CHIRAL METAL CATALYZED ENANTIOSELECTIVE SYNTHESIS OF PYRIDINYL PYRROLIDINE DERIVATIVES

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ABSTRACT

CHIRAL METAL CATALYZED ENANTIOSELECTIVE SYNTHESIS OF PYRIDINYL PYRROLIDINE DERIVATIVES

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Pyrrolidine skeleton can be found as core structures in many natural compounds. Almost all pyrrolidine derivatives show some biological activities and some of them are used as drugs. These compounds can be synthesized by 1,3-dipolar cycloaddition reaction of azomethine ylides with dipolarophiles. This strategy is one of the most efficient and atom economical reaction, because two "C-C" bonds and up to four stereogenic centers can be created in a single step. Our group has synthesized amino alcohol type chiral ligands having ferrocene and aziridine units in their structures. These ligands are shortly called **FAM** and used with a metal as chiral catalyst for the enantioselective synthesis of organic compounds. In this thesis these chiral catalysts and new derivatives (1-**NFAM** and **CFAM**) were screened for the first time in the literature for the enantioselective synthesis of pyridinyl substituted pyrrolidine derivatives. For the synthesis of pyrrolidine structures, 1,3-dipolar cycloaddition of azomethine ylides with electron deficient dipolarophiles were used. Imines, the precursors of azomethine ylides, were prepared by condensation of 2-, 3-, and 4-pyridinecarboxaldehyde with glycine methyl ester. Dimethyl maleate, tertiarybutyl acrylate, methyl acrylate, *N*-methylmaleimide, *trans*-chalcone, and vinylsulfone were used as the dipolarophiles. As the metal sources, silver, copper and zinc salts were tested. After optimizing the reaction conditions by changing many parameters, it was

found that **PFAM1** chiral ligand with silver is catalyzing the reaction better than the other ligands and metal sources by forming the product in 94% yield and 48% *ee*.

Keywords: Chiral Metal Catalyst, Azomethine Ylides, 1,3-Dipolar Cycloaddition, Pyridine Substituted Pyrrolidines, Enantioselective Synthesis

ÖZ

KİRAL METAL KATALİZÖRLERİYLE PİRİDİNİL PİROLİDİN TÜREVLERİNİN ENANTİOSEÇİCİ SENTEZİ

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Bir çok kiral doğal bileşiğin yapısında pirolidin ana iskeleti mevcuttur. Pirolidin yapısı içeren bileşiklerin tamamına yakını biyolojik aktivite göstermektedir, bir kısmıda ilaç olarak kullanılmaktadır. Bu yapıların sentezi için kullanılan önemli tepkimelerden biri azometin ylidlerin dipolarofiller ile 1,3-dipolar halkasal katılma tepkimesidir. Atom ekonomik olan bu tepkimeyle tek basamakta iki tane "C-C" bağı ve dört tane stereojenik merkez oluşturulabilmektedir. Grubumuz bir amino alkol türevi olan, yapısında ferrosen ve aziridin grupları içeren kısaca **FAM** olarak adlandırdığımız kiral bileşikleri sentezleyerek bir metal varlığında kiral katalizör olarak kullanıp organik bileşiklerin enantioseçici sentezini gerçekleştirmiştir. Bu tez kapsamında bu kiral katalizörler ve yeni türevleri (**1-NFAM** ve **CFAM**) piridinil substitue pirolidin bileşikleri enantioseçici olarak sentezinde literatürde ilk kez test edilmiştir. Pirolidin yapılarının sentezi azometin ylidlerin elektronca fakir dipolarofiller ile 1,3-dipolar halkasal katılma tepkimesi ile gerçekleştirilmiştir. Azometin ylidlerin öncüsü olan iminler, 2-, 3- ve 4-piridinkarbaldehitin glisin metil esteri ile kondenzasyonu ile hazırlanmıştır. Dipolarofil olarak dimetil maleat, *tert*-bütil akrilat, metil akrilat, *N*-metilmaleimid, *trans*-çalkon and vinilsulfon kullanılmıştır. Metal kaynağı olarak gümüş, bakır ve çinko tuzları denenmiştir. Tepkime şartlarının bir çok parametreye göre optimize edilmesi sonucunda **PFAM1** kiral ligandının gümüş ile birlikte diğer

kiral ligand ve metallerden daha iyi katalizleyerek ürünü %94 verim ve %48*ee* ile oluşturduğu bulunmuştur.

Anahtar Kelimeler: Kiral Metal Katalizörleri, Azometin Ylidleri, 1,3-Dipolar Halkasal Katılma Tepkimeleri, Piridin Sübstite Pirolidinler, Enantioselektif Sentez

To my family and my dear darling Aliekber Karabağ…

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LIST OF ABBREVIATIONS

ABBREVIATIONS

Ar: Aryl

BINAP: 2,2’-Bis(Diphenylphosphino)-1;1’binaphthyl

δ: Chemical Shift in Parts per Million

J: Coupling Constant

CFAM: Cyclohexyl-Substituted Ferrocenyl Aziridinyl Methanol

DCE: 1,2-Dichloroethane

1,3-DC: 1,3-Dipolar Cycloaddition

1-**NFAM**: 1-Naphtyl-Substituted Ferrocenyl Aziridinyl Methanol

PFAM: Phenyl-Substituted Ferrocenyl Aziridinyl Methanol

R_f: Retention Factor (TLC)

t_R: Retention Time

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CHAPTER 1

INTRODUCTION

1.1.Introduction to Chirality

A molecule or an object is said to be chiral if the molecule and its mirror image are nonsuperimposable to each other (Figure 1.1.) and they present as enantiomers in the nature. Enantiomers rotate plane polarized light in opposite directions by the same angle.[1] Also, these enantiomers can give different response to a particular chiral environment.[2] Biological systems have many examples of chiral molecules such as aminoacids (alanine, proline, etc.), sugars, alkaloids etc.[3] These chiral molecules present in not only biological systems but also in pharmaceuticals.[4] Chiral drugs can exist as a pair of enantiomers and much effort is needed to separate the enantiomers from each other.[5] Since the enantiomers of chiral drugs give different response in their interaction with enzymes, receptors, proteins and other chiral molecules, these different interactions may result in different biological activities.[6] In other words, biological systems can distinguish two enantiomers as if they are two different substances. For this reason, it is important to synthesize these compounds in their enantiomerically pure forms. This synthesis is the key process in modern chemistry and in the field of pharmaceuticals.[7]

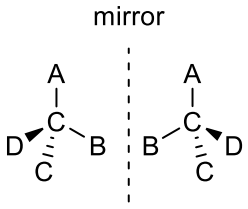


Figure 1.1. Mirror images of chiral molecules

1.2. Asymmetric Synthesis of Chiral Molecules

Asymmetric synthesis plays an important role in the production of single enantiomers. This synthesis favors one enantiomer over the other one. The enantiomers of one molecule sometimes can interact with the target receptor in biological system very differently and with a different response. For example, *S*-carvone smells like spearmint plant and *R*-carvone smells like caraway seed (Figure 1.2.). Since the difference of these enantiomers of carvone molecule are detected by the receptors in our noses, we smell identical odors of them.[8]

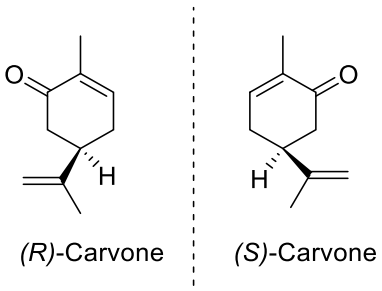


Figure 1.2. Mirror images of enantiomers of chiral Carvone molecule

In addition, when enantiomers are used in pharmaceuticals, they can behave very differently. For instance, morphinan derivative methorphan has two enantiomers having different effects in living systems. Although dextromethorphan, one of the enantiomers, is acting as an antitussive agent, the other enantiomer levomethorphan is a narcotic analgesic (Figure 1.3.).[9]

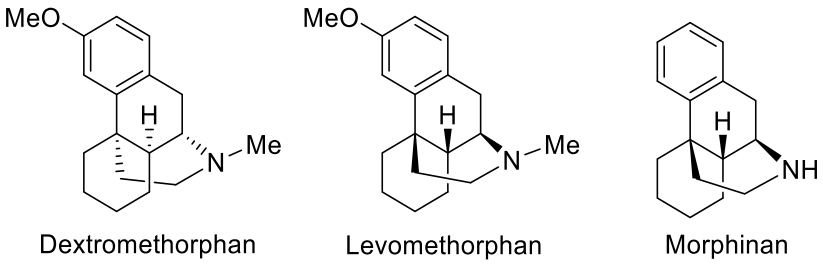


Figure 1.3. Morphinan and its derivatives

There are several strategies used to synthesize chiral molecules in their enantiomerically pure forms. Main strategies are the use of biocatalysts (enzymes), organocatalysts, chiral metal-ligand complexes, chiral auxiliaries, chiral pools and chiral resolutions.[10] Each strategy has its own advantages and disadvantages. For example, metal catalysts are very effective at low concentrations and applicable to many reactions in the production of stereoisomerically rich molecules. These catalysts have high activity and selectivity towards organic reactions and can be formed *in situ* by the combination of a metal salt and a chiral ligand.[11] By taking advantage of different kinds of organocatalysts, enantioselective synthesis can be made possible in more effective and environmentally more friendly ways. These types of catalyst do not contain any metal; therefore, it is not possible to contaminate environment. Organocatalysts are small organic molecules having oxygen, sulfur, nitrogen, phosphorous atoms in their structures.[12] Although organocatalysis are considerably useful in synthesis regarding to their effectivity in reaction rate, being non-toxic, and insensitive to humidity and air, these molecules are not yet very effective as the metal catalysts. Some commonly used organocatalysts from the literature are given in Figure 1.4.[13]

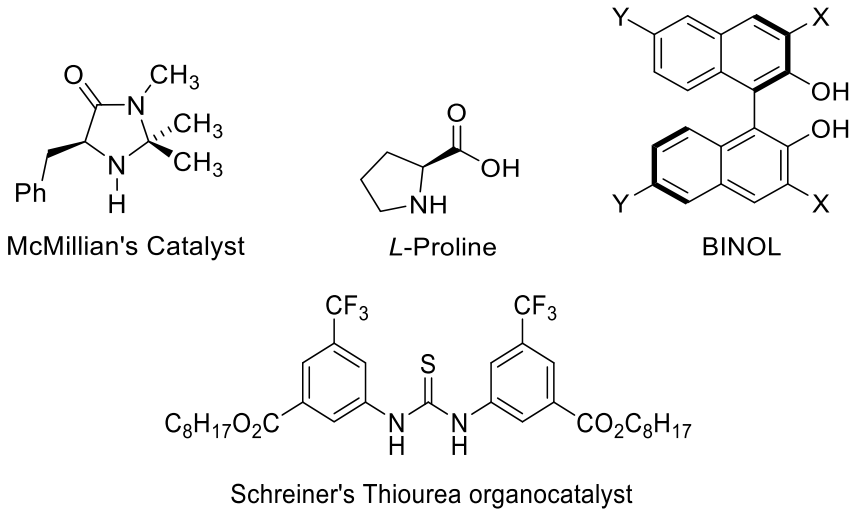


Figure 1.4. Some examples of organocatalysts known in the literature

Within the scope of this study, asymmetric synthesis of enantiomerically pure compounds is based on the utilization of chiral metal-ligand complexes, which are known as metal catalysts. In the reaction medium, it offers an effective asymmetric induction upon direct coordination of the substrate to the metal center.

1.3. Asymmetric Synthesis of Pyrrolidine Structures

Pyrrolidine structure is a nitrogen containing five-membered heterocycle and is present in natural bioactive products and drugs (Figure 1.5).[14]

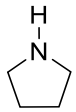
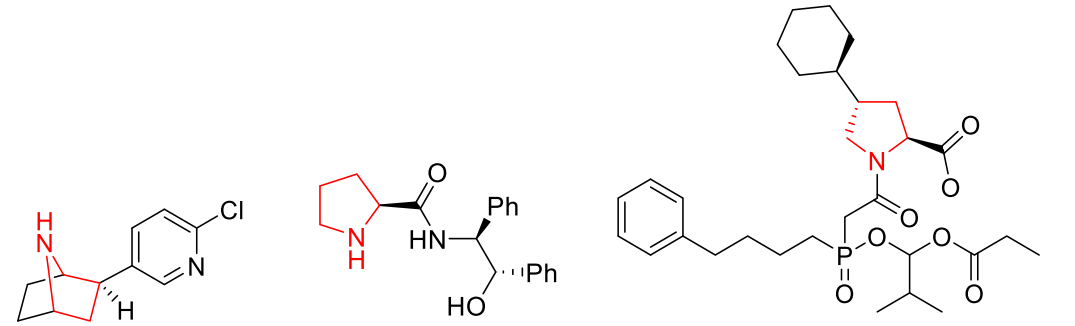


Figure 1.5. Pyrrolidine structure

In addition, pyrrolidines can be used as organocatalysts and the building blocks in the synthesis of many different organic molecules (Figure 1.6.).[15]



Analgesic Alkaloid Organocatalyst Angiotensin Converting Enzyme Inhibitor

Figure 1.6. Some examples of pyrrolidine ring containing compounds

Natural products and their molecular scaffolds are preserved in nature and many of these natural products have common scaffolds with different substituent templates.

Also, these substituted scaffolds have various bioactivities.[16] These substituted scaffolds of natural products are described as "primary scaffolds" and they are good point of origin for compound evolution.

For a long time, scientists tried to develop new methods to synthesize nitrogen containing heterocycles including pyrrolidines asymmetrically. Chiral pyrrolidines and their derivatives are found to be primary scaffolds and they are present in bioactive natural products.[17] Nature has a lot of examples with chiral pyrrolidine rings (Figure 1.7). Hyacinthacine A_4, for example, is a polyhydroxylated pyrrolizidine alkaloid showing inhibitor effect against diverse carbohydrate performing enzymes. (-)-Kainic acid is a common neurotoxin,[18] (-)-Swainsonine has anticancer, antitumor-proliferative, and antimetastatic activity,[14] (+)-Preussin shows antifungal activity.[19]

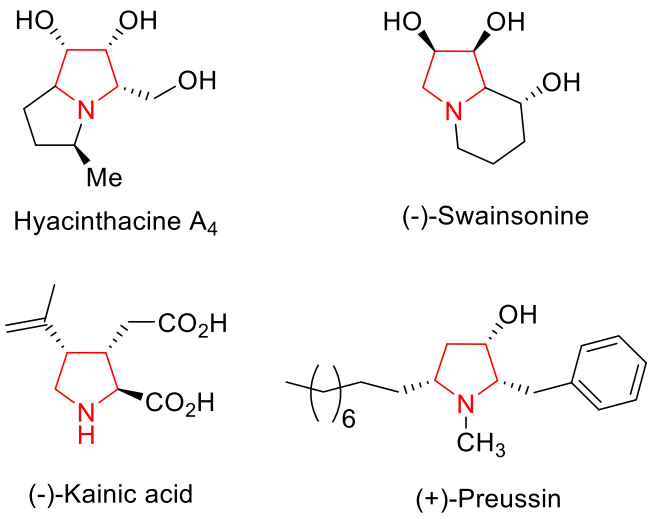


Figure 1.7. Natural products having pyrrolidine core

One of the important methods to get enantiopure pyrrolidine structures is the 1,3-dipolar cycloaddition (1,3-DC) reactions of azomethine ylides with electron-deficient dipolarophiles in the presence of metal catalysts (chiral ligand-metal complexes).[20]

1.4. 1,3-Dipolar Cycloaddition Reactions

In cycloaddition reactions, two reactants combine to form a cyclic molecule, forming two new sigma bonds while opening two π bonds.[21] [3+2]-Cycloadditions resulting in formation of 5-membered rings cannot be formed by octet-stabilized reactants with no formal charges.

As the name suggest, 1,3-dipoles are zwitterionic species with the charge separation between C1 and C3. These species can undergo cycloaddition reactions to produce 5-membered rings. 1,3-Dipole **1** 'a' possesses an incomplete valence shell with a positive charge and 'c' has an unshared electron pair with a negative charge (Figure 1.8.). The reaction of this 1,3-dipole with a dipolarophile, a multiple bond system **2**, yields five-membered ring through 1,3-DC.

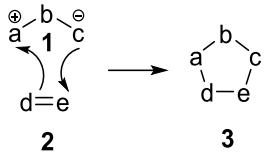


Figure 1.8. General designation of 1,3-dipolar cycloaddition reactions

As shown in Figure 1.9., 1,3-DC reaction is concerted reaction where the bond breakage and the bond formation take place at the same time with a cyclic electron shift. Diels-Alder reaction is also one-step concerted process.[22] Both 1,3-DC reactions and Diels-Alder reactions are mechanistically similar reactions as shown in Figure 1.9.

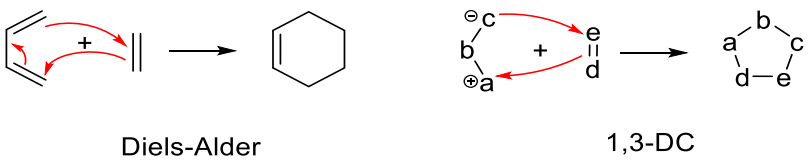


Figure 1.9. General schemes for 1,3-DC and Diels-Alder reactions

1.5. 1,3-Dipoles

1,3-Dipoles can be either in the form of allyl anion type with a bent structure or in the form of propargyl-allenyl type with a linear structure (Figure 1.10.). In allyl anion type dipole, nitrogen, oxygen and sulfur can occupy the central atom ‘b’. On the other hand, in propargyl-allenyl type dipole the central atom ‘b’ can be only the nitrogen.

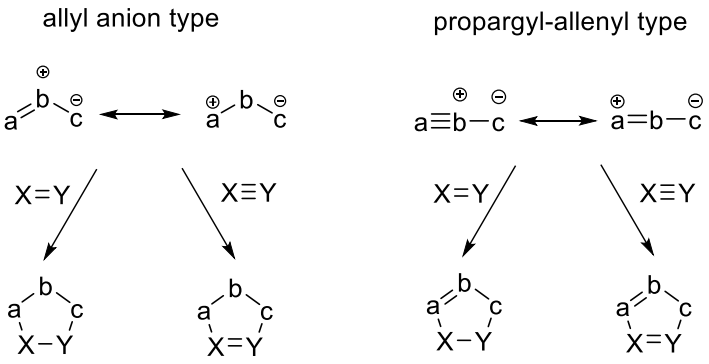


Figure 1.10. Structure of allyl anion and propargyl-allenyl type 1,3-dipoles

There are two types of classification of dipoles as shown in Tables 1.1 and 1.2. These structures are further classified according to the central heteroatom in the dipole structure.[21]

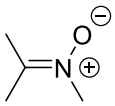
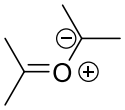
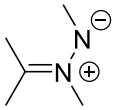
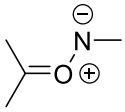
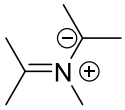
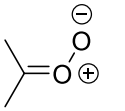
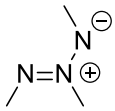
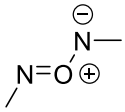
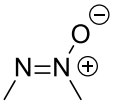
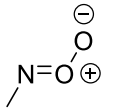
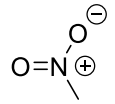
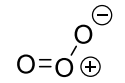
Allyl Anion Type	
Nitrogen-centered	**Oxygen-centered**
 Nitrones	 Carbonyl Ylides
 Azomethine Imines	 Carbonyl Imines
 Azomethine Ylides	 Carbonyl Oxides
 Azimines	 Nitrosoimines
 Azoxy Compounds	 Nitrosoxides
 Nitro Compounds	 Ozone

Table 1.1. Allyl anion type 1,3-dipoles

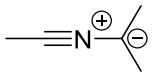
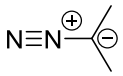
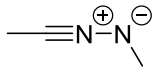
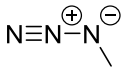
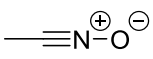
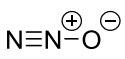
Propargyl-Allenyl Anion Type	
Nitrilium Betaines	**Diazonium Betaines**
 Nitrile Ylides	 Diazoalkenes
 Nitrile Imines	 Azides
 Nitrile Oxides	 Nitrous Oxide

Table 1.2. Propargyl-allenyl anion type 1,3-dipoles

Azomethine ylides are in the class of allyl anion-type dipoles composed of one nitrogen in the center and two terminal, planar sp^2 carbon atoms (Figure 1.11.).

