Development of Polymer Microsphere-immobilized Chiral Pyrrolidine Catalyst and Its Application to Multistep One-pot Asymmetric Synthesis

(高分子微粒子固定化キラルピロリジン触媒の開発と多工程ワンポット不斉合成への応用)

January, 2022

Doctor of Philosophy (Engineering)

MITHUN KUMAR DEBNATH

ミトウン ク マル デブナト

Toyohashi University of Technology

Date of Submission（January 7, 2022）

Department of Applied Chemistry and Life Science		Student ID Number	189402	Supervisor: Prof. Dr. Naoki Haraguchi Prof. Dr. Hideto Tsuji
Applicant's name	MITHUN KUMAR DEBNATH			

Abstract（Doctor）

Title of Thesis	Development of Polymer Microsphere-immobilized Chiral Pyrrolidine Catalyst and Its Application to Multistep One-pot Asymmetric Synthesis

Approx. 800 words

Transformation reaction with chiral catalyst is of increasing importance in process chemistry in organic synthesis. The most crucial challenge is developing a suitable synthesis procedure, that can produce the desired optically active compounds with low environmental impact, high economic feasibility, and high efficiency. If multiple transformation reactions using chiral catalysts can be consecutively carried out in a one reaction vessel, in that case, a highly efficient organic synthetic process can be realized. Unfortunately, one of the limitations is that multiple catalysts with contrary properties (e.g., acidic, and basic, oxidative, and reductive) cannot be used simultaneously.

"Site isolation" is an effective way to allow multiple catalysts to operate independently. Several site isolating materials are available, but their synthesis methods are complicated. Therefore, developing a general method that can smoothly perform one-pot catalytic reactions based on site isolation is strongly desired.

Polymer microspheres can be one of the promising candidates as the site isolating material. They possess exciting features such as large specific surface area, high mechanical strength, high dispersibility, insolubility, a simple separation process, low swelling tendency, and easy preparation. In this research, we have tried is to establish a one-pot reaction system based on site isolation using crosslinked polymer microsphere as a new site isolating material, which leads to a highly efficient one-pot organic synthetic process.

Chapter **I** describes the general introduction and background of the thesis.

Chapter **II** describes the synthesis of crosslinked polymer microsphere-immobilized chiral pyrrolidine catalysts and their application to asymmetric Michael addition reactions. The polymer microsphere-immobilized chiral pyrrolidine catalysts have been prepared via the precipitation polymerization using divinylbenzene, a comonomer, and a methacrylate monomer bearing a chiral *N*-Boc pyrrolidine moiety, followed by the removal of the *N*-Boc group. The resulting polymeric

catalysts were characterized by scanning electron microscopy, Fourier transform infrared spectroscopy, and elemental analysis. After the successful preparation of the polymeric catalyst, the catalytic performances of the polymeric catalysts were evaluated by carrying out asymmetric Michael addition reactions between aldehydes and alkyl vinyl ketones. The reaction proceeded with excellent yield and enantioselectivity when the polymeric catalysts were hydrophobic because the hydrophobic nature of the catalysts provided the suitable microenvironment for the reaction to occur. The effect of the molar ratios within the catalyst, catalyst loading, temperature, solvent, and substrate on the reaction yield and enantioselectivity were investigated in detail. Polar and non-polar organic solvents significantly affected the reaction yield and enantioselectivity. In the presence of polar solvents, the yield of the Michael adduct decreased significantly due to the restricted dispersion of hydrophobic polymeric catalysts in the reaction medium. On the other hand, the presence of non-polar organic solvents the yield of the reaction slightly increased but not satisfactorily due to the insolubility of the cocatalyst in non-polar solvents. The solvent-free condition was best suited for this reaction system. The recovery and reuse of a polymer microsphere-immobilized catalyst were performed, and the catalysts retained its original catalytic activity up to five cycles.

Chapter **III** describes the development of one-pot asymmetric two steps reaction system based on site isolation using crosslinked polymer microsphere as the site isolating precursor. The site isolation potential of the crosslinked polymer microspheres was demonstrated by carrying out a one-pot two steps deacetalization-asymmetric Michael addition reaction using crosslinked polymer microsphere-immobilized sulfonic acid and chiral pyrrolidine catalysts. The first step of the one-pot reaction sequence is the deacetalization of propionaldehyde diethyl acetal catalyzed by the acid catalyst to produce the intermediate compound propionaldehyde. The second step is the asymmetric Michael addition between the produced intermediate compound propionaldehyde and methyl vinyl ketone using chiral basic pyrrolidine catalyst. The pair of low-molecular-weight acid and base catalysts cannot catalyze the reaction due to the neutralization reaction among them. The final product was obtained with good yield and enantioselectivity when the acid and base organocatalysts are crosslinked polymer microsphere-immobilized. This result indicating that using crosslinked polymer microspheres site isolation can be achieved. The best catalytic activity was found for the hydrophobic chiral pyrrolidine catalyst and polymer microsphere-immobilized sulfonic acid catalysts pair with a good yield (82%) and enantioselectivity (91%). The recovery and reusability of the best catalysts pair were also performed, and they retained their original catalytic activity in the next cycles.

Chapter **IV** describes development of one-pot three steps asymmetric reaction based on site isolation using heterogeneous acid and base catalysts. The first step of the reaction, i.e., the asymmetric Michael addition reaction between the *tert*-butyl acetoacetate and *trans*-cinnamaldehyde was catalyzed by the chiral pyrrolidine catalyst. Then, the acid catalyst sequentially catalyzed the remaining two steps, i.e., hydrolysis and decarboxylation reactions. The low-molecular-weight acid and base catalysts pair even linear polymer-immobilized acid and base catalyst cannot afford the final product due to the deactivation of the catalytic sites by

neutralization reaction. Using the polymer microsphere-immobilized chiral pyrrolidine catalyst and silica gel immobilized acid catalyst pair, good yield and excellent enantioselectivity were obtained. Using the combination of polymer microsphere and silica gel, site isolation was achieved due to the insolubility and the 3-dimensional structure of the crosslinked polymer microsphere and silica gel microsphere. The active sites of acid and base cannot diffuse into each other and thus site isolation accomplished.

Chapter **V** describes the general summary of the thesis work.

Table of Contents

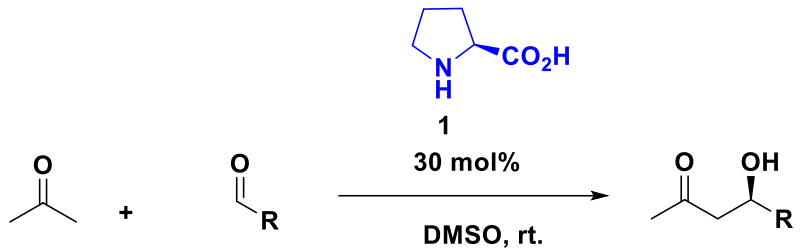
List of Abbreviations

aq.	aqueous
s	singlet
br	broad
d	doublet
m	multiplet
Calcd.	calculated
DMF	*N*,*N*-dimethylformamide
DVB	divinylbenzene
ee	enantiomeric excess
Equiv.	equivalent
EtOAc	ethyl acetate
EtOH	ethanol
Et	ethyl
GC	gas chromatography
h	hour
Pr^{i}	isopropyl
mg	milligram
mmol	milimole
MeOH	methanol
MVK	methyl vinyl ketone
Ph	phenyl
Pr	propyl
TEA	triethylamine
TREN	tris(2-aminoethyl)amine
THF	tetrahydrofuran

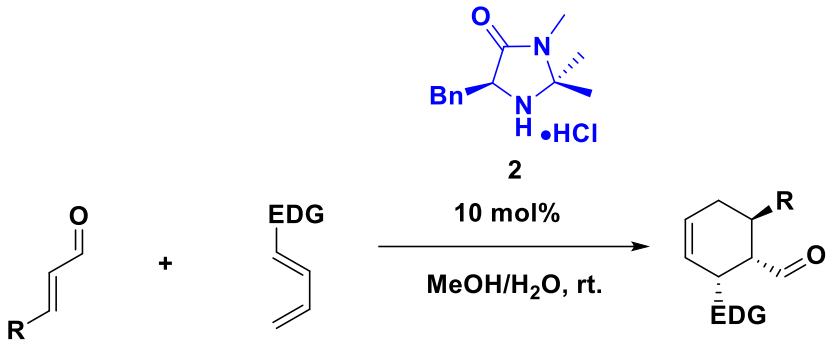
CHAPTER I

Introduction

Asymmetric organic synthesis involves the preparation of optically active organic compounds using small chiral molecules called catalysts. The chiral catalysts are of several types, such as organometallic catalysts, enzyme catalysts, and organocatalysts. In the case of organometallic catalysts, they are generally toxic due to the presence of metal atoms in their structure. Due to the presence of metal atoms in organometallic catalysts, they are very sensitive to air and water. A particular experimental setup is necessary to conduct the reaction using the organometallic catalysts. On the other hand, enzyme catalysts are highly substrate-specific. Finding a suitable enzyme catalyst for specific substrates is difficult and even the modification of the chemical structure of the enzyme is challenging. In this research, we have mainly focused on chiral organocatalysts due to having some limitations in the case of chiral organometallic catalysts and enzyme catalysts. Chiral organocatalysts are small chiral organic molecules that do not contain any metal atom in their structure. The advantages of organocatalysts are listed below: i) they are low cost, readily available, and economically attractive, ii) they offer mild reaction conditions, iii) they prevent metal contamination in the products, which is the vital feature applications in pharmaceutical chemistry. Until a few decades ago, it was believed that only the transition metal complexes and enzymes were the two main classes of efficient asymmetric catalysts.[1] Synthetic organic chemists have hardly used small chiral organic molecules as the catalyst for synthesizing chiral compounds in the last century. The field of asymmetric organocatalysis had bloomed after the publication of two novel catalytic reactions in the year of 2000, when List, Lerner, and Barbas reported an intermolecular aldol reaction catalyzed by proline catalyst in Scheme 1.1,[2] and MacMillan and co-workers reported an asymmetric Diels-Alder reaction catalyzed by imidazolidinone in Scheme 1.2.[3] After the publication of these two formative papers at the turn of the millennium, asymmetric organocatalysis began to attract the attention of the broader scientific community as a promising field in itself.



Scheme 1.1 Intermolecular asymmetric aldol reaction catalyzed by proline.



Scheme 1.2 Diels-Alder reaction catalyzed by the MacMillan imidazolidinone catalyst.

Several types of organocatalysts have been developed, and their chemical structures have been shown in Figure 1.1. Although several types of chiral organocatalysts have been developed, proline has been used as a promising chiral organocatalyst for different asymmetric chemical transformations, including the aldol,[2,4,5] α-Amination,[6-8] and Michael addition reactions.[9] Undoubtedly, proline is a powerful, robust, and diverse catalyst for different asymmetric chemical transformations, but it has some limitations. The major issue is its solubility in the reaction medium. Generally, polar solvents such as DMSO, DMF, or methanol are required to dissolve a significant amount of catalyst to make its homogeneous reaction mixture. The solvent compatibility issue of proline restricts its broad applicability in different chemical reactions. Another disadvantage of proline is its lower catalytic activity to catalyze a chemical reaction. [10-15] A example of a proline catalyzed asymmetric reaction with low catalytic activity has been depicted in Scheme 1.3. Different approaches have been taken to modify the chemical structure of proline in different times to improve the catalytic selectivity and enantioselectivity in asymmetric reactions.[16-23] The most important successors of the proline-derived catalysts are the diarylprolinols (Scheme 1.4).

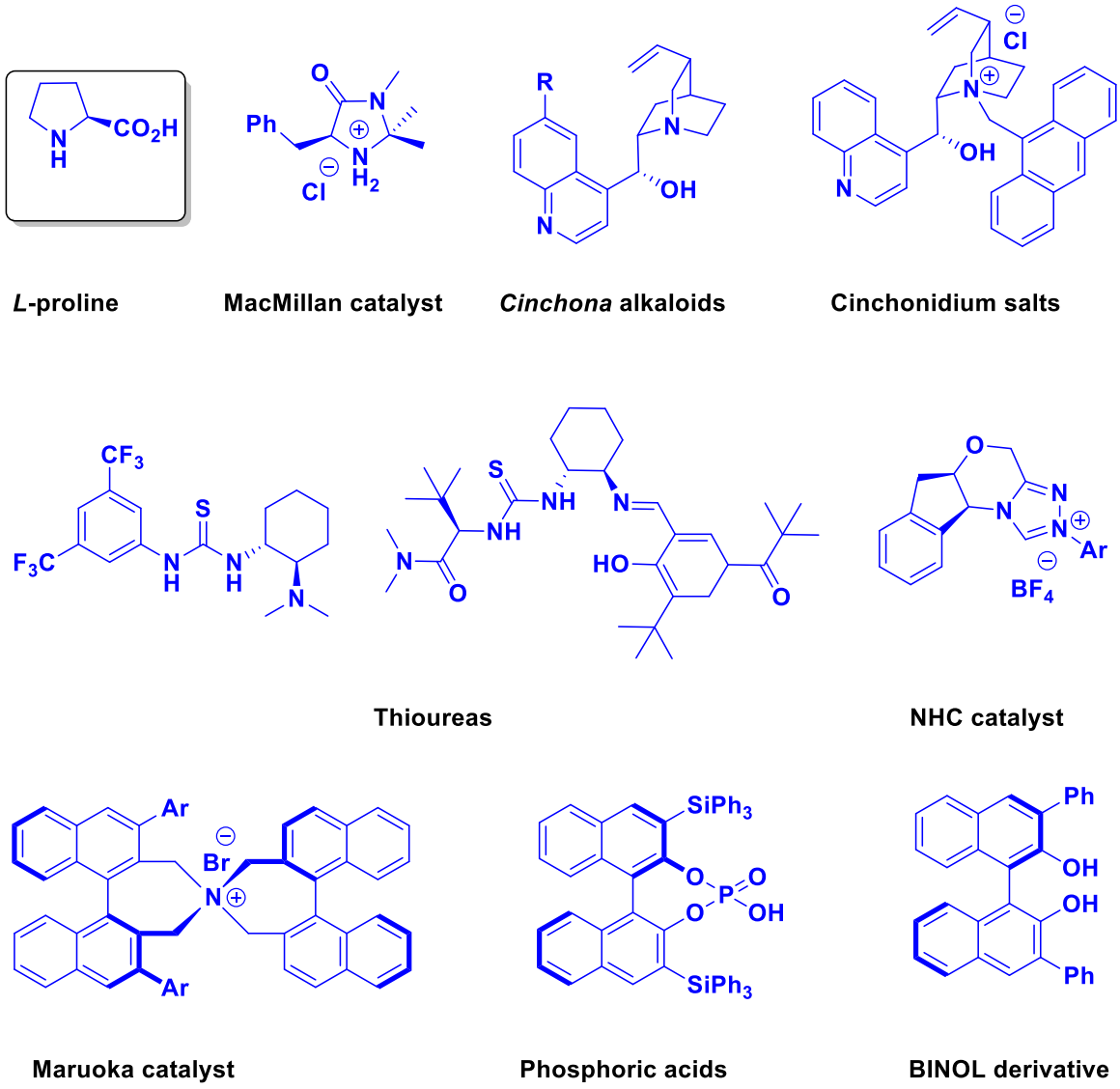
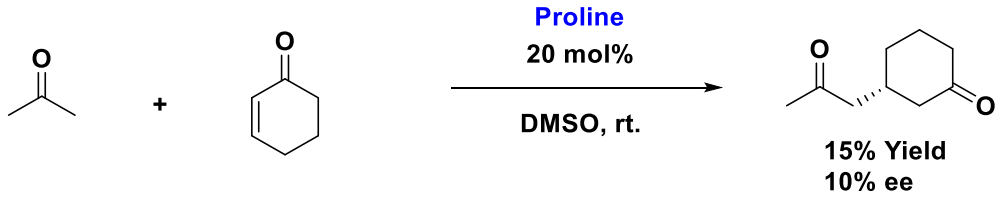
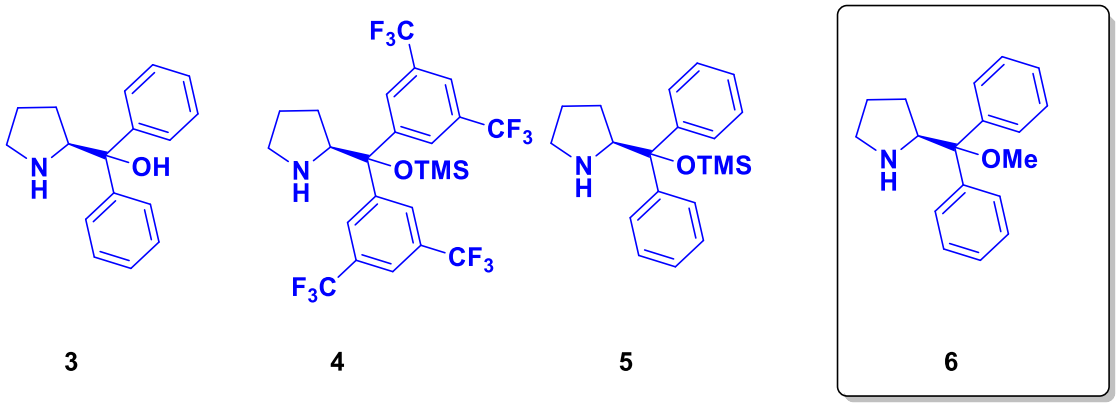


Figure 1.1 Chemical structure of chiral organocatalysts.

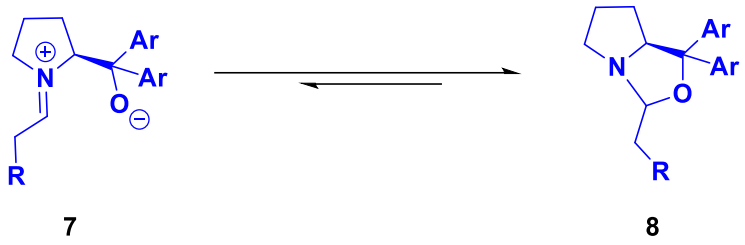


Scheme 1.3 Example of proline catalyzed reaction with low catalytic activity.



Scheme 1.4 Diarylprolinol organocatalysts.

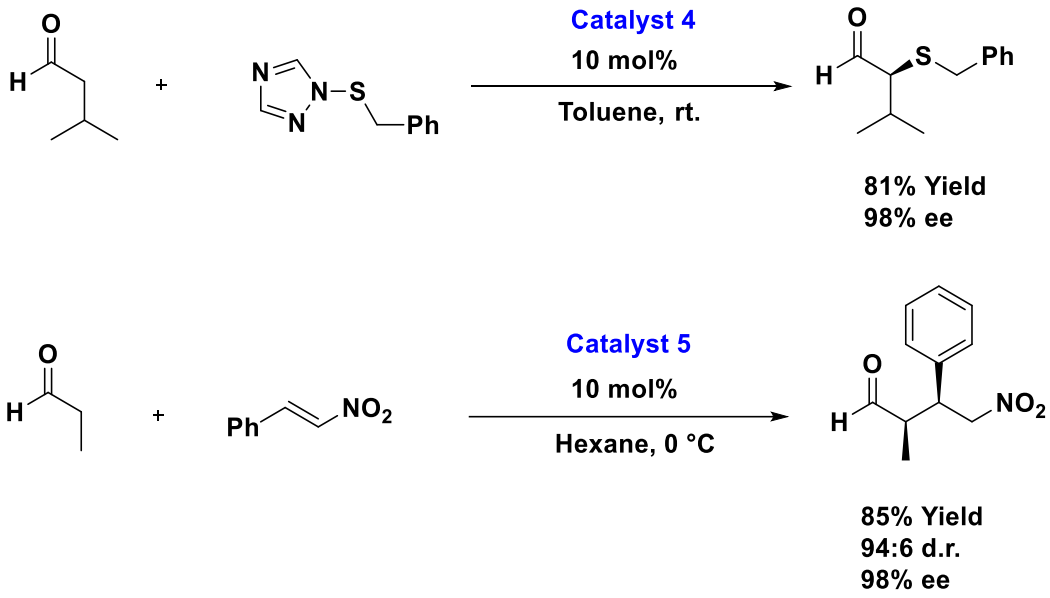
Initially, the *O*-unprotected diaryprolinol catalyst such as **3** was applied as a catalyst in the different chemical transformations such as Michael reaction,[24] Diels-Alder,[25] and α-functionalization of the aldehydes.[26-28] The catalyst **3** exhibited high selectivity but sometimes low reactivity towards the reactions mentioned above. Jørgensen and his research group pointed out the reason behind the low reactivity of the *O*-unprotected diaryprolinol catalyst. They found that *O*-unprotected diaryprolinol catalyst **7** is undergoing inhibition as a catalyst via the formation of parasitic oxazolidinones, **8**, in Scheme 1.5. [29] The protection of the free hydroxyl group with another protecting unit is essential to prevent the formation of oxazolidinones.



Scheme 1.5 Formation of catalytically inactive oxazolidinones.

In 2005, Jørgensen first reported the use of trimethylsilyl unit as a protecting group of the free hydroxyl unit and applied the diarylprolinol silyl ethers catalysts in the α-sulfenylation of aldehydes.[28] They screened a large number of easily accessible aryl groups as the substituents. They found that (3,5-bistrifluoromethyl)phenyl prolinol silyl ether **4** provided the best catalytic activity and enantioselectivity (Scheme 1.6). At the same time, Hayashi simultaneously reported the use of diarylprolinol silyl ether **5** in the

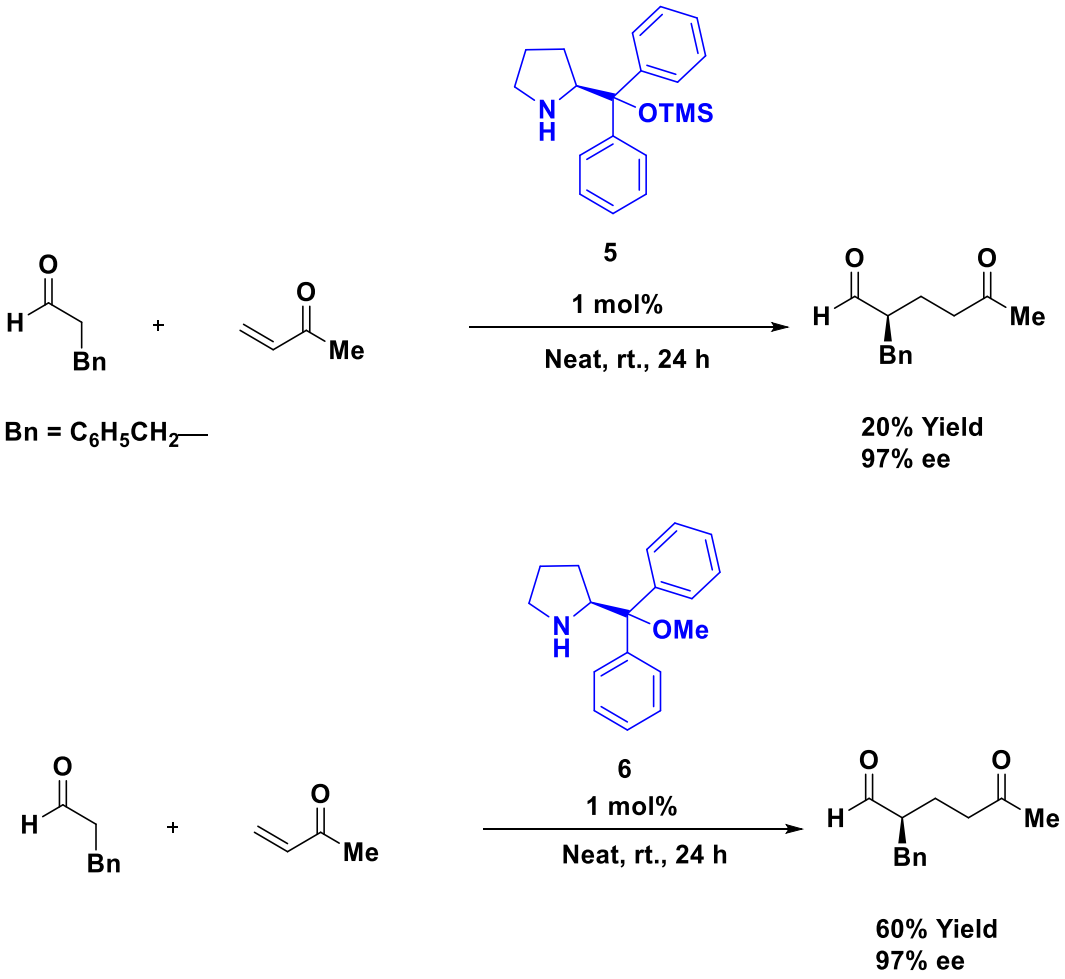
conjugate addition of aldehydes to nitro-olefins.[30] The catalyst **5** showed excellent yield and enantioselectivity (Scheme 1.6). Since the publication date is so close and the catalyst structure is so similar, the diarylprolinol silyl ethers **4** and **5** are referred to as Jørgensen-Hayashi catalysts.



Scheme 1.6 Early examples of asymmetric reactions catalyzed by Jørgensen-Hayashi catalysts.

After the discovery of the Jørgensen-Hayashi catalysts, it was immediately seized and bloomed upon in the literature to include a wide variety of hetero atom α-(F, Se, S),[31-34] β- conjugate addition,[35] epoxidation,[36-40] and Diels-Alder reactions.[41] Although the Jørgensen-Hayashi catalyst provides excellent catalytic activity and selectivity in various chemical transformations, the catalyst is less effective in asymmetric Michael addition of simple aldehydes to simple enones. Gellman reported a literature where the catalytic activity of the Jørgensen-Hayashi catalyst was very narrow in catalyzing the asymmetric Michael addition between simple aldehydes and enones (Scheme 1.7).[42] The trimethylsilyl ether **5** provided high enantioselectivity but low yield. Gellman replaced the trimethylsilyl ether to methyl ether and found excellent yield and enantioselectivity. The probable reason for the lower yield in the case of **5** is the sterically hindered trimethylsilyl ether substituent in the catalyst unit. The asymmetric Michael addition reaction between simple aldehydes and simple enones proceeds through the enamine intermediate formation. The bulky substituent trimethylsilyl ether creates a steric hindrance to forming the enamine intermediate between the catalyst and aldehyde

substrate. As a result, a low yield is obtained. In this research, we have used catalyst **6** as a chiral organocatalyst.



Scheme 1.7 Comparison of the catalytic activity between the catalysts **5** and **6**.

All the examples mentioned above of asymmetric organic synthesis we have discussed till now are in a single-step batch reaction system. The synthesis of the most useful complex organic compounds involves a series of chemical transformations of a very different nature, denoted as multistep synthesis.[43] Multistep synthesis enables the synthesis of numerous complex organic compounds, which are essential in drugs, agrochemicals, electronics, and adhesives. The multistep synthesis where the intermediate product separation and purification are worked up is conventionally termed a multistep batch reaction. In a multistep batch reaction, after completing the first reaction, the product is often necessary to isolate and purify and then apply to the second reaction step as a substrate (Figure 1.2).

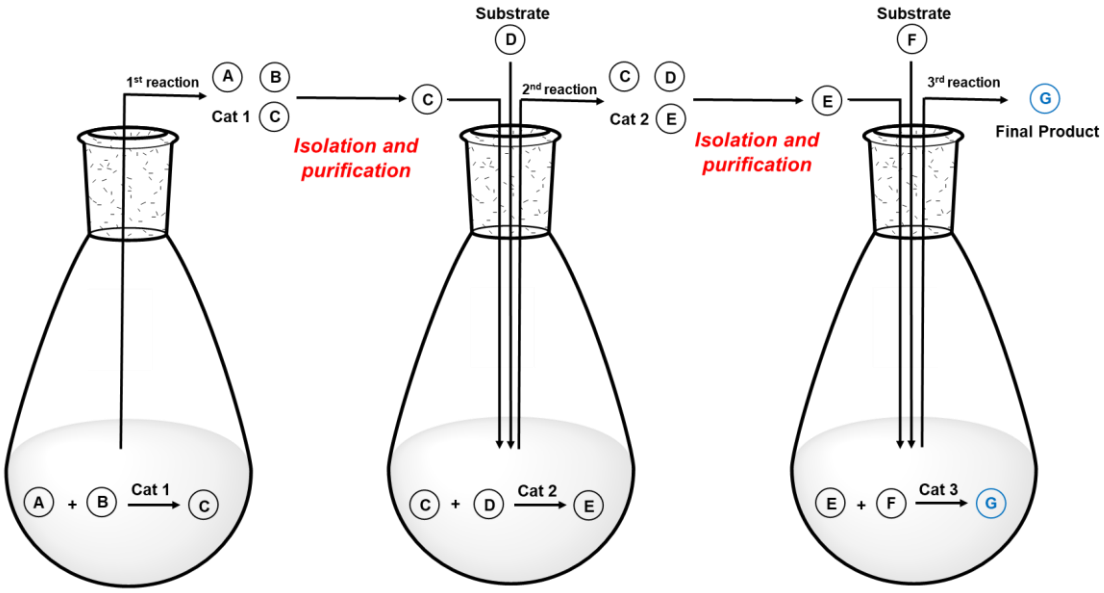
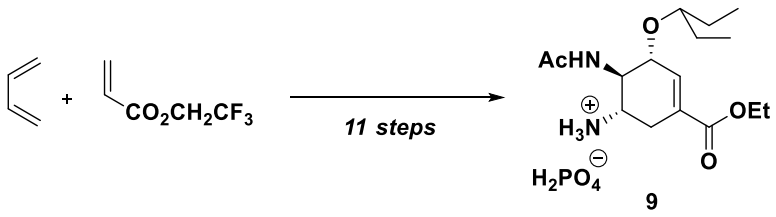


Figure 1.2 Multistep organic synthesis in the batch reaction system.

Numerous literature has been published on synthesizing biologically active complex compounds, mainly natural products using multistep batch reaction systems.[44-46] For example, Corey reported the synthesis of neuraminidase inhibitor (-)-oseltamivir phosphate **9** (Tamiflu) using total of eleven steps (Scheme 1.8).[46]



9

Scheme 1.8 Multistep synthesis of (-)-oseltamivir phosphate in the batch system.

Although the multistep organic synthesis in the batch process enables the formation of complex organic compounds, the process has some limitations. The limitations are listed below: i) it is often necessary to isolate and purify the product or intermediate compound after completing every reaction step. Generally, distillation, evaporation, recrystallization, and column chromatography techniques are employed to purify the intermediate compounds in the batch reaction system. However, these methods require extra energy, labor, time, and cost, ii) in case of multistep batch reaction if the intermediate compound is hazardous or toxic, then isolation and purification of the toxic compound is risky, and iii) if the intermediate compound is unstable, then the isolation

and purification of the compound is complicated and sometimes reduce the yield significantly of the final compound.

A one-pot reaction system may be one of the solutions to these limitations generated from the multistep batch reaction system. In a one-pot reaction system, several reaction sequences are conducted in the same reaction flask without the isolation and purification of the intermediate compound in a greener fashion (Figure 1.3).

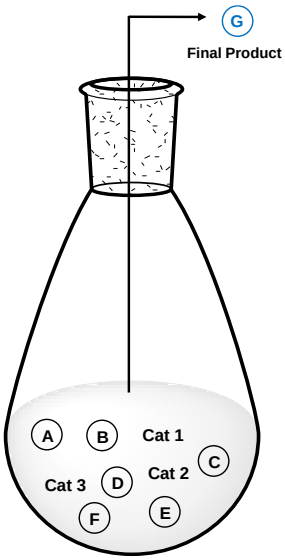
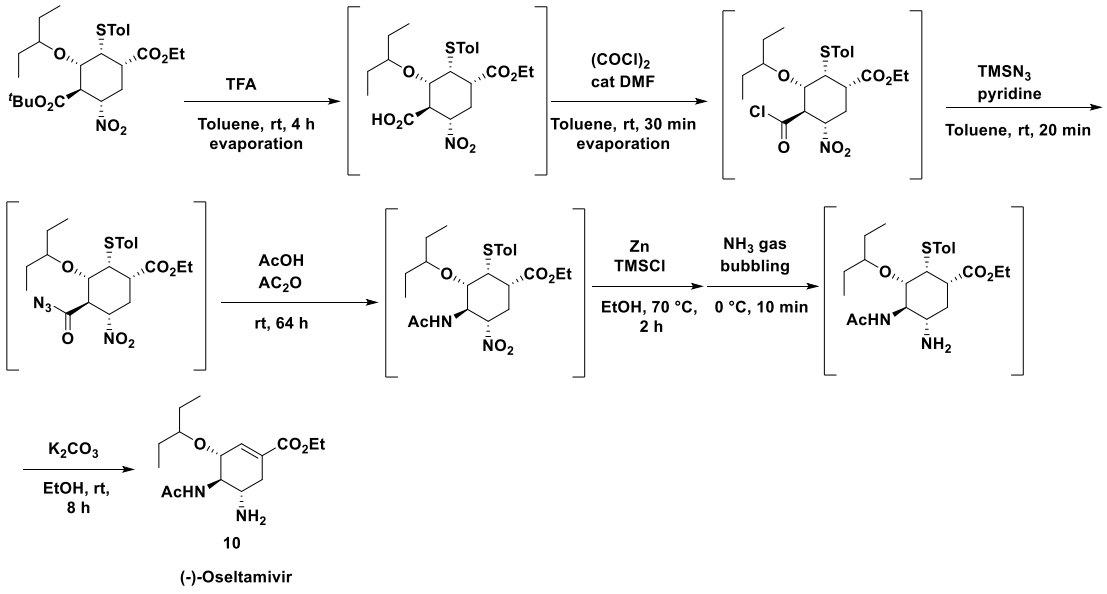


Figure 1.3 Multistep organic synthesis in a one-pot reaction system.



Scheme 1.9 Synthesis of (-)-oseltamivir in one-pot six-step reaction sequences.

The one-pot reaction system is greener due to the reduction of workup procedures and required purification steps compared to multistep batch reactions. In the case of a one-pot reaction, sometimes the same solvent is used in all the involved steps and thus reduces the consumption of chemicals. For example, Hayashi et al. reported the synthesis of neuraminidase inhibitor (-)-oseltamivir **10** in one-pot six-step reaction sequences (Scheme 1.9).[47] A similar compound where Corey and his group synthesized in eleven reaction steps in the batch system.[46]

Although a one-pot reaction system is effective in lowering the chemical waste, time, cost, and labor for the synthesis of the desired chiral compounds, it is challenging to employ the low-molecular-weight catalysts with contrary properties (acidic and basic; oxidative and reductive; and enamine and iminium) in a one-pot reaction. When the catalysts with contrary properties are applied in a one-pot reaction to catalyze the reaction sequentially, the catalysts are reacted with each other and thus diminish their catalytic ability. In this thesis, we will limit our discussion only to acid-base one-pot reaction. In general, when the low-molecular-weight acid and base catalysts pair are applied to a one-pot sequence, the neutralization reaction is occurred between the active sites of the acid-base catalysts to form salt and thus annihilate their catalytic performance (Figure 1.4). To carry out a one-pot reaction using low-molecular-weight acid and base catalyst pair, it is necessary to use the excess amount of either acid or base catalyst depending on the reaction condition.

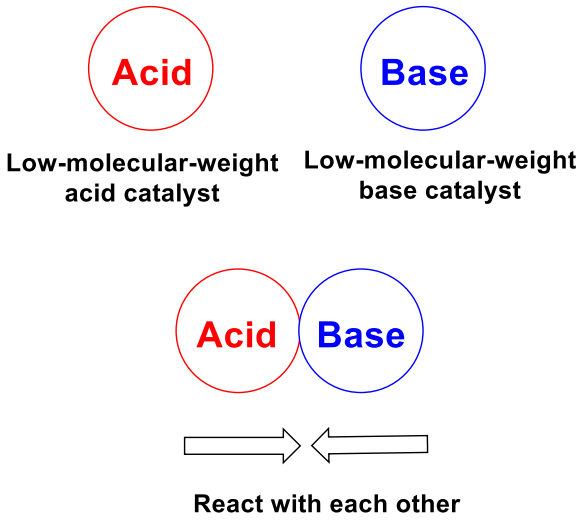
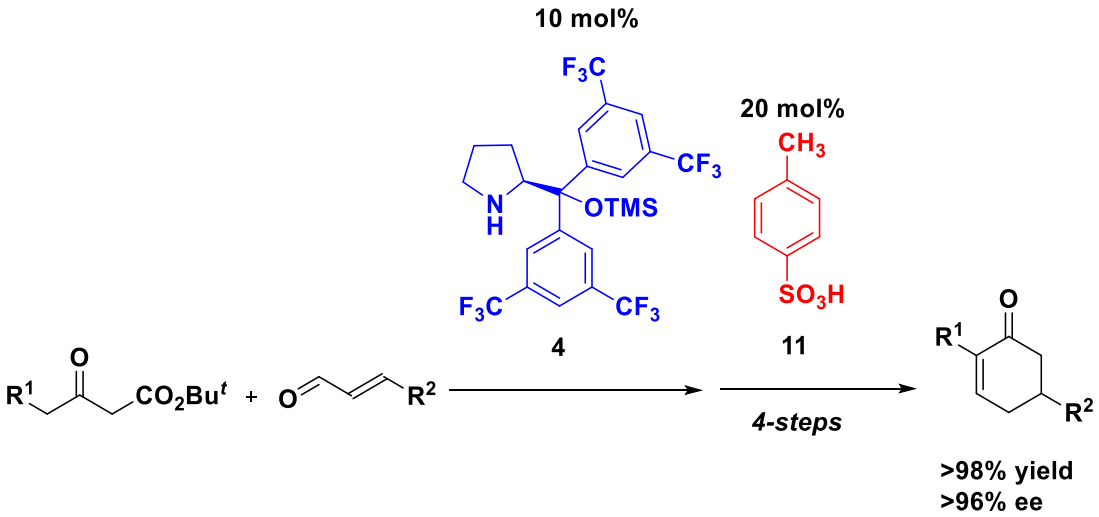


Figure 1.4 One-pot reaction sequence using low-molecular-weight acid and base catalysts.

The synthesis of optically active 2,5-disubstituted-cyclohexen-2-one derivatives from the reaction between *β*-ketoester and *α,β*-unsaturated aldehyde in a one-pot five steps process has been reported by using 2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyl-oxymethyl]pyrrolidine (**4**) and *p*-toluenesulfonic acid (*p*-TSA) (**11**) as the catalysts (Scheme 1.10).[48] The chiral amine facilitated the Michael addition of *β*-ketoester to *α,β*-unsaturated aldehyde and the Brønsted acid *p*-TSA catalyzed the remaining four steps to synthesize optically active 2,5-disubstituted-cyclohexen-2-one derivative in good yield and enantiomeric excess. The first step of the reaction was carried out using 10 mol% chiral prolinol catalyst **4** at room temperature and the remaining four steps were carried out using 20 mol% *p*-TSA (**11**) at 80 ºC. In this reaction sequence, it is necessary to use the excess amount of acid catalyst (**11**) to carry out the remaining four steps of the reaction because 10 mol% of *p*-TSA is reacting with 10 mol% of chiral base catalyst (**4**) and the remaining 10 mol% of *p*-TSA are acting as catalyst. Also, a slight excess of reagent was necessary to complete the first step of the reaction. The potential of this one-pot reaction system has been demonstrated by using a wide range of substrates to synthesize chemically important optically active 2,5-disubstituted cyclohex-2-enone derivatives.

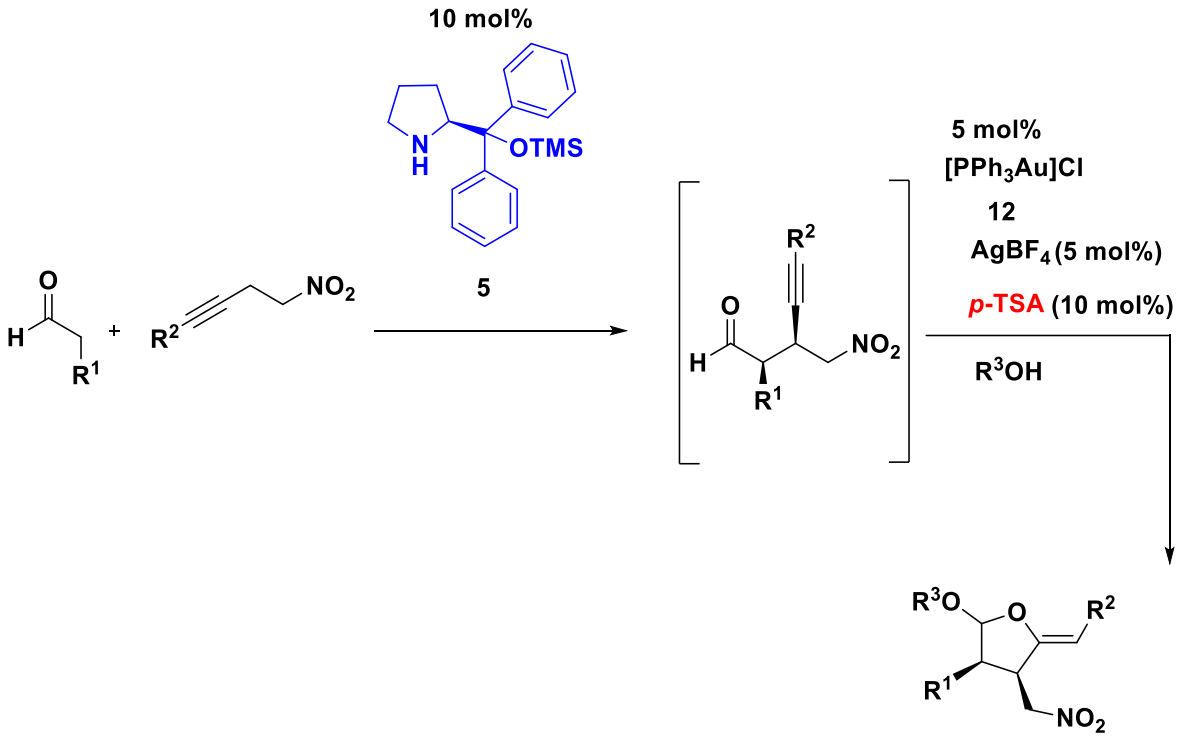


Scheme 1.10 One-pot five-step reactions using organocatalysts **4** and **11**.

An asymmetric tandem oxa-Michael/aldol condensation reaction process to synthesize chromene derivatives has been developed using chiral pyrrolidine derivative and 2-nitrobenzoic acid catalyst and cocatalyst, respectively.[49] The reaction proceeded

by the oxa-Michael addition of the *α,β*-unsaturated aldehyde to salicylic aldehyde and an intermolecular aldol condensation reaction to synthesize the chromene derivatives. The desired chromene derivatives were obtained with a low yield (10%) and enantioselectivity (9%) without cocatalyst 2-nitrobenzoic acid. The presence of cocatalyst significantly prompted the reaction yield and enantioselectivity of the products. This reaction system is applicable for a wide variety of substrate scopes.

The synthesis of nitro-substituted tetrahydrofuranyl ethers with high diastereo- and enantioselectivities has been carried out in a one-pot organocatalytic Michael addition/gold-catalyzed tandem acetalization/cyclization reaction process (Scheme 1.11). [50] The desired nitro-substituted tetrahydrofuranyl ethers were obtained by the enantioselective organocatalytic Michael addition of aldehydes to nitroenyne catalyzed by diphenylprolinol silyl ether and followed by tandem acetalization/cyclization reaction catalyzed by a gold catalyst (**12**) and *p*-TSA as additive. A slight excess of *p*-TSA relative to diphenylprolinol silyl ether was required to proceed with the response. The slight excess of *p*-TSA helps prevent the gold catalyst's deactivation by coordinating to the nitrogen atom of the diphenylprolinol silyl ether. It was found that no reaction occurred when the amount of organocatalyst diphenylprolinol silyl ether exceeded that of *p*-TSA.

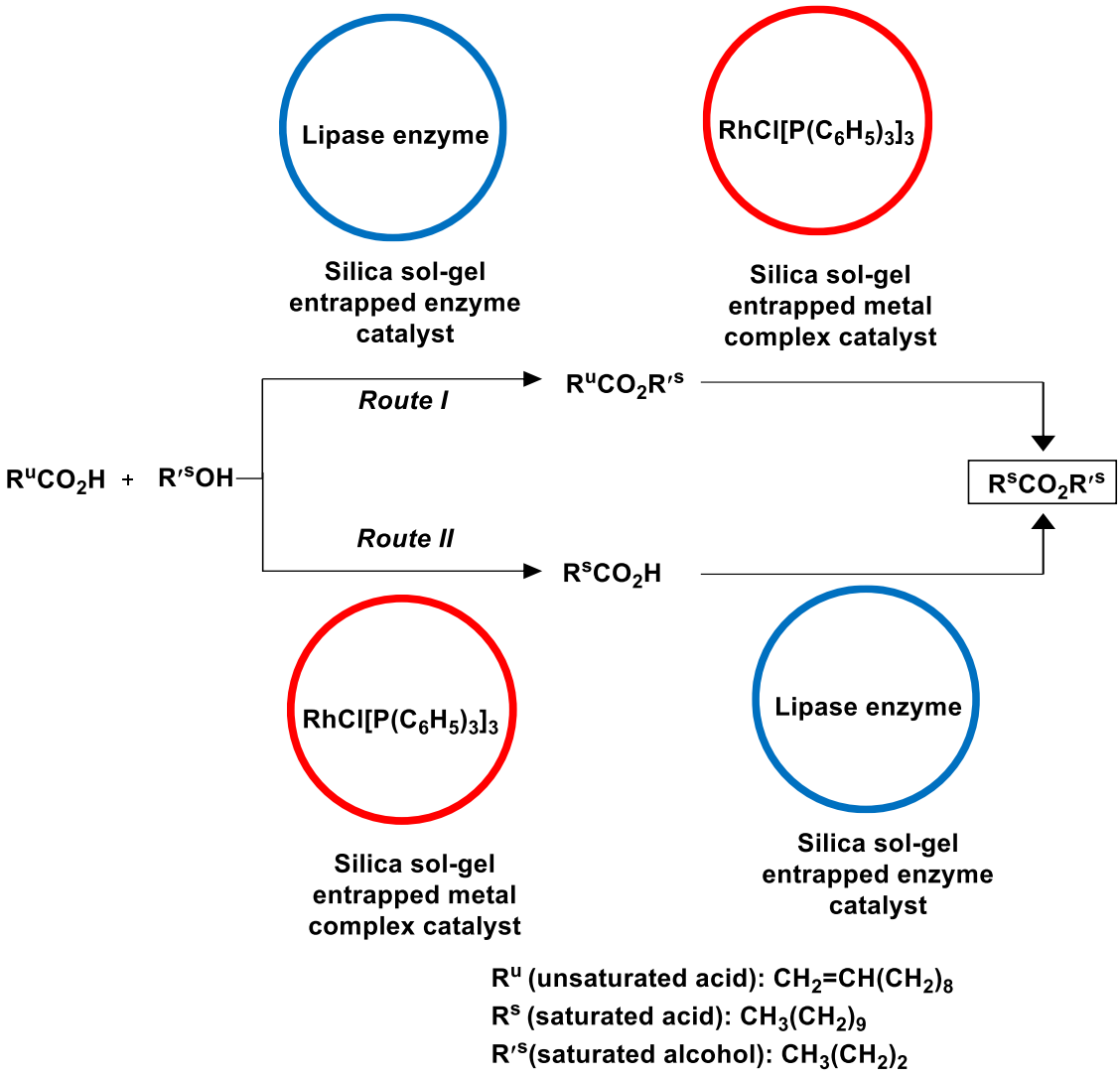


Scheme 1.11 One-pot asymmetric synthesis using organocatalysts **5** and **12.**

It has been found that the low-molecular-weight acid-base and liner polymer-immobilized acid-base catalysts pair also react with each other in a one-pot reaction system. To carry out a one-pot reaction sequence using acid and base catalysts where the acid and base catalysts will co-exist without interfering each other, it is necessary to isolate the active sites of the contrary catalysts so that both catalysts cannot react with each other and operate independently.

Site isolation is one of the effective ways to allow multiple catalysts with contrary properties independently into the same reaction vessel without the deactivation of the active sites of the catalyst's moiety. Site isolation is a process where the active sites of the antagonist catalysts is spatially and electrically separated in such a way so that they cannot react with each other but can catalyze the reaction efficiently. Several types of materials are available as site isolating precursors to develop the incompatible catalysts, including pickering emulsions,[51] sol-gel material,[52-55] micelles, [56-60] and polymer.[61-69]

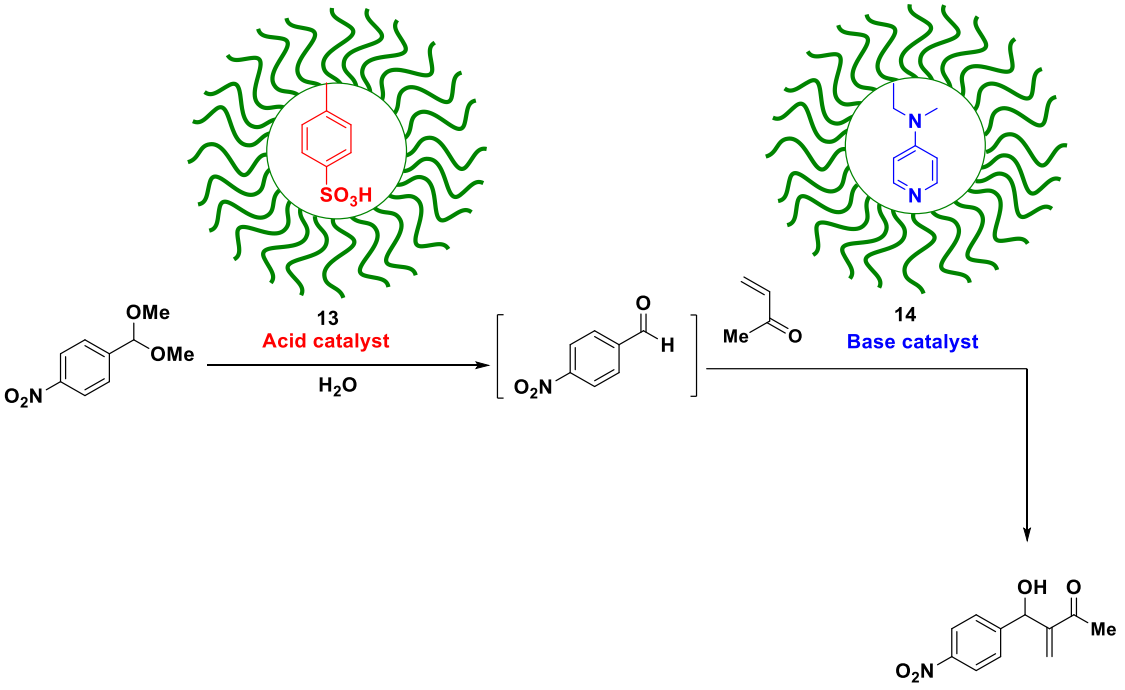
The site-isolated one-pot reaction sequence for the synthesis of saturated esters using sol-gel methodology with opposing reagents to an enzyme/metal catalysts pair has been reported successfully (Scheme 1.12).[52] The enzyme catalyst lipase and $RhCl[P(C_6H_5)_3]_3$ or $Rh_2Co_2(CO)_{12}$ were entrapped independently into the sol-gel matrixes and the catalyst pair were applied to the one-pot esterification and C-C double bond hydrogenation reaction to produce saturated esters. It was found that the sol-gel entrapped lipase and homogeneously dissolved $RhCl[P(C_6H_5)_3]_3$ afforded only 7% product indicating the deactivation of the catalysts pair. When both the catalysts were entrapped into the silica sol-gel matrixes separately, the yield of the reaction jumped 6.5-fold, confirming the site-isolation was achieved using the sol-gel matrixes. Both the sol-gel entrapped catalysts were recovered from the reaction mixture by simple filtration and reused in further runs without loss of catalytic activity. Although sol-gel entrapped catalysts can efficiently carry out the one-pot site-isolated reaction, their synthesis procedure is complex.



Scheme 1.12 One-pot multistep reactions using silica sol-gel entrapped catalysts.

A one-pot tandem reaction system has been developed using shell crosslinked micelle-immobilized acid and base catalysts.[56] The active acid (-COOH) and base sites (TREN) were isolated by covalently incorporating them into the shell and core of the single micelle, respectively. The shell crosslinked micelle support is based on an amphiphilic triblock copolymer of poly(2-oxazoline) with the orthogonal functional group on the side-chain that has been used to covalently crosslink the micelle and to separate two antagonist catalysts in two separate compartments of the micelle. The acid-base bifunctional catalysts were utilized as two-chamber nanoreactors for a prototypical tandem deacetalization-nitroaldol reaction to demonstrate the site-isolation efficiency of the micelle. The catalysts exhibited excellent catalytic activity.

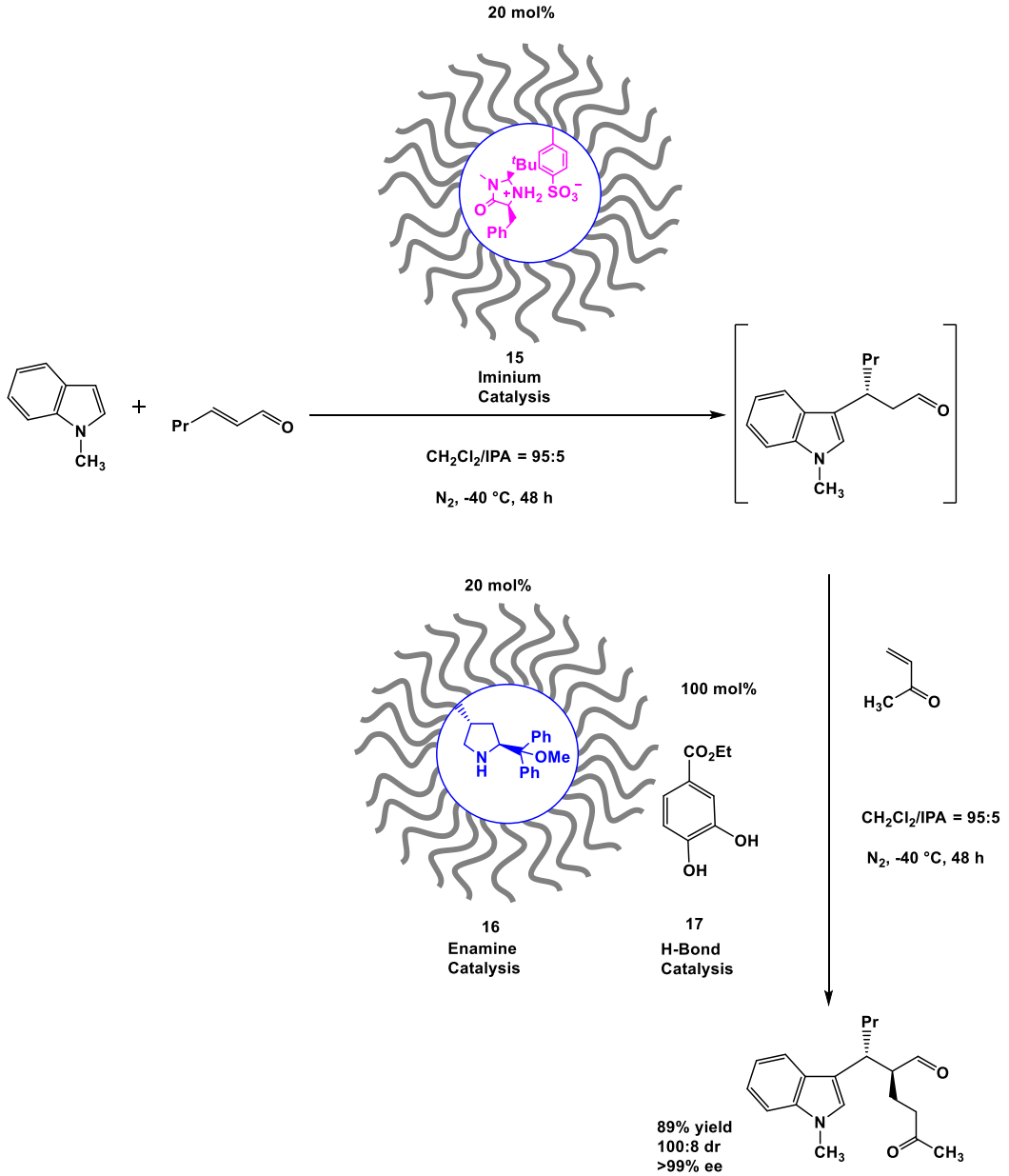
Fréchet reported a one-pot cascade reaction based on site isolation using star-branched polymer-immobilized acid and base catalysts (Scheme 1.13).[61] The acid and base sites were incorporated into the core of the star-branched polymers independently. The synthetic utility and site isolation efficiency of both acid-base catalysts was demonstrated by applying them to a one-pot two-step reaction sequence. The first step of the reaction was the deacetalization of the acetal mediated by the acid catalyst. The second step was the Baylis-Hillman reaction of produced intermediate aldehyde and methyl vinyl ketone catalyzed by the amine catalyst. The star-branched polymer incorporated both the acid and base catalysts catalyzed the reaction successfully with a good overall yield. The low-molecular-weight acid and base catalysts cannot afford the final product due to the formation of the salt as a result of an acid-base reaction. The reason behind the successful site isolation was the number of arms of the star-branched polymer that suppressed the mutual deactivation of acid and base sites, thus allowing acid and base-catalyzed reactions independently.



Scheme 1.13 One-pot cascade reaction using star-branched polymer-immobilized acid and base catalysts.

The same research group further expanded the scope of the site-isolated reaction system to asymmetric synthesis.[62] They have succeeded in multi-component one-pot

reactions by using two star-branched polymers in which the MacMillan (**15**) and diphenyl prolinol catalyst (**16**) are incorporated independently (Scheme 1.14). All the incompatible catalysts were incorporated into the core of the star-branched polymer and applied to a one-pot iminium, enamine, and hydrogen bond catalysis reaction sequences. The arms of the star-branched polymer providing the mutual deactivation of the active sites of the incompatible catalysts by preventing the penetration of the catalyst into the core of each other. High site isolation was achieved using the star-branched polymer incorporated incompatible catalysts with excellent overall yield (89%) and excellent enantioselectivity.



Scheme 1.14 One-pot asymmetric reaction using star-branched polymer-immobilized catalysts.

Although micelles and star polymers are effective in site isolation for the active sites of the catalysts with antagonist properties, they have some limitations. In the case of the micelle, the micelle's dynamic nature and inherent instability also make the synthesis of micelle-immobilized catalysts more complicated. The micelle's stability also depends on the nature of the solvents (e.g., alkaline or acidic). Therefore, the purification of the micelles needs a tedious workup. On the other hand, in the case of star-branched polymer incorporated acid and base catalysts, this method requires complicated synthesis because the chain length and the arm number of these star-branched polymers must be precisely controlled. The star-branched polymers with low arm numbers generally can penetrate the core of each other, and the site isolation cannot be accomplished. Developing a general method that can efficiently isolate the active sites of the incompatible catalysts and can smoothly perform one-pot catalytic reactions based on-site isolation is strongly desired.

The potential of the polymer microsphere as a new material for the site isolation of the active sites of the catalysts with contrary properties can be evaluated. Polymer microspheres are spherical polymeric particles whose diameter ranges from submicron to several microns (Figure 1.5).[70] These microspheres have the potential application in various fields, including electronics, chromatography, environmental science, biomedicine, coatings, adhesives, inks, paints, leather finishing, construction, and catalysis.[71-74] The reason for showing such a wide variety of applications listed above is because the polymer microspheres have some unique, valuable characteristics, including high surface area, good mechanical strength, stable dispersion, and can be easily recovered after use. The properties of the polymer microspheres can be easily tuned simply by changing the monomers. The hydrophobic-hydrophilic balance of the microspheres can also be modified easily to provide a suitable microenvironment for different types of applications.

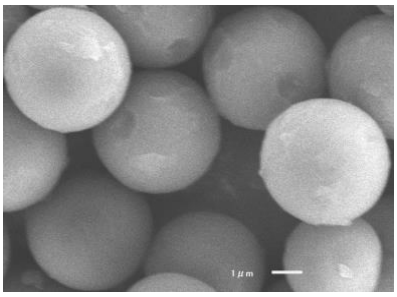


Figure 1.5 Polymer microsphere.

To use polymer microspheres as the site isolating precursor, it is essential to design polymer microspheres in such a way so that they can perform to isolate the active sites of the contrary catalysts effectively. The crosslinked polymer microspheres can serve as effective site isolating materials. When the crosslinked polymer microsphere-immobilized incompatible catalysts such as acid and base catalysts are applied to a one-pot reaction system, due to the 3-dimensional crosslinked polymer network and insolubility in the reaction medium, the microspheres cannot penetrate each other (Figure 1.6). Thus, the active sites of the acid and base catalysts cannot react with each other, and site isolation is accomplished. However, low-molecular-weight substrates and reagents easily penetrate the polymer microsphere and reach catalytic sites. Thus, the catalytic reaction occurs without the deactivation of the active sites of the acid and base catalysts.

