

CATALYTIC ASYMMETRIC ONE-POT SYNTHESIS OF PYRROLIDINES VIA 1,3-
DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

SEYLAN AYAN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

JULY 2013

Approval of the thesis:

**CATALYTIC ASYMMETRIC ONE-POT SYNTHESIS OF PYRROLIDINES VIA
1,3-DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES**

submitted by **SEYLAN AYAN** in partial fulfillment of the requirements for the degree of
Master of Science in Chemistry Department, Middle East Technical University by,

Prof. Dr. Canan Özgen
Dean, Graduate School of **Natural and Applied Sciences**

Prof. Dr. İlker Özkan
Head of Department, **Chemistry**

Prof. Dr. Özdemir Doğan
Supervisor, **Chemistry Dept., METU**

Examining Committee Members:

Prof. Dr. Metin Balcı
Chemistry Dept., METU

Prof. Dr. Özdemir Doğan
Chemistry Dept., METU

Prof. Dr. Metin Zora
Chemistry Dept., METU

Assoc. Prof. Dr. Adnan Bulut
Chemistry Dept., Kırıkkale University

Assist. Prof. Dr. Akın Akdağ
Chemistry Dept., METU

Date:

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

Name, Last name : Seylan Ayan

Signature :

ABSTRACT

CATALYTIC ASYMMETRIC ONE-POT SYNTHESIS OF PYRROLIDINES VIA 1,3-DIPOLAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES

Ayan, Seylan

MSc., Department of Chemistry

Supervisor: Prof. Dr. Özdemir Doğan

July 2013, 71 pages

In recent years one-pot reactions have been studied significantly by different research groups. These reactions provide complex molecules from very simple starting materials in a single step. For that reason it is considered as atom economical reaction and “green chemistry”. Asymmetric versions of these reactions are also being studied by organic groups for the synthesis of complex chiral compounds. In this respect, we have studied metal catalyzed one-pot reaction of azomethine ylides with electron deficient dipolarophiles using chiral ligands with silver metal. As the chiral ligands amino alcohol based ferrocenyl aziridinyl methanol (**FAM**) and phosphorous based phosphino ferrocenyl aziridinyl methanol (**PFAM**) were used. These ligands have an advantage of being synthesized easily on a gram scale starting from acryloyl ferrocene. Moreover, the yellow color of ferrocene ease the purification by flash column chromatography. For the one-pot reaction glycine methyl ester, aromatic aldehyde, dipolarophile, chiral ligand, and silver salt were mixed in the same reaction flask to form pyrrolidine derivatives. Analysis of the reaction products showed that pyrrolidine derivatives can be obtained with up to 99% yield and 86% enantioselectivity by this catalytic asymmetric one-pot reaction.

Keywords: One-pot reaction, Chiral catalysts, Asymmetric synthesis, 1,3-Dipolar Cycloaddition Reactions, Azomethine ylides, Pyrrolidine derivatives.

ÖZ

AZOMETİN İLÜRLERİN 1,3-DİPOLAR KATALİTİK ASİMETRİK TEK BASAMAK TEPKİMESİYLE PİROLİDİNLERİN SENTEZİ

Ayan, Seylan

Yüksek lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Özdemir Doğan

Temmuz 2013, 71 sayfa

Son yıllarda, tek basamak tipi reaksiyonlar farklı gruplar tarafından yoğun olarak çalışılmaktadır. Bu yöntemle kompleks moleküller basit başlangıç maddelerinden tek basamakta kolaylıkla sentezlenebilmektedir. Bu nedenle hem atom ekonomik hemde çevreci bir yöntemdir. Bu yöntemin asimetric uygulamaları organikçiler tarafından kullanılarak kiral kompleks moleküller sentezlenmektedir. Bu doğrultuda biz de metal katalizörlüğünde kiral ligandlarla azometin ilürlerin elektronca fakir dipolarifillerle basamak tepkimesini gümüş metali varlığında çalıştık. Kiral ligand olarak amino alkol yapısına sahip ferrosenil aziridinil metanol (**FAM**) ve fosfor içeren fosfino ferrosenil aziridinil metanol (**PFAM**) kullanılmıştır. Bu ligandların avantajı, gram ölçeğinde akrilolil ferrosenden başlayarak kolay bir şekilde sentezlenmeleridir. Bunun yanında, ferrosenin sarı rengi, kolon kromatografisi ile saflaştırma işleminde kolaylık sağlamaktadır. Basamak tipi tepkime için glisin metil esteri, aromatik aldehit, dipolarofil, kiral ligand ve gümüş tuzu aynı tepkime balonunda karıştırılarak pirolidin türevleri elde edilmiştir. Tepkime ürünleri analiz edildiğinde bu katalitik asimetric tek basamak tepkimesiyle pirolidin türevlerinin %99'a varan verim ve %86'ya varan enantiyoseçicilikle elde edilebileceği görülmüştür.