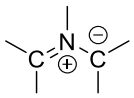


Figure 1.11. Structure of azomethine ylides

These ylides have a zwitterionic form with four-π electron system which overspread the C-N-C three-atom unit. Four resonance structures are possible as shown in Figure 1.12.[23]

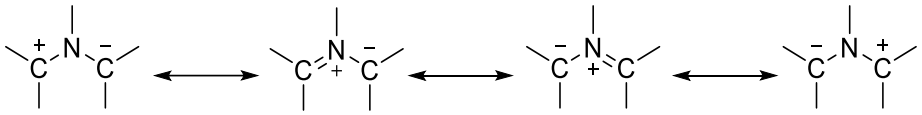


Figure 1.12. Resonance forms of azomethine ylides

In cycloaddition process, azomethine ylides and dipolarophiles interact in a [π^4s + π^2s]-fashion with a total 6π electron system like Diels-Alder reactions. According to Woodward-Hoffmann model, there is a suprafacial-suprafacial interaction between 1,3-dipole and dipolarophile which means interacting orbitals have favorable overlap with each other resulting in cyclic product.[24] The transition state is controlled by frontier molecular orbitals (FMO) of 1,3-dipole and dipolarophile. The reaction between azomethine ylides and electron deficient dipolarophiles is between HOMO of dipole and LUMO of dipolarophile. (Figure 1.13.).[25]

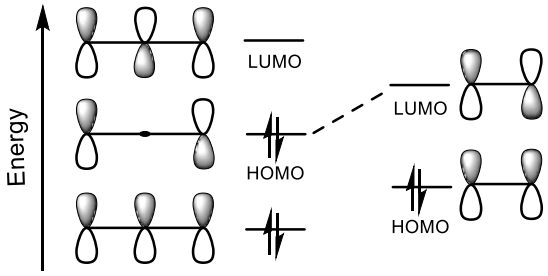
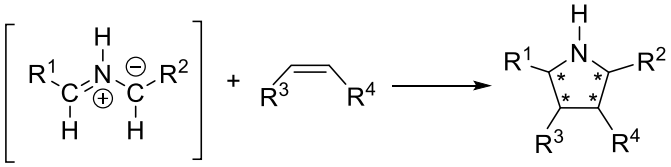
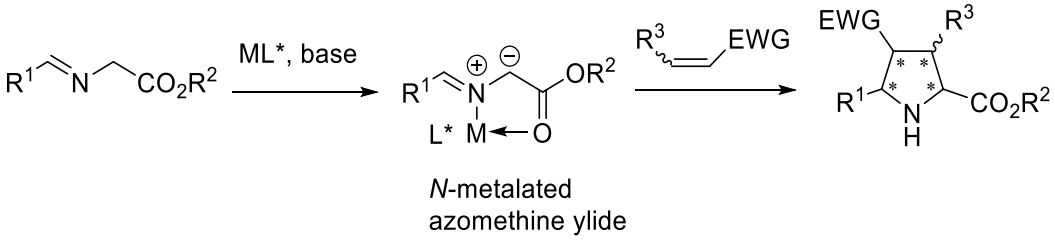


Figure 1.13. Woodward-Hoffman model of 1,3-DC reaction

1,3-Dipoles are reactive intermediates; therefore, they have to be prepared *in situ*. Their cycloadditions to alkene or acetylene dipolarophiles in the reaction medium result in the formation of two carbon-carbon bonds in a single step (Scheme 1.1.). In the presence of a chiral metal catalyst or an organocatalyst, 1,3-DC reactions of azomethine ylides with electron deficient dipolarophiles give rise to the enantiomerically enriched pyrrolidines (Scheme 1.2.).[26]



Scheme 1.1. Cycloaddition reaction of azomethine ylide with dipolarophiles



Scheme 1.2. Catalytic asymmetric 1,3-DC reaction of azomethine ylides

1.6. Literature Studies

Enantioselectivity of 1,3-DC reactions can be controlled by using a proper substrate (chiral 1,3-dipole or chiral alkene) or by using a chiral catalyst.

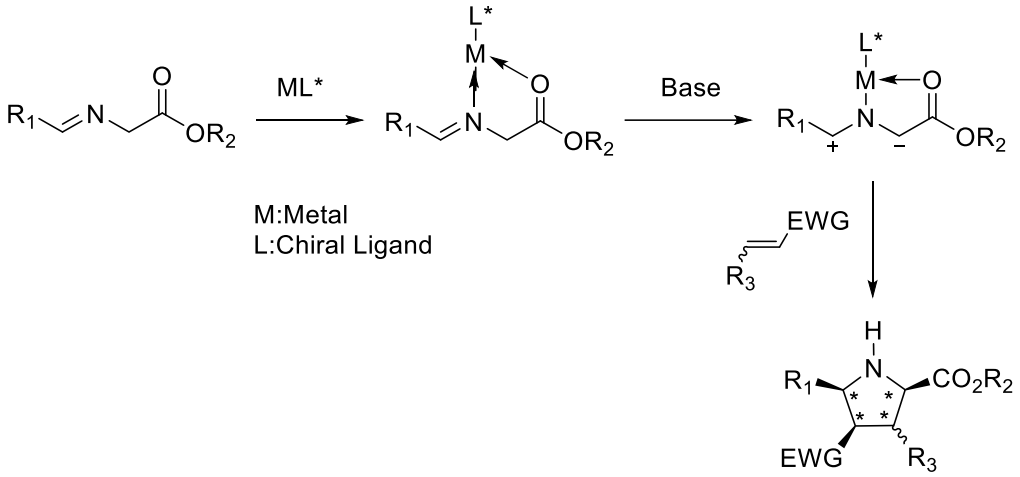
In literature, there are several strategies to get chiral pyrrolidines by 1,3-DC reactions.

- ✓ Introducing non-racemic chiral dipolarophile to the reaction medium[27]
- ✓ Introducing non-racemic chiral dipole to the reaction medium[28]
- ✓ Introducing chiral metal catalyst to the reaction medium [29]
- ✓ Introducing chiral organocatalyst to the reaction medium[30]

In our group, chiral metal catalyzed asymmetric 1,3-DC reaction of azomethine ylides has been studied to get enantiorich pyrrolidines.[31a] In this approach, chiral environment is provided by coordination of 1,3-dipole and electron deficient dipolarophile to chiral metal-ligand complex as shown in Scheme 1.2.

Although there are many examples in literature on the synthesis of aryl-substituted pyrrolidine by using both chiral metal catalysts and chiral organocatalysts, the efforts on the synthesis of pyridinyl-substituted pyrrolidines are quite limited. For this reason, it is important to develop new chiral catalysts for the synthesis of such biologically active compounds. In this thesis, we aimed to test the catalytic performance of our chiral **FAM** ligands in synthesizing 2-, 3-, and 4-pyridinyl-substituted pyrrolidines via asymmetric 1,3-DC reactions of azomethine ylides with different dipolarophiles. Once again, 1,3-dipolar cycloaddition reaction of azomethine ylides with dipolarophiles provides up to four stereocenters and two 'C-C' bonds in a single step while forming the pyrrolidine structure. Therefore, it is a very efficient way of synthesizing pyrrolidine structures. It is also important to mention that the literature related to the synthesis of pyridinyl-substituted pyrrolidines by 1,3-DC reports only one or two examples.[37-39]

In general, metal catalysts coordinate to 1,3-dipole and chiral ligand so that a chiral environment is formed (Scheme 1.3). Then, dipolarophile adds to this intermediate complex selectively from one face of the 1,3-dipole.



Scheme 1.3. Synthesis of chiral pyrrolidine structure in the presence of chiral metal-ligand catalyst

In Scheme 1.3., it is given that coordination of chiral metal-ligand catalyst by imine increases the acidity of α-CH_2 and promotes the proton abstraction by a base. This step leads to *in situ* formation of azomethine ylide. The coordination step of the chiral metal catalyst to imine is very crucial because it controls the enantioselectivity of the reaction. As the last step, the cycloaddition takes place with dipolarophile by forming stereochemically enriched pyrrolidines.

The first example of chiral-metal catalyzed asymmetric 1,3-DC reaction in literature is reported by Allway and Grigg.[32] They first showed that 1,3-DC reactions of azomethine ylides can be promoted by stoichiometric amounts of chiral Co, Mn, and Ag catalysts to give pyrrolidines in high selectivity and high yield.

Some contributing groups reported several reviews related with 1,3-DC reactions of azomethine ylides.[33] The first catalytic 1,3-DC reaction of azomethine ylides is introduced to the literature by Zhang[34] and Jorgensen.[35] While Zhang studied the chiral

Ag-catalyst to facilitate the reaction and control the enantioselectivity, Jorgensen used the chiral Zn-catalyst in enantioselective 1,3-DC reactions.

Our group have developed chiral phenyl substituted ferrocenyl aziridinyl methanol **(PFAM)** ligands and tested their catalytic activity in different organic reactions including 1,3-DC reaction.[31a]

In 2007, our group reported the synthesis and the use of novel chiral *ent*-**PFAM** ligands in asymmetric 1,3-DC reactions (Figure 1.14). Four diastereomers of these ligands were tested with different dipolarophiles in the presence of zinc-salt (10 mol%) which formed pyrrolidines in up to 90% *ee*.[31a]

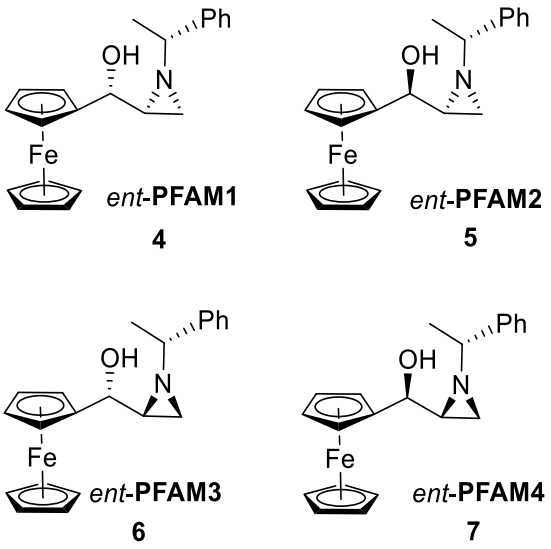


Figure 1.14. Structure of ***ent*-PFAM** ligands used by our group

In 2010, our group have synthesized phosphorous derivatives (**POFAM**) of the **FAM** ligands. Among the 6 novel diastereomeric **POFAM** ligands, **POFAM6** (Figure 1.15.) showed the highest performance, forming pyrrolidines in up to 99% yield and 77% *ee* with a silver metal (6 mol%).[31b]

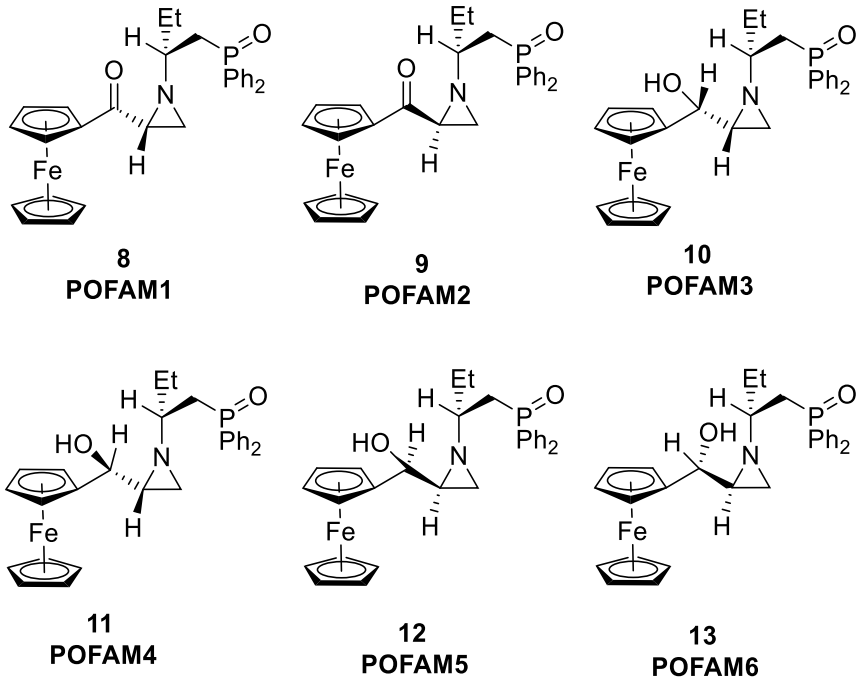
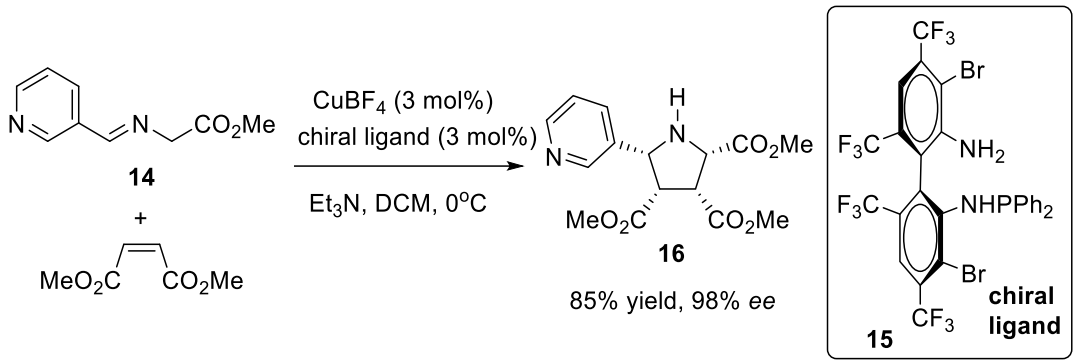


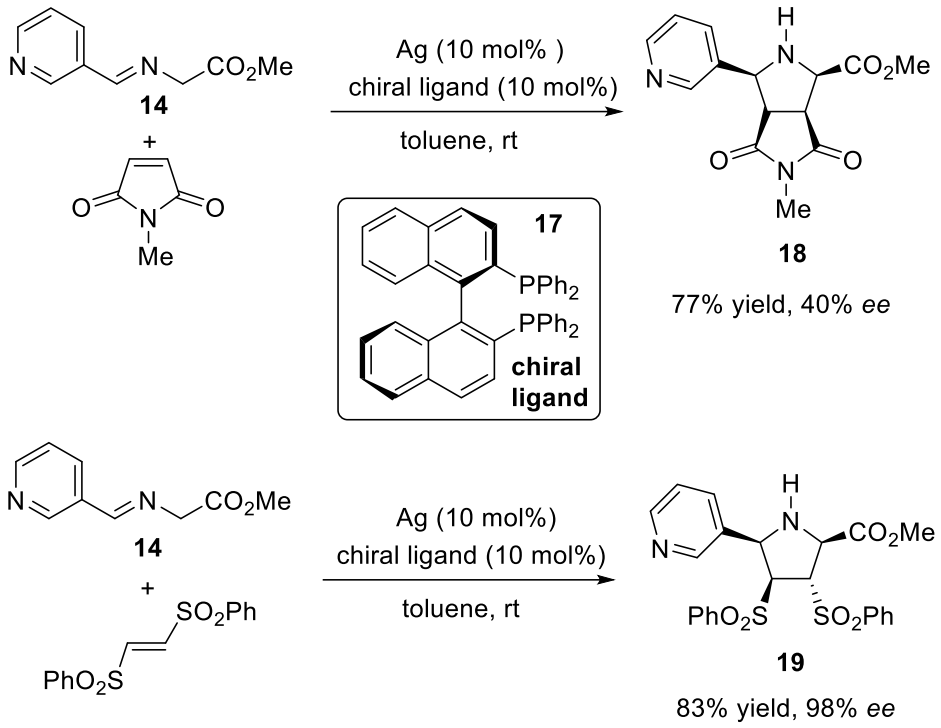
Figure 1.15. Structures of **POFAM** ligands

There are many groups including our group studying 1,3-DC reactions of azomethine ylides for the synthesis of aryl substituted pyrrolidines in literature.[36] Similar studies for the synthesis of pyridinyl substituted pyrrolidines are limited to one or two examples. One of these studies was reported by Wang and co-workers (Scheme 1.4). This group reported an example in their study having 3-pyridinyl substituted pyrrolidine structure.[37] In the presence of Cu/TF-BiphamPhos **(***N*,*P*-ligand**) 15** catalyst system, pyridinyl pyrrolidine was formed in 85% yield and 98% *ee*.



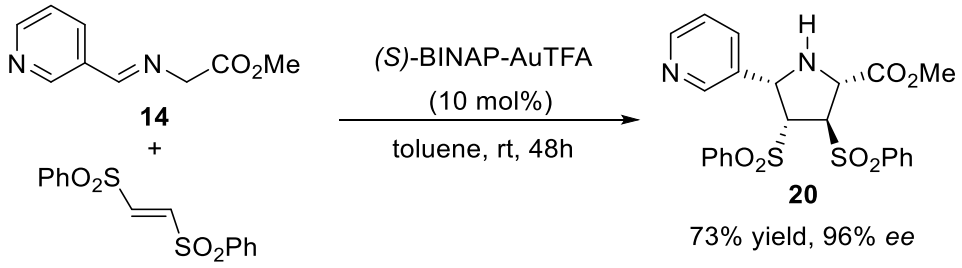
Scheme 1.4. 3-Pyridinyl substituted pyrrolidine structure reported by Wang and co-workers

Another study was reported by Sansano and co-workers (Scheme 1.5). This group also performed 3-pyridinyl-substituted pyrrolidine synthesis with two different dipolarophiles.[38] They were able to synthesize the pyridinyl-substituted pyrolidines in 70% yield with 40% *ee* by using *N*-methylmaleimide as the dipolarophile. The same group also reported this reaction by using *(S)*-BINAP-$AgClO_4$ catalyst system **17** and phenyl vinyl disulfone as the dipolarophile that formed the corresponding pyrrolidine structure in 83% yield with 98% *ee*.



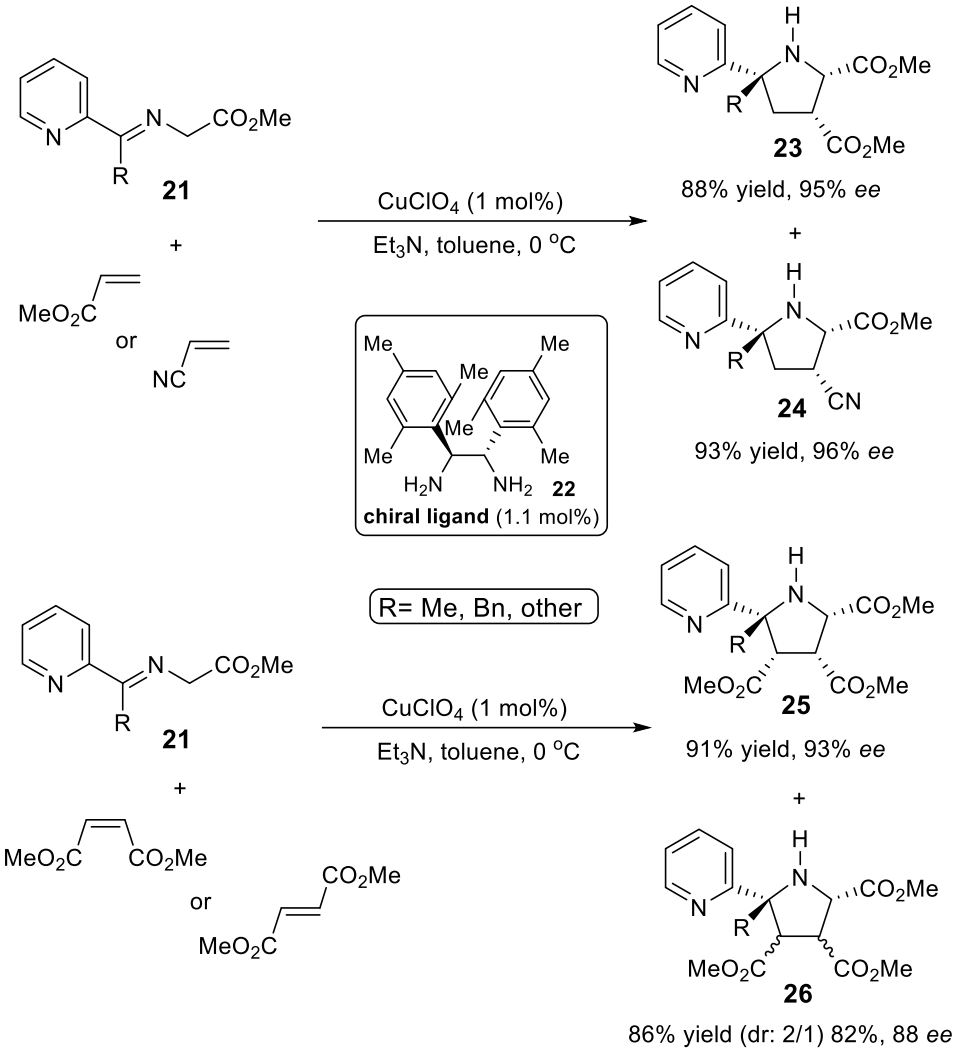
Scheme 1.5. 3-Pyridinyl substituted pyrrolidine synthesis by Sansano et.al.