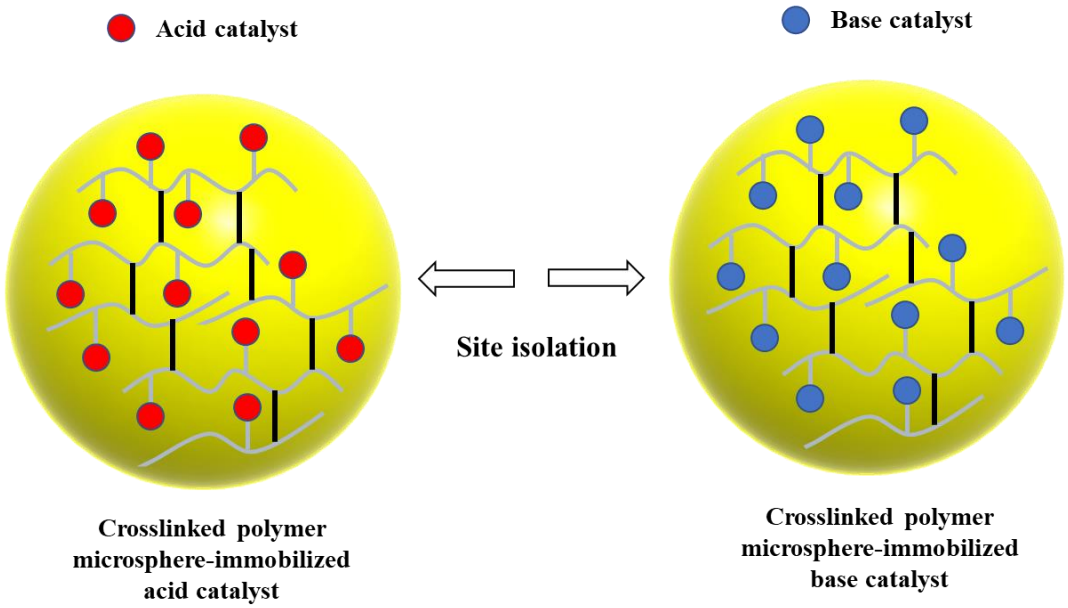
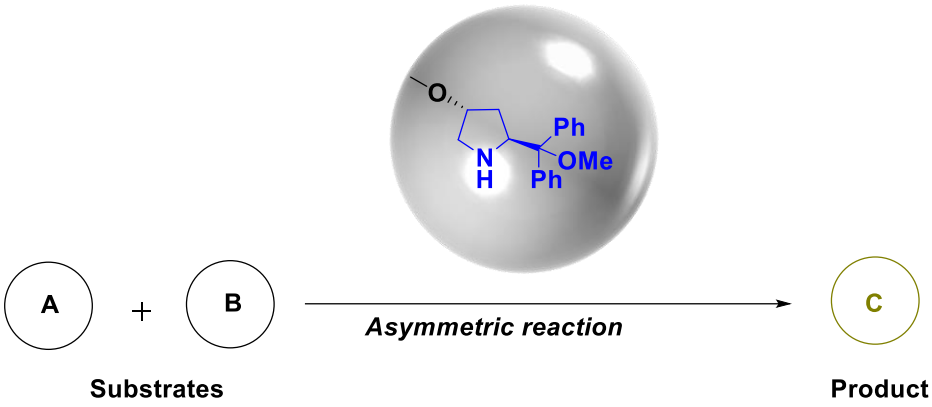


Figure 1.6 Crosslinked polymer microsphere-immobilized acid and base catalysts.

In general, it is not possible to co-exist the low-molecular-weight catalysts with contrary properties in a one-pot reaction system. Therefore, it is essential to isolate the active sites of the antagonist catalysts to develop a one-pot reaction system. Several techniques have been reported to isolate the active sites of the contrary catalysts, but the methods require complicated synthesis procedures. Therefore, an easy method has been introduced in this research to develop a site-isolated one-pot reaction system based on

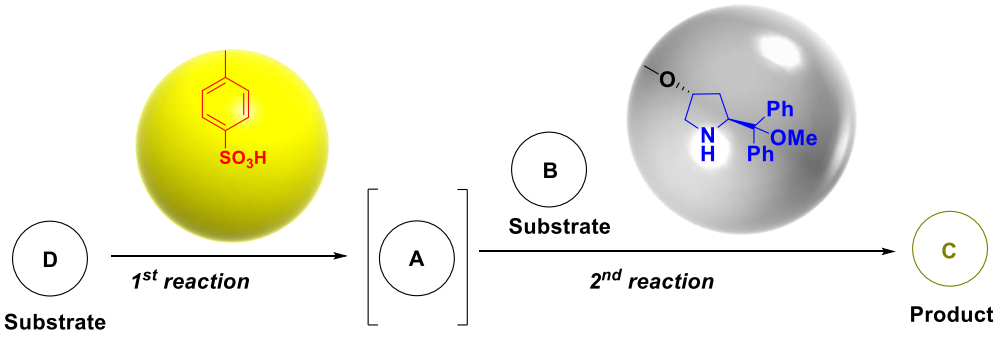
site isolation. This method will expand the scope of developing one-pot site isolated reaction systems in the future.

In **Chapter II**, an approach has been taken to establish an easy method for the development of low-molecular-weight chiral pyrrolidine catalysts using polymer microspheres as support material. The potential of the polymer microspheres as support material has been assessed by applying the polymer microsphere-immobilized chiral pyrrolidine catalysts to an asymmetric reaction (Scheme 1.15).



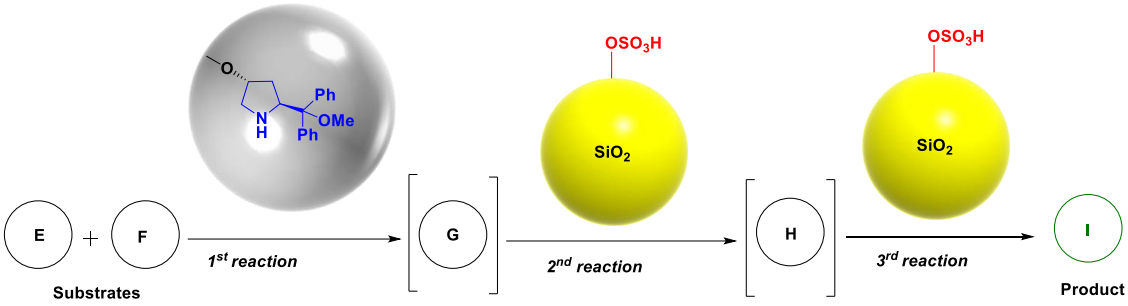
Scheme 1.15 Asymmetric reaction using polymer microsphere-immobilized chiral pyrrolidine catalysts.

In **Chapter III**, a one-pot acid-base reaction system based on site isolation has been tried to develop using crosslinked polymer microspheres-immobilized acid catalysts and chiral base catalysts (synthesized in chapter II). This research aims to evaluate the site isolation ability of the crosslinked polymer microspheres. The site isolation ability of the crosslinked polymer microsphere has been demonstrated by applying both the crosslinked polymer microsphere-immobilized acid and base catalysts to a one-pot two-step asymmetric reaction (Scheme 1.16).



Scheme 1.16 One-pot asymmetric reaction using polymer microsphere-immobilized acid and base catalysts.

In **Chapter IV**, an attempt has been taken to develop a one-pot multistep asymmetric reaction system based on site isolation using heterogeneous acid and base organocatalysts (Scheme 1.17). In chapter III, both the acid and base catalyst are crosslinked polymer microsphere-immobilized. In this research, the chiral base catalysts have been immobilized within the crosslinked polymer microsphere and the acid catalysts have been immobilized within the silica gel, respectively. The potential of polymer microsphere and silica-gel as site isolating materials has been evaluated by carrying out a one-pot three-step asymmetric reaction.



Scheme 1.17 One-pot multistep asymmetric reaction using heterogeneous acid and base organocatalysts.

References

[1] K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, 487.

[2] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[3] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[4] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798.

[5] W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386.

[6] B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656.

[7] N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bogevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254.

[8] A. Bogevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1790.

[9] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423.

[10] B. List, *Synlett* **2001**, *186*, 1675.

[11] J. M. Betancort, C. F. Barbas, *Org. Lett.* **2001**, *3*, 3737.

[12] D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299.

[13] J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas, *Tetrahedron Lett.* **2001**, *42*, 4441.

[14] M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108.

[15] D. Enders, M. R. M. Hüttl, *Synlett* **2005**, *6*, 991.

[16] Q. Gu, X. -F. Wang, L. Wang, X. -Y. Wu, Q. -L Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 1537.

[17] Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435.

[18] S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570.

[19] H. Sundén, N. Dahlin, I. Ibrahem, H. Adolfsson, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3385.

[20] N. Dahlin, A. Bogevig, H. Adolfsson, *Adv. Synth. Catal.* **2004**, *346*, 1101.

[21] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.

[22] A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry*. **2004**, *15*, 1831.

[23] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558.

[24] P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151.

[25] K. Juhl, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.

[26] M. Marigo, D. Fielenbach, A. Braunton, A. Kjoersgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703.

[27] N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790.

[28] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.

[29] J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.

[30] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[31] D. D. Steiner, N. Mase, C. F. Barbas, *Angew. Chem. Int. Ed.* **2005**, *44*, 3706.

[32] M. Tiecco, A. Carlone, S. Sternativo, F. Marini, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2007**, *46*, 6882.

[33] H. Sundén, R. Rios, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 7865.

[34] S. Sobhani, D. Fielenbach, M. Marigo, T. C. Wabnitz, K. A. Jørgensen, *Chem. Eur. J.* **2005**, *11*, 5689.

[35] H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307.

[36] B. P. Bondzic, T. Urushima, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 5434.

[37] G. L. Zhao, I. Ibrahem, H. Sundén, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1210.

[38] H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99.

[39] W. Zhuang, M. Marigo, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 3883.

[40] M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964.

[41] H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859.

[42] Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253.

[43] P. S. Baran, *J. Am. Chem. Soc.* **2018**, *140*, 4751.

[44] K. M. Bromfield, H. Grade´n, D. P. Hagberg, T. Olssonb, N. Kann, *Chem. Commun.* **2007**, *30*, 3183.

[45] M. Karpf, R.Trussardi, *Angew. Chem. Int. Ed.* **2009**, *48*, 5760.

[46] Y. -Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310.

[47] H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru, Y. Hayashi, *Chem. Eur. J.* **2010**, *16*, 12616.

[48] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, *47*, 4928.

[49] H. Sundén, I. Ibrahem, G. -L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574.

[50] S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem. Int. Ed.* **2009**, *48*, 8923.

[51] H. Yang, L. Fu, L. Wei, J. Liang, B. P. Binks, *J. Am. Chem. Soc.* **2015**, *137*, 1362.

[52] F. Gelman, J. Blum, D. Avnir, *J. Am. Chem. Soc.* **2002**, *124*, 14460.

[53] Y. Huang, B. G. Trewyn, H. T. Chen, V. S. -Y. Lin, *New J. Chem.* **2008**, *32*, 1311.

[54] F. Gelman, J. Blum, D. Avnir, *Angew. Chem. Int. Ed.* **2001**, *40*, 3647.

[55] H. Huang, C. A. Denard, R. Alamillo, A. J. Crisci, Y. Miao, J. A. Dumesic, S. L. Scott, H. Zhao, *ACS Catal.* **2014**, *4*, 2165.

[56] L. -C. Lee, J. Lu, M. Weck, C. W. Jones, *ACS Catal.* **2016**, *6*, 784.

[57] P. Cotanda, N. Petzetakis, R. K. O'Reilly, *MRS Commun.* **2012**, *2*, 119.

[58] M. Elsabahy, K. L. Wooley, *Chem. Soc. Rev.* **2012**, *41*, 2545.

[59] R. K. O'Reilly, C. J. Hawker, K. L. Wooley, *Chem. Soc. Rev.* **2006**, *35*, 1068.

[60] Y. Liu, Y. Wang, Y. Wang, J. Lu, V. Pinon III, M. Weck, *J. Am. Chem. Soc.* **2011**, *133*, 14260.

[61] B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Fréchet, *Angew. Chem. Int. Ed.* **2005**, *44*, 6384.

[62] Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322.

[63] A. W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem. Int. Ed.* **2007**, *46*, 5428.

[64] S. L. Poe, M. Kobašlija, D. T. McQuade, *J. Am. Chem. Soc.* **2006**, *128*, 15586.

[65] Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100.

[66] Y. Yang, X. Liu, X. Li, J. Zhao, S. Bai, J. Liu, Q. Yang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9164.

[67] R. J. R. W. Peters, I. Louzao, J. C. M. van Hest, *Chem. Sci.* **2012**, *3*, 335.

[68] J. Shi, L. Zhang, Z. Jiang, *ACS Appl. Mater. Interfaces* **2011**, *3*, 881.

[69] M. B. Runge, M. T. Mwangi, A. L. Miller II, M. Perring, N. B. Bowden, *Angew. Chem. Int. Ed.* **2008,** *47*, 935.

[70] H. Kawaguchi, *Prog. Polym. Sci.* **2000**, *25*, 1171.

[71] S. H. Zhang, X. Huang, N. S. Yao, C. Horvath, *J. Chromatogr. A* **2002**, *948*, 193.

[72] S. Ishikura, K. Ishii, R. Midzuguchi, *Prog. Org. Coat.* **1988**, *15*, 373.

[73] W. Funke, O. Okay, B. J. Müller, *Adv. Polym. Sci.* **1998**, *136*, 139.

[74] E. C. Peters, F. Svec, J. M. J. Fréchet, *Adv. Mater.* **1999**, *11*, 1169.

CHAPTER II

Synthesis of Polymer Microsphere-immobilized Chiral Pyrrolidine Catalysts and Their Application to Asymmetric Reactions

2.1 Introduction

Enantiomerically pure compounds are widely used in different research areas as aroma and flavoring chemicals,[1,2] as well as in agrochemistry,[3] non-linear optics,[4,5], and the synthesis of pharmaceuticals.[6] There have been numerous ongoing efforts to efficiently produce single enantiomers considering the economic feasibility and environmental impacts.[7] Pure enantiomers can often be obtained from asymmetric transformations using various chiral catalysts, including enzymes, organometallics, and organocatalysts. Chiral organocatalysts[8-20] do not incorporate metals in its structure, unlike chiral organometallic catalysts, reducing the risk of metal contamination in the product and the potential for environmental effects. The absence of metals in organocatalysts also increases the stability of the reaction system when in contact with air, oxygen, or moisture, which is advantageous regarding the manufacturing process compared to organometallic catalysts.

Although various organocatalysts are available, pyrrolidine and its derivatives have often been used to produce enantiomerically pure compounds over the past two decades. Because of the versatility of these compounds, there has been much research devoted to improving their catalytic performance, either by modifying the pyrrolidine ring or the substituent group. In 2005, Jørgensen et al.[21] and Hayashi et al.[22,23] independently reported using diphenylprolinol silyl ether as a new and effective organocatalyst. This compound, now termed the Jørgensen-Hayashi catalyst, is currently employed for various asymmetric transformations. Gellman et al. also synthesized a diphenyl prolinol methyl ether to promote the asymmetric Michael addition between unstable aldehydes and unmodified ketones.[24] The electron-donating methoxy group in this pyrrolidine derivative increases the electron density on the N atom of the pyrrolidine ring. This increased electron density results in the ready formation of enamine intermediates from

unstable aldehydes because these enamines are generated via the nucleophilic activation of the aldehyde based on its reaction with the pyrrolidine derivative.

Even though these chiral organocatalysts are very efficient, they have various drawbacks, including the requirement for relatively high catalyst loadings, longer reaction time, and difficult recovery and reuse.[25] These limitations have been addressed by using linear or crosslinked polymers,[26,27] Merrifield resin,[28] ionic liquids,[29] and dendrimers[30,31] as supports for the catalysts. One advantage of using a polymer as a support is the ability to control the hydrophobic-hydrophilic balance of the material by adjusting the monomeric composition of the polymer to provide a suitable microenvironment for asymmetric catalytic reactions.[32] Benaglia et al. applied a poly(ethylene glycol) (PEG)-immobilized L-proline to an aldol condensation reaction.[33-35] The polymeric catalyst represents a simplified analog of a type I aldolase enzyme. The polymer chain mimics the enzyme's peptide backbone and the proline is substituted for the enzyme's active sites. The polymeric catalyst could be successfully reused several times with little yield change and only minor selectivity losses. Wu et al. reported the synthesis of helical poly(phenyl isocyanide) bearing L-prolinol derivative as a pendant by living polymerization with controlled molecular weights and narrow molecular weight distributions.[36] The polymeric helical catalysts were applied on asymmetric Michael addition and aldol reaction. The catalytic activity of the helical polymeric catalyst was linearly correlated with the molecular weight (M_n) and optical activity of the polymeric catalyst. The stereoselectivity of the asymmetric Michael addition reaction was significantly amplified with the increase of molecular weight of the polymeric catalyst until the M_n reached 44.9 kDa. The catalyst was successfully recovered and reused in the Michael addition reaction for five cycles without losing catalytic activity and stereoselectivity. The helical polymeric catalyst was also used on the asymmetric aldol reaction. The enantiomeric excess (ee) and diastereomeric (dr) values of the aldol reaction product were found to be 99% and >99/1, respectively. The same research group further reported the synthesis of a series of helical phenyl isocyanide carrying L-proline derivatives and applied them on asymmetric aldol reactions.[37] They observed that after removing the *N*-Boc protecting group from the proline pendant, the left-handed helix was reversed to the right-handed helix. The helical catalysts showed excellent catalytic ability on asymmetric aldol reactions compared to small molecular

catalyst. The helical catalyst was recovered and reused up to four cycles without significant loss of its catalytic activity. Pericàs et al. reported the synthesis of polystyrene-immobilized (*S*)-α,α-diphenylprolinol trimethylsilyl ether using a triazole linker.[38] The combination of a polymer backbone, triazole linkers, and catalytic units in this material provided exceptional substrate selectivity that favored the formation of linear short-chain aldehydes with good yields and enantioselectivities. Werner et al. demonstrated a sustainable and easily recoverable catalyst comprising a bifunctional ammonium salt covalently bonded to polystyrene, intended to promote the reaction of CO_2 with epoxides.[39] The catalyst was readily recovered from the reaction mixture by simple filtration and retained its original activity and selectivity after use at temperatures as high as 100 °C. Wang et al. developed novel catalysts based on chiral pyrrolidine derivatives immobilized on Merrifield resin through a coupling reaction and used these materials to promote the Michael addition of ketones with nitrostyrenes.[28] These catalysts provided good yields, excellent enantioselectivity, and high diastereoselectivity. They could also be recovered and reused after up to five reaction cycles without loss of catalytic activity and stereoselectivity because of the Merrifield resin as a support material. Hansen et al. developed a highly scalable synthesis of acrylic polymer beads containing proline and prolineamide moieties.[40] The synthesis involved the transformation of non-polymerizable hydroxyproline to a novel monomeric proline (methacrylate) in a single step. The solid-immobilized organocatalyst was prepared by free-radical copolymerization without using any prefabricated solid support. The resulting acrylic beads showed highly desirable and adjustable swelling characteristics. The same group also reported the preparation of polymer-immobilized prolines, prolineamides, and Jørgensen-Hayashi catalysts, using an acrylic copolymerization method.[41] In the synthesis, the chiral organocatalysts were modified to produce functionalized methacrylic monomers capable of polymerizing with suitable comonomers to give crosslinked beads. These crosslinked catalysts were found to be applicable to reactions in polar solvents. Recently, our group developed gel-type polymer-immobilized chiral pyrrolidine derivatives and applied these catalysts to asymmetric Michael addition reactions.[42] Although these catalysts exhibited good reactivity and stereoselectivity, this prior work determined that it was necessary to improve the support polymer to achieve better catalytic performance.

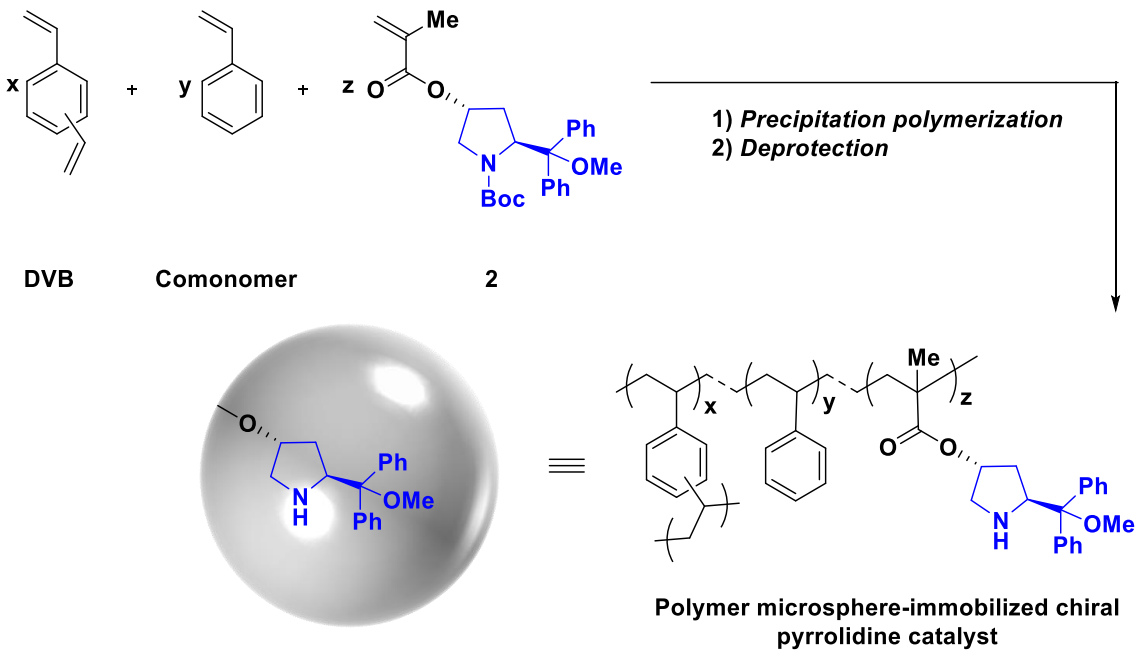
Polymer microspheres refer to spherical particles with diameters ranging from the sub-micron range to several microns.[43] These microspheres can be functionalized using various modification processes and have potential applications in electronics, coatings, adhesives, inks, leather finishing, paints, biomedicine, construction, chromatography, environmental science, and catalysis.[43-47] Applications such as those listed above arise because these microspheres have useful characteristics, including high specific surface areas and good mechanical strength, are readily dispersed, and can be easily recovered after use. These properties can also be tuned simply by changing the monomers. In particular, the hydrophobic-hydrophilic balance of the microspheres can be modified to provide suitable microenvironments for different chemical transformations.

Several polymerization techniques can prepare these microspheres, including emulsion, dispersion, and precipitation polymerizations.[48] Stöver et al. developed the first precipitation technique to synthesize monodisperse microspheres of divinylbenzene (DVB) without surfactants or stabilizers.[49-54] Other than precipitation polymerization, the techniques noted above require surfactants to prepare monodisperse microspheres. Unfortunately, both stabilizers and surfactants can adhere to the microsphere surfaces. Their complete removal by simple washing is quite challenging. This residual contamination can sometimes limit the potential of the application of microspheres in various research fields.

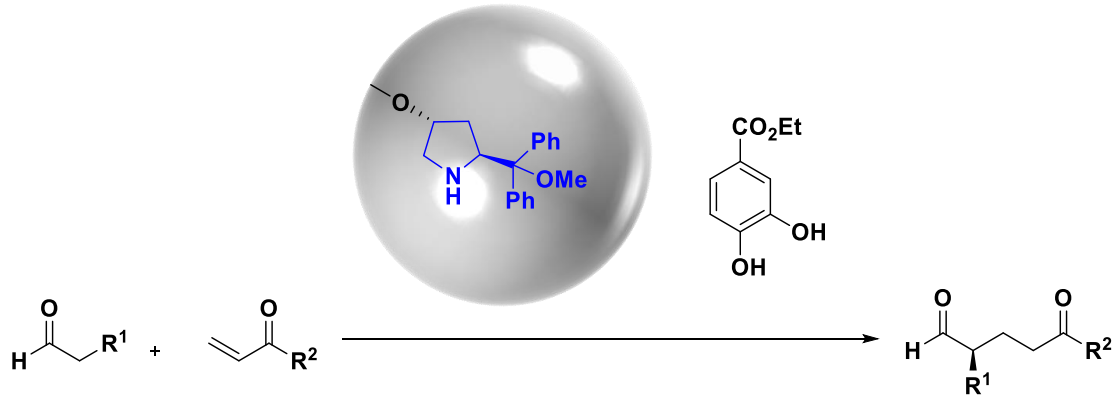
Interestingly, despite their useful features, microspheres are seldom used as polymeric supports for chiral catalysts in asymmetric reactions. Our own group previously synthesized monodisperse, crosslinked poly(divinylbenzene), and poly(methacrylic acid-*co*-ethylene glycol dimethacrylate) microspheres incorporating (1*R*,2*R*)-N^1-toluenesulfonyl-1,2-diphenylethylene-1,2-diamine ((*R*,*R*)-TsDPEN) moieties by precipitation polymerization. These polymer microsphere-immobilized chiral ligands were subsequently applied to the asymmetric transfer hydrogenation reactions of ketones and imines and demonstrated good reactivity and enantioselectivity.[48] We also found that the degree of crosslinking significantly affected both the yield and enantioselectivity obtained from such asymmetric reactions. More recently, we reported the synthesis of core-corona-type polymer microspheres immobilizing a cinchonidinium salt, based on a precipitation polymerization method, together with the application of the catalyst to the asymmetric alkylation reaction of a

glycine derivative.[55] The size of the core, the type and width of the corona, the grafting density, and the degree of crosslinking were all found to affect the catalytic reactivity of these catalysts. These polymeric catalysts showed good reactivity and excellent enantioselectivity (up to 99%). They demonstrated performance superior to those of the corresponding molecular catalysts.

In the present study, we examined the potential of crosslinked uniform polymer microspheres to serve as supports for a chiral organocatalyst intended to mediate asymmetric reactions. We report the synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts via precipitation polymerization using DVB, a comonomer, and a methacrylate monomer bearing a chiral *N*-Boc-pyrrolidine moiety, followed by removal of the *N*-Boc group (Scheme 2.1). The resulting catalysts were characterized by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), and elemental analysis. The catalytic performances of these polymer microspheres-immobilized catalysts were evaluated by carrying out asymmetric Michael addition reactions between aldehydes and alkyl vinyl ketones (Scheme 2.2). The effects of the chiral pyrrolidine derivative, comonomer, pyrrolidine derivative proportion in the catalyst, catalyst loading, temperature, solvent, and substrate were investigated in detail. The recovery and reuse of a polymer microsphere-immobilized catalyst was also assessed



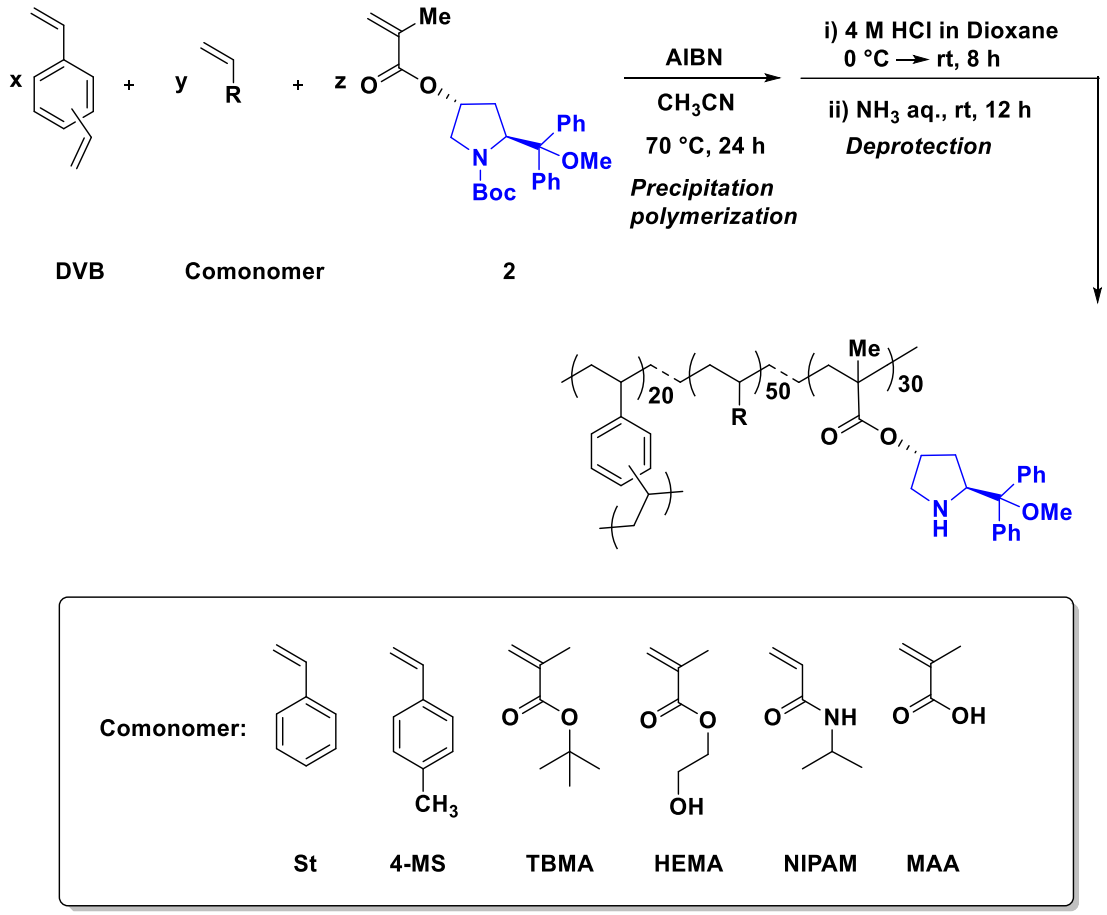
Scheme 2.1 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalyst.



Scheme 2.2 Asymmetric Michael addition reaction using polymer microsphere-immobilized chiral pyrrolidine catalyst.

2.2 Results and Discussion

2.2.1 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts by precipitation polymerization



Scheme 2.3 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts with variable comonomers.

A series of polymer microspheres with chiral pyrrolidine moieties was synthesized by precipitation polymerization followed by removing the *N*-Boc groups (Scheme 2.3). In these syntheses, DVB was used as a crosslinker while styrene (St), 4-methylstyrene (4-MS), *tert*-butyl methacrylate (TBMA), 2-hydroxyethyl methacrylate (HEMA), *N*-isopropyl acrylamide (NIPAM), and methacrylic acid (MAA) were used as comonomers to control the hydrophobic-hydrophilic balance of the polymeric catalyst. In initial trials,

Table 2.1 Characterization of polymer microsphere-immobilized chiral pyrrolidine catalysts.

Entry	Comonomer	Polymer	D_n (μm)[a]	U [a]
1	St	**PS3**	3.50	1.16
2	4-MS	**PMS**	3.79	1.23
3	TBMA	**PT**	2.63	1.08
4	HEMA	**PH**	2.06	1.02
5	NIPAM	**PN**	2.76	1.17
6	MAA	**PM**	4.20	1.02

[a] Determined by SEM images.

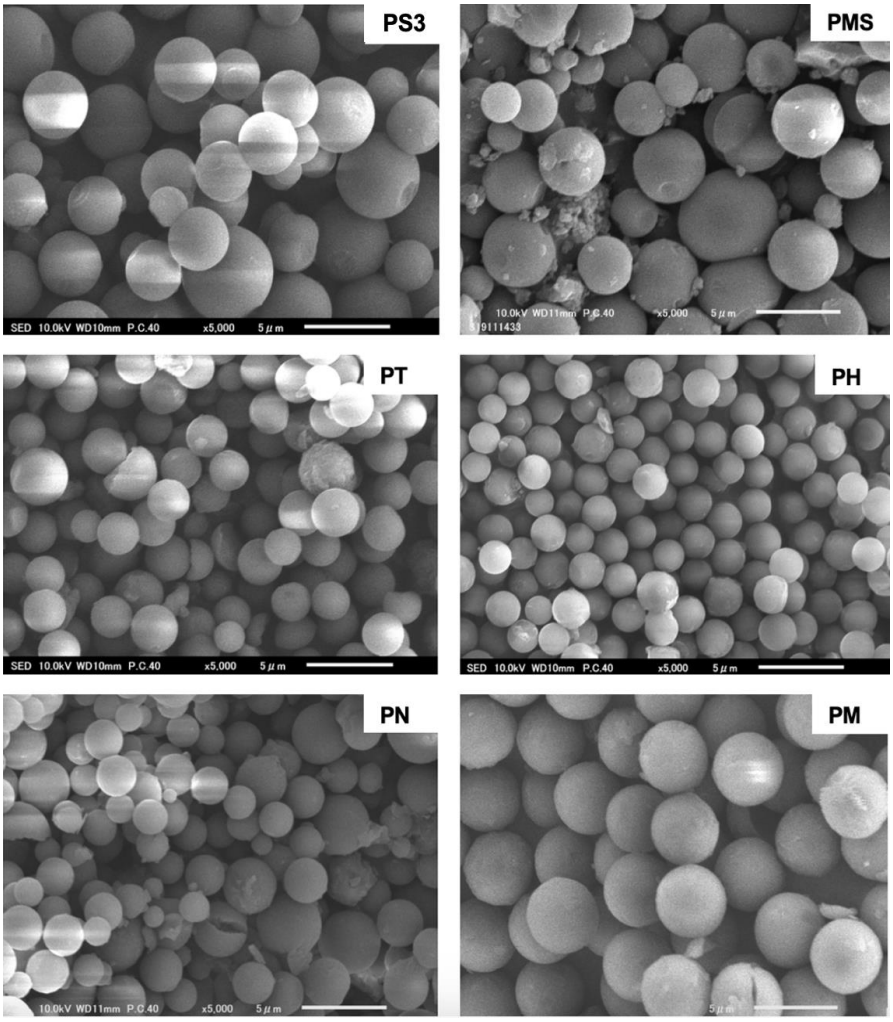


Figure 2.1 SEM images of polymer microsphere-immobilized chiral pyrrolidine catalysts. The scale bar in each image indicates 5 μm.

the molar ratio (x/y/z; see Scheme 2.3) was held constant at 20/50/30. Their characterization results are summarized in Table 2.1. The number average diameter (D_n) of the particles in each specimen was calculated based on SEM images acquired over areas with sizes in the micrometer range. These data indicated that the catalysts made with different comonomers had relatively similar particle sizes, although microspheres containing styrene and methacrylic acid comonomers were slightly larger. After removing the *N*-Boc groups, no significant variations in the microsphere's diameters were observed (Appendix A). The SEM images of these polymer microsphere-immobilized chiral pyrrolidine catalysts demonstrated the formation of uniform, spherical materials in each case (Figure 2.1). The polydispersity values (*U*) of those specimens made using HEMA, MAA, and TBMA as the comonomer were relatively low. This uniformity is attributed to the structural compatibility of each of these comonomers with the methacrylate monomer bearing the chiral pyrrolidine moiety. The FT-IR spectra acquired from the **PS3** before and after removing the *N*-Boc groups are shown in Figure 2.2. These spectra exhibit two characteristics absorption peaks at 1698 and 1721 cm^{-1} attributed to C=O bonds in the *N*-Boc and methacrylate moieties, respectively, confirming the successful polymerization of the pyrrolidine monomer. After the deprotection reaction, only the peak at 1721 cm^{-1} remained. In addition, a peak at 3393 cm^{-1} related to the amino groups in the pyrrolidine unit was observed. These results indicate that the precipitation polymerization and the deprotection reaction afforded the desired polymer microsphere-immobilized chiral pyrrolidine catalysts.

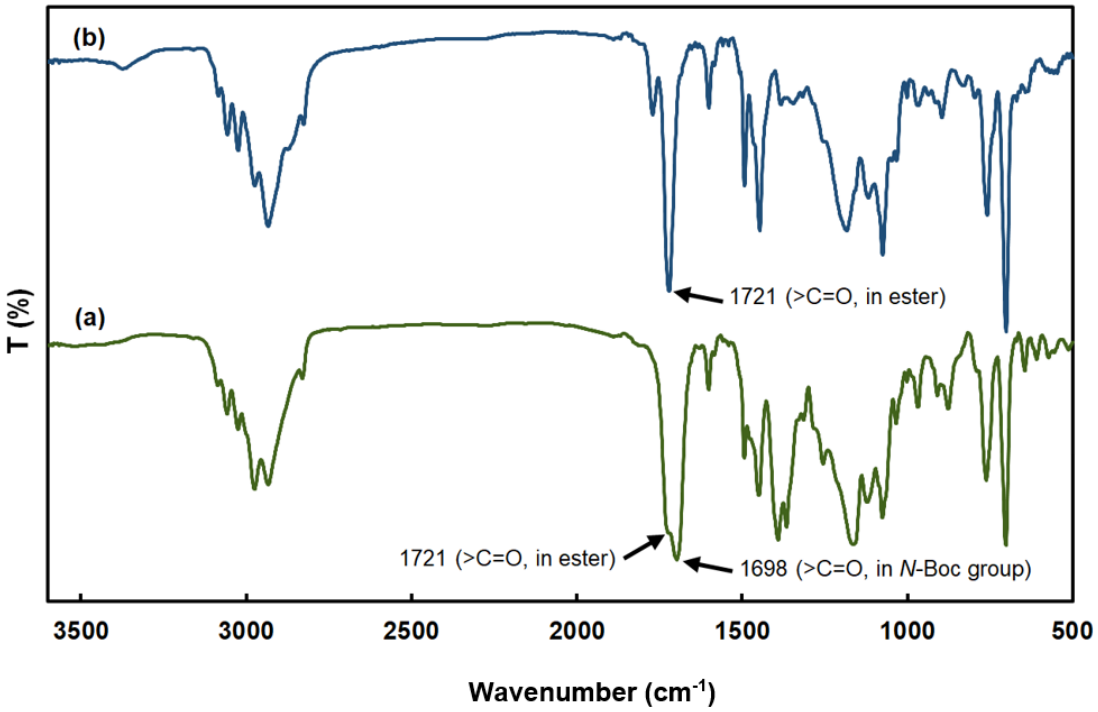


Figure 2.2 FT-IR spectra of the **PS3** (a) before and (b) after removing the *N*-Boc groups.

2.2.2 Asymmetric Michael addition reaction using polymer microsphere-immobilized pyrrolidine catalysts

The Michael addition reaction is a common and versatile means of forming C-C bonds in organic synthesis.[56] There have been numerous reports of asymmetric Michael addition reactions between different substrates. However, there are limited examples in the literature of the asymmetric Michael addition reactions of simple aldehydes with ketones.[57] In the present work, we examined the asymmetric Michael addition reactions of aldehydes (as the Michael donor) with alkyl vinyl ketones (as the Michael acceptor) catalyzed by polymer microsphere-immobilized chiral pyrrolidine catalysts made with different comonomers in the presence of ethyl 3,4-dihydroxy benzoate as a cocatalyst. These reactions proceeded via the nucleophilic activation of the aldehydes as a result of reactions with the polymeric pyrrolidine catalyst to form the corresponding enamines.[57] Simultaneously, the ethyl 3,4-dihydroxy benzoate electrophilically activated the methyl vinyl ketone by hydrogen bonding to the carbonyl oxygen.[58,59]

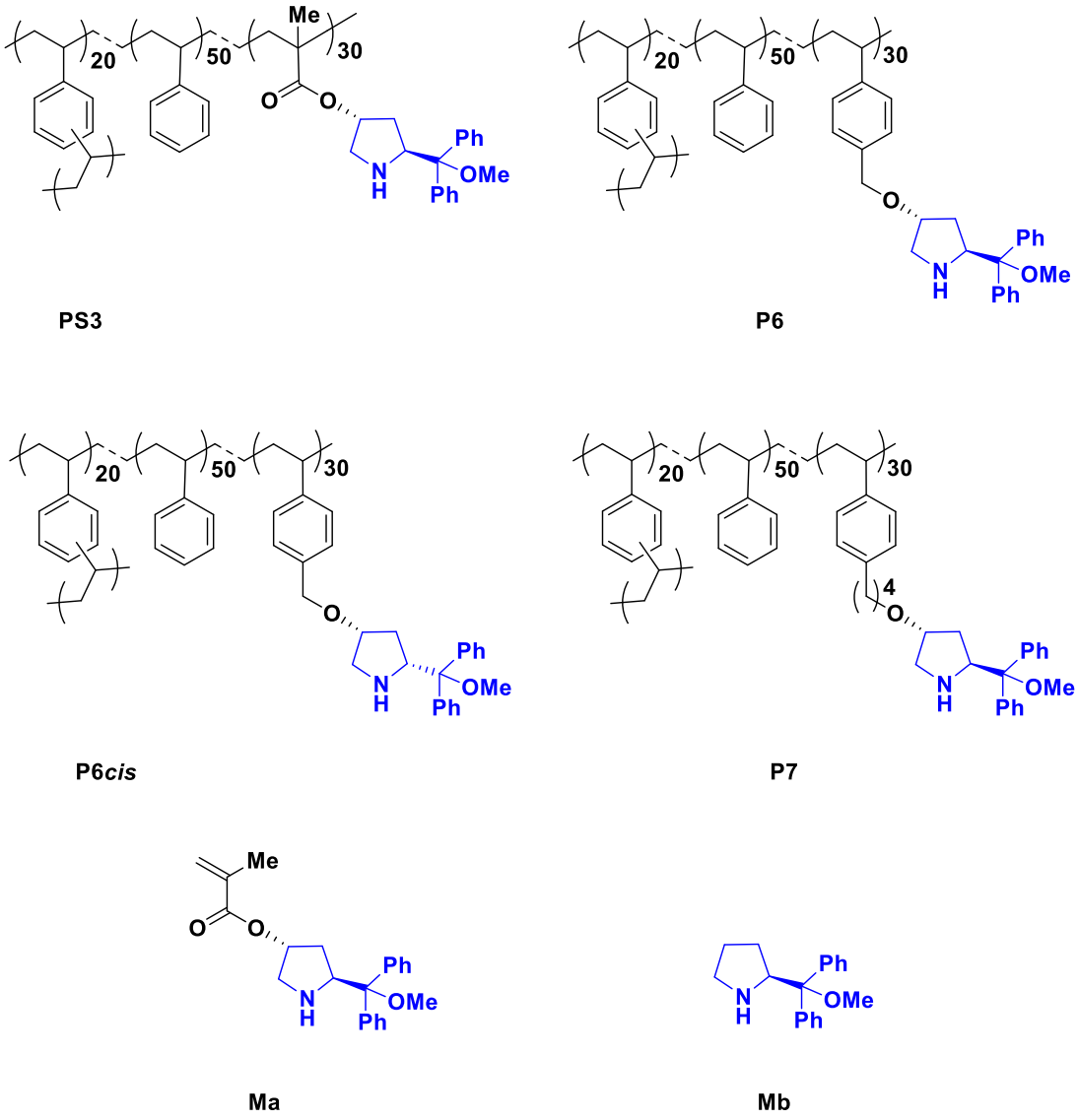
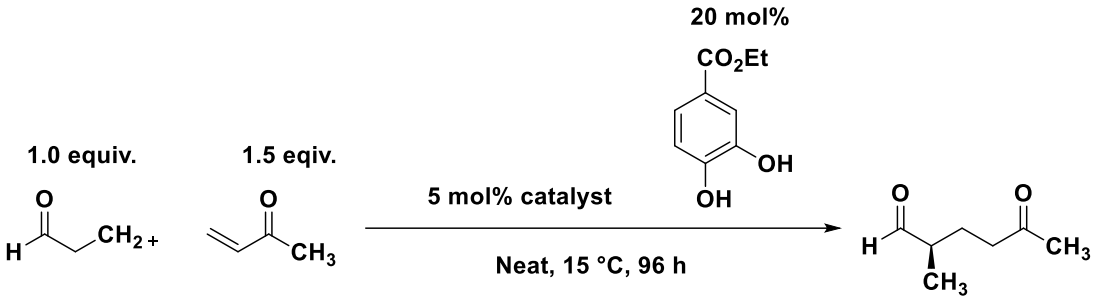


Figure 2.3 Polymer microsphere-immobilized pyrrolidine catalysts and molecular catalysts.

We first compared the catalytic activities and enantioselectivities obtained from the various catalysts (Figure 2.3) based on the reaction between propionaldehyde and methyl vinyl ketone in the presence of ethyl 3,4-dihydroxy benzoate and under solvent-free conditions at 15 ºC. The results are summarized in Table 2.2. In the absence of the pyrrolidine catalyst, the reaction did not proceed at all (Table 2, entry 1), while the use of molecular catalysts **Ma** and **Mb** gave the Michael adduct good yields with high enantioselectivities (Entries 2 and 3).

Table 2.2 Effects of chiral pyrrolidine catalysts on asymmetric Michael addition reaction.[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**none**	96	No reaction	nd[d]
2	**Mb**	36	82	97
3	**Ma**	48	92	92
4	**P6**	96	84	80
5	**P7**	96	87	87
6	**PS3**	96	92	91
7	**P6*cis***	96	88	91

[a] Reaction was conducted with propionaldehyde (1.00 mmol), methyl vinyl ketone (1.50 mmol), pyrrolidine catalyst (0.05 mmol), and ethyl 3,4-dihydroxy benzoate (0.20 mmol) at 15 °C for 96 h under Ar and solvent-free conditions.

[b] Determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after imination with (*S*)-1-methoxy-2-propylamine.

[d] nd stands for not determined.

When the polymer-immobilized chiral pyrrolidine catalyst with benzyl ether linkages (**P6**) was employed, the reaction afforded the product with good yield and high enantioselectivity (Entry 4). On the other hand, the version with alkyl ether linkages (**P7**) showed slightly higher reactivity and enantioselectivity than **P6** (Entry 5). Interestingly, the material having ester linkages (**PS3**) exhibited high reactivity along with the best enantioselectivity (Entry 6). The *cis*-type catalyst **P6*cis*** also exhibited the almost identical catalytic activity with the reverse configuration of the Michael adduct (Entry 7). Due to the best catalytic activity of **PS3**, this material was investigated further.

The effect of the comonomer was subsequently examined based on the same Michael addition reaction (Table 2.3). Regardless of the comonomer used to synthesize the

polymer, each catalyst showed good reactivity and enantioselectivity during the asymmetric Michael addition reaction. The hydrophobic polystyrene-based chiral pyrrolidine catalyst (**PS3**) exhibited high reactivity and enantioselectivity (Entry 1), and the hydrophobic poly(4-methylstyrene)-based **PMS** showed similar behavior (entry 2). Both the reactivity and enantioselectivity were slightly decreased when **PT**, **PH**, **PN,** or **PM** was used in the reaction (Entries 3-6). Incorporating hydrophobic comonomers in the polymeric catalyst allowed easier access of the hydrophobic substrates to the catalytic sites. It is also possible that the conformation of such sites was better suited to this reaction in the case that a hydrophobic comonomer was used.

Table 2.3 Effect of the comonomer.[a]

Entry	Catalyst	Comonomer	Yield (%)[b]	ee (%)[c]
1	**PS3**	St	92	91
2	**PMS**	4-MS	89	91
3	**PT**	TBMA	85	82
4	**PH**	HEMA	84	88
5	**PN**	NIPAM	85	89
6	**PM**	MAA	76	85

[a] Reaction was conducted with propionaldehyde (1.00 mmol), methyl vinyl ketone (1.50 mmol), pyrrolidine catalyst (0.05 mmol), and ethyl 3,4-dihydroxy benzoate (0.20 mmol) at 15 °C for 96 h under Ar and solvent-free conditions.

[b] Determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after imination with (*S*)-1-methoxy-2-propylamine

Table 2.4 Effects of molar ratio, catalyst loading, and temperature.[a]

Entry	Catalyst	DVB/St/2 (mol%)	Catalyst loading (mol%)	Yield (%)[b]	ee (%)[c]
1	**PS4**	20/60/20	5	91	91
2	**PS3**	20/50/30	5	92	91
3	**PS5**	20/40/40	5	97	91
4	**PS5**	20/40/40	3	54	91
5	**PS5**	20/40/40	1	26	92
6[d]	**PS5**	20/40/40	5	97	80
7[e]	**PS5**	20/40/40	5	27	93

[a] Reaction was conducted with propionaldehyde (1.00 mmol), methyl vinyl ketone (1.50 mmol), pyrrolidine catalyst (0.05 mmol), and ethyl 3,4-dihydroxy benzoate (0.20 mmol) at 15 °C for 96 h under Ar and solvent-free conditions.

[b] Determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after imination with (*S*)-1-methoxy-2-propylamine.

[d] Reaction was carried out at 30 °C and the yield after 60 h.

[e] Reaction was carried out at 0 °C.

Since the polystyrene-based chiral pyrrolidine catalyst (**PS3**) showed good reactivity during the asymmetric Michael addition reaction, we studied the effect of the molar ratios in the immobilized polymer and the catalyst loading on the reaction, using the series of catalysts **PS3-5** (see Table 2.4). In these specimens, the molar proportion of DVB was held constant while the proportions of styrene and the chiral pyrrolidine monomer (**2**) were changed. The results are summarized in Table 2.4. These data demonstrate that the reaction yield slightly increased with no change in enantioselectivity upon increasing the proportion of **2** from 20 to 40 mol% (Entries 1-3). The **PS5** showed the best catalytic activity because it contained the highest concentration of the catalytic moiety on the microspheres. In addition, these reactions were performed under solvent-free conditions, and so this increased catalyst concentration would have provided greater access of the substrate to catalytic sites. The effect of the catalyst loading was also examined, using the **PS5**, and an essentially quantitative yield was obtained when 5 mol% of **PS5** was employed (Entry 4), while lower loadings resulted in decreased yields with unaltered enantioselectivity (Entries 4 and 5).

The effect of temperature was further explored on the reaction rate and enantioselectivity of the Michael addition reaction. The increase of temperature up to 30 °C amplified the reaction rate. However, the enantioselectivity of the reaction significantly decreased (see Table 2.4 and entry 6). The enantioselectivity of the reaction was slightly increased up to 93% with a very low yield (27%) when the temperature was decreased to 0 °C (Entry 7).

Table 2.5 Solvent screening using **PS5**.[a]

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	DMF	4	85
2	MeOH	4	nd[d]
3	THF	2	90
4	CH_2Cl_2	22	90
5	toluene	28	93
6	hexane	50	82
7	none	97	91

[a] Reaction was conducted with propionaldehyde (1.00 mmol), methyl vinyl ketone (1.50 mmol), **PS5** (0.05 mmol), and ethyl 3,4-dihydroxy benzoate (0.20 mmol) in solvent (1.0 mL) at 15 °C for 96 h under Ar.

[b] Determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

[d] nd stands for not determined.

The effects of various solvents on the Michael addition reaction were assessed using a 5 mol% loading of the **PS5**, with the results summarized in Table 2.5. Unexpectedly, the yield was decreased when using the various solvents, such that only trace yields were obtained in polar solvents, even though the ethyl 3,4-dihydroxy benzoate cocatalyst is relatively soluble in such solvents (Entries 1-3). On the other hand, in non-polar solvents such as CH_2Cl_2 and toluene the yields were increased (Entries 4 and 5), while the reaction in hexane exhibited better reactivity (50% yield), but the enantioselectivity was decreased (entry 6). From these results, it is apparent that solvent-free conditions are preferable.

The substrate scope was examined using 5 mol% **PS5**, 1.0 equivalents of aldehydes, 20 mol% ethyl 3,4-dihydroxy benzoate, and 1.5 equivalents of methyl vinyl ketone or

ethyl vinyl ketone in conjunction with solvent-free conditions at 15 °C (Figure 2.4). The results indicated that the linear aldehydes gave the corresponding products **E8**, **E9**, and **E10** high yields. At the same time, isovaleraldehyde provided the product **E11** in moderate yield. The branching of the alkyl chain on this aldehyde may have inhibited the enamine formation from the **PS5** and isovaleraldehyde. Higher enantioselectivity values were observed when using long linear chain- or branched aldehydes compared to short-chain aldehydes. The alkyl chains of these aldehydes helped stabilize the transition state of the (*R*)-isomer in the reaction to produce a high ee value of the Michael adduct. The replacement of methyl vinyl ketone with ethyl vinyl ketone produced the corresponding product **E12**, **E13**, and **E14** with a lower yield than methyl vinyl ketone. The replacement of the methyl group by ethyl group in the case of ethyl vinyl ketone produces a steric constraint, making it less reactive to the reaction.

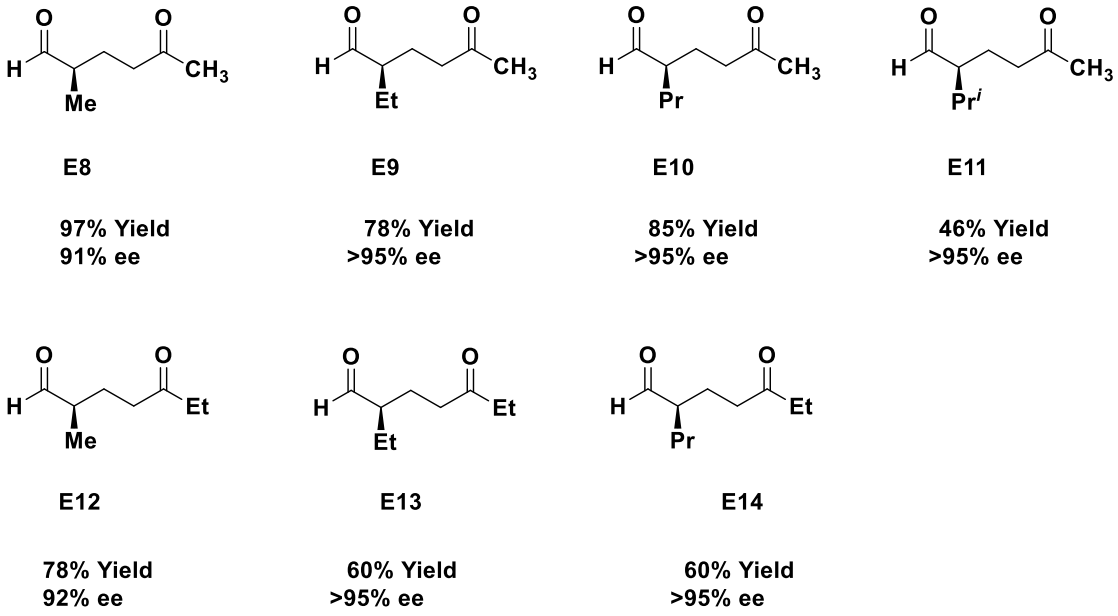


Figure 2.4 Substrate scope.

Because these polymeric catalysts comprised micron-sized particles, the recovery after use was remarkably straightforward compared with conventional crosslinked gel-type analogs. In the present work, the catalyst could be separated from the reaction mixture after using a simple centrifugation method. Trials were performed in which the recovered **PS5** was reused in subsequent reaction, with the results presented in Figure 2.5. Quantitative catalyst recovery was possible after each cycle, which is typically difficult when using gel-type or resin-type supported catalysts. The yield remained

constant up to the third cycle and then dropped at the fourth cycle. The reason for this loss of performance is unclear, although the lower yield remained constant during the fifth cycle. The catalyst also retained its original enantioselectivity up to five cycles.

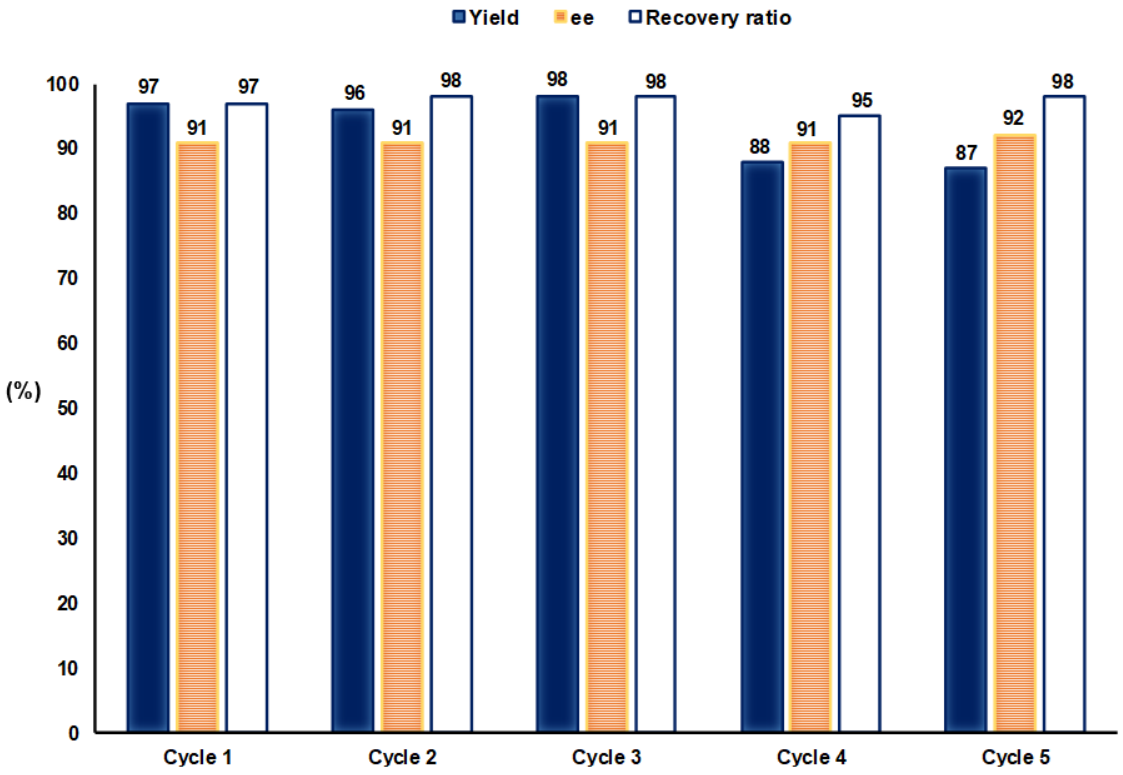
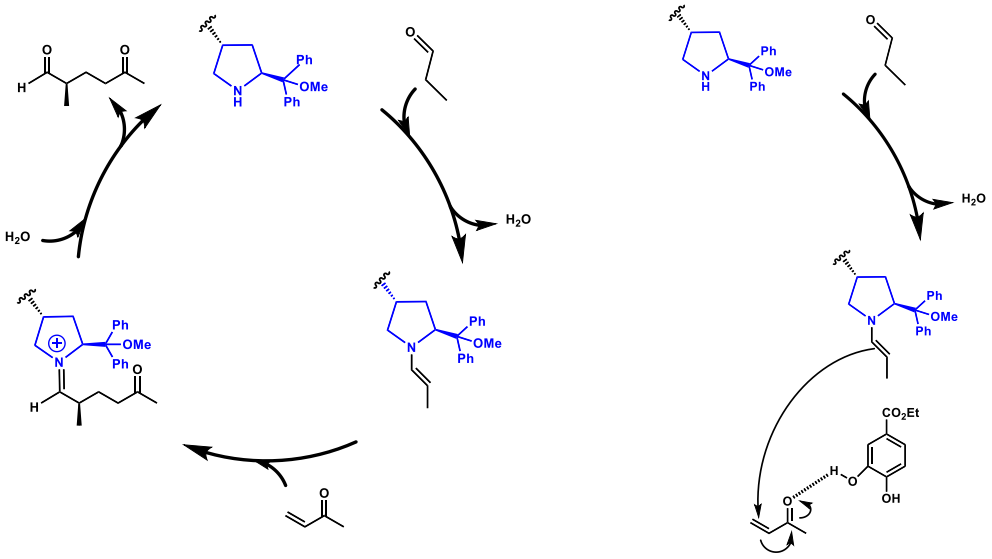


Figure 2.5 Results from trials reusing **PS5**.

2.2.3 Plausible reaction mechanism of asymmetric Michael addition between propionaldehyde and methyl vinyl ketone.

The pyrrolidine catalyst form enamine intermediate by the condensation reaction between -NH group of the pyrrolidine catalyst and propionaldehyde. The enamine intermediate further reacts with the methyl vinyl ketone to form the asymmetric Michael adduct with the release of free pyrrolidine catalyst (Scheme 2.4).



Scheme 2.4 Plausible reaction mechanism of asymmetric Michael addition reaction.

2.3 Conclusion

Polymer microsphere-immobilized chiral pyrrolidine catalysts made with various comonomers, and molar ratios were successfully synthesized by precipitation polymerization using a methacrylate monomer bearing a chiral *N*-Boc-pyrrolidine moiety followed by deprotection based on removal of the *N*-Boc group. These polymeric catalysts were applied to the asymmetric Michael addition reactions of aldehydes with alkyl vinyl ketones. Regardless of the comonomer used, good reactivity and enantioselectivity values were obtained under solvent-free conditions. The hydrophobic polystyrene-based catalyst **(PS5)** exhibited especially high reactivity (up to 97% yield) and enantioselectivity (up to 95%). It efficiently promoted the asymmetric Michael addition reactions of linear and branched aldehydes. The **PS5** showed good reusability for up to five cycles while retaining its original enantioselectivity. In this work, all the reactions were carried out using a batch process. However, the application of these polymeric catalysts to one-pot and continuous-flow processes is currently being investigated at our laboratory.

2.4 Experimental

2.4.1 Materials

N-(*tert*-Butoxycarbonyl)-*trans*-4-hydroxy-L-proline methyl ester, *tert*-butyldimethylchlorosilane, phenyl magnesium bromide, sodium hydride, tetra-*n*-butylammonium fluoride, iodomethane, methyl vinyl ketone (>95%), propionaldehyde (>98%), and ethyl 3,4-dihydroxybenzoate were purchased from the Tokyo Chemical Industry (TCI) Co. Ltd. and used as received. Imidazole (Wako Pure Chemical Industries Ltd., Japan), triethylamine (Wako Pure Chemical Industries Ltd., Japan), Ethyl vinyl ketone (>97%, Sigma-Aldrich), and (*S*)-1-methoxy-2-propylamine (99%, Sigma-Aldrich) were also all used as received. Butyraldehyde (>98%, TCI, Japan), valeraldehyde (>98%, TCI, Japan), and isovaleraldeyde (>98%, TCI, Japan) were further purified by distillation before use, and the purity of each was confirmed by nuclear magnetic resonance (NMR) spectroscopy. Styrene (Kishida Chemical Co. Ltd., Japan), 4-methylstyrene (TCI, Japan) and DVB (Nippon & Sumikin Chemical Co. Ltd., Japan) were washed with aqueous 10% NaOH and water, followed by distillation with CaH_2 under reduced pressure. 2-Hydroxyethyl methacrylate (Wako Pure Chemical Industries Ltd., Japan), *tert*-butyl methacrylate (Kishida Chemical Co. Ltd.) and methacrylic acid (TCI, Japan) were distilled under reduced pressure. Methacryloyl chloride (Wako Pure Chemical Industries Ltd., Japan) was purified by simple distillation, while *N*-isopropylacrylamide (TCI, Japan) was recrystallized from a mixture of hexane and acetone (90/10, v/v) and then dried at a low temperature under vacuum and 2,2'-azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and dried under vacuum prior to use.

