

ENANTIOSELECTIVE SYNTHESIS OF FURYL-SUBSTITUTED
PYRROLIDINES

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PYRROLIDINES**

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ABSTRACT

ENANTIOSELECTIVE SYNTHESIS OF FURYL-SUBSTITUTED PYRROLIDINES

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Asymmetric 1,3-Dipolar Cycloaddition (DC) reactions of azomethine ylides are important for the synthesis of pyrrolidines. These reactions may give enantiomerically pure compounds in the presence of a chiral catalyst in a single step. Therefore, many groups have studied this reaction to synthesize aryl-substituted pyrrolidines in enantiomerically rich form. Although the aryl-substituted pyrrolidine synthesis is very common, the studies involving the heteroaryl-substituted pyrrolidines are quite rare. In general, groups studying these reactions mainly focus on the aryl-substituted pyrrolidines and include one or two examples involving the heteroaryl-substituted pyrrolidines. Therefore, it is important to synthesize different derivatives of heteroaryl-substituted pyrrolidines and develop a chiral catalyst that produces these compounds in high yields and enantioselectivities. Our group is also involved in this field and developed two different types of chiral ligands, one is known as ferrocenyl aziridinyl methanol (**FAM**) and the other one is the phosphorous derivative of these ligands. Using both ligands, our group reported the enantioselective synthesis of aryl-substituted pyrrolidines in good yields and enantioselectivities. In this thesis, we have applied our **FAM** ligands (four diastereomers) and a new derivative, namely 1-naphthyl ferrocenyl aziridinyl methanol (**1-NFAM**, also four diastereomers), in the enantioselective synthesis of furyl-substituted pyrrolidines by using 1,3-DC reaction

of azomethine ylides. Our studies showed that **FAM** ligands can catalyze the 1,3-DC reaction of azomethine ylides to form furyl-substituted pyrrolidines in up to 87% yield and 72% enantioselectivity.

Keywords: Asymmetric synthesis, Azomethine ylides, Furyl-substituted pyrrolidine derivatives.

ÖZ

FURİL SÜBSTİTÜYE PİROLİDİN TÜREVLERİNİN ENANTİOSEÇİCİ SENTEZİ

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Asimetrik 1,3-dipolar halkasal katılma tepkimeleri pirolidin sentezi için önemli tepkimelerdir. Bu tepkimeler kiral katalizör varlığında tek basamakta enantiomerik saf bileşikler verirler. Bu sebeple birçok grup bu tepkimeleri enantiomerik bakımdan zengin aril sübstitüye pirolidin sentezlemek için çalışmıştır. Aril sübstitüye pirolidin sentezi yaygın olmasına rağmen heteroaril sübstitüye pirolidin içeren çalışmalar oldukça azdır. Genelde bu tepkimeleri çalışan gruplar esas olarak aril sübstitüye pirolidinlere odaklanmışlardır ve bu çalışmalarda heteroaril sübstitüye pirolidinlerin yalnızca bir veya iki örneği bulunmaktadır. Bu sebeple heteroaril sübstitüye pirolidinlerin farklı çeşitlerinin sentezlenmesi ve bu bileşiklerin yüksek verimde ve enantioseçicilikte sentezlenmesinde kullanılan kiral katalizörlerin geliştirilmesi önemlidir. Grubumuz da bu alanda çalışmış olup iki farklı kiral ligand geliştirmiştir. Bu kiral ligandlar ferosenil aziridinil metanol (**FAM**) ligandları ve bu ligandların fosforlu türevleridir. Bu ligandları kullanarak grubumuz verimi ve enantioseçiciliği iyi olan aril sübstitüye pirolidinlerin enantioseçici sentezini rapor etmiştir. Bu çalışma kapsamında furil sübstitüye azometin ylidlerin 1,3-dipolar halkasal katılma tepkimeleri metal ile koordine olan ve grubumuz tarafından sentezlenen ferosenil aziridinil metanol (**FAM**) olarak adlandırılan ve dört diastereomeri bulunan ligandlar ve bu ligandların türevleri olan ve 1- naftil ferosenil aziridinil metanol (**1-NFAM**)

olarak adlandırılan yine dört diastereomeri olan ligandlar varlığında gerçekleştirilmiştir. Çalışmamızdaki analiz sonuçlarına göre **FAM** ligandları kullanılarak yapılan asimetric 1,3-dipolar halkasal katılma tepkimeleri ile %87 verime ve %72 enantioseçiciliğe kadar ulaşan furil süstitüye pirolidin yapıları elde edilmiştir.

Anahtar Kelimeler: Asimetric sentez, Azometin yilidler, Furil süstitüye pirolidin türevleri.

To My Family

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LIST OF ABBREVIATIONS

ABBREVIATIONS

PFAM: Phenyl Substituted Ferrocenyl Aziridinyl Methanol

CFAM: Cyclohexyl Substituted Ferrocenyl Aziridinyl Methanol

1-NFAM: 1-Naphthyl Substituted Ferrocenyl Aziridinyl Methanol

DCE: 1,2-Dichloroethane

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

TLC: Thin Layer Chromatography

HPLC: High Performance Liquid Chromatography

R_f: Retention Factor (TLC)

t_r: Retention Time (HPLC)

ee: Enantiomeric Excess

CHAPTER 1

INTRODUCTION

1.1. Enantiomerically pure compounds

Chirality is an important property of asymmetry based on molecular symmetry. When the molecule and its mirror image are non-superposable, it is called as a chiral molecule. This property of molecule is important in many areas such as biochemistry, organic chemistry and especially pharmaceutical chemistry because our biological molecules are chiral molecules such as DNA, amino acids and sugars. Also, these mirror images are called enantiomers (Figure 1). They have same physical and chemical properties such as boiling or melting point, polarity, density etc. However, their odour, flavour and most importantly their biological activities can be different.

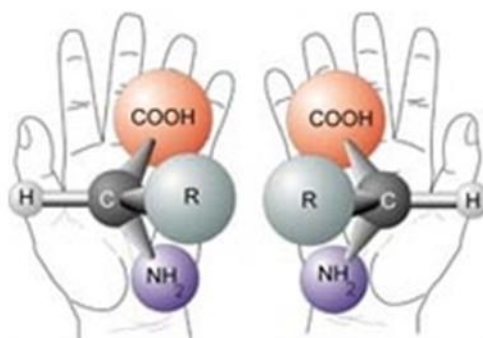


Figure 1. Enantiomers

The artificial sweetener aspartame has two enantiomers. Whereas D-aspartame is tasteless, taste of L-aspartame is sweet.¹ In addition, *R*-(-)-carvone smells like spearmint while *S*-(-)-carvone smells like caraway.² When chiral molecules are used

as drugs, they may behave differently. For example, for treatment of rheumatoid arthritis, *D*-penicillamine is used in chelation therapy while *L*-penicillamine is toxic because of its inhibition of action of pyridoxine, an essential B vitamin.³ Therefore, synthesis of enantiopure compounds is important.

Enantiomerically pure compounds can be synthesized using different methods. Those include along with resolution of racemates, the synthetic transformation from enantiopure starting compound and the stereoselective reactions using chiral reagents or auxiliaries,⁴ metal catalysts, organocatalysts and biocatalysts. Recently, the most commonly used methods are metal catalyst (metal-chiral ligand) and organocatalysts. Use of chiral catalyst is preferable because small amount of a chiral catalyst can produce a large amount of enantiopure product.

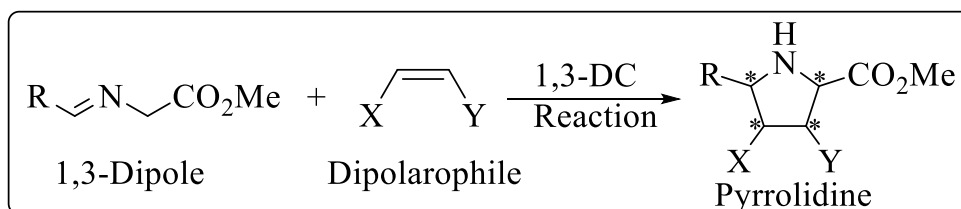
1.2. Asymmetric Cycloaddition Chemistry

As well as cyclic organic compounds, heterocyclic compounds are important in organic chemistry. Heteroatom in the ring gives these heterocyclic compounds physical and chemical properties different from that of all-carbon-ring analogs. They are found in numerous natural products and biochemical systems such as nucleic acids which carry the genetic information. Also, pigments, vitamins and antibiotics are examples of heterocycles like hallucinogens. These heterocyclic compounds can be used as drugs, pesticides, dyes and plastics.⁵ In addition, they may show different biological activities. Therefore, especially five-membered *N*-heterocycles are very important for scientist. The cycloaddition reaction is one of the common and efficient method for synthesizing heterocycles in high stereoselectivity in a single step.

1.2.1. 1,3-Dipolar Cycloaddition (1,3-DC) Reactions

1,3-Dipolar Cycloaddition (1,3-DC) reaction of azomethine ylides like Diels-Alder reaction is the most efficient method to construct five-membered *N*-heterocyclic compounds. This reaction is a highly atom economical process because two new carbon-carbon bonds and up to four stereogenic centers can be formed at the same time.⁶ In this type of reaction, 1,3-dipole also known as ylide, 4π electron component,

reacts with a dipolarophile, 2π electron component. In scheme 1, pyrrolidine formation by 1,3-DC reaction of an azomethine ylide with a dipolarophile is given as an example.



Scheme 1. Pyrrolidine formation by 1,3-DC reaction

1.2.1.1. 1,3-Dipoles or Ylides

General representation of 1,3-dipoles is ‘a-b-c’ structure (Figure 2). They have a delocalized electron over three atoms and a positive charge. Also, Pichon and co-workers stated that 1,3-dipoles should include 3 atoms with at least one heteroatom.⁷ There are two main groups of 1,3-dipole which are allyl-anion type and propargyl/allenyl-anion type.

The allyl-anion type of 1,3-dipole has a bent structure. It has four electrons in three parallel p_z orbitals which are perpendicular to plane of the dipole. The central atom ‘b’ can be oxygen, nitrogen or sulphur. Two resonance forms are obtained in octet structure. In these structures, three centers have an electron octet. Also, other two resonance forms in which ‘a’ or ‘c’ atom has an electron sextet can be obtained (Figure 2 and 3).⁸

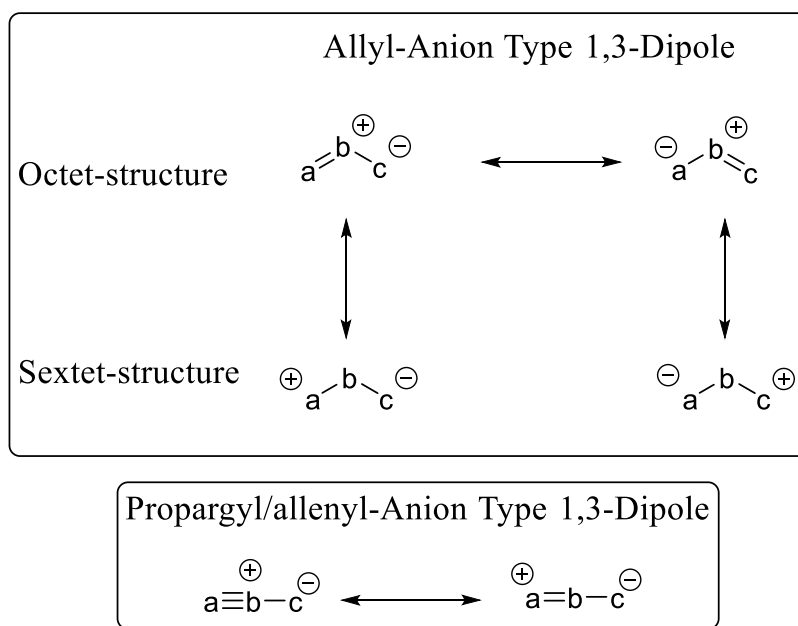


Figure 2. The resonance structures of 1,3-dipoles

On the other hand, the propargyl/allenyl-anion type of 1,3-dipole has a linear structure. Unlike allyl-anion type of 1,3-dipole, in this type the central atom 'b' can be just nitrogen. In addition, the former orbital is not directly involved in the resonance structures because this type has an extra π electron located in the plane orthogonal to the allenyl anion type molecular orbital (MO) (Figures 2 and 4).⁸

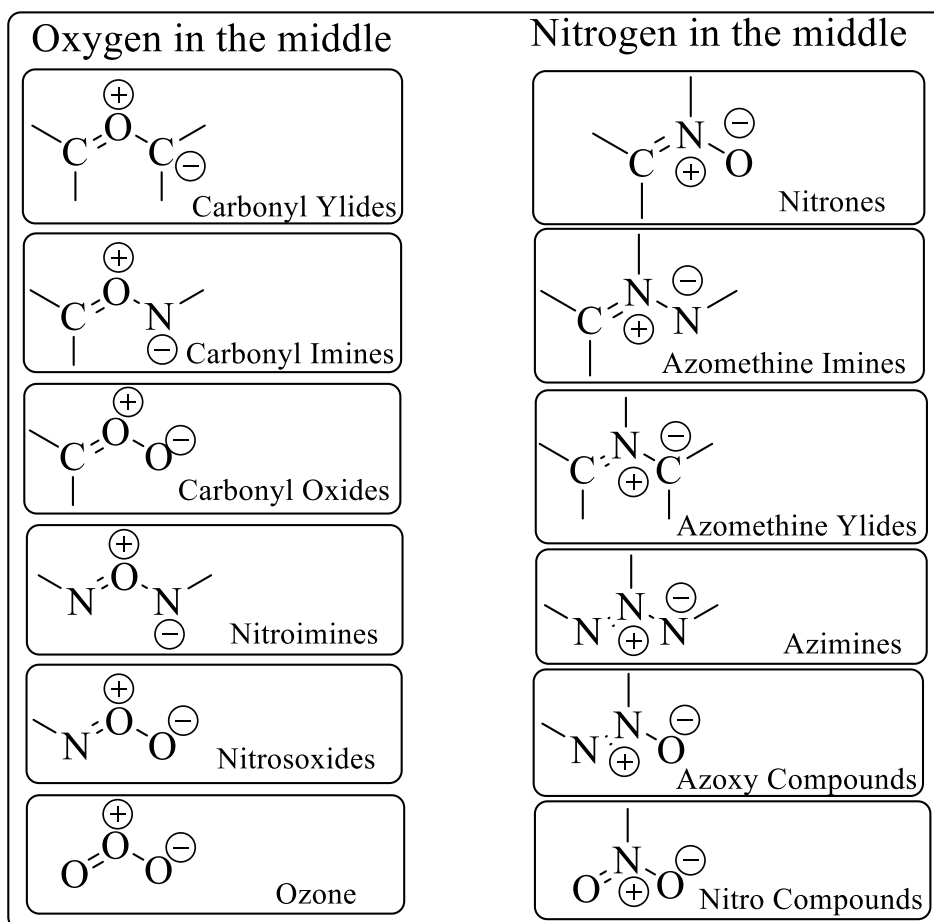


Figure 3. The allyl-anion type 1,3-dipoles

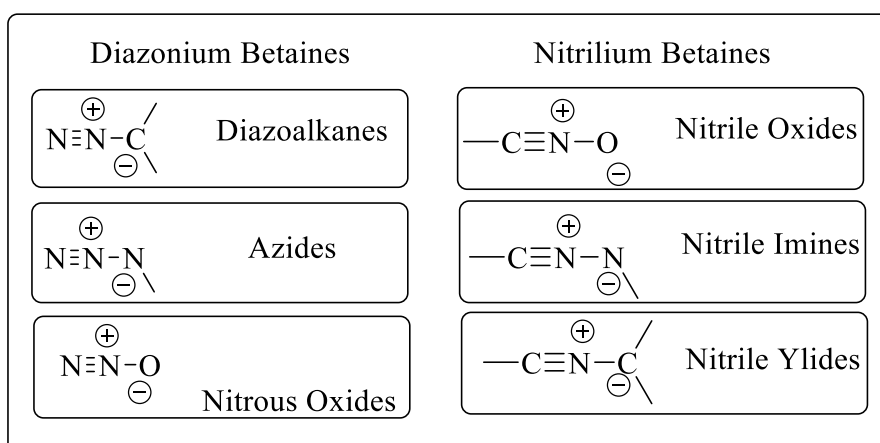


Figure 4. The propargyl/allenyl-anion type 1,3-dipole

Azomethine ylides are one type of allyl-anion type 1,3-dipoles. They are nitrogen-based dipoles. Pyrrolidines and pyrrolines, five-membered *N*-heterocycles, can be synthesized by 1,3-DC reaction of azomethine ylide. By this reaction, four new stereocentres can be obtained with high stereo- and regioselectivity. Therefore, azomethine ylides are common reagents used in total synthesis and pharmaceuticals. They are produced *in situ* and trapped immediately with dipolarophiles because they are very reactive and unstable (Scheme 1).⁹

In this thesis work, 1,3-DC reactions of heteroaryl-substituted azomethine ylide with different dipolarophiles were studied to synthesize furyl-substituted pyrrolidine which is a five-membered *N*-heterocycle.

1.2.1.2. Dipolarophile

In order to produce heterocyclic rings from azomethine ylides in a concerted mechanism, dipolarophiles are used in 1,3-DC reactions. They are 2π electron systems. There are many different types of dipolarophiles such as alkenes, ketones, allylic halides, alkynes and so on as shown in Figure 5.

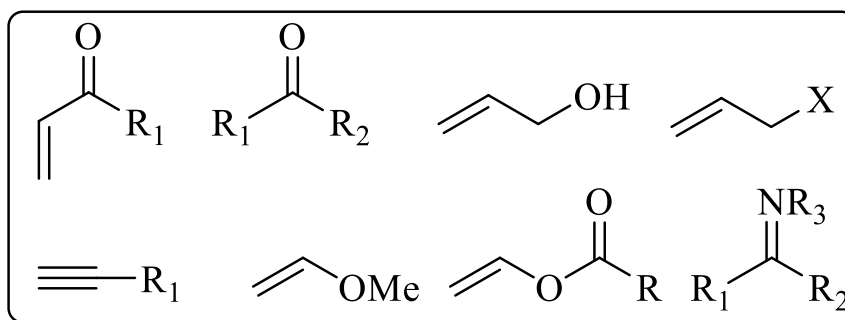


Figure 5. Different types of dipolarophiles used in 1,3-DC reaction

1.2.1.3. Pyrrolidine

Pyrrolidines, five-membered heterocycles (Figure 6), are found in many natural products and pharmaceuticals. Their synthesis is very important for scientists because they are biologically active compounds. There are many methods to synthesize pyrrolidines. An effective way to synthesize pyrrolidines is 1,3-DC reaction of azomethine ylides with dipolarophiles in the presence of a metal catalyst. In general, small amount of metal catalyst can produce large number of chiral pyrrolidines.

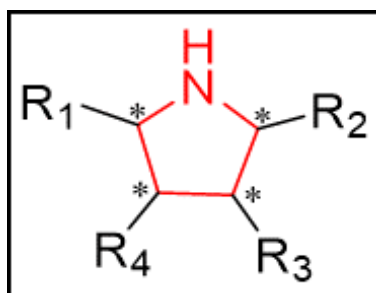


Figure 6. Structure of pyrrolidine

1.2.1.4. Organocatalyst and Metal-based Catalyst

There are two types of catalysts being used for asymmetric synthesis. Organocatalysts are low molecular weight organic molecules and small amount of organocatalyst can catalyze a chemical reaction. Organocatalysts have important roles in the construction of enantiopure compounds.¹⁰ Their low toxicity and insensitivity to moisture and oxygen are advantages in synthesizing pharmaceutical intermediates.¹¹

Other catalyst is the metal-based chiral catalyst. Chiral ligands forming complexes with transition metals provide the chiral environment for the asymmetric synthesis.

