METAL CATALYZED ASYMMETRIC SYNTHESIS OF THIENYL-SUBSTITUTED PYRROLIDINES BY 1,3-DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES

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METAL CATALYZED ASYMMETRIC SYNTHESIS OF THIENYL-SUBSTITUTED PYRROLIDINES BY 1,3-DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

METAL CATALYZED ASYMMETRIC SYNTHESIS OF THIENYL-SUBSTITUTED PYRROLIDINES BY 1,3-DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES

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September 2019, 64 pages

Pyrrolidines are structurally and biologically important heterocyclic compounds. One of the efficient methods for the synthesis of these compounds is 1,3-dipolar cycloaddition (1,3-DC) reaction of azomethine ylides with electron deficient dipolarophiles. Asymmetric synthesis of these compounds has been studied by many groups by using 1,3-DC reactions with chiral transition metal catalysts. In all these studies aryl-substituted pyrrolidines were synthesized mainly. In this thesis, heteroaryl-substituted pyrrolidines which were not explored in the literature will be synthesized by using chiral metal catalysts developed in our group. Chiral metal catalysts are composed of a metal and a chiral ligand. As the metal source, Cu-, Zn-, and Ag-salts were used with **FAM** (ferrocenyl aziridinyl methanol) chiral ligands. Besides the known **FAM** ligands, a new derivative, **CFAM** (cyclohexyl ferrocenyl aziridinyl methanol), was also synthesized for the first time in this thesis. With the **CFAM** chiral ligands, total of twelve chiral ligands (**PFAM1-4**, **CFAM1-4,** and 1-**NFAM1-4**) were screened for the synthesis of thienyl-substituted pyrrolidines. After optimizing all the reaction parameters (temperature, concentration, solvent, etc.), Ag-**PFAM1** catalyst system found to be the better one by forming thienyl-substituted pyrrolidines in 85% ee and 64% yield with *N*-methylmaleimide.

Keywords: 1,3-Dipolar cycloaddition reaction, Thienyl-substituted pyrrolidine, Azomethine ylide, Chiral ligand, Asymmetric synthesis.

ÖZ

TİYENİL-SÜBSTİTÜE PİROLİDİNLERİN METAL KATALİZÖRLÜĞÜNDE AZOMETİN YLİDLERİN 1,3-DİPOLAR HALKASAL KATILMA TEPKİMESİ İLE ASİMETRİK SENTEZİ

Bulut, Merve
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Eylül 2019, 64 sayfa

Pirolidinler yapısal ve biyolojik olarak önemli heterohalkalı bileşiklerdir. Bu bileşiklerin sentezi için en etkili yöntemlerden biri, azometin ilidlerin elektronca zayıf dipolarofillerle 1,3-dipolar halkasal katılma tepkimesidir.1,3-dipolar halkasal katılma tepkimesinden yararlanarak, bu bileşiklerin asimetrik sentezi kiral geçiş metali katalizörleriyle pek çok grup tarafından çalışılmıştır. Bütün çalışmalarda, ağırlıklı olarak aril-sübstitüe pirolidinler sentezlenmiştir. Bu tezde, grubumuz tarafından geliştirilen kiral metal katalizör kullanılarak, daha önce ayrıntılı çalışılmamış olan heteroaril-sübstitüe pirolidinler sentezlenmiştir. Kiral metal katalizörler metal ve kiral liganddan oluşmaktadır. Bu tezde, bakır, çinko ve gümüş tuzu metal kaynağı olarak **FAM** (ferrosenil-sübstitüye aziridinil metanol) ligandıyla test edilmiştir. Bilinen **FAM** ligandlarının yanı sıra bu bileşiklerin yeni türevleri, **CFAM** (siklohekzil-sübstitüye aziridinil metanol) de ilk defa bu tezde sentezlenmiştir. **CFAM** ile birlikte toplam olarak on iki kiral ligand (**PFAM1-4**, **CFAM1-4** ve 1-**NFAM1-4**) tiyenil-sübstitüe pirolidin sentezi için taranmıştır. Tepkime koşulları (sıcaklık, konsantrasyon, çözücü vb.) optimize edildikten sonra Ag-**PFAM1** katalizör sistemi *N*-metilmaleimid dipolarofiliyle tiyenil-sübstitüe pirolidin yapısını %85 ee ve %64 verimle oluşturduğu görülmüştür.

Anahtar Kelimeler: 1,3-Dipolar halkasal katılma tepkimeleri, Tiyenil-sübstitüye pirolidin, Azometin ylidler, Kiral ligand, Asimetrik sentez.

To my lovely sister, my dear mother and father and Arda…

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TABLE OF CONTENTS

LIST OF TABLES

TABLES

LIST OF FIGURES

FIGURES

LIST OF SCHEMES

SCHEMES

LIST OF ABBREVIATIONS

ABBREVIATIONS

CFAM:	Cyclohexyl Substituted Ferrocenyl Aziridinyl Methanol
PFAM:	Phenyl Substituted Ferrocenyl Aziridinyl Methanol
NFAM:	Naphthyl Substituted Ferrocenyl Aziridinyl Methanol
1,3-DC:	1,3-Dipolar Cycloaddition
HPLC:	High Performance Liquid Chromatography
DCM:	Dichloromethane
ACN:	Acetonitrile
THF:	Tetrahydrofuran
ee:	enantiomeric excess
HRMS:	High Resolution Mass Spectrometry
HOMO:	Highest Occupied Molecular Orbital
LUMO:	Lowest Unoccupied Molecular Orbital
FMO:	Frontier Molecular Orbitals
Fc:	Ferrocene

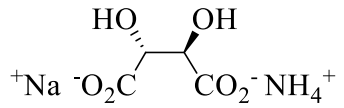
CHAPTER 1

INTRODUCTION

1.1. Chirality

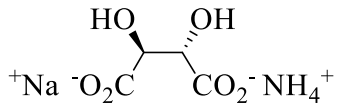
Chiral molecules have non-superimposable mirror images. A chiral molecule and its mirror image are called enantiomers. According to stereochemistry chiral molecules can be enantiomers or diastereomers. However, diastereomers are not the mirror image of each other. Although enantiomers have the same physical and chemical properties, they rotate the plane-polarized light by the same angle in the opposite direction.[1] Chemically, their reactivity against the other chiral molecules or reagents can be different as well.

Louis Pasteur contributed to the development of the chirality concept. In 1848, Pasteur separated two isomers of tartaric acid salts **1** and **2** by crystallization. He observed that the optical activity of these two isomers were different (Figure 1).[2,3] This discovery become a breakthrough in the field of stereochemistry.



(*R*,*R*)-Sodium ammonium tartrate

1



(*S*,*S*)-Sodium ammonium tartrate

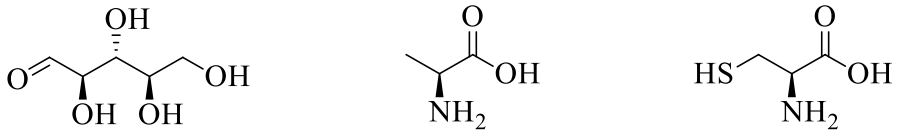
2

Figure 1. Structures of sodium ammonium tartrate salts.

1.1.1. Importance of Chirality in Biological Systems

Chirality is an important concept for human beings and also other living organisms because plenty of molecules such as ribose in RNA[4] and amino acids in

proteins[4] are chiral.[5] Figure 2 shows some biologically important chiral compounds such as *D*-Ribose (**3)** and also some amino acids like *L*-Alanine (**4**) and *L*-Cystein (**5**).[4]



D-ribose | *L*- Alanine | *L*-cystein

3 | **4** | **5**

Figure 2. Some biologically important chiral compounds.

Chirality is also a crucial phenomena in the pharmaceutical industry. Two enantiomers of the same drug may show different biological responses to human body. Generally, one enantiomer of the drug meets the required biological activity. The other enantiomer, on the other hand, can be toxic or removed from the body without showing any effect.[4] For instance, in the late 1950s, thalidomide drug caused a disaster. Doctors prescribed this drug to pregnant women as a sedative purposes.[5] This drug caused anomalies on babies such as missing hands, feet, and legs. This horrible result caused by *(S)*-enantiomer **7** of this drug (Figure 3). Even if one of the enantiomers is harmless to human body, the most reasonable pathway to prevent such cases, is to synthesize the desired enantiomers.[4]

Another chiral drug called ibuprofen is used as a pain killer and anti-inflammatory agent.[2] There is no restriction about selling the racemic form even though *(R)*-Ibuprofen **8** is not active because inversion of *(R)*-enantiomer to *(S)*-enantiomer **9** occurs spontaneously in the human body (Figure 3).[6]

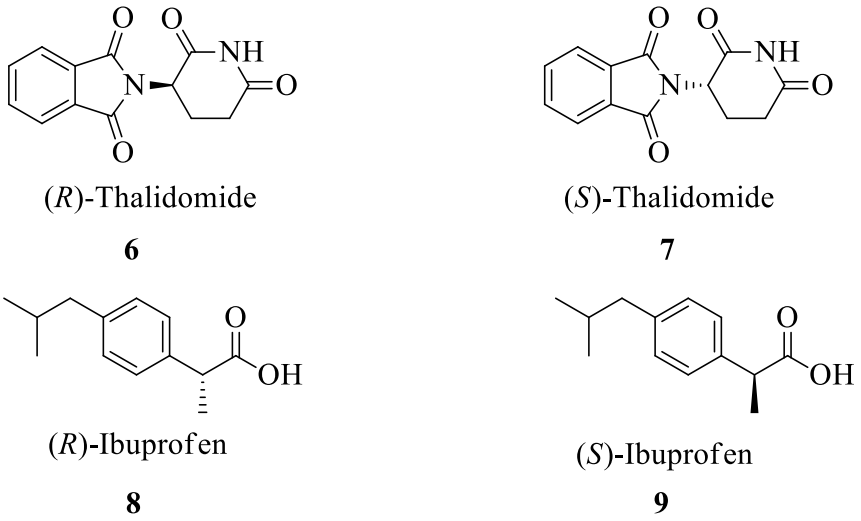


Figure 3. Enantiomers of Thalidomide and Ibuprofen drugs.

Besides the pharmaceutical industry, nature also provides us some chiral compounds like limonene. One enantiomers of this compound (**11**) is present in lemons and the other one (**10**) is present in oranges (Figure 4). These enantiomers are the origins of the smell of these fruits.[7]

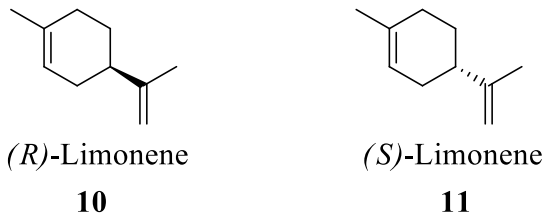


Figure 4. Enantiomers of limonene.

1.2. Asymmetric Synthesis

Asymmetric synthesis is a type of chemical reaction which selectively creates new configuration by generating new stereogenic centers[8] in a controlled way.[4] Synthesis of enantiomerically pure compounds is the main goal of asymmetric synthesis. Synthesizing enantiomers as a mixture causes separation problems. To prevent such problems and to save time and chemicals, it is necessary to use the tools of asymmetric synthesis.[9]

1.2.1. Resolution

According to classical definition, resolution is a way of separating enantiomers from each other.[8] Among the many resolution techniques, crystallization is the important one. Pasteur used this technique to separate tartaric acid salts as we mentioned earlier. By this technique, a mixture of enantiomers is converted to diastereomers and separated easily by crystallization. Other modern and effective method to separate enantiomers is chromatographic techniques like chiral HPLC. In this case, there is no need to convert enantiomers to diastereomers, so direct separation is possible.[3] On the other hand, there are some negative aspects of resolution attempts. Although separation of enantiomers is possible, the yield can only be 50% because in most cases the unwanted enantiomer is discarded. Therefore, this method is not atom economical.[10]

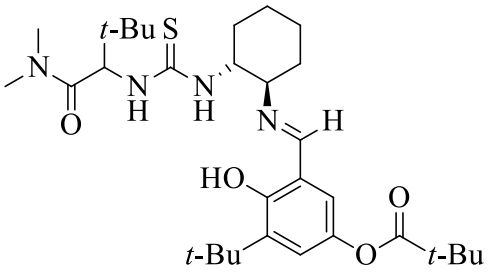
1.2.2. Chiral Entities

One possible way to achieve asymmetric synthesis is chiral pool. In this method, enantiopure natural compounds are used as starting materials. These types of compounds are called **chiral pool**,[11,12] such as amino acids and sugars.[11] In this method, one chooses a chiral starting material that has the same stereogenic center as the targeted product.[13] Thus, without changing stereogenic center of the starting material, desired product can be obtained.

These chiral pool compounds have some advantages. They are optically pure,[14] generally non-toxic and also commercially available.[15] In spite of these advantages, unfortunately, not all natural chiral compounds are easily accessible and cheap. For this reason, scientists face some difficulties such as long and multi-step reactions to obtain these materials.[16]

Another method is the use of **chiral auxiliaries**. These chiral compounds are attached to the substrates momentarily and removed at the end of the synthesis. Thus, this method can control the stereochemistry as long as chiral groups stay connected and provide new stereogenic center in a controlled way.[17] This method has been used by scientists in asymmetric synthesis for many years.[18] Although chiral auxiliaries providing high stereoselectivity to targeted products, they are not easily accessible and require two extra steps to get asymmetric synthesis.[19,20]

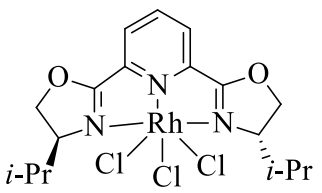
For the last twenty years, the most popular and preferred methods to perform asymmetric compounds is the use of **chiral catalysts**. The catalysts, in general, enhance the reaction rate by decreasing the activation energy of the process.[21] Compared to the other methods, the main advantages of chiral catalysts are not being consumed[22] during the process and used in catalytical amount. Thus, using small amount of a catalyst, it is possible to produce a large amount of product. Another advantage is the waste minimization.[21] There are different types of catalysts such as biocatalysts, metal catalysts, and organocatalysts. There are many examples to each class of these catalysts in literature.[10] The structure of one of the most popular thiourea organocatalyst (**12**) developed by Jacobsens' group is given in Figure 5.[23]



12

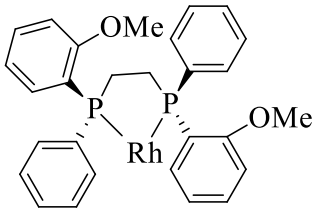
Figure 5. Jacobsen's thiourea catalyst

Since the purpose this thesis is the use of metal catalysts, we will focus mainly on these catalysts. Among the chiral catalysts, metal catalysts are the most studied ones. Metal catalysts involve a metal and a chiral ligand. There are many different metal catalysts developed and used in literature for different organic reactions to synthesize organic molecules in their enantiopure forms. Some examples are Rh-Pybox-^{i}Pr complex **13**,[24] (*R*,*R*)-Rh-DIPAMP **14**,[25] Ru-BINAP **15**[26] and Cu-Phosphino-oxazoline complex **16**[27] (Figure 6).



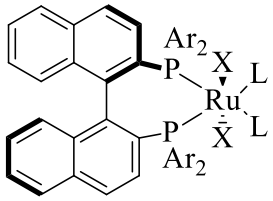
Rh-Pybox-*i*Pr complex

13



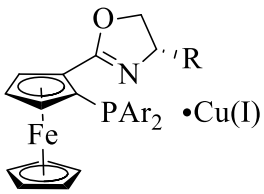
(R,R)-Rh-DIPAMP

14



Ru-BINAP

15

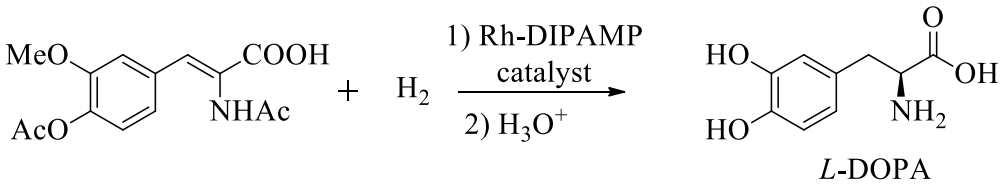


Cu-Phosphino-oxazoline complex

16

Figure 6. Examples to some metal catalysts.

Knowles introduced one of the first metal catalysts to the literature for the catalytic asymmetric hydrogenation in 1970s.[28] He developed Rh-DIPAMP[25] catalyst system, also used by industry, for the synthesis of the drug *L*-DOPA **17** used for the treatment of Parkinson's disease (Scheme 1).[25] He was awarded the Nobel prize along with Nayori and Sharpless in 2001.



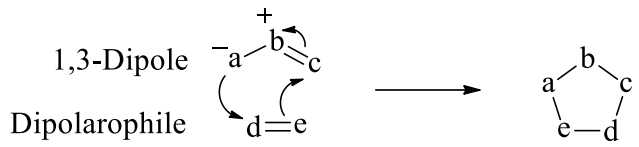
L-DOPA

17

Scheme 1. Industrial synthesis of *L*-DOPA by Rh-DIPAMP catalyst system.

1.3. Metal Catalysts Used for 1,3-Dipolar Cycloaddition (1,3-DC) Reactions

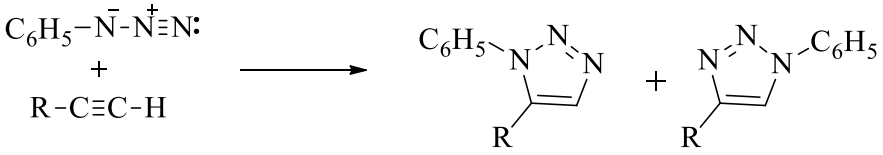
Before giving examples to metal catalysts used for the title reaction, we would like to give brief information about 1,3-Dipolar cycloaddition reactions. Because it is the main reaction used in this thesis. 1,3-DC reaction is taking place between a dipole (4π system) and a dipolarophile (2π system). According to Woodward–Hoffmann rules, 1,3-DC reactions are thermally allowed processes.[29] Scheme 2 shows the general mechanism of 1,3-DC reactions.



Scheme 2. General reaction mechanism of 1,3-DC.

1,3-DC reactions are one of the important reactions in synthesizing heterocyclic compounds. Depending on the dipole and the dipolarophile, two 'C-C' bonds and up to four stereogenic centers can be formed in one step.[30,31]

Huisgen is the pioneer of this reaction and he developed this chemistry in 1960s.[31] He studied the most of the of 1,3-dipoles such as azomethine ylides, nitrile oxides, nitrous oxides, azides etc. (see the types of 1,3-dipoles in Table 1).[32] Scheme 3 shows one example to Huisgen's study using phenylazide as 1,3-dipole and an acetylene as the dipolarophile.



Scheme 3. 1,3-DC reaction studied by Huisgen.

1.3.1. Frontier Molecular Orbital Theory (FMO) for 1,3-Dipolar Cycloaddition Reactions

Reactivity and regioselectivity of 1,3-DC reactions can be clarified by Frontier molecular orbital theory (FMO).[31,33] According to FMO theory, there are three types of interactions in 1,3-DC reactions based on the HOMO-LUMO energy gaps.[33] Type I uses HOMO of the dipole and LUMO of the dipolarophile. Type I also resembles Diels-Alder reaction where HOMO of the diene and LUMO of the dienophile interact with each other. In this thesis, we have used 1,3-DC reaction of azomethine ylides which mainly takes place by Type I interactions. In Type II both types of interactions are possible, HOMO-dipole and LUMO-dipolarophile or HOMO-dipolarophile and LUMO-dipole, because there is no energy difference. Finally, type III occurs between HOMO-dipolarophile and LUMO-dipole interactions as given in Figure 7.[31]

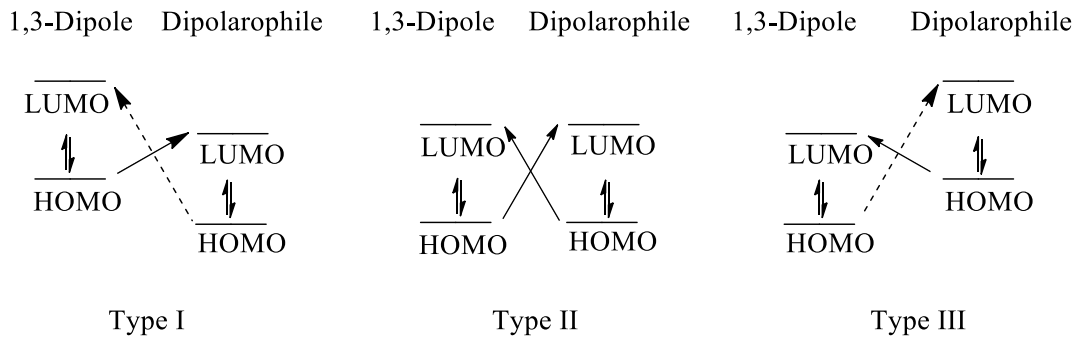


Figure 7. Frontier Molecular Orbital interactions in 1,3-DC reactions.