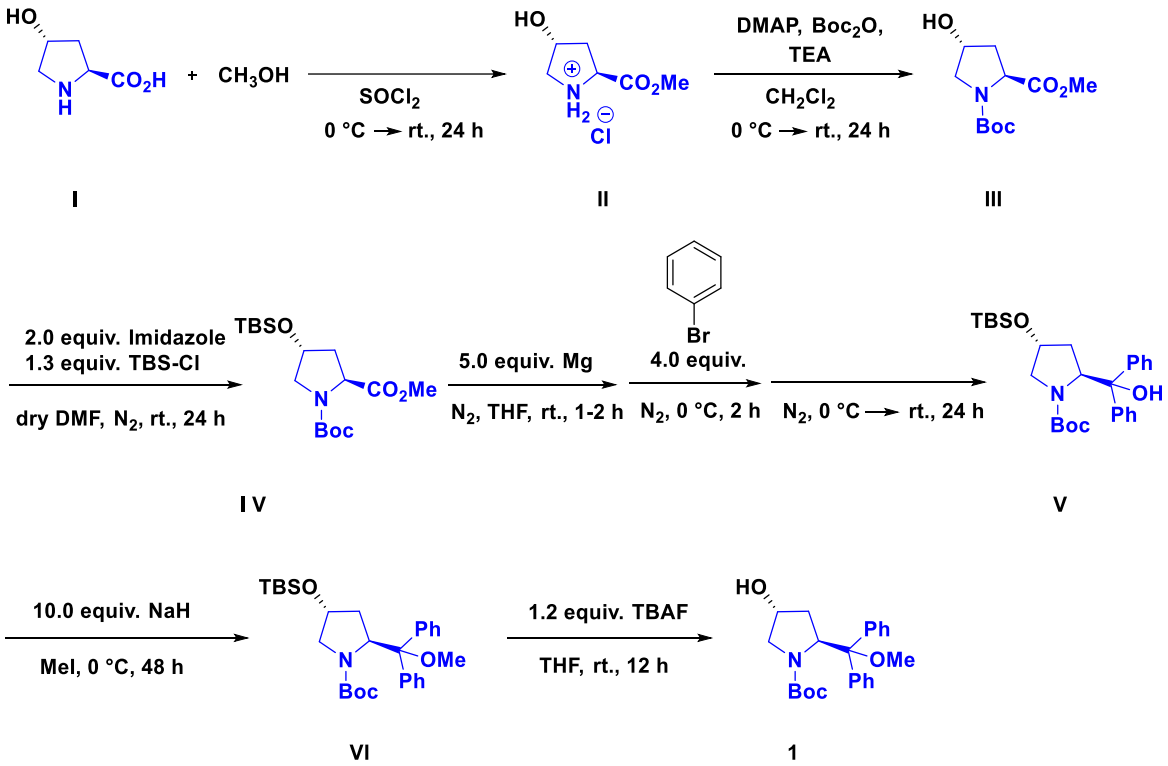
2.4.2 Measurements

Reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel plates (Merck 5554, $60F^{254}$). Column chromatography was performed with a silica gel column (Wakogel C-200, 100–200 mesh). NMR spectra were acquired at room temperature using JEOL JNM-ECS400 and JEOL JNM-ECX500 spectrometers with samples dissolved in $CDCl_3$ or CD_3CN. Chemical shifts are reported herein in units of parts per million (ppm), relative to tetramethylsilane (TMS) as a reference, while *J* values are reported in Hertz (Hz). HRMS (ESI) data were obtained using Bruker micrOTOF II-TTUH spectrometer. FT-IR spectra were recorded with a JASCO FT/IR-230

spectrometer and are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed at the Microanalytical Center of Kyoto University. Optical rotations were determined using a JASCODIP-149 digital polarimeter in conjunction with a 10 cm thermostatted microcell. SEM observations were conducted with a JSM-IT100 at an acceleration voltage of 10.0 kV. The number-averaged diameter (D_n), weight-average diameter (D_w), and polydispersity index (U) values for the polymer microspheres were calculated based on the SEM images.

*2.4.3 Synthesis of chiral compound **1***

The chiral compound **1** was prepared according to the reported literature.[24]



Scheme 2.5 Synthesis of chiral compound **1**.

In a 100 ml eggplant flask, 2.0 g of *trans*-4-hydroxy-L-proline **I** (15.2 mmol) was suspended in MeOH (50 mL) and cooled to 0 °C. Then 1.10 mL $SOCl_2$ (15.2 mmol, 1.00 equiv.) was added dropwise to the suspension. The reaction mixture was stirred for 24 h. Finally, the MeOH was removed from the reaction mixture under reduced pressure and the product **II** (2.83 g, >99 % yield) was obtained as colorless solid.

^{1}H-NMR (400 MHz, D_2O, δ, ppm) δ = 4.60-4.55 (m, 2H), 3.70-3.75 (3H), 3.40 (dd, *J* = 12.7, 3.8 Hz, 1H), 3.29 (dq, *J* = 12.6, 1.0 Hz, 1H), 2.40-2.34 (m, 1H), 2.21-2.13 (m, 1H).

In a 100 ml eggplant flask, 2.78 g of **II** (15.2 mmol) was suspended in CH_2Cl_2 (30 mL). Then, 4-dimethylaminopyridine (DMAP) 373 mg (3.05 mmol, 0.20 equiv.) and 5.0 mL of triethylamine (TEA) were added to the reaction mixture. The resulting reaction mixture was cooled to 0 °C. Di-*tert*-butyl dicarbonate (Boc_2O) 3.83 g (17.5 mmol, 1.15 equiv.) in CH_2Cl_2 (15 mL) were added dropwise to the same reaction mixture at 0 °C and the resulting mixture was stirred for 24 h. The reaction was quenched by adding H_2O and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL) and the collected organic layer was washed with 1 M citric acid solution. After washing, the organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by silica-gel column chromatography using a 10:1 (v/v) mixture of CH_2Cl_2 and MeOH as the eluent. Finally, the solvents were removed under reduced pressure to give white solid **III** (3.70 g, 99% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm) δ = 4.50-4.38 (m, 2H), 3.73 (s, 3H), 3.65 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.51 (dd, *J* = 42.6, 11.7 Hz, 1H), 2.33-2.26 (m, 1H), 2.11-2.05 (m, 1H), 1.44 (d, *J* = 18.6 Hz, 9H)

A 200 mL eggplant flask equipped with a magnetic stir bar was charged with compound **III** (2.62g, 10.68 mmol). Then, Imidazole (1.45g, 21.36 mmol), *tert*-butyldimethylsilyl chloride (TBS-Cl) (2.09g, 13.87 mmol), and dry DMF (13.20 mL) were added to the flask. The reaction mixture was magnetically stirred for 24 h under N_2 at room temperature. The reaction was quenched by adding water and the mixture was partitioned between 20 mL ethyl acetate and 20 mL water. The organic layer was collected and washed with water to remove any trace amount of DMF. After washing, the organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to give colorless liquid **IV** (4.63g; Yield >99%).

^{1}H-NMR (500 MHz, $CDCl_3$, δ, ppm) δ = 4.42-4.31 (m, 2H), 3.72 (s, 3H), 3.61-3.55 (m, 1H), 3.40-3.30 (m, 1H), 2.20-2.12 (m, 1H), 2.03-1.96 (m, 1H), 1.42 (d, *J* = 23.3 Hz, 9H), 0.85 (s, 9H), 0.05 (s, 6H)

N_2 gas was passed through a three-necked eggplant flask equipped with a magnetic stir bar. Then, Mg ribbon (1.52 g, 62.6 mmol), dry THF (10 mL), and Iodine (79 mg, 0.13 mmol) were added to the flask, and it was allowed to stir for 1-2 h under N_2 to activate the Mg ribbon. After the activation of the Mg ribbon, bromobenzene (5.24 mL, 50.08 mmol) was added at 0 °C and the reaction mixture stirred for 2 h. After 2 h, the compound **IV** (4.50g, 12.52 mmol) dissolved in dry THF (20 mL) was slowly added dropwise at 0 °C and stirred for 24 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl. The organic layer was separated, and the aqueous layer was extracted 5 times by 30 mL ethyl acetate. Finally, the organic layer was washed with 1 M HCl to remove any trace of Mg ribbon. After washing, the organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography using a 9:1 (v/v) mixture of hexane and EtOAc as the eluent. Finally, the solvents were removed under reduced pressure to give **V** (4.18 g, 69% yield) as white solid.

^{1}H-NMR (500 MHz, $CDCl_3$, δ, ppm) δ = 7.39-7.27 (m, 10H), 6.24-6.40 (1H), 5.03 (t, *J* = 6.7 Hz, 1H), 3.29-3.14 (m, 1H), 2.89-2.85 (m, 1H), 2.04 (t, *J* = 6.3 Hz, 2H), 1.43 (s, 9H), 0.77 (s, 10H), -0.13 (d, *J* = 7.3 Hz, 6H)

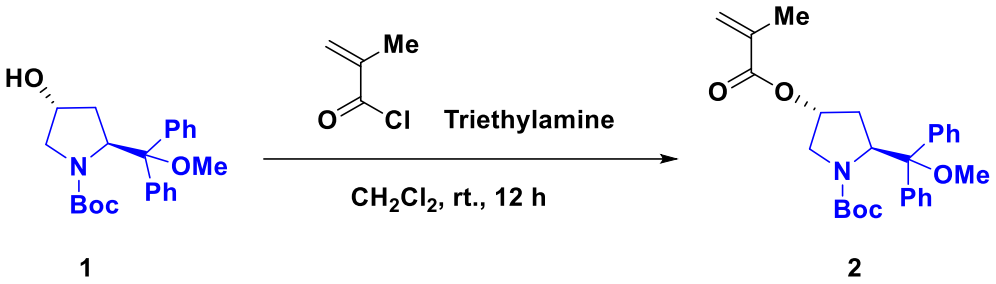
In a 50 mL eggplant flask equipped with a magnetic stir bar, sodium hydride (NaH) (1.0 g, 41.3 mmol) and methyl iodide (MeI) (3.0 mL) were added. Then **V** (2.00 g, 4.13 mmol) dissolved in MeI (3.0 mL) was added slowly dropwise into flask at 0 ºC. The reaction mixture was stirred for 48 h under Ar. The reaction was quenched by adding water. Excess MeI was removed under reduced pressure. The obtained residue was partitioned between 20 mL ethyl acetate and 20 mL water. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated to give crude product. The crude product was eluted through silica-gel column chromatography using a 10:1 (v/v) mixture of hexane and EtOAc. Finally, the solvents were removed under reduced pressure to obtain white solid **VI** (1.76 g; Yield 86%).

^{1}H-NMR (500 MHz, $CDCl_3$, δ, ppm) δ = 7.42-7.26 (m, 11H), 5.24-4.85 (m, 1H), 4.01-3.87 (m, 0H), 3.45-3.37 (m, 1H), 2.95 (s, 3H), 2.80-2.55 (m, 1H), 2.16-2.06 (m, 1H), 1.97-1.80 (m, 1H), 1.41 (s, 9H), 0.78 (s, 9H), -0.10 (s, 6H)

In a 50 mL eggplant flask equipped with a magnetic stirrer bar, 1.70 g (3.42mmol) of **VI** and 18.30 mL THF were added. The resulting reaction mixture was stirred for 5 minutes and then, 4.10 mL (4.10 mmol) tetra-*n*-butylammonium fluoride (TBAF) was added to the reaction mixture. The reaction was continued up to 12 h under Ar at room temperature. The reaction was quenched by adding saturated aqueous NH_4Cl solution and THF was removed under reduced pressure. After removing THF, the organic layer was collected using 20 mL EtOAc and 20 mL H_2O. The collected organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to give crude product. Next, the obtained crude product was eluted through silica-gel column chromatography using a 3:2 (v/v) mixture of hexane and EtOAc as the eluent. Finally, the solvents were removed under reduced pressure to obtain white foamy solid **1** (1.21g; Yield 92%).

^{1}H-NMR $CDCl_3$, δ, ppm) δ = 7.43-7.28 (m, 10H), 5.13-5.05 (m, 1H), 4.07-3.93 (m, 1H), 3.51-3.41 (m, 1H), 2.94 (s, 3H), 2.64-2.53 (m, 1H), 2.24 (td, J = 10.1, 4.1 Hz, 1H), 1.91-1.87 (m, 1H), 1.32 (s, 9H)

*2.4.4 Synthesis of methacrylate monomer bearing chiral N-Boc- pyrrolidine moiety (**2**)*



Scheme 2.6 Synthesis of chiral pyrrolidine moiety **2**.

A 50 mL eggplant flask equipped with a magnetic stir bar was charged with **1** (1.15 g, 2.99 mmol), triethylamine (1.70 mL, 12.2 mmol), and CH_2Cl_2 (4.3 mL). The mixture was cooled to 0 ºC and stirred under N_2 until the solution became transparent, after which the mixture was warmed to room temperature, and methacryloyl chloride (0.60 mL, 6.1 mmol) was added. The reaction mixture was subsequently stirred for 12 h under N_2 and then quenched by adding a saturated aqueous solution of $NaHCO_3$, following which the solvents were removed under reduced pressure. The residual material was extracted five times with a 1/1 (v/v) mixture of $CHCl_3$ and H_2O, and the combined $CHCl_3$ portions were

then dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated to give the crude product as a viscous liquid. This product was purified by silica gel column chromatography using a 7:1 (v/v) mixture of hexane and ethyl acetate as the eluent. Finally, the solvents were removed under reduced pressure to provide **2** (1.31 g, 2.90 mmol) as a highly viscous colorless liquid.

Yield: 97%; $[\alpha]_D$ = -0.13 (c = 1.5 g/dL in CH_2Cl_2 at 15 ºC); ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm) δ = 7.30-7.45 (m, 10H), 6.02 (s, 1H), 5.51 (s, 1H), 4.76-5.24 (m, 2H), 3.77 (br, 1H), 3.51 (br, 1H), 2.99 (s, 3H), 2.61 (br, 1H), 2.41 (br, 1H), 2.12 (br, 1H), 1.87 (s, 3H), 1.31 (br, 9H)

^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm) δ = 166.99, 155.39, 140.70, 139.68, 138.70, 136.18, 129.71, 129.33, 127.69, 127.36, 125.67, 86.72, 79.65, 74.45, 64.71, 61.01, 52.78, 35.04, 28.27, 17.70.

High resolution mass spectrometry (HRMS; ESI, $[M+Na]^+$ positive); calc. 474.2268; found: 474.2251; Δppm= -3.60.

*2.4.5 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalyst (**PS3**)*

A 30 mL high density polyethylene (HDPE) narrow-mouth bottle was charged with DVB (0.121 g, 0.929 mmol), styrene (0.246 g, 2.36 mmol), **2** (0.634 g, 1.40 mmol), CH_3CN (29 mL), and AIBN (20 mg, 0.12 mmol, 2 wt% relative to the total monomer mass) under N_2. The mixture was then heated in an incubator at 70 ºC while rotating the bottle horizontally at 9 rpm for 24 h. Subsequently, the reaction was quenched by adding hydroquinone, and the mixture was cooled to room temperature. Soluble oligomeric and polymeric products were separated from the insoluble material by centrifugation. The insoluble product was washed once with tetrahydrofuran (THF), once with methanol, and three times with THF. This material was dried under vacuum at 40 ºC for 24 h to give the polymer microsphere-immobilized chiral pyrrolidine catalyst bearing *N*-Boc groups (**PS'3**) as a white solid (0.38 g).

Yield: 38%; FT-IR (KBr): ν (cm^{-1}) = 1698 (C=O, in *N*-Boc) and 1721 (C=O, in ester).

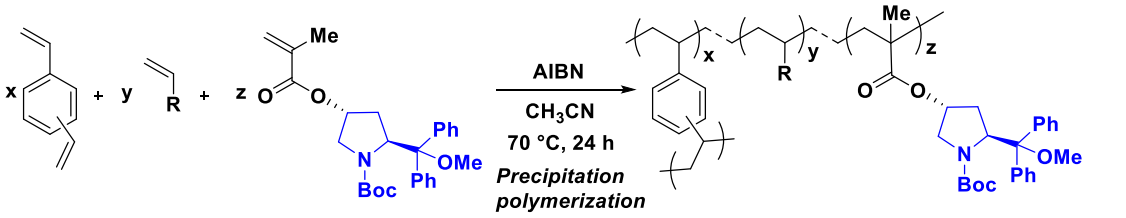
A Schlenk test tube equipped with a magnetic stir bar was charged with **PS'3** (0.34 g, 0.48 mmol) and cooled to 0 ºC, after which a 4 M HCl solution in dioxane (1.25 mL, 5.00 mmol) was added slowly under Ar and the reaction mixture was stirred at room

temperature. After 8 h, an aqueous NH_3 solution (1.70 mL, 25.5 mmol) was gradually added, and the mixture was stirred for a further 12 h under Ar. Following the deprotection reaction, the polymeric catalyst was washed sequentially with a 1/1 (v/v) mixture of H_2O and THF, methanol, and THF, then dried under vacuum at 40 ºC for 24 h to give **PS3** (0.29 g) as a yellow solid.

Yield: 99%; FT-IR (KBr): ν (cm^{-1}) = 1721 (C=O, in ester).
Elemental analysis for $C_{12.58}H_{13.48}N_{0.30}O_{0.90}$: calcd: C, 82.44%; H, 7.41% and N, 2.29%, found: C, 80.22%; H, 7.43% and N, 2.61%.
Catalyst content: 1.63 mmol/g.

2.4.6 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalyst with variable comonomer

The polymer microsphere-immobilized different chiral pyrrolidine catalysts have been synthesized by changing the variable comonomer and keeping the DVB as constant crosslinker. The results of the polymerization have been summarized in Table 2.6. The removal of the *N*-Boc group from the polymeric catalyst moiety was carried out and the results of the deprotection reaction have been summarized in Table 2.7.



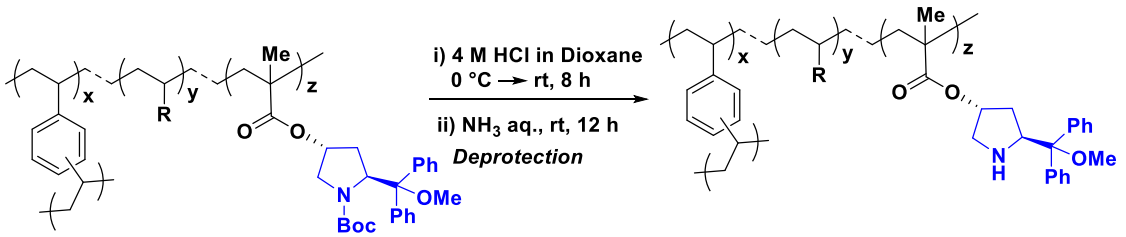


Table 2.6 Data of polymerization for the polymer microsphere-immobilized chiral pyrrolidine catalysts with variable comonomer.

Polymer	x/y/z (mol%)	DVB	Comonomer	Monomer 2	Yield (%)
PS'4	20/60/20	146 mg (1.12 mmol)	St, 349 mg (3.35 mmol)	505 mg (1.12 mmol)	40
PS'5	20/40/40	104 mg (0.799 mmol)	St, 169 mg (1.62 mmol)	728 mg (1.61 mmol)	40
PMS'	20/50/30	118 mg (0.906 mmol)	4-MS, 268 mg (2.27 mmol)	614 mg (1.36 mmol)	34
PT'	20/50/30	90 mg (0.691 mmol)	TBMA, 245 mg (1.72 mmol)	466 mg (1.03 mmol)	40
PH'	20/50/30	92 mg (0.707 mmol)	HEMA, 229 mg (1.76 mmol)	478 mg (1.06 mmol)	51
PN'	20/50/30	96 mg (0.737 mmol)	NIPAM, 208 mg (1.84 mmol)	497 mg (1.10 mmol)	40
PM'	20/50/30	102 mg (0.783 mmol)	MAA, 170 mg (1.97 mmol)	530 mg (1.17 mmol)	60

Table 2.7 Data for the deprotection reaction of polymer microsphere-immobilized pyrrolidine catalyst.

Weight of *N*-Boc group protected catalyst	4 M HCl (mL)	NH_3 aq. (mL)	*N*-Boc group deprotected polymeric catalyst	Yield (%)
PS4', 0.38 g (0.42 mmol)	1.05	1.40	**PS4**	99
PS5', 0.35 g (0.56 mmol)	1.40	1.90	**PS5**	99
PMS', 0.30 g (0.41 mmol)	1.05	1.40	**PMS**	84
PT', 0.28 g (0.36 mmol)	0.90	1.20	**PT**	90
PH', 0.36 g (0.48 mmol)	1.20	1.60	**PH**	99
PN', 0.27 g (0.37 mmol)	0.95	1.30	**PN**	97
PM', 0.42 g (0.61 mmol)	1.55	2.10	**PM**	99

*2.4.7 Asymmetric Michael addition reaction between propionaldehyde and methyl vinyl ketone using **PS3***

A Schlenk test tube was charged with propionaldehyde (58 mg, 1.0 mmol), **PS3** (31 mg, 0.050 mmol), ethyl 3,4-dihydroxybenzoate (36 mg, 0.20 mmol), and methyl vinyl ketone (105 mg, 1.50 mmol), after which the reaction mixture was stirred at 15 ºC for 96 h under Ar. The yield was determined from the ^{1}H NMR spectrum of the crude reaction mixture, following which the product was extracted from the mixture by three centrifugations using THF. After extraction, the THF was removed using a rotary evaporator and the crude product was purified by silica-gel column chromatography using a 3:1 (v/v) mixture of hexane and ethyl acetate as the eluent

to give a colorless liquid. The enantiomeric excess (ee) of this product was determined from its ^{1}H NMR spectrum after an imination reaction with (*S*)-1-methoxy-2-propylamine.

References

[1] R. Z. Wojtasiak, *Food Chem*. **2004**, *86*, 113.

[2] G. Flores, G. P. Blanch, M. L. Ruiz del Castillo, *Food Chem*. **2013**, *141*, 2982.

[3] R. Celis, B. Gámiz, M. A. Adelino, M. C. Hermosín, J. Cornejo, *Sci. Total Environ.* **2013**, *444*, 288.

[4] M. Kauranen, T. Verbiest, J. J. Maki, A. Persoons, *Synth. Met.* **1996**, *81*, 117.

[5] J. Lu, L. Wu, L. Jing, X. Xu, X. Zhang, *Dyes Pigm.* **2012**, *94*, 169.

[6] R. N. Patel, *Coord. Chem. Rev.* **2008**, *252*, 659.

[7] A. A. Elmekawy, J. B. Sweeney, D. R. Brown, *Catal. Sci. Technol.* **2015**, *5*, 690.

[8] Y. Zhang, L. Zhao, S. S. Lee, J. Y. Yinga, *Adv. Synth. Catal.* **2006**, *348*, 2027.

[9] J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719.

[10] A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, Germany **2005**.

[11] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[12] S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985.

[13] B. List, *Tetrahedron* **2002**, *58*, 5572.

[14] E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481.

[15] H. Gröger, J. Wilken, *Angew. Chem. Int. Ed.* **2001**, *40*, 529.

[16] B. List, *Synlett* **2001**, *11*, 1675.

[17] M. Kumar, R. I. Kureshy, S. Saravanan, S. Verma, A. Jakhar, N. H. Khan, *Org. Lett.* **2014**, *16*, 2798.

[18] D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[19] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[20] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

[21] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.

[22] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *117*, 4284.

[23] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[24] Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253.

[25] S. Llopis, T. García, Á. Cantín, A. Velty, U. Díaz, A. Corma, *Catal. Sci. Technol.* **2018**, *8*, 5835.

[26] A. Lu, T. P. Smart, T. H. Epps, D. A. Lonbottom, R. K. O'Reilly, *Macromolecules* **2011,** *44*, 7233.

[27] A. Bañón-Caballero, G. Guillena, C. Nájera, *Helvetica Chimica Acta* **2012**, *95*, 1831.

[28] J. Liu, P. Li, Y. Zhang, K. Ren, L. Wang, G. Wang, *Chirality* **2010**, *22*, 432.

[29] L. -Y. Wu, Z. -Y. Yan, Y. -X. Xie, Y. -N. Niu, Y. -M. Liang, *Tetrahedron:Asymmetry* **2007**, *18*, 2086.

[30] A. -M. Caminade, A. Ouali, M. Keller, J. -P. Majoral, *Chem. Soc. Rev.* **2012**, *41*, 4113.

[31] E. Bellis, G. Kokotos, *J. Mol. Catal. A: Chem.* **2005**, *241*, 166.

[32] D. C. Sherrington, *British Polym. J.* **1980**, *12*, 70.

[33] M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171.

[34] M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2002**, *344*, 533.

[35] M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *J. Mol. Catal A: Chem.* **2003**, 204,157.

[36] L. Shen, L. Xu, X. -H. Hou, N. Lu, Z. -Q. Wu, *Macromolecules.* **2018**, *51*, 9547.

[37] L. Zhou, B. -F. Chu, X. -Y. Xu, L. Xu, N. Lu, Z. -Q. Wu, *ACS Macro Lett.* **2017**, *6*, 824.

[38] E. Alzaa, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 3051.

[39] C. Kohrt, T. Werner, *ChemSusChem* **2015**, *8*, 2031.

[40] T. E. Kristensen, K. Vestli, K. A. Fredriksen, F. K. Hansen, T. Hansen, *Org. Lett.* **2009**, *11*, 2968.

[41] T. E. Kristensen, K. Vestli, M. G. Jakobsen, F. K. Hansen, T. Hansen, *J. Org. Chem.* **2010**, *75*, 1620.

[42] H. Ochiai, A. Nishiyama, N. Haraguchi, S. Itsuno, *Org. Process Res. Dev.* **2020**, *24*, 2228.

[43] H. Kawaguchi, *Prog. Polym. Sci.* **2000**, *25*, 1171.

[44] S. H. Zhang, X. Huang, N. S. Yao, C. Horvath, *J. Chromatogr. A* **2002**, *948*, 193.

[45] S. Ishikura, K. Ishii, R. Midzuguchi, *Prog. Org. Coat.* **1988**, *15*, 373.

[46] W. Funke, O. Okay, B. J. Müller, *Adv. Polym. Sci.* **1998**, *136*, 139.

[47] E. C. Peters, F. Svec, J. M. J. Fréchet, *Adv. Mater.* **1999**, *11*, 1169.

[48] N. Haraguchi, A. Nishiyama, S. Itsuno, *J. Polym. Sci. Part A: Polym. Chem.* **2010**,

48, 3340.

[49] W. H. Li, H. D. H. Stöver, *J. Polym Sci Part A: Polym. Chem*. **1993**, *31*, 3257.

[50] W. H. Li, H. D. H. Stöver, *J. Polym. Sci. Part A: Polym. Chem.* **1998**, *36*, 1543.

[51] W. H. Li, H. D. H. Stöver, *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 2899.

[52] J. S. Downey, G. McIsaac, R. S. Frank, H. D. H. Stöver, *Macromolecules* **2001**, *34*, 4534.

[53] W. H. Li, H. D. H. Stöver, *Macromolecules* **2000**, *33*, 4354.

[54] R. Takekoh, W. H. Li, N. A. D. Burke, H. D. H. Stöver, *J. Am. Chem. Soc.* **2005**, *128*, 240.

[55] M. W. Ullah, N. T. P. Thao, T. Sugimoto, N. Haraguchi. *Mol. Catal.* **2019**, *473*, 110392.

[56] Z. Zeng, P. Luo, Y. Jiang, Y. Liu, G. Tang, P. Xu, Y. Zhao, G. M. Backburn, *Org. Biomol. Chem.* **2011**, *9*, 6973.

[57] P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151.

[58] T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598.

[59] P. R. Schreiner, *Chem. Soc. Rev*. **2003**, *32*, 289.

CHAPTER III

Development of One-pot Asymmetric Reaction Using Polymer Microsphere-immobilized Acid and Base Catalysts

3.1 Introduction

Chemical transformation with the chiral catalysts to prepare enantiopure compounds is of increasing importance in organic synthetic chemistry because it can supply useful medicines, pesticides, and building blocks.[1-4] The synthesis of enantiopure compounds is the most challenging task met by organic chemists. The most crucial challenge is developing suitable synthesis procedures to produce the desired optically active compounds with low negative environmental impact, high economic feasibility, and high efficiency. For example, suppose multiple transformation reactions can be consecutively carried out in a one reaction vessel. In that case, a highly efficient organic synthetic process can be realized, which will circumvent the above issues. This process is often termed a one-pot reaction sequence. Thus, the one-pot reaction process can mitigate chemical waste, save time, energy, and labor of isolation and purification of the product.

Several "one-pot" reactions have been reported with much attention in the field of organic synthetic chemistry.[5,6] Unfortunately, one of the limitations is that multiple catalysts with contrary properties (e.g., acidic and basic, oxidative and reductive) cannot be used simultaneously. The undesired interactions of the contrary type of catalysts lead to the diminished performance of the active species, which compromises the formation of the target compounds.[7] The issue is one of the significant factors limiting the versatility of the one-pot reaction. Developing a practical one-pot synthetic process using multiple chiral catalysts with contrary properties provides a method with excellent total efficiency in synthesizing numerous beneficial optically active compounds.

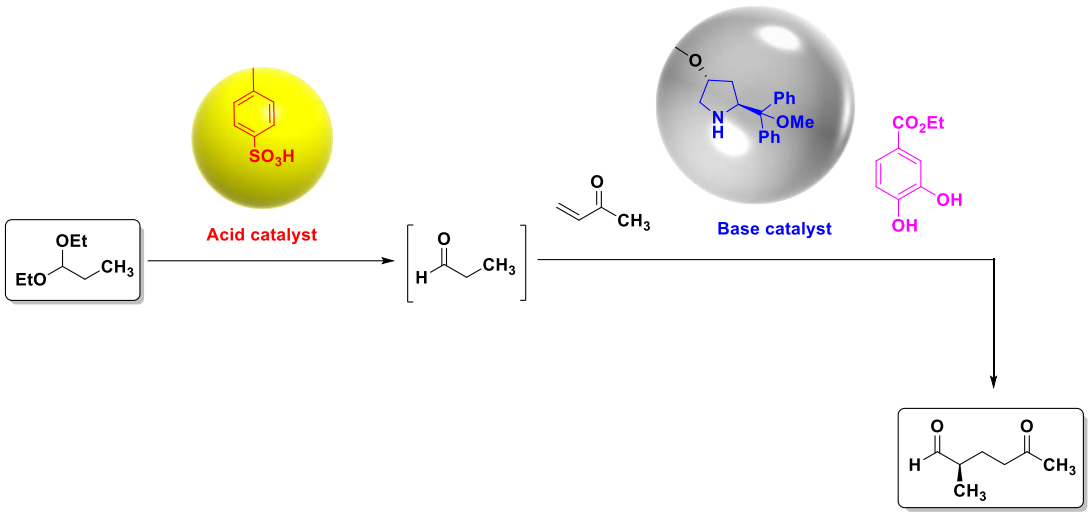
"Site isolation" is a very effective way for allowing multiple catalysts to operate independently, wherein the incompatible catalysts are spatially separated from each other to avoid undesired reaction among them. Site isolation can be achieved by using sol-gel materials,[8-11] polymers,[12-22] pickering emulsions,[23] and micelles.[24-28] Although several research groups have reported one-pot reactions based on site isolation, in

particular, Fréchet and coworkers have succeeded in three successive one-pot reactions by using two star-branched polymers in which an acid and a base catalysts are incorporated independently into the core of the star polymers.[14] The same research group further reported the synthesis of two stars-branched polymers, each containing acid groups and base group in its core and applied to a one-pot two-step deacetalization-Baylis-Hillman reaction.[15] The results clearly showed that encapsulation of acidic and basic catalysts within the highly branched star polymer suppresses their mutual deactivation, providing a site-isolated reaction system. Using the star-branched polymer, the concept of site isolation provided a new tool for designing the catalysts with the contrary property. Although the star-branched polymers are effective as site isolating material, this method requires complicated synthesis because the chain length and the arm number of these star-branched polymers must be precisely controlled. C. W. Jones et al. reported the synthesis acid and base bifunctional shell crosslinked micelle nanoreactor for one-pot deacetalization-nitroaldol condensation reaction sequences.[24] The bifunctional acid-base shell crosslinked micelle catalyzed the one-pot reaction with a good yield. Nevertheless, the synthesis procedure of micelle-immobilized acid and base catalysts with contrary properties is quite challenging due to the micelle's inherent instability and dynamic nature. So, developing a general method that can effectively perform one-pot catalytic reactions based on site isolation is strongly desired.

Although different site isolating materials are available, crosslinked polymer microspheres can be one of the promising candidates as a site isolating material for incompatible catalysts. Polymer microspheres are spherical polymer particles having a diameter from micrometer to several micrometer ranges. They possess exciting features such as large specific surface area, high mechanical strength, high dispersibility, simple separation process, low swelling tendency, and accessible synthesis method.[29] Previously, our research group successfully synthesized core-shell, core-corona, and uniform-type polymer microsphere-immobilized chiral catalysts and applied them to different asymmetric chemical transformations in the batch reaction systems.[29-32] The polymeric chiral catalysts catalyzed those different asymmetric transformations with excellent yield and enantioselectivity. Despite having numerous interesting features of crosslinked polymer microspheres, there is no research report where polymer microspheres have been used as site isolating materials for the incompatible catalysts. In this work, we have tried to circumvent the synthesis complexity for the site isolation of

the acid and base catalyst's active sites and establish an easy reaction system for the one-pot reactions based on site isolation.

Herein, we describe the synthesis of crosslinked polymer microsphere-immobilized sulfonic acid by simple precipitation polymerization and apply them to a one-pot deacetalization-asymmetric Michael addition reaction sequence in conjugation with crosslinked polymer microsphere-immobilized chiral pyrrolidine catalysts (synthesized in Chapter II). The ultimate objective of this research is to establish a one-pot reaction system based on site isolation using polymer microsphere as a new site isolating material and which leads to a highly efficient organic synthetic process from the viewpoint of labor-saving of isolation, purification of the product, time-saving, and energy-saving. High site isolation efficiency can be expected due to the steric hindrance and electrical repulsion of the crosslinked polymer microsphere. A precisely designed polymer microspheres polymer network provides a microenvironment for asymmetric reactions. It is expected that the reaction rate of one-pot synthesis and the stereoselectivity can be improved by the polymer network. Since the isolation and purification of the intermediate product can be omitted by a one-pot reaction, chemicals, energy, and time can be saved. To the best of our knowledge, there is no report where crosslinked polymer microspheres have been used as site-isolating particles to design acid and base organocatalysts. The polymer microsphere-immobilized catalysts were characterized by SEM, FT-IR, and elemental analysis. To demonstrate the site-isolation efficiency of the crosslinked polymer microspheres, the one-pot two-step deacetalization-asymmetric Michael addition reaction was carried out (Scheme 3.1). The effect of molar ratio, catalyst loading, H_2O, additive, amount of MVK (methyl vinyl ketone), solvent, and hydrophobic-hydrophilic nature of the polymer microsphere-immobilized pyrrolidine catalysts, and recyclability test was investigated on the reaction course in detail.

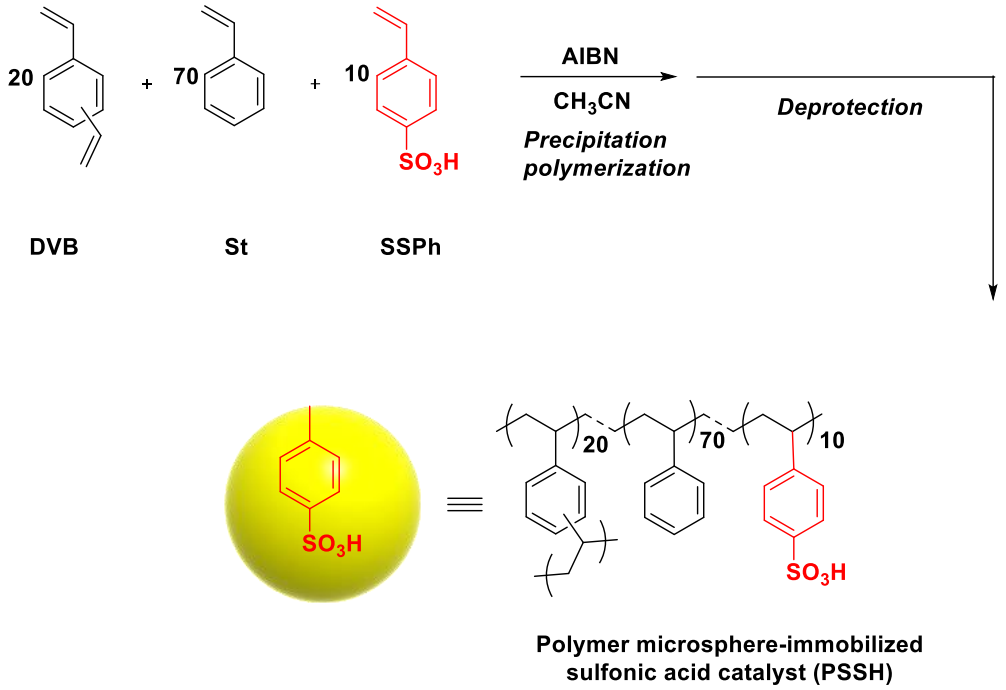


Scheme 3.1 One-pot deacetalization-asymmetric Michael addition reaction based on site isolation.

3.2 Results and Discussion

*3.2.1 Synthesis of polymer microsphere-immobilized sulfonic acid catalyst (**PSSH**)*

The crosslinked polymer microspheres-immobilized sulfonic acid catalyst **PSSH** was prepared by the precipitation polymerization of DVB as a crosslinker, styrene, and styrene monomer having phenyl group protected sulfonic acid moiety **SSPh** and followed by the deprotection reaction (Scheme 3.2). The molar ratio of DVB/St/**SSPh** was set to 20/70/10 mol%, respectively. From the SEM image of polymer microsphere-immobilized sulfonic acid catalyst (**PSSH**), it was apparent that all the microspheres are spherical (Figure 3.1). The number average diameter (D_n) of **PSSH** was found to be to1.02 μm. The polydispersity (U) of the **PSSH** was 1.01, indicating highly monodisperse polymer microsphere-immobilized sulfonic acid catalysts were obtained.



Scheme 3.2 Synthesis of polymer microsphere-immobilized sulfonic acid catalyst (**PSSH**).

The sulfur (S) content within the polymer microspheres was repeatedly measured by the sulfur titration method (2.79%) was in close agreement with that of the calculated value (2.73%). Furthermore, from the FT-IR spectrum of **PSSH**, the characteristic absorption peaks of >S=O were found at 1177 and 1217 cm^{-1} (Appendix B), confirming the successful incorporation of the sulfonic acid moiety into the polymer microspheres.

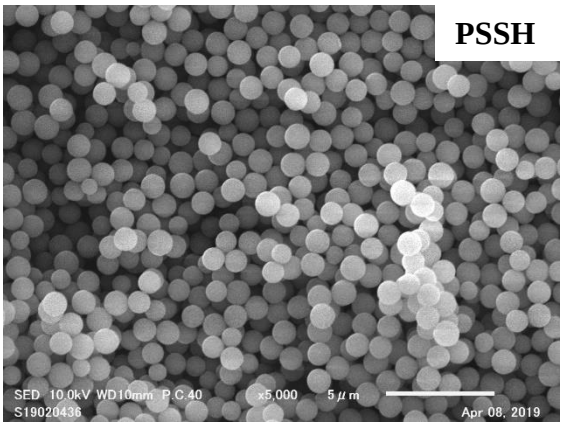


Figure 3.1 SEM images of the polymer microsphere-immobilized sulfonic acid catalyst (**PSSH**).

3.2.2 One-pot deacetalization-Michael addition reaction

Several types of acid and base catalysts such as low molecular acid catalyst *p*-toluenesulfonic acid (***p*-TSA**), linear polymer-immobilized sulfonic acid catalyst (**Linear-SH**), polymer microsphere immobilized sulfonic acid catalyst **PSSH**, low-molecular-weight chiral pyrrolidine catalyst (**Mb**), polymer microsphere-immobilized chiral pyrrolidine catalysts **PS3**, and **PS4** were applied to the one-pot deacetalization-asymmetric Michael addition reaction sequence to check the site isolation efficiency of the various acid and base catalysts pair (Figure 3.2). The first step of the reaction involves the deacetalization of propionaldehyde diethyl acetal catalyzed by sulfonic acid moiety in the presence of water to form intermediate compound propionaldehyde and the formation of ethanol as the by-product.

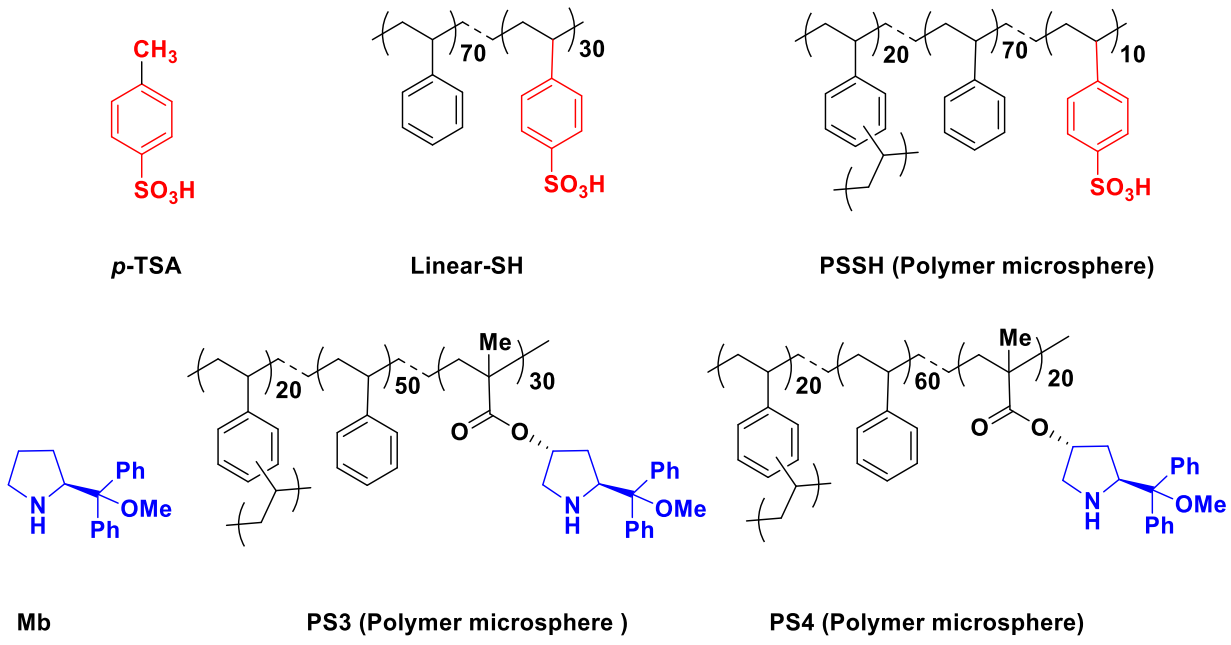


Figure 3.2 Several types of sulfonic acid and chiral pyrrolidine catalyst's structure.

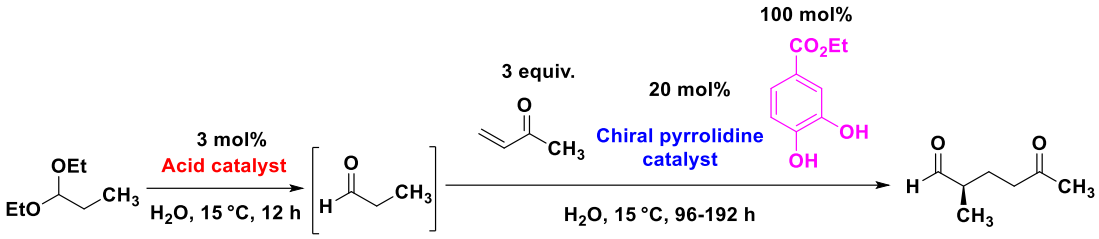


Table 3.1 Effect of acid and base catalysts on the one-pot deacetalization-Michael addition reaction sequence.[a]

Entry	Sulfonic acid catalyst	Pyrrolidine catalyst	Yield (%)[b]	ee (%)[c]
1	***p*-TSA**	**Mb**	81	0
2	***p*-TSA**	**PS3**	9	nd[d]
3	**Linear-SH**	**PS3**	75	18
4	**PSSH**	**PS4**	76[e]	83

[a] Reaction conditions: In a Schlenk test tube equipped with a magnetic stir bar, 0.50 mmol propionaldehyde diethyl acetal, 3 mol% acid catalyst, and 5 equiv. of H_2O was charged and stirred at 15 °C for 12 h; After 12 h, 20 mol% pyrrolidine catalyst, 100 mol% ethyl 3,4-dihydroxy benzoate, and 3 equiv. of MVK were added to the same reaction mixture. The reaction mixture was stirred at 15 °C for 192 h under Ar.

[b] Overall yield determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

[d] nd stands for not determined.

[e] Yield after 96 h.

The second step is the asymmetric Michael addition reaction between the intermediate compound propionaldehyde and methyl vinyl ketone in the presence of cocatalyst ethyl 3,4-dihydroxy benzoate in the absence of any additional solvent to produce the chiral product (*R*)-2-methyl-5-oxohexanal. The asymmetric Michael addition reaction proceeds via nucleophilic activation between the intermediate aldehydes (enamine formation) and chiral pyrrolidine catalyst.[33] The role of cocatalyst ethyl 3,4-dihydroxybenzoate is to electrophilically activate the unmodified enone (MVK) via hydrogen bond donation to the carbonyl oxygen.[34,35] The results have been summarized in Table 3.1. The low-molecular-weight ***p*-TSA** and pyrrolidine catalyst **Mb** were applied to the one-pot reaction and the overall yield of the reaction was 81%, with a complete racemized product (Entry 1). In entry 2, when the ***p*-TSA** and polymer microsphere-immobilized pyrrolidine catalyst **PS3** were applied to the reaction, the yield of the reaction was very

low due to the reaction of ***p*-TSA** with the -NH group of the pyrrolidine catalyst in **PS3**. The undesired reaction among the active sites of both catalysts diminished the catalytic efficiency of the pyrrolidine catalyst to catalyze the asymmetric Michael addition reaction in the second step. The linear polymer-immobilized sulfonic acid catalyst **Linear-SH** and **PS3** catalysts pair proceeded the reaction with 75% overall yield and 18% ee in entry 3. The lower enantioselectivity may result from unwanted interference of the linear polymer immobilized sulfonic acid with the chiral base catalyst **PS3** in the second step, indicating the incomplete site isolation of the active acid sites by the linear polymer. In entry 4, when both the acid and base catalysts are the crosslinked polymer microsphere-immobilized then a good overall yield (76%), and ee (83%) were observed within the short reaction time (96 h). The crosslinked polymer network and the 3D structure of the polymer microspheres provide a strong steric shield to prevent the mutual deactivation among the acid and base catalyst sites. The steric hindrance created by the polymer microspheres contributes to increasing the ee of the produced chiral product. Thus, polymer microsphere-immobilized acid catalyst (**PSSH**) and chiral base catalyst (**PS4**) pair provide a site-isolated reaction system with high efficiency.

Table 3.2 Effect of molar ratio **2**, catalyst loading, and H_2O amount on one-pot deacetalization-Michael addition reaction sequence.[a]

Entry	Catalyst	Catalyst loading (mol%)	H_2O (equiv.)	DVB/St/2 (mol%)	Yield (%)[b]	ee (%)[c]
1	**PS4**	20	5	20/60/20	76	83
2	**PS3**	20	5	20/50/30	82	91
3	**PS5**	20	5	20/40/40	74	86
4	**PS3**	15	5	20/50/30	47	92
5	**PS3**	5	5	20/50/30	29	92
6	**PS3**	20	7	20/50/30	71	86
7	**PS3**	20	15	20/50/30	71	85

[a] Reaction conditions: In a Schlenk test tube equipped with a magnetic stir bar, 0.50 mmol propionaldehyde diethyl acetal, 3 mol% **PSSH,** and 5 to 15 equiv. of H_2O was charged and stirred at 15 °C for 12 h; After 12 h, 5 to 20 mol% chiral pyrrolidine catalyst, 100 mol% ethyl 3,4-dihydroxy benzoate, and 3 equiv. MVK was added to the same reaction mixture. The reaction mixture was stirred at 15 °C for 96 h under Ar.

[b] Overall yield determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

The effect of the molar ratio of chiral pyrrolidine monomer **2** within the microsphere on the catalytic activity of the polymeric catalysts has been evaluated by applying them to the one-pot reaction. The results have been summarized in Table 3.2. It was observed that, with the increasing molar ratio of monomer **2**, the reactivity and enantioselectivity of the polymer microsphere-immobilized pyrrolidine catalysts increased (Entries 1 and 2). This enhanced reactivity could be due to the increment of the density of pyrrolidine moiety within the polymer microsphere. On the other hand, the overall yield of the reaction slightly decreased in entry 3, where the density of chiral pyrrolidine moiety is maximum. The slightly lower yield results from the catalysts crowding created by the pyrrolidine moiety within the microspheres in the case of **PS5**. Among all the three types of chiral polymeric catalysts, the catalyst **PS3** showed the best reactivity and enantioselectivity.

The effect of the catalyst loading was also investigated on the overall yield and enantioselectivity of the one-pot reaction using **PS3**. The catalyst amount was reduced from 20 mol% to 5 mol%. The overall yield of the reaction was decreased proportionally with the decreasing of the catalyst amount due to decreasing of available active catalytic sites within the microsphere-immobilized pyrrolidine catalyst (Entries 1, 4, and 5). Initially, 5 equivalent of H_2O was used to carry out the deacetalization reaction of propionaldehyde diethyl acetal by polymer microsphere-immobilized sulfonic acid catalyst **PSSH**. The excess amount of water 7 and 15 equiv. was used in the reaction (Entries 6 and 7). The overall yield and enantioselectivity of the reaction were found almost identical for 7 and 15 equiv. of H_2O, but lower than 5 equiv. H_2O in entry 2. The catalyst **PSSH** is hydrophobic, so the presence of a large amount of water retards the efficiency of the catalysts by creating restricted dispersion into the reaction medium. The increase of H_2O also facilitates the insolubility of cocatalyst ethyl 3,4-dihydroxy benzoate in the reaction medium. As a result, lower overall yield and enantioselectivity were observed in 7 and 15 equiv. of H_2O.

The role of additives is to activate the enone MVK via hydrogen bond formation to the carbonyl oxygen. Several additives capable of forming a hydrogen bond with MVK were applied to the reaction system (Table 3.3). Propionic acid and trifluoracetic acid were used as additives, and the reaction's overall yield was very low (Entries 1 and 2). In

the presence of H_2O, propionic acid and trifluoroacetic acid are acting as an acid, and probably reacting with the -NH group of the **PS3.** This undesired acid-base reaction diminished the catalytic activity of the pyrrolidine catalyst **PS3** to catalyze the asymmetric Michael addition reaction. The aromatic acids were also used as additives. The reaction yield slightly increased with lower enantioselectivity (Entries 3 and 4). The ester-type additive ethyl 3,4-dihydroxy benzoate was used as an additive in entry 5. The overall yield and enantioselectivity were significantly increased. The improvement of yield and enantioselectivity of the reaction is due to the chemical nature of ethyl 3,4-dihydroxy benzoate. It was found that the ester type ethyl 3,4-dihydroxy benzoate functions as a suitable additive for this type of acid-base one-pot reaction. Further, the amount of ethyl 3,4-dihydroxy benzoate was reduced from 100 mol% to 50 mol%. The reaction yield was also reduced to nearly 50% (Entry 6), indicating 100 mol% additives is the optimized amount for the reaction.

Table 3.3 Effect of additive on one-pot deacetalization-Michael addition reaction sequence.[a]

Entry	Additive	Yield (%)[b]	ee (%)[c]
1	Propionic acid	6	nd[d]
2	Trifluoroacetic acid	4	nd[d]
3	Benzoic acid	62	74
4	2,5 dihydroxybenzoic acid	32	27
5	Ethyl 3,4-dihydroxy benzoate	82	91
6[e]	Ethyl 3,4-dihydroxy benzoate	43	86

[a] Reaction conditions**:** In a Schlenk test tube equipped with a magnetic stir bar, 0.50 mmol propionaldehyde diethyl acetal, 3 mol% **PSSH**, and 5 equiv. of H_2O was charged and stirred at 15 °C for 12 h; After 12 h, 20 mol% pyrrolidine catalyst **PS3**, 100 mol% of each additive, and 3 equiv. MVK was added to the same reaction mixture. The reaction mixture was stirred at 15 °C for 96 h under Ar.

[b] Overall yield determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

[d] nd stands for not determined.

[e] 50 mol% ethyl 3,4-dihydroxy benzoate.

Table 3.4 Effect of MVK amount on one-pot deacetalization-Michael addition reaction sequence.[a]

Entry	MVK (equiv.)	Yield (%)[b]	ee (%)[c]
1	1.5	68	82
2	3	82	91
3	6	95	85
4[d]	6	21	89
5[e]	6	66	90

[a] Reaction conditions: In a Schlenk test tube equipped with a magnetic stir bar, 0.50 mmol propionaldehyde diethyl acetal, 3 mol% **PSSH**, 5 equiv. of H_2O was stirred at 15 °C for 12 h; After 12 h, 20 mol% pyrrolidine catalyst **PS3**, 100 mol% of ethyl 3,4-dihydroxy benzoate, and 1.5 to 6 equiv. MVK were added to the same reaction mixture. The reaction mixture was stirred at 15 °C for 96 h under Ar.

[b] Overall yield determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

[d] Reaction was carried out at 4 °C.

[e] 15 mol% **PS3** were used.

The effect of MVK on the reaction yield and enantioselectivity was examined using 1.5-6 equiv. of MVK (Table 3.4 and Entries 1-3). It was observed that the yield and enantioselectivity of the reaction increased with the increase of MVK amount (Entry 2). Further, with the increasing MVK amount, the overall yield of the reaction increased, but enantioselectivity was lowered in entry 3. The reason of decreasing of enantioselectivity is still unknown. In entry 4, the reaction was carried at 4 °C with 6 equiv. MVK, and the yield significantly decreased due to the low temperature. Finally, reducing the catalyst amount to 15 mol% in entry 5 found a low yield but almost identical enantioselectivity comparable with entry 2. From the above result, it was observed 3 equiv. of MVK providing the best result for this one-pot reaction system.

The polarity of the solvents significantly affects the reactivity of the catalysts. Here, the catalyst **PS3** is hydrophobic. Polar solvents create an unfavorable environment to disperse the catalyst **PS3** in the reaction medium. In the case of highly polar solvents EtOH, the yield of the reaction was very low, and the reverse reaction of deacetalization was experienced (Table 3.5 and entries 1, 2, and 5). The reason of the reverse reaction could be explained by Le Chatelier's principle on the equilibrium state of a reversible

reaction. The deacetalization process is a reversible equilibrium reaction, and in the deacetalization step, EtOH is produced as a by-product. The addition of EtOH as solvent increased the concentration of EtOH, favoring the backward reaction. A large amount of propionaldehyde diethyl acetal was found unreacted in the reaction medium at the end of the reaction when EtOH was used as the solvent. When the polarity of solvents gradually decreased, the yield slightly increased in entries 3-4. In entries 5, and 6 the mixture of organic polar and non-polar solvents was used. However, the overall yield of the reaction was slightly increased with the increase of enantioselectivity. From the overall evaluation, we found that the one-pot deacetalization-Michael addition reaction proceeded smoothly with good overall yield and enantioselectivity in the absence of any additional solvents compared to solvent medium (Entry 8). Further, the reaction was carried out at 30 °C in solvent-free condition, the overall yield of the reaction reached 99% after 48 h. However, the enantioselectivity of the chiral product significantly decreased (Entry 9).

Table 3.5 Effect of solvent on one-pot deacetalization-Michael addition reaction sequence.[a]

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1[d]	EtOH	2	nd[e]
2	EtOH	8	84
3	CH_3CN	33	84
4	$CHCl_3$	34	92
5	Toluene/EtOH (50/50, v/v)	14	91
6	Toluene/^{i}PrOH (95/5, v/v)	38	92
7	Et_2O	5	nd[e]
8	none	82	91
9[f]	none	99	46

[a] Reaction conditions: In a Schlenk test tube equipped with a magnetic stir bar, 0.50 mmol propionaldehyde diethyl acetal, 3 mol% **PSSH,** 5 equiv. of H_2O was charged and stirred at 15 °C for 12 h; After 12 h, 20 mol% pyrrolidine catalyst **PS3**, 100 mol% each additive, 3 equiv. MVK, and 0.20 mL of each solvent were added to the same reaction mixture. The reaction mixture was stirred at 15 °C for 96 h under Ar.

[b] Overall yield determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

[e] nd stands for not determined.

[d] Reaction was carried out using 0.50 mL EtOH.

[f] Reaction was carried out at 30 °C, and yield after 48 h.

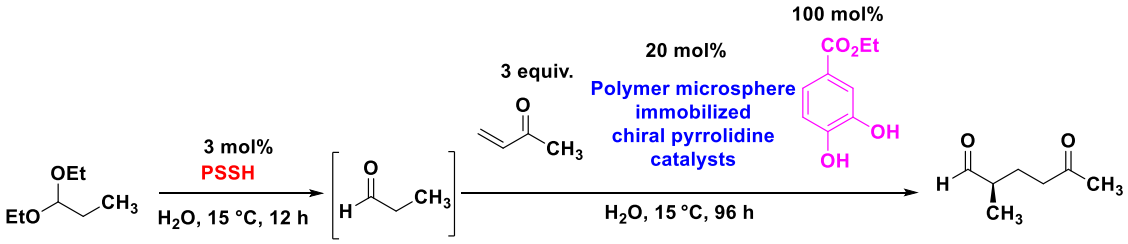


Table 3.6 Effect of comonomer on one-pot deacetalization-Michael addition reaction sequence.[a]

Entry	Prolinol catalyst	Comonomer	Yield (%)[b]	ee (%)[c]
1	**PM**	MAA	62	75
2	**PN**	NIPAM	38	50
3	**PH**	HEMA	41	83
4	**PT**	TBMA	85	61
5	**PMS**	4-MS	91	77
6	**PS3**	St	82	91

[a] Reaction conditions: In a Schlenk test tube equipped with a magnetic stir bar, 0.50 mmol propionaldehyde diethyl acetal, 3 mol% **PSSH,** 5 equiv. of H_2O was charged and stirred at 15 °C for 12 h; After 12 h, 20 mol% polymeric chiral pyrrolidine catalysts, 100 mol% ethyl 3,4-dihydroxy benzoate, and 3 equiv. MVK were added to the same reaction mixture. The reaction mixture was stirred at 15 °C for 96 h under Ar.

[b] Overall yield determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR after the imination with (*S*)-1-methoxy-2-propylamine.

The effect of comonomers on the reactivity of the polymeric pyrrolidine catalysts was examined in detail. To investigate the effect of comonomers on the reactivity of the polymeric catalysts, variable hydrophilic and hydrophobic types of comonomers were used for the synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts (discussed in Chapter II). The polymer microsphere-immobilized chiral pyrrolidine catalysts and **PSSH** catalyst pairs were applied to the one-pot reaction two steps reaction system in the absence of any additional solvent. The results have been summarized in Table 3.6. We expected that the hydrophilic types of polymeric pyrrolidine catalysts will

perform the best for this type of acid-base of one-pot reaction due to the presence of H_2O and polar EtOH in the reaction medium. Nevertheless, the hydrophobic type of pyrrolidine catalysts showed good yield and enantioselectivity instead of hydrophilic type catalysts. On the other hand, in entries 1-3, the pyrrolidine catalysts are hydrophilic due to the presence of hydrophilic comonomer showed low yield and low enantioselectivity. As we move from entries 4-6, the overall yield significantly increased when the catalysts are hydrophobic in nature due to the presence of comonomers TBMA, 4-MS, and St, respectively within the microspheres. The hydrophobic types of pyrrolidine catalyst **PMS,** where 4-MS as comonomer showed the maximum yield but low enantioselectivity (Entry 5). Among all the hydrophobic types of catalyst, **PS3** contained styrene as comonomer in entry 6 showed good overall yield 82%, and enantioselectivity 91%. It is observed that the hydrophobic nature of the polymeric pyrrolidine catalysts provides a suitable microenvironment for the substrate molecules to reach the catalytic sites within the polymer microspheres than hydrophilic types of polymeric pyrrolidine catalysts.

The recovery and reuse of the **PSSH** and **PS3** catalysts pair were also performed. The catalysts were recovered from the reaction mixture using THF as a solvent by a simple centrifugation method. The recovered catalysts were washed with THF, MeOH, and acetone repeatedly until the complete removal of ethyl 3,4-dihydroxy benzoate from the microspheres and dried under vacuum at 40 ºC for 24 h. The catalyst pair was further applied to the one-pot reaction sequence. The overall yield and enantioselectivity were almost identical to the fresh catalyst pair (Figure 3.3).

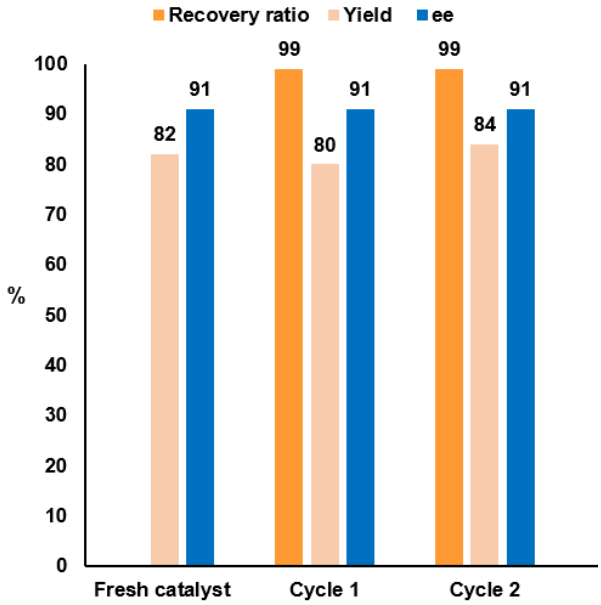


Figure 3.3 Results from trials reusing **PSSH** and **PS3**.

3.3 Conclusion

In this research, we have successfully designed crosslinked polymer microsphere-immobilized sulfonic acid catalysts. The as-prepared polymeric acid and base catalysts (synthesized in Chapter II) were applied to the one-pot reaction. The hydrophobic type of chiral polymeric pyrrolidine catalysts containing styrene as comonomer (**PS3**) showed good reactivity compared to hydrophilic type catalysts. The one-pot reaction proceeded smoothly without any additional solvents compared to the solvent medium. The concept of site isolation is old, but site isolation of the active sites of the two incompatible catalysts using polymer microsphere is new. To the best of our knowledge, this is the first report where polymer microspheres have been used to isolate two antagonist organocatalysts to apply a one-pot deacetalization-Michael addition reaction. This study successfully developed a methodology for a one-pot acid-base asymmetric reaction system based on site isolation using crosslinked polymer microsphere-immobilized acid and base catalysts. This research will substantially expand the chemical toolbox of the site isolation process for the incompatible catalysts with contrary properties.