Anahtar kelimeler: Tek basamak tepkimesi, Kiral katalizör, Asimetric sentez, 1,3-Dipolar Halkasal Katılma Tepkimeleri, Azometin ilürler, Pirolidin türevleri.

To my family and Dr. Gürcan Günaydin...

ACKNOWLEDGEMENTS

I would like to express my deep sense of gratitude to my teacher and supervisor Prof. Dr. Özdemir Doğan, who has helped me a lot to learn and think more about chemistry. I thank him for his friendship, constant encouragement, excellent guidance, sincere advice, and endless support during all the tough times of my master life. His continuous efforts in my career will never be forgotten.

I would like to thank Assoc. Prof. Dr. Adnan Bulut for his precious advices, positive energy and friendship provided warm working medium in lab. I would like to express my special thanks to Assoc. Prof. Dr. Konstantin V. Kudryavtsev for his endless guidance, advice, criticism, encouragements. I also would like to thank TÜBİTAK (Project No: 210T075) and BAP for financial support throughout my M.S. study

Many thanks to all my friends and colleagues who helped me throughout these years. Especially, I would like to express my gratitude to Eylem Canbolat, Alkım Aydın, Ayşegül Hisar who are always a forethoughtful friend for me throughout this period. Special acknowledgements to Şevkican Cevher and all current and previous members of the D-Block Organic Chemistry Research Group members for their friendship and help.

I would like to express my deepest appreciation to my parents Gülcan and Abidin Ayan and my brother Alper ayan for their love, encouragement and support throughout this study.

Finally my sincere appreciation and cordial gratitude is devoted to my beloved friend Dr. Gürcan Günaydın especially for his endless patience, encouragement, support, and love whenever I needed throughout this study.

TABLE OF CONTENTS

ABSTRACT.....	v
ÖZ.....	vi
ACKNOWLEDGEMENTS.....	viii
TABLE OF CONTENTS.....	ix
LIST OF TABLES.....	xii
LIST OF FIGURES.....	xiii
LIST OF SCHEMES.....	xiv
CHAPTERS	
1. INTRODUCTION.....	1
1.1 Introduction to enantiomerically pure compounds.....	1
1.1.1 Asymmetric Cycloaddition Chemistry.....	2
1.1.1.1 1,3-Dipolar Cycloaddition (DC) Reactions.....	2
1.1.1.1.1 1,3-DIPOLES OR YLIDES.....	3
1.1.1.1.1.1 ALLYL ANION-TYPE DIPOLES.....	3
1.1.1.1.1.2 PROPARGYL/ALLENYL ANION-TYPE DIPOLES.....	4
1.1.1.1.2 Dipolarophile.....	5
1.1.1.1.3 Mechanistic Approach of 1,3-Dipolar Cycloaddition Reaction.....	5
1.1.1.1.4 Similarity between the 1,3-DCR and Diels-Alder type reactions.....	8
1.1.1.1.5 Azomethine Ylides and Their 1,3-Dipolar Cycloaddition Reactions.....	8
1.1.1.1.6 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides.....	10
1.2 Aim of work.....	19
2. RESULTS AND DISCUSSION.....	21
2.1 The Synthesis of Chiral P-FAM Ligands.....	21
2.1.1 Synthesis of Aziridines.....	21
2.1.2 Synthesis of Tosylated Aziridines.....	22

