The polymer can be characterized using various analytical techniques, such as nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), elemental analysis, gel-permeation chromatography (GPC), vapor pressure osmometry (VPO), membrane osmometry (MO), thermal gravimetric analysis (TGA), and differential scanning calorimetry (DSC). The efficiency of the catalyst depends on several factors, like as

- The solubility of the monomer or
- The tolerance of the catalyst toward chemical functions present in the monomers

In this polymerization, it is important for obtainment of high molecular weight polymers to conduct the polymerization under the high monomer concentration with repetitive removal of ethylene by-product from the reaction medium. ADMET polymerization is an intermolecular metathesis reaction of monomers containing two vinyl (or propenyl) groups as well as condensation polymerization with certain equilibrium.

The mechanism of ADMET reaction, first described by Wagener, Boncella, and Nel in 1991 is shown in figure **8**. It is a step-growth polycondensation reaction that is driven by the removal of a small molecule, or condensate. Every step in the reaction cycle is reversible and in equilibrium. This reaction is normally done by using reduced pressure, or in some cases a continuous flow of argon or nitrogen to remove the condensates as it forms and this is very important factor for the formation of high molecular weight ADMET polymer.

The ADMET reaction cycle contains two metallocyclobutane intermediates, [**h**] and [**j**]. The first one [**h**] is formed by the association of monomer or oligomer with the alkylidene [**g**] that contains another monomer or the growing polymer chain. The second one [**j**] which is formed when the monomer associates with the methyledene [**i**]. By removal of ethylene molecule from [**j**] an alkylidene [**g**] that contains the growing polymer chain. The ‘true’ catalyst in this reaction is the methyledene complex [**i**]. The repetition of this cycle shown in the figure **7** leads to high molecular weight polymers with high conversion.

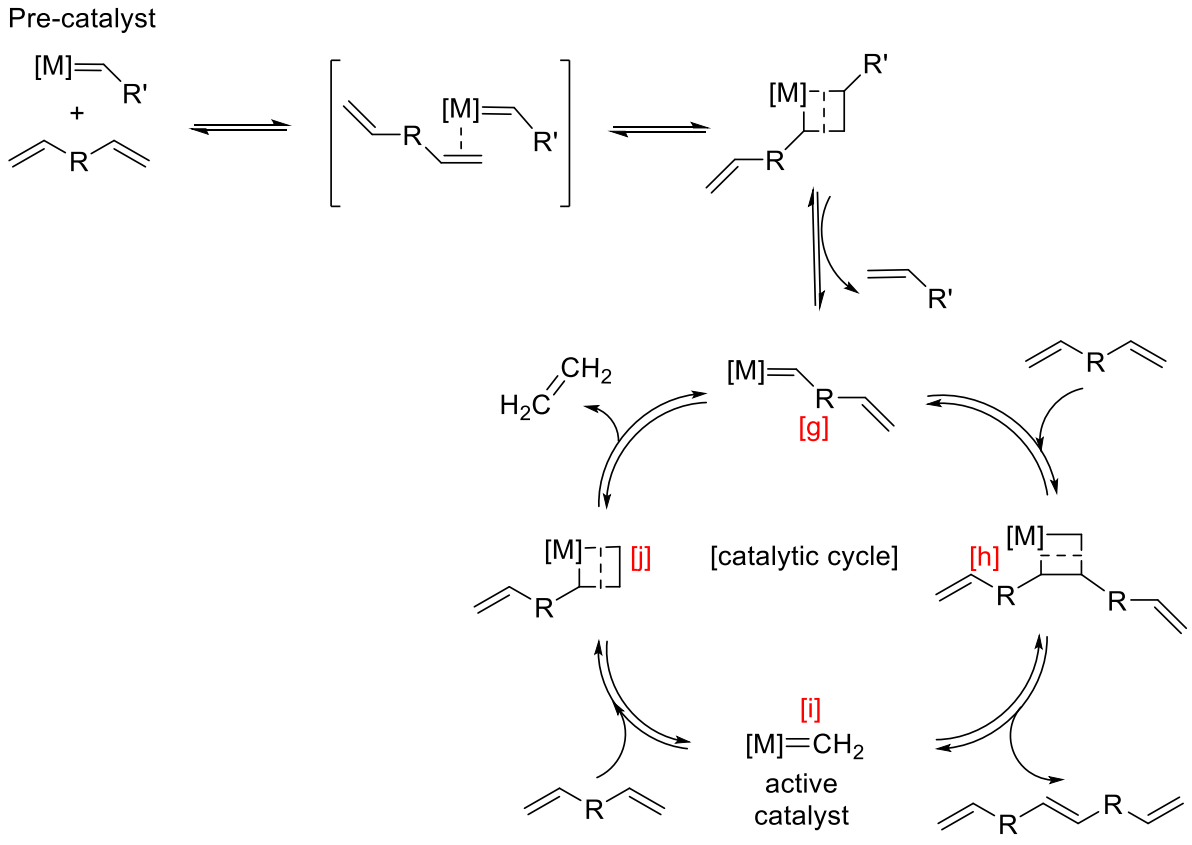
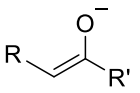


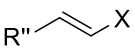
Figure 7. General mechanism of ADMET reaction.[36]

1.8 Michael addition reaction

Michael addition[37] is a nucleophilic addition reaction in which a michael donor-generally an enolate (a nucleophile), and a michael acceptor-generally a conjugated system with an electron withdrawing group such as cyano, nitro, keto or ester, react to each other to from a new addition product. The Michael addition reaction is a great tool which can be used to increase the number of carbons of a molecule and make larger molecules by formation of new carbon–carbon bonds. This is very useful method for the formation of new C–C bond in organic compounds. It is a thermodynamically controlled reaction; the reaction donors are active methylene such as malonates and nitroalkanes, and the acceptors are activated olefins such as α, β-unsaturated compounds.



[Michael donor: Nucleophile]



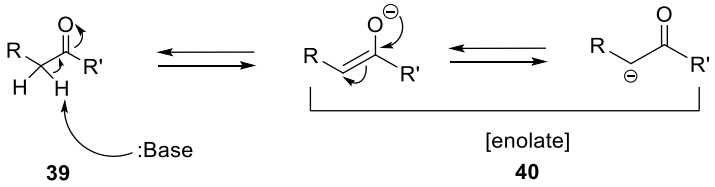
[Michael acceptor: Electrophile]

X= any electron withdrawing groups such as cyano, nitro, keto or ester, etc.

❖ Michael reaction: general mechanism

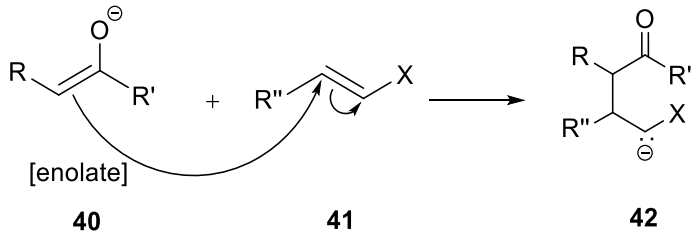
Step 1

The R and R' substituents on the nucleophile (a Michael donor) **38** are electron-withdrawing groups such as acyl and cyano making the methylene hydrogen more acidic forming the carbanion on reaction with base. An enolate **39** is formed in the presence of a base by the removal of alpha hydrogen from the carbonyl containing compound **38**.



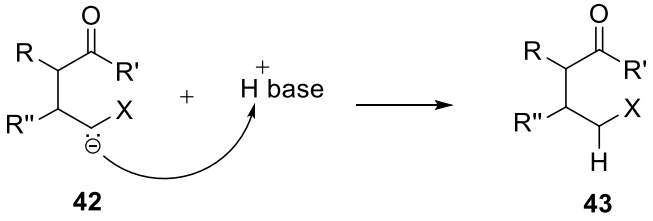
Step 2

The enolate **39** acts as a Michael donor which reacts with the Michael acceptor (α, β-unsaturated compound) **40** to produce the molecule **41**.

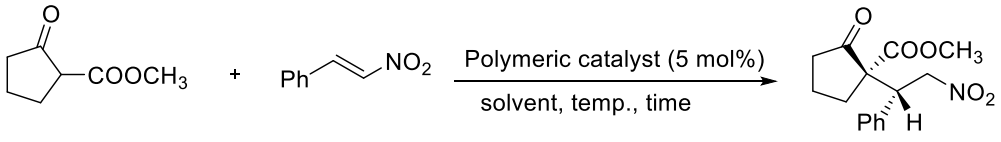


Step 3

Finally, the base got regenerated from **41** forming the final product **42**.



Currently, many researchers are very much passionate to explore the scope of asymmetric Michael addition reaction. Chiral phase transfer catalysis is one of the most important methods for the study of asymmetric Michael addition reaction. Many chiral phase transfer catalysts have been synthesized from cinchona alkaloids and successfully applied in different asymmetric reaction as a chiral organocatalyst. As, for example, we have chosen the enantioselective Michael addition reaction of methyl 2-oxocyclopentanecarboxylate to *trans*-β-nitrostyrene and we investigated various factors on this asymmetric Michael reaction which is catalyzed by the chiral polymeric organocatalysts **33**, **35** and others (scheme **9**).



44 **45** **46**

Scheme 9. The enantioselective Michael addition of methyl 2-oxocyclopentanecarboxylate **44** to *trans*-β-nitrostyrene **45**.

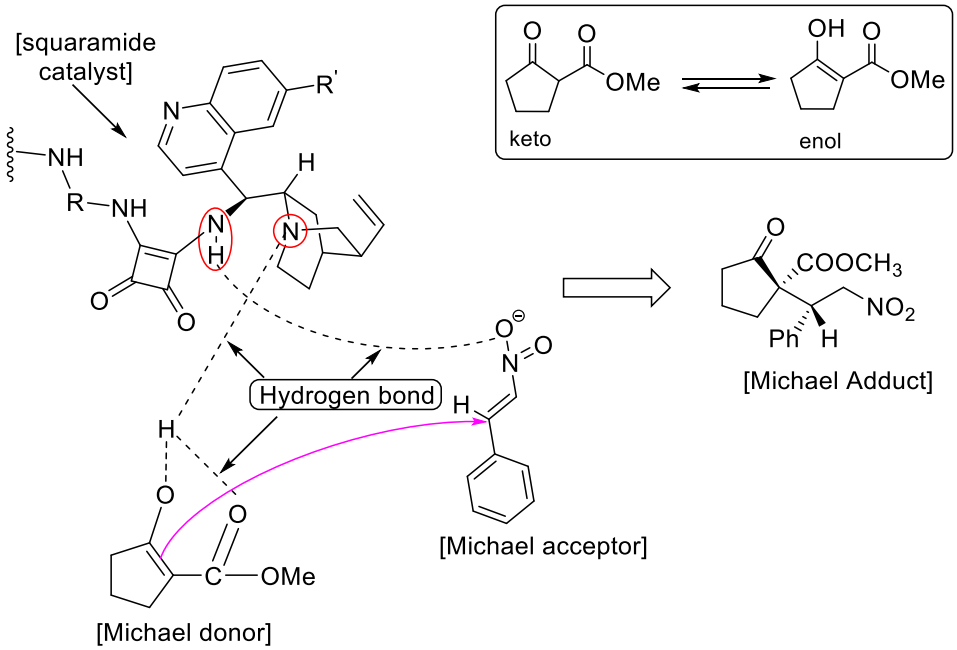
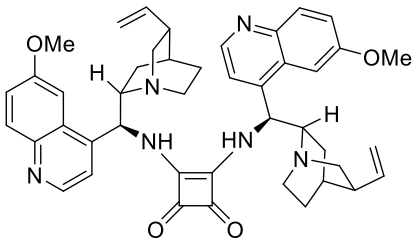


Figure 8. Plausible reaction pathway for squaramide catalyzed asymmetric Michael Addition.

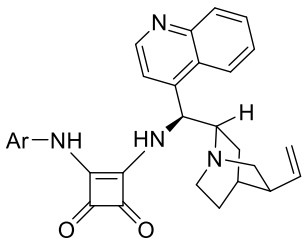
1.9 Cinchona alkaloids-derived squaramides as bifunctional chiral organocatalyst for the enantioselective Michael addition/others asymmetric reactions.

1.9.1 Cinchona alkaloids in enantioselective synthesis and catalysis

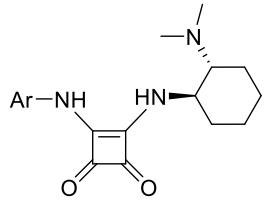
Cinchona alkaloids have various functionalities. These functional groups play an important role in creating chirality in asymmetric products by themselves or by chemically modified forms of them. They have a secondary hydroxy group at 9-position in their structure and this secondary alcohol group can be converted to C9-amino derivative by Mitsunobu-type azide formation, followed by the Staudinger reaction according to the literatures.[38,39] In the field of catalytic enantioselective organic synthesis, the natural cinchona alkaloids as well as modified forms of them are frequently used as a versatile source for organocatalysts as chiral phase-transfer catalyst (PTCs).[40] Cinchona alkaloids are a popular and good natural source of practical organocatalyst due to their commercial availability and also low cost. After the introduction of the first phase-transfer catalysts using cinchona alkaloid in 1981, now many of cinchona alkaloid-derived phase-transfer catalysts have been successfully synthesized and applied to various asymmetric synthesis as organocatalyst. The squaramides derived from different cinchona alkaloids can play a vital role as an excellent PTCs in various asymmetric transformations. The cinchona squaramide, which act as a PTCs in various asymmetric reactions,[41] is easily prepared by a simple chemical reaction of the 9-amino group of modified cinchona alkaloids with other chemical substances under suitable reaction conditions. The squaramide moiety in PTCs catalysts has proven to be a powerful hydrogen-bonding donor in organocatalysis process.



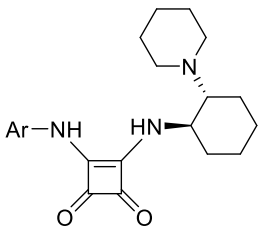
47



48a: Ar = 3,5-$(CF_3)_2C_6H_3$
48b: Ar = 4-$CF_3C_6H_4$



49a: Ar = 3,5-$(CF_3)_2C_6H_3$
49b: Ar = 4-$CF_3C_6H_4$

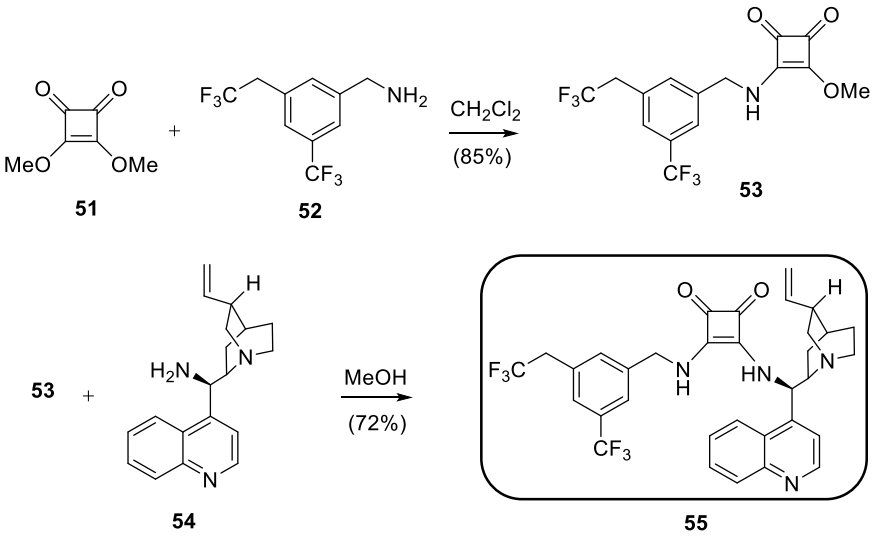


50a: Ar = 3,5-$(CF_3)_2C_6H_3$
50b: Ar = 4-$CF_3C_6H_4$

Figure 9. Structures of different squaramide organocatalysts

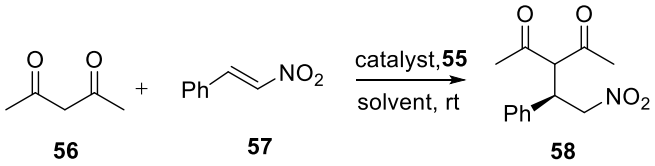
1.9.2 The pioneer works for chiral squaramide derivatives as hydrogen bond catalysts.[42]

The pioneer works on chiral cinchona squaramide catalyzed enantioselective Michael addition was described by Rawal and his co-workers in 2008. They developed a new family of H-bonding catalysts based on the squaramide moiety (scheme **1**).



Scheme 10. Synthesis of chiral squaramide catalyst, **9**

The new squaramide **55** was synthesized by stirring of dimethyl squarate **51** with an amine **52** in CH_2Cl_2 solvent involving the first substitution reaction at room temperature. Then repeating the process with 9-amino derivative of cinchona alkaloid gives the disubstituted cinchona squaramide **55**. The bisamides of squaric acid could act as an important core activation unit for dual H-bonding catalysis.[43,44] The (–)-cinchonine-substituted derivative **55** to be an effective H-bond donor catalyst for the conjugate addition of 2,4-pentanedione **56** to *β*-nitrostyrene **57**.



Scheme 11. The conjugate addition of 2,4-pentanedione to *β*-nitrostyrene.

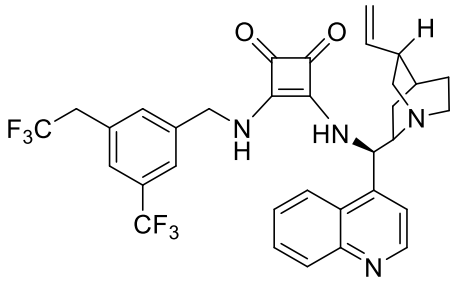
The asymmetric Michael addition reaction was carried out in ether at room temperature with 2.0 mol % of catalyst **55**, the conjugate addition product **58** was obtained in 88% yield and 96% ee (Table1, entry1). The same reaction was performed in toluene gave the product in higher yield and ee (entry 2). The best result was obtained with methylene chloride; the reaction proceeded faster and higher yield and excellent ee was obtained (entry 3). The improved enantioselectivity was maintained when the catalyst loading was reduced to 0.5 mol % (entry 4). Even, the reaction proceeded well with 0.1 mol% catalyst loading and slightly reduction of ee value and good isolated yield were found (entry 5).

Table 1. Evaluation of **55** as a catalyst for the conjugate addition of 2,4-pentanedione to *β*-nitrostyrene.[a]

entry	mol % of **55**	solvent	time, h	yield, %	ee, %
1	2.0	Et_2O	24	88	96
2	2.0	PhMe	24	94	98
3	2.0	CH_2Cl_2	7	98	>99
4	0.5	CH_2Cl_2	8	94	>99
5	0.1	CH_2Cl_2	20	97	96

[a] Reactions were carried out on 0.50 mmol of **57** with 2.0 equiv of **56** and 0.5 mol % **55** in 1.5 mL of solvent.

Next, the scope of this squaramide catalyzed conjugate addition reaction was examined. Various substituted *β*-nitro styrenes were reacted with 2, 4-pentanedione **56** in the presence of 0.5 mol % of catalyst **55** and all afforded consistently high yields and enantioselectivities. A somewhat longer reaction time was required for 4-methoxy-*β*-nitrostyrene due to its inherently lower reactivity toward nucleophiles. Then the asymmetric reaction was done using various 1,3-dicarbonyl compounds as nucleophiles. In all cases, the conjugate addition products were obtained in good to excellent yields and also excellent enantioselectivities. In all these reactions, the cinchona squaramide catalyst **55** can act as a bifunctional catalyst, analogously to Takemoto's catalyst.[45] For the conjugate addition reactions of 1,3-dicarbonyl compounds to nitroolefins, (–)-cinchonine-derive squaramide **55** was an excellent active organocatalyst, affording the conjugate addition products in high yields and excellent enantioselectivities.



55

Figure 10. The cinchonine derived squaramide catalyst, **55** developed by Rawal's group.[42]

1.9.3 Highly enantioselective Michael addition of thiols to *trans*-chalcones using bifunctional cinchona alkaloid-squaramide catalysts.[46]

The asymmetric sulfa-Michael conjugated addition of thiols to *trans*-chalcones is presented by using chiral squaramide catalysts. Moderate to excellent yields and high enantioselectivities (up to 99% ee) were achieved under mild conditions. A variety of bifunctional squaramide organocatalysts were synthesized and identified **59e** as a most efficient and enantioselective catalyst for the conjugate addition of various thiols to *trans*-chalcones.

The enantiopure sulphides are an important structural feature of various types of pharmaceuticals and natural products and are extremely versatile building blocks that can undergo synthetically useful

transformations.[47] This enantioselective sulfa-Michael addition reaction represents a simple and versatile approach towards valuable optically active sulfur compounds.

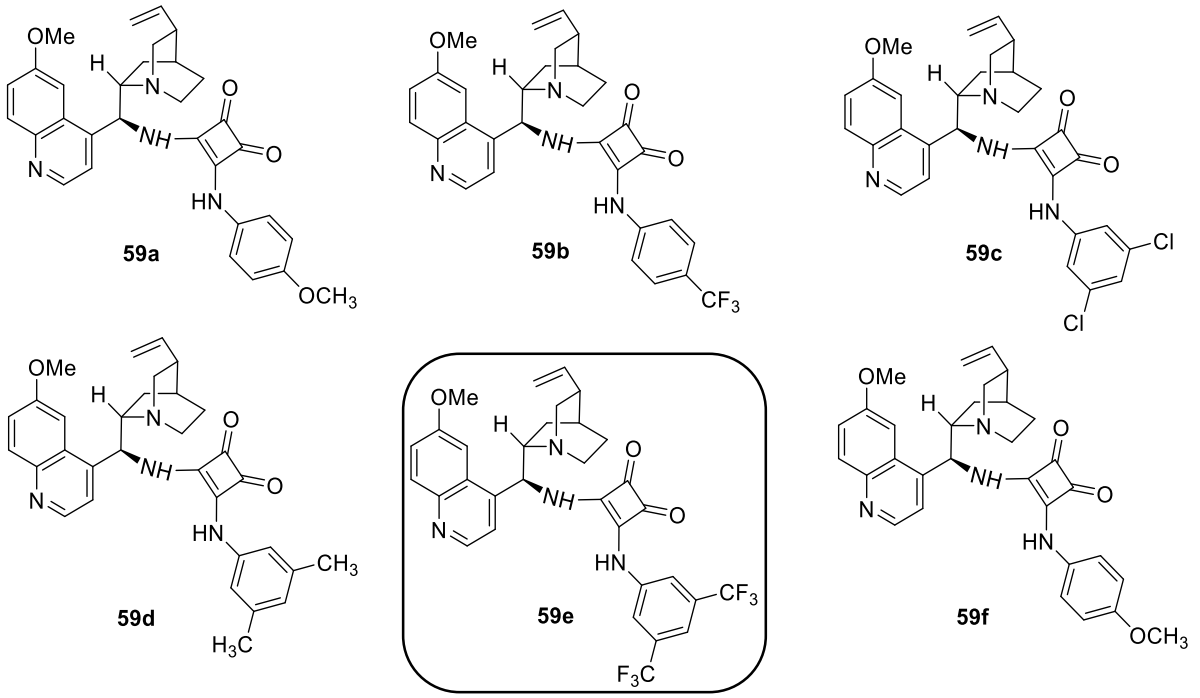
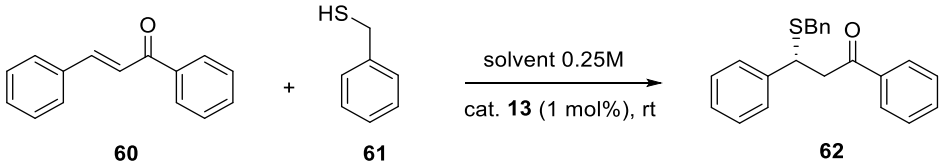


Figure 11. Structures of new squaramide-substituted Cinchona alkaloid catalysts, **59**.

The addition reaction of benzyl thiol to *trans*-chalcone was conducted using newly designed cinchona squaramide catalysts to determine the catalytic activity of the catalysts **59a-59f** (Table **1**). Firstly, used of the catalysts **59a** and **59b**, which have different substituents on the *para* position of the aromatic rings. Electron-withdrawing group on the aryl group decreased the reaction time, but asymmetric product was found with same ee value (entry 2). Of the *meta* position substituted catalysts **59c-59e**, **59d** and **59e** showed marked superiority on enantioselectivity. Using the catalyst **59e** which contains two CF_3 groups on the aromatic ring a value of 92% ee was obtained. This outcome indicate that steric hindrance of the aromatic rings and acidity of the squaramide N–H groups were related directly to the stereoselectivity and chemical yield of the asymmetric products. The unsatisfactory result with cyclohexyl-substituted squaramide catalyst **59f** indicated the irreplaceable role of the aromatic group in the enhancement of catalyst activity and selectivity.

Table 2. Asymmetric conjugate addition of benzyl thiol **61** to *trans*-chalcone **60** with squaramide catalysts **59**.[a]



60 **61** **62**

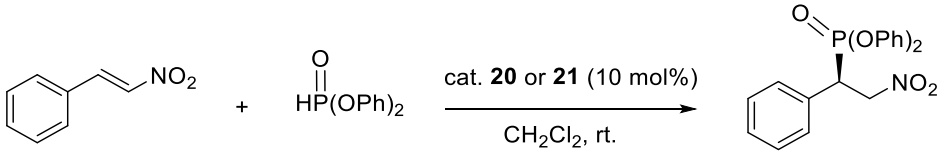
entry	solvent	catalyst	time, h	yield, %[b]	ee, %[c]	Config.
1	CH_2Cl_2	**13a**	6	81	63	*R*
2	CH_2Cl_2	**13b**	3	91	63	*R*
3	CH_2Cl_2	**13c**	3	90	62	*R*
4	CH_2Cl_2	**13d**	10	81	84	*R*
5	CH_2Cl_2	**13e**	3	98	92	*R*
6	CH_2Cl_2	**13f**	12	48	33	*R*

[a]The reaction between *trans*-chalcone **60** (0.25 mmol) and benzyl thiol **61** (0.375 mmol) was carried out with 1 mL solvent in the presence of 1 mol% catalyst at room temperature. [b]Yield of isolated product. [c]Determined by HPLC analysis using a Chiracel OJ-H column.

After finding the squaramide catalyst **59e** as the best catalyst for this reaction, then the screening of solvents in the Michael reaction of benzyl thiol and *trans*-chalcone at room temperature was performed. The absolute configuration of the C-3 position of **62** was determined to be ***R*** by comparison with the reported optical rotation data.[48]

1.9.4 Squaramide-catalyzed enantioselective Michael addition of diphenyl phosphite to nitroalkenes.[49]

The enantioselective Michael addition reaction of diphenyl phosphite to nitroalkene was successfully catalyzed by the squaramide catalyst. The easily prepared squaramide would be a remarkably effective catalyst for this Michael addition reaction. The reaction provides a simple, highly enantioselective synthesis of chiral β-nitro phosphonates, which are the important building blocks to biologically active β-amino phosphonic acids. The high yields and uniformly excellent enantioselectivities obtained for both aryl- and alkyl-substituted nitroalkenes, including those bearing acidic protons or sterically-demanding substituents, point to the unique capability of the squaramide moiety.



63 **64** **65**

Scheme 12. Michael addition of diphenyl phosphite **64** to *trans*-β-nitrostyrene **63**.

This asymmetric reaction to prepare β-nitro phosphonates **65** using squaramide catalysts is so important due to its metal-free catalysis. There have been only two reported works regarding the use of metal-free

catalysts for the conjugate addition reaction of phosphites.[50-52] Wang, et al., showed that natural quinine successfully promotes this reaction to afford the phosphite addition products in modest to very good enantioselectivities.[50] Using an intricate, axially chiral biaryl guanidine derivative to promote the conjugate addition by Terada et al., higher ee values were obtained.[51] In 2007, Wang et al. reported the use of achiral thiourea to promote the addition of diphenyl phosphite to *trans*-β-nitrostyrene with the conjugated product with 21% yield and 8% *ee* after a reaction time of 24 h.[50] Due to the structural difference between thioureas and squaramides, particularly the spacing between the two donor hydrogen atoms in thioureas and squaramides the reactivity must differ in case of squaramide.

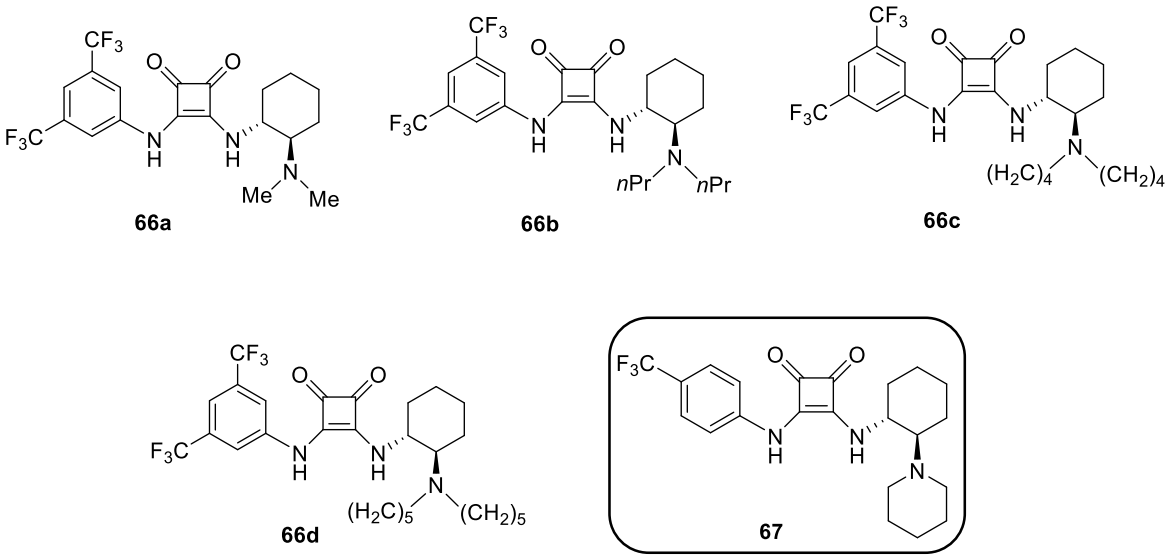
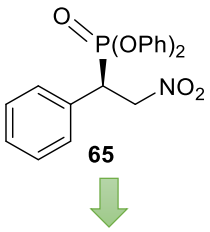


Figure 12. The structures of squaramide catalysts, **66** and **67**.



with cat. **66a** (10 mol %): CH_2Cl_2, rt., 45 min. conv. 98%, *ee*: 81%

with cat. **66d** (10 mol %): CH_2Cl_2, rt., 30 min. conv. 97%, *ee*: 95%

with cat. **66b** (10 mol %): CH_2Cl_2, rt., 1 h, conv. 96%, *ee*: 84%

with cat. **66c** (10 mol %): CH_2Cl_2, rt., 30 min. conv. 98%, *ee*: 88%

with cat. **67** (10 mol %): CH_2Cl_2, rt., 15 min. conv. 99%, *ee*: 96%

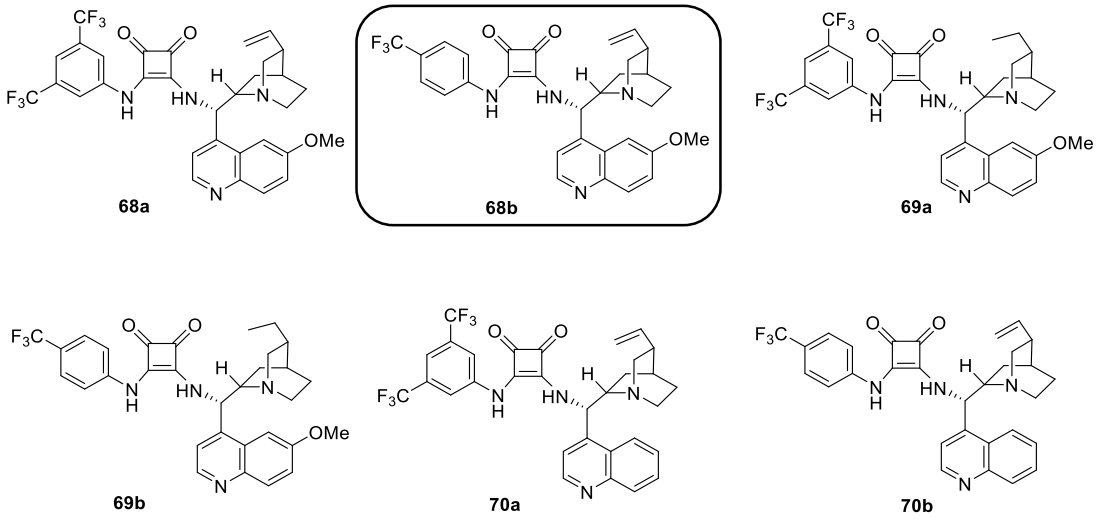
Reactions were carried out on 0.20 mmol of **63** with 1.25 equiv of **64** and 10 mol% **66** or **67** in 1.0 mL CH_2Cl_2 at room temperature.

The addition reaction of *trans*-β-nitrostyrene **63** and diphenyl phosphite **64** at room temperature readily promoted by using dimethyl-substituted squaramide **66a** with 98% conversion after just 45 min, and

afforded the addition product in 81% *ee*. The study of relationship between catalyst structure and reaction enantioselectivity was performed to find out the optimal catalyst. Firstly, the effect of changing the substituents on the nitrogen atom of the catalyst was examined using catalysts **66b**, **66c** and **66d**. In case of catalyst **66b**, slightly improved enantioselectivity was observed due to the presence of bulkier *n*-propyl groups on the nitrogen. Using the cyclic amine derivatives containg catalysts such as the pyrrolidine-substituted catalyst **66c** and piperidine substituted catalyst **66d** gave the products with somewhat higher enantioselectivities up to 95% *ee*. Because of the relative conformational rigidity of these substituents in the catalyst **66d**, which allows a more favorable transition state, a high *ee* value was found. Finally, catalyst **67** was used on this asymmetric reaction and highest level of conversion (99%) and enantioselectivity (99% *ee*) was obtained.

1.9.5 Chiral squaramide-catalyzed sulfa-Michael/Aldol cascade for the asymmetric synthesis of spirocyclic tetrahydrothiophene chromanone derivatives.[53]

In 2014, Du, et al. presented an effective asymmetric sulfa-Michael/aldol cascade reaction for the construction of stereoselective chiral spirocyclic tetrahydrothiophene chromanone derivatives in a single operation by using readily available bifunctional squaramide organocatalysts. The reaction provides the asymmetric products in high isolated yields and with good diastereoselectivity and enantioselectivity. The important features of the present protocol include a wide substrate range, a relatively low catalyst loading, and amenability to gram-scale synthesis providing many opportunities for possible industrial applications.



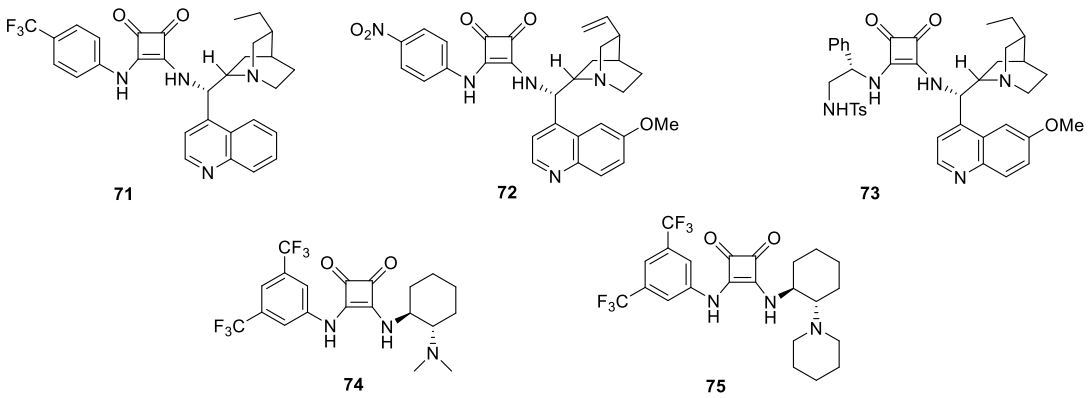
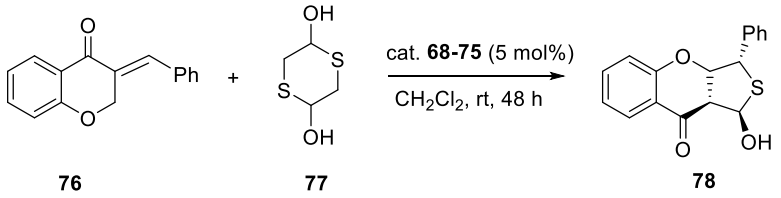


Figure 13. Structures of squaramide organocatalysts.

To know the applicability of the squaramide organocatalysts, **68-75** on the proposed asymmetric cyclization reaction, (*E*)-3-benzylidene-chroman-4-one was treated with 1,4-dithiane-2,5-diol at room temperature in CH_2Cl_2 in the presence of 5 mol% quinine-derived squaramide **68a** (Figure **5**). The catalyst **68a** is one of the most successful bifunctional tertiary amine-squaramide catalysts, has been applied to many asymmetric reactions. The sulfa-Michael/aldol cascade reaction was completed within 48 h affording desired spirocyclic tetrahydrothiophene **78** in excellent yield (76%) with good stereoselectivities (84:16 *dr*, 79% *ee*) (Table 4, entry 1).



Scheme 13. Asymmetric sulfa-Michael addition reaction.

However, it was not possible to distinguish the diastereoisomers by TLC and failed to separate them by silica gel column chromatography. The effects of various chiral squaramide catalysts were examined on this asymmetric reaction to know the catalytic activities; the results are outlined in Table **4**. Under the same conditions, reactions using catalyst **69a** or **69b** reached completion of the reaction more quickly gave slightly higher yields than were achieved with **68** although there are no change in stereoselectivities. Hence, it was found that hydroquinine has a higher catalytic activity than quinine. Using the electron-withdrawing, $–NO_2$ group containing catalyst **72** the asymmetric product was obtained with some higher stereoselectivity and also higher isolated yield of product (entry 11).

Table 4. Asymmetric sulfa-Michael addition reaction between **76** and **77** catalyzed by **68-75**.[a]

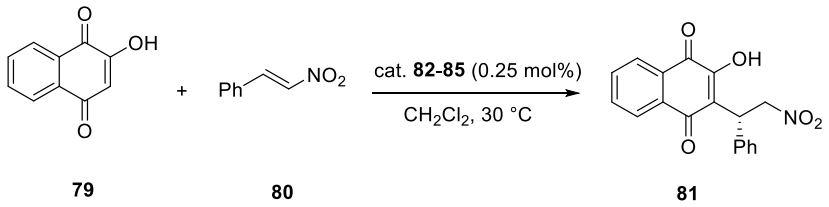
entry	catalyst	yield, %[b]	*dr*, %[c]	*ee*, %[c]
1[d]	**68a**	76	84:16	79
2[e]	**68a**	78	95:5	80
3	**68a**	92	90:10	84
4[f]	**68a**	92	87:13	80
5	**68b**	86	92:8	87
6	**69a**	94	88:12	82
7	**69b**	94	89:11	81
8	**70a**	84	93:7	86
9	**70b**	76	86:14	78
10	**71**	90	87:13	80
11	**72**	93	91:9	85
12	**73**	32	97:3	33
13	**74**	67	91:9	62
14	**75**	83	90:10	56

[a]Reactions were carried out with **76** (0.20 mmol) and **77** (0.22 mmol) in dichloromethane (1.0 mL) catalyzed by **5** mol-% catalyst for 48 h. [b]Isolated yields after column chromatography. [c] Determined by HPLC analysis. [d]The reaction was conducted with 0.1 mmol of **77**. [e]The reaction was conducted with 0.15 mmol of **77**. [f]The reaction was conducted with 0.3 mmol of **77**.

The cinchonidine or hydrocinchonidine derived squaramide catalysts **70-71** were also applied to this reaction, although no improvements in stereoselectivity were observed compared to the previously used catalysts. The use of multi-hydrogen bonding catalyst **73** was also done and very low of isolated yield and enantioselectivity was found. Squaramide catalysts **74** and **75** derived from (1*S*, 2*S*)-cyclohexane-1,2-diamine (Table 4, Entries 13 and 14) were also evaluated, although inferior yields and selectivities were obtained. After screening of different catalysts, squaramide **68b** was found to be the best catalyst in terms of induction of diastereoselectivity and enantioselectivity for this asymmetric reaction.

After finding the best catalyst **68b** for this asymmetric transformation, further optimization was carried out using squaramide **68b** as the catalyst. The reaction solvent, catalyst loading condition, temperature and additive were all factors that were intensively investigated.

1.9.6 Chiral squaramide-catalyzed highly enantioselective Michael addition of 2-hydroxy-1, 4-naphthoquinones to nitroalkenes.[54]



Scheme 14. Asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to *trans*-β-nitrostyrene.

A series of chiral squaramide-based bifunctional organocatalysts have been synthesized and successfully applied to promoting the asymmetric Michael addition of 2-hydroxy-1, 4-naphthoquinones to nitroalkenes. Significantly, very low amount of catalyst loading (0.25 mol %) is highly effective to

give good-to-excellent yields and excellent enantioselectivities (95-98% ee) under mild reaction conditions. This catalytic asymmetric reaction provides a valuable and easy access to chiral napthoqui-

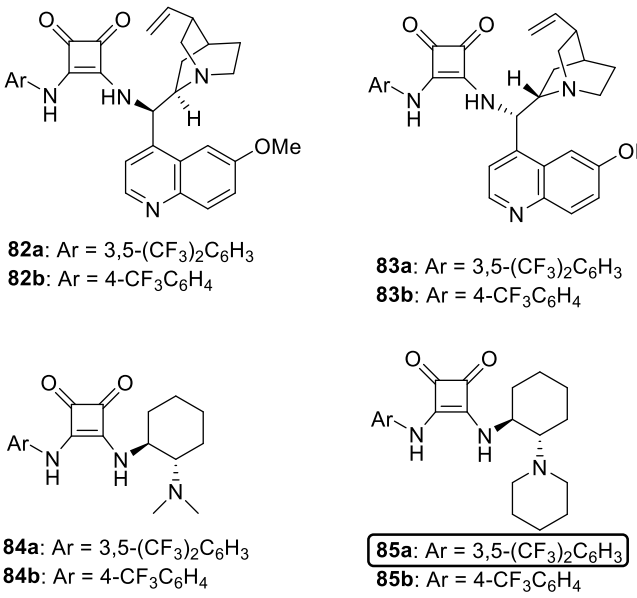


Figure 14. Structures of squaramide organocatalysts.

none derivatives, which possess the versatile transformation possibilites and potential biological activity. Given the highly modular nature and facile synthesis, chiral squaramides may represent a kind of good hydrogen-bonding organocatalyst. Among all squaramide catalysts, catalyst **85b** was selected as the best catalyst for the synthesis of the asymmetric compound **81**. The asymmetric results are summarized in the table **5**.

Table 5. Screening of organocatalysts for the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone **79** to β-nitrostyrene **80**.[a]

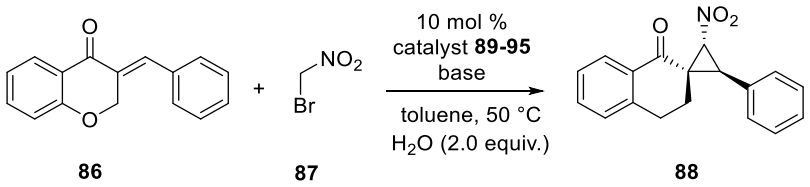
entry	catalyst	yield of **81**, %[b]	ee of **81**, %[c]	config.
1	**82a**	94	91	*R*
2	**82b**	96	92	*R*
3	**83a**	96	-87	*S*
4	**83b**	96	-86	*S*
5	**84a**	95	89	*R*
6	**84b**	96	87	*R*
7	**85a**	97	97	*R*
8	**85b**	97	98	*R*

[a]Reactions were carried out with β-nitrostyrene **80** (0.2 mmol) and 2-hydroxy-1,4-naphthoquinone **79** (0.2 mmol) in CH_2Cl_2 (0.5 mL). [b]Isolated yield, [c]Determined by HPLC using a Daicel Chiralcel OJ-H column.

1.9.7 Chiral squaramide-catalyzed Michael/Alkylation cascade reaction for the asymmetric synthesis of nitro-spirocyclopropanes.[55]

A new diastereoselective and enantioselective cyclopropanation reaction has been developed by employing a Michael/alkylation cascade reaction between (*E*)-3-arylenechroman-4-one or (*E*)-2-arylideneindan-1-one derivatives and a bromonitroalkane with a chiral squaramide catalyst in moderate to good yields (54-90%) and with excellent diastereo-(97:3 to 99:1) and enantioselectivities (98 to >99%

ee). This reaction provides an easy way to prepare spirocyclopropane derivatives that have three adjacent stereogenic centers.



Scheme 15. Asymmetric Michael/alkylation cascade reaction between (*E*)-3-arylenechroman-4-one and a bromonitroalkane.

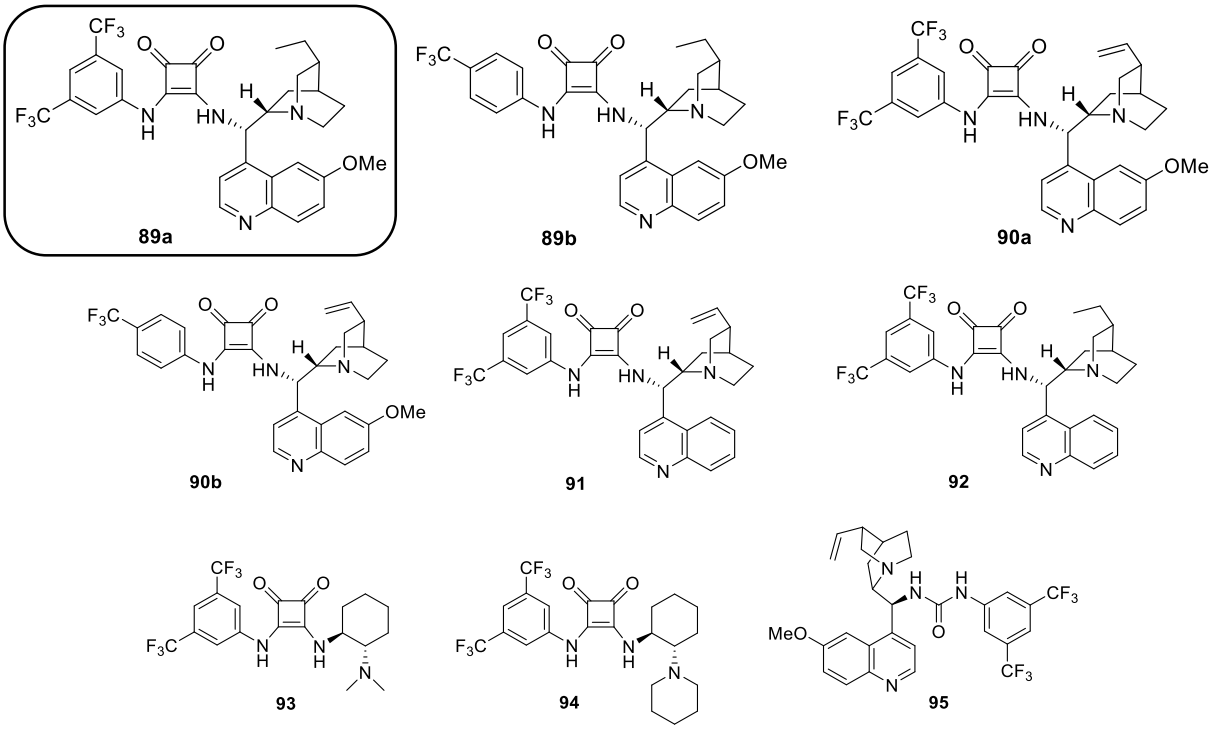


Figure 15. Structures of squaramide organocatalysts.

Table 6. Asymmetric Michael/alkylation cascade reaction between (*E*)-3-arylenechroman-4-one **86** and a bromonitroalkane **87** catalyzed by squaramide catalysts **89**-**95**.[a]

entry	catalyst	base	yield, %[b]	*dr*[c]	*ee*, %[c]
1	**89a**	K_2CO_3	77	98:2	99
2	**89b**	K_2CO_3	49	99:1	99
3	**90a**	K_2CO_3	48	98:2	99
4	**90b**	K_2CO_3	34	98:2	99
5	**91**	K_2CO_3	43	98:2	99
6	**92**	K_2CO_3	63	99:1	99
7	**93**	K_2CO_3	30	98:2	91
8	**94**	K_2CO_3	16	99:1	86
9	**95**	K_2CO_3	31	98:2	99

[a]Reactions were carried out with **86** (0.2 mmol) **87** (1.0 mmol), catalyst (10 mol%), K_2CO_3 (1.0 equv.) and H_2O (2.0 equiv.) in toluene (0.5 mL) at 50 °C for 60 h. [b]Isolated yield, [C]Diastereomeric ratio (*dr*) and *ee* values were determined by chiral HPLC analysis.

After the catalyst screening it is found that the hydroquinine-derived squaramide catalyst **89a** is the best catalyst for this asymmetric transformation, as it provided better isolated yields and excellent stereoselectivity than those obtained by the other catalysts.

1.9.8 Highly enantioselective Michael addition of nitroalkanes to chalcones using chiral squaramides as hydrogen bonding organocatalysts.[56]

Squaramide-based chiral organocatalysts were synthesized and applied as hydrogen bonding organocatalysts in the enantioselective Michael addition of nitroalkanes to chalcones. These organocatalysts promoted the Michael addition with low catalyst loading under high temperature (80 °C), affording the desired *R* or *S* enantiomers of the products flexibly in high yields with excellent enantioselectivities (93-96% ee) by the appropriate choice of organocatalysts.

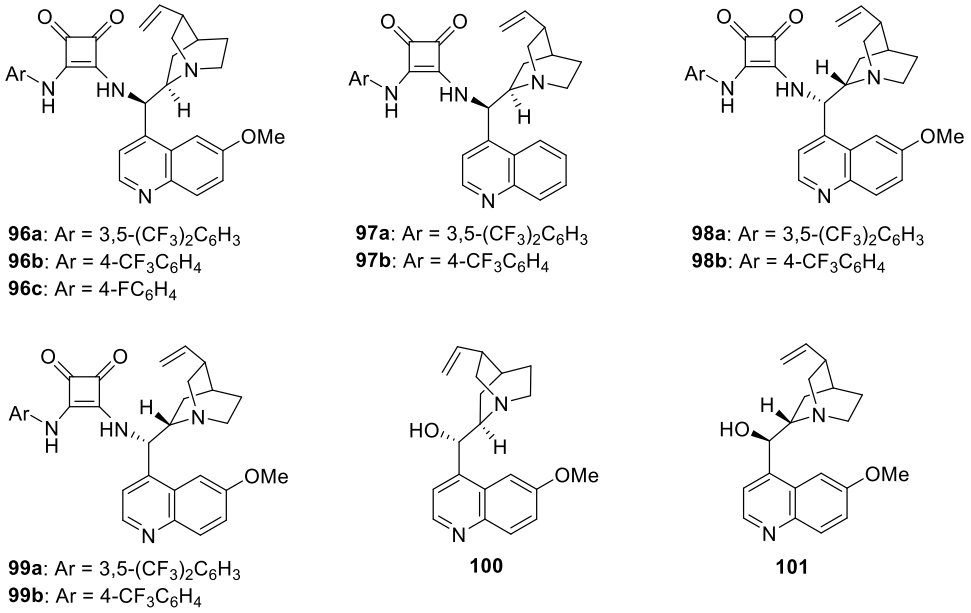
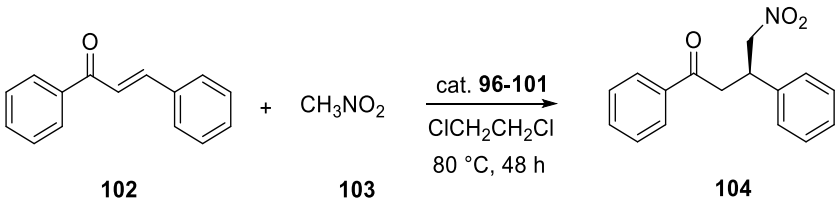


Figure 16. Structures of screened organocatalysts.

Table 7. Asymmetric Michael reaction between chalcone **102** and nitromethane **103** catalyzed by squaramide catalysts **96-101**.[a]



102 **103** **104**

entry	catalyst	loading (mol %)	yield, %[b]	*ee*, %[c]	config.
1	**96a**	10	97	94	*S*
2	**96b**	10	92	93	*S*
3	**96c**	10	73	93	*S*
4	**97a**	10	93	93	*S*
5	**97b**	10	81	92	*S*
6	**98a**	10	>99	94	*R*
7	**98b**	10	84	94	*R*
8	**99a**	10	94	94	*R*
9	**99b**	10	80	94	*R*
10	**100**	10	13	33	*R*
11	**101**	10	12	19	*S*

[a]Reactions were carried out with 0.25 mmol of chalcone **102** and 2.5 mmol of nitromethane **103** in 0.5 mL of CH_2ClCH_2Cl. [b]Isolated yields. [c]Determined by HPLC, using a Chiralpak IA column.

The screening of the squaramide-based organocatalysts **96-99** was conducted under the optimized conditions and results are summarized in Table 7. High enantioselectivities (92-94% ee) were obtained in all the cases. Using the quinidine and cinchonine-derived catalysts **96-97** gave the *S*-configured products, whereas the quinine and cinchonidine-derived catalysts **52-53** provided the *R*-configured products with the same efficiency. It is also noted that the acidity of the hydrogen bond donor motifs had a certain effect on their catalytic activity. The catalysts with 3,5-$(CF_3)_2$ substitution on the aromatic ring gave better yields than the ones with 4-CF_3 and 4-F substitutions, which demonstrated that the activity of the catalyst was improved with the increasing of the acidity. Quinidine **100** and quinine **101** were also applied on the same reaction for comparison, but very low yields and enantioselectivities were found. The best catalysts were **96a** and **98a** which gave the *R* and *S* enantiomers in excellent yields and enantioselectivities.

1.9.9 Chiral squaramide-catalyzed highly diastereo- and enantioselective direct Michael addition of nitroalkanes to nitroalkenes.[57]

A Highly stereoselective direct Michael addition of nitroalkanes to nitroalkenes has been developed by using squaramide-catalysts, **105-109**. This squaramide catalysts were very much effective to give the corresponding Michael adducts in high yields and high diastereoselectivities (up to 95:5 *dr*) and excellent enantioselectivities (up to 97% *ee*). This method provides a facile way to get optically active 1,3-dinitro compounds.

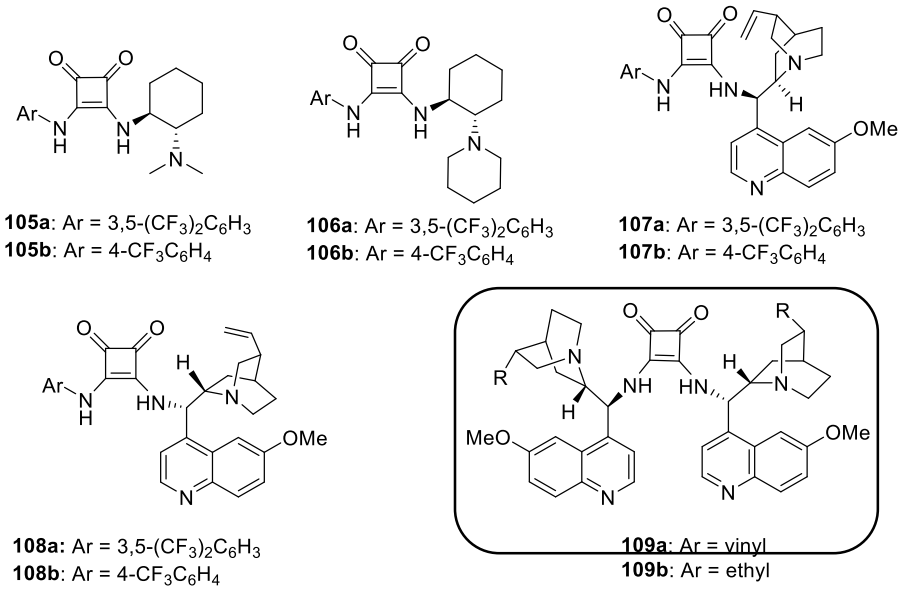
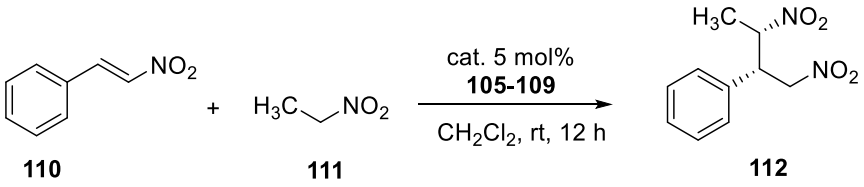


Figure 17. Screened squaramide organocatalysts.

Table 8. Asymmetric Michael reaction between nitroalkenes **110** and nitromethane **111** catalyzed by squaramide catalysts **105-109**.[a]



110 **111** **112**

entry	catalyst	yield, %[b]	*dr*, (*syn*/*anti*)[c]	*ee*, (*syn*)%[d]
1	**105a**	70	85:15	79
2	**105b**	74	80:20	43
3	**106a**	82	75:25	88
4	**106b**	32	80:20	87
5	**107a**	75	83:17	-82
6	**107b**	67	83:17	-67
7	**108a**	90	83:17	91
8	**108b**	62	81:19	86
9	**109a**	94	85:15	93
10	**109b**	96	80:20	91

[a]Reactions were carried out with 0.20 mmol of β-nitrostyrene **110** and 1.0 mmol of nitromethane **111** in 0.5 mL of CH_2Cl_2 at room temperature for 12 h, [b]Isolated yields after column chromatography. [c]Determined by chiral HPLC analysis. [d]Enantiomeric excess for the major syn-diastereomer was determined by chiral HPLC analysis.

Among the above all squaramides, the catalyst **109a** is the best catalyst for this Michael addition reaction in terms of isolated yield and stereoselectivities.

1.9.10 Squaramide-catalyzed highly enantioselective Michael addition of malononitrile to chalcones.[58]

Chiral quinine-derived squaramide catalyzed highly enantioselective Michael addition of malononitrile to chalcones has been described. This organocatalytic reaction smoothly occurred with a very low

catalyst loading (0.5 mol%) to give the Michael adducts in high yields and good enantioselectivities (up to 96% ee) under mild reaction conditions.

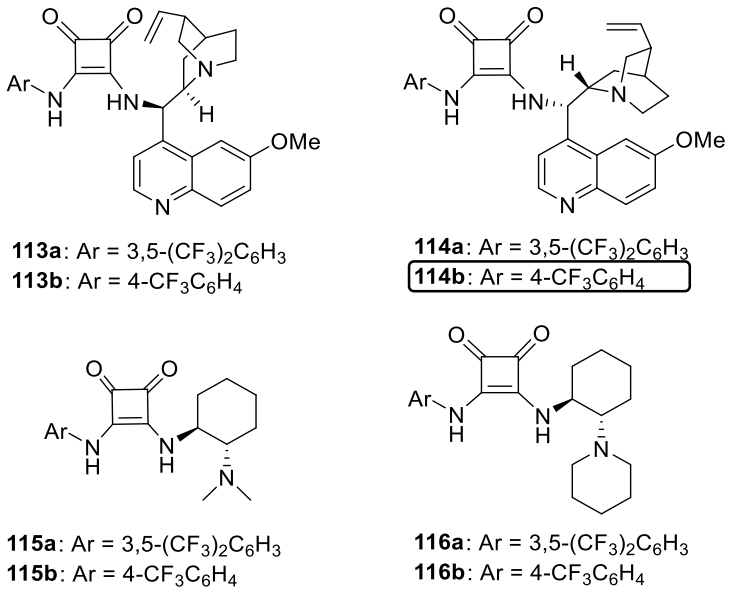
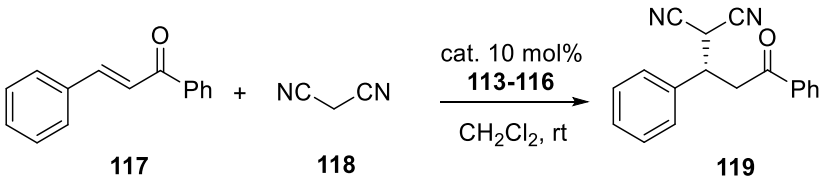


Figure 18. Screened squaramide catalysts.

Table 9. Asymmetric Michael addition of *trans*-chalcones **117** to malononitrile **118** catalyzed by squaramide catalysts **113-116**.[a]



entry	catalyst	yield, (%)[b]	*ee*, %[c]	config.
1	**113a**	75	33	*R*
2	**113b**	83	59	*R*
3	**114a**	73	82	*S*
4	**114b**	78	86	*S*
5	**115a**	82	81	*S*
6	**115b**	80	79	*S*
7	**116a**	68	81	*S*
8	**116b**	74	79	*S*

[a]Reactions were carried out with 0.20 mmol of *trans*-chalcone **117** and 0.24 mmol of malononitrile **118** in 0.5 mL of CH_2Cl_2 at room temperature for 24 h, [b]Isolated yields after column chromatography. [c]Determined by chiral HPLC analysis.

The squaramide catalyst **114b** is the best catalyst for this Michael addition reaction in terms of isolated yield and stereoselectivity.

1.9.11 Cinchona-based squaramide-catalysed cascade aza-Michael-Michael addition: enantioselective construction of functionalized spirooxindole tetrahydroquinolines.[59]

An efficient chiral bifunctional tertiary amine-squaramide catalysed enantioselective aza-Michael-Michael addition reaction of 2-tosylaminoenones to 3-ylidenoxindoles has been disclosed in here. The corresponding cascade double Michael adducts were obtained in excellent yields with excellent

diastereoselectivities (>25:1 *dr*) and high enantioselectivities (up to 94% *ee*) under mild reaction conditions.

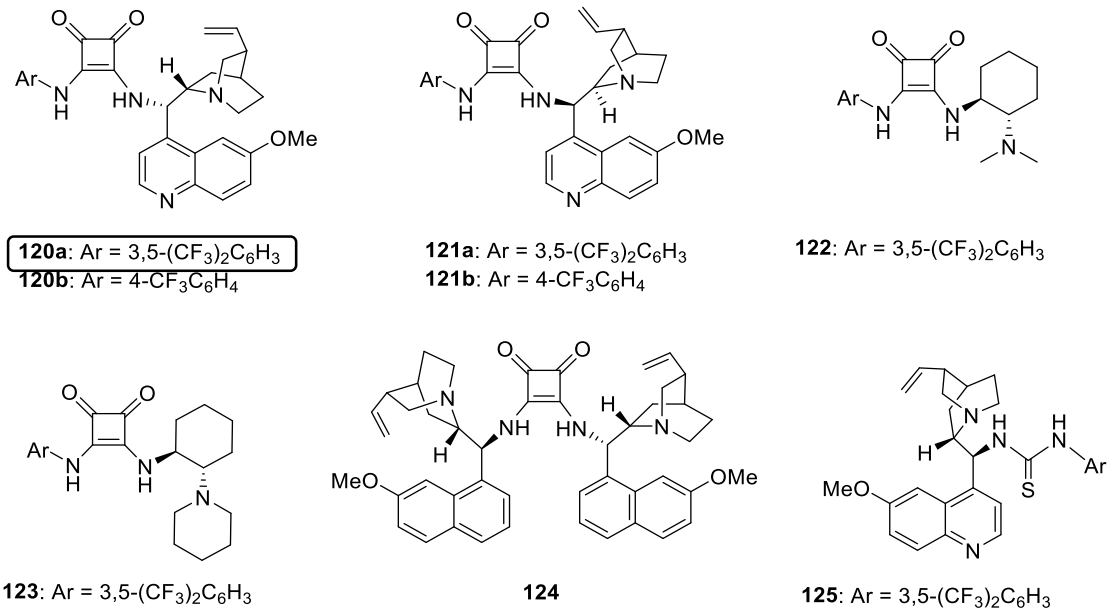
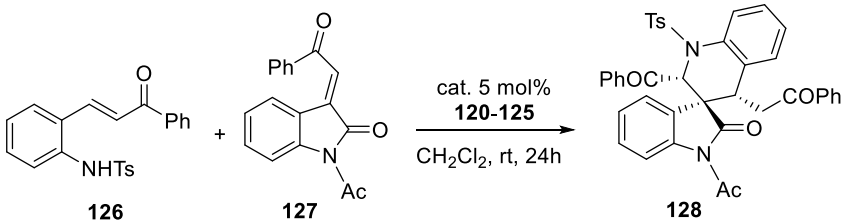


Figure 19. Screened squaramide catalysts.

Table 10. Asymmetric cascade aza-Michael-Michael addition of **126** to **127** catalyzed by squaramide catalysts **120-125**.[a]



entry	catalyst	yield, %[b]	*dr*, %[c]	*ee*, %[d]	config.
1	**120a**	99	>25:1	88	2'*R*,3'*S*,4'*S*
2	**120b**	93	>25:1	88	2'*R*,3'*S*,4'*S*
3	**121a**	92	>25:1	-80	2'*S*,3'*R*,4'*R*
4	**121b**	90	>25:1	-81	2'*S*,3'*R*,4'*R*
5	**122**	90	>25:1	38	2'*R*,3'*S*,4'*S*
6	**123**	78	>25:1	69	2'*R*,3'*S*,4'*S*
7	**124**	86	>25:1	49	2'*R*,3'*S*,4'*S*
8	**125**	86	>25:1	63	2'*R*,3'*S*,4'*S*

[a]Reactions were carried out with 0.11 mmol of **126** and 0.10 mmol of **127** in 0.5 mL of CH_2Cl_2 at room temperature for 24h, [b]Isolated yields after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis.

Therefore, squaramide **120a** was identified as the best catalyst for this asymmetric transformation.

1.9.12 Squaramide-catalyzed enantioselective Friedel-Crafts reaction of indoles with imines.[60]

The squaramide catalyzed asymmetric Friedel-Crafts reaction of indoles with *N*-tosyl imines has been successfully occurred to provide 3-indolyl methanamine product in 85-96% yields and 84-96% ee.

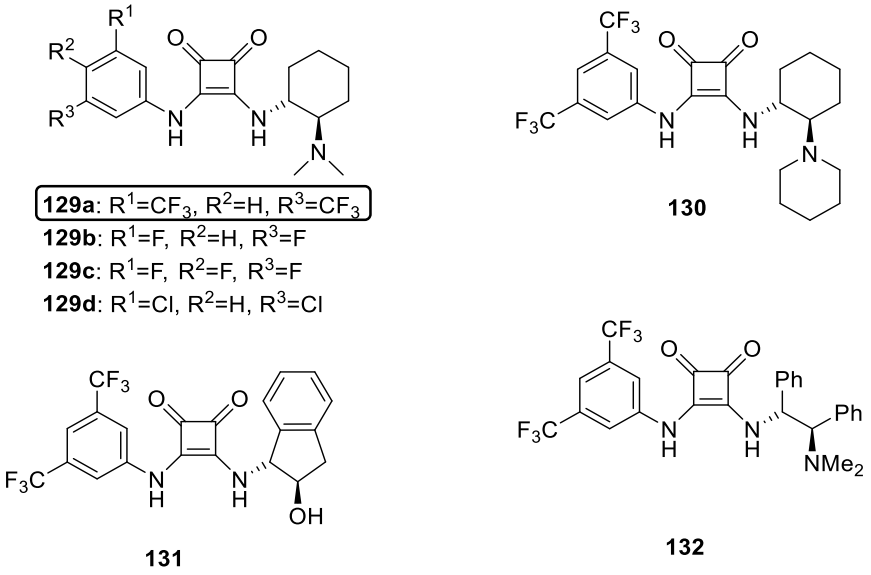
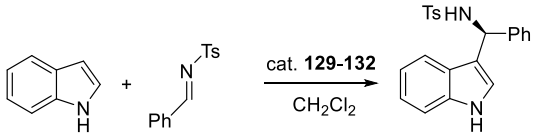


Figure 20. Structures of squaramide-based H-bonding catalysts.

Table 11. Enantioselective Friedel-Crafts reaction of indole **133** with *N*-tosyl imine **134** catalyzed by squaramide catalysts **129-132**.[a]



entry	catalyst	yield, %[b]	*ee*, %[c]	config.
1	**129a**	80	94	*S*
2	**129b**	48	84	*S*
3	**129c**	49	85	*S*
4	**129d**	50	86	*S*
5	**130**	24	4	*S*
6	**131**	90	0	*S*
7	**132**	81	92	*S*

[a]Reactions were carried out with **133** (1M), **134** (3.0 equiv.), catalyst (2.5 mol-%) in CH_2Cl_2 at 50 °C for 24 h. [b]Isolated yields, [C]Determined by chiral HPLC analysis (Chiralcel OD-H).

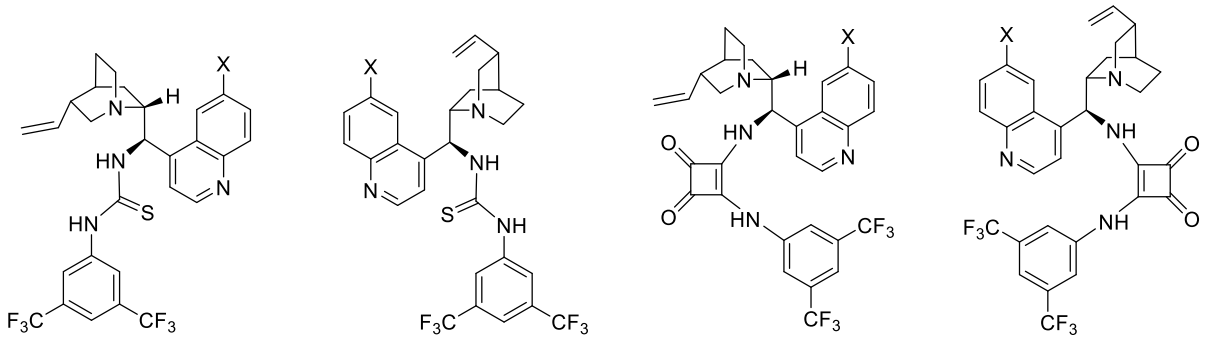
Three catalysts having the core structure of **129a** but differing in the substituents on the aryl ring were examined, and all were found to provide inferior results (table **11**, entries 2-4). Interestingly, catalyst **130** which provided excellent enantioselectivity the reported Michael addition of diphenyl phosphite to nitroalkenes, was a poor catalyst for this reaction, giving a nearly racemic product. The 1-amino-2-indanol containing squaramide **131** while it afforded the product in excellent yield with no

enantioselectivity. On the other hand, the 1,2-diphenylethylenediamine derived catalyst **132** was quite effective and gave the addition product in 81% yield and 92% ee. This study showed that catalyst **129a** to afford the best yield and enantioselectivity for this asymmetric Friedel-Crafts reaction.

1.9.13 Chiral squaramide-catalyzed enantioselective decarboxylative addition of β-keto acids to isatin imines.[61]

The enantioselective decarboxylative addition reaction of various β-keto acids with isatin imine derivatives has been described in here using an efficient quinine squaramide-catalyst. Through this methodology, various 3-substituted-3-amino-2-oxindole derivatives were synthesized in good yields (up to 91%) and good enantioselectivity (up to 98% ee) using 20 mol% of the organocatalyst. A wide range of substituted isatin imines and β -keto acids reacted well under the optimized reaction conditions.