Sansano and co-workers carried out another study for the synthesis of 3-pyridinyl substituted pyrrolidines (Scheme 1.6).[39] This time, they used *(S)*-BINAP-AuTFA (10 mol%) chiral catalyst system and reported the cycloadduct in 73% yield with 96% *ee*.



Scheme 1.6. Another work performed by Sansano group

Aron's group reported a more comprehensive study for the synthesis of 2-pyridinyl-substituted pyrrolidines as shown in Scheme 1.7.[40]

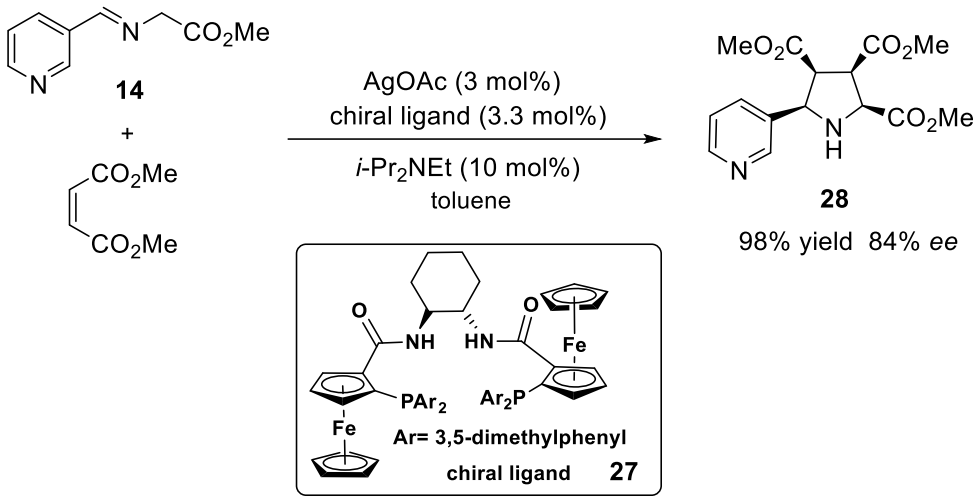


Scheme 1.7. 2-Pyridinyl-substituted pyrrolidine structures reported by Aron et.al.

They reported the synthesis of different 2-pyridinyl substituted pyrrolidines by using diamine-Cu (1 mol%) catalyst system **22** which formed pyrrolidine structures in very good yields and enantioselectivities.

The asymmetric synthesis of pyridinyl-substituted pyrrolidines was also studied by Zhang and co-workers (Scheme 1.8.).[34] By using a chiral ligand having amino and phosphorous group with AgOAc, 3-pyridinyl-substituted pyrrolidine was obtained in

98% yield with 84% *ee*. In this study, *i*-Pr_2NEt was used as a base and just one 3-pyridinyl-substituted pyrrolidine structure was reported.



Scheme 1.8. Study of Zhang and co-workers

Limited number of studies in literature towards the asymmetric synthesis of pyridinyl-substituted pyrrolidines by using 1,3-DC reaction of azomethine ylides with chiral metal catalysts motivated us to try our **FAM** ligands for the same reaction.

1.7. Aim of This Study

Pyrrolidines are structurally and biologically important compounds. Therefore, the synthesis, especially the asymmetric synthesis, of these compounds are still attracting the attention of researchers. Although heteroaryl-substituted pyrrolidines are also biologically active compounds, the research related to the asymmetric synthesis of these compounds are very limited. In general, 1,3-DC reactions are studied with aryl-substitıted imines, heteroaryl-substituted ones are present as one or two examples in these studies. In another words these is no systematic study based on the pyridinyl-substituted pyrrolidines by using 1,3-DC reaction of azomethine ylides. For this reason, we aim to study the asymmetric synthesis of pyridinyl-substituted pyrrolidines

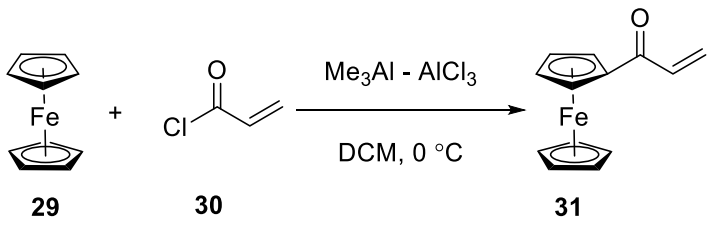
by using our chiral **FAM** ligands with a metal by employing 1,3-DC reaction of azomethine ylides. In doing so, we planned to synthesize 2-, 3-, and 4-pyridinyl-substituted pyrrolidines by using different dipolarophiles in each case. Our group has previously synthesized *ent*-**PFAM** ligands and tested their catalytic activity in 1,3-DC reactions of aryl-substituted pyrrolidines. In this thesis work, besides using **PFAM** chiral ligands (four diastereomers), new derivatives of **CFAM** (cyclohexyl substituted ferrocenyl aziridinyl methanol, four diastereomers) and 1-**NFAM** (1-naphthyl substituted ferrocenyl aziridinyl methanol, also four diastereomers) chiral ligands will also be screened with a metal (Cu, Zn, and Ag) for the asymmetric synthesis of pyridinyl-substituted pyrrolidines via 1,3-DC reactions of azomethine ylides.

CHAPTER 2

RESULTS AND DISCUSSIONS

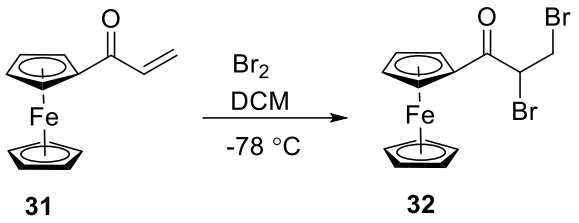
2.1. Synthesis of Chiral PFAM Ligands

In our group, *ent*-**PFAM** ligands were previously synthesized by using the Gabriel-Cromwell reaction.[31a] Four diastereomers of the **PFAM** ligands were also synthesized by using the same procedures but the chiral amine with opposite configuration as explained in the following paragraphs. First step in the ligand synthesis started with the synthesis of acryloyl ferrocene. Our group developed a convenient protocol. According to this protocol, acryloyl chloride and ferrocene were reacted in the presence of $AlMe_3$-$AlCl_3$ Lewis acids to yield acryloyl ferrocene in 95% yield (Scheme 2.1). It was a very clean reaction, so only extraction was enough to isolate the desired product **31** in pure form.



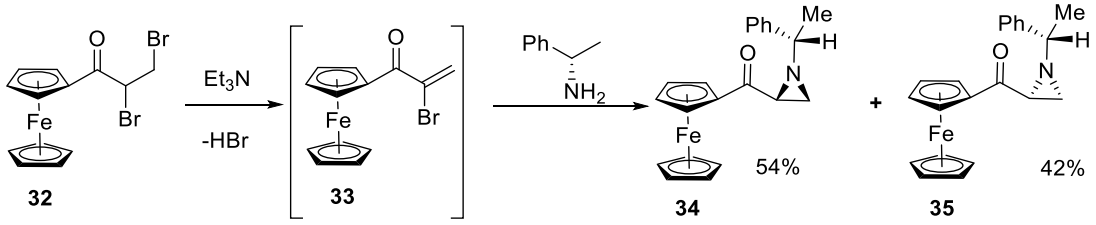
Scheme 2.1. Synthesis of acryloyl ferrocene **31**

The next step was bromination of acryloyl ferrocene **31**, which was carried out at -78 ℃ to yield dibromo compound **32** in about quantitative yield with minor amount of HBr-eliminated form **33** after simple filtration through a silica gel column (Scheme 2.2).[31b]



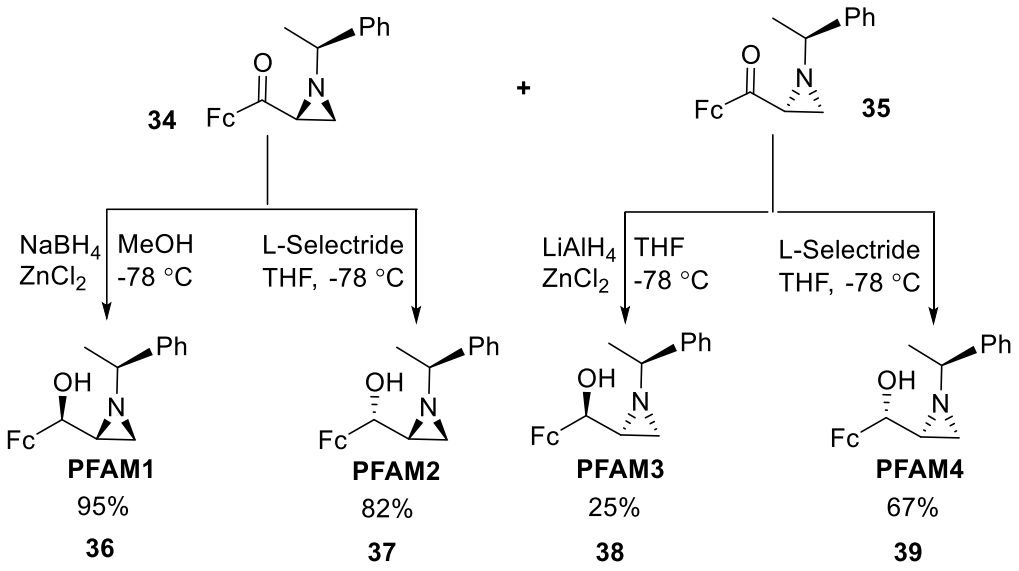
Scheme 2.2. Bromination of acryloyl ferrocene **31**

Third step in the synthesis of **FAM** ligands was achieved by the use of the Gabriel-Cromwell reaction. Simply, a mixture of dibromo compound and small amount of HBr-eliminated form **33** were mixed with Et_3N which converts compound **32** completely to **33** simply by eliminating HBr. Then, the addition of *(S)*-1-phenylethylamine into the same reaction flask yielded a diastereomeric mixture of aziridinyl ketones **34** and **35** in 54% and 42% yields, respectively, after flash column chromatography (Scheme 2.3).



Scheme 2.3. Aziridination of brominated ferrocene via Gabriel-Cromwell reaction

The last step in the ligand synthesis was the reduction of ketones to corresponding alcohols. The reduction of the ketones was done by following the procedures adopted from Yun's group as shown in Scheme 2.4.[41] The configurational assignment was based on the X-ray analysis of *ent*-**PFAM1** reported previously.[31a]



Scheme 2.4. Synthesis of **PFAM** chiral ligands

After completing the synthesis of **PFAM** ligands and having the other derivatives 1-**NFAM** and **CFAM** in hand (structures are given in Figure 2.1), synthesized by the other group members following the steps used for **PFAM** ligands, we were ready to test their catalytic activity for the enantioselective synthesis of pyridinyl substituted pyrrolidines by 1,3-DC reaction.

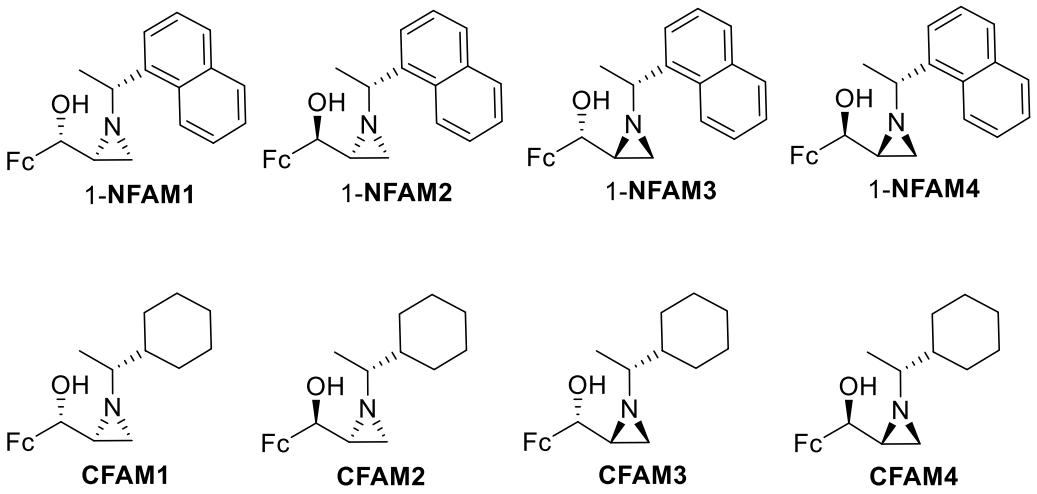


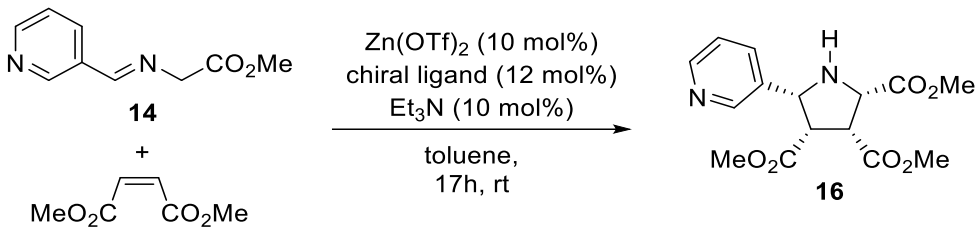
Figure 2.1. Structures of **1-NFAM** and **CFAM** ligands

2.2. Enantioselective 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

One of the starting materials for the 1,3-DC reaction is imines. Therefore, imines corresponding to 2-, 3-, and 4-pyridinyl-substituted imines were prepared first by adopting the literature procedure.[33] These imines can survive for about one month in cold under nitrogen atmosphere.

After the preparation of imines, first we screened the ligands in 1,3-DC reaction using $Zn(OTf)_2$ as the metal source and dimethyl maleate as the dipolarophile. The results of these studies were summarized in Table 2.1.

Table 2.1. Ligand screening studies



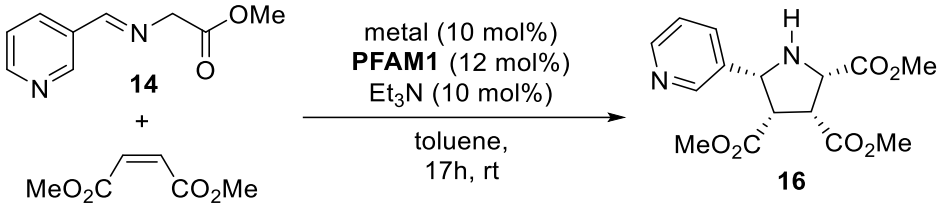
Entry	Ligand	Yield[a] (%)	*ee*[b] (%)
1	**CFAM1**	8	9
2	**CFAM2**	38	racemic
3	**CFAM3**	22	racemic
4	**CFAM4**	24	13
5	**PFAM1**	30	17
6	**PFAM2**	24	racemic
7	**PFAM3**	7	15
8	**PFAM4**	67	racemic
9	1-**NFAM1**	14	11
10	1-**NFAM2**	13	racemic
11	1-**NFAM3**	12	racemic
12	1-**NFAM4**	15	17

[a] Isolated chemical yields.
[b] Determined by chiral HPLC using Chiralpak OD-H column.

As can be seen from the Table 2.1, all the chiral ligands formed the products either at low enantioselectivity or no selectivity at all with $Zn(OTf)_2$. Although the enantioselectivities were not satisfactory, we determined **PFAM1** to be the better ligand than the others in terms of both yield and *ee* (entry 5). At this point, our main concern was the enantioselectivity rather than the yield. After deciding on the chiral ligand as **PFAM1**, we continued further optimizations by using this ligand.

We tried different metal sources for the second optimization. In deciding the type of the metals, we looked at the literature reporting the similar studies. Besides $Zn(OTf)_2$, we tested AgOAc, $Cu(CH_3CN)_4BF_4$ and Et_2Zn by using the same imine and dipolarophile. The results of these studies were summarized in Table 2.2.

Table 2.2. Metal screening studies



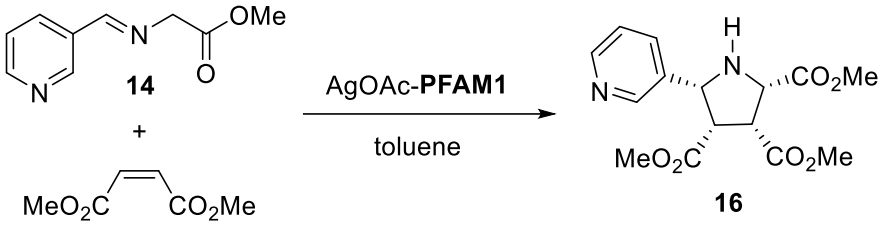
Entry	Metal	Yield[a] (%)	*ee*[b] (%)
1	$Zn(OTf)_2$	30	17
2	AgOAc	67	25
3	$Cu(CH_3CN)_4BF_4$	55	9
4	Et_2Zn	25	13

[a] Isolated chemical yields.
[b] Determined by chiral HPLC using Chiralpak OD-H column

Metal screening studies showed that AgOAc was providing the product in better yield and *ee* than the other metals (entry 2). The lowest enantioselectivity was observed with the copper salt (entry 3). From the metal screening studies, we decided to continue further optimization of reaction conditions by using AgOAc with **PFAM1** ligand.

After determining metal and the ligand, we continued optimization studies by changing reaction temperature, time, and catalyst loading (mol%). The results of these optimizations were summarized in Table 2.3.

Table 2.3. Further optimization of reaction condition



Entry	Rxn time and temp.	Ligand (mol%)	Metal (mol%)	Yield[a] (%)	*ee*[b] (%)
1	17h, rt	**PFAM1** (12)	AgOAc (10)	67	25
2	17h rt	**PFAM1** (12)	AgOAc (5)	88	13
3	17h, -20 ℃	**PFAM1** (12)	AgOAc (5)	92	45
4	17h, -20 ℃	**PFAM1** (20)	AgOAc (10)	84	51
5	4h, 0 ℃ to rt	**PFAM1** (12)	AgOAc (5)	74	11
6	4h, 0 ℃ to rt	**PFAM1** (6)	AgOAc (5)	72	31
7	4h, 0 ℃ to rt	**PFAM1** (20)	AgOAc (16.7)	35	50
8	4h, 0 ℃ to rt	**PFAM1** (30)	AgOAc (25)	32	57
9	4h, 0 ℃ to rt	**PFAM1** (40)	AgOAc (20)	27	67

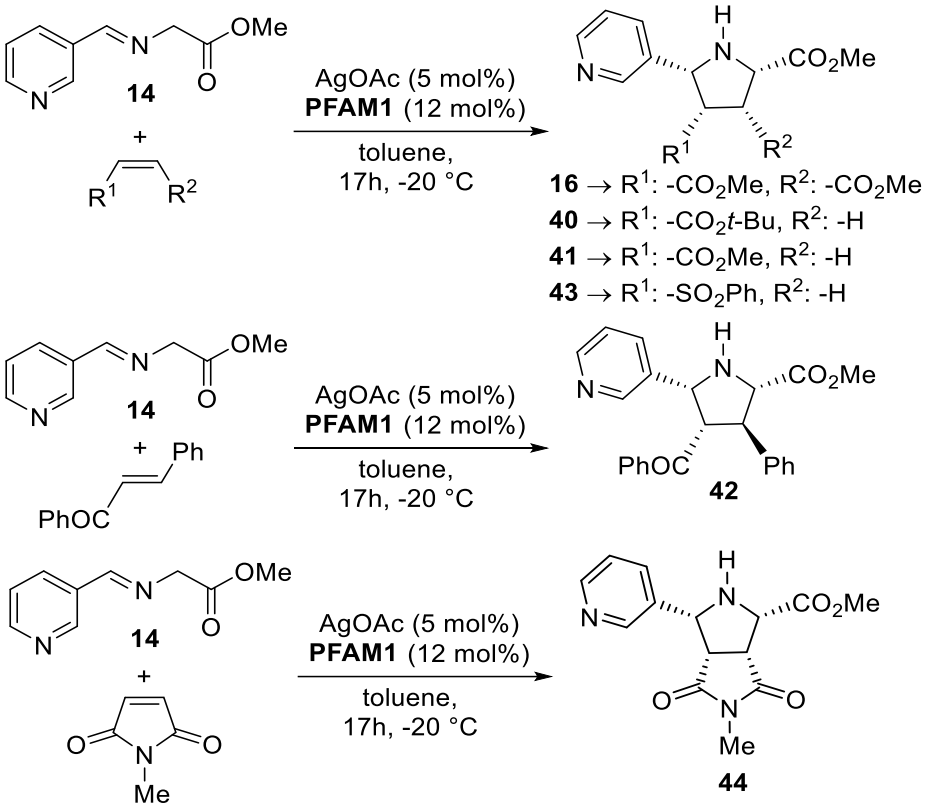
[a] Isolated chemical yields.
[b] Determined by HPLC using Chiralpak OD-H column.