2.1.3	Phosphorylation of tosylated aziridiny ketones	23
2.1.4	Reduction of phosphorylated aziridiny ketones.....	23
2.2	The Asymmetric One-pot 1,3-Dipolar Cycloaddition Reaction by Using Chiral POFAM Ligands	24
2.2.1	Ligand screening studies of asymmetric cascade 1,3-Dipolar Cycloaddition Reaction.....	25
2.2.2	Additive screening studies	26
2.2.3	Solvent screening studies	26
2.2.4	Temperature and concentration screening studies	27
2.2.5	Silver salt screening studies	28
2.2.6	Optimization studies at different AgOAc-ligand ratio	29
2.3.1	Enantioselective asymmetric one-pot 1,3-Dipolar Cycloaddition Reaction of various aldehyde and dipolarophiles	30
3.	CONCLUSION.....	33
4.	EXPERIMENTAL	35
4.1	General Consideration	35
4.1.1	General Procedures	35
4.1.2	Materials	35
4.1.3	Instrumentation.....	35
4.2	Synthesis and Characterization of Chiral Ligands.....	36
4.2.1	Synthesis of acryloyl ferrocene	36
4.2.2	Bromination of acryloyl ferrocene	36
4.2.3	Synthesis of aziridiny ketones	36
4.2.4	Synthesis of tosylated aziridiny ketone 33	37
4.2.5	Synthesis of tosylated aziridiny ketone 34	37
4.2.6	Synthesis of phosphino aziridine 35 and phosphineoxy aziridine 17	37
4.2.7	Synthesis of phosphino aziridine 36 and phosphineoxy aziridine 18	38
4.2.8	Synthesis of phosphine and phosphineoxy ferrocenyl aziridiny methanols (<i>R, R, R</i>) 37 and 19	38

4.2.9	Synthesis of phosphine and phosphineoxy ferrocenyl aziridinyl methanols (<i>S, R, R</i>) 38 and 20	38
4.2.10	Synthesis of phosphine and phosphineoxy ferrocenyl aziridinyl methanols (<i>S, S, R</i>) 39 and 21	39
4.2.11	Synthesis of phosphine and phosphineoxy ferrocenyl aziridinyl methanols (<i>R, S, R</i>) 40 and 22	39
4.4	Representative general Procedure for Asymmetric One-pot 1,3-DC Reaction..	40
4.4.1	(<i>2S, 3R, 4S, 5R</i>)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate .. 41	40
4.4.2	(<i>2S, 3R, 4S, 5R</i>)-Trimethyl 5-(4-chlorophenyl) pyrrolidine-2,3,4-tricarboxylate 42	40
4.4.3	(<i>2S,3R,4S,5R</i>)-trimethyl 5-(4-bromophenyl)pyrrolidine-2,3,4-tricarboxylate 43	41
4.4.4	(<i>2S, 3R, 4S, 5R</i>)-Trimethyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate 44	41
4.4.5	(<i>2S, 3R, 4S, 5R</i>)-Trimethyl 5-(naphthalen-1-yl)pyrrolidine-2,3,4-tricarboxylate 45	41
4.4.6	(<i>2S, 3R, 4S, 5R</i>)-Trimethyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate 46	42
4.4.7	(<i>2S, 4S, 5R</i>)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate 47	42
4.4.8	(<i>1S, 2R, 4S, 5R</i>)-Methyl octahydro-7-methyl-6,8-dioxo-4-phenyl-3, 7-diazabicyclo [3.3.0]pyrrole-2-carboxylate 48	42
4.4.9	(<i>2S, 4S, 5R</i>)-Methyl 4-cyano-5-phenylpyrrolidine-2-carboxylate 49 .	43
4.5	General procedure for racemic cycloaddition reactions.....	43
	REFERENCES	45
	APPENDIX A	49

LIST OF TABLES

TABLES

Table 1. Ligand screening studies	24
Table 2. Additive screening studies.....	25
Table 3. Solvents screening studies	26
Table 4. Temperature and concentration screening studies.....	27
Table 5. Silver salt screening studies.....	27
Table 6. Different AgOAc-ligand ratio studies	28
Table 7. Comparison of pyrrolidine derivatives result.....	29