1.3. Mechanistic Approach to 1,3-Dipolar Cycloaddition Reaction

Huisgen and his colleagues stated that mechanism of 1,3-DC reactions is a concerted process.¹² They also claimed that the reaction needs small activation enthalpy to produce cycloadduct and the reactions of 1,3-dipoles with alkene are stereospecifically suprafacial. Therefore, their studies showed that the 1,3-DC reactions proceed through a concerted pathway. In the concerted 1,3-DC reaction, the stereochemistry of final cycloadduct and that of dipole and dipolarophile are invariable. When *trans*-dipolarophile reacts with dipole, *trans*-cycloadduct is obtained. To get only *cis*-cycloadduct, *cis*-dipolarophile should be used (Figure 7).

On the other hand, at the beginning, Firestone claimed that 1,3-DC reactions have stepwise mechanism via diradical intermediate.¹³ However, in this mechanism, 180° rotation of C-C bond takes place in diradical intermediate state so the mixture of *cis*- and *trans*- cycloadduct can be obtained (Figure 8). Therefore, the stereospecificity of the reaction is ruined. At the end, Firestone accepted that 1,3-DC reactions proceed through concerted mechanism.¹⁴

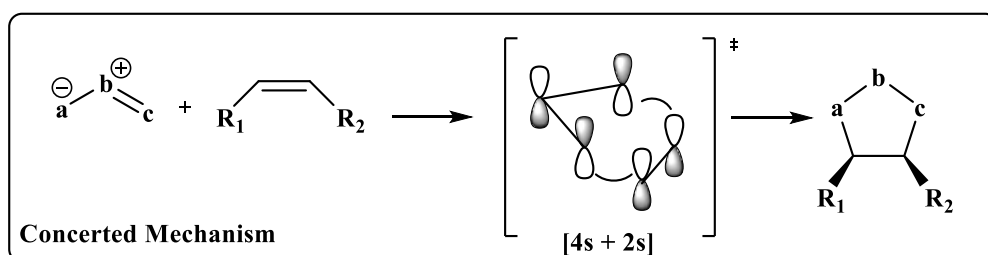


Figure 7. Concerted mechanism of 1,3-DC reaction

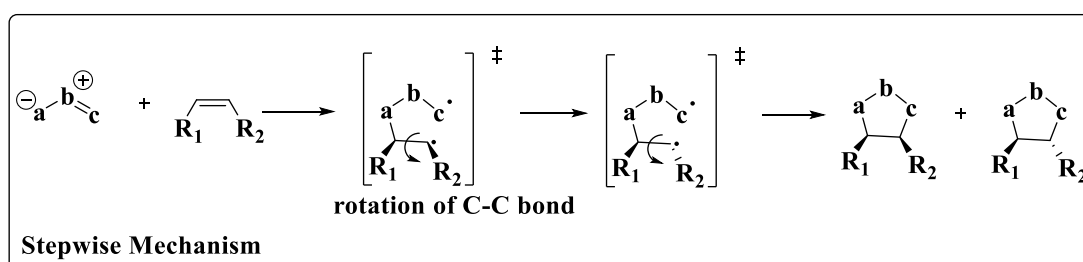


Figure 8. Stepwise mechanism of 1,3-DC reaction

The transition state of concerted 1,3-DC reaction is controlled by frontier molecular orbitals (FMO) of dipole and dipolarophile. Based on the FMO energies between dipole and dipolarophile interactions, Sustman stated that there are three types of 1,3-DC reaction (Figure 9).¹⁵

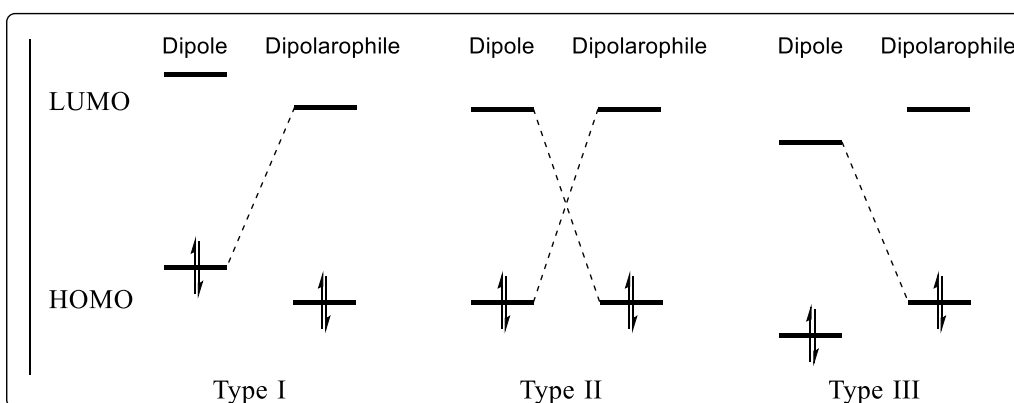


Figure 9. The classification of 1,3-DC reactions based on FMOs

In type 1 reactions, there is an interaction between $\text{HOMO}_{\text{dipole}}$ and $\text{LUMO}_{\text{dipolarophile}}$ and for carbonyl ylide, azomethine imines and azomethine ylides; this type of reaction is representative.

In type 2, both energy gaps of dipole and dipolarophile are similar. As a result, two-way interactions can take place. One of them is $\text{HOMO}_{\text{dipolarophile}}$ and $\text{LUMO}_{\text{dipole}}$. The other one is $\text{LUMO}_{\text{dipolarophile}}$ with $\text{HOMO}_{\text{dipole}}$. This is typical for nitrones, nitrile oxides and azides.

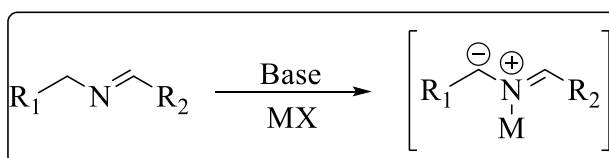
In the case of type 3, $\text{HOMO}_{\text{dipolarophile}}$ interacts with $\text{LUMO}_{\text{dipole}}$. Nitrous oxide or ozone reacts with dipolarophiles via this type of interactions.

Electron-donating or electron-withdrawing groups on dipolarophile or dipole can affect 1,3-DC reaction. Because these groups can change FMO energies. As a result, 1,3-DC reaction can proceed in different HOMO-LUMO pathways – either type 1, type 2 or type 3. In type 1, electron-withdrawing group (EWG) on dipolarophile reduces the energy of $\text{LUMO}_{\text{dipolarophile}}$ so the reaction is accelerated. However, when dipolarophile including electron-donating group (EDG) is used, reaction is decelerated because of the raised energy of $\text{HOMO}_{\text{dipolarophile}}$.¹⁶ In the case of type 2, both EDG and EWG groups on dipolarophile accelerate the reaction as EDG raise energy of the HOMO whereas EWG lowers the energy of LUMO.¹⁷ In type 3, EDG on dipolarophile

raises the energy of HOMO of the dipolarophile. Consequently, the rate of the reaction increases.¹⁸

1.4. 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides

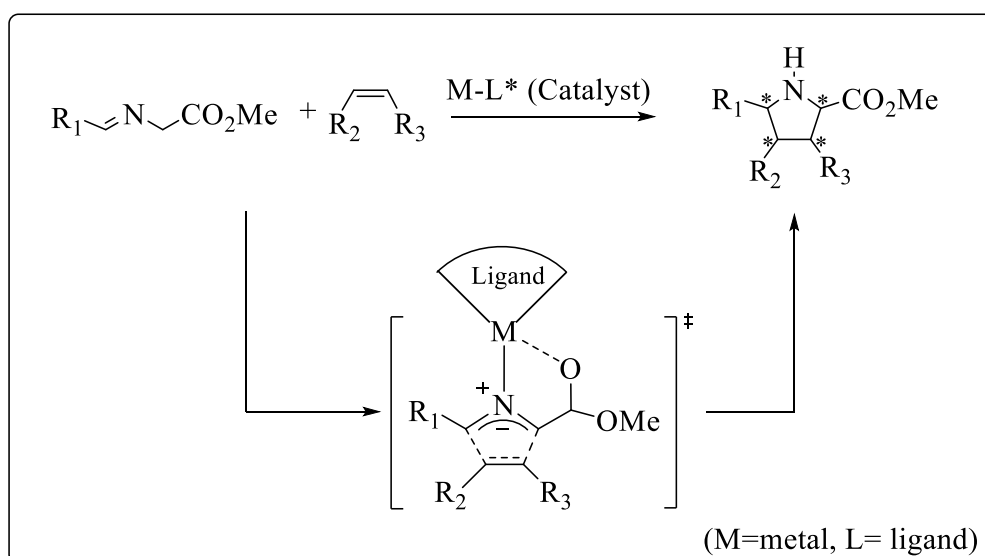
Azomethine ylides are the kind of bent allyl anion-type 1,3-dipoles and they contain 4 electrons distributed over the π orbitals of a C-N-C group.¹⁹ Generally, they are formed *in situ* due to their high reactivity. There are different ways to generate azomethine ylides, such as condensation of aldehyde with amine,²⁰ photolysis or thermolysis of aziridines,²¹ deprotonation of iminium salts,²² or most commonly proton abstraction from imines (Scheme 2).²³



Scheme 2. Proton abstraction from imine

1.5. Enantioselective 1,3-DC Reactions of Azomethine Ylides Using Chiral Catalysts

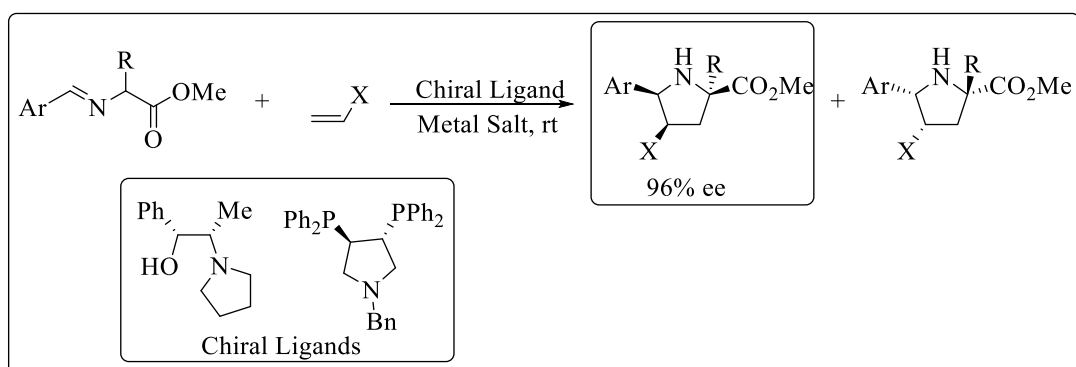
In the field of pharmaceuticals and agrochemicals, enantioselective synthesis is the key process to obtain enantiomerically pure compounds, because different enantiomers may have different biological activities. Using asymmetric catalysis for cycloaddition reactions, enantiomerically pure compounds can be synthesized in one step. This cycloaddition reaction is a very atom economical way to create more than one stereogenic centres and two “C-C” bonds in one step. 1,3-DC reaction of azomethine ylides with dipolarophiles in the presence of a chiral catalyst leads to the formation of pyrrolidines enantioselectively (Scheme 3). The catalyst used in the reaction is dissociated from the cycloadduct and it can be used for another catalytic cycle.



Scheme 3. Pyrrolidine synthesis using chiral catalyst

In general, azomethine ylides of α -iminoesters are used in 1,3-DC reactions because they can be easily stabilized in the presence of a Lewis acid catalyst that coordinates easily to azomethine ylide. Different metals such as Ag, Cu and Zn can coordinate both to the ligand and azomethine ylide.

Since the first study reported by Grigg and co-workers in 1991,²⁴ many groups studied 1,3-DC reaction of azomethine ylides using different chiral ligands and metals. Although Grigg's work did not involve using metal-ligand chiral catalyst in catalytic amount, it was the first study in literature. Using chiral manganese and cobalt complexes, enantioselectivity could be achieved in 1,3-DC reactions of azomethine ylides derived from α -iminoester. They obtained up to 96% ee and the yields were ranged between 45-84% (Scheme 4).

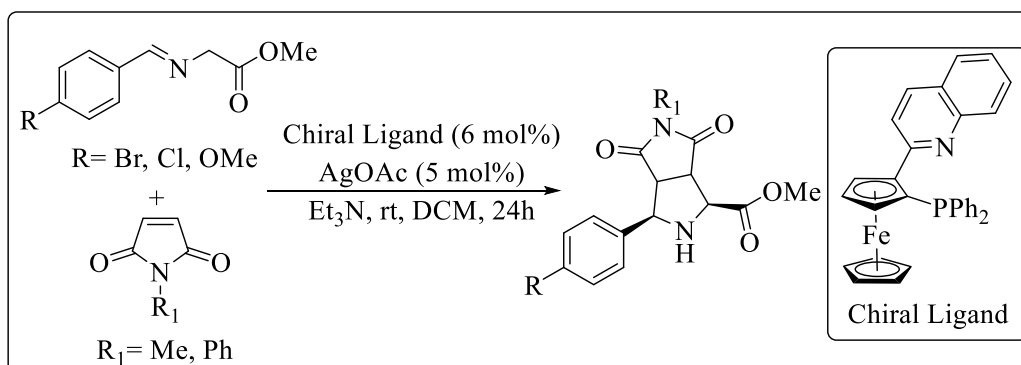


Scheme 4. Grigg and co-workers' study

1.6. Asymmetric 1,3- Dipolar Cycloaddition Reactions Using Ferrocene-based Chiral Ligands in Literature

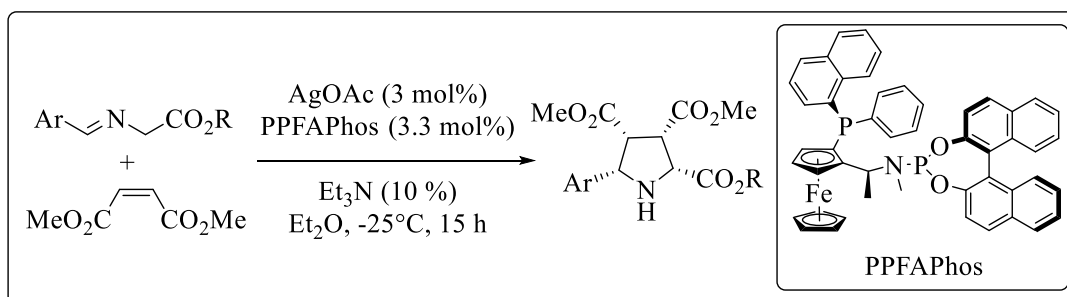
Ferrocene and its derivatives have been widely used since the discovery of ferrocene in 1950s.²⁵ Due to structural inertness to many reaction conditions, it is used in all fields of organometallic chemistry. Ferrocene based chiral ligands have been used in asymmetric synthesis. Adequate rigidity, ease of derivatization, planar chirality when substituted with a chiral unit, steric bulkiness, thermal stability and tolerance to oxygen and moisture makes ferrocene derivatives a suitable chiral ligand for asymmetric synthesis.²⁶

In one of the studies, chiral 1,2-*P,N*-bidentate ferrocene based ligand was used for 1,3-DC reactions involving different imines (precursors of intermediate azomethine ylides) and dipolarophiles. This chiral ligand provided aryl-substituted pyrrolidine structures in up to 93% enantioselectivity (Scheme 5).²⁷



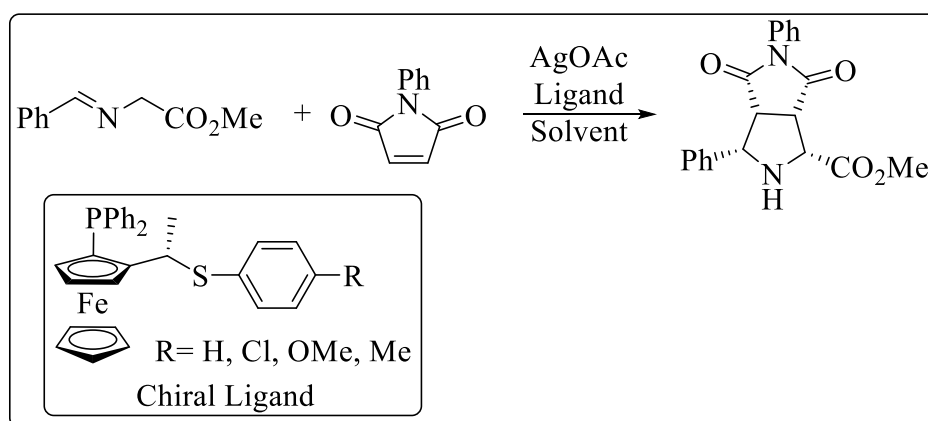
Scheme 5. Utepova and co-workers' study

In other study, chiral ferrocene-based phosphine–phosphoramidite ligand having a stereogenic *P*-center was used for enantioselective Ag(I)-catalyzed [3+2] cycloaddition reaction of azomethine ylides. This catalyst system also provided aryl-substituted pyrrolidines in up to 99% enantioselectivity (Scheme 6).²⁸



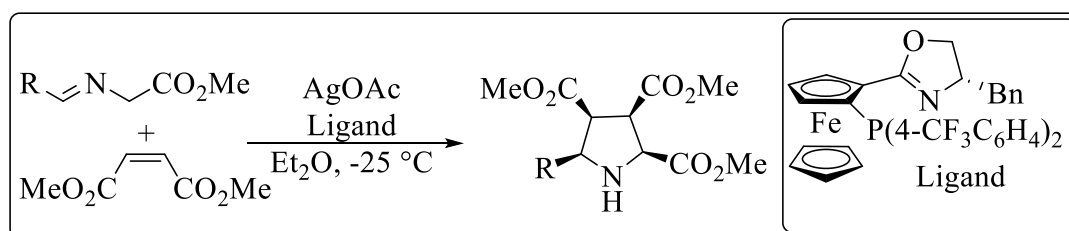
Scheme 6. Yu and co-workers' study

Zhou et al. reported another ferrocene derived *P,S*-bidentate ligand for the asymmetric 1,3-DC reaction yielding aryl substituted pyrrolidines in up to 93% enantioselectivity (Scheme 7).²⁹



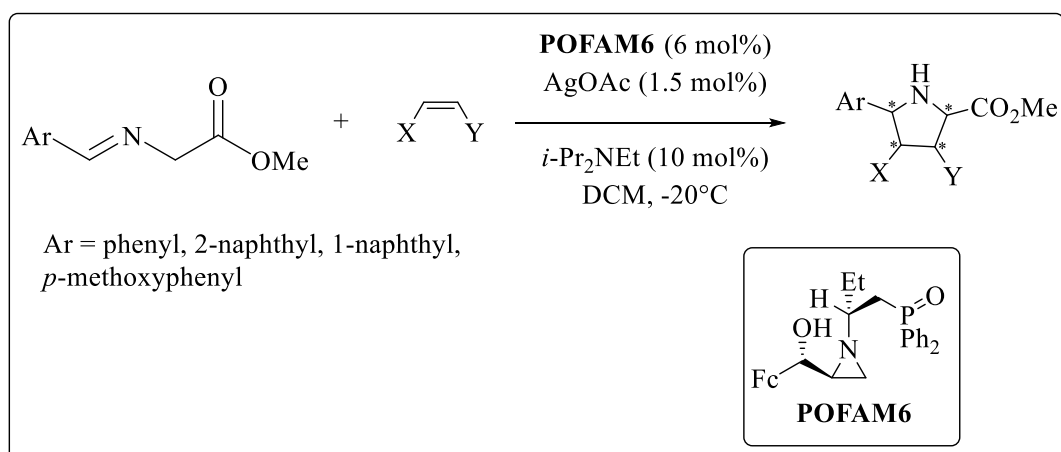
Scheme 7. Zeng and Zhou's study

Zhou et al. reported another study by using ferrocene based *N,P*-bidentate ligands which provided pyrrolidines in up to 98% enantioselectivity (Scheme 8).³⁰