3.4 Experimental

3.4.1 Materials and reagents

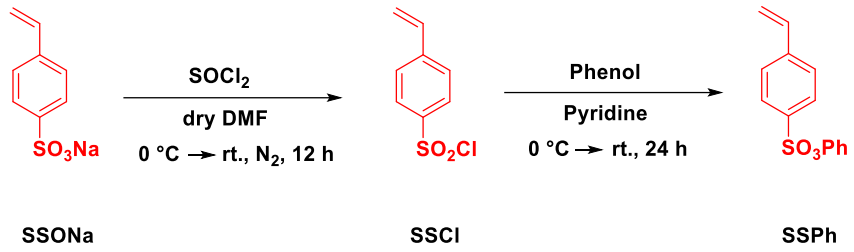
Imidazole (Wako Pure Chemical Industries Ltd., Japan), *N*-(*tert*-Butoxycarbonyl)-*trans*-4-hydroxy-L-proline methyl ester (Tokyo Chemical Industry (TCI) Co., Ltd.), iodomethane (TCI, Japan), *tert*-butyldimethylchlorosilane (TCI, Japan), phenylmagnesium bromide (TCI, Japan), sodium hydride (TCI, Japan), tetra-*n*-Butylammonium Fluoride (TCI, Japan), triethylamine (Wako Pure Chemical Industries Ltd., Japan), methyl vinyl ketone (>95%, TCI, Japan), ethyl 3,4-dihydroxybenzoate (TCI, Japan), (*S*)-1-Methoxy-2-propylamine (99%, Sigma-Aldrich), and propionaldehyde diethyl acetal (97%, Sigma-Aldrich) were used as received. Styrene (Kishida Chemical Co. Ltd., Osaka, Japan), 4-methylstyrene (TCI, Japan), and divinylbenzene (DVB) (Nippon & Sumikin Chemical Co. Ltd., Japan) were washed with aqueous 10% NaOH and water, followed by distilling with CaH_2 under reduced pressure. 2-hydroxyethyl methacrylate (Wako Pure Chemical Industries Ltd., Japan), *tert*-butyl methacrylate (Kishida Chemical Co. Ltd.), and methacrylic acid (TCI, Japan) were distilled under reduced pressure. Methacryloyl Chloride (Wako Pure Chemical Industries Ltd., Japan) was purified by normal distillation. *N*-isopropylacrylamide (TCI, Japan) was recrystallized from a mixture of hexane and acetone (90/10, *v/v*) and dried at a low temperature under a vacuum. Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and dried under a vacuum prior to use.

3.4.2 Measurements

NMR spectroscopy was recorded on JEOL JNM-ECS400 and JEOL JNM-ECX500 spectrometers in $CDCl_3$ or CD_3CN at room temperature. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as a reference, and the *J* values were reported in Hertz (Hz). Reactions were monitored by TLC using Merck precoated silica gel plates (Merck 5554, 60F254). Column chromatography was performed with a silica gel column (Wakogel C-200, 100–200 mesh). FT-IR spectra were recorded with a JASCO FT/IR-230 spectrometer and are reported in reciprocal centimeter (cm^{-1}). Elemental analyses were performed at the Microanalytical Center of Kyoto University. Optical rotations were taken on a JASCODIP-149 digital polarimeter using a 10-cm thermostatted microcell. HRMS (ESI) data were obtained using Bruker micrOTOF II-TTUH spectrometer. SEM measurements were conducted by using JSM-IT100 at an

acceleration voltage of 10.0 kV. Number-averaged diameter (D_n), weight-averaged diameter (D_w), and polydispersity index (U) of polymer microsphere were calculated using SEM images.

3.4.3 Synthesis of phenyl group protected sulfonic acid monomer ***SSPh***



Scheme 3.3 Synthesis of **SSPh**.

In a 100 mL eggplant flask equipped with a magnetic stir bar, 5.0 g, 24.25 mmol sodium *p*-styrenesulfonate (**SSONa)**, dry DMF (7.5 ml) were added and stirred the reaction mixture for five minutes under N_2 at 0 ºC. Then 12.4 mL thionyl chloride ($SOCl_2$) was added very slowly and the resulting reaction mixture was stirred for 12 h. The reaction flask was covered with aluminum foil to prevent the light from passing through it. After 12 h, the product was extracted by using Et_2O (50.0 mL in each time) five times and the product was further washed with Et_2O several times. Finally, the product **SSCl** (5.04 g, 24. 87 mmol, >99% yield) was obtained after removing the solvent under reduced pressure.

^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm) δ = 8.05-7.93 (m, 2H), 7.65 (dd, J = 24.4, 8.2 Hz, 2H), 6.79 (dd, J = 17.4, 11.0 Hz, 1H), 5.99-5.90 (m, 1H), 5.56-5.50 (m, 1H)

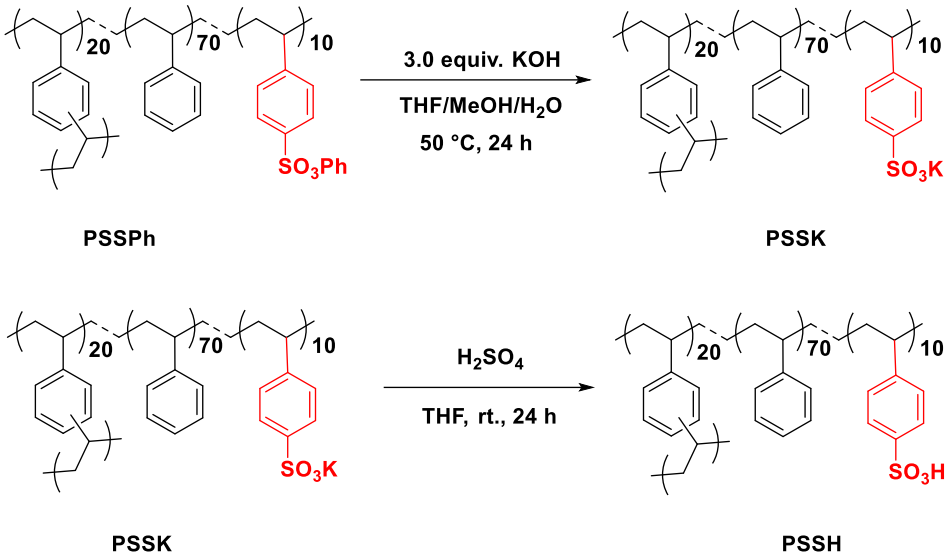
In a 50 mL eggplant flask equipped with a magnetic stir bar charged with phenol (2.34 g, 24.86 mmol) and pyridine (10 mL) and the reaction flask was transferred to the ice bath. Then, **SSCl** (5.0 g, 24.67 mmol) was added to the reaction mixture and the flask was covered with the aluminum foil. The reaction mixture was allowed to stir for 24 h and then, the organic layer was collected using a mixture 105 ml of $CHCl_3$ and 60 ml of HCl and finally, washed with 60 mL of HCl and then 50 mL 5% K_2CO_3 two times in each case. The filtration and the removal of solvent gave the crude product. Next, the crude product was purified through silica-gel column chromatography using a 3:2 (v/v)

mixture of hexane and CH_2Cl_2 as eluent. Finally, the product **SSPh** (2.93 g, 11.26 mmol, 45% yield) was obtained after removing solvents under reduced pressure.

^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm) δ = 7.77 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.52 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.32-7.22 (m, 4H), 7.00-6.97 (m, 2H), 6.75 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.92 (d, *J* = 17.1 Hz, 1H), 5.48 (d, *J* = 11.0 Hz, 1H)

*3.4.4 Synthesis of polymer microsphere-immobilized acid catalyst **PSSH***

A 30 mL HDPE narrow-mouth bottle was charged with DVB (0.21 g, 1.61 mmol), styrene (0.58 g, 5.57 mmol), styrene monomer bearing phenyl group protected sulfonic acid derivative **SSPh** (0.21 g, 0.81 mmol), CH_3CN (29 mL), and AIBN (20 mg, 0.122 mmol, 2 wt% of relative total monomer) under N_2. The mixture was heated in an incubator at a constant temperature of 70 ºC, with rolling the bottle horizontally at 9 rpm for 24 h. The reaction was quenched by adding hydroquinone as an inhibitor, and the reaction mixture was cooled to room temperature. The soluble oligomer and polymer were separated from the insoluble fraction by centrifugation. The insoluble fraction was washed with tetrahydrofuran (THF), methanol (MeOH), and acetone five times repeatedly. The insoluble polymer microspheres were dried under vacuum at 40 °C for 24 h to give white product **PSSPh** (0.45 g, 45% yield). The final polymer microsphere-immobilized sulfonic acid catalyst **PSSH** was obtained by the deprotection of the phenyl group from the polymeric microsphere using the following scheme according to our previously reported literature (Scheme 3.4).[30]



Scheme 3.4 Deprotection of the phenyl group from the sulfonic acid moiety.

3.4.5 Determination of the sulfur (S) content

The sulfur content in polymeric catalyst **PSSH** was determined by oxygen flask method. The method is consisted of a combustion procedure and followed by titrimetric determination. The burning of polymeric catalyst **PSSH** in oxygen yields water soluble sulfur-containing products and which are determined titrimetrically. The combustion procedure was carried out in a conical flask into the stopper, which is fused one end of a piece of platinum wire. The platinum wire provides a means of the holding substance clear of the absorbing liquid during combustion. The absorbing liquid consists of 0.1 M NaOH (1.0 mL), distilled water (3.0 mL), and hydrogen peroxide (10 drops). A small amount of **PSSH** was wrapped in a piece of ashless filter paper, secured the package in the platinum gauze, and inserted one end of a narrow strip of filter paper. The free end of the narrow strip was lightened and immediately inserted into the stopper. After completing the combustion procedure, the flask was shaken continuously for 20 minutes and kept for 20 minutes by placing little water around the rim of the flask. The stopper was withdrawn carefully and rinsed stopper, platinum wire, platinum gauze, and sides of the flask with water. The total solution volume was reduced to 3-4 mL by boiling and cooled to room temperature. Next, the 20 mL EtOH, two drops of bromophenol blue, and 0.1 M HNO_3 were added until the solution became yellow. Finally, six drops of dimethylsulphonazo(III) were added as an indicator and titrated with standardized barium perchlorate solution until the blueish color turned green.

3.4.6 General procedure for one-pot deacetalization asymmetric Michael addition reaction

A Schlenk test tube was charged with propionaldehyde diethyl acetal (0.5 mmol), 3 mol% polymer microsphere-immobilized acid catalyst **PSSH** (0.015 mmol), and H_2O (5 equiv., 2.5 mmol). The reaction mixture was stirred at 15 °C for 12 h. After 12 h, 20 mol% polymers microsphere-immobilized chiral pyrrolidine catalyst (0.1 mmol), 100 mol% ethyl 3,4-dihydroxybenzoate (0.5 mmol), and methyl vinyl ketone (3.0 equiv., 1.5 mmol) were added to the same reaction mixture. The mixture was stirred at 15 ºC for 96 h under Ar. The overall yield of the reaction was measured from the ^{1}H NMR of the crude reaction mixture. The chiral product was extracted from the mixture by centrifugation method using THF three times. Then, THF was removed using rotary evaporator, and the crude product was purified by silica-gel column chromatography (3:1 hexane-ethyl acetate as eluent) to give colorless liquid. The enantiomeric excess (ee) was measured by ^{1}H NMR after imination with the (*S*)-1-methoxy-2-propylamine.[36]

References

[1] P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, **2007**.

[2] A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, **2005**.

[3] I. Ojima. *Catalytic Asymmetric Synthesis* Wiley-VCH, **2000**.

[4] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley Interscience, **1994**.

[5] J. Zhou, *Multicatalyst System in Asymmetric Catalysis*, Wiley, **2015**.

[6] L. F. Tietze, G. Brasche, *Domino Reactions in Organic Synthesis*, Wiley-VCH, **2006**.

[7] G. Szőllősi. *Catal. Sci. Technol.* **2018**, *8*, 389.

[8] F. Gelman, J. Blum, D. Avnir, *J. Am. Chem. Soc.* **2002**, *124*, 14460.

[9] Y. Huang, B. G. Trewyn, H. T. Chen, V. S. -Y. Lin, *New J. Chem.* **2008**, *32*, 1311.

[10] F. Gelman, J. Blum, D. Avnir, *Angew. Chem. Int. Ed.* **2001**, *40*, 3647.

[11] F. Gelman, J. Blum, D. Avnir, *J. Am. Chem. Soc.* **2000**, *122*, 11999.

[12] H. Huang, C. A. Denard, R. Alamillo, A. J. Crisci, Y. Miao, J. A. Dumesic, S. L. Scott, H. Zhao, *ACS Catal.* **2014**, *4*, 2165.

[13] B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Fréchet, *Angew. Chem. Int. Ed.* **2005**, *44*, 6384.

[14] Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322.

[15] B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Fréchet, *Angew. Chem.* **2005**, *117*, 6542.

[16] A. W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem. Int. Ed.* **2007**, *46*, 5428.

[17] S. L. Poe, M. Kobašlija, D. T. McQuade, *J. Am. Chem. Soc.* **2006**, *128*, 15586.

[18] Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100.

[19] Y. Yang, X. Liu, X. Li, J. Zhao, S. Bai, J. Liu, Q. Yang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9164.

[20] R. J. R. W. Peters, I. Louzao, J. C. M. van Hest, *Chem. Sci.* **2012**, *3*, 335.

[21] J. Shi, L. Zhang, Z. Jiang, *ACS Appl. Mater. Interfaces* **2011**, *3*, 881.

[22] M. B. Runge, M. T. Mwangi, A. L. Miller II, M. Perring, N. B. Bowden, *Angew. Chem. Int. Ed.* **2008**, *47*, 935.

[23] H. Yang, L. Fu, L. Wei, J. Liang, B. P. Binks, *J. Am. Chem. Soc.* **2015**, *137*, 1362.

[24] L. -C. Lee, J. Lu, M. Weck, C. W. Jones, *ACS Catal.* **2016**, *6*, 784.

[25] P. Cotanda, N. Petzetakis, R. K. O'Reilly, *Chem. Commun.* **2012**, *2*, 119.

[26] M. Elsabahy, K. L. Wooley, *Chem. Soc. Rev.* **2012**, *41*, 2545.

[27] R. K. O'Reilly, C. J. Hawker, K. L. Wooley, *Chem. Soc. Rev.* **2006**, *35*, 1068.

[28] Y. Liu, Y. Wang, Y. Wang, J. Lu, V. Pinon III, M. Weck, *J. Am. Chem. Soc.* **2011**, *133*, 14260.

[29] N. Haraguchi, A. Nishiyama, S. Itsuno, *J. Polym. Sci. Part A: Polym. Chem.* **2010**, *48*, 3340.

[30] M. W. Ullah, N. Haraguchi, *Catalysts* **2019**, *9*, 960.

[31] M. W. Ullah, N. T. P. Thao, T. Sugimoto, N. Haraguchi, *Mol. Catal*. **2019**, *473*, 110392.

[32] M. W. Ullah, N. Haraguchi, *J. Polym. Sci. Part A: Polym. Chem.* **2019**, *57*, 1296.

[33] P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151.

[34] T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598.

[35] P. R. Schreiner, *Chem. Soc.* Rev. **2003**, *32*, 289.

[36] Y. Chi, S. H. Gellman, Org. Lett. 2005, *7*, 4253

CHAPTER IV

Development of One-pot Multistep Asymmetric Reactions Using Heterogeneous Acid and Base Organocatalysts

4.1 Introduction

Optically active compounds are the key ingredients of active pharmaceutical ingredients and life science products. Organocatalysis has gained considerable attention to prepare active pharmaceutical ingredients from the last few decades in chemistry due to the metal-free catalysis process rather than organometallic complexes.[1-4] The organocatalytic process is appealing for obtaining life science products and active pharmaceutical compounds to avoid metal poisoning with the consequences. On the other hand, the organocatalysis process serves mild and simple reaction conditions that offer easy handling and safety issues following the green chemistry aspect. Undoubtedly, organocatalysis provides some advantages for producing active pharmaceutical compounds. However, sometimes the benefits have been tolerated using a large excess of solvent, reagent, catalyst, and longer reaction time. The aforementioned collective disadvantages of the organocatalysis process arise another issue called chemical waste from the reaction system. It has been reported that for the preparation of 1 kg of active pharmaceutical compounds, on average, 25-100 kg of chemical waste is generated.[5,6] The management of chemical waste is also a vital issue in the chemical industry. In 2005, the U.S. Environmental Protection Agency reported that nearly 25.1 billion pounds of chemical waste were generated from the chemical industry. Only 36% of them (8.96 billion pounds) were recycled.[7] This large amount of non-recycled chemical waste is a significant threat to the natural environment. The development of an efficient and straightforward reaction process is inevitable to reduce the production of chemical waste generation.

The one-pot reaction process can be one of the sustainable reaction paths to minimize the chemical waste generated from the reaction system. In a one-pot reaction system, multiple reactions are carried out sequentially to produce the desired final product without the isolation of intermediate and thus help save energy, labor, time, and reagents. Thus one-pot reaction systems provide significant benefits to the chemical world, lowering the adverse effect of chemical waste.[8-17] Jørgensen and his

research group reported the synthesis of optically active 2,5-disubstituted-cyclohexen-2-one derivatives from the reaction between *β*-ketoester and *α,β*-unsaturated aldehyde in a one-pot five steps process by using 2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyl-oxymethyl]pyrrolidine and *p*-toluenesulfonic acid (*p*-TSA) as the catalysts.[18] The chiral pyrrolidine derivative facilitated the Michael addition of *β*-ketoester to *α,β*-unsaturated aldehyde, and the Brønsted acid *p*-TSA catalyzed the remaining four steps to synthesize chemically important optically active 2,5-disubstituted-cyclohexen-2-one derivative in good yield and enantiomeric excess (ee) without the use of large excess of reagent and solvent. The reaction system offers an extended range of substrate applicability. Córdova and his research group developed an asymmetric tandem oxa-Michael/aldol condensation reaction sequence to synthesize chromene derivatives using chiral pyrrolidine derivative and 2-nitrobenzoic acid catalyst and cocatalyst, respectively.[19] The reaction proceeded by the oxa-Michael addition of the *α,β*-unsaturated aldehyde to salicylic aldehyde and followed by an intermolecular aldol condensation reaction to synthesize the chromene derivatives with good yield and enantioselectivity. The desired chromene derivatives were obtained with very low yield (10%) and enantioselectivity (9%) without cocatalyst 2-nitrobenzoic acid. However, the presence of cocatalyst significantly prompted the reaction yield and enantioselectivity (88%). Alexakis and his group reported an asymmetric one-pot organocatalytic Michael addition/gold-catalyzed tandem acetalization/cyclization reaction process to obtain nitro-substituted tetrahydrofuranyl ethers with excellent diastereo- and enantioselectivities.[20] The desired nitro-substituted tetrahydrofuranyl ethers were obtained by the enantioselective organocatalytic Michael addition of aldehydes to nitroenyne catalyzed by diphenylprolinol silyl ether and followed by tandem acetalization/cyclization reaction catalyzed by a gold catalyst and *p*-TSA as additive. A slight excess of *p*-TSA relative to diphenylprolinol silyl ether was required to proceed with the response. It was found that no reaction occurred when the amount of organocatalyst diphenylprolinol silyl ether exceeded that of *p*-TSA. The slight excess of *p*-TSA helps prevent the gold catalyst's deactivation by coordinating to the nitrogen atom of the diphenylprolinol silyl ether. Hayashi and his colleagues reported the synthesis of functionalized cyclic 1,3-diene derivatives with good yield and excellent enantioselectivity by a one-pot six-step reaction process using diphenylprolinol silyl ether and (ethyl 2-(triphenylphosphoranylidene)acetate) as a

catalyst in presence of benzoic acid.[21] The reaction proceeded with the vinylogous Michael addition, hydration, and oxy-Michael reaction to produce tetrahydrochromate derivative and followed by retro oxy-Michael reaction, isomerization, and Wittig reaction. The reaction systems provided a wide range of substrate applicability to form the desired products on a large scale.

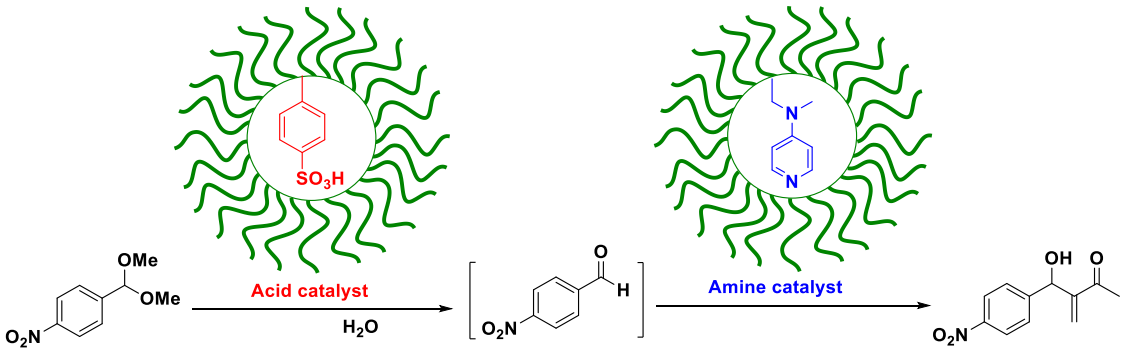
Although several research articles on one-pot reactions have been reported in the field of organic synthesis, one of the limitations is that multiple catalysts with contrary properties (e.g., acidic and basic, oxidative and reductive) cannot be used simultaneously in the same reaction vessel. The catalysts with opposite properties in the one-pot reaction course react with each other and thus diminish their catalytic performances to catalyze the desired reaction. Site isolation is one of the effective ways to operate multiple catalysts independently, in which the active sites of contrary catalysts are spatially separated in such a way so that they cannot interact with each other. However, the substrate molecules can reach the active sites. Several types of site-isolating materials are available to achieve site isolation of the active sites of the catalysts, such as micelles,[22-26] pickering emulsions,[27] sol-gel materials,[28-31] and polymers.[32-40] Different research groups reported one-pot reactions based on site-isolation, in particular, Fréchet and his colleagues have succeeded in one-pot two-step deacetalization-Baylis-Hillman reaction reactions by using two star-branched polymers in which an acid and a base catalyst were incorporated independently into the core of the star polymers (Scheme 4.1).[41] The arms of the star polymer provided steric hindrance to suppress the mutual interaction between active sites of acid and base catalysts, thus providing high site-isolation efficiency. Although star polymer incorporated acid-base catalysts provide good site isolation performance, the synthesis procedure of star polymer is quite complex. Even the arms number of the star polymer must be precisely controlled to achieve good site isolation efficiency. So, developing a general method that can efficiently synthesize site isolated catalysts and smoothly perform catalytic one-pot site-isolated reactions is strongly desired.

The different site isolating materials are available, but polymer microspheres can be one of the promising candidates for the site isolation of the catalysts with contrary properties. Polymer microspheres possess exciting features such as large specific surface area, high mechanical strength, high dispersibility, a simple separation process,

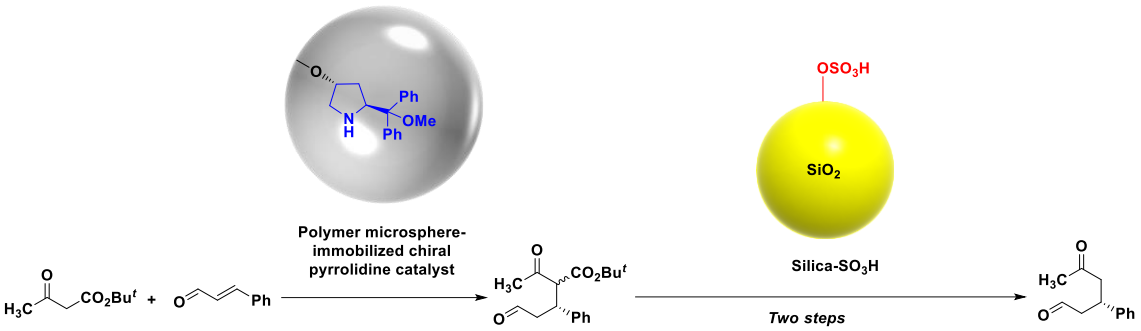
and an easy preparation method.[42] High site isolation could be achieved due to the steric hindrance and electrical repulsion of the crosslinked polymer network.

On the other hand, silica-immobilized acid-base catalysts are also used as an efficient catalyst for the one-pot tandem reactions.[43] The silica-immobilized catalysts provide some advantages such as low coast, avoidance of polymeric swelling, and providing a free-flowing solid of ease handling.[44] Using the silica gel, it is possible to immobilize the large amount of acid or base content within silica gel microspheres, which is quite difficult for polymer microspheres. These exciting collective features make the silica particles a promising solid-support material for heterogenization of low-molecular-weight catalysts.

Herein, we report a one-pot three-step asymmetric transformation to synthesize optically active compounds using polymer microsphere-immobilized chiral pyrrolidine catalysts and silica gel -immobilized acid catalysts under the green chemistry principles (Scheme 4.2). The acid and base catalysts pair was applied to a one-pot three-step asymmetric synthesis and the catalyst pair was able to produce the chiral compound with good overall yield (70%) and enantioselectivity (89%). This research introduces a practical, flexible, and efficient chemical route to prepare optically active compounds based on site isolation where the base catalysts are immobilized within the microspheres and the acid catalysts are immobilized on the surface of the silica microspheres.



Scheme 4.1 One-pot reaction using star-branched polymer-immobilized acid and base organocatalysts.

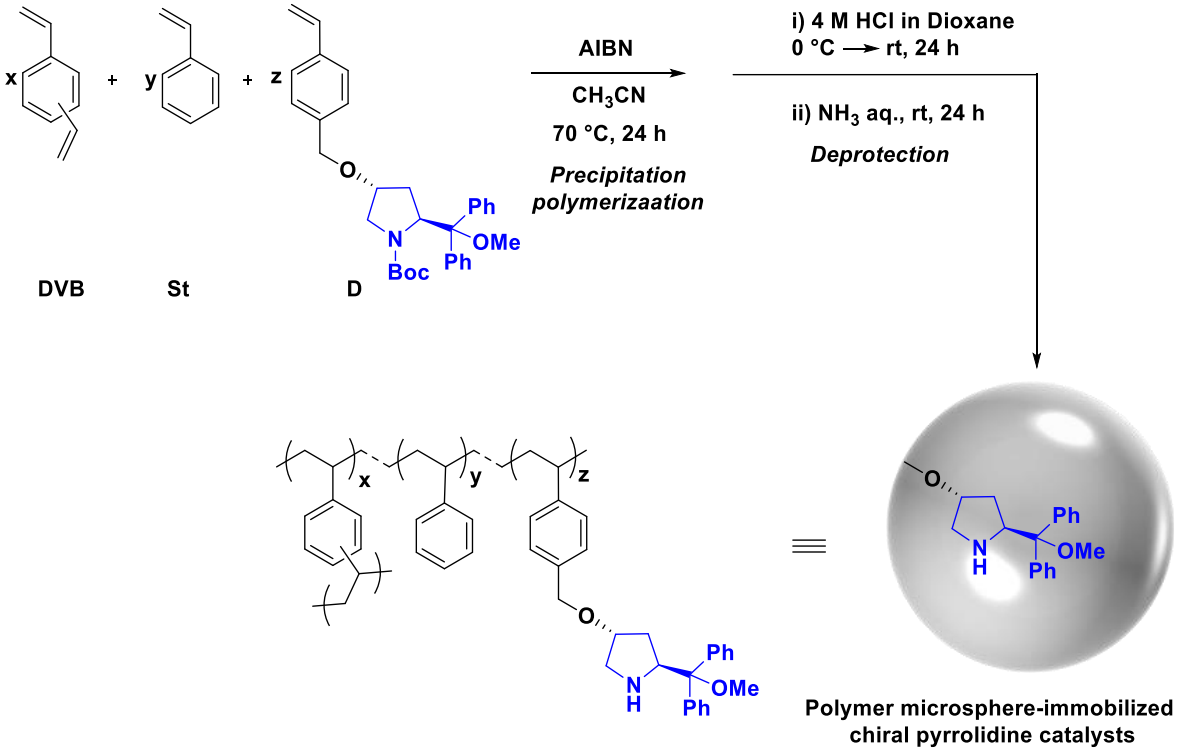


Scheme 4.2 One-pot multistep reaction using acid and base catalysts.

4. 2 Results and Discussion

4.2.1 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts

Polymer microsphere-immobilized chiral pyrrolidine catalysts were prepared by the precipitation polymerization and followed by the removal of the *N*-Boc group (Scheme 4.3). In the synthesis, DVB was used as a crosslinker, St as comonomer, and vinyl benzyl ether bearing chiral prolinol derivative **D**. In every microsphere, the molar ratio of DVB was kept constant, and the molar ratio of St and **D** were changed.



Scheme 4.3 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts.

Table 4.1 Characterization of polymer microsphere-immobilized chiral pyrrolidine catalysts.

Entry	Polymer	x/y/z (mol%)	D_n (μm)[a]	U[a]
1	**M10**	20/70/10	1.99	1.22
2	**M20**	20/60/20	3.14	1.33
3	**M30**	20/50/30	4.08	1.14

[a] Determined from SEM images.

The results of the polymerization have been summarized in Table 4.1. The isolated yield of the polymer microsphere-immobilized chiral pyrrolidine derivatives was moderate (20%-26%) due to using the minimum amount of DVB in each polymer microsphere. The yield of the isolated polymer microsphere can be improved by increasing the molar ratio of DVB.

The number average diameter of the polymeric particles was calculated using SEM images acquired over areas with sizes in the micrometer (μm) range. Almost identical diameters were observed before and after the removal of the *N*-Boc group. The uniform and spherical material in each case from the SEM images confirm the successful incorporation of the chiral prolinol moiety into the microspheres (Figure 4.1). The FT-IR spectra obtained from the **M10** before, and removal of *N*-Boc groups are shown in Appendix C. The characteristic absorption peak at 1698 cm^{-1} attributed to C=O bonds in the *N*-Boc confirming the successful polymerization of the prolinol monomer **D**. The disappearance of the peak at 1698 cm^{-1} after the deprotection reaction confirmed the successful removal of the *N*-Boc group from the prolinol catalyst moiety. These results indicate that the precipitation polymerization and the deprotection reaction afforded the desired polymer microsphere-immobilized chiral pyrrolidine catalysts.

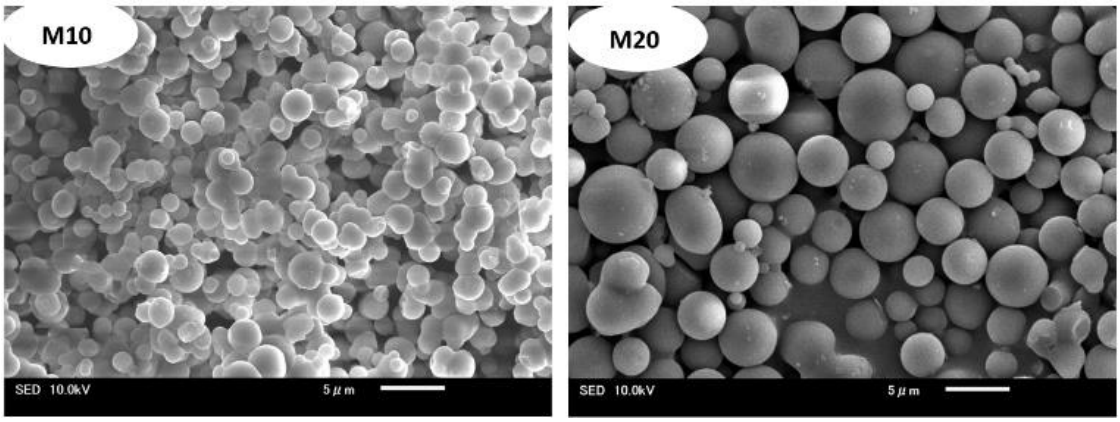
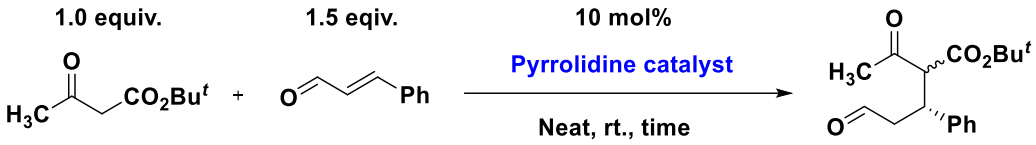


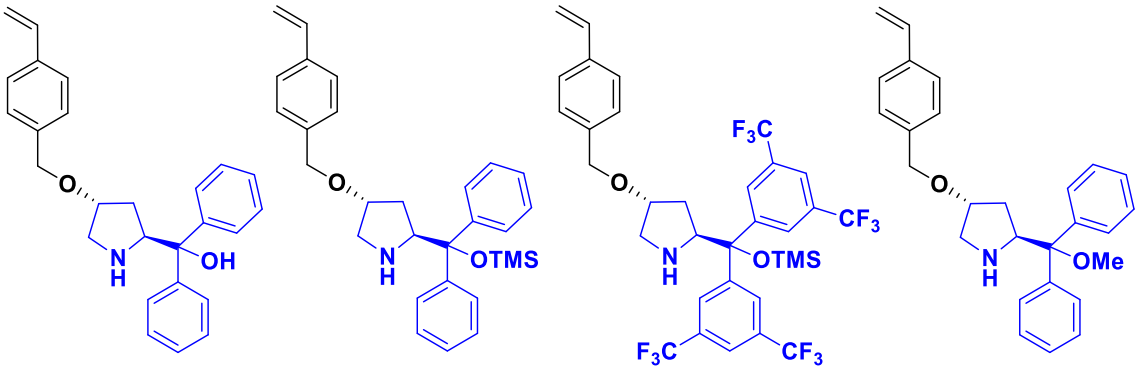
Figure 4. 1 SEM images of polymer microsphere-immobilized chiral pyrrolidine catalysts.

4.2.2 Asymmetric Michael addition reaction using low-molecular-weight chiral pyrrolidine catalysts

The optimization of the chiral pyrrolidine catalysts was started with the asymmetric Michael addition reaction between *tert*-butyl acetoacetate and *trans*-cinnamaldehyde under the solvent-free neat condition at room temperature. Only 8% Michael adduct was obtained when the chiral pyrrolidine catalyst **A** was employed in the reaction (Table 4.2, Entry 1). The reaction smoothly proceeded with the excellent yield (97%) and enantioselectivity (98%) of the Michael adduct using catalyst **B** (Entry 2). The chiral pyrrolidine catalysts **C** and **D** were also provided nearly the identical enantioselectivity as of catalyst **B**. Although the catalysts **B**, **C**, and **D** showed almost identical enantioselectivity, the diphenylprolinol methyl ether **D** showed slightly higher reactivity than other catalysts (Entry 4). Therefore, catalyst **D** was further used as a polymerizable chiral pyrrolidine derivative to prepare polymer microsphere-immobilized chiral pyrrolidine catalysts and employed them to organocatalytic asymmetric Michael addition reaction and one-pot reaction sequences based on site isolation.

Table 4.2 Organocatalytic asymmetric Michael addition reaction.[a]





A B C D

Entry	Pyrrolidine catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**A**	12	8	nd[d]
2	**B**	12	97	98
3	**C**	12	82	99
4	**D**	8	98	97

[a] All the reactions were carried out on a 0.25 mmol scale under solvent-free conditions at room temperature.

[b] Determine by ^{1}H NMR.

[c] Enantiomeric excess determined by chiral GC-analysis after hydrolysis and decarboxylation of the Michael adduct.

[d] nd stands for not determined.

4.2.3 Asymmetric Michael addition reaction using polymer microsphere-immobilized chiral pyrrolidine catalysts

The catalytic efficiency of the polymer microsphere-immobilized chiral pyrrolidine catalysts was further evaluated by the asymmetric Michael addition reaction between *tert*-butyl acetoacetate and *trans*-cinnamaldehyde under the solvent-free neat condition

at room temperature. Initially, the polymer microsphere-immobilized catalyst **M30** was applied to the reaction. The catalyst **M30** afforded the Michael adduct with excellent

Table 4.3 Organocatalytic asymmetric Michael addition reaction using polymeric catalysts.[a]

Entry	Polymeric catalyst	x/y/z (mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**M30**	20/50/30	36	95	96
2	**M20**	20/60/20	36	95	87
3	**M10**	20/70/10	36	99	96
4[d]	**M10**	21/70/10	24	98	95
5[e]	**M10**	20/70/10	12	98	79

[a] All the reactions were carried out on a 0.25 mmol scale under solvent-free condition at room temperature.

[b] Determined by ^{1}H NMR.

[c] Enantiomeric excess was determined by chiral GC-analysis after hydrolysis and decarboxylation of the Michael adduct.

[d] 2.0 equiv. of *trans*-cinnamaldehyde were used.

[e] Reaction was carried out using 2.0 equiv. of *trans*-cinnamaldehyde at 40 °C.

yield (95%) and enantioselectivity (96%). We further studied the effect of molar ratios in immobilized polymer microspheres using the series of catalysts **M30-10** (see Table 4.3). In each polymer microspheres, the molar proportion of DVB was constant while the molar proportion of styrene and chiral prolinol monomer (**D**) was changed. The enantioselectivity decreased with no change in yield upon lowering the molar proportion of **D** from 30 to 20 mol% (Entries 1 and 2). However, the reaction yield and enantioselectivity slightly increased, further decreasing the **D**'s molar proportion (Entry 3). The catalyst **M10** showed the best catalytic performance because of its hydrophobic nature. The catalysts **M10** contains the maximum proportion of polystyrene content within its structure. The highest ratio of polystyrene made the polymer microsphere more hydrophobic by its chemical nature. The hydrophobic nature of polymeric catalysts and substrates provided a suitable microenvironment to occur the reaction with a slightly higher yield in the case of **M10**. The diameter of the polymeric catalysts

also plays a vital role in enhancing the higher reactivity of **M10**. The diameter of the polymeric catalysts is the minimum for the **M10** among all the other catalysts providing increased surface area, which is another reason for enhanced reactivity for the catalysts **M10**. The substrate amount was also further explored on the reaction rate and enantioselectivity by increasing *trans*-cinnamaldehyde from 1.5 to 2.0 equiv. The reaction rate increased upon increasing *trans*-cinnamaldehyde with a 99% yield within 24 h (Entry 4). The effect of temperature on the reaction rate and enantioselectivity was further investigated by increasing the reaction temperature from room temperature to 40 °C. The reaction rate increased with the increase of temperature, but the enantioselectivity was also decreased. From these results, it is apparent that the catalyst **M10**, room temperature, and 2.0 equiv. of *trans*-cinnamaldehyde is a preferable reaction condition for this reaction system.

4.2.4 One-pot asymmetric reactions using chiral pyrrolidine and acid catalysts

The catalytic activity of the different acid and base catalysts pair was evaluated by applying them to the one-pot three steps asymmetric synthesis of the optically active compound. The reaction proceeded with the formation H_2O and CO_2 as major by-products, along with isobutene. The reaction initiated with the asymmetric Michael addition between *tert*-butyl acetoacetate and *trans*-cinnamaldehyde catalyzed by chiral

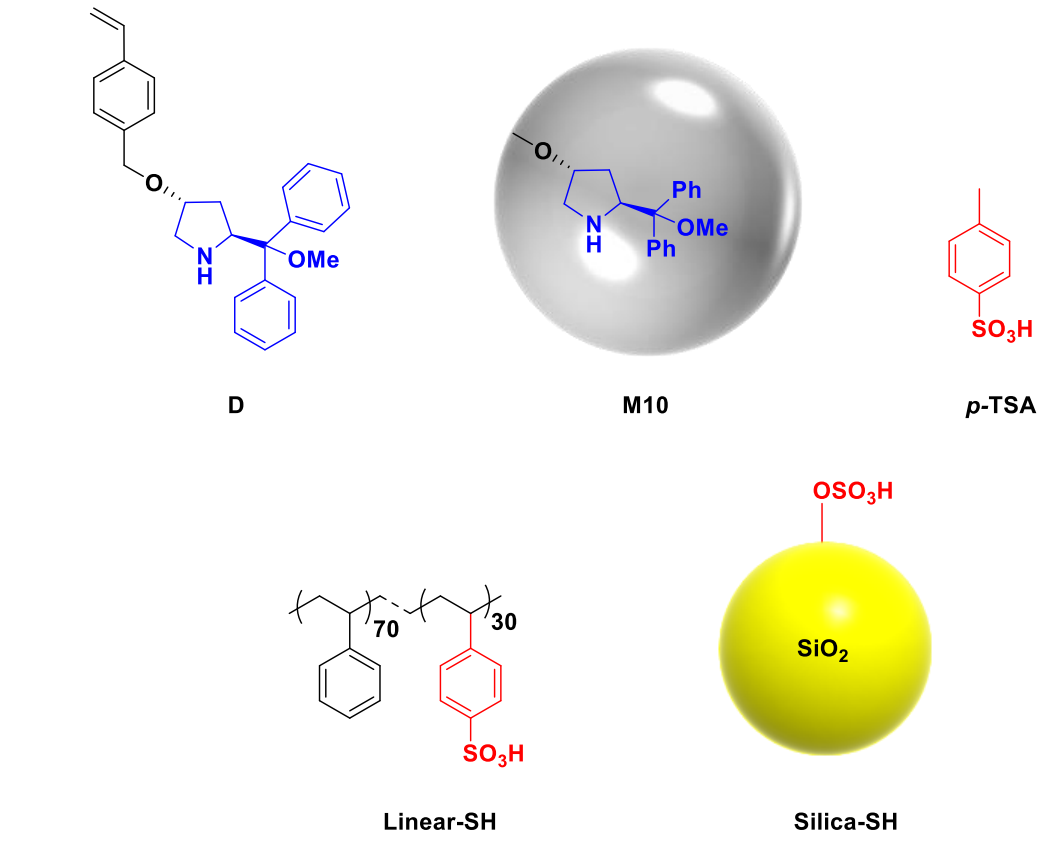
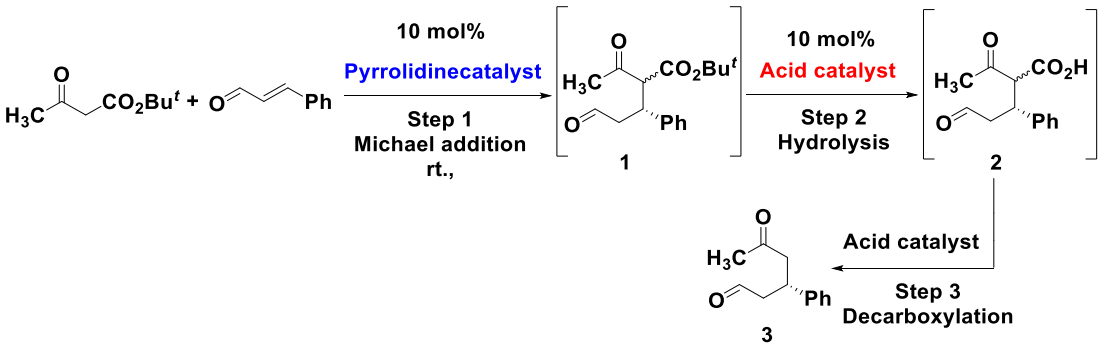


Figure 4.2 Chemical structure of several chiral pyrrolidine and acid catalysts.

pyrrolidine catalyst under the solvent-free neat condition at room temperature. The remaining two steps of the reaction were catalyzed by the acid catalyst in the presence of CH_2Cl_2 as solvent at room temperature for 24 h. Several types of chiral pyrrolidine and acid catalysts such as low molecular weight chiral prolinol catalyst (**D**), polymer microsphere-immobilized pyrrolidine catalyst (**M10**), *p*-toluenesulfonic (***p*-TSA**), linear polymer-immobilized sulfonic acid catalyst (**Linear-SH**), and silica gel -immobilized sulfonic acid catalyst (**Silica-SH**) were applied to the one-pot three steps chemical transformations (Figure 4.2). The results have been summarized in Table 4.4.

Table 4.4 One-pot three steps reaction.[a]



Entry	Pyrrolidine catalyst	Acid catalyst	Overall yield of 3 (%)[b]	ee (%)[c]
1	**D**	***p*-TSA**	0	nd[d]
2	**D**	**Linear-SH**	0	nd[d]
3	**D**	**Silica-SH**	2	nd[d]
4	**M10**	***p*-TSA**	0	nd[d]
5	**M10**	**Linear-SH**	<1	nd[d]
6	**M10**	**Silica-SH**	52	87
7[e]	**M10**	**Silica-SH**	70	89
8[f]	**M10**	**Silica-SH**	68	88

[a] In a Schlenk test tube *tert*-butyl acetoacetate (0.25) mmol was added to a mixture of pyrrolidine catalyst (10 mol%, 0.025 mmol), and *trans*-cinnamaldehyde (2 equiv., 0.50 mmol). The reaction mixture was stirred at room temperature under neat conditions until the complete consumption of *tert*-butyl acetoacetate. After the complete consumption of *tert*-butyl acetoacetate, 0.20 ml CH_2Cl_2 and acid catalyst (10 mol%, 0.025 mmol) were added. The reaction mixture was stirred at room temperature for 24 h.

[b] Determined by ^{1}H NMR.

[c] Enantiomeric excess was determined by chiral GC-analysis.

[d] nd stands for not determined.

[e] 30 mol% **M10** were used as the catalyst.

[f] Catalysts were used in entry 7.

The low-molecular-weight pyrrolidine catalyst **D** and ***p*-TSA**, and **D** and **Linear-SH** catalysts pair when applied to the reaction system. The first step of the reaction only proceeded. The remaining two steps of the reaction did not proceed at all (Entries 1 and 2). In entry 3, the catalyst pair **D** and **Silica-SH** afforded product **3** only 2%. These results indicate that the neutralization reaction occurred between the acid catalyst and the chiral base prolinol catalyst from entries 1-3. The polymer microsphere-immobilized chiral pyrrolidine catalyst **M10** in conjugation with ***p*-TSA,** and **Linear-SH** catalyst could not afford the final product **3** (Entries 4 and 5) result of the neutralization reaction between the active acid and base sites of the catalyst. In Entry 6, when the microsphere-immobilized pyrrolidine catalyst **M10** was used in conjugation with silica gel-immobilized acid catalyst **Silica-SH**, the final product **3** was obtained

with good yield and excellent enantioselectivity. The 3D structure and insolubility of the polymer microsphere and silica gel, respectively, provide steric shielding so that the active sites of the base and acid catalysts can not penetrate each other, and site isolation is achieved. The increase of catalyst loading from 10-30 mol% of **Silica-SA** further increased the yield and enantioselectivity (89%) of product **3** (Entry 7). The catalysts were recovered by simple centrifugation from the reaction mixture and reused in the next cycle. The reused catalyst retained its almost identical catalytic activity as of the fresh catalysts (Entry 8).

4.3 Conclusion

We have reported the synthesis of polymer microsphere-immobilized chiral pyrrolidine catalysts by simple precipitation polymerization. The chiral polymeric catalysts catalyzed the asymmetric Michael addition reaction between the *tert*-butyl acetoacetate and *trans*-cinnamaldehyde under the solvent-free neat condition at room temperature with excellent yield and enantioselectivity to afford the Michael adduct. The potential of the polymer microsphere as a site isolating material in the presence of other site isolating material such silica gel has been evaluated by applying in a one-pot three steps acid-base asymmetric reactions. It was found that the polymeric pyrrolidine catalyst in conjugation with silica gel-immobilized acid catalyst provided a site-isolated one-pot reaction system with good yield and enantioselectivity.

4.4 Experimental

4.4.1 Materials and Chemicals

N-(*tert*-Butoxycarbonyl)-*trans*-4-hydroxy-L-proline methyl ester, *tert*-butyldimethylchlorosilane, phenyl magnesium bromide, sodium hydride, tetra-*n*-butylammonium fluoride, iodomethane, Imidazole (Wako Pure Chemical Industries Ltd., Japan), and triethylamine (Wako Pure Chemical Industries Ltd., Japan), was used as received. *tert*-butyl acetoacetate (>98%, Sigma-Aldrich) was further purified by distillation before use, and the purity was confirmed by nuclear magnetic resonance (NMR) spectroscopy. Styrene (Kishida Chemical Co. Ltd., Japan), 4-methylstyrene (TCI, Japan), vinyl benzyl chloride (TCI, Japan), and DVB (Nippon & Sumikin Chemical Co. Ltd., Japan) were washed with aqueous 10% NaOH and water, followed by distillation with CaH_2 under reduced pressure. *trans*-cinnamaldehyde (TCI, Japan)

was further purified under reduced pressure prior to use. 2,2'-azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and dried under vacuum prior to use.

4.4.2 Measurements

Reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel plates (Merck 5554, $60F^{254}$). Column chromatography was performed with a silica gel column (Wakogel C-200, 100–200 mesh). NMR spectra were acquired at room temperature using JEOL JNM-ECS400 and JEOL JNM-ECX500 spectrometers with samples dissolved in $CDCl_3$. Chemical shifts are reported herein in units of parts per million (ppm), relative to tetramethylsilane (TMS) as a reference, while *J* values are reported in Hertz (Hz). FT-IR spectra were recorded with a JASCO FT/IR-230 spectrometer and are reported in reciprocal centimeters (cm^{-1}). SEM observations were conducted with a JSM-IT100 at an acceleration voltage of 10.0 kV. The number-averaged diameter (D_n), weight-average diameter (D_w), and polydispersity index (U) values for the polymer microspheres were calculated based on the SEM images. G.C. chromatogram was acquired with GC-2014, Shimadzu gas chromatography.

*4.4.3. Synthesis of polymerizable chiral pyrrolidine catalyst **D***

(2*S*,4*R*)-4-Hydroxy-2-(methoxydiphenylmethyl)pyrrolidine-1-carboxylate *tert*-butyl ester (**1**) was prepared according to a literature procedure.[48] The eggplant flask was replaced with nitrogen gas, the compound **1**(1.0 g, 2.60 mmol), NaH (0.33 g, 13.75 mmol), and dry DMF (10.0 mL). The mixture was stirred at 0 °C for 1 h. Then, the mixture was stirred at room temperature for 1 h and VBC (0.55 mL, 3.90 mmol) was added slowly. The reaction mixture was allowed to stir for 24 h at room temperature. The reaction was quenched by adding $NaHCO_3$ and 30 ml CH_2Cl_2. The organic layer was separated, and the aqueous layer extracted 5 times with CH_2Cl_2. The organic layer was washed with 30 mL water 2 times and dried over anhydrous MgSO4. The MgSO4 was removed by filtration, and the CH_2Cl_2 was removed under reduced pressure to give crude product. Then, the crude product was purified by silica gel column chromatography using a mixture of hexane/EtOAc = 9/1 as eluent to give chiral prolinol catalyst **D** as viscous liquid (1.20 g, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm) δ = 7.42-7.18 (m, 16H), 6.69 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.72 (d, *J* = 18.0 Hz, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.38-4.24 (m, 2H), 3.89-

3.75 (m, 1H), 3.53-3.39 (m, 1H), 2.96 (s, 3H), 2.68-2.54 (m, 1H), 2.24-2.20 (m, 2H), 1.85-2.07 (1H), 1.40 (s, 10H)

*4.4.4 Synthesis of polymer microsphere-immobilized chiral pyrrolidine catalyst (**M10**)*

The chiral pyrrolidine monomer **D** was prepared according to the published literature.[45] A 30 mL high density polyethylene (HDPE) narrow-mouth bottle was charged with DVB (0.174 g, 1.34 mmol), styrene (0.491 g, 4.71 mmol), **D** (0.338 g, 0.676 mmol), CH_3CN (29 mL), and AIBN (20 mg, 0.12 mmol, 2 wt% relative to the total monomer mass) under N_2. The mixture was then heated in an incubator at 70 °C while rotating the bottle horizontally at 9 rpm for 24 h. The reaction was subsequently quenched by adding hydroquinone, and the mixture was cooled to room temperature. Soluble oligomeric and polymeric products were separated from the insoluble material by centrifugation. The insoluble product was washed once with tetrahydrofuran (THF), once with methanol, three times with THF, and once with acetone. This material was dried under a vacuum oven at 40 °C for 24 h to give the polymer microsphere-immobilized chiral prolinol catalyst bearing *N*-Boc groups (**M'10**) as a white solid (0.26 g).

Yield: 26%; FT-IR (KBr): ν (cm^{-1}) = 1698 (C=O, in *N*-Boc)

A Schlenk test tube equipped with a magnetic stir bar was charged with **M'10** (0.24 g, 0.16 mmol) and cooled to 0 °C, after which 4 M HCl solution in dioxane (0.45 mL, 1.80 mmol) was added slowly under Ar. The reaction mixture was stirred at room temperature. After 24 h, an aqueous NH_3 solution (0.60 mL, 9.0 mmol) was gradually added. The mixture was stirred for a further 24 h under Ar. Following the deprotection reaction, the polymeric catalyst was washed sequentially with a 1/1 (v/v) mixture of H_2O and THF, methanol, THF, and acetone, then dried under vacuum at 40 °C for 24 h to give **M10** (0.21 g) as a yellow solid.

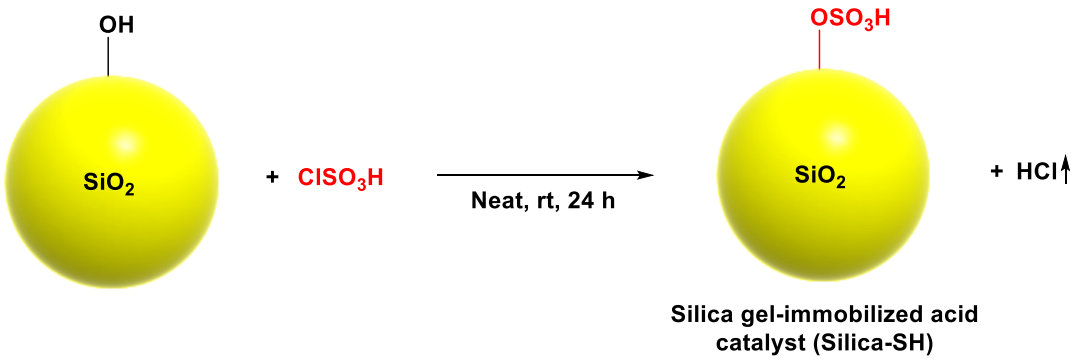
Yield: 94%; Catalyst content: 0.715 mmol/g.

*4.4.5 Synthesis of a silica gel-immobilized acid catalyst (**Silica-SH**)*

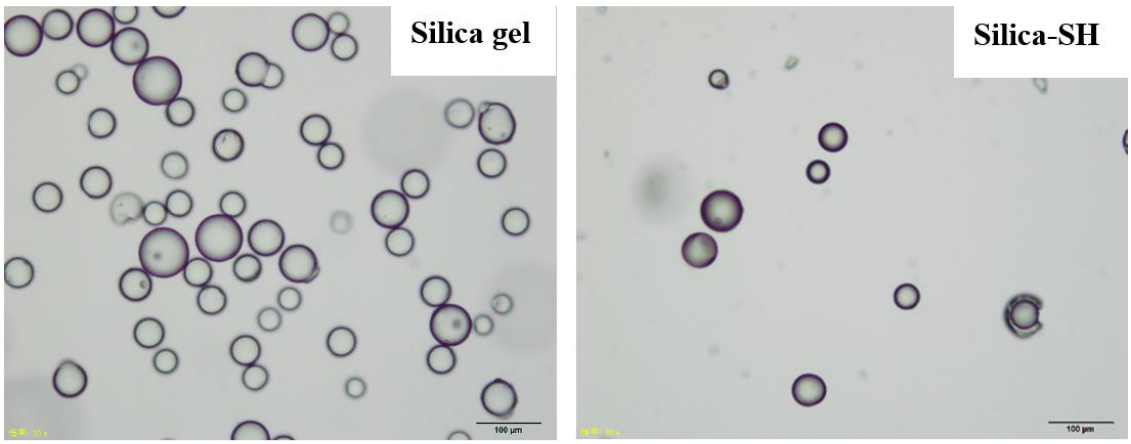
The silica-immobilized acid catalyst was prepared according to the published literature using the following Scheme (4.4). [2,3] Silica gel (CHROMATOREX PSQ 60B) was dried at 100 °C under vacuum for 24 h to remove the free absorb water from the

silica gel. After the drying, a 100 mL three neck round-bottomed flask was charged with 4.0 g of silica gel and fitted with a magnetic stirrer. Then chlorosulfonic acid (1.79 g, 15.36 mmol) was added dropwise to the silica gel at room temperature. Immediately, HCl emerged from the reaction vessel, and the HCl gas was neutralized by passing through an absorber tube containing solid NaOH. The reaction was carried out in a well-ventilated hood. After adding chlorosulfonic acid, the resulting reaction mixture was stirred for 24 h. After the completion of the reaction, the silica-immobilized acid (**Silica-SH**) was dried at 100 °C for 72 h under reduced pressure to give 5.20 g of **Silica-SH**. The complete removal of free chlorosulfonic acid was confirmed by measuring the round-bottomed flask's weight at different time intervals until it reached the constant weight.

Catalyst content: 2.85 mmol/g.



Scheme 4.4 Synthesis of a silica gel-immobilized acid catalyst.



$D_n = 49$ µm
$U = 1.05$

$D_n = 49$ µm
$U = 1.05$

Figure 4.3 Optical microscope image of Silica gel and **Silica-SH**. The scale bar is 100 µm.

The **Silica-SH** catalyst has been characterized by optical microscope image (Figure 4.3). From the optical microscope images it was found that the **Silica-SH** catalysts are spherical in shape. The diameter and polydispersity was identical for the fresh silica gel and silica gel-immobilized acid catalysts. The successful incorporation of the sulfonic acid content was confirmed the characteristic I.R. absorption peak of >S=O at 1178 cm^{-1} within the **Silica-SH** (Figure 4.4).

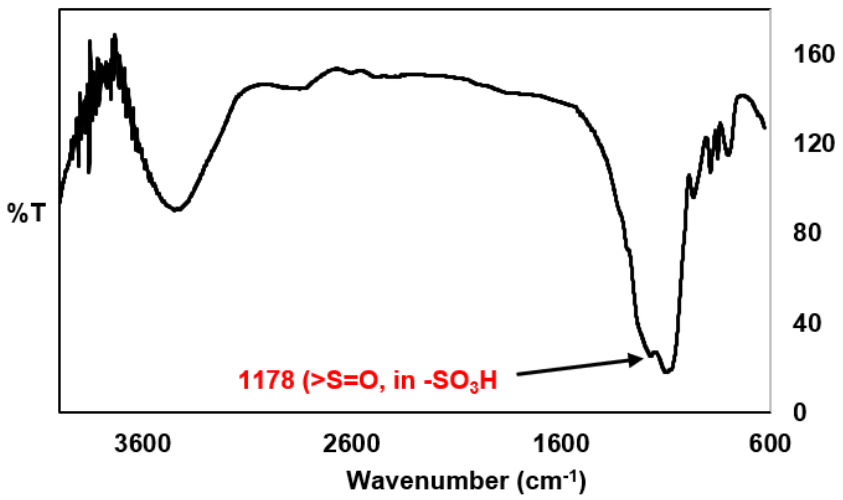
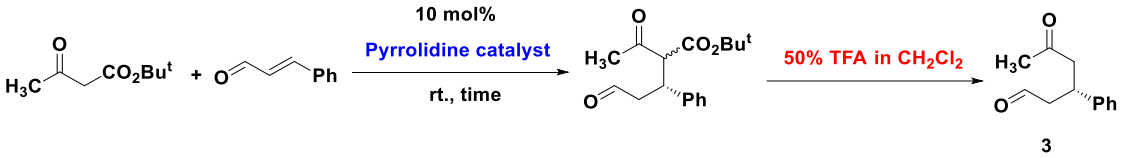


Figure 4.4 FT-IR spectra of **Silica-SH**.

4.4.6 General procedure of asymmetric organocatalytic Michael addition reaction and determination of enantiomeric excess

In a Schlenk test tube equipped with a magnetic stir bar, *tert*-butyl acetoacetate (0.25 mmol) was added to a mixture of 10 mol% chiral pyrrolidine catalyst **M10** (0.025 mmol) and 1.5 equiv. of *trans*-cinnamaldehyde (0.37 mmol). The reaction mixture was stirred at room temperature under Ar. After the complete consumption of the *tert*-butyl acetoacetate, 50% trifluoroacetic acid (TFA) in CH_2Cl_2 (0.5 mL) was added to the reaction and the resulting mixture and stirred for 1 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The organic layer dried over $MgSO_4$, filtered, and concentrated to give crude product. The crude product was purified by silica gel flash chromatography 9:1 (v/v) mixture of CH_2Cl_2 and Et_2O as eluent to give a liquid product **3**. The Enantiomeric excess (ee) was determined by GC analysis on a Astec G-TA chiral stationary phase (T1 = 70 °C; T2 = 165 °C, rate = 10 °C/min; Inject temperature = 110 °C; FID temperature = 180 °C. Spectroscopic data are in accordance with literature values.[18,49]



4.4.7. General procedure of one-pot three steps reaction

In a Schlenk test tube equipped with a magnetic stirring bar, *tert*-butyl acetoacetate (0.25 mmol) was added to a mixture of 10 mol% chiral pyrrolidine catalyst (0.025 mmol) and 2 equiv. of *trans*-cinnamaldehyde (0.50 mmol). The reaction mixture was stirred at room temperature until the complete consumption of *tert*-butyl acetoacetate under Ar. Next, the reaction mixture was stirred at room temperature after adding CH_2Cl_2 (0.20 mL) and 10 mol% acid catalyst (0.025 mmol) to the same reaction mixture. The crude product was extracted three times by centrifugation using THF. After extraction, the THF was removed using a rotary evaporator. Finally, the crude product was purified by silica-gel column chromatography using a 9:1 (v/v) mixture of CH_2Cl_2 and Et_2O as eluent to give a liquid product **3**.

References

[1] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[2] A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**.

[3] J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719.

[4] B. List, *Chem. Commun.* **2006**, *8*, 819.

[5] K. Kümmerer, *Annu. Rev. Environ. Resour.* **2010**, *35*, 57.

[6] M. B. J. Atkinson, S. Oyola-Reynoso, R. E. Luna, D. K. Bwambokc, M. M. Thuo, *RSC Adv.* **2015**, *5*, 597.

[7] US EPA, 2005 Toxics Release Inventory (TRI) Public Data Release Report, United StateEnvironmental Protection Agency, Washington DC, USA. http://www.epa.gov/tri.

[8] C. Aubert, L. Fensterbank, V. Gandon, M. Malacria, *Top. Organomet. Chem.* **2006**, *19*, 259.

[9] G. Balme, D. Bouyssi, N. Monteiro, *Top. Organomet. Chem.* **2006**, *19*, 115.

[10] J. M. Bowness, *Science* **1966**, *152*, 1370.

[11] C. Bruneau, S. Derien, P. H. Dixneuf, Top. *Organomet. Chem.* **2006**, *19*, 295.

[12] Y. Chi, S. T. Scroggins, J. M. J. Frechet, *J. Am. Chem. Soc.* **2008**, *130*, 6322.

[13] A. Corma, *Catal. Rev.: Sci. Eng.* **2004**, *46*, 369.

[14] M. Malacria, *Chem. Rev.* **1996**, *96*, 289.

[15] S. F. Mayer, W. Kroutil, K. Faber, *Chem. Soc. Rev.* **2001**, *30*, 332.