Figure 8a shows the molecular orbitals and their relative energy levels of the dipole and the dipolarophile. Figure 8b shows type I bonding interaction of $HOMO_{dipole}$-$LUMO_{dipolarophile}$. Figure 8c shows type III bonding interactions of $HOMO_{dipolarophile}$- $LUMO_{dipole}$.

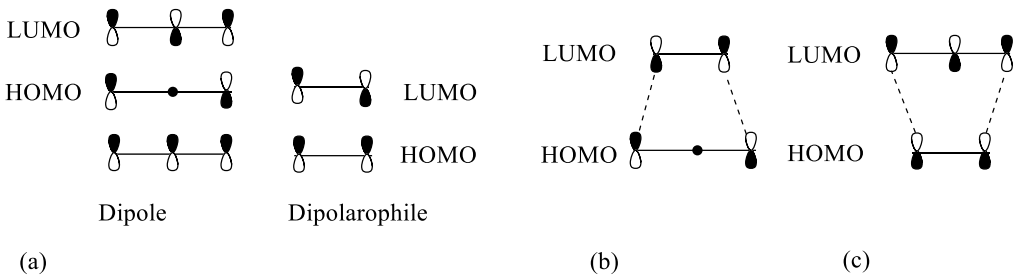


Figure 8. (a) π-Orbitals of the dipole and dipolarophile, (b) type I bonding FMO, (c) type III bonding FMO.

1.3.2. Stereochemisty of 1,3-Dipolar Cycloaddition Reaction

1,3-DC reactions are generally stereospecific due to concerted mechanism. If a *cis*-dipolarophile is used, *cis*-product is obtained. Likewise, when a *trans*-dipolarophile is used, *trans*-product is obtained as shown in Figure 9.[33]

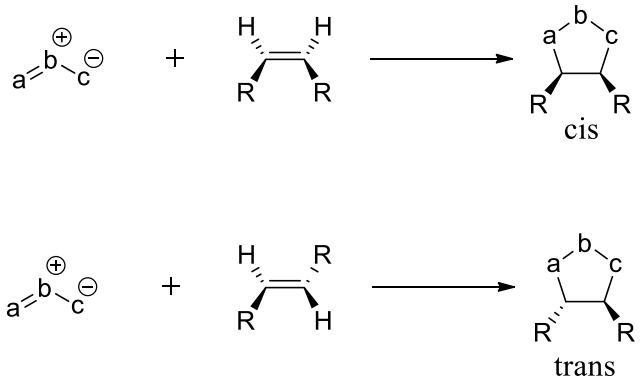


Figure 9. Conserved stereochemistry of 1,3 DC reaction.

1.3.3. Dipolarophiles and Dipoles of 1,3-Dipolar Cycloaddition Reactions

Generally, alkenes and alkynes are used as dipolarophile in 1,3-DC reactions. In addition to alkenes and alkynes, carbonyl (C=O), imine (C=N), nitroso (N=O), and nitrile (C≡N) groups can act as dipolarophiles.[33]

There are two different kinds of 1,3-dipoles (commonly called ylides). These are allyl anion and propargyl/allenyl anion type. Allyl anion type can be represented in two resonance structure as octet and sextet. In octet resonance structure, central atom has a positive charge. Negative charge travels between terminal atoms. In sextet structure, central atom is neutral, terminal atoms are positively and negatively charged. Allyl anion type has a bent structure because four electrons are delocalized in p_z orbitals which are orthogonal to the plane of the ylide.[33]

In the propargyl anion type resonance structure, central atom has positive charge and one of the terminal atoms is negative or one terminal atom is positively charged and the other one is negatively charged. This type of dipole always has a nitrogen as the central atom. Also, the propargyl anion type 1,3-dipoles have linear structure because of the extra double bond. This double bond is orthogonal to the delocalized system and its orbitals cannot contribute to the resonance structure (Figure 10).[29]

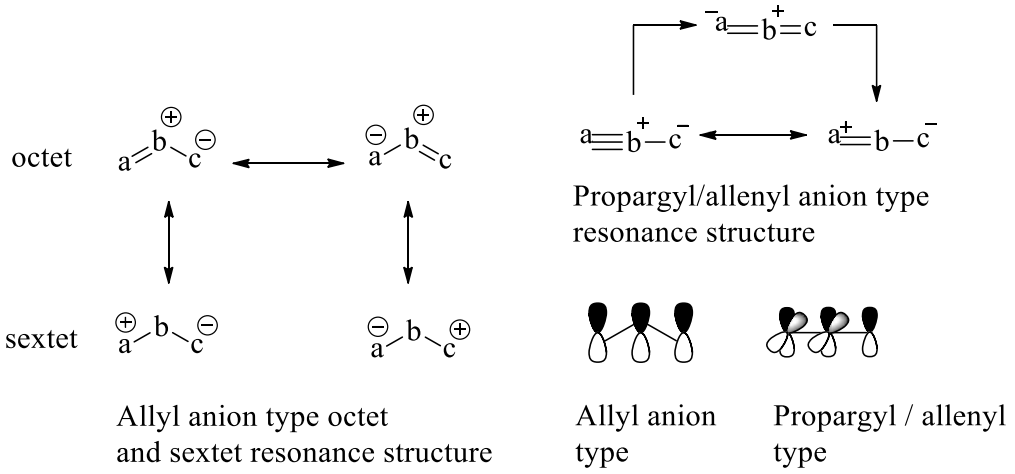
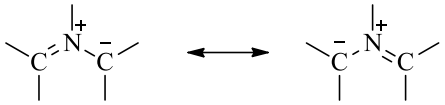
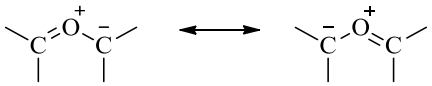
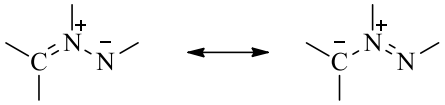
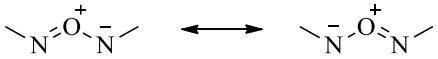
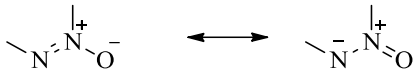
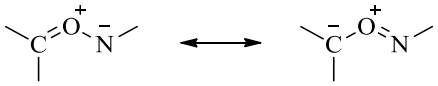
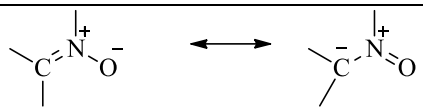
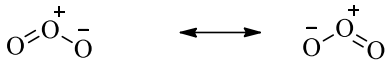
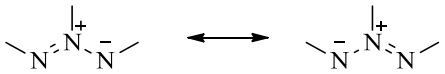
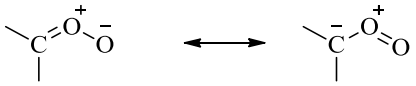
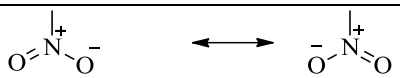
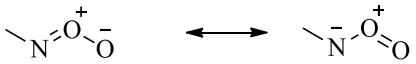
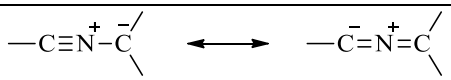
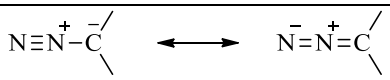
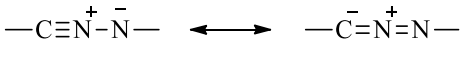
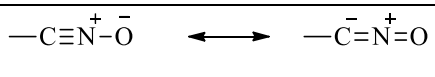
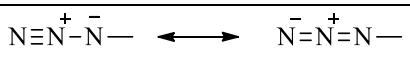


Figure 10. Resonance structures of 1,3-dipoles

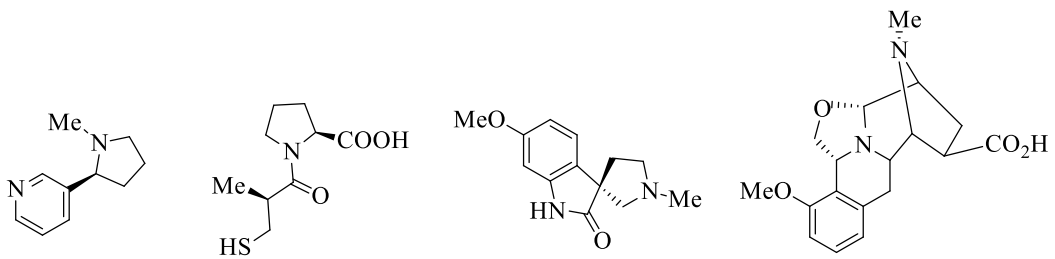
Table 1 shows some commonly known 1,3-dipoles which belong to both types.

Table 1. Some widely used 1,3-dipoles.

Allyl Anion Type	
N-Centered	**O- Centered**
 Azomethine Ylide	 Carbonyl Ylide
 Azomethine Imine	 Nitrosimine
 Azoxy Compound	 Carbonyl Imine
 Nitrone	 Ozone
 Azimine	 Carbonyl Oxide
 Nitro Compound	 Nitroso Oxide
Propargyl/Allenyl Type	
 Nitrile Ylide	 Diazoalkane
 Nitrile Imine	 Nitrous Oxide
 Nitrile Oxide	 Azide

1.3.4. Metal Catalyzed Asymmetric Synthesis of Pyrrolidines by 1,3-DC Reaction of Azomethine Ylide in the Literature

Azomethine ylides are widely used as reactive intermediates of 1,3-DC reactions. Two of the most commonly used methods to create azomethine ylides are aziridine ring opening by thermolysis or photolysis and by deprotonation of imines.[34] When azomethine ylides are trapped with dipolarophiles, pyrrolidines are formed.[29] Pyrrolidine structure is very important in organic chemistry because they are present in many natural products.[35] Also, they are crucial for pharmaceutical industry in designing some drugs.[36] Figure 11 illustrates some biologically active pyrrolidine compounds, nicotine (**18**), captopril (**19**), horsfiline (**20**), and quinocarcin (**21**).

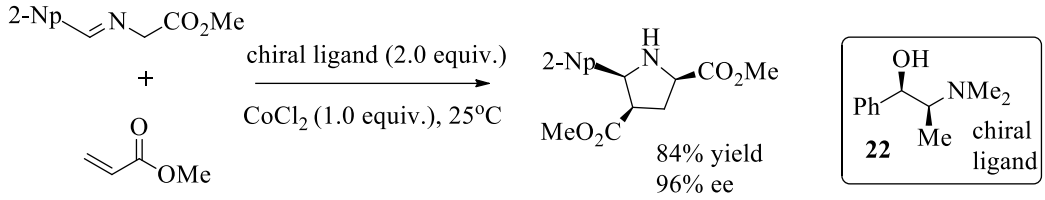


Nicotine **18** | Captopril **19** | Horsfiline **20** | Quinocarcin **21**

Figure 11. Some biologically active compounds bearing pyrrolidine ring.

For the metal-catalyzed asymmetric synthesis of pyrrolidines by 1,3-DC reaction of azomethine ylides, Co(II), Ag(I), Mg(II), Mn(II), Li(I), Ti(IV), Cu(I), and Zn(II) are used as the metals with a variety of chiral ligands.

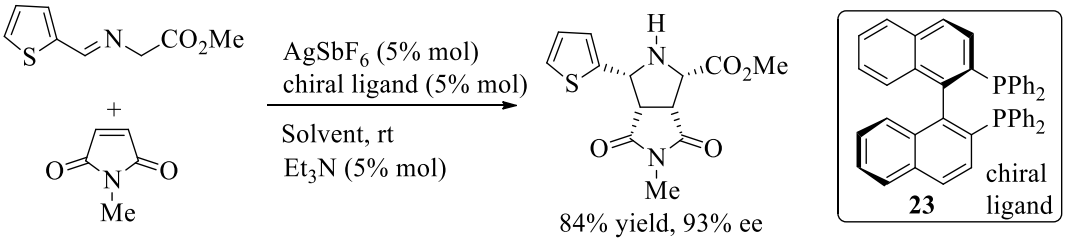
Grigg is the pioneer of the enantioselective 1,3-DC reactions of azomethine ylides by using chiral metal-ligand system. He used molar equivalent of cobalt-ephedrine **22** complex to synthesize pyrrolidines in up to 84% yield and 96% ee (Scheme 4).[37]



Scheme 4. 1,3-DC reaction reported by Grigg and co-workers.

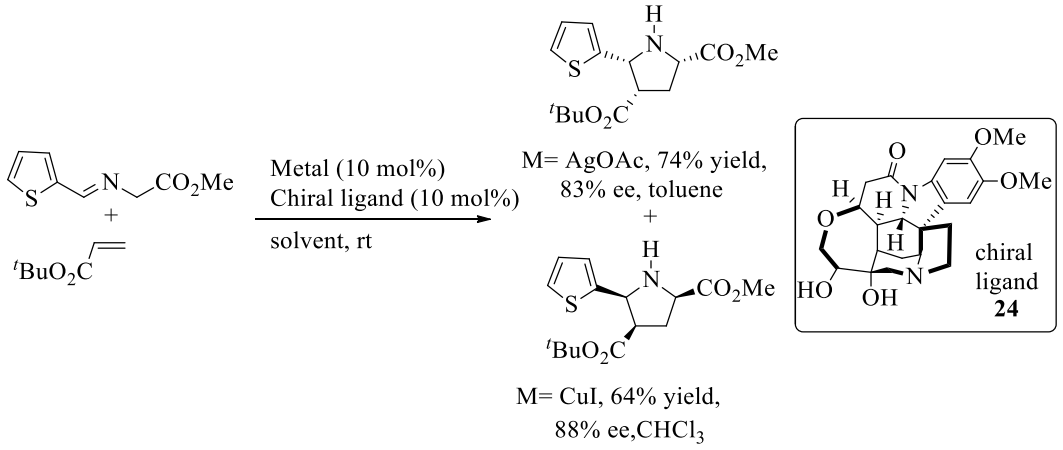
Since the first work published by Grigg, many groups have studied metal catalyzed asymmetric synthesis of pyrrolidines by 1,3-DC reaction of azomethine ylides. Many of these studies involved the synthesis of aryl-substituted pyrrolidines and only in very few cases, heteroaryl-substituted pyrrolidines were reported as one or two examples. In another words, there is no comprehensive study for the heteroaryl-substituted pyrrolidine derivatives by using 1,3-DC reactions of azomethine ylides with chiral metal catalysts. These studies are summarized in the following paragraphs.

One of the studies related with the heteroaryl-substituted pyrrolidine synthesis by using 1,3-DC of azomethine ylides with a metal catalyst was reported by Sansano and co-workers.[37] This group used silver as the metal source and BINAP **23** as the chiral ligand to synthesize thienyl-substituted pyrrolidine in 93% ee and 84% yield (Scheme 5).[38]



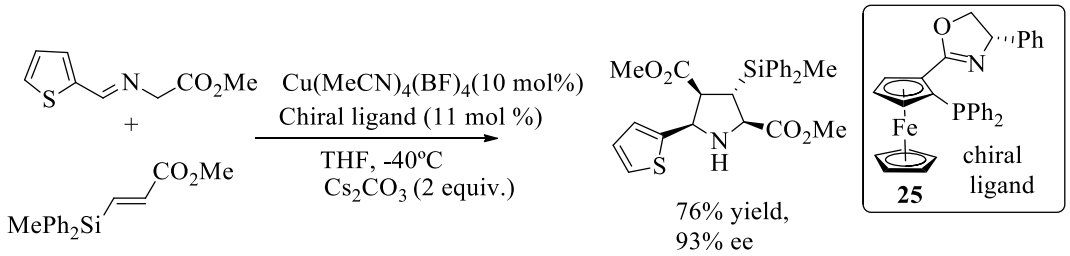
Scheme 5. BINAP-chiral ligand was used by Sansano and co-workers.

Oh and co-workers also studied the same reaction by using two different metals with *tert*-butyl acrylate. Using a rather complex chiral ligand, they reported the cycloadduct in 74% yield with 83% ee with silver and 64% yield and 88% ee with copper as shown in Scheme 6.[39]



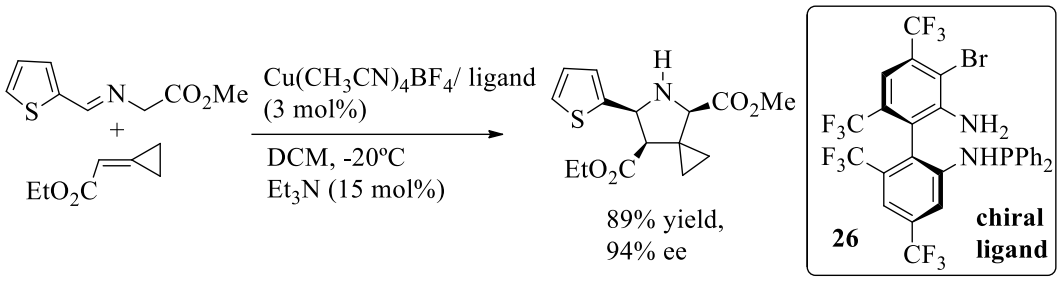
Scheme 6. Study of Oh and co-workers.

In the recent study reported by Deng and co-workers, thienyl-substituted imine and *β*-methyldiphenylsilyl acrylate were used to synthesize pyrrolidine heterocycle in high selectivity and remarkable yield. In this study, Cs_2CO_3 was used as a base with planar-chiral ferrocene *P,N*-ligand **25**. This catalyst system formed cycloadduct in 76% yield with 93% ee (Scheme 7).[40]



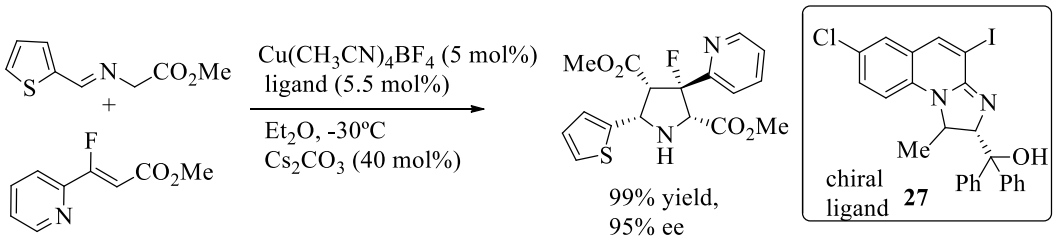
Scheme 7. Ferrocene-based P,N ligand used by Deng and co-workers.

In another study, reported by Wang and co-workers, thienyl-substituted pyrrolidine was synthesized from a very special dipolarophile by using Cu(I) salt with *(S)*-TF–BiphamPhos ligand **26**. The cycloadduct was isolated in 89% yield with 94% ee (Scheme 8).[41]



Scheme 8. Copper-catalyzed 1,3-DC reaction reported by Wang and co-workers.

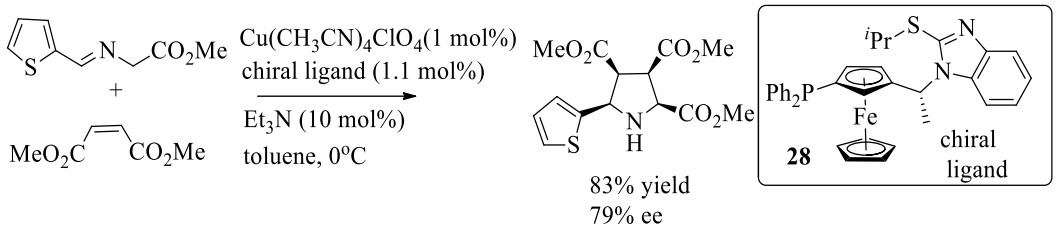
In an interesting study, Deng and co-workers studied 1,3-DC reaction to access thienyl-substituted pyrrolidine with Cu(I)-*N,O*-ligand **27** catalyst. In this study, pyridiyl- and thienyl- substituted cycloadduct was obtained in 99% yield and 95% ee (Scheme 9).[42]



Scheme 9. Pyridiyl- and thienyl- substituted cycloadduct reported by Deng and co-workers.

According to study reported by Hu and co-workers, chiral ferrocenyl *P,S*-ligand **28** and Cu(I) salt used as a catalyst for the reaction of thienyl-substituted

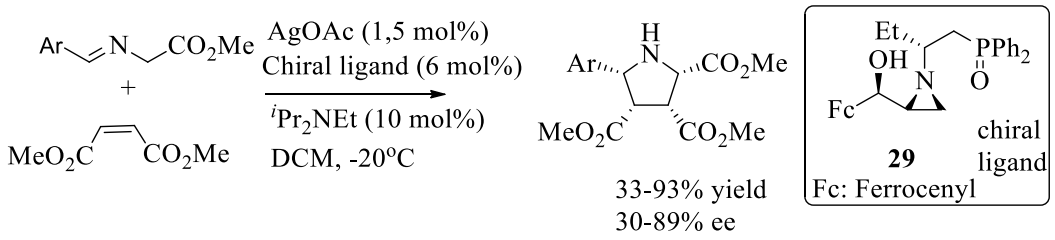
azomethine ylide and dimethyl maleate in toluene. This chiral catalyst system provided the cycloadduct in 83% yield and 79% ee with minor amount of *exo*-product (Scheme 10).[43]



Scheme 10. 1,3-DC reaction reported by Hu and co-workers.