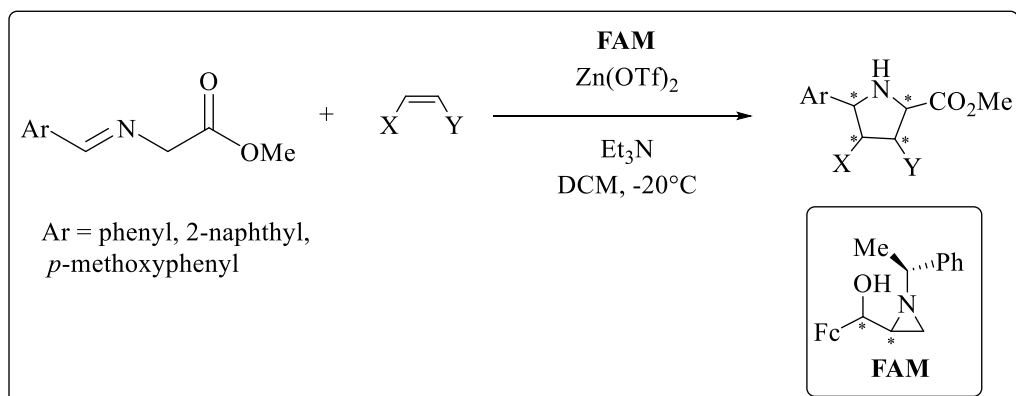
Scheme 8. Use of ferrocene based *N,P*-bidentate ligand reported by Zhou group

Our group also studied 1,3-DC reactions of azomethine ylides by using ferrocenyl aziridinyl methanol (**FAM**) chiral ligands with Zn used as the metal source and reported aryl-substituted pyrrolidines in up to 95% enantioselectivity (Scheme 9).³¹



Scheme 9. Use of **FAM** ligands in 1,3-DC reaction of azomethine ylides

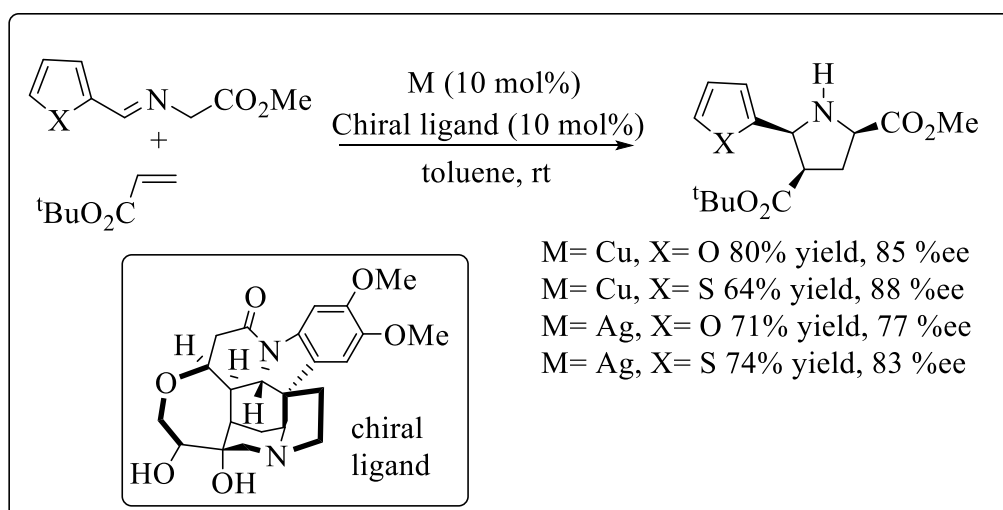
Our group reported another study by using phosphorous derivatives of **FAM** ligands with Ag. This catalyst system gave aryl substituted pyrrolidines in up to 89% enantioselectivity (Scheme 10).³²



Scheme 10. Use of phosphorous derivative of **FAM** ligands in 1,3-DC reaction of azomethine ylides

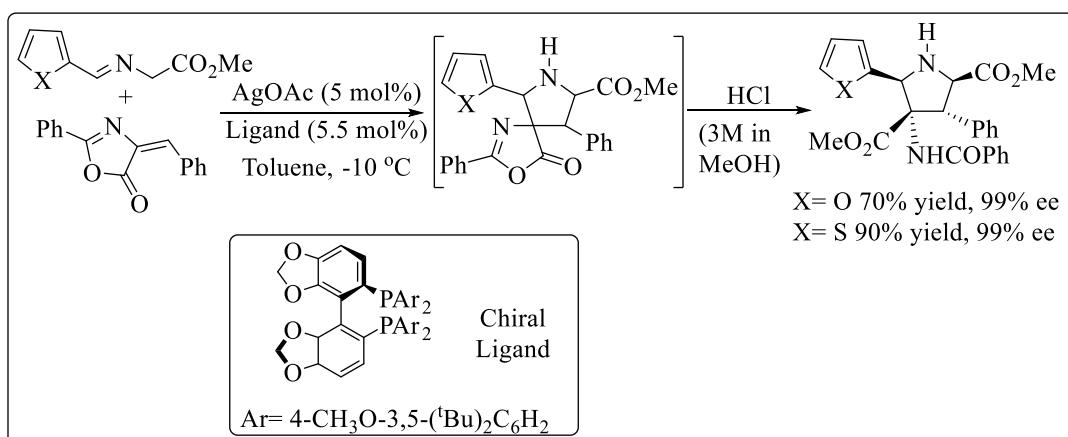
1.7. Metal Catalysed Asymmetric 1,3-Dipolar Cycloaddition Reactions Involving Heteroaryl Substituted Pyrrolidine Synthesis

Heterocyclic compounds in general are biologically active compounds. Therefore, having heteroaryl group in pyrrolidine structure is expected to improve the biological activity of these compounds. As mentioned before the synthesis of chiral heteroaryl-substituted pyrrolidines is limited. One of these studies was reported by Oh and colleagues. This group used silver and copper as the metal sources with rather complex chiral ligand and reported 85% enantioselectivity with only *tert*-butyl acrylate for the furyl and thiofuryl-substituted pyrrolidines (Scheme 11, only two examples).³³



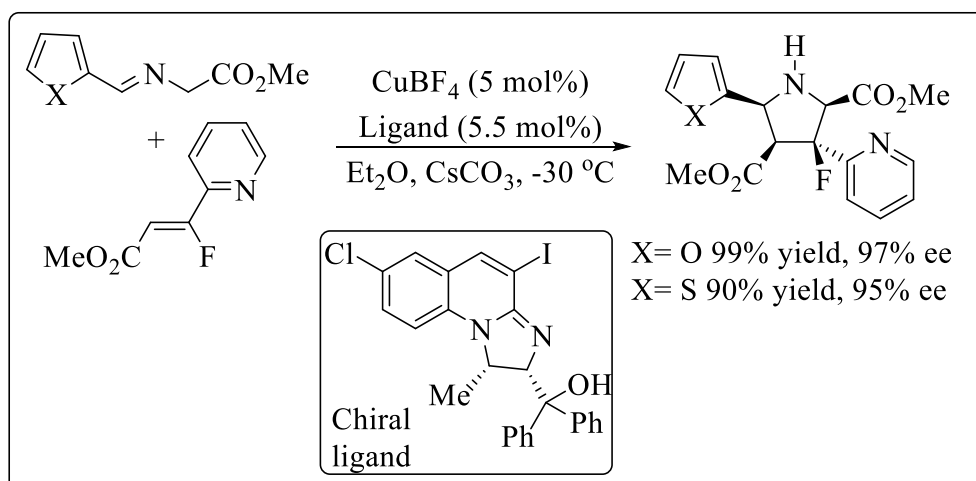
Scheme 11. Synthesis of furfuryl- and thiofurfuryl-pyrrolidines by Oh and co-workers

Related with the heteroaryl-substituted pyrrolidine synthesis by 1,3-DC reaction, Carretero and co-workers reported up to 99% enantioselectivity of the product by using phosphorous based chiral ligand with Ag (Scheme 12, only two examples).³⁴



Scheme 12. Carretero and co-workers' study

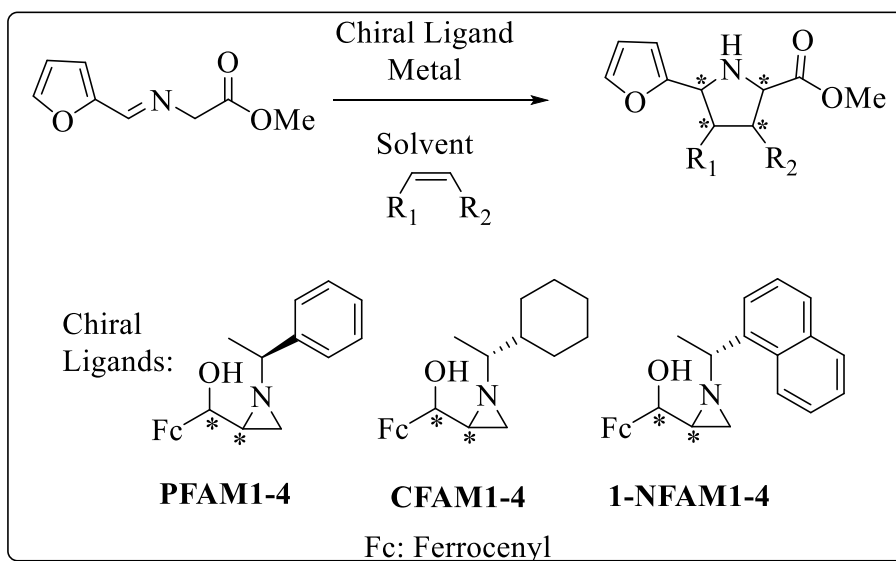
In another study, Deng et al. used copper salt for 1,3-DC reaction to get heteroaryl substituted pyrrolidines in up to 97% enantioselectivity. They used both pyridinyl- and fluoro-substituted dipolarophile which is not a commonly used one (Scheme 13, only two examples).³⁵



Scheme 13. Deng and co-workers' study

1.8. Aim of The Study

Synthesis of pyrrolidines in enantiomerically pure forms by efficient and economical way is important due to biological activity of these compounds. 1,3-DC reaction of azomethine ylides is one of the best methods to synthesize pyrrolidine structures. In literature, different metal catalysts (metal-chiral ligand) have been developed and used successfully for 1,3-DC reaction of azomethine ylides with dipolarophiles to synthesize aryl-substituted pyrrolidines. However, there are only a few examples reported in literature for the enantioselective synthesis of furyl-substituted pyrrolidines using the same chemistry. Therefore, we aimed to explore this chemistry to synthesize variety of furyl-substituted pyrrolidines. In doing so, we wanted to use **FAM** chiral ligands developed by our group. Besides, screening the known **FAM** ligands, we also wanted to synthesize new 1-naphthyl-substituted derivative of these ligands (**1NFAM**, four diastereomers) in this thesis. Basically, total of 12 structurally and stereochemically different **FAM** ligands (**PFAM**, **CFAM**, and **1NFAM**, each composed of four diastereomers) were screened with an aim to synthesize furyl-substituted pyrrolidines (Scheme 14).



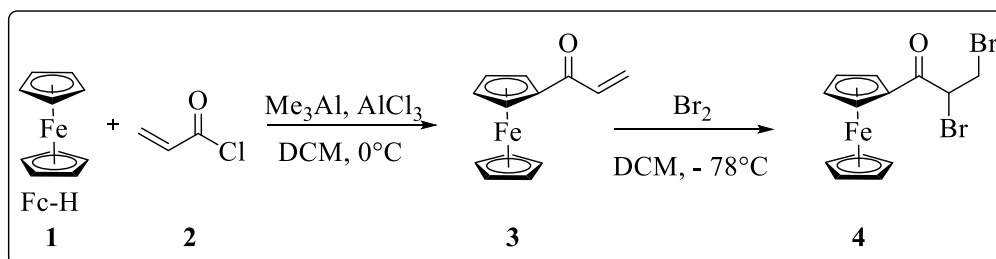
Scheme 14. Metal-catalyzed asymmetric synthesis of furyl-substituted pyrrolidines

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of New 1-Naphthyl-Ferrocenyl-Aziridinyl-Methanol (1NFAM) Ligands

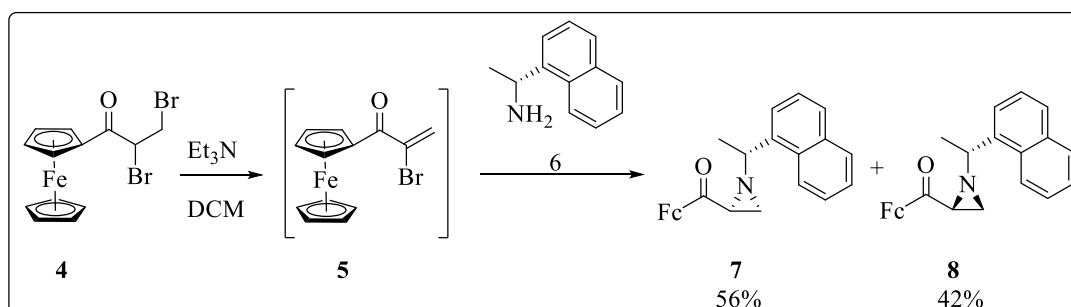
1-NFAM ligands were synthesized by following the literature procedure reported by Dogan's research group.³⁶ This synthesis started with the Friedel-Crafts reaction of ferrocene and acryloyl chloride in the presence of a mixed Lewis acid $\text{Me}_3\text{Al}-\text{AlCl}_3$, which provided acryloyl ferrocene **3** in 97% yield. Then, bromination of acryloyl ferrocene **3** in DCM at -78°C , this protocol was developed by our group, gave the desired product **4** in 95% yield (Scheme 15).³⁶



Scheme 15. Synthesis and bromination of acryloyl ferrocene

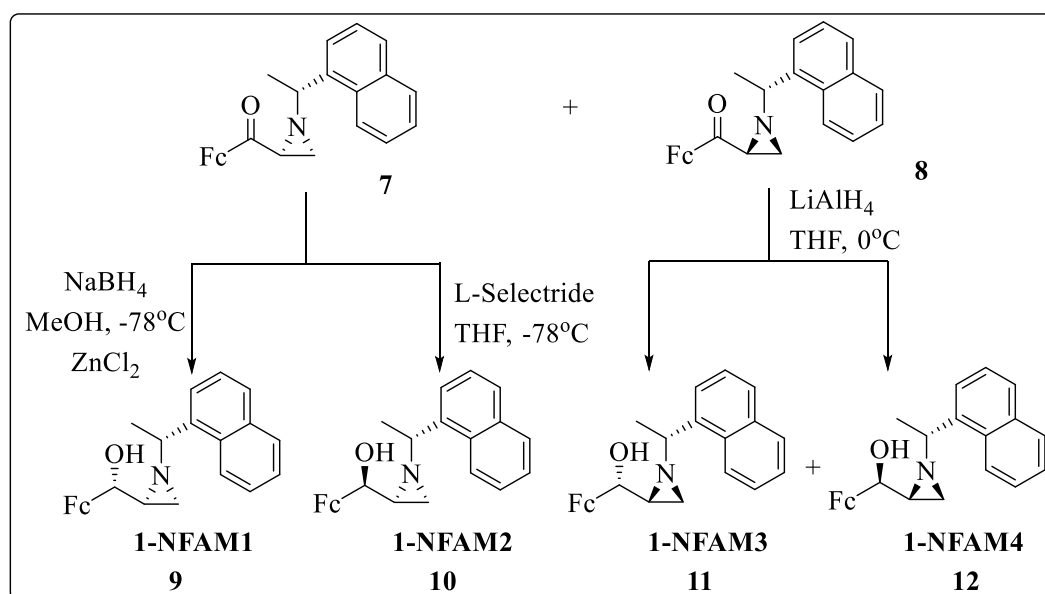
The next step was the aziridine formation reaction by using the modified Gabriel-Cromwell reaction.³⁷ First, dibromo compound **4** was stirred with trimethylamine to obtain α -bromoacryloyl ferrocene **5** by elimination of HBr. Then, addition of (*R*)-1-naphtylethylamine **6** to the reaction flask formed a diastereomeric mixture of aziridinyl ketones **7** and **8**. These ketones were purified and separated easily

by flash column chromatography and obtained in 56% and 42% yields, respectively (Scheme 16).



Scheme 16. Synthesis of aziridinyl ketones by Gabriel-Cromwell reaction

The last step for the synthesis of **1-NFAM** ligands was the reduction of the carbonyl group. This reduction was achieved under different reaction conditions by using a procedure developed by a Korean group.³⁸ As a result, all four diastereomers of ketones **7** and **8** were obtained as shown in Scheme 17. In assigning the absolute configurations of **1-NFAM** ligands, we made analogy with our previously synthesized **FAM** ligands based on NMR data and R_f values on TLC.³⁶ Ketone **7**, first isomer on TLC, was reduced by NaBH_4 at -78°C in MeOH to get **1-NFAM1** chiral ligand **9** in 92% yield. Using L-selectride as the reducing reagent in THF at -78°C , the same ketone **7** gave **1-NFAM2** ligand **10** in 71% yield. On the other hand, reduction of the second ketone **8** by using LiAlH_4 at 0°C in THF provided a diastereomeric mixture of **1-NFAM3** ligand **11** and **1-NFAM4** ligand **12** in 28% and 62% yields, respectively, after flash column chromatography.



Scheme 17. Reduction of aziridinyl ketones

Besides **1-NFAM1-4** chiral ligands, **CFAM1-4** and **PFAM1-4** chiral ligands were also synthesized by using the same procedures. In order to synthesize **PFAM1-4** chiral ligands, (*S*)-1-phenylethylamine was used in aziridination step and in order to synthesize **CFAM1-4** chiral ligands, (*R*)-cyclohexylethylamine was used in the aziridination step, the structures of these chiral ligands are shown in Figure 10. As a result of all these syntheses, total of 12 stereoisomerically and structurally different ligands were in hand to be tested in asymmetric 1,3-DC reactions of furyl-substituted azomethine ylides.