[16] T. J. J. Müeller, *Top. Organomet. Chem.* **2006**, *19*, 149.

[17] K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

[18] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, *47*, 4928.

[19] H. Sundén, I. Ibrahem, G. -L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574.

[20] S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem. Int. Ed.* **2009**, *48*, 8923.

[21] Y. Hayashi, Y. Suga, N. Umekubo, *Org. Lett.* **2020**, *22*, 8603.

[22] L. -C. Lee, J. Lu, M. Weck, C. W. Jones, *ACS Catal.* **2016**, *6*, 784.

[23] P. Cotanda, N. Petzetakis, R. K. O'Reilly, *MRS Commun.* **2012**, *2*, 119.

[24] M. Elsabahy, K. L. Wooley, *Chem. Soc. Rev.* **2012**, *41*, 2545.

[25] R. K. O'Reilly, C. J. Hawker, K. L. Wooley, *Chem. Soc. Rev.* **2006**, *35*, 1068.

[26] Y. Liu, Y. Wang, Y. Wang, J. Lu, V. Pinon III, M. Weck, *J. Am. Chem. Soc.* **2011**, *133*, 14260.

[27] H. Yang, L. Fu, L. Wei, J. Liang, B. P. Binks, *J. Am. Chem. Soc.* **2015**, *137*, 1362.

[28] F. Gelman, J. Blum, D. Avnir, *J. Am. Chem. Soc.* **2002**, *124*, 14460.

[29] Y. Huang, B. G. Trewyn, H. T. Chen, V. S. -Y. Lin, *New J. Chem.* **2008**, *32*, 1311.

[30] F. Gelman, J. Blum, D. Avnir, *Angew. Chem. Int. Ed.* **2001**, *40*, 3647.

[31] H. Huang, C. A. Denard, R. Alamillo, A. J. Crisci, Y. Miao, J. A. Dumesic, S. L. Scott, H. Zhao, *ACS Catal.* **2014**, *4*, 2165.

[32] B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Fréchet, *Angew. Chem. Int. Ed.* **2005**, *44*, 6384.

[33] Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322.

[34] A. W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem. Int. Ed.* **2007**, *46*, 5428.

[35] S. L. Poe, M. Kobašlija, D. T. McQuade, *J. Am. Chem. Soc.* **2006**, *128*, 15586.

[36] Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100.

[37] Y. Yang, X. Liu, X. Li, J. Zhao, S. Bai, J. Liu, Q. Yang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9164.

[38] R. J. R. W. Peters, I. Louzao, J. C. M. van Hest, *Chem. Sci.* **2012**, *3*, 335.

[39] J. Shi, L. Zhang, Z. Jiang, *ACS Appl. Mater. Interfaces* **2011**, *3*, 881.

[40] M. B. Runge, M. T. Mwangi, A. L. Miller II, M. Perring, N. B. Bowden, *Angew. Chem. Int. Ed.* **2008**, *47*, 935.

[41] B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Fréchet, *Angew. Chem.* **2005**, *117*, 6542.

[42] N. Haraguchi, A. Nishiyama, S. Itsuno, *J. Polym. Sci. Part A: Polym. Chem.* **2010**, *48*, 3340.

[43] N. R. Shiju, A. H. Alberts, S. Khalid, D. R. Brown, G, Rothenberg, *Angew. Chem. Int. Ed.* **2011**, *50*, 9615.

[44] S. Faisal, P. K. Maity, Q, Zang, T. B. Samarakoon, R. L. Sourk, P. R. Hanson, *ACS Comb. Sci.* **2016**, *18*, 387.

[45] H. Ochiai, A. Nishiyama, N. Haraguchi, S. Itsuno, *Org. Process Res. Dev.* **2020**, *24*, 2228.

[46] M. A. Zolfigo, *Tetrahedron* **2001**, *57*, 9509.

[47] S. Pathak, K. Debnath, A. Pramanik, *Beilstein. J. Org. Chem.* **2013**, *9*, 2344.

[48] Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253.

[49] G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115***,** 830.

CHAPTER V

Summary

The uniform polymer microspheres-immobilized chiral pyrrolidine catalysts have been prepared via precipitation polymerization using DVB as a crosslinker, a comonomer, and a methacrylate monomer bearing a chiral pyrrolidine moiety, followed by the removal of the *N*-Boc group. The potential of the polymer microspheres as support material has been evaluated by applying the polymeric catalysts to asymmetric Michael addition reaction between the aldehydes and alkyl vinyl ketones. The effect of comonomer, molar ratios within the catalyst, catalyst loading, temperature, solvent, and substrate scope was investigated on the catalytic performance in detail. The reaction was found to proceed smoothly at 15 ºC in the absence of any solvent. Among all catalysts investigated in this study, The hydrophobic polymer microsphere-immobilized catalyst **PS5** provided the best catalytic activity (up to 97% yield and 95% enantioselectivity). **PS5** exhibited higher catalytic activity for the short-chain aldehydes in the reaction. **PS5** showed high recovery and reusability performance without the deterioration of its enantioselectivity up to five cycles. This research work contributes to polymer chemistry by introducing polymer microsphere as one of the promising support materials for the immobilization of organocatalysts as well as organometallic catalysts.

On the basis of the successlul application of the polymer microsphere-immobilized chiral pyrrolidine catalysts for the asymmetric reaction, the polymeric catalysts were applied to a one-pot reaction system based on site isolation. The site isolation efficiency of the polymer microsphere was demonstrated by applying polymer microsphere-immobilized sulfonic acid and chiral pyrrolidine catalysts to a one-pot deacetalization-asymmetric Michael addition reaction. The one-pot reaction involves two-step reactions. The first step reaction is the acid catalyst mediated deacetalization reaction to produce intermediate propionaldehyde. The second step is the chiral pyrrolidine catalyzed asymmetric Michael addition reaction between propionaldehyde and methyl vinyl ketone. The use of low-molecular-weight sulfonic acid and chiral pyrrolidine catalyst and linear polymer-immobilized acid catalyst and pyrrolidine catalyst was not effective for the one-pot reaction. The final chiral product was obtained in good yield with high enantioselectivity only when the combination of the polymer microsphere-immobilized sulfonic acid and chiral pyrrolidine catalysts were employed. Further, the effect of molar

ratio of monomers within the catalyst, catalyst loading, H_2O amount, additive, methyl vinyl ketone, solvent, and the hydrophobic-hydrophilic balance of the polymer microsphere-immobilized pyrrolidine catalyst was investigated on the overall yield and enantioselectivity. The reaction proceeded smoothly in the absence of any additional solvent. The catalyst **PSSH** and the polystyrene-based pyrrolidine catalysts **PS3** afforded the final asymmetric product with good yield (82%) and excellent enantioselectivity (91%) based on site isolation. The catalysts were also recovered and reused from the reaction mixture by simple centrifugation. The catalytic activity of the reused catalysts was identical to fresh catalysts. This research exhibited the promising possibility of polymer microspheres that will be one of the effective site isolating materials for the site isolation of the incompatible catalysts such as reductive-oxidative and enamine-iminium type catalysts.

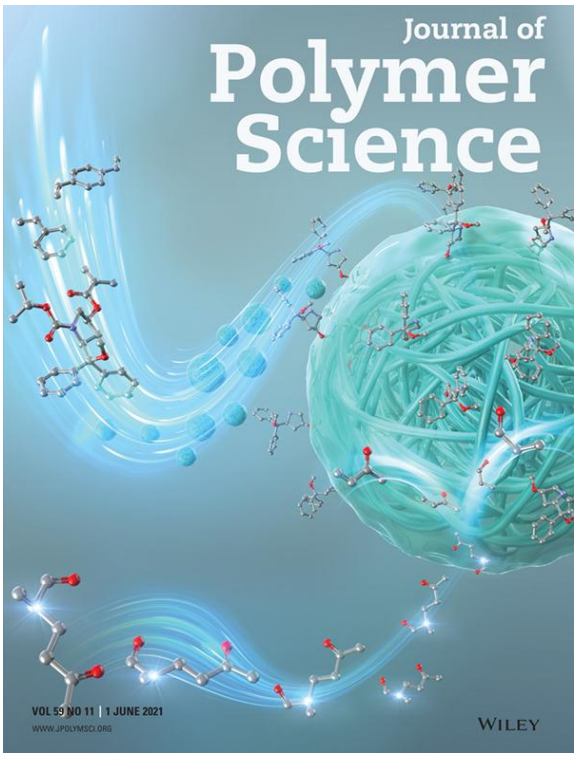
A one-pot three-step reaction using heterogeneous acid and base catalysts has been successfully developed. The polymer microsphere-immobilized chiral pyrrolidine catalysts were applied to the asymmetric Michael addition reaction between *tert*-butyl acetoacetate and *trans*-cinnamaldehyde under the solvent-free condition at room temperature. The effect of molar ratio of monomers within the catalyst, temperature, and substrate amount was investigated on the catalytic performance. The hydrophobic polymer microsphere-immobilized catalyst **M10** afforded the Michael adduct with excellent yield (98%) and enantioselectivity (95%). The site isolation efficiency of **M10** was evaluated by the one-pot three-step asymmetric reaction in conjugation with several acid catalysts. Among these acid and base catalysts, **M10** and silica gel-immobilized acid catalyst **Silica-SH** afforded the final product with good yield and enantioselectivity. The catalysts were recovered from the reaction mixture and applied to the reuse. The catalysts retained their original catalytic activity. This system will be versatile and effective for one-pot multistep reaction based on site isolation.

ACHIEVEMENTS

A.1 List of Papers

1. **M. K. Debnath**, W. Oyama, Y. Ono, T. Sugimoto, R. Watanabe, N. Haraguchi,* "Synthesis of polymer microsphere-supported chiral pyrrolidine catalysts by precipitation polymerization and their application to asymmetric Michael addition reactions," *J. Polym. Sci.* **2021**, *59*, 1072.

This research article has been featured on the top cover page of the *Journal of Polymer Science*. https://onlinelibrary.wiley.com/toc/26424169/2021/59/11



2. **M. K. Debnath**, Y. Ono, N. Haraguchi,* "One-pot Reaction Catalyzed by Site-isolated Polymer Microsphere-immobilized Organocatalysts," *ChemSusChem* (accepted) 2021.

3. **M. K. Debnath,** Y. Hashimoto, N. Haraguchi,* "Asymmetric One-pot Reaction Catalyzed by Polymer Microsphere-immobilized Chiral Pyrrolidine Catalysts and Silica-immobilized Sulfonic Acid," *Chem. Lett.* (accepted) 2021.

A.2 List of Presentations at International Conference

1. **M. K. Debnath**, N. Haraguchi, "Design of polymer microsphere-immobilized chiral prolinol derivative: application in one-pot acid-base reaction by using site-isolation," ACS *SPRING 2021, MACROMOLECULAR CHEMISTRY: THE SECOND CENTURY,* San Antonio, Texas, USA, 5-16th April **2021**.

A.3 List of Presentations at Domestic Conferences

1. **M. K. Debnath**, N. Haraguchi, "Development of one-pot multistep reactions by using polymer microsphere-immobilized chiral prolinol derivative," *70th SPSJ Annual Meeting*, *Japan,* 26-28th May **2021**.

2. N. Haraguchi, **M. K. Debnath**, "Design of polymer microsphere-immobilized chiral prolinol derivative and Michael addition reaction," *69th Symposium on Macromolecules, Japan,* 16-18th September **2020**.

3. **M. K. Debnath**, Md. W. Ullah, N. Haraguchi, "Development of one-pot asymmetric Michael addition reaction catalyzed by polymer microsphere-supported chiral pyrrolidine catalyst," *50th Annual Meeting of UCRS in Chubu Area, Japan*, 9-10th November **2019**.

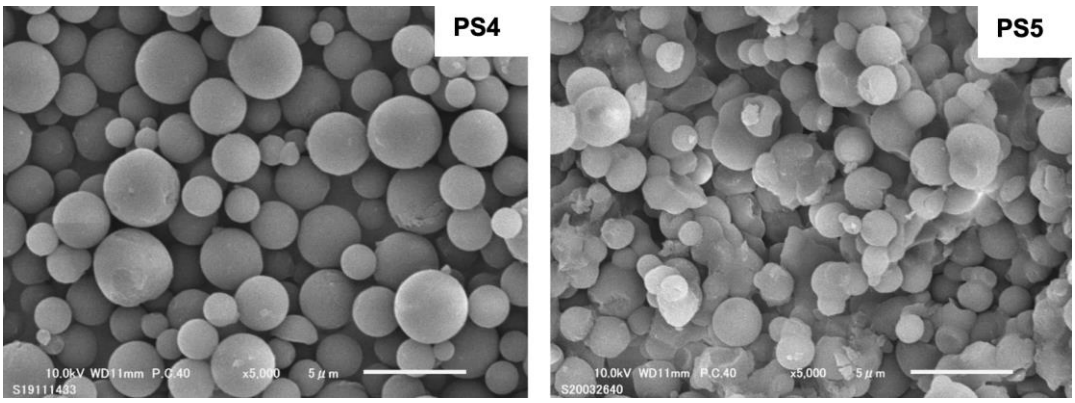
A.4 Membership

1. Society of Polymer Science, Japan: Tokyo, Japan.
2. The American Chemical Society: Washington, DC, USA.
3. Royal Society of Chemistry, UK.

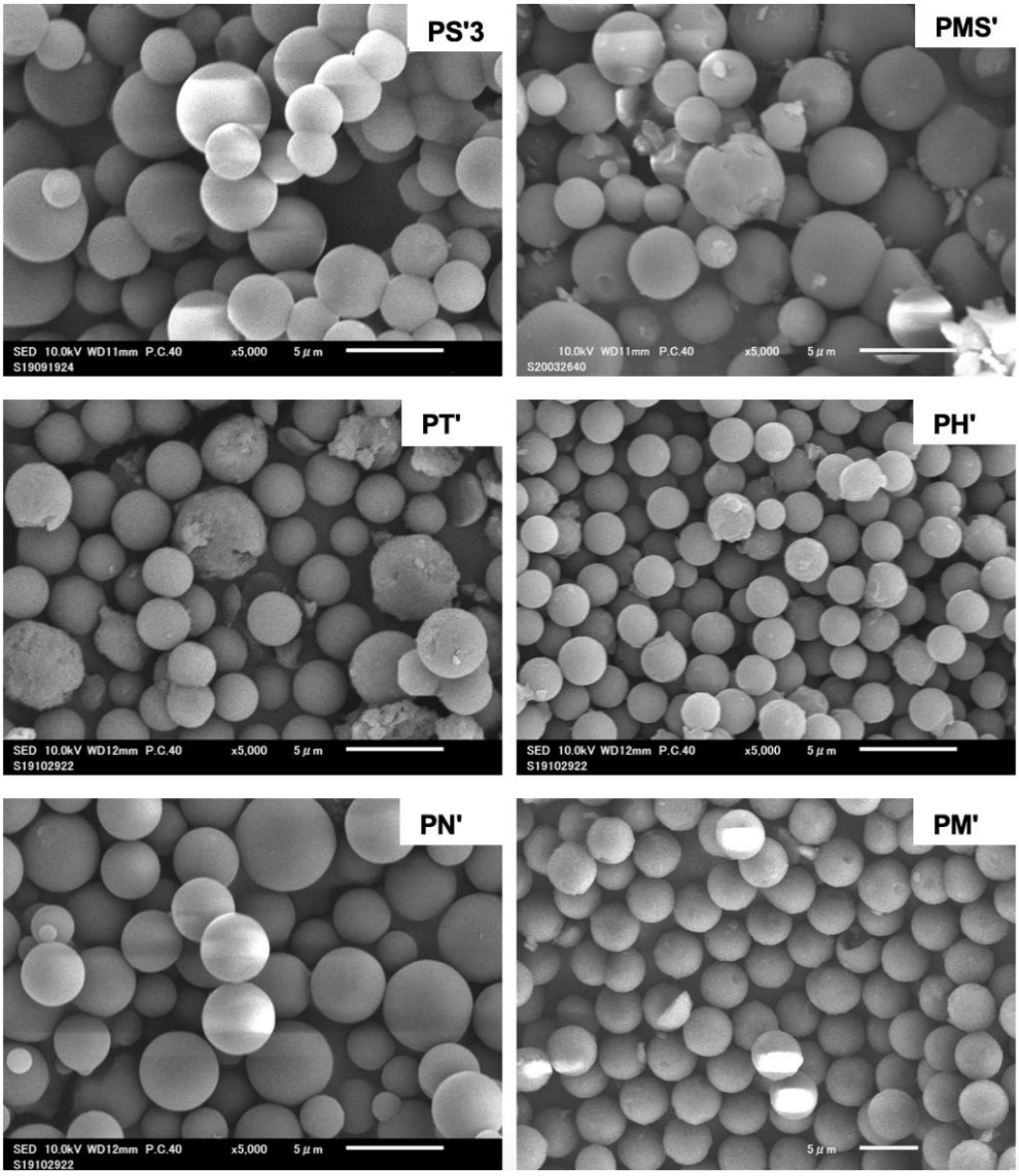
APPENDIX A

Supplementary Information for Chapter II

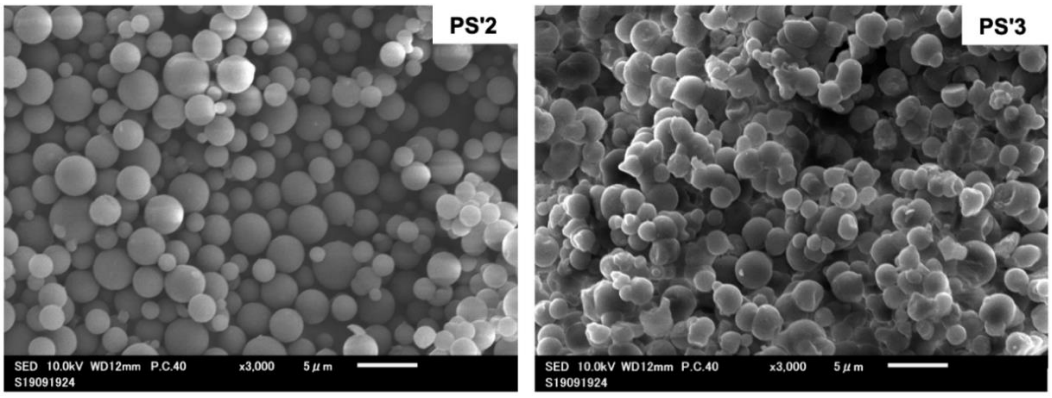
A.1 SEM images



SEM images of **PS4** and **PS5.**



SEM images of polymer microsphere-supported chiral pyrrolidine catalyst before deprotection.



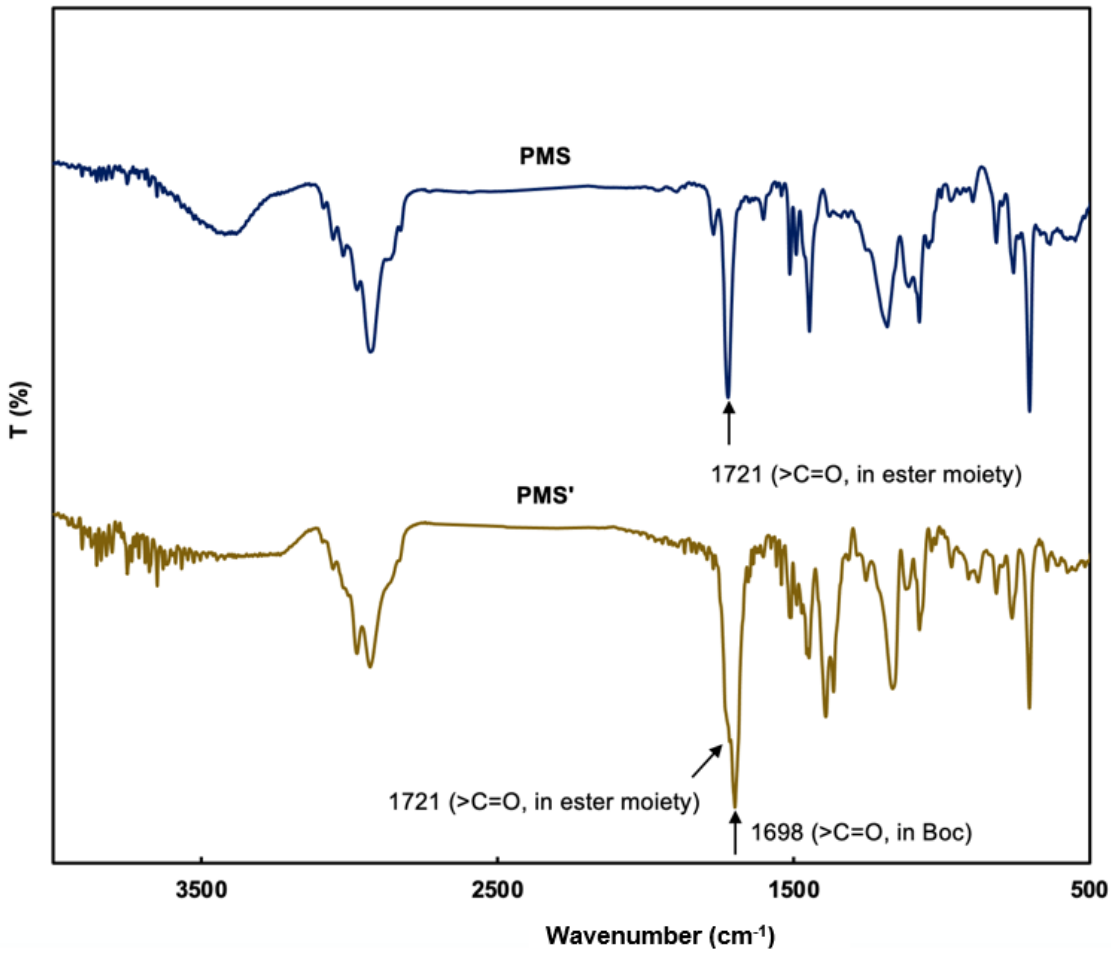
SEM images of polymer microsphere-supported chiral pyrrolidine catalyst before deprotection .

A.2 Characterization of polymer microsphere-immobilized chiral pyrrolidine catalysts before and after deprotection.

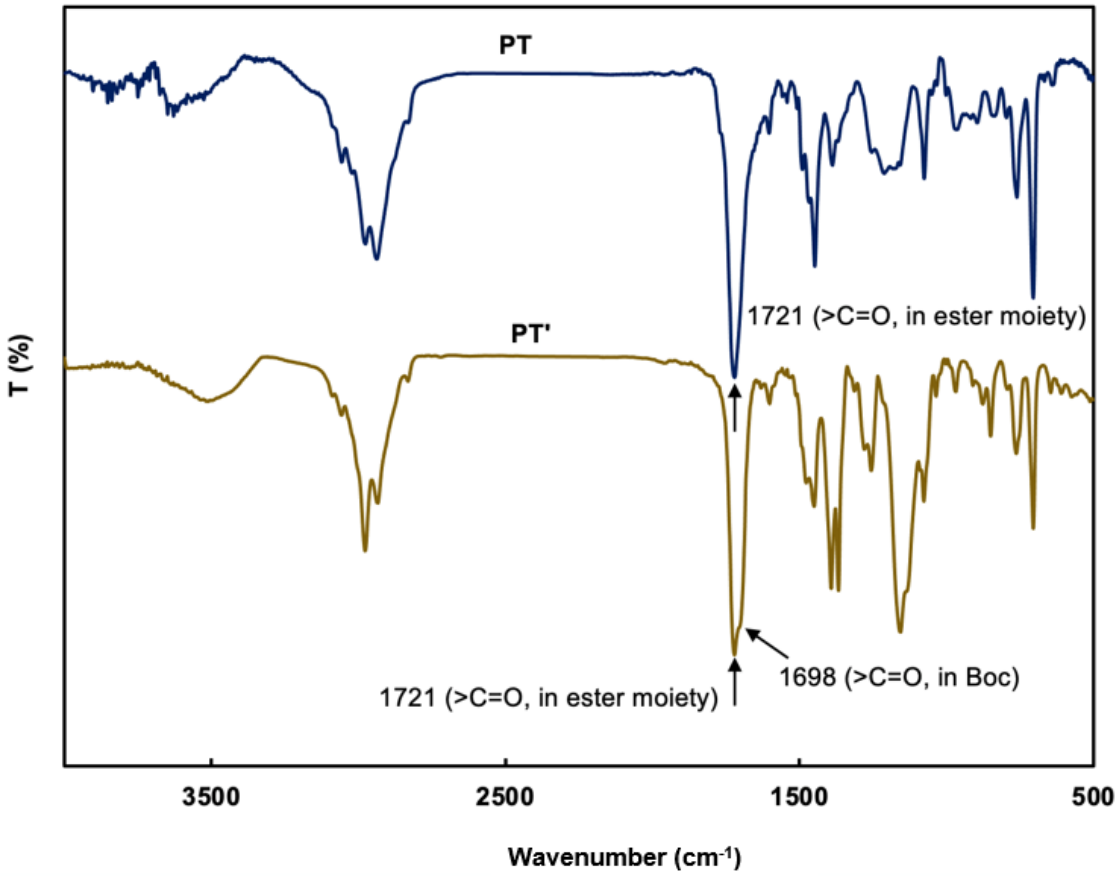
Entry	Comonomer	x/y/z [mol%]	Polymer	Before deprotection		After deprotection	
				D_n (μm)[a]	U[a]	D_n (μm)[a]	U[a]
1	St	20/50/30	**PS3**	3.57	1.14	3.50	1.16
2	St	20/60/20	**PS4**	2.58	1.19	2.56	1.24
3	St	20/40/40	**PS5**	1.95	1.26	1.87	1.23
4	4-MS	20/50/30	**PMS**	3.89	1.28	3.79	1.23
5	TBMA	20/50/30	**PT**	2.73	1.12	2.63	1.08
6	HEMA	20/50/30	**PH**	2.12	1.02	2.06	1.02
7	NIPAM	20/50/30	**PN**	2.78	1.30	2.76	1.17
8	MAA	20/50/30	**PM**	4.24	1.01	4.20	1.02

[a] Determined by SEM images.

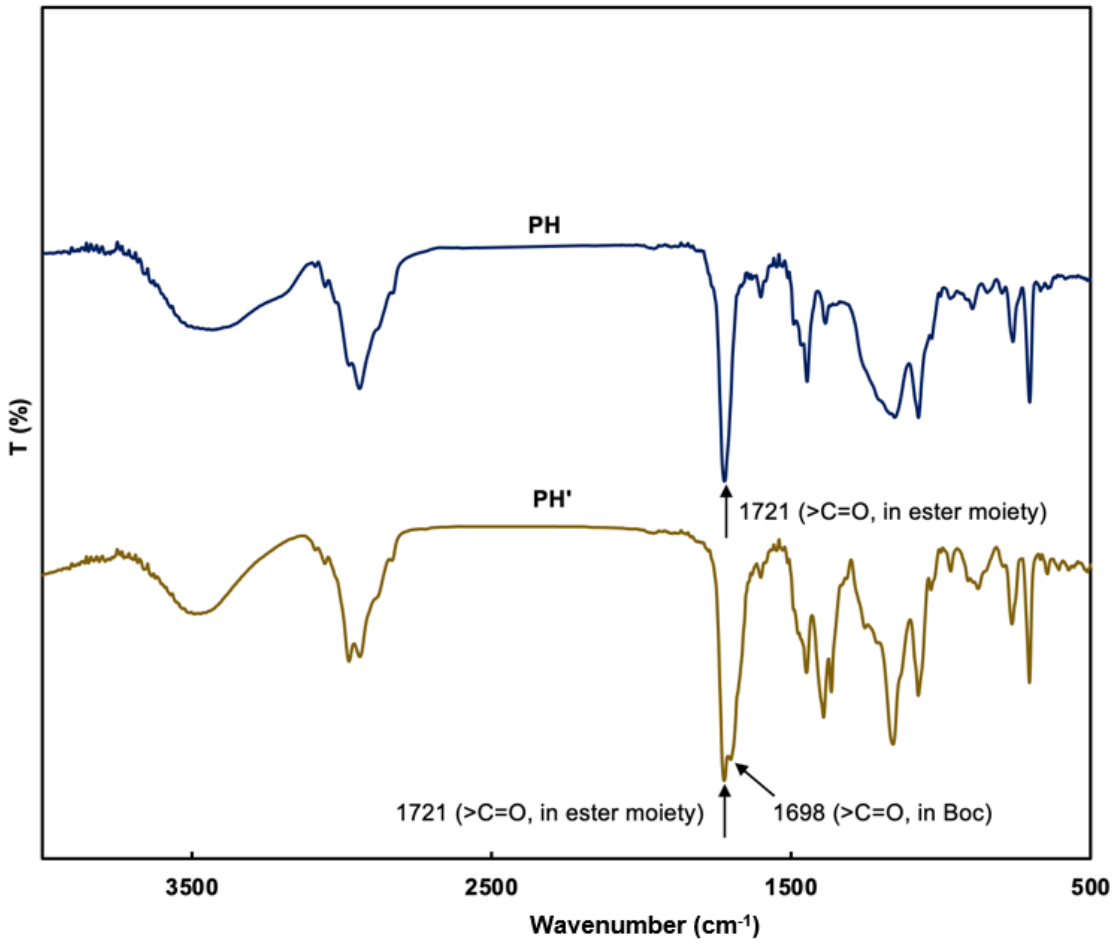
A.3 FT-IR spectra



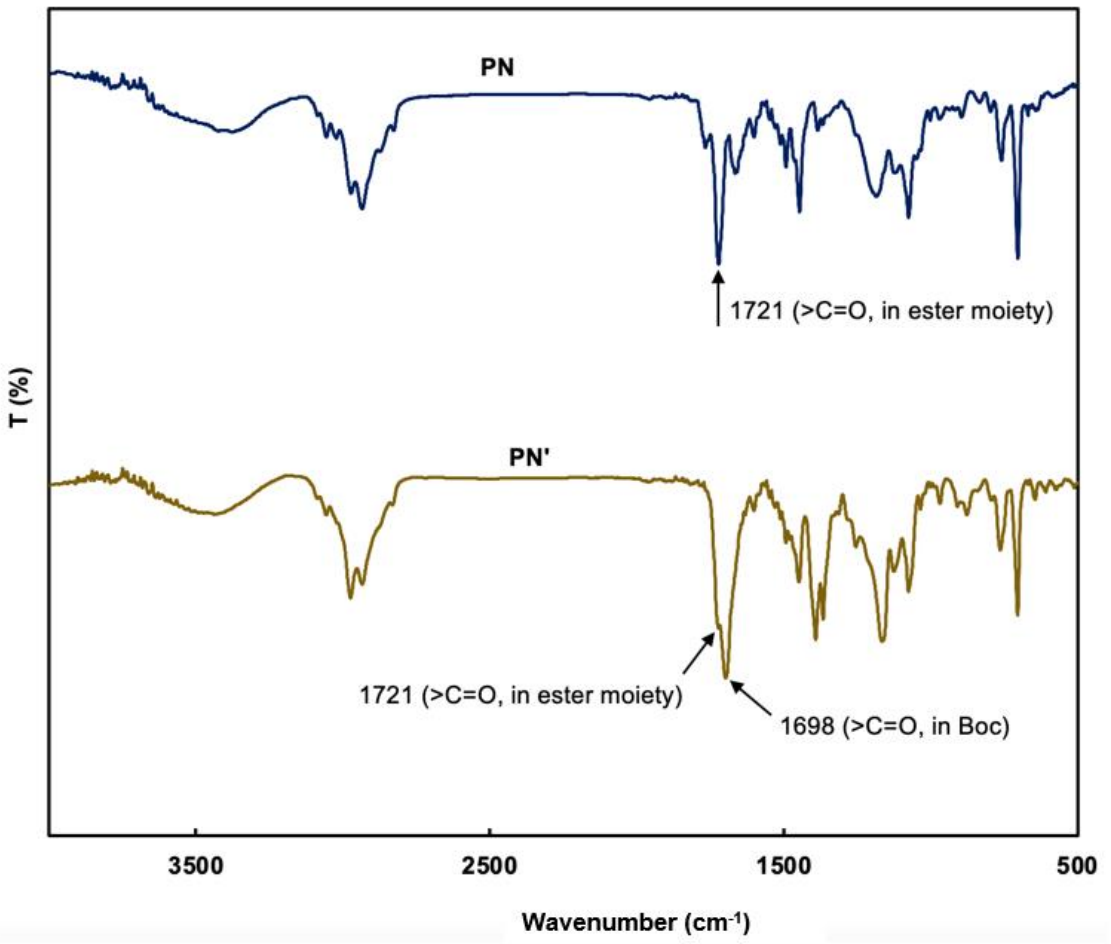
FT-IR spectra of **PMS'** (before deprotection) and **PMS** (after deprotection).



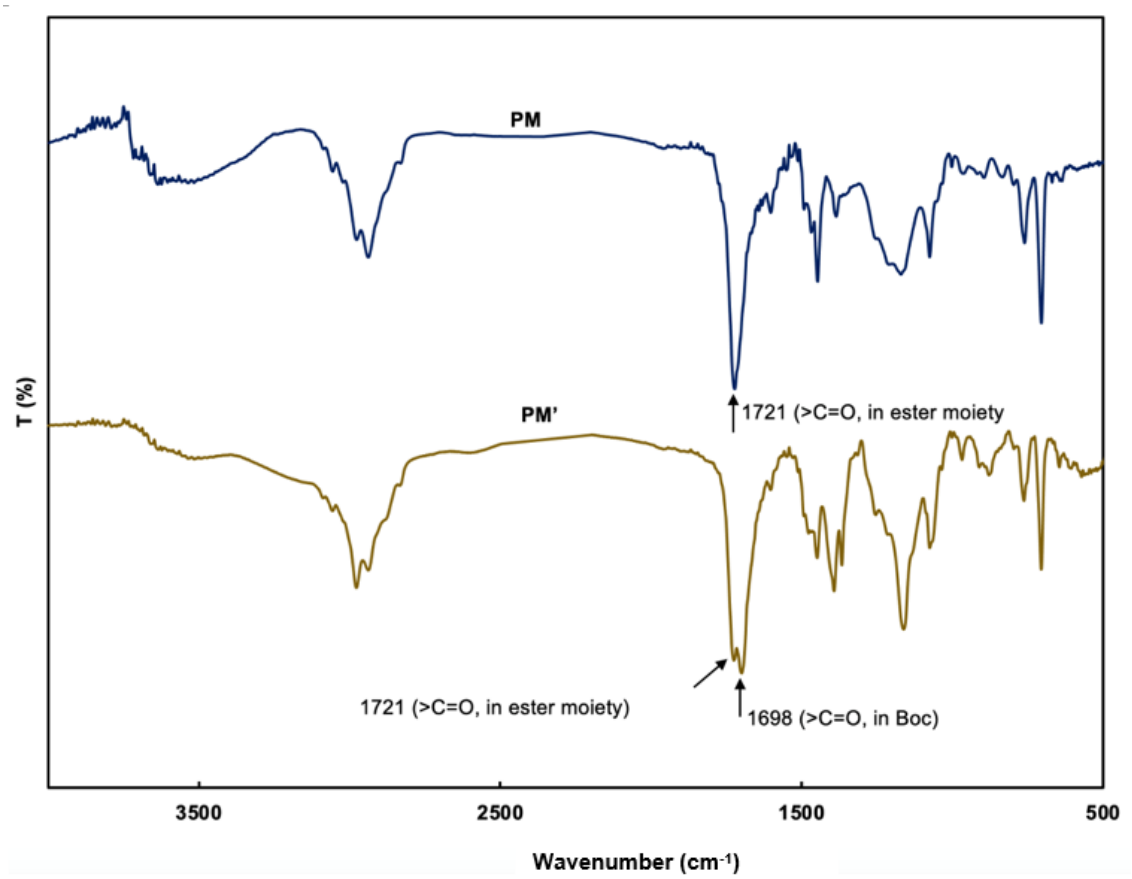
FT-IR spectra of **PT'** (before deprotection) and **PT** (after deprotection).



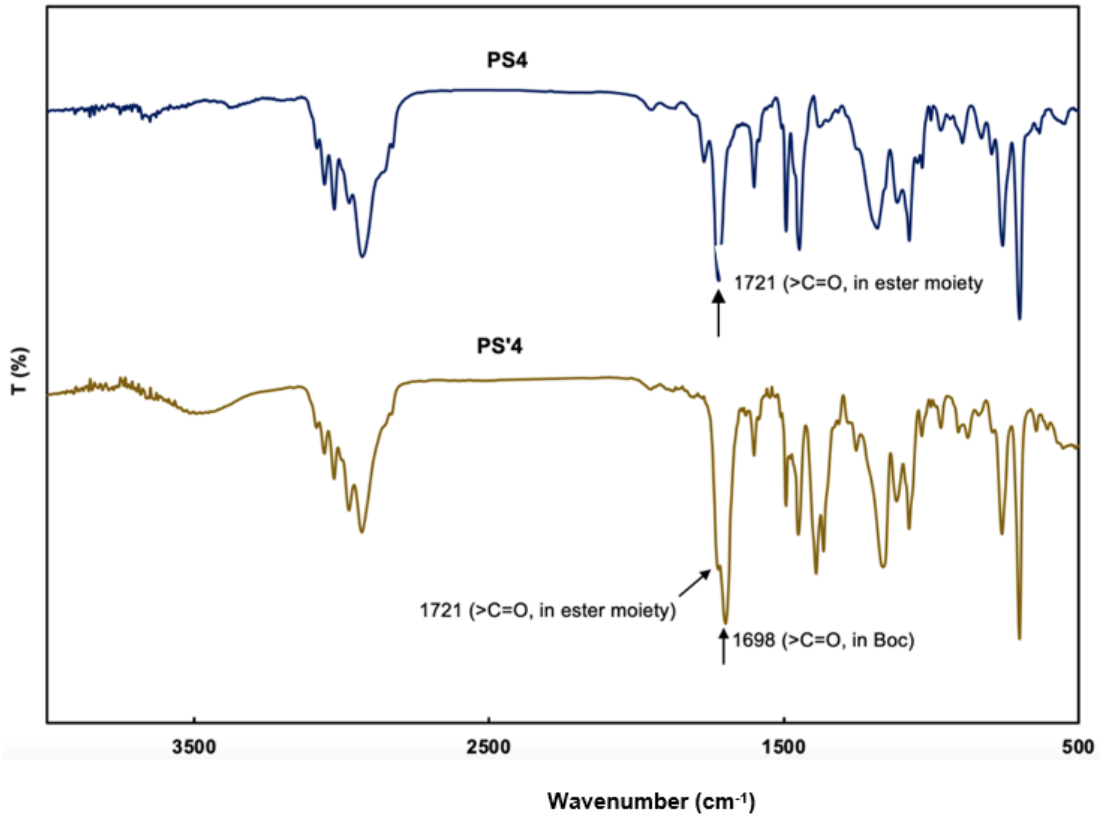
FT-IR spectra of **PH'** (before deprotection) and **PH** (after deprotection).



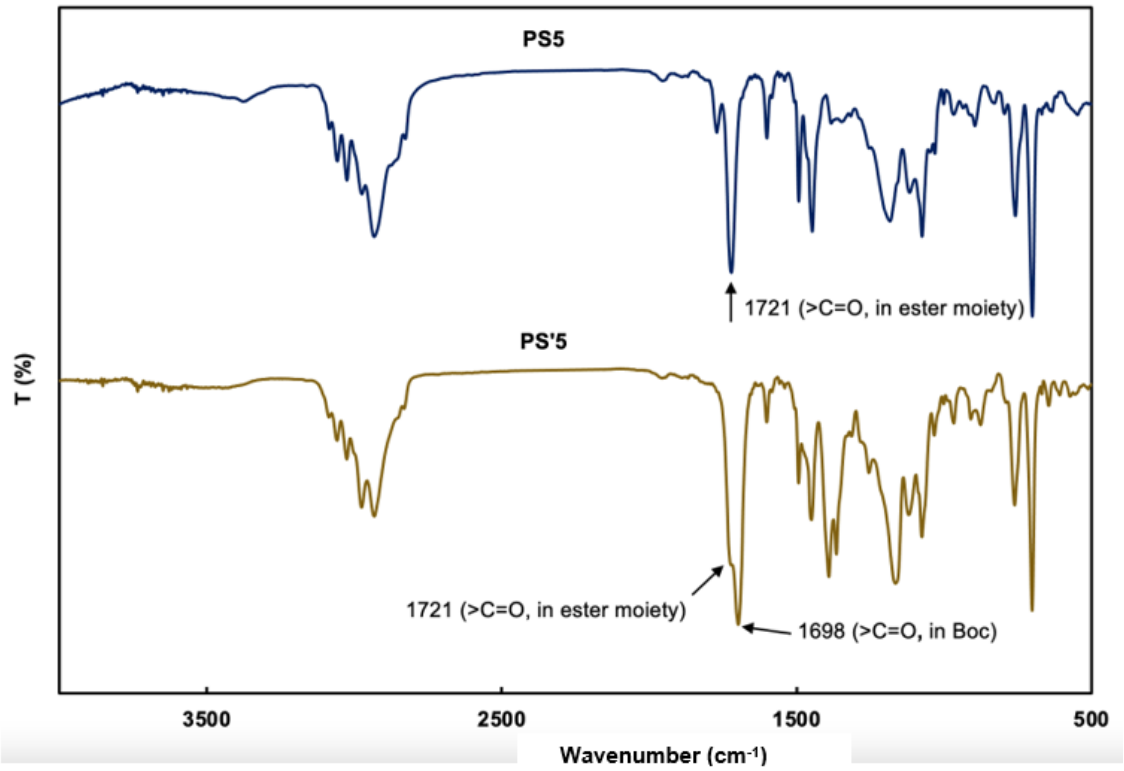
FT-IR spectra of **PN'** (before deprotection) and **PN** (after deprotection).



FT-IR spectra of **PM'** (before deprotection) and **PM** (after deprotection).

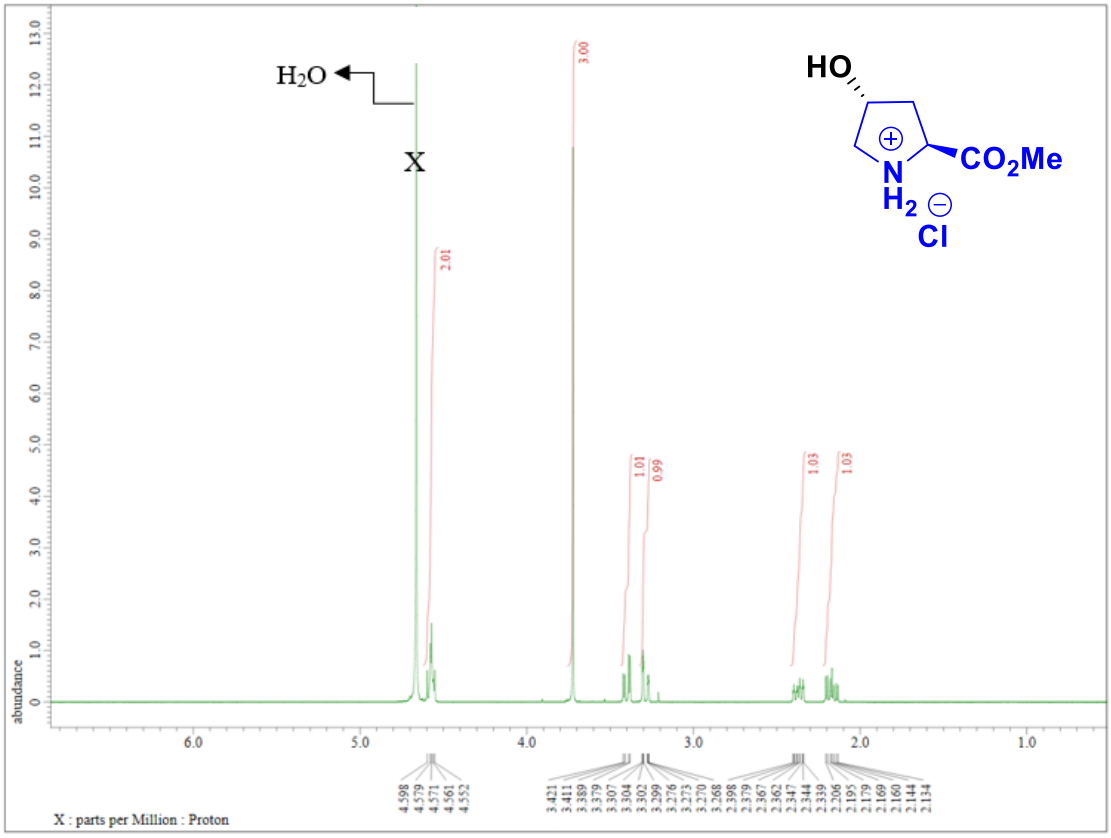


FT-IR spectra of **PS'4** (before deprotection) and **PS4** (after deprotection).

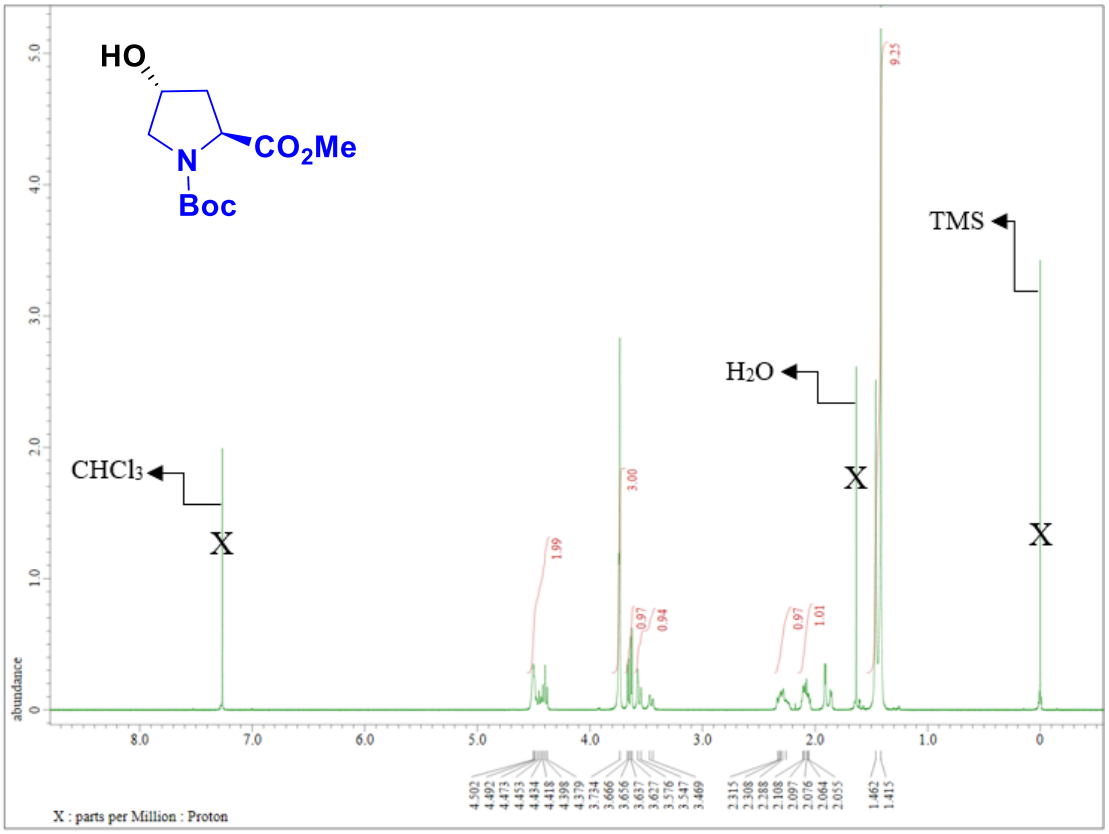


FT-IR spectra of **PS'5** (before deprotection) and **PS5** (after deprotection).

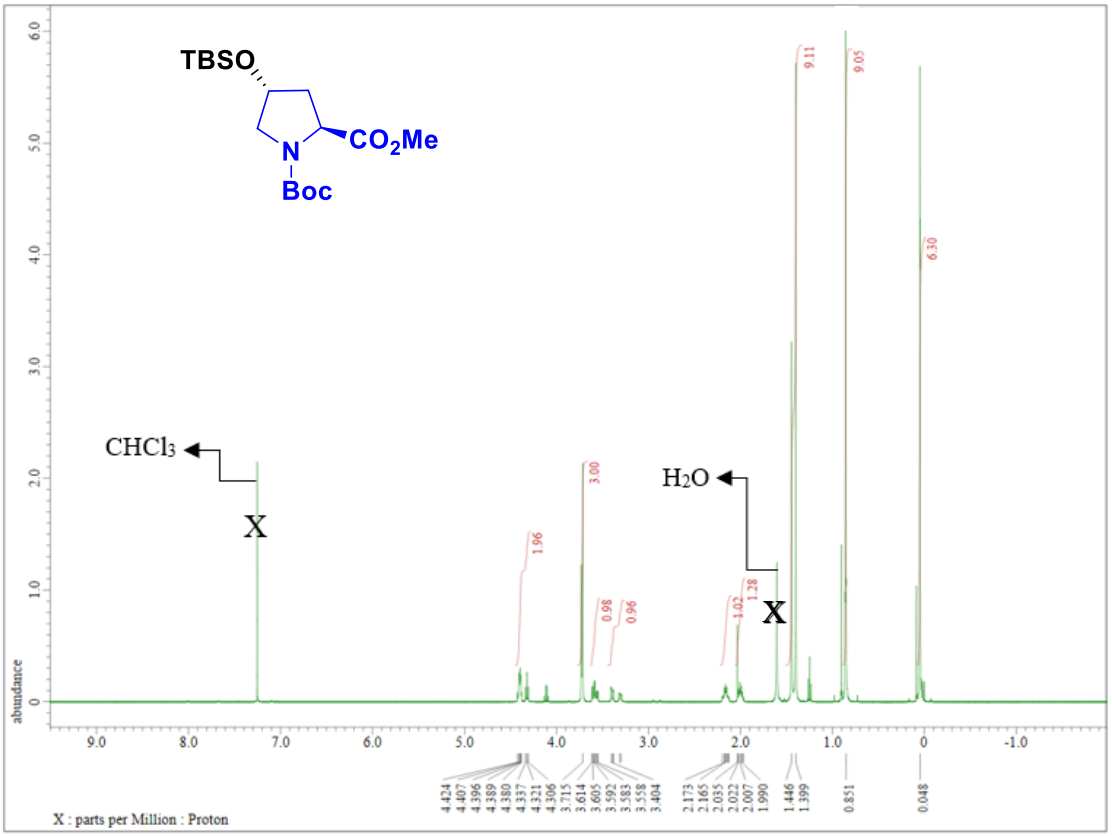
A.4 ^{1}H NMR and ^{13}C NMR Spectra



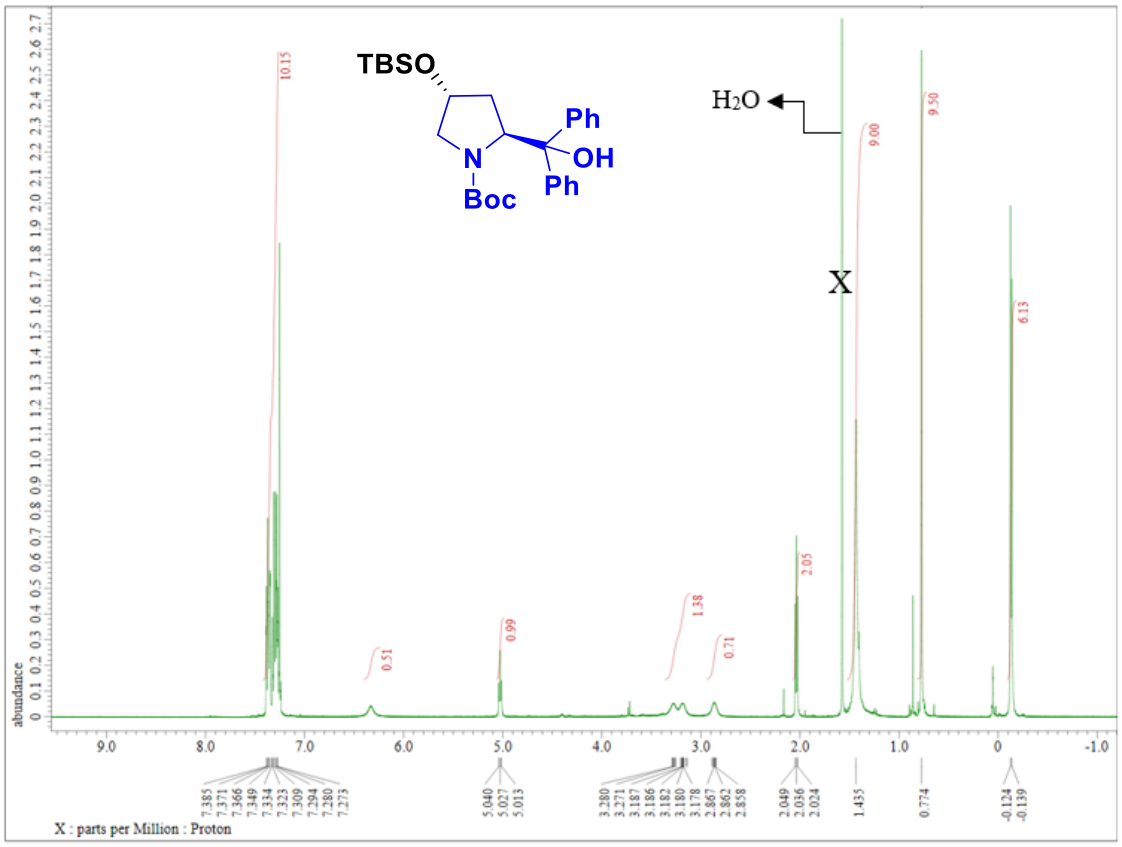
^{1}H NMR spectra of compound **II** in D_2O.



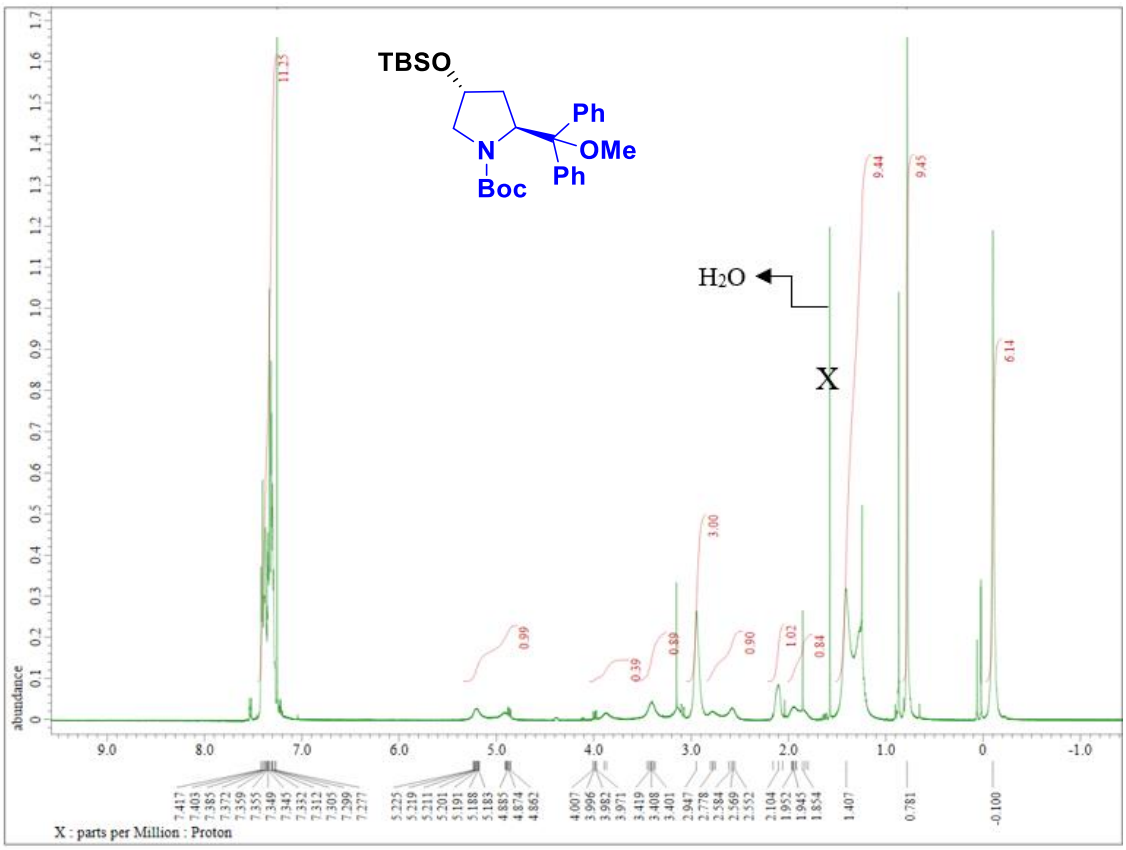
^{1}H NMR spectra of compound **III** in $CDCl_3$.



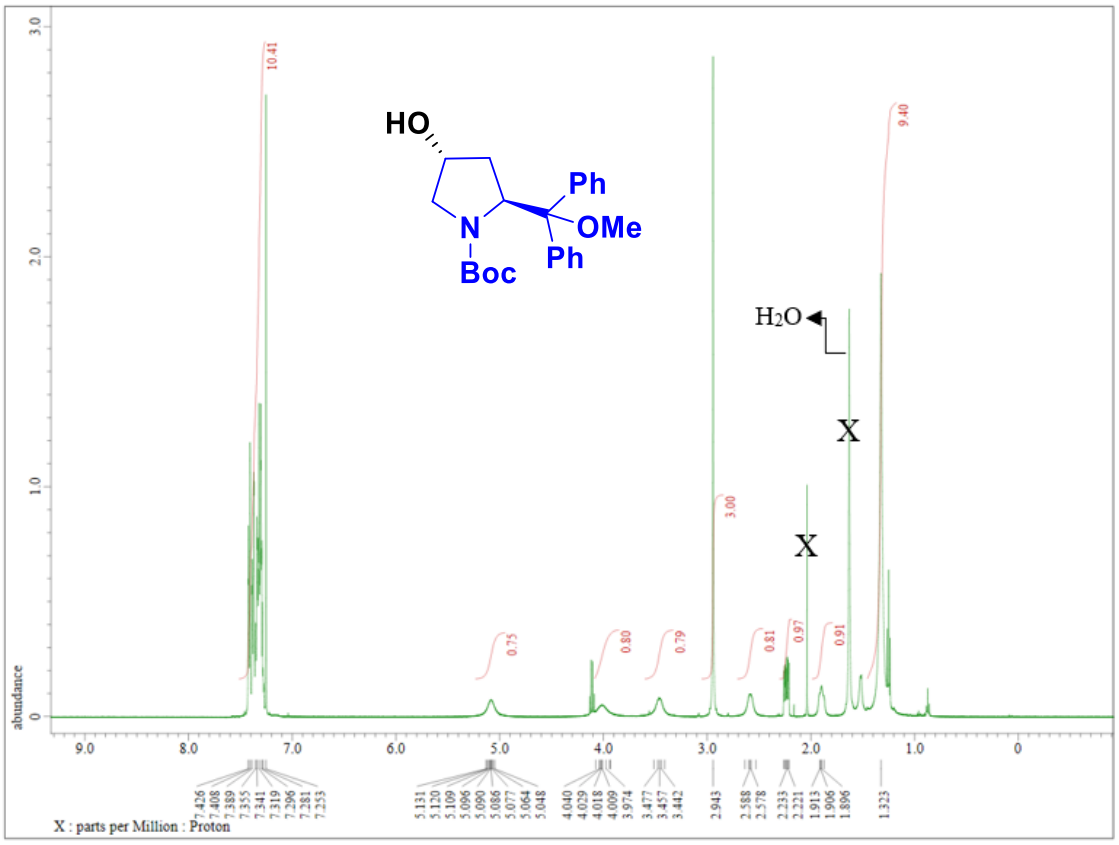
^{1}H NMR spectra of compound **IV** in $CDCl_3$.



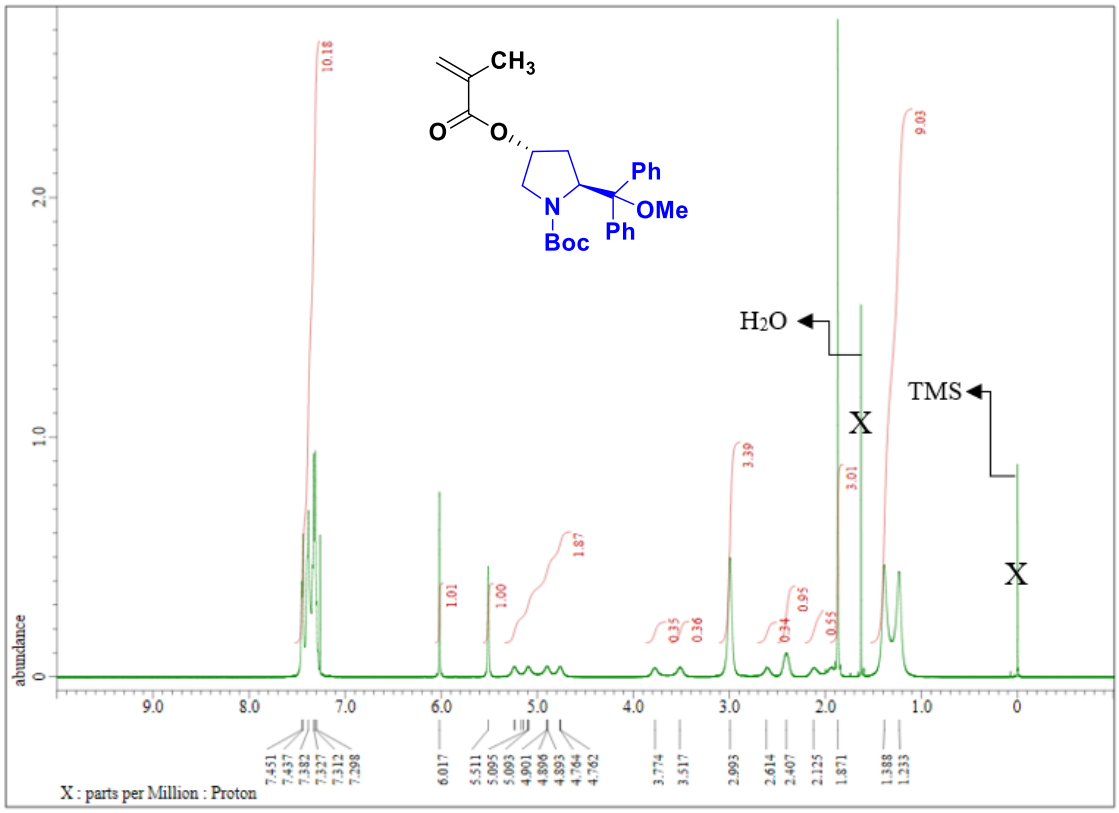
^{1}H NMR spectra of compound **V** in $CDCl_3$.