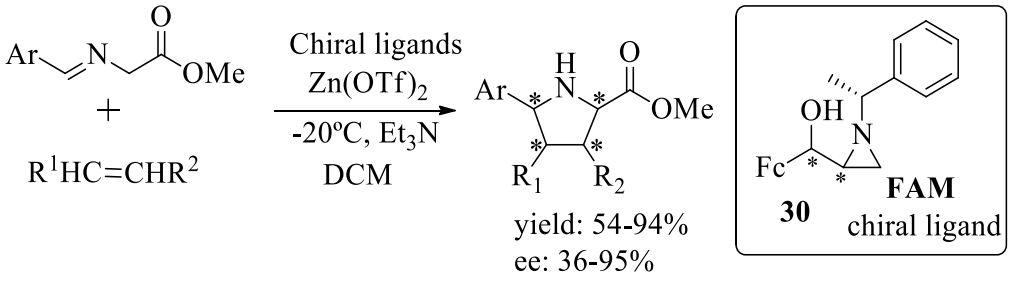
In all these studies, heteroaryl-substituted pyrrolidines took place as only one or two examples. Main part of the studies involved aryl-substituted pyrrolidines. In other words, there is no systematic study for the synthesis of thienyl- or heteroaryl-substituted pyrrolidines by using 1,3-DC reaction.

Our group also involved in this field and developed new metal catalysts for the asymmetric synthesis of pyrrolidines by 1,3-DC. In one of these studies, phosphine oxide ferrocenyl aziridinyl methanol **29** was used as the chiral ligand with silver as a metal source to form aryl-substituted pyrrolidines in 33-99% yield and 30-89% ee (Scheme 11).[44]



Scheme 11. 1,3-DC reaction reported by Dogan group using phosphorous oxide chiral ligand.

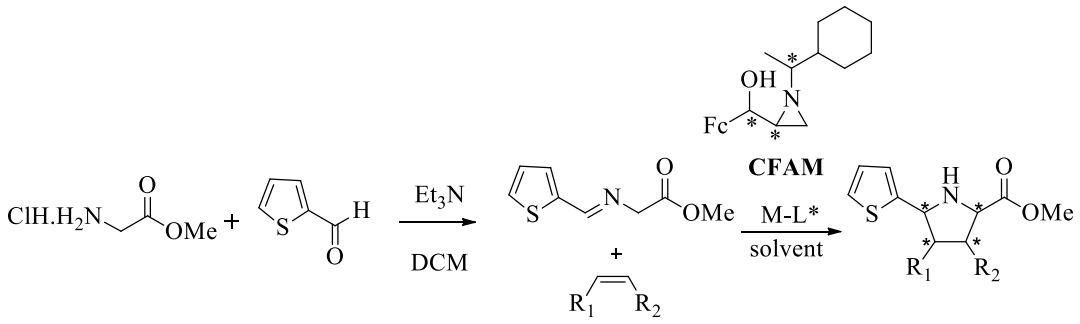
In the second study, our group used chiral **FAM** (phenyl-substituted ferrocenyl aziridinyl methanol (**30**) ligands with $Zn(OTf)_2$ to yield aryl-substituted pyrrolidines in 63-94% yield with 36-95% enantioselectivity (Scheme 12).[45]



Scheme 12. Use of **FAM** ligands in 1,3-DC reactions.

1.4. Aim of the Thesis

Pyrrolidine units are found in the structure of many natural products and some drugs. Therefore, they are synthetically and pharmacologically important compounds. Syntheses of pyrrolidines in their enantiopure forms is still attracting the attention of organic chemists worldwide. One of the most efficient methods for the asymmetric synthesis of pyrrolidines is chiral metal catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides with electron deficient dipolarophiles. In literature, different chiral metal catalysts (metal-chiral ligand) have been developed and used for this reaction. Our group has also been involved in this field and developed chiral **FAM** ligands that were used with different metals for the enantioselective aryl-substituted pyrrolidines successfully. Although literature is full of chiral metal catalyst used for aryl-substituted pyrrolidine synthesis, there are only one or two examples reported for heteroaryl-substituted pyrrolidines in some of these studies. In this thesis, we aimed to use our **FAM** ligands with different metals for the asymmetric synthesis of thienyl-substituted pyrrolidines by 1,3-DC reaction of azomethine ylides (Scheme 13). In doing so we also aimed to synthesize a new derivative of **FAM** ligand which is called **CFAM** (cyclohexyl ferrocenyl aziridinyl methanol).



Scheme 13. General reaction scheme of thienyl-substituted pyrrolidines with **CFAM** ligands.

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of Chiral CFAM ligands

Since our purpose in this thesis was to screen chiral **FAM** ligands and find out their catalytic performance for enantioselective synthesis of thienyl-substituted pyrrolidines, first we synthesized **CFAM1-4**, **PFAM1-4** and 1-**NFAM1-4** ligands (Figure 12).

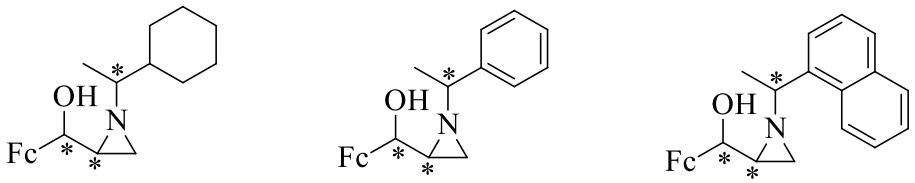
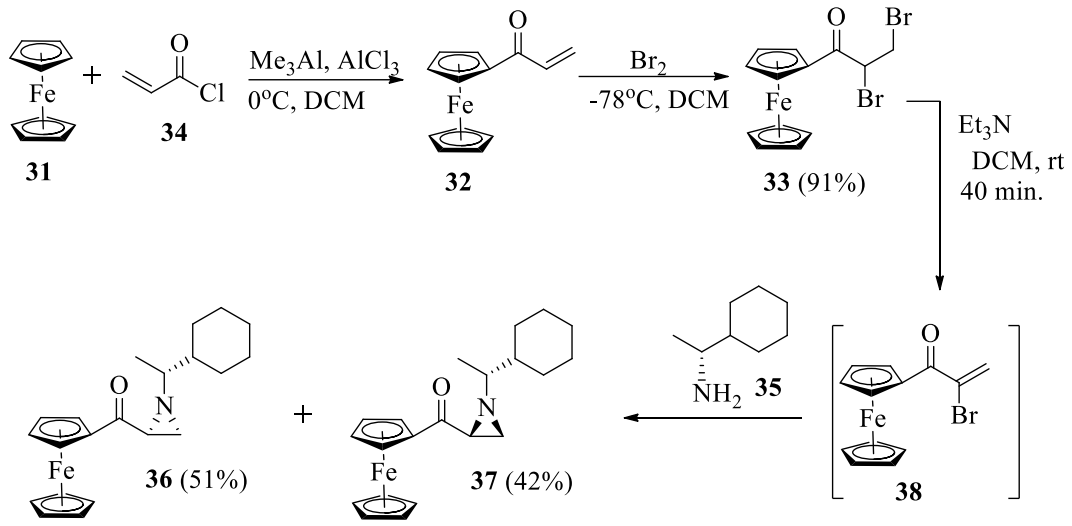


Figure 12. General structure of **CFAM, PFAM, and NFAM** ligands

Among these ligands **CFAM** (cyclohexyl ferrocenyl aziridinyl methanol) was synthesized for the first time in this thesis by using the known procedures reported by our group.[45]

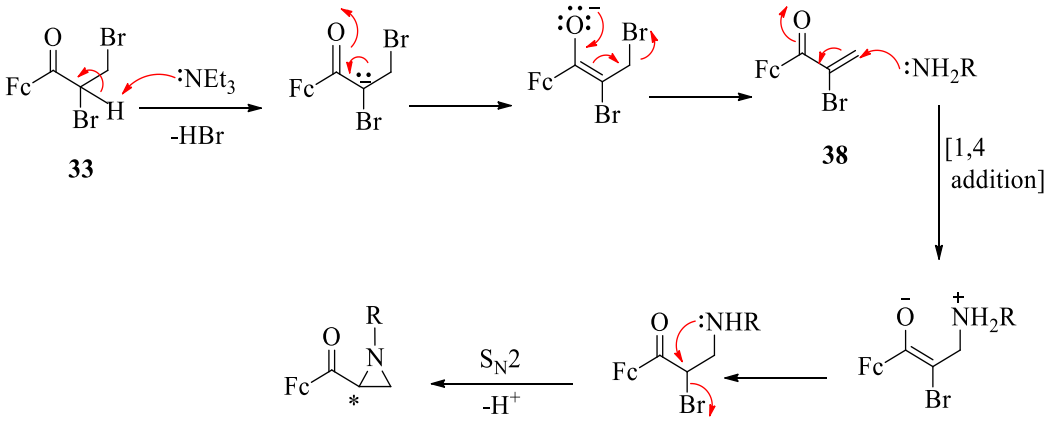
For the synthesis of **CFAM** ligands, we started from ferrocene **31** and acryloyl chloride **34**. Reaction of these two compounds by the Friedel-Craft acylation in the presence of mixed Lewis acids $AlCl_3$-Me_3Al provided the corresponding acryloyl ferrocene **32** in almost quantitative yield. In the next step, simple bromination was carried out. Although it looks like a simple bromination reaction, it has to be done carefully by adding the cooled (-78 ^oC) bromine solution in DCM to the solution of acryloyl ferrocene in DCM at -78 ^oC at once. After obtaining dibromo compound **33**

in >90% yield in a very short reaction time, it was treated with Et_3N to get α-bromoacryloyl ferrocene **38**. Without isolating this compound, chiral amine *(R)*-(-)-1-cyclohexylethylamine (**35**) was added to the same reaction flask which resulted in the formation of two diastereomeric ketones **36** and **37** in 42% and 51% yields respectively (Scheme 14). This reaction is also known as Gabriel-Cromwell reaction.[46]



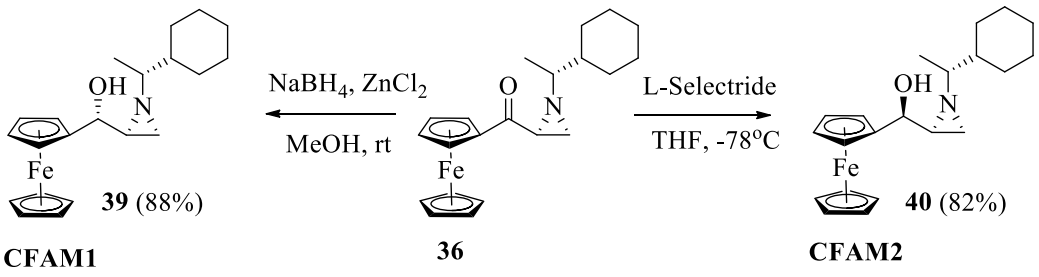
Scheme 14. Synthesis of cyclohexyl-substituted aziridinyl ketones.

Gabriel-Cromwell reaction is a one-pot reaction and following steps are taking place according to the proposed mechanism shown in Scheme 15. In the first step, Et_3N eliminates HBr and then conjugate addition of chiral amine takes place. After conjugate addition, α-protonation is achieved. Final step is the aziridination by a S_N2 reaction.



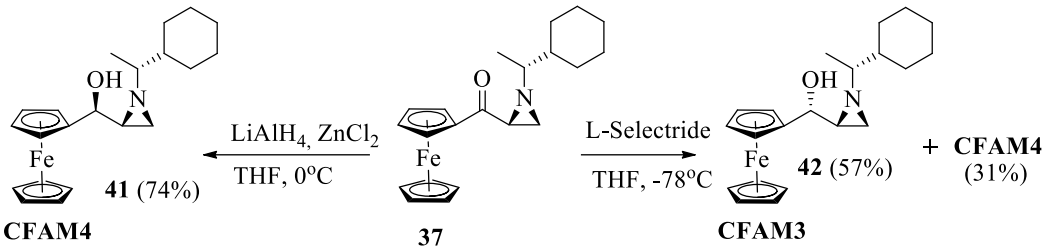
Scheme 15. Proposed mechanism for Gabriel-Cromwell Reaction.

The last step in ligand synthesis was the reduction of carbonyl group. In this step, we followed a procedure which was developed by Korean group.[47] For this purpose, different reagents were used to obtain all possible stereoisomers. Reduction of ketone **36** with $NaBH_4$ in the presence of $ZnCl_2$ provided **CFAM1** (**39**) in 88% yield as a single diastereomer (Scheme 15). Configurational assignments (*R, R, R)* were made by making analogy with previously known **PFAM1** ligand where the absolute configuration was determined by X-ray analysis.[45] Reduction of the same ketone **36** by using L-selectride formed the second diastereomer **CFAM2** (**40**) in 82% yield (Scheme 16).



Scheme 16. Formation of **CFAM1** and **CFAM2** from ketone **36**.

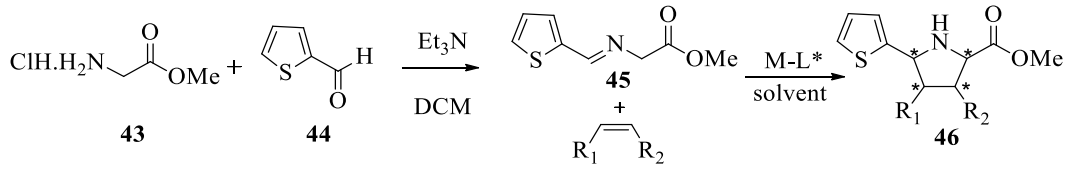
Reduction of ketone **37** was achieved by using $LiAlH_4$-$ZnCl_2$ which provided **CFAM4** (**41**) ligand in 74% yield. In this step, the other diastereomer **CFAM3** (**42**) was also formed in trace amount. When L-Selectride was used for the reduction of the same ketone, mixture of **CFAM3** and **CFAM4** was obtained with 57% and 31% yield. (Scheme 17). Diastereomers were separated easily by flash-column chromatography on silica gel. $NaBH_4$-$ZnCl_2$ was not effective in this case which was attributed to steric reasons.



Scheme 17. Formation of **CFAM3** and **CFAM4** from ketone **37**.

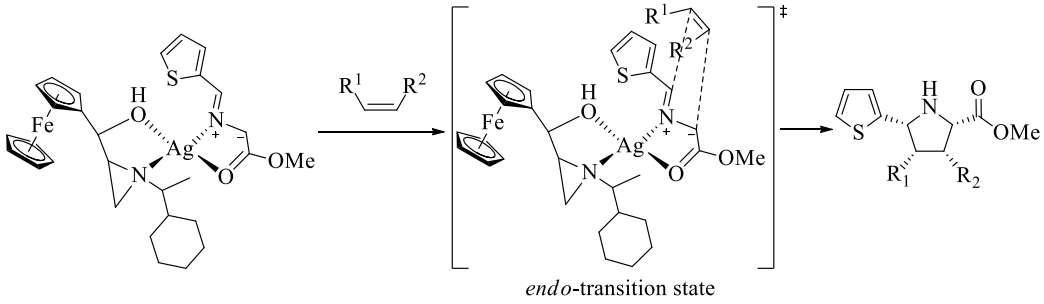
2.2. Synthesis of Thienyl-Substituted Pyrrolidine Derivatives

In order to test the catalytic effect of chiral **FAM** ligands in 1,3-DC reaction of azomethine ylides, thienyl-substituted imine was synthesized first by condensing glycine methyl ester hydrochloride (**43**) with 2-thiophenecarboxaldehyde (**44**). The reaction of this imine with electron deficient dipolarophile in the presence of a metal and **FAM** ligands yielded thienyl-substituted pyrrolidines **46** as shown in Scheme 18.



Scheme 18. Formation of thienyl-substituted pyrrolidines from thienylimine.

Based on the literature studies and our previous studies for the metal catalyzed asymmetric synthesis of pyrrolidines by 1,3-DC reactions, the following transition state was proposed (Scheme 19). In this transition state, imine and chiral ligand were coordinated to the metal and then dipolarophile was added from the *re*-face of the azomethine ylide in an *endo*-mode (substitutents on the azomethine ylide nitrogen and the group on the dipolarophile are on the same side). Dipolarophile may also coordinate to the metal depending on the functional group.



Scheme 19. Proposed transition states for 1,3-DC reaction.

After the synthesis of **CFAM** ligands, we had total of 12 structurally and stereoisomerically different ligands to be screened for the 1,3-DC reaction. The structure of **PFAM1-4** (phenyl ferrocenyl aziridinyl methanol) and 1-**NFAM1-4** (1-naphthyl ferrocenyl aziridinyl methanol) ligands synthesized by other group members were given in Figure 13.

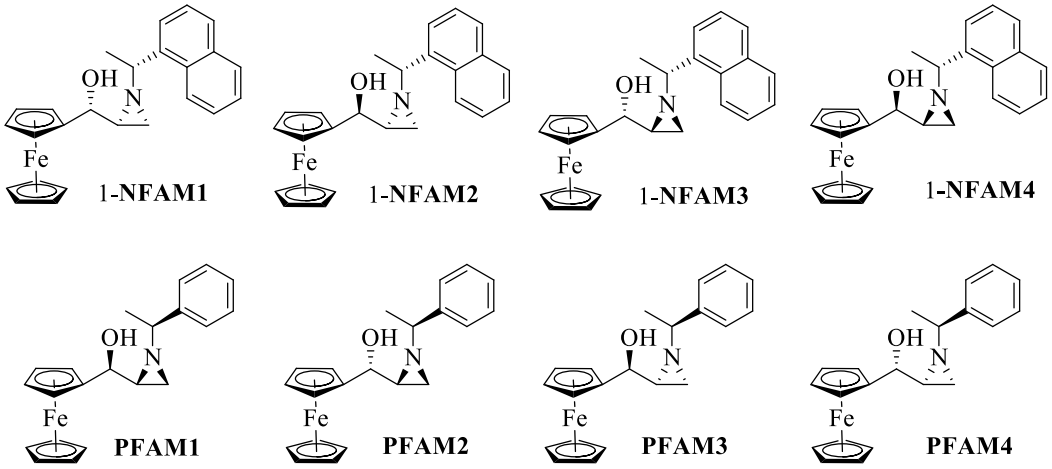
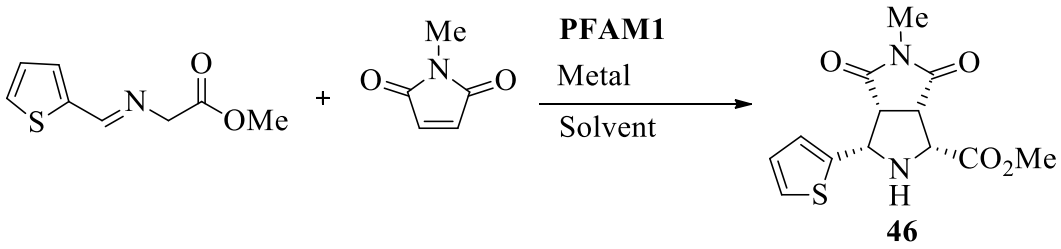


Figure 13. Structure of **PFAM** and 1-**NFAM** ligands.

2.3. Optimization Studies of 1,3-DC Reactions

In order to optimize reaction parameters for 1,3-DC, we started with the metals. For this purpose, we selected copper, zinc, and silver salts because these metals have already been tested in literature and good results were obtained in similar reactions. As shown in Table 2, **PFAM1** chiral ligand, *N*-methylmaleimide, thienylimine, and metals were tried one by one by using the literature procedure.[39] In the case of copper salt, product was formed in a short time in reasonably good yield even at low temperatures without enantioselectivity (entries 1-3). Increasing the amount of chiral ligand with the same metal source at an extended reaction time resulted in low yield and very low enantioselectivity (entry 4). Zinc as the metal source gave very similar results obtained with copper salt, very low ee and good yield after 17 hours reaction time (entry 5). Finally, silver acetate gave promising results, 49% ee and 65% yield (entry 6), therefore we selected this metal source for further optimizations. In order to increase selectivity and yield, we double the amount of ligand. (Entry 7)

Table 2. Metal screening studies.