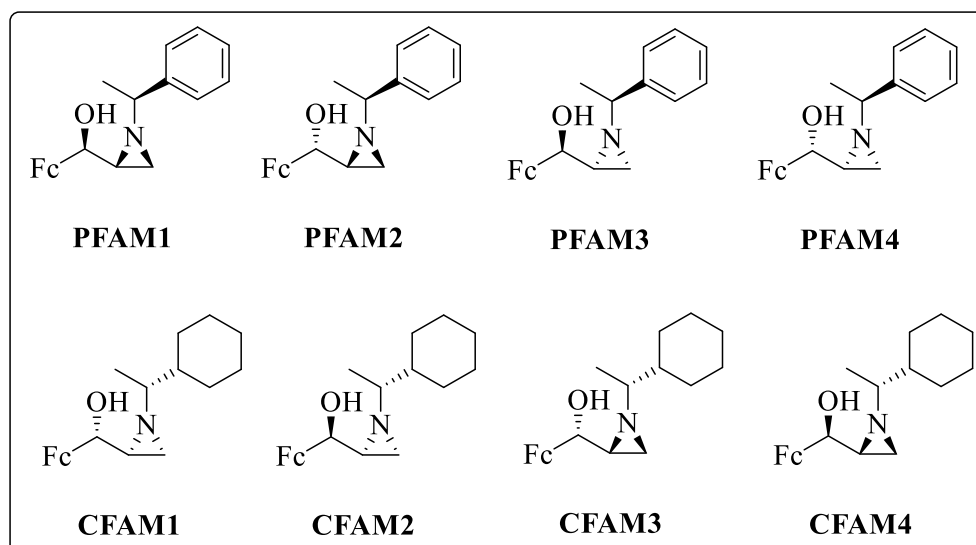
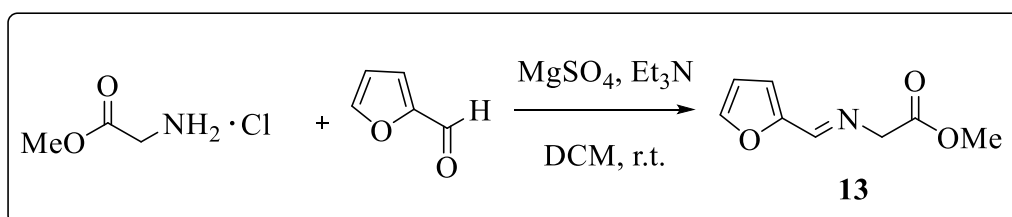


Figure 10. Structures of **PFAM** and **CFAM** ligands

2.2. Synthesis of Furyl-Substituted Imino Ester

Methyl (*E*)-2-((furan-2-ylmethylene)amino)acetate, a furyl-substituted imino ester **13**, was synthesized as reported in literature³⁹ by using furfural and glycine methyl ester.³⁹ The crude furyl-substituted iminoester **13** was pure enough to be used without any purification in 1,3-DC reaction (Scheme 18).

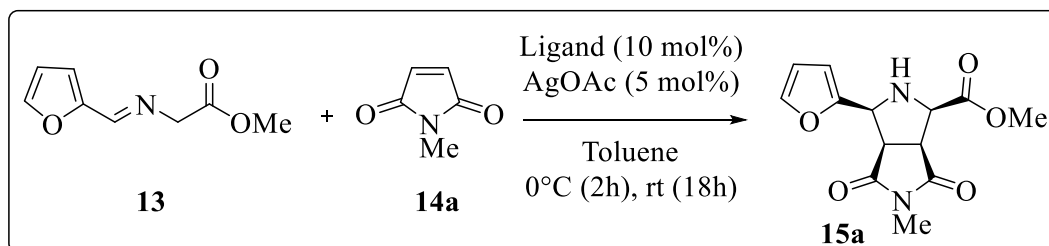


Scheme 18. Synthesis of imino ester **13**

2.3. The Asymmetric 1,3- Dipolar Cycloaddition Reactions

After synthesizing **FAM** ligands and imine, we were ready to test the catalytic performance of the ligands with a metal in 1,3-DC reaction of azomethine ylides to obtain furyl-substituted pyrrolidines.

Firstly, the ligand screening studies were performed by following the literature procedure using AgOAc as the metal source and *N*-methylmaleimide **14** as the dipolarophile.⁴⁰ The results of these studies were summarized in Table 1.

Table 1. Ligand screening studies

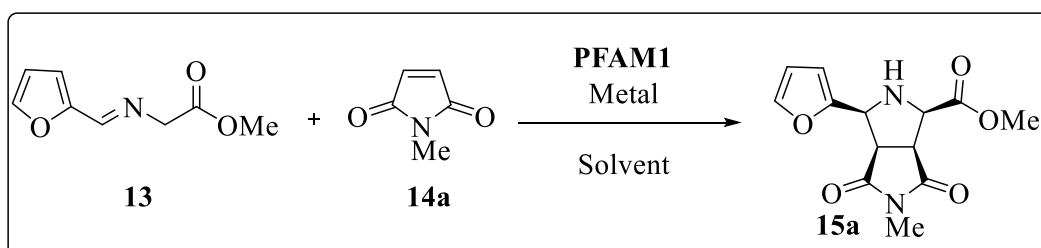
Entry	Ligand	Yield (%) ^a	ee (%) ^b
1	PFAM1	76	61
2 ^c	PFAM2	40	54
3	PFAM3	24	66
4 ^c	PFAM4	74	65
5 ^c	1-NFAM1	66	67
6	1-NFAM2	64	34
7 ^c	1-NFAM3	96	30
8	1-NFAM4	55	30
9 ^c	CFAM1	37	63
10	CFAM2	47	44
11 ^c	CFAM3	47	38
12	CFAM4	83	50

^aIsolated yield. ^bDetermined by chiral AS-H column. ^c*ent*-**15a** formed as the major stereoisomer.

As can be seen from Table 1, five of the ligands **PFAM1** (61% ee, entry 1), **PFAM3** (66% ee, entry 3), **PFAM4** (65% ee, entry 4), **1-NFAM1** (67% ee, entry 5) and **CFAM1** (63% ee, entry 9) formed the product in relatively high enantioselectivity. On the other hand, among these five ligands only **PFAM1**, **PFAM4** and **1-NFAM1** gave the product in acceptable yields, 76%, 74% and 66%, respectively. From the results of the ligand screening studies, we decided to continue further optimizations of reaction conditions by using **PFAM1** and **PFAM4** ligands. Because these two ligands formed the pyrrolidine in high yield and ee.

Next optimization of the reaction conditions was the metal screening studies. Based on the literature, we decided on screening three different metals, Ag, Zn, and Cu. The results of these studies were summarized in Table 2.

Table 2. Metal screening studies



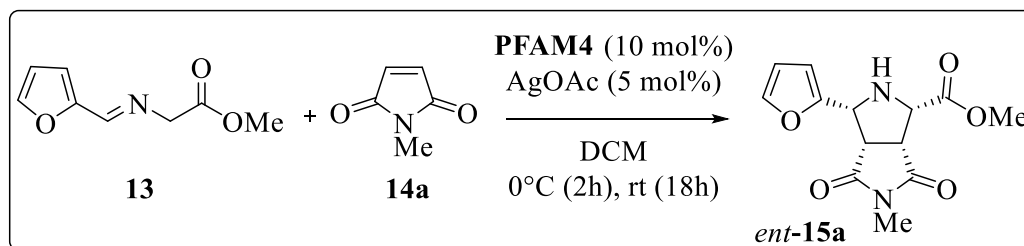
Entry	Metal	Solvent	Time, Temp	Yield (%) ^a	ee (%) ^b
1	Zn(OTf) ₂	DCM	20h, 0°C	21	15
2	Zn(Et) ₂	DCM	20h, 0°C	15	Rac. ^c
3	Cu(CH ₃)	Et ₂ O	24h, -30°C	40	30
4	AgOAc	Toluene	0°C (2h), rt (18h)	76	61
5	AgSbF ₆	Toluene	0°C (2h), rt (18h)	10	4

^aIsolated yield. ^bDetermined by chiral AS-H column. ^cRacemic.

First we tried two different zinc sources, zinc (II) trifluoromethane sulfonate ($\text{Zn}(\text{OTf})_2$) and diethylzinc (ZnEt_2) by applying the literature procedure.³⁶ Both of the zinc sources produced cycloadduct **15a** in low yield and 15% ee to no enantioselectivity (entries 1 and 2). As the second metal, we tried copper tetrakis(acetonitrile)copper(I)tetrafluoroborate ($\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$).⁴¹ This metal provided the cycloadduct **15a** in slightly better yield and ee (entry 3) as compared to zinc. As the third metal, we tried two different silver salts, AgOAc and AgSbF₆.⁴⁰ Although AgSbF₆ yielded cycloadduct **15a** in very low yield and ee (entry 5), AgOAc yielded the product **15a** in highest yield (76%) and ee (61%) among the metals tried. Therefore, AgOAc was used for the further optimizations.

In general, depending on the reaction, metal catalysts may show concentration dependence. Therefore, we also wanted to see whether our catalyst system (Ag-**PFAM4**) could show concentration dependence. For this purpose, we run the 1,3-DC reaction at three different concentrations as outlined in Table 3.

Table 3. Reactions run at different concentrations

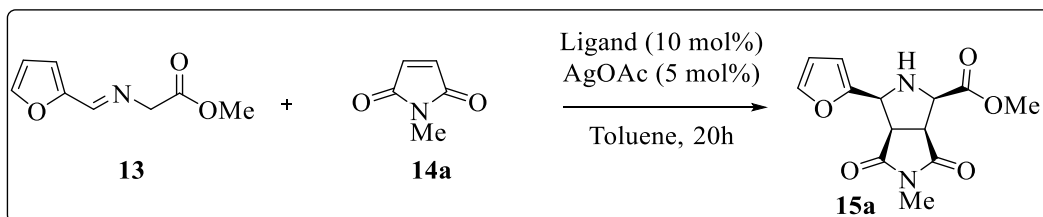


Entry	Molarity (M)	Yield (%) ^a	ee (%) ^b
1	0.1	13	59
2	0.2	86	67
3	0.3	54	56

^aIsolated yield. ^bDetermined by chiral AS-H column.

As can be seen from Table 3, running the reaction at different molarities, enantioselectivity of the reaction was not affected significantly. However, the yield was much better at 0.2 M concentration of the reaction mixture (entry 2). From the concentration studies, we decided to run the reactions at 0.2 M.

After screening ligands, metals and concentrations of the 1,3-DC reactions of furfuryl-substituted azomethine ylide with *N*-methylmaleimide, the effect of temperature was also studied as another reaction parameter (Table 4).

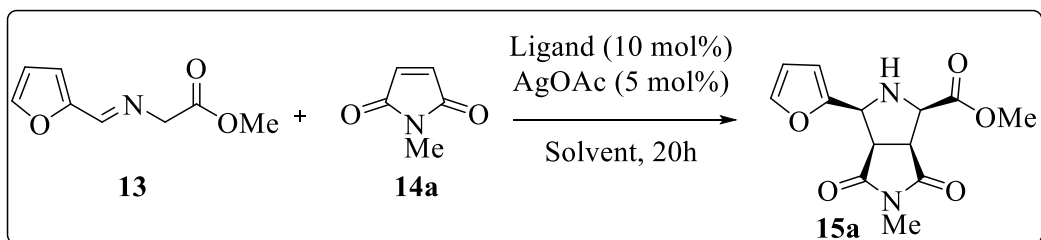
Table 4. Temperature screening studies

Entry	Ligand	Temperature	Yield (%) ^a	ee (%) ^b
1	PFAM1	0°C (2h), rt (18)	76	61
2	PFAM1	-20°C	79	56
3 ^c	PFAM4	0°C (2h), rt (18)	74	65
4 ^c	PFAM4	-20°C	40	37
5 ^c	1-NFAM1	0°C (2h), rt (18)	66	67
6 ^c	1-NFAM1	-20°C	88	35
7 ^c	1-NFAM3	0°C (2h), rt (18)	96	30
8 ^c	1-NFAM3	-20°C	57	32

^aIsolated yield. ^bDetermined by chiral AS-H column. ^c*ent*-**15a** formed as the major stereoisomer.

For the temperature screening studies, besides **PFAM1** and **PFAM4** ligands, **1-NFAM1** and **1-NFAM3** ligands were also used. Because, in ligand screening experiments, **1-NFAM1** also gave the cycloadduct in acceptable yield and ee (Table 1, entry 5). **1-NFAM3**, on the other hand, formed the product in the highest yield (Table 1, entry 7). At two different reaction temperatures, 0°C to room temperature and -20°C, the reaction yield and ee with **PFAM1** ligand was not affected significantly (entries 1 and 2). However, in the case of **PFAM4**, both the yield and ee were lower at -20°C than the reaction run at 0°C to rt (entries 3 and 4). For **1-NFAM1**, when temperature was decreased, the yield increased from 66% to 88% while enantioselectivity decreased from 67% to 35% (entries 5 and 6). In the case of **1-NFAM3** ligand, the yield at -20°C decreased from 96% to 57% and the ee was not affected considerably (entries 7 and 8). Temperature screening studies showed that **PFAM1** and **PFAM4** ligands are behaving similarly when the reaction was run at 0°C to rt. Therefore, we continued solvent screening studies by using these two ligands.

After seeing the results of temperature effect on the 1,3-DC reactions, the effect of different solvents was studied by using **PFAM1** and **PFAM4** ligands. The results were summarized in Table 5.

Table 5. Solvent screening studies

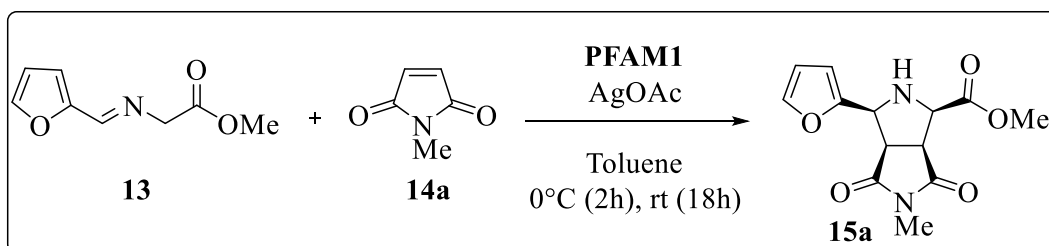
Entry	Solvent	Ligand	Temperature	Yield (%) ^a	ee (%) ^b
1	DCM	PFAM1	-20°C	52	21
2	Toluene	PFAM1	-20°C	79	56
3 ^c	DCM	PFAM4	0°C (2h), rt (18)	86	67
4 ^c	THF	PFAM4	0°C (2h), rt (18)	30	45
5 ^c	Toluene	PFAM4	0°C (2h), rt (18)	49	46
6 ^c	DCE	PFAM4	0°C (2h), rt (18)	84	38
7 ^c	Et ₂ O	PFAM4	0°C (2h), rt (18)	66	32

^aIsolated yield. ^bDetermined by chiral AS-H column. ^c*ent*-**15a** formed as the major stereoisomer.

Using **PFAM1**, only two solvents, DCM and toluene, were tested. Toluene was determined as the proper solvent for **PFAM1** in terms of both chemical yield (79%) and enantioselectivity (56%) values in 1,3-DC reactions (entry 2). On the other hand, five different solvents, DCM, THF, toluene, DCE and Et₂O were used with **PFAM4** ligand. For this ligand, the highest yield and ee were obtained in DCM (entry 3).

Finally, the effect of ligand-metal ratio on the yield and ee of the 1,3-DC reaction was investigated by using **PFAM1** ligand (Table 6).

Table 6. Ligand/metal ratio screening studies

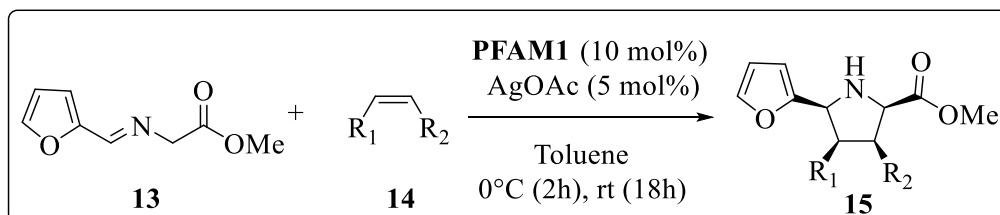


Entry	Ligand/metal (mol%)	Yield (%) ^a	ee (%) ^b
1	20/10	48	66
2	10/10	79	63
3	10/5	76	61
4	5/2.5	50	50
5	10/2	66	48

^aIsolated yield. ^bDetermined by chiral AS-H column.

As can be seen from Table 6, high ligand concentration had the opposite effect on the yield but no significant effect on the value of ee (entries 1-3). By keeping the ligand concentration at 10 mol% and lowering the metal concentration from 10 to 5 mol% resulted in no significant change on the yield and ee of the reaction (entries 2 and 3). By keeping the ligand/metal ratio same and reducing the amount of the catalyst to half, both the yield and ee were lowered (entries 3 and 4). In trying to find out the lowest metal loading by holding the ligand loading at 10 mol%, both the yield and ee were lowered from 76 to 66% and 61 to 48%, respectively (entries 3 and 5).

After optimizing reaction parameters in terms of ligands, metals, temperature, concentration, solvents, and metal/ligand ratio by using *N*-methylmaleimide as the dipolarophile, we also wanted to see the applicability of our catalyst system on different dipolarophiles. For this purpose, 1,3-DC reaction was run by using **PFAM1** ligand (10 mol%), AgOAc (5 mol%), and toluene at rt and 0.2 M reaction concentration. The results of these studies were summarized in Table 7.

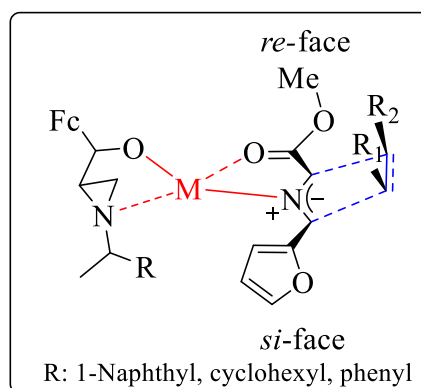
Table 7. Dipolarophile screening studies

Entry	Dipolarophile	Yield (%) ^a	ee (%)
1 ^b		76	61
2 ^b		53	64
3 ^b		38	40
4 ^c		79	5
5 ^b		87	14
6 ^b		70	18
7 ^d		22	6

^aIsolated yield. ^bDetermined by chiral AS-H. ^cDetermined by chiral OD. ^dDetermined by chiral AD-H columns.

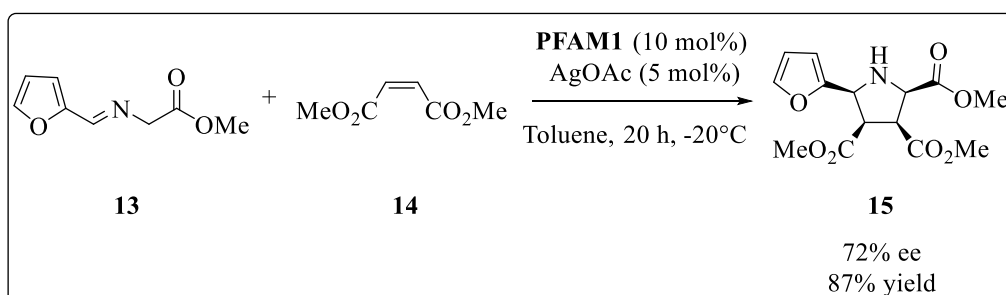
The dipolarophile screening studies showed that under optimized reaction conditions, our catalyst system provided the cycloadducts corresponding to *N*-methylmaleimide and dimethyl maleate in reasonable to acceptable yields and enantioselectivities (entries 1 and 2). *tert*-Butyl acrylate resulted in the formation of cycloadduct in low yield and ee (entry 3). The other dipolarophiles, methyl acrylate, acrylonitrile and chalcone formed the cycloadducts in reasonably good yields but poor enantioselectivities (entries 4, 5, and 6). Lowest yield and ee was observed in the case of phenyl vinyl sulfone (entry 7). These studies showed that each dipolarophile requires further optimizations of the reaction parameters which is a generally observed case for these types of reactions.