The catalytic ability of cinchonine thiourea catalyst **136a**, cinchonidine thiourea **137a**, quinine thiourea **137b** and quinidine thiourea **136b** (Figure **21**) for the organocatalytic Mannich reaction of isatin imine with 3-oxo-3-phenylpropanoic acid in DCM in the presence of 4Å molecular sieves at room temperature (Table **9**, entries1-4).



136a: X=H; *epi*CNT
136b: X=OMe; *epi*QDT

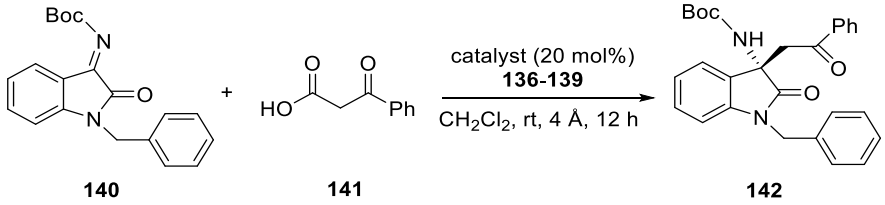
137a: X=H; *epi*CDT
137b: X=OMe; *epi*QNT

138a: X=H; *sq*CN
138b: X=OMe; *sq*QD

139a: X=H;*sq*CD
139b: X=OMe; *sq*QN

Figure 21. Structures of the organocatalysts.

Table 12. Enantioselective Decarboxylative Addition of Isatin Imine **140** to β-Keto acid **141**.[a]



140 **141** **142**

entry	catalyst	yield, %[b]	ee, %[C]	config.
1	**136a**	82	12	*R*
2	**136b**	92	1	*R*
3	**137a**	83	33	*S*
4	**137b**	87	22	*S*
5	**138a**	89	3	*R*
6	**138b**	86	4	*R*
7	**139a**	84	20	*S*
8	**139b**	89	41	*S*

[a]Reaction conditions: 0.1 mmol *N*-benzylisatin imine **140**, 0.12 mmol of 3-oxo-3-phenylpropanoic acid **141**, 4 Å molecular sieves (50 mg) and catalyst (20 mol%) in dry solvent (0.5 mL). [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis.

The desired adduct **142** was isolated in good to excellent yield (82-92%) with enantiomeric excesses from 1% to 33% (Table 9). After this cinchonine-squaramide **138a** and cinchonidine-squaramide **139a** were used as organocatalyst for this reaction which yielded the desired product **141** with ee of 3% (89% yield) and ee of 20% (84% yield), respectively (Table 9, entries 5 and 7). The use of quinidine-derived squaramide organocatalyst **138b** gave the product in 86% yield with 4% enantiomeric excess (Table 9, entry 6). But the use of quinine squaramide **139b** for the reaction of *N*-benzyl isatin imine with 3-oxo-3-phenylpropanoicacid provides **142** in 89% yield with 41% enantiomeric excess (Table 9, entry 8). So, among the different screened organocatalysts, the quinine-squaramide, **139b** was found to be the best catalyst providing **96** in 89% yield with 41% ee.

1.9.14 Organocatalytic enantioselective Strecker reaction of imines containing a thiazole moiety by using a cinchona-based squaramide catalyst.[62]

The first organocatalytic highly enantioselective Strecker reaction for the synthesis of α-amino nitriles that contain a thiazole moiety by using a cinchona-based squaramide catalysts has been described. The corresponding product **152** was obtained in good to excellent yields (up to 99%) with excellent enantioselectivities (up to 98% *ee*) by starting from aromatic-substituted imines.

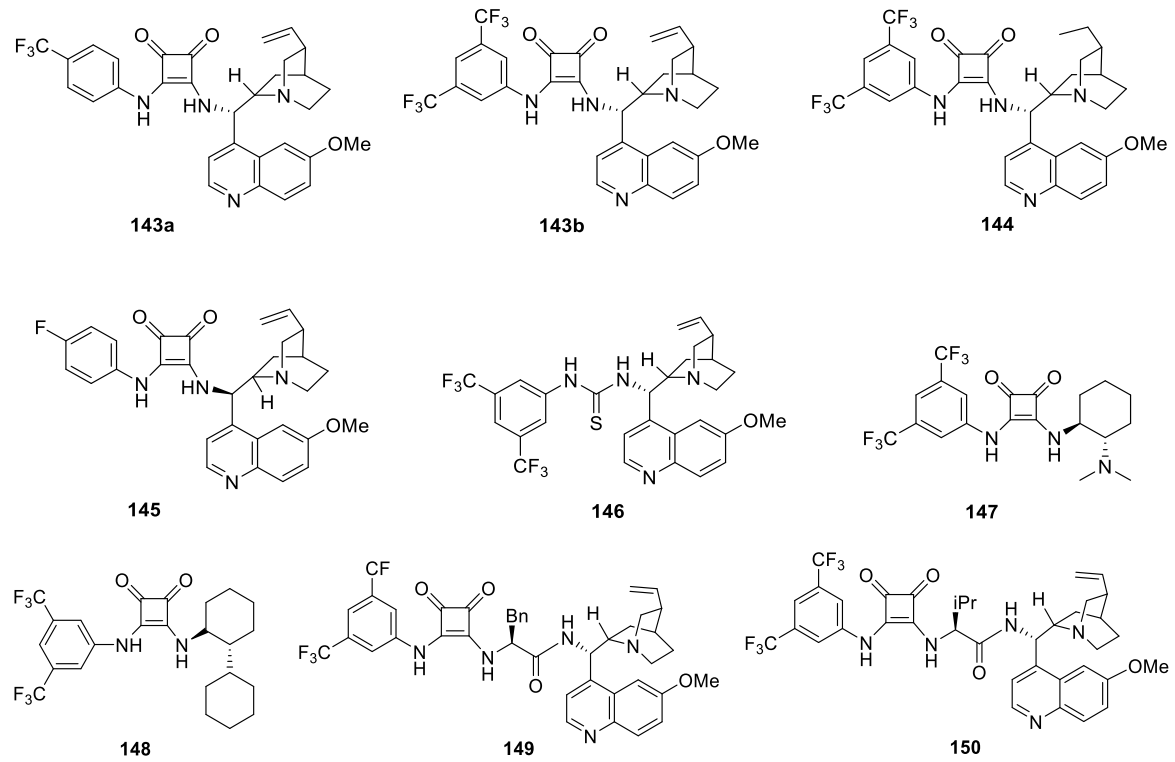
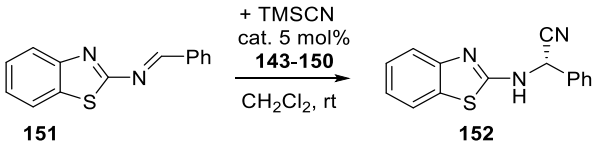


Figure 22. Structures of the organocatalysts.

Table 13. Screening of catalysts for the enantioselective Strecker reaction of imine **151** with TMSCN.[a]



entry	catalyst	time, h	yield, %[b]	*ee*,%[c]	config.
1	**143a**	24	90	45	*S*
2	**143b**	24	99	43	*S*
3	**144**	24	99	16	*S*
4	**145**	24	97	-38	*R*
5	**146**	24	99	23	*S*
6	**147**	24	99	16	*S*
7	**148**	24	90	9	*S*
8	**149**	24	85	59	*S*
9	**150**	24	87	76	*S*

[a]Reactions were carried out by using imine **151** (23.8 mg, 0.1 mmol) and TMSCN (19.8 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) at room temperature. [b]Isolated yield after purification by column chromatography. [c]Determined by HPLC analysis using Daicel Chiralpak AD-H column.

The addition reaction of trimethylsilyl cyanide (TMSCN) to imine **151** by using 5 mol% cinchona-based squaramide **143b** as the catalyst. This model reaction proceeded at room temperature for 24 h in CH_2Cl_2 successfully. Next, many other organocatalysts were prepared and evaluated in this model reaction. Cinchona-based squaramide catalysts **143**–**145** all gave product **152** in excellent yields with low to moderate enantioselectivities (16-45% ee, Table 13, entries 1-4). Quinine-based thiourea **146**

gave the corresponding adduct **152** in 99% yield with 23% ee (entry 5). Squaramides **147** and **148** which were derived from (1*S*, 2*S*)-1,2-diaminocyclohexane, afforded the product in high yields, but the enantioselectivities were also very low (entries 6 and 7). Two trifunctional squaramides **149**, **150** such as squaramide **149** derived from L-phenylalanine and quinine, was used to give the corresponding adduct **152** in 85% yield with 59% ee (entry 8). Squaramide **150** derived from L-valine and quinine, afforded a better yield and enantioselectivity (87% yield, 76% ee; entry 9).

1.9.15 Enantioselective α-amination of 1, 3-dicarbonyl compounds using squaramide derivatives as hydrogen bonding catalysts.[63]

Various squaramides were synthesized and successfully applied to be a highly effective catalyst for the enantioselective α-hydrazination of 1,3-dicarbonyl compounds with azodicarboxylate. All reactions can be conducted under mild conditions, with low catalyst loading, and afford the products in generally excellent yields and enantioselectivities. These results not only provide further demonstration of squaramides as highly effective hydrogen bonding catalysts but also calibration of their usefulness versus other hydrogen bond donor catalysts for the preparation of optically active nitrogen compounds.

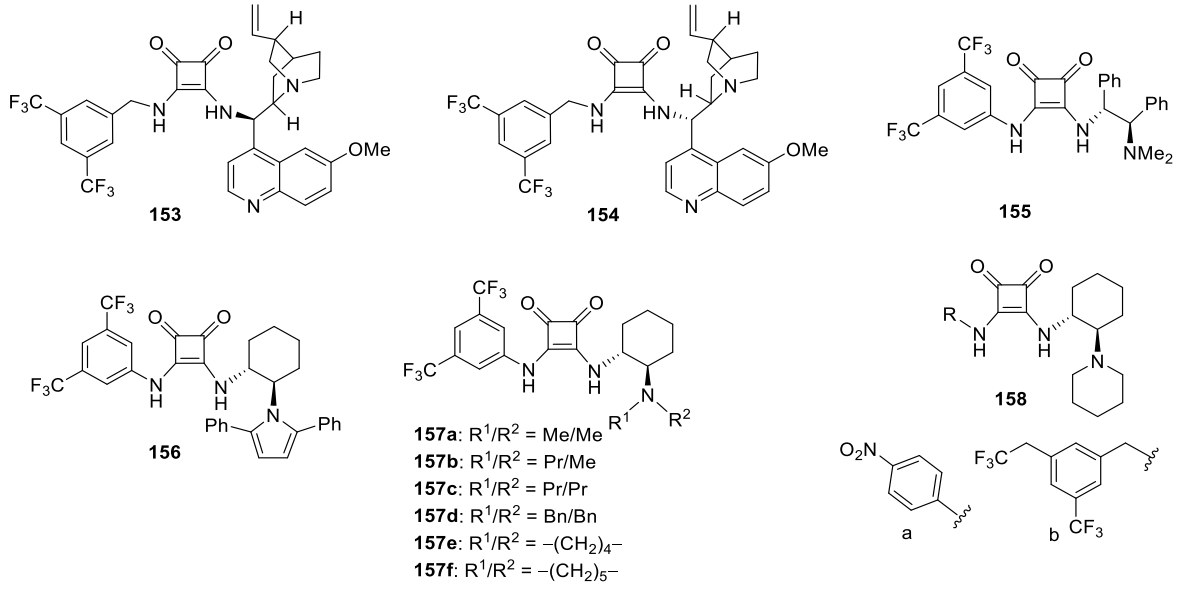
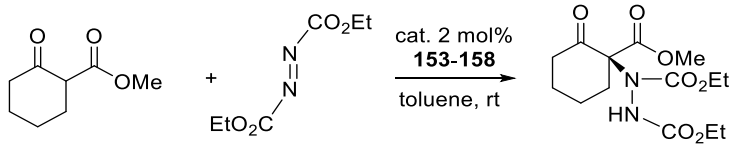


Figure 23. Structures of the organocatalysts.

Catalyst **153** and **154** are the pseudoenantiomeric cinchona alkaloid with an amine derived did not function well for the present transformation (entries 1, 2). Investigation of the effect of the tertiary amino group led to the discovery of another suitable catalyst **157e** which contains a piperidinyl group acts as the best catalyst for this asymmetric transformation.

Table 14. Screening of catalysts for the enantioselective α-amination of 1, 3-dicarbonyl compound.[a]



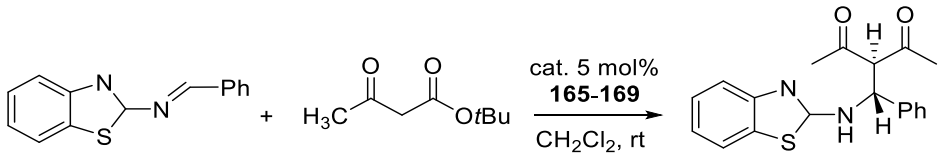
159 160 161

entry	catalyst	time, h	yield, %[b]	*ee*, %[c]	config.
1	**153**	15	58	10	*S*
2	**154**	15	65	29	*S*
3	**155**	60	71	5	*S*
4	**156**	48	22	0	*S*
5	**157a**	0.5	98	88	*S*
6	**157b**	1	83	69	*S*
7	**157c**	1	78	69	*S*
8	**157d**	30	81	32	*S*
9	**157e**	24	70	25	*S*
10	**157f**	0.5	90	89	*S*
11	**158a**	3	91	88	*S*
12	**158b**	2	84	66	*S*

[a]Reactions were performed with 0.75 mmol of **159** 0.5 mmol of **160** and 2 mol % of catalyst in 0.5 mL of toluene at rt, unless otherwise stated. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

1.9.16 Highly enantioselective Mannich reactions of imines with *tert*-butyl acetoacetate catalyzed by squaramide organocatalyst.[64]

The highly enantioselective Mannich reactions of imines bearing a benzothiazole moiety with *tert*-butyl acetoacetate, catalyzed by a cinchona-based squaramide organocatalyst have been described in here. The corresponding benzothiazole β-keto ester derivative **164** was obtained in high yield (up to 99%) and with excellent enantioselectivities (up to 98% ee).



162 163 164

Scheme 7. Squaramide-catalyzed enantioselective Mannich reaction of imine **162** with *tert*-butyl acetoacetate **163**.

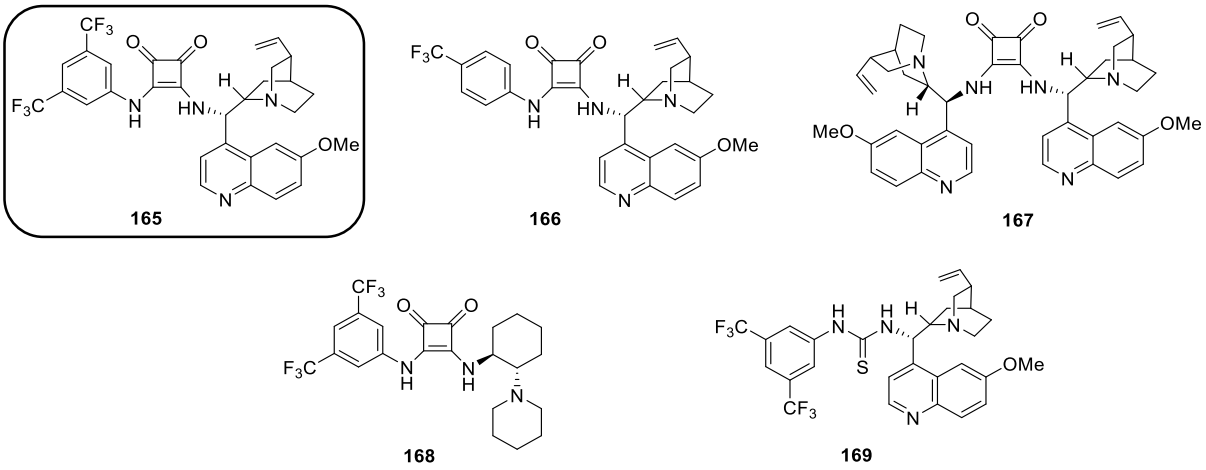


Figure 24. Structures of the organocatalysts.

Table 15. Screening of the organocatalysts for the enantioselective Mannich reaction of *tert*-butyl acetoacetate **163** with imine **162** [a]

entry	catalyst	yield, %[b]	*dr*[c]	ee, %[c]	config.
1	**165**	99	60:40	91/89	*R*,*S*
2	**166**	99	57:43	81/79	*R*,*S*
3	**167**	97	54:46	85/83	*R*,*S*
4	**168**	96	49:51	59/53	*R*,*S*
5	**169**	99	49:51	86/82	*R*,*S*

[a]Reaction conditions: imine **162** (47.6 mg, 0.2 mmol) and *tert*-butyl acetoacetate **163** (0.2 mmol) in CH_2Cl_2 (1 mL) at room temperature. [b]Isolated yield after column chromatography purification., [c]Determined by chiral HPLC analysis. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis using Daicel Chiralpak IA column.

The asymmetric Mannich reaction was performed in the presence of 5 mol% catalyst **165** in CH_2Cl_2 for 24 h at room temperature, and the corresponding products were obtained in excellent yield (99%) and with high enantioselectivities (91% and 89% ee) (Table 1, entry 1). Then other four squaramide catalysts **166-169** (Fig. 24) were evaluated with the same conditions on this reaction. When mono-CF_3 substituted quinine-based squaramide catalyst **166** was used in this reaction, the corresponding product **164** was obtained in excellent yield (99%) and with high enantioselectivities (81% and 79% *ee*, 57:43 *dr*) (Table 2, entry 2). After the completion of catalysts screening it was found that squaramide catalyst **165** was the best catalyst for the Mannich reaction of imines bearing a heterocycle moiety with *tert*-butyl acetoacetate.

1.9.17 Organocatalytic enantioselective construction of isatin-derived *N*-alkoxycarbonyl 1,3-aminonaphthols via the aza-Friedel craft reaction using sterically encumbered hydrocarbon-substituted quinine-based squaramide.[65]

A new 2-adamantyl-substituted quinine-derived squaramide catalyst is synthesized and successfully applied on the facile synthesis of chiral naphthoxazepine precursors via the aza-Friedel-Crafts reaction of *N*-alkoxycarbonyl isatin ketimines with naphthol using. The reaction afforded the chiral-tetra substituted 3-amino-2oxindoles with excellent enantioselectivity (> 99% ee) and quantitative yields.

This methodology is important for the efficient preparation of sterically hindered hydrocarbon substituents in squaramide organocatalysts.

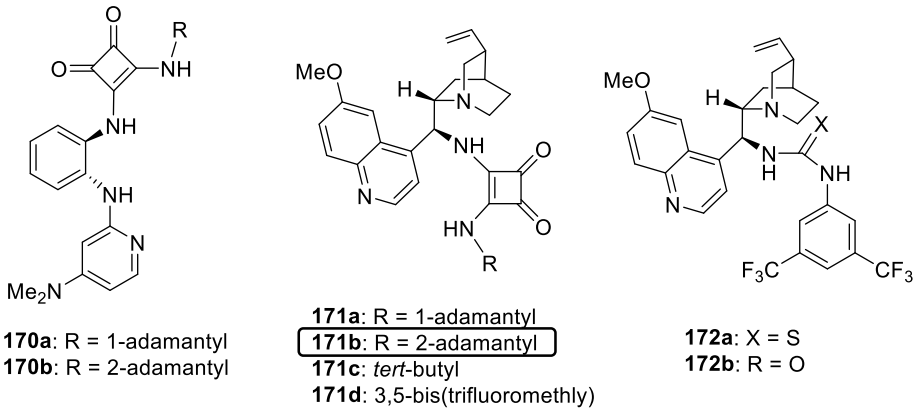
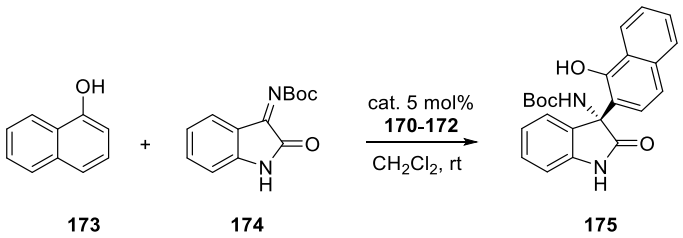


Figure 25. Structures of the organocatalysts

Table 16. Screening of the organocatalysts for the enantioselective construction of isatin-derived *N*-alkoxycarbonyl 1,3-aminonaphthols.[a]



entry	catalyst	time, h	yield, %[b]	ee, %[c]	config.
1	**170a**	60	68	-8	*S*
2	**170b**	60	94	-7	*S*
3	**171a**	19	71	60	*R*
4	**171b**	16	99	90	*R*
5	**171c**	19	60	60	*R*
6	**171d**	13	98	70	*R*
7	**172a**	19	71	44	*R*
8	**172b**	19	81	21	*R*

[a]Reaction conditions: imine **173** (0.055 mmol, 1.1 eq.) and **174** (0.050 mmol, 1 eq.) in CH_2Cl_2 (0.5 mL) at room temperature. [b]Isolated yield after column chromatography purification., [c]Determined by chiral HPLC analysis.

From the above study, it was found that catalyst **171b** can act as the best catalyst for this asymmetric transformation.

1.9.18 Squaramide-catalysed enantioselective Mannich reaction of imines bearing a heterocycle with malonates.[66]

Cinchona-based squaramide organocatalysts have been developed and successfully applied on the enantioselective Mannich reaction of imines bearing a heterocycle with malonates afforded the β-amino ester derivatives containing a heterocycle moiety in high yields (up to 99%) and excellent

enantioselectivities (up to 98%). The imines with an electron-withdrawing group afforded the adducts with better yields than those bearing an electron-donating group in this reaction.

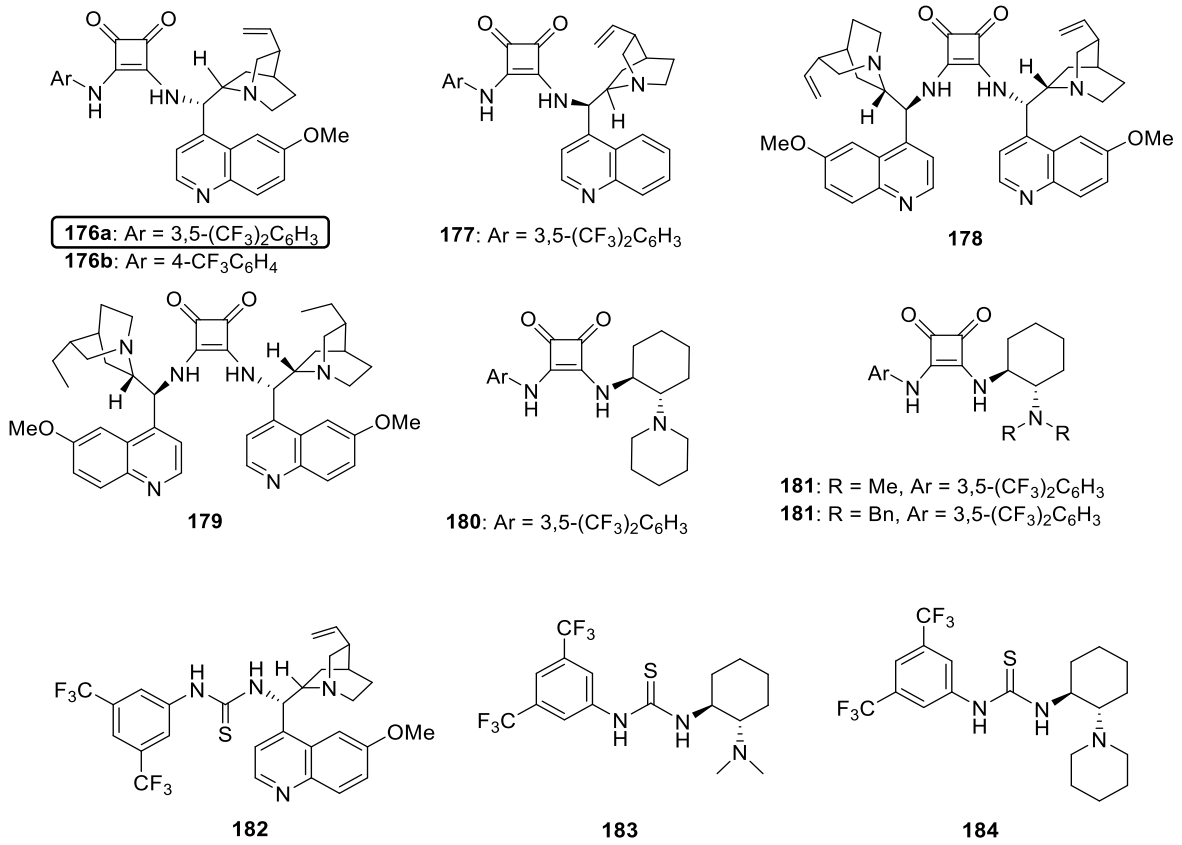
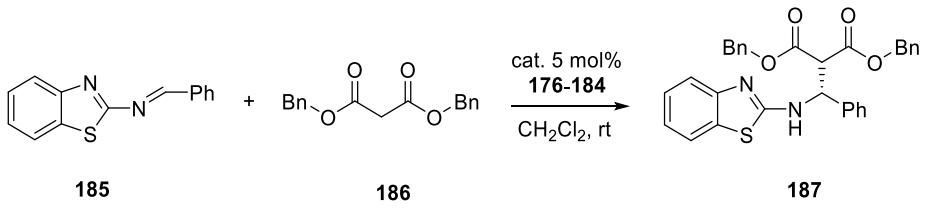


Figure 26. Screened organocatalysts.

Table 17. Screening of the organocatalysts for the enantioselective Mannich reaction of dibenxyl malonate **186** with imine **185**.[a]



entry	catalyst	time, h	yield, %[b]	ee, %[c]	config.
1	**130a**	24	99	94	*R*
2	**130b**	24	92	86	*R*
3	**131**	24	97	-76	*S*
4	**132**	24	93	55	*R*
5	**133**	24	99	63	*R*
6	**134**	24	91	84	*R*
7	**135**	24	90	94	*R*
8	**136**	24	38	0	*R*
9	**137**	24	99	99	*R*
10	**138**	24	99	91	*R*
11	**139**	24	99	92	*R*

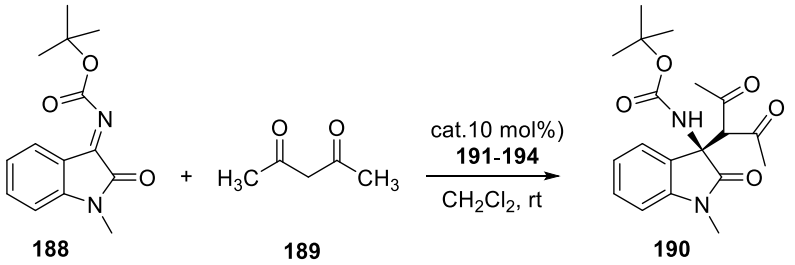
[a]Reaction conditions: imine **185** (0.20 mmol) and dibenzyl malonate **186** (0.60 mmol) in CH_2Cl_2 (2 mL) at room temperature. [b]Isolated yield after column chromatography purification., [c]Determined by chiral HPLC analysis using Daicel Chiralpak IB column.

From the catalysts screening, it was found that catalyst **176a** can act as the best catalyst for this asymmetric transformation.

1.9.19 Asymmetric Mannich reaction: highly enantioselective synthesis of 3-amino-oxindoles via chiral squaramide based H-bond donor catalysis.[67]

The catalytic activity of chiral squaramide catalysts for asymmetric Mannich reaction of 1,3-diketones with isatin (*N*-Boc) ketimines in dichloromethane at room temperature has been reported. The corresponding 3-substituted 3-amino-oxindole derivatives were obtained in high yields and excellent enantioselectivities under mild reaction conditions with low catalyst loading (3 mol %). This method affords valuable and simple access to enantiomerically pure 3-substituted-3-aminoxindole derivatives.

Table 18. Enantioselective Mannich reaction of *N*-Boc ketimine **188** to pentane-2,4-dione **189**.[a]



188 189 190

entry	catalyst	time, h	yield, %[b]	ee, %[c]	config.
1	**191a**	4	92	93	*S*
2	**191b**	4	94	95	*S*
3	**191c**	4	92	95	*S*
4	**192a**	5	91	92	*S*
5	**192b**	5	93	94	*S*
6	**193a**	4	95	92	*S*
7	**193b**	4	96	97	*S*
8	**194a**	4	92	90	*R*
9	**194b**	4	94	93	*R*

[a]Reaction conditions: *N*-Boc **188** (0.25 mmol) and pentane-2,4-dione **189** (0.30 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. [b]Isolated yield after column chromatography purification., [c]Determined by chiral HPLC analysis using Daicel Chiralpak IC column.

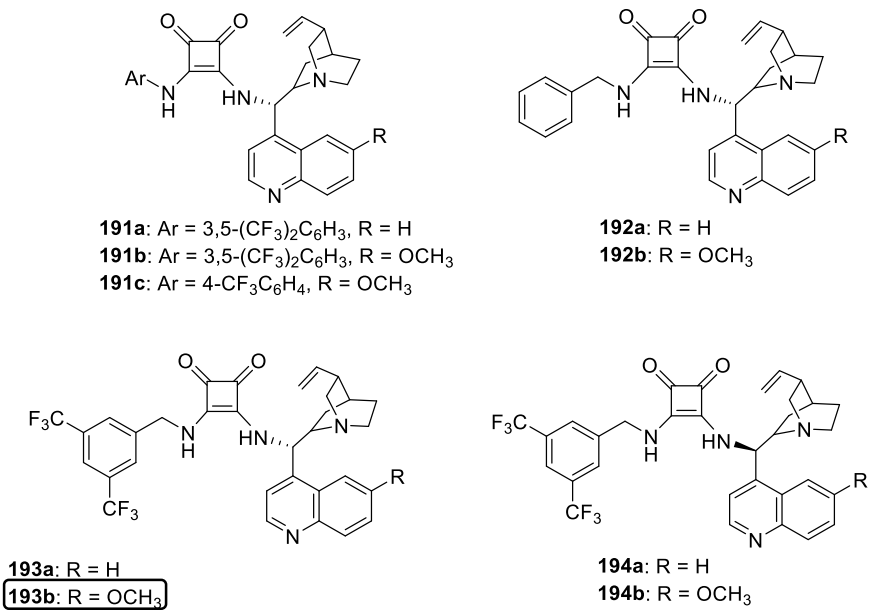


Figure 27. Structures of squaramide based bifunctional catalysts

From the catalysts screening, it was found that catalyst **193b** can act as the best catalyst for this asymmetric transformation.

1.9.20 References

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Chapter 2

Synthesis of cinchona alkaloid-derived squaramide polymers as bifunctional chiral organocatalysts for the enantioselective Michael addition of β-ketoesters to nitroolefins

2.1 INTRODUCTION

Cinchona alkaloids are easily obtained from the bark of the cinchona tree, and have various functionalities including a quinuclidine tertiary nitrogen, a secondary alcohol, a quinoline ring, and a terminal olefin in their structure. Cinchona alkaloids and their derivatives have been widely used as chiral organocatalysts in asymmetric synthesis.[1-5] Cinchona-substituted squaramides have been shown to be highly efficient chiral organocatalysts in asymmetric Michael-type reactions.[6] They are easily prepared from 9-amino derivatives of cinchona alkaloids.[7] The acidic NH of the squaramide can act as a H-bond donor, whereas the tertiary nitrogen of the quinuclidine of cinchona alkaloids may act as both a H-bond acceptor and a base in the asymmetric Michael addition[8-20] The asymmetric Michael reaction is an essential C–C bond forming reaction, and can be applied to the synthesis of various important chiral building blocks. Cinchona squaramide derivatives have shown high catalytic activity in asymmetric Michael reactions. For example, Rawal et al. reported that cinchona squaramides showed excellent catalytic activity in the enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkenes.[17]

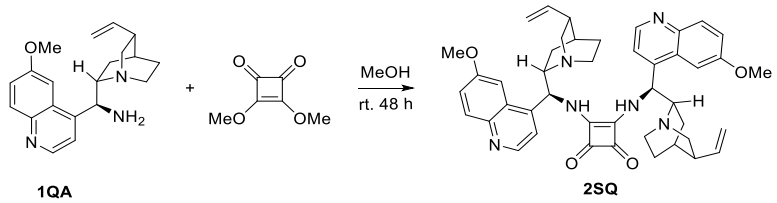
Development of polymer-immobilized chiral catalysts is always attractive due to their easy recovery and reuse. Insoluble polymeric catalysts are necessary for the application of the catalysts to continuous flow systems. Conventional polystyrene supported cinchona squaramide organocatalysts have been prepared and applied in such systems.[21, 22] However, dimeric cinchona squaramides have not yet been attached to the polymer side chain. More interestingly, polymers with a chiral backbone, using the cinchona squaramide structure as the repeat unit, have not been synthesized. We have reported the syntheses of main chain type chiral polymers containing cinchona-based organocatalysts using a variety of polymerization techniques, including the Menshutkin reaction,[23] ether formation,[24] Mizoroki-Heck coupling,[25] and ion exchange.[26,27] These polymerization reactions are all suitable for cinchona-based polymer synthesis. The chiral polymers prepared by these reactions have proven to be excellent catalysts for asymmetric transformations. In some cases, even higher stereoselectivities compared to those of the original monomeric catalysts were achieved by using the chiral polymeric catalysts, mainly due to their specific conformation created by the chiral main chain polymers. From these results, we realized that polymeric cinchona alkaloid derivatives could play a significant role in asymmetric catalysis. Since cinchona alkaloids contain a double bond in their structure, we proposed that this functionality may be suitable for Mizoroki-Heck coupling polymerization.[28-30] Although some achiral polymers have been already synthesized by using the Mizoroki-Heck reaction,[31] there are no examples of chiral polymer synthesis using this method except for our previous report[25] We have prepared dimeric cinchona

squaramide organocatalysts, which were easily polymerized with aromatic diiodides under the conditions of the Mizoroki-Heck coupling reaction. Herein, we report the synthesis of chiral cinchona squaramide polymers and their application as catalysts in the enantioselective Michael addition of β-ketoesters to nitroolefins.

2.2 RESULTS AND DISCISSION

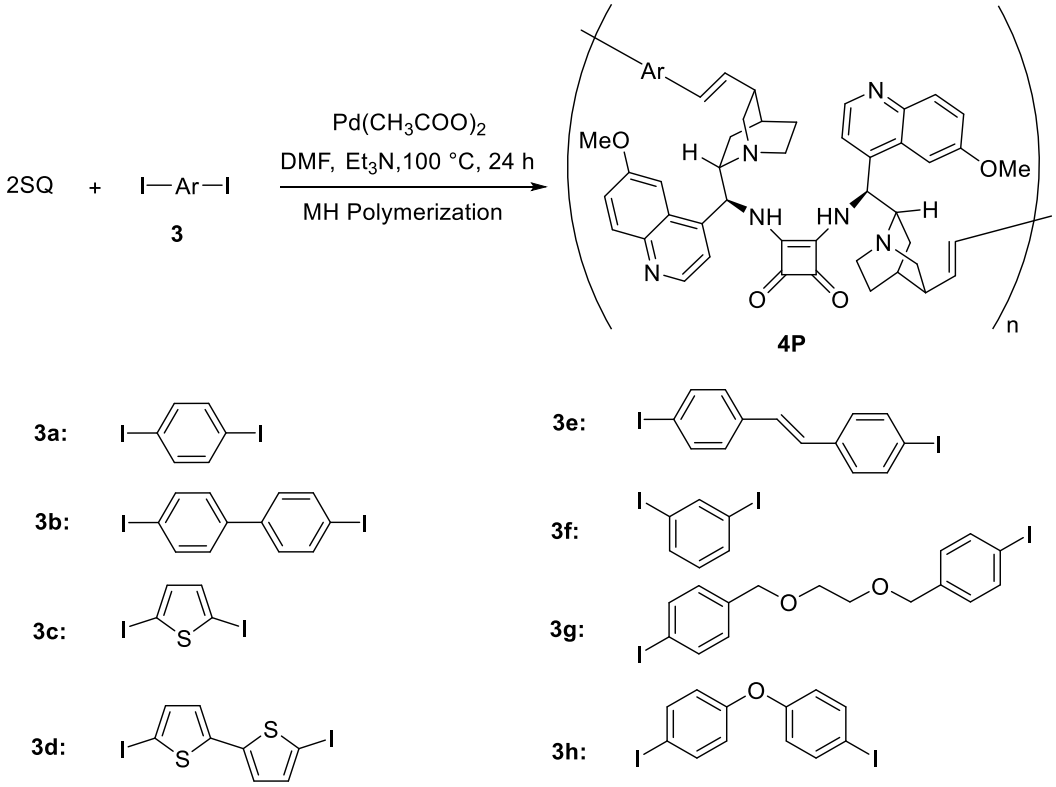
2.2.1 Synthesis of chiral polymers of cinchona alkaloid-substituted squaramide

Dimeric cinchona squaramide **2SQ** possesses two terminal double bonds, which is ideal for Mizoroki-Heck (MH) polymerization. Starting from quinine, the 9-amino derivative **1QA** was prepared and allowed to react with dimethylsquarate to give **2SQ** in 94% yield (Scheme **1**).[6] The double bonds of **2SQ** were able to react with aromatic diiodides such as diiodobenzene under the conditions of the Mizo-



Scheme 1. Preparation of cinchona-substituted squaramide, **2SQ**

roki-Heck reaction. As shown in Scheme **2**, repetitive Mizoroki-Heck reactions occurred between dimeric cinchona squaramide **2SQ** and various aromatic diiodides to give chiral polymers **4P**. In our previous paper, we reported the Mizoroki-Heck polymerization of cinchonidinium dimers.[32] We found that the previously reported reaction conditions were suitable for the synthesis of the chiral squaramide polymers (Scheme **2**). Polycondensation of squaramide **2SQ** and aromatic diiodides **3** in the presence of $Pd(OAc)_2$ gave the corresponding chiral polymers **4P** in high yields (Table **1**). Mizoroki-Heck polymerization using aromatic diiodides containing an iodophenyl structure proceeded smoothly to give the corresponding polymers **4P**. However, heterocyclic diiodides containing a thiophene ring failed to polymerize under these reaction conditions, even at elevated reaction temperatures and higher catalyst loading (entries 3–6). Mizoroki-Heck reactions of diiodothiophene derivatives may require different reaction conditions.[33,34] The chiral polymers obtained were soluble in polar solvents such as DMF and DMSO. In other commonly used organic solvents including CH_2Cl_2, $CHCl_3$, MeOH, EtOAc, and THF, the polymers were insoluble. Various low-molecular-weight cinchona squaramide organocatalysts have been synthesized and successfully used as catalysts for asymmetric Michael additions.[35]



Scheme 2. Synthesis of cinchona alkaloid-derived squaramide chiral polymers **4P** by Mizoroki-Heck coupling.

Figure 1. Image of squaramide, **SQ** and corresponding polymer, **4PaSQ**

Figure 2. Suspension of polymer, **4PaSQ** in ether.

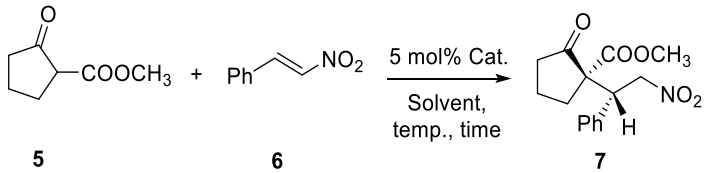
2.2.2 Catalytic performance of the cinchona squaramide polymers, 4P

In order to evaluate the catalytic activity of the chiral cinchona squaramide polymers **4P**, the asymmetric Michael addition of methyl 2-oxocyclopentanecarboxylate **5** to *trans*-β-nitrostyrene **6** was chosen as a model reaction (Scheme **3**). Firstly, we examined the dimeric cinchona squaramide **2SQ** as an organocatalyst in the asymmetric Michael reaction. Although unsymmetrically substituted cinchona squaramides have been shown to be superior organocatalysts compared with symmetrical dimeric cinchona squaramides,[36] dimeric organocatalyst **2SQ** showed excellent performance in the asymmetric reaction. The reaction between **5** and **6** with **2SQ** in CH_2Cl_2 at room temperature proceeded smoothly to give the Michael adduct **7** in 95% yield with 91% ee (Table 2, entry 1). A high level of diastereoselectivity (79:1) was also attained with this catalyst. This result encouraged us to apply the corresponding polymeric catalysts in the same reaction. Firstly, we trialled polymeric catalyst **4PaSQ**. Although **4PaSQ** was totally insoluble in CH_2Cl_2, the reaction occurred at room temperature to give the corresponding adduct in 71% yield with 97% ee (entry 2). Due to the heterogeneous system, a longer reaction time was required for the polymeric catalyst. Interestingly, the enantioselectivity obtained with the polymeric catalyst **4PaSQ** was higher than that obtained with the corresponding low-molecular-weight catalyst **2SQ**. The polymeric chiral organocatalyst may provide a suitable microenvironment for an efficient asymmetric reaction. The choice of solvent also influenced the catalytic activity and the enantioselectivity of the reaction as shown in Table **2**.

Table 1. Synthesis of chiral squaramide polymers **4P** from **2SQ** and diiodides **3**.

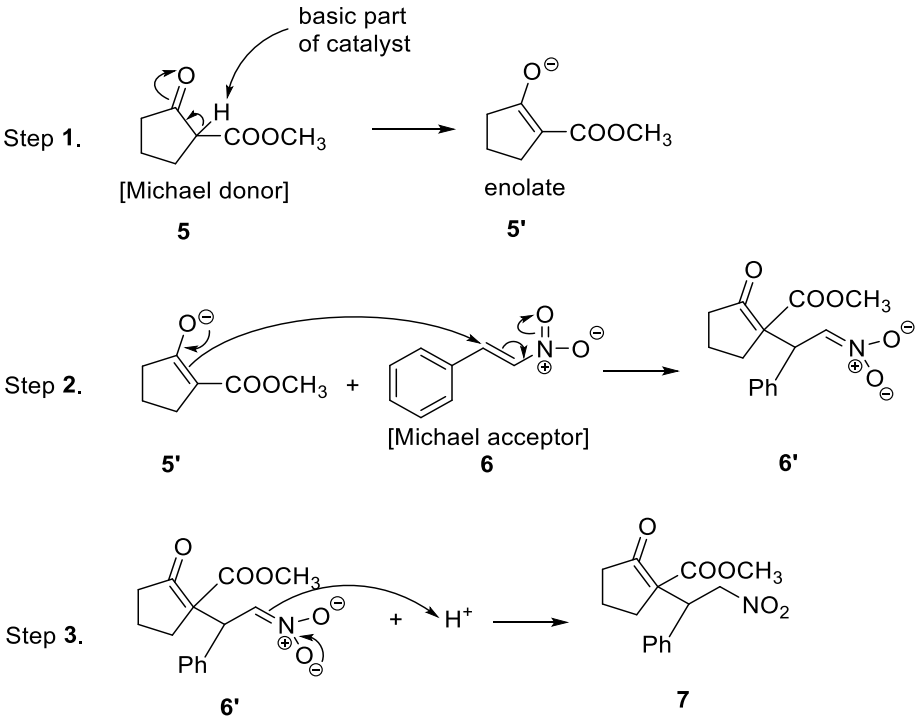
entry	diiodides	polymer	yield, %	M_n[b]	M_w[b]	M_w/M_n[b]
1	**3a**	**4PaSQ**	97	7800	8400	1.07
2	**3b**	**4PbSQ**	98	5400	5700	1.05
3	**3c**	**4PcSQ**	nr	nd	nd	nd
4	**3d**	**4PdSQ**	nr	nd	nd	nd
[c]5	**3d**	**4PdSQ**	nr	nd	nd	nd
[d]6	**3d**	**4PdSQ**	nr	nd	nd	nd
7	**3e**	**4PeSQ**	>99	4300	5000	1.16
8	**3f**	**4PfSQ**	80	4500	4800	1.06
9	**3g**	**4PgSQ**	>99	4100	4500	1.09
10	**3h**	**4PhSQ**	>99	3900	4200	1.07

[a]Polymerized in DMF at 100 °C for 24 h.
[b]Determined by SEC using DMF as a solvent at a flow rate of 1.0 mL min^{-1} at 40 °C (polystyrene standard).
[c]Polymerized at 120 °C, [d]Using 12 mg of $Pd(OAc)_2$.



Scheme 3. Asymmetric Michael addition of methyl 2-oxocyclopentanecarboxylate **5** to *trans*-β-nitrostyrene **6**.

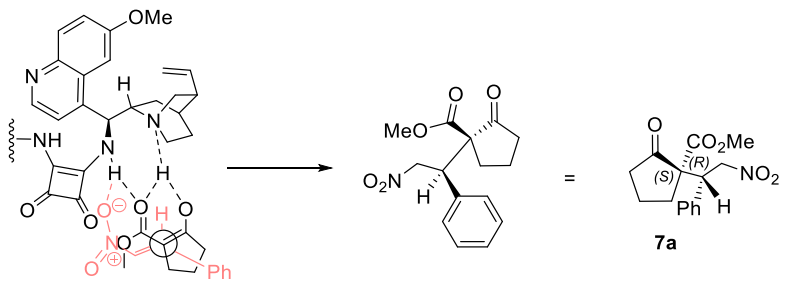
In case of this above asymmetric Michael addition reaction, the Michael donor, methyl 2-oxocyclopentanecarboxylate **5** is deprotonated by the bifunctional squaramide chiral polymeric catalyst to form the enolate (step **1**). Then formation of a new C–C bond is occurred by the reaction of enolate and a Michael acceptor *trans*-β-nitrostyrene **6**. Finally, addition of a proton which is formed from the deprotonation process to give the desire addition asymmetric product **7**.



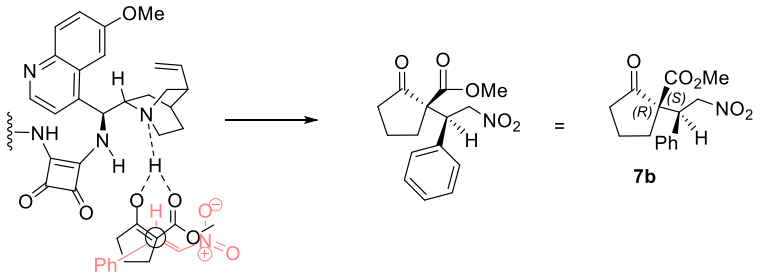
Scheme 4. General reaction mechanism of squaramide catalyzed asymmetric Michael Addition reaction.

There are four possible isomers are formed in the asymmetric Michael addition reaction of methyl 2-oxocyclopentanecarboxylate **5** to *trans*-β-nitrostyrene **6**. The expected transition states of the asymmetric reaction between **5** and **6** with quinine-based squaramide catalyst. The transition state leading to **7a** may be the most stable among them.

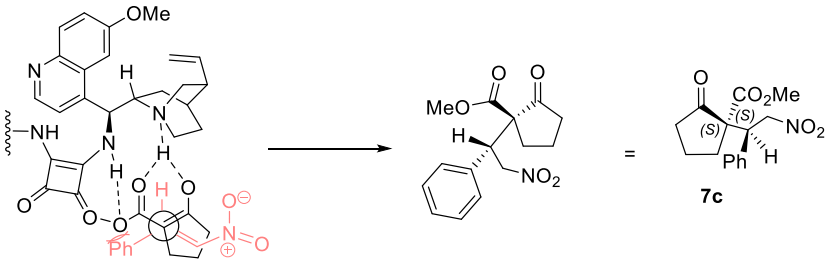
1 Major diastereomer (major enantiomer)



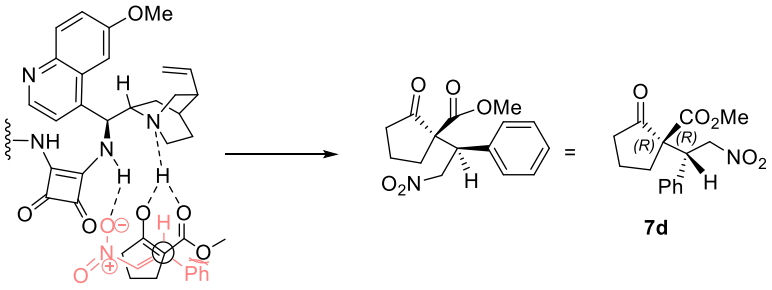
2 Major diastereomer (minor enantiomer)



3 Minor diastereomer (major enantiomer)



4 Minor diastereomer (minor enantiomer)



When the reaction was performed in methanol, the product was obtained in good yield but with a diminished enantioselectivity (entry 3). Use of polar, aprotic solvents such as THF and EtOAc gave comparable results to CH_2Cl_2, with Michael adduct **7** being provided in 93% and 96% ee respectively (entries 4 and 5). In toluene, however, a much decreased enantioselectivity was observed (entry 6). Lowering the reaction temperature to –10 °C gave no reaction in MeOH, CH_2Cl_2 and ethyl acetate, even after a longer reaction time (entries 7–9). We therefore chose dichloromethane and ethyl acetate as the ideal solvents for the reaction, as Michael adduct **7** was produced with the highest enantioselectivity and diastereoselectivity in these solvents (entries 2 and 6).

We then trialled polymeric catalysts **4PbSQ**-**4PhSQ** containing differing linker structures to see the effect of the polymer structure on the stereoselectivity of the reaction. The results of the asymmetric reaction using these polymeric catalysts are summarized in Table **3**. Catalyst **4PbSQ** (entries 4, 5, and 7), with a biphenyl linker, showed similar performance to that of **4PaSQ** (entries 2, 3, and 5 in Table2). In ethyl acetate, **4PbSQ** was still active at –10 °C (entry 8). Catalyst **4PfSQ** uses a meta-substituted

phenyl linker, which could result in a different polymer main chain conformation from that of **4PaSQ**. This may explain why a longer reaction time was required to complete the reaction with **4PfSQ** which formed the product in a slightly reduced enantioselectivity and diastereoselectivity (entry 10).

Table 2. Optimization of reaction conditions: solvent screening for the enantioselective Michael addition of β-ketoester **5** to nitroolefin **6**.

entry	catalyst	solvent	temp.,°C	reaction time, h	yield ,%[b]	*dr*[c]	*ee*, %[c]
1	**2SQ**	CH_2Cl_2	rt.	2	95	79:1	91
2	**4PaSQ**	CH_2Cl_2	rt.	30	71	28:1	97
3	**4PaSQ**	MeOH	rt.	16	86	32:1	91
4	**4PaSQ**	THF	rt.	36	77	23:1	93
5	**4PaSQ**	EtOAc	rt.	22	66	20:1	96
6	**4PaSQ**	Toluene	rt.	43	55	16:1	88
7	**4PaSQ**	MeOH	-10	41	0	nd	nd
8	**4PaSQ**	CH_2Cl_2	-10	42	0	nd	nd
9	**4PaSQ**	EtOAc	-10	40	0	nd	nd

[a]Reactions were carried out with **5** (0.50 mmol), *trans*-β-nitrostyrene **6** (0.55 mmol) and the monomeric and polymeric catalyst (5 mol%) in 2.5 mL solvent.
[b]Isolated yield of product after column chromatography. [c]Determined by chiral HPLC (Chiralcel OD-H).

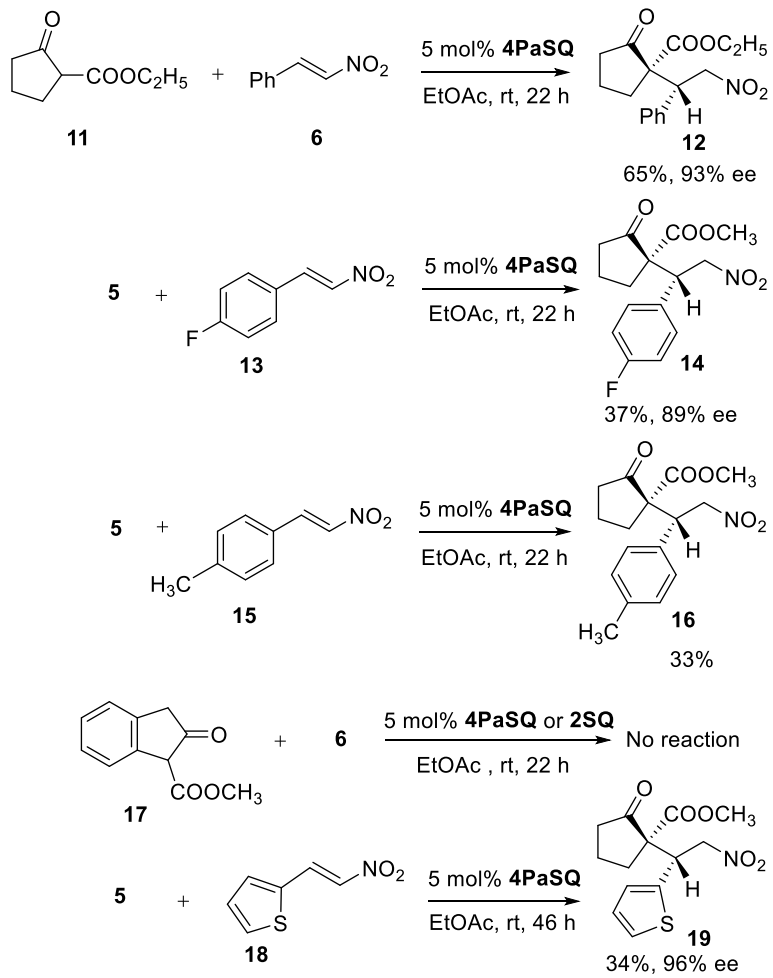
Table 3. Optimization of reaction conditions: catalyst screening for the enantioselective Michael addition of β-ketoester **5** to nitroolefins **6**.

entry	catalyst	solvent	temp., °C	reaction time, h	yield, %[b]	*dr*[c]	*ee*, %[c]
[d]1	**4PaSQ**	MeOH	rt.	16	66	54:1	95
[e]2	**4PaSQ**	MeOH	rt.	15	74	43:1	94
[f]3	**4PaSQ**	MeOH	rt.	19	78	54:1	94
4	**4PbSQ**	CH_2Cl_2	rt.	30	63	34:1	91
5	**4PbSQ**	MeOH	rt.	16	56	34:1	93
[g]6	**4PbSQ**	MeOH	rt.	16	52	43:1	99
7	**4PbSQ**	EtOAc	rt.	22	76	18:1	95
8	**4PbSQ**	EtOAc	-10	29	54	19:1	96
9	**4PeSQ**	EtOAc	rt.	21	60	17:1	90
10	**4PfSQ**	EtOAc	rt.	30	60	13:1	94
11	**4PgSQ**	EtOAc	rt.	20	63	21:1	95
12	**4PhSQ**	EtOAc	rt.	20	69	22:1	92

[a]Reactions were carried out with **5** (0.50 mmol), *trans*-β-nitrostyrene **6** (0.55 mmol) and polymeric catalyst (5 mol%) in 2.5 mL solvent.
[b]Isolated yield of product after column chromatography.
[c]Determined by chiral HPLC (Chiralcel OD-H).
[d]The recovered polymer catalyst **4PaSQ** (from entry 3, Table 2) was used.
[e]The recovered polymer catalyst **4PaSQ** (from entry 1, Table 3) was used.
[f]The recovered polymer catalyst **4PaSQ** (from entry 2, Table 3) was used.
[g]The recovered polymer catalyst **4PbSQ** (from entry 5, Table 3) was used.

A flexible linker structure as in **4PgSQ** gave no significant influence on the catalytic activity and the stereoselectivity (entry 11). Using a stilbene linker (**4PeSQ**) or a diphenyl ether linker (**4PhSQ**) gave the Michael adduct in somewhat lower enantioselectivities (entries 9, 12). Since the chiral polymers developed in this study were insoluble in commonly used organic solvents as mentioned before, the reaction occurred in a heterogeneous system. After the reaction was completed, the polymers were easily separated and recovered by simple filtration. After washing of the polymer with organic solvents the recovered polymeric catalyst was able to be reused for the following reaction. We therefore examined the recyclability of the polymeric catalysts. Recovered **4PaSQ** and **4PbSQ** were used as catalysts in the same reaction (entries 1–3, 6). In both cases, enantio- and diastereoselectivities obtained with the recovered polymeric catalysts were higher than those of the original experiment. In the case of the recovered polymeric catalyst **4PbSQ**, an enantioselectivity of 99% was attained for the major diastereomer of the Michael adduct (entry 6).

We further applied the chiral polymers as catalysts of the asymmetric Michael addition for other substrates. In the presence of the chiral polymer **4PaSQ**, the reaction between ethyl 2-oxocyclopentanecarboxylate **11** and *trans*-β-nitrostyrene in ethyl acetate occurred smoothly to give the



Scheme 4. Substrates scope of enantioselective Michael additions of β-ketoesters to nitroolefins.

corresponding Michael adduct **12** with moderate yield and high enantioselectivity (93% ee) (Scheme **4**). 4-Fluoro-*trans*-β-nitrostyrene **13** and 4-methyl-*trans*-β-nitrostyrene **15** also reacted with **5** in the presence of **4PaSQ** to give adducts **14** and **16** respectively. Unfortunately, in the case of **16**, stereoselectivities of the reaction were not determined due to difficulties of peak separation of the stereoisomers of **16** in HPLC analysis. No reaction was observed with **17** using both polymeric (**4PaSQ**) and monomeric (**2SQ**) catalysts. 2-thiophene derivative **18** reacted with **5** to give the corresponding Michael adduct **19** in lower yield (34%) with 96% ee (Scheme **4**).

2.3 CONCLUSIONS

In conclusion, we have successfully synthesized novel chiral polymers **4P** by Mizoroki-Heck (MH) polymerization, which contain a cinchona-based squaramide structure in their main chain repeat unit. The chiral polymers acted as excellent catalysts for the enantioselective Michael addition of β-ketoesters to nitroolefins. The asymmetric reaction proceeded smoothly to give the Michael adduct in high levels of enantioselectivity and diastereoselectivity. Insolubility of the chiral polymeric catalysts enabled us to separate the catalysts from the reaction mixture by simple filtration. The recovered catalysts maintained their catalytic activities and stereoselectivities.

2.4 EXPERIMENTAL

2.4.1 Materials and general considerations

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. Reactions were monitored by thin-layer chromatography using pre-coated silica gel plates (Merck 5554, 60F254). Column chromatography was performed using a silica gel column (Wakogel C-200, 100–200 mesh). 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 $CDCl_3$ for ^{13}C NMR. Chemical shifts were reported in ppm using TMS as a reference, and the *J* values were recorded in Hertz. IR spectra were recorded on a JEOL JIR-7000 FTIR spectrometer and are reported in cm^{-1}. High-performance liquid chromatography (HPLC) was performed with a Jasco HPLC system composed of a DG-980-50 three-line degasser, a PU-980 HPLC pump, and a CO-965 column oven equipped with a chiral column (Chiralpak OD-H, Daicel) with hexane/2-propanol as the eluent. A Jasco UV-975 UV detector was used for peak detection. Size exclusion chromatography (SEC) was performed using a Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as the carrier solvent at a flow rate of 1.0 mL min-1 at 40 °C. Two polystyrene gel columns of bead size 10 μm were used. A calibration curve was made to determine the number average molecular weight (Mn) and molecular weight distribution (M_w/M_n) values with polystyrene standards. Optical rotation was recorded using a JASCO DIP-149 digital polarimeter using a 10 cm thermostatted microcell.

2.4.2 General procedure for the synthesis of cinchona-derived squaramide, 2SQ

Dimethylsquarate (439.4 mg, 3.09 mmol) was added to a stirred solution of the epi-aminoquinine **1QA** (2.50 g, 7.73 mmol) in methanol at room temperature. The reaction was monitored by TLC. After stirring for 48 h at room temperature under argon gas, the precipitate was filtered, washed with cold methanol (2–3 times), and then dried in vacuo to afford the crude squaramide as a white solid. The solid compound was purified by silica gel (100–200 mesh) column chromatography with DCM/MeOH = 5/5 as an eluent to give the desired compound **2SQ** in 94% yield as white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.78 (d, J = 4.2 Hz, 1H), 7.98 (d, J = 9.6 Hz, 1H), 7.80 (s, 1H), 7.57 (s, 1H), 7.46 (dd, J = 2.0 and 9.6 Hz, 1H), 5.85–6.00 (m, 2H), 4.93–5.01 (m, 2H), 3.93 (s, 3H), 3.03–3.33 (m, 4H), 2.57–2.64 (m, 1H), 2.18 (s, 1H), 1.42–1.50 (m, 4H), 0.50 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 141.04, 131.87, 127.49, 122.43, 118.87 (br s), 114.54, 101.12 (br s), 61.33 (br s), 55.93, 52.77 (br s), 50.49, 40.78, 39.37, 27.84, 25.80 ppm. IR (KBr) ν 2945, 2921, 2861, 1797, 1667, 1623, 1587, 1541, 1512, 1474, 1245, 848, 693 cm^{-1}.

2.4.3 Synthesis of cinchona alkaloid chiral polymers 4P by Mizoroki-Heck polycondensation

Synthesis of polymer 4PaSQ

Squaramide **2SQ** (250.0 mg, 0.3449 mmol) and Diiodobenzene **3a** (113.8 mg, 0.3449 mmol) were placed in a 30 mL flask, to which was added two equivalents of triethylamine (95.62 µL, 0.6898 mmol). After adding Palladium acetate (4 mg) and DMF (3 mL) the reaction mixture was stirred for 24 h at 100 °C. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether. This solution was washed with water then THF. The compounds were dried in a vacuum oven for 3 h at 40 °C to afford the desired polymer **4PaSQ** in 99% yield as brownish solid. $[\alpha]^{25}_{D}$ = –109.5 (c 1.0 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.86 (1H), 7.30–8.00 (aromatic H), 6.19–6.39 (vinylic H), 3.95 (OCH_3), 2.90, 2.30, 2.10, 1.15, 0.87 (quinuclidine H) ppm. IR (KBr) ν 3853, 3420, 2932, 2584, 2370, 2079, 1793, 1683, 1620, 1597, 1508, 1429, 1385, 1252, 1109, 1019, 967, 844, 713, 617 cm^{-1}. M_n (SEC) = 5.4 x 10^3, M_w/M_n = 1.05.

Synthesis of polymer 4PbSQ

Squaramide **2SQ** (250.0 mg, 0.3449 mmol) and Diiodobiphenyl **3b** (140.0 mg, 0.3449 mmol) were taken in a 30 mL flask and added double moles of triethylamine (95.62 µL, 0.6898 mmol) to the mixture. After adding Palladium acetate (4 mg) and DMF solvent (3 mL) reaction mixture was stirred for 24 hours at 100 °C. Then evaporate the solvent and treatment with diethyl ether and washed by water then THF. After that the compounds were dried over in vacuum oven for 3 hours at 40 °C to afford the desired polymer **4PbSQ** in 98% yield as brownish solid. $[\alpha]^{25}_{D}$ = –109.5 (c 1.0 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.86 (1H), 7.21–8.03 (aromatic H), 6.21–6.48 (vinylic H), 3.96 (OCH_3),

2.89, 2.73, 2.31, 2.05, 1.18, 0.89 (quinuclidine H) ppm. IR (KBr) *v* 3853, 3734, 3648, 3446, 2931, 2369, 2325, 1792, 1683, 1620, 1585, 1508, 1473, 1224, 1024, 826, 714, 617 cm^{-1}. M_n (SEC) = 5.4 x 10^3, M_w/M_n = 1.05.

Synthesis of polymer 4PeSQ

Squaramide **2SQ** (250.0 mg, 0.3449 mmol) and 4, 4'-Diiodo-*trans*-stilbene **3e** (149.0 mg, 0.3449 mmol) were taken in a 30 mL flask and added double moles of triethylamine (95.62 µL, 0.6898 mmol) to the mixture. After adding Palladium acetate (4 mg) and DMF solvent (3 mL) reaction mixture was stirred for 24 hours at 100 °C. Then evaporate the solvent and treatment with diethyl ether and washed by water then THF. After that the compounds were dried over in vacuum oven for 3 h at 40 °C to afford the desired polymer **4PeSQ** in >99% yield as brownish solid. $[\alpha]^{25}_D$ = –136.1 (*c* 1.0 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.86 (1H), 7.19–8.03 (aromatic H), 6.16–6.41 (vinylic H), 3.94 (OCH_3), 2.96, 2.36, 1.91, 1.38, 0.82 (quinuclidine H) ppm. IR (KBr) *v* 3853, 3734, 3648, 3446, 2933, 2369, 2310, 1791, 1683, 1583, 1508, 1429, 1224, 1023, 960, 828, 713, 614 cm^{-1}. M_n (SEC) = 4.3 x 10^3, M_w/M_n = 1.16.

Synthesis of polymer 4PfSQ

Squaramide **2SQ** (250.0 mg, 0.3449 mmol) and 1, 3-Diiodobenzene **3f** (113.8 mg, 0.3449 mmol) were taken in a 30 mL flask and added double moles of triethylamine (95.62 µL, 0.6898 mmol) to the mixture. After adding Palladium acetate (4 mg) and DMF solvent (3 mL) reaction mixture was stirred for 24 hours at 100 °C. Then evaporate the solvent and treatment with diethyl ether and washed by water then THF. After that the compounds were dried over in vacuum oven for 3.0 h at 40 °C to afford the desired polymer **4PfSQ** in 80% yield as brownish solid. $[\alpha]^{25}_D$ = –105.4 (*c* 1.0 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.82 (1H), 7.33–8.04 (aromatic H), 6.20–6.42 (vinylic H), 3.95 (OCH_3), 2.94, 2.32, 2.10, 1.97, 1.14, 0.87 (quinuclidine H) ppm. IR (KBr) *v* 3443, 2584, 2933, 2862, 1682, 1620, 1588, 1509, 1433, 1227, 1291, 848 cm^{-1}. M_n (SEC) = 4.5 x 10^3, M_w/M_n = 1.06.

Synthesis of polymer 4PgSQ

Squaramide **2SQ** (235.0 mg, 0.3242 mmol) and 1,2-bis((4-iodobenzyl)oxy)ethane **3g** (160.2 mg, 0.3242 mmol) were taken in a 30 mL flask and added double moles of triethylamine (89.87 µL, 0.6484 mmol) to the mixture. After adding Palladium acetate (4 mg) and DMF solvent (3 mL) reaction mixture was stirred for 24 hours at 100 °C. Then evaporate the solvent and treatment with diethyl ether and washed by water then THF. After that the compounds were dried over in vacuum oven for 3.0 h at 40 °C to afford the desired polymer in >99% yield as brownish solid. $[\alpha]^{25}_D$ = –83.3 (*c* 1.0 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.89 (1H), 7.24–7.98 (aromatic H), 6.20–6.40 (vinylic H), 4.50 (methylene H), 3.97 (OCH_3), 2.90, 1.87, 1.35, 0.81 (quinuclidine H) ppm. IR (KBr) *v* 3443, 2933, 2864, 1793, 1682, 1620, 1588, 1509, 1433, 1362, 1227, 1091, 848 cm^{-1}. M_n (SEC) = 4.1 x 10^3, M_w/M_n = 1.09.

Synthesis of polymer 4PhSQ

Squaramide **2SQ** (80.8 mg, 0.1114 mmol) and 4, 4'-Diiododiphenyl ether **3h** (47.0 mg, 0.1114 mmol), were taken in a 30 mL flask and added double moles of triethylamine (30.88 µL, 0.2228 mmol) to the mixture. After adding Palladium acetate (3 mg) and DMF solvent (2 mL) reaction mixture was stirred for 24 hours at 100 °C. Then evaporate the solvent and treatment with diethyl ether and washed by water then THF. After that the compounds were dried over in vacuum oven for 3 h at 40 °C to afford the desired polymer in >99% yield as brownish solid. $[\alpha]^{25}_{D}$ = –72.4 (*c* 1.0 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.87 (1H), 6.98–8.03 (aromatic H), 6.34 (vinylic H), 3.97 (OCH_3), 2.97, 2.31, 1.86, 0.86 (quinuclidine H) ppm. IR (KBr) *v* 3553, 3392, 3255, 2942, 1798, 1665, 1621, 1598, 1540, 1510, 1473, 1364, 1240, 1101, 1025, 912, 847, 693, 622 cm^{-1}. M_n (SEC) = 3.9 x 10^3, M_w/M_n = 1.07.

2.4.4 Representative procedure for the enantioselective Michael addition of β-ketoesters to nitroolefins

The asymmetric reaction was carried out by adding methyl 2-oxocyclopentanecarboxylate **5** (63 µL, 0.50 mmol), *trans*-β-nitrostyrene **6** (82.05 mg, 0.55 mmol) and catalyst (5 mol %) to a vessel with 2.5 mL of solvent. The reaction mixture was then stirred at room temperature for the time specified. After consumption of substrate **5** (monitored by TLC) the reaction mixture was then filtered through a filter paper. The filtrate was then concentrated in vacuo and the compound was purified by silica gel (100-200 mesh) column chromatography with hexane/EtOAc = 6/1 as an eluent to afford the desired addition compound as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.29–7.23 (m, 5H), 5.14 (dd, *J* = 13.8 Hz, 3.8 Hz, 1H), 5.00 (dd, *J* = 13.8 Hz, 10.7 Hz, 1H), 4.08 (dd, *J* = 10.8 Hz, 3.8 Hz, 1H), 3.74 (s, 3H), 2.38–2.33 (m, 2H), 2.04–1.84.

The other asymmetric Michael addition reactions were performed in the same manner and the results are summarized in Tables **2**, **3**, and Scheme **4**.

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Chapter 3

Synthesis of chiral main-chain polymers of diamine connected cinchona squaramides by Mizoroki–Heck polymerization and their application to asymmetric catalysis

3.1 INTRODUCTION

In asymmetric synthesis, the use of chiral organocatalysts has played an important role in synthetic strategy mainly because of their high performance and lack of toxic metal species. Chiral organocatalysts have made significant contributions to green chemical processes. Cinchona alkaloids and their derivatives have been widely used as chiral organocatalysts in asymmetric synthesis,[1-6] because they show excellent catalytic activity for several asymmetric reactions. Cinchona alkaloids have various functionalities including a quinuclidine tertiary nitrogen, a secondary alcohol, a quinoline ring, and a vinylic unit in their structure. The chemical modification of the functionalities enables us to design catalysts suitable for a range of tasks, including polymeric catalysts.[7-9]

Important chiral cinchona-derived organocatalysts are their squaramide derivatives, which were successfully introduced in the pioneering work of Rawal.[10] Cinchona-derived squaramide derivatives show highly efficient catalytic activity for asymmetric Michael type reactions.[11,12] The cinchona-squaramides possess an acidic NH that can act as an H-bond donor, and the tertiary nitrogen of the quinuclidine of cinchona alkaloids may serve as both an H-bond acceptor and a base in asymmetric Michael addition reactions. Based on the seminal work of Rawal and coworkers on cinchona squaramide organocatalysts[10] various modifications to the cinchona squaramides have been developed and utilized in different types of Michael addition reactions.[13–24] Fine-tuning the cinchona squaramide catalysts for each asymmetric reaction has resulted in efficient catalytic activity for this type of reaction. The asymmetric Michael addition reaction is a powerful tool for C–C bond formation and can be applied to the synthesis of different types of important chiral building blocks. Besides their applications in asymmetric catalysis, the cinchona-squaramides have been successfully applied to molecular recognition[25] and supramolecular assemblies based on their efficient formation of hydrogen bonds.[26]

Polymer immobilized catalysts have recently attracted much attention in organic synthesis. Chiral catalysts attached to crosslinked polymers having a random structure, such as polystyrene, have also been extensively used in asymmetric synthesis. Some of these polymeric systems have been utilized in continuous flow systems because of their insolubility.[27] In comparison with random polymer-immobilized chiral catalysts, chiral polymers containing a chiral catalyst moiety in the main chain repeat unit of the polymer have not been studied significantly. We have developed some chiral polymers containing cinchona alkaloid moieties in their main chain structure using polymerization techniques such as etherification polymerization,[28] Mizoroki–Heck (MH) polymerization,[29-31] ion-exchange polymerization,[32,33] and neutralization polymerization.[34,35] The chiral polymers previously prepared have been applied to various kinds of asymmetric transformations and show excellent catalytic

activities. The fine tuning of the catalyst conformation is easily achieved in the case of chiral main chain polymers. Interestingly, some main chain chiral polymer catalysts show higher stereoselectivities than those of the original low-molecular-weight catalysts. This could be due to the specific conformations created by the chiral main chain polymers.[7-9]

In this article, we focus on novel cinchona squaramide dimers containing diamine linkers and their polymers prepared by MH polymerization. The cinchona squaramide dimers we have developed in this study contain two terminal olefin structures at the C-3 position of both cinchona moieties. One of the most reliable C–C bond forming reaction for such olefinic double bonds is the Mizoroki–Heck (MH) coupling reaction with aromatic iodides.[36–38] Although some achiral polymers have been synthesized using the MH reaction,[39] but there have been no examples of chiral polymer synthesis using this method except for our previous report.[29-31] For the synthesis of novel chiral polymers from the cinchona squaramide dimers, we applied MH polymerization.