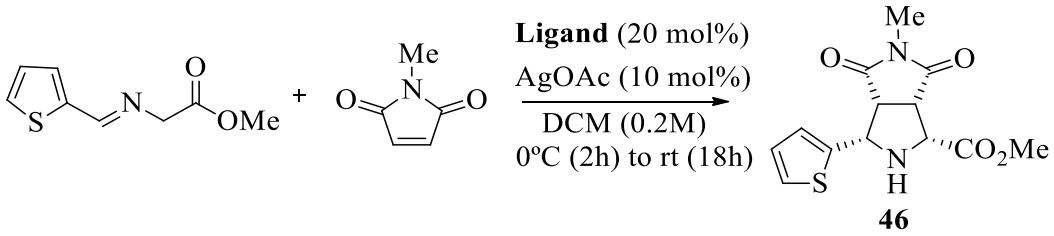


Entry	**Metal**	**Ligand / Metal Ratio**[c] (mol%)	**Solvent** (molarity)	**Temp.** and **Time**	**ee**[a] (%)	**Yield**[b] (%)
1[d]	$Cu(CH_3CN)_4BF_4$	3/3	DCM (0.66 M)	0°C 30 min	racemic	83
2	$Cu(CH_3CN)_4BF_4$	3/3	DCM (0.1 M)	0°C 20 min	racemic	75
3	$Cu(CH_3CN)_4BF_4$	3/3	DCM (0.1 M)	-40°C 30 min	racemic	80
4	$Cu(CH_3CN)_4BF_4$	6/3	Toluene (0.1 M)	0°C to rt 3 days	11	55
5[e]	$Zn(OTf)_2$	11.5/10	Toluene (0.55 M)	rt, 17h	7	86
6	AgOAc	10/10	DCM (0.2 M)	0ºC to rt 19h	49	65
7[f]	AgOAc	20/10	DCM (0.2 M)	0ºC to rt 19h	63	93

[a]Determined by HPLC using chiral AS-H column. [b]Isolated yield. [c]Given accordingly to mol of starting imine. [d]Ref 48 was followed. [e]Ref 49 was followed. [f]Ref 39 was followed.

After determining the metal source, we continued optimization studies by screening the **FAM** ligands. The results of these studies were summarized in Table 3.

Table 3. Ligand screening studies.



46

Entry	FAM Ligands	Ee[a] (%)	Yield[b] (%)
1	**PFAM1**	63	93
2	**PFAM2**	5	46
3	**PFAM3**	11	33
4	**PFAM4**	59 (*ent*-**46**)	75
5	**CFAM1**	65 (*ent*-**46**)	75
6	**CFAM2**	3	65
7	**CFAM3**	9	78
8	**CFAM4**	83	75
9	1-**NFAM1**	7	60
10	1-**NFAM2**	5	87
11	1-**NFAM3**	3	63
12	1-**NFAM4**	33	71

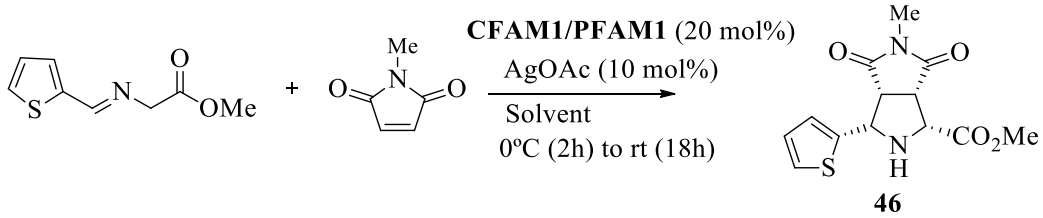
[a]Determined by HPLC with chiral AS-H column. [b]Isolated yield.

All reactions were done with 20/10 ligand metal ratio (in mol%), at same reaction time, with the same dipolarophile and in DCM by adopting the literature procedure.[38] As can be seen from the table, **PFAM1** (entry 1), **PFAM4** (entry 4), **CFAM1** (entry 5) and **CFAM4** (entry 8) formed the cycloadduct in promising yields and enantioselectivities. For the other ligands, yields were usually good to acceptable but the ee was low, the highest being 33% (entry 12). For us, the surprising results were the enantioselectivities of the naphthyl series. Because of the size of the naphthyl group, our expectation for this ligand was to obtain higher ee than phenyl (**PFAM**)

and cyclohexyl (**CFAM**) substituted ligands. From the ligand screening studies, based on the yield and ee, we decided to continue further optimizations of 1,3-DC reaction by using **PFAM1** and **CFAM4** ligands.

After determining the metal source and ligands, we continued optimization studies by screening the solvents. The results of these studies were summarized in Table 4.

Table 4. Solvent screening studies.



46

Entry	FAM Ligands	Solvent (0.20 M)	ee[a] (%)	Yield[b] (%)
1	**PFAM1**	DCM	63	93
2	**PFAM1**	Toluene	83	79
3	**PFAM1**	THF	73	82
4	**PFAM1**	ACN	31	44
5	**CFAM4**	DCM	83	75
6	**CFAM4**	Toluene	79	62
7	**CFAM4**	THF	61	56
8	**CFAM4**	ACN	59	55

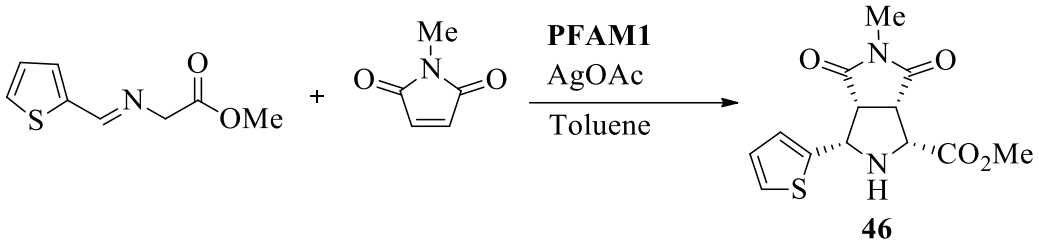
[a]Determined by HPLC with chiral AS-H column. [b]Isolated yield.

THF, DCM, acetonitrile (ACN), and toluene were used in solvent screening experiments. Acetonitrile gave the lowest ee and yield with both ligands (entries 4 and 8). Toluene gave the highest ee (entry 2) with **PFAM1** ligand but with lower yield than DCM and THF (entries 1 and 3). In the case of **CFAM4** ligand, DCM formed the

product in higher yield and ee than the other solvents (entries 5-8). From the results of the solvent screening studies, we eliminated **CFAM4** ligand and decided to continue further studies by using toluene and **PFAM1** ligand, because toluene with **PFAM1** ligand formed the product in same ee (83%, entries 2 and 5) but better yield than DCM with **CFAM4** ligand.

After choosing metal source, ligand and the solvent, we continued the optimization studies by changing catalyst loading, reaction time and equivalence of the dipolarophile. The results of these studies were summarized in Table 5.

Table 5. Optimization of catalyst loading, reaction time and dipolarophile equivalence.



46

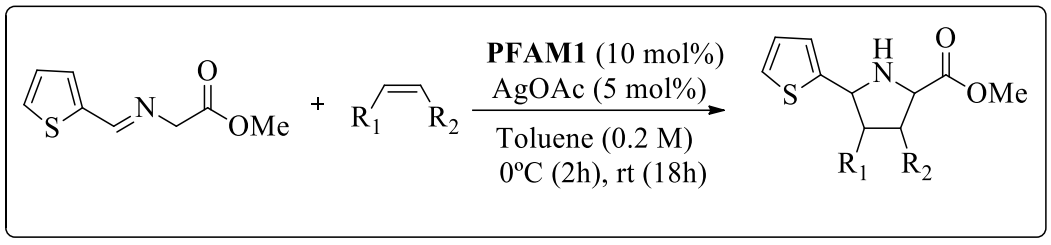
Entry	**Ligand/Metal Ratio** (mol %)	**Rxn. Conc.** (M)	**Rxn. Time.** (h)	**ee** (%)[a]	**Yield** (%)[b]
1	20/10	0.2	20	83	79
2	10/5	0.2	20	79	46
3	10/5	0.2	44	83	53
4	10/5	0.5	20	51	53
5[c]	10/5	0.2	9	69	90
6[c]	10/5	0.2	20	77	64
7[c]	10/5	0.2	44	85	64
8	5/2.5	0.2	20	45	90

[a]Determined by HPLC with chiral AS-H column. [b]Isolated yield. [c]2 Equiv. of dipolarophile was used. [d]Given accordingly to mol of starting imine.

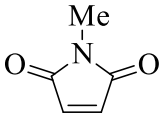
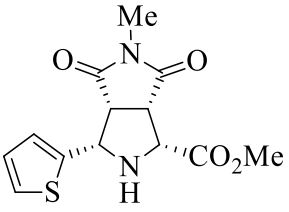
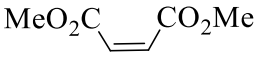
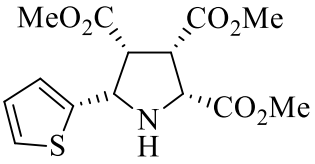
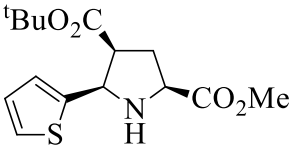
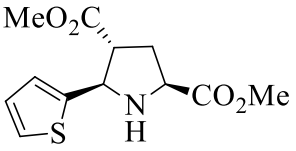
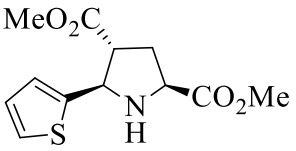
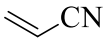
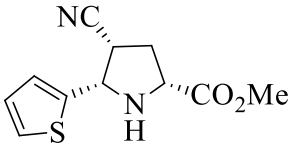
As can be seen from Table 5, lowering the catalyst loading from 20/10 mol% to 10/5 mol%, ee was lowered from 83% to 79% and yield was lowered from 79% to 49% (entries 1 and 2). Increasing the reaction time at 10/5 mol% catalyst loading provided the same ee (83%, entry 3) but the yield was still low (53%). Increasing the reaction concentration from 0.2M to 0.5M did not improve the yield and ee (entry 4). Changing the dipolarophile equivalence from 1.5 to 2.0 increased the yield, however ee did not change significantly (entries 2 and 6). From these optimization studies, we decided to carry out the 1,3-DC reactions at 10/5 mol% catalyst loading for 20h and with 2 equivalence of the dipolarophile.

After determining the metal source (AgOAc), chiral ligand (**PFAM1**), solvent (toluene), catalyst loading (ligand/metal, 10/5 mol%), reaction concentration (0.2M) and time (20h), we wanted to see the applicability of our catalyst on the other dipolarophiles. For this purpose, besides *N*-methylmaleimide commonly used dipolarophiles in 1,3-DC reactions, dimethyl maleate, *tert*-butyl acrylate, methyl acrylate, and acrylonitrile were used. The results of these studies were summarized in Table 6. As can be seen from the table, yields for all the dipolarophiles are acceptable but the enantioselectivity except *N*-methylmaleimide is low. Extending reaction time with methyl acrylate increased the yield but didn't change the ee (entry 4 and 5).

Table 6. Dipolarophile screening studies.



Entry	Dipolarophile	Product	ee (%)	Yield[d] (%)

1[a]		 **46**	77	64
2[a]		 **47**	53	65
3[a]		 **48**	11	75
4[b]		 **49**	9	68
5[b,e]		 **49**	9	77
6[c]		 **50**	15	74

[a]Determined by HPLC with chiral AS-H column. [b]Determined by HPLC with chiral OD column. [c]Determined by HPLC with chiral AD-H column. [d]Isolated yield. [e]Rxn. time was 44h.

Absolute configuration of all the cycloadducts were determined by using the literature data. We compared our HPLC data (same chiral column was used, and the retention times were compared) and NMR spectra with the literature.[50,43,39,51,52]

CHAPTER 3

CONCLUSION

In this thesis, we have synthesized a new derivative of **FAM** chiral ligands, **CFAM1-4** (cyclohexyl ferrocenyl aziridinyl methanol), successfully by using the known procedures. The catalytic performance of these chiral ligands (**CFAM1-4**) and eight other derivatives **PFAM1-4** and 1-**NFAM1-4** were tested in 1,3-DC of azomethine ylides with different dipolarophiles for the enantioselective synthesis of thienyl-substituted pyrrolidines. Although reasonable yields were obtained with all dipolarophiles, enantioselectivity except with *N*-methylmaleimide (85%) and dimethylmaleate (53%) were low. Although we have done lots of optimization reactions using *N*-methylmaleimide as the dipolarophile, it seemed necessary to do further optimizations for the other dipolarophiles as well.

CHAPTER 4

EXPERIMENTAL

4.1. General Consideration

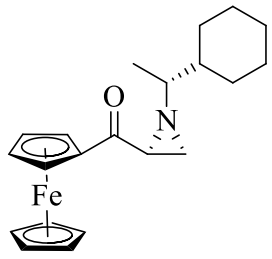
All solvents were distilled before the usage. In the all the cycloadducts and ligands preparation steps flash column chromatography were used to purify compounds on silica gel Merck, 230–400 mesh ASTM. TLC analyses were colored with ninhydrin or phosphomolybdic acid. Agilent 1100 HPLC system determined ee (enantiomeric excess) values for cycloadducts by using Chiralpak Daicel AS-H, AD-H or OD columns at 210, 215 and 254 nm with hexane:*i*-PrOH eluent system. Rudolph Research Analytical Autopol III Polarimeter were used to evaluate optical rotation. Mass analysis were done with Agilent 6224 TOF-LC/MS instrument 120. IR spectra were obtained by Thermo Scientific Nicolet IS10 FT-IR instruments and are reported in cm^{-1}. All ^{1}H-NMR and ^{13}C-NMR samples were prepared in $CDCl_3$ and recorded at Brucker spectrospin Avance III DPX-400 Ultra shield instrument at 400 and 100 MHz. ^{1}H-NMR data are reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ 0.00), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet), coupling constant (Hz) and integration.

4.2. Synthesis and Characterization

4.2.1. Ketone Synthesis and Characterization

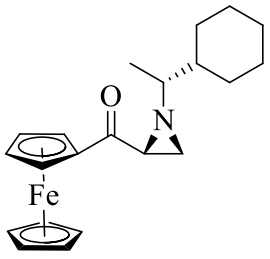
Acryloyl ferrocene **32** and dibromo **33** compounds' synthesis was achieved according to procedure which was developed by Dogan's group previously.[44] To complete ketone synthesis dibromo **32** (2.0 g, 5 mmol) was dissolved in dry DCM (33 ml, 0.15M) and then converted to monobromo **38** with Et_3N (1.04 ml, 7.5mmol) under

nitrogen at room temperature. After 40 minutes *(R)*-(-)-1-cyclohexyl ethyl amine (1.47 ml, 10 mmol) **35** was added. Crude product purification done by silica column chromatography with 4:1 Hexane: EtOAc. Ketone 1 **36** was synthesized in 51% yield and ketone 2 **37** was synthesized in 42% yield.



36

Orange solid, mp: 137-138°C. R_f = 0.65 (5:2 Hexane:EtOAc). $[\alpha]_D^{22.7}$ = +56.2 (*c* = 0.006, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.99 (dt, *J* = 2.6, 1.3 Hz, 1H), 4.90 (dt, *J* = 2.5, 1.3 Hz, 1H), 4.53 (dd, *J* = 3.7, 2.3 Hz, 2H), 4.23 (s, 5H, ferrocene), 2.41 (dd, *J* = 6.4, 3.1 Hz, 1H), 2.36 (dd, *J* = 2.9, 1.8 Hz, 1H), 1.90 (t, *J* = 11.0 Hz, 2H), 1.77 (dd, *J* = 6.5, 1.7 Hz, 3H), 1.69 (d, *J* = 11.9 Hz, 1H), 1.62 – 1.45 (m, 1H), 1.36 – 1.23 (m, 3H), 1.18 (d, *J* = 6.3 Hz, 3H, CH_3), 1.15 – 0.95 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.8 (C=O), 78.3 C), 72.3, 72.2, 70.7, 69.8, 69.7, 69.5, 43.8, 40.6, 38.1, 30.3, 29.1, 26.6, 26.45, 26.38, 17.6 (CH_3). IR (cm^{-1}): 2926, 2852, 1656, 1457, 1391, 1254, 1068, 815. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{28}FeNO$ 366.1520 [M+H]: and found 366.1521.



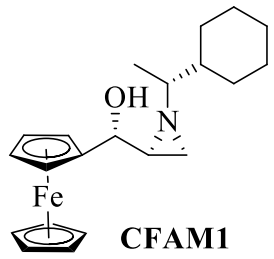
37

Tile red viscous oil, R_f = 0.41 (5:2 Hexane:EtOAc). $[\alpha]_D^{25.8}$ = +14.1 (*c* = 0.006, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.95 – 4.93 (m, 1H), 4.92 – 4.89 (m, 1H), 4.56 – 4.53 (m, 2H), 4.24 (s, 5H, ferrocene), 2.57 (dd, *J* = 6.6, 3.0 Hz, 1H), 2.24 – 2.19 (broad t, *J* = 2.1 Hz, 1H), 1.90 (broad d, *J* = 11.7 Hz, 1H), 1.74 (broad d, *J* = 11.2 Hz, 4H), 1.66 (dd, *J* = 6.6, 1.8 Hz, 2H), 1.59 – 1.47 (m, 1H), 1.42 – 1.32 (m, 1H), 1.42 – 1.32 (m, 3H), 1.13 (d, *J* = 6.4 Hz, 3H, CH_3), 1.11 – 1.05 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.2 (C=O), 78.6, 72.39, 72.36, 70.5, 69.83, 69.80, 69.4, 43.7, 43.4, 35.0, 30.5, 28.4, 26.7, 26.4, 16.6 (CH_3). IR (cm^{-1}): 2923, 2851, 1662, 1451, 1374, 1254, 1070, 821, 735. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{28}FeNO$ 366.1520 [M+H]: and found 366.1529.

4.2.2. Ligand Synthesis and Characterization

4.2.2.1. Synthesis of CFAM1 (*R,R,R*)

Ketone 1 **36** (0.4 g, 1.10 mmol) was dissolved in MeOH (13.54 ml, 0.08M) at room temperature. $ZnCl_2$ (0.224 g, 1.65 mmol) was added to coordinate. After 1 hour, $NaBH_4$ (0.083 g, 2.19 mmol) was added. Product formation was checked by TLC. Reaction was completed at room temperature. Reaction was hydrolyzed with water and extraction done with saturated NH_4Cl solution and EtOAc. Organic layer was dried with $MgSO_4$. Crude product purification done by silica column chromatography with 3:1 Hexane: EtOAc. **CFAM1 39** was obtained with 88% yield.



CFAM1

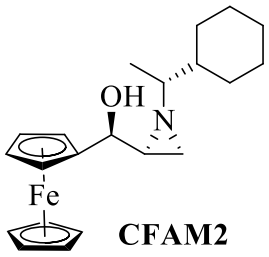
39

Yellow solid, mp: 61-63°C. R_f = 0.48 (3:1 Hexane:EtOAc). $[\alpha]_D^{26.5}$ = +31.8 (*c* = 0.025, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.44 (broad d, *J* = 4.0 Hz, 1H), 4.27 (broad s, 1H), 4.22 (broad s, 1H), 4.18 (s, 5H, ferrocene), 4.14 (broad s, 1H), 2.75 (broad singlet, 1H, OH), 1.83 (d, *J* = 3.3 Hz, 1H), 1.80 – 1.68 (m, 4H), 1.68 – 1.52 (m, 1H), 1.46 – 1.39 (m, 1H), 1.37 (d, *J* = 6.3 Hz, 1H), 1.35 – 1.28 (m, 1H), 1.27 – 1.15 (m, 3H), 1.15 – 1.09 (m, 1H), 1.07 – 0.98 (m, 3H), 0.94 (d, *J* = 6.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 89.5, 68.9, 68.4, 67.83, 67.77, 67.70, 66.9, 66.1, 43.8, 40.7, 31.5, 30.1, 28.7, 26.6, 26.5, 26.4, 17.0 (CH_3). IR (cm^{-1}): 3392, 2922, 2851, 1446, 1073, 816. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{30}FeNO$ 368.1677 [M^+]: and found 368.1718.

4.2.2.2. Synthesis of CFAM2 *(S,R,R)*

Ketone 1 **36 (**0.05 g, 0.137 mmol) was dissolved in dry THF (2 ml, 0.07 M) at -78ºC. L-Selectride (0.2 ml, 1M in THF solution) was added to the flask fastly. Reaction was stirred 2 hours at -78ºC and 1 hour at 0ºC. When color change was observed from orange to light orange, reaction medium was warmed to room temperature. 2 ml of 10% NaOH was added and stirred 15 minutes. Following, extraction was done, and

organic phase passed through silica column. Compound was collected and dissolved 5 ml in THF. 5 ml 10% NaOH was added and stirred 2 hours at room temperature. After extraction step, crude product purification done by silica column chromatography. **CFAM2 40** was obtained with 82% yield.