In the literature, the cycloadducts formed by 1,3-DC reactions of furyl-substituted imine with *tert*-butyl acrylate, methyl acrylate and acrylonitrile exist. Therefore, these cycloadducts and their absolute configurations were characterized based on the analogy with same compounds in literature using their chiral HPLC data and NMR spectra. The rest of the cycloadducts (entries 1, 2, 6 and 7) do not exist in the literature. They were characterized making an analogy with previous cycloadduct structures and similar cycloadduct structures in literature by comparing their optical rotations and chiral HPLC data according to proposed transition state (Scheme 19). Considering these data and proposed transition state, all 1,3-DC reactions proceeded over *endo*-approach of dipolarophile to azomethine ylide. Also, by using **PFAM1**, **PFAM3**, **1-NFAM2**, **1-NFAM4**, **CFAM2** and **CFAM4** ligands, *re*-facial selectivity with these dipolarophiles were observed comparing with the values of furyl-substituted pyrrolidines in literature. On the other hand, by using **PFAM2**, **PFAM4**, **1-NFAM1**, **1-NFAM3**, **CFAM1** and **CFAM3** ligands, *si*-facial selectivity with *N*-methylmaleimide were observed.



Scheme 19. Proposed *endo-re* transition state

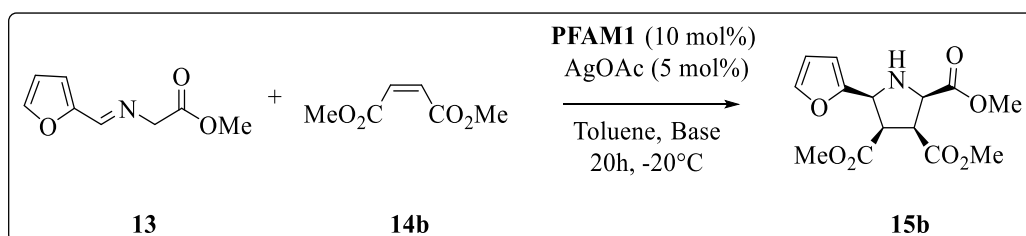
By knowing that 1,3-DC reactions may require further optimizations for every dipolarophile, we repeated 1,3-DC reaction with dimethyl maleate at -20°C without changing the other parameters. As can be seen in scheme 20, both the yield and ee increased from 53 to 87% and from 64 to 72%. These are the highest numbers for our catalyst system in forming the furyl-substituted pyrrolidines. Also, at the same condition, *N*-methyl maleimide and *tert*-butyl acrylate as dipolarophiles were used to synthesize furyl-substituted pyrrolidines. For *N*-methyl maleimide, the results were similar (Table 1, entries 1 and 2). For *tert*-butyl acrylate, at 0°C to rt, the enantioselectivity was 40% and the yield was 38% (Table 7, entry 3). At -20°C , both values decreased (8% ee and 30% yield).



Scheme 20. Temperature change for dimethyl maleate

Since in only two cases, our catalyst gave cycloadducts in reasonable yields and enantioselectivities, we wanted to see the effect of additives on the 1,3-DC reaction as the last reaction parameter. In metal catalyzed reactions, additives can make significant differences. Using the optimized reaction parameters, Et₃N, DIEA, DBU and PPh₃ were added to reaction mixture as additives. Results are summarized in Table 8.

Table 8. Additive screening studies



Entry	Additive (base)	Yield (%) ^a	ee (%) ^b
1	-	87	72
2	Et ₃ N	35	56
3	DIEA	54	64
4	DBU	11	4
5	PPh ₃	56	Rac ^c

^aIsolated yield. ^bDetermined by chiral AS-H column. ^cRacemic

Results in Table 8 indicated that additives in general lowered both the yield and the ee values of the reaction (entries 2-5. The reaction carried out without using the additive formed the product in higher yield and ee (entry 1).

CHAPTER 3

CONCLUSION

Asymmetric 1,3-dipolar cycloaddition (1,3-DC) reactions of azomethine ylides are one of the very well-known cycloaddition reactions for the synthesis of enantiomerically pure pyrrolidines. In a single step, two new C-C bonds are formed in up to 4 stereogenic centres. This reaction is also an atom economical process. In this study, metal-catalyzed asymmetric 1,3-DC reaction of azomethine ylide with electron deficient dipolarophiles were studied by using our chiral **FAM** ligands to synthesize chiral furyl-substituted pyrrolidines.

In the first part of the thesis, a new series of **FAM** (ferrocenyl aziridinyl methanol) ligands, **1-NFAM1-4** (1-naphthyl ferrocenyl aziridinyl methanol) were synthesized by using the literature procedure reported by our group. The catalytic performance of **1-NFAM1-4**, **CFAM1-4** and **PFAM1-4** ligands with a metal were tested as a chiral catalyst for the first time in the enantioselective synthesis of furyl-substituted pyrrolidines. After optimizing the reaction parameters, it was found that Ag-**PFAM1** ligand in toluene at 0.2 M reaction concentration at 0 °C to rt forming the product with *N*-methylmaleimide in 76% yield and 61% ee. However, in order to obtain the cycloadduct in high yield (87%) and ee (72%), it was necessary to run the reaction with dimethyl maleate at -20 °C. The 1,3-DC reaction of azomethine ylides with other dipolarophiles also formed the cycloadducts but in low yields and enantioselectivities.

CHAPTER 4

EXPERIMENTAL

4.1. General Consideration

4.1.1. General Procedure

All reactions were performed in dried round-bottom flask or schlenk tube under reduced pressure and then filled with nitrogen to provide inert atmosphere. AgOAc is light and moisture sensitive so it is wrapped by aluminum foil. All column chromatography was performed using silica gel (E. Merck Silica Gel 60, particle size: 0.040- 0.063 mm, 230-400 mesh ASTM) and TLC (Merck 250 μ m Silica Gel 60 F₂₅₄ plates) was used to check separation of compounds. Ninhydrin and phosphomolybdic acid were used as the colouring agent for TLC checking. Enantiomeric excess (ee) was specified by chiral HPLC. Racemic compounds were prepared in the absence of chiral ligands using metal. Acryloyl ferrocene **3** and dibromo compound **4** were prepared following procedure in literature.³⁶ Furyl-substituted azomethine ylide **13** was produced according to general procedure in the literature.³⁹

4.1.2. Chemicals

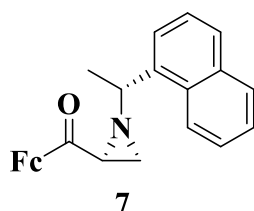
Before using, toluene, dichloromethane (DCM) and 1,2-dichloroethane (DCE) were distilled over calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled and kept over sodium and benzophenone. When THF or Et₂O are dried, the colour of solution turns a deep blue. Triethylamine (Et₃N) and *N,N*-diisopropylethylamine (DIPEA) were distilled and kept over KOH pellets. 4Å Molecular sieves (MS) were activated at 120°C in the drying oven. Liquid aldehyde and dimethyl maleate were distilled and kept over molecular sieves.

4.1.3. Instrumentation

To analyse products, ^1H - and ^{13}C - NMR spectra were determined using a Bruker spectrosopin Avance III DPX-400 Ultra shield instrument at 400 and 100 MHz respectively. In NMR, chemical shifts were reported in δ , ppm with multiplicity (s= singlet, br= broad singlet, d= doublet, dd= doublet of doublet, t= triplet, q= quartet, m= multiplet) and coupling constant was reported in Hz. Tetramethylsilane was reference in δ 0.00. Enantiomeric excess (ee) was specified by chiral HPLC and retention times of cycloproducts were identified comparing with same compounds in the literature and confirmed by that of racemic products. NMR samples of all products were prepared in CDCl_3 or acetone- d_6 . Using Rudolph Research Analytical Autopol III Polarimeter in 1 dm cell, optical rotations were measured and reported as $[\alpha]_D^{26}$ (c in mg/mL solvent). Isopropanol bath cooled by cryostat (HAAKE EK90) was used for overnight reactions at 0°C or below zero.

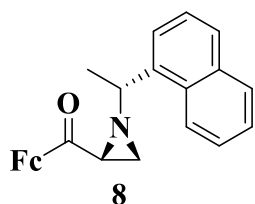
4.2. Synthesis and Characterizations of Chiral Ligands

4.2.1. Synthesis of 1-Naphthyl Aziridinyl Ketones 7 and 8



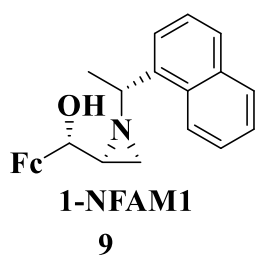
The aziridinyl ketones **7** and **8** were synthesized following procedure given in the literature.³⁶

Ketone 7: Brown-orange solid, mp: $75\text{-}76^\circ\text{C}$. $R_f = 0.54$ (4:1 Hexane:EtOAc). $[\alpha]_D^{26.5} = +54.8$ ($c = 0.025$, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ 8.08 (d, $J = 7.7$ Hz, 1H), 8.03 (d, $J = 6.9$ Hz, 1H), 7.93 – 7.86 (m, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.59 – 7.46 (m, 3H), 5.10 – 5.0 (m, 1H), 5.01 – 5.00 (m, 1H), 4.59 (dd, $J = 3.6, 2.2$ Hz, 2H), 4.28 (s, $J = 20.2$ Hz, 5H), 3.42 (q, $J = 6.5$ Hz, 1H), 2.78 (dd, $J = 6.5, 3.1$ Hz, 1H), 2.36 (d, $J = 1.9$ Hz, 1H), 1.70 (d, $J = 6.5$ Hz, 3H), 1.68 (dd, $J = 6.5, 1.1$ Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 200.2, 139.6, 133.6, 130.5, 128.9, 127.4, 125.7, 125.6, 125.2, 124.1, 122.8, 78.0, 72.45, 72.38, 69.7, 69.6, 43.6, 35.9, 23.1. IR (cm^{-1}): 2973, 1659, 1455, 1255, 1069, 800, 749. HRMS-EI (m/z): calculated for $\text{C}_{25}\text{H}_{24}\text{FeNO}$ [$\text{M}+\text{H}$]: 410.1207 and found 410.1273.



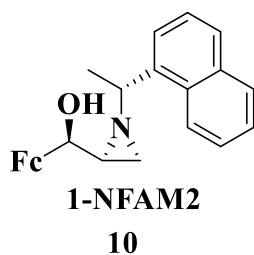
8: Brown solid, mp: 180-182°C. $R_f = 0.41$ (4:1 Hexane:EtOAc). $[\alpha]_D^{22.7} = +221.6$ ($c = 0.006$, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ 7.98 – 7.91 (m, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 2H), 7.48 (td, $J = 7.6, 3.8$ Hz, 2H), 4.64 (s, 1H), 4.60 (s, 1H), 4.40 – 4.37 (m, 2H), 3.77 (s, 5H), 3.43 (q, $J = 6.4$ Hz, 1H), 2.56 (t, $J = 3.2$ Hz, 1H), 2.53 (t, $J = 4.9$ Hz, 1H), 2.02 (t, $J = 5.2$ Hz, 1H), 1.68 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 199.5, 139.9, 133.7, 130.5, 129.0, 127.6, 125.9, 125.8, 125.3, 124.3, 78.4, 72.3, 72.2, 69.5, 69.4, 69.3, 69.1, 41.5, 37.6, 22.8. IR (cm^{-1}): 2965, 1650, 1453, 1253, 1001, 800, 779. HRMS-EI (m/z): calculated for $\text{C}_{25}\text{H}_{24}\text{FeNO}$ [$\text{M}+\text{H}$]: 410.1207 and found 410.1273.

4.2.2. Synthesis of Naphtyl-substituted Ferrocenyl Aziridinyl Methanol (*R,R,R*)



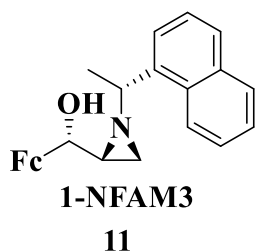
Ketone **7** (3.7 mmol) was dissolved in MeOH (0.1M) and cooled to -78°C . Then, ZnCl_2 was added (5.6 mmol). After 1 h, NaBH_4 (7.5 mmol) was added and solution was stirred for 2 h. TLC showed that there was no starting material. The solution was hydrolyzed with distilled water and extracted with DCM. The aqueous layer was extracted one more time with DCM. The organic layers were dried over MgSO_4 , concentrated and purified by column chromatography on silica gel using 4:1 hexane/EtOAc. Orange oil. $R_f = 0.59$ (4:1 Hexane:EtOAc). $[\alpha]_D^{32.0} = +66.5$ ($c = 0.01$, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ 8.01 (d, $J = 5.6$ Hz, 1H), 7.87 (dd, $J = 6.7, 3.0$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.55 – 7.43 (m, 3H), 4.64 (d, $J = 4.1$ Hz, 1H), 4.36 – 4.33 (m, 1H), 4.31 – 4.29 (m, 1H), 4.23 (s, 5H), 4.21 – 4.17 (m, 2H), 3.40 (q, $J = 6.8$ Hz, 1H), 2.07 – 2.02 (m, 1H), 1.92 (d, $J = 3.5$ Hz, 1H), 1.49 (d, $J = 6.5$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 140.1, 133.6, 130.5, 128.8, 128.0, 127.1, 125.6, 125.1, 123.7, 122.9, 89.4, 68.4, 68.1, 67.8, 67.7, 67.0, 66.0, 44.1, 29.9, 23.1. IR (cm^{-1}): 3422, 2970, 1238, 1102, 1000, 799, 776. HRMS-EI (m/z): calculated for $\text{C}_{25}\text{H}_{26}\text{FeNO}$ [$\text{M}+\text{H}$]: 412.1364 and found 412.1380.

4.2.3. Synthesis of Naphthyl Ferrocenyl Aziridinyl Methanol (*S,R,R*) **10**

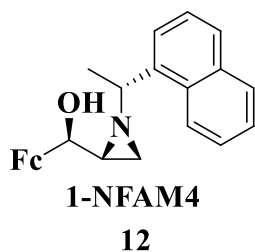


Ketone **7** (2.78 mmol) was dissolved in THF (16 mL, distilled over Na-benzophenone) in a reaction flask. The flask was cooled to -78 °C and L-Selectride (4 mL, from 1M THF solution) was added slowly over 30 min. After stirring about 1h, TLC showed no starting material. To the reaction flask was added 10% NaOH solution (15 mL) followed by EtOAc (20 mL) and the two layers were separated. The aqueous layer was extracted one more time with EtOAc (25 mL). The combined organic layers were dried over MgSO₄ concentrated and purified by flash chromatography on silica gel using 3:1 hexane/EtOAc. These extraction and column chromatography were repeated respectively once more to get rid of L-Selectride totally. Dark orange oil. $R_f = 0.69$ (2:1 Hexane:EtOAc). $[\alpha]_D^{25.4} = +62.1$ ($c = 0.0125$, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ 8.00 (d, $J = 5.3$ Hz, 1H), 7.92 (d, $J = 7.2$ Hz, 1H), 7.87 (dt, $J = 7.6, 2.6$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.56–7.42 (m, 3H), 4.38 (t, $J = 1.8$ Hz, 1H), 4.27 – 4.25 (m, 1H), 4.25 (s, 5H), 4.20 (t, $J = 1.9$ Hz, 2H), 3.31 (q, $J = 6.5$ Hz, 1H), 2.89 (d, $J = 4.8$ Hz, 1H), 1.98 (td, $J = 6.1, 3.4$ Hz, 1H), 1.83 (d, $J = 3.5$ Hz, 1H), 1.56 (d, $J = 6.5$ Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 140.4, 133.7, 130.7, 128.9, 127.2, 125.7, 125.7, 125.2, 123.8, 123.0, 90.7, 70.6, 68.5, 67.9, 67.8, 66.4, 65.9, 46.0, 31.7, 23.4. IR (cm⁻¹): 3431, 2922, 2853, 1016, 799, 778. HRMS-EI (m/z): calculated for C₂₅H₂₆FeNO [M+H]: 412.1364 and found 412.1405.

4.2.4. Synthesis of Naphtyl-substituted FAMs (*R,S,R*) **11** and (*S,S,R*) **12**



Ketone **8** (0.49 mmol) was dissolved in THF (5 mL, distilled over Na-benzophenone) and cooled to 0°C. Then, LiAlH₄ (0.49 mmol) was added and solution was stirred for 30 min. TLC showed that there was no starting material. The solution was hydrolyzed with distilled water and extracted with EtOAc. The aqueous layer was extracted one more time with EtOAc. The organic layers were dried over MgSO₄, concentrated. Then, two isomers of FAM were obtained together. They were separated from each other by column chromatography on silica gel using 4:1 hexane/EtOAc. **11**: Light Brown viscous oil, *R_f* = 0.64 (3:1 Hexane:EtOAc). $[\alpha]_D^{26.5} = -15.1$ (*c* = 0.025, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): 8.26 (s, 1H), 8.01 (s, 1H), 7.97 – 7.89 (m, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.45 (m, 3H), 4.10 (s, 1H), 4.05 (s, 5H), 3.98 (dt, *J* = 2.5, 1.3 Hz, 1H), 3.94 (td, *J* = 2.4, 1.3 Hz, 1H), 3.89 (dt, *J* = 2.5, 1.3 Hz, 1H), 3.42 (q, *J* = 5.8 Hz, 1H), 2.94 (s, 1H), 1.91 (d, *J* = 3.4 Hz, 1H), 1.80 (td, *J* = 6.2, 3.3 Hz, 1H), 1.70 (d, *J* = 6.4 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 140.4, 134.0, 130.8, 129.1, 127.7, 125.8, 125.7, 125.4, 124.4, 123.1, 89.9, 70.9, 68.3, 67.6, 67.5, 66.2, 66.1, 44.0, 32.1, 22.6. HRMS-EI (*m/z*): calculated for C₂₅H₂₆FeNO [*M*+*H*]: 412.1364 and found 412.1394.



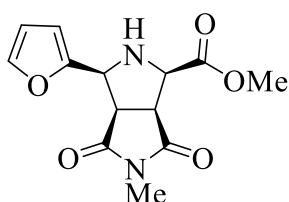
12: Orange solid, mp: 149-150°C. *R_f* = 0.63 (2:1 Hexane:EtOAc). $[\alpha]_D^{26.2} = -52.0$ (*c* = 0.025, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ 7.90 – 7.85 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.44 (m, 3H), 4.40 (d, *J* = 2.3 Hz, 1H), 4.10 – 4.07 (m, 2H), 4.06 (s, 5H), 4.05 – 4.03 (m, 2H), 3.42 (q, *J* = 6.8 Hz, 1H), 2.78 (s, 1H), 2.17 (d, *J* = 3.6 Hz, 1H), 1.79 (dt, *J* = 6.7, 3.4 Hz, 1H), 1.58 (d, *J* = 6.5 Hz, 4H). ¹³C NMR (CDCl₃, 100 MHz): δ 140.3, 133.8, 130.7, 129.0, 127.4, 125.8, 125.3, 123.7, 123.0, 89.3, 68.4, 67.9, 67.6, 66.8, 66.7, 66.3, 42.5, 30.1, 22.7. IR (cm⁻¹): 3469, 2975, 2864, 1231, 1103, 998, 830, 775. HRMS-EI (*m/z*): calculated for C₂₅H₂₆FeNO [*M*+*H*]: 412.1364 and found 412.1404.

4.3. Synthesis and Characterizations of Cycloadducts

4.3.1. Synthesis of Cycloadducts

All cycloadducts were synthesized based on procedure given in the literature.⁴⁰ Differently, as ligands, derivatives of **FAM** ligands, **1-NFAM**, **CFAM** and **PFAM** chiral ligands, were used. They were synthesized by our group as mentioned before. Also, only furyl-substituted azomethine ylide was used.