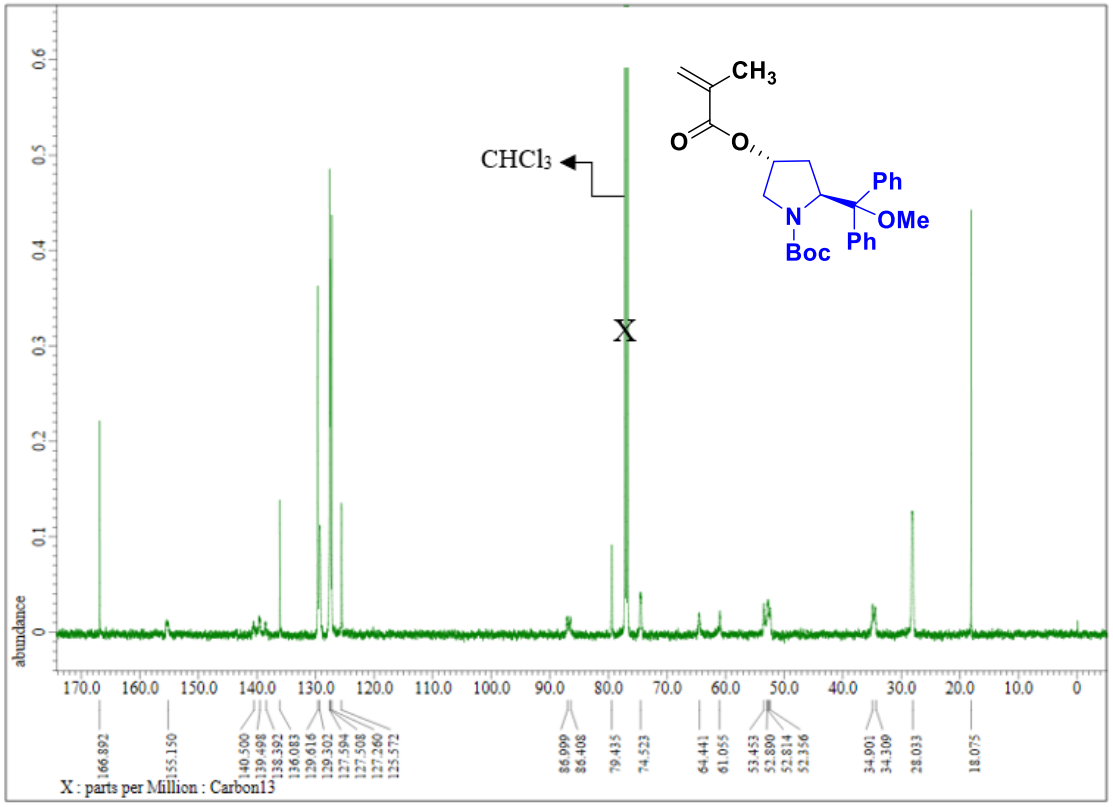
^{1}H NMR spectra of compound **VI** in $CDCl_3$.



^{1}H NMR spectra of compound **1** in $CDCl_3$.



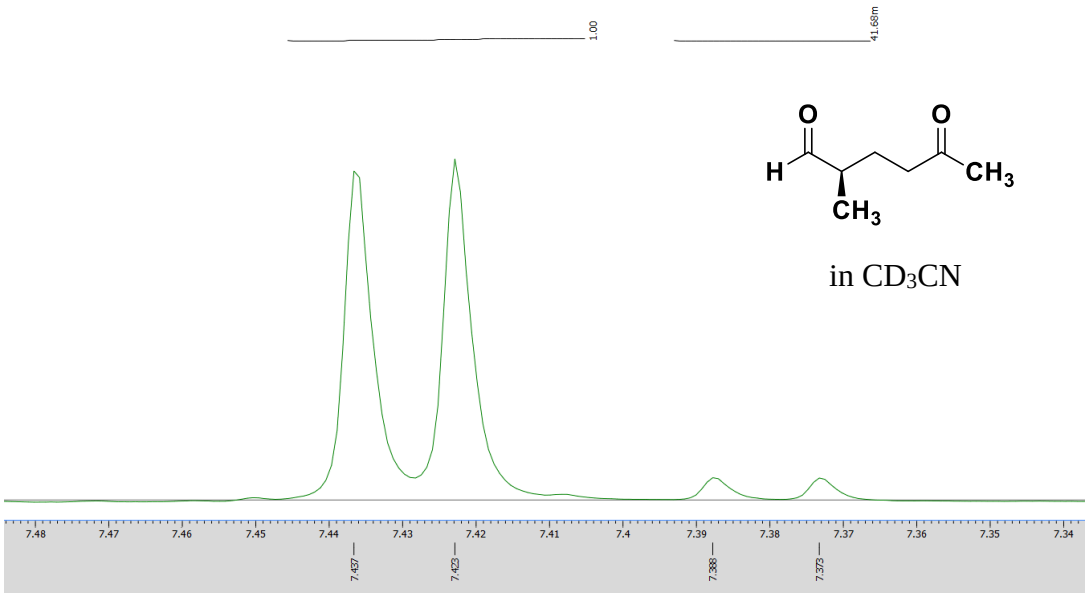
^{1}H NMR spectra of monomer **2** in $CDCl_3$.



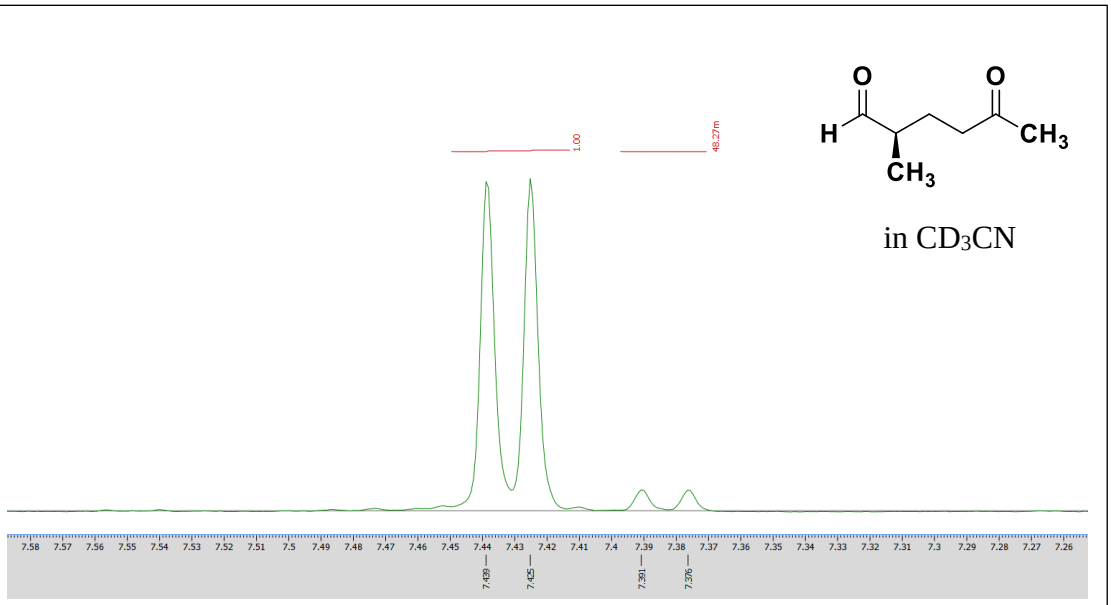
^{13}C NMR spectra of **2** in $CDCl_3$.

A.5 Enantiomeric data

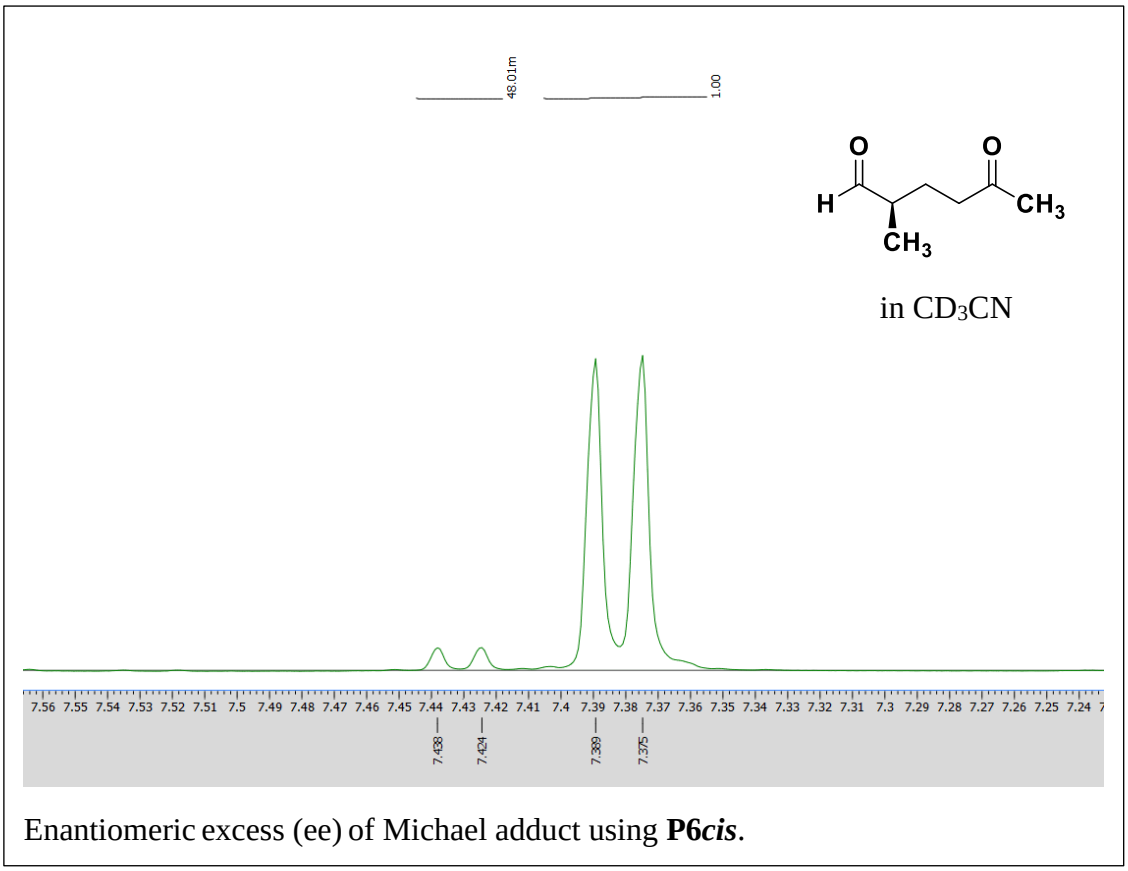
The enantiomeric excess (ee) of the Michael adducts were determined according to the reported literature.[1] Spectroscopic data are in accordance with the literature.[1]



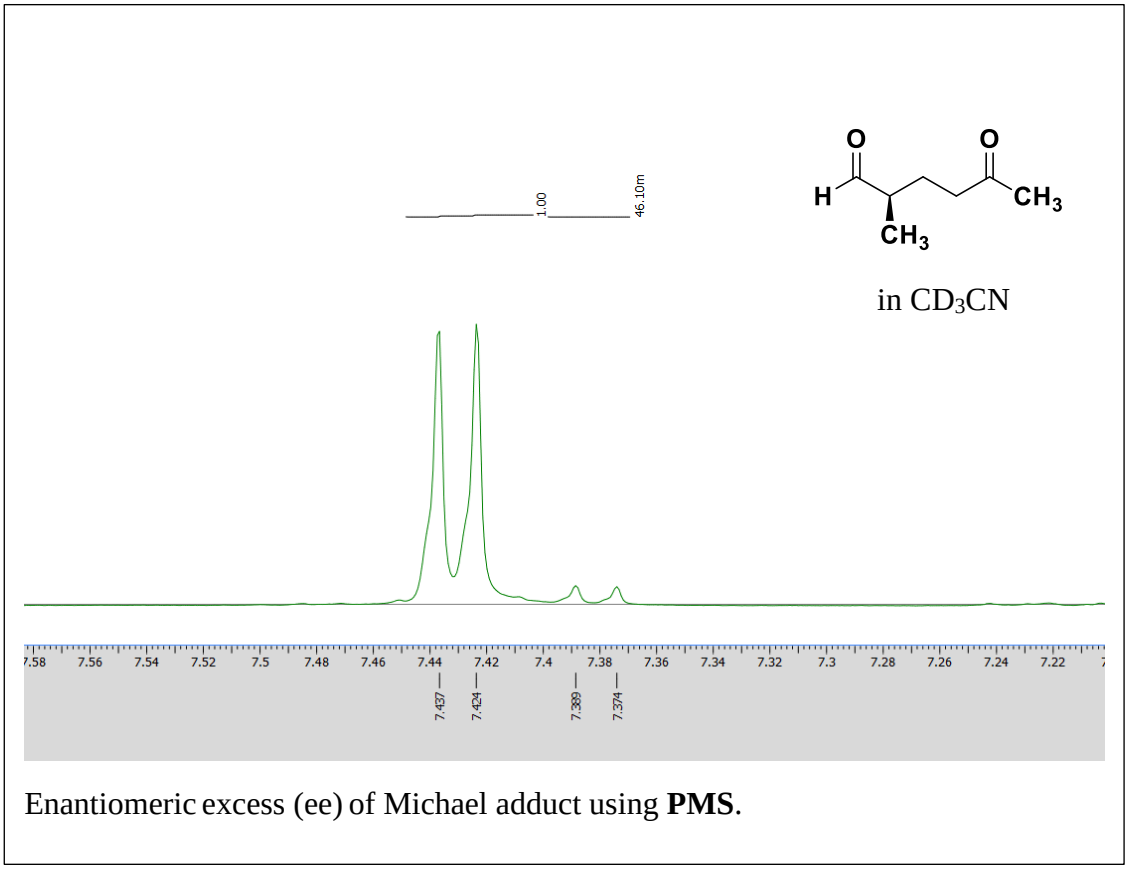
Enantiomeric excess (ee) of Michael adduct using **Ma**.



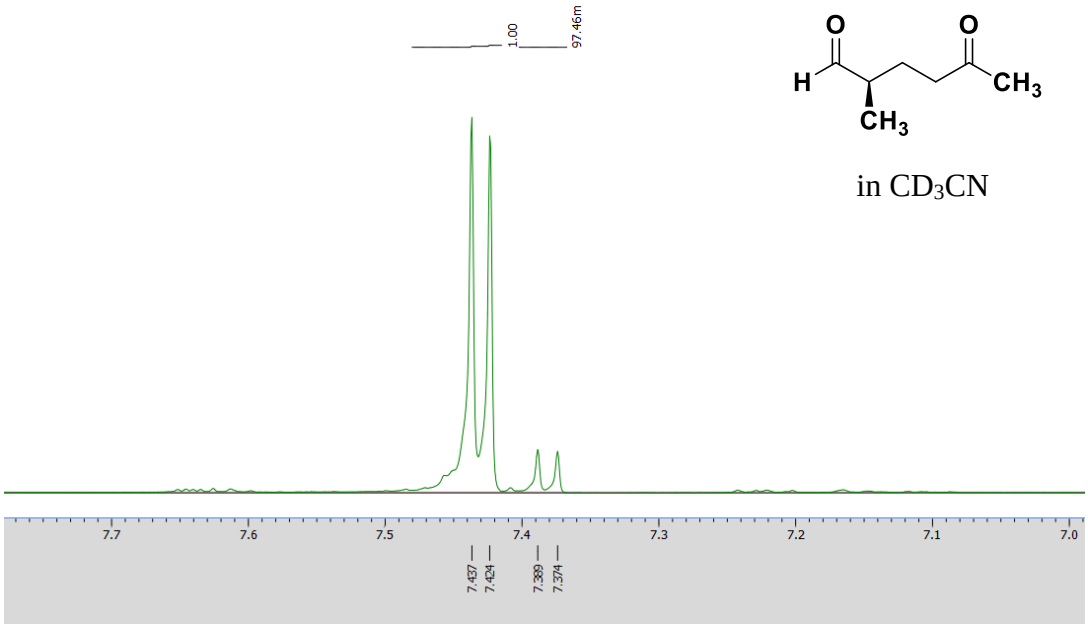
Enantiomeric excess (ee) of Michael adduct using **PS3**.



Enantiomeric excess (ee) of Michael adduct using **P6*cis***.

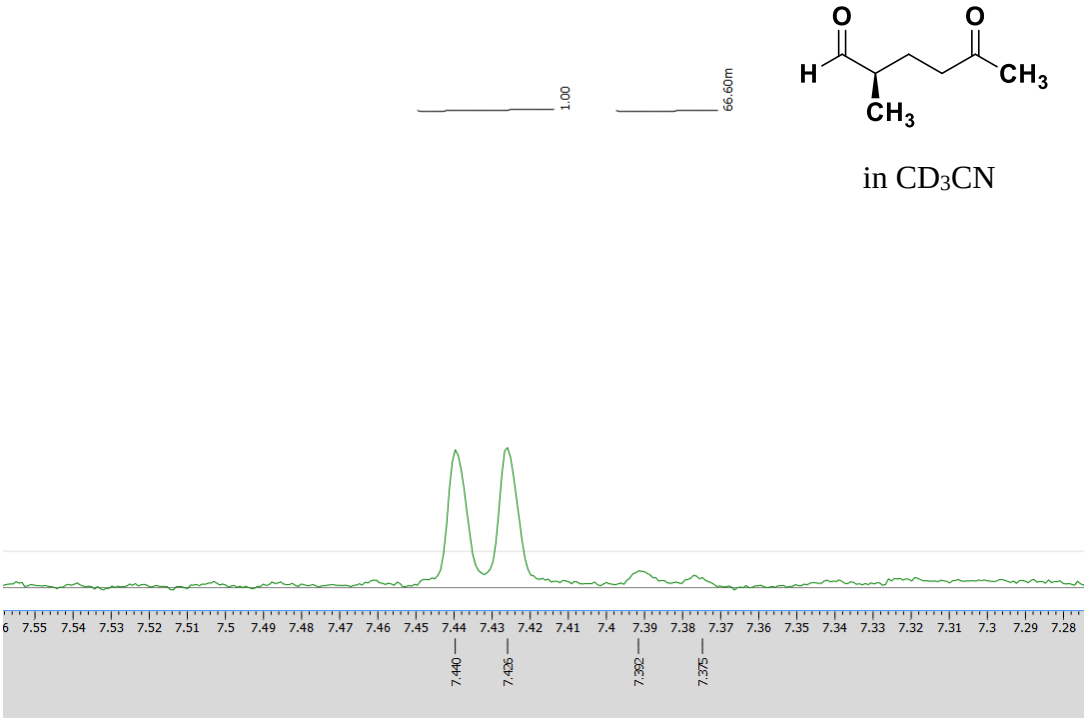


Enantiomeric excess (ee) of Michael adduct using **PMS**.



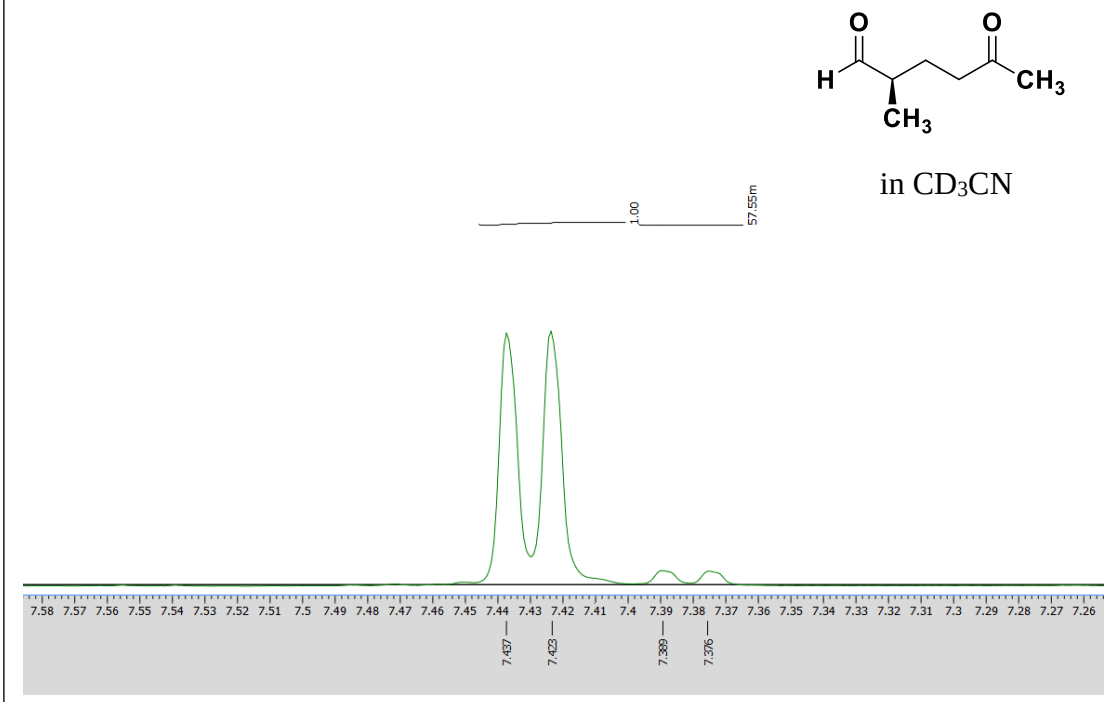
in CD_3CN

Enantiomeric excess (ee) of Michael adduct using **PT**.

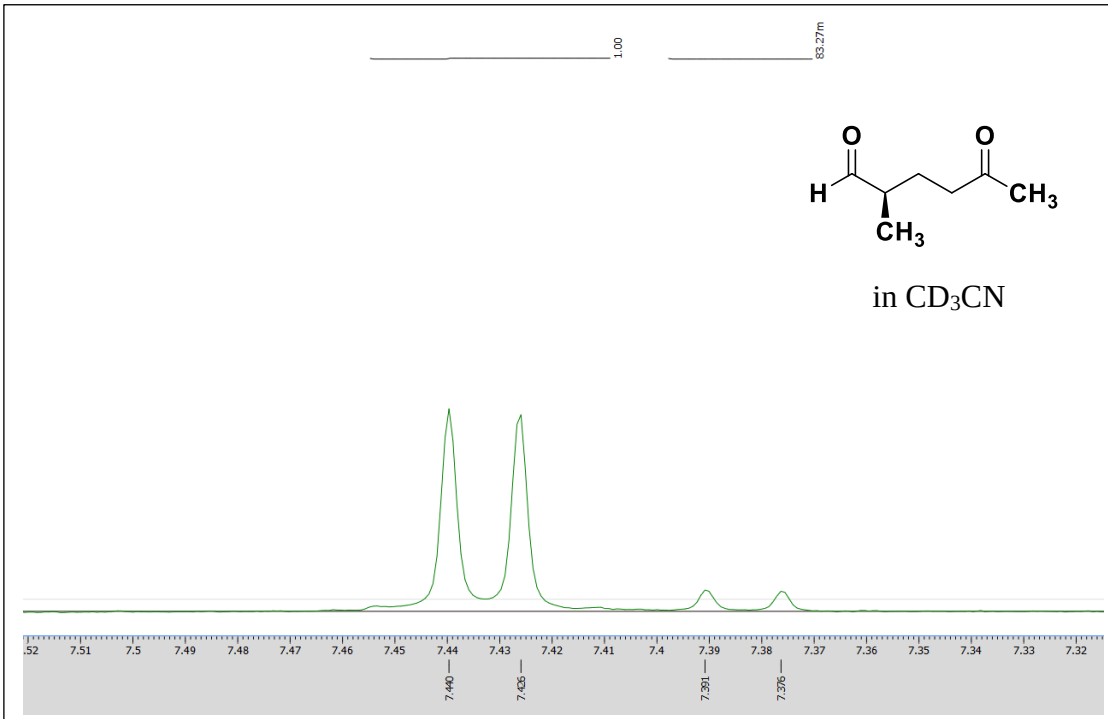


in CD_3CN

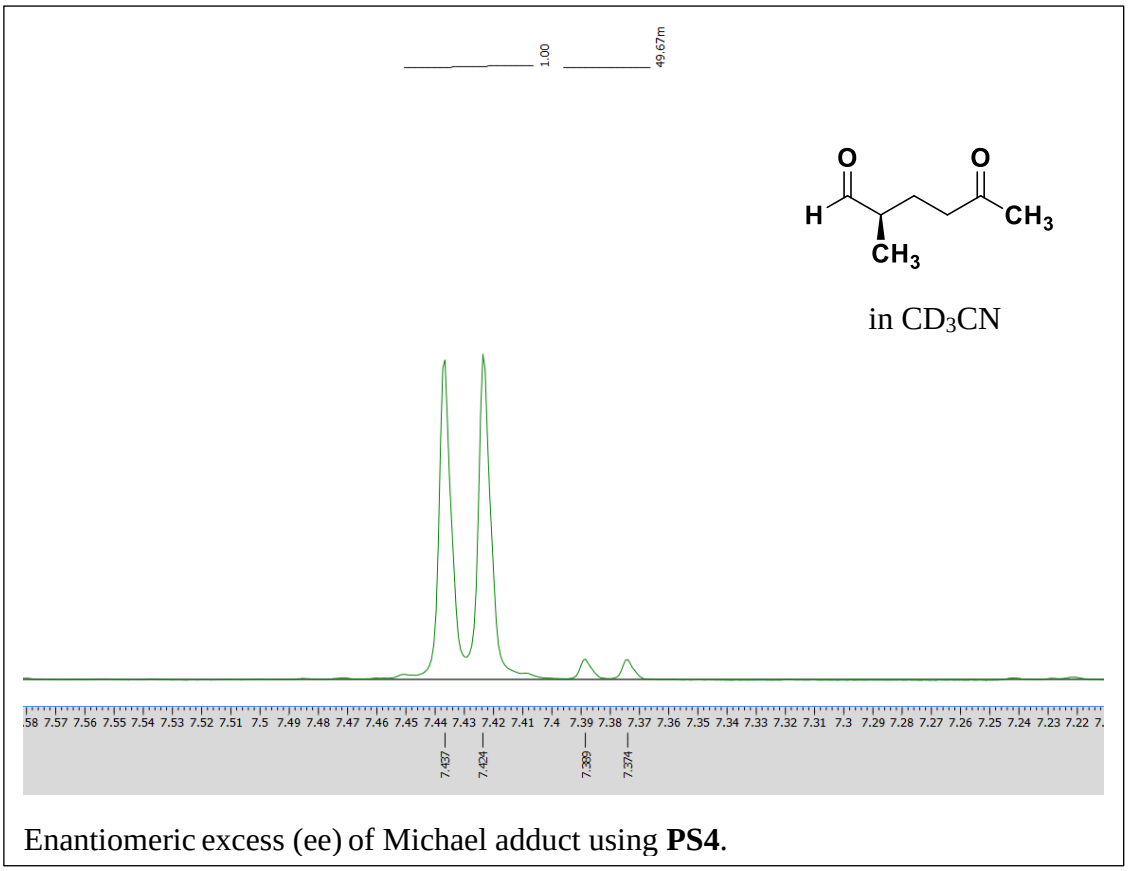
Enantiomeric excess (ee) of Michael adduct using **PH**.



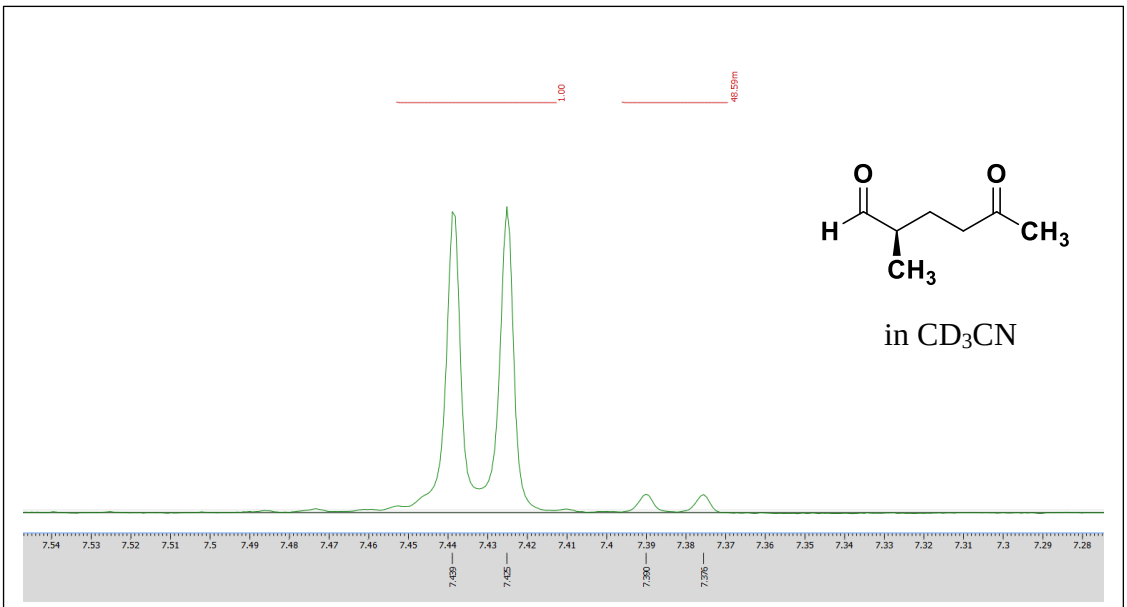
Enantiomeric excess (ee) of Michael adduct using **PN**.



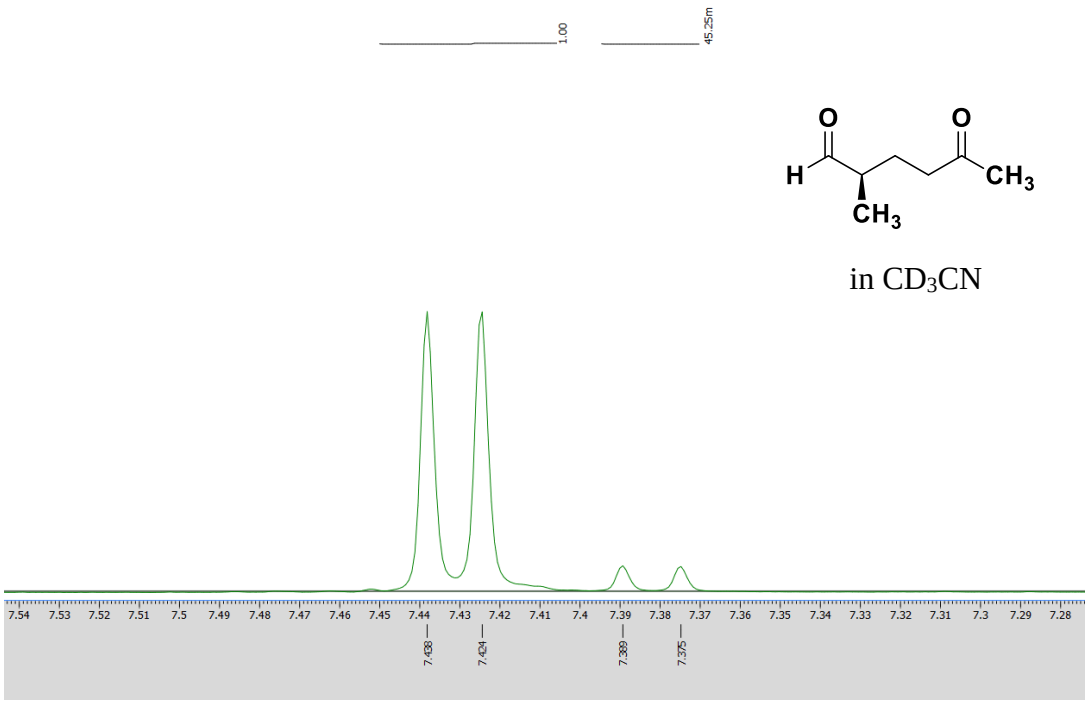
Enantiomeric excess (ee) of Michael adduct using **PM**.



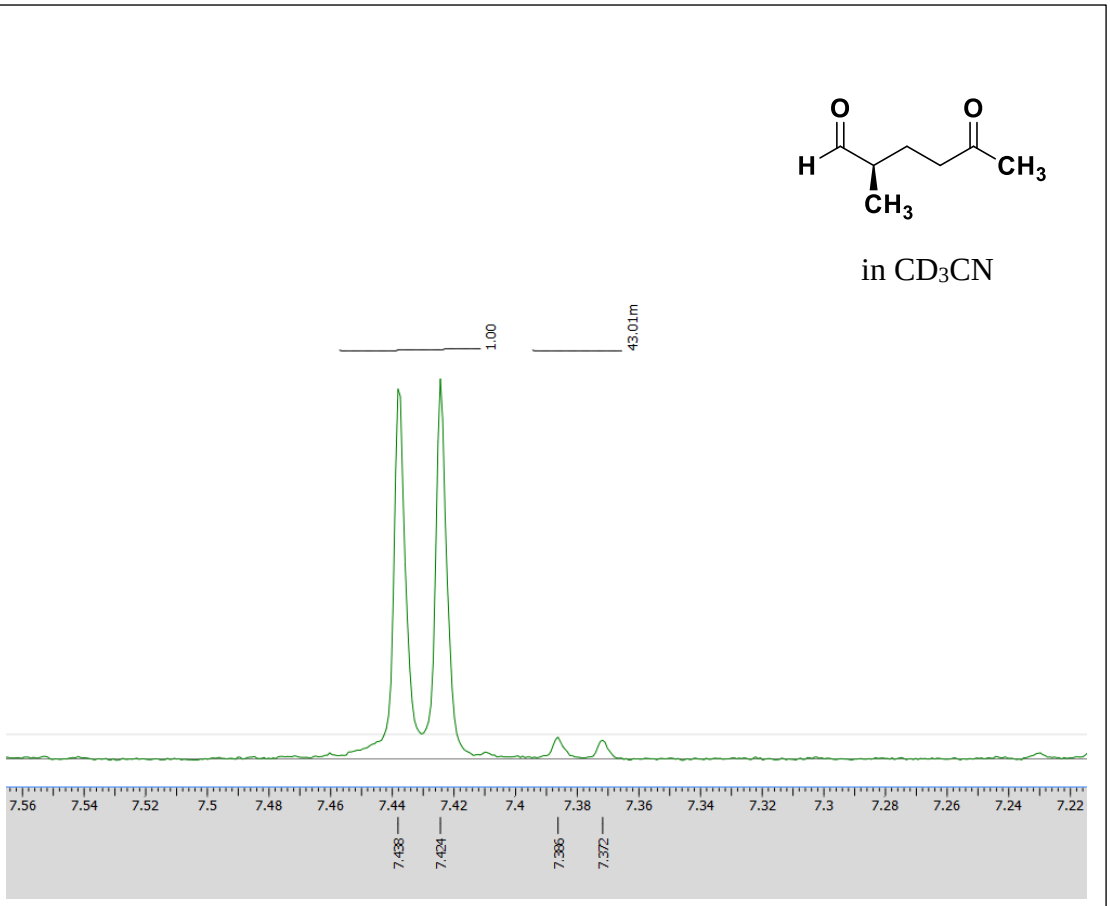
Enantiomeric excess (ee) of Michael adduct using **PS4**.



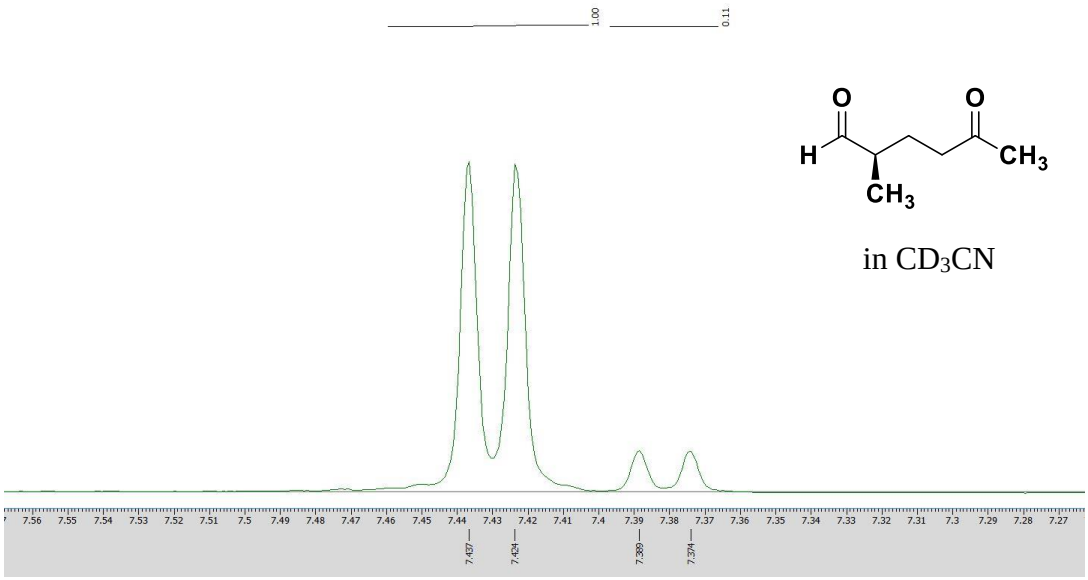
Enantiomeric excess (ee) of Michael adduct using **PS5**.



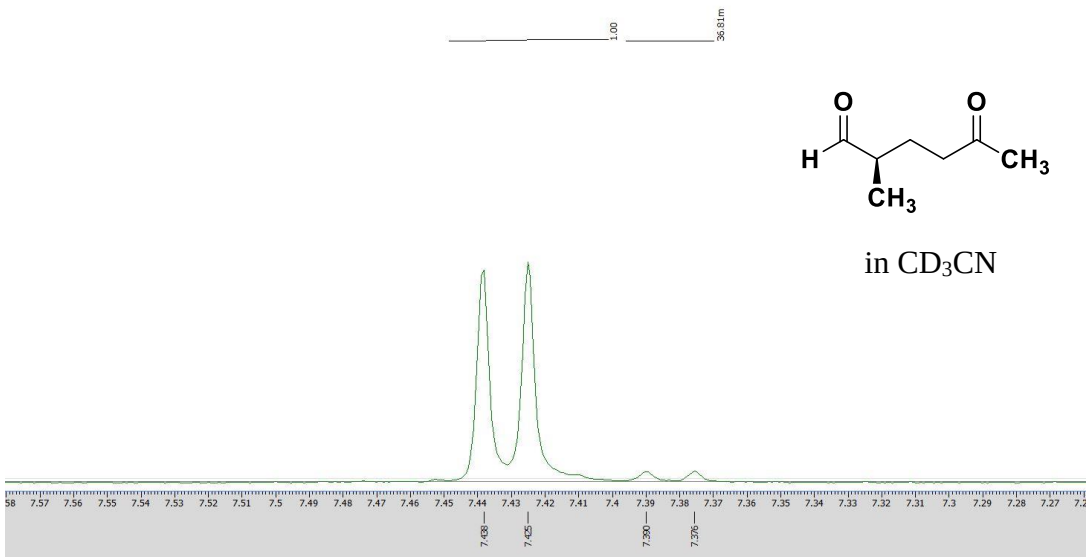
Enantiomeric excess (ee) of Michael adduct using **PS5** (with 3 mol%).



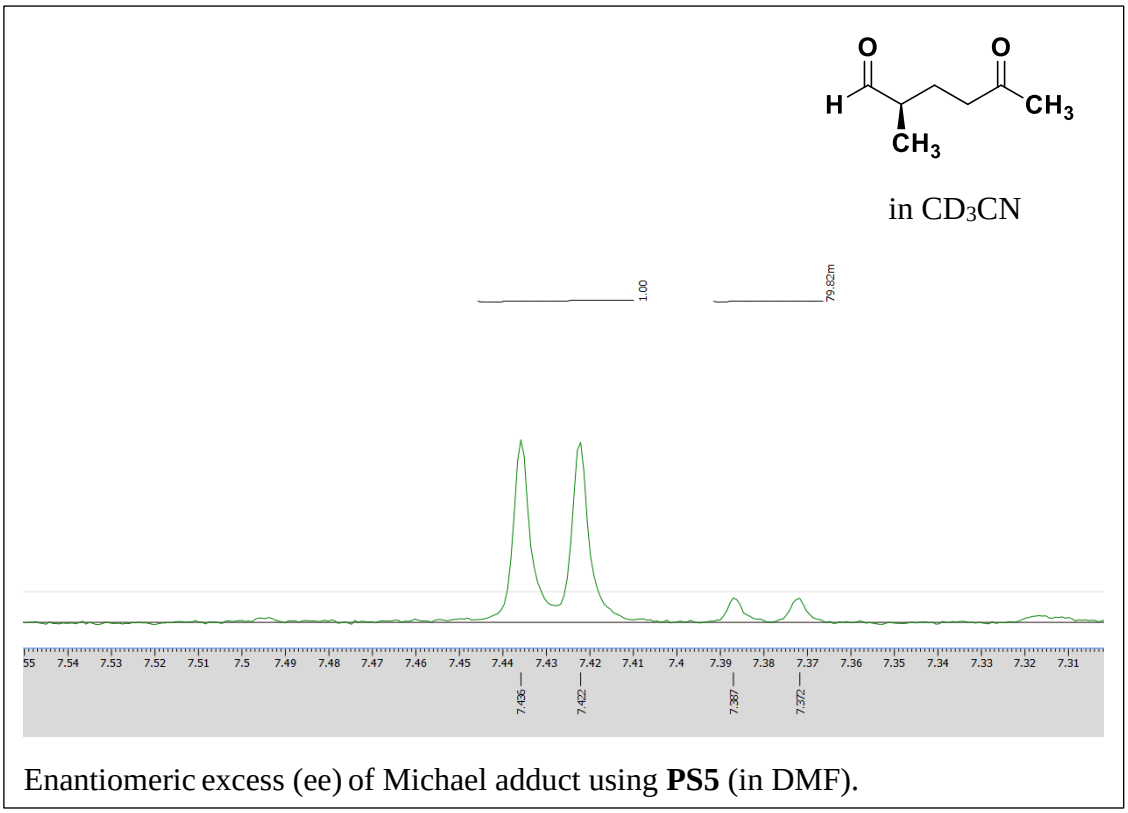
Enantiomeric excess (ee) of Michael adduct using **PS5** (with 1 mol%).



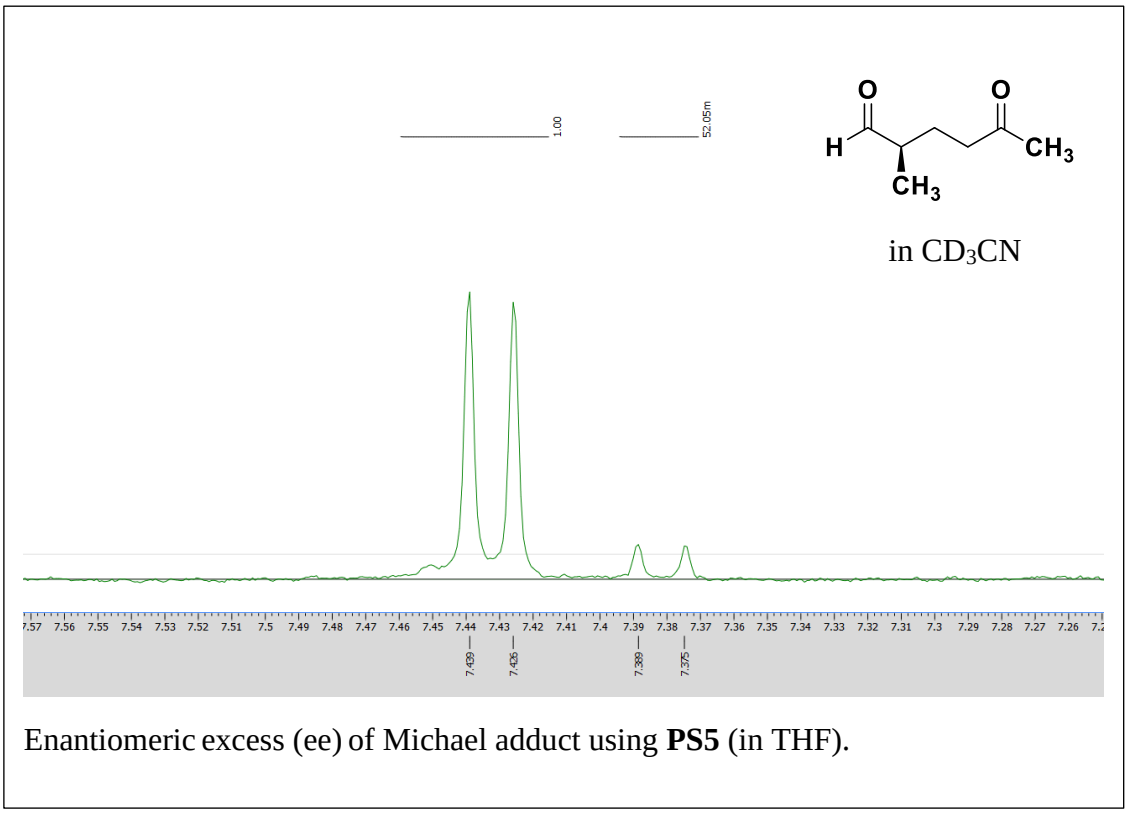
Enantiomeric excess (ee) of Michael adduct using **PS5** (at 30 °C).



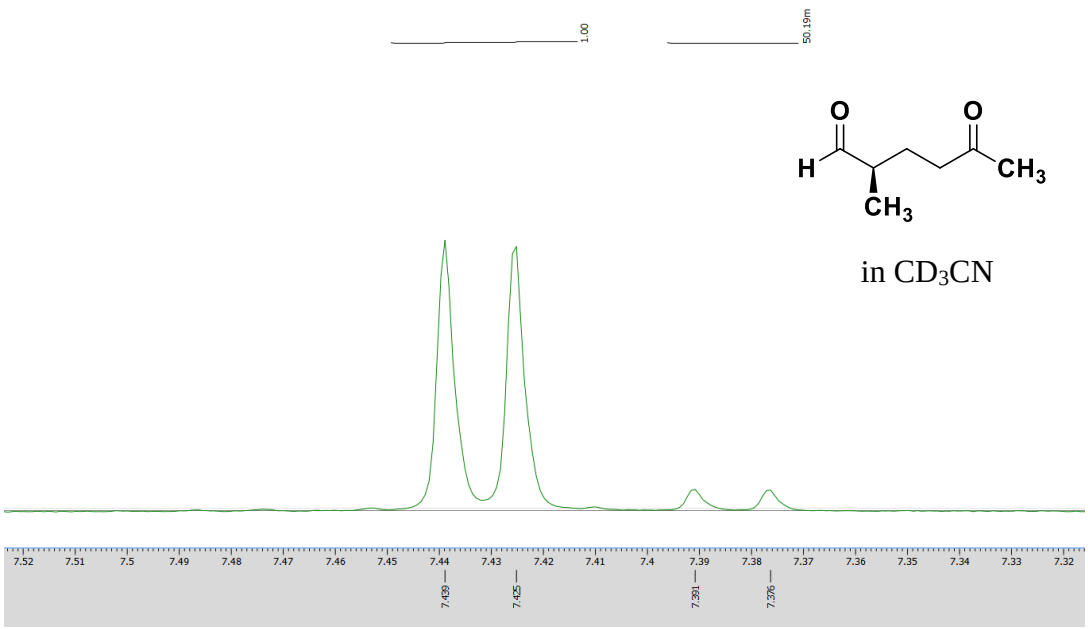
Enantiomeric excess (ee) of Michael adduct using **PS5** (at 0 °C).



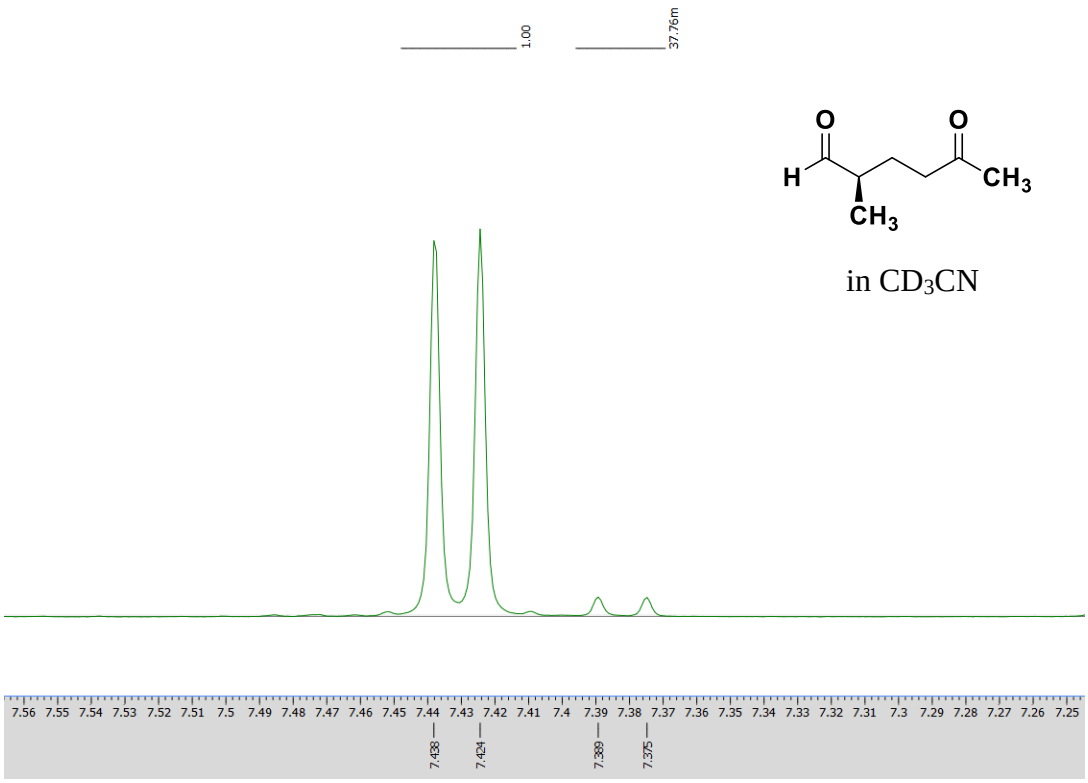
Enantiomeric excess (ee) of Michael adduct using **PS5** (in DMF).



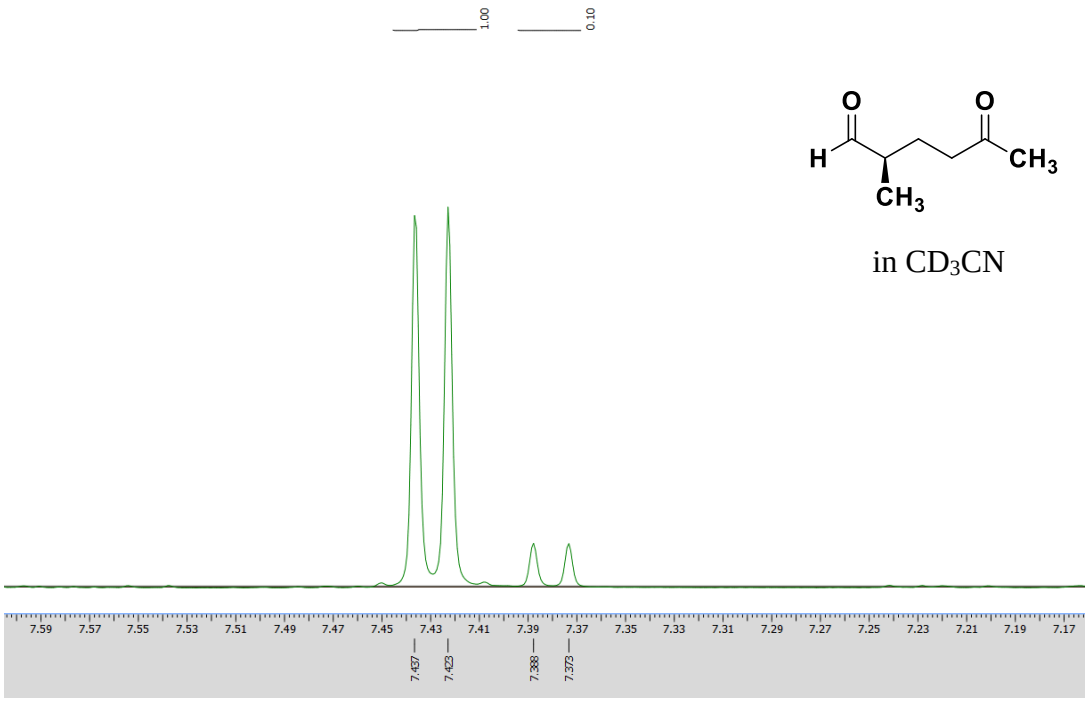
Enantiomeric excess (ee) of Michael adduct using **PS5** (in THF).



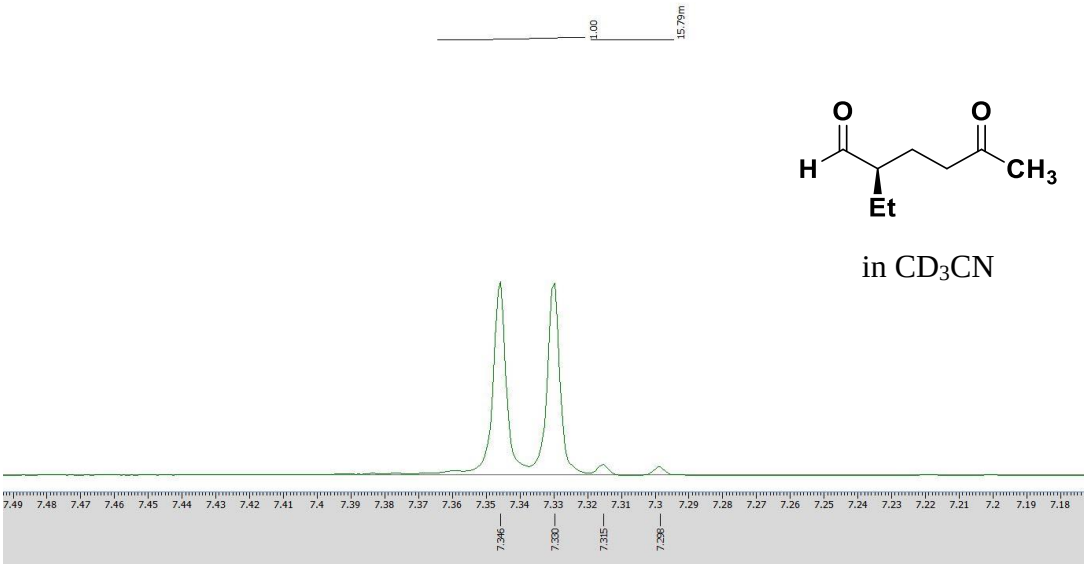
Enantiomeric excess (ee) of Michael adduct using **PS5** (in CH_2Cl_2).



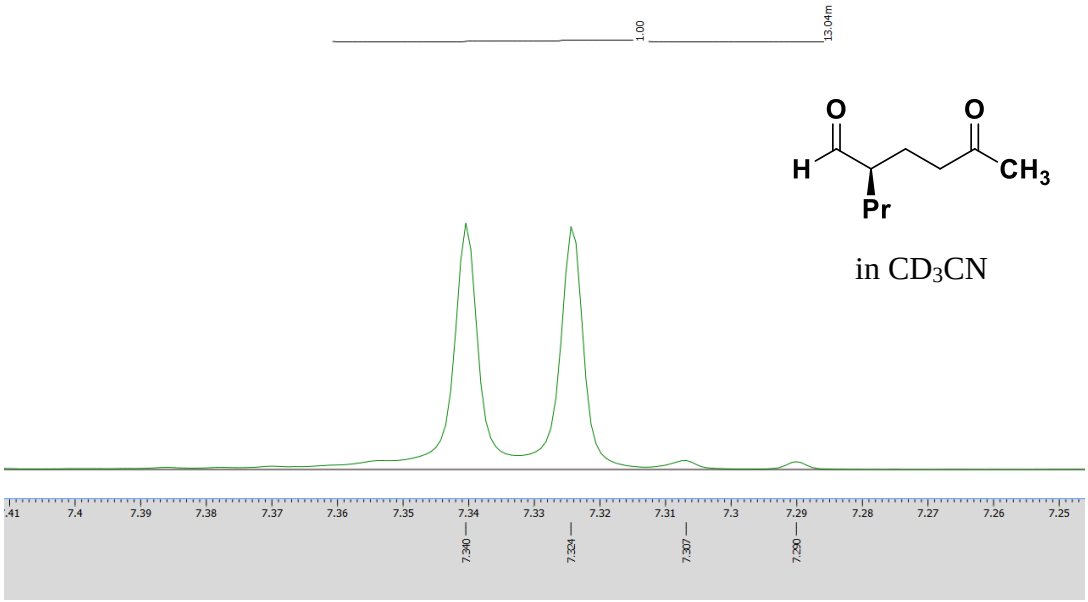
Enantiomeric excess (ee) of Michael adduct using **PS5** (in toluene).



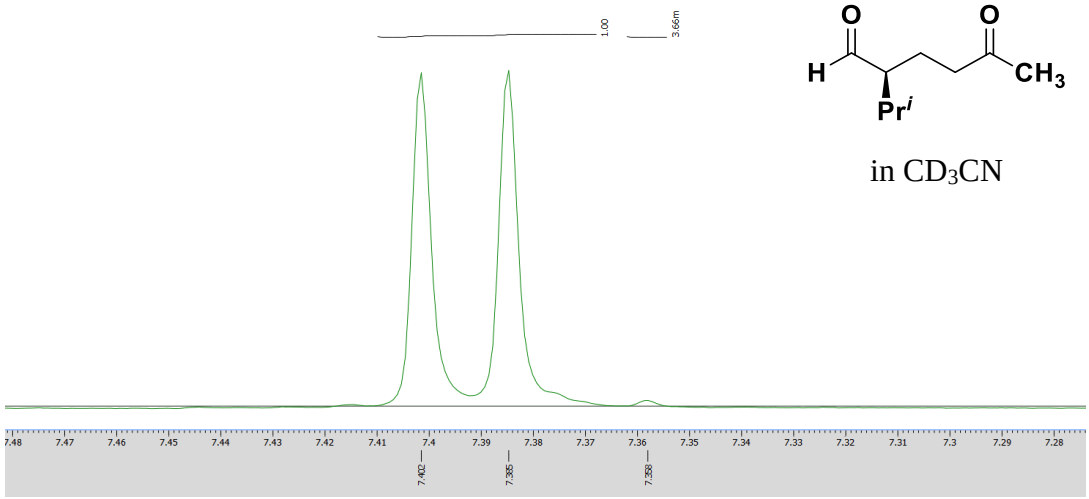
Enantiomeric excess (ee) of Michael adduct using **PS5** (in hexane).



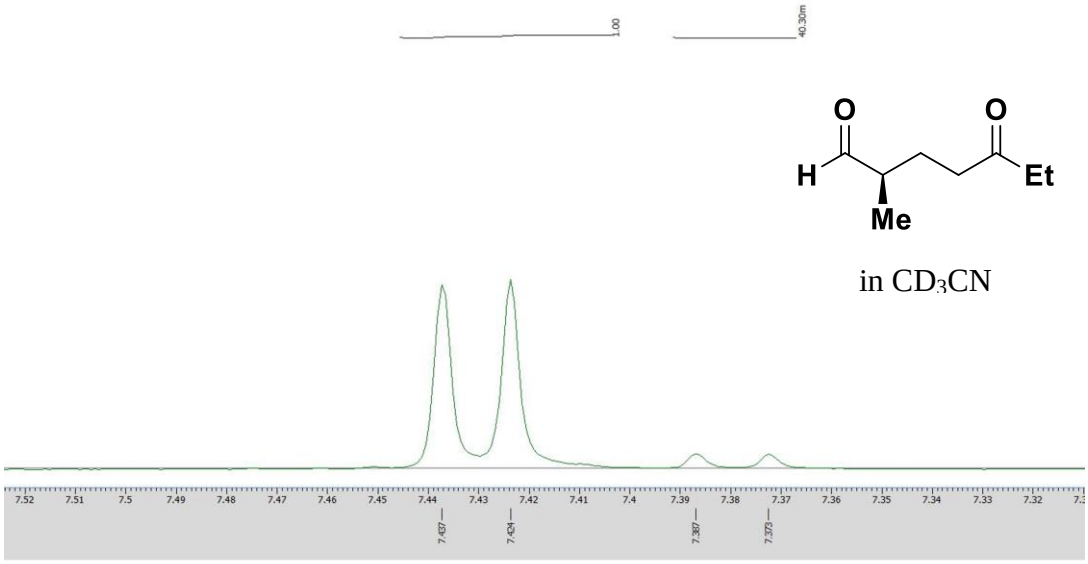
Enantiomeric excess (ee) of Michael adduct **E9**.



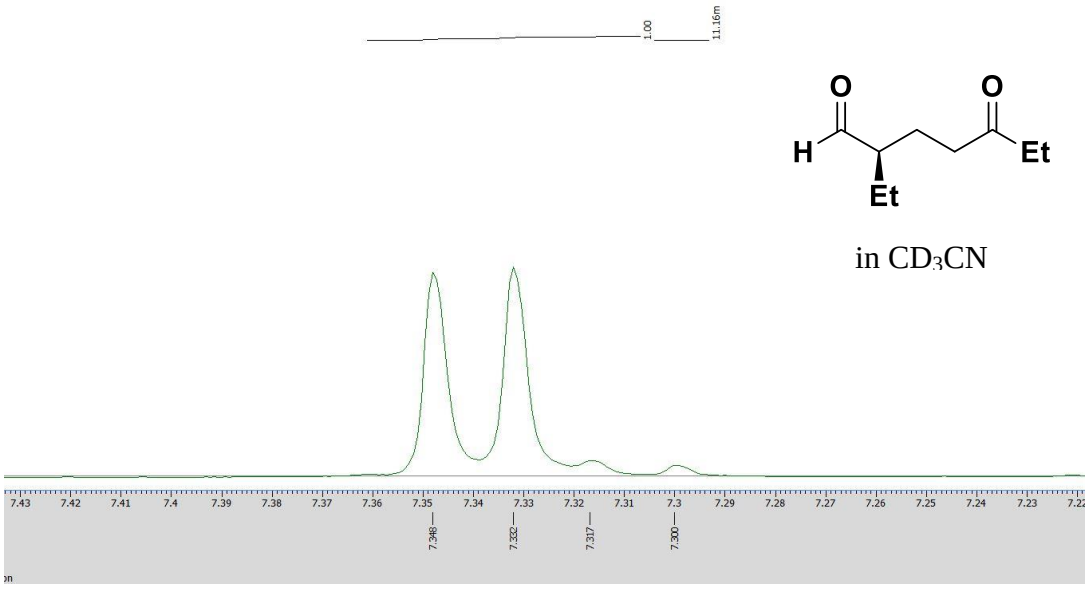
Enantiomeric excess (ee) of Michael adduct **E10**.