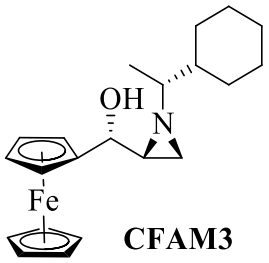
CFAM2

40

Light orange oil, R_f = 0.57 (2:1 Hexane:EtOAc). $[\alpha]_D^{25.1}$ = +40.3 (*c* = 0.025, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.21 (broad d, *J* = 1.8 Hz, 1H), 4.15 (s, 1H), 4.12 (broad s, 5H), 4.08 (s, 1H), 3.95 (d, *J* = 1.8 Hz, 1H), 2.85 (broad singlet, 1H, OH), 1.79 – 1.57 (m, 6H), 1.51 (td, *J* = 6.3, 3.4 Hz, 2H), 1.37 (d, *J* = 6.4 Hz, 2H), 1.25 – 1.02 (m, 6H), 0.95 (d, *J* = 6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 90.8, 70.7, 69.4, 68.5, 67.8, 67.6, 66.3, 66.0, 43.9, 42.8, 33.5, 30.4, 28.9, 26.7, 26.6, 26.5, 17.4 (CH_3). IR (cm^{-1}): 3422, 2921, 2851, 1450, 1048, 1018, 1000, 814. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{30}FeNO$ 368.1677 [M^+]: and found 368.1726.

4.2.2.3. Synthesis of CFAM3 *(R,S,R)*

Ketone **37 (**0.12 g, 0.329 mmol) was dissolved in dry THF (7 ml, 0.047 M) at -78ºC. L-Selectride (0.1 ml, 1M in THF solution) was added to the flask. Reaction was stirred 2 hours at -78ºC. Following, additional 0.1 ml L-Selectride was added to the flask and stirred 1 hour at 0ºC. When color change was observed from orange to light orange, reaction medium was warmed to room temperature. 1.5 ml of 10% NaOH was added and stirred 15 minutes. Following, extraction was done, and organic phase passed through silica column. **CFAM3** and **CFAM4** were separated. Compounds was collected and separately dissolved 1.5 ml in THF. 1.5 ml 10% NaOH was added each other and stirred 2 hours at room temperature. After extraction step, crude product purification done by silica column chromatography. **CFAM3 42** was obtained with 57% yield and **CFAM4 41** was obtained with 31% yield.



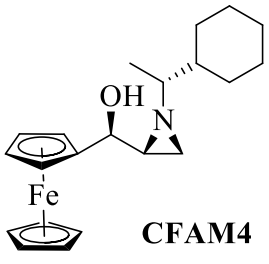
CFAM3

42

Yellow, mp: 86-87°C. R_f = 0.40 (2:1 Hexane:EtOAc). $[\alpha]_D^{27.9}$ = -10.5 (*c* = 0.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.22 (broad s, 1H), 4.12 (broad s, 6H), 4.08 (broad s, 2H), 2.60 (broad singlet, 1H, OH), 1.77 (d, *J* = 11.4 Hz, 1H), 1.73 – 1.50 (m, 6H), 1.46 – 1.24 (m, 2H), 1.25 – 0.97 (m, 7H), 0.93 (d, *J* = 6.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 91.1, 70.2, 69.4, 68.5, 67.8, 67.6, 66.1, 65.7, 44.6, 42.6, 30.5, 27.0, 26.8, 26.7, 26.3, 15.1 (CH_3). IR (cm^{-1}): 3327, 2918, 2848, 1446, 1103, 1045, 999, 805. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{30}FeNO$ 368.1677 [M^+]: and found 368.1726.

4.2.2.4. Synthesis of CFAM4 *(R,S,R)*

Ketone 2 **37** (0.4 g, 1.10 mmol) was dissolved in THF (14 ml, 0.08 M) at 0ºC. After stirring the reaction for 1 hour, $LiAlH_4$ (0.04 g, 1.10 mmol) was added to reaction flask. Reaction was finished after 1 hour and hydrolyzation was done with water. Following, extraction was done with DCM and water. Crude product purification done by silica column chromatography with 4:1 Hexane: EtOAc. **CFAM4 41** ligand was obtained with 74% yield.



CFAM4

41

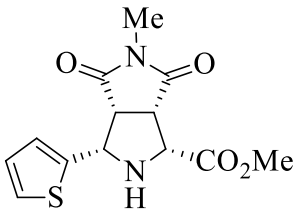
Yellow solid, mp: 75-77°C. R_f = 0.52 (1:1 hexane:EtOAc). $[\alpha]_D^{26.6}$ = -21.2 (*c* = 0.025, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.40 (broad d, *J* = 4.4 Hz, 1H), 4.29 (broad s, 1H), 4.24 (broad s, 1H), 4.20 (s, 5H), 4.17 (broad s, 1H), 2.96 (broad singlet, 1H, OH), 1.83 (d, *J* = 3.3 Hz, 1H), 1.80 – 1.68 (m, 5H), 1.68 – 1.52 (m, 3H), 1.37 – 1.29 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 2H), 1.24 – 1.05 (m, 3H), 1.02 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 89.8, 69.1, 68.3, 67.9 (), 67.8, 67.7, 67.0, 66.0, 43.9, 43.2, 30.0, 28.5, 28.2,

26.60, 26.58, 26.3, 16.2 (CH_3). IR (cm^{-1}): 3389, 2920, 2850, 1451, 1076, 811. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{30}FeNO$ 368.1677 [M^+]: and found 368.1733.

4.2.3. Catalytic Asymmetric Cycloaddition Synthesis and Characterization

1,3 dipole (imine) (1 eq) was added to pre-dried schlenk tube under nitrogen atmosphere. Reaction flask was cooled to at 0ºC. Ligand were added and dissolved in solvent for 15 minutes. After 15 minutes silver acetate was added and Schlenk tube was covered with alumina. 1 hour was waited and molecular sieve and dipolarophile was added. (amount of metal, dipolarophile and ligand was shown in tables). After 2 hours reaction temperature was brought to room temperature. Crude product purification done by silica column chromatography with Hexane: EtOAc.

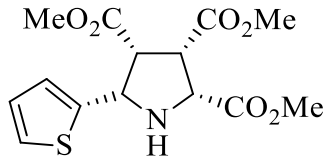
4.2.3.1. Characterizations of (1*R*, 3*S*, 3a*R*, 6a*S*)-methyl 5-methyl-4,6-dioxo-3-(thiophen-2-yl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate



46

White solid, ee determined by HPLC using chiral AS-H column at 220 nm with hexane/2-propyl alcohol: 70/30, flow rate: 1.0 ml/min. Retention time: t_1 =18 min. and t_2= 40 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (dd, *J* = 5.0, 1.2 Hz, 1H) 7.09 (dt, J = 3.5, 1.0 Hz, 1H), 7.02 (dd, J = 5.1, 3.5 Hz, 1H), 4.81 (dd, J = 8.8, 5.3 Hz, 1H), 4.04 (dd, J = 6.5, 5.0 Hz, 1H), 3.88 (s, 3H), 3.57 (t, *J* = 7.0 Hz 1H), 3.42 (t, J = 8.2 Hz, 1H), 2.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.81, 174.50, 169.77, 140.60, 126.97, 125.26, 125.13, 61.32, 59.64, 52.31, 49.61, 48.13, 25.11.

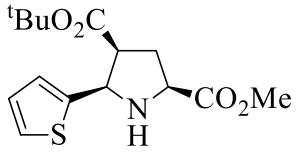
4.2.3.2. Characterizations of (2*R*, 3*S*, 4*R*, 5*S*)-trimethyl 5-(thiophen-2-yl) pyrrolidine-2,3,4-tricarboxylate



47

White solid, ee determined by HPLC using chiral AS-H column at 220 nm with hexane/2-propyl alcohol: 70/30, flow rate: 1.0 ml/min. Retention time: t_1 =7.5 min. and t_2= 18.5 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (m, 1H), 7.03 (m, 1H), 6.97 (m, 1H), 4.64 (m, 1H), 4.17 (d, *J* = 9.2 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.71–3.67 (m, 1H), 3.54 (t, 6.4 Hz, 1H), 3.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.85, 170.76, 170.52, 139.91, 126.82, 124.97, 124.71, 61.95, 61.37, 52.47, 52.38, 52.16, 51.62, 51.11.

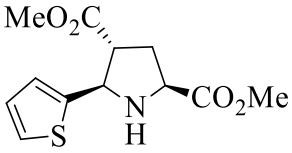
4.2.3.3. (2*S*, 4*S*, 5*R*)-4-tert-butyl 2-methyl 5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate



48

Yellow liquid, ee determined by HPLC using chiral AS-H column at 220 nm with hexane/2-propyl alcohol: 95/5, flow rate: 1.0 ml/min. Retention time: t_1 =9 min. and t_2= 15.7 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (dd, J = 5.0, 1.3 Hz, 1H), 6.99 (m, 1H), 6.95 (dd, J = 5.0, 3.5 Hz, 1H), 4.68 (d, J = 7.6 Hz, 1H), 3.94 (t, J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.27 (q, J = 7.5 Hz, 1H), 2.51–2.30 (m, 2H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.55, 171.12, 143.22, 126.57, 124.92, 124.25, 80.94, 61.15, 59.59, 52.28, 50.60, 33.35, 27.61.

4.2.3.4. (2S,4R,5R)-dimethyl 5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate

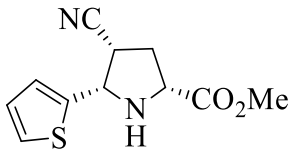


49

Orange-brown liquid, ee determined by HPLC using chiral OD column at 220 nm with hexane/2-propyl alcohol: 80/20, flow rate: 1.0 ml/min. Retention time: t_1 =7.5 min. and t_2= 14 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.98-7.0 (m, 1H), 6.95 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.79 (d, *J* = 7.5

Hz, 1H), 3.98 (t, *J* = 8.4, 1H), 3.82 (s, 3H), 3.43 (s, 3H), 3.33 (q, *J* = 7.6 Hz, 2H), 2.43 (ddd, *J* = 8.3, 7.3, 2.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.55, 172.36, 143.07, 126.69, 124.68, 124.58, 61.08, 59.43, 52.35, 51.59, 49.87, 32.50.

4.2.3.5. (2R,4R,5S)-methyl 4-cyano-5-(thiophen-2-yl)pyrrolidine-2-carboxylate



50

Yellow solid, ee determined by HPLC using chiral AD-H column at 215 nm with hexane/2-propyl alcohol : 95/5, flow rate: 1.0 ml/min. Retention time: t_1 =40 min. and t_2= 44 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, *J* = 5.2 Hz, 1H), 7.11 (d, *J* =3.6 1H), 6.97 (dd, *J* = 5.6, 3.6 Hz, 1H), 4.63 (d, *J* = 6.4 Hz, 1H), 3.91 (t, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 3.27 (q, *J* = 6.5 Hz, 1H), 2.59–2.42 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.59, 141.51, 127.17, 125.37, 125.34, 118.75, 60.35, 58.53, 52.66, 36.29, 33.80.

REFERENCES

1. Solomons, G.; Craig, F.; Snyder S. *Organic Chemistry* 11th Ed. John Wiley & Sons: Singapore, **2014**.
2. Davies N. M.; Teng X. W. *Adv. Pharm.* **2003**, *1*, 242-252.
3. Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci*. **2006**, *2*, 85-100.
4. Stephenson, G. R. *Advanced Asymmetric Synthesis* 1st Ed. Blackie Academic & Professional: London, **1996**.
5. Mohan, S. J.; Mohan, E. C.; Yamsani, M. R.; *Int. J. Pharm. Sci. Nanotechnol*. **2009**, *1*, 309-316.
6. Geisslinger, G.; Stock, K. P.; Bach, G. L.; Loew, D.; Brune, K. *Agents Actions*. **1989**, *27*, 455-457.
7. Fu, L.; Zhang, Y.; Wei, Z. H.; Wang, H. F. *Chirality* **2014**, *26*, 509-520.
8. Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis* 1st Ed. Pergamon: Oxford, **1996**.
9. Ahad, A.; Farooqui, M. *Sci. Revs. Chem. Commun.* **2015**, *5*, 93-103.
10. Koskinen, A. *Asymmetric Synthesis of Natural Products*. 1st Ed. John Wiley & Sons: Chichester, **1993**.
11. Gademann, K. S. *Asymmetric Synthesis II More Methods Appl*ications 1st Ed. Wiley-VCH: Weinheim, **2013**
12. Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology* 1st Ed. CRC Press: Florida, **1996**.
13. Li, F. Z.; Li, S.; Zhang, P. P.; Huang, Z. H.; Zhang, W. B.; Gong. J.; Yang, Z. *Chem. Commun*. **2016**, *52*, 12426-12429.

14. Chida, N.; Sato, T. *Comprehensive Chirality: Chiral Pool Synthesis: Chiral Pool Syntheses Starting from Carbohydrates* 1st Ed. Elsevier Ltd.: Oxford **2012**.

15. Paek, S. M.; Jeong, M.; Jo, J.; Heo Y. M.; Han, Y. T.; Yun, H. *Molecules* **2016**, *21*, 951-964

16. Taylor, M. S.; Jacobsen, E. N. *PNAS* **2004**, *35*, 5368-5373.

17. Meggers, E. *Chem. Eur. J*. **2010**, *16*, 752-758.

18. Evans, D. A.; Helmchen, G.; Ruping, M. *Asymmetric Synthesis The Essentials: Chiral Auxiliaries in Asymmetric Synthesis* 1st Ed. Wiley-VCH: Weinheim, **2007**.

19. Gnas, Y.; Glorius, F. *Synthesis* **2006**, *12*, 1899-1930.

20. Heravi, M. M.; Zadsirjan, V.; Farajpour B. *RSC Adv*. **2016**, *6*, 30498-30551.

21. Rothenberg, G. *Catalysis Concepts and Green Applications* 1st Ed. Wiley-VCH: Weinheim, **2008**.

22. Steinborn, D. *Fundamentals of Organometallic Catalysis* 1st Ed. Wiley-VCH: Weinheim, **2012**.

23. Vachal, P.; Jacobsen, E.N. *J. Am. Chem. Soc*. **2002**, *124*, 10012-10014.

24. Nlshiyama, H.; Sakaguchi, H.; Nakamura, T.; Horlhata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846-848.

25. Knowles, W. S. *Adv. Synth. Catal*. **2003**, *345*, 3-13.

26. Noyori, J. *Adv Synth Catal*. **2003**, *345*, 15-32.

27. Yan, X. X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X. L.; Wu, Y.D. *Angew. Chem. Int.* Ed. **2006,** *45*, 1979-1983.

28. Halpern, J.; Trost, B. M. *PNAS* **2004**, *101*, 5347.

29. Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863-909

30. Pellissier, H. *Tetrahedron* **2007**, *63*, 3235-3285.

31. Emamian, S. R.; Ali-Asgari. S.; Zahedi, E. *J. Chem Sci*. **2014**, *126*, 293-302.

32. Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565-598.

33. Kumar, S.; Kumar, V.; Singh, S. P. *Pericyclic Reactions: Cheletropic Reactions and 1,3-Dipolar Cycloadditions* 1st Ed. Elsevier: Oxford, **2015**.

34. Jannatun, Z.; Pandey, J. *IJRASET* **2017**, *5*, 536-553.

35. Narayan, R.; Potowski, M.; Jia, Z. J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296−1310.

36. Wang, Z. P.; Wu, Q.; Jiang, J.; Li, Z. R.; Peng, X. J.; Shao, P. L.; He, Y. *Org. Chem. Front.* **2018**, *5*, 36-40.

37. Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366-5412.

38. Mancebo-Aracil, J.; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; de Lima, E. C.; & Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596-1606.

39. Kim, H. Y.; Shih, H.; Knabe, W. E.; Oh, K. *Angew. Chem. Int Ed.* **2009**, *48*, 7420-7423.

40. Tian, F.; He, F. S.; Deng, H.; Yang, W. L.; Deng, W. P. *Org. Lett.* **2018**, *20*, 3838-3842.

41. Wang, C. J.; Liang, G.; Xue, Z. Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250-17251.

42. Yang-Zi Liu, Y-Z.; Shang,S-J.; Yang,W-L.; Luo, X. Deng, W-P. *J. Org. Chem.* **2017**, *82*, 11141-11149.

43. Han, F. Z.; Yu, S. B.; Zhang, C.; Hu, X. P. *Tetrahedron* **2015**, *72*, 2616-2622.

44. Eröksüz, S.; Dogan, Ö.; Garner, P. P. *Tetrahedron: Asymmetry* **2010**, *21*, 2535-

2541.

45. Dogan, O.; Koyuncu, H.; Garner, P.; Bulut, A.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 4687-4690.

46. a) Nagel, D. L.; Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3911. b) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 1049.

47. Yun, J. M.; Sim, T. B.; Hahm, H. S.; Lee, W. K. *J. Org. Chem.* **2003**, *68*, 7675.

48. Liu, Y.; Shang, S.; Yang, W.; Luo, X.; Deng, W. *J. Org. Chem.* 2**017**, *82*, 11141-11149.

49. Dogan, O.; Zeytinci, S.; Bulut, A. *Synth. Commun.* **2005**, *35*, 1067-1076.

50. Nájera, C.; Retamosa, M. D. G.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025-4028.

51. Caleffi, G. S.; Larrañaga, O.; Ferrandiz-Saperas, M.; Costa, P. R. R.; Nájera, C.; de Cozar, A.; Cossio F.P.; Sansano, J. M. *J. Org. Chem.* **2019**, *84*, 10593-10605.

52. Xiong, Y.; Du, Z.; Chen, H.; Yang, Z.; Tan, Q.; Zhang, C.; Zhu, L.; Lan, Y.; Zhang, M. *J. Am. Chem. Soc.* **2019**, *141*, 961−971.

APPENDICES

A. NMR Spectra

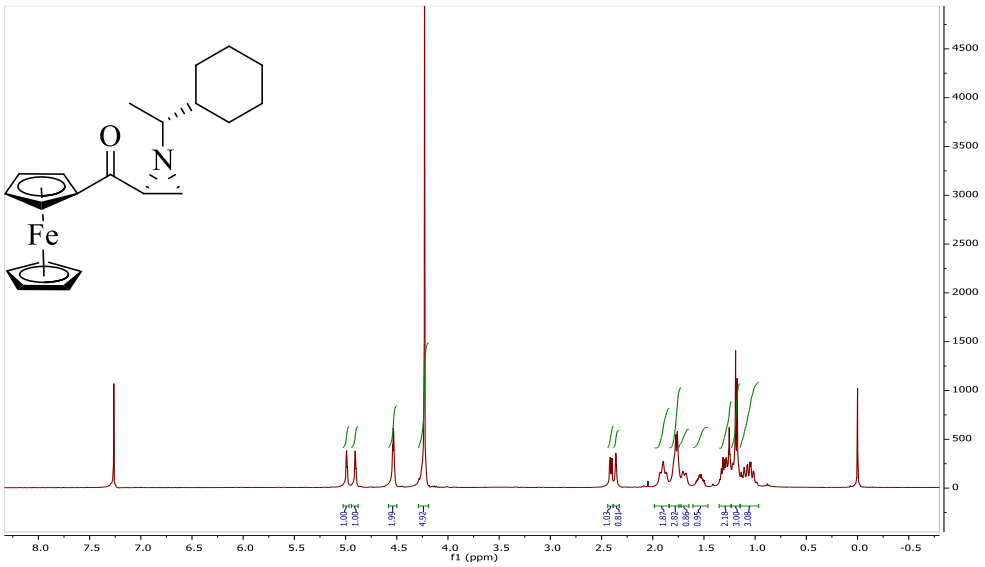


Figure A.1. ^{1}H-NMR Spectrum of compound **36.**

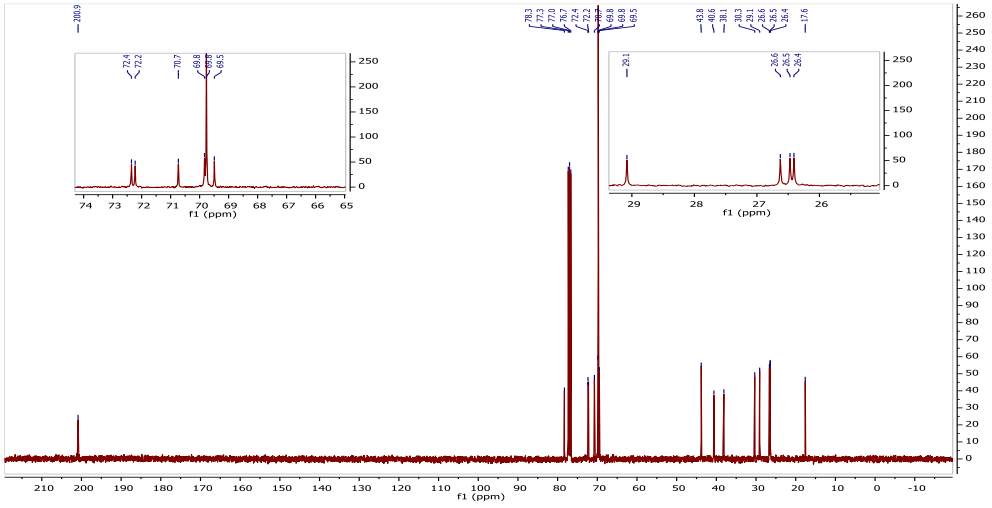


Figure A.2. ^{13}C-NMR Spectrum of compound **36.**

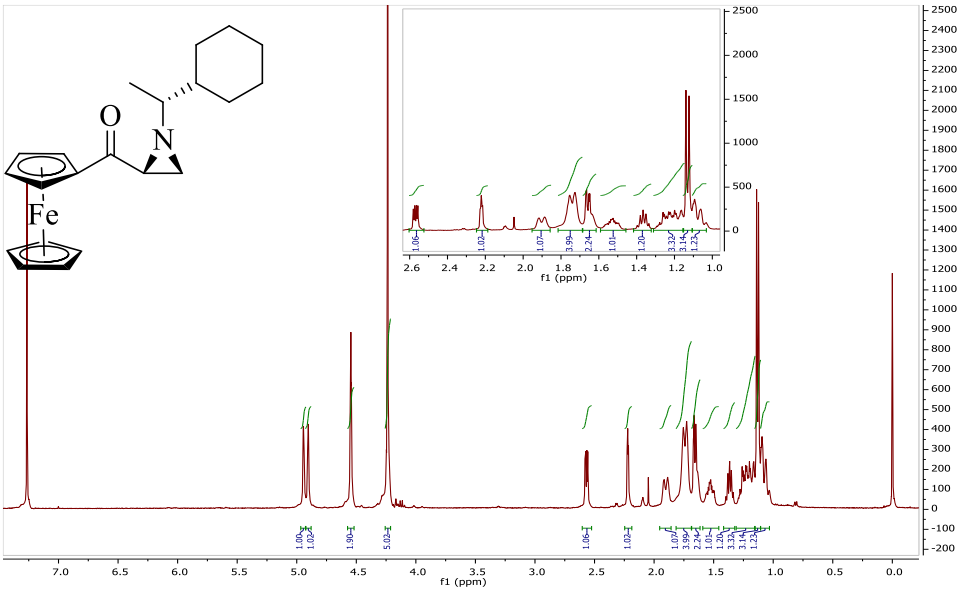


Figure A.3. ^{1}H-NMR Spectrum of compound **37**.