LIST OF FIGURES

FIGURES

Figure 1. Enantiomers	1
Figure 2. General representation of 1,3-DC reactions	2
Figure 3. Allyl anion types dipoles	3
Figure 4. Allyl anion type of 1,3-dipoles	4
Figure 5. Propargyl/Allenyl Anion-type Dipoles	4
Figure 6. Propargyl/Allenyl Anion-type of 1,3-dipoles	5
Figure 7. Dipolarophiles used in 1,3-DC reaction	5
Figure 8. Mechanisms of 1,3-DC reaction	6
Figure 9. Stereochemistry of 1,3-DC reaction	7
Figure 10. The classification of 1,3-DC reactions according to FMOs	7
Figure 11. Similarity between 1,3-DCR and Diels-Alder Reaction.....	8
Figure 12. Azomethine ylides	9
Figure 13. The cycloadditions of azomethine ylides with alkenes	10
Figure 14. Examples of biologically active compounds containing pyrrolidine ring	10
Figure 15. Pyrrolidine synthesis by using chiral metal catalyst.....	11
Figure 16. Chiral phosphine ligands used by Zhang and co-workers	14
Figure 17. Pyrrolidine derivatives under optimized reaction conditions	16
Figure 18. Chiral phosphine oxide ligands used by Dogan and co-workers	17
Figure 19. Transition state for <i>exo</i> selectivity	18

LIST OF SCHEMES

SCHEMES

Scheme 1 Proton abstraction from imine derivatives.....	9
Scheme 2 Photolysis or thermolysis of aziridines.....	9
Scheme 3 Decomposition of <i>N</i> -alkyl- <i>N</i> -methoxymethyl- <i>N</i> (trimethylsilyl) methylamines.....	9
Scheme 4 First asymmetric 1,3-DC reaction of azomethine ylides studied by Grigg and co-workers.....	12
Scheme 5 1,3-DC reaction using chiral ligand 5 with AgOTf.....	13
Scheme 6 1,3-DC reaction of azomethine ylides studied by Zhang and co-workers.....	14
Scheme 7 1,3-DC reaction of azomethine ylides studied by Schreiber and co-workers...	15
Scheme 8 1,3-DC reaction of azomethine ylides studied by Carreira and co-workers.....	15
Scheme 9 1,3-DC reaction of azomethine ylides studied by Zhou and co-workers.....	16
Scheme 10 1,3-DC reaction of azomethine ylides studied by Dogan and co-workers.....	17
Scheme 11 1,3-DC reaction of azomethine ylides studied by Komatsu and co-workers...	18
Scheme 12 Synthesis of acryloyl ferrocene from ferrocene and acryloyl chloride.....	20
Scheme 13 Bromination of acryloyl ferrocene.....	20
Scheme 14 Bromination of acryloyl ferrocene.....	21
Scheme 15 Tosylation of aziridinyl ketones.....	21
Scheme 16 Synthesis of phosphino aziridinyl ketones.....	22
Scheme 17 Synthesis of phosphino and phosphineoxy aziridinyl methanol ligands.....	23
Scheme 18 Synthesis of phosphineoxy aziridinyl methanol ligands.....	23

LIST OF ABBREVIATIONS

Ar	: aryl (also argon)
BINAP	: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
δ	: chemical shift in parts per million downfield from tetramethylsilane
J	: coupling constant
DCM	: Dichloromethane
1,2-DCE	: 1,2-dichloroethane
1,3-DC	: 1,3-Dipolar Cycloaddition
DIPEA	: Diisopropylethylamine
EWG	: Electron withdrawing group
PFAM	: Phosphino Ferrocenyl Aziridinyl Methanones and Methanols
POFAM	: Phosphineoxy Ferrocenyl Aziridinyl Methanones and Methanols
R_f	: retention factor (TLC)
t_R	: retention time (in HPLC)
TEA	: Triethylamine
TMEDA	: Tetramethylethylenediamine
TMS	: Tetramethylsilane, also Trimethylsilyl

CHAPTER 1

INTRODUCTION

1.1 Introduction to enantiomerically pure compounds

As Pasteur said "The universe is chiral." Most of the organic compounds, agrochemicals, pharmaceuticals, cosmetics, nutrients and pesticides are chiral. Chiral compounds that are non-superimposable mirror images are called enantiomers (*Figure 1*).