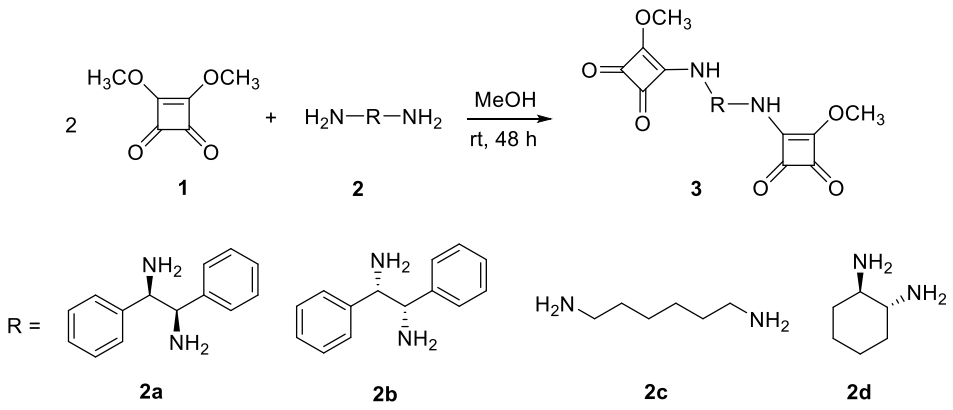
To evaluate the catalytic activity and the stereoselectivity of the polymeric organocatalysts, the resulting main chain chiral polymers were used as polymeric chiral organocatalysts for the asymmetric Michael addition of β-ketoesters to nitroolefins. The effects of the chiral polymer structure on the catalytic activity and stereoselectivity of the asymmetric reaction have been investigated. Because of their insolubility in commonly used organic solvents, we also surveyed the recycling of the polymer organocatalysts.

3.2 RESULTS AND DISCUSSION

3.2.1 Synthesis of cinchona squaramide polymers

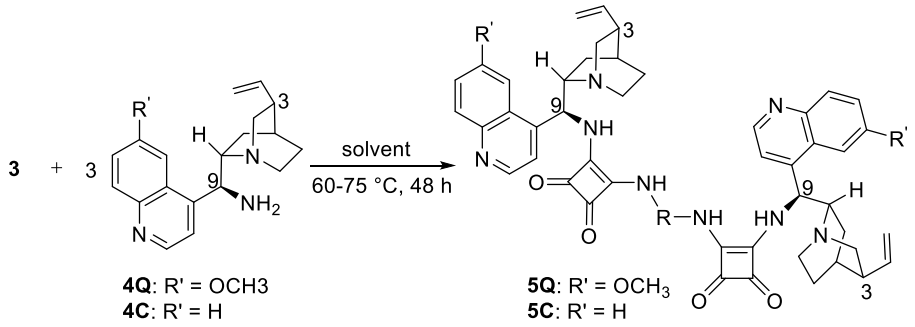
Dimethylsquarate **1** is highly reactive towards primary amines, yielding squaramides. Thus, two equivalents of dimethylsquarate **1** easily reacted with diamines **2** to give the squaramide dimers **3** in high yield. We prepared different kinds of squaramide dimers **3** from several diamines **2**, including chiral diamines (Scheme **1**). When (*R*,*R*)-DPEN, **2a** and (*S*,*S*)-DPEN, **2b** were used as chiral diamine, the squaramide dimer **3a** and **3b** were obtained with 68% and 63% of yields. The isolated yield were obtained after washing with solvent and column chromatography. In case of achiral diamine **2c** the dimeric compound was found with very low of yield (41%) due to solubility problem of dimeric compound **3c** but excellent yield of product **3d** (95%) was obtained using another chiral diamine **2d**.

The remaining methoxy groups in the dimers **3** are still active towards amines and the hydroxyl group at C-9 of the cinchona alkaloid can be easily transformed into the amino derivative. The C-9-amino derivative of quinine **4Q** was synthesized by Mitsunobu type azide formation, followed by the Staudinger reaction according to the reported procedure.[40] A squaramide dimer **3** was then allowed to react with the amino group of **4Q** to give the cinchona squaramide dimer **5Q** as shown in Scheme **2**.



Scheme 1. Synthesis of squaramide dimers **3.**

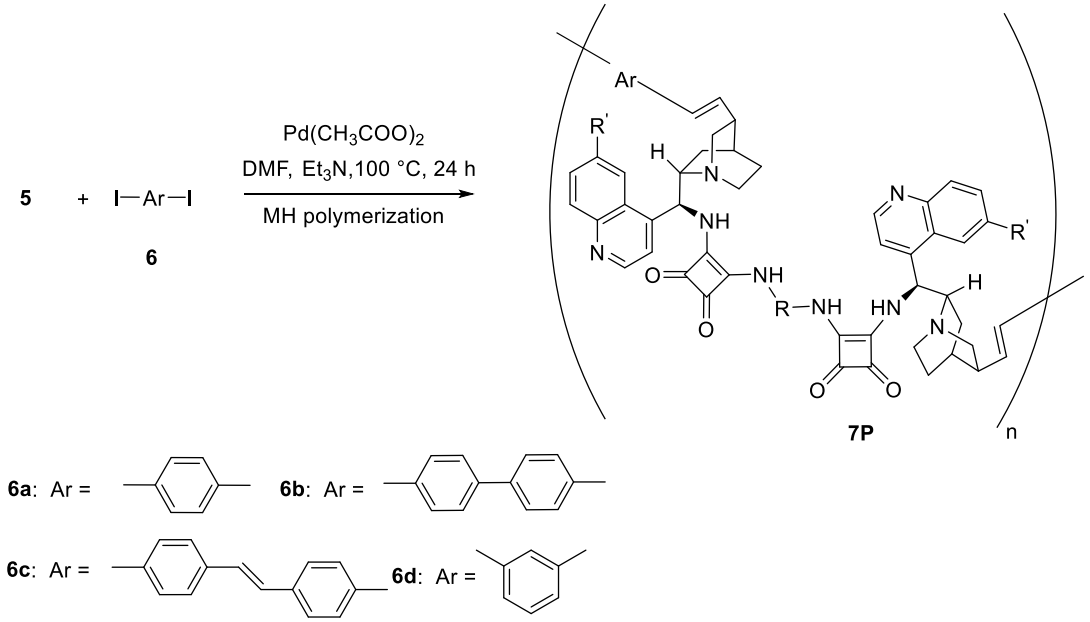
This reaction required the use of excess amount of 4Q (3 equiv.) at a high reaction temperature (60–75 ˚C) in chloroform, mainly because of the steric hindrance of the cinchona derived amine. When C9-amino derivative of quinine 4Q was used to prepare two cinchona squaramide dimers 5Qa and 5Qb the isolated products were found with 77% and 79% yield respectively. In the case of 1,6-hexanediamine 2c tetrahydrofuran (THF) was used as the solvent because 2c was well soluble in THF and from this reaction 5Qc was obtained with very low of yield, 35% due to isolation problem.



Scheme 2. Synthesis of cinchona squaramide dimers **5**.

In case of **5Qd** good isolated yield was gained (75%). When cinchonidine derived amine **4C**[41] was used instead of **4Q** the corresponding cinchona squaramide dimeric compounds **5Ca** and **5Cb** were obtained with somewhat lower isolated yields, 55% and 43% respectively.

The cinchona squaramide dimers **5Q**, **5C** possess two C3-vinyl groups in their structure. These vinyl groups are applicable to the Mizoroki–Heck (MH) reaction with aromatic iodides. When diiodo aromatic compounds are used with cinchona squaramide dimers **5** repeated MH reactions occur to give chiral polymers (Scheme 3). Thus, repeated MH reactions occurred between cinchona squaramide dimers **5** and various aromatic diiodides **6** in the presence of $Pd(OAc)_2$ catalyst to give chiral squaramide polymers **7P** (Scheme 3). After polymerization, the reaction mixture was precipitated in ether to give the polymer powder. The polymers **7PQaa**, **7PQba**, **7PQca**, **7PQda** were synthesized by the MH polymerization of quinine based squaramide dimers **5Qa**, **5Qb**, **5Qc** and **5Qd** with the diiodo compound 1,4-diiodobenzene **6a**.



Scheme 3. Synthesis of cinchona squaramide polymers **7P** by Mizoroki-Heck (MH) coupling polymerization.

Cinchonidine-based squaramide containg polymers **7PCaa** and **7PCba** were prepared from dimeric compounds **5Ca** and **5Cb** with same diiodo compound **6a**. Moreover, another two polymers **7PQab**, **7PQbb** were obtained from quinine based squaramide dimers **5Qa**, **5Qb** and 4, 4'-Diiodobiphenyl compound **6b**. Finally, from the MH reaction of dimeric compound **5Qa** and the two different diiodo compounds 4, 4'-Diiodo-*trans*-Stilbene **6c** and 1,3- diiodobenzene **6d** the polymeric compounds **7PQac**, **7PQad** were synthesized. The chiral polymers **7P** were soluble only in highly polar solvents such as dimethylformamide (DMF) and dimethylsulfoxide (DMSO).

Table 1. Synthesis of cinchona squaramide polymers **7P** by MH polymerization of **5** and **6**.[a]

entry	diiodides	polymer	yield, %	M_w[b]	M_n[b]	M_w/M_n[b]
1	**6a**	**7PQaa**	80	4400	4300	1.02
2	**6a**	**7PQba**	95	4400	4200	1.05
3	**6a**	**7PQca**	99	4000	3800	1.05
4	**6a**	**7PQda**	73	5100	4800	1.06
5[c]	**6a**	**7PCaa**	96	4200	3900	1.07
6[c]	**6a**	**7PCba**	>99	4200	3900	1.07
7	**6b**	**7PQab**	>99	3900	3700	1.05
8	**6b**	**7PQbb**	>99	4300	4000	1.08
9	**6c**	**7PQac**	>99	3900	3700	1.05
10	**6d**	**7PQad**	>99	3800	3600	1.06

[a]Polymerization was performed in DMF at 100 °C for 24 h.

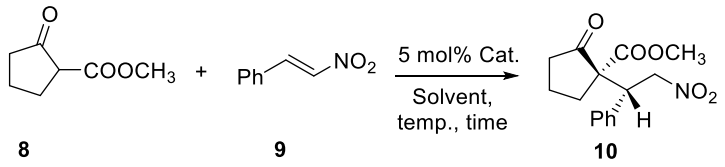
[b]Determined by size exclusion chromatography using DMF as a solvent at a flow rate of 1.0 mL min^{-1} at 40 °C (polystyrene standard).

[c]Polymerization time was 48 h. Q: Quinine-based dimer and C: Cinchonidine-based dimer.

They were not soluble in commonly used organic solvents including ether, chloroform, THF, hexane, toluene, ethyl acetate, and methanol. Table **1** summarizes the results of the MH polymerization of cinchona squaramide dimers **5** and aromatic diiodides **6**. In all cases, chiral polymers **7P** having molecular weights of about 4000 were obtained in high yield. When cinchonidine derivative **5C** was used for the MH polymerization, a longer reaction time was required to obtain a high yield of polymer **7P** (entries 5, 6).

3.2.2 Catalytic performance of the cinchona squaramide dimers, 5 and their polymers, 7P

To investigate the catalytic activity of the novel cinchona squaramide derivatives, asymmetric Michael addition reactions between 2-oxocyclopentanecarboxylate 8 and *trans*-β- nitrostyrene 9 was tested with cinchona squaramide dimers 5 as asymmetric catalysts. Rawal's original cinchona squaramide (11, Figure 1) derived from cinchonine, shows excellent catalytic activity in asymmetric Michael reactions.[10] The reaction of 8 and 9 gave the chiral product in 75% yield with 93% ee for the major diastereomer using 11 as the catalyst. Our cinchona squaramide dimers 5 also showed high performance in the same reaction.



8 **9** **10**

Scheme 3. Asymmetric Michael addition of methyl 2-oxocyclopentanecarboxylate **8** to *trans*-β-nitrostyrene **9**.

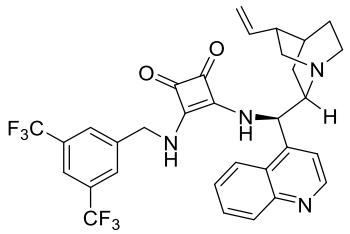
Table 2. Asymmetric Michael addition reaction of β-ketoester **8** to nitrostyrene **9** using squaramide dimers **5** as catalyst.[a]

entry	catalyst	solvent	reaction time, h	yield, %[b]	*dr*[c]	% *ee*[c]
1	**5Qa**	THF	22	76	>100:1	98
2	**5Qa**	MeOH	24	67	11:1	92
3	**5Qa**	CH_2Cl_2	42	69	52:1	96
4	**5Qb**	THF	26	79	>100:1	94
5	**5Qc**	THF	30	75	35:1	84
6	**5Qd**	THF	16	70	19:1	70
7	**5Ca**	THF	31	45	65:1	90
8	**5Cb**	THF	30	46	>100:1	87
9[d]	**11**	CH_2Cl_2	24	75	50:1	93

[a]Reactions were carried out with **8** (0.5 mmol), *trans*-β-nitro-styrene **9** (0.55 mmol), and catalyst **5Q, 5C** (5 mol%) in solvent (2.5 mL) at rt.

[b]Isolated yield of the product after purification by column chromatography.

[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H). [d]Using Rawal's original cinchonine-based squaramide catalyst, **11**.



11

Figure 1. Cinchonine-derived squaramide **11**.

Table **2** summarizes the results of asymmetric Michael reaction of **8** and **9** using **5** as catalysts. In the presence of **5Qa** the reaction smoothly occurred in THF at room tem temperature to give the Michael adduct **10** in 76% isolated yield with 98% ee for the major diastereomer (Table 2, entry 1). The diastereomeric ratio (*dr*) of the product was also very high (>100:1). The main stereoisomer of four possible isomers obtained in this reaction was **10**. The same reaction in methanol proceeded to give **10** but with lower stereoselectivity, diastereoselectivity, and enantioselectivity (entry 2). In dichloromethane, a somewhat longer reaction time was required compared to that in THF (entry 3). The effect of the diamine linker (**R** in 5) was also investigated. **5Qb** prepared from (*S*,*S*)-amine **2b** had a slightly decreased enantioselectivity compared to that obtained with **5Qa** (entry 4). An appropriate combination of the cinchona moiety and diamine linker in this catalyst is **5Qa** prepared from (*R*,*R*)-amine **2a**. The use of a flexible achiral methylene chain linker **2c** resulted in lower stereoselectivity in the asymmetric induction (entry 5). The (*R*,*R*)-1,2-diaminocyclohexane linker **2d** also resulted in lower stereoselectivity (entry 6). The cyclohexane ring may induce an unfavorable conformation at the catalytic site. Cinchonidine derived squaramide dimers also catalyzed the same reaction with somewhat lower reactivity and stereoselectivity (entries 7, 8).

Table 3. Asymmetric Michael addition reaction of β-ketoester **8** to nitroolefin **9** using polymers **7P** as catalysts at rt in THF.[a]

entry	catalyst	solvent	reaction time, h	yield, %[b]	*dr*[c]	% *ee*[c]
1	**7PQaa**	THF	22	68	60:1	95
2	**7PQba**	THF	24	71	33:1	97
3	**7PQca**	THF	40	75	46:1	93
4	**7PQda**	THF	50	57	28:1	90
5	**7PCaa**	THF	22	72	68:1	95
6	**7PCba**	THF	22	68	55:1	96

[a]Reactions were carried out with **8** (0.50 mmol), *trans*-β-nitrostyrene **9** (0.55 mmol) and the polymeric catalyst **7P** (5 mol%) in solvent (2.5 mL).

[b]Isolated yield of the product after purification by column chromatography.

[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H).

The results obtained by using cinchona squaramide dimers **5** encouraged us to apply the corresponding polymers **7P** for catalysis in the same asymmetric reaction. The chiral polymer **7PQaa** prepared from **5Qa** and 1,4-diiodobenzene **6a** was first used as a polymeric catalyst. **7PQaa** was insoluble in commonly used organic solvents and was, thus, suspended in THF. The substrates **8** and **9** were dissolved in THF and **7PQaa** was added to initiate the reaction. Even in the heterogeneous system using the insoluble polymeric catalyst, the reaction proceeded smoothly (Table **3**). After stirring for 22 h at room temperature, the consumption of **8** was confirmed by thin-layer chromatography (TLC). The polymeric chiral catalyst **7PQaa** suspended in the reaction mixture was easily removed by filtration. The desired product was isolated from the filtrate. In the presence of **7PQaa** the asymmetric Michael reaction smoothly occurred in THF to give **10**. The stereoselectivity (*dr* = 60:1, 95% *ee*) obtained with **7PQaa** was as high as that with the corresponding low-molecular-weight catalyst **5Qa** (Table 2, entry 1, vs. Table 3, entry 1). Of the chiral polymeric catalysts **7PQba** gave the highest enantioselectivity in THF solvent (Table 3, entry 2). The cinchonidine-derived polymers **7PCaa** and **7PCba** also showed a high level of stereoselectivities (entries 5, 6).

Interestingly, most of the chiral polymer catalysts 7P afforded the chiral product 10 with higher enantioselectivities compared to those of the corresponding low-molecular-weight catalysts 5 under the same reaction conditions (Table 2, 3). Some conformational differences between the catalytic sites of dimeric catalysts 5 and those of chiral polymers 7P might give rise to a positive effect on the enantioselectivity in the asymmetric reaction.

Table 4. Asymmetric Michael addition reaction of β-ketoester **8** to nitroolefin **9** using polymeric catalyst **7PQaa** in different solvents.[a]

entry	solvent	temp., °C	reaction time, h	yield, %[b]	*dr*[c]	% *ee*[c]
1	CH_2Cl_2	rt.	40	66	65:1	99
2	EtOAc	rt.	24	59	41:1	92
3	CH_3CN	rt.	45	52	>100:1	99
4	THF	rt.	22	68	60:1	95
5	MeOH	rt.	19	69	33:1	99
6	Hexane	rt.	25	70	51:1	97
7	Toluene	rt.	60	73	22:1	88
8	MeOH	-10	46	75	>100:1	97
9	CH_2Cl_2	-10	46	74	>100:1	99
10	CH_2Cl_2	40	5	82	>100:1	99

[a]Reactions were carried out with **8** (0.50 mmol), *trans*-β-nitrostyrene **9** (0.55 mmol) and the polymeric catalyst (5 mol%) in solvent (2.5 mL).

[b]Isolated yield of the product after purification by column chromatography.

[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H).

Next, we surveyed the solvent effects on the catalytic performances of the chiral cinchona squaramide polymers **7P**. In addition to THF, we chose dichloromethane, ethyl acetate, acetonitrile, hexane, and

toluene as examples of commonly used organic solvents. The **7P** polymers were all insoluble in these solvents. The asymmetric reaction proceeded in the heterogeneous system in these solvents. The reaction smoothly occurred to give **10** with even higher enantioselectivities of up to 99% ee. In dichloromethane, the asymmetric reaction occurred with polymeric catalyst **7PQaa** to give 10 in a diastereomeric ratio 65:1 (Table 4, entry 1). The enantioselectivity of the major diastereomers was 99% ee. This results also shows the higher stereoselectivity in the asymmetric induction compared with that obtained with the corresponding low-molecular-weight dimeric catalyst **5Qa** in the same solvent (Table 2, entry 3).

Table 5. Asymmetric Michael addition reaction of β-ketoester **8** to nitroolefin **9** using different polymeric catalysts at rt in methanol.[a]

entry	catalyst	yield, %[b]	*dr*[c]	%*ee*[c]
1	**7PQaa**	69	33:1	99
2	**7PQba**	71	35:1	98
3	**7PQbb**	68	39:1	98
4	**7PQac**	73	34:1	96
5	**7PQad**	72	30:1	97

[a]Reactions were carried out with **8** (0.50 mmol), *trans*-β-nitrostyrene **9** (0.55 mmol), and the polymeric catalyst **7PQ** (5 mol%) in MeOH (2.5 mL).

[b]Isolated yield of the product after purification by column chromatography.

[c]The diastereomeric ratio (*dr*) and enantioselectivity (**ee**) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H).

Acetonitrile and methanol were also suitable solvents for the same reaction with **7PQaa** giving **10** in 99% ee (entries 3, 5). In acetonitrile, an even higher diastereoselectivity (>100:1) was obtained with **7PQaa**. Toluene gave a lower stereoselectivity with the polymeric catalyst (entry 7). The effect of temperature on the catalytic performance was also investigated. The use of a higher reaction temperature reduced the reaction time required to achieve completion (entry 10). In dichloromethane, the stereoselectivity was not influenced by changing the reaction temperature in the range of –10 to 40 °C (entries 1, 9, and 10). Interestingly, very high stereoselectivity was maintained, even under reflux conditions, in dichloromethane (entry 10).

We then used some other cinchona squaramide polymer organocatalysts for the same asymmetric reaction. Table **5** summarizes the results obtained by using **7PQ** in methanol at room temperature. In all cases, excellent stereoselectivities were obtained with **7PQ**. Various combinations of **R** and **Ar** in **7PQ** (R' = OMe) were chosen for the polymeric catalyst structure and showed no significant effect on the stereoselectivities, as shown in Table **5**.

Because the chiral polymers were completely insoluble in commonly used organic solvents, the asymmetric reactions were carried out in a heterogeneous system. The use of the **7P** polymeric organocatalysts allowed easy separation of the catalyst from the reaction mixture by simple filtration.

The recovered polymer could be reused several times in the same asymmetric reaction. The catalyst recyclability was examined by using the **7PQaa** polymeric organocatalyst in methanol. After the reaction had completed, the polymer was easily separated from the reaction mixture and washed with organic solvent. After completing the reaction, reaction solvent, MeOH was completely removed by rotary evaporator. Then again diethyl ether solvent was added to the reaction mixture and stirring with spatula and taking the reaction vessel for settle down. After sometimes, the ether solvent with asymmetric products was removed by Pasteur pipette and collected to another vessel. This same procedure was repeated for 3–4 times and collected solvent by same way to add with previous vessel. Finally, the polymer was dried over by vacuum pump. Then the recovered polymer was then used for subsequent reactions. Although the second reuse gave somewhat lower enantioselectivity (Table 6, entry 1), the catalytic performance of **7PQaa** was maintained for several repeated cycles.

We applied chiral polymer **7PQaa** as an organocatalyst in the asymmetric Michael addition of various kinds of substrates. The reaction between ethyl 2-oxocyclopentanecarboxylate and *trans*-β-nitrostyrene proceeded smoothly in methanol to give the corresponding asymmetric product in high yield with excellent enantioselectivity (Table 7, entry 1). Methyl 2- oxocyclopentanecarboxylate **8** was allowed

Table 6. Recycle use of polymeric catalyst **7PQaa** at rt.[a]

entry	yield, %[b]	*dr*[c]	%*ee*[c]
original	69	33:1	99
cycle **1st**	88	40:1	97
cycle **2nd**	84	35:1	98
cycle **3rd**	82	39:1	98
cycle **4th**	82	39:1	96
cycle **5th**	79	31:1	96
cycle **6th**	76	30:1	96
cycle **7th**	81	29:1	97

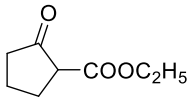
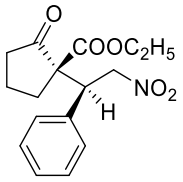
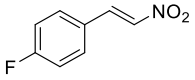
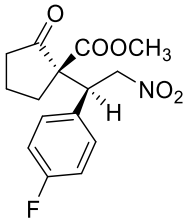
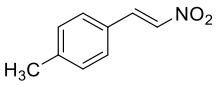
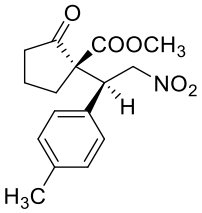
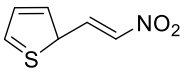
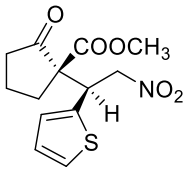
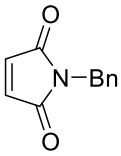
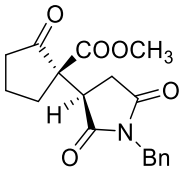
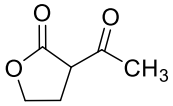
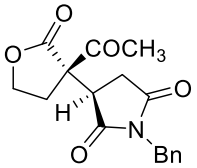
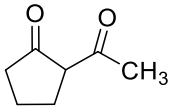
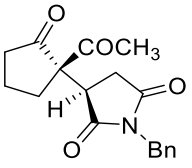
[a]Reactions were carried out with **8** (0.50 mmol), *trans*-β-nitrostyrene **9** (0.55 mmol), and the polymeric catalyst **7PQaa** (5 mol%) in MeOH (2.5 mL).

[b]Isolated yield of the product after purification by column chromatography.

[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H).

to react with several Michael acceptors including 4-fluoro-*trans*-β-nitrostyrene, 4-methyl-*trans*-β-nitrostyrene, (2-nitrovinyl)thiophene, and *N*-benzylmaleimide. The reactions occurred smoothly in the presence of **7PQaa** to give the corresponding Michael adducts (Table 7, entries 2–5). The stereoselectivities of the chiral products obtained from methyl-*trans*-β-nitrostyrene (entry 3) and *N*-benzylmaleimide (entry 5) were not determined because of the incomplete separation of the products by chiral high-performance liquid chromatography analysis. The reactivity of *N*-benzylmaleimide as a Michael acceptor was relatively low compared to those of the nitroolefins (Table 7, entries 5–7). Finally,

Table 7. Asymmetric Michael addition reaction of different combinations of Michael donors and acceptors using **7PQaa**.[a]

entry	Michael donor	Michael acceptor	asymmetric compound	reaction time, h	yield, %[b]	*dr*[c]	% *ee*[c]
1		**9**		19	92	87:1	95
2	**8**			19	78	>100:1	97
3	**8**			45	81	nd[d]	nd[d]
4	**8**			20	83	44:1	98
5	**8**			48	58	nd[d]	nd[d]
6		**12**		48	56	6:1	<1
7		**12**		48	29	21:1	-5

[a]Reactions were carried out with the Michael donor (0.50 mmol), Michael acceptor (0.55 mmol), and **7PQaa** (5 mol%) in MeOH (2.5 mL). [b]Isolated yield of the product after purification by column chromatography. [c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral HPLC (Chiralcel OD-H) for entries 1–4 and (Chiralcel AD-H) for entries 5–7. [d]*dr* and *ee* were not determined due to the incomplete separation of the products by chiral HPLC.

almost racemic products were obtained in the products with α-acetylbutyrolactone and 2-acetylcyclopentanone (entries 6, 7).

3.3 CONCLUSIONS

In summary, we have successfully synthesized novel chiral cinchona squaramide dimers **5**. Mizoroki–Heck (MH) polymerization smoothly occurred between **5** and various kinds of aromatic diiodides to give chiral polymers **7P**. Although the **7P** polymers were insoluble in commonly used organic solvents, the Michael reaction of β-ketoesters to nitroolefins was efficiently catalyzed by **7P** to afford the corresponding Michael adducts with high stereoselectivity. In particular, in the case of the reaction of 2-oxocyclopentanecarboxylate **8** and *trans*-β-nitrostyrene **9** in the presence of **7P**, one stereoisomer **10** was produced almost exclusively of four possible stereoisomers with high diastereoselectivity (*dr* >100:1) and high enantioselectivity (up to 99% *ee*). The insolubility of the chiral polymeric catalysts allowed us to recover the catalysts from the reaction mixture by simple filtration for reuse several times without significant loss of catalytic activity.

3.4 EXPERIMENTAL SECTION

3.4.1 Materials and general considerations

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. Reactions were monitored by thin-layer chromatography using pre-coated silica gel plates (Merck 5554, 60F254). Column chromatography was performed using a silica gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro melting apparatus, and the values were not corrected. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in $CDCl_3$ or [D_6]DMSO 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 $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in parts-per-million (ppm) using TMS as a reference, and the *J* values are reported in hertz. IR spectra were recorded on a JEOL JIR-7000 Fourier transform (FT)-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) electrospray ionization (ESI) spectra were recorded on a microTOF-Q II HRMS/MS instrument (Bruker). High-performance liquid chromatography (HPLC) was performed with a Jasco HPLC system composed of a DG-980-50 three-line degasser, a PU-980 HPLC pump, and a CO-965 column oven equipped with a chiral column (Chiralpak OD-H, Daicel) with hexane/2-propanol as the eluent. A Jasco UV-975 UV detector was used for peak detection. Size-exclusion chromatography (SEC) was performed using a Tosoh HLC 8020 instrument with UV (254 nm) or refractive index detection. DMF was used as the carrier solvent at a flow rate of 1.0 mL min^{-1} at 40 °C. Two polystyrene gel columns of 10-μm bead size were used. A

calibration curve was made to determine the number average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards. The optical rotation was recorded using a JASCO DIP-149 digital polarimeter using a 10-cm thermostatted microcell.

3.4.2 Synthesis of squaramide dimer, 3

Synthesis of 3a

(1*R*, 2*R*)-1,2-Diphenylethylenediamine **2a** (743 mg, 3.50 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione **1** (995 mg, 7.00 mmol) were added to a flask. Then, MeOH (30 mL) solvent was added to this mixture and stirred for 48 h at room temperature under argon gas. The reaction was monitored by TLC and the solvent was removed in vacuo to afford the crude product as a white solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 9/1 as an eluent to afford the desired compound **3a** in 68% yield as a white solid. mp: 253–255 °C. $[\alpha]_{25}^{D} = -12.2$ (c 0.500 g/dL in DMF). R_f: 0.44 (CH_2Cl_2/MeOH = 9/1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.99 (s, 2H), 7.12–7.24 (m, aromatic, 10H), 4.80 (d, J = 3.2 Hz, 2H), 4.39 (s, OCH_3, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 192.6, 181.2, 181.1, 170.5, 138.3, 128.8, 128.6, 127.6, 63.7, 61.8 ppm. IR (KBr) ν 3237, 1801, 1704, 1596, 1513, 1390, 1130, 1049, 919, 699, 609, 590 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{20}N_2O_6$ $[M+Na]^+$: 455.1219 found: 455.1276.

Synthesis of 3b

(1*S*, 2*S*)-1,2-Diphenylethylenediamine **2b** (743 mg, 3.50 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione 1 (995 mg, 7.00 mmol) were added to a flask. Then, MeOH (30 mL) solvent was added to this mixture and stirred for 48 h at room temperature under argon gas. The reaction was monitored by TLC and the solvent was removed in vacuo to afford the crude product as a white solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 5/5 as an eluent to afford the desired compound **3b** in 63% yield as a white solid. mp: 251–252 °C. $[\alpha]^{25}_{D} = +9.8$ (*c* 0.515 g/dL in DMF). R_f: 0.36 (CH_2Cl_2/MeOH= 5/5). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 9.00 (s, 2H), 7.11–7.23 (m, aromatic, 10H), 4.81 (d, J = 5.6 Hz, 2H), 4.38 (s, OCH_3, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 192.6, 181.2, 181.1, 170.5, 138.2, 128.7, 63.7, 61.8 ppm. IR (KBr) ν 3238, 3036, 1804, 1705, 1622, 1529, 1465, 1378, 1353, 1065, 1019, 926, 699, 577 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{20}N_2O_6$ $[M+Na]^+$: 455.1219 found: 455.1205.

Synthesis of 3c

Hexamethylenediamine **2c** (174 mg, 1.50 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione 1 (426 mg, 3.00 mmol) were added to a flask. Then, MeOH (15 mL) solvent was added to this mixture and stirred for 48 h at room temperature under argon gas. The reaction was monitored by TLC and the solvent was removed in vacuo to afford the crude product as a white solid. The solid compounds were

purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 9/1 as an eluent to afford the desired compound 3c in 41% yield as a white solid. mp: 189–190 ˚C; R_f: 0.57 (CH_2Cl_2/MeOH = 9/1) ^{1}H NMR (400 MHz, DMSO-d_6, 25 ˚C) δ 8.77 (br, s, 1H), 8.55 (br, s, 1H), 4.27 (br, s, 6H), 3.45 (br, 2H), 3.23 (br, 2H), 1.47–1.50 (br, 2H), 1.26 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ˚C) δ 189.5, 176.9, 172.2, 60.0, 43.7, 43.3, 30.3, 29.7, 25.3 ppm. IR (KBr) ν 3253, 3054, 2942, 1803, 1688, 1638, 1530, 1443, 1378, 1340, 1071, 1042, 927, 821, 742, 616 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{20}N_2O_6$ $[M+Na]^+$: 359.1219 found: 359.1351.

Synthesis of 3d

(1*R*,2*R*)-1,2-Cyclohexanediamine **2d** (400 mg, 3.50 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione **1** (995 mg, 7.00 mmol) were added to a flask. Then, MeOH (30 mL) solvent was added to this mixture and stirred for 48 h at room temperature under argon gas. The reaction was monitored by TLC and the solvent was removed in vacuo to afford the crude product as a white solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with at first CH_2Cl_2/MeOH = 9/1 and then EtOAc/CH_2Cl_2 = 9.5/0.5 as eluents to afford the desired compound **3d** in 95% yield as white solid. mp: 132–133 °C. $[\alpha]^{25}_D$ = +184.4 (*c* 0.630 g/dL in DMF). R_f: 0.47 (CH_2Cl_2/MeOH = 9/1). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.87 (s, 1H), 8.63 (s, 1H), 4.28 (br, s, 6H), 3.75 (s, 2H), 1.89 (d, *J* = 12.4, 2H), 1.68 (d, *J* = 6.4, 2H), 1.42 (d, *J* = 9.6, 2H), 1.19 (br, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ˚C) δ 189.1, 182.2, 177.3, 171.9, 60.1, 57.7, 57.0, 32.6, 32.0, 23.9 ppm. IR (KBr) ν 3514, 3231, 2939, 2862, 1804, 1710, 1260, 1156, 936, 825, 705, 612 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{18}N_2O_6$ $[M+Na]^+$: 357.1063 found: 357.1186.

3.4.3 Synthesis of cinchona squaramide dimer, 5

Synthesis of 5Qa

3a (173 mg, 0.400 mmol) was added to a stirred solution of the 9-amino derivative of quinine **4Q** (323.4 mg, 1.00 mmol) in $CHCl_3$ (10 mL) in a flask and stirred for 48 h at 75 °C under argon gas. The reaction was monitored by TLC. Then, the precipitate was washed with EtOAc and dried in vacuo to afford the crude product as a solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 9/1 as an eluent to afford the desired pure compound **5Qa** in 77% yield as white solid. mp: 262–263 °C [dec.]. $[\alpha]^{25}_D$ = –133.9 (*c* 0.275 g/dL in DMF). R_f: 0.32 (CH_2Cl_2/MeOH = 9/1). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.75 (s, 1H), 8.26 (s, 1H), 7.04–8.04 (m, aromatic H), 5.92 (m, 2H), 5.49 (s, 2H), 4.97–5.06 (m, 2H), 3.85 (s, 3H), 2.70–3.43 (m, 4H), 2.30 (s, 1H), 1.41–1.59 (m, 4H), 0.63–0.83 (br, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ˚C) δ 182.6, 182.1, 167.1, 157.9, 147.8, 144.3, 142.1, 139.0, 131.5, 128.4, 127.1, 121.9, 114.4, 101.6, 61.5, 58.5,

55.6, 27.3 26.1 ppm. IR (KBr) ν 3205, 2938, 1776, 1554, 1451, 1358, 1231, 1094, 1033, 978, 914, 847, 762, 700 cm^{-1}. HRMS (ESI) calcd for $C_{62}H_{62}N_8O_6$ $[M+H]^+$: 1015.4871 found: 1015.4881.

Synthesis of 5Qb

3b (144 mg, 0.333 mmol) was added to a stirred solution of the 9-amino derivative of quinine **4Q** (323.4 mg, 1.00 mmol) in $CHCl_3$ (10 mL) in a flask and stirred for 48 h at 75 °C under argon gas. The reaction was monitored by TLC. Then, the precipitate was washed with EtOAc and dried in vacuo to afford the crude product as a solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 9/1 as an eluent to afford the desired pure compound **5Qb** in 79% yield as white solid. mp: 277–279 °C [dec.]. $[\alpha]^{25}_D$ = –46.4 (*c* 0.225 g/dL in DMF). R_f: 0.15 (CH_2Cl_2/MeOH = 9/1). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.71 (s, 1H), 7.10–7.97 (m, aromatic H), 5.92 (m, 2H), 5.52 (s, 2H), 4.97–5.02 (m, 2H), 3.81 (s, 3H), 2.67–3.51 (m, 4H), 2.20 (s, 1H), 1.24–1.52, 0.56–0.79 (s, 2H), (m, 4H) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C) δ 182.6, 181.7, 166.8, 157.6, 147.6, 144.2, 142.2, 139.2, 131.4, 128.5, 127.0, 121.8, 114.2, 101.4, 61.1, 55.5, 48.6, 27.2, 26.0 ppm. IR (KBr) ν 3192, 2936, 2863, 1796, 1654, 1356, 1229, 1094, 1030, 978, 912, 849, 698 cm^{-1}. HRMS (ESI) calcd for $C_{62}H_{62}N_8O_6$ $[M+H]^+$: 1015.4871 found: 1015.4885.

Synthesis of 5Qc

3c (112 mg, 0.333 mmol) was added to a stirred solution of the 9-amino derivative of quinine **4Q** (323.4 mg, 1.00 mmol) in THF (10 mL) in a flask and stirred for 48 h at 60 °C under argon gas. The reaction was monitored by TLC. Then, the precipitate was washed with EtOAc and dried in vacuo to afford the crude product as a solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 9/1 as an eluent to afford the desired pure compound **5Qc** in 35% yield as white solid. mp: 229–231 °C. $[\alpha]^{25}_D$ = –51.9 (*c* 0.290 g/dL in DMF). R_f: 0.37 (CH_2Cl_2/MeOH =7/3). ^{1}H NMR (400 MHz, DMSO, 25 °C) δ 8.77 (s, 1H), 7.43–7.96 (m, aromatic H), 5.95 (m, 2H), 4.96–5.05 (m, 2H), 3.91(s, 3H), 2.66 (m, 4H), 2.25 (s, 1H), 1.18–1.56 (m, 4H), 0.57–0.82 (br, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6 25 °C) δ 182.1, 167.7, 166.7, 157.9, 147.8, 144.2, 142.2, 131.5, 127.6, 121.9, 114.5, 101.7, 58.7, 55.7, 43.2, 30.5, 27.4, 26.3, 25.4 ppm. IR (KBr) ν 3238, 2935, 1796, 1658, 1357, 1228, 1092, 915, 847, 465 cm^{-1}. HRMS (ESI) calcd for $C_{54}H_{62}N_8O_6$ $[M+H]^+$: 919.4871 found: 919.4886.

Synthesis of 5Qd

3d (111 mg, 0.333 mmol) was added to a stirred solution of the 9-amino derivative of quinine **4Q** (323.4 mg, 1.00 mmol) in $CHCl_3$ (10 mL) in a flask and stirred for 48 h at 75 °C under argon gas. The reaction was monitored by TLC. Then, the precipitate was washed with EtOAc and dried in vacuo to afford the crude product as solid. The solid compounds were purified by column chromatography on silica gel (100–200 mesh) with MeOH/CH_2Cl_2 = 9.5/0.5 as an eluent and also using a solubility test in MeOH to afford the desired pure compound **5Qd** in 75% yield as white solid. mp: 267–269 °C; $[\alpha]^{25}_D$ = –181.7

(*c* 0.225 g/dL in DMF). R_f: 0.29 (MeOH/CH_2Cl_2 = 9.5/0.5). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.79 (s, 1H), 7.43–7.98 (m, aromatic H), 5.99 (m, 2H), 4.98–5.06 (m, 2H), 3.93 (s, 3H), 3.39 (m, 4H), 2.69–3.39 (m, 4H), 2.29 (s, 2H), 1.90 (d, 2H), 1.17–1.76 (m, 4H), 0.56–0.82 (br, 2H) ppm.^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 182.4, 181.5, 166.8, 157.8, 147.8, 144.3, 143.6, 142.1, 131.5, 127.4, 121.9, 114.3, 101.5, 58.5, 55.5, 34.2, 27.3, 26.2, 23.7 ppm. IR (KBr) ν 3205, 2937, 2863, 1795, 1621, 1359, 1230, 1098, 1030, 981, 916, 849, 687 cm^{-1}. HRMS (ESI) calcd for $C_{54}H_{60}N_8O_6$ $[M+H]^+$: 917.4714 found: 917.4752.

Synthesis of 5Ca

3**a** (144 mg, 0.333 mmol) was added to a stirred solution of the 9-amino derivative of cinchonidine **4C** (293.4 mg, 1.00 mmol) in $CHCl_3$ (10 mL) in a flask and stirred for 48 h at 75 °C under argon gas. The reaction was monitored by TLC. Then the precipitate was washed with EtOAc and dried in vacuo to afford the crude product as a solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 8.5/1.5 as an eluent to afford the desired pure compound **5Ca** in 55% yield as white solid. mp: 254–256 °C [dec.]. $[\alpha]^{25}_D$ = –43.3 (*c* 0.275 g/dL in DMF). R_f: 0.45 (CH_2Cl_2/MeOH = 8.5/1.5). ^{1}H NMR (100 MHz, DMSO-d_6, 25 °C) δ 8.90 (s, 1H), 8.40 (s, 1H), 7.04–8.26 (m, aromatic H), 5.92 (m, 2H), 5.49 (s, 2H), 5.00 (m, 2H), 2.73–3.56 (m, 4H), 2.33 (s, 1H), 1.91-2.08 (m, H), 1.23–1.58 (m, 4H), 0.69–0.86 (br, 2H) ppm. ^{13}C NMR (400 MHz, DMSO-d_6, 25 °C) N/D because of solubility problem. IR (KBr) ν 3223, 2940, 2865, 1796, 1674, 1579, 1450, 1345, 979, 913, 766, 698, 624 cm^{-1}. HRMS (ESI) calcd for $C_{60}H_{58}N_8O_4$ $[M+H]^+$: 955.4659 found: 955.4675.

Synthesis of 5Cb

3b (144 mg, 0.333 mmol) was added to a stirred solution of the 9-amino derivative of cinchonidine **4C** (293.4 mg, 1.00 mmol) in $CHCl_3$ (10 mL) in a flask and stirred for 48 h at 75 °C under argon gas. The reaction was monitored by TLC. Then, the precipitate was washed with EtOAc and dried in vacuo to afford the crude product as solid. The solid compounds were purified by silica gel (100–200 mesh) column chromatography with CH_2Cl_2/MeOH = 8.2/1.8 as the eluent to afford the desired pure compound **5Cb** in 43% yield as white solid. mp: 239–242 °C [dec.]. $[\alpha]^{25}_D$ = –16.1 (*c* 0.225 g/dL in DMF). R_f: 0.53 (CH_2Cl_2/MeOH = 8.2/1.8). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.84 (s, 1H), 8.39 (s, 1H), 7.16–8.06 (m, aromatic H), 5.87 (s, 2H), 5.51 (s, 2H), 4.94 (m, 2H), 2.63–3.05 (m, 4H), 2.20 (s, 1H), 1.23–1.49 (m, 4H), 0.59–0.85 (br, 2H) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C) δ 181.9, 166.8, 150.4, 148.1, 142.1, 130.0, 128.6, 127.2, 123.4, 119.4, 114.3, 67.3, 55.4, 37.9, 27.1, 23.1 ppm. IR (KBr) ν 3206, 2939, 1795, 1678, 1580, 1345, 979, 913, 768, 699, 618 cm^{-1}. HRMS (ESI) calcd for $C_{60}H_{58}N_8O_4$ $[M+Na]^+$: 977.4479 found: 977.4474.

3.4.4 Synthesis of cinchona squaramide containing chiral polymers, 7P

Synthesis of polymer 7PQaa

A mixture of squaramide dimer **5Qa** (250 mg, 0.246 mmol), 1,4-diiodobenzene **6a** (81.2 mg, 0.246 mmol) in the presence of palladium acetate (4 mg) and two equivalents of triethylamine (68.20 µL, 0.492 mmol) was stirred in DMF (3 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue was precipitated in diethyl ether (70–80 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PQaa** in 80% yield as brownish solid. $[\alpha]^{25}_{D}$ = –55.9 (*c* 0.315 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.82 (1H), 6.86–7.95 (aromatic H), 6.21–6.47 (vinylic H), 5.51(s, 2H), 3.81 (OCH_3), 2.89, 2.72, 2.32, 1.98, 1.89, 1.75, 1.55, 1.35, 1.22, 0.85 (quinuclidine H) ppm. IR (KBr) ν 3434, 3172, 2935, 1797, 1680, 1621, 1579, 1510, 1227, 1027, 850, 700, 619 cm^{-1}. M_n (SEC) = 4.3×10^3, M_w/M_n = 1.02.

Synthesis of polymer 7PQba

A mixture of squaramide dimer **5Qb** (100 mg, 0.098 mmol), 1,4-diiodobenzene **6a** (32.5 mg, 0.098 mmol) in the presence of Palladium acetate (2 mg) and two equivalents of triethylamine (27.16 µL, 0.196 mmol) was stirred with DMF (2 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3-4 h to afford the desired polymer **7PQba** in 95% yield as brownish solid. $[\alpha]^{25}_{D}$ = –73.6 (*c* 0.075 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.84 (1H), 7.08-8.51 (aromatic H), 6.01-6.50 (vinylic H), 5.48 (2H), 3.91 (OCH_3), 2.94, 2.73, 2.30, 1.94, 1.55, 1.23, 1.06, 0.85 (quinuclidine H) ppm. IR (KBr) ν 3414, 2935, 1798, 1680, 1621, 1579, 1451, 1227, 1027, 969, 850, 700, 619 cm^{-1}. M_n (SEC) = 4.2 x 10^3, M_w/M_n = 1.05.

Synthesis of polymer 7PQca

A mixture of squaramide dimer **5Qc** (50.0 mg, 0.054 mmol), 1,4-diiodobenzene **6a** (17.9 mg, 0.054 mmol) in the presence of Palladium acetate (2 mg) and two equivalents of triethylamine (15 µL, 0.108 mmol) was stirred with DMF (1 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PQca** in 99% yield as brownish solid. $[\alpha]^{25}_{D}$ = –62.2 (*c* 0.290 g/mL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.82 (1H), 7.44-8.16 (aromatic H), 6.18-6.50 (vinylic H), 3.89 (OCH_3), 3.09, 2.94, 2.73, 2.66, 2.32, 1.98, 1.40, 1.07, 0.86, (quinuclidine H) ppm. IR (KBr) ν 3436, 2936, 1796, 1677, 1621, 1590, 1529, 1227, 1094, 850, 618 cm^{-1}. M_n (SEC) = 3.8 x 10^3, M_w/M_n = 1.05.

Synthesis of polymer 7PQda

A mixture of squaramide dimer **5Qd** (100 mg, 0.108 mmol), 1,4-diiodobenzene **6a** (35.9 mg, 0.108 mmol) in the presence of Palladium acetate (4 mg) and two equivalents of triethylamine (30 µL, 0.216 mmol) was stirred with DMF (2 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer 7PQda in 73% yield as brownish solid. $[\alpha]^{25}_{D}$ = –89.7 (*c* 0.075 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.84 (1H), 7.48–8.15 (aromatic H), 6.19–6.53 (vinylic H), 3.91 (OCH_3), 2.88, 2.73, 2.32, 2.08, 1.98, 1.82, 1.54, 1.23, 1.07, 0.85 (quinuclidine H) ppm. IR (KBr) *v* 3452, 3207, 2934, 1795, 1677, 1621, 1586, 1512, 1451, 1359, 1227, 1094, 1026, 850 cm^{-1}. M_n (SEC) = 4.8 x 10^3, M_w/M_n = 1.06.

Synthesis of polymer 7PCaa

A mixture of squaramide dimer **5Ca** (100 mg, 0.104 mmol), 1,4-diiodobenzene **6a** (34.5 mg, 0.104 mmol) in the presence of Palladium acetate (2 mg) and two equivalents of triethylamine (29 µL, 0.208 mmol) was stirred with DMF (1.5 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PCaa** in 96% yield as brownish solid. $[\alpha]^{25}_{D}$ = –46.9 (*c* 0.055 g/mL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.98 (br, 1H), 7.08-8.46 (aromatic H), 5.96-6.40 (vinylic H), 5.51 (s, 2H), 2.93, 2.73, 2.33, 1.94, 1.56, 1.34, 1.17, 1.07, (quinuclidine H) ppm. IR (KBr) *v* 3414, 2936, 1798, 1677, 1578, 1511, 1448, 1240, 968, 849, 767, 700, 619 cm^{-1}. M_n (SEC) = 3.9 x 10^3, M_w/M_n = 1.07.

Synthesis of polymer 7PCba

A mixture of squaramide dimer **5Cb** (40.0 mg, 0.041 mmol), 1,4-diiodobenzene **6a** (13.8 mg, 0.041 mmol) in the presence of Palladium acetate (2 mg) and two equivalents of triethylamine (12 µL, 0.082 mmol) was stirred with DMF (1 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PCba** in >99% yield as brownish solid. $[\alpha]^{25}_{D}$ = –38.1 (*c* 0.050 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.96 (br, 1H), 8.96 (br, 1H), 7.34–8.52 (aromatic H), 5.98–6.38 (vinylic H), 5.48 (2H), 2.92, 2.68, 2.32, 2.08, 1.98, 1.56, 1.35, 1.08, 0.66 (quinuclidine H) ppm. IR (KBr) *v* 3436, 2936, 1725, 1691, 1678, 1581, 1550, 1502, 1483, 1443, 767 cm^{-1}. M_n (SEC) = 3.9 x 10^3, M_w/M_n = 1.07.

Synthesis of polymer 7PQab

A mixture of squaramide dimer **5Qa** (100 mg, 0.098 mmol), 4,4'-Diiodobiphenyl **6b** (40.0 mg, 0.098 mmol) in the presence of Palladium acetate (3 mg) and two equivalents of triethylamine (27 µL, 0.196 mmol) was stirred with DMF (1.5 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PQab** in >99% yield as brownish solid. $[\alpha]^{25}_{D}$ = – 44.7 (*c* 0.285 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.81 (br, 1H), 6.95–8.14 (aromatic H), 6.21–6.58 (vinylic H), 5.53 (2H), 3.82–3.91 (OCH_3), 2.92, 2.71, 2.32, 2.00, 1.57, 1.24, 1.08, 0.86 (quinuclidine H) ppm. IR (KBr) *v* 3434, 3171, 2935, 1796, 1679, 1621, 1580, 1511, 1227, 1026, 849, 700, 617 cm^{-1}. M_n (SEC) = 3.7 x 10^3, M_w/M_n = 1.05.

Synthesis of polymer 7PQbb

A mixture of squaramide dimer **5Qb** (100 mg, 0.098 mmol), 4,4'-Diiodobiphenyl **6b** (40.0 mg, 0.098 mmol) in the presence of Palladium acetate (3 mg) and two equivalents of triethylamine (27 µL, 0.196 mmol) was stirred with DMF (1.5 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PQbb** in >99% yield as brownish solid. $[\alpha]^{25}_{D}$ = – 41.7 (*c* 0.055 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.85 (1H), 7.09–8.15 (aromatic H), 5.98–6.55 (vinylic H), 5.48 (2H), 3.78–3.91 (OCH_3), 2.93, 2.73, 2.31, 2.08, 1.89, 1.56, 1.09, 0.85 (quinuclidine H) ppm. IR (KBr) *v* 3435, 3181, 2937, 1797, 1755, 1679, 1621, 1579, 1443, 1228, 1027, 700, 619 cm^{-1}. M_n (SEC) = 4.0 x 10^3, M_w/M_n = 1.08.

Synthesis of polymer 7PQac

A mixture of squaramide dimer **5Qa** (100 mg, 0.098 mmol), 4, 4'-Diiodo-*trans*-stilbene **6c** (42.5 mg, 0.098 mmol) in the presence of Palladium acetate (3 mg) and two equivalents of triethylamine (27 µL, 0.196 mmol) was stirred with DMF (1.5 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PQac** in >99% yield as brownish solid. $[\alpha]^{25}_{D}$ = –73.1 (*c* 0.055 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.83 (br, 1H), 6.96–8.18 (aromatic H), 5.99–6.57 (vinylic H), 5.52 (2H), 3.83–3.91 (OCH_3), 2.93, 2.71, 2.32, 1.99, 1.56, 1.24, 1.09, 0.86 (quinuclidine H) ppm. IR (KBr) *v* 3426, 3171, 2934, 1796, 1679, 1621, 1579, 1511, 1442, 1226, 1024, 965, 849, 700, 618 cm^{-1}. M_n (SEC) = 3.7 x 10^3, M_w/M_n = 1.05.

Synthesis of polymer 7PQad

A mixture of squaramide dimer **5Qa** (100 mg, 0.098 mmol), 1,3-diiodobenzene **6d** (32.5 mg, 0.098 mmol) in the presence of Palladium acetate (3 mg) and two equivalents of triethylamine (27 µL, 0.196 mmol) was stirred with DMF (1.5 mL) in a flask. After completion of the reaction, the reaction mixture was cooled to room temperature. Then the solvent was removed in vacuo and the crude residue precipitated in diethyl ether (50–60 mL) for 3–4 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3–4 h to afford the desired polymer **7PQad** in >99% yield as brownish solid. $[\alpha]^{25}_{D}$ = – 69.9 (*c* 0.055 g/dL in DMF). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.83 (br, 1H), 7.09–8.16 (aromatic H), 5.98–6.54 (vinylic H), 5.52 (2H), 3.84–3.90 (OCH_3), 2.92, 2.73, 2.32, 2.08, 1.94, 1.56, 1.09, 0.86 (quinuclidine H) ppm. IR (KBr) *v* 3434, 3171, 2936, 1797, 1679, 1621, 1580, 1511, 1450, 1228, 1027, 970, 851, 700, 620 cm^{-1}. M_n (SEC) = 3.6 x 10^3, M_w/M_n = 1.06.

3.4.5 Representative procedure for the enantioselective Michael addition of β-ketoesters to nitroolefins

The asymmetric Michael reaction was carried out with methyl 2-oxocyclopentanecarboxylate **8** (63 µL, 0.50 mmol) and *trans*-β-nitrostyrene **9** (82.05 mg, 0.55 mmol) in a vessel with 2.5 mL of solvent using squaramide or the polymeric organocatalysts (5 mol %). The reaction mixture was then stirred at room temperature for the specified time. After the consumption of substrate **8** (monitored by TLC), the solvent was evaporated by rotary evaporation. After washing with ether, the solution was then filtered through a filter paper to recover the used catalysts from the reaction mixture. The filtrate was concentrated in vacuo, and the compound was purified by silica gel (100–200 mesh) column chromatography with hexane/EtOAc = 6.0/1.0 as an eluent to afford the desired addition compound as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.29–7.23 (m, 5H), 5.14 (dd, *J* = 13.8 Hz, 3.8 Hz, 1H), 5.00 (dd, *J* = 13.8 Hz, 10.7 Hz, 1H), 4.08 (dd, *J* = 10.8 Hz, 3.8 Hz, 1H), 3.74 (s, 3H), 2.38–2.33 (m, 2H), 2.04–1.84.

The other asymmetric Michael additions were performed in the same manner; the results are summarized in Tables **2**, **3**, **4**, **5**, **6**, and **7**.

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Chapter 4

Synthesis of Cinchona Alkaloid-derived Chiral Squaramide Polymers by ADMET Polymerization and Their Application to Asymmetric Catalysis

4.1 INTRODUCTION

Acyclic diene metathesis (ADMET) is a special type of olefin metathesis[1] that could be used for synthesis of high molecular weight polymers. ADMET is a step-growth polycondensation reaction that is driven by the removal of a small molecule, or condensate. The term ADMET had been known in scientific literature since the 1970s, but Wagener and his coworkers reported the first successful ADMET polymerization.[2] The mechanism of ADMET reaction was demonstrated by Wagener, Boncella, and Nel in 1991.[3] This polymerization technique could be used to make a variety of polymers and polymer architectures that are not possible by applying other polymerization methods. A variety of polymers synthesized by Wagener group, including unsaturated poly[carbo(dimethyl)silanes[4]; unsaturated polyether[5]; unsaturated polycarbonates[6]; unsaturated polyamines[7]; unsaturated polyacetals[8]; main-chain boronate ADMET polymers[9]; carbosilane/carbosiloxane-based ADMET homopolymers, and copolymers[10,11]; unsaturated polyesters[12]; amino acid-based chiral polymers[13] and more. Almost all polymers have been synthesized using the ADMET polymerization are achiral except the amino acid based chiral polymers.[13] There is no example of chiral cinchona alkaloid-derived polymer synthesis using ADMET polymerization. For the preparation of different types of catalysts, cinchona alkaloids and their derivatives have been widely used, and the most important application of cinchona alkaloids is their use as chiral organocatalysts in asymmetric synthesis.[14–18] Since cinchona alkaloids have various functionalities such as a quinuclidine tertiary nitrogen, a secondary alcohol, a quinoline ring, and a vinylic unit, it is feasible to modify the functionalities for designing new catalysts such as polymeric catalysts.[19–21] Cinchona squaramide derivatives are one of the important chiral organocatalysts which were successfully introduced in the pioneering work of Rawal,[22] and these showed highly efficient catalytic activity for asymmetric Michael-type reactions.[23,24]

Low-molecular-weight cinchona-derived squaramide organocatalysts are good catalyst for various asymmetric reactions [25–32] although those have some drawbacks. Recyclability of cinchona squaramide organocatalyst is one of them. Recently, polymer-immobilized chiral organocatalysts have significant attention in asymmetric organic synthesis. We have developed some chiral polymers containing cinchona alkaloid moieties in their main chain structure using different polymerization techniques such as etherification polymerization,[33] Mizoroki–Heck (MH) polymerization,[34-36] ion-exchange polymerization,[37,38] and neutralization polymerization.[39,40] Due to the creation of specific conformations by the chiral main chain polymers, the chiral polymers have been showed excellent catalytic activities to various kinds of asymmetric reactions.

In this chapter, we report the novel cinchona squaramide dimers containing polymers prepared by ADMET polymerization using the Hoveyda-Grubbs 2nd generation catalysts (HG_2). The cinchona squaramide dimers we have previously prepared[34,36] contain two terminal vinyl groups in both cinchona moieties. ADMET polymerization has been already reported as a viable synthetic route to prepare high molecular weight polymers containing various functionalities. For the synthesis of novel chiral polymers from the previously prepared cinchona squaramide dimers, we applied acyclic diene metathesis (ADMET) technique.

In this article, we discuss a novel chiral polymer synthesis involving cinchona alkaloid-derived squaramide dimers by ADMET polymerization and the application of this polymers to asymmetric reaction as an organocatalyst. To examine the catalytic activity and the stereoselectivity of the synthesized ADMET polymers as chiral organocatalysts, the chiral polymers were used as catalysts for the enantioselective Michael addition of β-ketoesters to nitroolefins. The Michael addition reaction is an excellent pathway for C–C bond formation in organic synthesis and can be applied to the synthesis of different types of important chiral compounds. Since the resulting ADMET polymers were insoluble in some commonly used organic solvents, we also examined the recycling of the Chiral ADMET polymeric organocatalysts.

4.2 RESULTS AND DISCUSSION

4.2.1 Synthesis of cinchona squaramide polymers by acyclic diene metathesis (ADMET) Polymerization

In our previous paper, we reported that dimethylsquarate easily reacts with 9-amino derivatives of quinine as well as cinchonidine and cinchonine to give corresponding squaramide dimers **1** in quantitative yield according to a reported procedure.[34] We also synthesized another modified cinchona squaramide dimer, **2** according to literature procedure.[36] Dimethylsquarate is also highly reactive towards primary amines. Thus, two equivalents of dimethylsquarate easily reacted with diamine to give the squaramide dimer **2** in high yields. We prepared one squaramide dimer **2** from diamine, (*R*,*R*)-DPEN with C9-amino derivative of quinine. (Figure **1**). The C9-amino derivative of quinine, cinchonidine and cinchonine were synthesized by Mitsunobu-type azide formation, followed by the Staudinger reaction according to the reported procedure.[41,42]

All cinchona squaramide dimers contain two vinyl groups in their structure. Thus, these squaramide dienes are applicable to ADMET polymerization. Since the ADMET reaction proceeded quantitatively on the vinyl positions of the cinchona squaramide, we investigated the synthesis of chiral polymers by means of a repetitive ADMET reaction. The ADMET reaction of squaramide diene **1a** and Hoveyda-Grubbs 2nd generation catalyst, **HG_2A** occurred smoothly in dry DMF to provide chiral polymers **1Pa** containing cinchona squaramide moieties in their main chain structure (Scheme **2**). After completing

the polymerization, the reaction mixture was precipitated in ether to give the polymer powder. The chiral polymers **1P**, **2P** were soluble in dichloromethane, methanol, chloroform and also highly polar solvents such as dimethylformamide (DMF), dimethylsulfoxide (DMSO). They were not soluble in commonly used organic solvents including ether, THF, hexane, toluene, acetonitrile and ethyl acetate. Table **1** summarizes the results of the ADMET polymerization of cinchona squaramide dienes. The chiral polymers **1P** having molecular weights of about in the range of 32,000–56,000 were obtained.

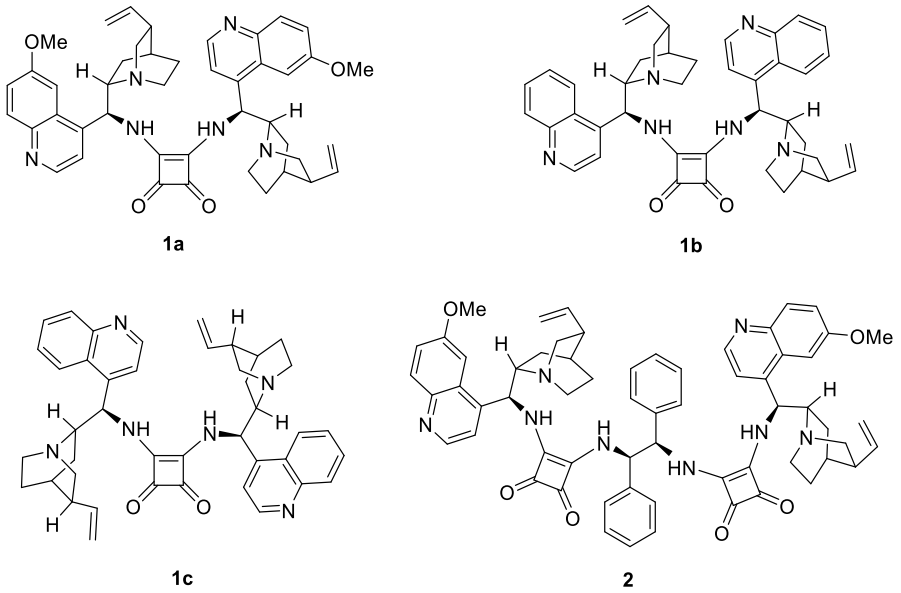
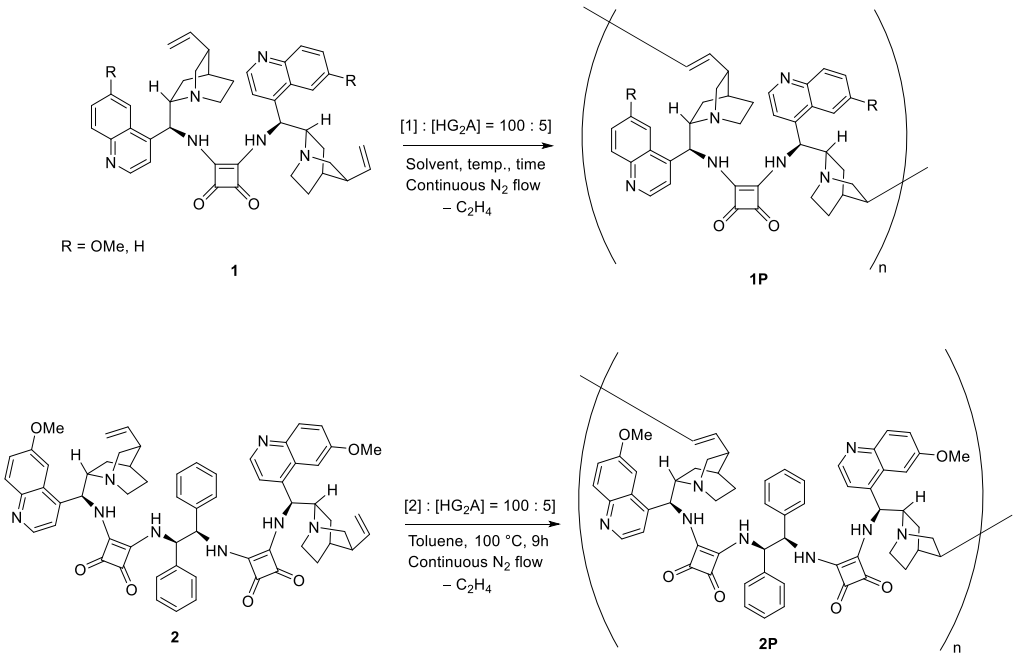


Figure 1. Cinchona squaramide dimers **1** and **2**.

We examined various reaction conditions for the ADMET polymerization of quinine-based squaramide dimer **1a** (0.200 mmol) and Hoveyda-Grubbs 2nd generation catalyst **HG$_2$A**. Table **1** summarizes the result of the ADMET polymerization under various reaction conditions. Polymerization with Hoveyda-Grubbs catalyst **HG$_2$A** in dry DMF for 24 h give polymer with high M_n value but lower yield of product (entry 1). Almost same M_n value was obtained when the polymerization occurred using double moles of catalyst for same reaction time with some higher yield of polymer (entry 2). With the increasing of catalyst loading, the ADMET polymers were formed with the decreasing of M_n value and higher isolated yield of polymer since the reaction time was 48 h (entries 3, 4, 5). Thus catalyst loading has significant effect on the formation of polymer. Maximum molecular weight M_n (50,000) and better isolated yield were found when the reaction time was 36 h in Dry DMF solvent (entry 8). The highest molecular weight M_n (56,000) and good yield of polymer were obtained using de-oxidized *o*-dichlorobenzene solvent at 100 °C temperature for 24 h (entry 9). Using de-oxidized toluene solvent, polymer reaction was proceeded smoothly with expected result after a very short time compare to other entries (entries 10, 11, 12). Almost same result was observed when Hoveyda-Grubbs 2nd generation catalyst HG$_2$B were used (entries 13). Table **2** summarizes the results of ADMET polymers using different cinchona squaramides with HG$_2$A catalyst at 100 °C temperature for the same reaction time 9 h.



Scheme 1. Synthesis of ADMET polymers of cinchona squaramide dienes **1** and **2** using Hoveyda-Grubbs 2nd generation catalyst **HG$_2$A**.

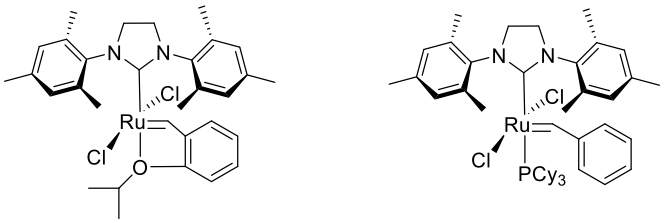
Table 1. Synthesis of cinchona squaramide polymer **1Pa** by ADMET polymerization in dry DMF solvent.[a]

entry	polymer	catalyst, mol %	solvent, mL	time, h	yield, %	M_n[b]	M_w[b]	M_w/M_n[b]
1	1Pa	0.005	1.0	24	58	46,000	53,000	1.15
2	**1Pa**	0.01	1.0	24	70	44,000	52,000	1.18
3	**1Pa**	0.01	1.0	48	77	44,000	51,000	1.16
4	**1Pa**	0.02	1.0	48	78	37,000	53,000	1.43
5	**1Pa**	0.03	1.0	48	80	32,000	46,000	1.44
6	**1Pa**	0.01	0.5	24	81	49,000	58,000	1.18
7	**1Pa**	0.01	0.5	30	80	49,000	55,000	1.12
8	**1Pa**	0.01	0.5	36	88	50,000	60,000	1.20
9[c]	**1Pa**	0.01	0.5	24	77	56,000	74,000	1.32
10[d]	**1Pa**	0.01	1.0	12	81	48,000	54,000	1.13
11[d]	**1Pa**	0.01	0.5	9	92	42,000	46,000	1.10
12[e]	**1pa**	0.01	1.0	25	52	49,000	56,000	1.14
13[f]	**1Pa**	0.01	0.5	24	74	41,000	47,000	1.14

[a]Polymerization was performed in dry DMF using 0.200 mmol of squaramide diene (**1a**) and different (mmol) of Hoveyda-Grubbs 2nd generation catalyst, HG$_2$A. [b]Determined by size exclusion chromatography using DMF (0.5 wt.% of LiCl salt) as a solvent at a flow rate of 1.0 mL/min at 40 °C (polystyrene standard). [c]Using de-oxidized o-dichlorobenzene solvent at 100 °C, [d]Solvent was de-oxidized Toluene at 100 °C, [e]Solvent was de-oxidized Toluene and at 85 °C, fHoveyda-Grubbs 2nd generation catalyst, HG$_2$B was used.

In case of cinchonidine and cinchonine based squaramides **1b**, **1c** the ADMET polymers were obtained with high isolated yields and high M_n values after 9 h (entries 2, 3). Finally, we used another diamine

linker containing squaramide dimer **2** with dry DMF solvent and very high molecular weight with good isolated yield was obtained (entry 4).



HG$_2$A **HG$_2$B**

Figure 2. Hoveyda-Grubbs 2nd generation catalysts, **HG$_2$**

Table 2. Synthesis of cinchona squaramide polymers **1P**, **2P** by ADMET polymerization in Toluene.[a]

entry	polymer	diene	time, h	yield, %	M_n[b]	M_w[b]	M_w/M_n[b]
1	**1Pa**	1a	9	92	42000	46000	1.10
2	**1Pb**	1b	9	93	54000	55000	1.02
3	**1Pc**	1c	9	77	47000	49000	1.04
4[c]	**2P**	2	9	86	74000	75000	1.01

[a]Polymerization was performed in 0.5 mL de-oxidized Toluene solvent at 100 °C for 9 h using 0.200 mmol of squaramide dienes **1** and **2**, Hoveyda-Grubbs 2nd generation catalyst, HG$_2$A (0.010 mmol).