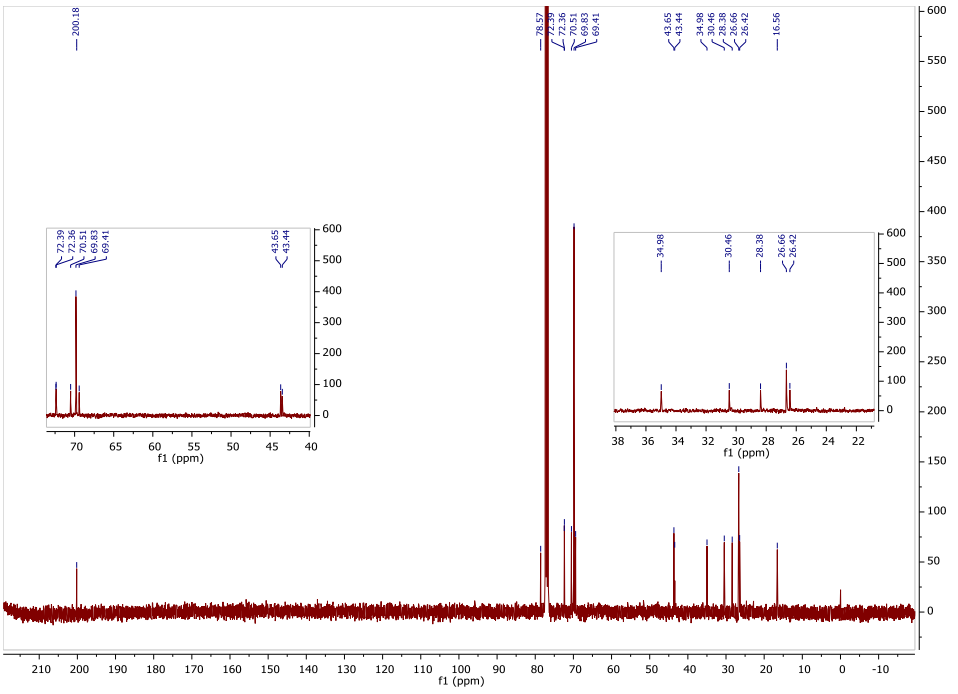


Figure A.4. ^{13}C-NMR Spectrum of compound **37.**

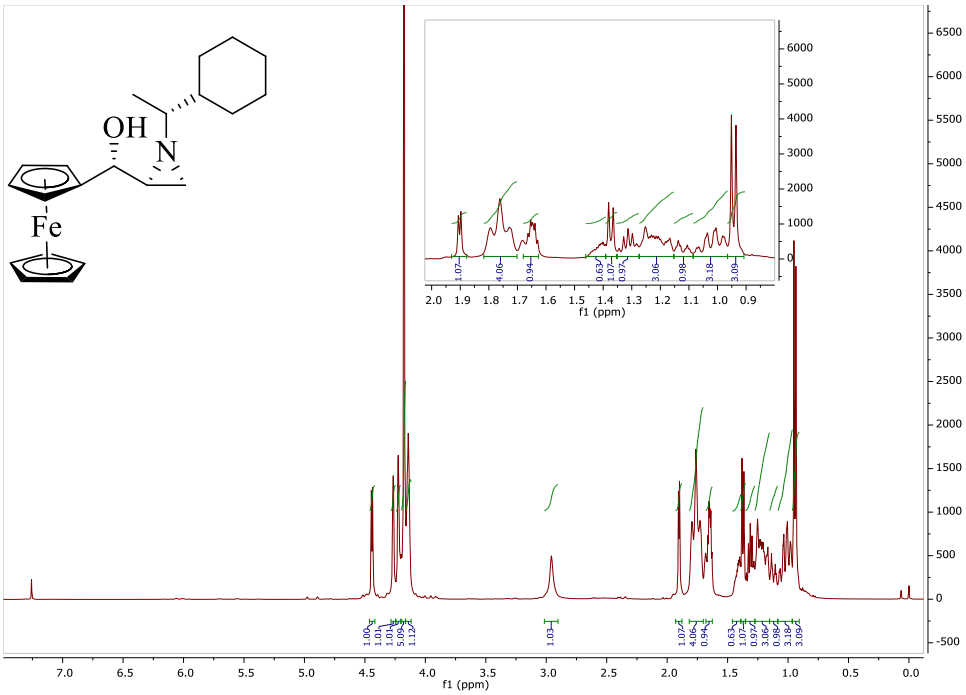


Figure A.5. ^{1}H-NMR Spectrum of compound **39.**

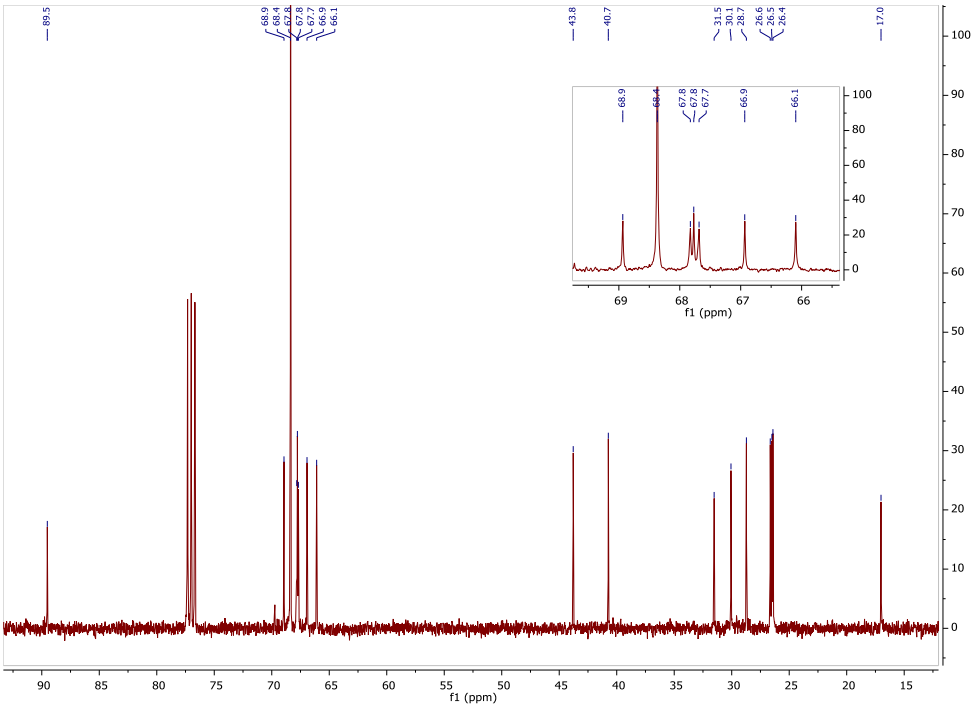


Figure A.6. ^{13}C-NMR Spectrum of compound **39**.