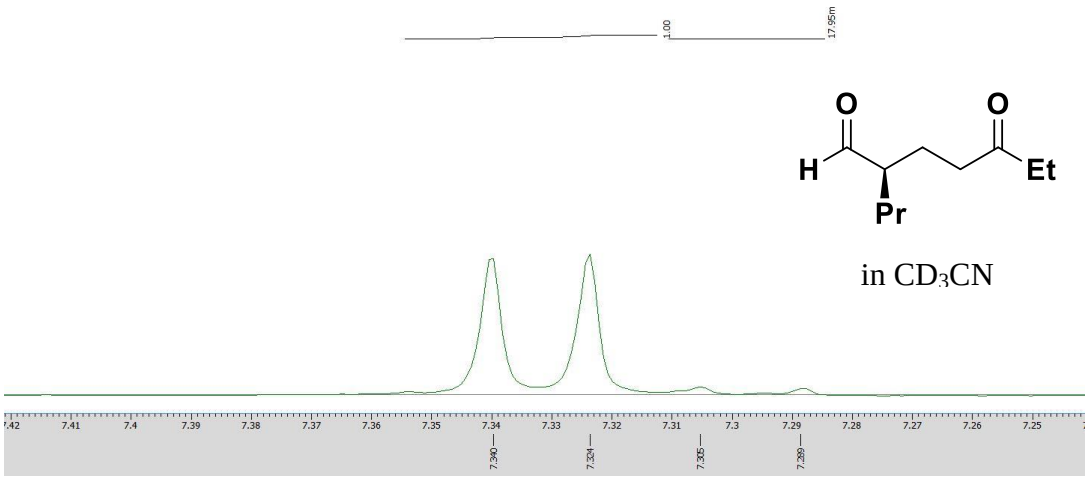
Enantiomeric excess (ee) of Michael adduct **E11**.



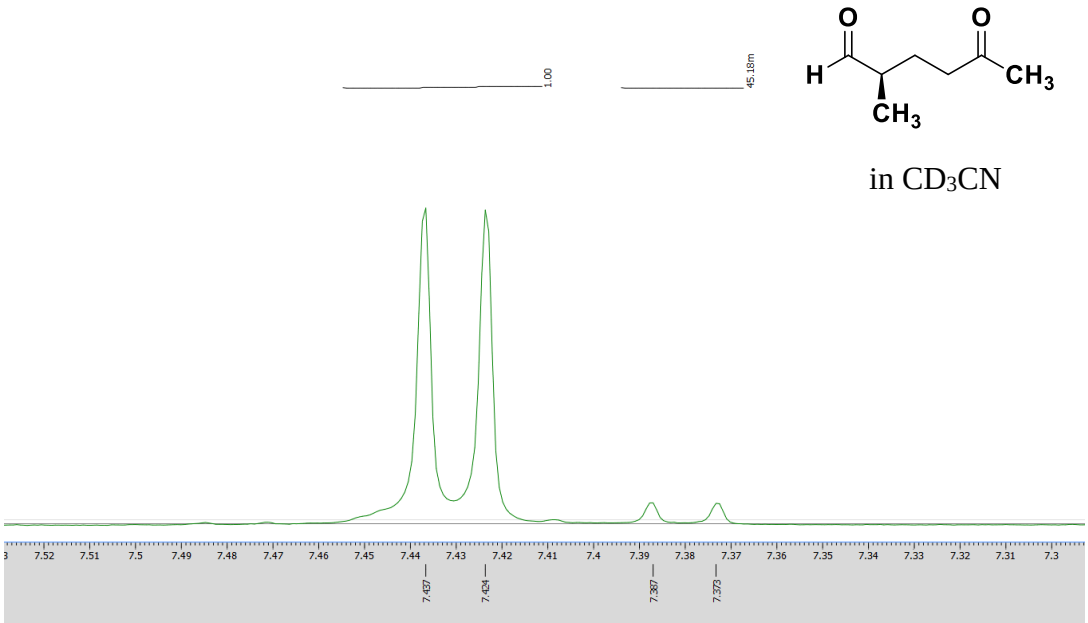
Enantiomeric excess (ee) of Michael adduct **E12**.



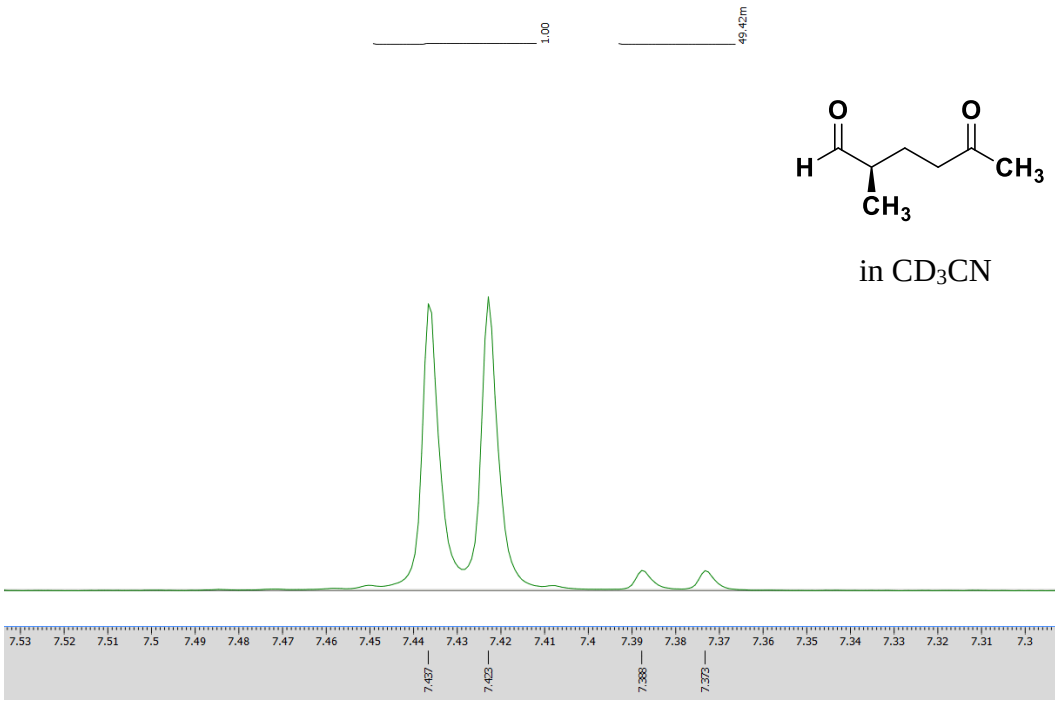
Enantiomeric excess (ee) of Michael adduct **E13**.



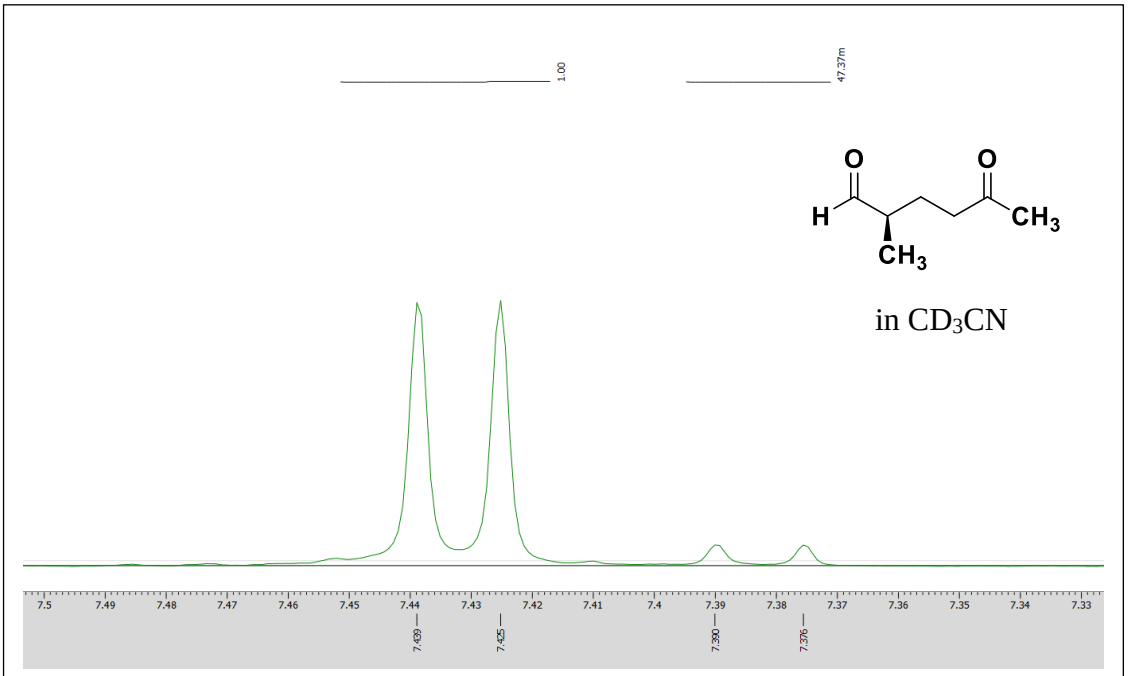
Enantiomeric excess (ee) of Michael adduct **E14**.



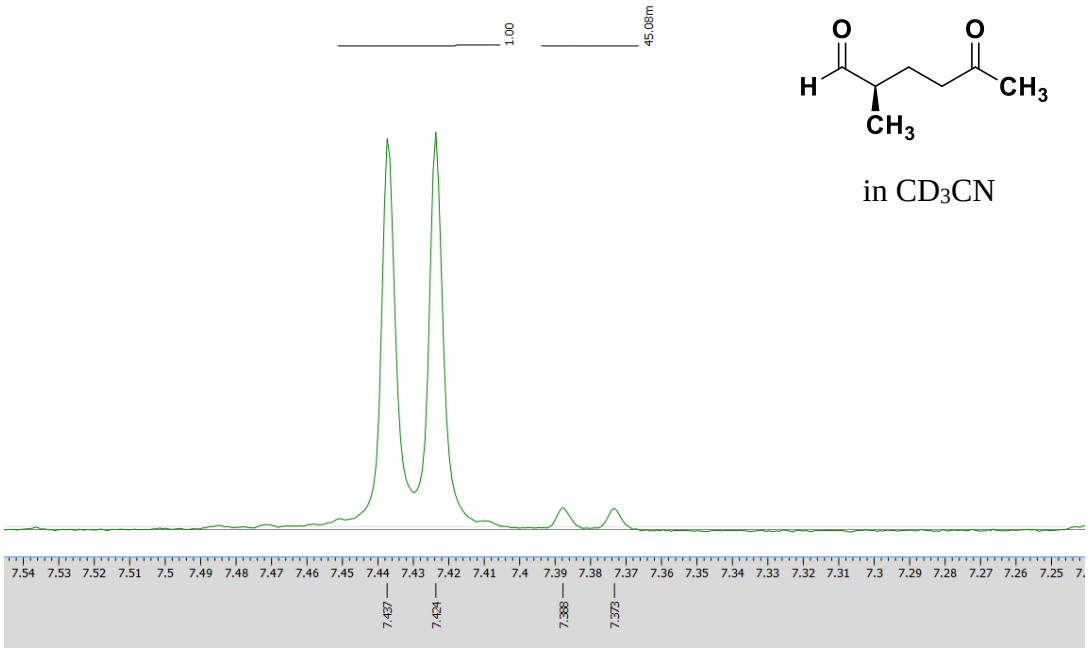
Enantiomeric excess (ee) of Michael adduct (cycle 1).



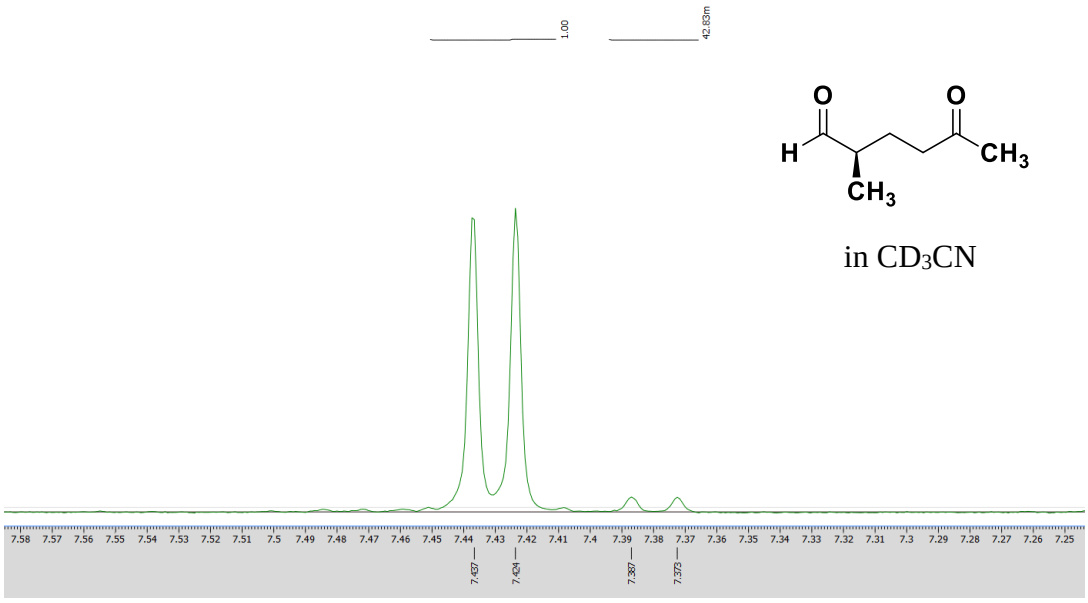
Enantiomeric excess (ee) of Michael adduct (cycle 2).



Enantiomeric excess (ee) of Michael adduct (cycle 3).



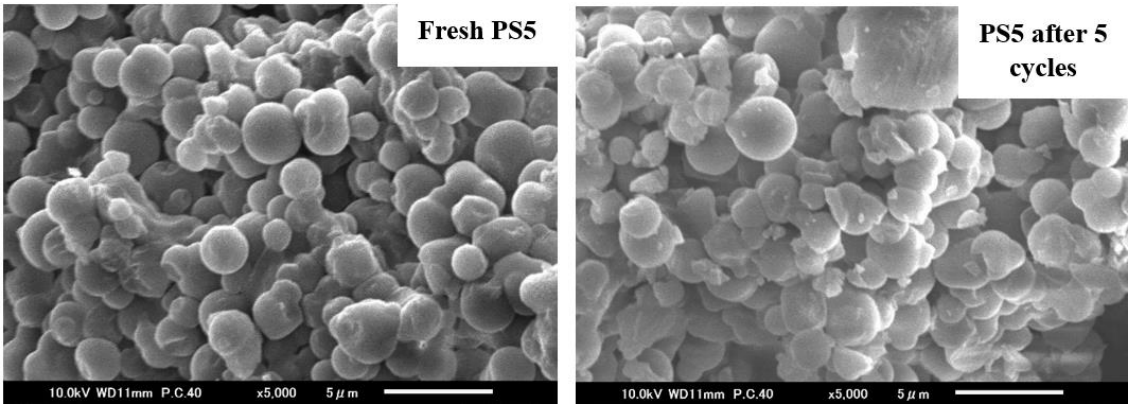
Enantiomeric excess (ee) of Michael adduct (cycle 4).



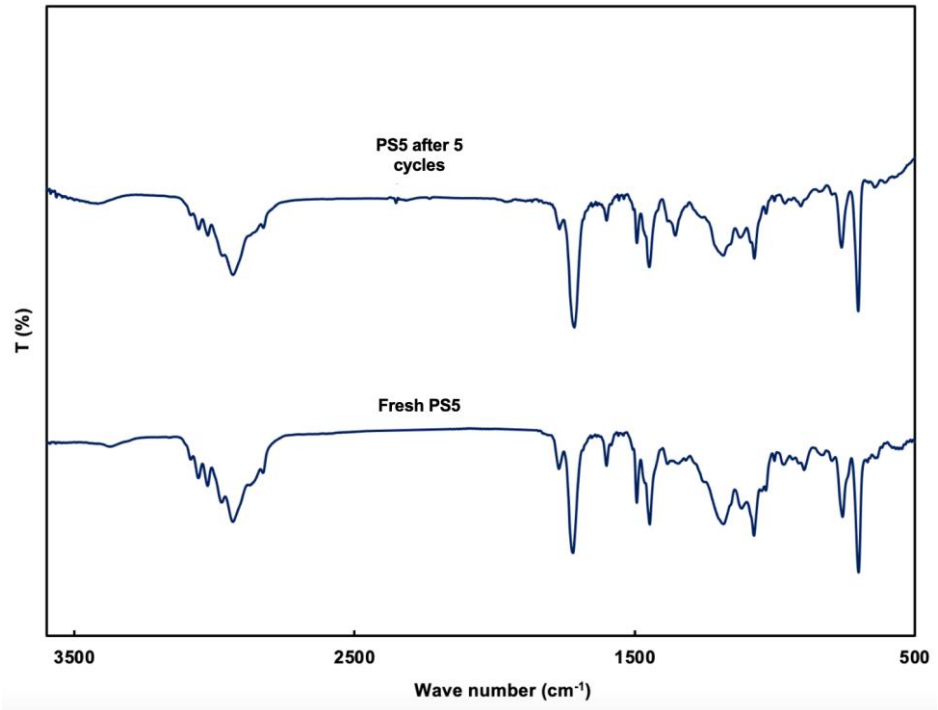
Enantiomeric excess (ee) of Michael adduct (cycle 5).

A.7 Test of recyclability

The test of recyclabilty was started with 3.0 mmol propionaldehyde, 0.15 mmol **PS5,** 0.60 mmol ethyl 3,4-dihydroxybenzoate, and 4.50 mmol methyl vinyl ketone at 15 °C. In every cycle, the reaction was carried out for 96 h under Ar. After the completion of every cycle, the catalyst **PS5** was recovered by simple centrifugation method using THF as extraction solvent. The recovered polymeric catalyst was washed with THF, MeOH, H_2O, and THF. The complete removal of the ethyl 3,4-dihydroxybenzoate from the polymeric catalyst was confirmed by the test of TLC method.



Sem images of fresh **PS5** and **PS5** after 5 cycles.



FT-IR spectra of fresh and recycled catalyst **PS5** after five cycles.

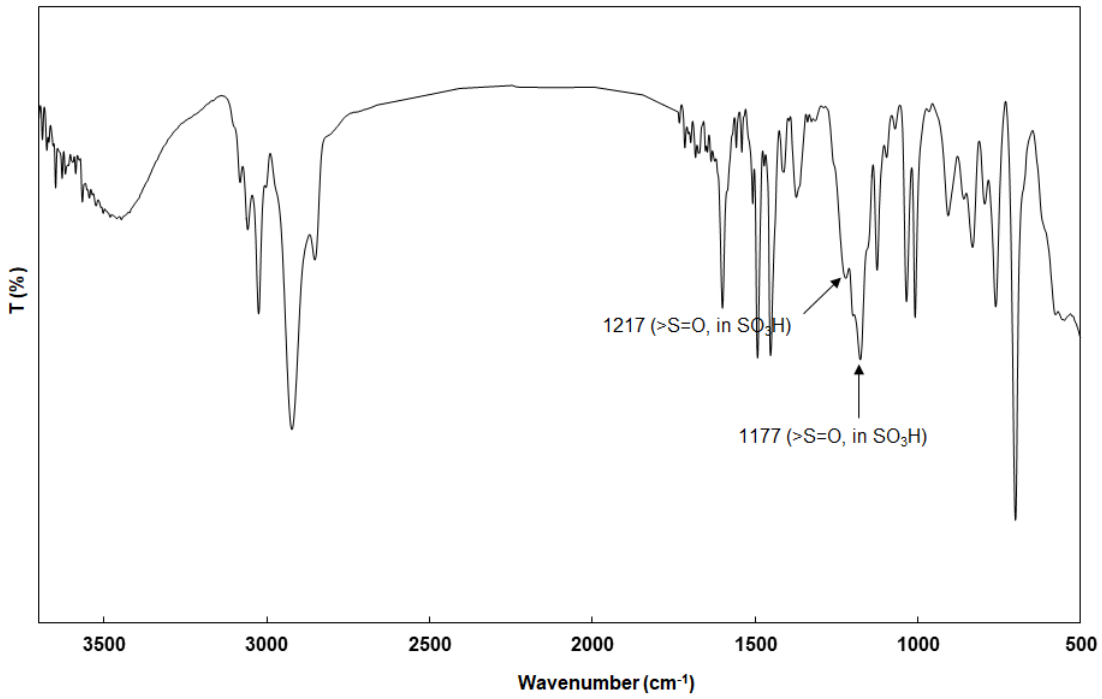
Reference

[1] Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253.

APPENDIX B

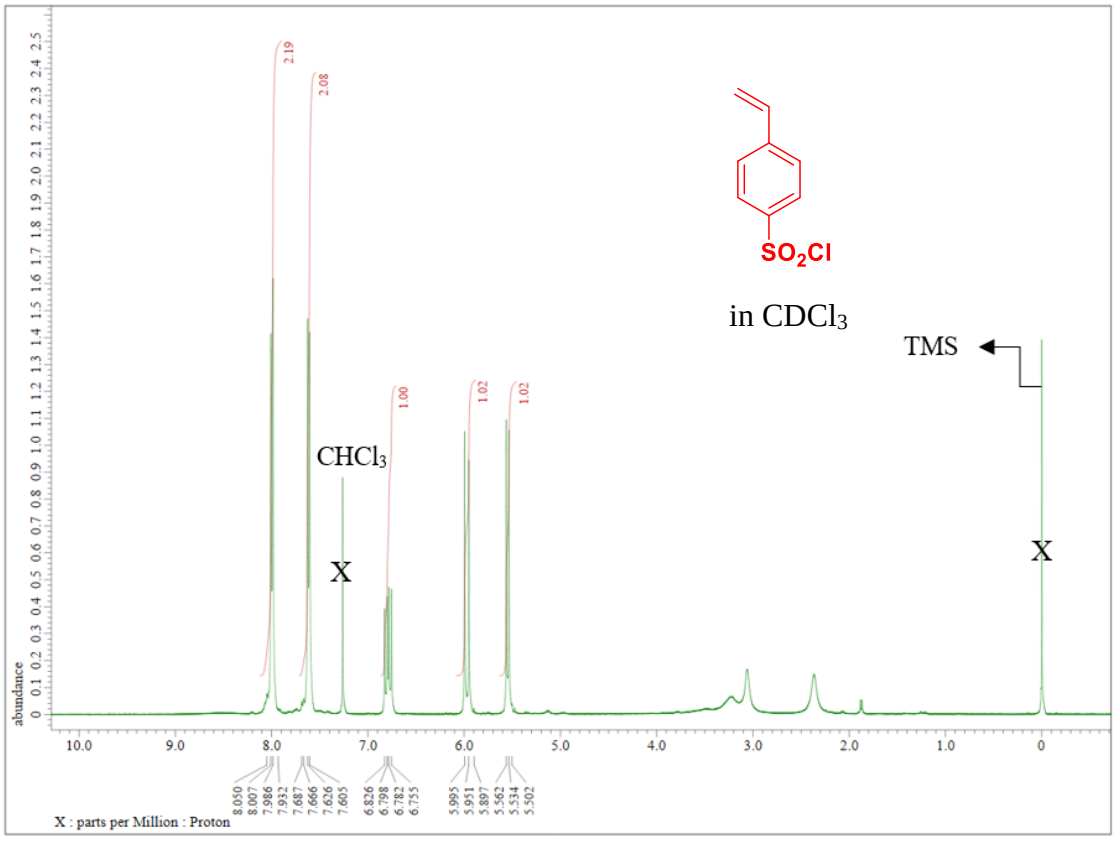
Supplementary Information for Chapter III

B.1 FT-IR spectra

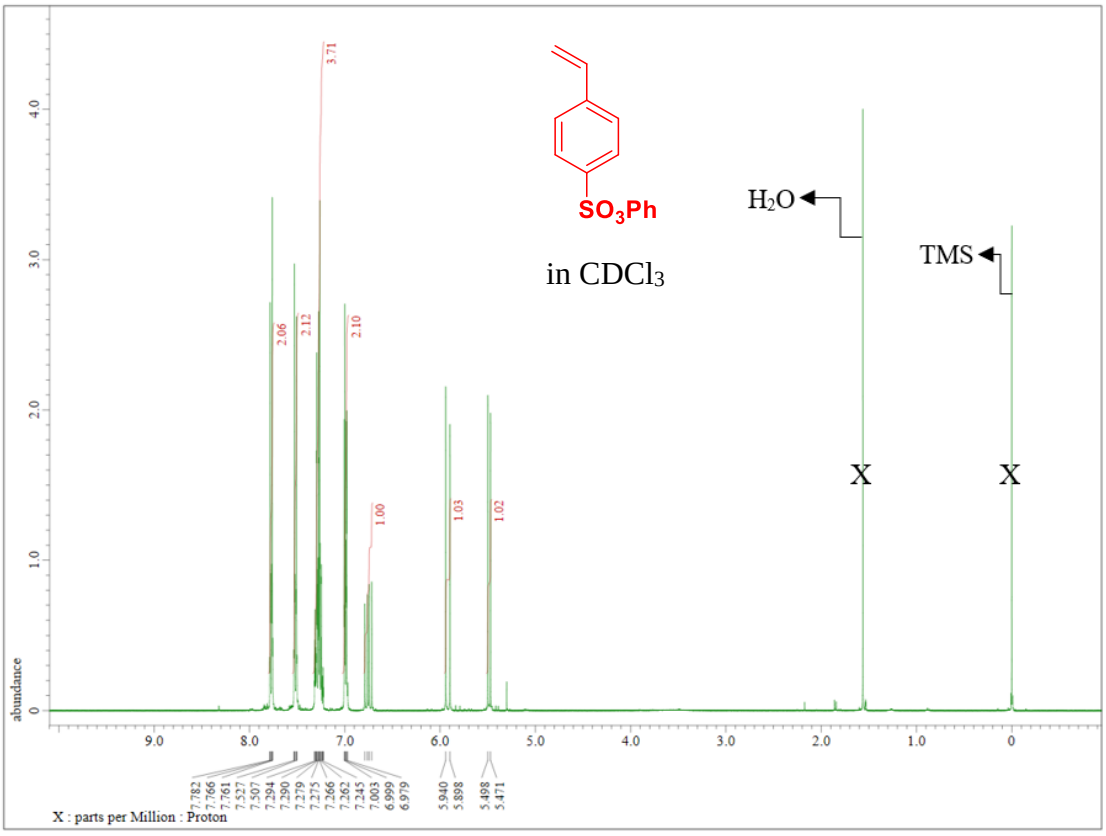


FT-IR spectra of **PSSH**.

B.2 ^{1}H NMR spectra

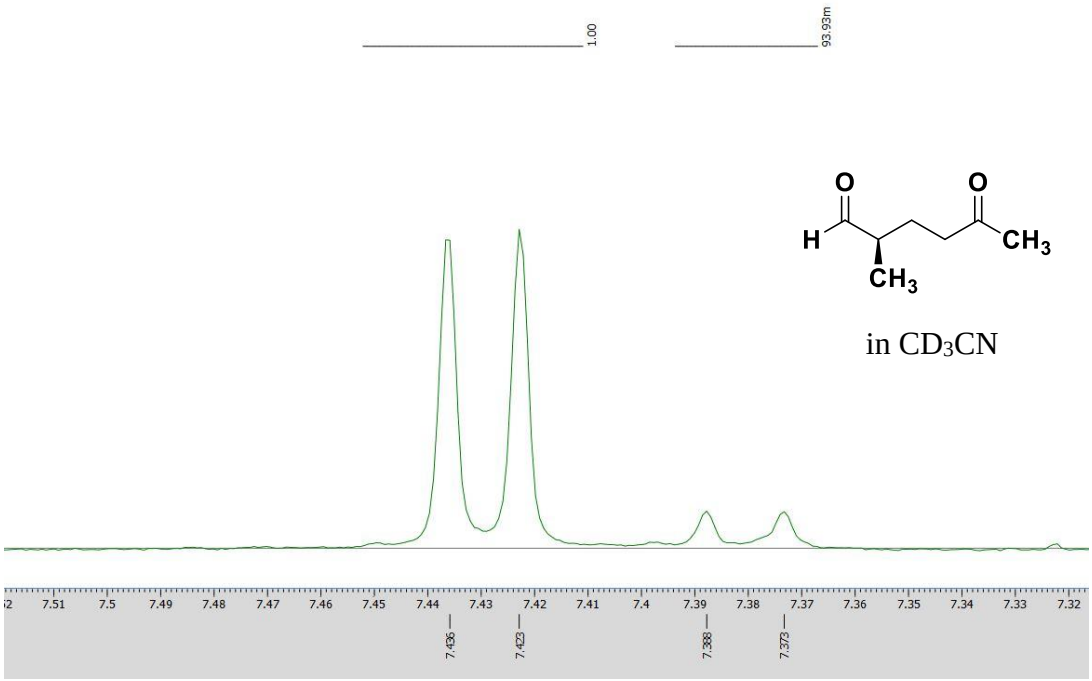


^{1}H NMR spectra of **SSCl**.

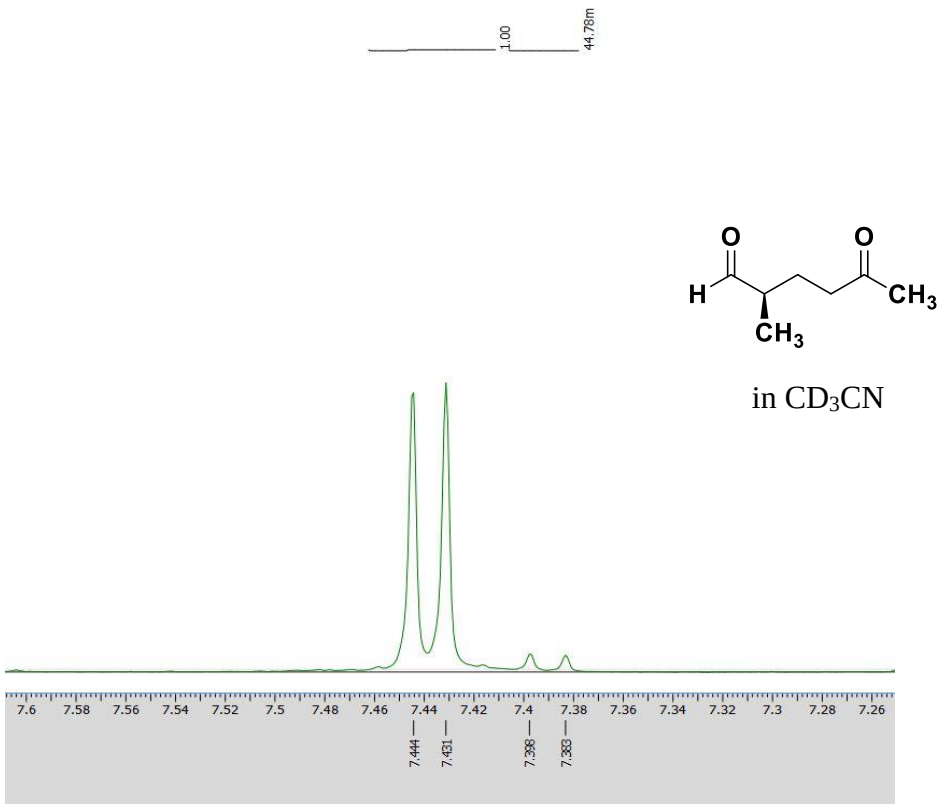


^{1}H NMR spectra of **SSPh**.

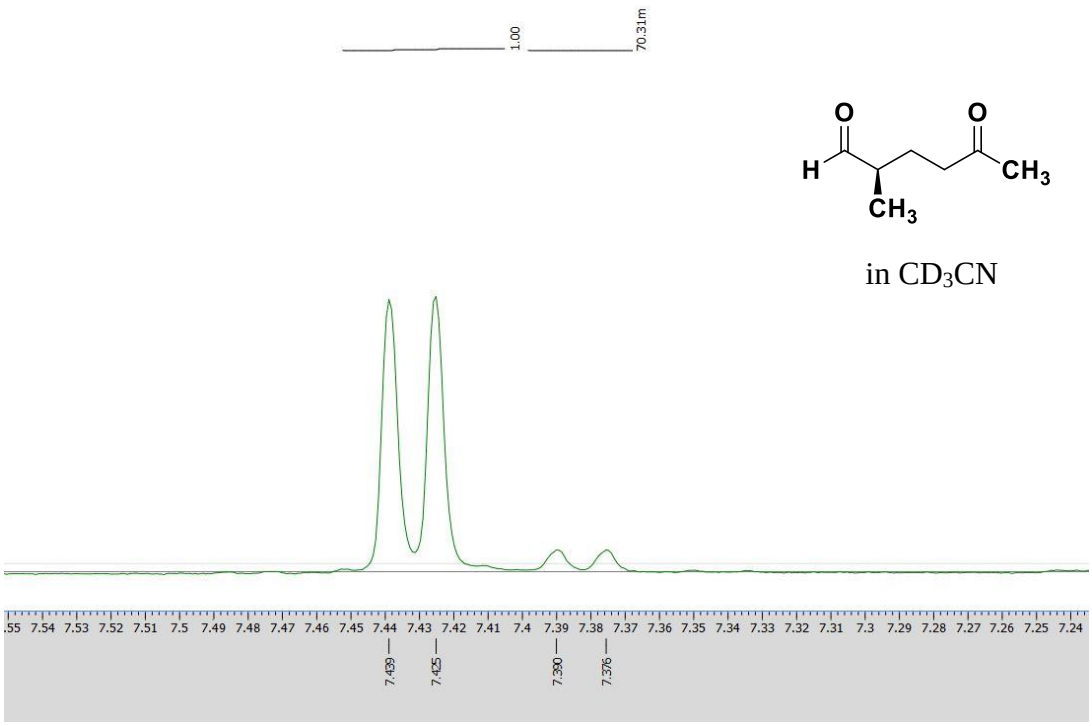
B.3 Enantiomeric excess (ee) data of the Michael adduct



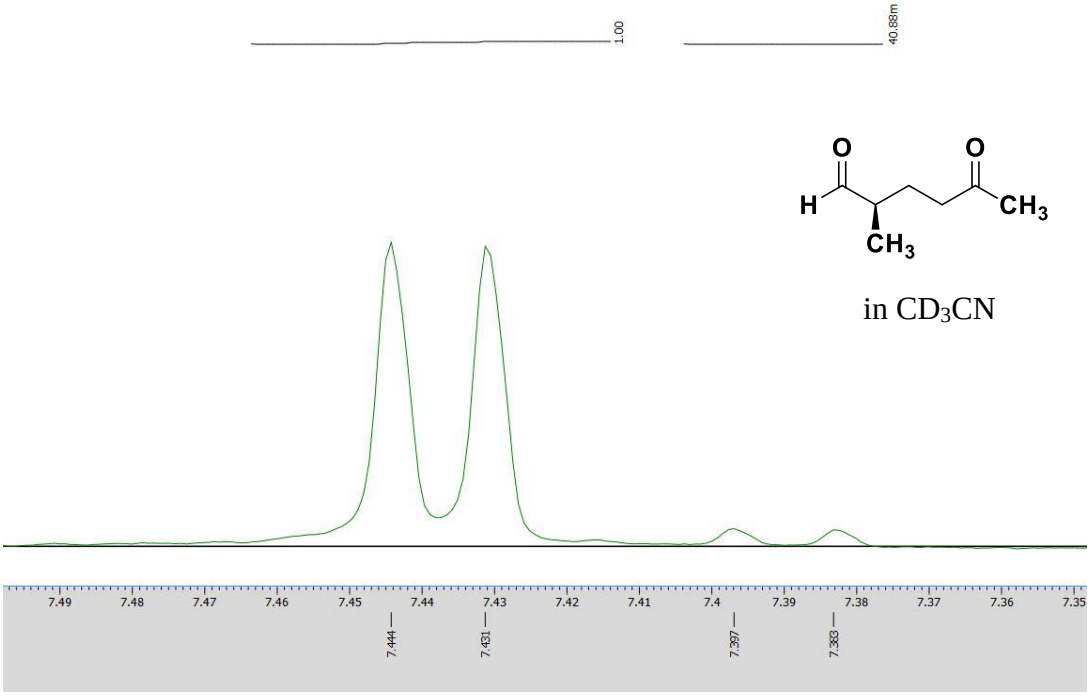
Enantiomeric excess (ee) of Michael adduct using **PS4**.



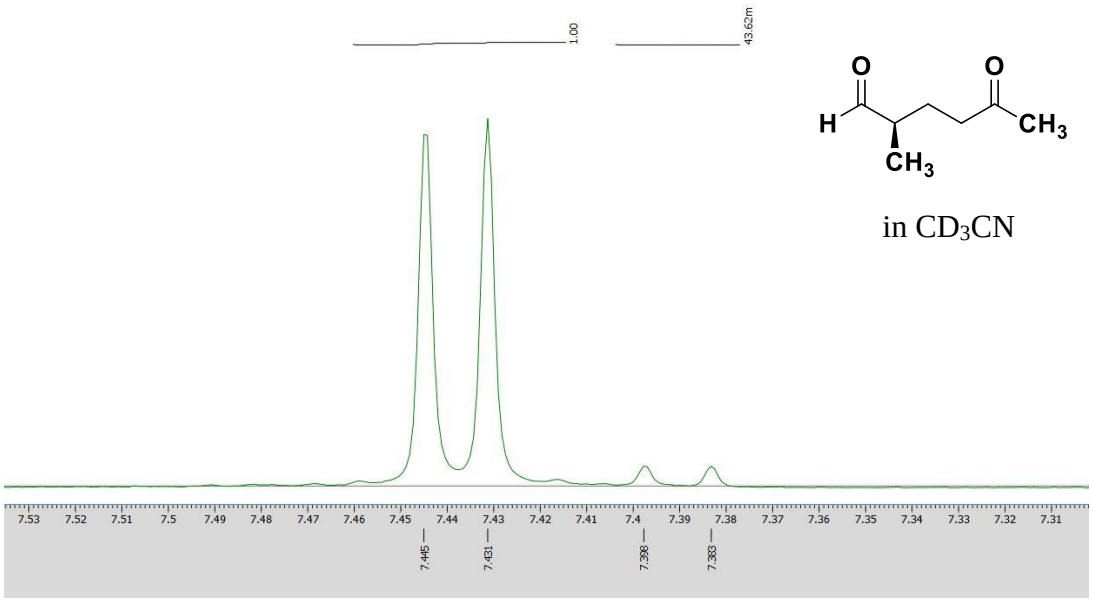
Enantiomeric excess (ee) of Michael adduct using **PS3**.



Enantiomeric excess (ee) of Michael adduct using **PS5**.

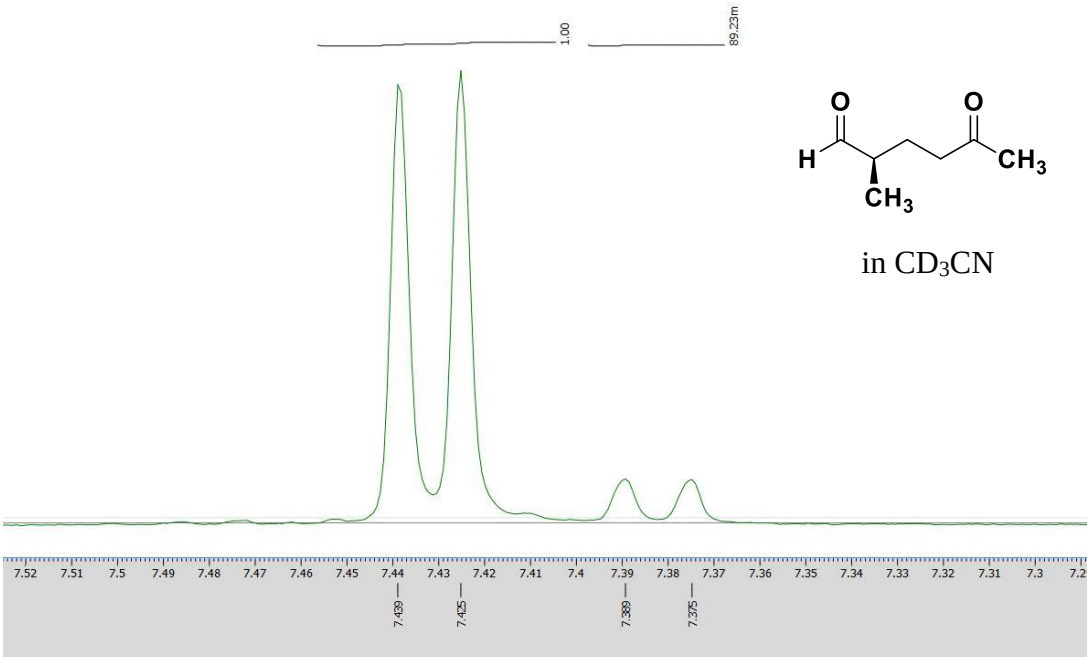


Enantiomeric excess (ee) of Michael adduct using **PS3** (with 15 mol%).



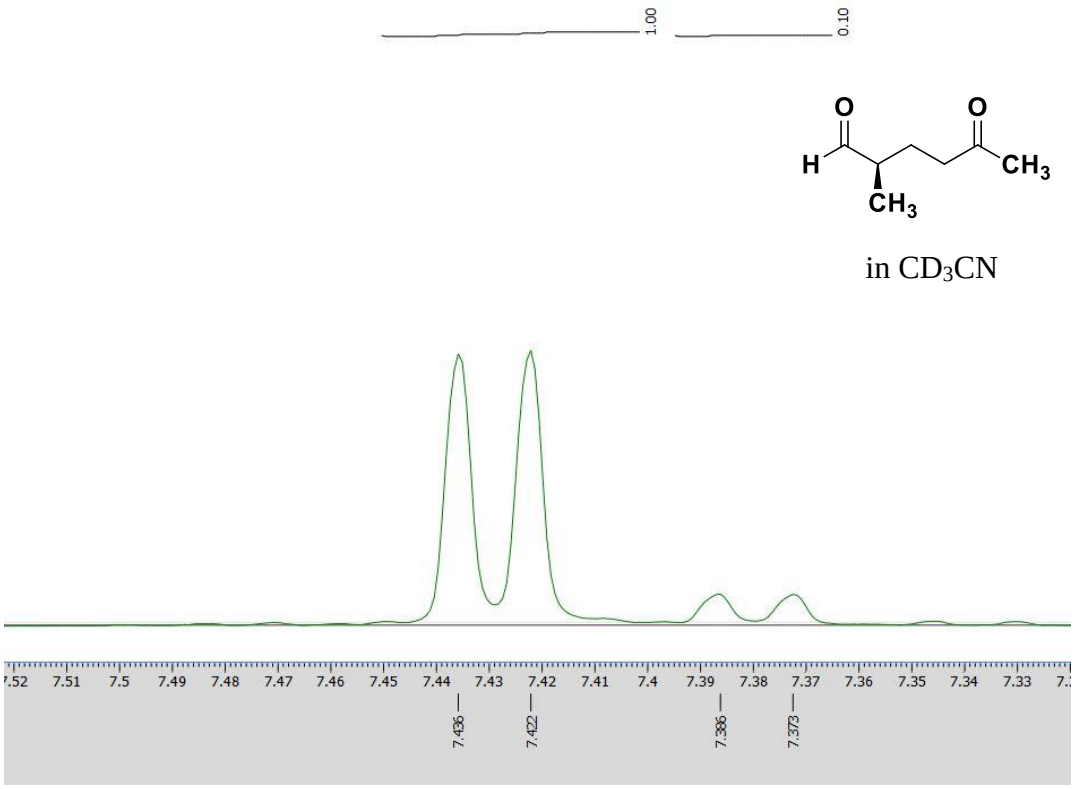
in CD_3CN

Enantiomeric excess (ee) of Michael adduct using **PS3** (with 5 mol%).

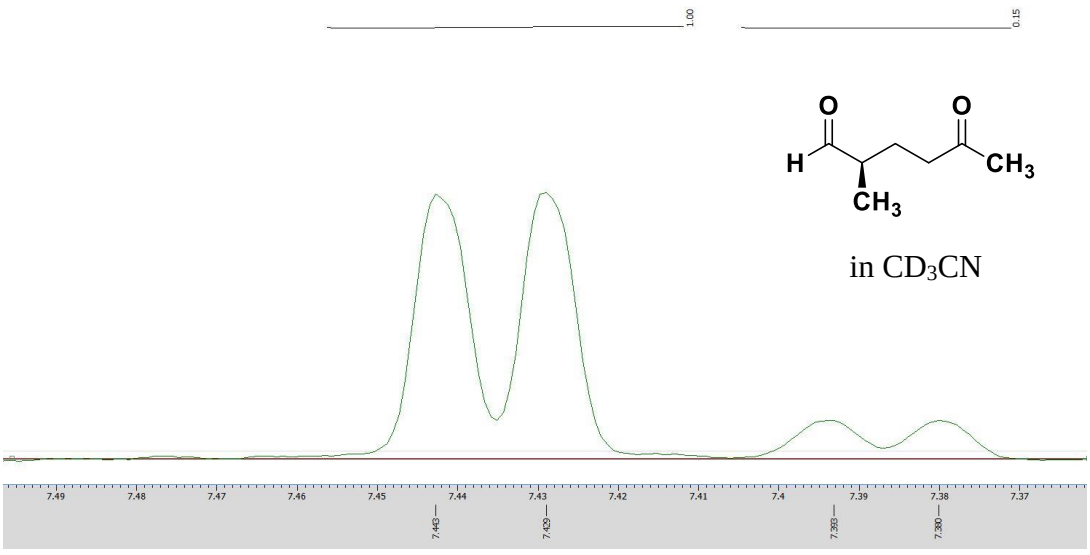


in CD_3CN

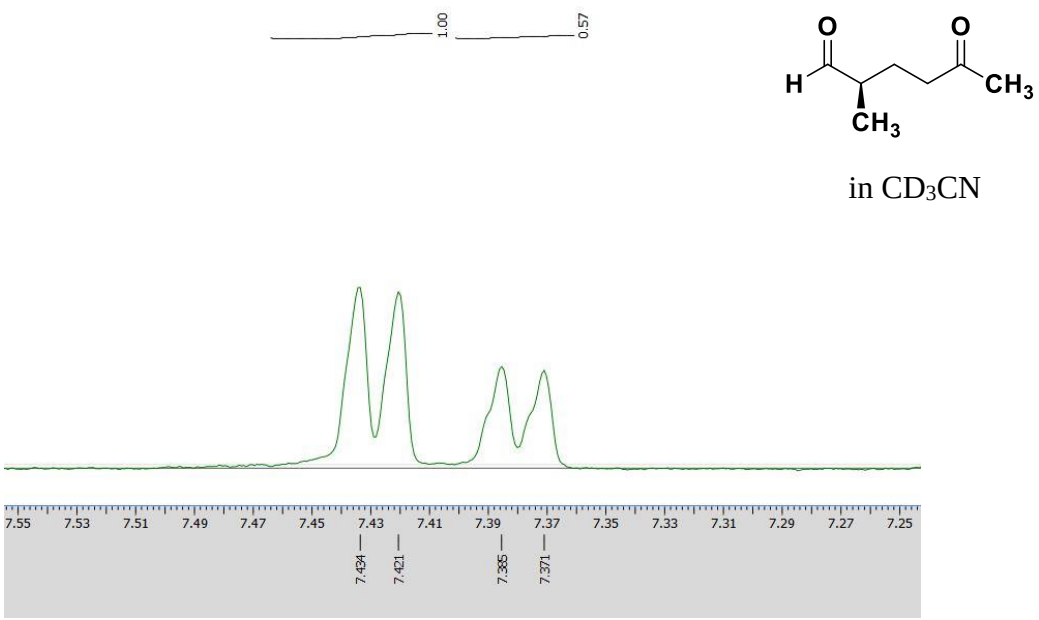
Enantiomeric excess (ee) of Michael adduct using 20 mol% **PS3** (with 7 equiv. H_2O).



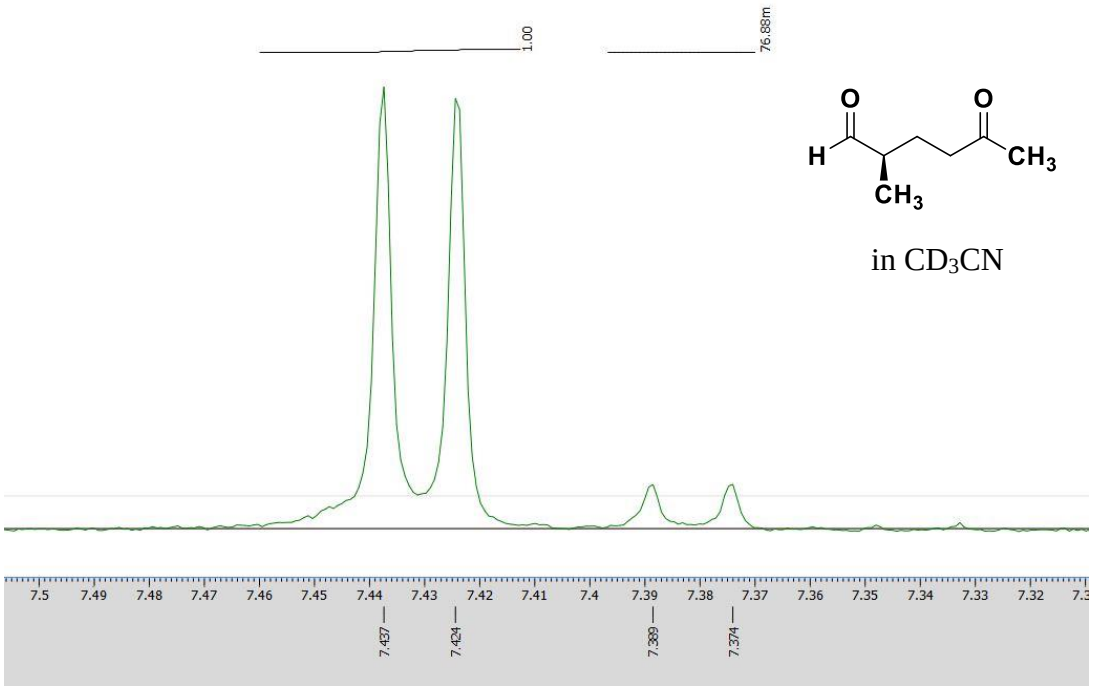
Enantiomeric excess (ee) of Michael adduct using 20 mol% **PS3** (with 15 equiv. H_2O).



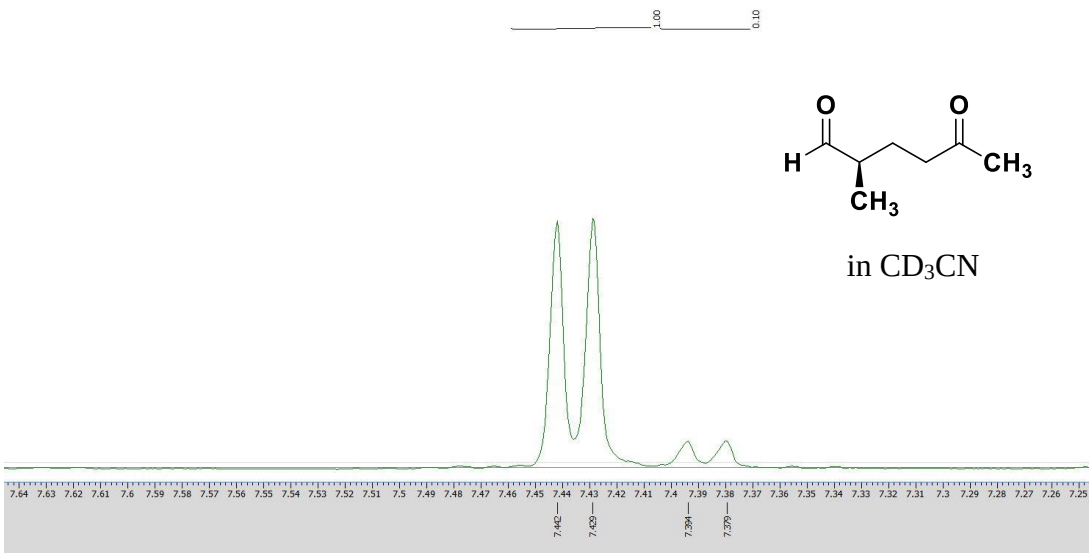
Enantiomeric excess (ee) of Michael adduct using **PS3** (with benzoic acid as additive).



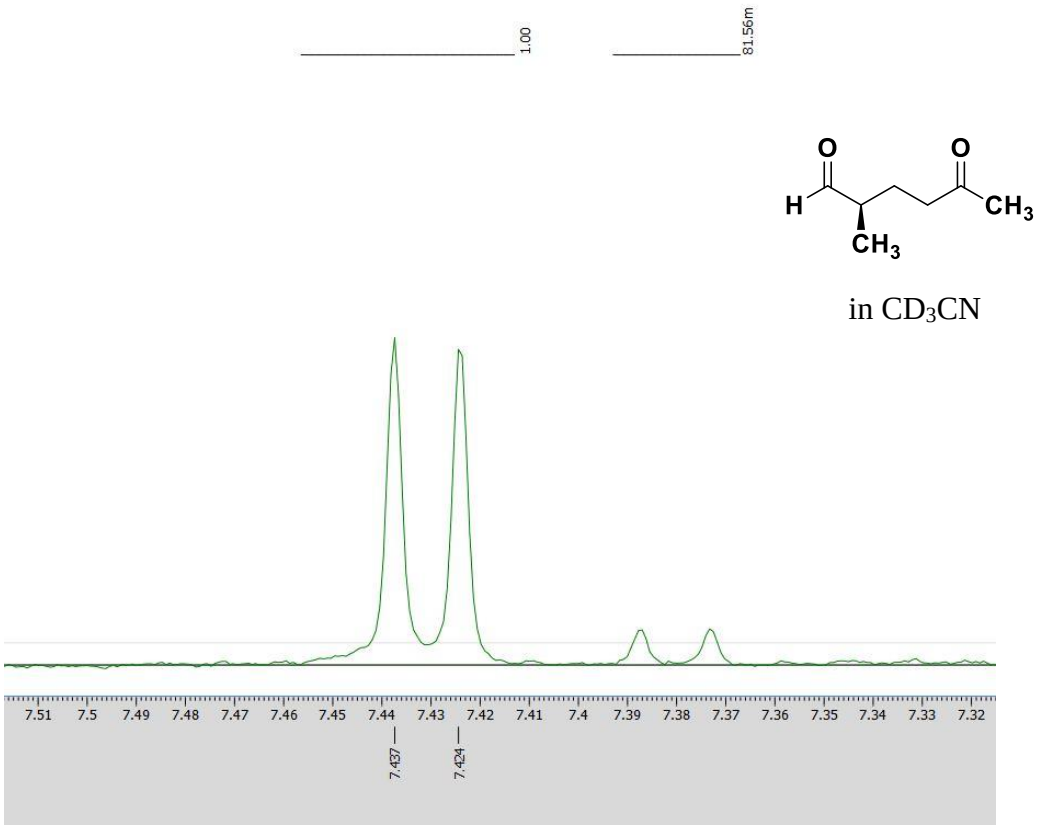
Enantiomeric excess (ee) of Michael adduct using **PS3** (with 2,5 dihydroxy benzoic acid as additive).



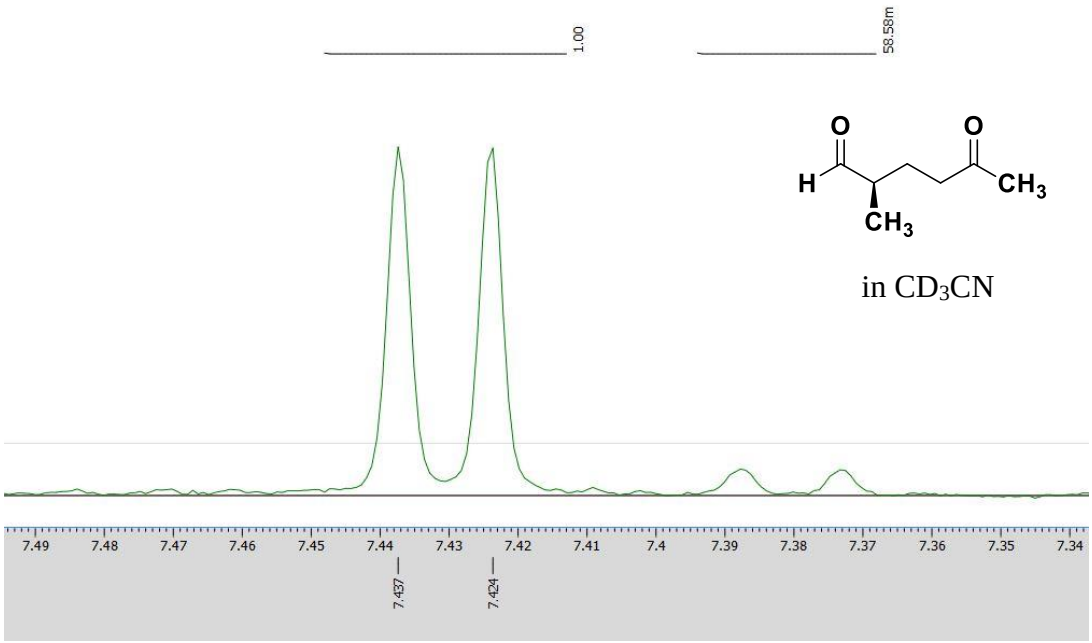
Enantiomeric excess (ee) of Michael adduct using **PS3** (with 50 mol% ethyl 3,4-dihydroxy benzoate as additive).



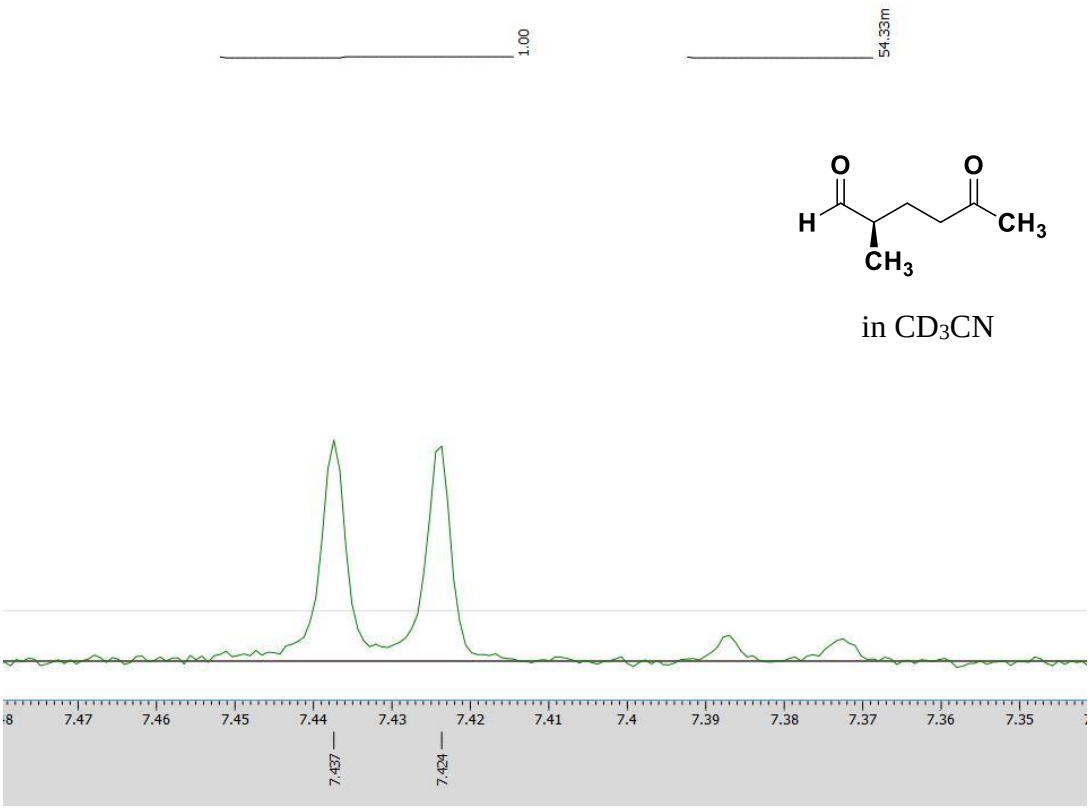
Enantiomeric excess (ee) of Michael adduct using **PS3** (with 1.5 equiv. of MVK).



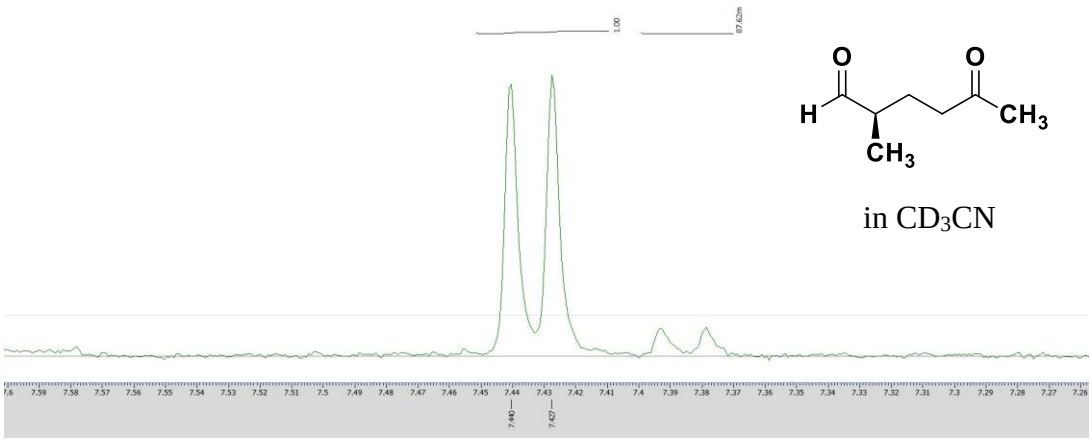
Enantiomeric excess (ee) of Michael adduct using **PS3** (with 6 equiv. MVK).