[b]Determined by size exclusion chromatography using DMF (0.5 wt.% of LiCl salt in case of entry 1 and 0.5 wt.% of LiBr salt in case of entries 2–4) as a solvent at a flow rate of 1.0 mL/min at 40 °C (polystyrene standard).

[c]Polymerization solvent was dry DMF.

4.2.2 Catalytic performance of the cinchona squaramide ADMET polymer (1P, 2P)

To evaluate the catalytic activity of the resulting novel cinchona squaramide containing chiral ADMET polymers, the enantioselective Michael addition reactions between 2-oxocyclopentanecarboxylate **3** and *trans*-β-nitrostyrene **4** was investigated with the chiral ADMET polymer **1Pa**. The solvent effect on the catalytic performances of the chiral cinchona squaramide polymer **1Pa** was tested. We chose dichloromethane, methanol, THF, ethyl acetate, ether, toluene, hexane, chloroform and acetonitrile, as examples of commonly used organic solvents. Among these solvents the **1Pa** polymer was soluble only in methanol, dichloromethane and chloroform solvents. In case of other organic solvents polymer **1Pa** was insoluble. The asymmetric reaction proceeded in the homogeneous and also heterogeneous system in these solvents at room temperature.

The reaction smoothly occurred to give 5 with excellent enantioselectivity of up to 98% *ee* and good isolated yields. The asymmetric reaction was smoothly proceeded in dichloromethane solvent by using polymeric catalyst, 1Pa and poor isolated yield with good stereoselectivity was obtained after a long reaction time, 48 h (Table 3, entry 2).

Table 3. Asymmetric Michael addition reaction of β-ketoester **3** to nitroolefin **4** using ADMET polymer **1Pa** as catalyst.[a]

entry	solvent	temp., °C	reaction time, h[b]	yield, %[c]	*dr*[d]	% *ee*[d]
1[e]	CH_2Cl_2	rt.	2	95	79:1	91
2	CH_2Cl_2	rt.	48	45	59:1	96
3	MeOH	rt.	6	75	33:1	95
4	THF	rt.	9	78	24:1	97
5	EtOAc	rt.	9	50	32:1	97
6	Ether	rt.	40	60	52:1	97
7	Toluene	rt.	28	15	54:1	95
8	Hexane	rt.	16	77	37:1	93
9	$CHCl_3$	rt.	24	25	15:1	87
10	Acetonitrile	rt.	9	81	52:1	98
11	Acetonitrile	0	25	95	>100:1	98
12	Acetonitrile	-10	25	99	>100:1	98
13	Acetonitrile	70	7	91	21:1	94

[a]Reactions were carried out with **3** (0.50 mmol), *trans*-β-nitrostyrene **4** (0.55 mmol), and polymeric catalyst **1Pa** (5 mol%) in solvent (2.5 mL).

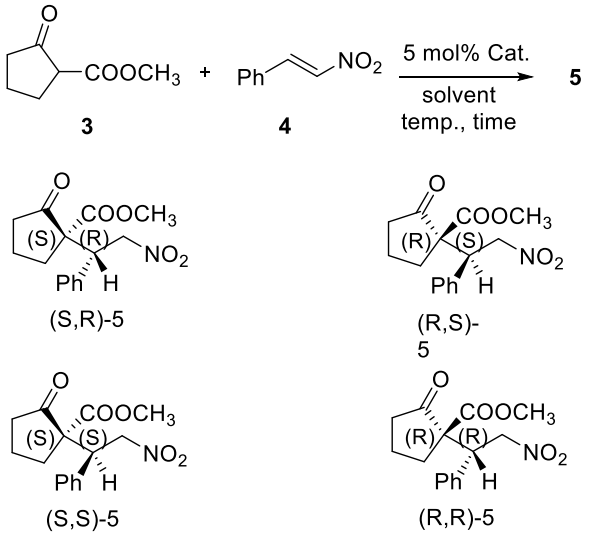
[b]At the reaction time specified, the consumption of substrate **3** was confirmed by TLC.

[c]Isolated yield of the product after purification by column chromatography.

[d]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H) and the configuration of major product is (*S*,*R*). [e]squaramide, **1a** was used as a catalyst.

In methanol, the asymmetric reaction occurred to give **5** with 75% of isolated yield in a diastereomeric ratio of 33:1 even reaction time was very short. The enantioselectivity of the major diastereomers was 95% *ee* (Table 3, entry 3). Same enantioselectivities (up to 97% *ee*) but a big difference of isolated yields were found when the reactions were performed in THF and ethyl acetate solvents for same reaction time, 9 h (entries 4, 5). Higher reaction time was required to proceed the asymmetric reactions with ether, toluene and hexane solvents and a little drops of enantioselectivity was obtained (entries 6, 7, 8). Chloroform gave a lower stereoselectivity and isolated yield with this same polymeric catalyst (entry 9). In case of acetonitrile solvent, excellent enantioselectivity and 81% of isolated yield were obtained with polymeric catalyst **1Pa** after 9h (entry 10).

The effect of temperature on the catalytic performance of ADMET polymer **1Pa** was also investigated. The use of a lower reaction temperature the reaction required 25 h to achieve the completion. In acetonitrile, the excellent stereoselectivities with very high isolated yields were obtained at 0 °C and also -10 °C temperature up to 98% ee with 99% of isolated yield (entries 11, 12). By increasing the reaction temperature to 70 °C, a very low diastereoselectivity (*dr* 21:1) and little drops of enantioselectivity was found after a short reaction time of 7h. (entry 13).



Scheme 2. Asymmetric Michael addition of methyl 2-oxocyclopentanecarboxylate, **3** to *trans*-β-nitrostyrene, **4**

Table **4**. Asymmetric Michael addition reaction of β-ketoester **3** to nitroolefin **4** using ADMET polymers, **1P** and **2P** as catalyst.[a]

entry	catalyst	yield, %[b]	*dr*[c]	% *ee*[c]
1	**1Pa**	81	52:1	98
2	**1Pb**	75	68:1	91
3	**1Pc**	97	>100:1	95[d]
4	**2P**	67	95:1	97

[a]Reactions were carried out with **3** (0.50 mmol), *trans*-β-nitrostyrene **4** (0.55 mmol), and catalysts **1P**, **2P** (5 mol%) in acetonitrile (2.5 mL) at rt.

[b]Isolated yield of the product after purification by column chromatography.

[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H) and the configuration of major product is (*S*,*R*).

[d]The configuration of major asymmetric product is (*R*,*S*).

We then used some other cinchona squaramide ADMET polymer organocatalysts for the same asymmetric reaction. Table **4** summarizes the results obtained by using polymers **1P** and **2P** in acetonitrile at room temperature. In all cases, excellent stereoselectivities were obtained with ADMET polymers. The best results were obtained by using cinchonine-based squaramide polymer **1Pc** up to 97% of isolated yield and >100:1 *dr* with 95% *ee* (entry 3). In case of (1*R*,2*R*)-DPEN diamine liker containing squaramide polymer, **2P** poor isolated yield and excellent stereoselectivity were also found (entry 4).

As the chiral ADMET polymers were soluble and also insoluble in some commonly used organic solvents the asymmetric reactions were carried out in a homogeneous and also a heterogeneous system. The use of the ADMET polymeric organocatalysts allowed easy separation of the catalyst from the reaction mixture by using decantation process. The recyclability test was carried out by using the 1Pc

polymeric organocatalyst in acetonitrile solvent at room temperature. After the completion of reaction, the polymer was easily separated from the reaction mixture and washed with ether for 3 times. The recovered polymer was then used for subsequent reactions in the same asymmetric reaction. Although the third and fourth reuse gave somewhat lower enantioselectivity (Table 5, entry 3, 4), the catalytic performance of 1Pc was maintained for several repeated cycles.

Table 5. Recycle use of polymeric catalyst **1Pc** at rt.[a]

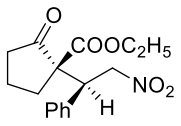
cycle	yield, %[b]	*dr*[c]	% *ee*[c]
original	97	>100:1	95
1st	73	54:1	97
2nd	93	59:1	97
3rd	90	39:1	94
4th	82	46:1	93
5th	72	51:1	95

[a]Reactions were carried out with **3** (0.50 mmol), *trans*-β-nitrostyrene **4** (0.55 mmol), and the polymeric catalyst **1Pc** (5 mol %) in acetonitrile (2.5 mL).

[b]Isolated yield of the product after purification by column chromatography.

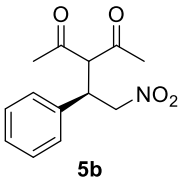
[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral high-performance liquid chromatography (HPLC, Chiralcel OD-H) and the configuration of major product is (*R*,*S*).

Scheme 3. Asymmetric Michael addition reaction of different combinations of Michael donors and acceptors using ADMET polymer, **1Pc** [a]



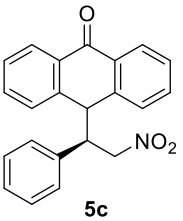
5a

yield: 87%
dr: >100:1
ee: 94%



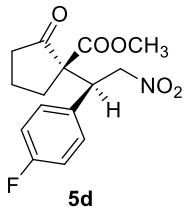
5b

yield: 79%
ee: 45%



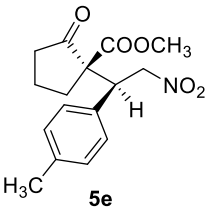
5c

yield: 72%
ee: 12%



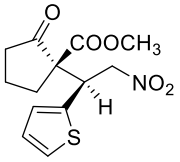
5d

yield: 95%
dr: 89:1
ee: 93%



5e

yield: 82%
dr: n/d
ee: 91%



5f

yield: 80%
dr: 50:1
ee: 96%

[a]Reactions were carried out with the Michael donor (0.50 mmol), Michael acceptor (0.55 mmol), and **1Pc** (5 mol%) in acetonitrile (2.5 mL).
[b]Isolated yield of the product after purification by column chromatography.
[c]The diastereomeric ratio (*dr*) and enantioselectivity (*ee*) were determined by chiral HPLC (Chiralcel OD-H) for compounds **5a, 5d-5f** and the configuration of the major asymmetric product is (*R,S*); (Chiralcel AD-H) for compound **5b**, the configuration is *R* and (Chiralcel AS-H) for compound **5c**, the configuration is *R*.
[d]*dr* was not determined due to the incomplete separation of the products by chiral HPLC.

Finally, we applied the chiral ADMET polymer **1Pc** as an organocatalyst in the asymmetric Michael addition of various kinds of substrates. The reaction between ethyl 2-oxocyclopentanecarboxylate and *trans*-β-nitrostyrene proceeded smoothly in acetonitrile to give the corresponding asymmetric product, **5a** in high yield with excellent diastereoselectivity up to >100:1 *dr* and high enantioselectivity (Scheme **4**). The substrate *trans*-β-nitrostyrene **4** was allowed to react with another two Michael donors including pentane-2,4-dione and anthrone and in both of cases very low enantioselectivity was found with good isolated yields, compounds 5b and 5c. The Michael acceptor methyl 2-oxocyclopentanecarboxylate **3** was also smoothly reacted with 4-fluoro-*trans*-β-nitrostyrene, 4-methyl-*trans*-β-nitrostyrene and (2-nitrovinyl)thiophene in the presence of **1Pc** organocatalyst to give the corresponding Michael adducts with good yields and high enantioselectivities, compounds **5d**, **5e** and **5f**. The diastereoselectivity of the chiral product **5e** obtained from methyl-*trans*-β-nitrostyrene was not determined because of the incomplete separation of the products by chiral high-performance liquid chromatography analysis.

4.3 CONCLUSIONS

In summary, we have successfully synthesized the cinchona squaramide containing chiral ADMET polymers. Acyclic diene metathesis polymerization smoothly occurred between cinchona squaramide dienes **1**, **2** and Hoveyda-Grubbs 2nd generation catalyst, **HG_2** under optimal reaction conditions to give chiral polymers **1P**, **2P**. As the chiral polymers were soluble and also insoluble in commonly used organic solvents, the Michael reaction of β-ketoesters to nitroolefins was efficiently catalyzed by ADMET polymers to afford the corresponding Michael adducts with high stereoselectivity and isolated yields. In particular, in the case of the reaction of methyl 2-oxocyclopentanecarboxylate **3** and *trans*-β-nitrostyrene **4** in the presence of polymer **1Pc** one stereoisomer **5** was produced almost exclusively of four possible stereoisomers with high diastereoselectivity (*dr* >100:1) and high enantioselectivity (up to 95% *ee*). The insoluble and soluble polymeric organocatalysts allowed us to recover the catalysts from the reaction mixture by decantation process for reuse several times on the same asymmetric reaction without significant loss of catalytic activity.

4.4 EXPERIMENTAL SECTION

4.4.1 Materials and general considerations

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. Reactions were monitored by thin-layer chromatography using pre-coated silica gel plates (Merck 5554, 60F254). Column chromatography was performed using a silica gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro melting apparatus, and the values were not corrected. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in $CDCl_3$ or [D_6]DMSO 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 $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in parts-per-million (ppm) using TMS as a reference, and the *J* values are reported in hertz. IR spectra were recorded on a JEOL JIR-7000 Fourier transform (FT)-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) electrospray ionization (ESI) spectra were recorded on a microTOF-Q II HRMS/MS instrument (Bruker). High-performance liquid chromatography (HPLC) was performed with a Jasco HPLC system composed of a DG-980-50 three-line degasser, a PU-980 HPLC pump, and a CO-965 column oven equipped with a chiral column (Chiralpak AS-H, OD-H and AD-H Daicel) with hexane/2-propanol as the eluent. A Jasco UV-975 UV detector was used for peak detection. Size-exclusion chromatography (SEC) was performed using a Tosoh HLC 8020 instrument with UV (254 nm) or refractive index detection. DMF with 0.5 wt. % LiCl/LiBr salt was used as the carrier solvent at a flow rate of 1.0 mL min^{-1} at 40 °C. Two polystyrene gel columns of 10-µm bead size were used. A calibration curve was made to determine the number average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards. The optical rotation was recorded using a JASCO DIP-149 digital polarimeter using a 10-cm thermostatted microcell.

4.4.2 Synthesis of cinchona squaramide containing chiral ADMET polymer

Synthesis of polymer 1Pa

Squaramide **1a** (145.0 mg, 0.200 mmol) and Hoveyda-Grubbs 2nd generation catalyst (**HG$_2$A**) (6.26 mg, 0.010 mmol) were taken in a dried Schlenk tube, then set it into oil bath with condenser. After setting the desire reaction temperature (100 °C) the slang tube with reactant and catalyst were again dried over 2 hours with a vacuum pump. After that the vacuum was replaced by argon gas and connected it with continuous N_2 gas flow. Then 0.5 mL of de-oxidized toluene solvent was added to this mixture. After 9 h, the reaction mixture was cooled to room temperature and this was quenched by diethyl ether. Then the crude mixture was precipitated in diethyl ether (70–80 mL) for 3 times. The solid precipitate was

filtered and dried in a vacuum oven at 40 °C for 3 h to afford the desired polymer **1Pa** in 92% yield **as** brownish solid. $[\alpha]^{25}_{D}$ = –228.4 (*c* 0.085 g/dL in DMF at 26.8 °C). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.77–8.80 (1H), 7.44–7.99 (aromatic H), 5.87–5.98 (vinylic H), 5.47–5.54 (2H), 4.92–5.09 (m, 2H), 3.94–3.99 (OCH_3), 3.03, 2.72, 2.66, 2.33, 2.18, 2.12, 1.98, 1.50, 1.42, 0.77, 0.49 (quinuclidine H) ppm. IR (KBr) ν 3379, 3210, 2934, 2863, 1793, 1361, 1258, 1084, 1030, 975, 848, 715, 692, 625 cm^{-1}. M_n (SEC) = 4.2×10^4, M_w/M_n = 1.10.

Synthesis of polymer 1Pb

Squaramide **1b** (133.0 mg, 0.200 mmol) and Hoveyda-Grubbs 2nd generation catalyst (**HG$_2$A**) (6.26 mg, 0.010 mmol) were taken in a dried Schlenk tube, then set it into oil bath with condenser. After setting the desire reaction temperature (100 °C) the Schlenk tube with reactant and catalyst were again dried over 2 hours with a vacuum pump. After that the vacuum was replaced by argon gas and connected it with continuous N_2 gas flow. Then 0.5 mL of de-oxidized toluene solvent was added to this mixture. After 9 h, the reaction mixture was cooled to room temperature and this was quenched by diethyl ether. Then the crude mixture was precipitated in diethyl ether (70–80 mL) for 3 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3 h to afford the desired polymer **1Pb** in 93% yield as brownish solid. $[\alpha]^{25}_{D}$ = – 109.30 (*c* 0.175 g/dL in DMF at 26.1 °C). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.47–8.98 (1H), 7.63–8.09 (aromatic H), 5.83–6.01 (vinylic H), 5.54 (2H), 4.91-4.99 (m, 2H), 3.19, 3.07, 3.03, 2.67, 2.58, 2.54, 2.34, 2.18, 1.98, 1.50, 1.42, 1.32, 1.17, 1.04, 0.85, 0.51 (quinuclidine H) ppm. IR (KBr) ν 3380, 3237, 2936, 2866, 1794, 1675, 1337, 1240, 1079, 975, 849, 767, 622 cm^{-1}. M_n (SEC) = 5.4×10^4, M_w/M_n = 1.02.

Synthesis of polymer 1Pc

Squaramide **1c** (133.0 mg, 0.200 mmol) and Hoveyda-Grubbs 2nd generation catalyst (**HG$_2$A**) (6.26 mg, 0.010 mmol) were taken in a dried Schlenk tube, then set it into oil bath with condenser. After setting the desire reaction temperature (100 °C) the Schlenk tube with reactant and catalyst were again dried over 2 hours with a vacuum pump. After that the vacuum was replaced by argon gas and connected it with continuous N_2 gas flow. Then 0.5 mL of de-oxidized toluene solvent was added to this mixture. After 9 h, the reaction mixture was cooled to room temperature and this was quenched by diethyl ether. Then the crude mixture was precipitated in diethyl ether (70–80 mL) for 3 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3 h to afford the desired polymer **1Pc** in 77% yield as brownish solid. $[\alpha]^{25}_{D}$ = + 90.99 (*c* 0.175 g/dL in DMF at 26.0 °C). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.37, 8.43, 8.84, 8.98 (1H), 7.48–8.26 (aromatic H), 5.71–6.08 (vinylic H), 5.43 (2H), 5.02–5.15 (m, 2H), 3.05, 2.89, 2.72, 2.67, 2.34, 2.10, 1.55, 1.45, 1.26, 1.09, 0.93, 0.76, 0.65 (quinuclidine H)

ppm. IR (KBr): ν = 3380, 3208, 2936, 2863, 1793, 1672, 1360, 1258, 1239, 1085, 1030, 975, 848, 692, 624 cm^{-1}. M_n (SEC) = 4.7×10^4, M_w/M_n = 1.04.

Synthesis of polymer 2P

Squaramide **2** (76.0 mg, 0.075 mmol) and Hoveyda-Grubbs 2nd generation catalyst (**HG_2A**) (2.50 mg, 0.004 mmol) were taken in a dried Schlenk tube, then set it into oil bath with condenser. After setting the desire reaction temperature (100 °C) the Schlenk tube with reactant and catalyst were again dried over 2 hours with a vacuum pump. After that the vacuum was replaced by argon gas and connected it with continuous N_2 gas flow. Then 0.5 mL of dry DMF solvent was added to this mixture. After 9 h, the reaction mixture was cooled to room temperature and this was quenched by diethyl ether. Then the crude mixture was precipitated in diethyl ether (70–80 mL) for 3 times. The solid precipitate was filtered and dried in a vacuum oven at 40 °C for 3 h to afford the desired polymer 2P in 86% yield as brownish solid. $[\alpha]^{25}_D$ = – 77.81 (*c* 0.075 g/dL in DMF at 26.8 °C). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.42, 8.74 (1H), 7.04–8.08 (aromatic H), 5.99 (vinylic H), 5.48 (s, 2H), 5.17 (2H), 3.84 (OCH_3), 3.54, 2.88, 2.72, 2.66, 2.54, 2.49, 2.34, 2.28, 2.21, 1.62, 1.52, 1.35, 1.22, 1.03, 0.84 (quinuclidine H) ppm. IR (KBr) ν3383, 3226, 2934, 2862, 1794, 1670, 1601, 1510, 1458, 1341, 1108, 912, 842, 767, 610 cm^{-1}. M_n (SEC) = 7.4×10^4, M_w/M_n = 1.01.

4.4.3 Representative procedure for the enantioselective Michael addition of β-ketoesters to nitroolefins using chiral ADMET polymer

Methyl 2-oxocyclopentanecarboxylate **3** (63 µL, 0.50 mmol) and *trans*-β-nitrostyrene **4** (82.05 mg, 0.55 mmol) were taken in a vessel with 2.5 mL of solvent. Then the ADMET polymeric organocatalyst (5 mol %) was added to this mixture. The reaction mixture was then stirred at room temperature for the specified time. After the consumption of substrate **3** (monitored by TLC), the solvent was evaporated by rotary evaporator. After washing with ether, the solution with asymmetric compound was collected by pipette using decantation process to recover the used catalysts from the reaction mixture. The solution was concentrated in vacuo, and the compound was purified by column chromatography on silica gel (100–200 mesh) with hexane/EtOAc = 6.0/1.0 as an eluent to afford the desired asymmetric compound as a colorless oil. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ 7.29–7.23 (m, 5H), 5.14 (dd, *J* = 13.8 Hz, 3.8 Hz, 1H), 5.00 (dd, *J* = 13.8 Hz, 10.7 Hz, 1H), 4.08 (dd, *J* = 10.8 Hz, 3.8 Hz, 1H), 3.74 (s, 3H), 2.38–2.33 (m, 2H), 2.04–1.84.

The other asymmetric Michael additions were performed in the same manner; the results are summarized in Tables **3**, **4**, **5** and scheme **4**.

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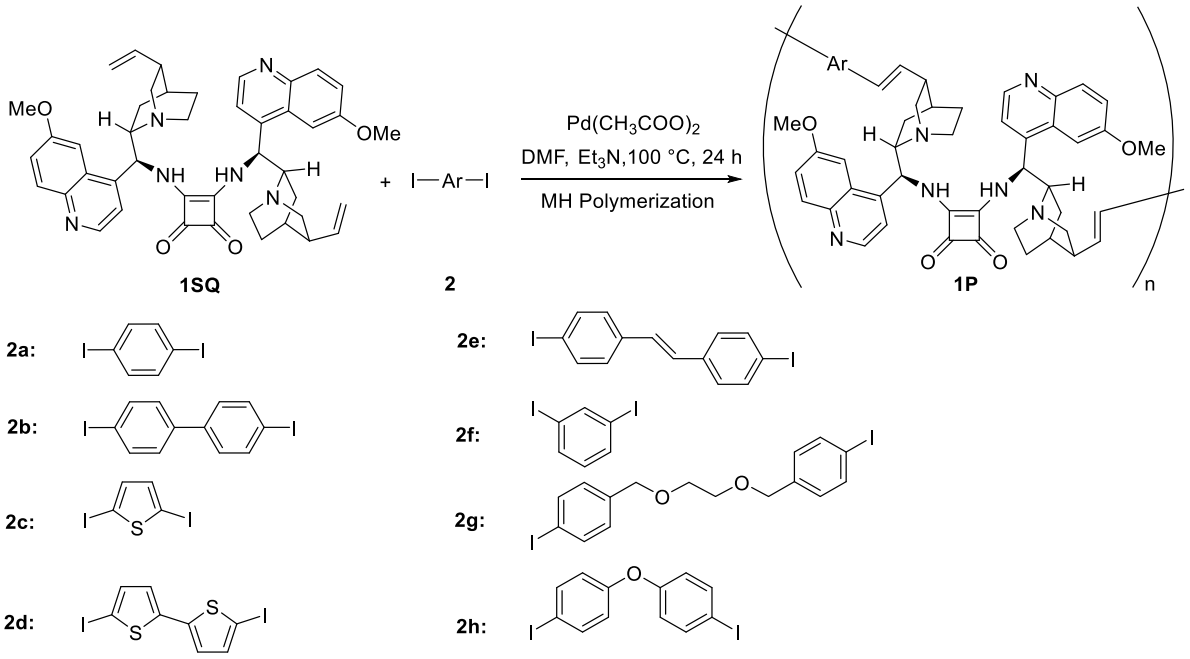
Summary

In my doctoral course study, I have synthesized different types of main-chain chiral polymers having cinchona derived-squaramide unit in their main-chain structure using Mizoroki-Heck polymerization and acyclic diene metathesis (ADMET) polymerization. The synthesized polymeric catalysts were applied in enantioselective Michael addition of methyl 2-oxocyclopentanecarboxylate to *trans*-β-nitrostyrene as an organocatalyst.

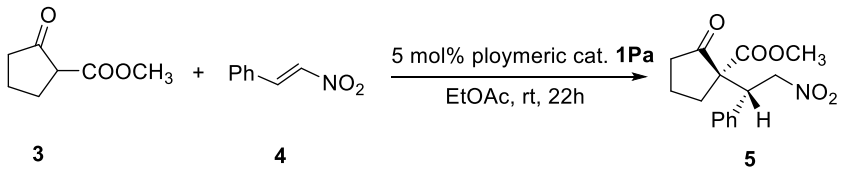
5.1 Synthesis of cinchona alkaloid-derived squaramide polymers as bifunctional chiral organocatalysts for the enantioselective Michael addition of β-ketoesters to nitroolefins

In chapter **3**, the successful synthesis of main-chain chiral squaramide polymeric catalysts and their application in asymmetric Michael addition reaction have been described in details.

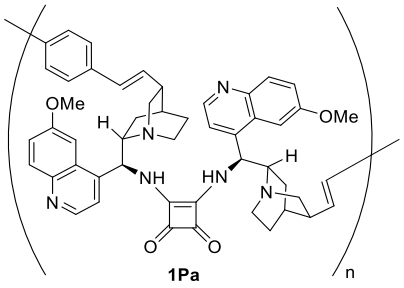


Scheme 1. Synthesis of main-chain squaramide polymer using MH polymerization.

Table 1. The enantioselective Michael addition of β-ketoester **3** to nitroolefin **4**.



entry	catalyst	solvent	temp., °C	reaction time, h	yield ,%[b]	*dr*[c]	*ee*, %[c]
1	**1SQ**	CH_2Cl_2	rt.	2	95	79:1	91
2	**1Pa**	CH_2Cl_2	rt.	30	71	28:1	97
5	**1Pa**	EtOAc	rt.	22	66	20:1	96

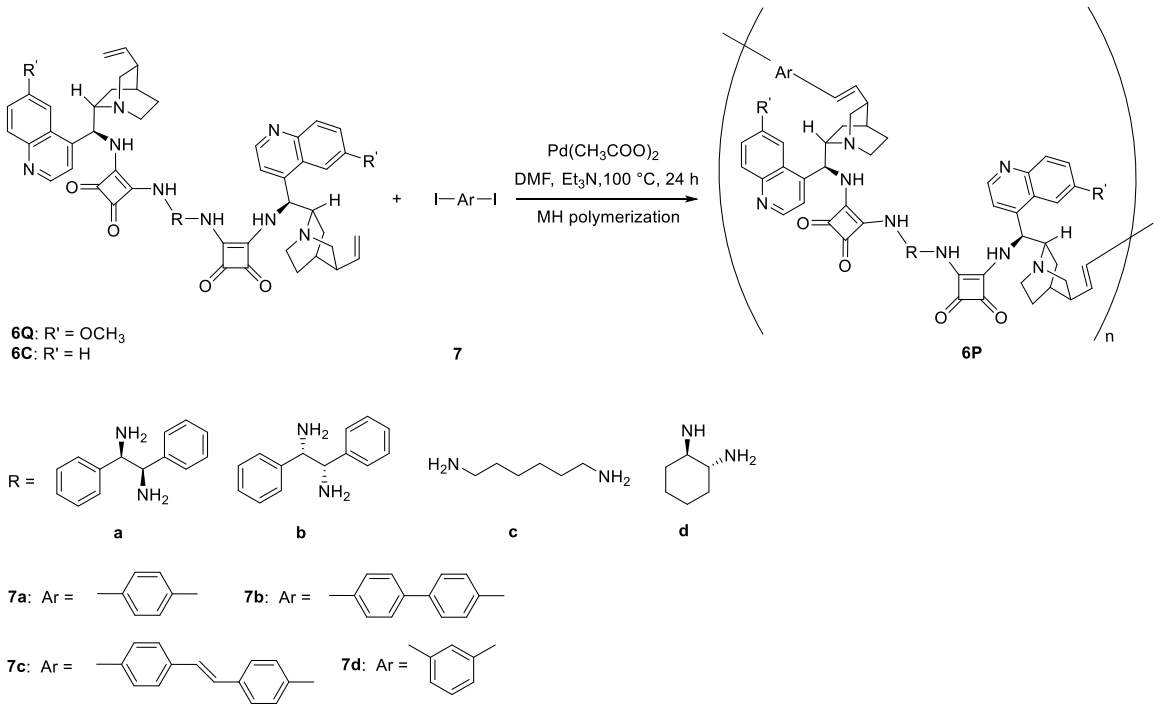


1Pa

The chiral main-chain squaramide polymers **1P** were successfully synthesized by the reaction between cinchona-derived squaramide **1SQ** and different aromatic diiodo compounds **2** by Mizoroki-Heck polymerization (Scheme **1**). These polymeric organocatalysts were applied in enantioselective Michael addition of methyl 2-oxocyclopentanecarboxylate to *trans*-β-nitrostyrene and the asymmetric compounds were obtained in good yield with high enantioselectivity up to 97% ee (Table **1**). The polymeric organocatalysts were used for recycling test on the same reaction successfully.

5.2 Synthesis of chiral main-chain polymers of diamine connected cinchona squaramides by Mizoroki–Heck polymerization and their application to asymmetric catalysis

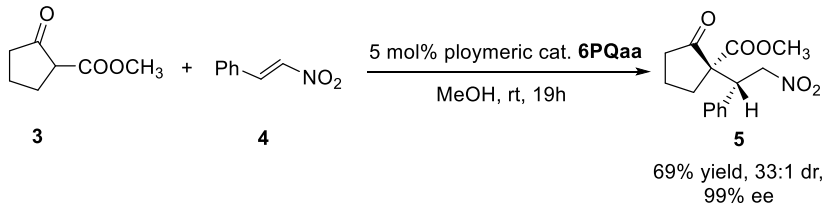
In chapter **4**, I synthesized novel cinchona squaramide dimers that contain two cinchona squaramide units connected by diamines and the novel chiral polymers of that cinchona squaramides. The olefinic double bonds in these dimers were used for Mizoroki–Heck polymerization with aromatic diiodides to give the corresponding chiral polymers in good yields.



Scheme 2. Synthesis of main-chain diamine connected squaramide polymers using MH polymerization.

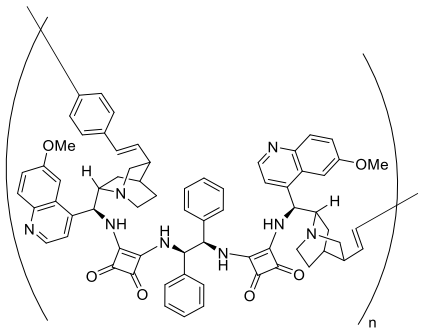
We have surveyed the effect of the chiral polymer structure on the catalytic activity and enantioselectivity of the asymmetric reaction. The novel squaramides and also polymers were applied

in asymmetric Michael addition of β-ketoesters to nitroolefins to obtain the asymmetric compounds in good yields with excellent stereoselectivities. Scheme **2** shows the preparation of main-chain squaramide chiral polymeric organocatalysts **6P** by the reaction between diamine-connected cinchona squaramides **6** and various diiodo compounds **7** using MH polymerization technique.



Scheme 3. The enantioselective Michael addition of β-ketoester **3** to nitroolefin **4**.

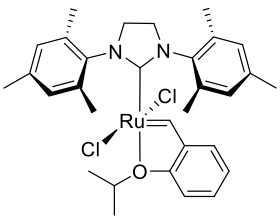
Using the chiral main-chain polymeric organocatalyst **6PQaa** in this above asymmetric reaction (scheme **3**), the addition adduct was obtained in good yields with excellent enantioselectivity up to 99% ee. The used polymeric catalyst was also recovered and reused several times without significant loss of catalytic activity.



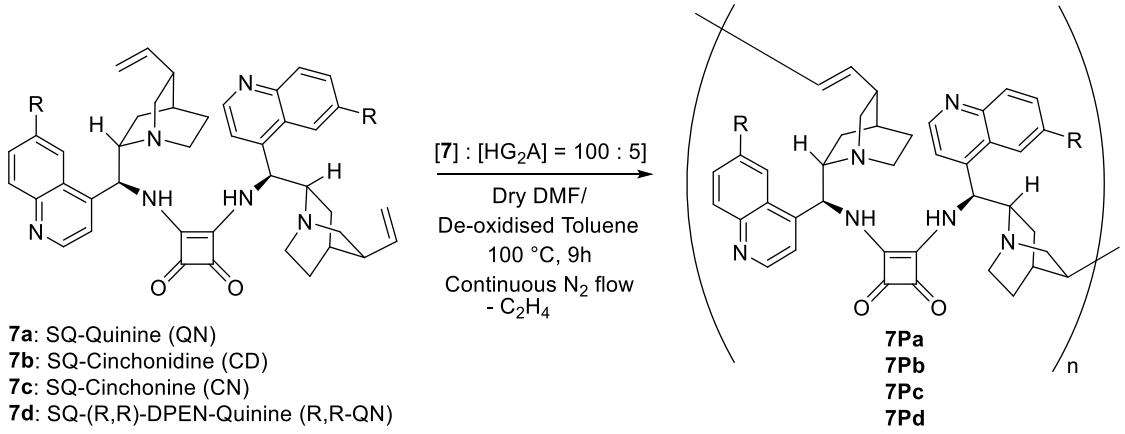
6PQaa

5.3 Synthesis of cinchona alkaloid-derived chiral squaramide polymers by ADMET polymerization and their application to asymmetric catalysis

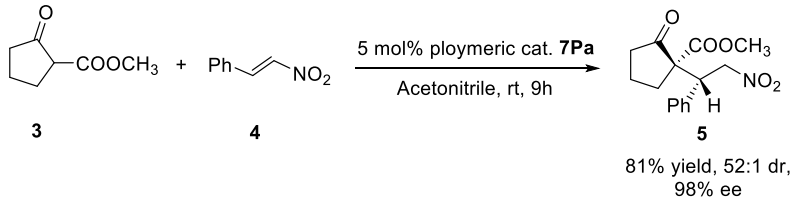
In chapter **5,** I have synthesized novel chiral cinchona alkaloid-derived squaramide polymers by ADMET Polymerization. The first synthesis of high molecular weight cinchona alkaloid-derived chiral squaramide polymers by acyclic diene metathesis (ADMET) polymerization is described using the Hoveyda-Grubbs 2nd generation catalysts (**HG_2**). I have synthesized novel chiral polymeric catalysts **7P** containing cinchona squaramide moieties in the main chain of the polymer using ADMET reaction in between diene **7** and Hoveyda-Grubbs 2nd generation catalysts (**HG_2**).



Hoveyda-Grubbs 2nd generation catalysts (**HG_2**)



Scheme 4. Synthesis of main-chain squaramide polymers using ADMET polymerization



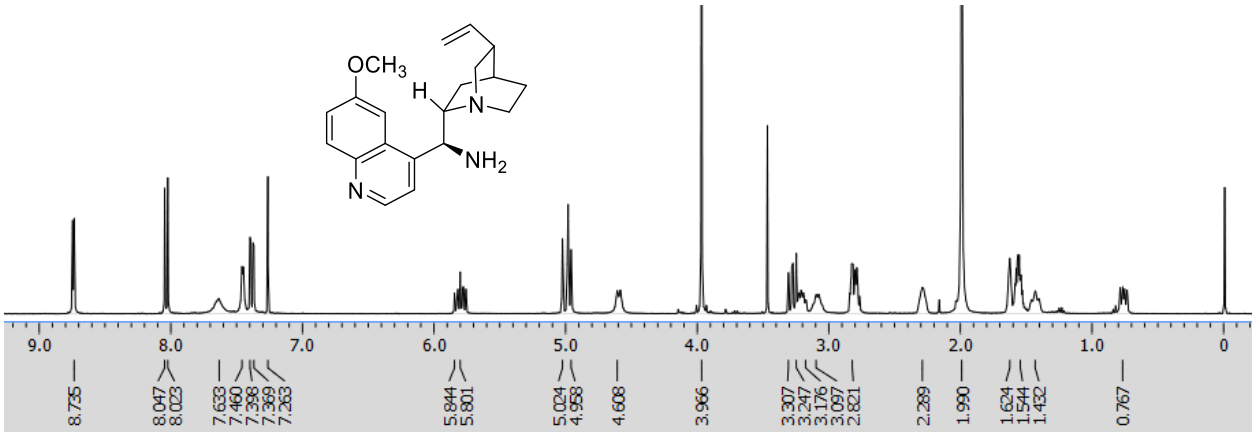
Scheme 5. The enantioselective Michael addition of β-ketoester **3** to nitroolefin **4**.

The chiral ADMET polymers **7P** were also used as organocatalysts in the same asymmetric Michael addition and the addition products were obtained in good yields with excellent stereoselectivities up to 52:1 *dr* and 98% *ee* (using polymeric catalyst **7Pa**). These polymeric catalysts were also easily recovered from the reaction mixture and reused several times.

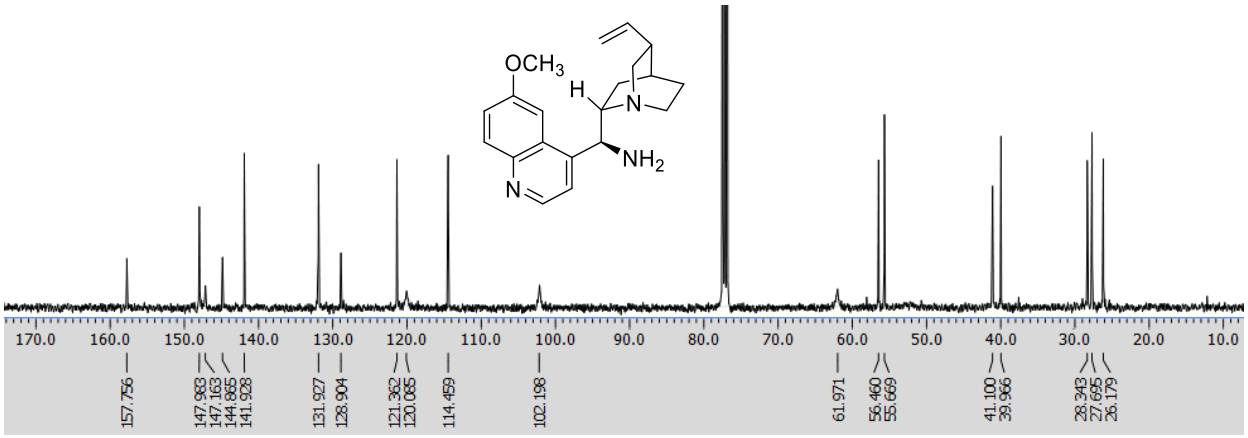
From the study of asymmetric catalysis on the enantioselective Michael addition reaction, it was found that the catalytic activity and stereoselectivity of the chiral ADMET polymers were higher than the corresponding chiral Mizoroki-Heck polymers. But in case of diamine connected squaramide containing chiral polymers somewhat higher enantioselectivity and better recyclability results were observed.

Spectra of different compounds for chapter 2

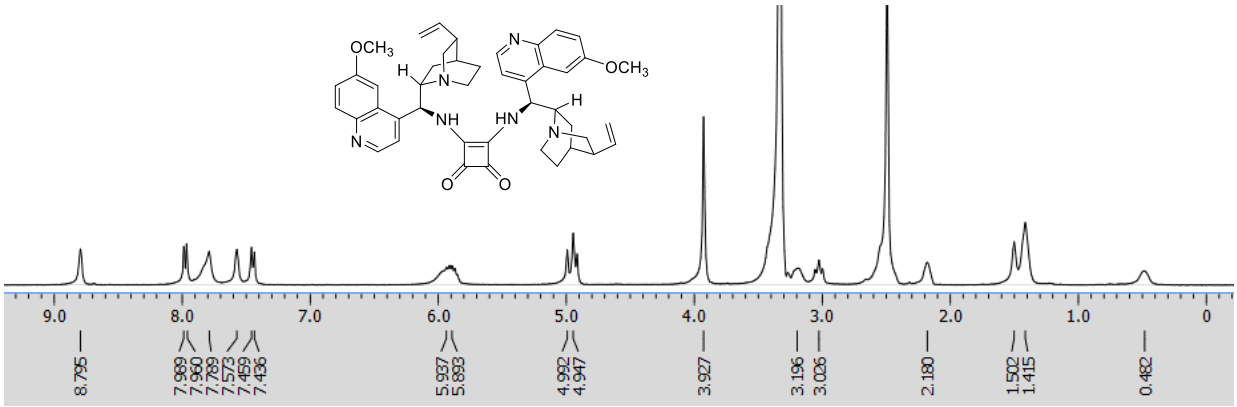
^{1}H NMR of 1QA in $CDCl_3$



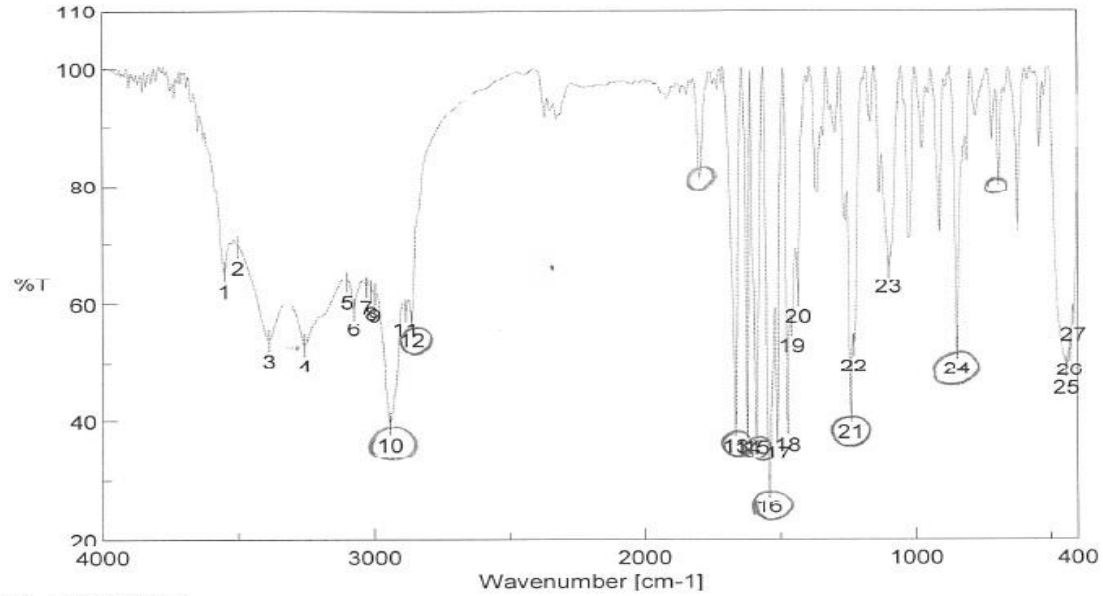
^{13}C NMR of 1QA in $CDCl_3$



^{1}H NMR of 2SQ in DMSO-d_6



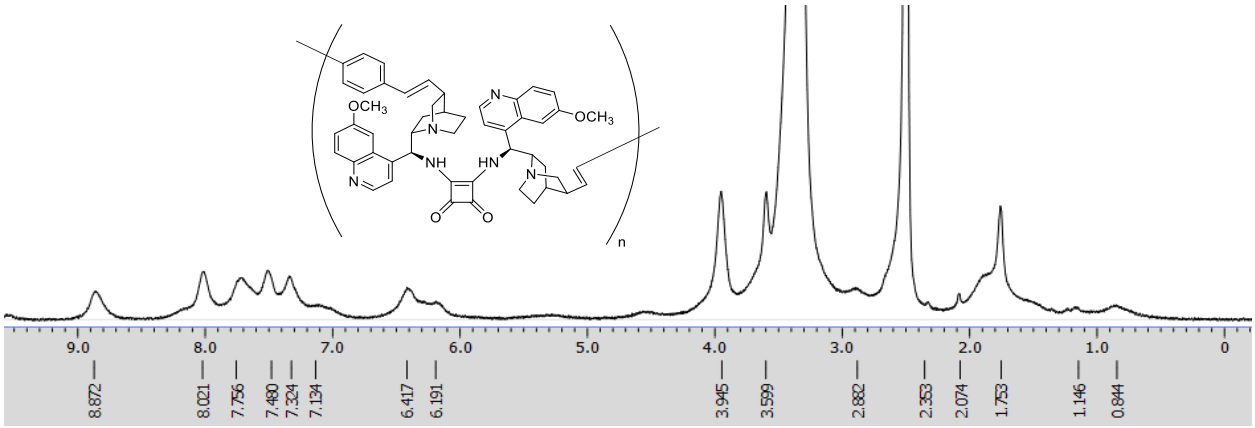
IR spectra of 2SQ



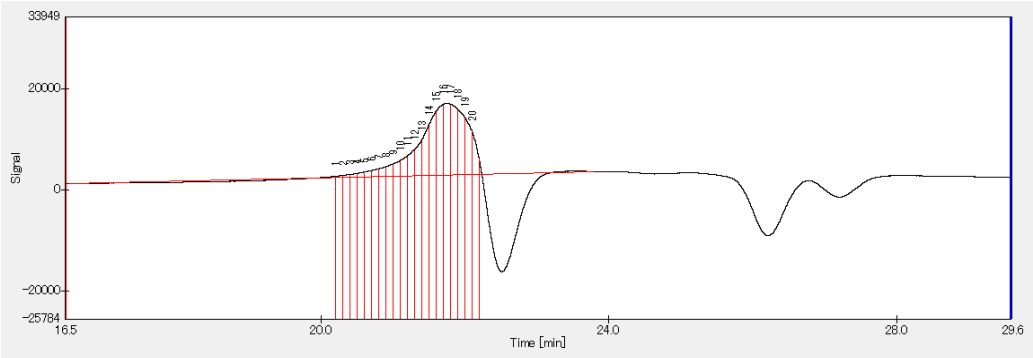
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3552.24	65.368	2	3501.13	69.515
3	3387.35	53.7184	4	3256.22	52.8729
5	3100.01	63.6811	6	3074.94	59.015
7	3029.62	62.8479	8	3010.34	61.8873
9	2997.6	61.5223	10	2942.84	39.4229
11	2884.02	58.8683	12	2860.88	57.1449
13	1665.23	39.1905	14	1621.84	38.9402
15	1589.06	39.0108	16	1540.85	28.868
17	1510.95	37.9538	18	1473.35	39.4366
19	1457.92	56.1654	20	1433.82	61.3214
21	1240	41.5145	22	1228.43	52.751
23	1101.15	66.1675	24	847.561	52.2753
25	440.655	48.9943	26	428.12	52.0515

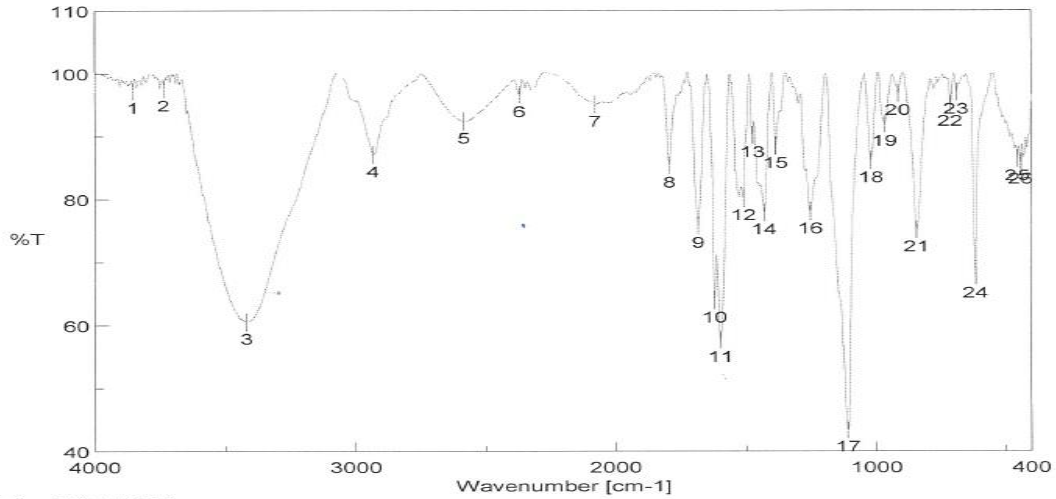
^{1}H NMR of polymer, 4PaSQ in DMSO-d_6



SEC data of polymer, 4PaSQ



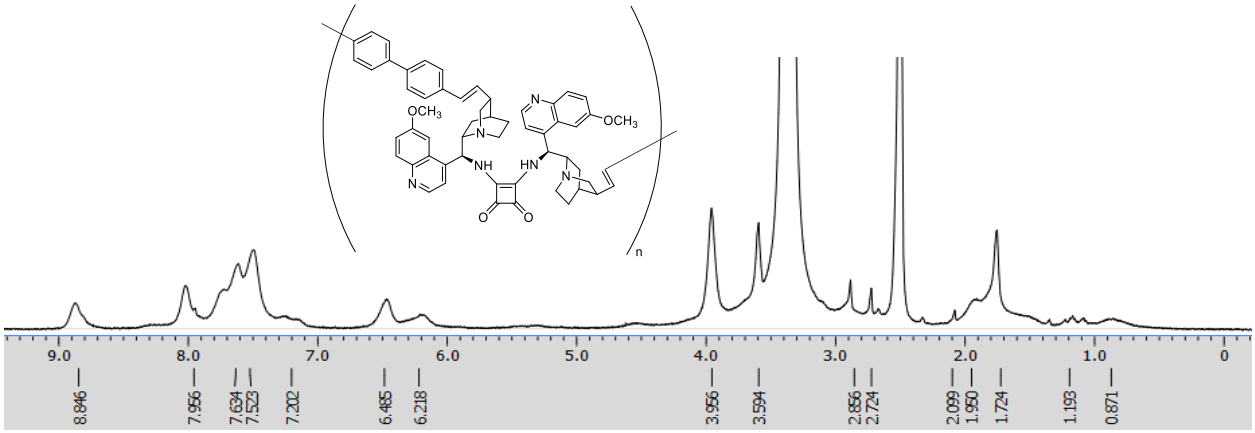
IR spectra of polymer, 4PaSQ



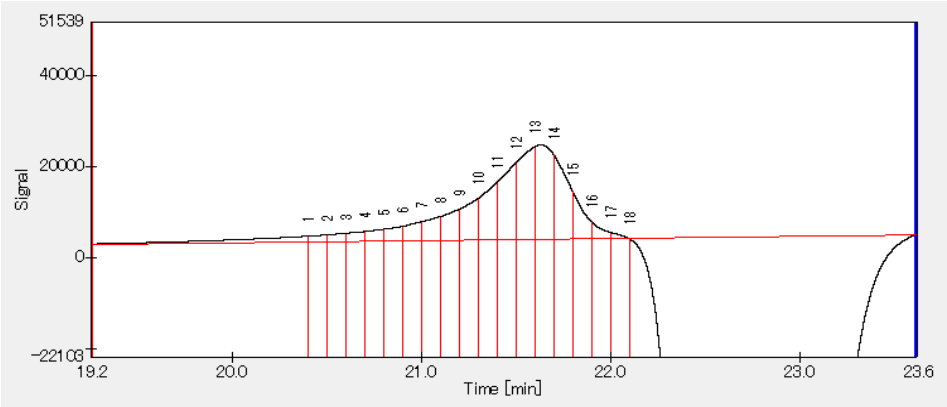
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3853.08	97.1749	2	3734.48	97.5209
3	3420.14	60.5028	4	2932.23	87.034
5	2584.15	92.3299	6	2370.09	96.5196
7	2079.85	94.9717	8	1793.47	85.2968
9	1683.55	75.7856	10	1620.88	63.9089
11	1597.73	57.6259	12	1508.06	80.1368
13	1474.31	90.0858	14	1429.96	77.8891
15	1385.6	88.3842	16	1252.54	78.0097
17	1109.83	43.4362	18	1019.19	86.0665
19	967.126	91.8367	20	916.022	96.7704
21	844.669	75.1655	22	713.533	95.0045
23	690.391	96.9221	24	617.109	67.7748
25	453.19	86.3353	26	440.655	85.8084

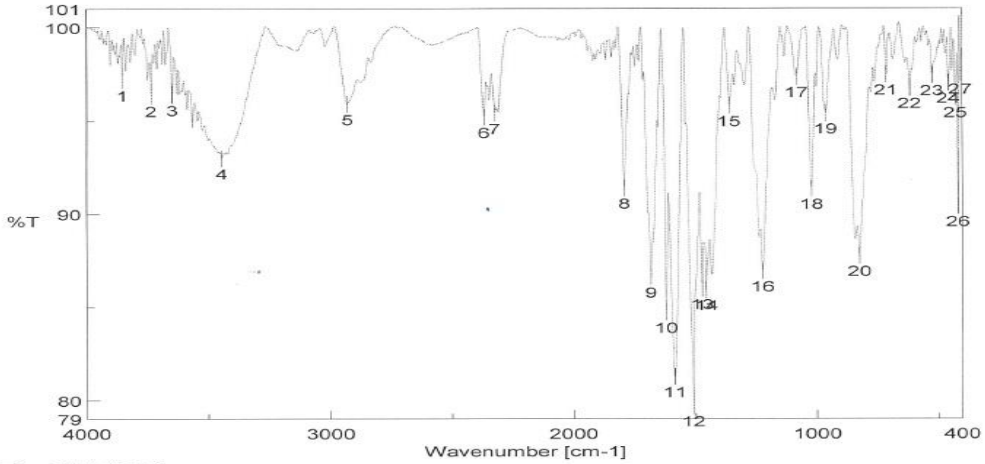
^{1}H NMR of polymer, 4PbSQ in DMSO-d_6



SEC data of polymer, 4PbSQ



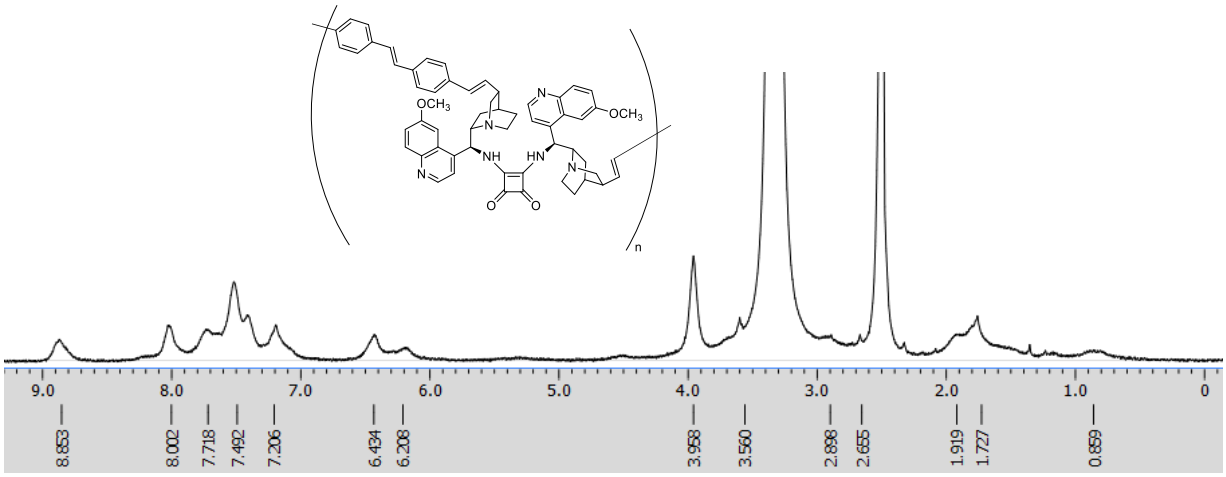
IR spectrum of polymer, 4PbSQ



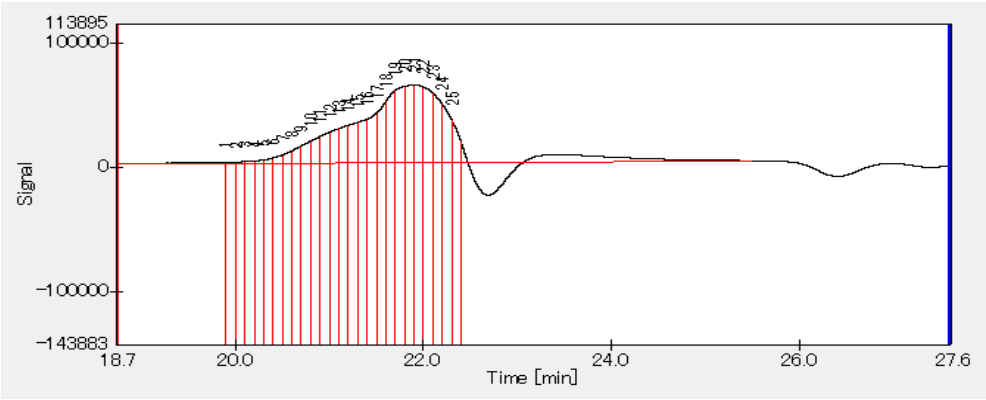
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
~~1~~	3853.08	97.1631	~~2~~	3734.48	96.3435
~~3~~	3648.66	96.3931	~~4~~	3446.17	92.985
~~5~~	2931.27	95.8853	~~6~~	2369.12	95.1863
~~7~~	2325.73	95.3893	~~8~~	1792.51	91.3773
~~9~~	1683.55	86.5799	~~10~~	1620.88	84.6975
~~11~~	1585.2	81.2703	~~12~~	1508.06	79.6923
~~13~~	1473.35	85.9639	14	1455.99	85.908
15	1361.5	95.7839	~~16~~	1224.58	86.9166
17	1084.76	97.33	~~18~~	1024.02	91.3511
19	965.198	95.3844	~~20~~	826.348	87.7281
~~21~~	714.497	97.4534	~~22~~	617.109	96.7393
23	524.543	97.4116	24	457.047	97.009
25	427.155	96.2392	26	417.513	90.3971
27	406.907	97.4958			

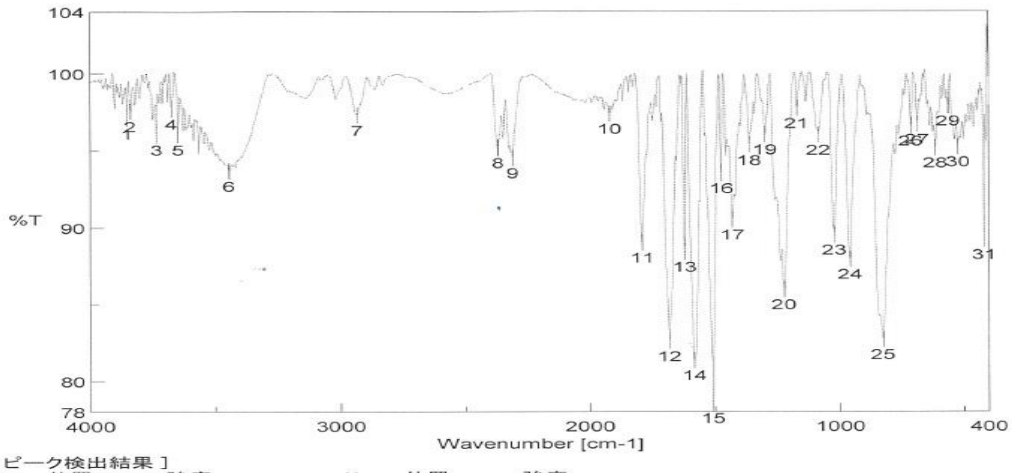
^{1}H NMR of polymer, 4PeSQ in DMSO-d_6



SEC data of polymer, 4PeSQ



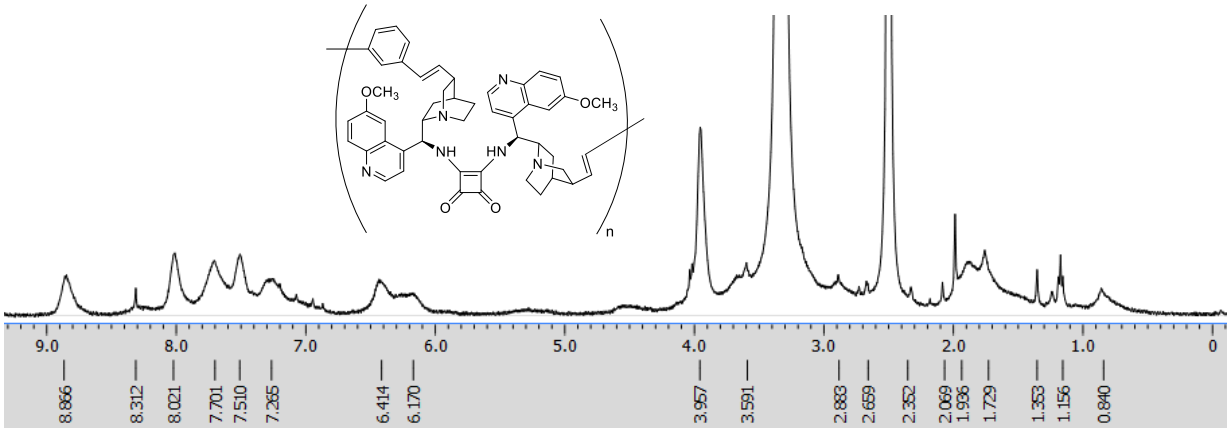
IR spectrum of polymer, 4PeSQ



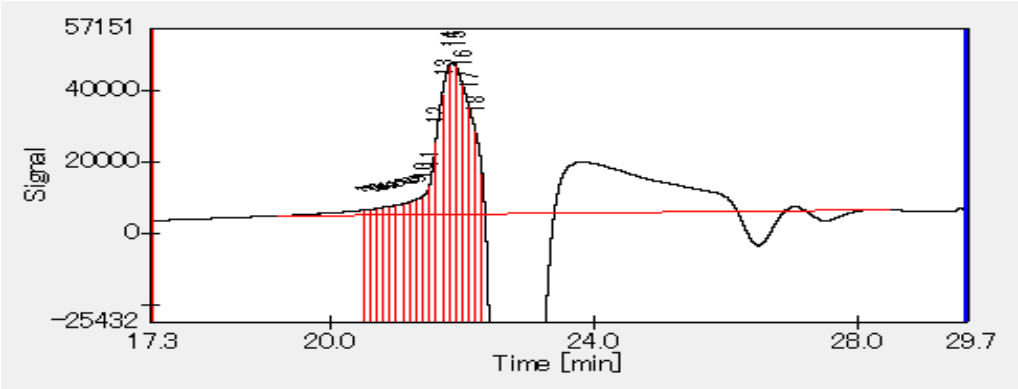
［ピーク検出結果］

No.	位置	強度	No.	位置	強度
~~1~~	3853.08	97.0462	2	3839.58	97.5305
~~3~~	3734.48	96.0197	4	3675.66	97.7011
~~5~~	3648.66	96.0227	6	3446.17	93.6645
~~7~~	2933.2	97.2806	8	2369.12	95.1673
~~9~~	2310.3	94.5081	10	1920.75	97.3634
~~11~~	1791.55	89.0107	~~12~~	1683.55	82.577
13	1621.84	88.4126	~~14~~	1583.27	81.3392
~~15~~	1508.06	78.5598	16	1473.35	93.5087
~~17~~	1429.96	90.4966	18	1361.5	95.3204
19	1298.82	96.0137	~~20~~	1224.58	85.948
21	1171.54	97.7169	22	1084.76	95.9833
~~23~~	1023.05	89.5089	~~24~~	960.377	87.925
~~25~~	828.277	82.6813	~~26~~	713.533	96.5596
27	688.463	96.6649	~~28~~	614.217	95.1406
29	563.112	97.8635	30	523.579	95.206

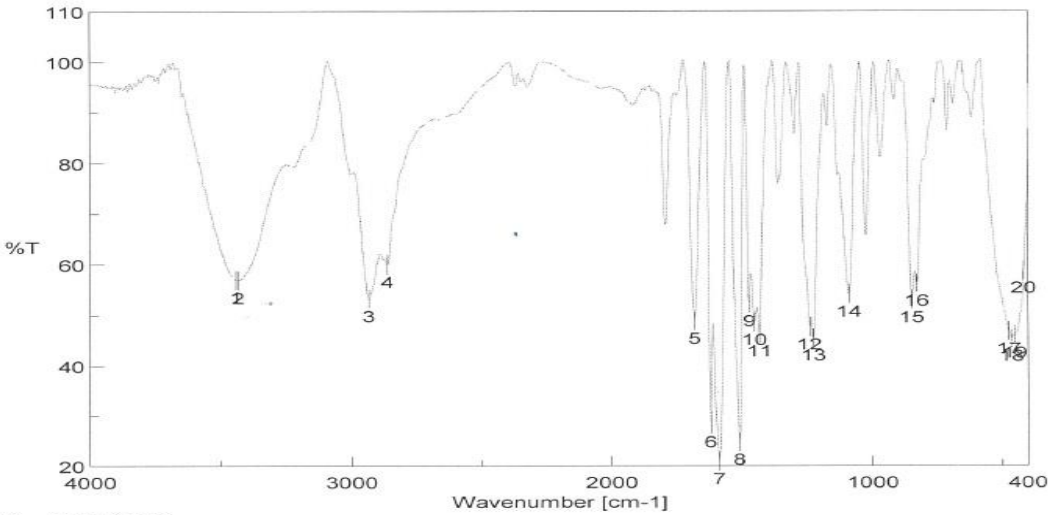
^{1}H NMR of polymer, 4PfSQ in DMSO-d_6



SEC data of polymer, 4PfSQ



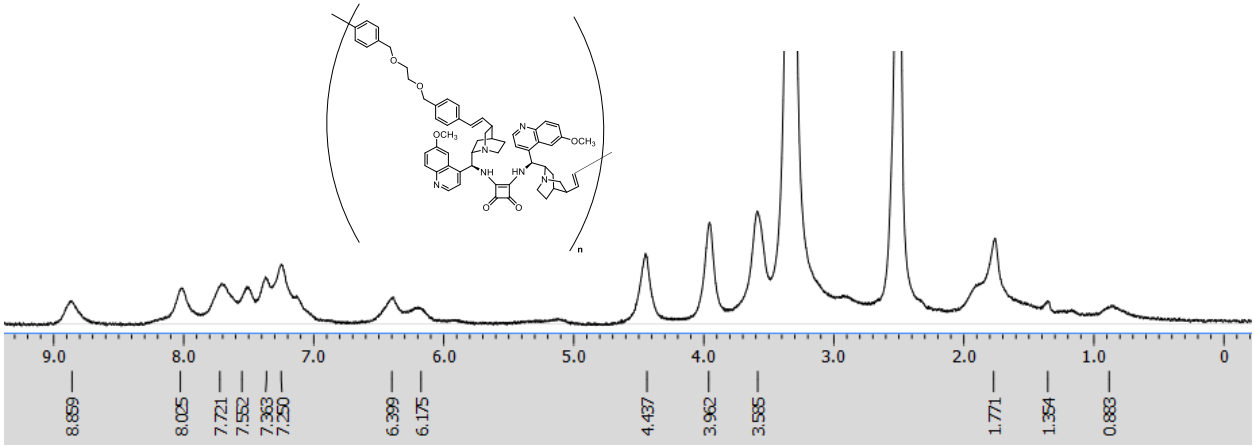
IR spectrum of polymer, 4PfSQ



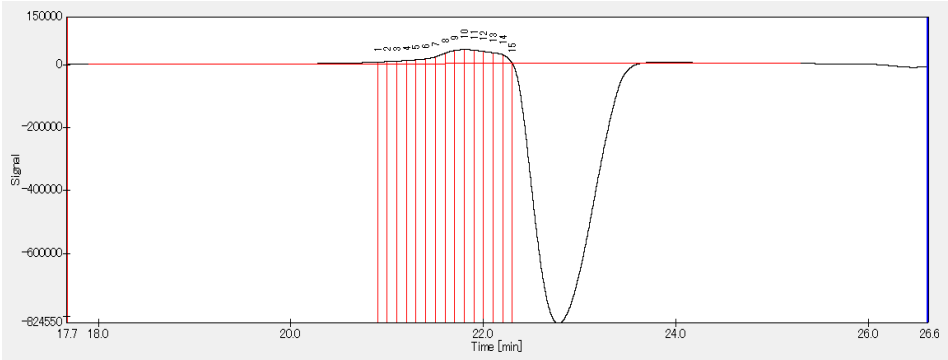
［ピーク検出結果］

No.	位置	強度	No.	位置	強度
~~1~~	3443.28	56.9415	2	3433.64	56.8379
~~3~~	2933.2	53.2285	~~4~~	2862.81	59.9464
~~5~~	1682.59	48.8274	~~6~~	1620.88	28.1786
~~7~~	1588.09	20.8822	~~8~~	1509.99	24.7014
9	1473.35	52.2588	10	1453.1	48.6067
~~11~~	1433.82	46.3119	12	1241.93	47.6585
~~13~~	1227.47	45.5001	~~14~~	1091.51	54.0933
~~15~~	848.525	52.9717	16	830.205	56.2188
17	474.403	46.7718	18	463.796	45.3023
19	451.261	45.9389	20	416.549	58.7177