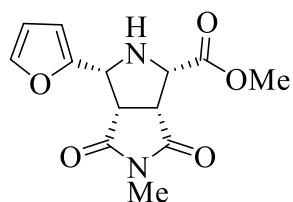
4.3.2. Characterizations of methyl (1R,3S,3aR,6aS)-3-(furan-2-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **15a**



15a

Based on the procedure in the literature, **15a** was obtained in 76% yield and 61% ee as a white solid, mp: 163.8-166.0 °C. $R_f = 0.41$ (EtOAc). $[\alpha]_D^{30.2} = -28.7$ ($c = 0.01$, DCM). ^1H NMR (CDCl_3 , 400 MHz): δ 7.39 (t, $J = 1.3$ Hz, 1H), 6.36 (d, $J = 1.7$ Hz, 2H), 4.57 (t, $J = 9.0$ Hz, 1H), 4.03 (dd, $J = 9.3$, 7.2 Hz, 1H), 3.88 (s, 3H), 3.59 (d, $J = 7.4$ Hz, 1H) 3.46 (t, $J = 8.2$ Hz 1H), 2.93 (s, 3H), 2.66 (t, $J = 9.3$ Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 174.59, 173.80, 168.83, 148.42, 141.47, 109.38, 106.99, 60.94, 57.65, 51.41, 48.35, 24.06. HPLC: Chiralpak AS-H column, UV detection at 210 nm, eluent: hexane:2-propanol 50:50, flowrate: 1 mL/min, $t_R = 8.200$ min (minor), $t_R = 15.707$ min (major). IR (cm^{-1}): 3349, 3124, 2955, 2853, 1732, 1692, 1504, 1097. HRMS-EI (m/z): calculated for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_5$ [M+H]: 279.09810 and found 279.09791.

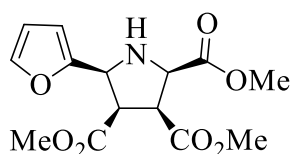
4.3.3. Characterizations of methyl (1S,3R,3aS,6aR)-3-(furan-2-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate **ent-15a**



ent-15a

Based on the procedure in the literature, **ent-15a** was obtained in 74% yield and 65% ee as a white solid, HPLC: Chiralpak AS-H column, UV detection at 210 nm, eluent: hexane:2-propanol 50:50, flowrate: 1 mL/min, $t_R = 9.027$ min (major), $t_R = 17.650$ min (minor).

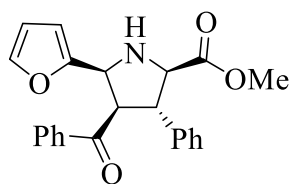
4.3.4. Characterizations of trimethyl (2R,3S,4R,5S)-5-(furan-2-yl)pyrrolidine-2,3,4-tricarboxylate **15b**



15b

Based on the procedure in the literature, **15b** was obtained in 87% yield and 72% ee as a white solid, mp: 82.6-84.6 °C. $R_f = 0.33$ (EtOAc). $[\alpha]_D^{30.4} = -36.8$ ($c = 0.01$, DCM). ^1H NMR (CDCl_3 , 400 MHz): δ 7.33 (t, $J = 1.3$ Hz, 1H), 6.31 (d, $J = 1.3$ Hz, 2H), 4.48 (d, $J = 7.0$ Hz, 1H), 4.10 (d, $J = 8.8$ Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.64 (dd, $J = 8.8, 7.7$ Hz, 1H), 3.48 (t, $J = 7.3$ Hz, 1H), 3.44 (s, 3H), 3.28 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.81, 170.52, 150.73, 141.84, 110.20, 106.90, 61.57, 59.16, 52.46, 52.10, 51.72, 50.97, 50.51. HPLC: Chiralpak AS-H column, UV detection at 210 nm, eluent: hexane:2-propanol 70:30, flowrate: 1 mL/min, $t_R = 7.007$ min (minor), $t_R = 15.480$ min (major). IR (cm^{-1}): 3313, 3000, 2950, 1740, 1722, 1505, 1174. HRMS-EI (m/z): calculated for $\text{C}_{14}\text{H}_{18}\text{NO}_7$ $[\text{M}+\text{H}]$: 312.10833 and found 312.10824.

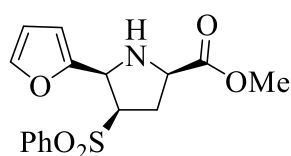
4.3.5. Characterizations of methyl (2R,3S,4R,5S)-4-benzoyl-5-(furan-2-yl)-3-phenylpyrrolidine-2-carboxylate **15f**



15f

Based on the procedure in the literature, **15f** was obtained in 87% yield and 18% ee as a white solid, mp: 129-131 °C. $R_f = 0.43$ (1:1 Hexane:EtOAc). $[\alpha]_D^{30.7} = +10.8$ ($c = 0.01$, DCM). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.69-7.63 (m, 2H), 7.41-7.13 (m, 9H), 7.02 (t, $J = 1.3$ Hz, 1H), 6.02 (d, $J = 1.4$ Hz, 2H), 4.97 (d, $J = 8.0$ Hz, 1H), 4.40 (t, $J = 8.1$ Hz, 1H), 4.14 (t, $J = 8.3$ Hz, 1H), 4.06 (d, $J = 8.5$ Hz, 1H), 3.66 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 197.19, 173.27, 151.61, 141.92, 140.77, 136.80, 132.82, 128.79, 128.38, 128.11, 127.84, 127.16, 110.15, 108.06, 67.12, 60.10, 59.29, 52.42, 51.18. HPLC: Chiralpak AS-H column, UV detection at 210 nm, eluent: hexane:2-propanol 95:5, flowrate: 1 mL/min, $t_R = 29.107$ min (minor), $t_R = 37.240$ min (major). IR (cm^{-1}): 3295, 3123, 2951, 1739, 1722, 1673, 1504, 1174, 732. HRMS-EI (m/z): calculated for $\text{C}_{23}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]$: 376.15488 and found 376.15497.

4.3.6. Characterizations of methyl (2R,4R,5R)-5-(furan-2-yl)-4-(phenylsulfonyl)pyrrolidine-2-carboxylate **15g**



15g

Based on the procedure in the literature, **15g** was obtained in 33% yield and 6% ee as a white solid, mp: 132-134 °C. $R_f = 0.29$ (EtOAc). $[\alpha]_D^{31.0} = -1.4$ ($c = 0.01$, DCM). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.63-7.36 (m, 5H), 7.08 (d, $J = 1.7$ Hz, 1H), 6.27 (d, $J = 3.2$ Hz, 1H), 6.22 (t, $J = 2.4$ Hz, 1H), 4.55 (s, 1H), 3.96 (s, 1H), 3.74 (s, 3H), 2.73 (s, 2H), 2.49 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 172.37, 149.73, 142.44, 138.58, 133.19, 129.06, 127.97, 110.34, 109.25, 66.15, 58.37, 56.90, 52.55, 50.65, 29.75. HPLC: Chiralpak AD-H column, UV detection at 210 nm, eluent: hexane:2-propanol 70:30, flowrate: 0.7 mL/min, $t_R = 23.867$ min (minor), $t_R = 69.887$ min (major). IR (cm^{-1}): 3284, 3133, 2954, 2920, 2850, 1731, 1504, 1305, 1140, 752. HRMS-EI (m/z): calculated for $\text{C}_{16}\text{H}_{18}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]$: 336.09057 and found 336.09024.

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APPENDICES

A. NMR Spectra

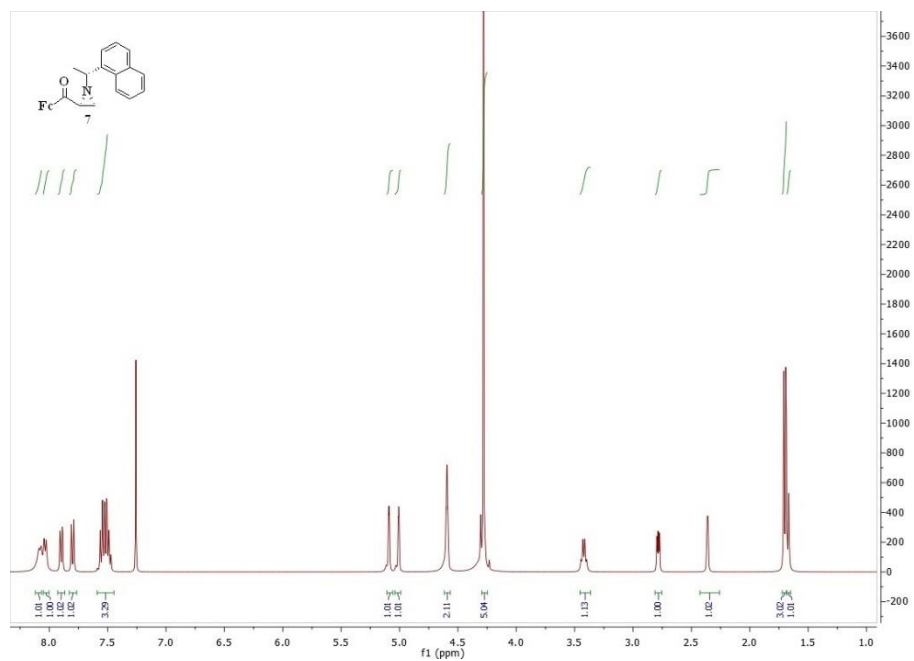


Figure 11. ^1H -NMR spectrum of compound 7

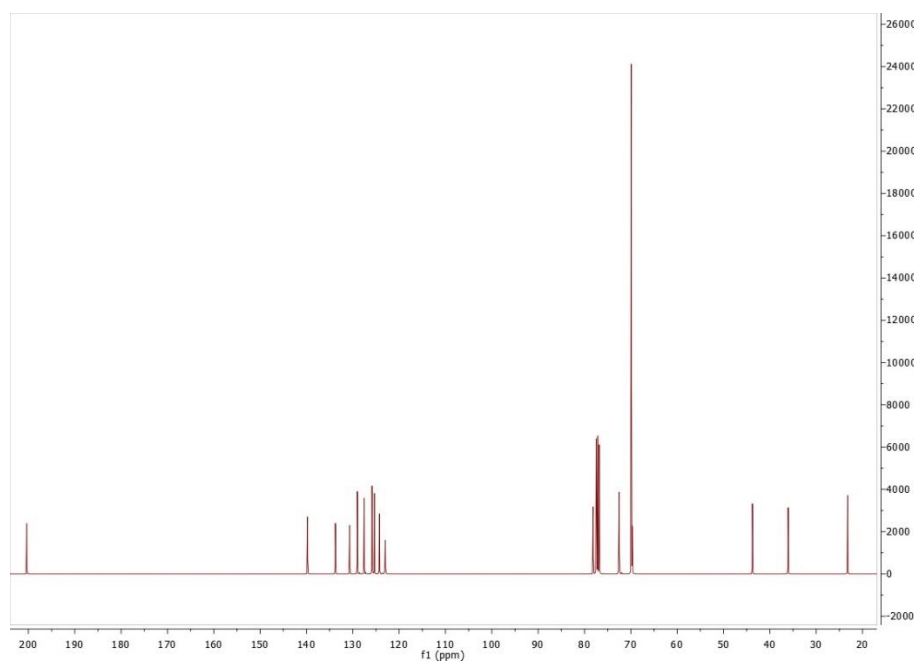


Figure 12. ^{13}C -NMR spectrum of compound 7

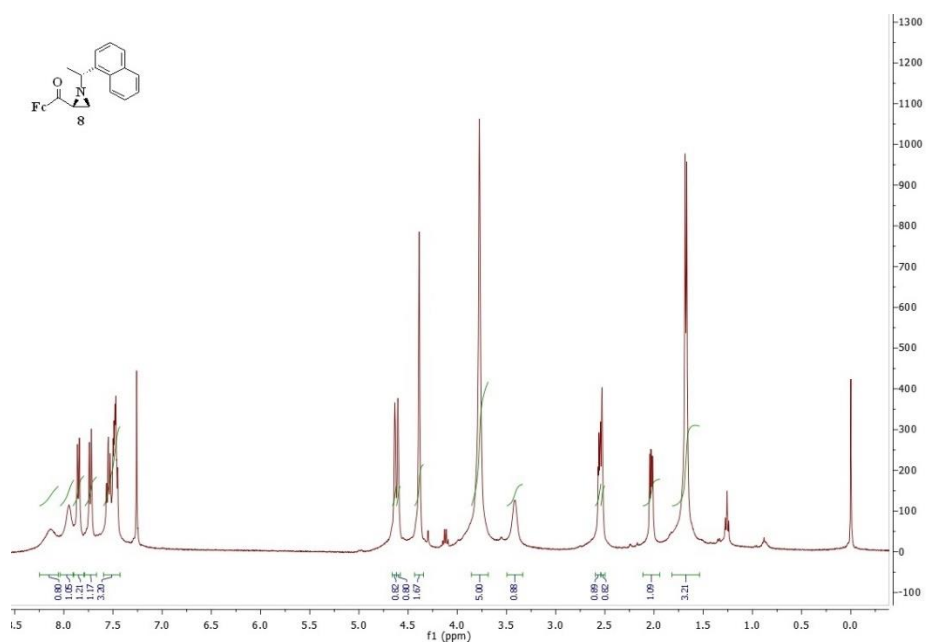


Figure 13. ¹H-NMR spectrum of compound 8

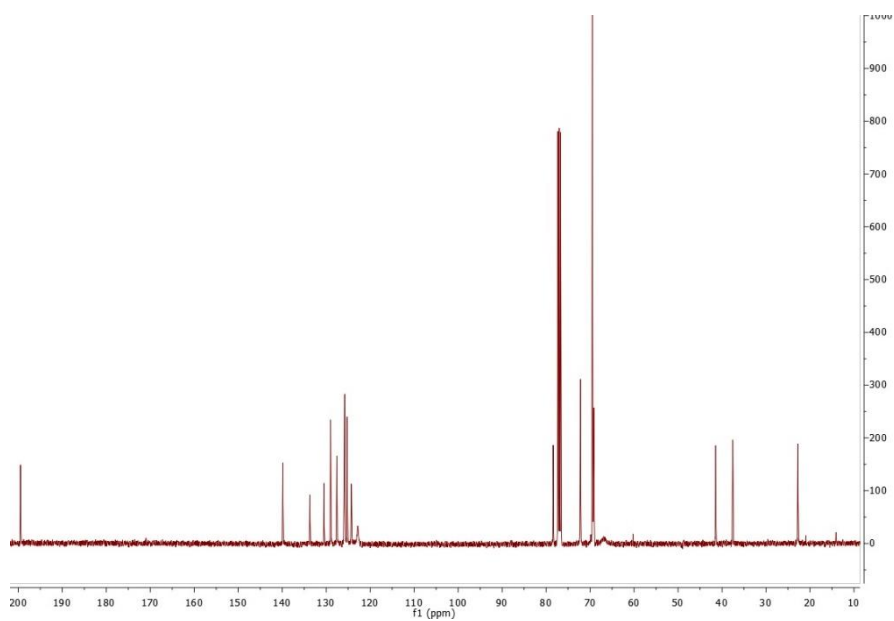
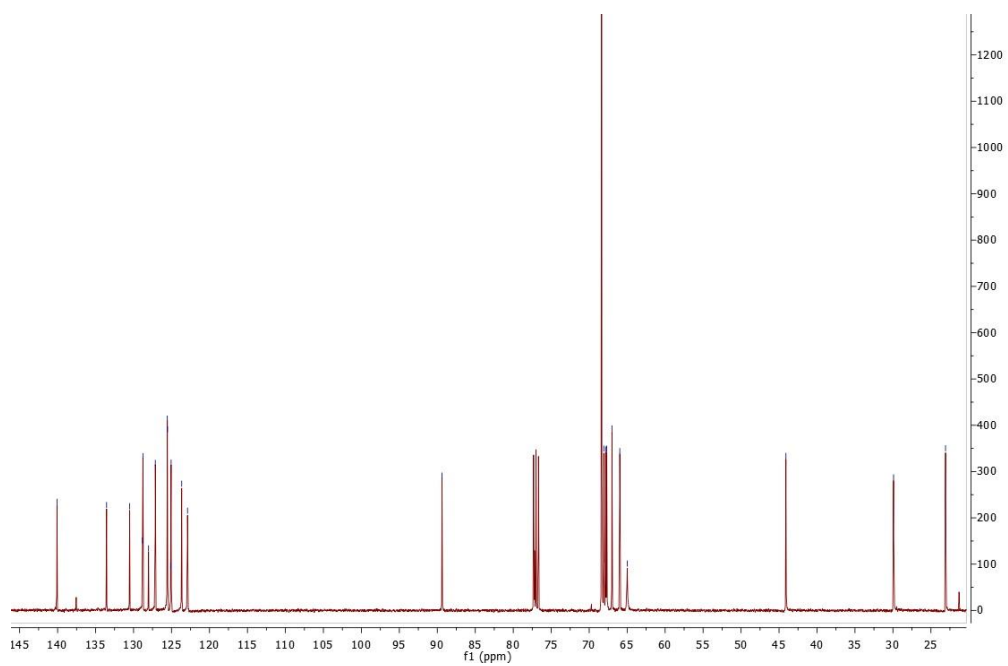
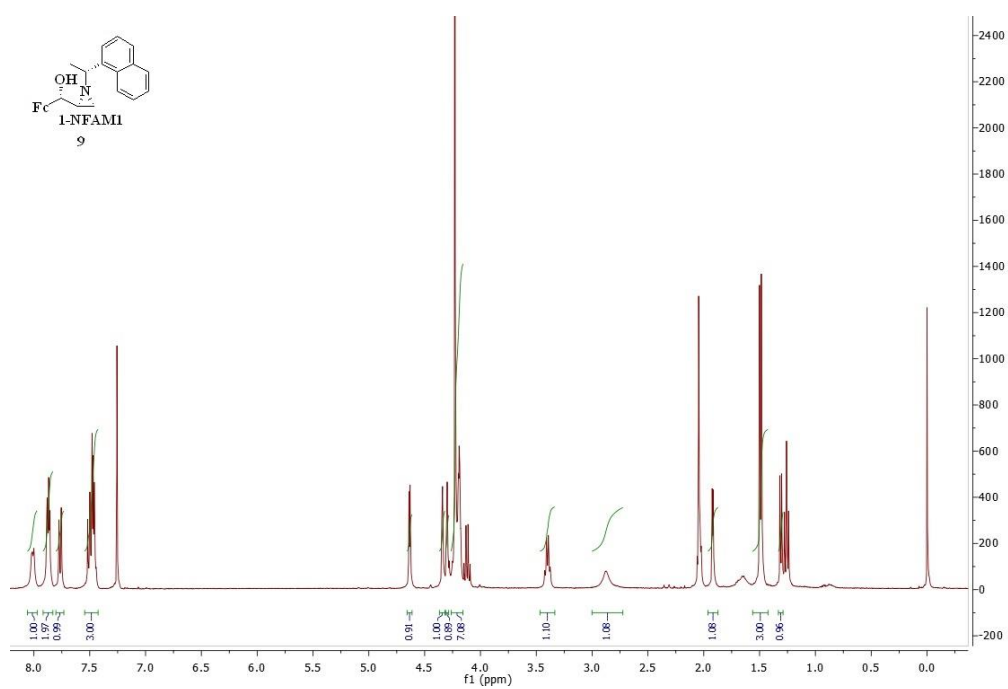