The ratio of chiral metal-ligand catalyst is very important in metal catalyzed asymmetric reactions. Therefore, optimization studies were done by changing metal to ligand ratio. In first two entries, only the amount of silver salt was reduced from 10 mol% to 5 mol%. This change resulted in increase in chemical yield from 67% to 88% but decrease in *ee* from 25% to 13%. Lowering the reaction temperature to -20 ^{o}C at low metal concentration increased both the yield and *ee* of the reaction (entry 3). When

the amount of the ligand was increased from 10 mol% to 20 mol% at -20 ^{o}C, the yield decreased to 84% but *ee* increased to 51% (entry 4). We have also lowered reaction time to 4 hours which provided the product in acceptable yield but the *ee* was low (entry 5). Interestingly, lowering the ligand amount to 6 mol% at shorter reaction time *ee* was higher compared to the results in entry 5. We have also increased ligand amount up to 40 mol% and metal amount up to 25 mol%. In general, *ee* was acceptable but the yield was low (entries 7-9). From the results of these optimization studies, we decided to use 5 mol% AgOAc and 12 mol% **PFAM1** and carry out the 1,3-DC reactions at -20 ℃ for further studies.

After determining chiral ligand, metal, temperature, and the catalyst loading, we repeated 1,3-DC reaction with different dipolarophiles under these conditions. The results of these studies were summarized in Table 2.4.

Table 2.4. Dipolarophile screening



Entry	Dipolarophile	Yield[a] (%)	*ee*[b] (%)
1	MeO_2C CO_2Me	92	45
2	$CO_2{}^tBu$	82	racemic
3	CO_2Me	63	racemic
4	Ph COPh	83	13
5	SO_2Ph	40	10
6	Me N O O	76	racemic

[a]Isolated chemical yields.
[b] Determined by HPLC using Chiralpak OD-H column

Dipolarophile screening studies showed that the yield of 1,3-DC reaction is good to acceptable except the phenyl vinyl sulfone case where the product is formed in 40 % yield (entry 5). *trans*-Chalcone formed the product in good yield 83% with %13 *ee* (entry 4). The results of this table showed that the enantioselectivity of our catalyst system is dipolarophile dependent. It means that reaction parameters need to be optimized for each dipolarophile. This observation was also reported by other groups for similar reactions. Structural and configurational assignments were based on the literature reports. The cycloadducts obtained from dimethylmaleate and methylacrylate are known in the literature. Therefore, we compared our data with the literature to assign the configuration.[37,42] Based on the stereochemistry of the known compounds, we propose the following transition state for the selectivity of the 1,3-DC reaction (Figure 2.2).

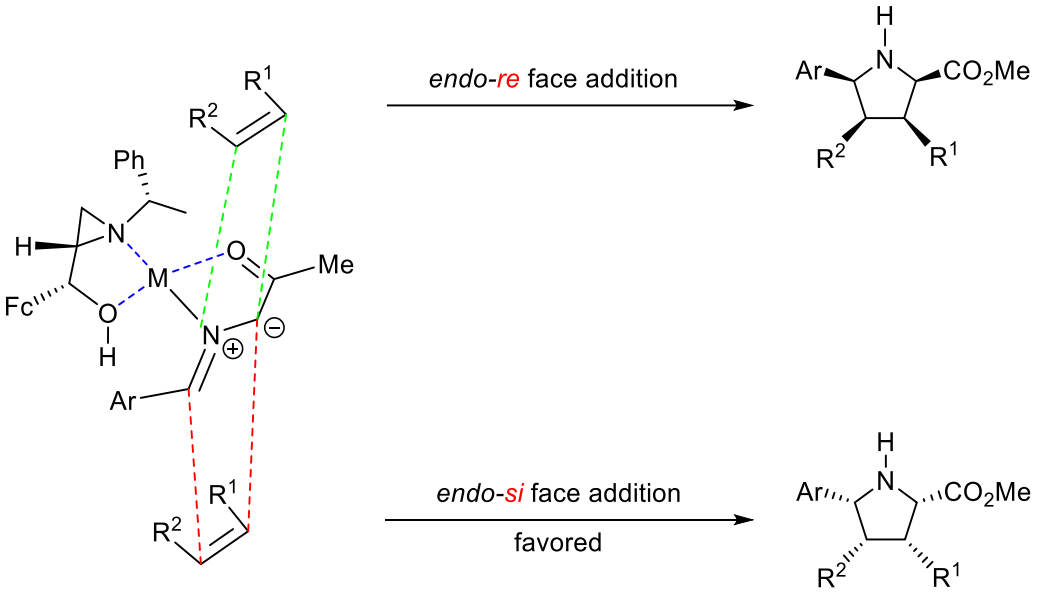


Figure 2.2. Proposed transition state

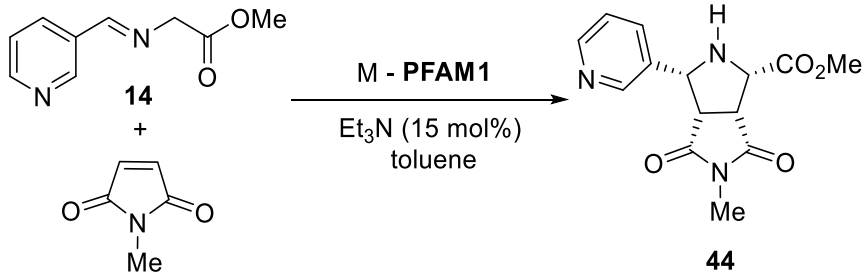
According to this transition state in Figure 2.2, the chiral ligand and the azomethine ylides are coordinated to the metal from their oxygens and nitrogens. The

dipolarophile is approaching the planar azomethine ylide from its lower face in an *endo*-mode (substituents on the dipolarophile are through the metal).

Cycloadducts obtained from *N*-methylmaleimide, *tert*-butlyacrylate, *trans*-chalcone, and phenyl vinyl sulfone are not reported in the literature. Therefore, full analysis of these compounds was obtained.

As mentioned before, our catalyst system showed dipolarophile dependency. Therefore, we tried a different metal source to see whether yield and enantioselectivity could be improved for *N*-methylmaleimide. For this purpose, we adapted the experimental procedure reported by Wang and co-workers.[29] The results of these studies were summarized in Table 2.5.

Table 2.5. Optimization studies for *N*-methylmalemide using copper salt

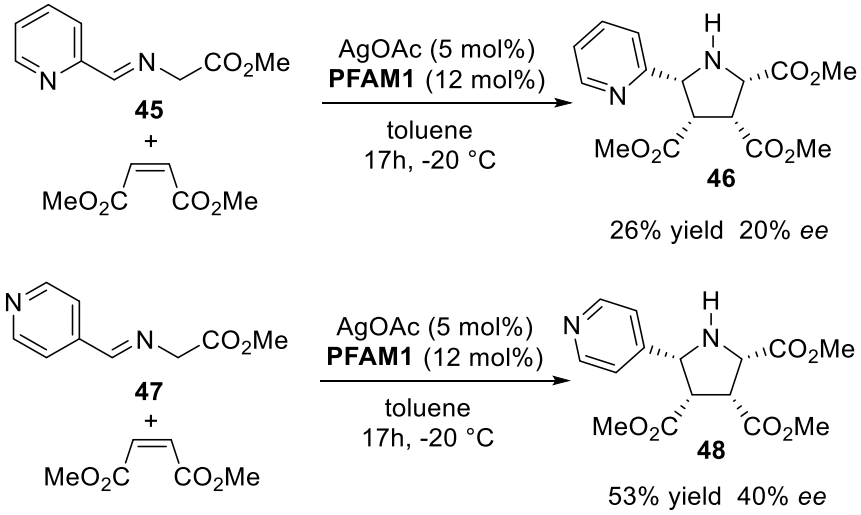


Entry	Rxn Conditions	Ligand (mol%)	Metal (mol%)	Yield[a] (%)	*ee*[b] (%)
1[c]	17h -20 °C	**PFAM1** (12)	AgOAc (5)	76	Racemic
2	17h rt	**PFAM1** (6)	$Cu(CH_3CN)_4BF_4$ (6)	42	33
3	17h -20 °C	**PFAM1** (6)	$Cu(CH_3CN)_4BF_4$ (6)	40	15
4	17h rt	**PFAM1** (20)	$Cu(CH_3CN)_4BF_4$ (17)	16	racemic
5	17h rt	**PFAM1** (30)	$Cu(CH_3CN)_4BF_4$ (25)	24	racemic

[a] Isolated chemical yields.
[b] Determined by HPLC using Chiralpak OD-H column.
[c] without base

As can be seen from Table 2.5, although 33% enantioselectivity was observed with this metal, better than silver acetate, the yield was low, and the other optimizations did not give satisfactory results.

Besides optimizing reaction conditions and screening different dipolarophiles, we also studied 1,3-DC reaction of 2- and 4-pyridinyl substituted imines. Using the optimized conditions decided from Table 2.4, 1,3-DC reactions were carried out with these imines as outlined in Scheme 2.5.

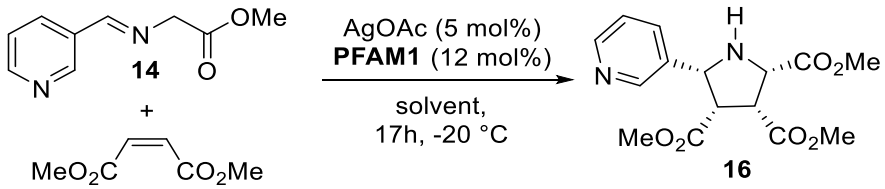


Scheme 2.5. 1,3-DC reactions carried out with 2- and 4-pyridinyl substituted imines

The results in Scheme 2.5 showed that under the same conditions used for 3-pyridinyl case, 4-pyridinylimine also formed the product in similar enantioselectivity but in low yield. In the case of 2-pyridinylimine both the *ee* and yield were low. Related with the 2-pyridinyl and 4-pyridinylimines, it is also important to note that both of them are less stable than 3-pyridinylimine. Although all the imines were prepared fresh and checked by ^{1}H NMR, the spectra for 2- and 4-pyridinylimines were not as pure as that of 3-pyridinylimine. This may have some effect on the results of the 1,3-DC reactions of these imines.

As the final optimization, we also wanted to see the effect of different solvents on 1,3-DC reactions with our catalyst system. For this purpose, the reaction was repeated under optimized conditions by using common organic solvents which are DCM, THF, DCE and Et_2O. The results of these studies were summarized in Table 2.6.

Table 2.6. Solvent screening



Entry	Solvent	Yield[a] (%)	*ee*[b] (%)
1	Toluene	92	45
2	THF	92	31
3	DCM	72	15
4	DCE	93	23
5	Et_2O	94	48

[a] Isolated chemical yields.
[b] Determined by HPLC using Chiralpak OD-H column.

Solvent screening studies showed that the results of diethyl ether were slightly better than those of toluene by forming the product in 94% yield with 48% *ee* (entries 1 and 5). Although ether gave slightly higher yield and *ee* than toluene, 48% *ee* was not encouraging enough to repeat the reaction with other dipolarophiles using this solvent. Since ether is more volatile than toluene, the molarity change of the reaction is more possible during the reaction time in the case of ether; therefore, toluene is chosen as a better solvent.

CHAPTER 3

CONCLUSION

Within the scope of this thesis, the asymmetric 1,3-DC reactions of pyridinyl-substituted azomethine ylides with different dipolarophiles have been studied for the first time by using our **FAM** ligands. For this purpose, three different **FAM** ligands, **PFAM**, 1-**NFAM** and **CFAM**, were synthesized and their catalytic performance were tested. Since each ligand is composed of four diastereomers, total of 12 ligands were screened in this study. Besides screening ligands for 1,3-DC reaction, the reaction conditions were also optimized in terms of temperature, solvent, metal, time etc. All these optimizations were done with 3-pyridinylimine. Using the optimized conditions 2-pyridinyl- and 4-pyridinylimines were also studied for the 1,3-DC reaction of azomethine ylides.

Under the optimized reaction conditions our catalyst system, different dipolarophiles were also screened. These studies showed that our catalyst system did not show consistency among the dipolarophiles, enantioselectivities and yields were different for each dipolarophile. This can be attributed to the functional groups on the dipolarophiles. Because some of the dipolarophiles may coordinate the metal better than the others at the transition state. As a result, this effects the *ee* and yield of the reaction. Our optimization studies were carried out with dimethyl maleate which was used as the dipolarophile. All the studies carried out in this thesis showed that 3-pyridinylimine forms the cycloadduct with dimethyl maleate in higher yield (94%) and *ee* (48%) by using AgOAc (5 mol%) and **PFAM1** (12 mol%) at -20 ℃. One solution to increase the yield and *ee* with the other dipolarophiles could be further optimization of the reaction parameters for each dipolarophile which was not possible in the time of this thesis.

CHAPTER 4

EXPERIMENTAL

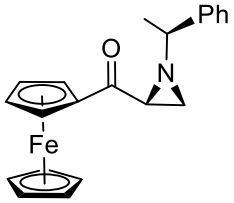
4.1. General Experimental Procedure

Commercially available reagents were purchased from Sigma-Aldrich, Across and Merck. All enantioselective reactions were carried on inert atmosphere under nitrogen and in a dried and vacuumed glassware. Reagents, catalyst and solvents were dried and purified before using. Reactions were followed by TLC under UV-light at 254 nm. Ninhydrin and phosphomolybdic acid were used to color the UV-inactive spots. For purification of crude products, flash column chromatography on silica gel (230-400 mesh) was used. Enantioselectivity of cycloadducts were detected by HPLC using DAICEL Chiralpak OD-H and AS-H Columns eluting with *i*-PrOH-hexane mixture. ^{1}H and ^{13}C NMR spectra of synthesized compounds were observed by Brucker Spectrospin Avance III DPX-400 instrument at 400 MHz and 100 MHz relative to TMS. Agilent 6224 TOF-LC/MS instrument120 was used for mass analysis of cycloadducts not known in the literature. IR spectra were obtained by using Bruker Platinum ATR-IR instruments and were reported in cm^{-1}. Synthesis of **PFAM** ligands were carried out according to the literature procedure.[31a]

4.2. Synthesis of Chiral PFAM Ligands

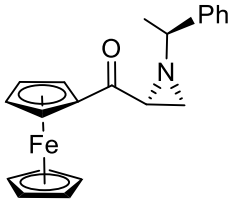
4.2.1. Synthesis and of Phenyl Substituted Ferrocenyl Aziridinyl Ketone 1 and Ketone 2

The title compounds were synthesized by using the literature procedure, all the spectral data are in agreement with the reported values.[31a]



34

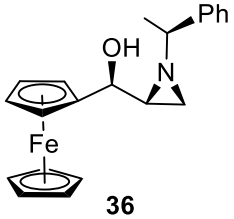
Ketone 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 7.0 Hz, 2H), 7.37 (t, J = 7.4 Hz, 3H), 7.31-7.28 (m, 1H), 5.06-5.02 (m, 1H), 4.97-4.94 (m, 1H), 4.59-4.55 (m, 2H), 4.26 (s, 5H), 2.68-2.62 (m, 2H), 2.27 (dd, J = 3.2, 1.5 Hz, 1H), 1.71 (dd, J = 6.5, 1.5 Hz, 1H), 1.56 (d, J = 6.5 Hz, 3H).



35

Ketone 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.25-7.19 (m, 1H), 4.73-4.63 (m, 2H), 4.44 (t, J = 2.0 Hz, 2H), 3.89 (s, 5H), 2.61 (q, J = 6.6 Hz, 1H), 2.56 (dd, J = 6.5, 3.1 Hz, 1H), 2.41 (dd, J = 3.2, 1.6 Hz, 1H), 1.87 (dd, J = 6.5, 1.6 Hz, 1H), 1.52 (d, J = 6.6 Hz, 3H).

4.2.2. Synthesis and Characterization of PFAM1

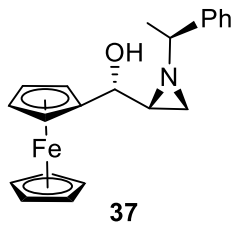


36

The synthesis of **PFAM1** was done by the reduction of phenyl substituted aziridinyl ketone 1. The reduction was done according to the literature procedure.[31a] Apart from this reported procedure, reduction was also done in the presence of different reducing agent with a different procedure. Ketone 1 was taken (1.0 g, 0.27 mmol) and dissolved in fresh distilled THF (10 mL) at room temperature. Then $LiAlH_4$ (0.02 g, 0.5 mmol) was added. After 15 mins, TLC showed no starting material was left in the reaction medium. The reaction mixture was hydrolyzed with distilled water (10 mL). The extraction was done with EtOAc and organic phase was washed with saturated NH_4Cl solution. Then, the combined organic layer was dried over $MgSO_4$. The concentrated crude product was purified by flash column chromatography on silica gel (4:1 hexane/EtOAc). **PFAM1 36** was obtained in 95 yield % as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 4.53 (d, J = 4.3 Hz, 1H), 4.31 (br, 1H), 4.28 (br, 1H), 4.21 (s, 5H), 4.20-4.16 (m, 2H), 2.76 (br, 1H), 2.62 (q, J = 6.5 Hz, 1H), 1.91-1.87 (m, 1H), 1.84 (d, J = 3.5 Hz, 1H), 1.58

(s, 1H), 1.34 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 128.4, 127.1, 126.8, 89.7, 68.8, 68.6, 68.3, 68.1, 68.0, 67.9, 67.2, 66.1, 43.8, 30.1, 23.6.

4.2.3. Synthesis and Characterization of PFAM2



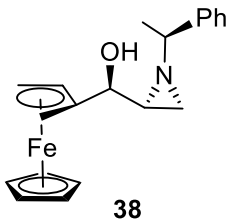
37

The synthesis of **PFAM2** was done by the reduction of phenyl substituted aziridinyl ketone 1. The reduction was done according to the literature procedure.[31a] In addition to this procedure, after flash column chromatography 2 hours hydrolysis was done in order to get rid of L-Selectride. The concentrated crude compound was purified by flash column chromatography on silica gel (4:1 hexane/EtOAc). **PFAM2 37** was obtained in a good yield %82 as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.26 (m, 4H), 7.22-7.19 (m, 1H), 4.28 (br, 1H), 4.16 (s, 6H), 4.12 (t, J = 2.2 Hz, 2H), 4.05 (d, J = 6.0 Hz, 1H), 2.71 (br, 1H), 2.47 (q, J = 6.6 Hz, 1H), 1.80-1.74 (m, 1H), 1.68 (d, J = 3.5 Hz, 1H), 1.35 (d, J = 6.4 Hz, 3H), 1.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 128.4, 127.1, 126.8, 90.7, 70.6, 69.1, 68.6, 67.9, 67.8, 66.4, 65.9, 45.5, 31.5, 23.6.

4.2.4. Synthesis and Characterization of PFAM3 and PFAM4

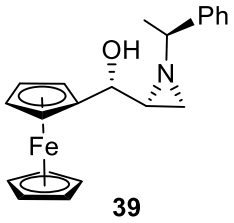
The synthesis of **PFAM3** and **PFAM4** was done by the reduction of phenyl substituted aziridinyl ketone 2. The reduction was done according to the literature procedure.[31a] Apart from this reported procedure, the reduction was also done in the presence of different reducing agent with a different procedure. Ketone 2 was taken (1.0 g, 2.8 mmol) and dissolved in fresh distilled THF (27 mL) at room temperature. Then, $LiAlH_4$ (0.11 g, 5.6 mmol) was added. After 15 mins, TLC showed no starting material was left in the reaction medium and two isomers were formed which were **PFAM3** and **PFAM4**. The reaction mixture was hydrolyzed with distilled water. The extraction was done with EtOAc and organic phase washed with distilled water. Then, organic

layer was dried over $MgSO_4$. The obtained isomers **PFAM3** and **PFAM4** were separated by flash column chromatography on silica gel (4:1 hexane/EtOAc).



38

PFAM3 38 was obtained in 43 yield % as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.26 (m, 4H), 7.25-7.20 (m, 1H), 4.06 (s, 5H), 4.02-3.92 (m, 3H), 3.82-3.70 (m, 1H), 2.58-2.43 (m, 1H), 2.13-2.01 (m, 1H), 1.98-1.85 (m, 1H), 1.81 (s, 1H), 1.63 (br, 1H), 1.57-1.51 (m, 1H), 1.50-1.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 128.7, 127.5, 127.0, 89.8, 70.7, 69.6, 68.4, 67.7, 66.4, 66.1, 60.4, 43.7, 32.1, 22.7, 14.2.



39

PFAM4 39 was obtained in a 51 yield % as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.26 (m, 4H), 7.26-7.22 (m, 1H), 4.32 (br, 1H), 4.09 (s, 5H), 4.06-3.94 (m, 3H), 2.67 (s, 1H), 2.65-2.57 (m, 1H), 2.11-1.98 (m, 1H), 1.86-1.74 (m, 1H), 1.68 (br, 1H), 1.50-1.44 (m, 1H), 1.45-1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 128.5, 127.1, 126.7, 89.3, 69.3, 68.4, 68.0, 67.8, 67.0, 66.7, 66.5, 42.3, 30.0, 23.2, 14.2.