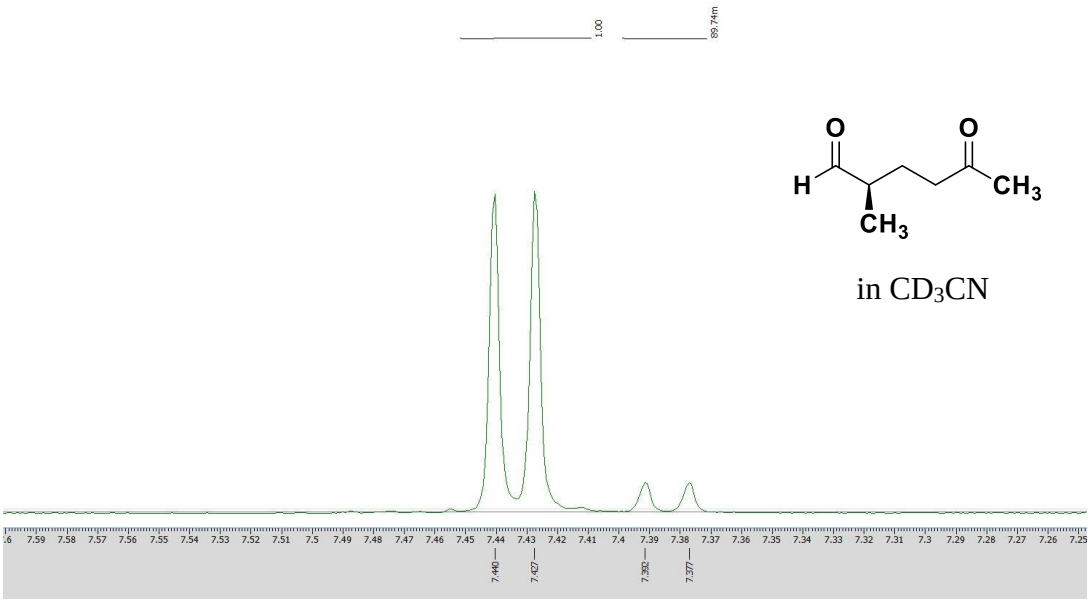
Enantiomeric excess (ee) of Michael adduct using **PS3** (with 6 equiv. MVK at 4 °C).



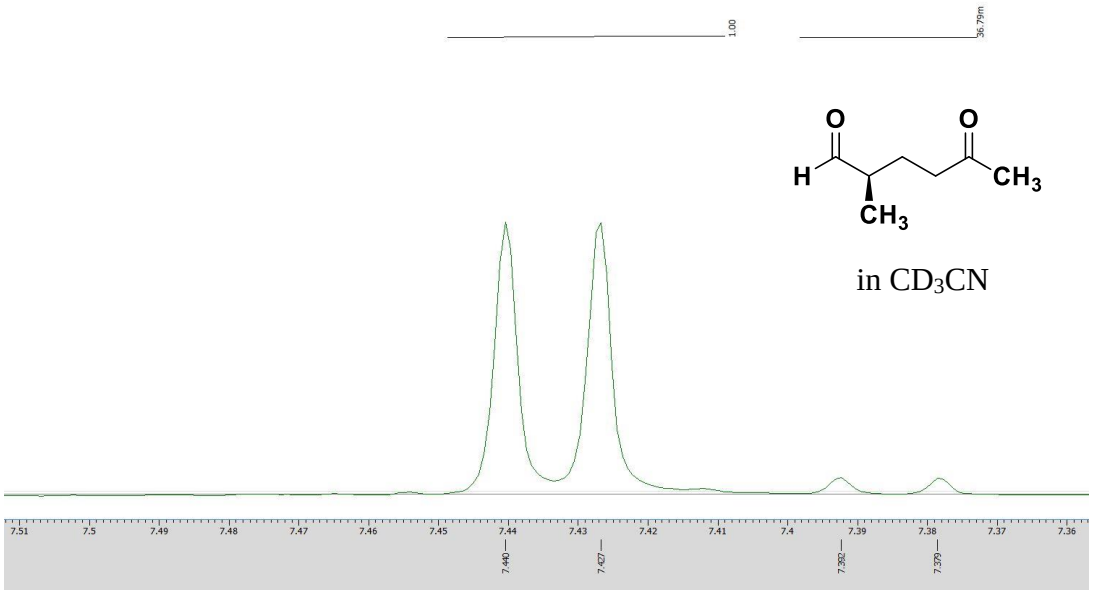
Enantiomeric excess (ee) of Michael adduct using 15 mol% **PS3** (with 6 equiv. MVK).



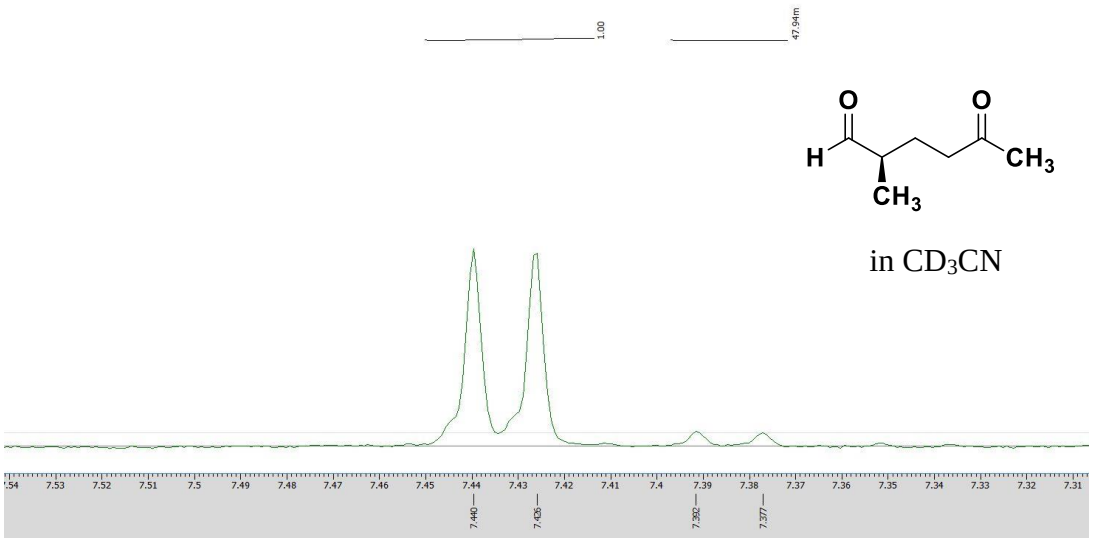
Enantiomeric excess (ee) of Michael adduct using **PS3** (in EtOH).



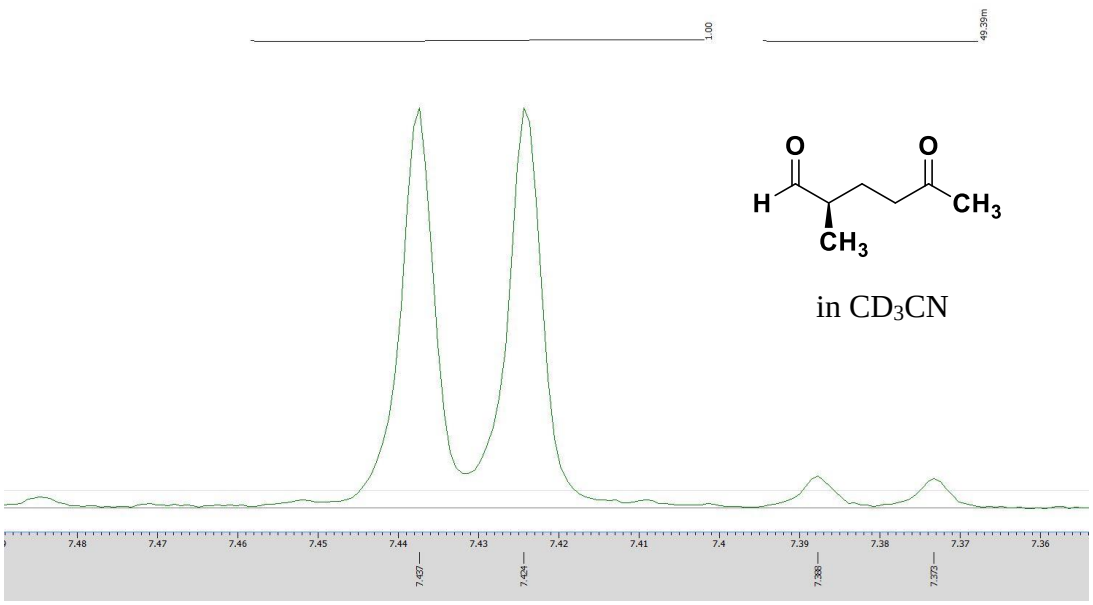
Enantiomeric excess (ee) of Michael adduct using **PS3** (in CH_3CN).



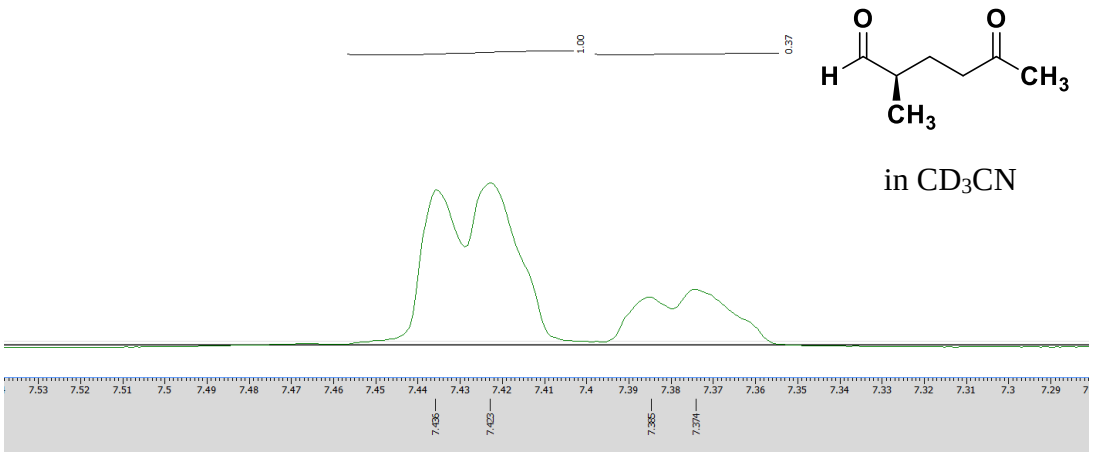
Enantiomeric excess (ee) of Michael adduct using **PS3** (in $CHCl_3$).



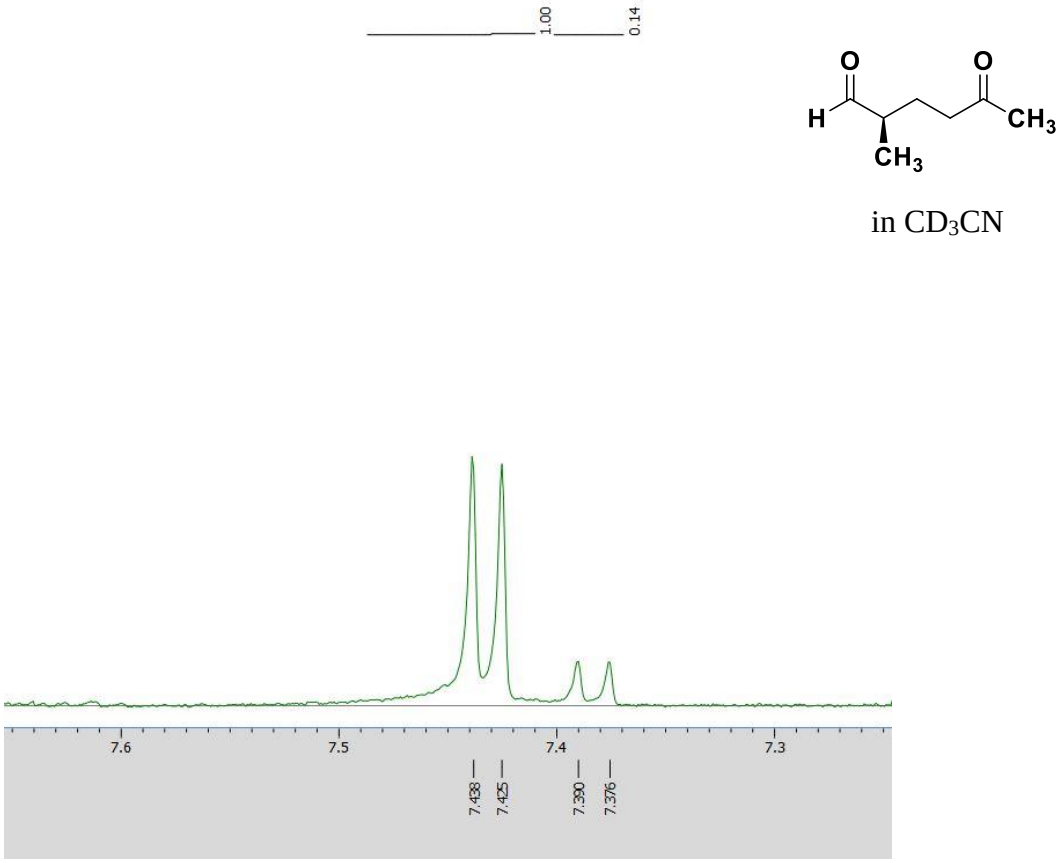
Enantiomeric excess (ee) of Michael adduct using **PS3** (inToluene/EtOH : 1/1, v/v) .



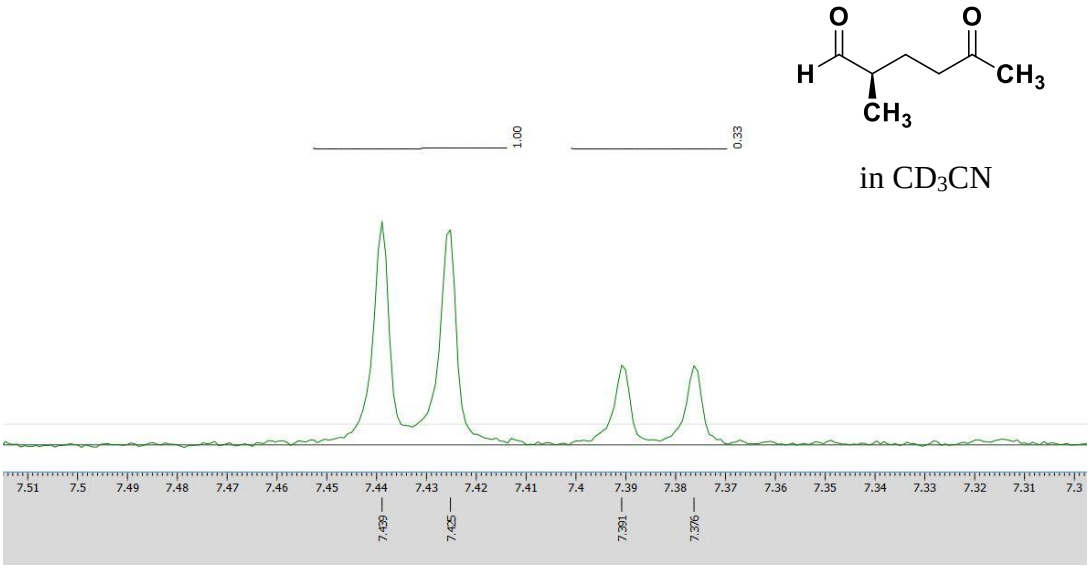
Enantiomeric excess (ee) of Michael adduct using **PS3** (in Toluene/^{i}PrOH : 95/5, v/v).



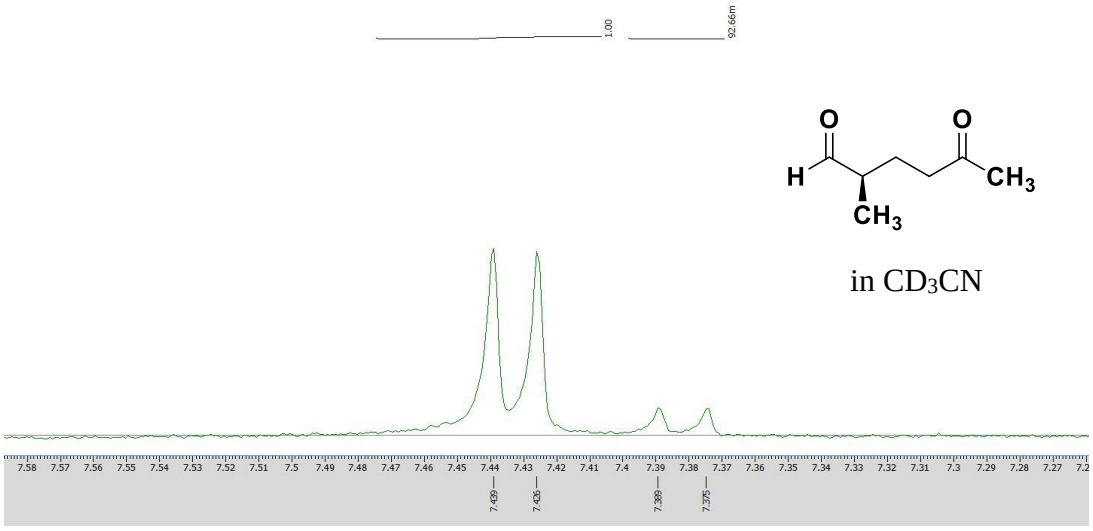
Enantiomeric excess (ee) of Michael adduct using **PS3** (at 30 °C).



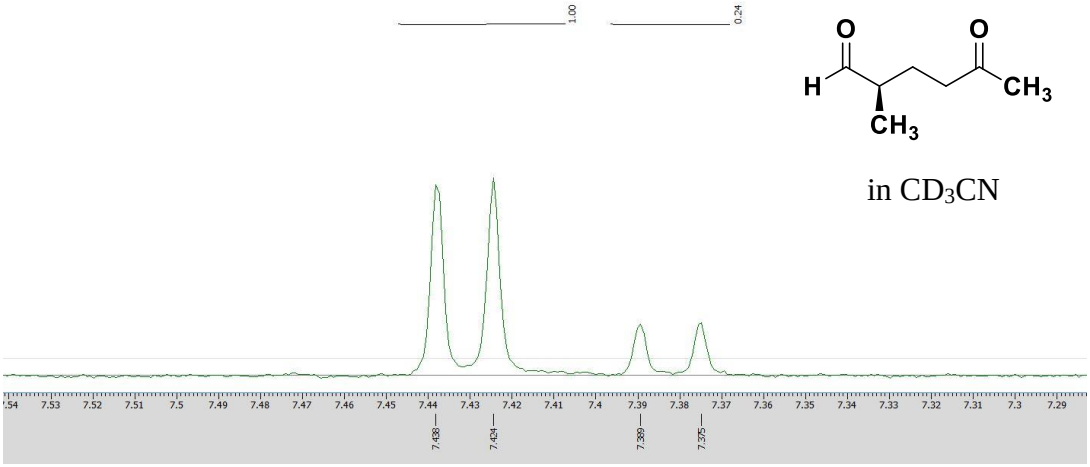
Enantiomeric excess (ee) of the Michael adduct using **PM**.



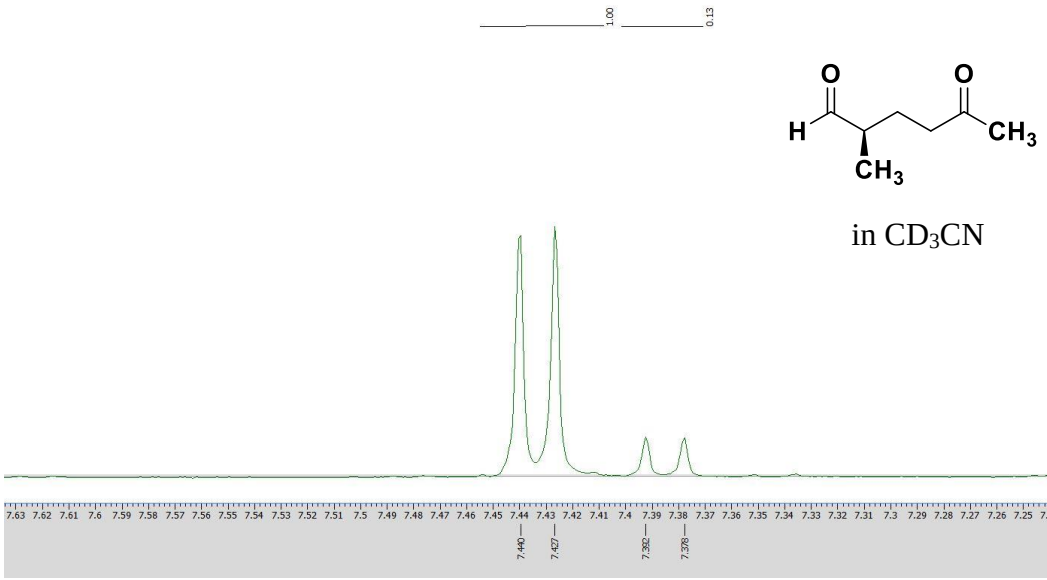
Enantiomeric excess (ee) of the Michael adduct using **PN**.



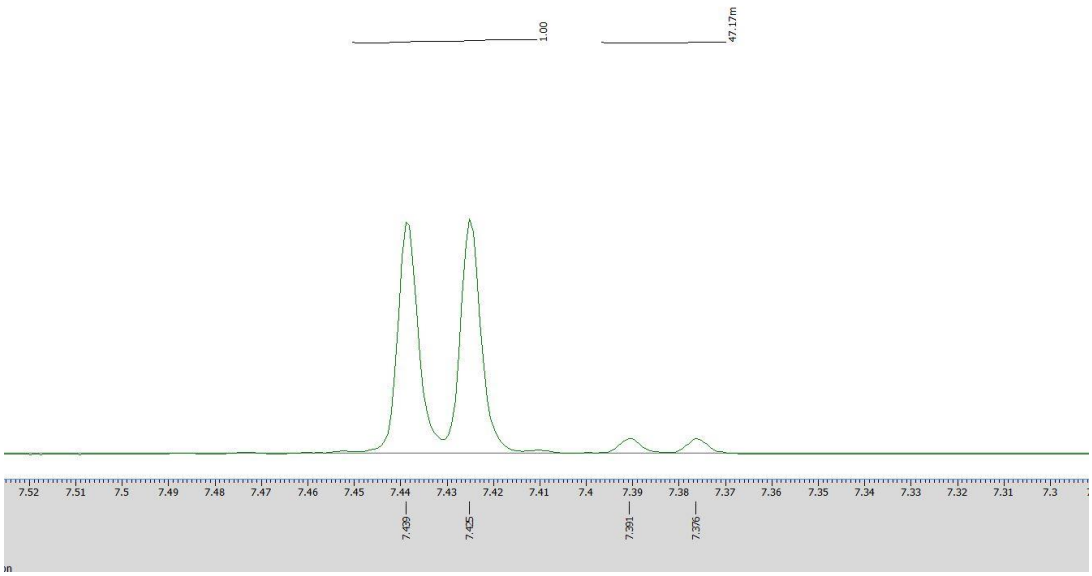
Enantiomeric excess (ee) of Michael adduct using **PH**.



Enantiomeric excess (ee) of Michael adduct using **PT**.



Enantiomeric excess (ee) of Michael adduct using **PMS**.

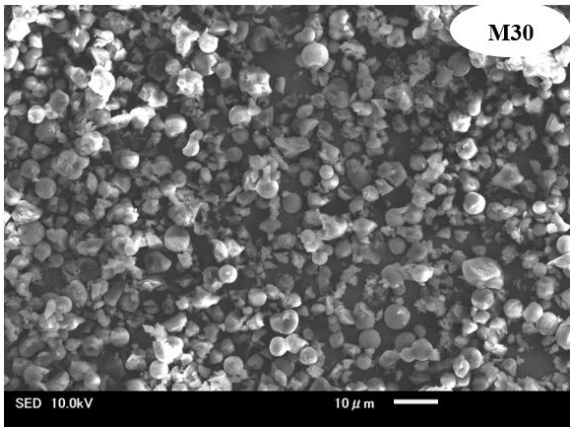


Enantiomeric excess (ee) of Michael adduct using **PS3** in cycle 1.

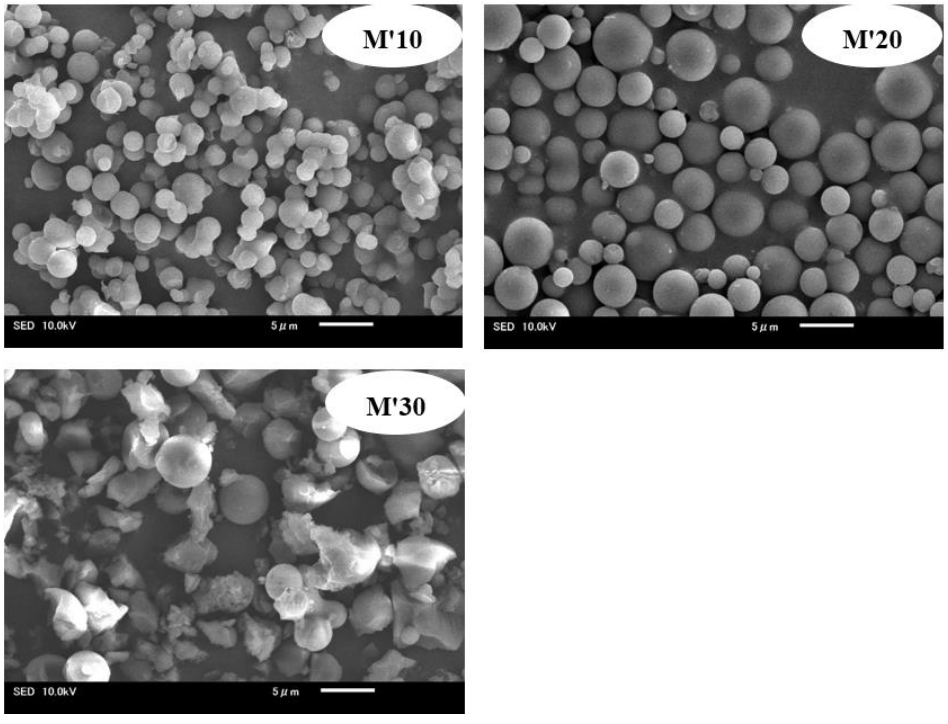
APPENDIX C

Supplementary Information for Chapter IV

C. 1 SEM images

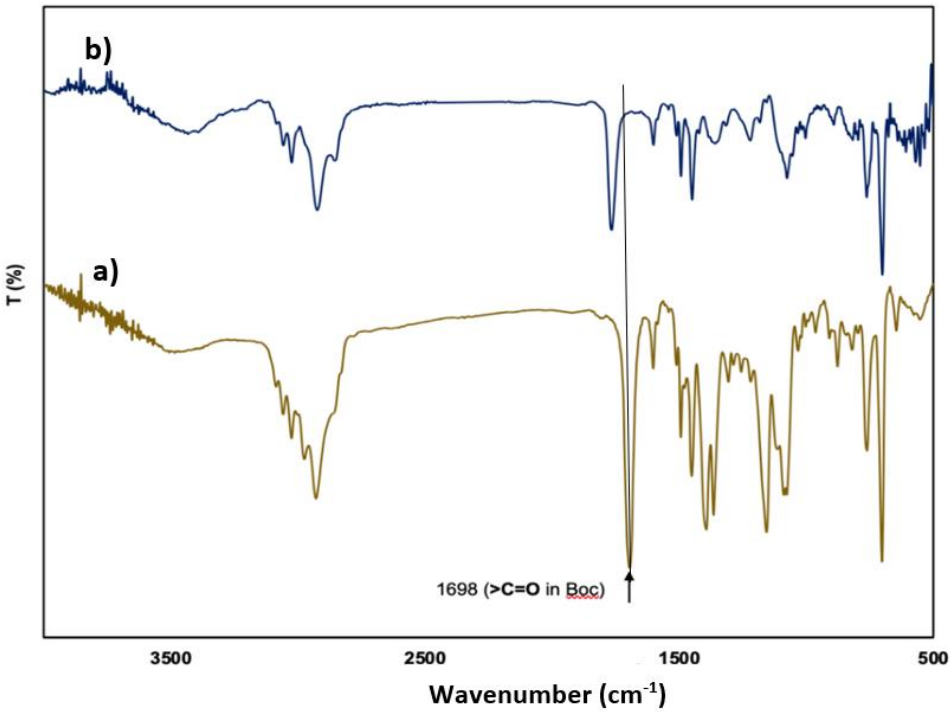


SEM image of **M30**



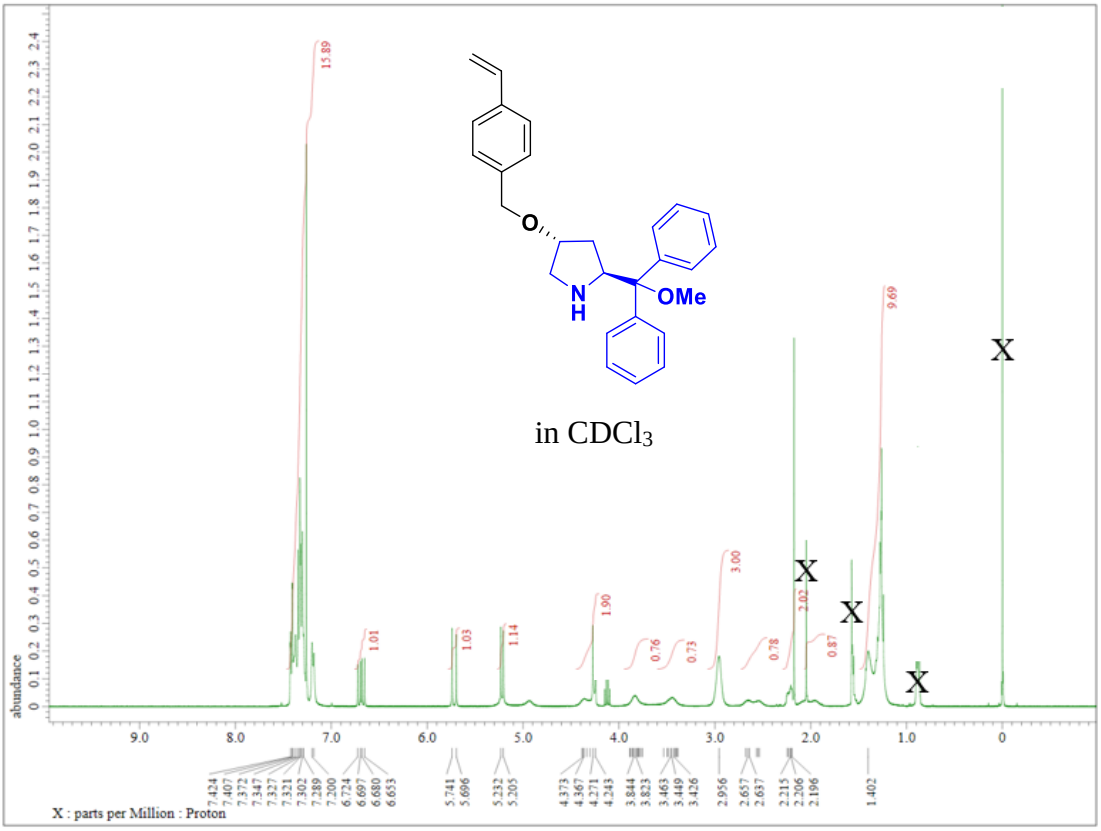
SEM image of polymer microsphere-immobilized chiral pyrrolidine catalysts before deprotection of the *N*-Boc group.

C. 2 FT-IR spectra

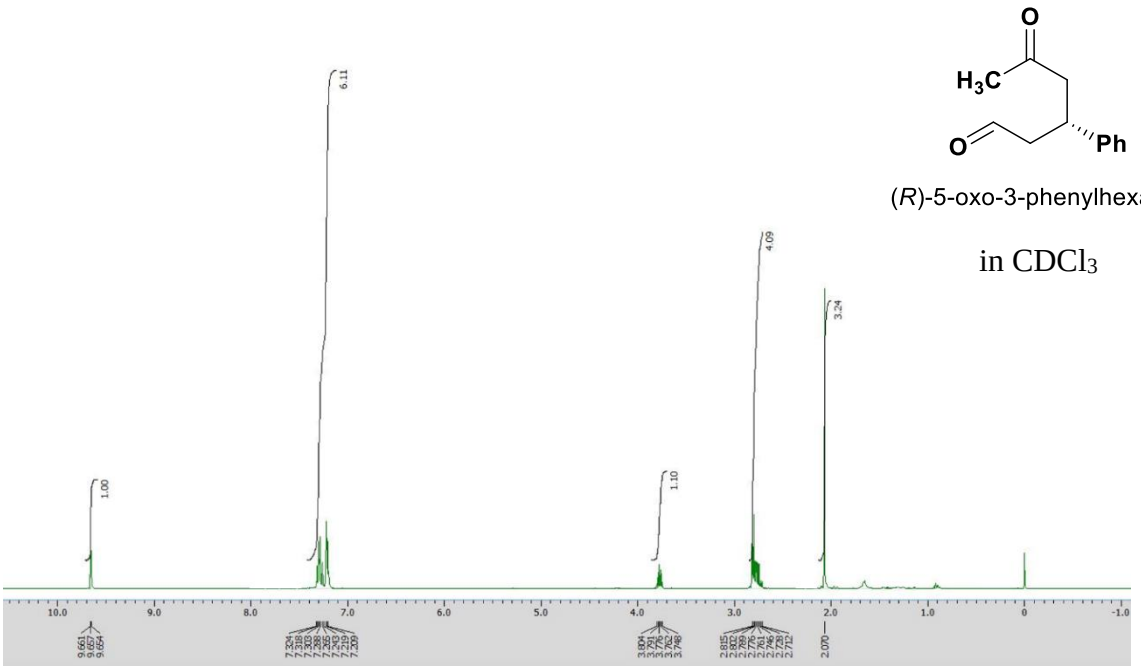


FT-IR spectra of the **M10** (a) before and (b) after removal of the *N*-Boc group.

C. 3 ^{1}H NMR spectra



^{1}H NMR spectra of **D**.



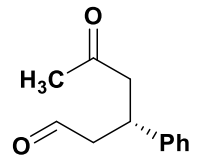
^{1}H NMR spectra of the chiral product **3**.

C. 4 Leaching experiment

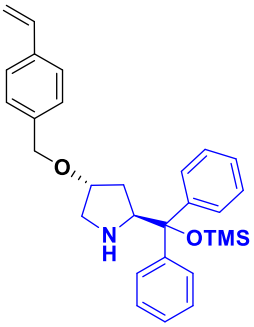
0.025 mmol of **Silica-SH** was added in 0.20 ml of CH_2Cl_2, and the resulting mixture was stirred for 24 h. After that, the catalyst **Silica-SH** was separated from the mixture. The supernatant has experimented with the litmus paper. The color of the litmus paper does not change, indicating no leaching of sulfonic acid moiety from **Silica-SH** has occurred.

C. 5 Enantiomeric excess (ee) data of the optically active compound

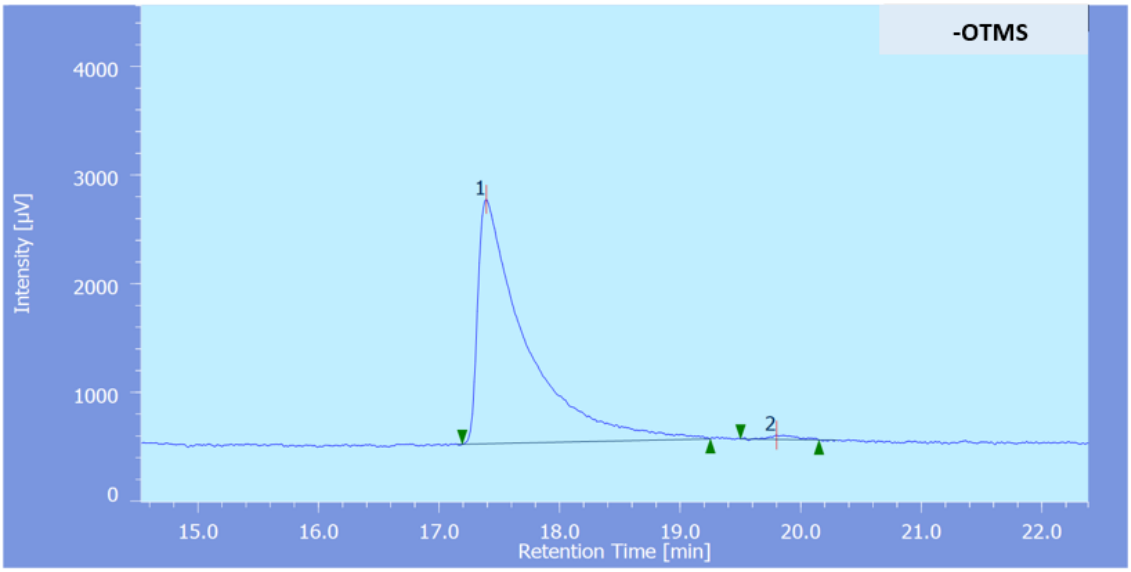
The Enantiomeric excess (ee) was determined by GC analysis on a Astec G-TA chiral stationary phase (T1 = 70 °C; T2 = 165 °C, rate = 10 °C/min; Inject temperature = 110 °C; FID temperature = 180 °C. Spectroscopic data are in accordance with literature values.[1,2]



(*R*)-5-oxo-3-phenylhexanal

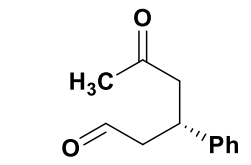


Catalyst **B**

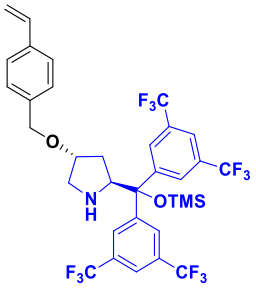


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.392	61797	2248	98.972	98.306	N/A	14619	4.923	4.914	
2	Peak-002	1	19.800	642	39	1.028	1.694	N/A	38111	N/A	1.087	

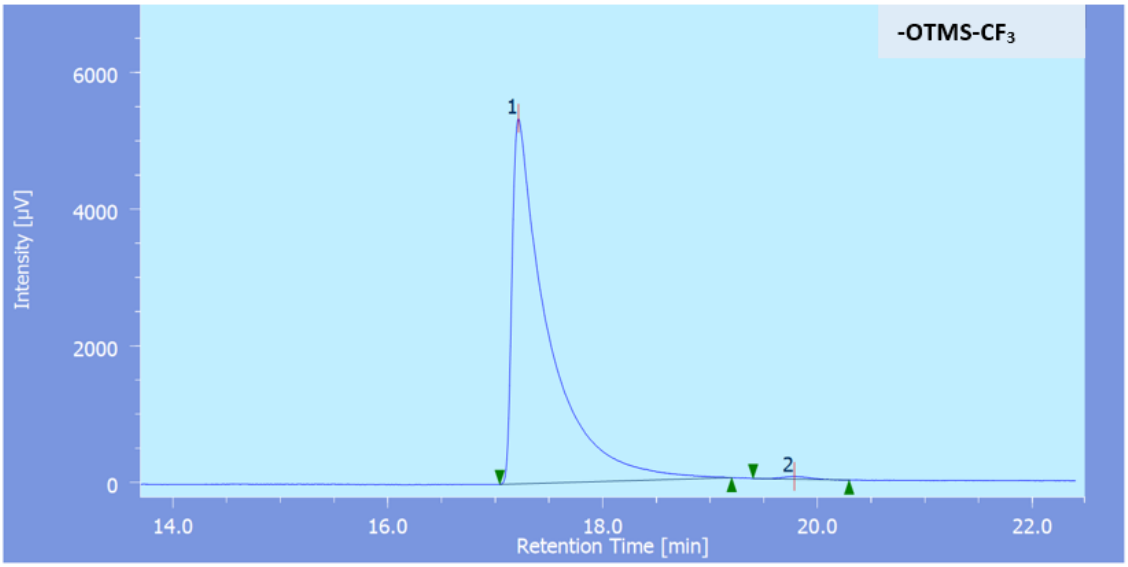
Enantiomeric excess (ee) of the optically active compound using catalyst **B**.



(*R*)-5-oxo-3-phenylhexanal

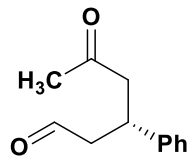


Catalyst **C**

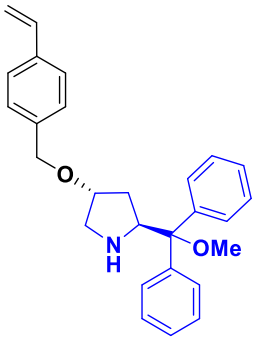


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.217	123740	5348	99.430	99.261	N/A	20407	5.399	4.746	
2	Peak-002	1	19.783	709	40	0.570	0.739	N/A	28198	N/A	1.196	

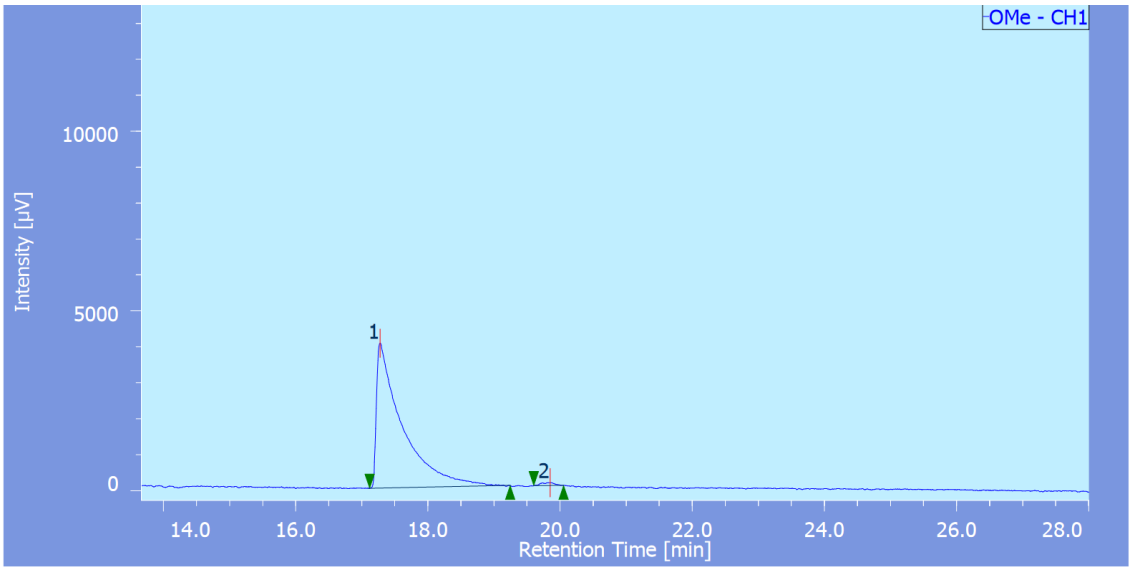
Enantiomeric excess (ee) of the optically active compound using catalyst **C**.



(*R*)-5-oxo-3-phenylhexanal

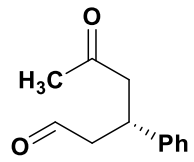


Catalyst **D**

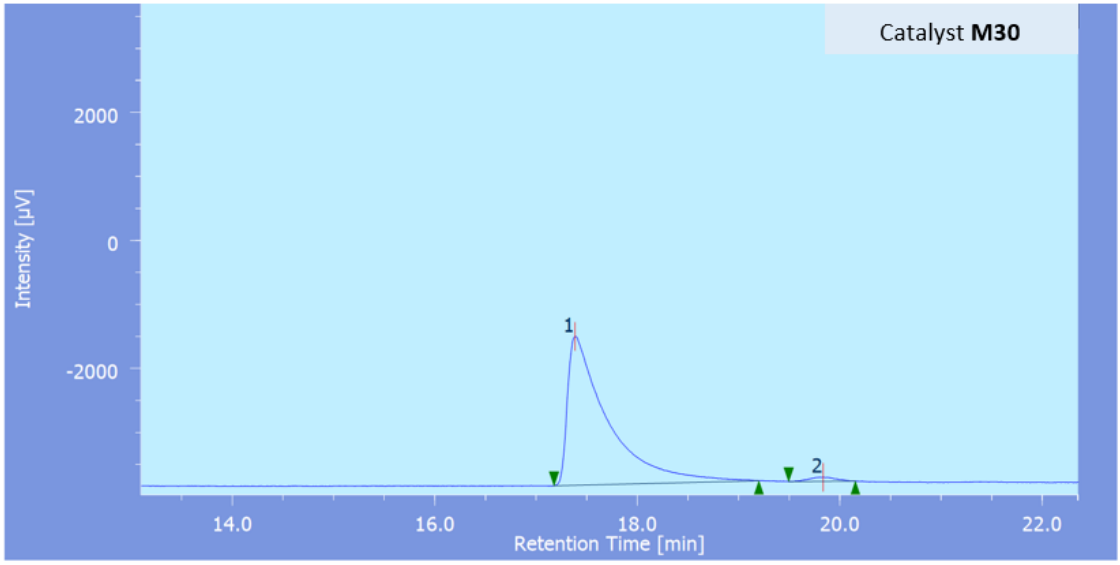


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.275	108558	4023	98.948	98.090	N/A	14576	5.253	6.262	
2	Peak-002	1	19.850	1154	78	1.052	1.910	N/A	37397	N/A	0.821	

Enantiomeric excess (ee) of the optically active compound using catalyst **D**.

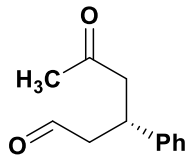


(*R*)-5-oxo-3-phenylhexanal

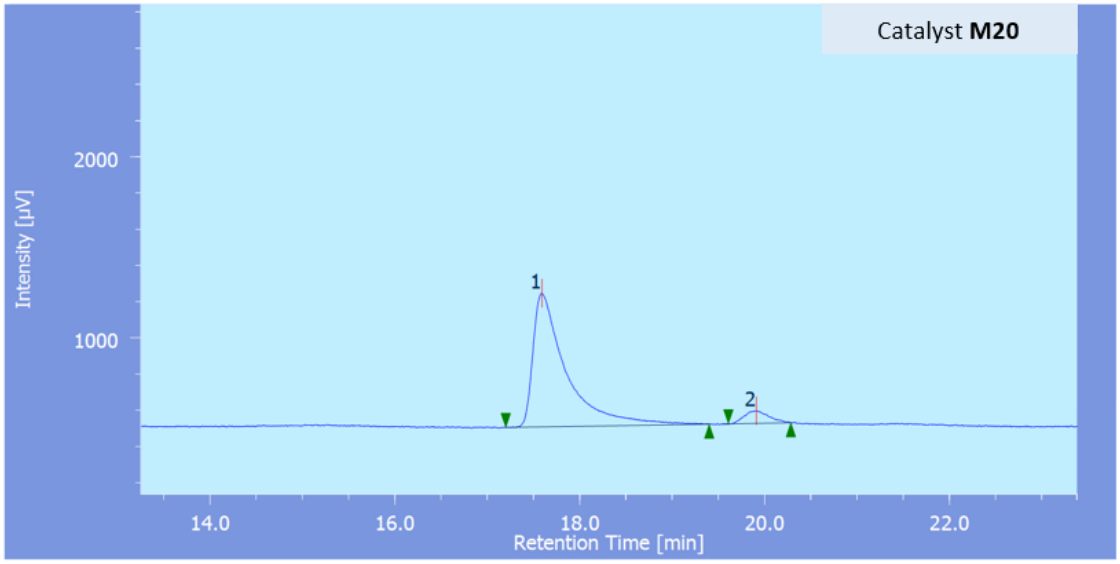


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.383	64118	2325	98.139	97.265	N/A	13177	4.426	4.352	
2	Peak-002	1	19.833	1216	65	1.861	2.735	N/A	24758	N/A	1.021	

Enantiomeric excess (ee) of the optically active compound using catalyst **M30**.

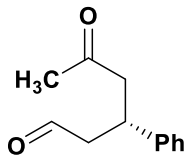


(*R*)-5-oxo-3-phenylhexanal

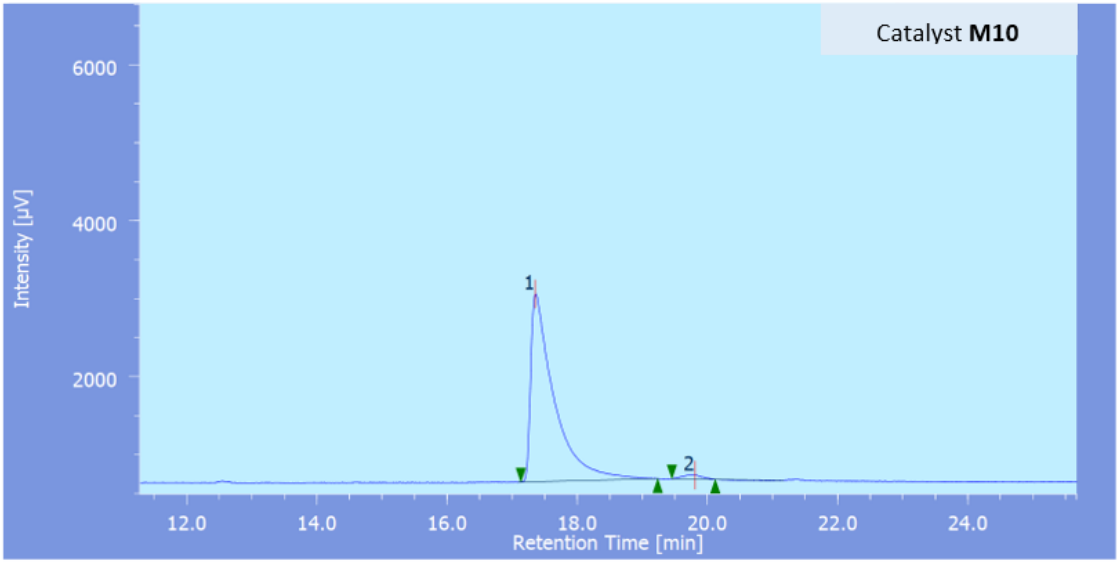


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.592	18465	738	93.512	91.375	N/A	16727	4.474	3.039	
2	Peak-002	1	19.908	1281	70	6.488	8.625	N/A	25950	N/A	1.223	

Enantiomeric excess (ee) of the optically active compound using catalyst **M20**.

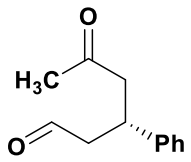


(*R*)-5-oxo-3-phenylhexanal

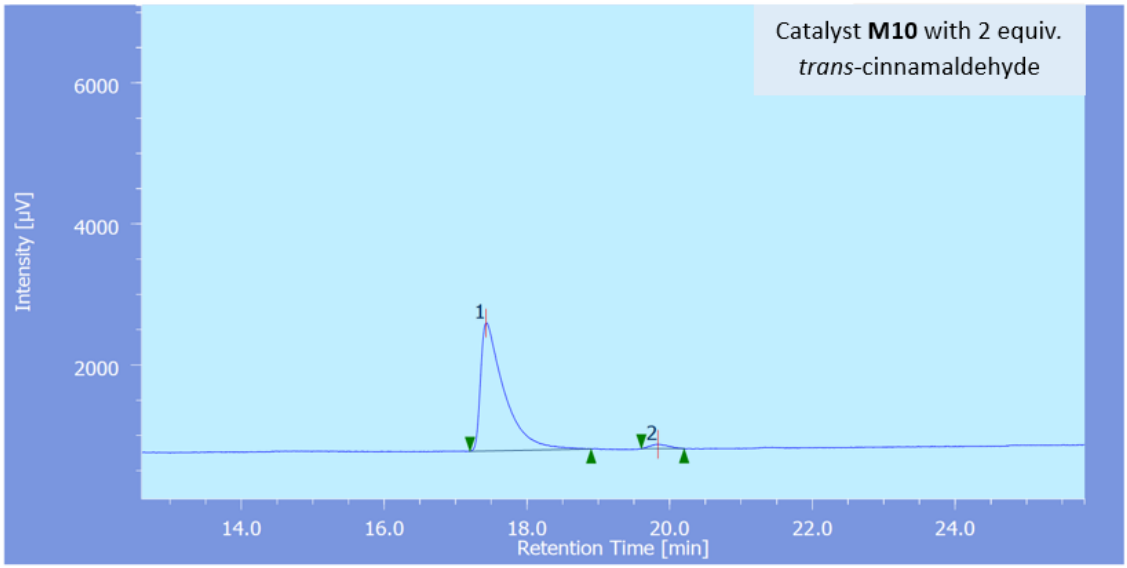


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.358	60177	2408	98.259	97.888	N/A	15314	4.386	3.746	
2	Peak-002	1	19.808	1066	52	1.741	2.112	N/A	20077	N/A	0.928	

Enantiomeric excess (ee) of the optically active compound using catalyst **M10**.

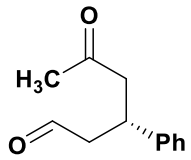


(*R*)-5-oxo-3-phenylhexanal

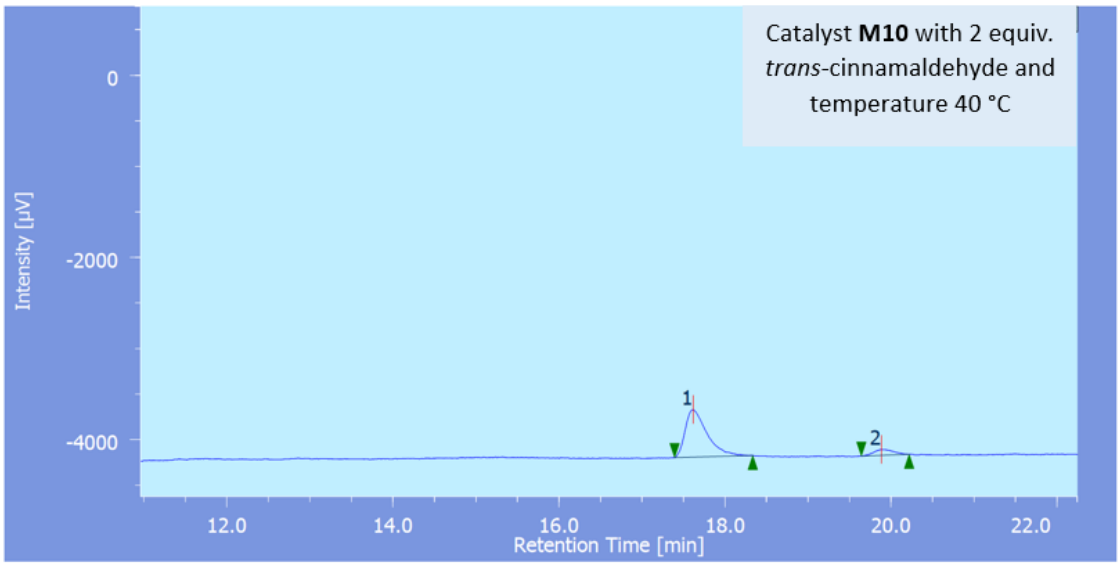


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.425	41724	1813	97.434	96.713	N/A	16341	4.534	2.972	
2	Peak-002	1	19.833	1099	62	2.566	3.287	N/A	23284	N/A	1.280	

Enantiomeric excess (ee) of the optically active compound using catalyst **M10** with 2 equiv. of *trans*-cinnamaldehyde.

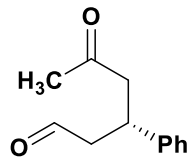


(*R*)-5-oxo-3-phenylhexanal

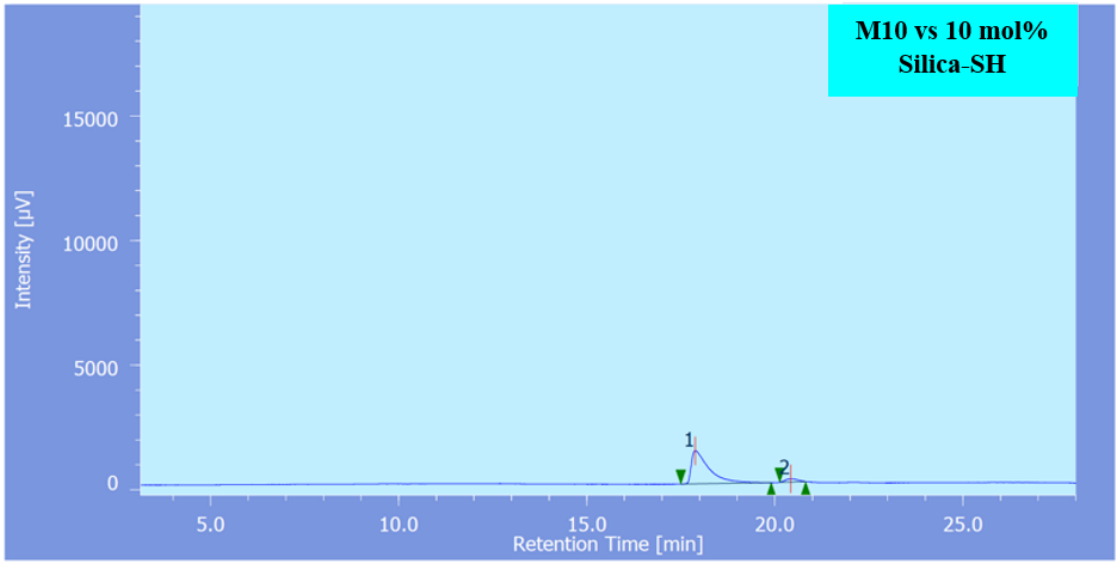


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Unknown	1	17.617	9459	521	89.681	88.782	N/A	23716	4.986	1.755	
2	Unknown	1	19.883	1088	66	10.319	11.218	N/A	30678	N/A	1.208	

Enantiomeric excess (ee) of the optically active compound using catalyst **M10** with 2 equiv. of *trans*-cinnamaldehyde at 40 °C.

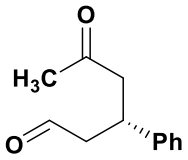


(*R*)-5-oxo-3-phenylhexanal

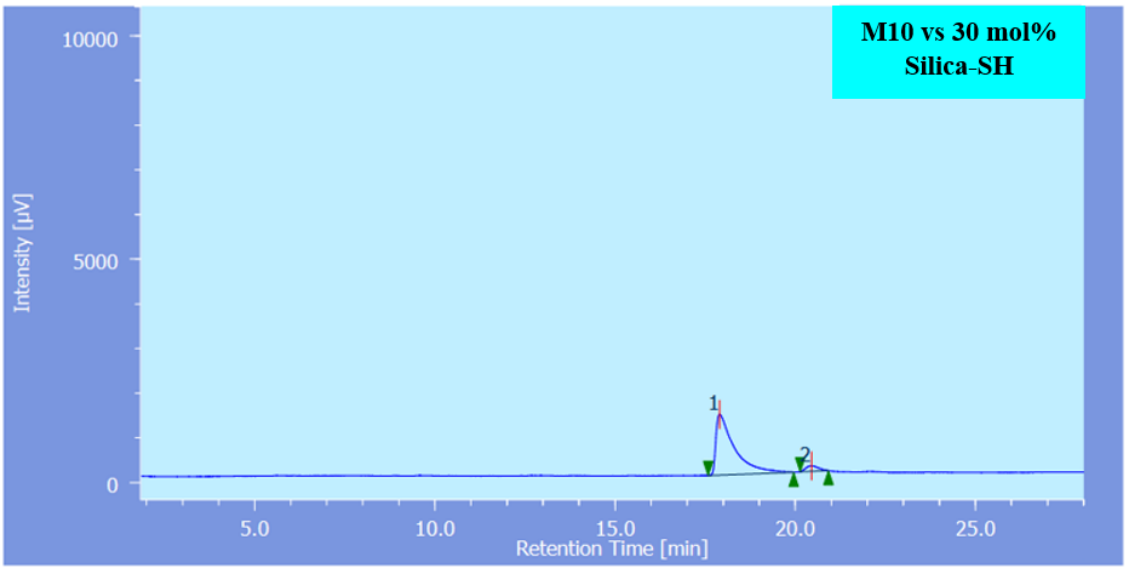


#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.883	43996	1327	93.659	90.998	N/A	8668	3.609	3.483	
2	Peak-002	1	20.417	2979	131	6.341	9.002	N/A	16312	N/A	1.198	

Enantiomeric excess (ee) of the optically active compound using catalyst **M10** vs 10 mol% **Silica-SH**.



(*R*)-5-oxo-3-phenylhexanal



#	ピーク名	CH	tR [min]	面積 [μV·sec]	高さ [μV]	面積%	高さ%	定量値	NTP	分離度	シンメトリー係数	警告
1	Peak-001	1	17.900	48618	1351	94.677	92.051	N/A	7831	3.482	4.081	
2	Peak-002	1	20.442	2733	117	5.323	7.949	N/A	15596	N/A	1.274	

Enantiomeric excess (ee) of the optically active compound using catalyst **M10** vs 30 mol% **Silica-SH**.

References

[1] G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830.

[2] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, *47*, 4928.

ACKNOWLEDGMENTS

First and foremost, I am grateful to my God, who has given me the strength to complete this work successfully.

I would like to express my best regards, profound gratitude, and heartfelt respect to my honorable and favorite supervisor Prof. Dr. Naoki Haraguchi, for his constant supervision, skilled and authoritative guidance, valuable critics, and encouragement during the research and writing of this thesis. I am amazed by his creativity, desire for chemistry, and friendly gesture during my entire study, which has fueled my research. I have learned from him how a researcher can propose and execute a research plan successfully with high precision. He has been a constant source of inspiration and knowledge in my life.

I would like to express my most profound sense of gratitude to Prof. Dr. Shinichi Itsuno for his scientific and scholastic guidance, enthusiastic encouragement, wise advice, and affectionate surveillance throughout the entire period of my research. I am highly grateful to my honorable thesis examiners, Prof. Dr. Hideto Tsuji and Prof. Dr. Kazutaka Shibatomi, for their insightful comments on my thesis. I am incredibly grateful to Dr. Ikuhide Fujisawa for his help and co-operation during my research.

I am grateful to all respected teachers of the Department of Applied Chemistry and Life Science, Toyohashi University of Technology, for their kind help, valuable suggestions, and inspiration during the progress of this work. I want to thank MEXT for providing me with the scholarship for my PhD study.

I want to express my heartiest regards and great sense of gratitude to my MSc supervisor Prof. Dr. Hasan Ahmad, Department of Chemistry, University of Rajshahi, Bangladesh, for recommending me to join the research group of Prof. Naoki Haraguchi.

I am also grateful to my present and past lab mates, Thao, Sugimoto, Ooi, Sasaki, Hashimoto, Watanabe, Takatsuka, Takeuchi, Sadia, Ali, Shibata, Shinya, Yamada, Tatsumi, Jason, Jimmy, Daniel, and Lida for their valuable advice, help, and co-operation.

Finally, I am thankful to my beloved parents for their patience, co-operation, and unconditional moral and mental support during this endeavor.

Mithun Kumar Debnath

Dedicated to My Supervisor

Prof. Naoki Haraguchi

And

My Parents