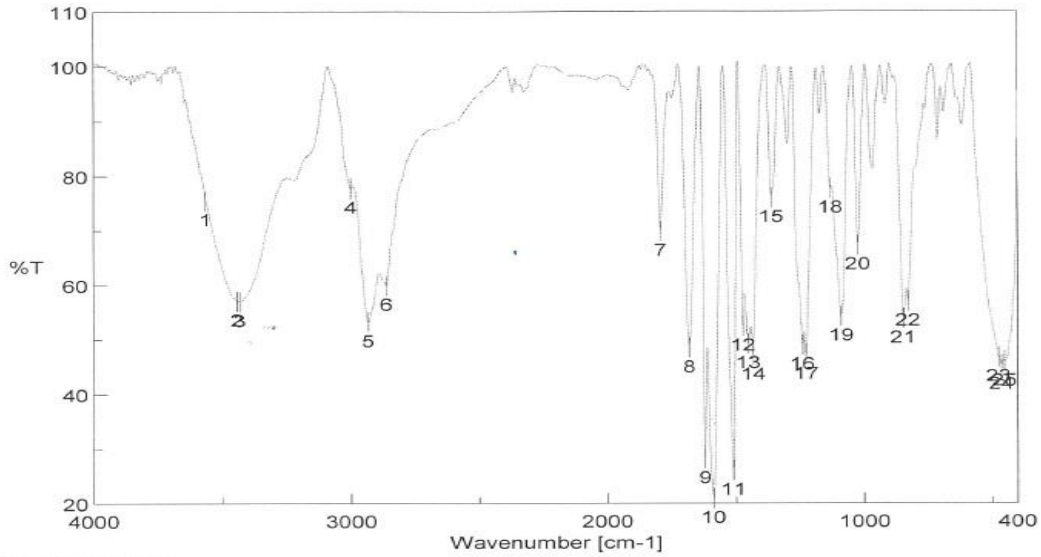
^{1}H NMR of polymer, 4PgSQ in DMSO-d_6



SEC data of polymer, 4PgSQ



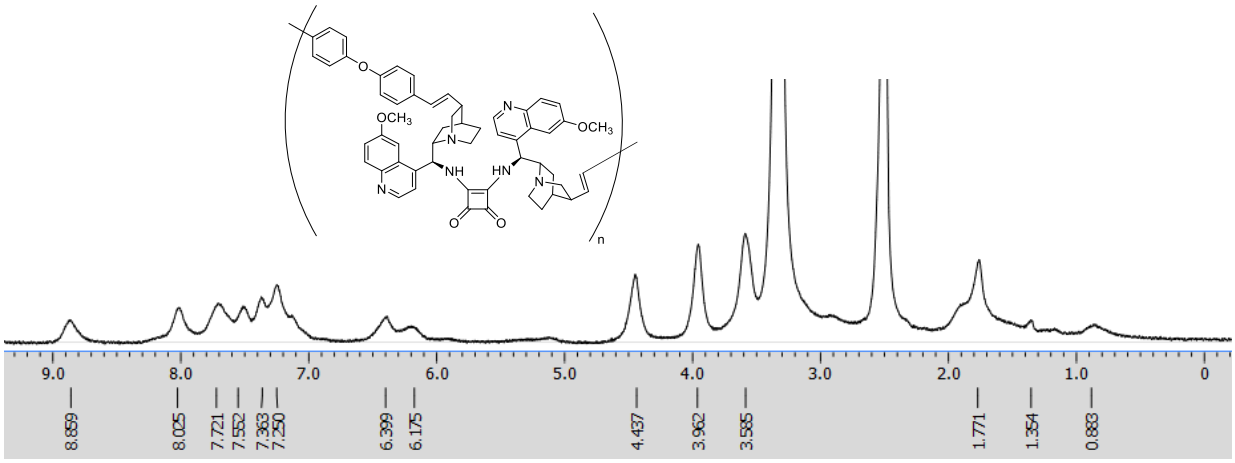
IR spectrum of polymer, 4PgSQ



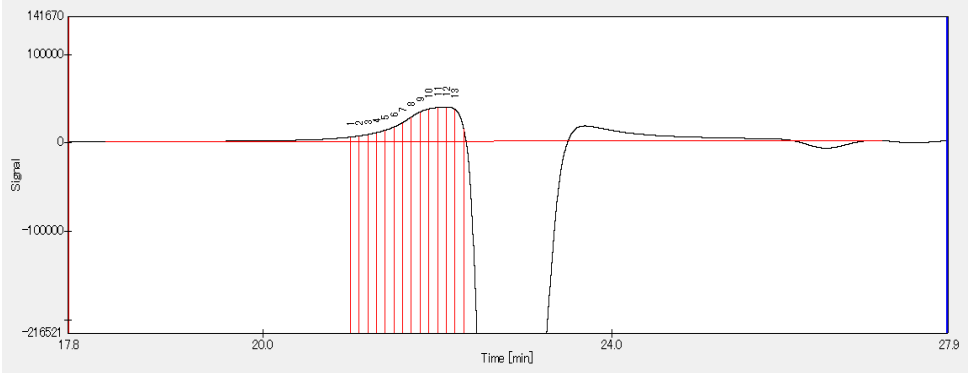
［ピーク検出結果］

No.	位置	強度	No.	位置	強度
1	3564.77	75.459	~~2~~	3443.28	57.0139
3	3433.64	56.9052	4	3000.69	77.6901
~~5~~	2933.2	53.1404	6	2862.81	59.8582
~~7~~	1793.47	69.8484	~~8~~	1682.59	48.4169
~~9~~	1620.88	28.2019	~~10~~	1588.09	20.8963
~~11~~	1509.99	26.0682	12	1473.35	52.3763
13	1453.1	49.1632	~~14~~	1433.82	47.0448
~~15~~	1362.46	75.9985	16	1241.93	48.9245
~~17~~	1227.47	47.1556	18	1132.97	77.7168
~~19~~	1091.51	54.184	20	1025.94	67.2634
~~21~~	848.525	53.7371	22	830.205	56.8827
23	474.403	46.671	24	463.796	45.2135

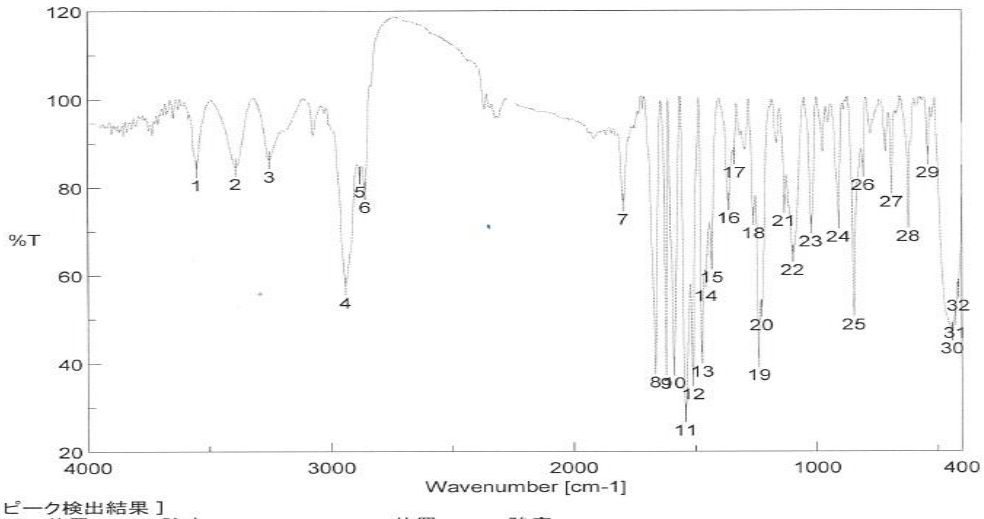
^{1}H NMR of polymer, 4PhSQ in DMSO-d_6



SEC data of polymer, 4PfSQ



IR spectrum of polymer, 4PhSQ



[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3553.2	84.3128	2	3392.17	84.6753
3	3255.25	86.2672	4	2942.84	57.5038
5	2883.06	82.8087	6	2860.88	79.3135
7	1798.3	76.4814	8	1665.23	39.5423
9	1621.84	39.2338	10	1589.06	39.3688
11	1540.85	28.6109	12	1510.95	36.8418
13	1473.35	41.9645	14	1457.92	59.0549
15	1433.82	63.3006	16	1364.39	76.732
17	1341.25	87.1475	18	1261.22	73.322
19	1240	41.2188	20	1228.43	52.4487
21	1135.87	76.0696	22	1101.15	64.9207
23	1025.94	71.4043	24	912.165	72.4866
25	847.561	52.5628	26	810.92	84.2733
27	693.284	80.4048	28	622.895	72.6071
29	541.899	87.1258	30	440.655	47.1085

HPLC data of the products obtained from enantioselective Michael Addition of methyl 2-oxocyclopentanecarboxylate, 5 to *trans*-β-nitrostyrene, 6

Table 2, entry 1
91% ee

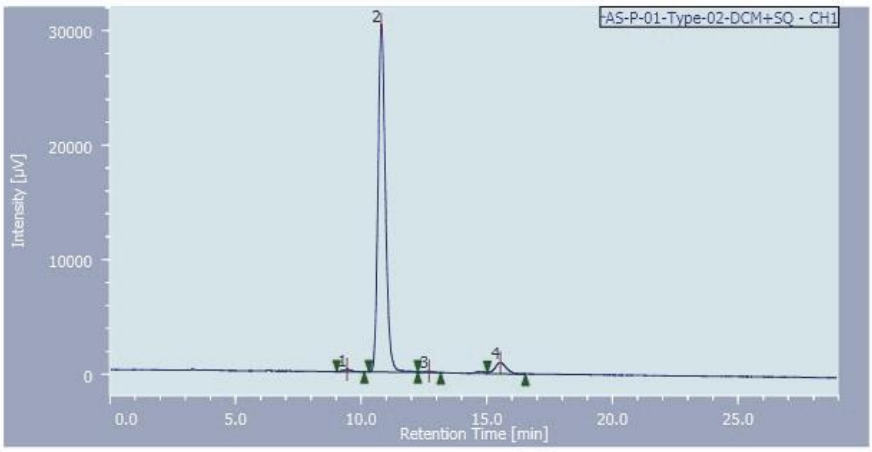


Table 2, entry 2
97% ee

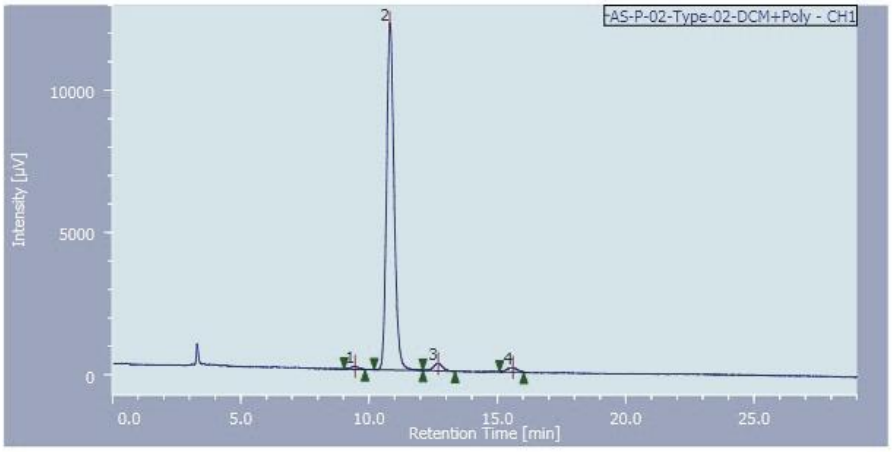


Table 2, entry 3
91% ee

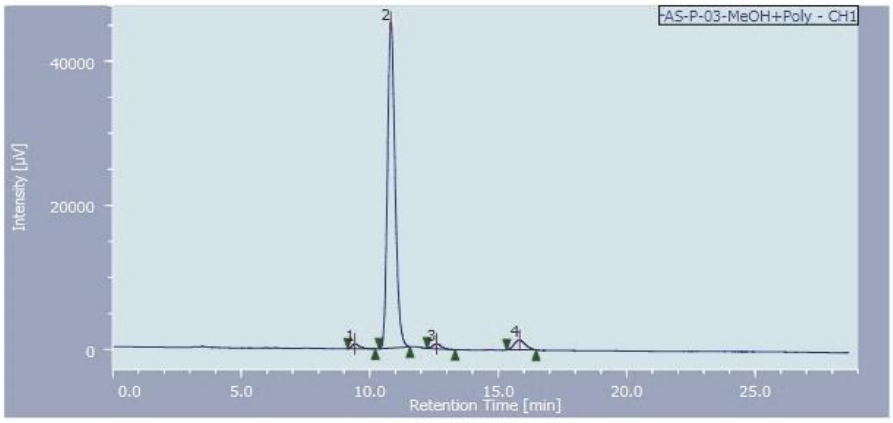


Table 2, entry 4
93% ee

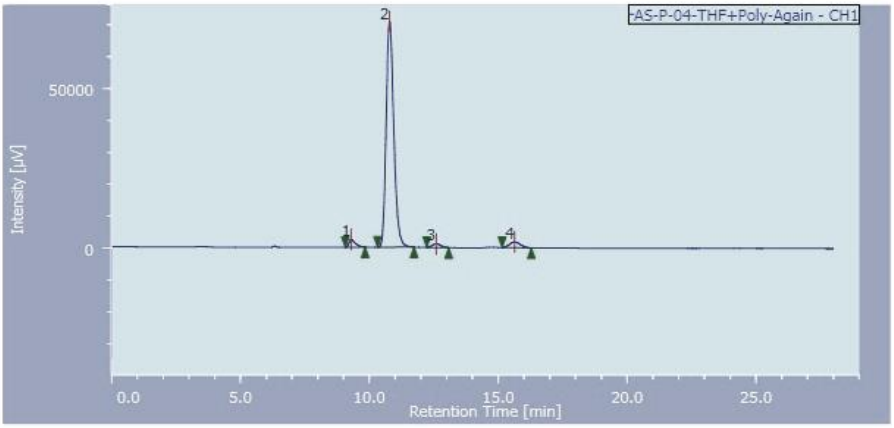


Table 2, entry 5
96% ee

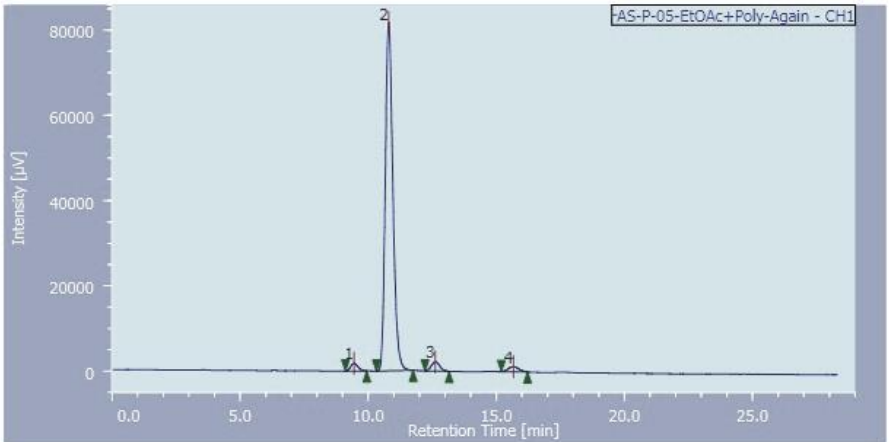


Table 2, entry 6
88% ee

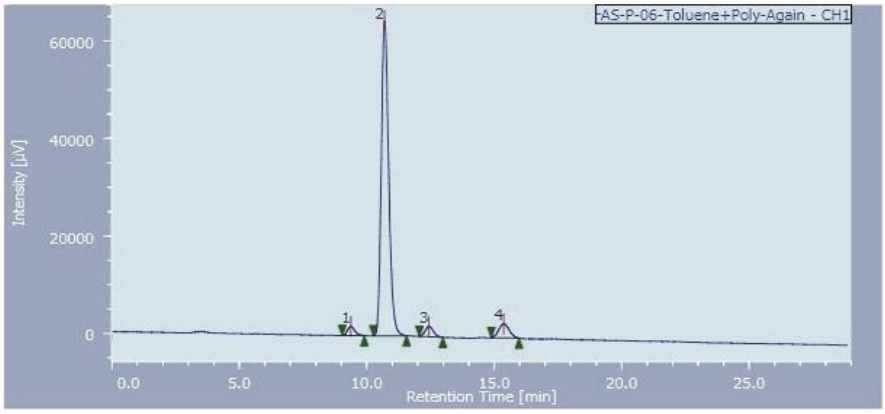


Table 3, entry 1
95% ee

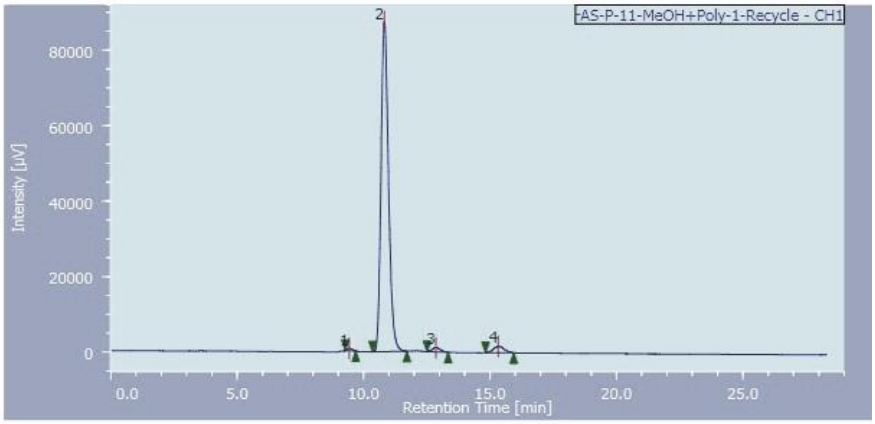


Table 3, entry 2
94% ee

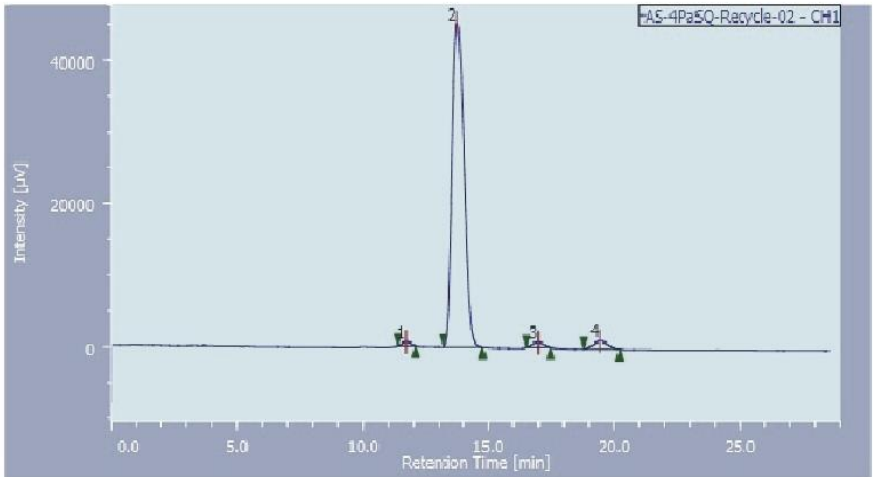


Table 3, entry 3
94% ee

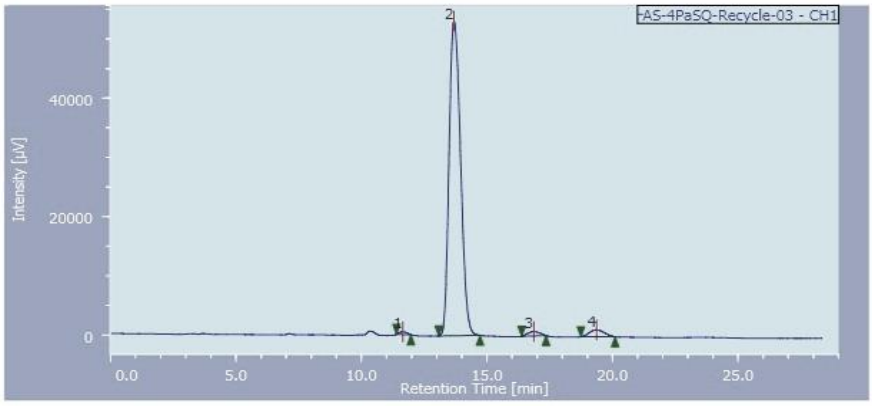


Table 3, entry 4
91% ee

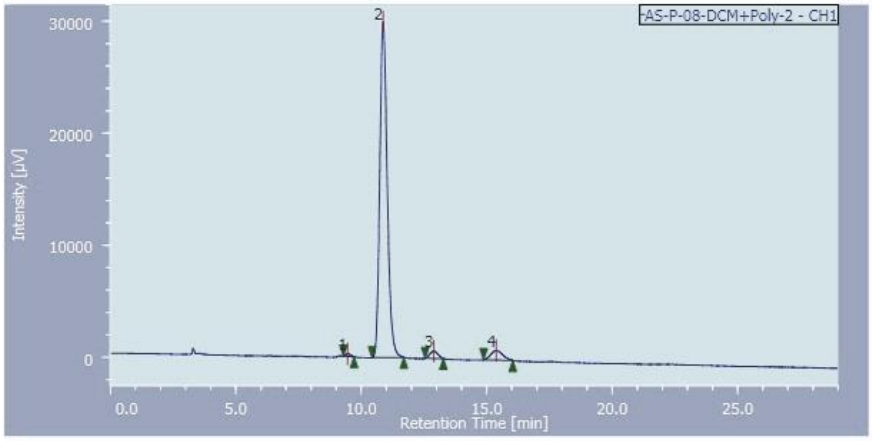


Table 3, entry 5
93% ee

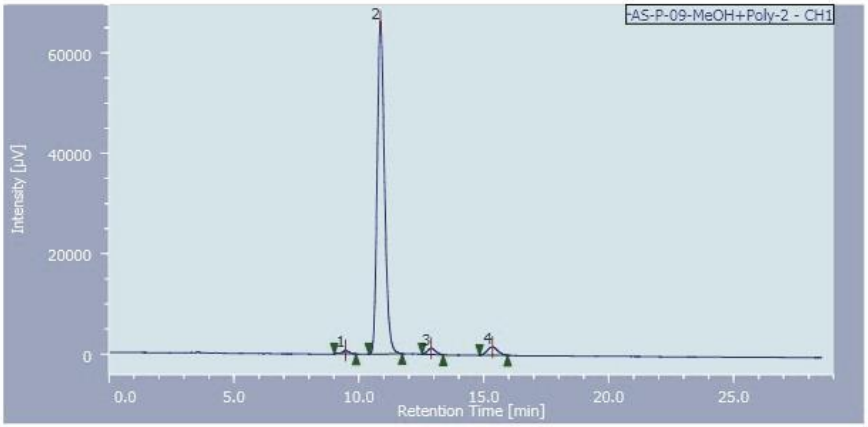


Table 3, entry 6
96% ee

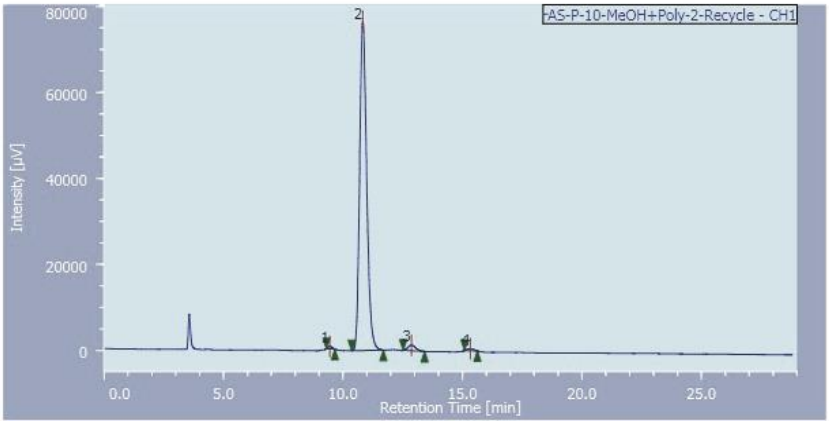


Table 3, entry 7
95% ee

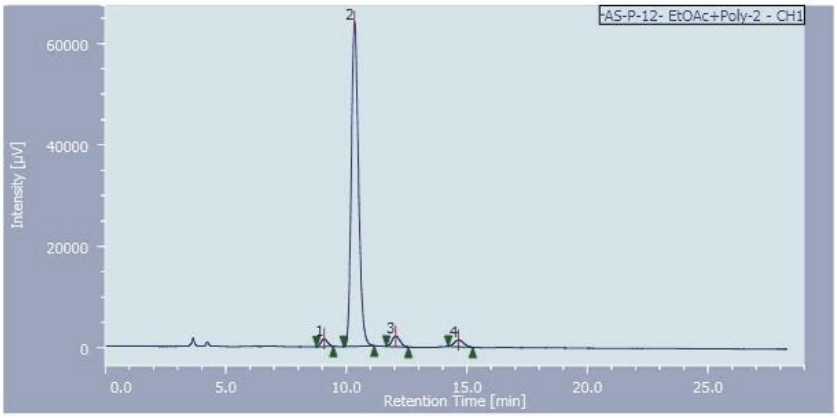


Table 3, entry 8
96% ee

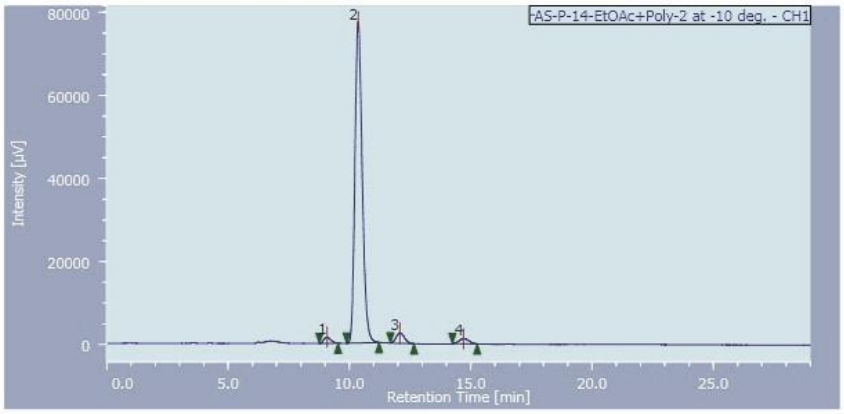


Table 3, entry 9
90% ee

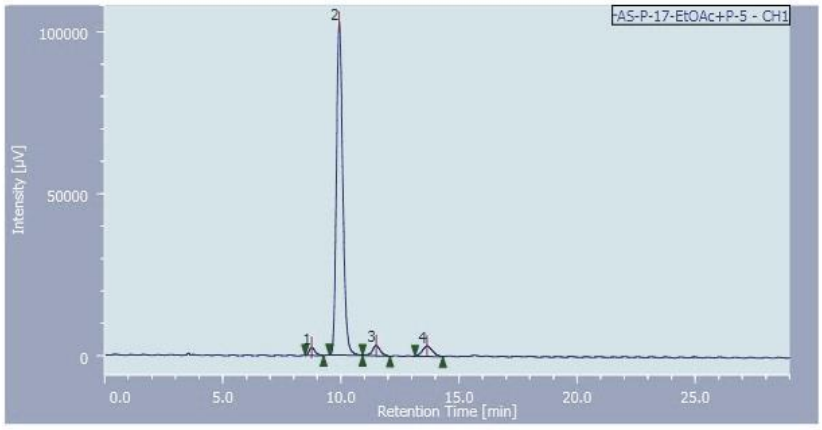


Table 3, entry 10
94% ee

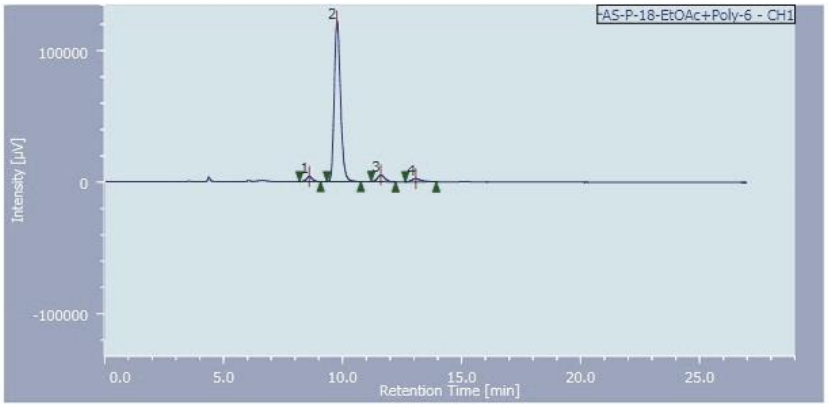


Table 3, entry 11
95% ee

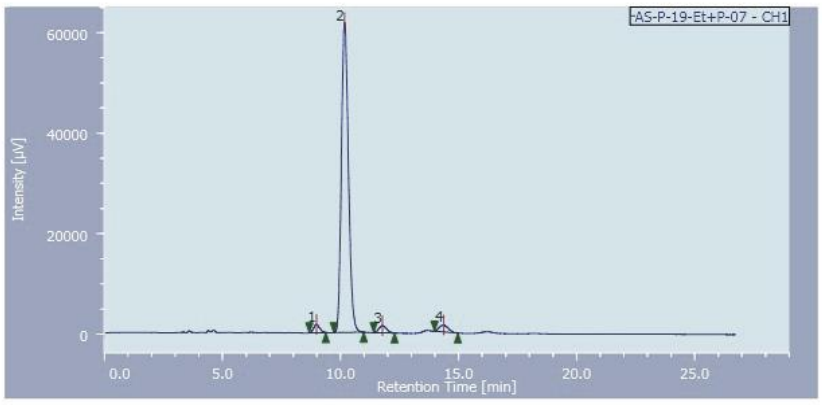
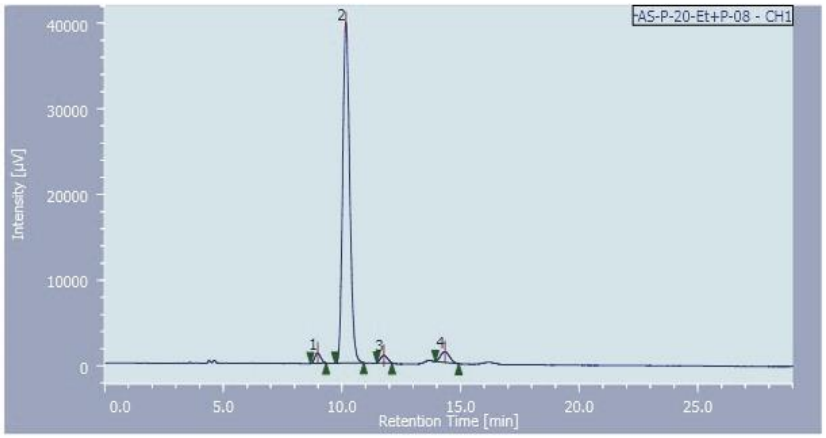
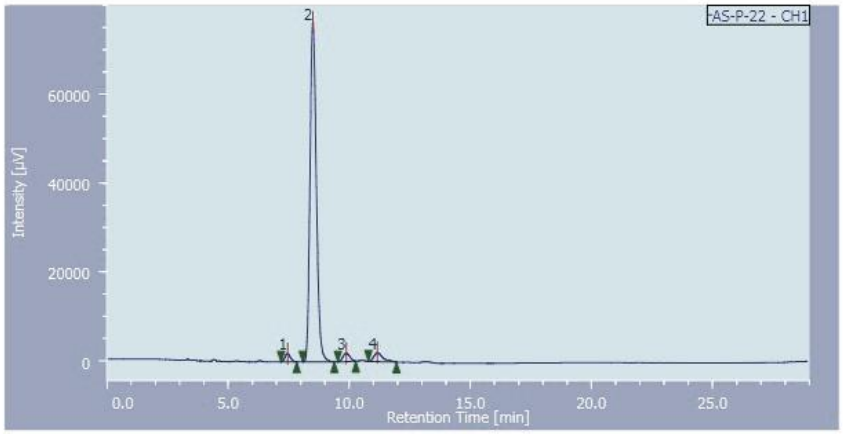


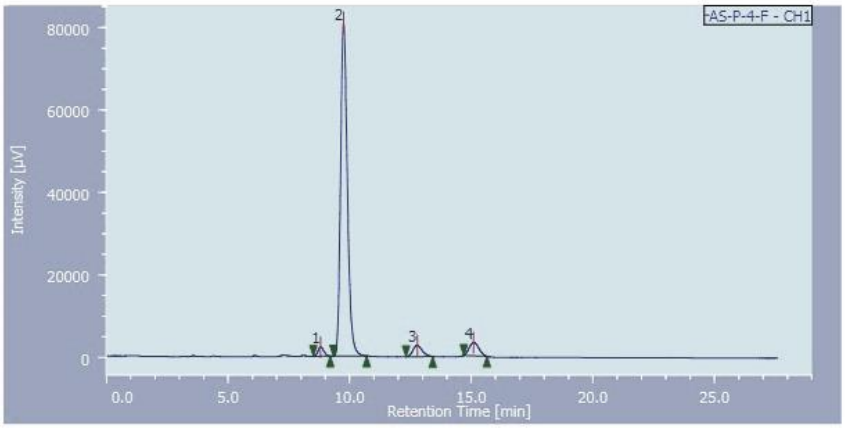
Table 3, entry 12
92% ee



Scheme 4-1
93% ee

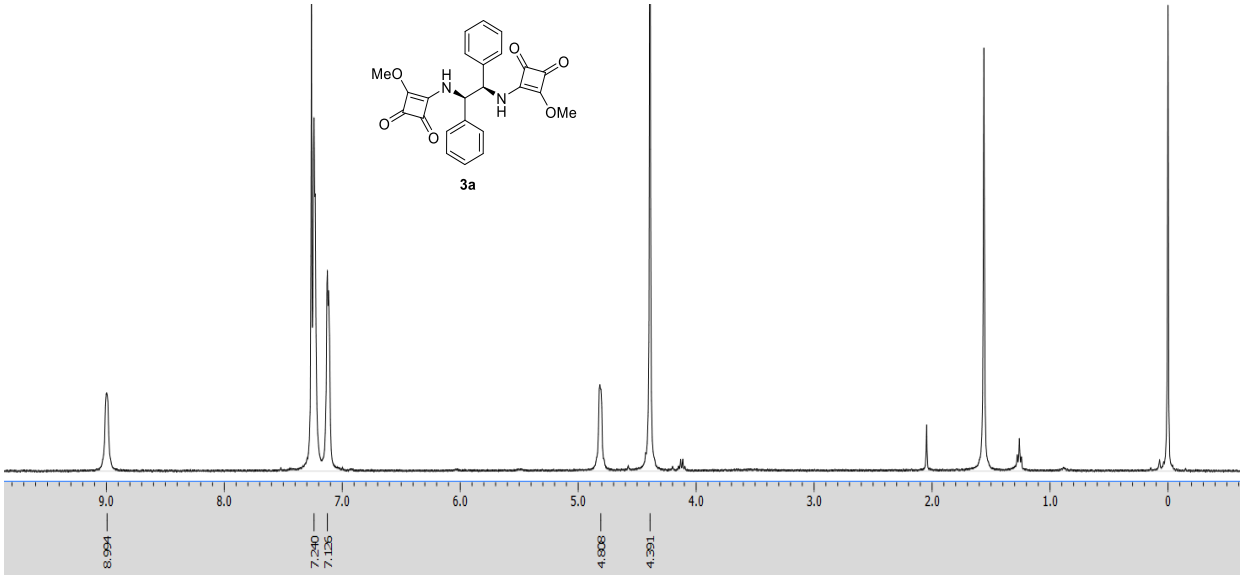


Scheme 4-2
89% ee

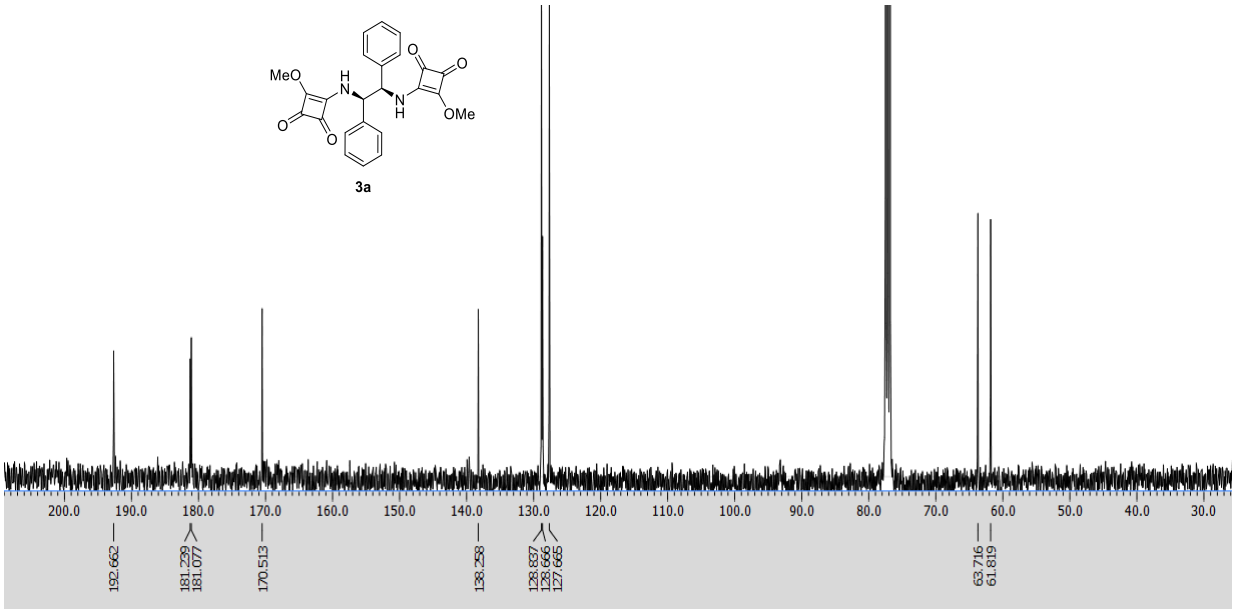


Spectra of different compounds for chapter 3

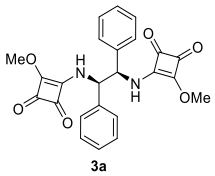
^{1}H NMR of 3a in $CDCl_3$



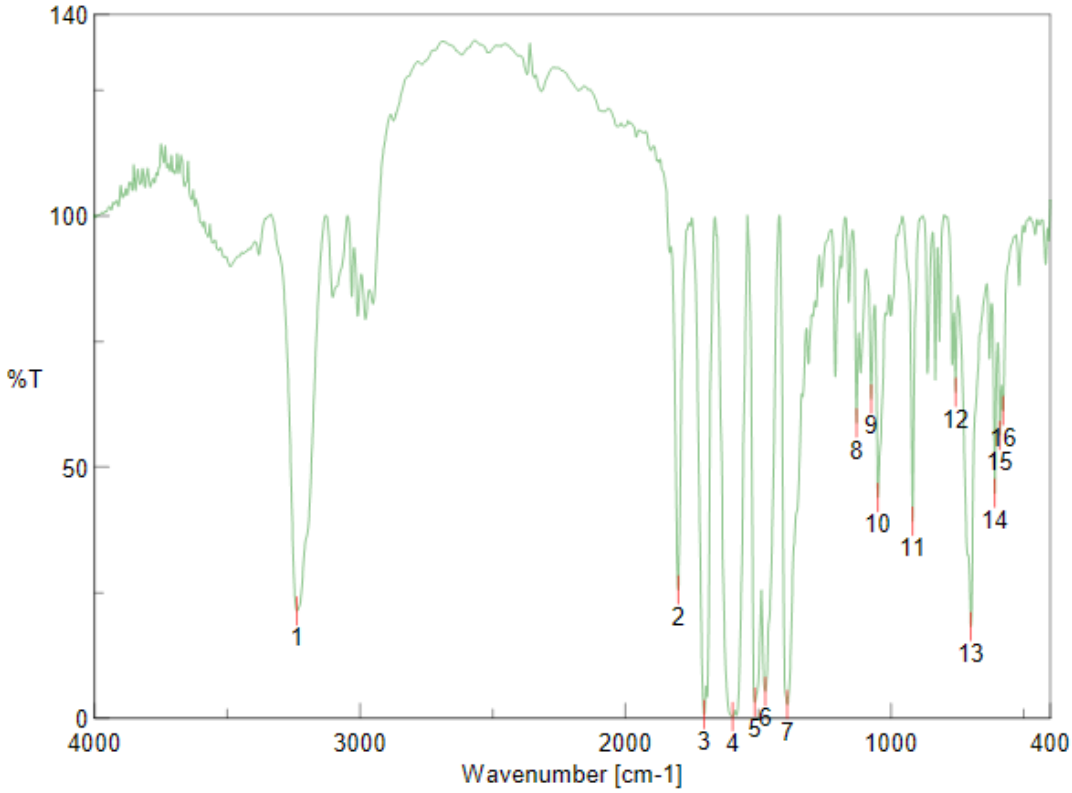
^{13}C NMR of 3a in $CDCl_3$



IR spectrum of 3a



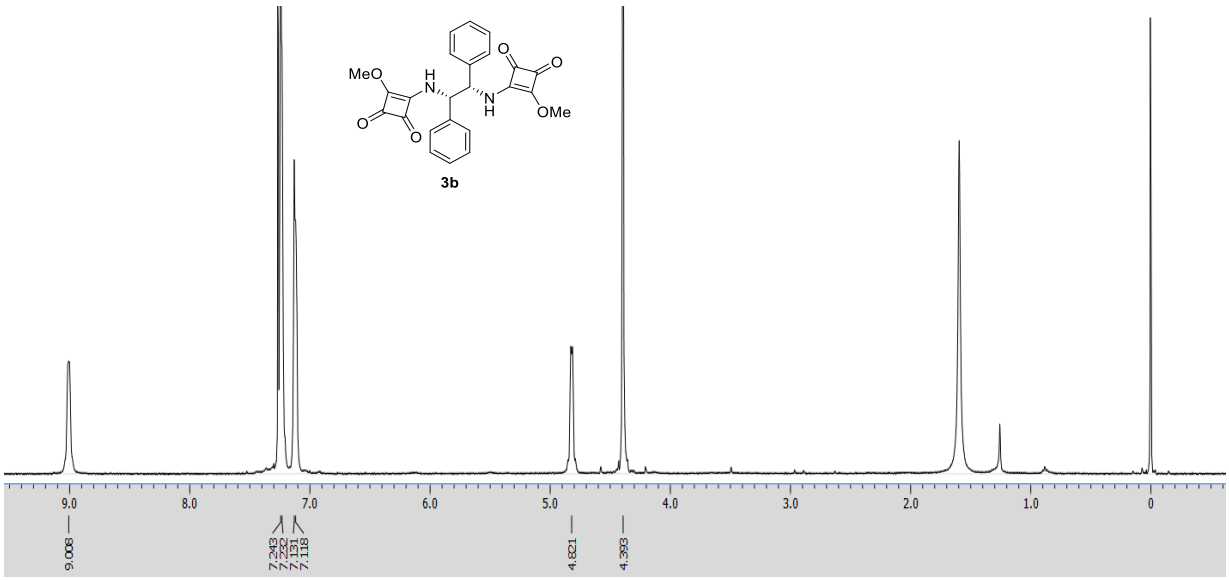
3a



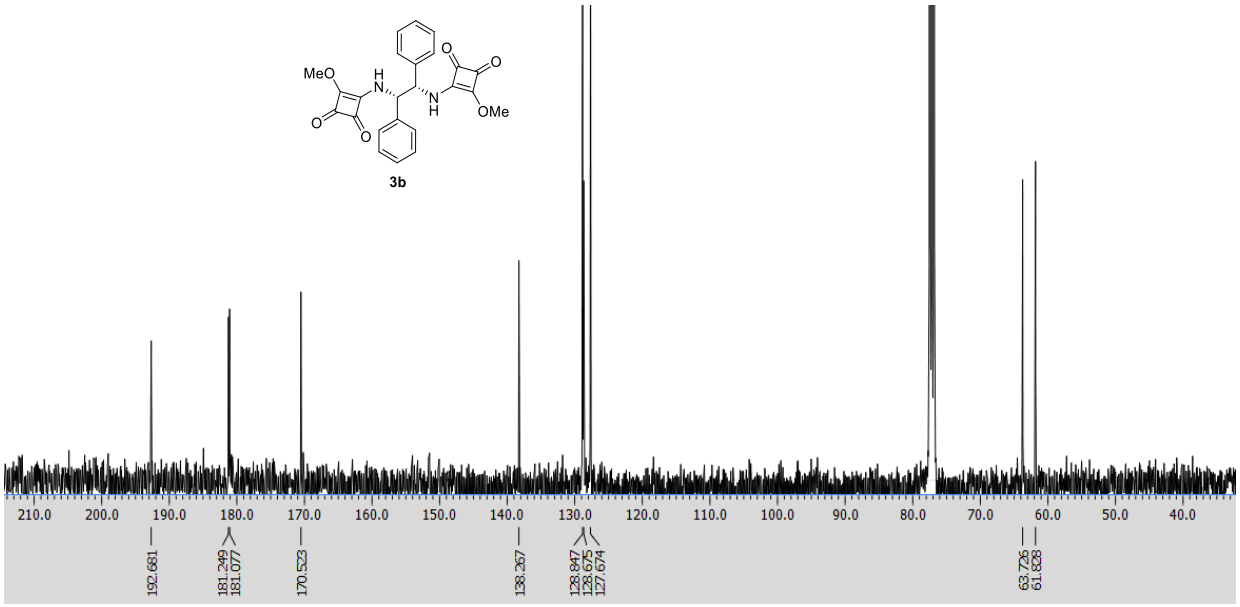
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3236.93	21.3325	2	1801.19	25.4757
3	1703.8	0.709274	4	1595.81	0.288431
5	1512.88	3.12437	6	1473.35	5.31696
7	1390.42	2.67004	8	1130.08	58.734
9	1075.12	63.5214	10	1049.09	43.9065
11	918.914	39.2001	12	756.923	64.8513
13	699.069	18.2144	14	609.396	44.7615
15	590.111	56.21	16	577.576	61.1904

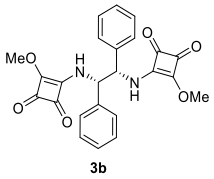
^{1}H NMR of 3b in $CDCl_3$



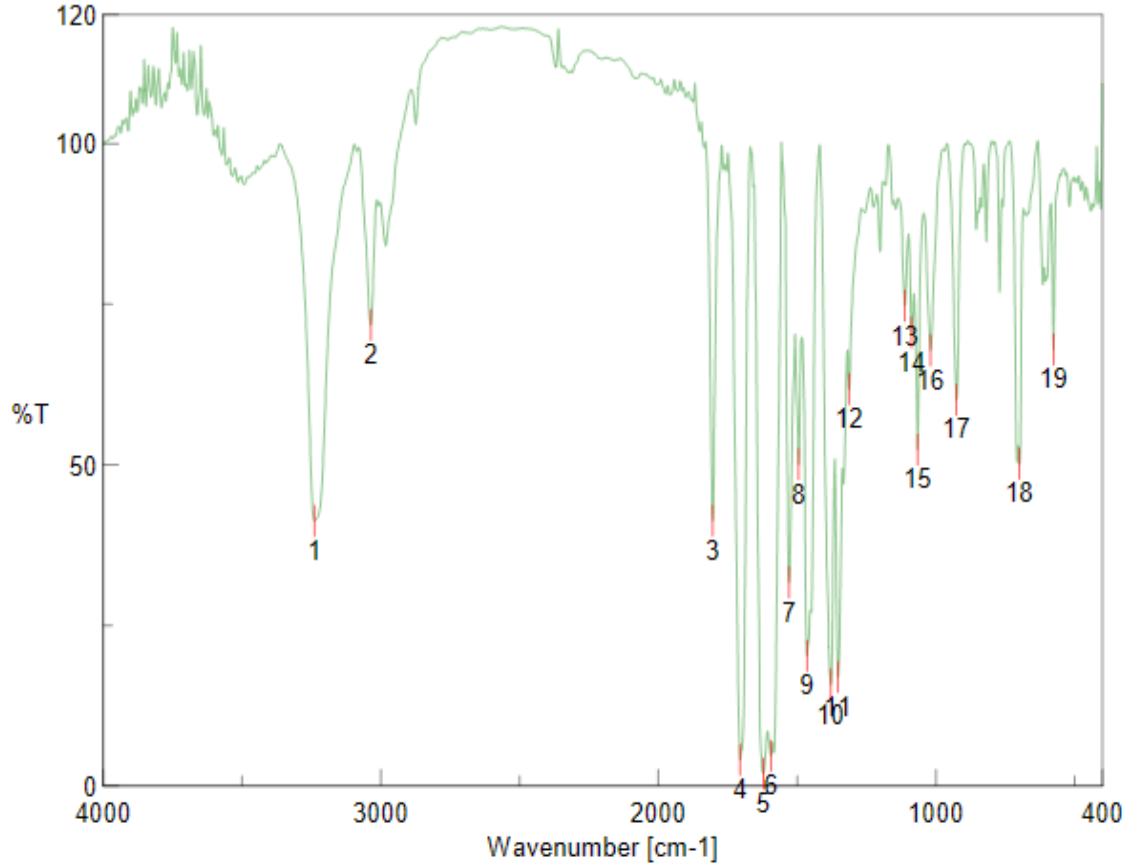
^{13}C NMR of 3b in $CDCl_3$



IR spectrum of 3b



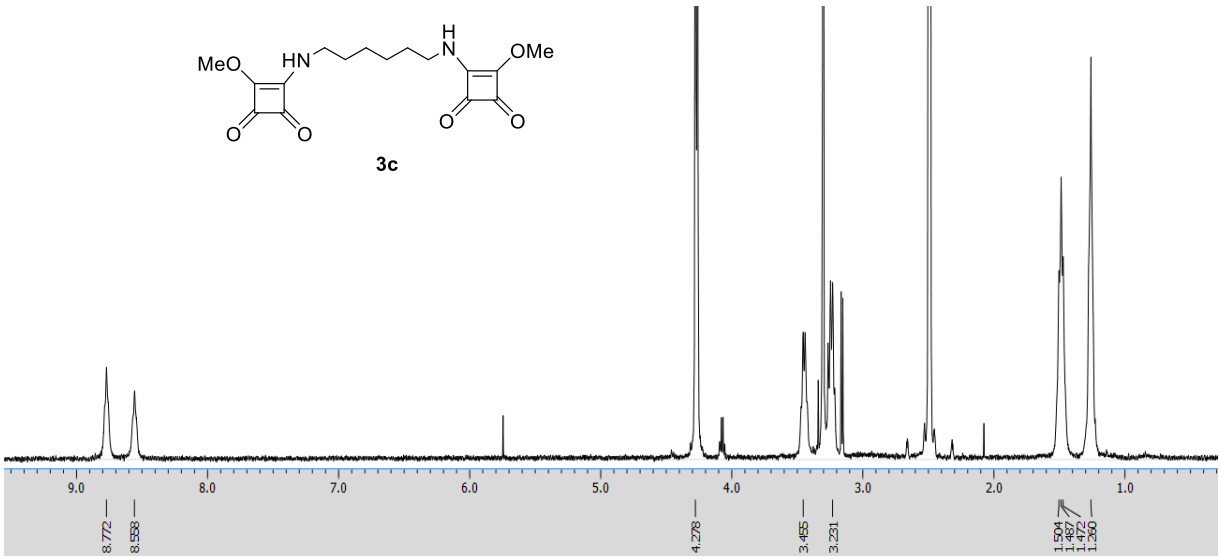
3b



[ピーク検出結果]

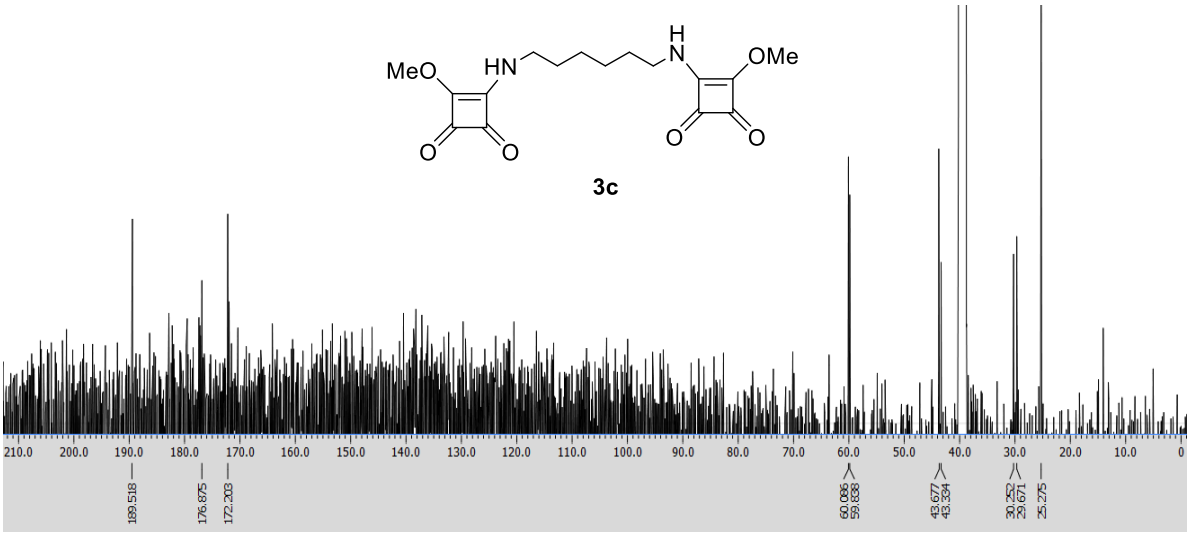
No.	位置	強度	No.	位置	強度
1	3237.9	41.2228	2	3036.37	71.6817
3	1804.08	41.2448	4	1704.76	4.06332
5	1621.84	1.8977	6	1593.88	4.64351
7	1529.27	31.6316	8	1494.56	50.0234
9	1464.67	20.2274	10	1377.89	15.7106
11	1352.82	16.9337	12	1312.32	61.7439
13	1111.76	74.6742	14	1087.66	70.5771
15	1065.48	52.3013	16	1019.19	67.7719
17	925.664	60.0711	18	699.069	50.0866
19	576.612	67.9007			

^{1}H NMR of 3c in DMSO-d_6

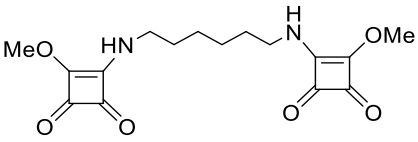


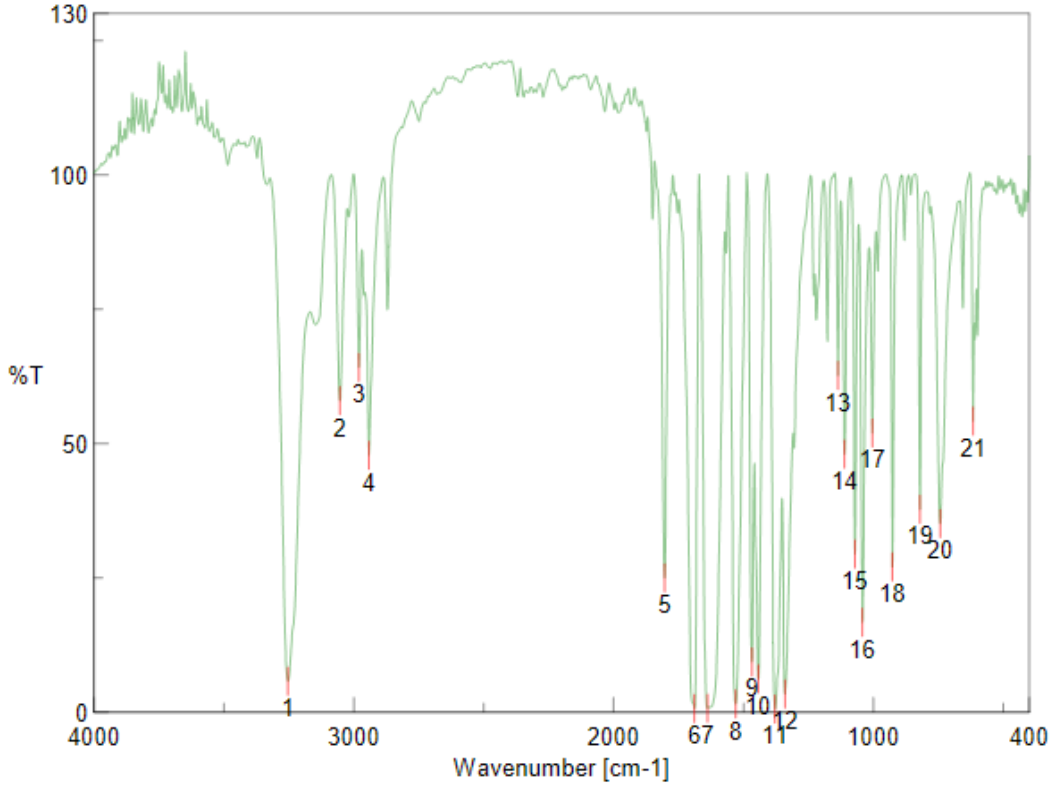
^{13}C NMR of 3c in DMSO-d_6

[NMR spectrum is not clear due to solubility problem]



IR spectrum of 3c

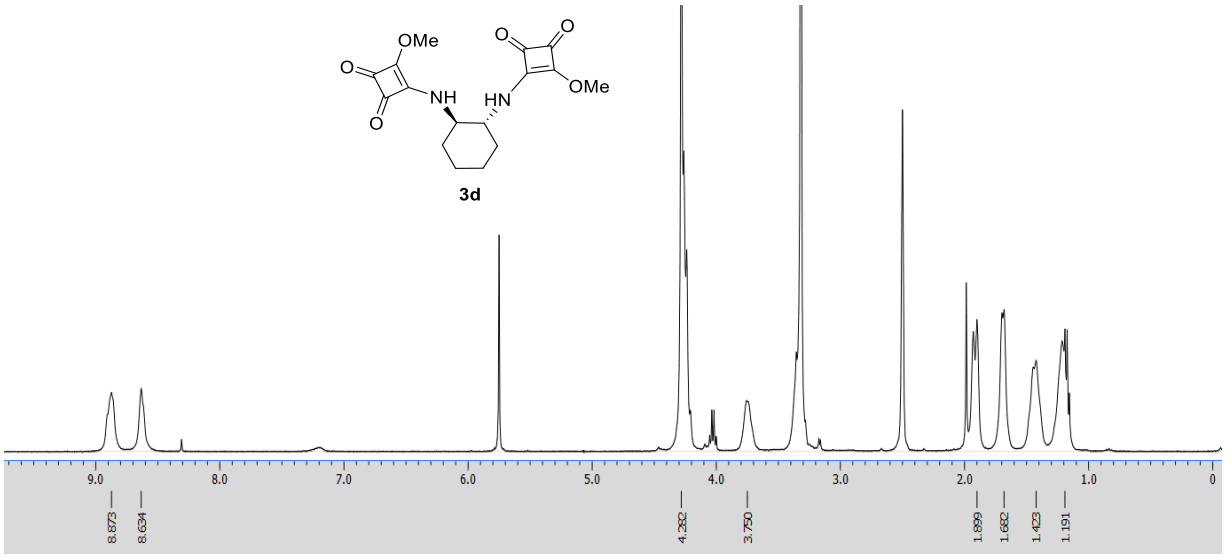




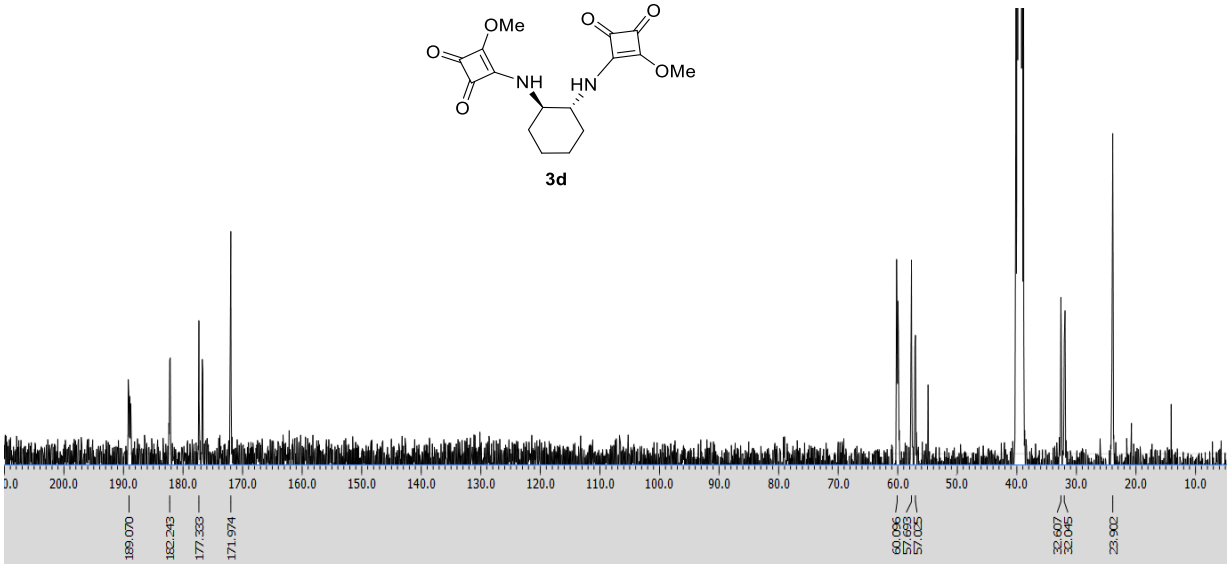
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3253.32	5.74945	2	3053.73	57.9635
3	2980.45	64.1414	4	2941.88	47.7834
5	1803.12	24.9862	6	1688.37	0.662815
7	1638.23	0.694051	8	1530.24	1.5248
9	1467.56	9.37201	10	1443.46	6.18239
11	1377.89	0.523067	12	1340.28	3.36139
13	1135.87	62.645	14	1110.8	48.0039
15	1071.26	29.4278	16	1042.34	16.708
17	1003.77	51.9395	18	926.628	27.0051
19	820.563	37.7389	20	742.46	35.097
21	616.145	54.1844			

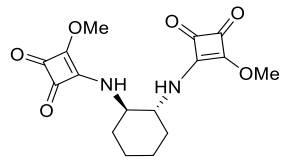
^{1}H NMR of 3d in DMSO-d_6



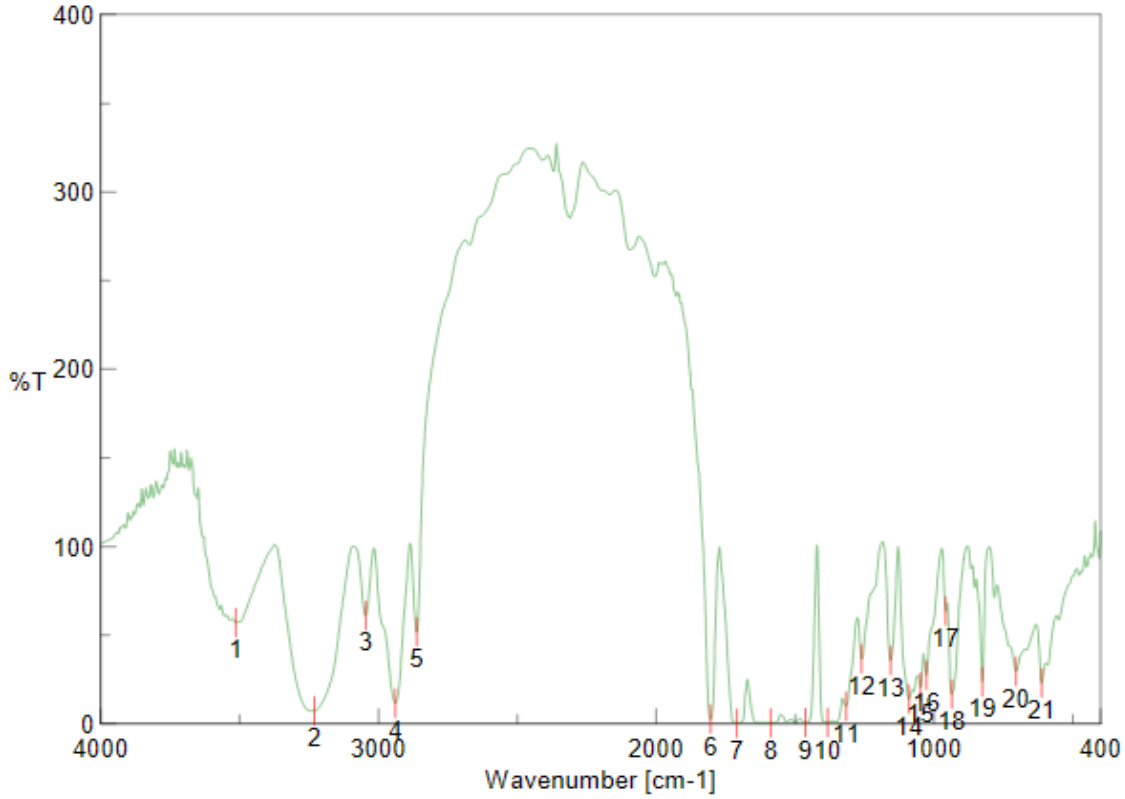
^{13}C NMR spectrum of 3d in DMSO-d_6



IR spectrum of 3d



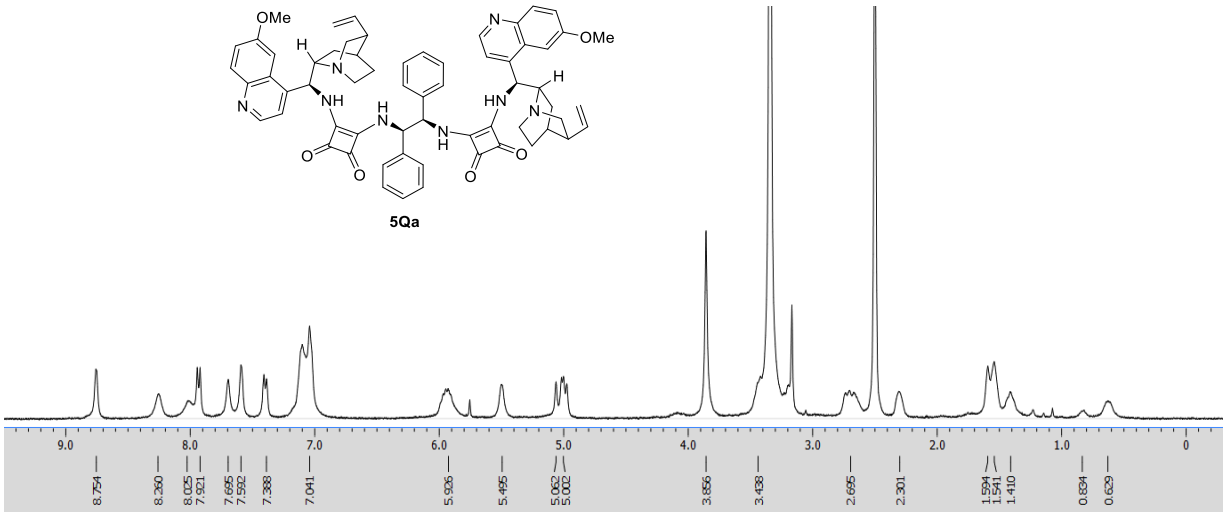
3d



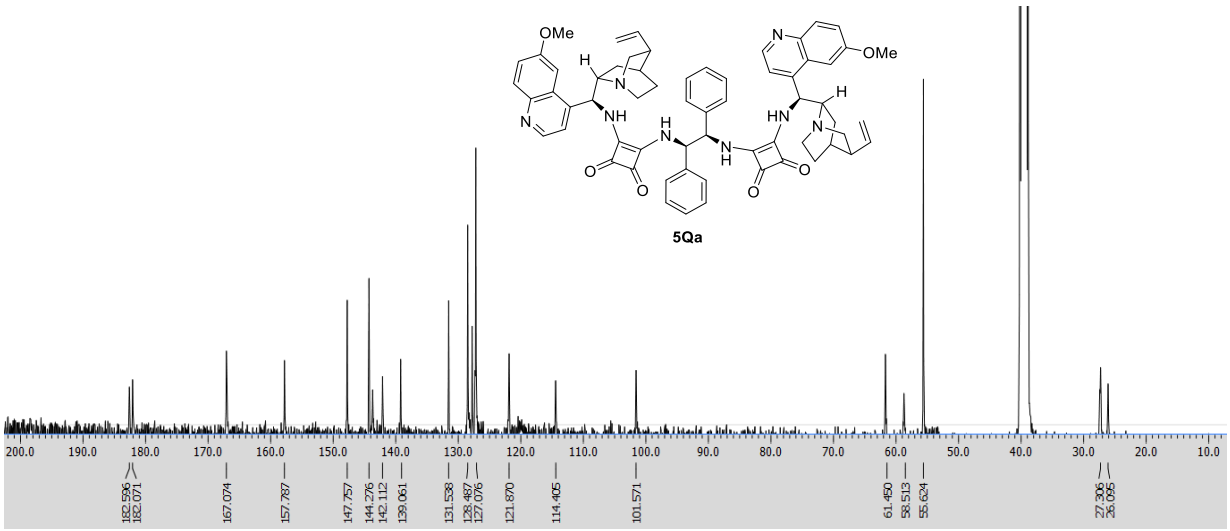
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3513.67	56.9515	2	3231.15	7.08271
3	3046.01	60.9103	4	2938.98	11.4771
5	2861.84	51.6533	6	1804.08	2.45073
7	1709.59	0.244992	8	1587.13	0.301383
9	1462.74	0.524033	10	1382.71	0.568128
11	1316.18	9.72716	12	1260.25	36.4204
13	1156.12	35.6109	14	1090.55	13.7686
15	1048.12	20.3942	16	1027.87	27.2353
17	957.484	63.4526	18	936.271	16.6292
19	825.384	23.4701	20	704.855	29.3909
21	612.288	22.7727			