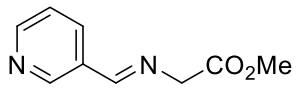
4.3. General Imine Formation Procedure

Glycine methyl ester hydrochloride (1.2 eq) was dissolved in DCM and then $MgSO_4$ (1.6 eq) and Et_3N (1.4 eq) were added respectively. This mixture was stirred for 1 hour at room temperature. At the end of this stirring time, the corresponding aldehyde (1.0 eq) was added. The reaction mixture was left stirring overnight at room temperature. In the morning the reaction mixture was filtered to remove solids. Then the filtrate was washed with distilled water and the organic phase was dried over $MgSO_4$, filtered and concentrated to obtain pure imine. All the data for 2- and 3-pyridinyl-substituted

imines are in accordance with the literature.[37,40] 4-Pyridinylimine was also synthesized with this procedure.

4.3.1. (*E*)-[(Pyridin-4-ylmethylene)-amino]-acetic acid methyl ester

Using the general procedure, the imine was synthesized starting from glycine methyl ester and 4-pyridinylcarboxyaldehyde as a yellow oil in 80% yield.



14

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 6.1 Hz, 2H), 8.24 (s, 1H), 7.58 (d, J = 6.1 Hz, 2H), 4.41 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 169.7, 163.4, 150.2, 142.1, 121.9, 61.5, 52.0.

4.4. General Procedures for Enantioselective Pyrrolidine Synthesis via 1,3-Dipolar Cycloaddition

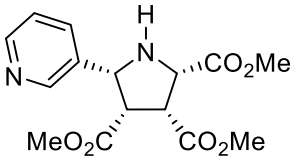
4.4.1. $Zn(OTf)_2$-Based Procedure

Dry $Zn(OTf)_2$ (10 mol%) was put into a dried reaction flask under N_2. (Commercial $Zn(OTf)_2$ was dried by azeotroping with toluene under N_2 and then removing the residual solvent under vacuum). The reaction flask was then connected to a vacuum line and heated with a heat gun for 2 minutes. This procedure was repeated 3 times. Chiral ligand (12 mol%) dissolved in freshly distilled toluene (1 mL) was added to the reaction flask at rt. The homogeneous mixture was stirred at this temperature for about 1h. To this mixture was added sequentially, the imine (1 eq), dry Et_3N (10 mol%) and the dipolarophile (1.1 eq). The resulting mixture was stirred for overnight under N_2 atmosphere. In the morning, crude reaction mixture was applied directly to flash column chromatography on silica gel for purification.

4.4.2. AgOAc-Based Procedure

AgOAc was put into a previously dried and vacuumed reaction flask under N_2. Chiral ligand was dissolved in freshly distilled toluene (1 mL) and added to the reaction flask at rt. The homogeneous mixture was stirred at this temperature for half an hour. To this mixture, imine was added (1 eq) and the reaction mixture was stirred for another half an hour. Then dipolarophile (1.5 eq) was added and the resulting mixture was stirred for overnight under N_2 atmosphere. In the morning crude product was applied directly to flash column chromatography on silica gel for purification.

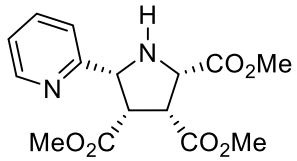
4.4.2.1. *(2S,3R,4S,5R)*-Trimethyl 5-(pyridin-3-yl) pyrrolidine-2,3,4-tricarboxylate



16

Compound **16** was synthesized by using AgOAc procedure. It was obtained in 94% yield as light-yellow solid. $[\alpha]^{29}_D$ = -41.5 (*c* 0.01, $CHCI_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.45 (d, *J* = 5.3 Hz, 1H), 7.72 (d, *J* = 4.2 Hz, 1H), 7.26-7.18 (m, 1H), 4.47 (d, *J* = 7.2 Hz, 1H), 4.11 (d, *J* = 8.7 Hz, 1H), 3.74 (s, 3H), 3.68 (t, *J* = 8.2 Hz, 1H), 3.63 (s, 3H), 3.58 (t, *J* = 7.6 Hz, 1H), 3.28 (s, 1H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.7, 170.6, 149.0, 148.7, 134.5, 133.3, 123.3, 62.7, 62.1, 52.5, 52.2, 52.1, 51.6, 50.7; 51% *ee*, HPLC (Chiralpak OD-H column, *i*-PrOH-hexane 15/85, UV detection: 205 nm, 0.8 mL/min, t_r = 63.05 and 78.33 min).

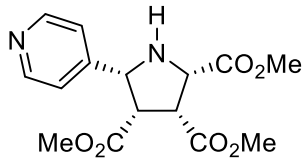
4.4.2.2. *(2S,3R,4S,5R)*-Trimethyl 5-(pyridin-2-yl) pyrrolidine-2,3,4-tricarboxylate



46

Compound **46** was synthesized by using AgOAc procedure. It was obtained in 26% yield as a yellow oil. R_f = 0.42, EtOAc/MeOH 5:1. IR (neat, cm^{-1}) 3294, 3002, 2952, 2850, 1732, 1434, 1198. ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 4.6 Hz, 1H), 7.72-7.62 (m, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.23-7.12 (m, 1H), 4.59 (d, J = 6.7 Hz, 1H), 4.28 (d, J = 9.3 Hz, 1H), 3.80 (s, 3H), 3.78-3.75 (m, 1H), 3.70 (s, 1H), 3.67 (s, 3H), 3.49 (s, br, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.7, 169.4, 155.3, 147.8, 135.5, 121.6, 120.8, 65.2, 60.9, 51.5, 51.1, 50.4, 50.3, 50.2; HRMS calcd for $C_{15}H_{18}N_2O_6$ $[M+H]^+$ 323.1200, found 323.1240; 20% *ee*, HPLC (Chiralpak OD-H column, *i*-PrOH-hexane 15/85, detector: 205 nm, 0.8 mL/min, t_r = 46.08 and 55.65 min)

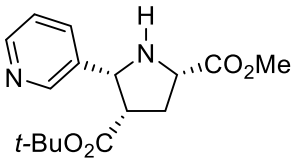
4.4.2.3. *(2S,3R,4S,5R)*-Trimethyl 5-(pyridin-4-yl) pyrrolidine-2,3,4-tricarboxylate



48

Compound **48** was synthesized by using AgOAc procedure. It was obtained in 53% yield as light orange solid, mp: 124.4-126.4 ℃. R_f = 0.46, EtOAc/MeOH 5:1. IR (neat, cm-1) 3228, 2946, 1743, 1713, 1431, 1186. $[\alpha]^{29}_D$ = -14.0 (*c* 0.01, $CHCI_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.60-8.49 (m, 2H), 7.35-7.25 (m, 2H), 4.43 (d, J = 6.8 Hz, 1H), 4.17 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H), 3.74-3.71 (m, 1H), 3.68 (s, 3H), 3.64-3.59 (m, 1H), 3.27 (s, 3H), 3.05 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.4, 170.4, 149.7, 146.6, 121.9, 64.1, 62.0, 52.5, 52.3, 51.8, 51.6, 51.0; HRMS calcd for $C_{15}H_{18}N_2O_6$ $[M+H]^+$ 323.1200, found 323.1250; 40% *ee*, HPLC (Chiralpak OD-H column, *i*-PrOH-hexane 15/85, detector: 205 nm, 0.8 mL/min, t_r = 50.78 and 73.57 min).

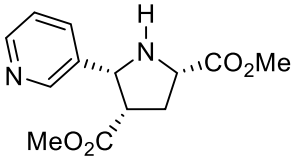
4.4.2.4. *(2S,4S,5R)*-4-(*tert*-Butyl) 2-methyl-5-(pyridin-3-yl) pyrrolidine-2,4-dicarboxylate



40

Compound **40** was synthesized by using AgOAc procedure. It was obtained in 82% yield as a light-yellow solid, mp: 173-175 ℃. IR (neat, cm^{-1}) 3286, 2972, 2952, 1744, 1703, 1427, 1148. ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.43-8.36 (m, 1H), 7.70-7.61 (m, 1H), 7.20-7.13 (m, 1H), 4.42 (d, J = 5.6 Hz, 1H), 3.93-3.83 (m, 1H), 3.71 (s, 3H), 3.24-3.17 (m, 1H), 2.96 (s, br, 1H), 2.38-2.21 (m, 2H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 171.2, 149.0, 148.6, 135.3, 134.9, 123.3, 81.2, 62.8, 59.7, 52.4, 49.9, 33.5, 27.5; HRMS calcd for $C_{16}H_{22}N_2O_4$ $[M+H]^+$ 307.1700, found 307.1662; racemic, HPLC (Chiralpak OD-H column, *i*-PrOH-hexane 15/85, detector: 205 nm, 0.8 mL/min, t_r = 17.94 and 20.59 min).

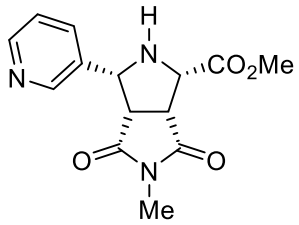
4.4.2.5. *(2S,4S,5R)*-Dimethyl 5-(pyridin-3-yl) pyrrolidine-2,4-dicarboxylate



41

Compound **41** was synthesized by using AgOAc procedure. It was obtained in 63% yield as a light-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 8.47-8.41 (m, 1H), 7.78-7.60 (m, 1H), 7.25-7.13 (m, 1H), 4.54 (d, J = 8.0 Hz, 1H), 3.96 (t, J = 8.2 Hz, 1H), 3.76 (s, 3H), 3.32 (q, J = 7.3 Hz, 1H), 3.20 (s, 3H), 3.09 (s, br, 1H), 2.39 (dd, J = 8.1, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 172.4, 148.8, 148.7, 135.2, 134.4, 123.2, 62.9, 59.7, 52.3, 51.4, 49.3, 32.8; racemic, HPLC (Chiralpak OD-H column, *i*-PrOH-hexane 15/85, detector: 205 nm, 0.8 mL/min, t_r = 37.31 and 43.39 min).

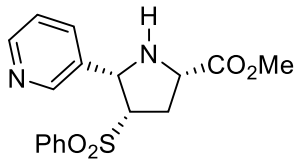
4.4.2.6. (*2S,3R,4S,5R)*-Methyl 5-methyl-4,6-dioxo-3-(pyridin-3-yl) octahydropyrrolo[3,4-c] pyrrole-1-carboxylate



44

Compound **44** was synthesized by using AgOAc procedure. It was obtained in 76% yield as white solid, mp: 183.8-185 ℃. R_f = 0.36, EtOAc/MeOH 5:1. IR (neat, cm^{-1}) 3224, 2953, 2850, 2161, 1771, 1745, 1700, 1430, 1216. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.51 (d, J = 4.9 Hz, 1H), 7.71-7.52 (m, 1H), 7.27-7.21 (m, 1H), 4.47 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 7.0 Hz, 1H), 3.83 (s, 3H), 3.56 (t, J = 7.3 Hz, 1H), 3.42 (t, J = 8.1 Hz, 1H), 2.83 (s, 3H), 2.47 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 174.5, 169.9, 149.6, 148.8, 134.8, 132.5, 123.2, 61.6, 61.5, 52.4, 49.1, 47.8, 25.1; HRMS calcd for $C_{14}H_{15}N_3O_4$ $[M+H]^+$ 290.1100, found 290.1143; racemic, HPLC (Chiralpak AS-H column, *i*-PrOH-hexane 50/50, detector: 205 nm, 1.0 mL/min, t_r = 9.73 and 20.43 min).

4.4.2.7. *(2S,4S,5S)*-Methyl 4-(phenylsulfonyl)-5-(pyridin-3-yl) pyrrolidine-2-carboxylate

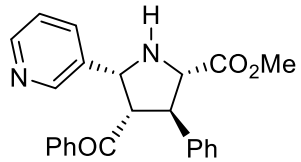


43

Compound **43** was synthesized by using AgOAc procedure. It was obtained in 40% yield as white solid, mp: 147.2-148.7 ℃. R_f = 0.46, EtOAc/MeOH 5:1. IR (neat, cm^{-1}) 3284, 2957, 2922, 2160, 2026, 1976, 1735, 1304, 1137. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50-8.44 (m, 1H), 8.44 (s, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.52-7.32 (m, 4H), 7.33-7.27 (m, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.17-4.05 (m, 1H), 4.00 (t, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.09-3.88 (s, br, 1H), 2.80-2.72 (m, 1H), 2.61-2.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 147.9, 146.9, 138.9, 133.6, 129.2, 127.7, 123.5, 100.0, 66.3, 61.5, 58.5, 52.7, 31.4.; HRMS calcd for $C_{17}H_{18}N_2O_4S$ $[M+H]^+$ 347.1100, found 347.1066; racemic, HPLC (Chiralpak OD-

H column, *i*-PrOH-hexane 15/85, detector: 205 nm, 0.8 mL/min, t_r = 31.69 and 47.84 min).

4.4.2.8. *(2R,3R,4S,5S)*-Methyl 4-benzoyl-3-phenyl-5-(pyridin-3-yl) pyrrolidine-2-carboxylate



42

Compound **42** was synthesized by using AgOAc procedure. It was obtained in 83% yield as white solid, mp: 179.8-182 ℃. R_f = 0.62, EtOAc/MeOH 5:1. IR (neat, cm^{-1}) 3319, 2955, 1736, 1670, 1430, 1211, 1172. $[\alpha]^{29}_D$ = +18.0 (*c* 0.01, $CHCI_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 7.59 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.53-7.42 (m, 2H), 7.45-7.05 (m, 9H), 7.07-6.99 (m, 1H), 4.95 (d, *J* = 8.7 Hz, 1H), 4.48 (t, *J* = 8.3 Hz, 1H), 4.14 (d, *J* = 9.0 Hz, 1H), 4.10-4.00 (m, 1H), 3.66 (s, 3H), 2.77 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 173.1, 148.8, 140.1, 137.0, 135.1, 135.1, 133.4, 128.9, 128.6, 128.0, 127.7, 127.3, 123.3, 67.4, 63.6, 60.0, 52.4, 52.2; HRMS calcd for $C_{24}H_{22}N_2O_3$ $[M+H]^+$ 387.1700, found 387.1714; 13% *ee*, HPLC (Chiralpak OD-H column, *i*-PrOH-hexane 15/85, detector: 205 nm, 0.8 mL/min, t_r = 36.44 and 47.09 min).