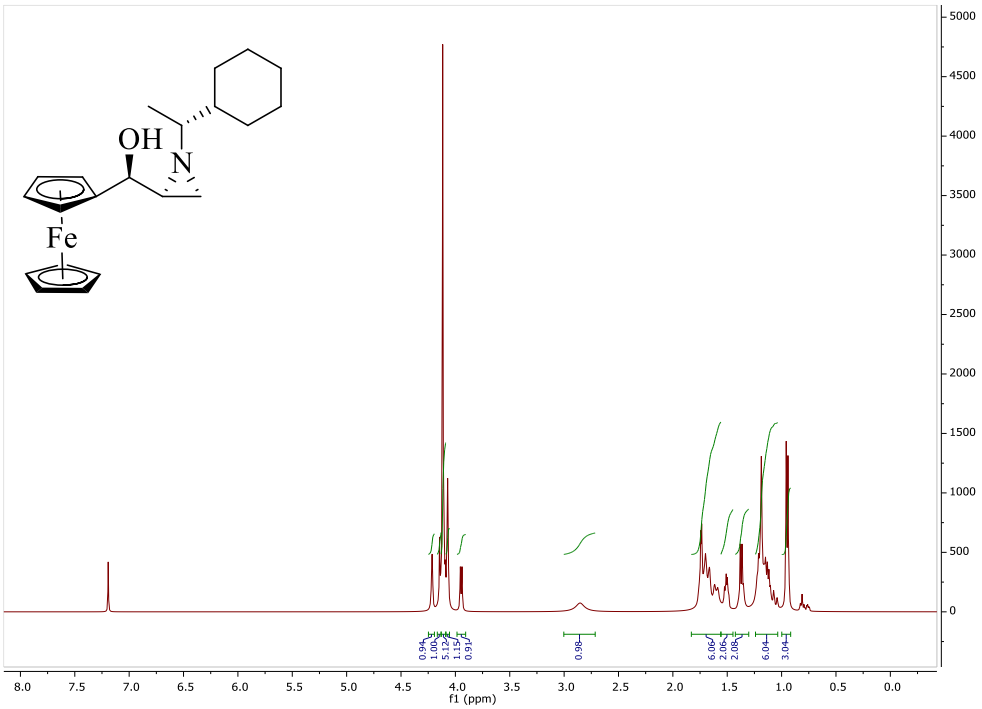


Figure A.7. ^{1}H-NMR Spectrum of compound **40.**

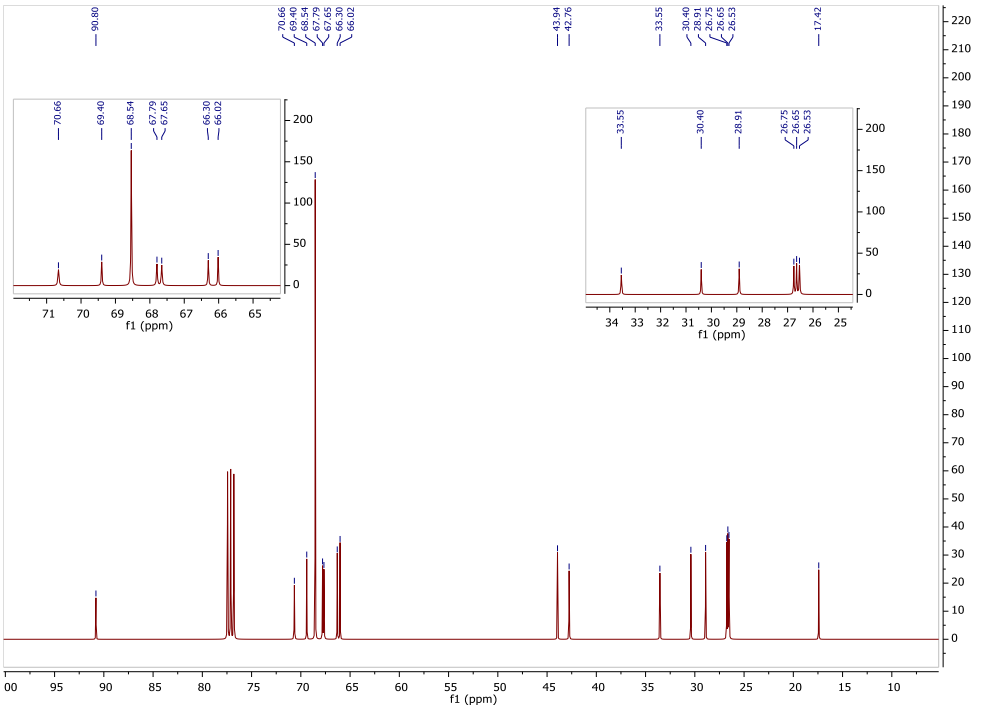


Figure A.8. ^{13}C-NMR Spectrum of compound **40.**

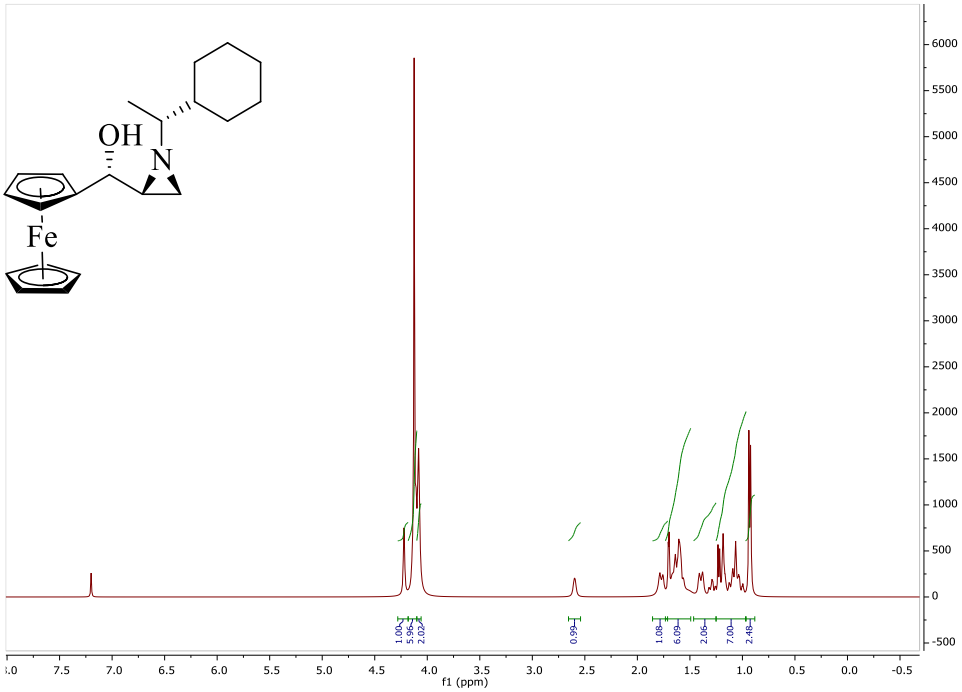


Figure A.9. ^{1}H-NMR Spectrum of compound **42.**

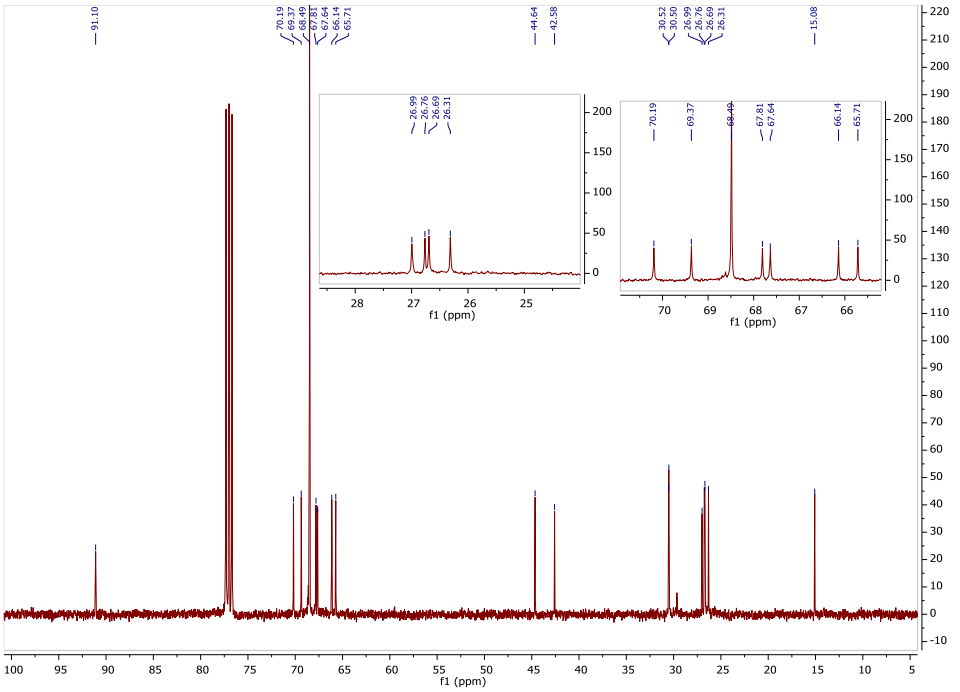


Figure A.10. ^{13}C-NMR Spectrum of compound **42.**

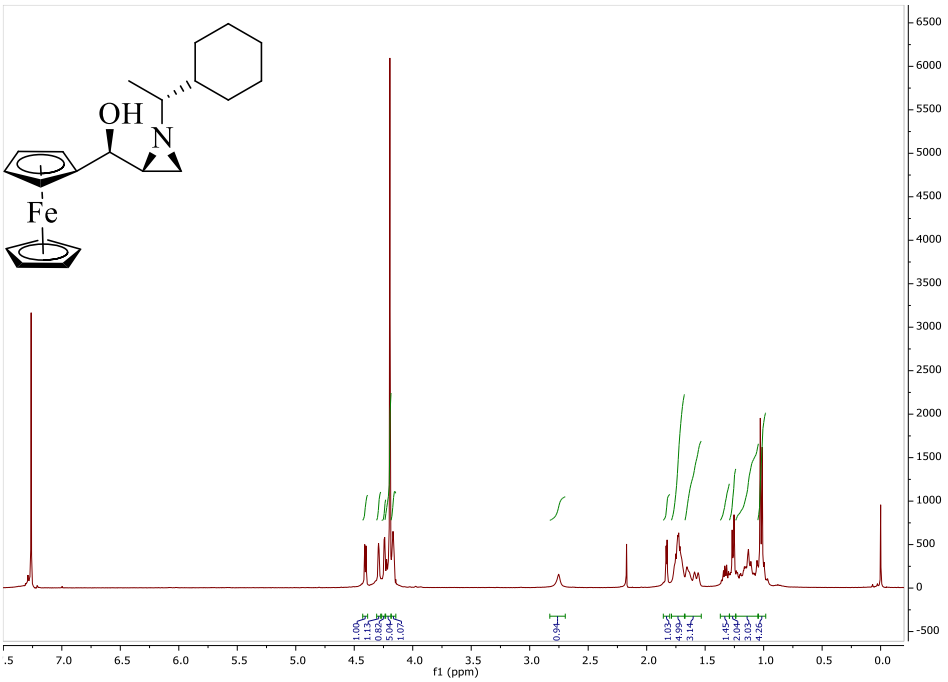


Figure A.11. ^{1}H-NMR Spectrum of compound **41.**

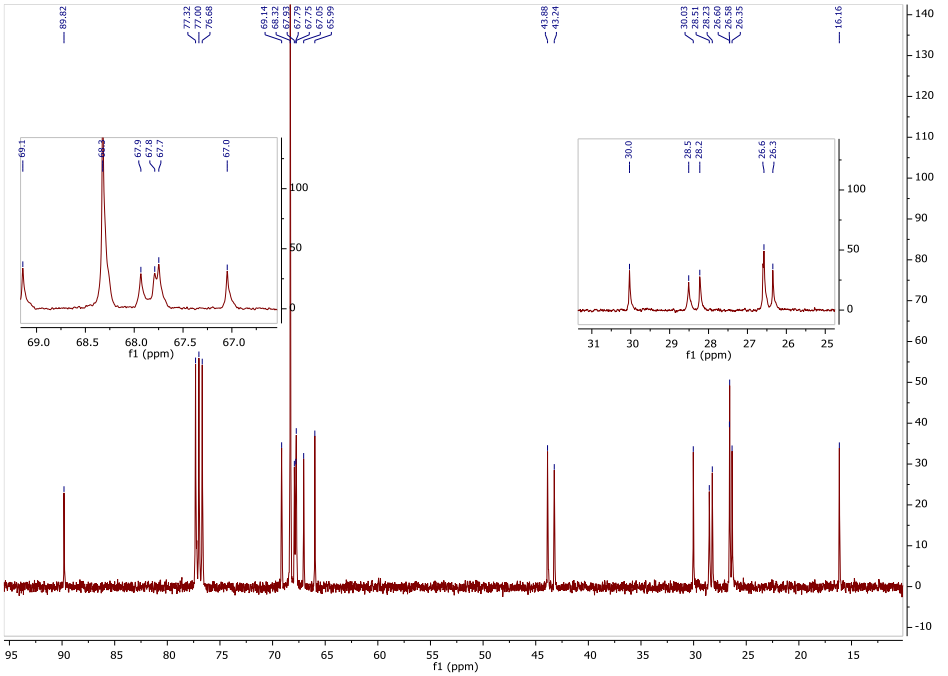


Figure A.12. ^{13}C-NMR Spectrum of compound **41.**

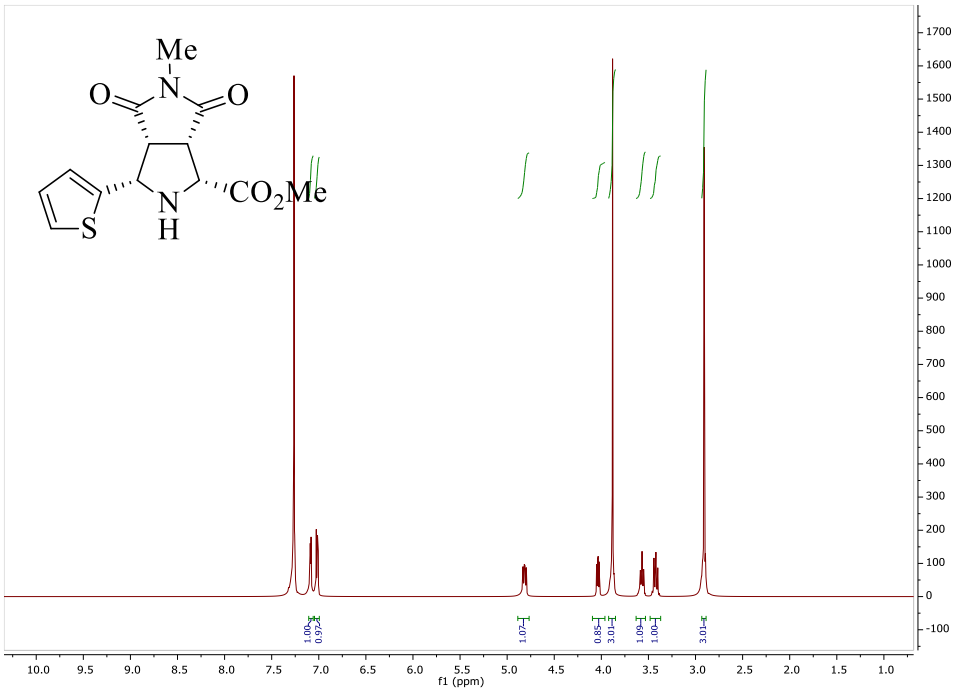


Figure A.13. ^{1}H-NMR Spectrum of compound **46.**

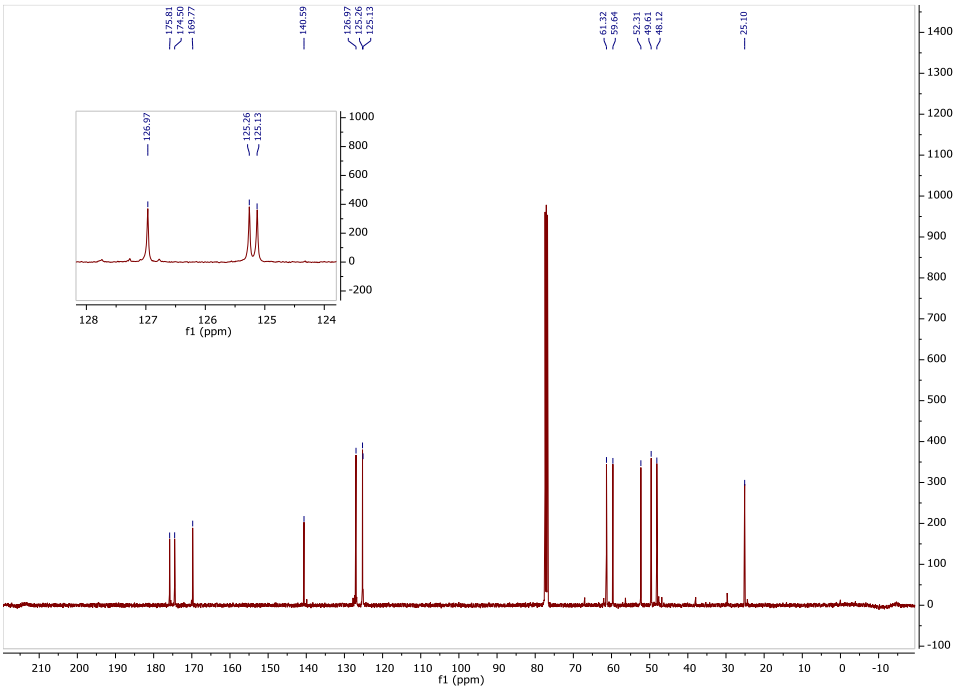


Figure A.14. ^{13}C-NMR Spectrum of compound **46.**

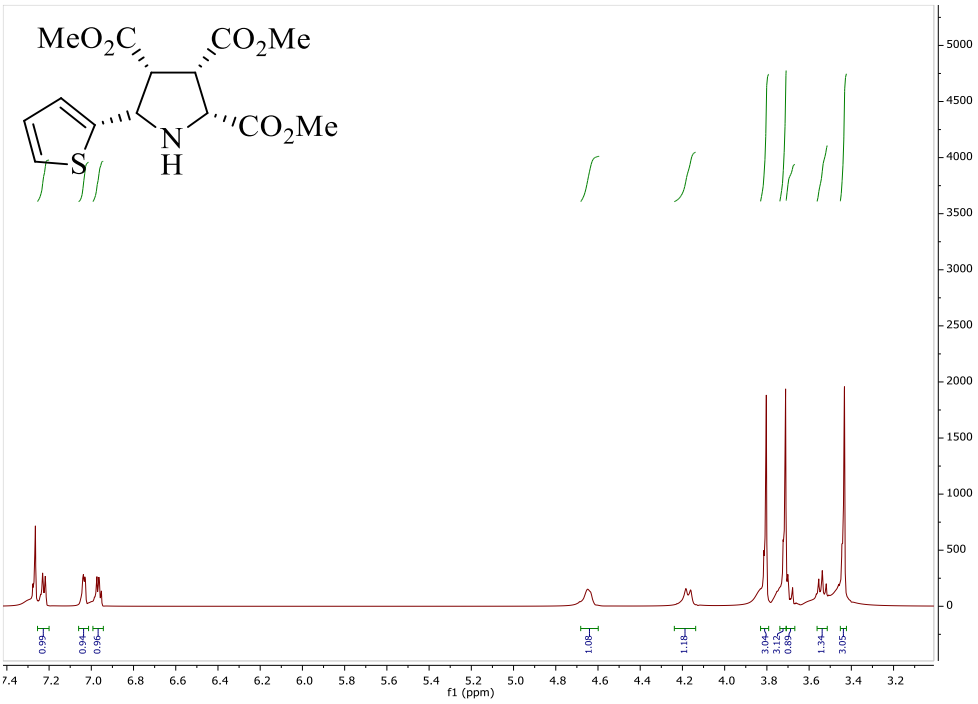


Figure A.15. ^{1}H-NMR Spectrum of compound **47**.

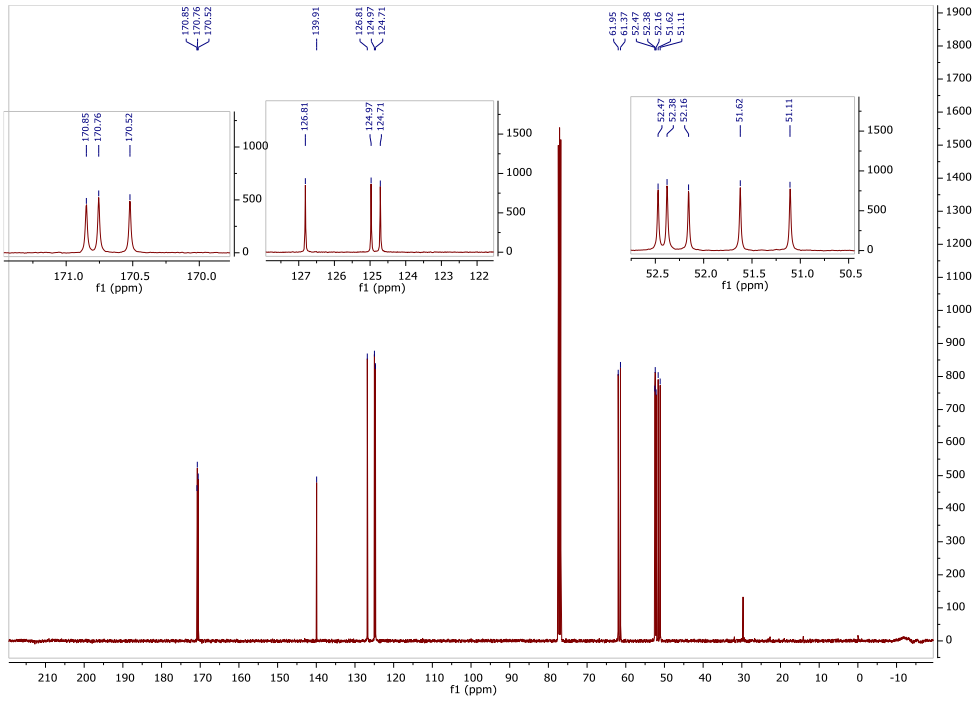


Figure A.16. ^{13}C-NMR Spectrum of compound **47**.

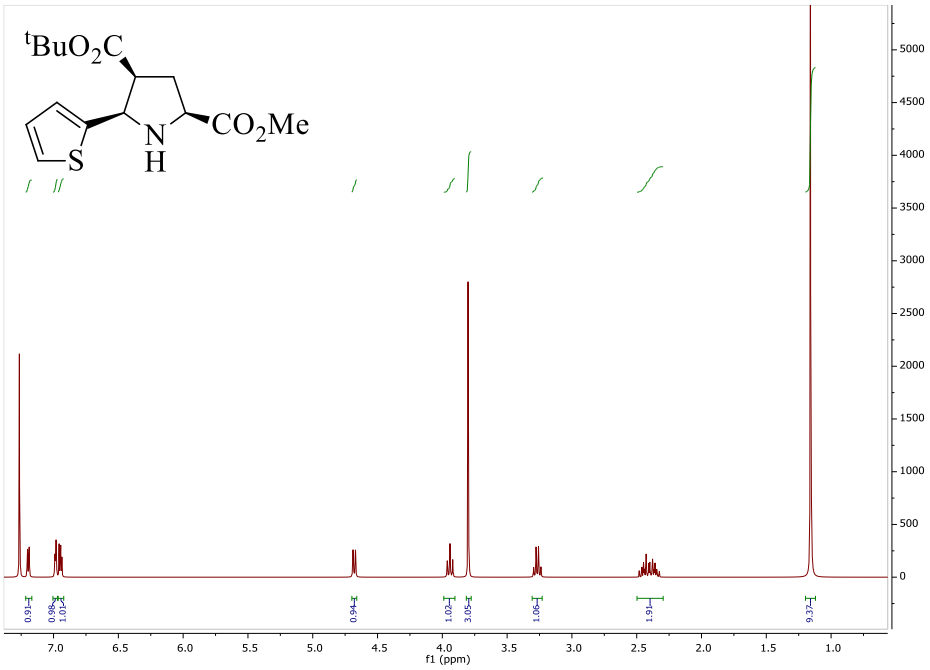


Figure A.17. ^{1}H-NMR Spectrum of compound **48**.

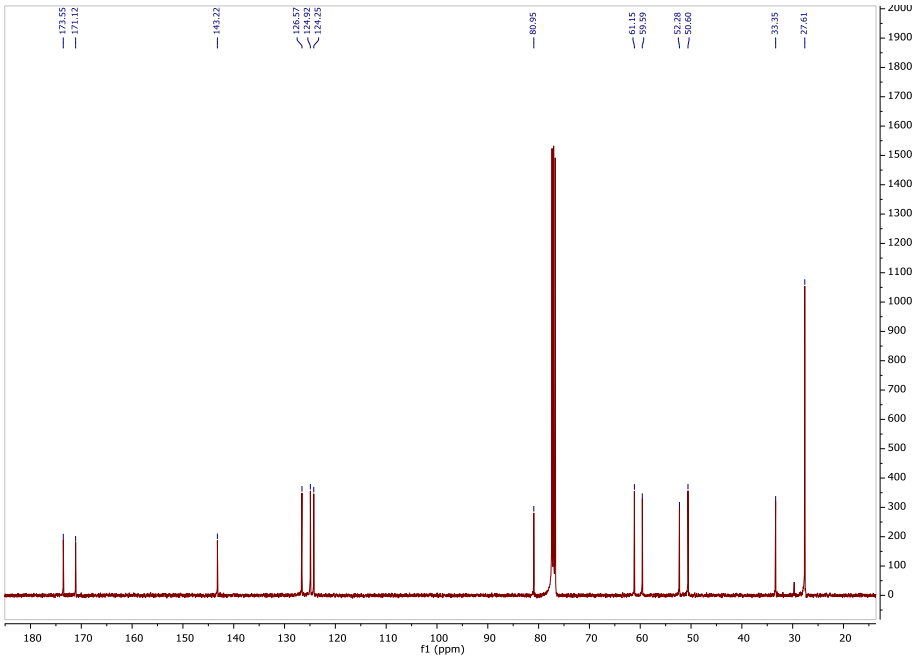


Figure A.18. ^{13}C-NMR Spectrum of compound **48**.

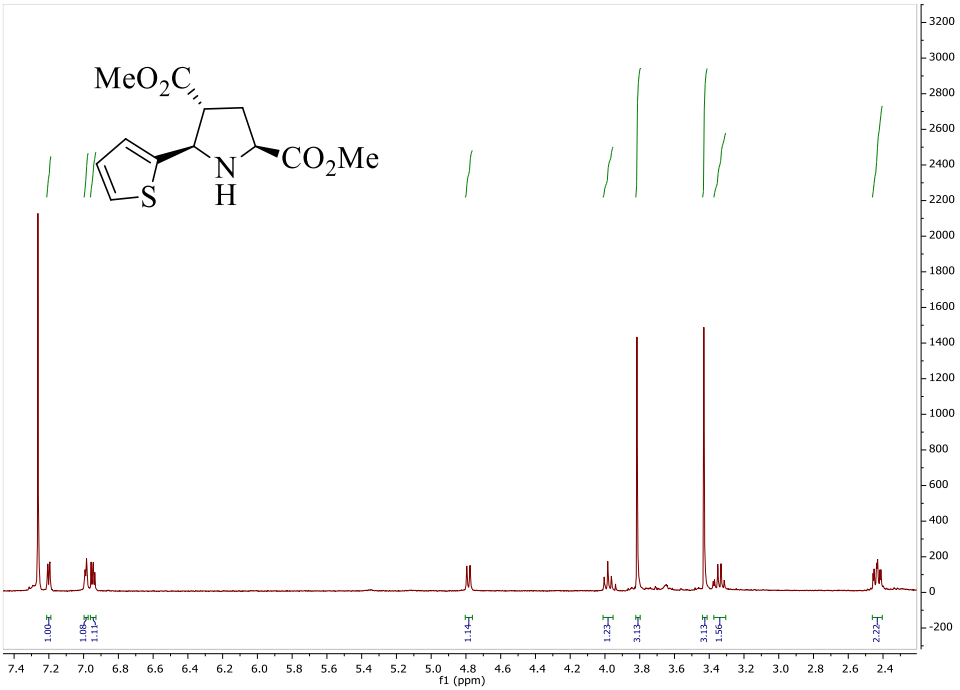


Figure A.19. ^{1}H-NMR Spectrum of compound **49**.

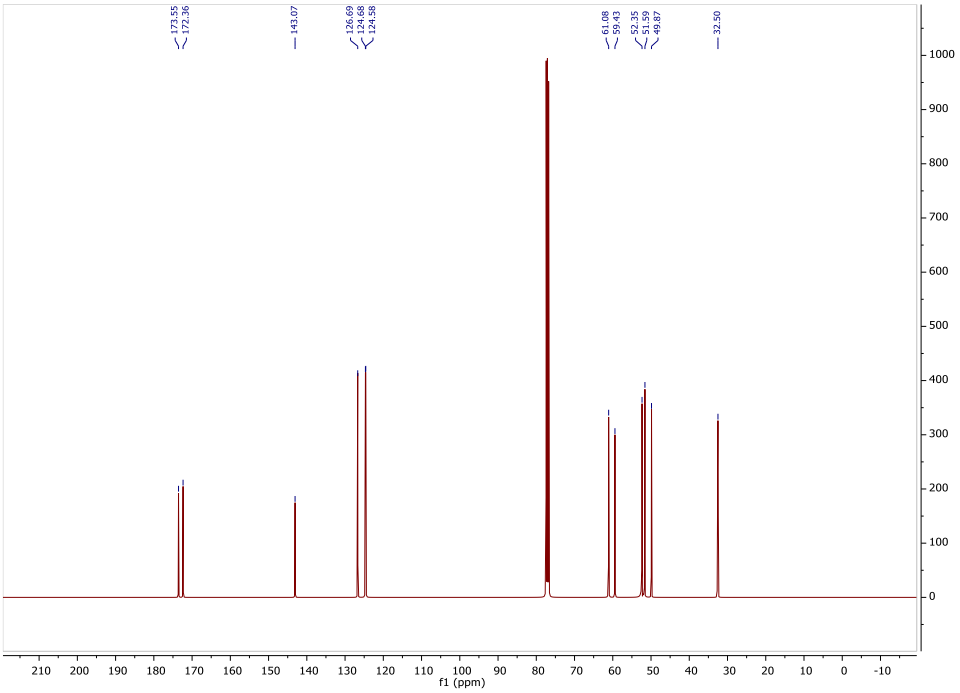


Figure A.20. ^{13}C-NMR Spectrum of compound **49**.

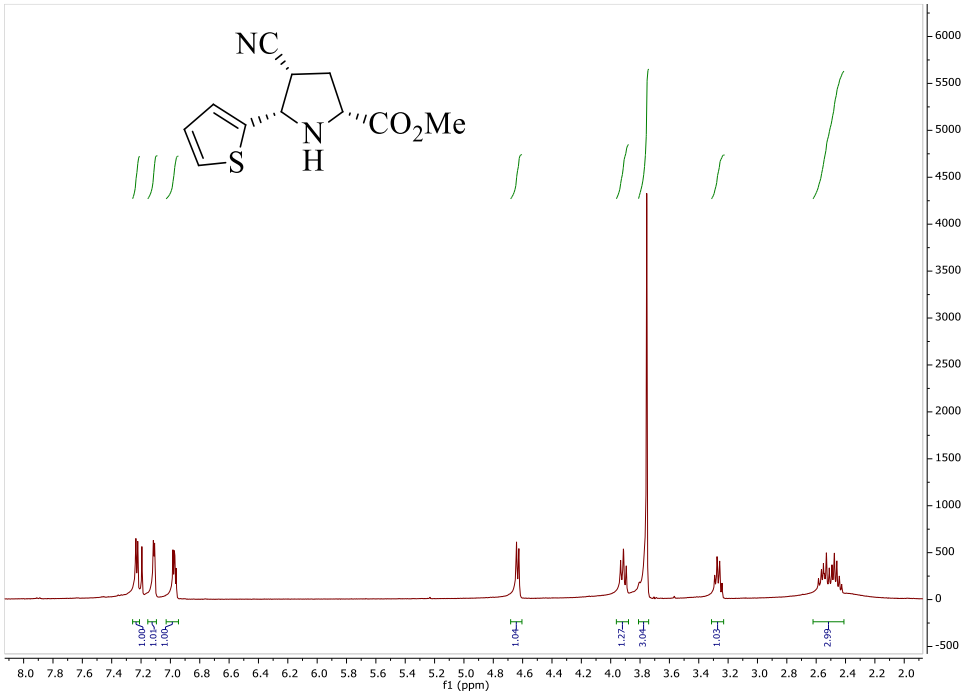


Figure A.21. ^{1}H-NMR Spectrum of compound **50**.