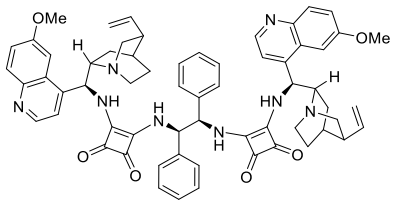
^{1}H NMR of 5Qa in DMSO-d_6



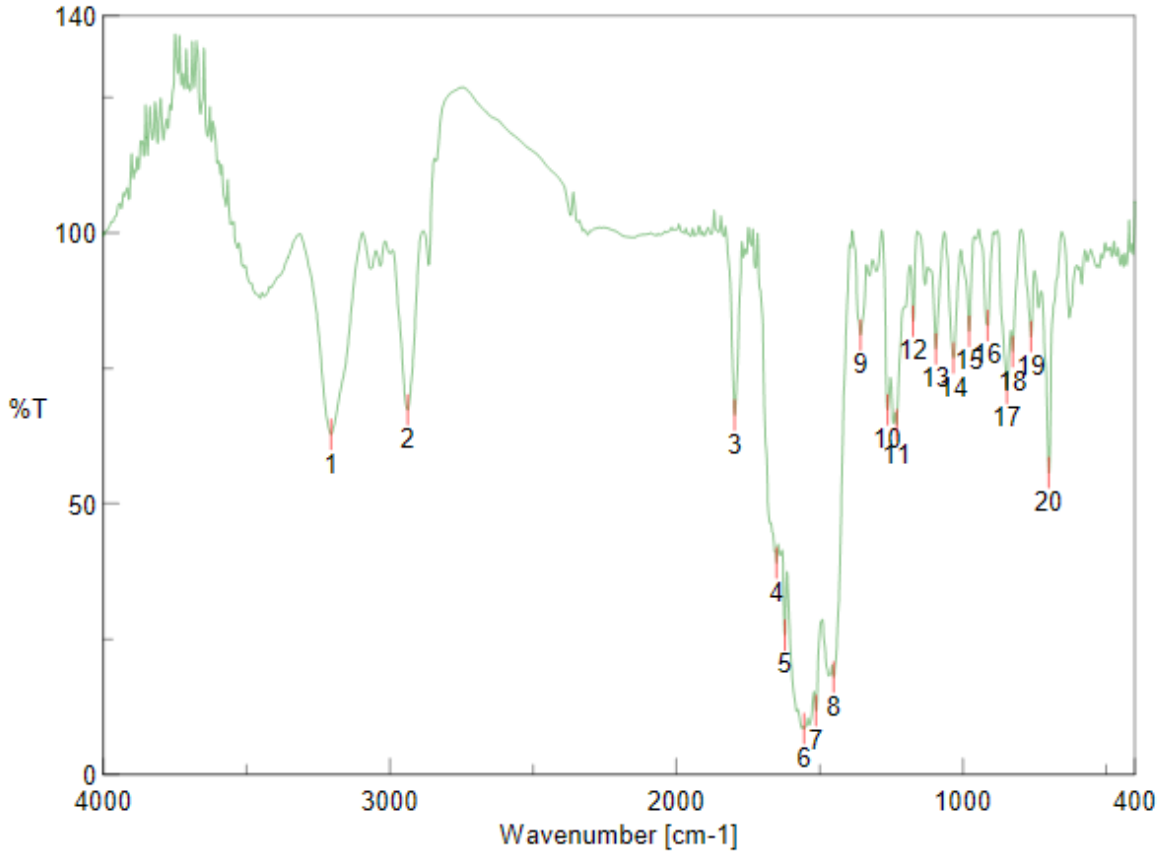
^{13}C NMR of 5Qa in DMSO-d_6



IR spectrum of 5Qa



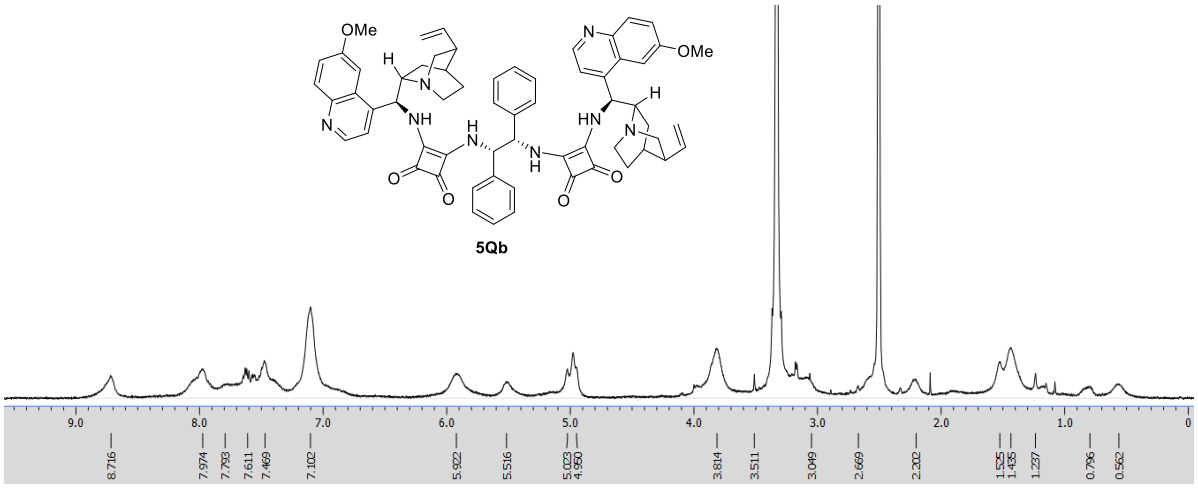
5Qa



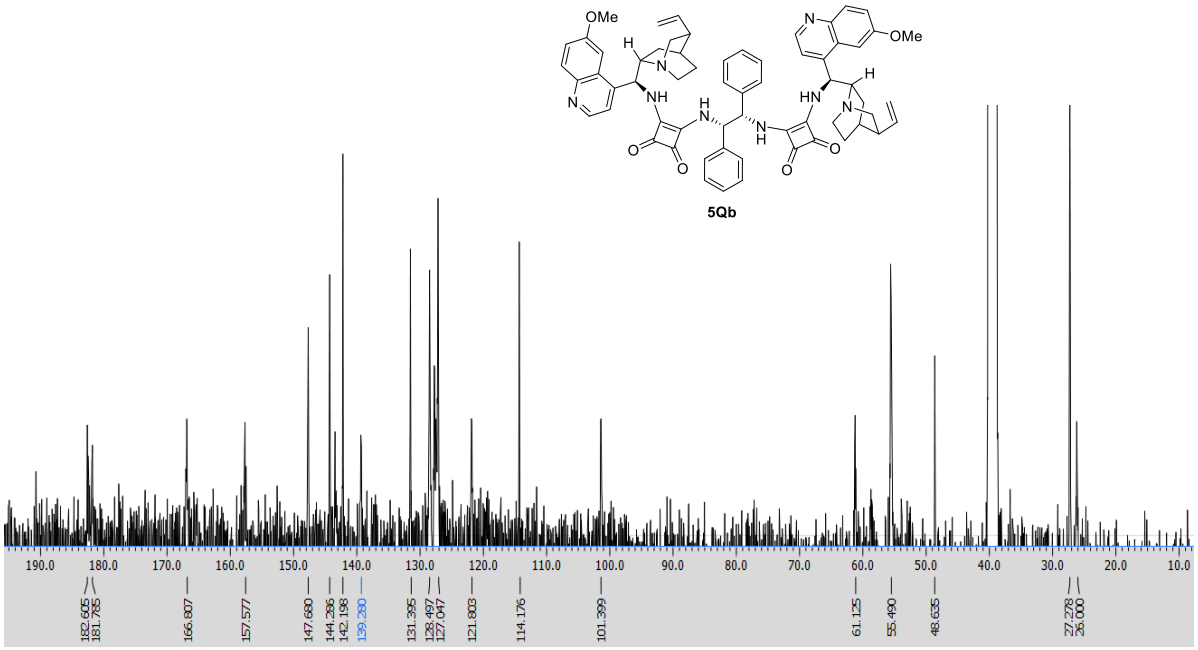
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3205.11	62.7551	2	2938.02	67.2857
3	1796.37	66.2841	4	1650.77	39.0294
5	1621.84	25.6847	6	1554.34	8.45669
7	1512.88	11.768	8	1451.17	17.9495
9	1357.64	81.0823	10	1263.15	67.3039
11	1231.33	64.5025	12	1173.47	83.666
13	1094.4	78.5349	14	1032.69	76.8385
15	977.733	81.7817	16	914.093	82.8543
17	846.597	71.2276	18	826.348	77.9939
19	761.744	80.775	20	700.034	55.6852

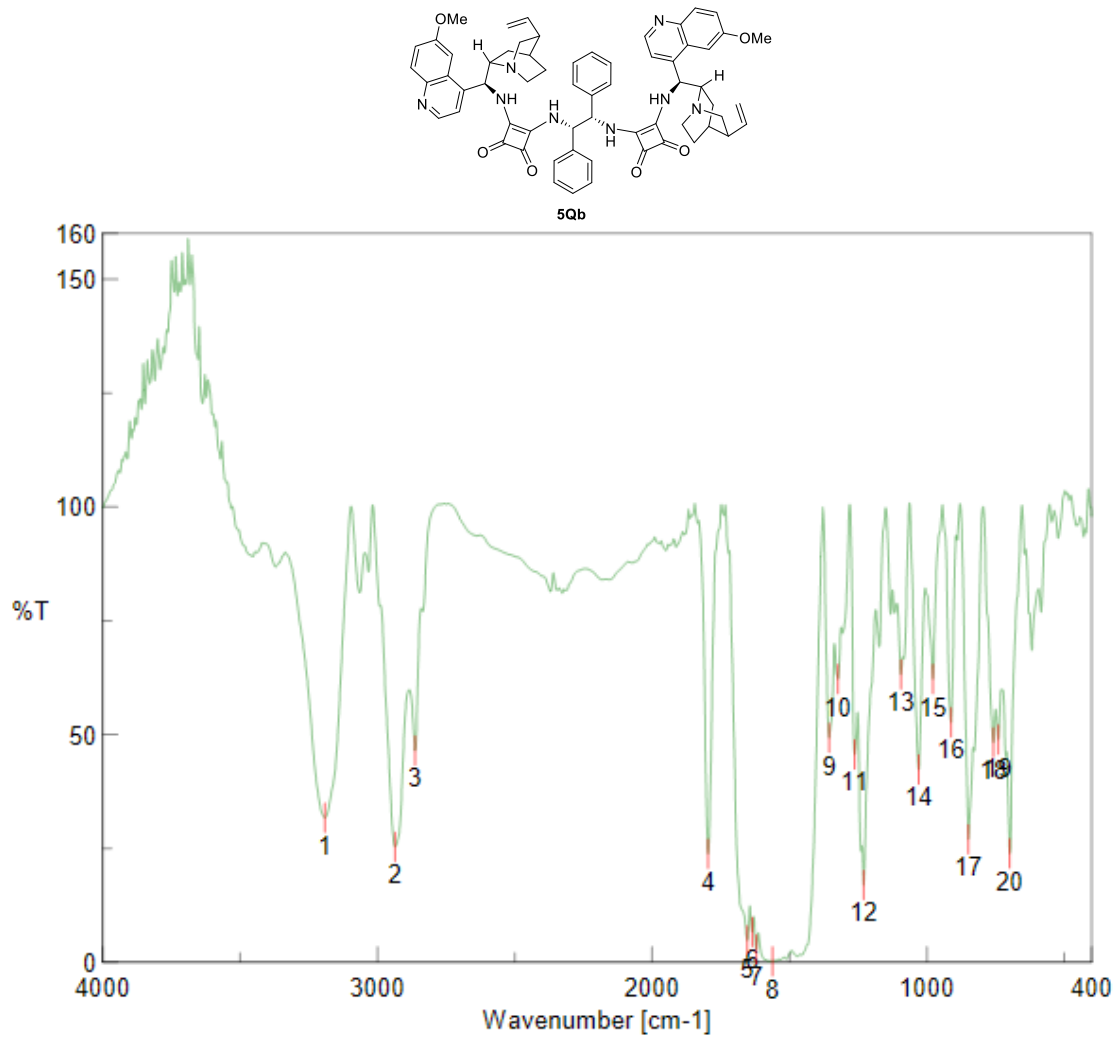
^{1}H NMR of 5Qb in DMSO-d_6



^{13}C NMR spectrum of 5Qb in DMSO-d_6



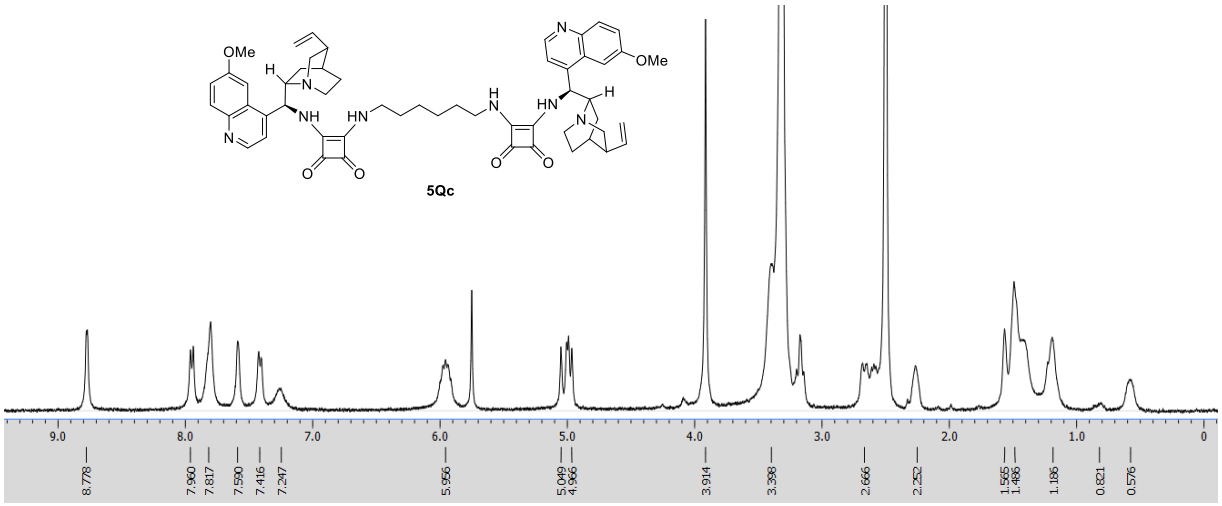
IR spectrum of 5Qb



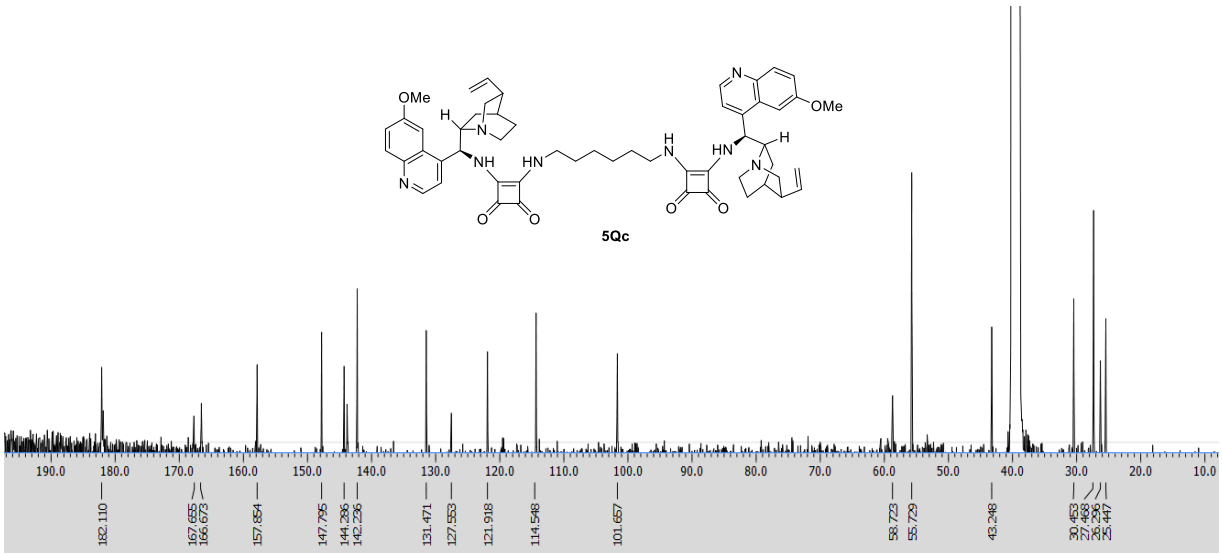
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3191.61	31.6718	2	2936.09	25.3016
3	2862.81	46.4116	4	1796.37	23.7503
5	1653.66	4.71574	6	1636.3	6.61171
7	1620.88	2.69798	8	1562.06	0.11884
9	1355.71	49.2315	10	1322.93	62.1429
11	1263.15	45.54	12	1229.4	16.8975
13	1094.4	63.1534	14	1029.8	42.2128
15	977.733	62.1126	16	912.165	52.6046
17	848.525	26.9284	18	757.888	48.221
19	740.531	48.8386	20	698.105	23.8338

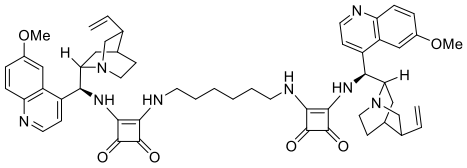
^{1}H NMR of 5Qc in DMSO-d_6



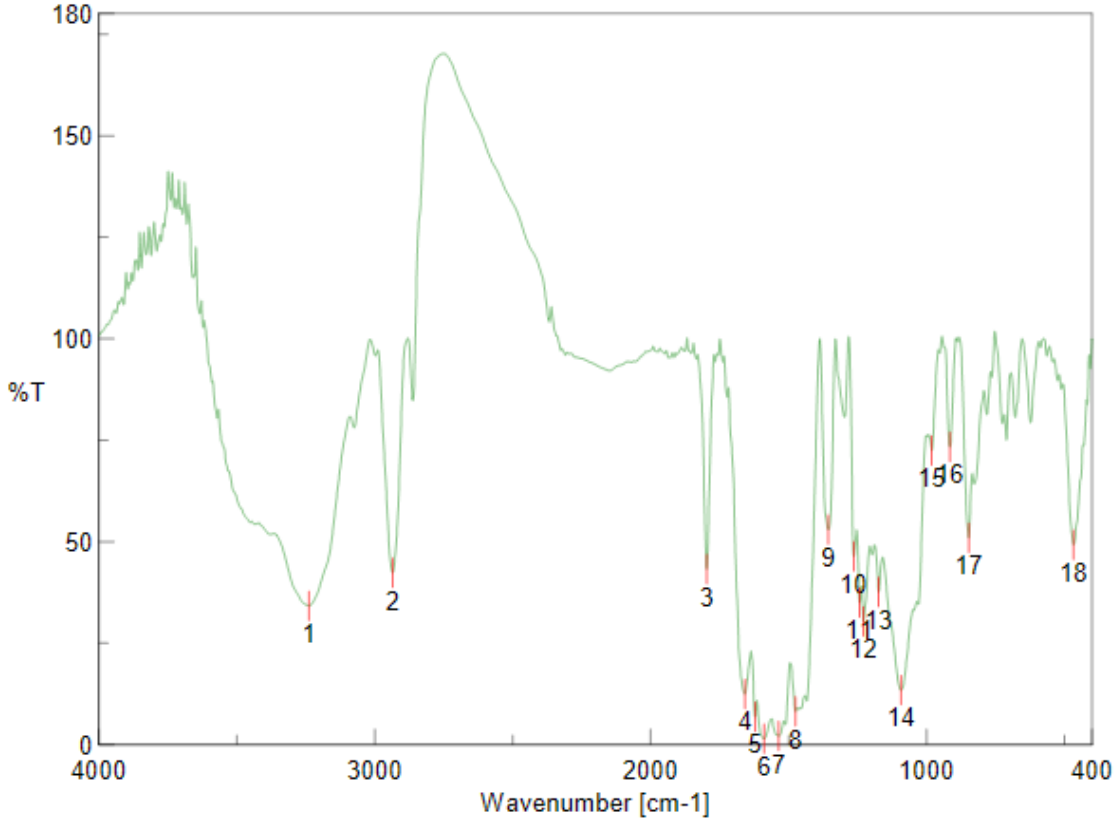
^{13}C NMR of 5Qc in DMSO-d_6



IR spectrum of 5Qc



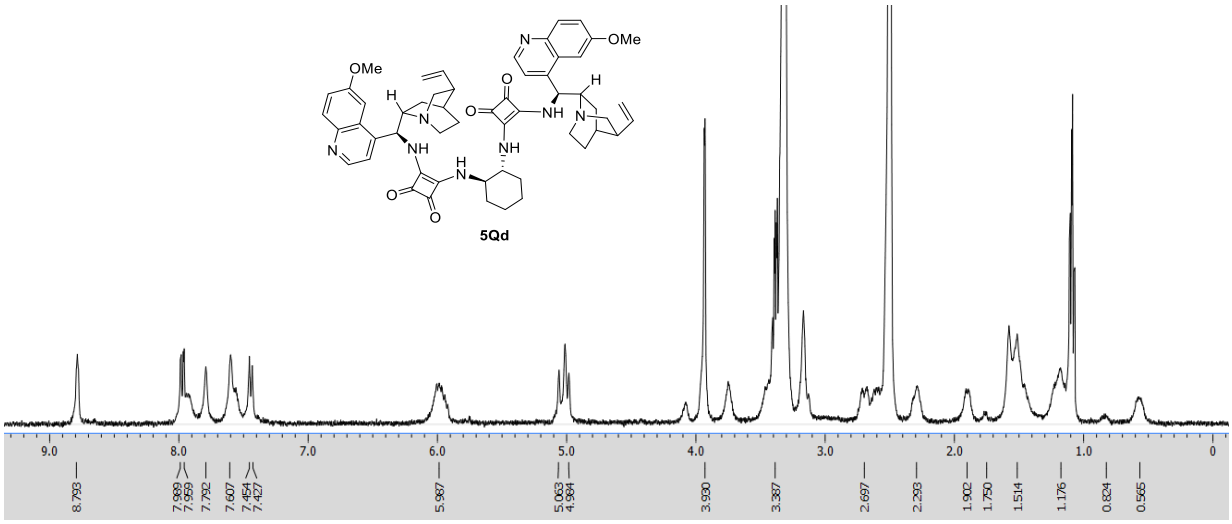
5Qc



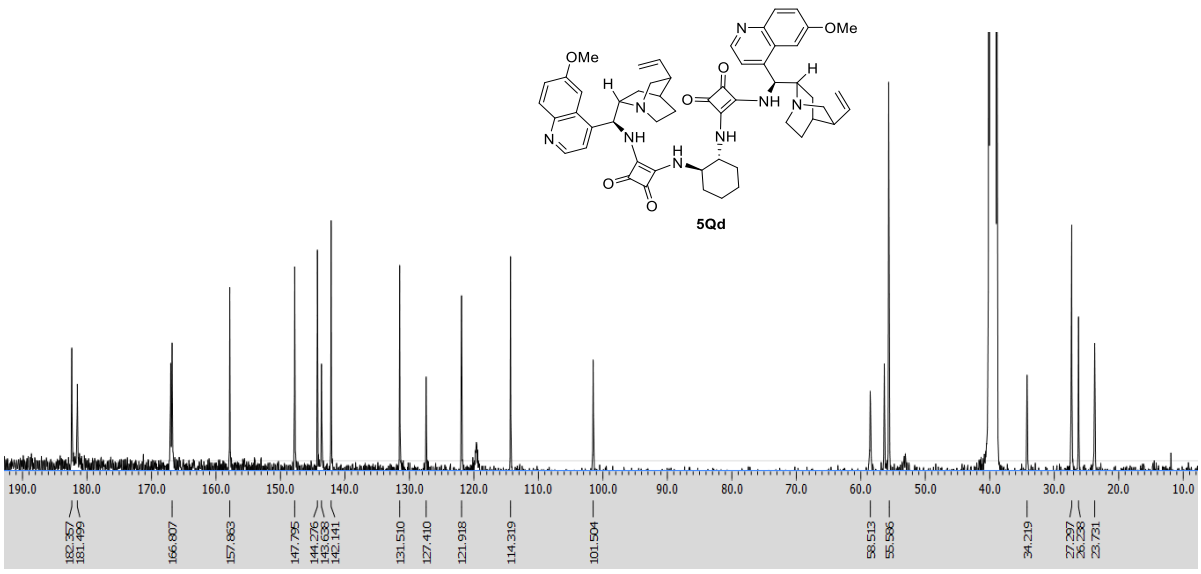
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3237.9	34.1326	2	2935.13	42.2746
3	1796.37	43.2127	4	1658.48	12.3948
5	1621.84	6.79689	6	1589.06	1.42432
7	1536.02	2.07883	8	1475.28	8.1542
9	1356.68	52.9112	10	1264.11	46.3525
11	1242.9	34.941	12	1228.43	30.3306
13	1173.47	37.6046	14	1092.48	13.3774
15	980.625	72.3982	16	915.058	73.2848
17	846.597	50.8778	18	466.689	49.1503

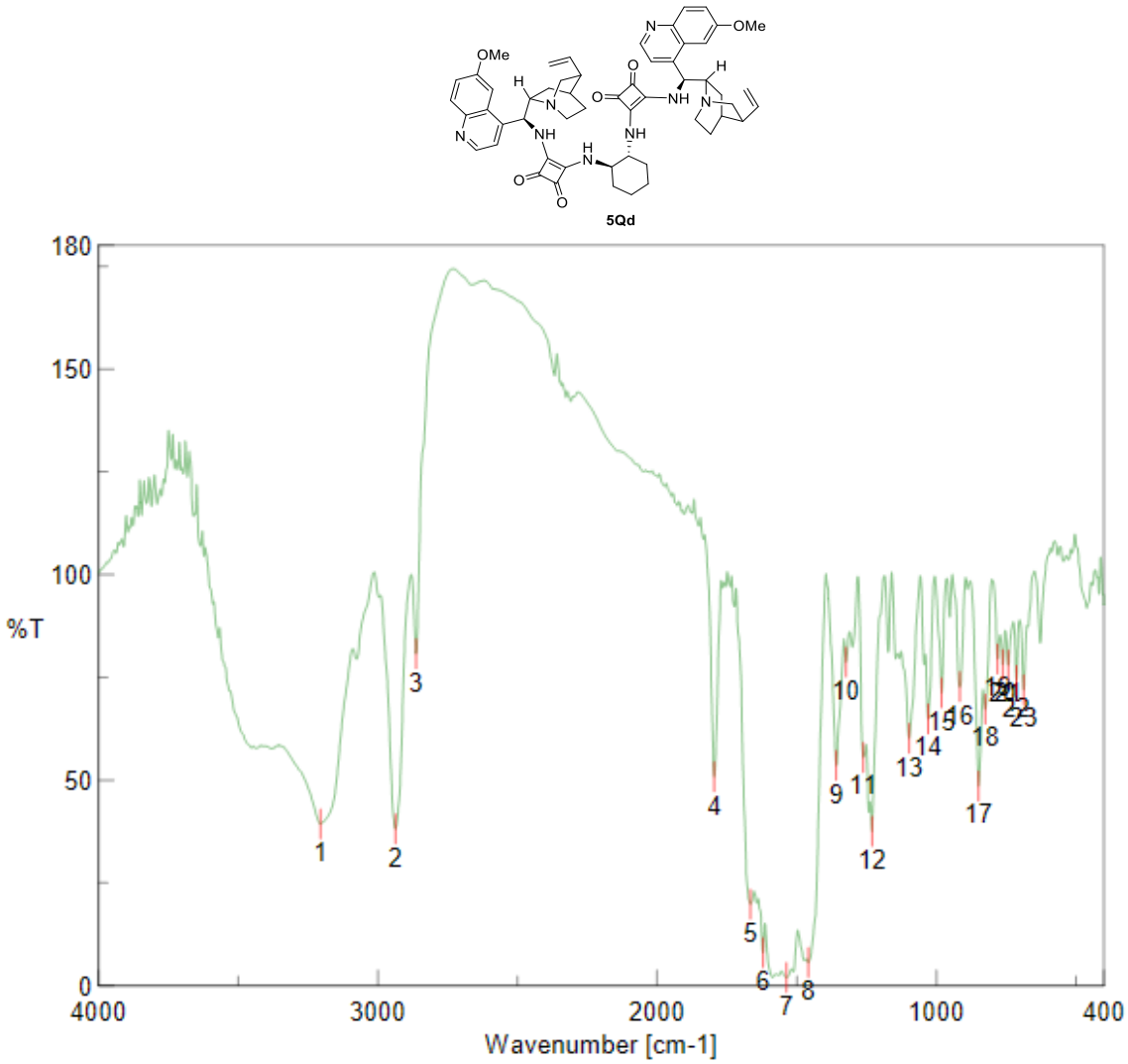
^{1}H NMR of 5Qd in DMSO-d_6



^{13}C NMR of 5Qd in DMSO-d_6



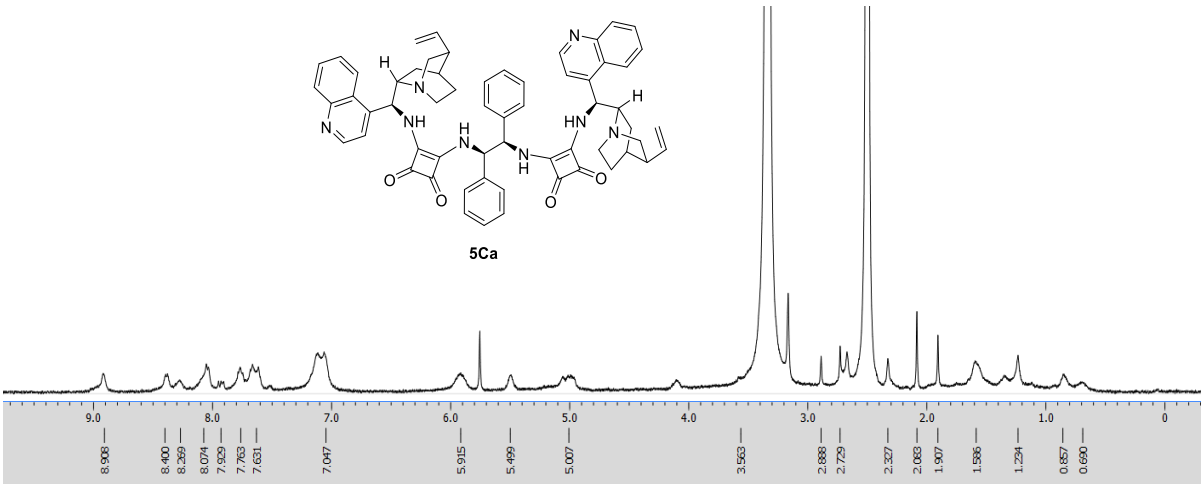
IR spectrum of 5Qd



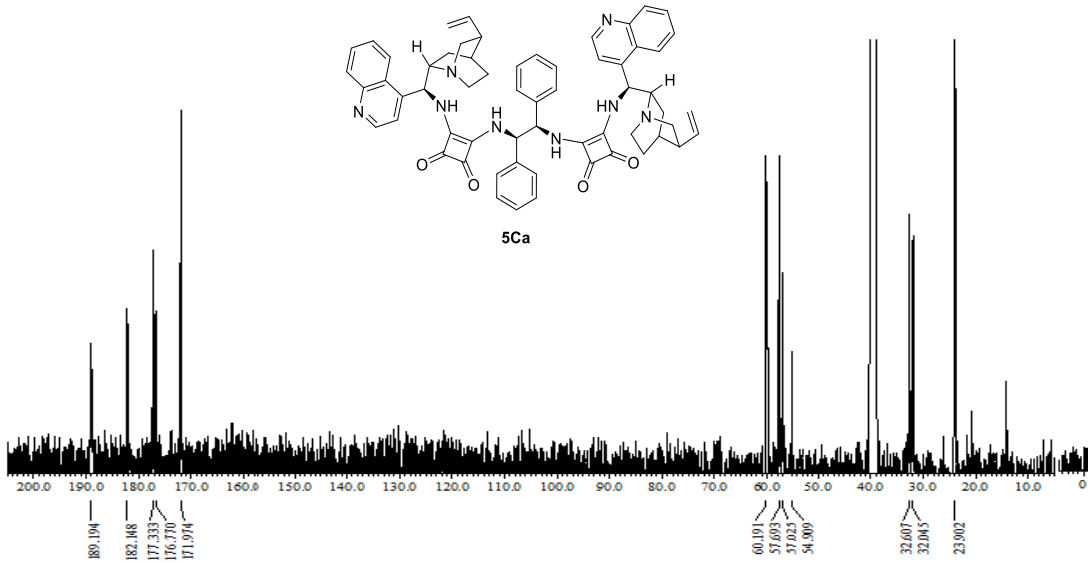
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3205.11	39.2783	2	2937.06	38.1059
3	2862.81	80.6781	4	1795.4	50.7186
5	1666.2	19.724	6	1620.88	8.01483
7	1536.99	1.9113	8	1458.89	5.62645
9	1358.6	53.5377	10	1322.93	78.6624
11	1261.22	55.4803	12	1230.36	37.5275
13	1098.26	60.1135	14	1029.8	64.817
15	980.625	71.16	16	916.022	72.6546
17	848.525	48.5306	18	824.42	67.2309
19	781.029	79.3924	20	761.744	78.0782
21	742.46	77.8961	22	713.533	74.1914
23	687.498	71.956			

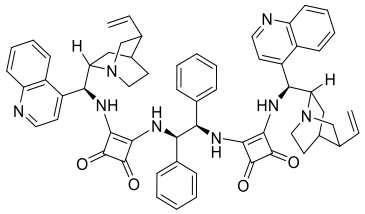
^{1}H NMR of 5Ca in DMSO-d_6



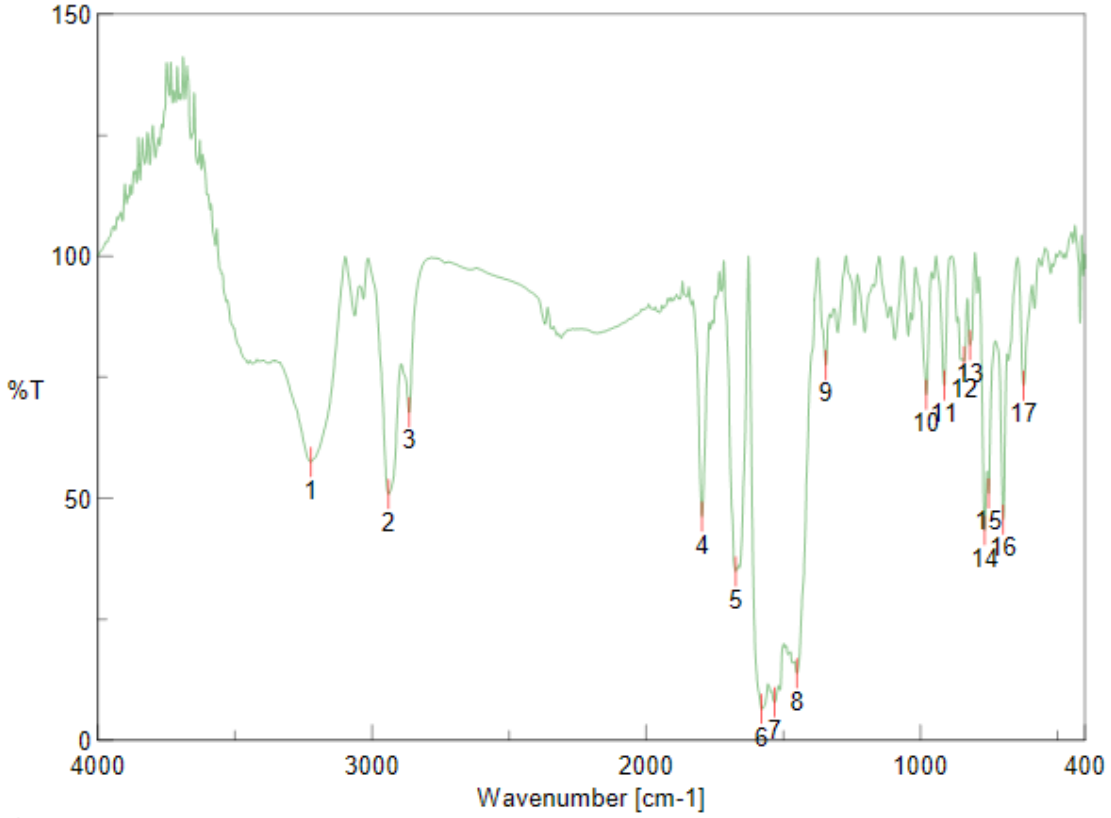
^{13}C NMR of 5Ca in DMSO-d_6



IR spectrum of 5Ca



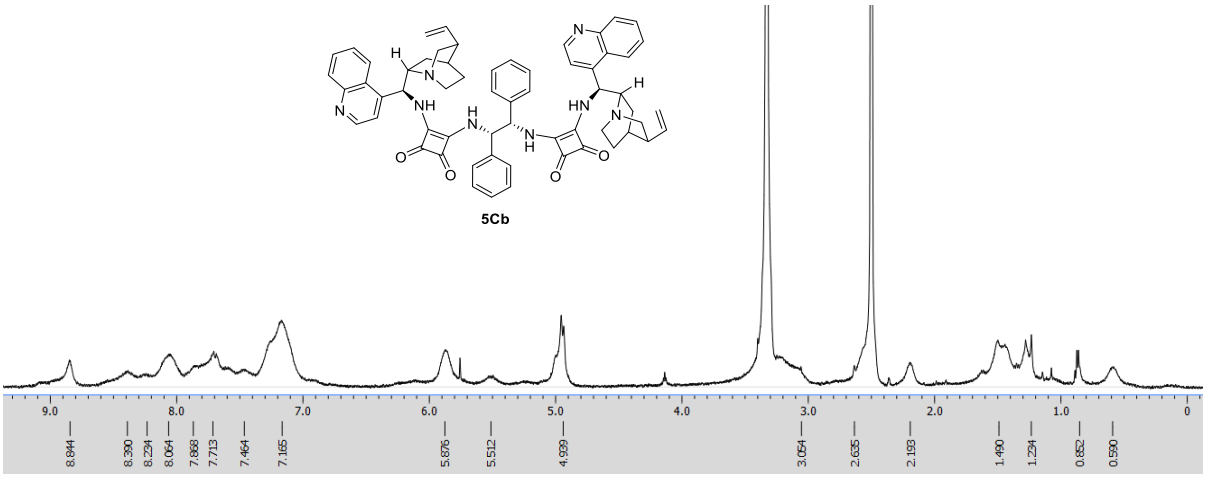
5Ca



[ピーク検出結果]

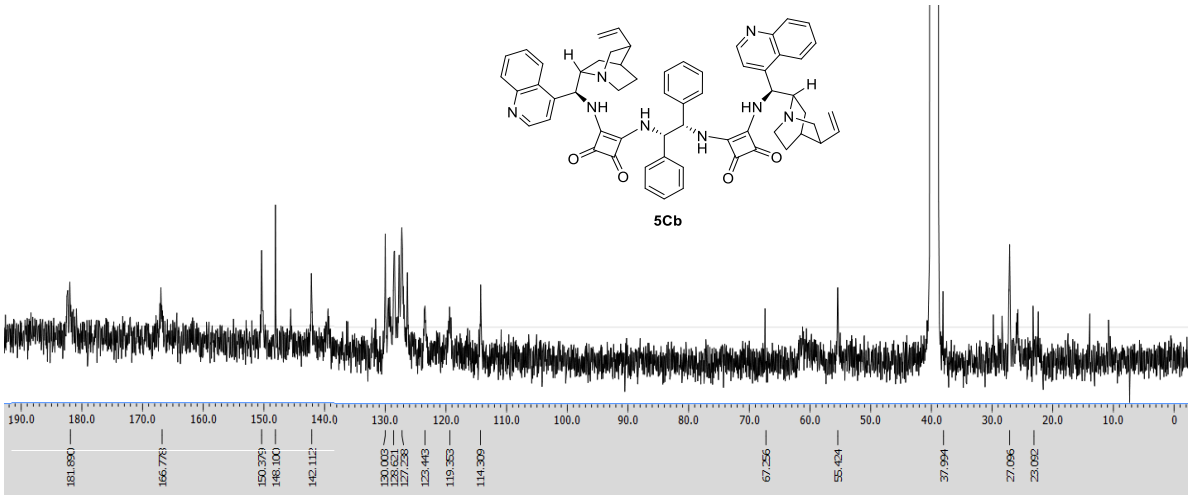
No.	位置	強度	No.	位置	強度
1	3223.43	57.4387	2	2939.95	50.8232
3	2864.74	67.7048	4	1796.37	46.169
5	1673.91	34.7978	6	1579.41	6.40434
7	1531.2	7.79373	8	1450.21	13.8027
9	1345.11	77.4771	10	978.697	71.3413
11	913.129	73.2791	12	839.847	78.2796
13	819.598	81.5792	14	765.601	43.3538
15	751.138	50.9707	16	698.105	45.5059
17	623.859	73.2277			

^{1}H NMR of 5Cb in DMSO-d_6

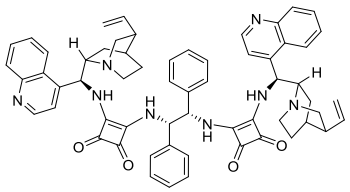


^{13}C NMR of 5Cb in DMSO-d_6

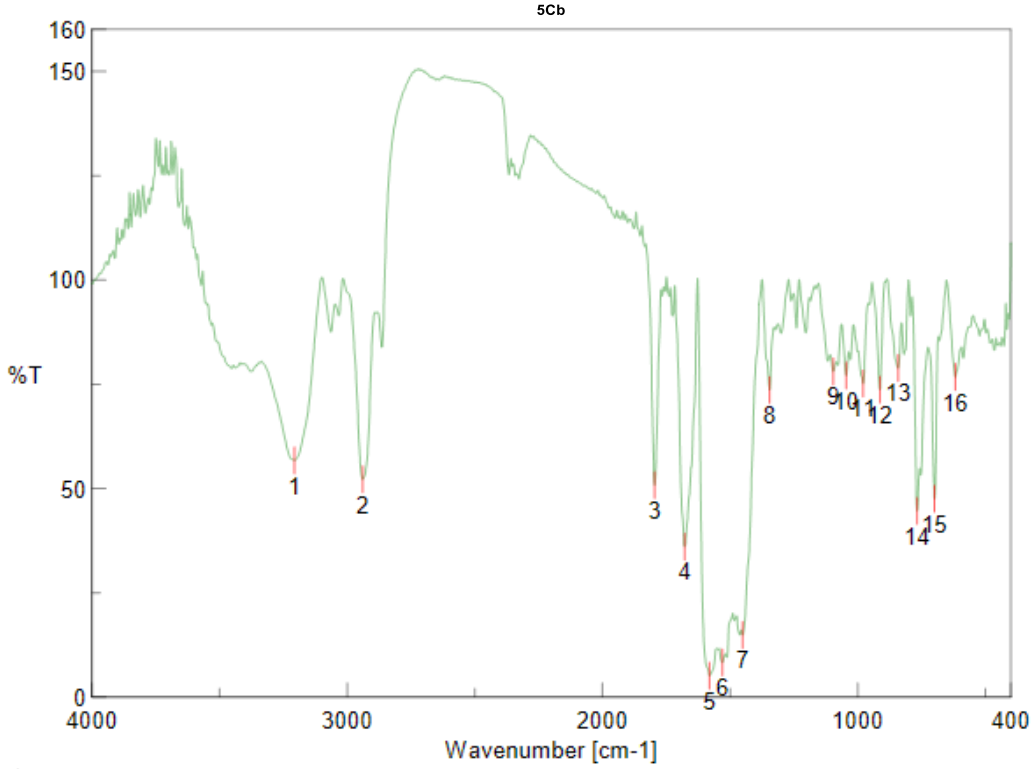
[NMR spectrum is not clear due to solubility problem]



IR spectrum of 5Cb



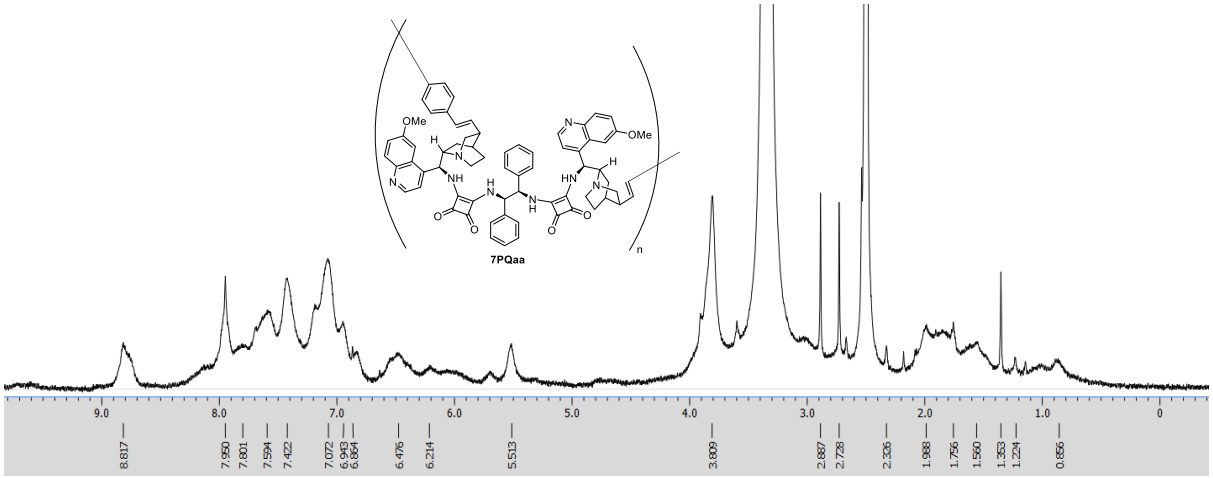
5Cb



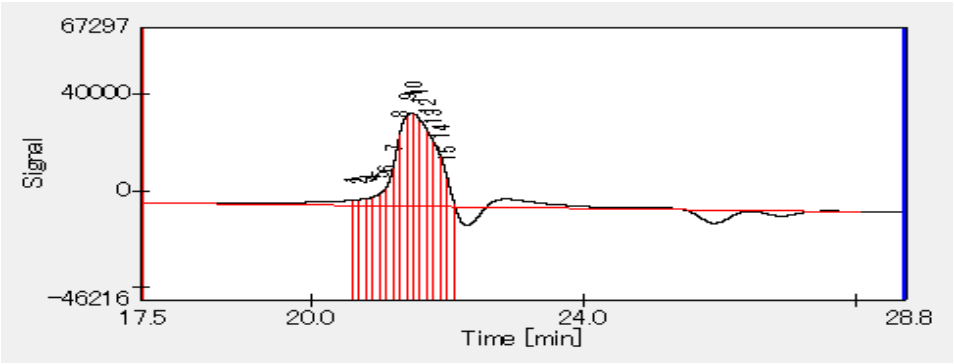
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3206.08	56.7017	2	2938.98	52.1682
3	1795.4	50.7471	4	1677.77	36.0204
5	1580.38	5.02607	6	1530.24	8.24798
7	1451.17	14.8498	8	1345.11	73.5501
9	1095.37	78.0198	10	1045.23	77.0406
11	978.697	75.1363	12	913.129	73.6398
13	841.776	78.8131	14	767.53	44.5956
15	699.069	47.4975	16	618.074	76.7139

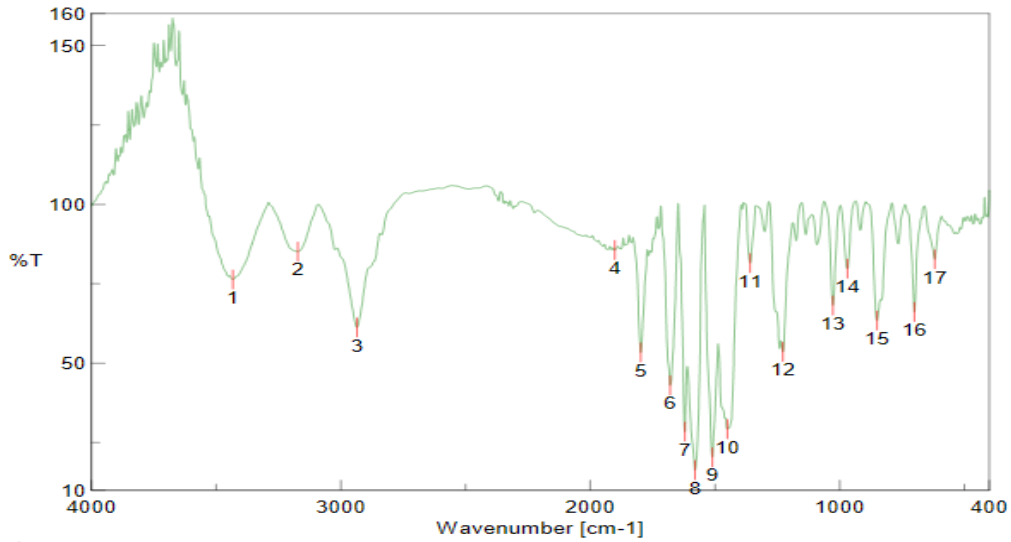
^{1}H NMR of 7PQaa in DMSO-d_6



SEC data of polymer, 7PQaa



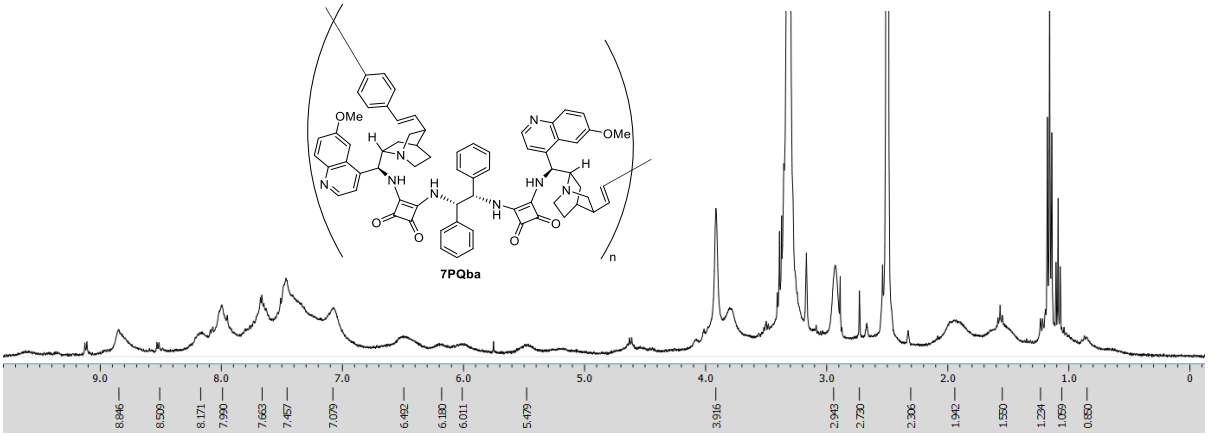
IR spectrum of polymer, 7PQaa



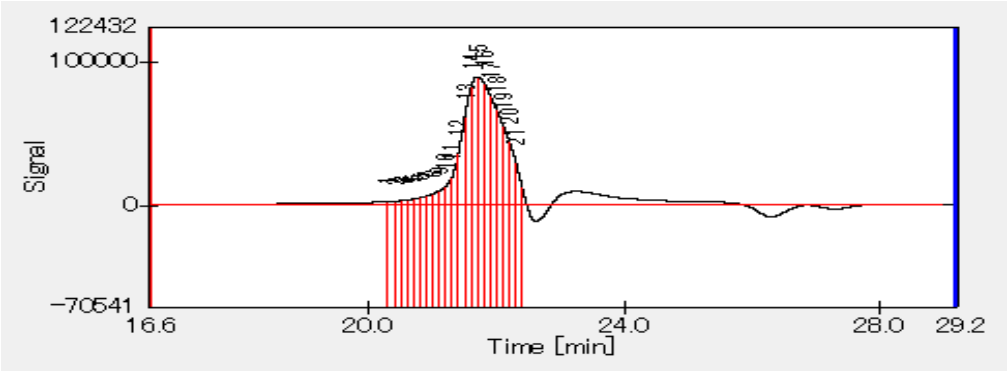
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3433.64	76.3211	2	3172.33	85.0642
3	2935.13	61.2301	4	1901.47	85.5837
5	1797.33	53.3281	6	1679.69	43.015
7	1620.88	28.3718	8	1579.41	16.2832
9	1509.99	20.3229	10	1450.21	29.2364
11	1358.6	81.4543	12	1227.47	53.5352
13	1026.91	68.1115	14	969.055	79.7307
15	850.454	63.4071	16	700.034	66.0717
17	619.038	82.6626			

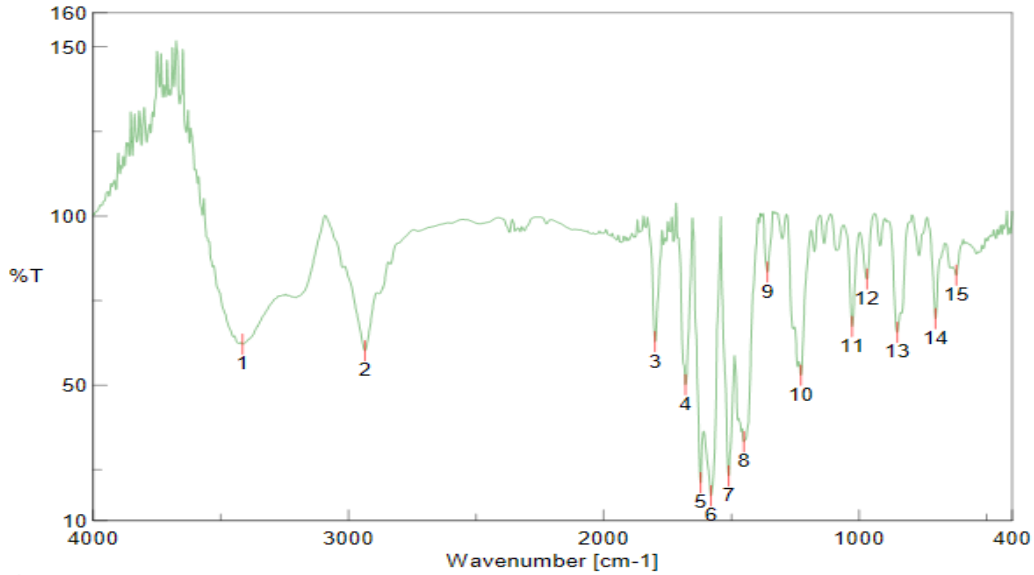
^{1}H NMR of 7PQba in DMSO-d_6



SEC data of polymer, 7PQba



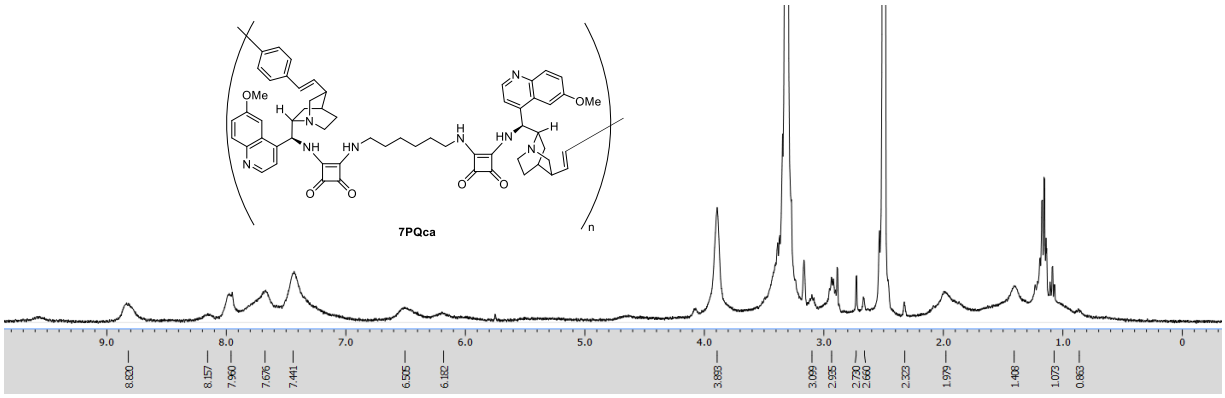
IR spectrum of 7PQba



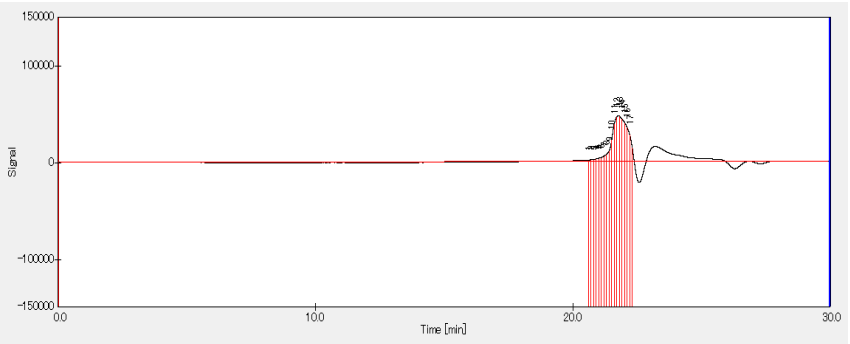
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3414.35	62.1002	2	2935.13	60.1435
3	1798.3	62.8219	4	1679.69	50.0929
5	1620.88	21.1608	6	1579.41	17.2772
7	1510.95	23.1471	8	1451.17	33.2336
9	1358.6	83.3915	10	1227.47	52.924
11	1026.91	67.2874	12	969.055	81.3204
13	850.454	65.6023	14	700.034	69.6558
15	619.038	82.4544			

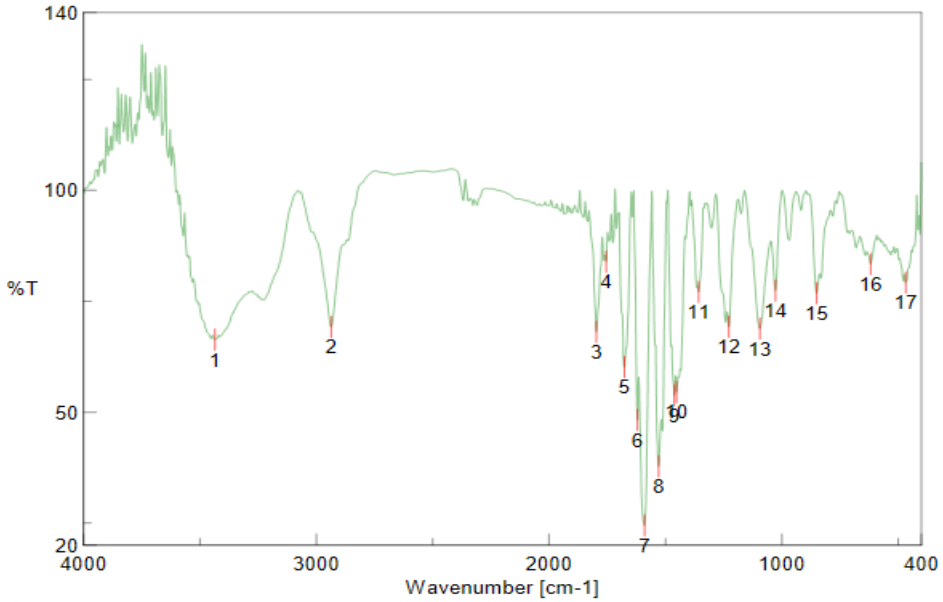
^{1}H NMR spectrum of 7PQca in DMSO-d_6



SEC data of polymer, 7PQca



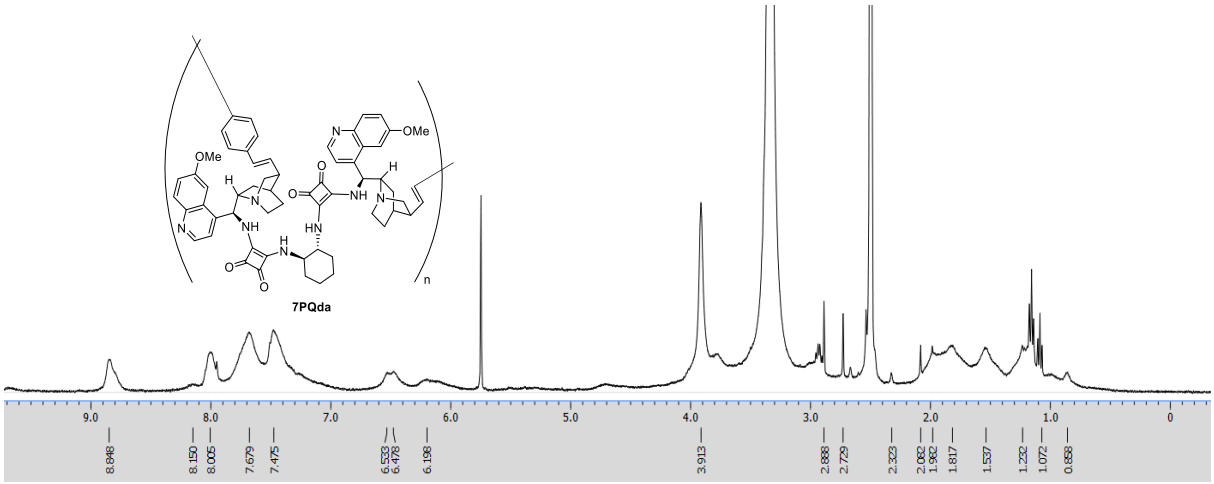
IR spectrum of 7PQca



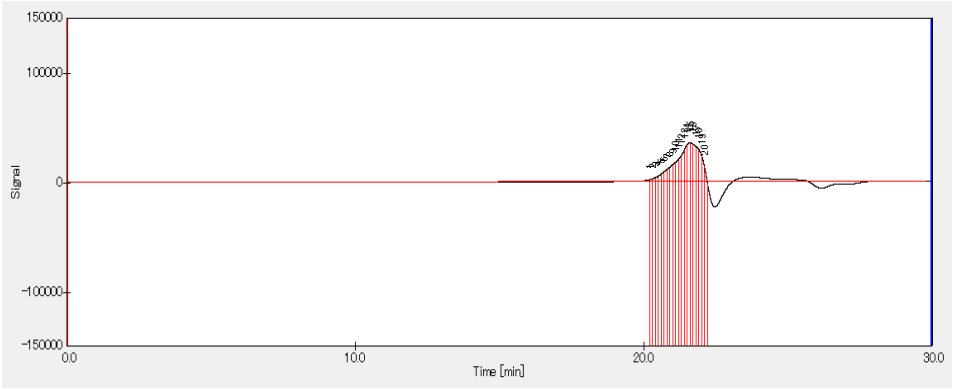
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3435.56	66.3135	2	2936.09	69.1707
3	1796.37	68.0382	4	1754.9	83.8657
5	1676.8	60.1198	6	1620.88	48.2071
7	1590.02	24.3963	8	1529.27	37.7096
9	1461.78	53.6877	10	1452.14	54.4842
11	1357.64	77.096	12	1227.47	69.1851
13	1094.4	68.8165	14	1027.87	77.3195
15	850.454	76.7849	16	618.074	83.2964
17	467.653	79.152			

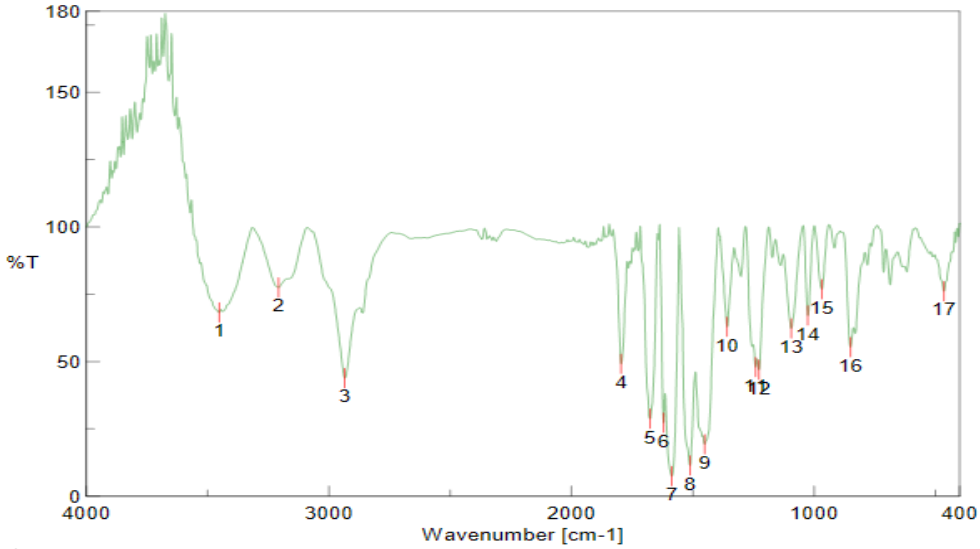
^{1}H NMR of polymer, 7PQda in DMSO-d_6



SEC data of polymer, 7PQda



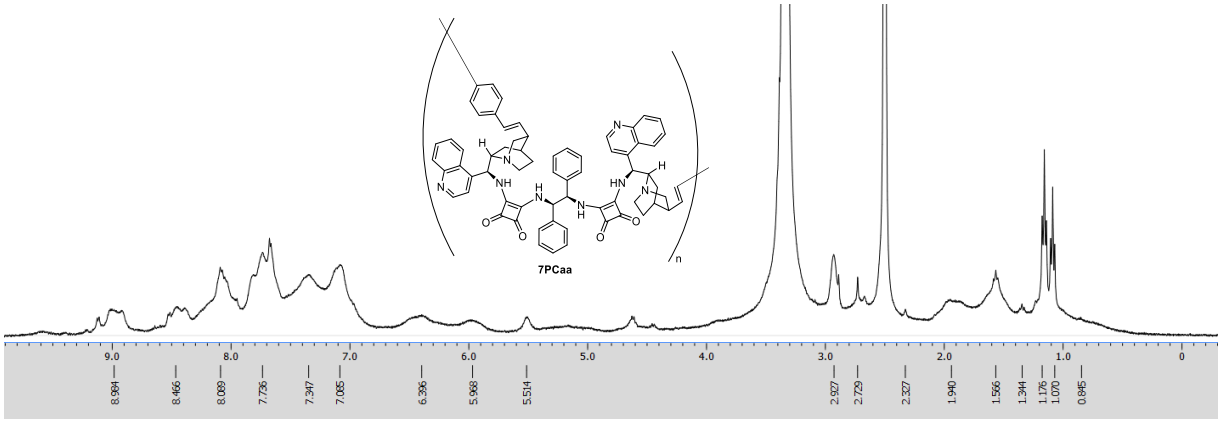
IR spectrum of polymer, 7PQda



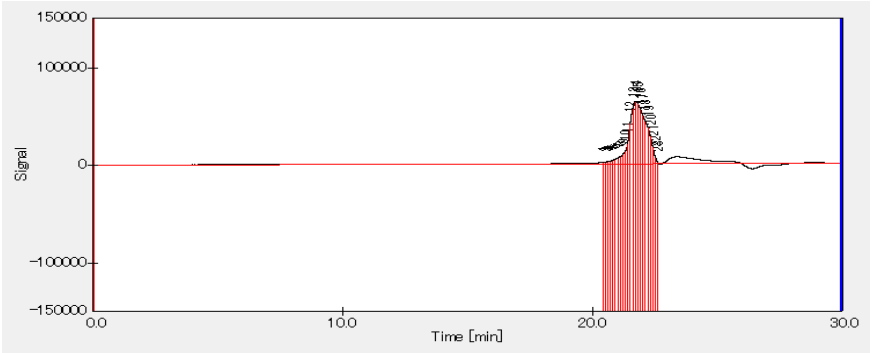
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3451.96	68.1515	2	3207.04	77.4611
3	2934.16	43.7946	4	1795.4	49.0738
5	1676.8	28.7732	6	1620.88	27.2555
7	1586.16	7.42229	8	1511.92	11.3514
9	1451.17	19.259	10	1358.6	62.8948
11	1240.97	47.8884	12	1227.47	46.9122
13	1094.4	62.2797	14	1025.94	67.0506
15	968.09	76.8216	16	850.454	55.3063
17	464.761	76.0441			

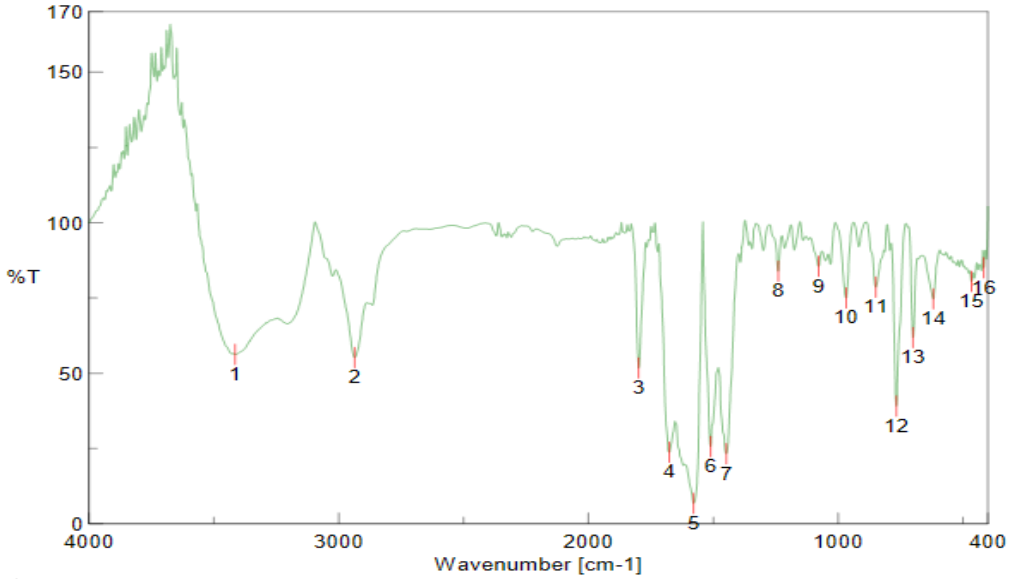
^{1}H NMR of polymer, 7PCaa in DMSO-d_6



SEC data of polymer, 7PCaa



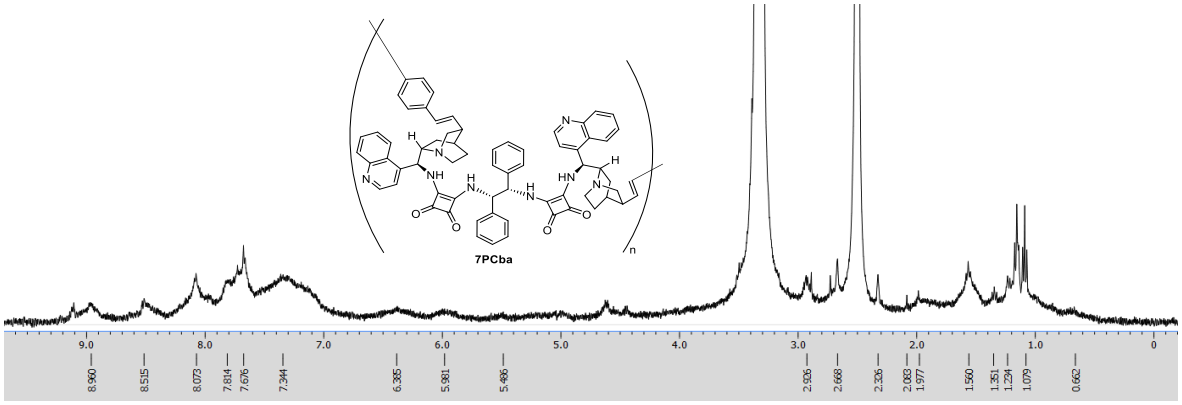
IR spectrum of polymer, 7PCaa



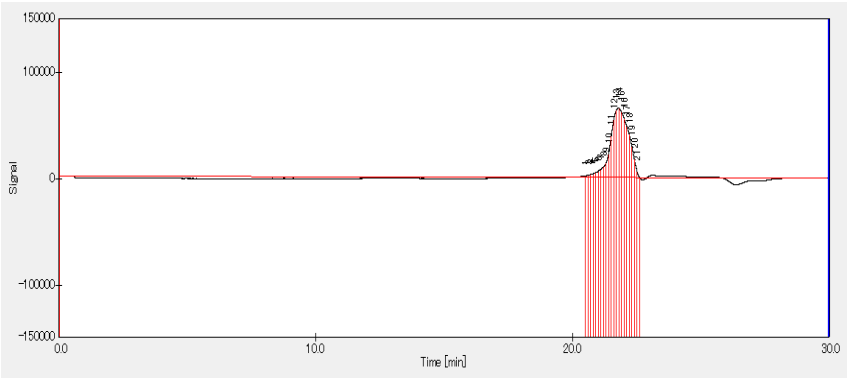
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3414.35	56.1622	2	2936.09	55.1092
3	1798.3	51.6731	4	1676.8	23.6865
5	1578.45	6.74102	6	1510.95	25.6095
7	1448.28	23.1696	8	1240	83.8396
9	1078.01	85.4486	10	968.09	74.9364
11	849.49	78.5089	12	766.566	38.9978
13	700.034	61.804	14	619.038	74.6198
15	465.725	80.475	16	416.549	84.9921

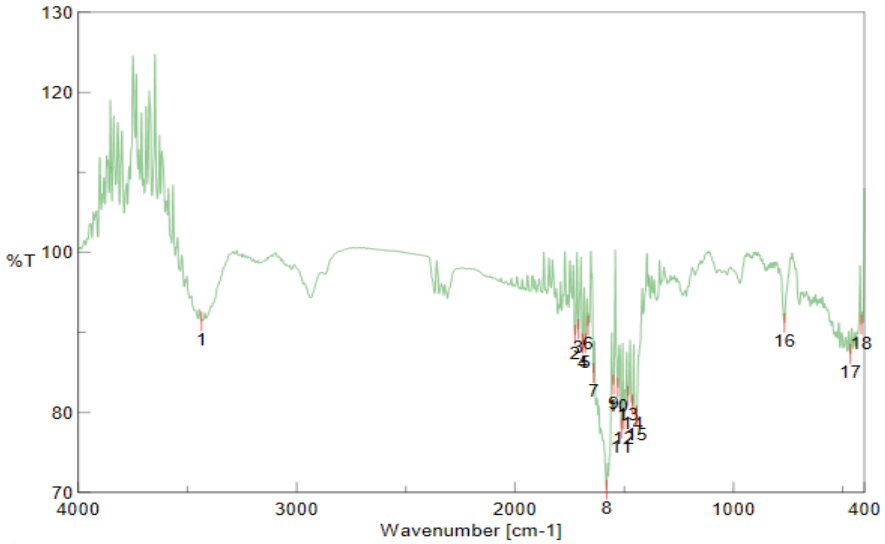
^{1}H NMR of polymer, 7PCba in DMSO-d_6
[NMR spectrum is not clear due to solubility problem]