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APPENDICES

A. NMR Spectrum of Compounds

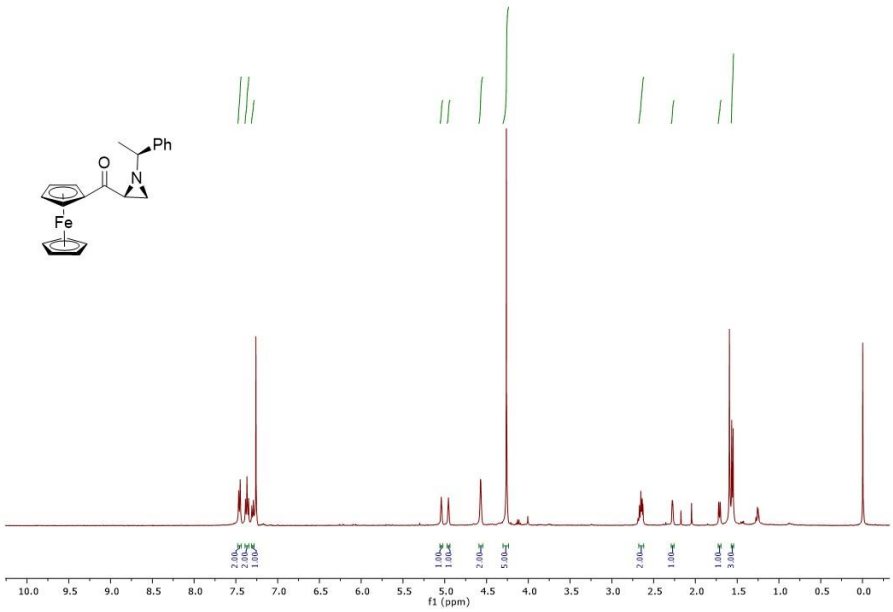


Figure A 1. ^{1}H-NMR Spectrum of Compound **34**

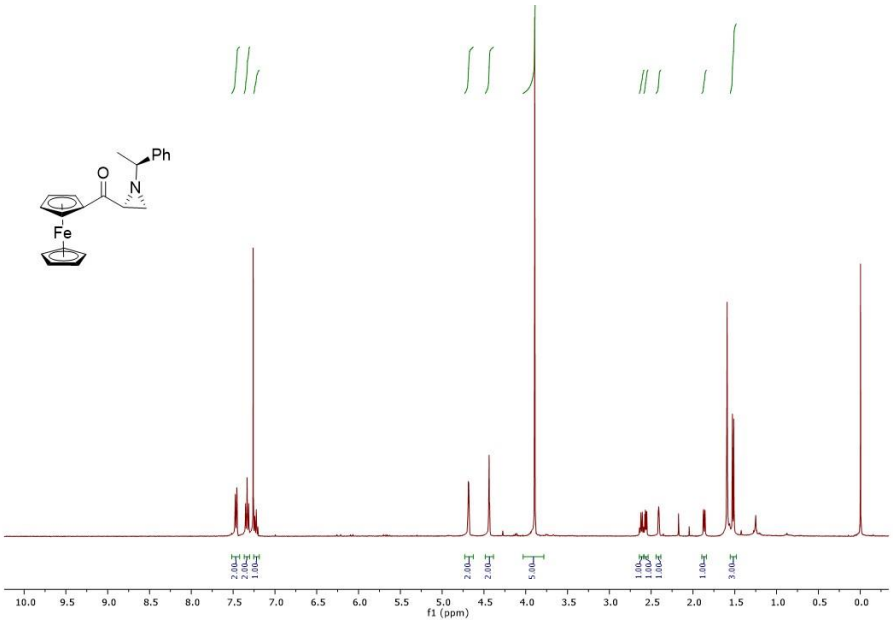


Figure A 2. [1]H-NMR Spectrum of Compound **35**

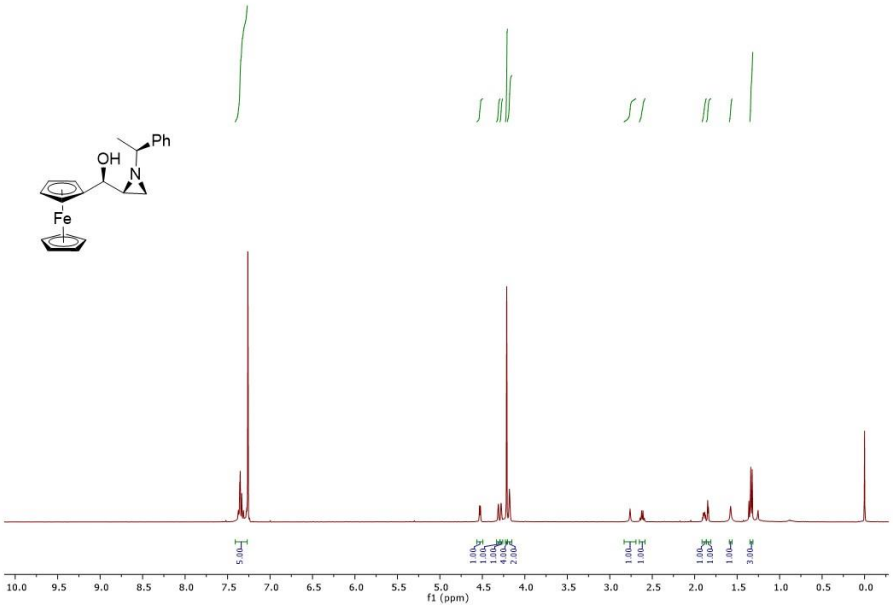


Figure A 3. [1]H-NMR Spectrum of Compound **36**

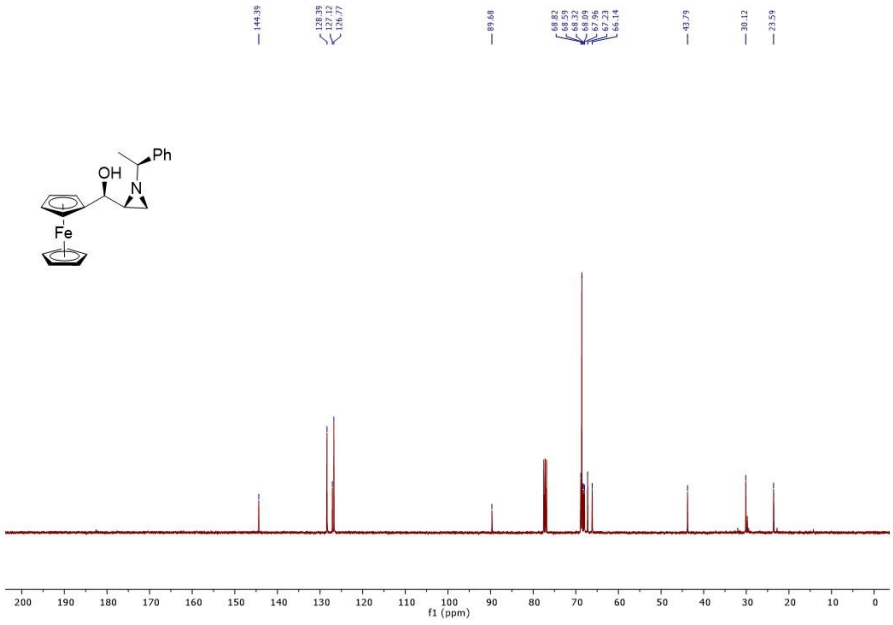


Figure A 4. ^{13}C-NMR Spectrum of Compound **36**

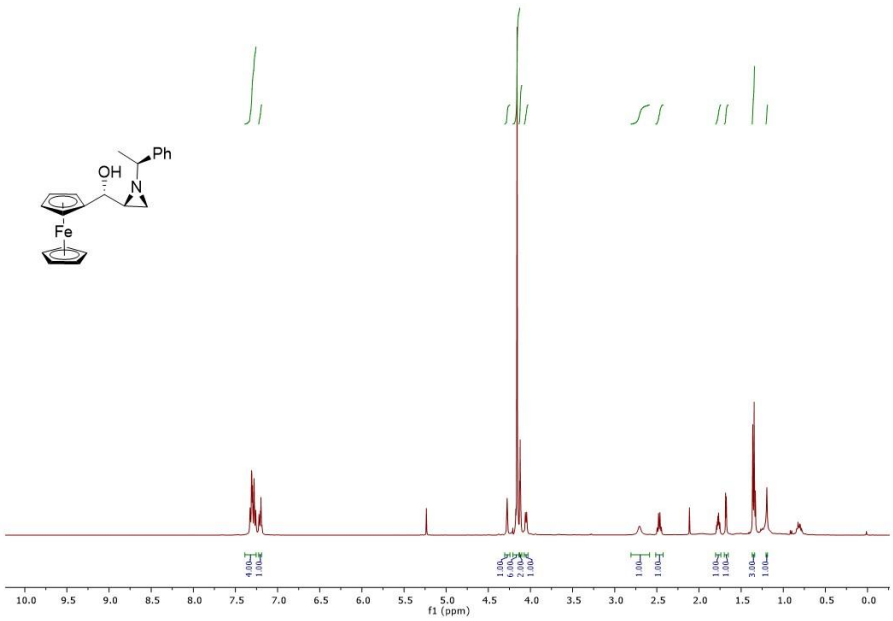


Figure A 5. ^{1}H-NMR Spectrum of Compound **37**

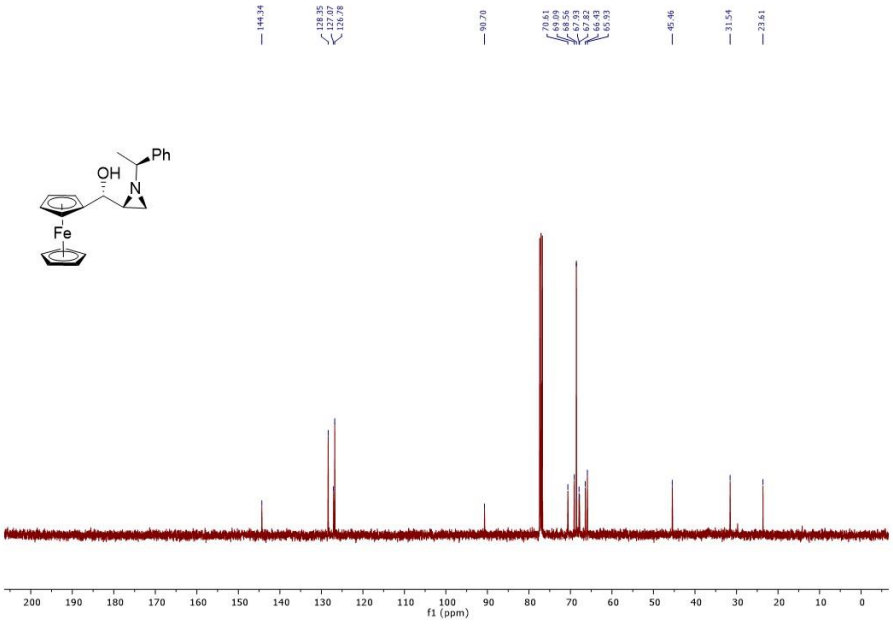


Figure A 6. ^{13}C-NMR Spectrum of Compound **37**

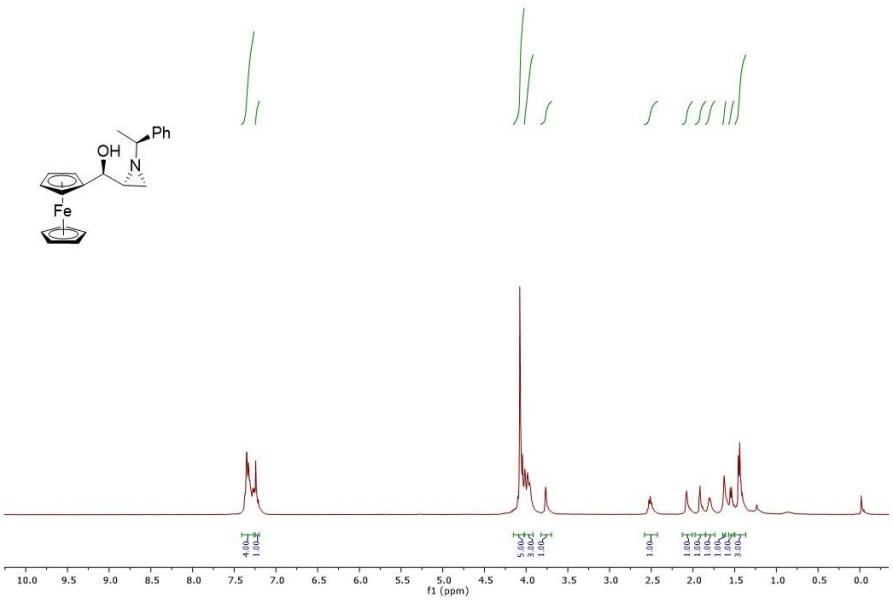


Figure A 7. ^{1}H-NMR Spectrum of Compound **38**

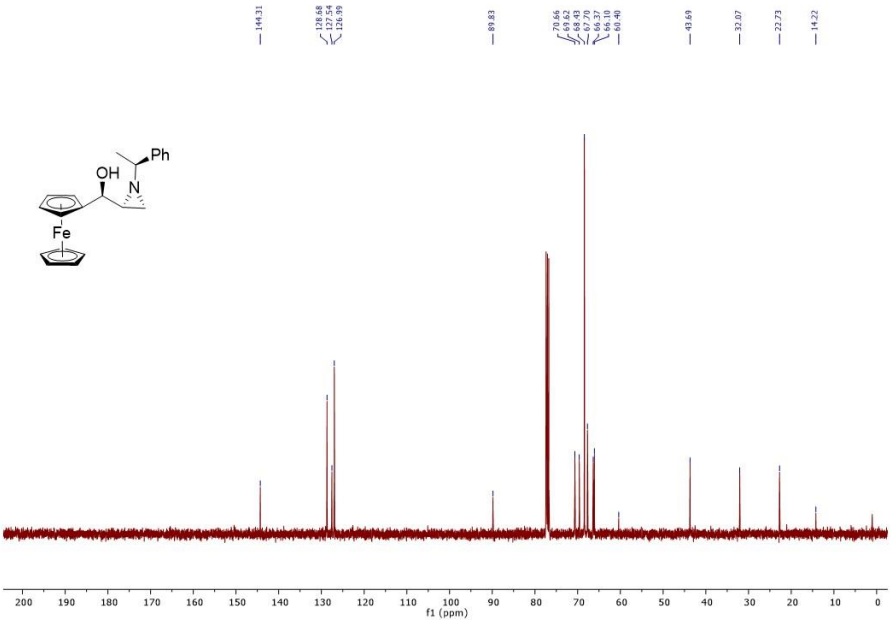


Figure A 8. ^{13}C-NMR Spectrum of Compound **38**

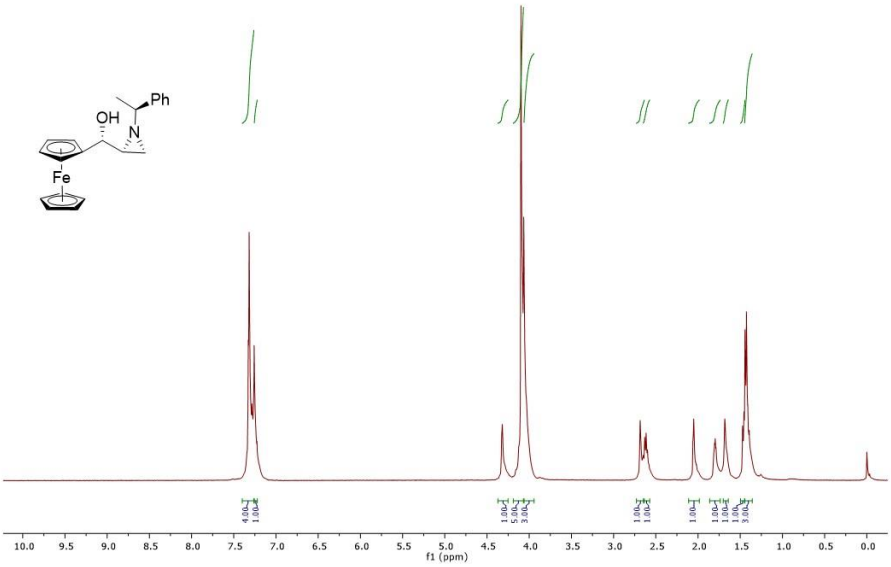


Figure A 9. ^{1}H-NMR Spectrum of Compound **39**

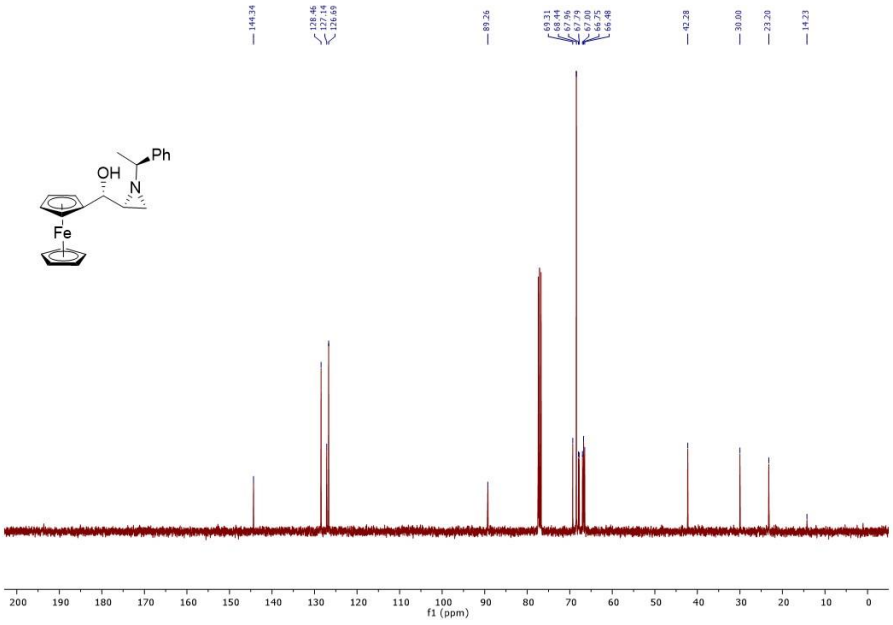


Figure A 10. ^{13}C-NMR Spectrum of Compound **39**

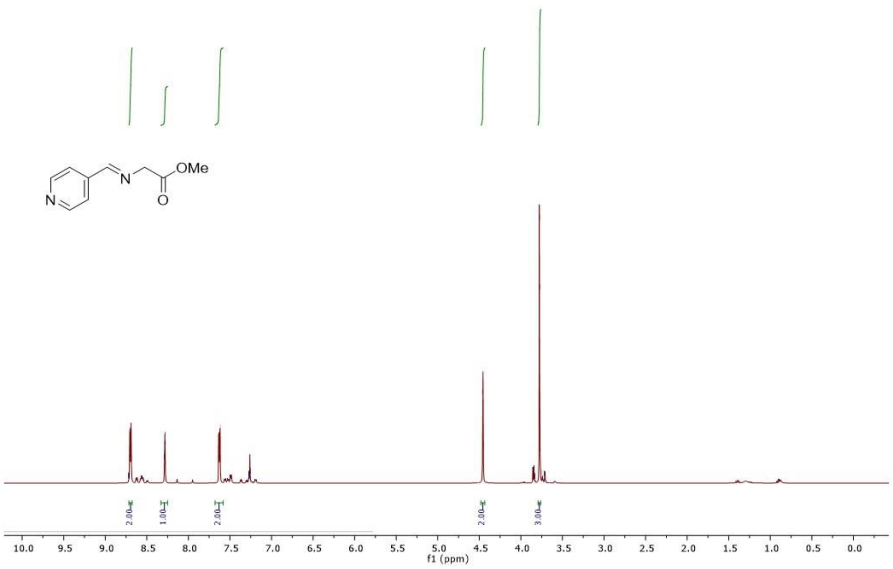


Figure A 11. ^{1}H-NMR Spectrum of Compound **14**

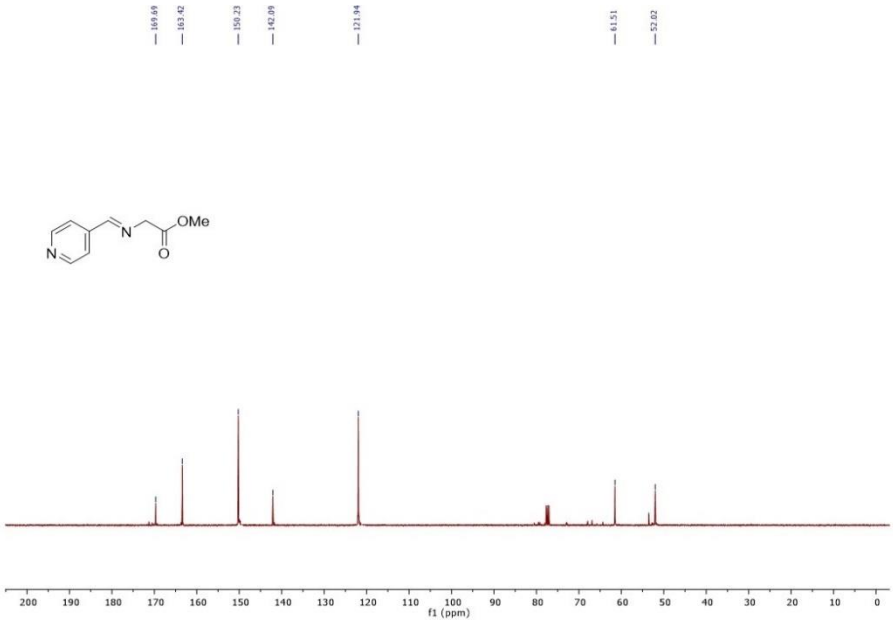


Figure A 12. ^{13}C-NMR Spectrum of Compound **14**

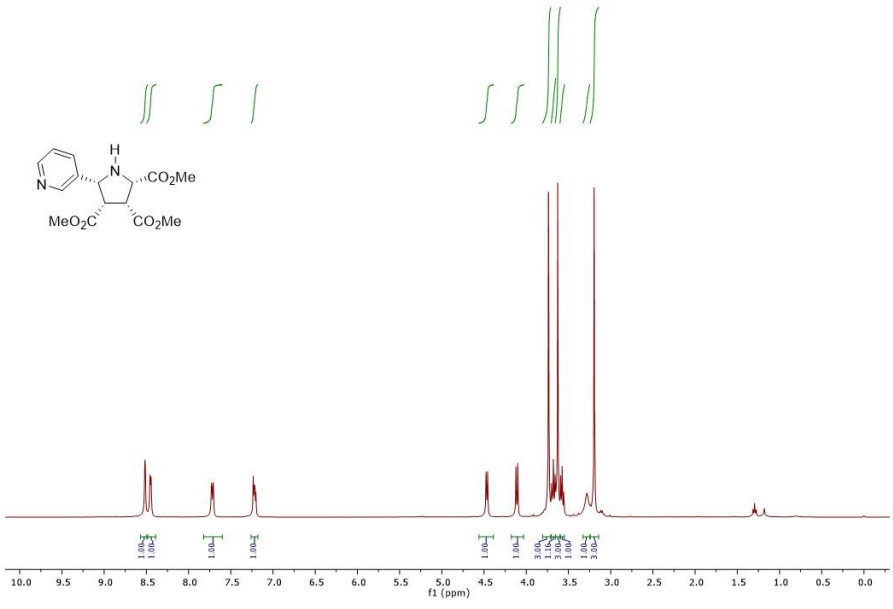


Figure A 13. ^{1}H-NMR Spectrum of Compound **16**

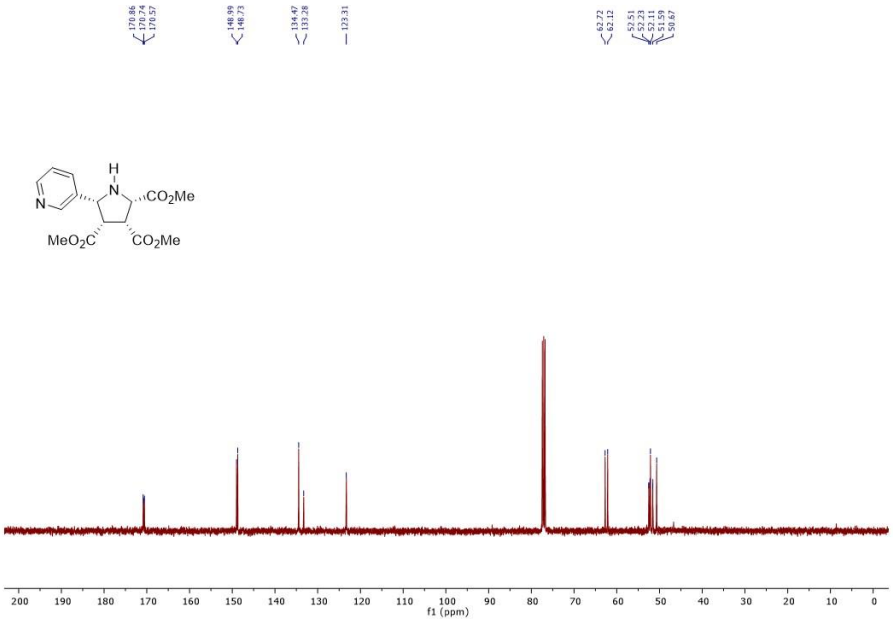


Figure A 14. ^{13}C-NMR Spectrum of Compound **16**

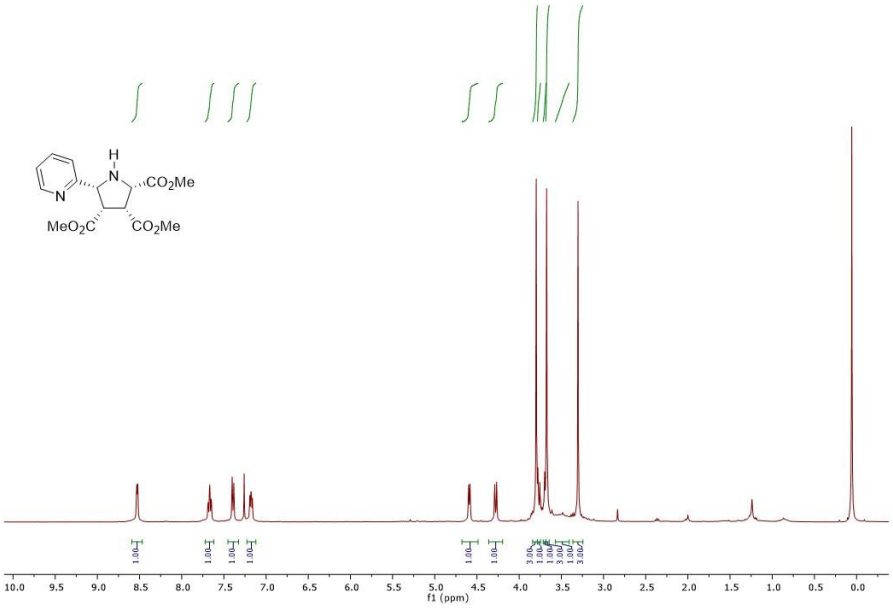


Figure A 15. ^{1}H-NMR Spectrum of Compound **46**

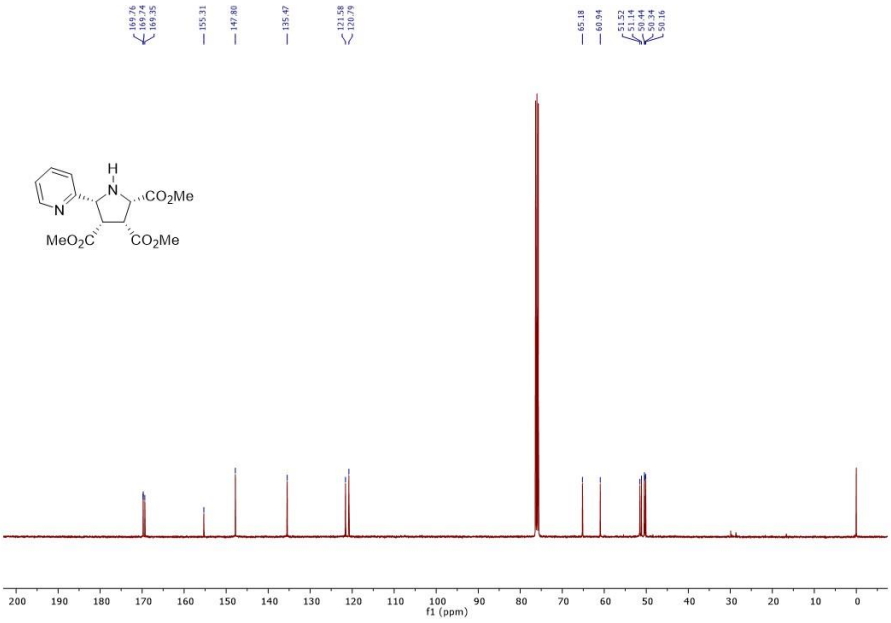


Figure A 16. ^{13}C-NMR Spectrum of Compound **46**

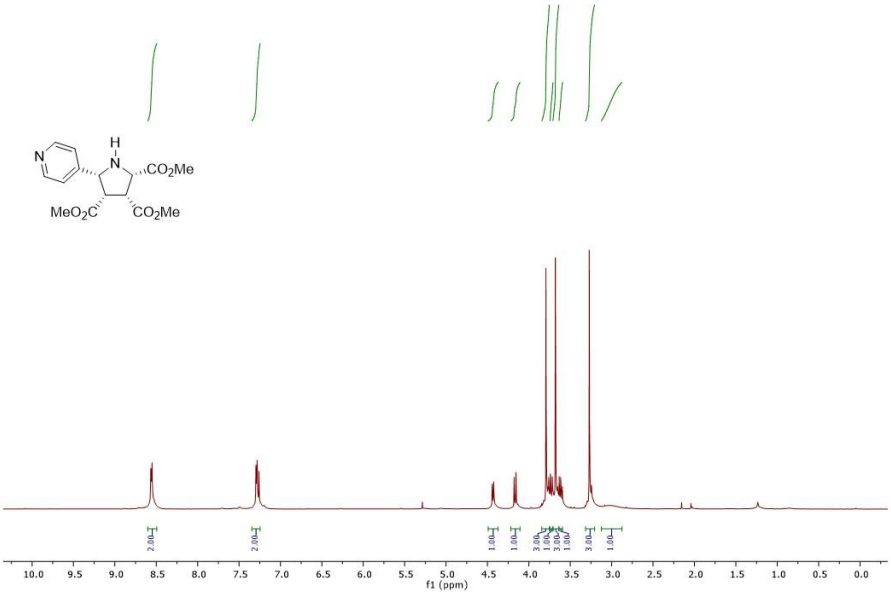


Figure A 17. ^{1}H-NMR Spectrum of Compound **48**

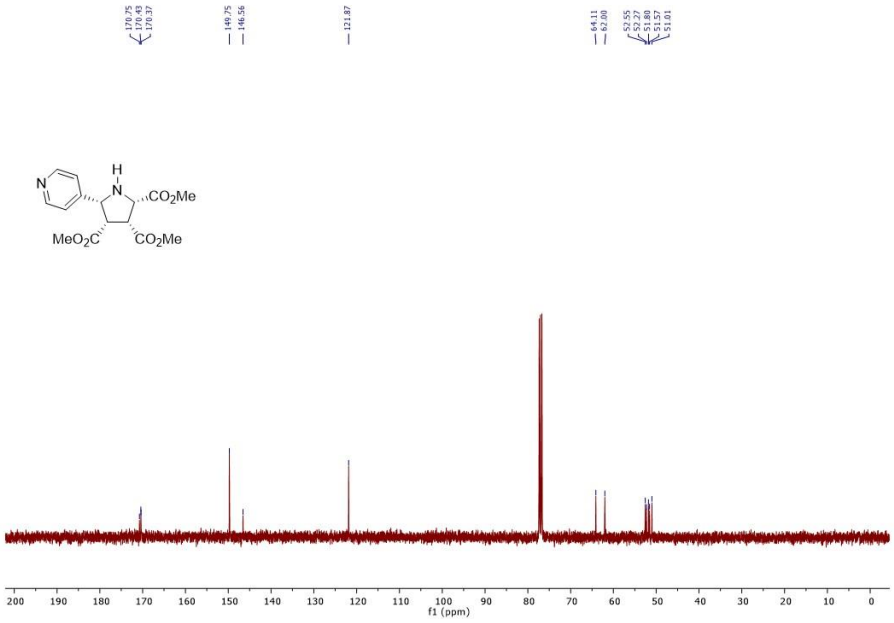


Figure A 18. ^{13}C-NMR Spectrum of Compound **48**

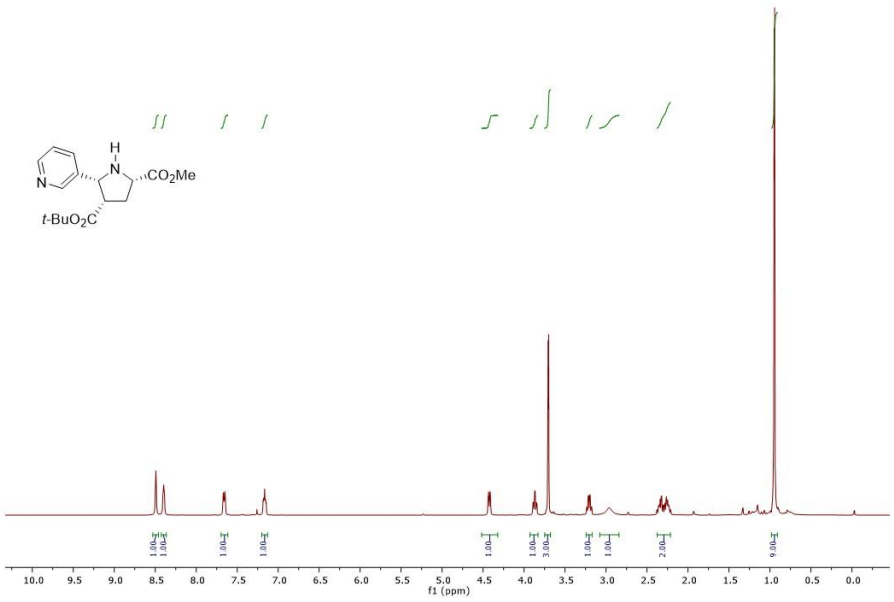


Figure A 19. ^{1}H-NMR Spectrum of Compound **40**

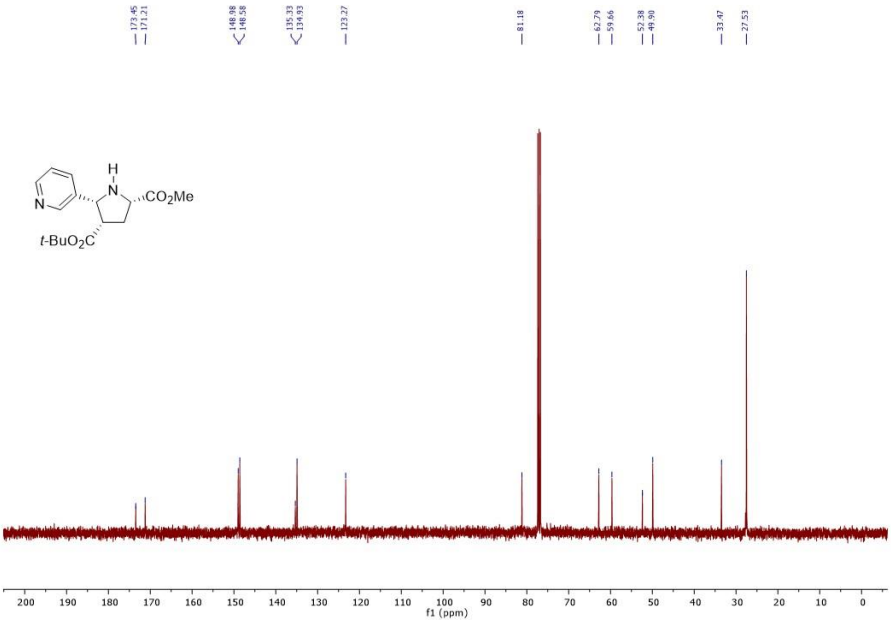


Figure A 20. ^{13}C-NMR Spectrum of Compound **40**

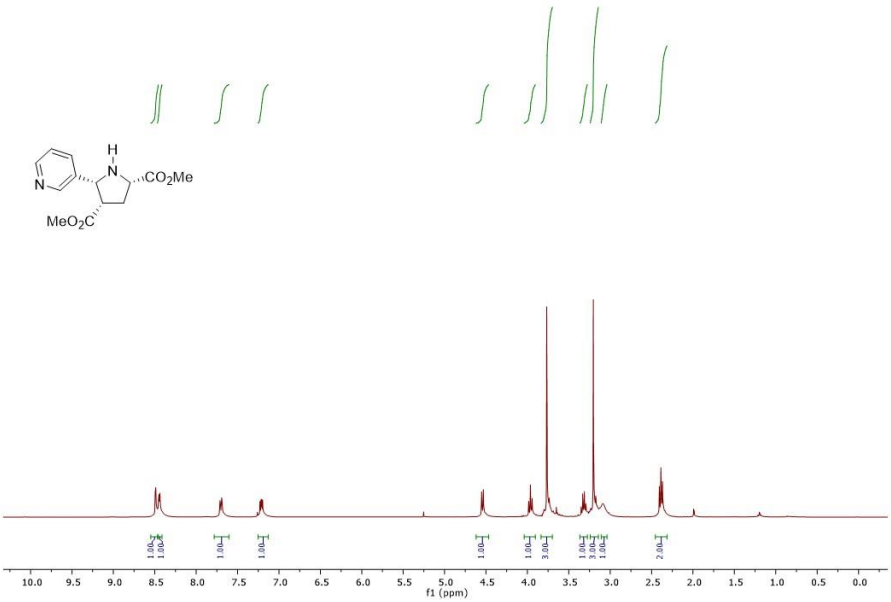


Figure A 21. ^{1}H-NMR Spectrum of Compound **41**

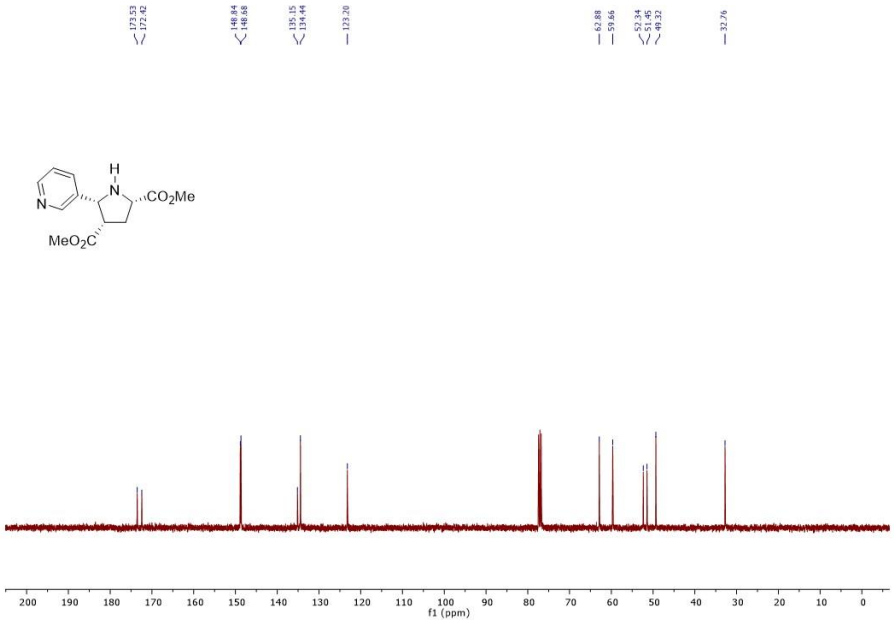


Figure A 22. ^{13}C-NMR Spectrum of Compound **41**

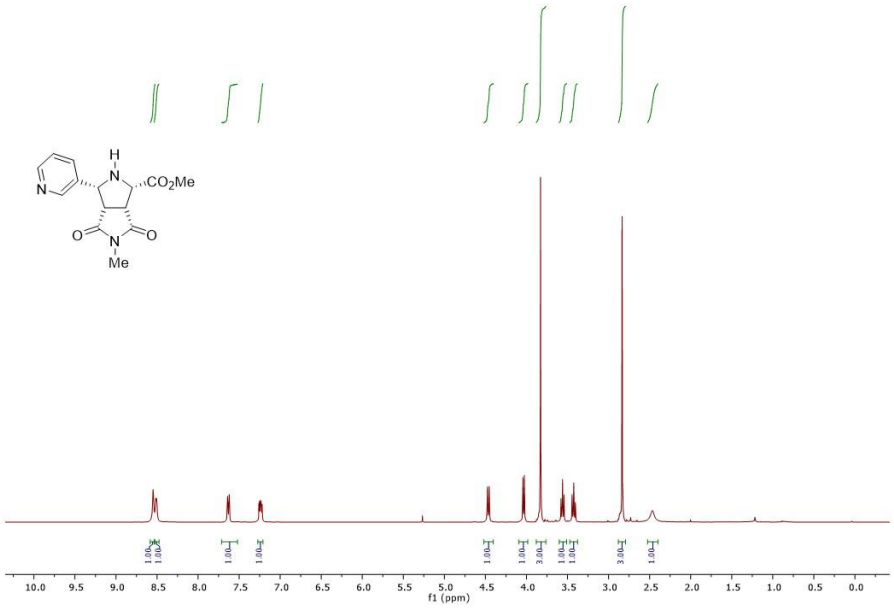


Figure A 23. ^{1}H-NMR Spectrum of Compound **44**

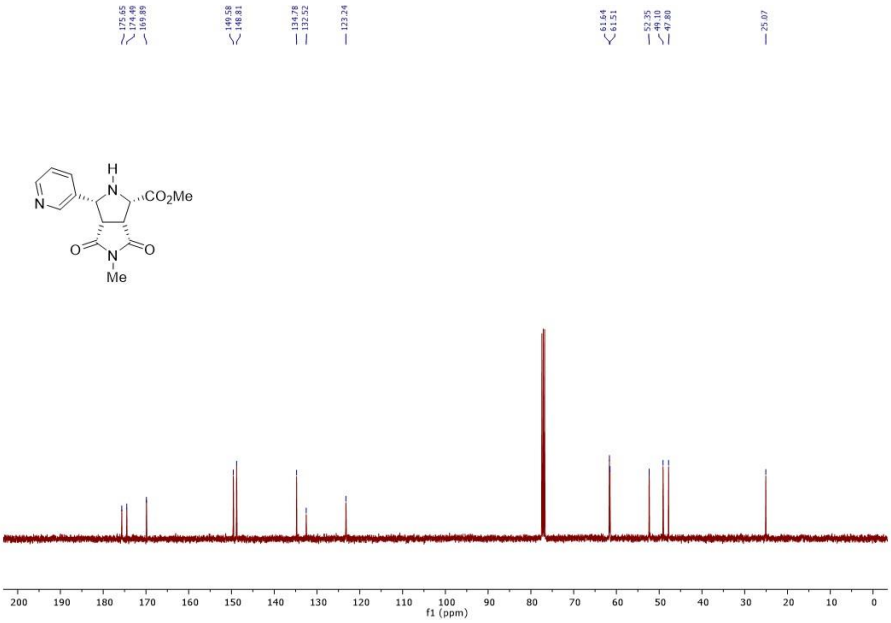