Figure 14. ¹³C-NMR spectrum of compound 8



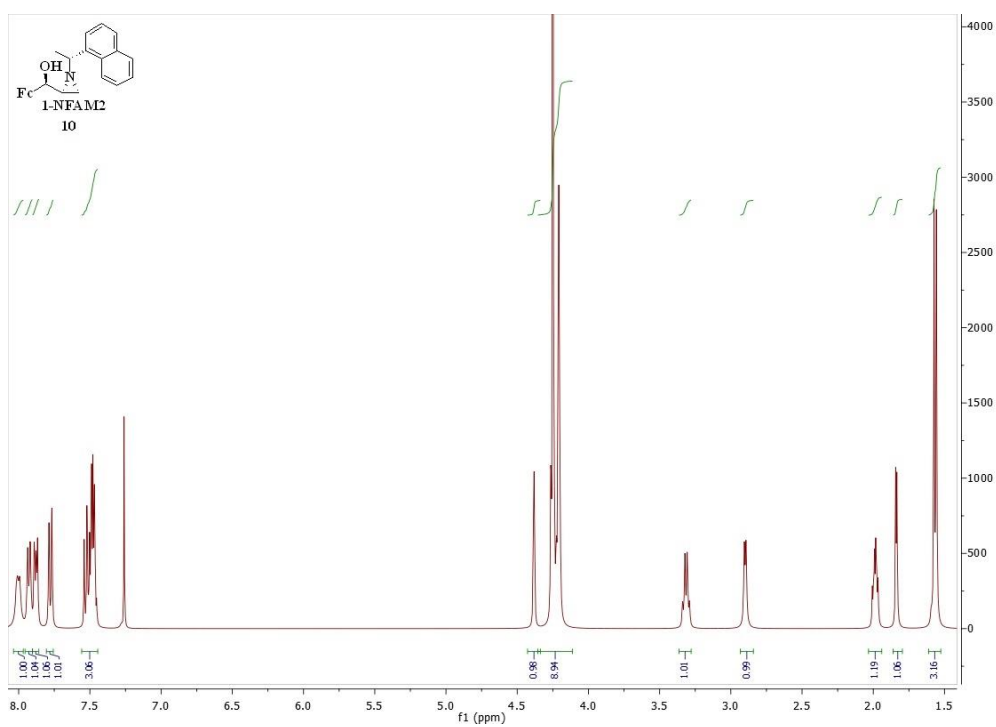


Figure 17. ^1H -NMR spectrum of compound **10**

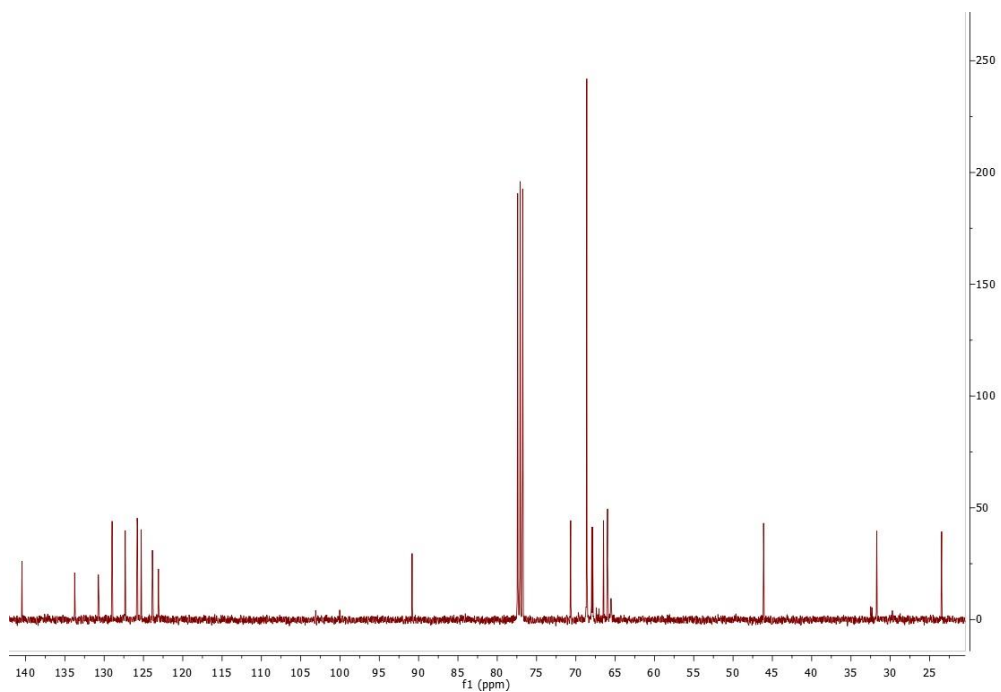


Figure 18. ^{13}C -NMR spectrum of compound **10**

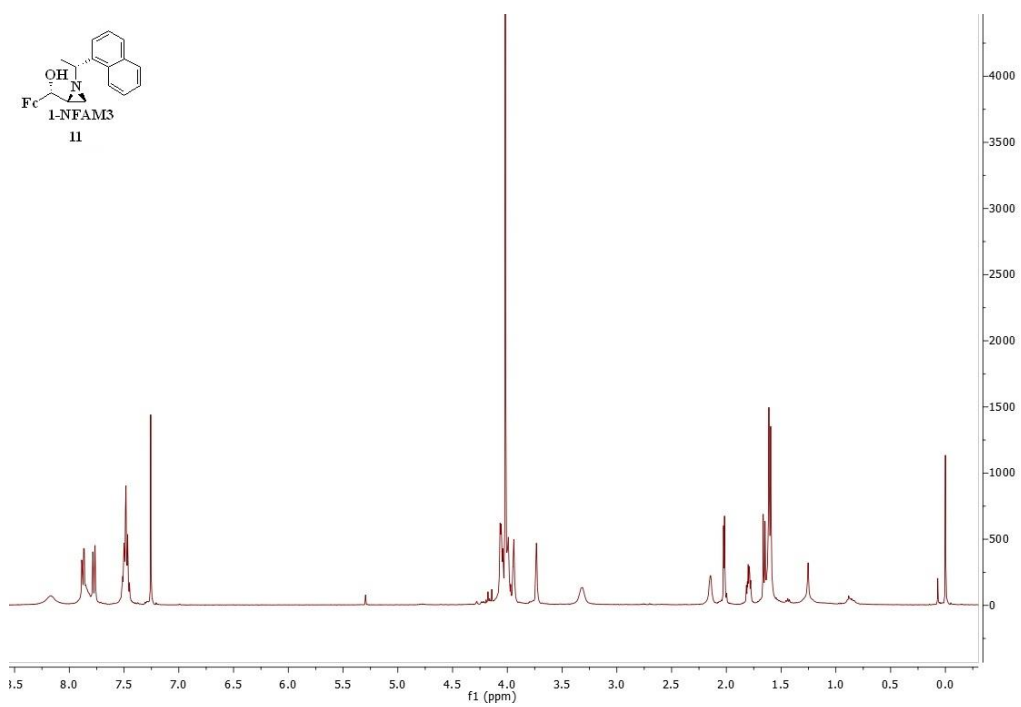


Figure 19. ¹H-NMR spectrum of compound 11

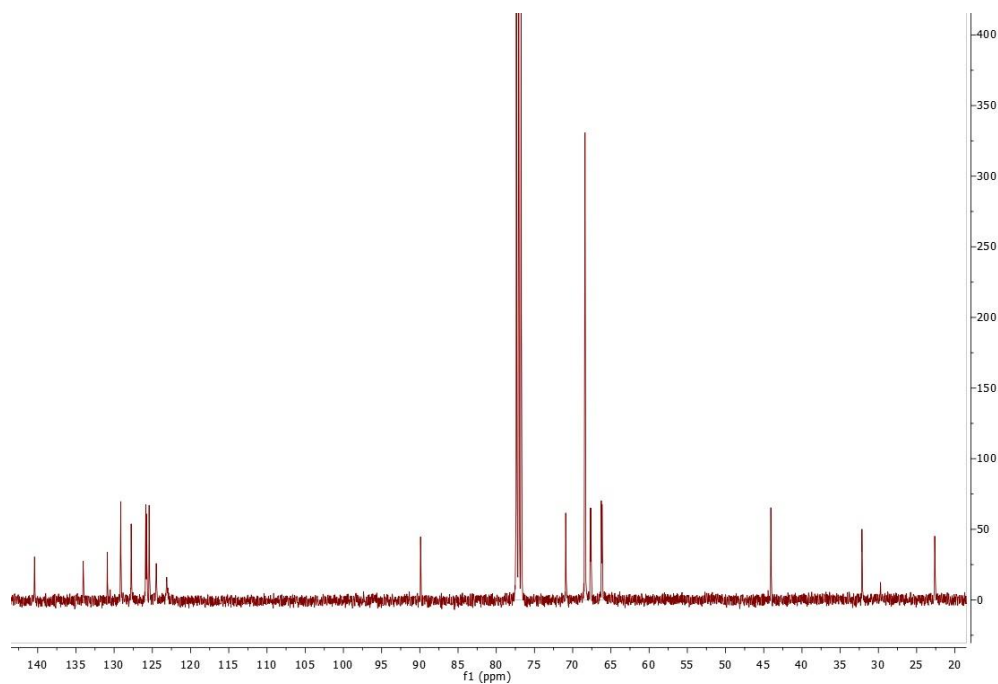
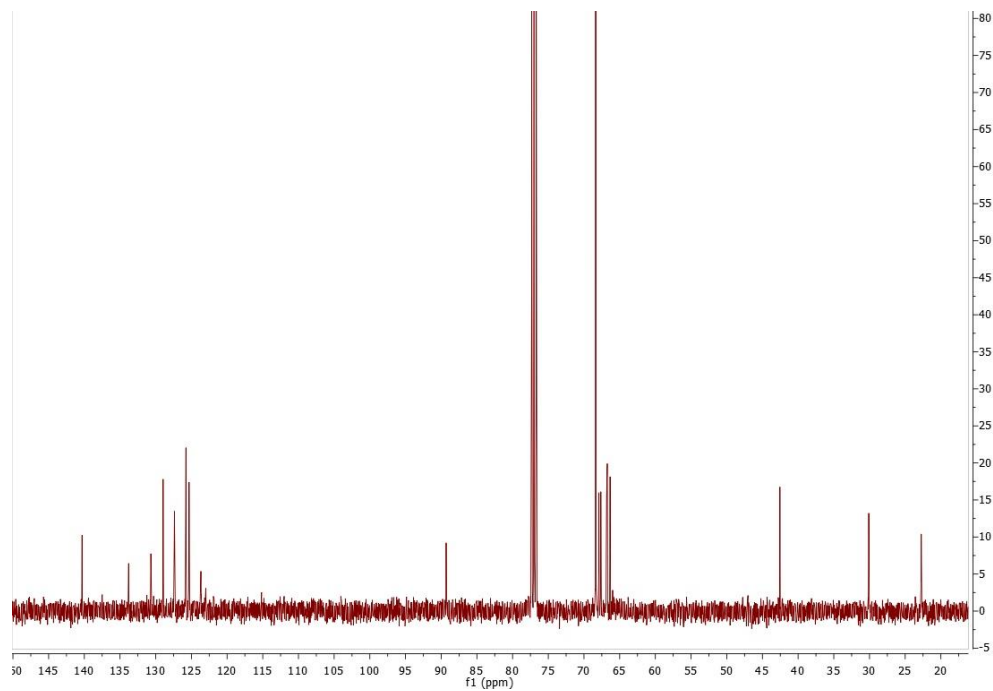
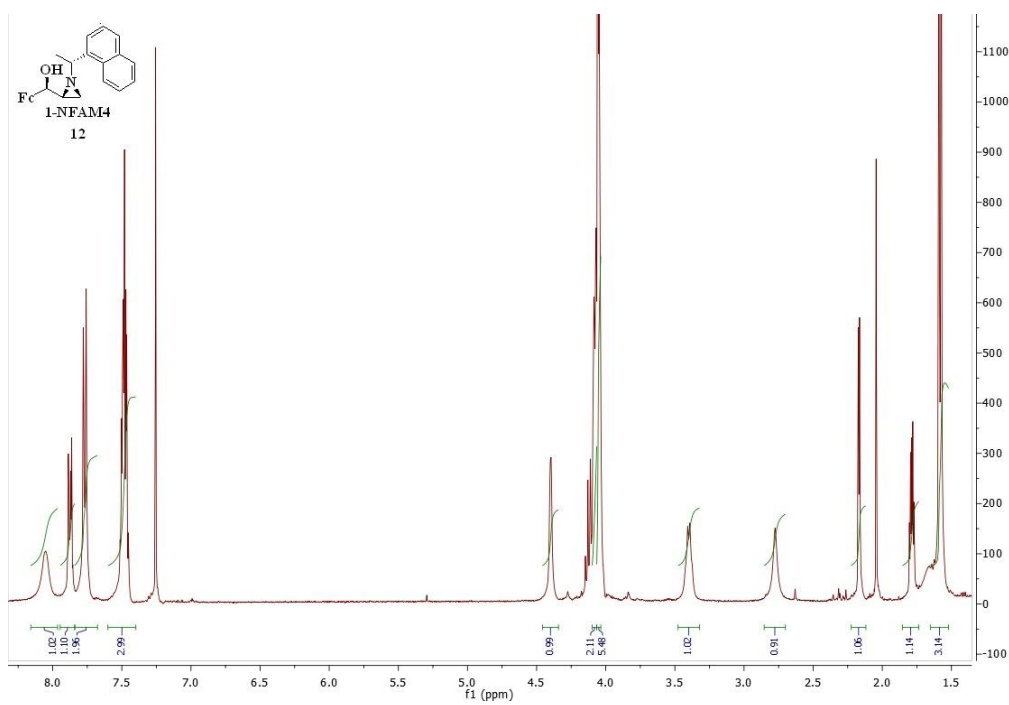