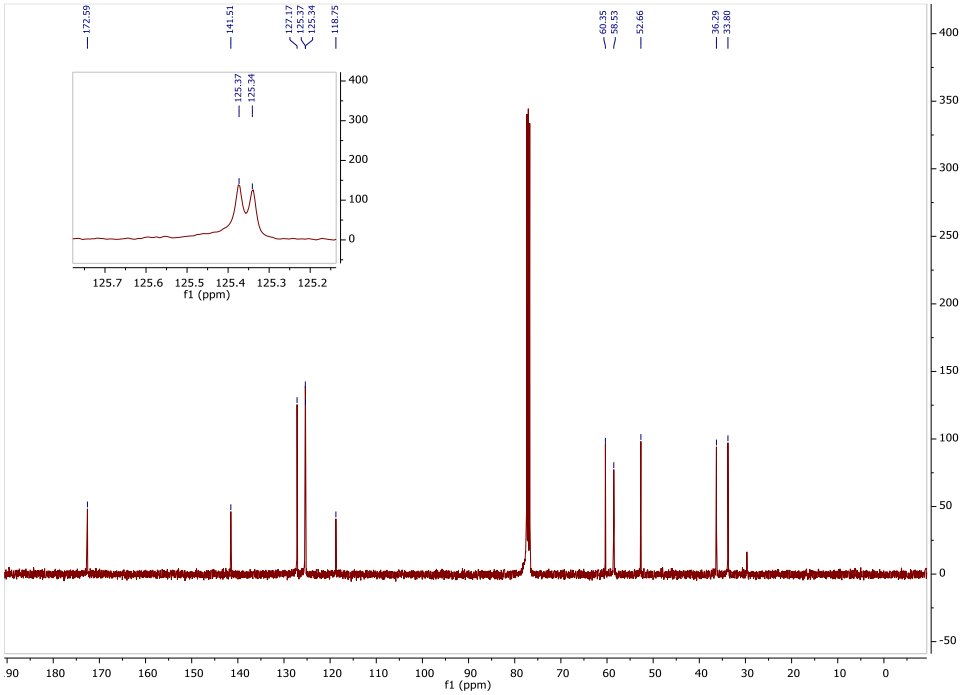
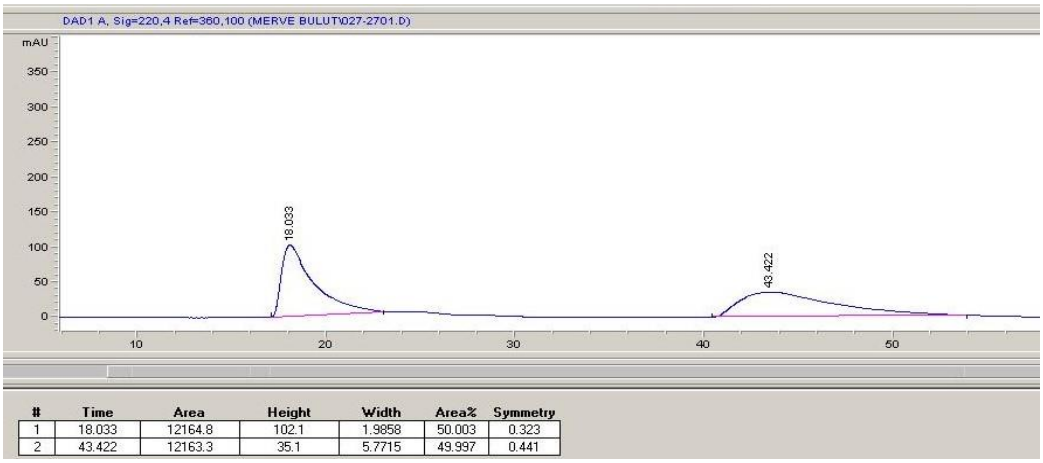


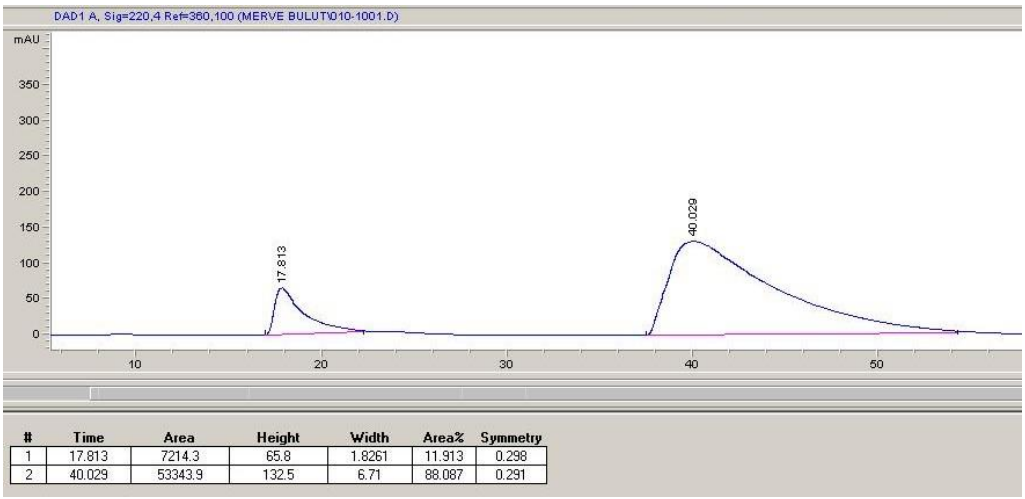
Figure A.22. ^{13}C-NMR Spectrum of compound **50**.

B. HPLC Chromatograms



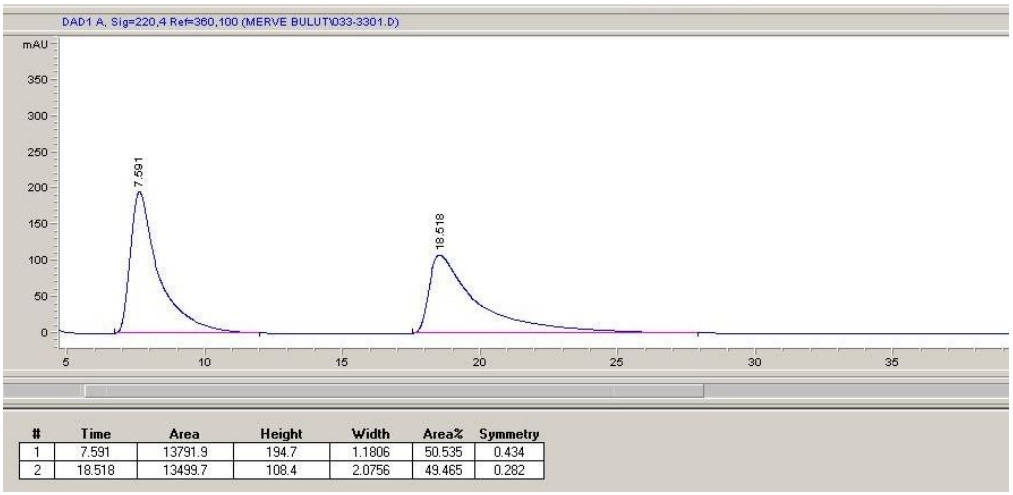
#	Time	Area	Height	Width	Area%	Symmetry
1	18.033	12164.8	102.1	1.9858	50.003	0.323
2	43.422	12163.3	35.1	5.7715	49.997	0.441

Figure B.1. HPLC Chromatogram of compound **46** (Rac.)



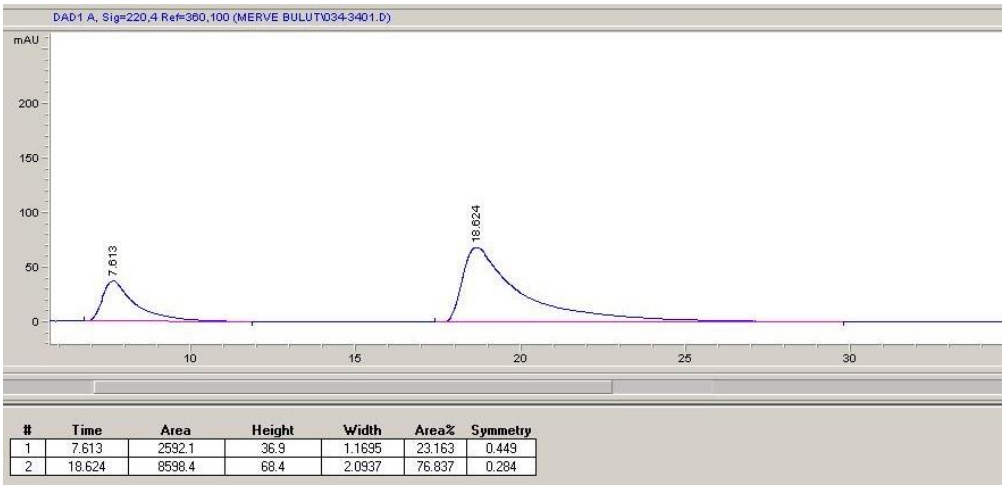
#	Time	Area	Height	Width	Area%	Symmetry
1	17.813	7214.3	65.8	1.8261	11.913	0.298
2	40.029	53343.9	132.5	6.71	88.087	0.291

Figure B.2. HPLC Chromatogram of compound **46** (77% ee)



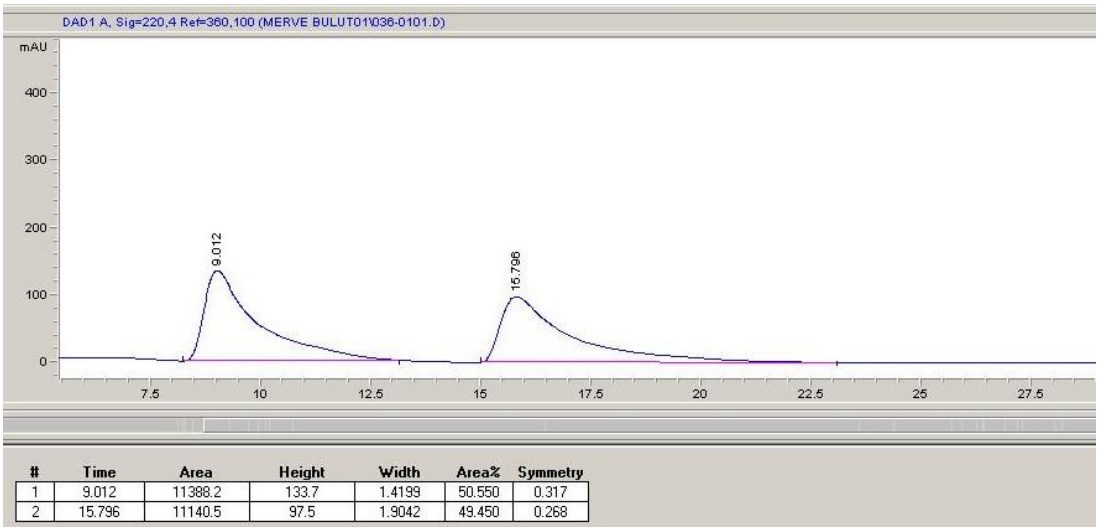
#	Time	Area	Height	Width	Area%	Symmetry
1	7.591	13791.9	194.7	1.1806	50.535	0.434
2	18.518	13499.7	108.4	2.0756	49.465	0.282

Figure B.3. HPLC Chromatogram of compound **47** (Rac.)



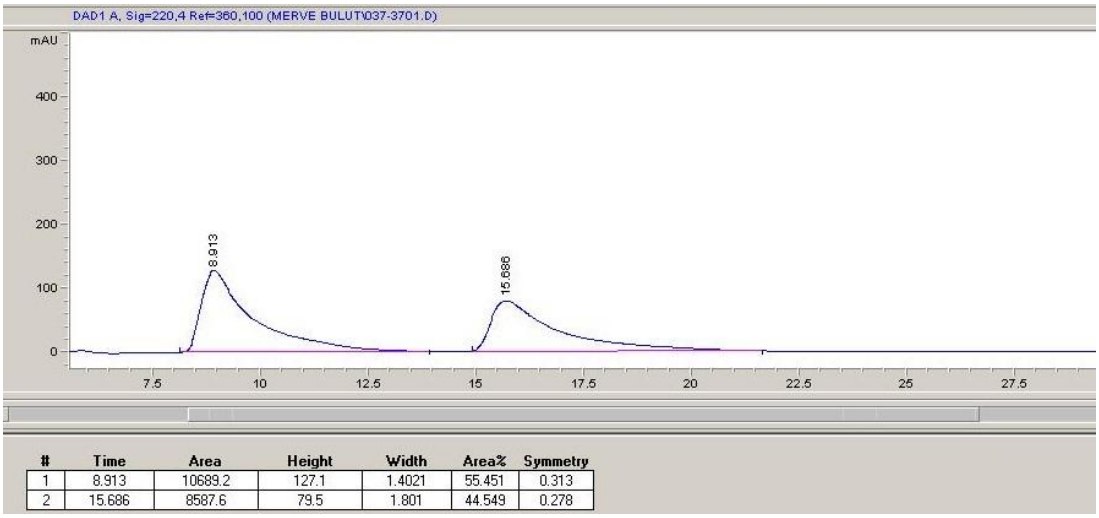
#	Time	Area	Height	Width	Area%	Symmetry
1	7.613	2592.1	36.9	1.1695	23.163	0.449
2	18.624	8598.4	68.4	2.0937	76.837	0.284

Figure B.4. HPLC Chromatogram of compound **47** (53% ee)



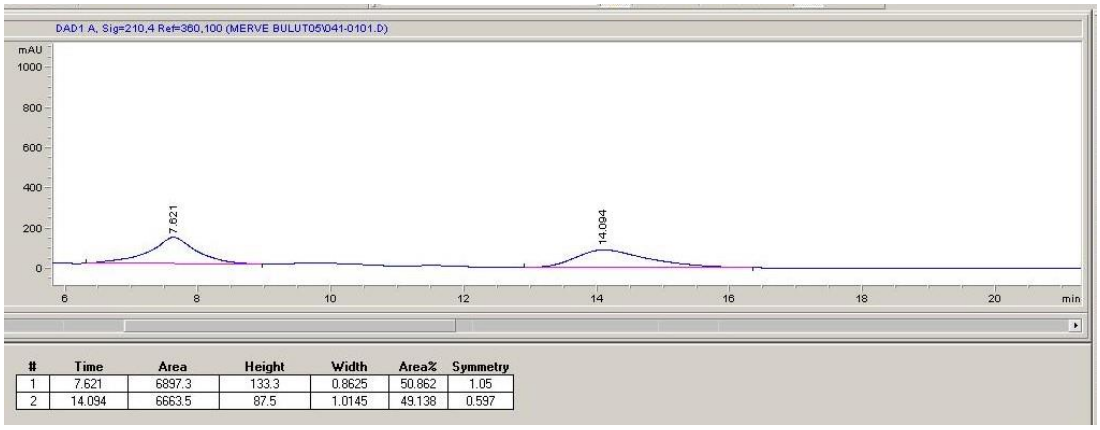
#	Time	Area	Height	Width	Area%	Symmetry
1	9.012	11388.2	133.7	1.4199	50.550	0.317
2	15.796	11140.5	97.5	1.9042	49.450	0.268

Figure B.5. HPLC Chromatogram of compound **48** (Rac.)



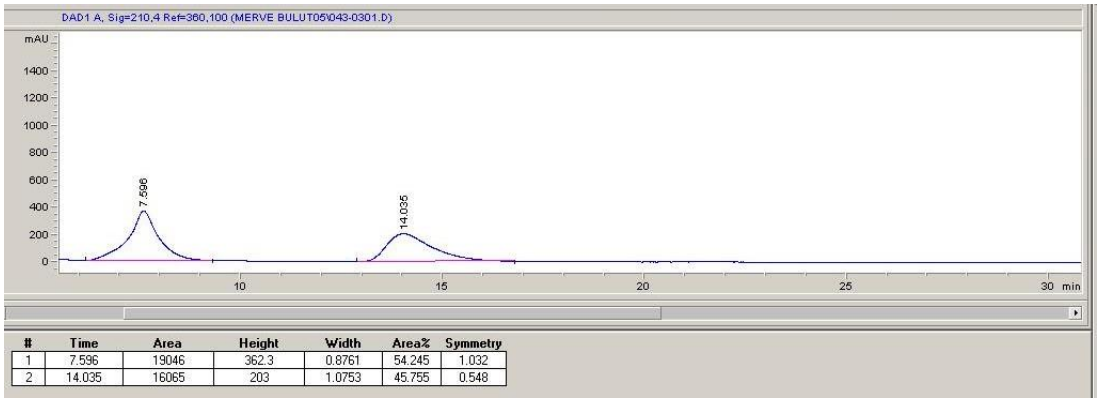
#	Time	Area	Height	Width	Area%	Symmetry
1	8.913	10689.2	127.1	1.4021	55.451	0.313
2	15.686	8587.6	79.5	1.801	44.549	0.278

Figure B.6. HPLC Chromatogram of compound **48** (11% ee)



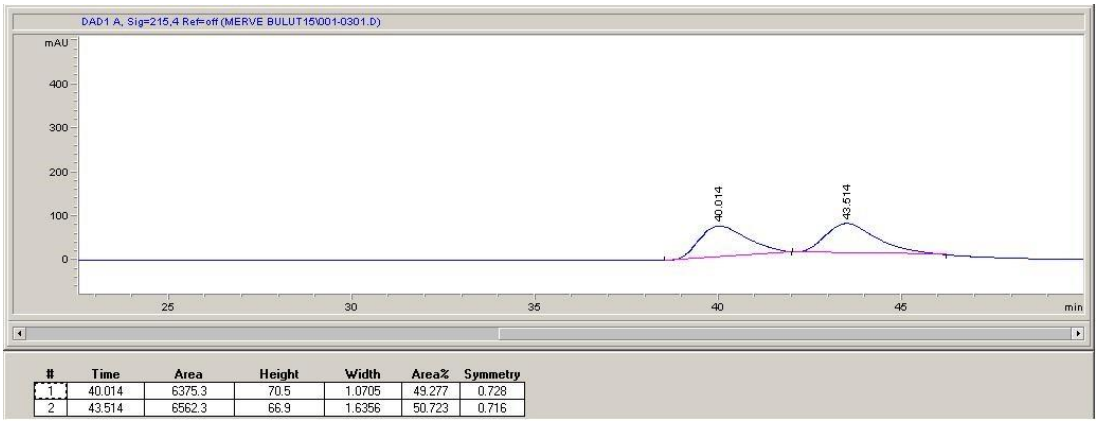
#	Time	Area	Height	Width	Area%	Symmetry
1	7.621	6897.3	133.3	0.8625	50.862	1.05
2	14.094	6663.5	87.5	1.0145	49.138	0.597

Figure B.7. HPLC Chromatogram of compound **49** (Rac.)



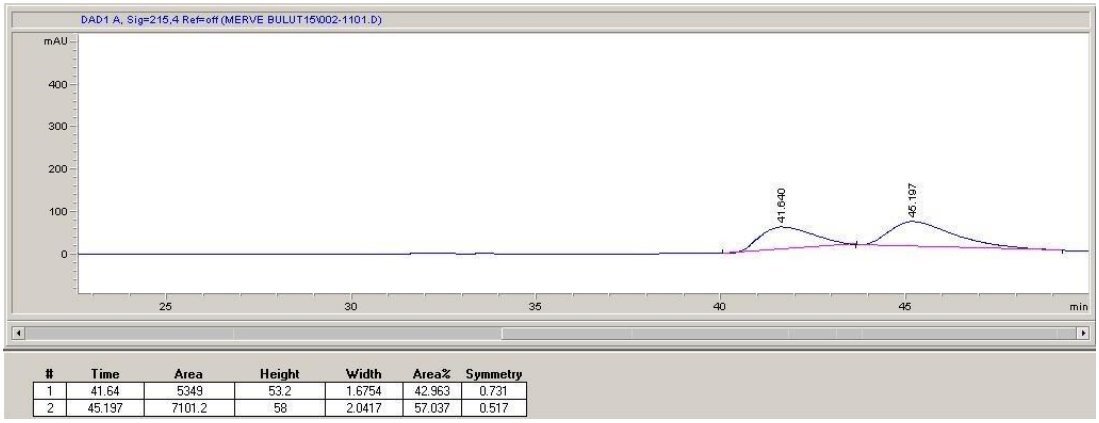
#	Time	Area	Height	Width	Area%	Symmetry
1	7.596	19046	362.3	0.8761	54.245	1.032
2	14.035	16065	203	1.0753	45.755	0.548

Figure B.8. HPLC Chromatogram of compound **49** (9% ee)



#	Time	Area	Height	Width	Area%	Symmetry
1	40.014	6375.3	70.5	1.0705	49.277	0.728
2	43.514	6562.3	66.9	1.6356	50.723	0.716

Figure B.9. HPLC Chromatogram of compound **50** (Rac.)



#	Time	Area	Height	Width	Area%	Symmetry
1	41.64	5349	53.2	1.6754	42.963	0.731
2	45.197	7101.2	58	2.0417	57.037	0.517

Figure B.10. HPLC Chromatogram of compound **50** (15% ee)