Figure A 24. ^{13}C-NMR Spectrum of Compound **44**

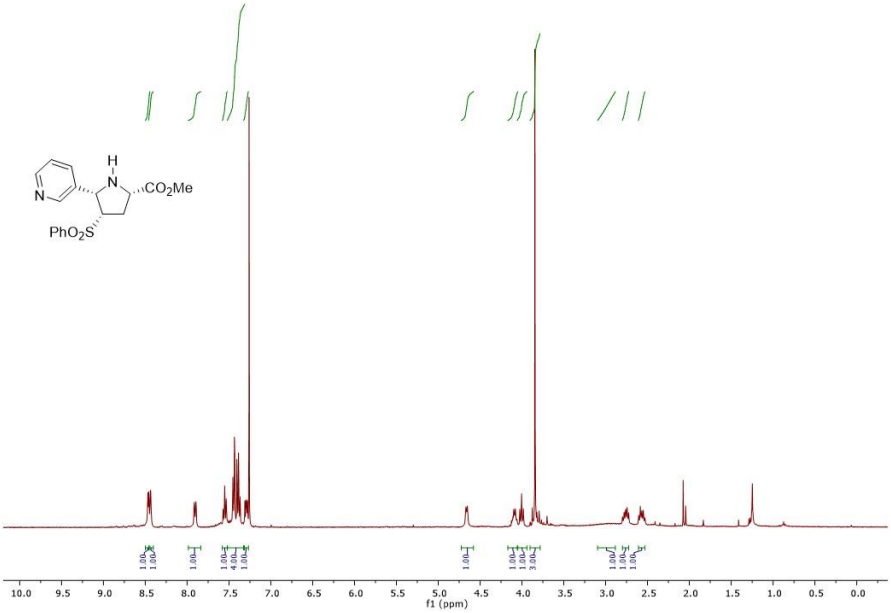


Figure A 25. ^{1}H-NMR Spectrum of Compound **43**

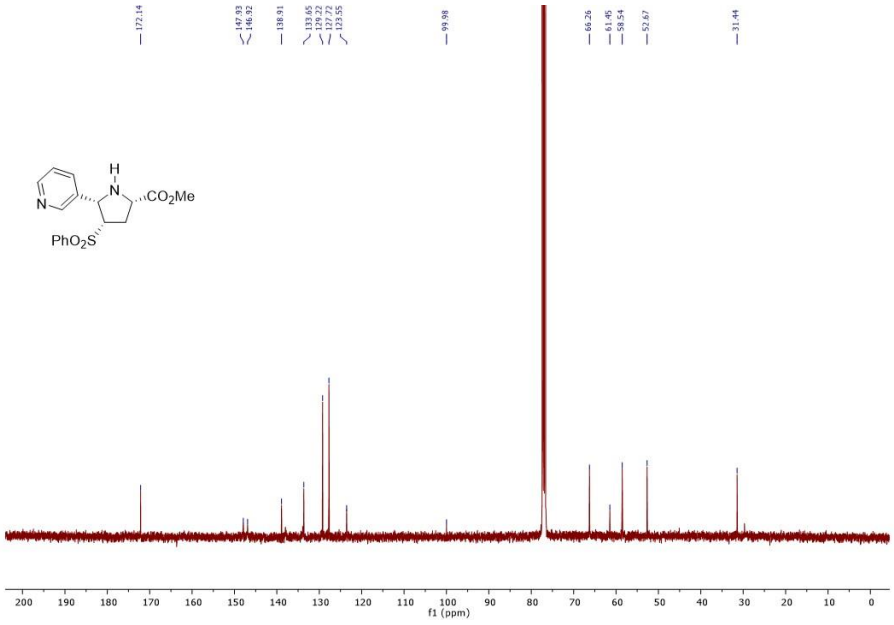


Figure A 26. ^{13}C-NMR Spectrum of Compound **43**

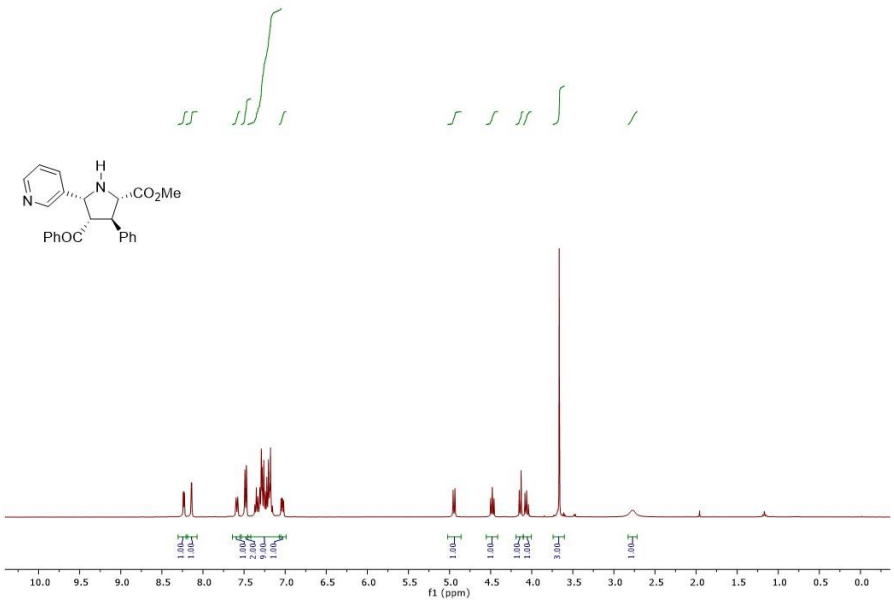


Figure A 27. ^{1}H-NMR Spectrum of Compound **42**

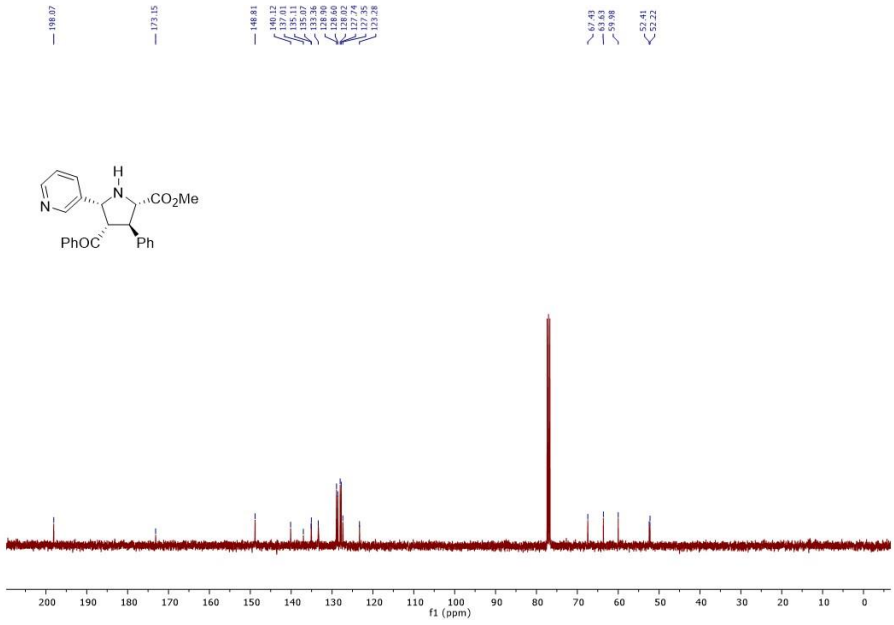
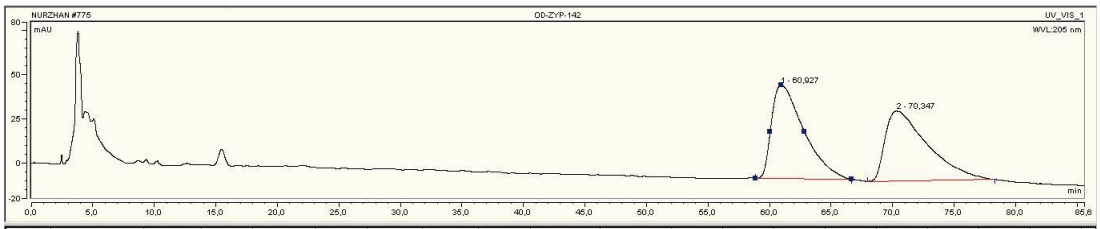
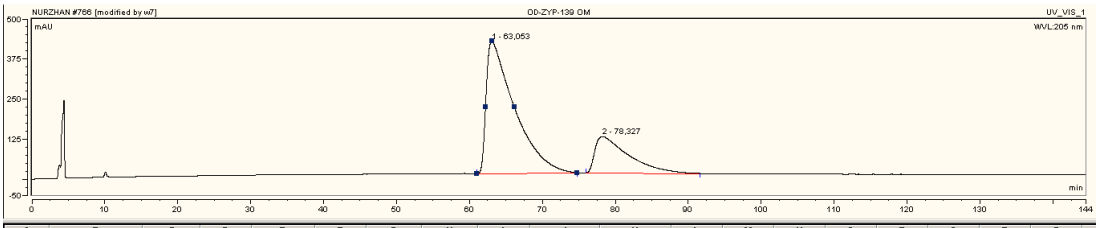


Figure A 28. ^{13}C-NMR Spectrum of Compound **42**

B. HPLC Spectra of Compounds

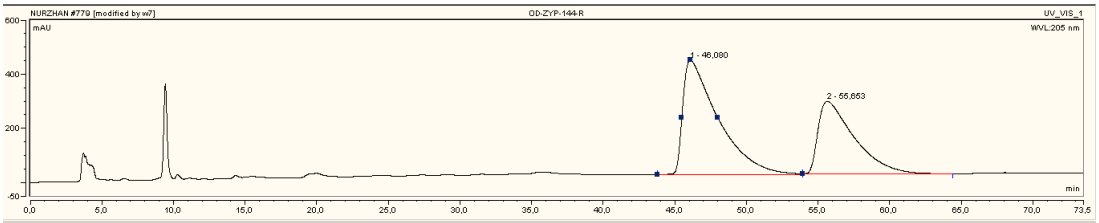


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	60,927	161,0441	n.a.	BMB	52,967	50,32	1,72
2	n.a.	70,347	158,9978	n.a.	BMB	39,606	49,68	n.a.
Total:			320,0419	0,0000		92,564	100,00	

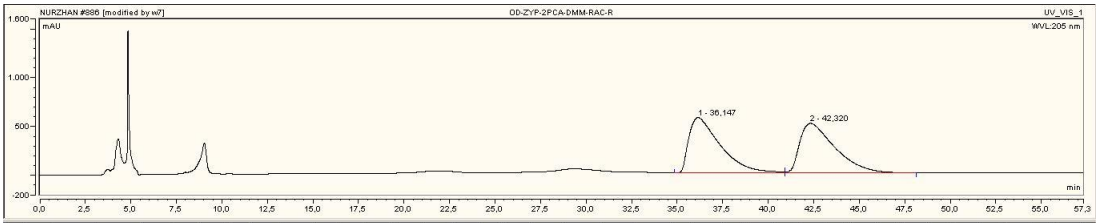


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	63,053	##########	n.a.	BMB*	411,662	75,19	2,07
2	n.a.	78,327	607,6266	n.a.	BMB*	113,385	24,81	n.a.
Total:			##########	0,0000		525,047	100,00	

Figure B 1. HPLC Spectrum of Compound **16**

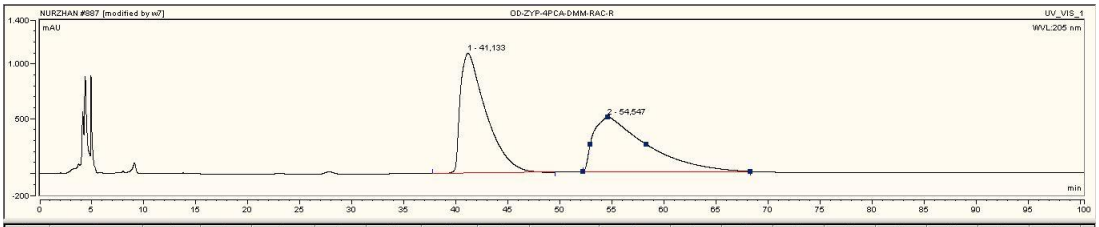


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	46,080	##########	n.a.	BM	422,877	50,39	2,21
2	n.a.	55,653	791,7743	n.a.	MB	269,705	39,61	n.a.
Total:			##########	0,0000		692,582	100,00	

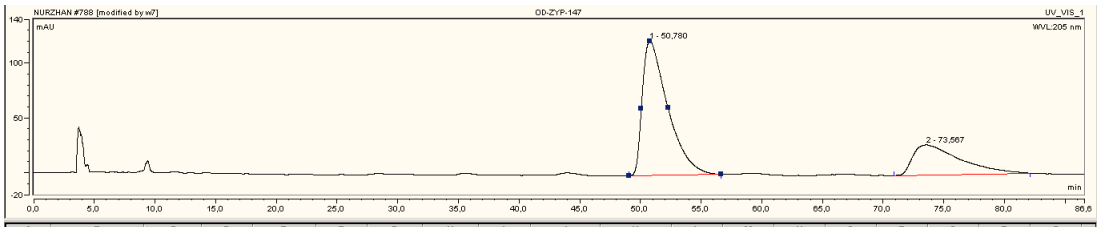


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	36,147	##########	n.a.	BM	567,450	50,13	1,89
2	n.a.	42,320	##########	n.a.	MB	507,039	49,87	n.a.
Total:			##########	0,0000		1074,489	100,00	

Figure B 2. HPLC Spectrum of Compound **46**

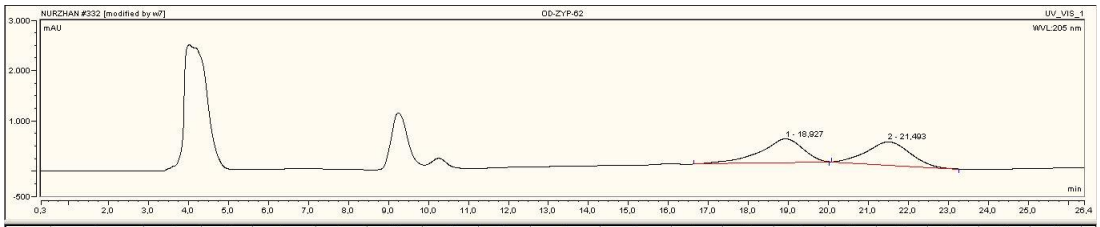


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	41,133	##########	n.a.	BMB*	1094,766	51,39	1,98
2	n.a.	54,547	##########	n.a.	BMB*	498,717	48,61	n.a.
Total:			##########	0,0000		1593,483	100,00	

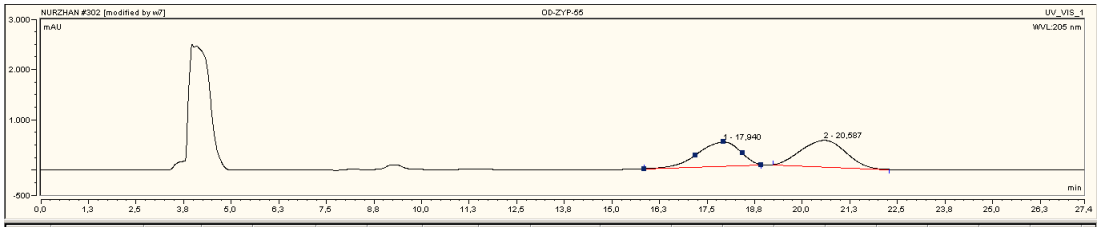


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	50,780	297,0097	n.a.	BMB	122,363	70,52	4,31
2	n.a.	73,567	124,1837	n.a.	BMB	27,689	29,48	n.a.
Total:			421,1934	0,0000		150,052	100,00	

Figure B 3. HPLC Spectrum of Compound **48**

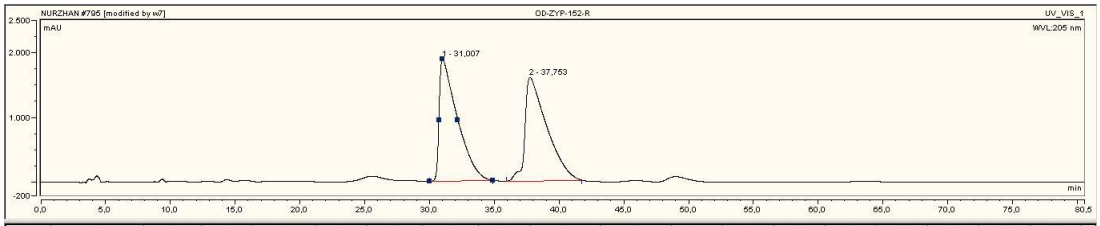


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	18,927	560,4405	n.a.	BMB*	470,214	50,26	1,35
2	n.a.	21,493	574,4851	n.a.	BMB*	459,680	49,74	n.a.
Total:			##########	0,0000		929,894	100,00	