Figure 20. ¹³C-NMR spectrum of compound 11



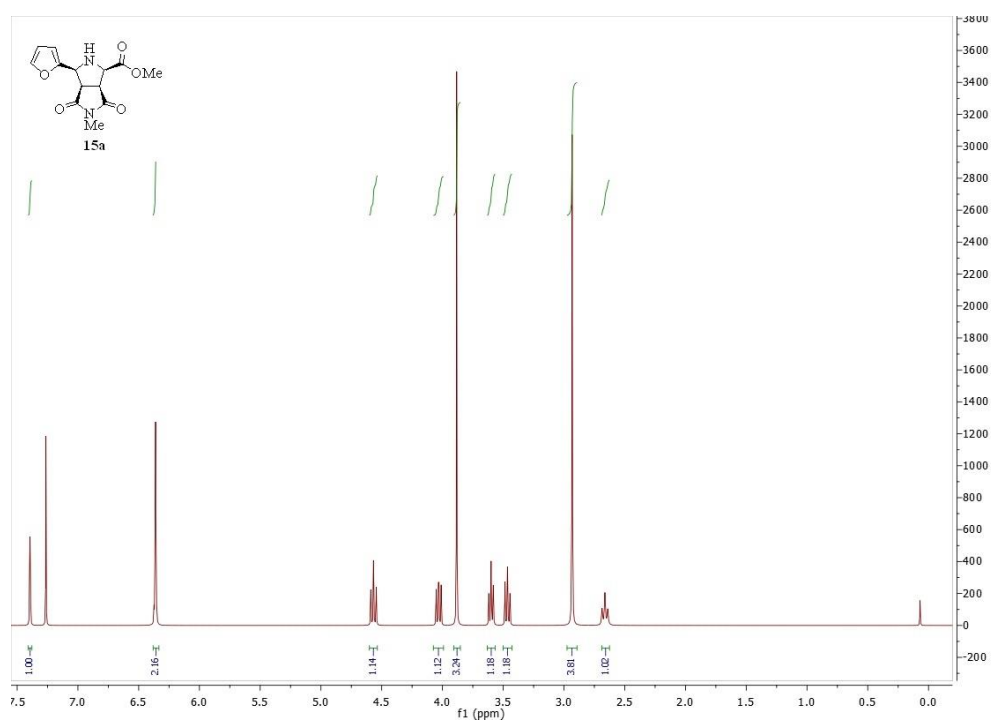


Figure 23. ¹H-NMR spectrum of compound **15a**

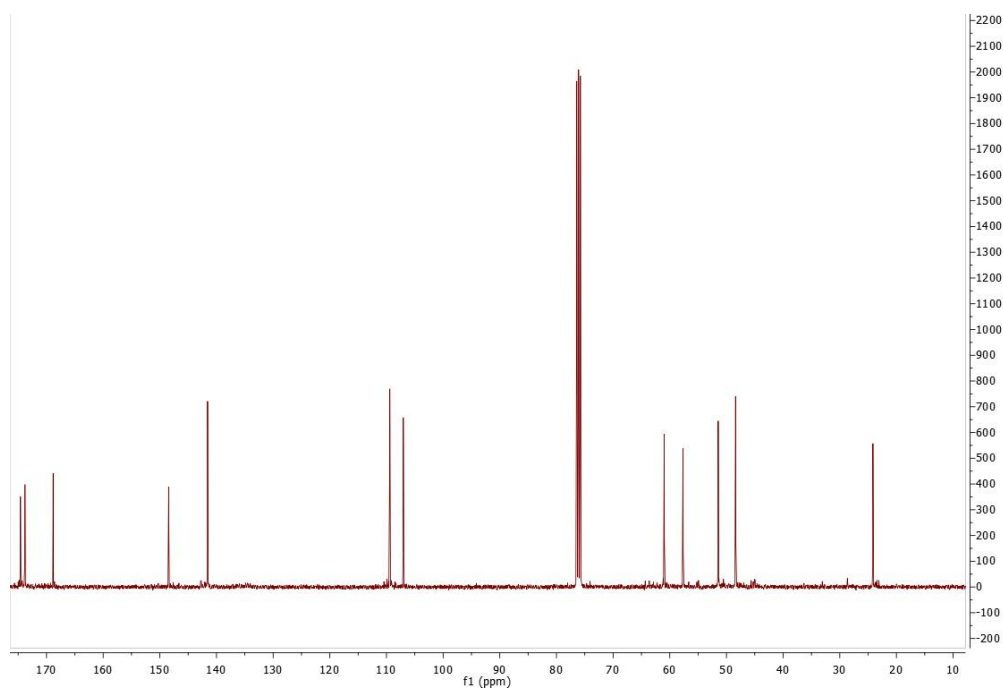


Figure 24. ¹³C-NMR spectrum of compound **15a**

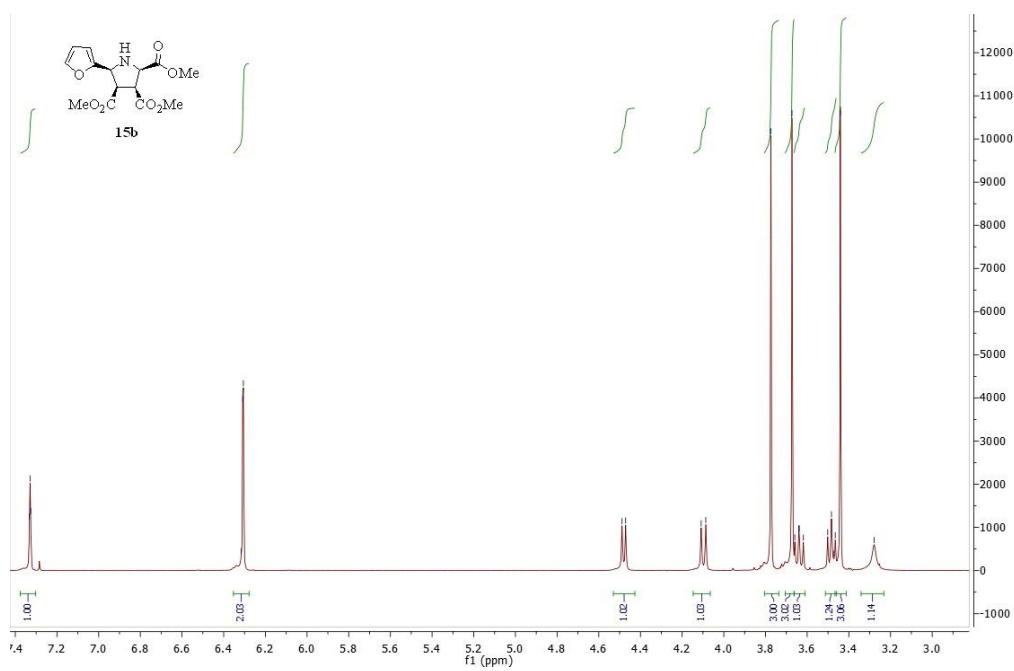


Figure 25. $^1\text{H-NMR}$ spectrum of compound **15b**

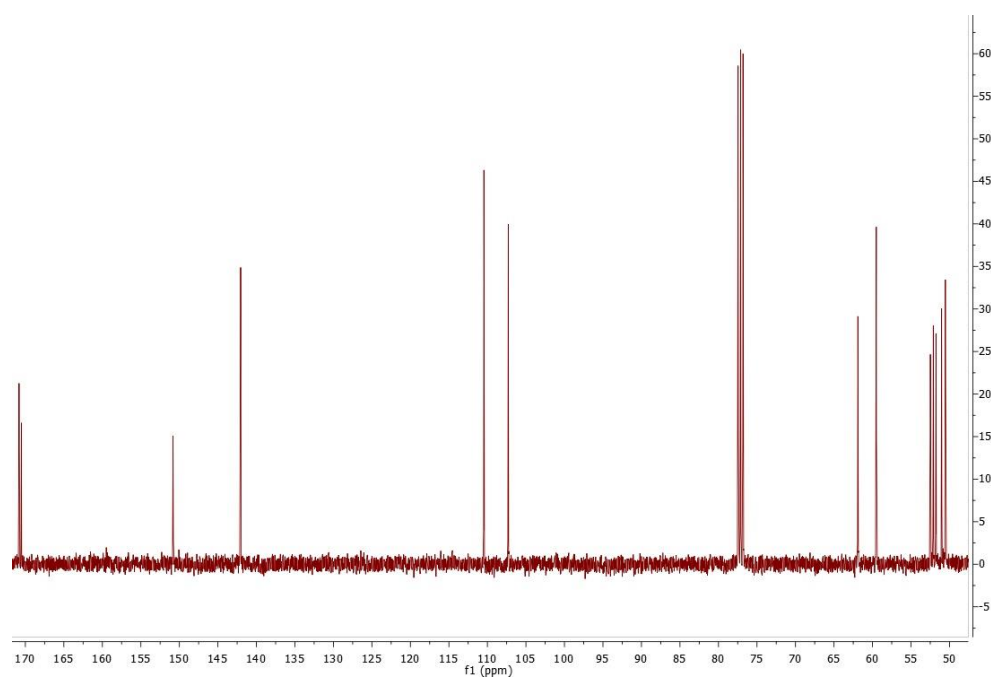


Figure 26. $^{13}\text{C-NMR}$ spectrum of compound **15b**

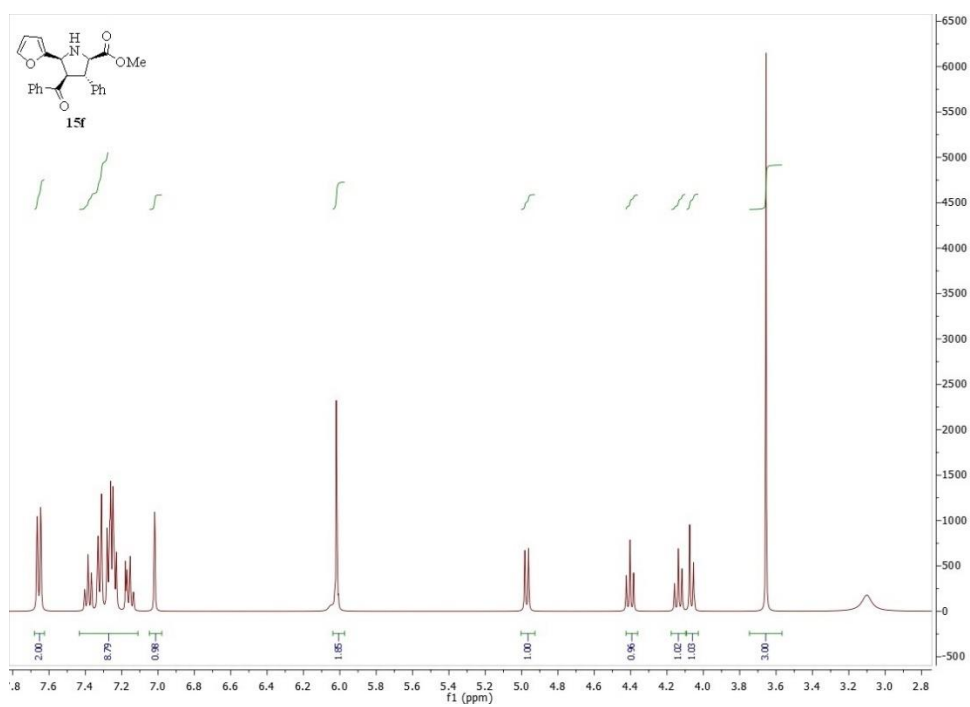


Figure 27. ¹H-NMR spectrum of compound **15f**

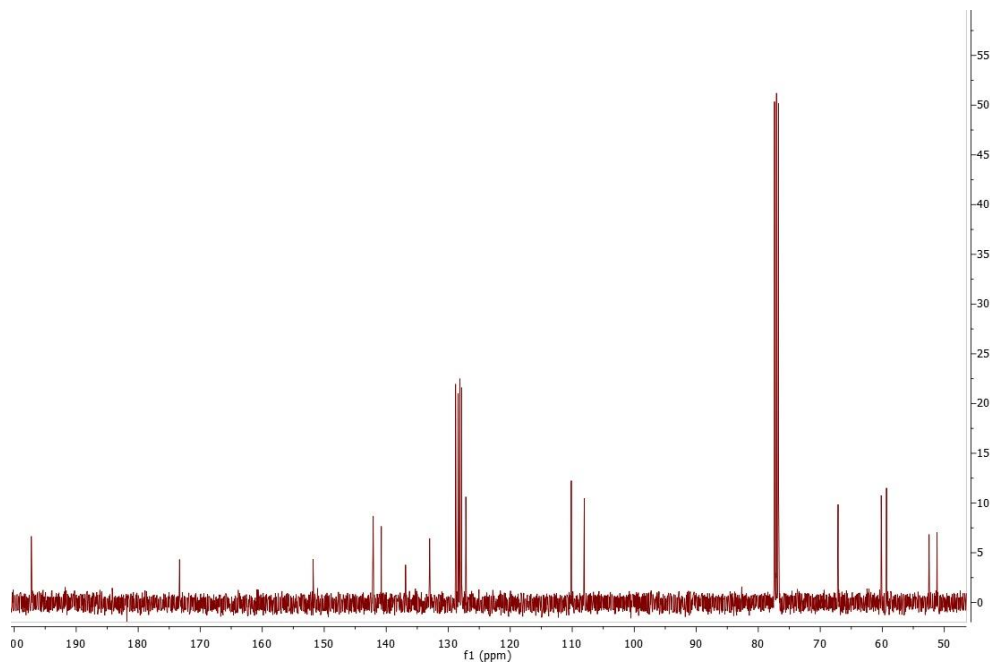


Figure 28. ¹³C-NMR spectrum of compound **15f**

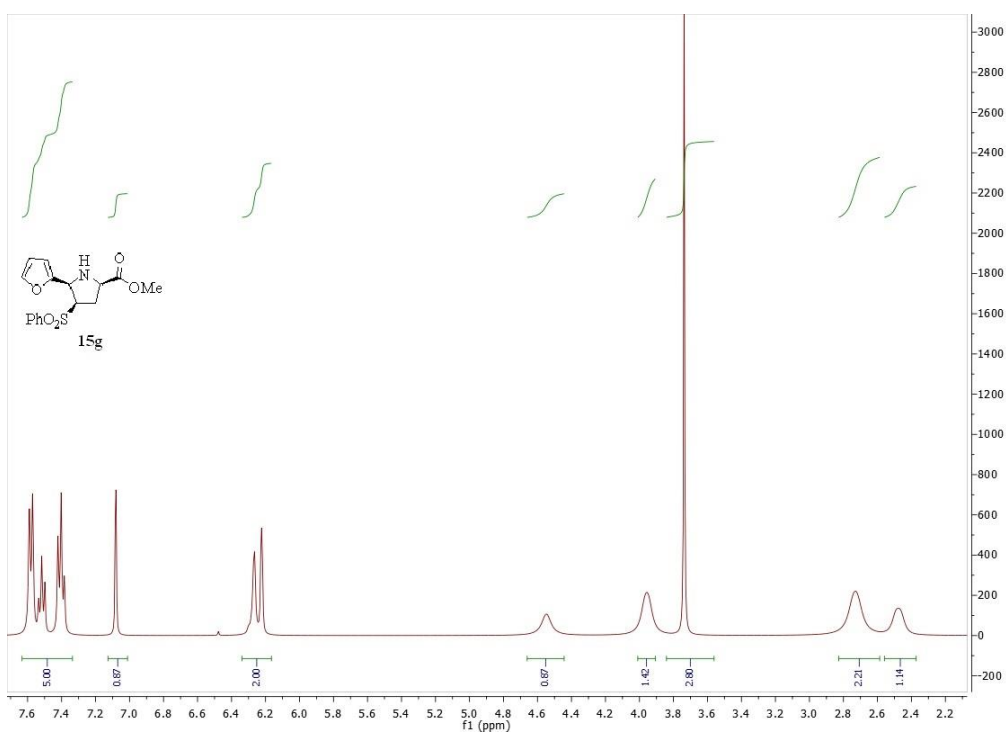


Figure 29. ¹H-NMR spectrum of compound **15g**

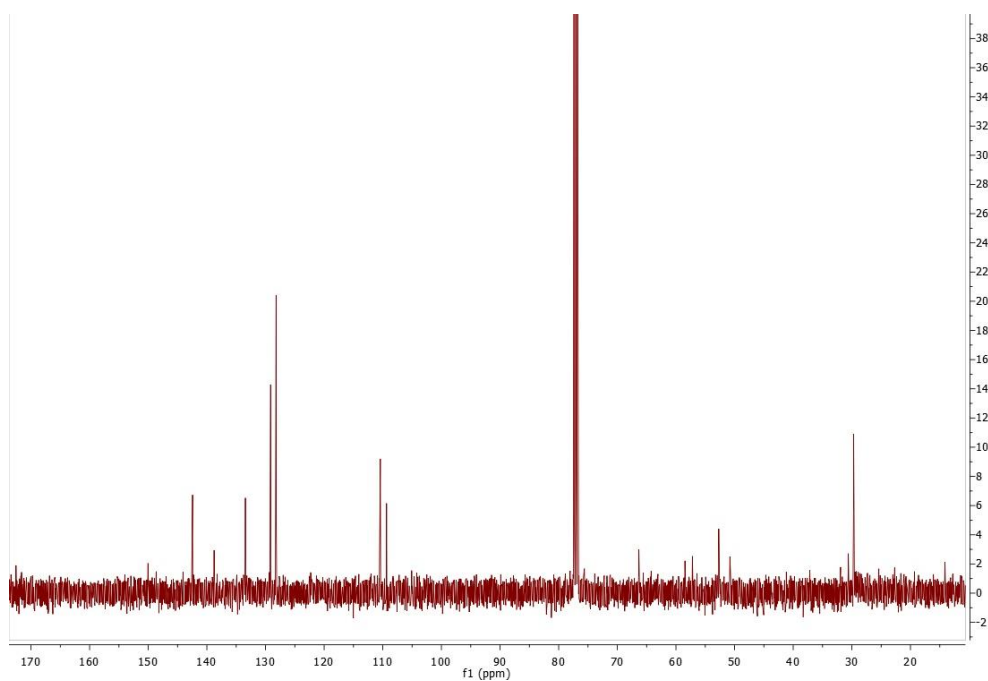


Figure 30. ¹³C-NMR spectrum of compound **15g**

B. HPLC Chromatograms

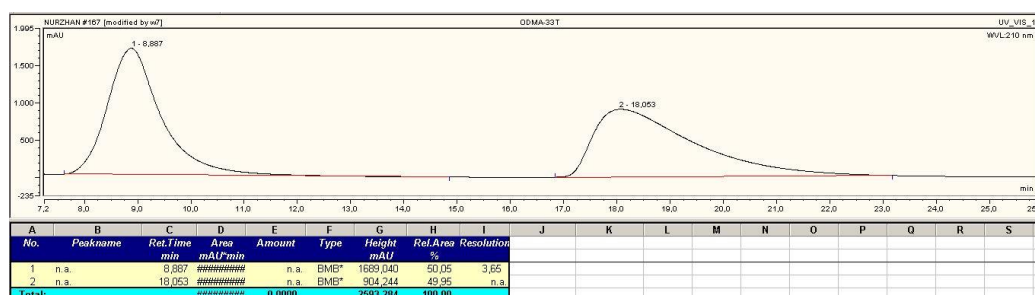


Figure 31. HPLC chromatogram of compound 15a (Rac.)

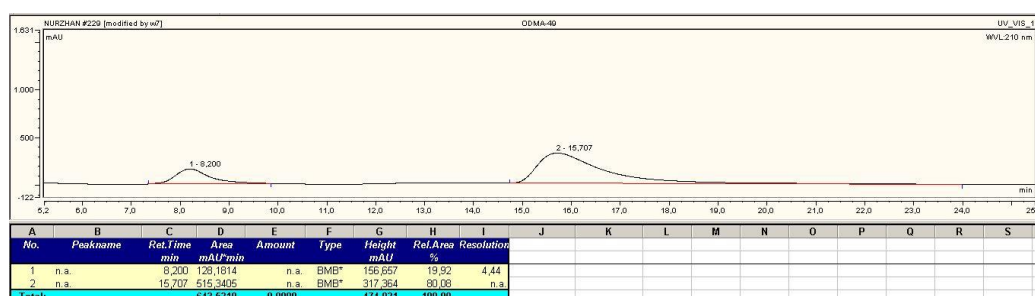


Figure 32. HPLC chromatogram of compound 15a

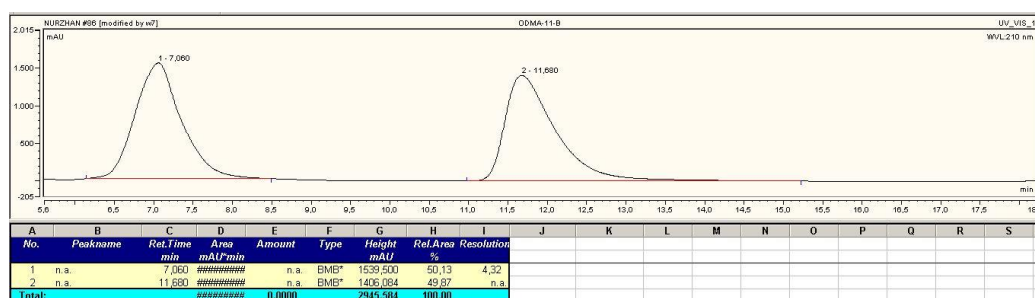


Figure 33. HPLC chromatogram of compound 15b (Rac.)

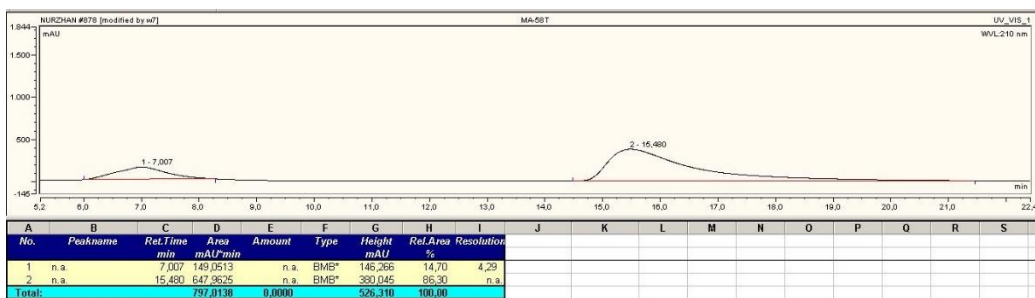


Figure 34. HPLC chromatogram of compound 15b

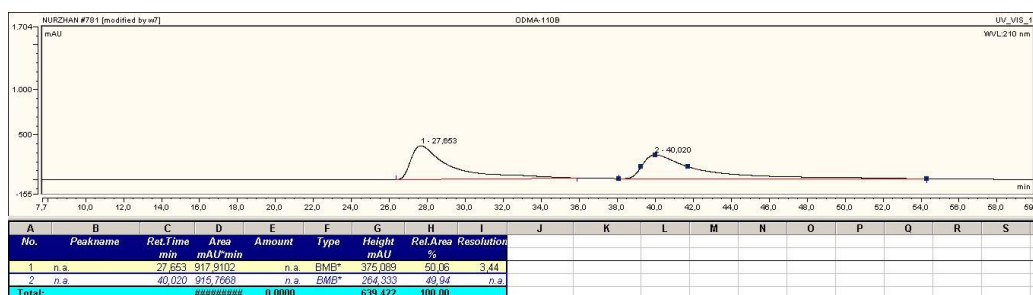


Figure 35. HPLC chromatogram of compound 15f (Rac.)

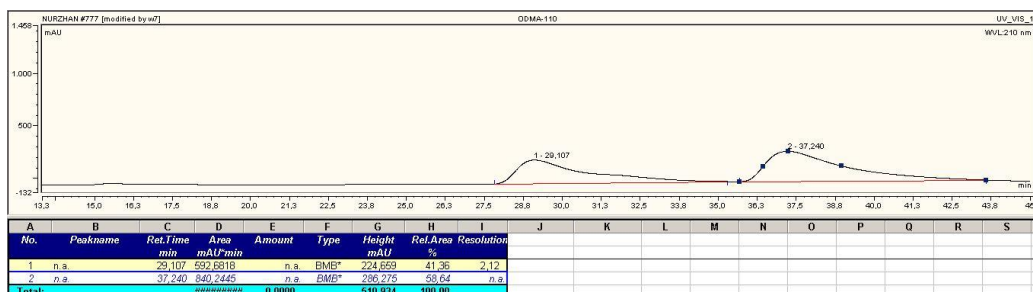


Figure 36. HPLC chromatogram of compound 15f



Figure 37. HPLC chromatogram of compound 15g (Rac.)

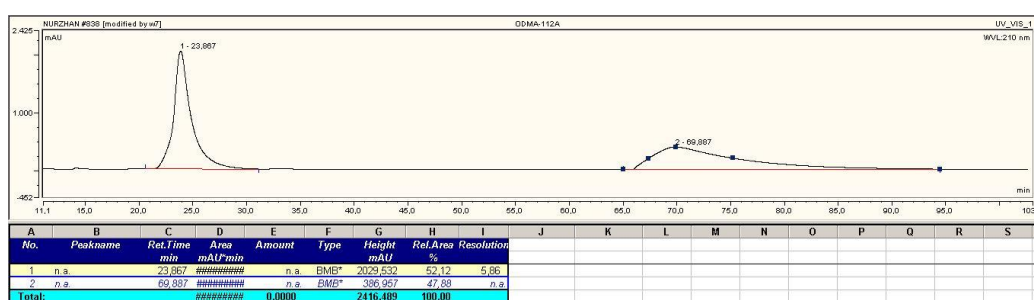


Figure 38. HPLC chromatogram of compound 15g