SEC data of polymer, 7PCba



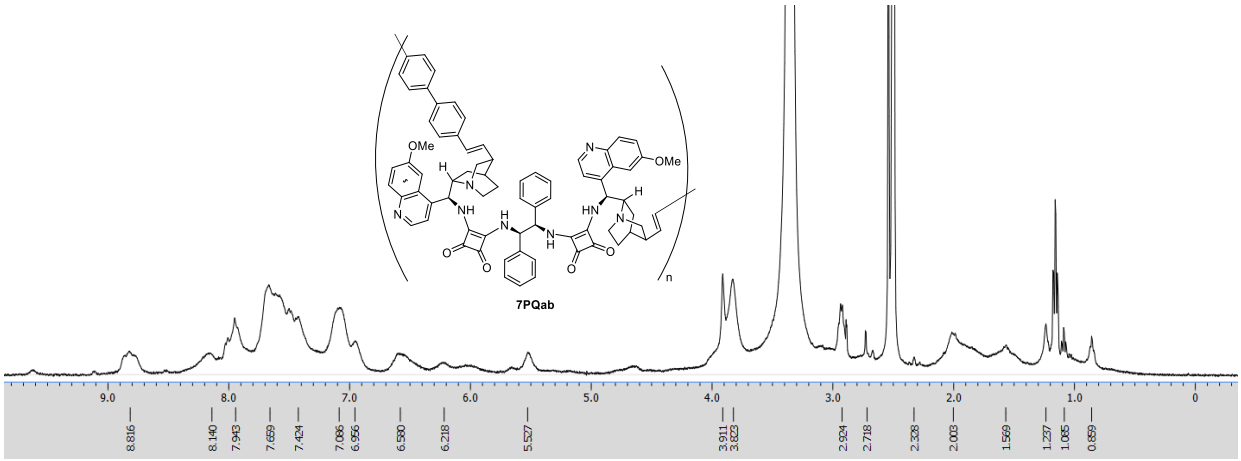
IR spectrum of polymer, 7PCba



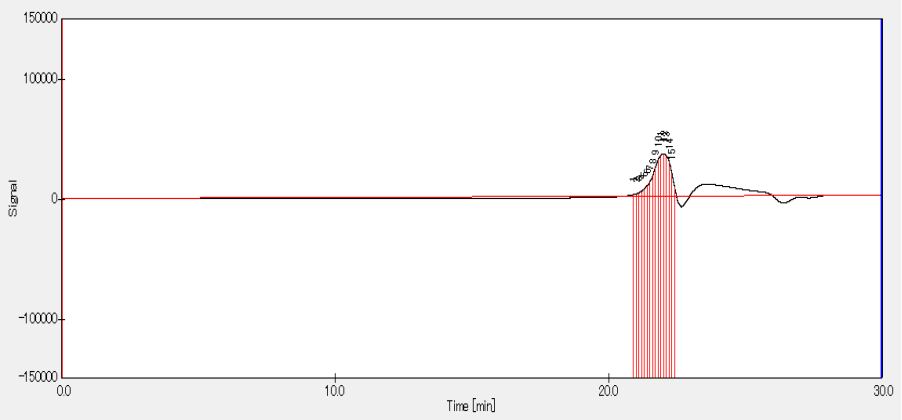
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3435.56	91.3863	2	1725.01	89.6664
3	1709.59	90.3757	4	1691.27	88.5728
5	1677.77	88.6	6	1665.23	90.8663
7	1640.16	84.9218	8	1581.34	70.3197
9	1549.52	83.4517	10	1529.27	83.0617
11	1512.88	77.9928	12	1502.28	79.0814
13	1482.99	82.0133	14	1461.78	80.9469
15	1443.46	79.5888	16	766.566	91.1643
17	464.761	87.2912	18	414.62	90.9473

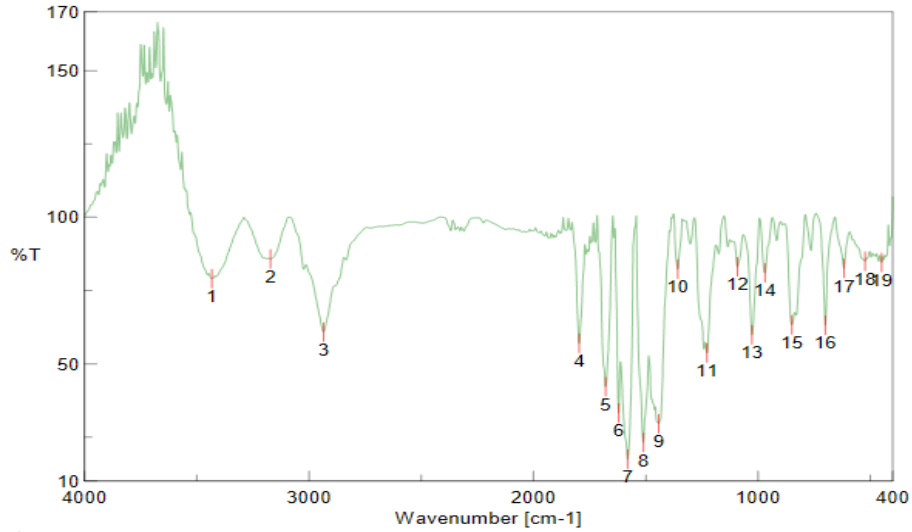
^{1}H NMR of polymer, 7PQab in DMSO-d_6



SEC data of polymer, 7PQab



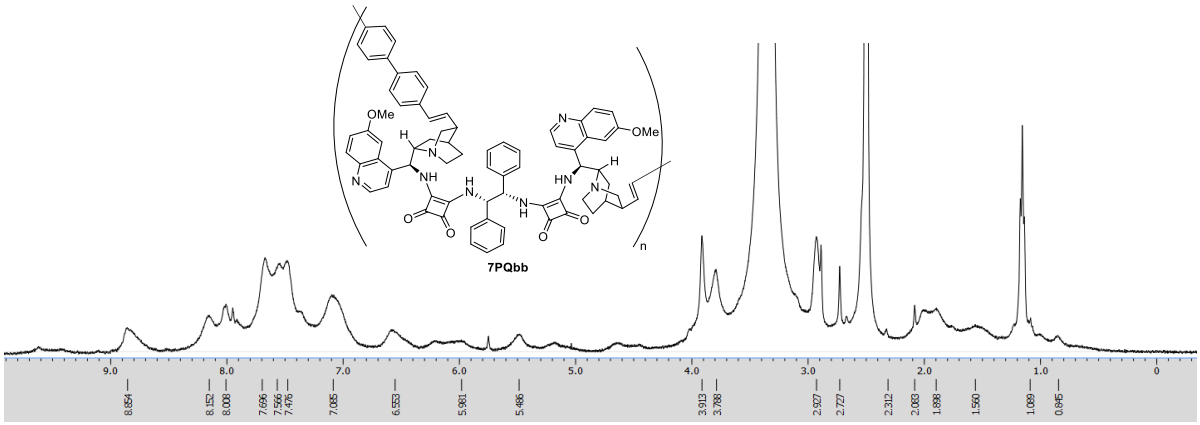
IR spectrum of polymer, 7PQab



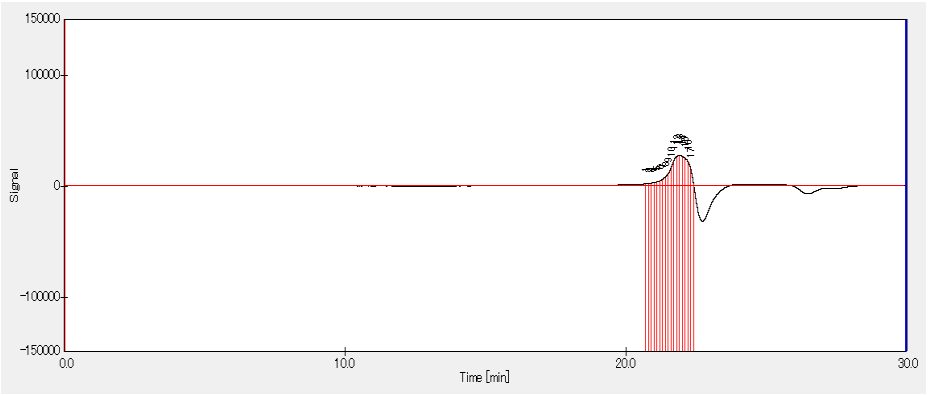
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3433.64	79.0035	2	3171.36	85.7309
3	2935.13	60.7901	4	1796.37	56.9067
5	1678.73	42.1022	6	1620.88	33.1454
7	1580.38	17.3901	8	1510.95	23.0831
9	1442.49	29.5065	10	1357.64	82.2249
11	1227.47	53.621	12	1091.51	83.0474
13	1026.91	59.8056	14	969.055	80.9887
15	849.49	63.2453	16	700.034	63.1188
17	617.109	82.4964	18	523.579	84.8827
19	449.333	84.5352			

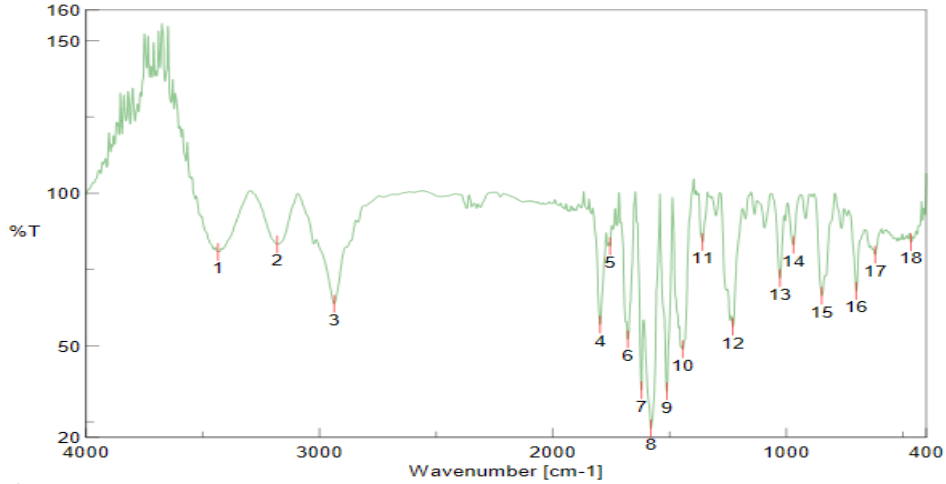
^{1}H NMR of 7PQbb in DMSO-d_6



SEC data of polymer, 7PQbb



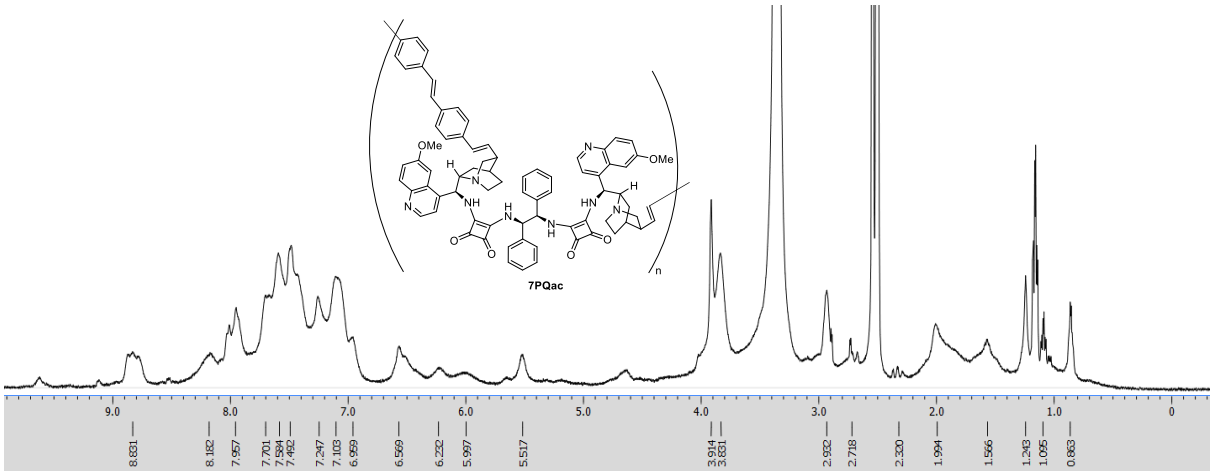
IR spectrum of polymer, 7PQbb



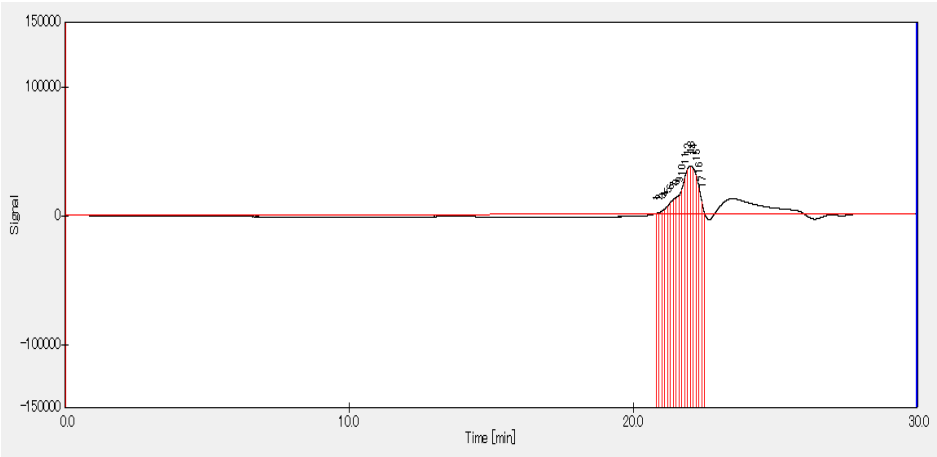
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3434.6	80.688	2	3181.01	83.234
3	2937.06	63.7216	4	1797.33	56.9242
5	1754.9	82.5648	6	1678.73	52.0989
7	1620.88	35.4532	8	1579.41	22.8618
9	1511.92	35.0334	10	1443.46	48.8024
11	1358.6	83.9981	12	1228.43	56.202
13	1026.91	72.0868	14	969.055	83.0694
15	847.561	66.3102	16	700.034	67.9054
17	619.038	79.8633	18	465.725	83.8985

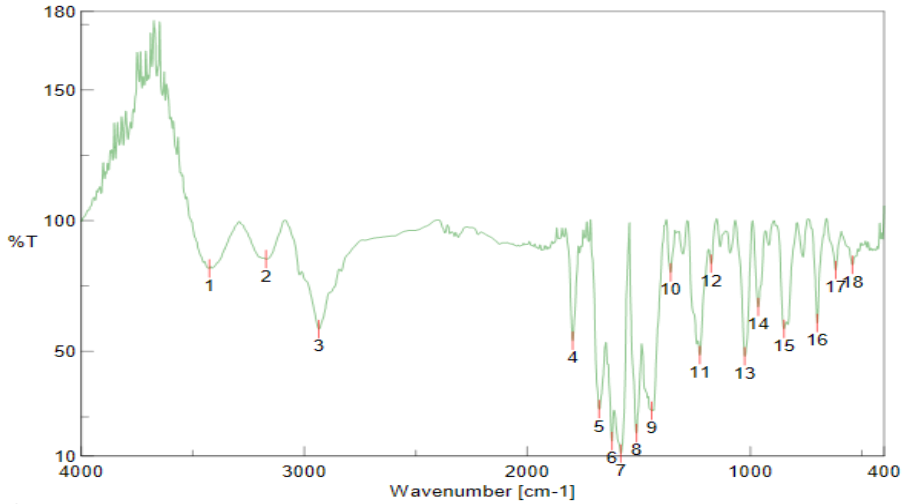
^{1}H NMR spectrum of 7PQac in DMSO-d_6



SEC data of polymer, 7PQac



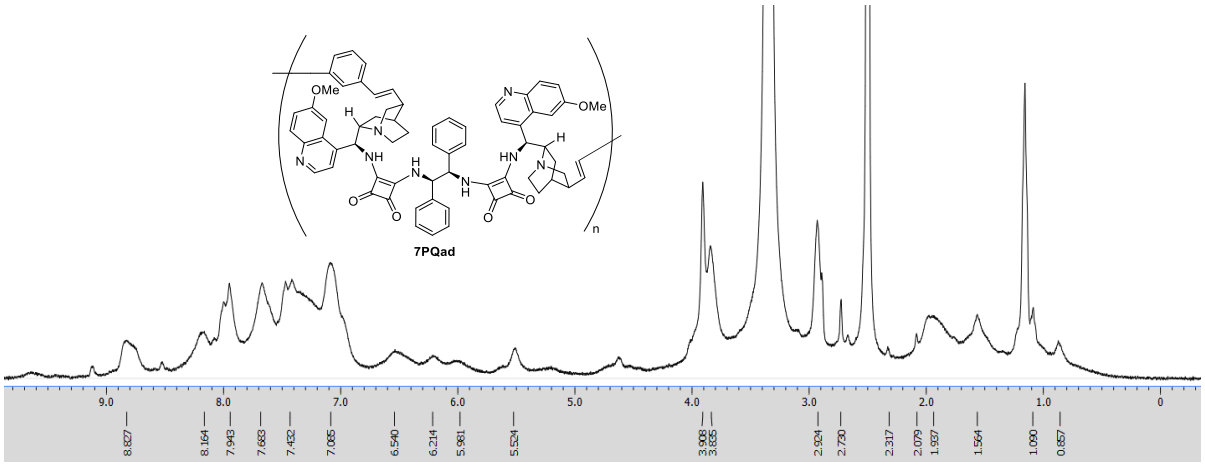
IR spectrum of polymer, 7PQac



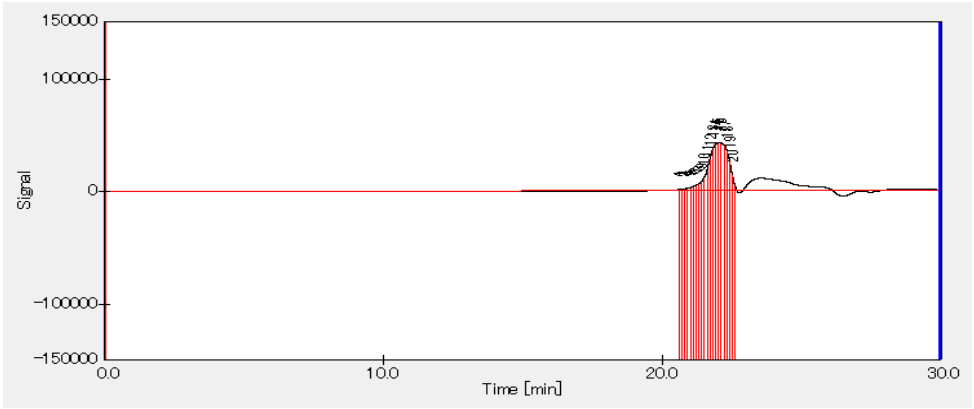
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3425.92	81.7092	2	3171.36	85.2462
3	2934.16	58.503	4	1796.37	54.0649
5	1677.77	27.8834	6	1620.88	15.684
7	1580.38	10.8199	8	1510.95	18.6796
9	1442.49	27.2239	10	1357.64	80.1906
11	1226.5	48.534	12	1175.4	83.5456
13	1024.98	48.114	14	964.233	66.9648
15	849.49	58.5487	16	700.034	60.8544
17	617.109	81.09	18	541.899	83.0994

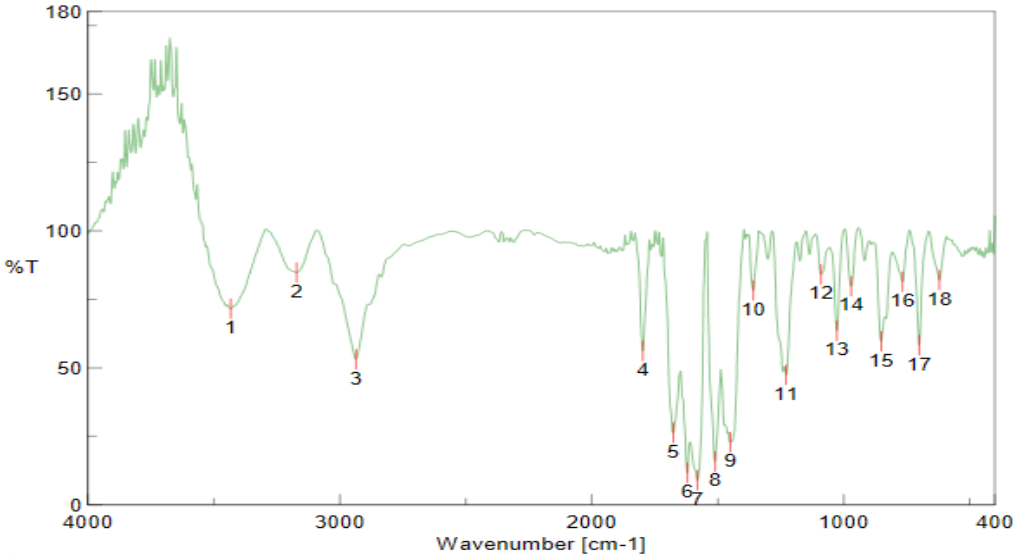
^{1}H NMR of polymer, 7PQad in DMSO-d_6



SEC data of polymer, 7PQad



IR spectrum of polymer, 7PQad



[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3433.64	71.5187	2	3171.36	84.7369
3	2936.09	53.0733	4	1797.33	56.1384
5	1676.8	26.2997	6	1620.88	11.5771
7	1580.38	8.90275	8	1510.95	15.7136
9	1450.21	22.8037	10	1358.6	78.2266
11	1228.43	47.3595	12	1090.55	84.0442
13	1026.91	63.4703	14	970.019	79.7834
15	851.418	59.6454	16	766.566	81.3806
17	700.034	58.2195	18	620.002	82.0371

Table 2, entry 2
98% ee

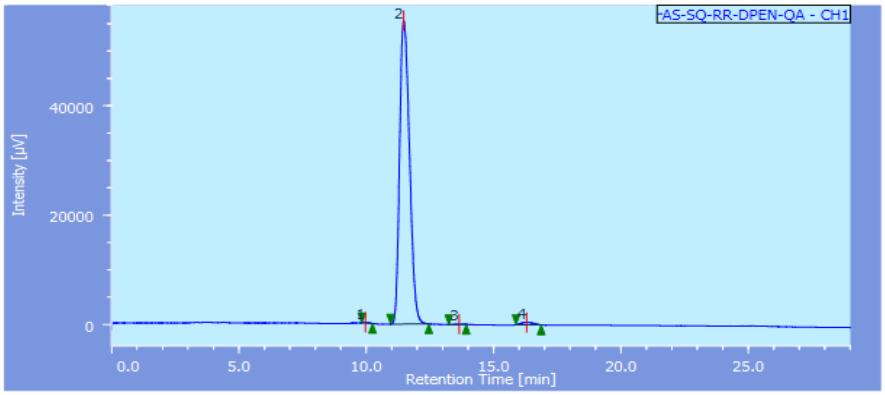


Table 2, entry 3
92% ee

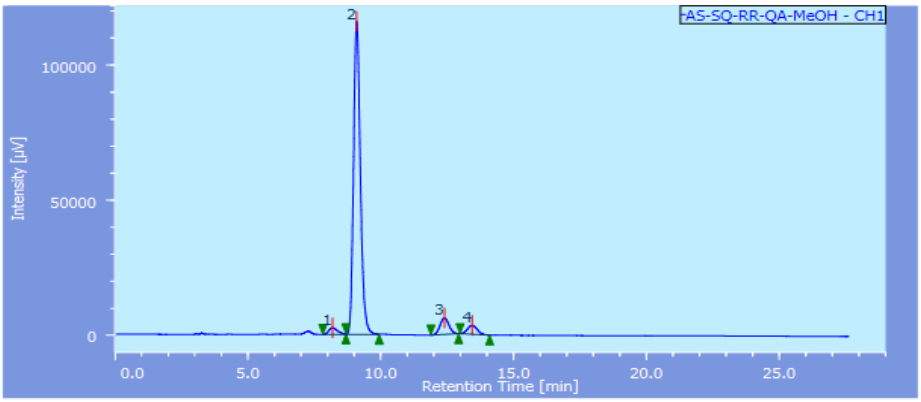


Table 2, entry 4
96% ee

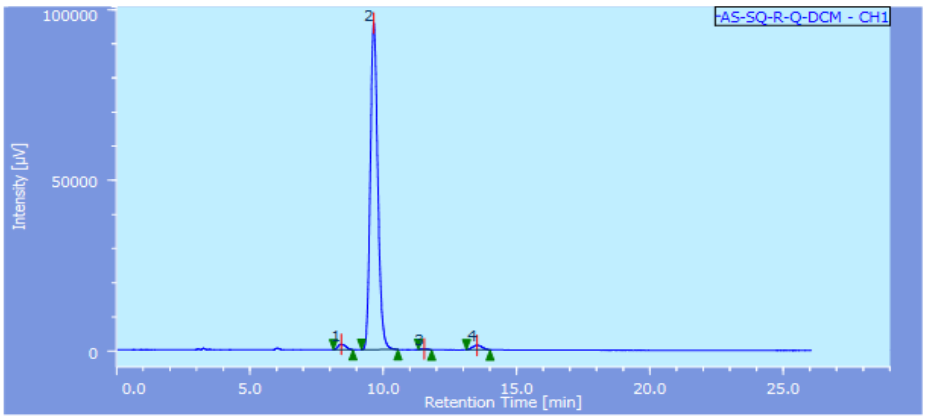


Table 2, entry 5
94% ee

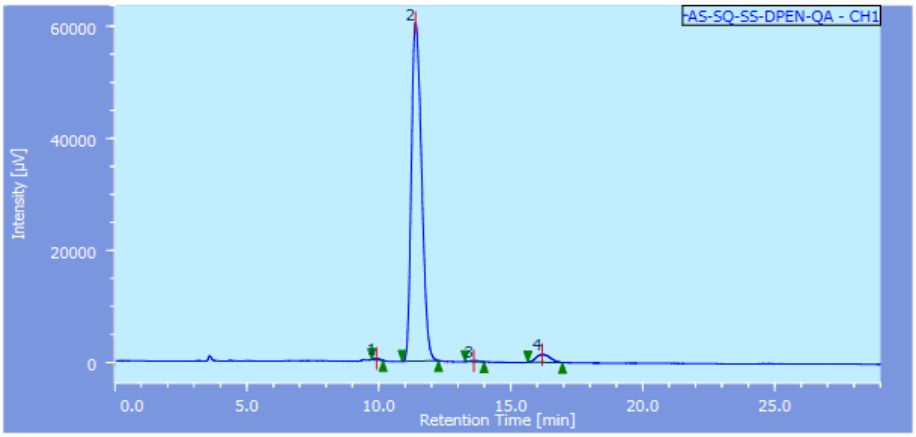


Table 2, entry 6
84% ee

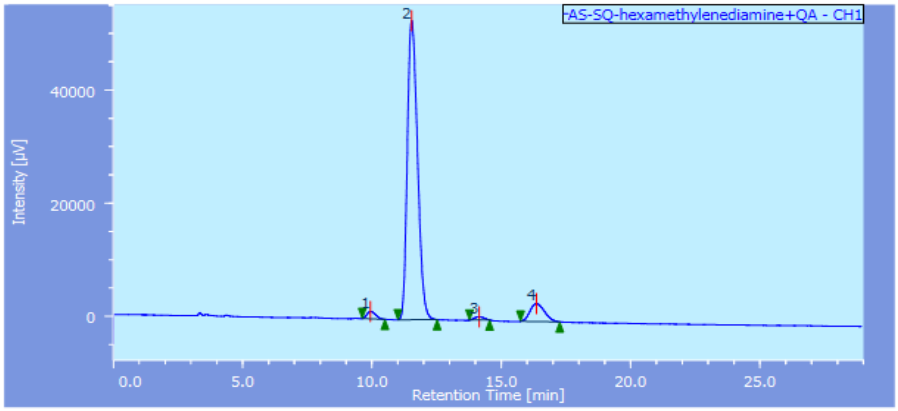


Table 2, entry 7
70% ee

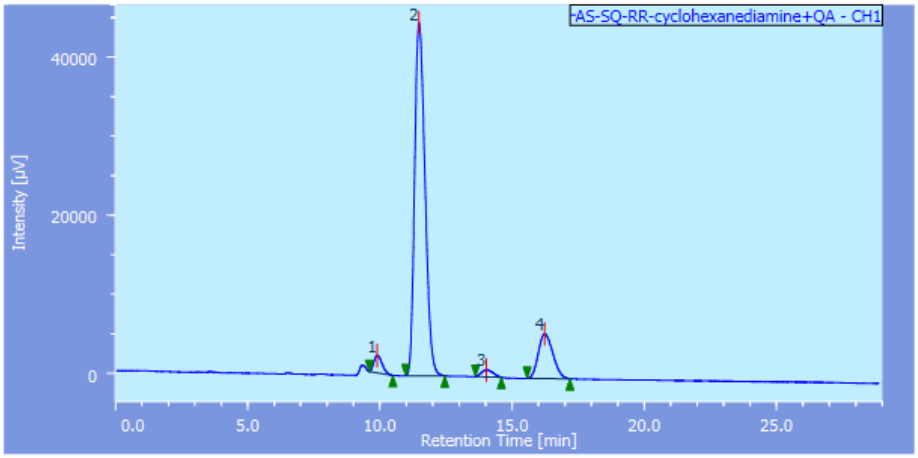


Table 2, entry 8
90% ee

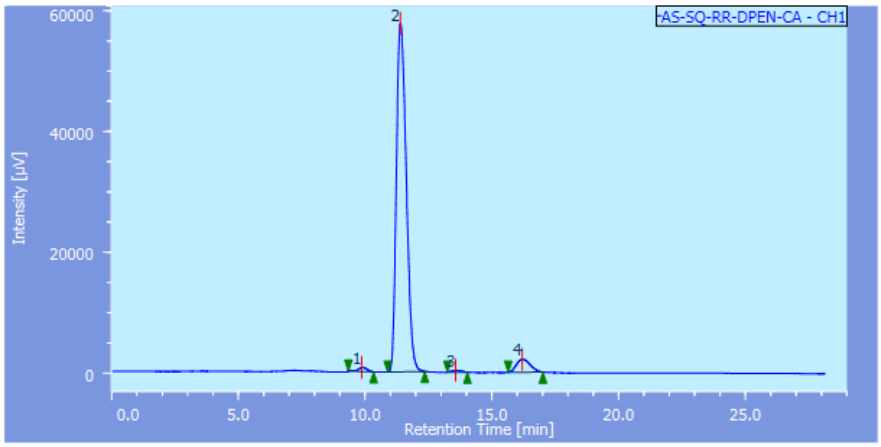


Table 2, entry 9
87% ee

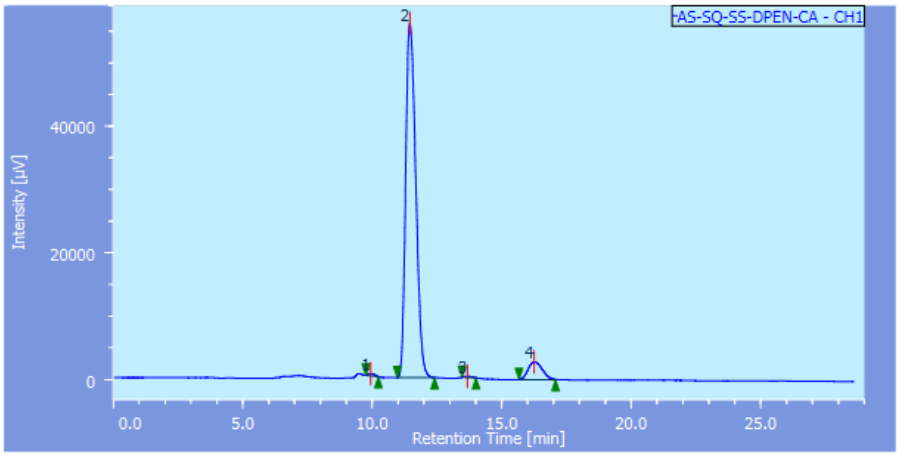


Table 3, entry 1
95% ee

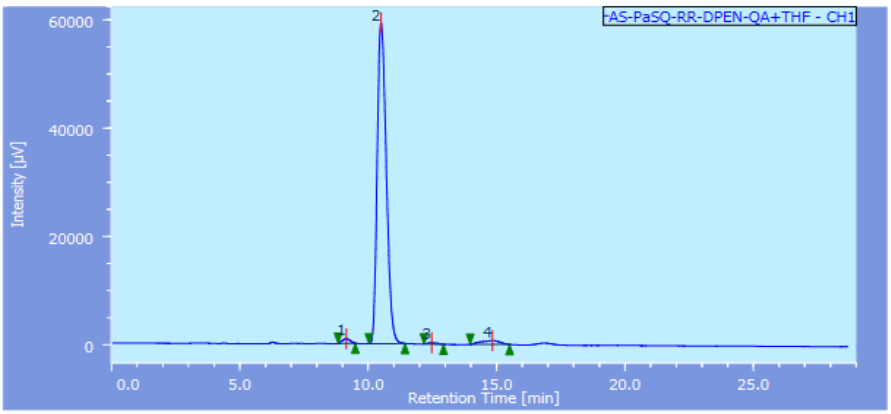


Table 3, entry 2
97% ee

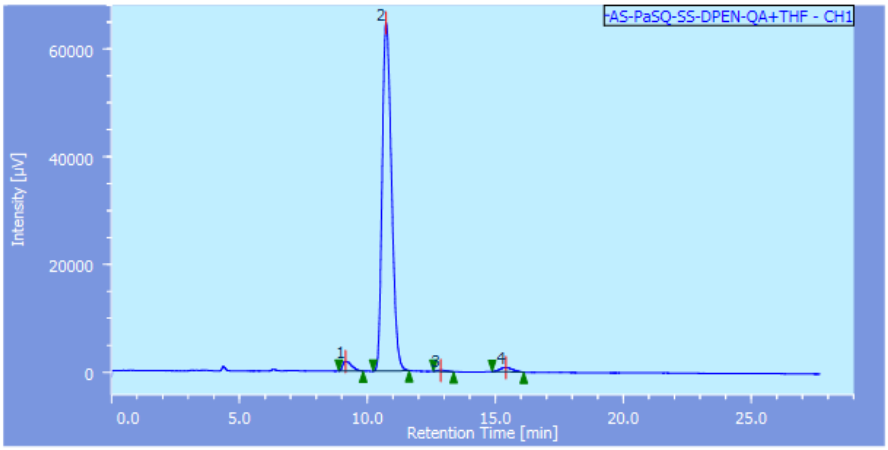


Table 3, entry 3
93% ee

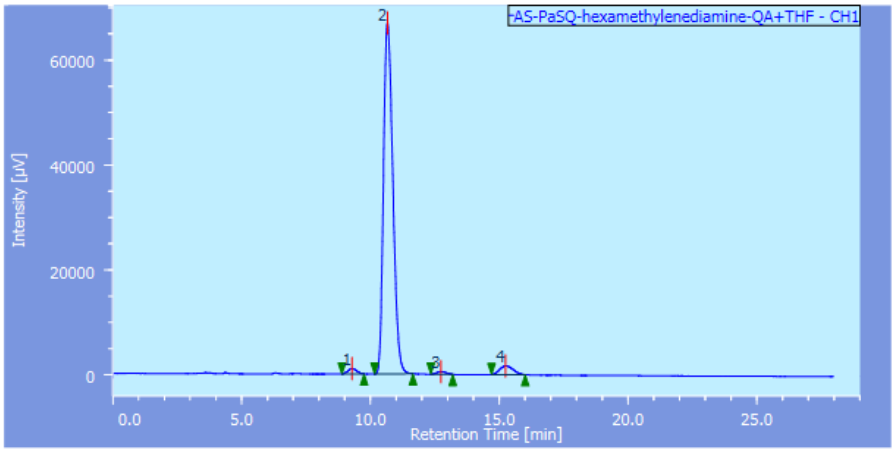


Table 3, entry 4
90% ee

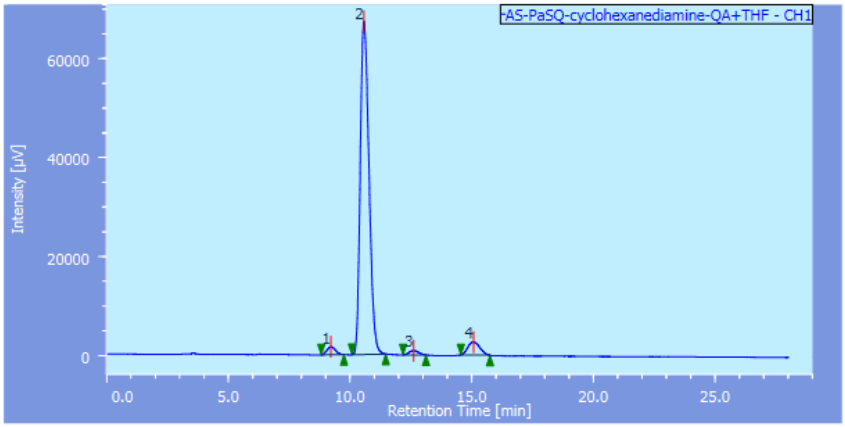


Table 3, entry 5
95% ee

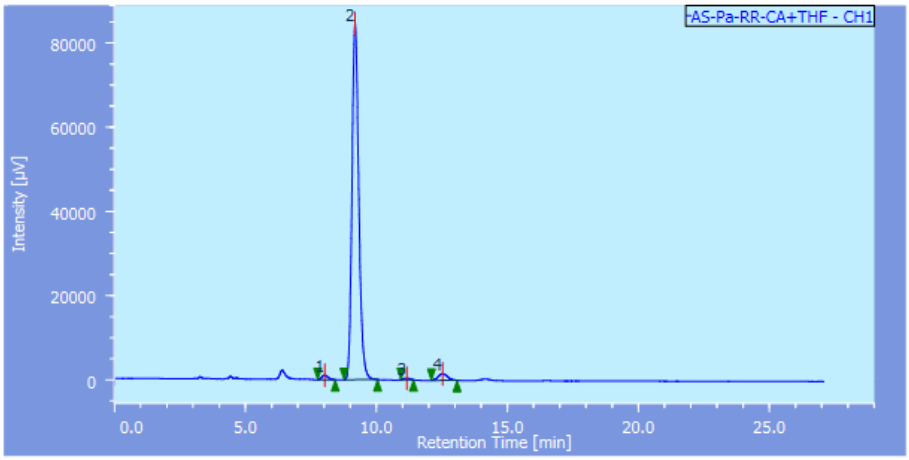


Table 3, entry 6
96% ee

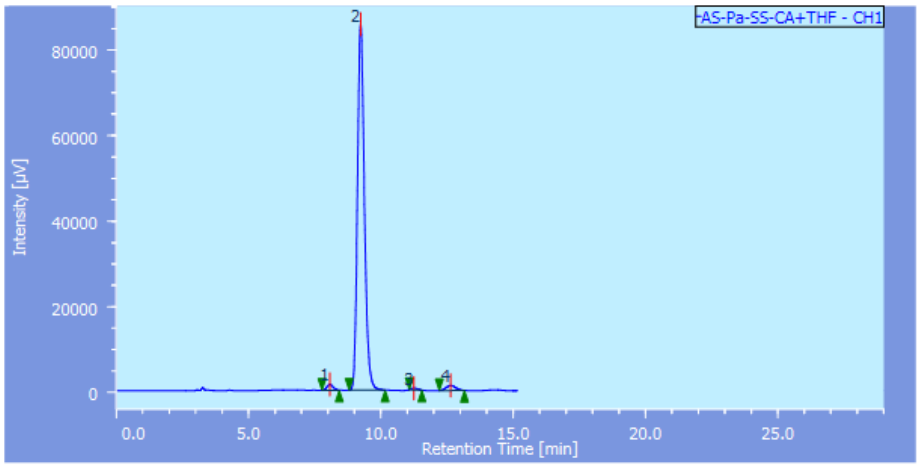


Table 4, entry 1
99% ee

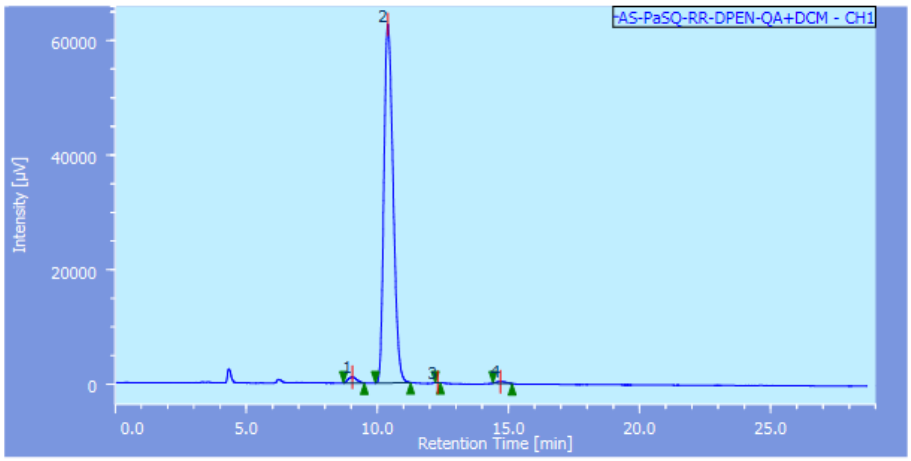


Table 4, entry 2
92% ee

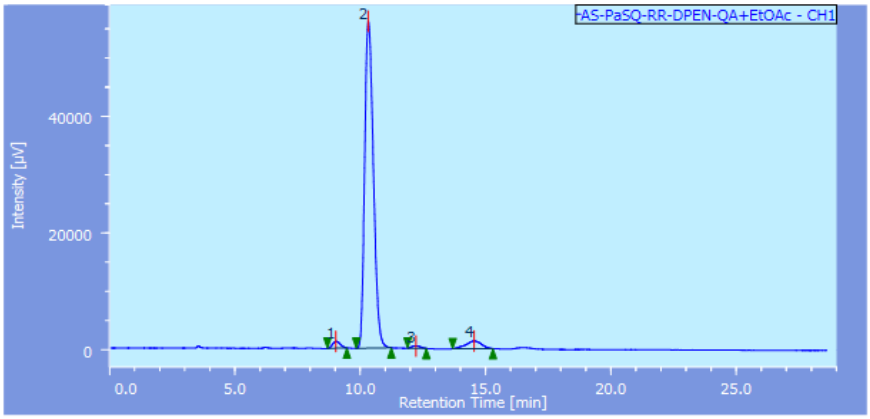


Table 4, entry 3
99% ee

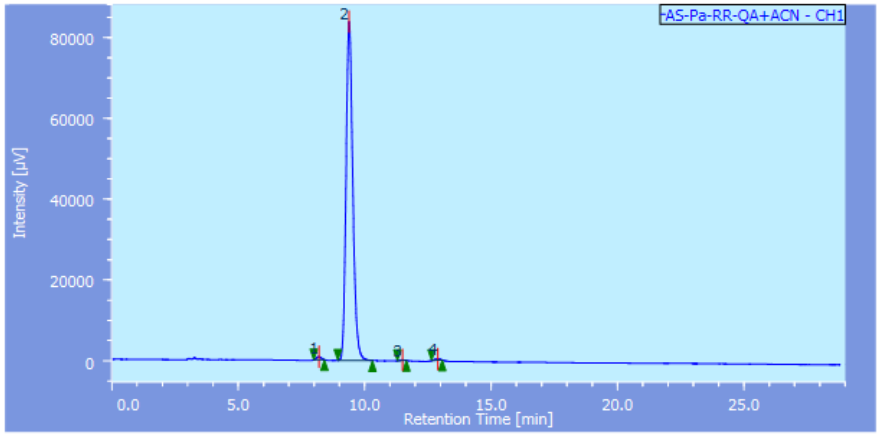
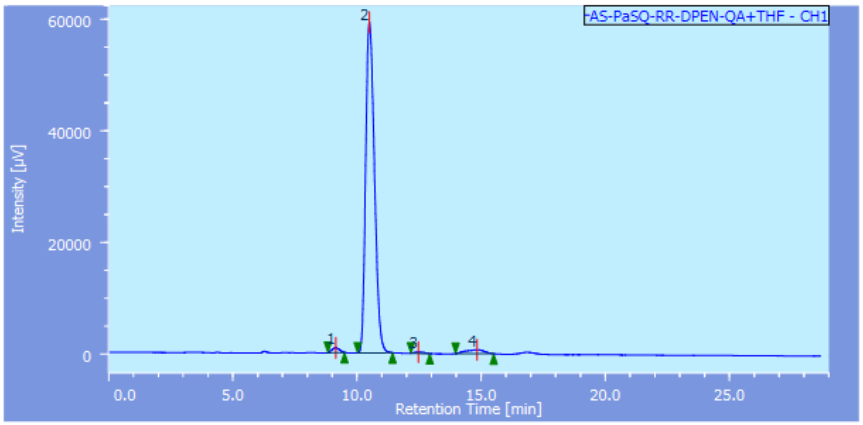


Table 4, entry 4
95% ee



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99% ee

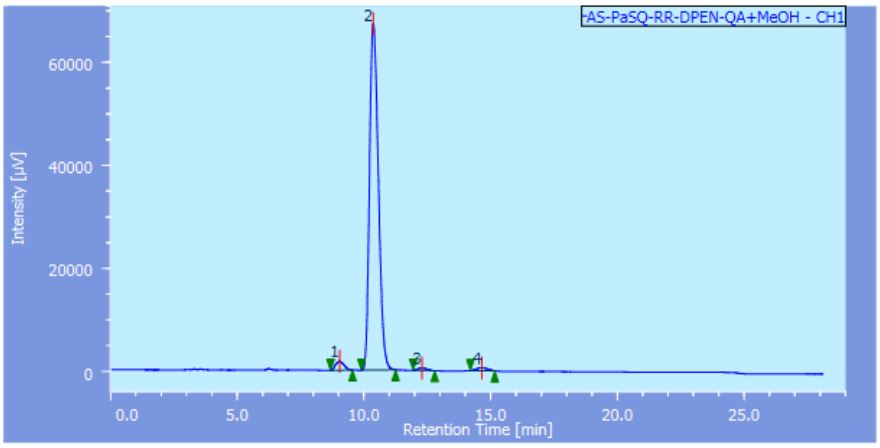


Table 4, entry 6
97% ee

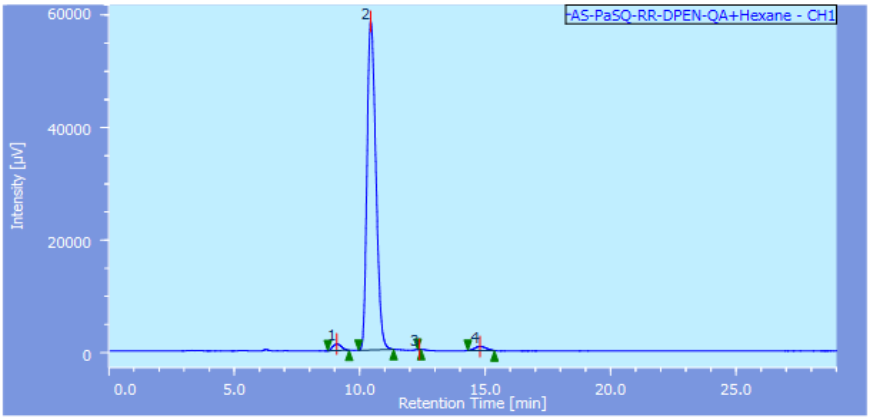


Table 4, entry 7
88% ee

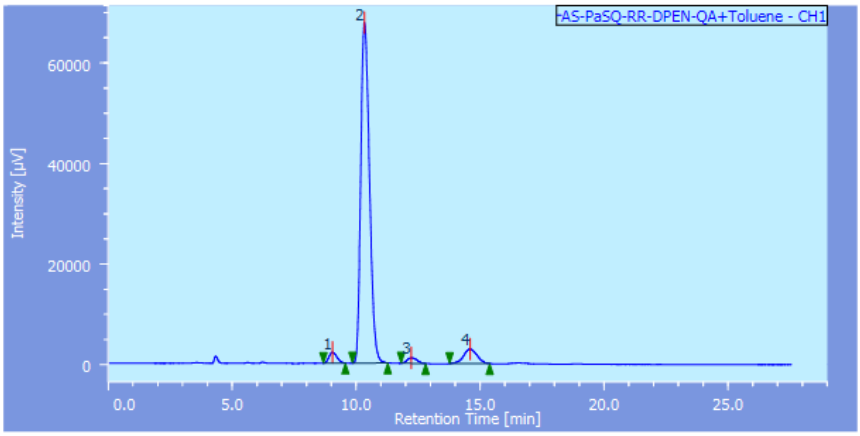


Table 4, entry 8
97% ee

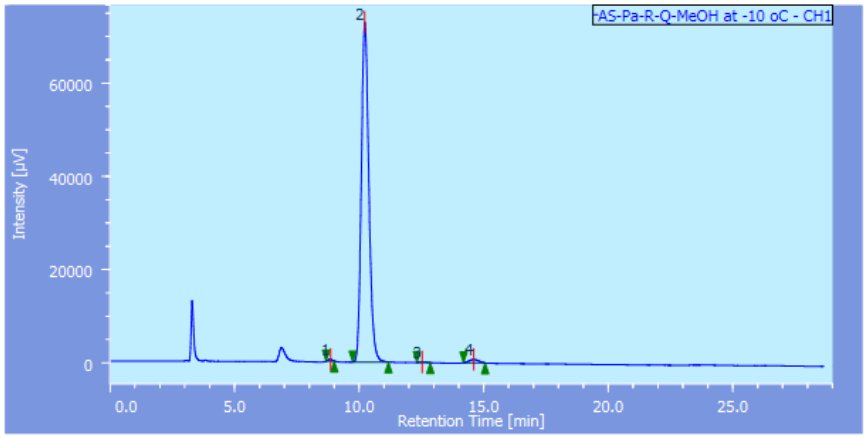


Table 4, entry 9
99% ee

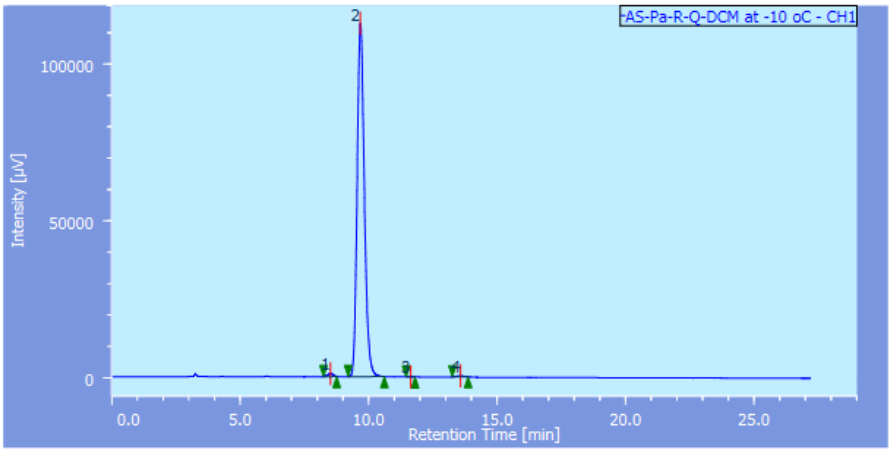


Table 4, entry 10
99% ee

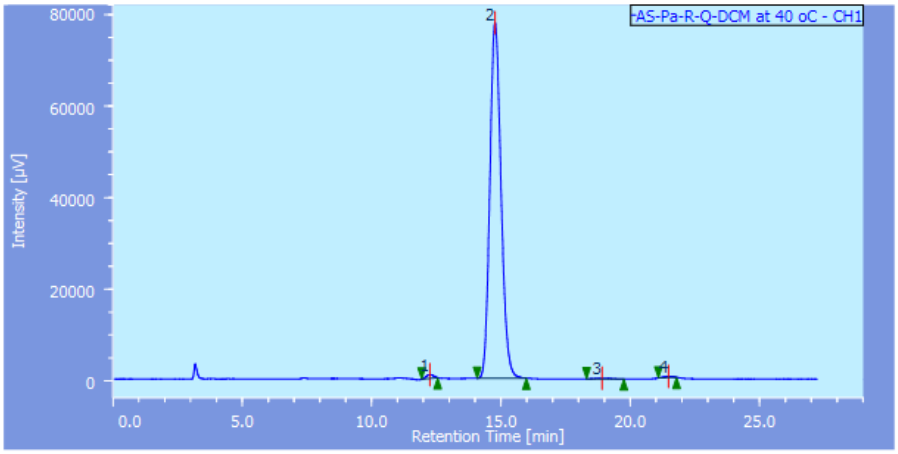


Table 5, entry 1
99% ee

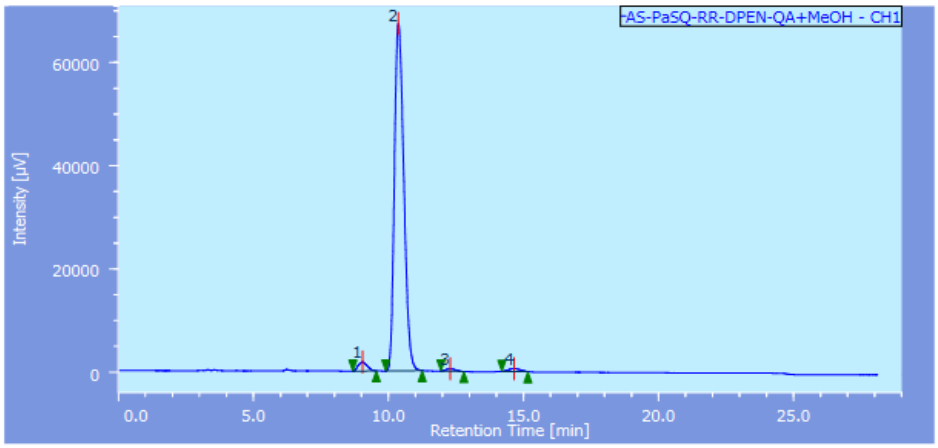
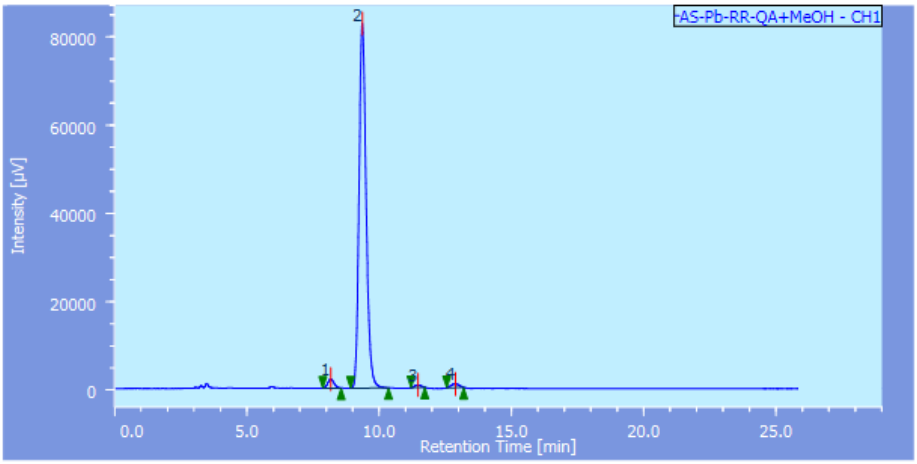


Table 5, entry 2
98% ee



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98% ee

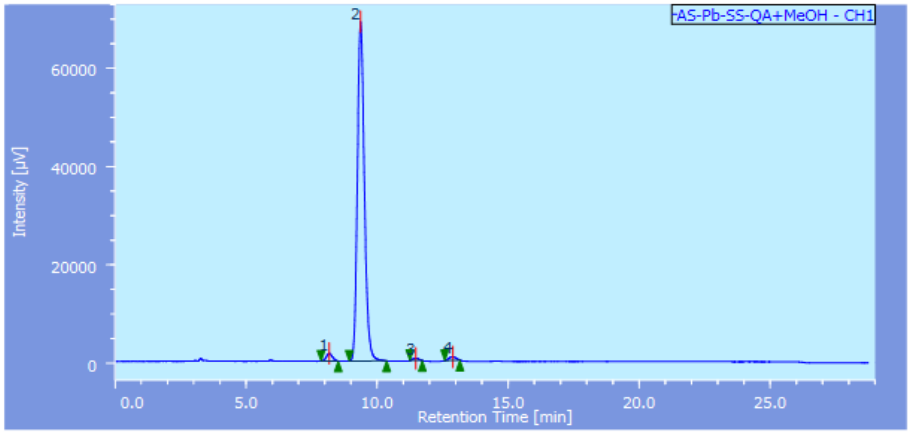


Table 5, entry 4
96% ee

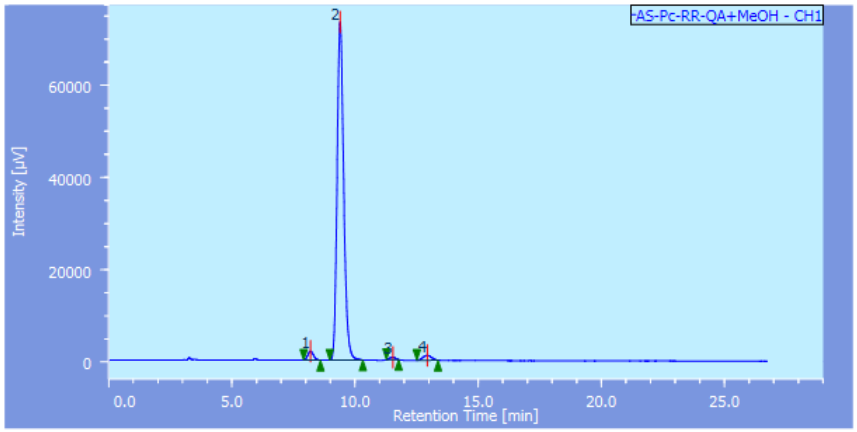


Table 5, entry 5
97% ee

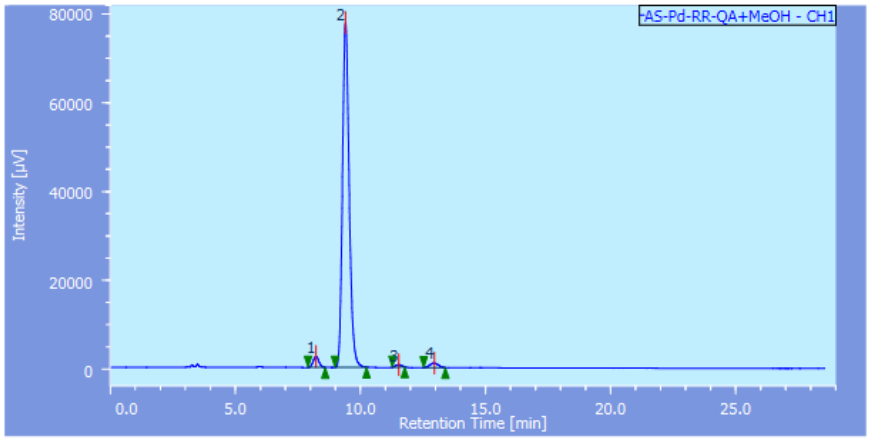


Table 6, entry 1
99% ee

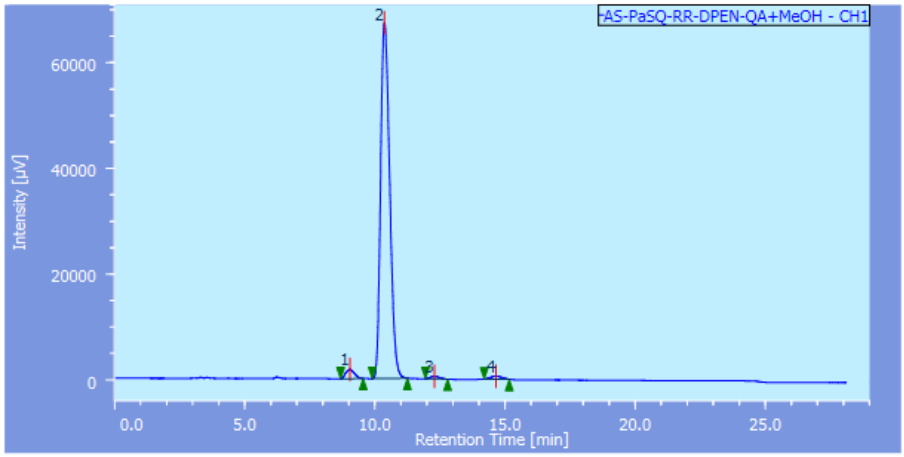


Table 6, entry 2
97% ee

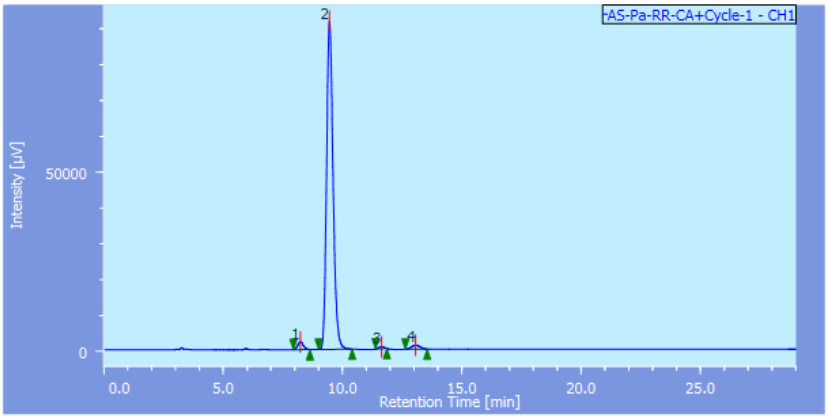


Table 6, entry 3
98% ee

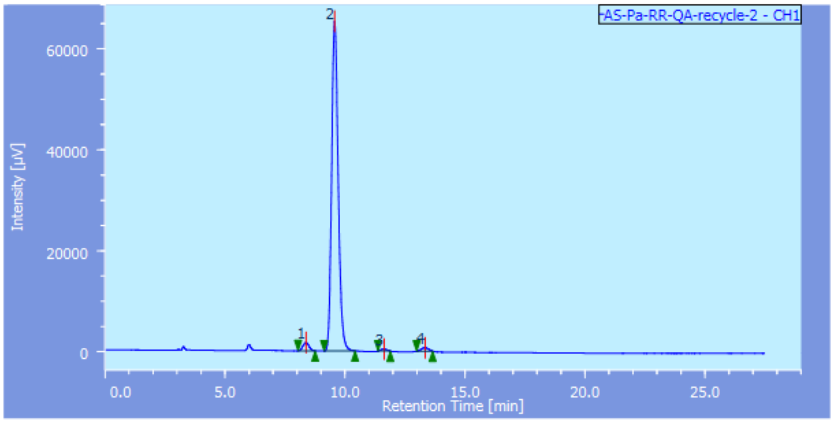


Table 6, entry 4
98% ee

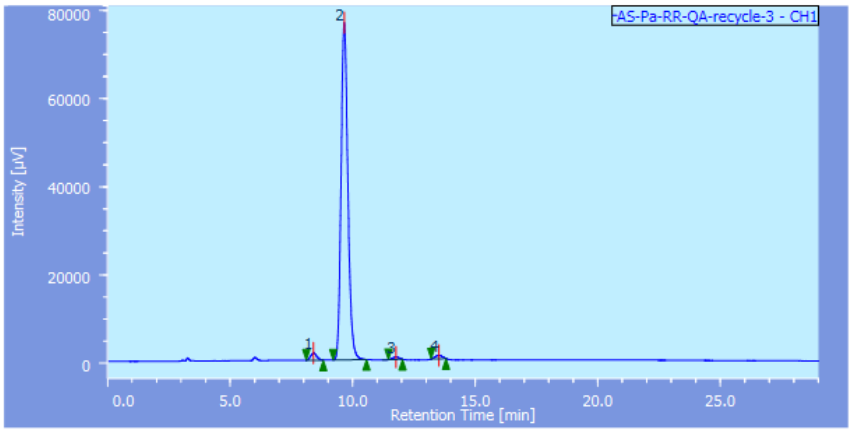


Table 6, entry 5
96% ee

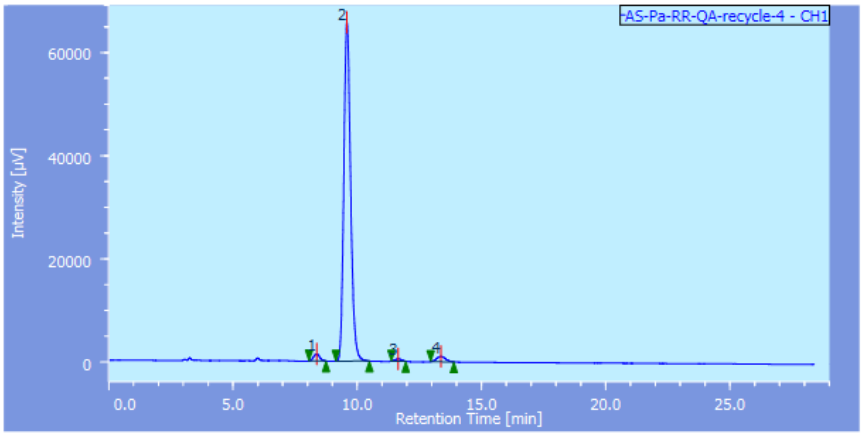


Table 6, entry 6
96% ee

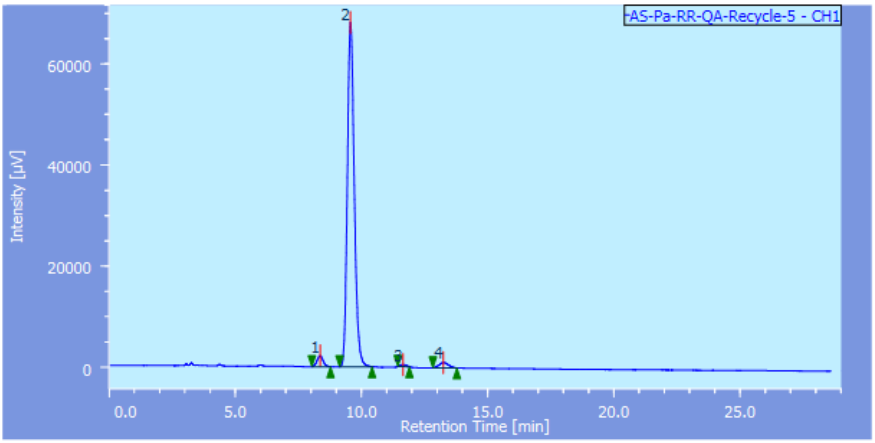


Table 6, entry 7
96% ee

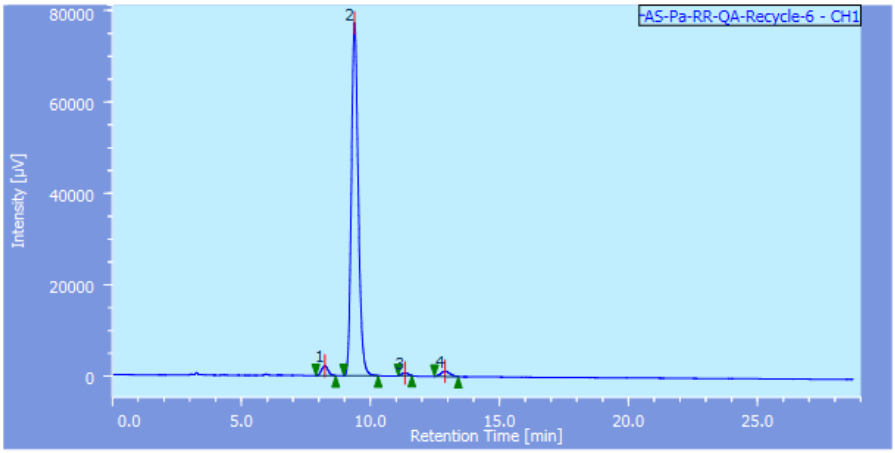


Table 6, entry 8
97% ee

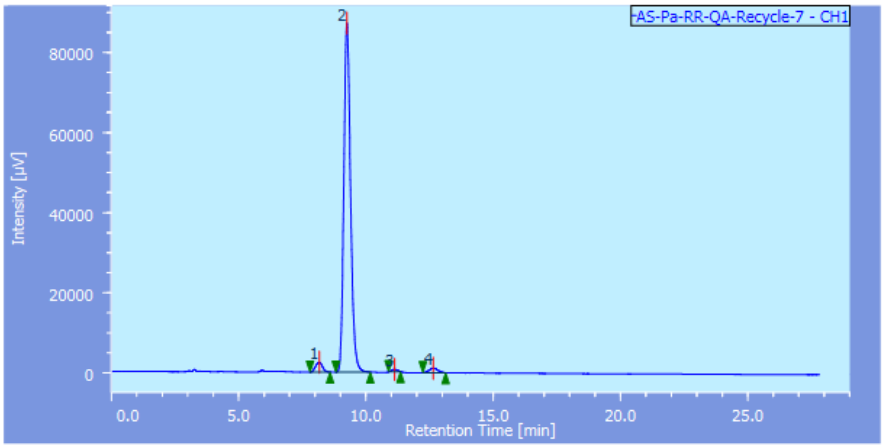


Table 7, entry 1
95% ee

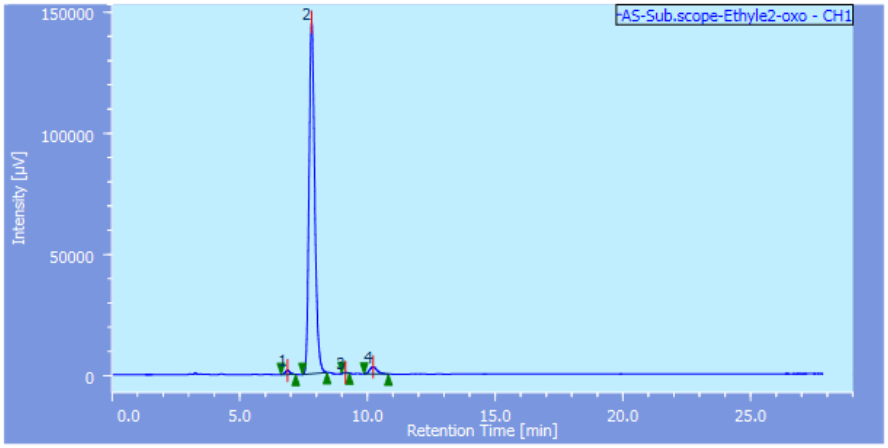


Table 7, entry 2
97% ee

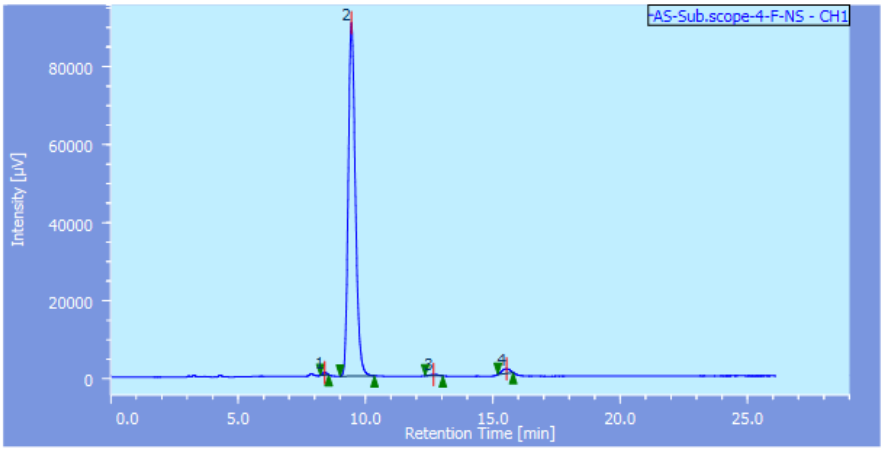


Table 7, entry 3
ee: N/D

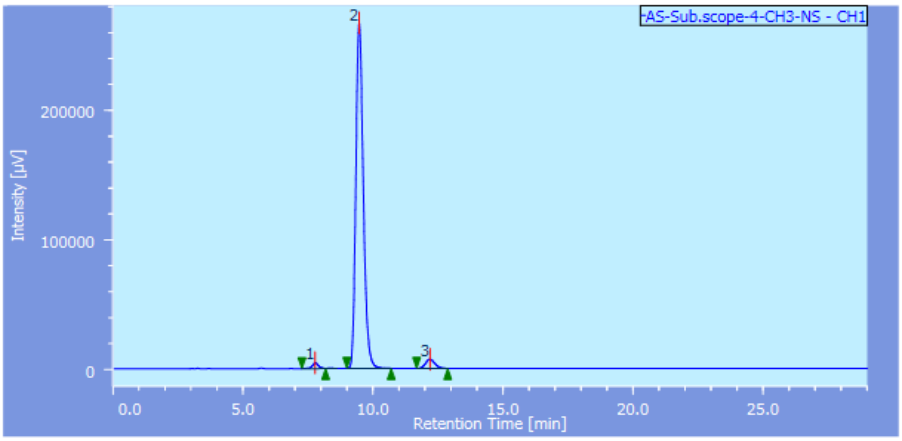


Table 7, entry 4
98% ee

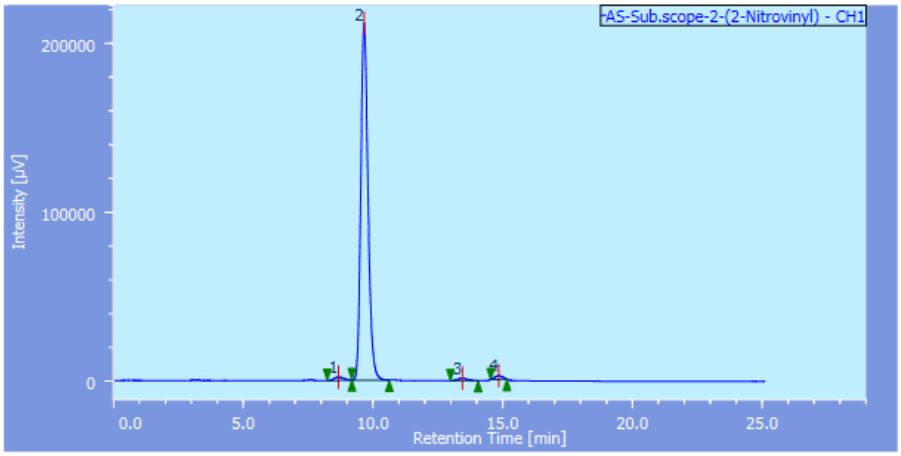


Table 7, entry 5
***ee*: N/D**

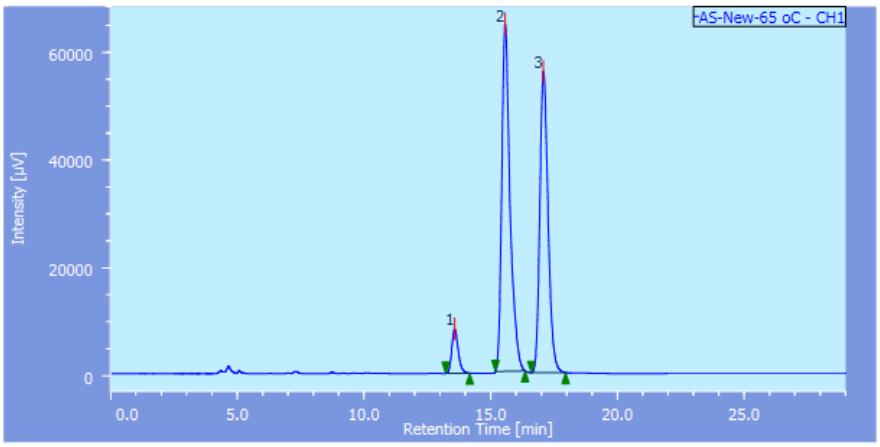


Table 7, entry 6
<1% ee

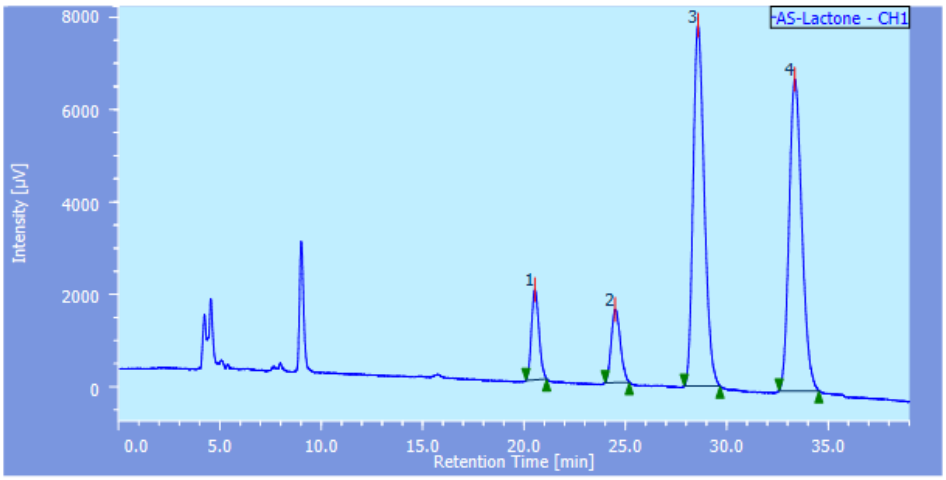
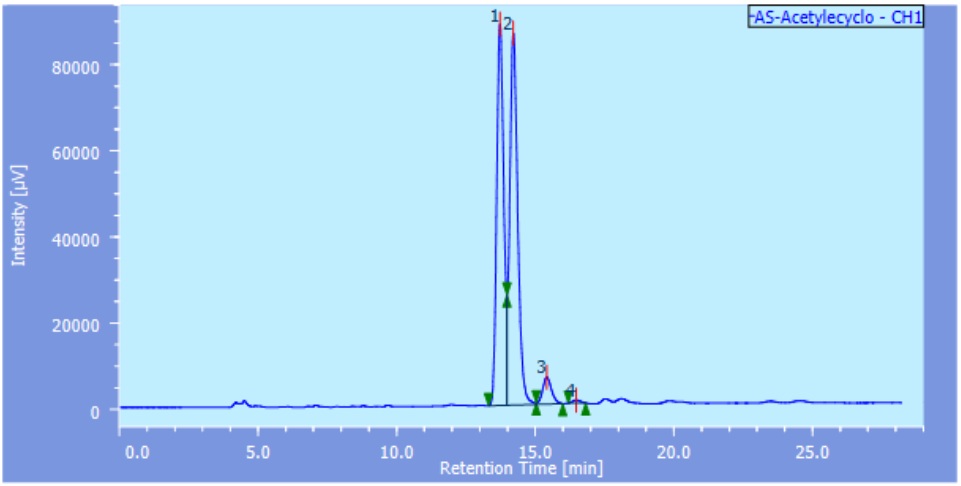
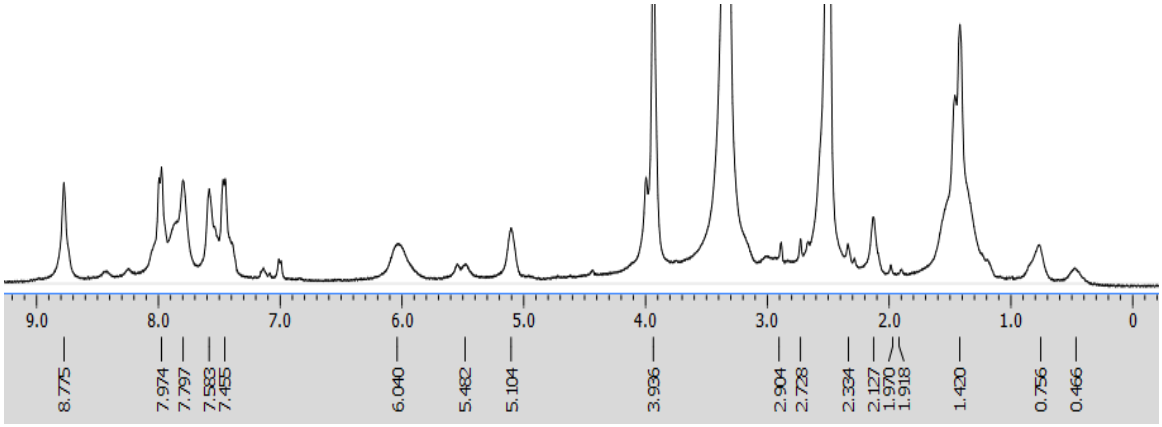