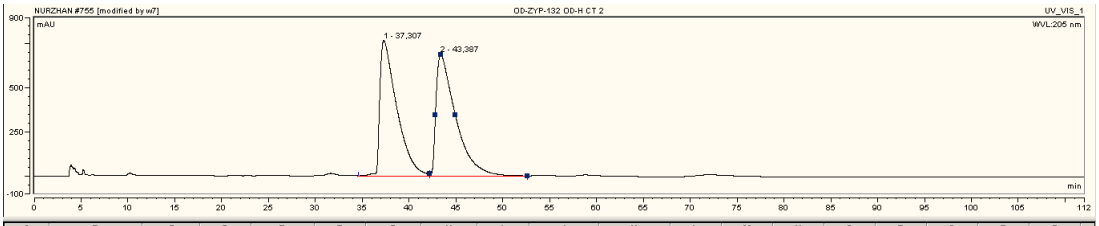


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	17,940	608,9010	n.a.	BMB*	477,132	46,03	1,22
2	n.a.	20,587	713,7994	n.a.	BMB*	527,751	53,97	n.a.
Total:			##########	0,0000		1004,883	100,00	

Figure B 4. HPLC Spectrum of Compound **40**

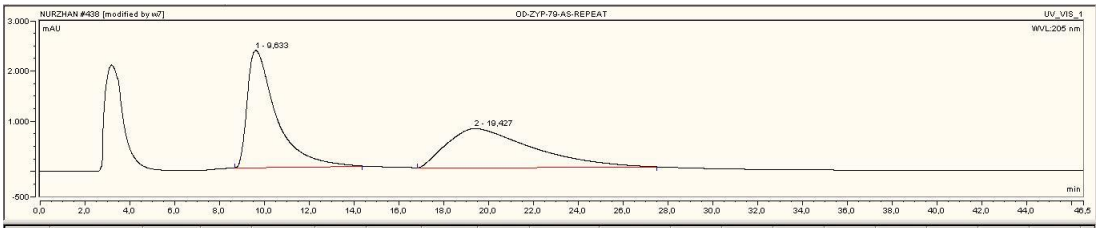


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	31,007	##########	n.a.	BMB*	1882,644	49,55	2,47
2	n.a.	37,753	##########	n.a.	BMB*	1592,816	50,45	n.a.
Total:			##########	0,0000		3475,459	100,00	

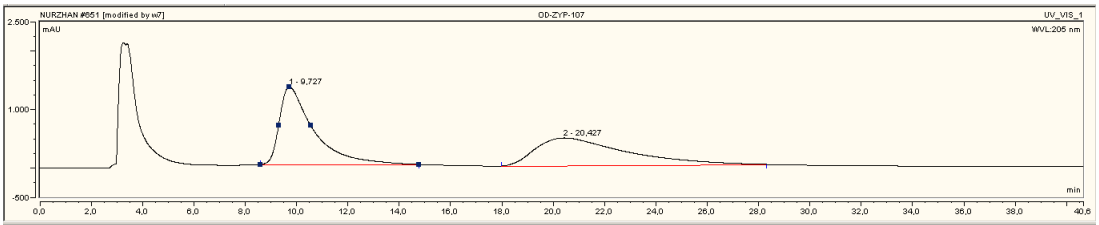


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	37,307	##########	n.a.	BM *	768,478	49,03	1,79
2	n.a.	43,387	##########	n.a.	MB*	688,014	50,97	n.a.
Total:			##########	0,0000		1456,492	100,00	

Figure B 5. HPLC Spectrum of Compound **41**

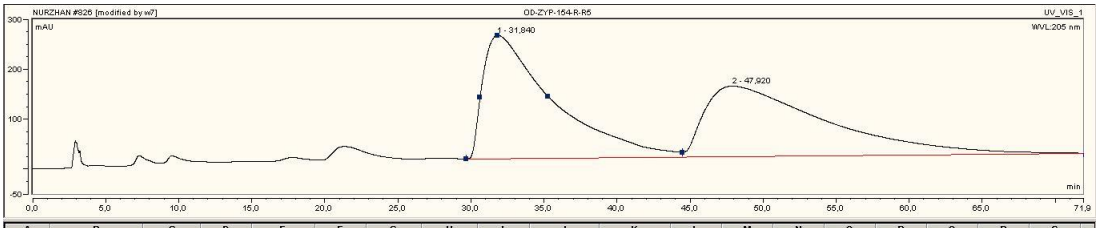


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	9,633	##########	n.a.	BMB*	2329,821	50,36	2,18
2	n.a.	19,427	##########	n.a.	BMB*	776,281	49,64	n.a.
Total:			##########	0,0000		3106,102	100,00	

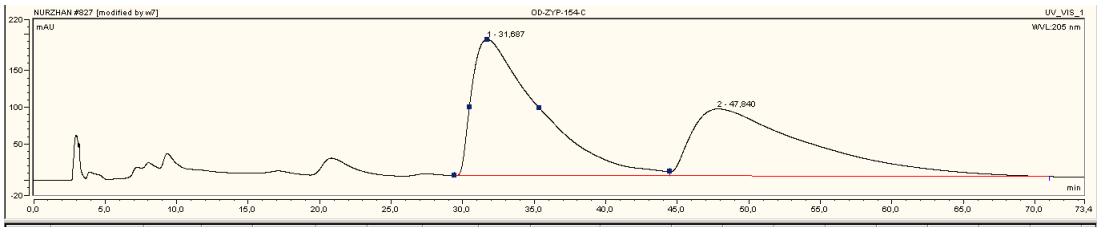


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	9,727	##########	n.a.	BMB*	1323,665	51,46	2,58
2	n.a.	20,427	##########	n.a.	BMB*	474,017	48,54	n.a.
Total:			##########	0,0000		1797,682	100,00	

Figure B 6. HPLC Spectrum of Compound **44**

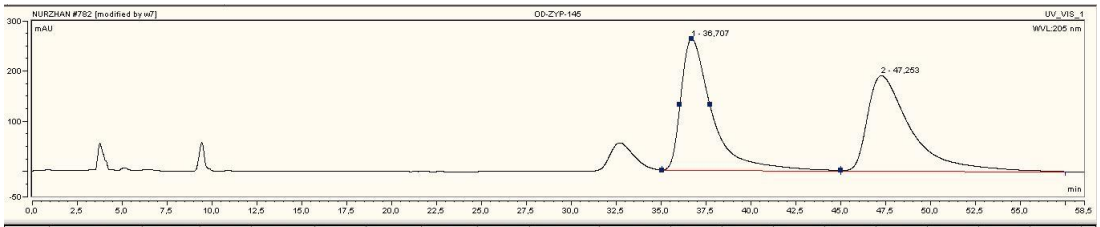


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	31,840	##########	n.a.	BM	246,999	50,50	1,44
2	n.a.	47,920	##########	n.a.	MB	140,896	49,50	n.a.
Total:			##########	0,0000		387,895	100,00	

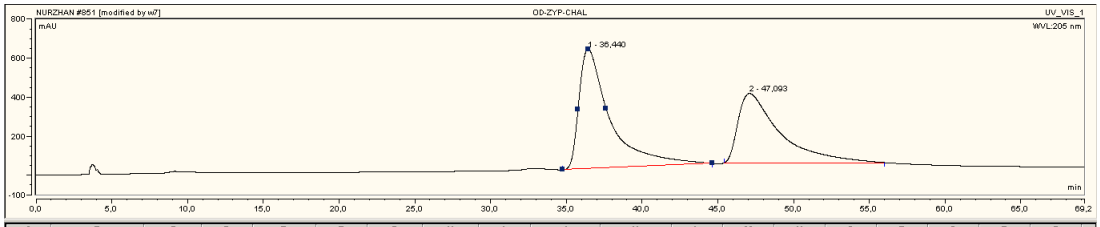


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	31,687	##########	n.a.	BM *	186,053	54,05	1,44
2	n.a.	47,840	670,4091	n.a.	MB*	91,629	45,95	n.a.
Total:			##########	0,0000		277,682	100,00	

Figure B 7. HPLC Spectrum of Compound **43**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	36,707	525,1284	n.a.	BM *	261,901	49,85	3,13
2	n.a.	47,253	528,3028	n.a.	MB*	190,009	50,15	n.a.
Total:			##########	0,0000		451,910	100,00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	36,440	##########	n.a.	BMB*	612,144	56,35	2,84
2	n.a.	47,093	##########	n.a.	BMB*	355,530	43,65	n.a.
Total:			##########	0,0000		967,674	100,00	

Figure B 8. HPLC Spectrum of Compound **42**