Table 7, entry 7
- 5 % ee

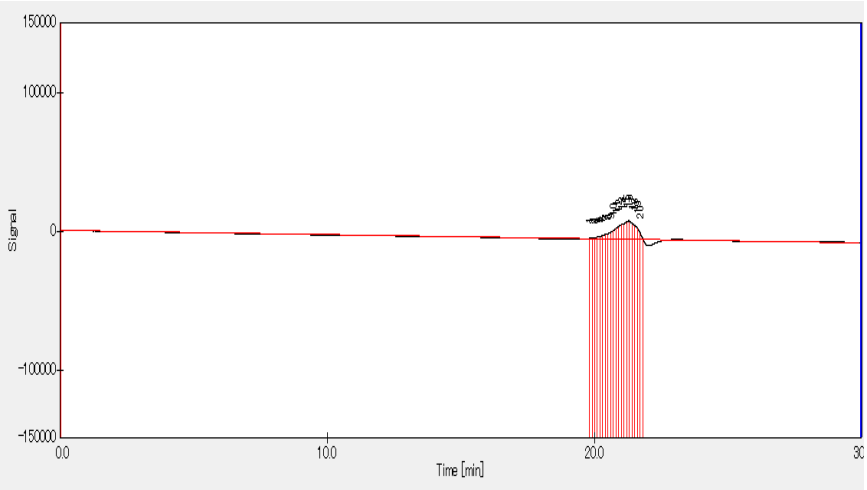


Spectra of different compounds for chapter 4

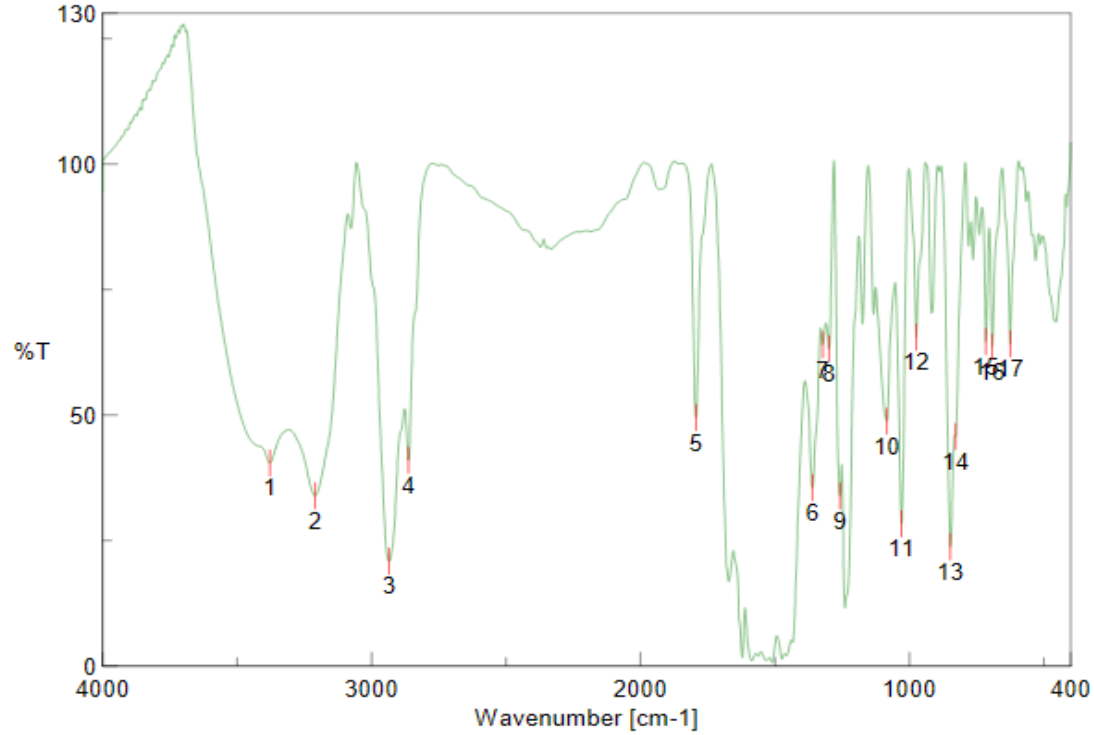
^{1}H NMR spectrum of polymer, 1Pa in DMSO-d_6



SEC data of polymer, 1Pa



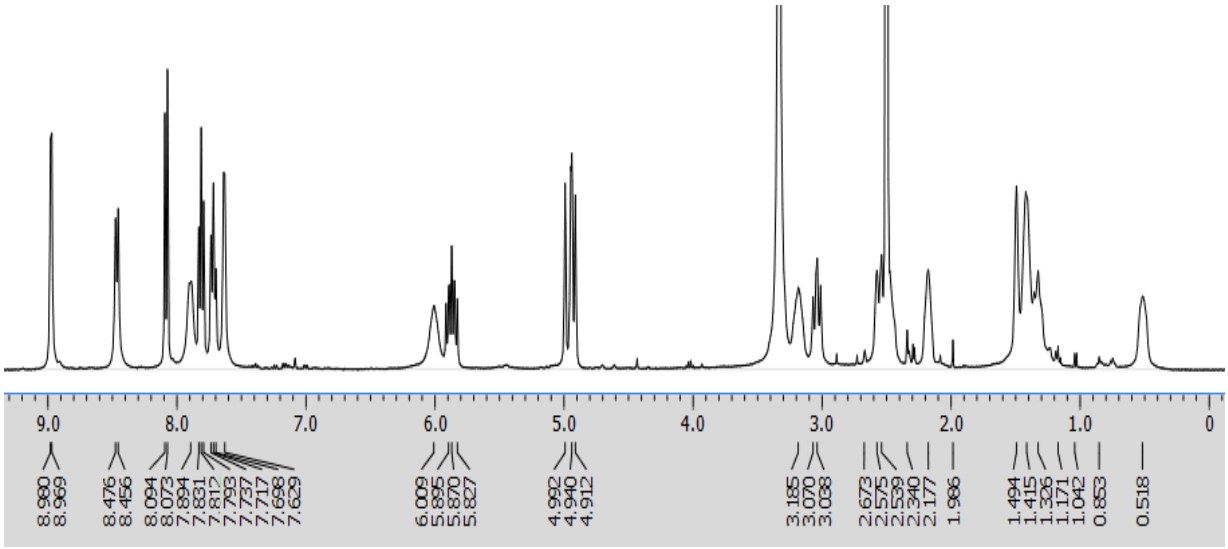
IR spectrum of polymer, 1Pa



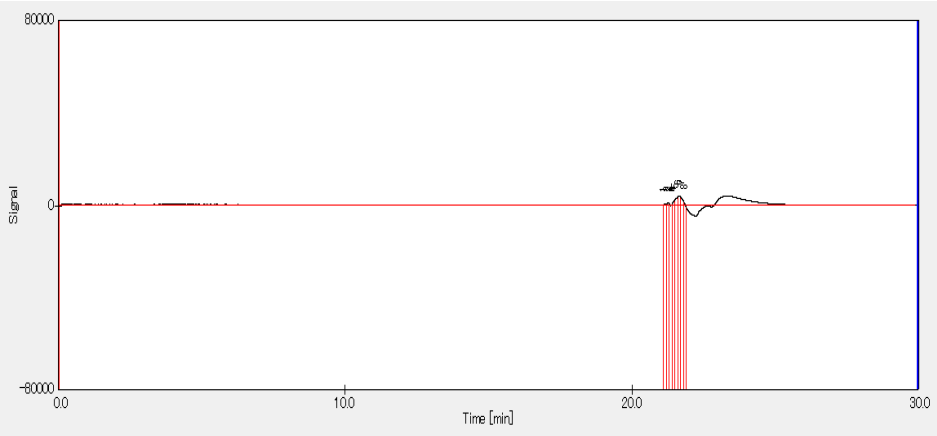
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3378.67	40.4085	2	3209.93	33.9026
3	2934.16	20.8419	4	2862.81	40.9717
5	1793.47	49.4825	6	1360.53	35.4967
7	1321.96	63.9834	8	1298.82	63.2067
9	1258.32	33.8353	10	1083.8	48.7327
11	1029.8	28.3264	12	974.84	65.4984
13	847.561	23.7353	14	828.277	45.6948
15	715.461	64.6403	16	692.32	63.5461
17	624.823	64.1501			

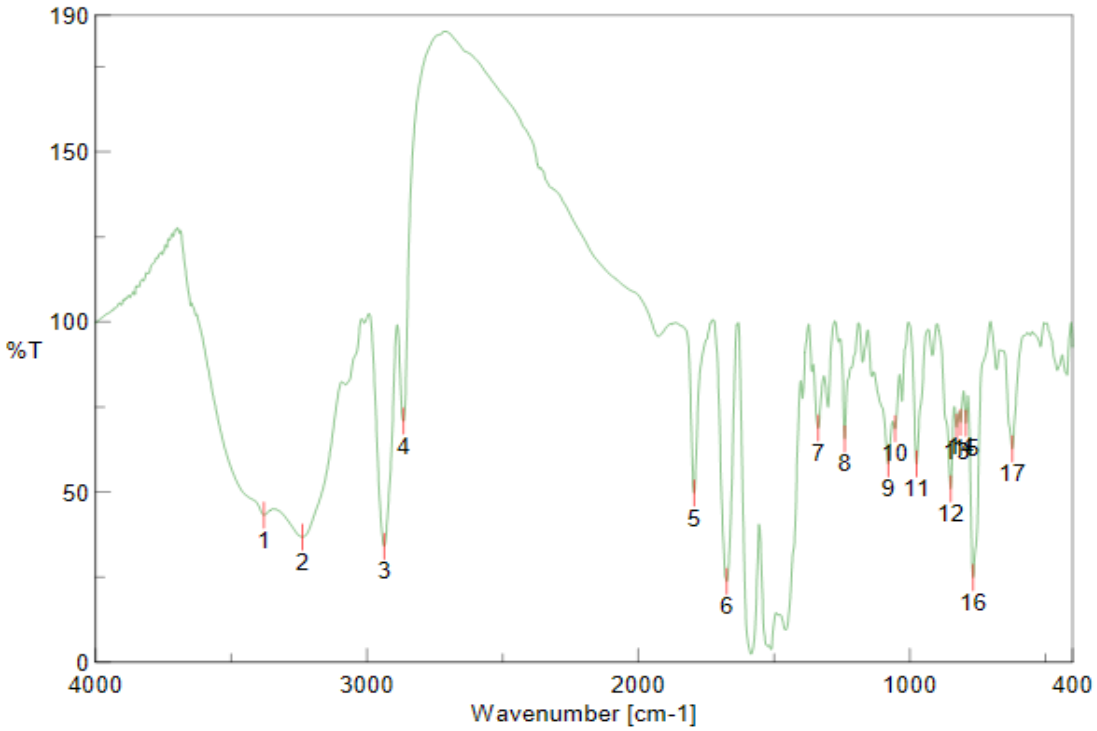
^{1}H NMR spectrum of polymer, 1Pb in DMSO-d_6



SEC data of polymer, 1Pb



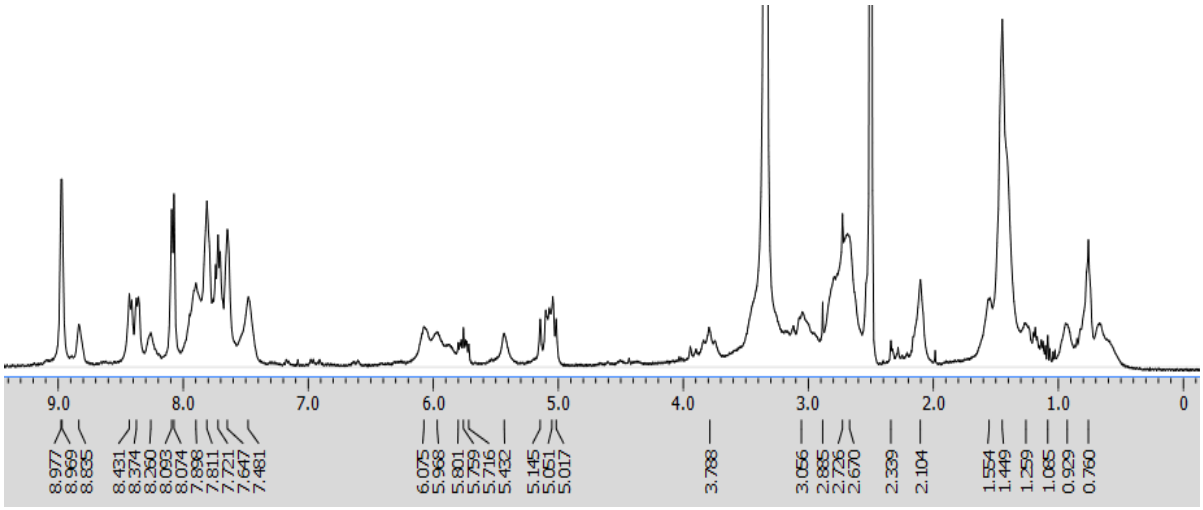
IR spectrum of polymer, 1Pb



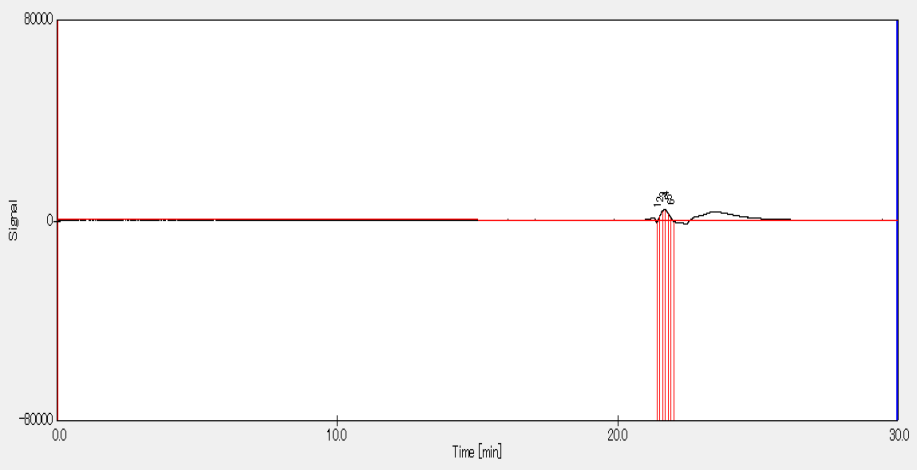
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3379.64	43.1594	2	3236.93	36.695
3	2936.09	33.9734	4	2865.7	70.7693
5	1794.44	49.6407	6	1674.87	23.6632
7	1337.39	68.7085	8	1240	65.5555
9	1078.98	58.2615	10	1053.91	68.5649
11	974.84	58.219	12	849.49	50.9021
13	827.312	69.0001	14	812.849	70.3912
15	792.6	70.1161	16	766.566	24.7736
17	621.931	62.6525			

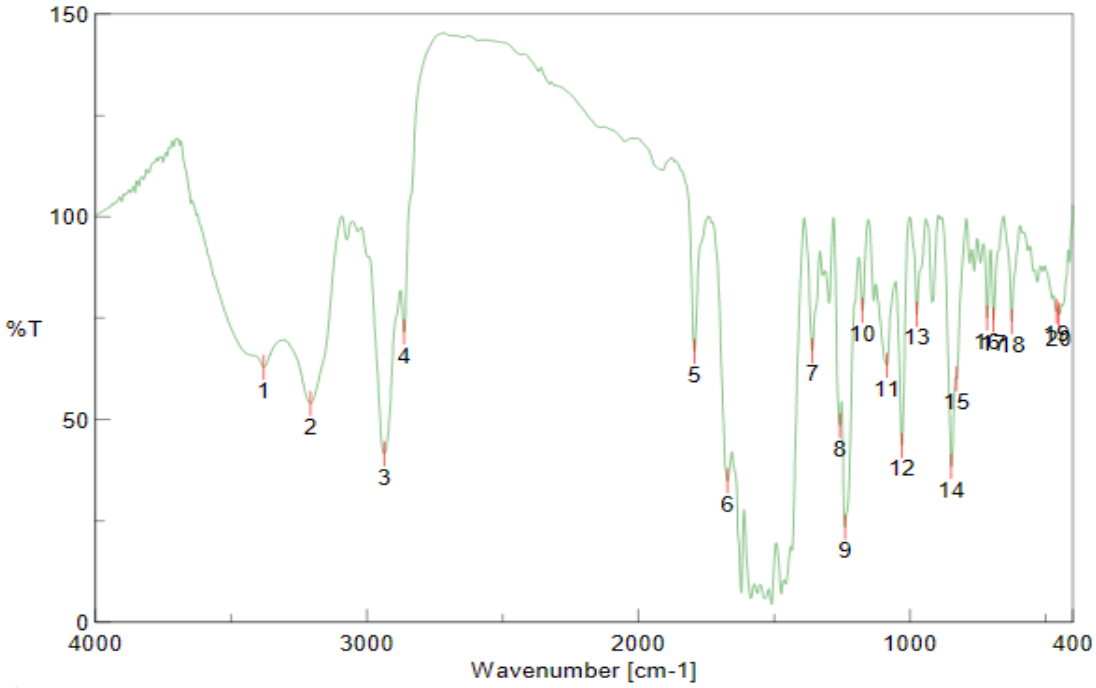
^{1}H NMR spectrum of polymer, 1Pc in DMSO-d_6



SEC data of polymer, 1Pc



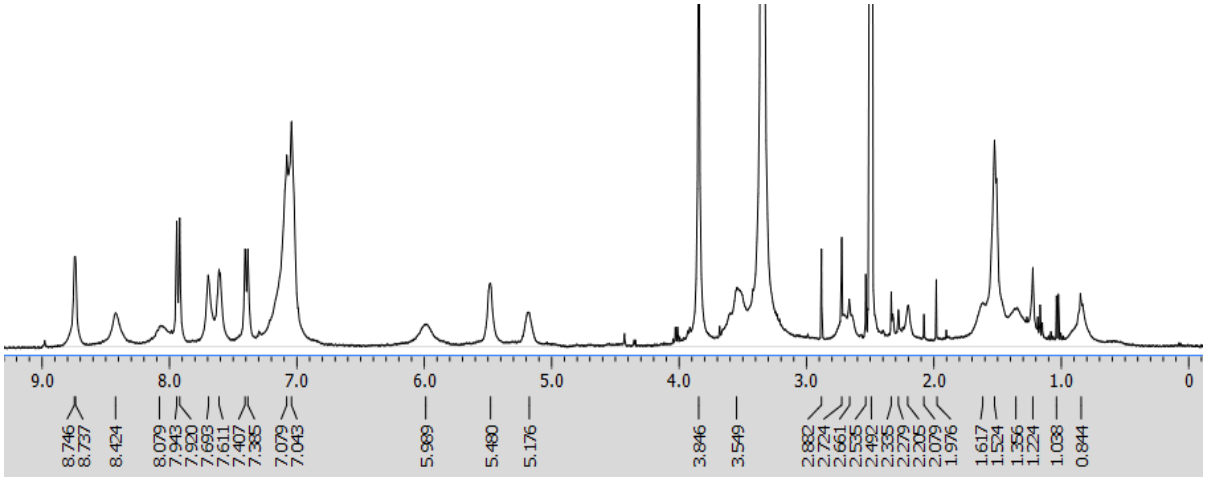
IR spectrum of polymer, 1Pc



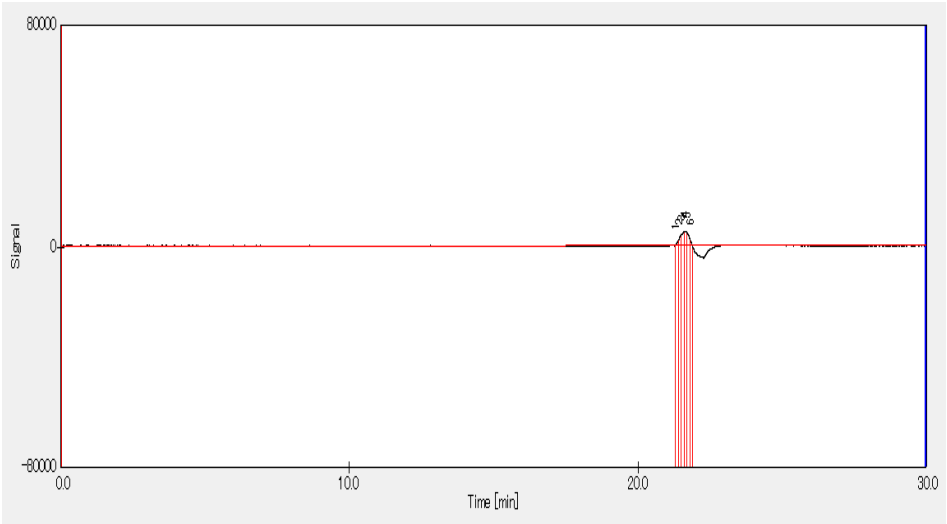
[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3380.6	62.8279	2	3208	53.9169
3	2936.09	41.502	4	2862.81	71.5161
5	1793.47	66.7422	6	1671.98	34.7941
7	1359.57	66.9221	8	1258.32	48.3685
9	1239.04	23.4191	10	1174.44	76.9319
11	1084.76	63.3131	12	1029.8	43.5066
13	974.84	75.9144	14	847.561	38.3649
15	828.277	59.9847	16	715.461	75.0475
17	692.32	74.5336	18	624.823	74.0939
19	460.904	76.67	20	451.261	75.7662

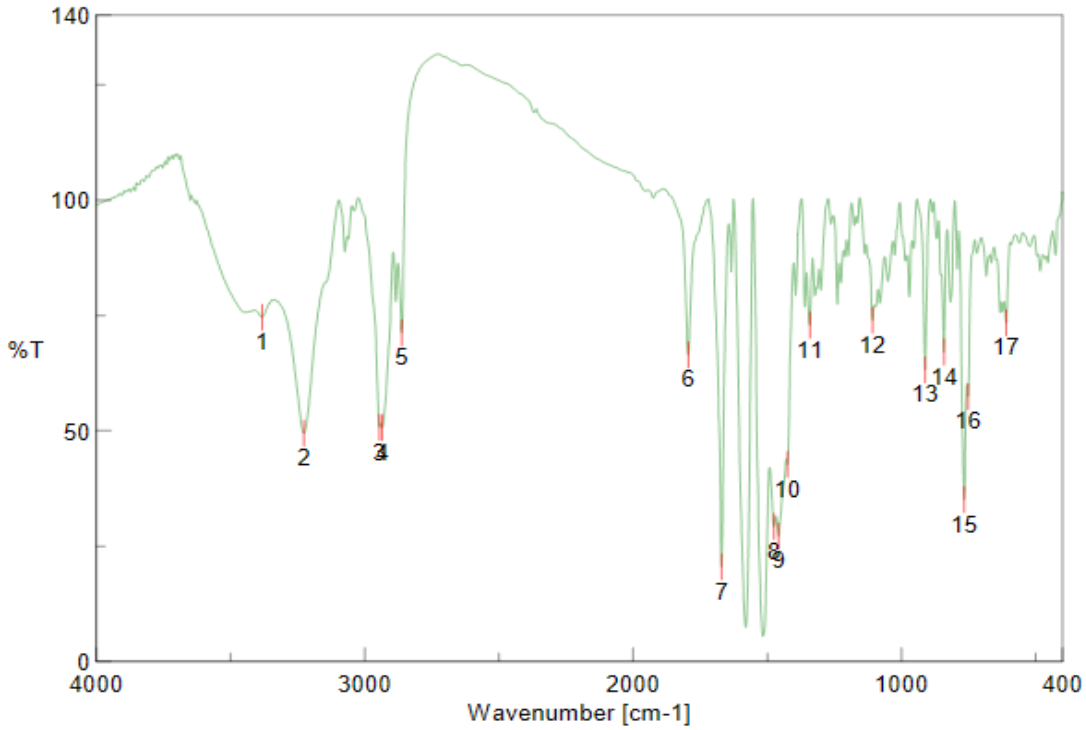
^{1}H NMR spectrum of polymer, 2P in DMSO-d_6



SEC data of polymer, 2P



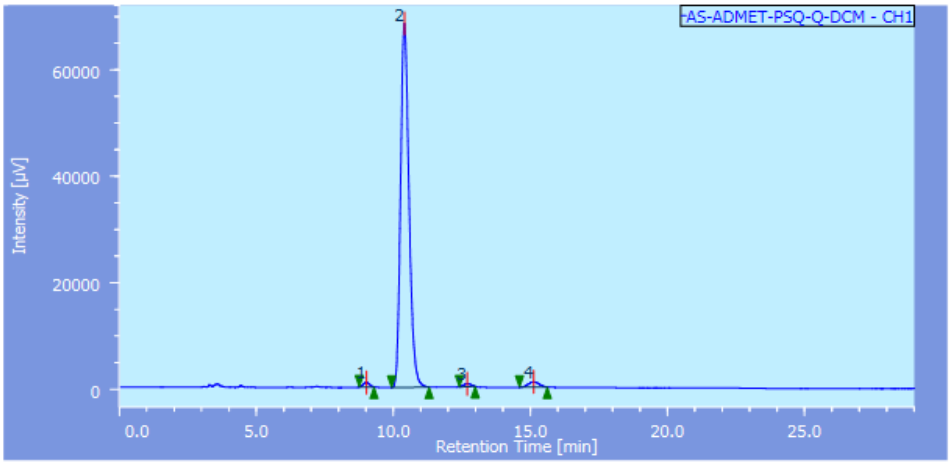
IR spectrum of polymer, 2P



[ピーク検出結果]

No.	位置	強度	No.	位置	強度
1	3382.53	74.5495	2	3226.33	49.4192
3	2945.73	50.6771	4	2934.16	50.6647
5	2861.84	71.167	6	1794.44	66.4468
7	1670.05	20.4988	8	1475.28	29.2195
9	1457.92	27.1092	10	1425.14	42.6482
11	1341.25	72.8182	12	1107.9	73.9321
13	912.165	63.1877	14	841.776	67.0274
15	766.566	35.0399	16	752.102	57.4023
17	610.36	73.3235			

Table 3, entry 2
96% ee



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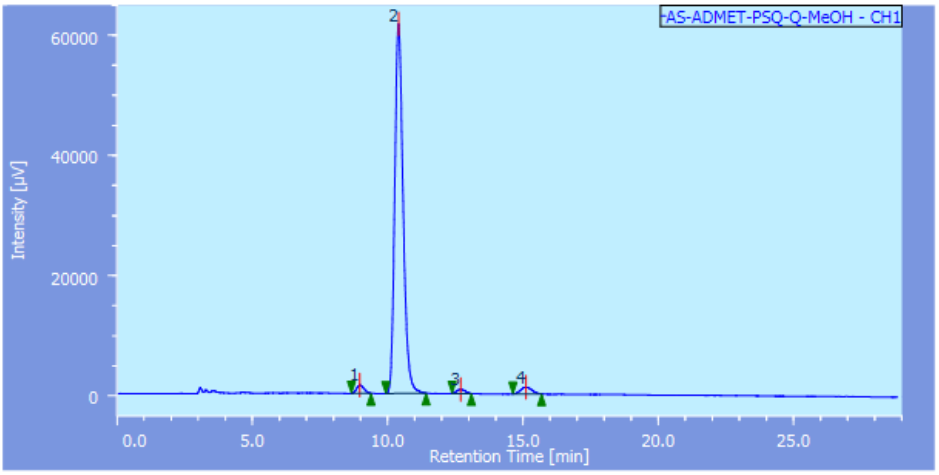

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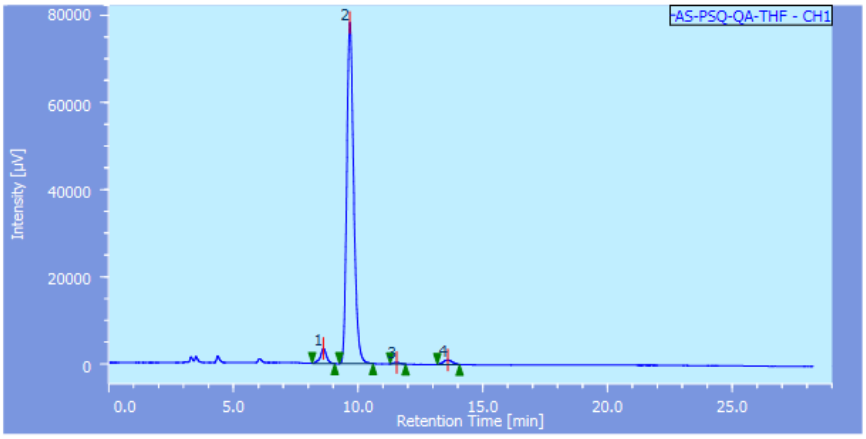

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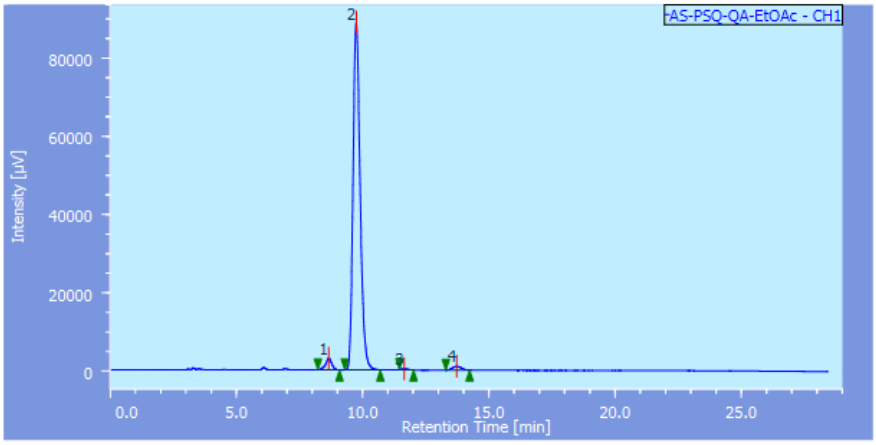

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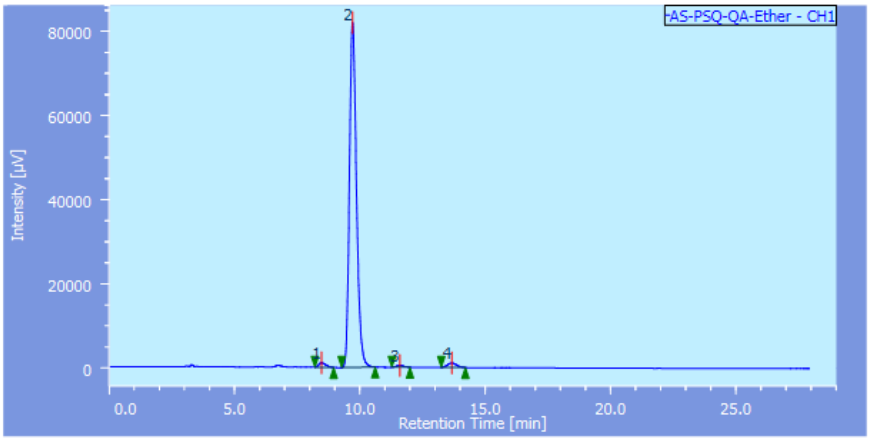

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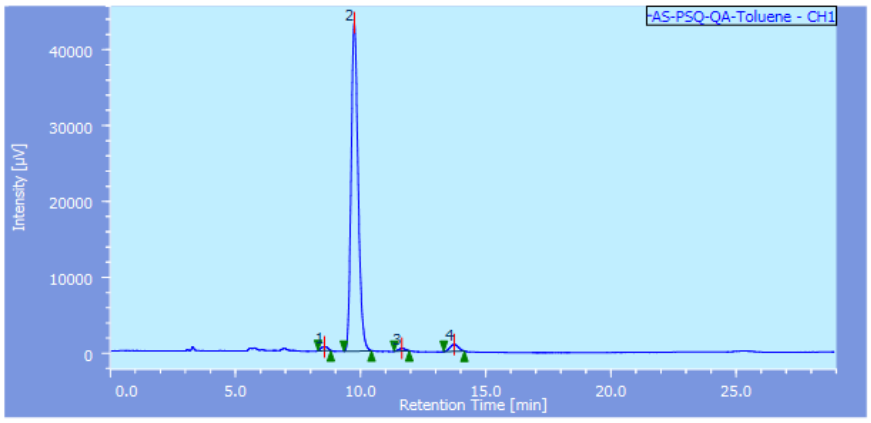

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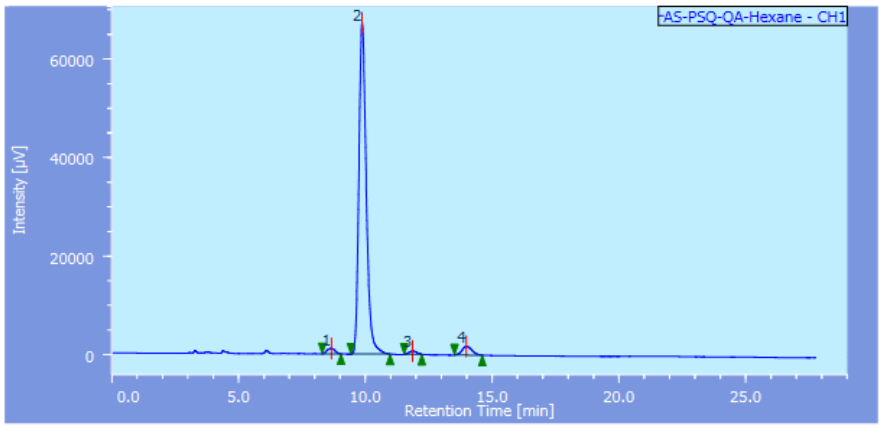

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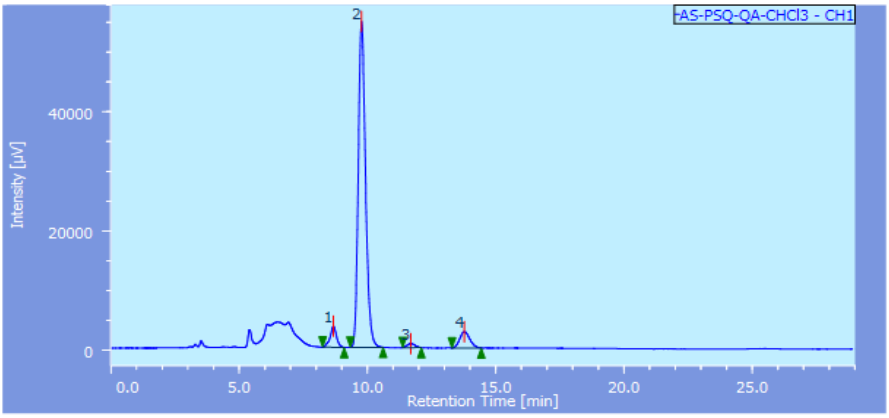

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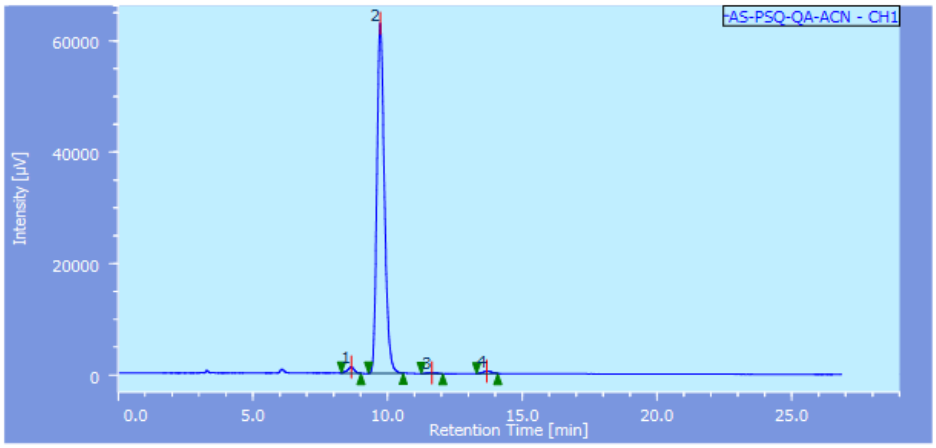

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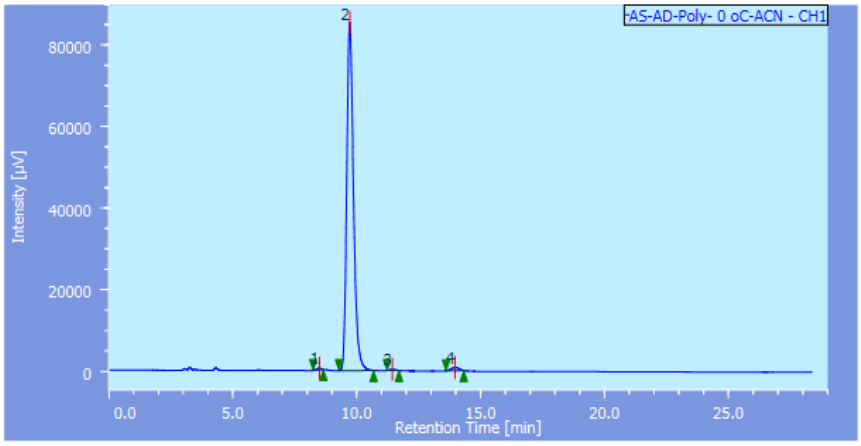

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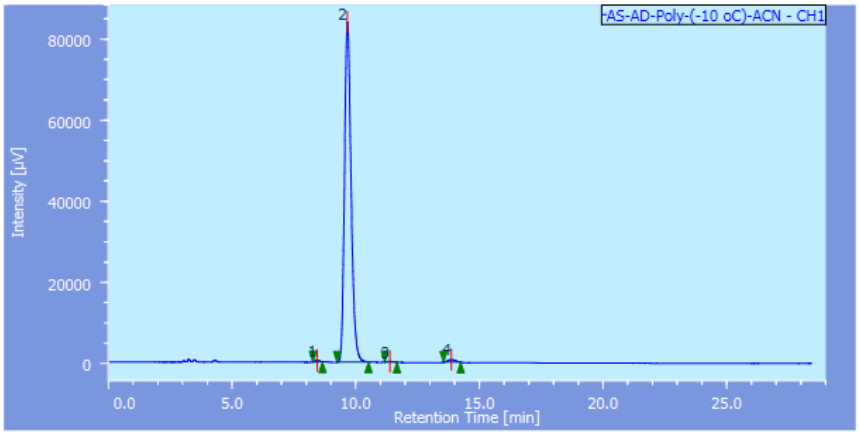

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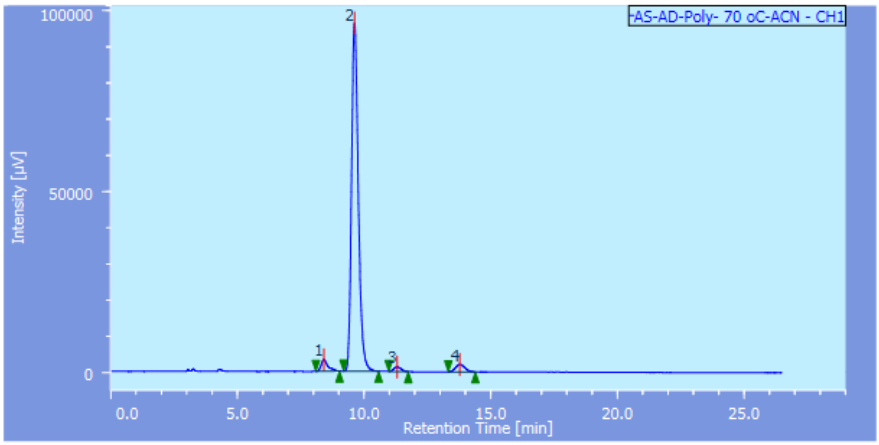

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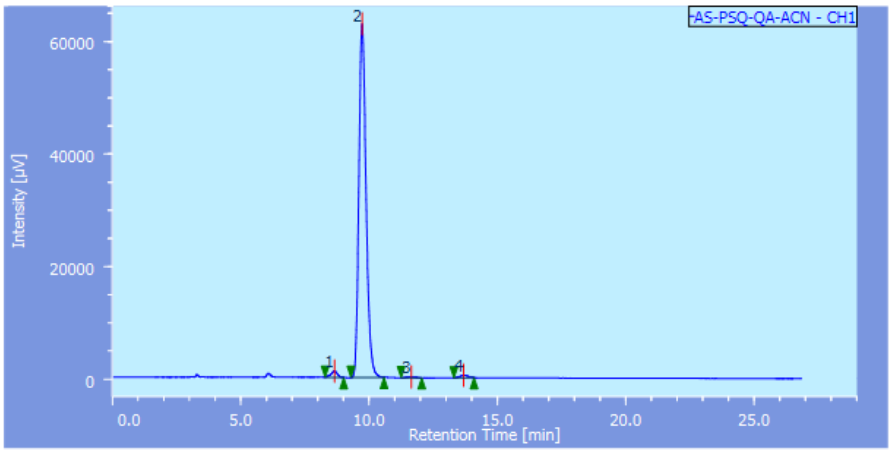

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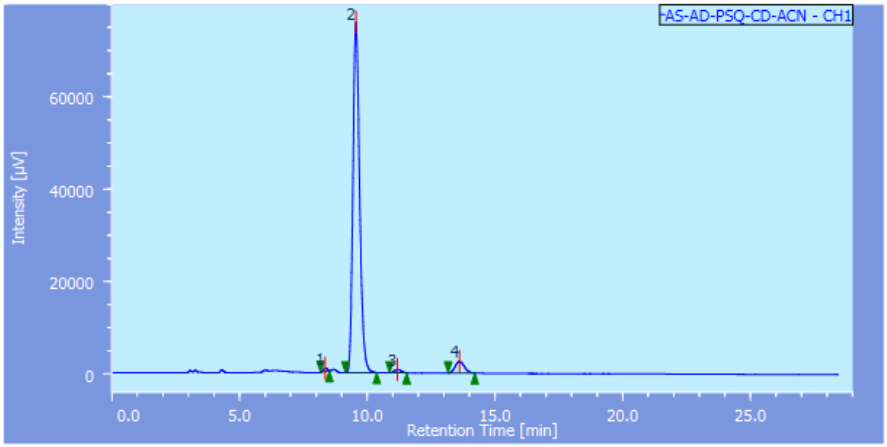

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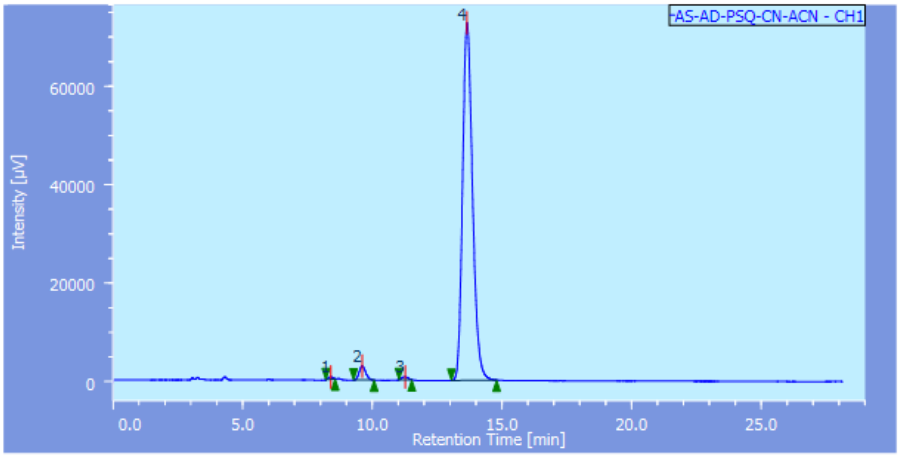

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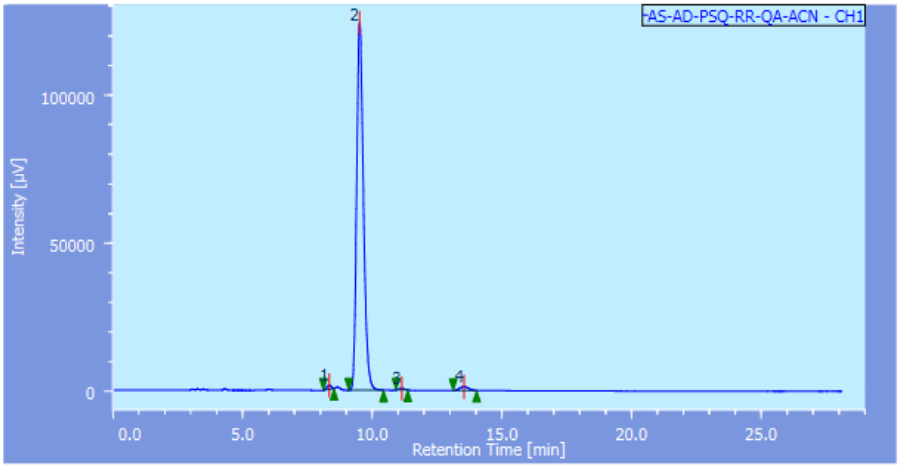

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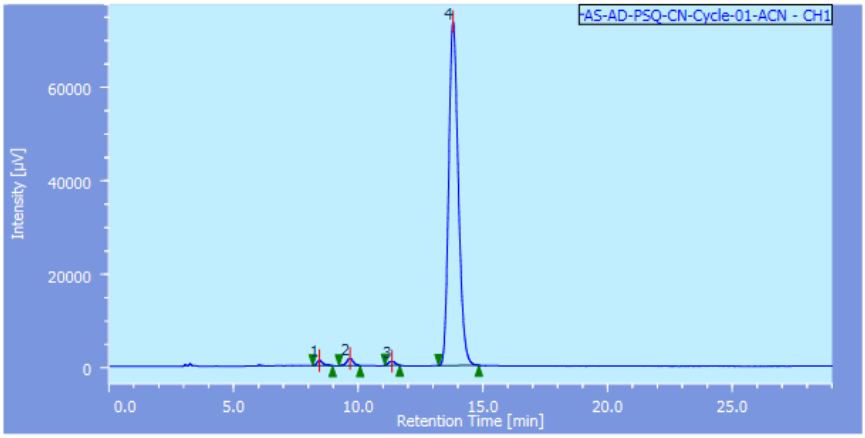

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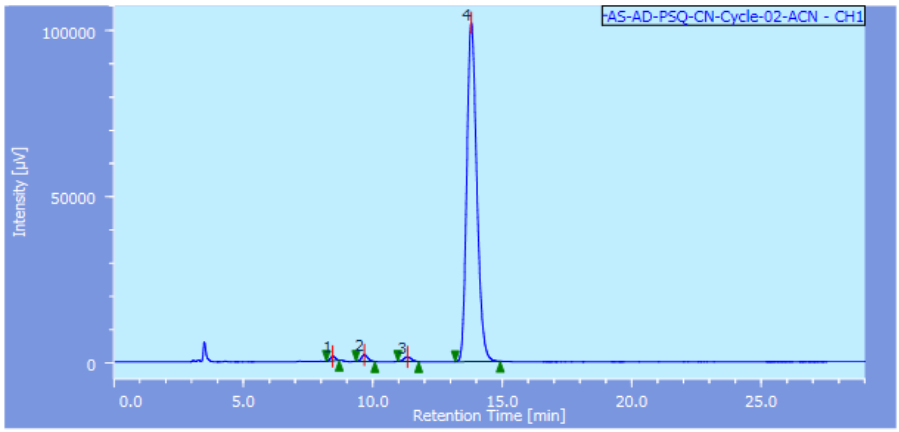

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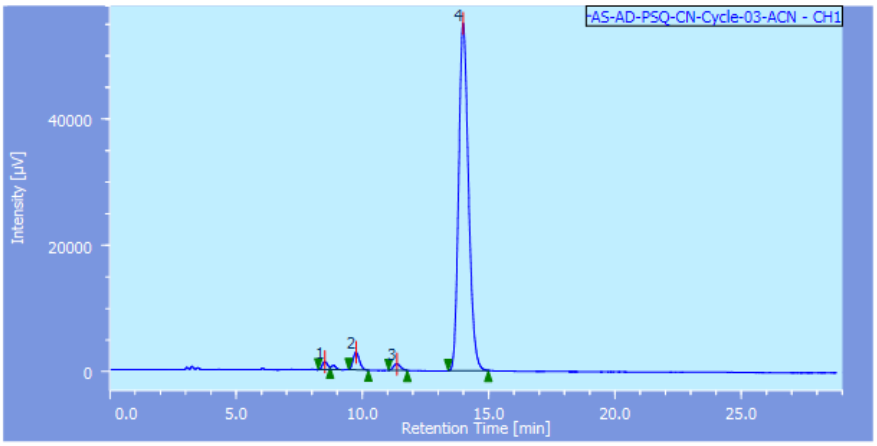

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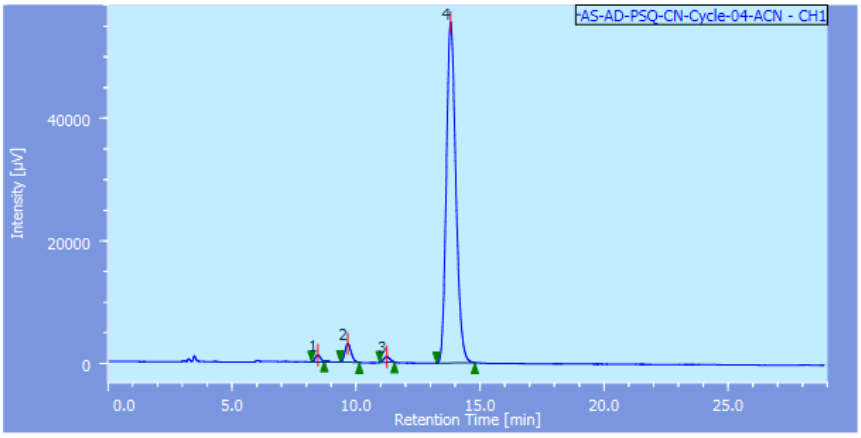

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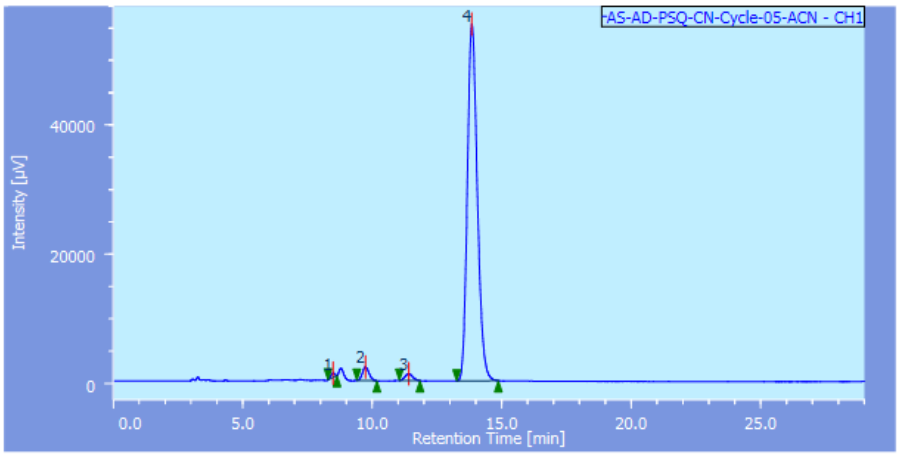
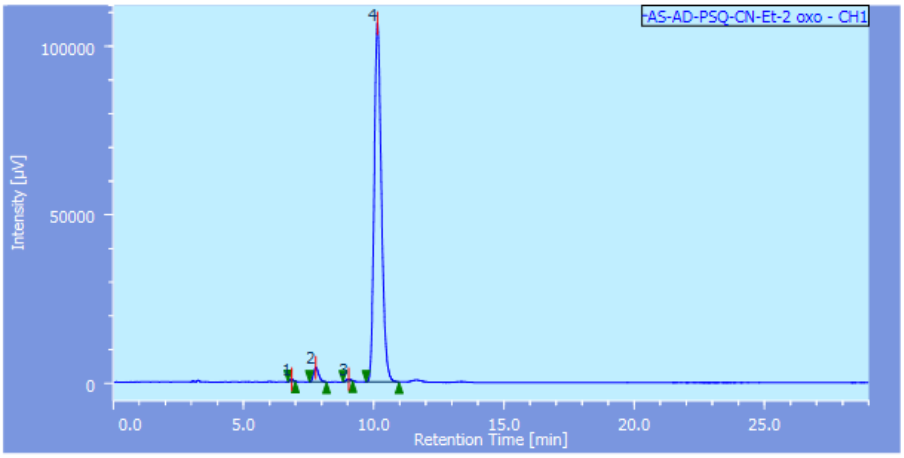


Scheme 4
94% ee



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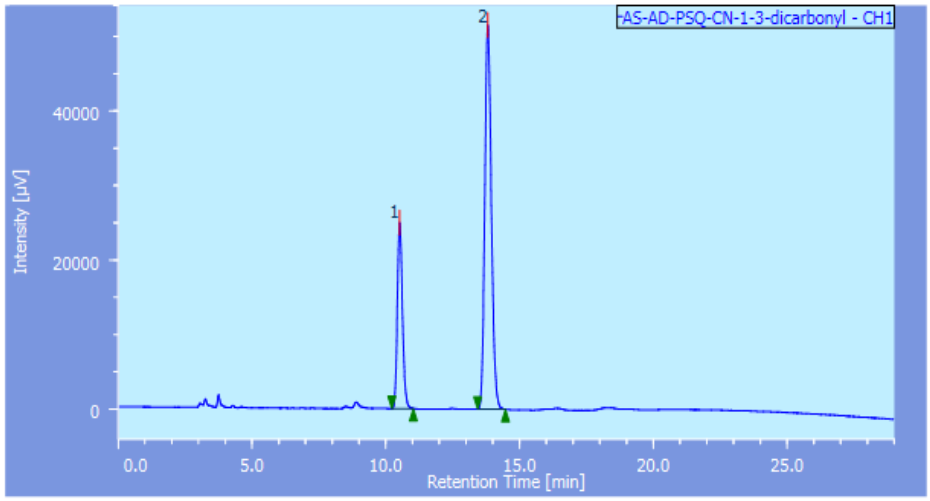
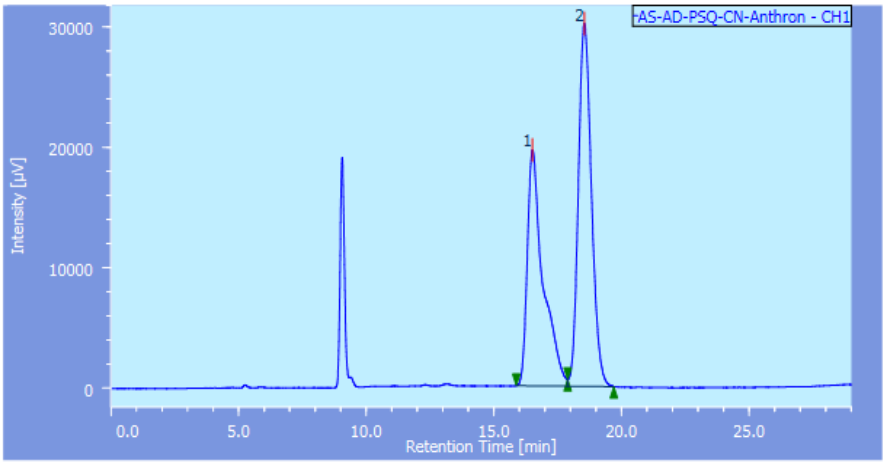
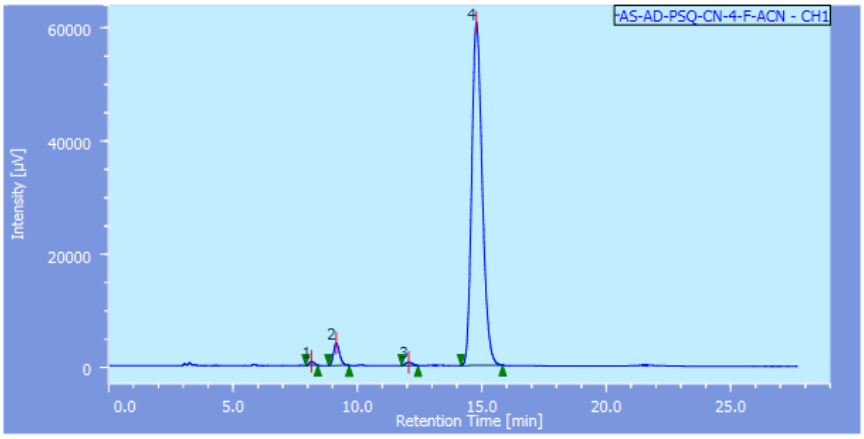


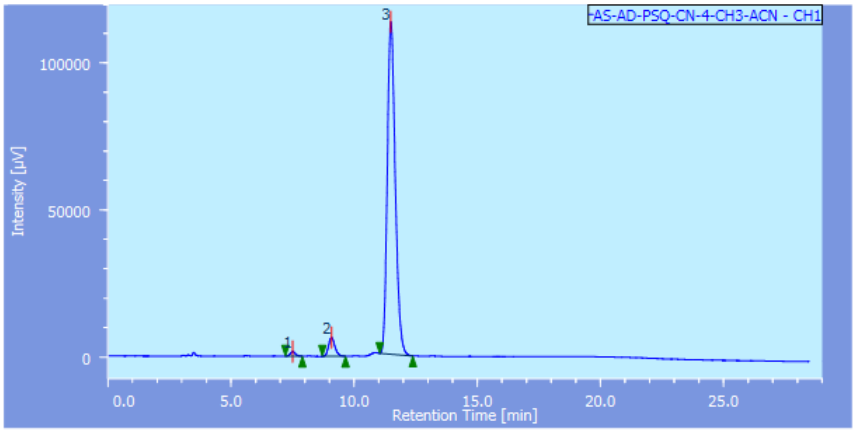
Scheme 4
12% ee



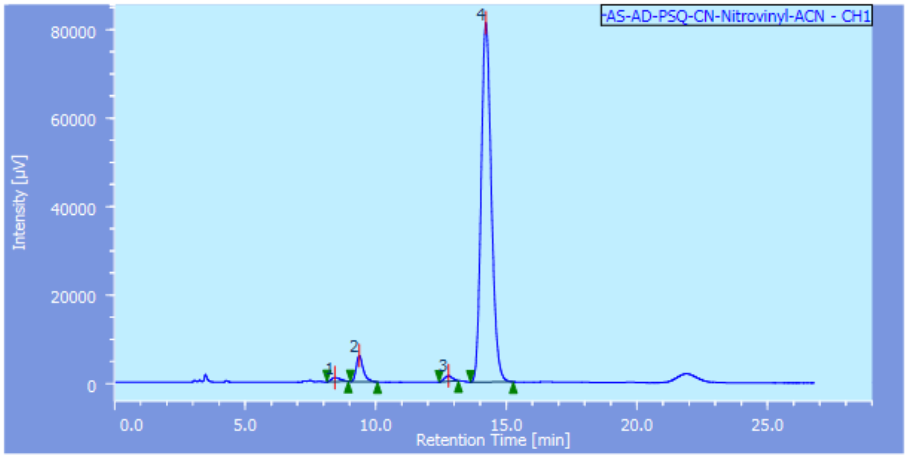
Scheme 4
93% ee



Scheme 4
91% ee



Scheme 4
96% ee



List of Papers/Journals with Referee's Review:

1. **Mohammad Shahid Ullah** and Shinichi Itsuno, "Synthesis of Cinchona Alkaloid Derived Chiral Squaramide Polymers by ADMET Polymerization and Their Application to Asymmetric Catalysis'' *Chemistry Letters* **2018**, *47*, 1220-1223.

2. **Mohammad Shahid Ullah** and Shinichi Itsuno, "Chiral Polymers of Cinchona Squaramides as Highly Efficient Catalysts in Asymmetric Michael Addition Reaction" *ACS Omega* **2018**, *3*, 4573-4582.

3. **Mohammad Shahid Ullah** and Shinichi Itsuno, "Synthesis of cinchona alkaloid squaramide polymers as bifunctional chiral organocatalysts for the enantioselective Michael addition of β-ketoesters to nitroolefins" *Molecular Catalysis* **2017**, *438*, 239 - 244.

4. Shohei Takata, Yuta Endo, **Mohammad Shahid Ullah** and Shinichi Itsuno, "Synthesis of cinchona alkaloid sulfonamide polymers as sustainable catalysts for the enantioselective desymmetrization of cyclic anhydrides" *RSC Adv*. **2016**, *6*, 72300-72305.

5. Shinichi Itsuno and **Mohammad Shahid Ullah**, "Immobilized Catalysts for Asymmetric Reactions", *Thieme, Science of Synthesis*, **2018**, (In press).

Conferences:

[**1**] **Mohammad Shahid Ullah**, Naoki Haraguchi and Shinichi Itsuno "Enantioselective Michael Addition Mediated by Cinchona Alkaloid-Derived Polymeric Bifunctional Chiral Organocatalyst Containing Squaramide" 47th Annual meeting of Union of Chemistry-Related Societies in Chubu Area, Toyohashi, Japan, November-**2016**. [Poster: 2P36]

[**2**] **Mohammad Shahid Ullah**, Naoki Haraguchi and Shinichi Itsuno "Synthesis of Cinchona Alkaloid Squaramide Polymers as Bifunctional Chiral Organocatalysts for the Enantioselective Michael Addition of β-Ketoester to Nitroolefin" **The 11th SPSJ International Polymer Conference, Fukuoka, Japan. 2016/12/13~16. [Oral: 16C04]**

[**3**] **Mohammad Shahid Ullah**, Naoki Haraguchi and Shinichi Itsuno "Synthesis of Main-Chain Chiral Polymers Containing Cinchona Alkaloid Squaramides and Their Application to Asymmetric Catalysis" The 66th SPSJ Annual Meeting, Chiba, Japan. **2017**/05/29~31. [Oral: 1K27]