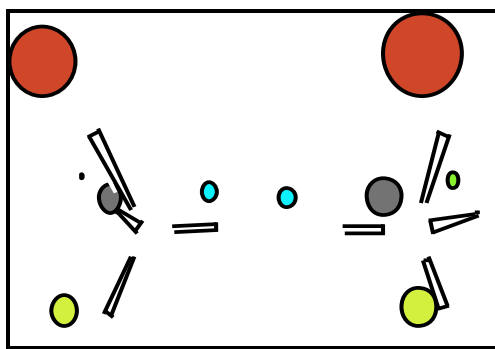


Figure 1. Enantiomers

The enantiomers show different biological activities; as a result one should consider them as two distinct compounds. It is important to synthesize these types of compounds in enantiomerically pure forms. Because, enantiomers may behave differently especially when they are used as drugs.

How can enantiomerically pure compounds be synthesized?

- Resolution of racemates (expensive and disposal of another enantiomer)
- Starting from enantiomerically pure compounds (must be available)
- Chiral reagents (limited with the reaction type)
- Use of chiral auxiliaries
- Metal catalysts (metal+chiral ligand)
- Organocatalysts
- Biocatalysts (enzymes)

In recent years, metal catalysts and organocatalysts are the most commonly employed techniques. Because small amount of a catalyst can produce large amount of a enantiomerically enriched product. Therefore these methods are considered to be more economical and environmentally friendly [1].

1.1.1 Asymmetric Cycloaddition Chemistry

The carbo- and heterocyclic compounds show different biological activities therefore they are very important for the total syntheses of complex molecules. In addition, carbo- and heterocyclic compounds are found in innumerable natural products and pharmaceuticals. Therefore all of these cyclic compounds, especially five- and six-membered N-heterocycles, continue to attract attention of researchers [2]. One of the efficient methods for constructing heterocyclic units is cycloaddition reaction. Cycloaddition reactions are very important in synthetic organic chemistry, since these reactions have advantages of forming heterocyclic structures in high stereoselectivity in a single step [3]. Since 1,3-dipolar cycloaddition (DC) reaction of azomethine ylides is used in this study, this method will be discussed in more details in the following pages.

1.1.1.1 1,3-Dipolar Cycloaddition (DC) Reactions

The 1,3-DC reaction is a classical reaction in organic chemistry for constructing five membered heterocycles up to four stereogenic centers. These five membered heterocycles are very important for both scientists and industry, because they are found in many complex natural products, pharmaceuticals, biologically active compounds and building blocks in organic synthesis [4]. The 1,3-DC reaction takes place between 1,3-dipole or ylide **1** which is 4π electron component and dipolarophile **2** which is 2π electron component (*Figure 2*) [5]. They react in a $[\pi 4_s + \pi 2_s]$ -fashion to form five membered heterocyclic ring system **3**.

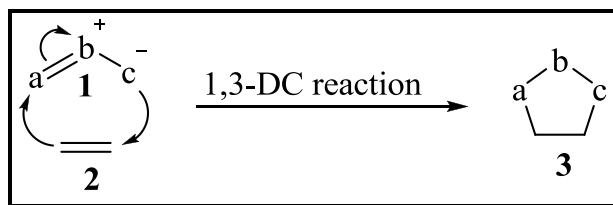


Figure 2. General representation of 1,3-DC reactions

Although there are different methods for the syntheses of heterocyclic compounds, the 1,3-DC reaction offers a remarkably wide range of utility in the synthesis of five-membered heterocycles [6]. The history of 1,3-dipoles and 1,3-DC reaction began with;

- Curtius who discovered diazoacetic ester (1883) [7].
- Buchner studied the reaction of diazoacetic ester with α,β -unsaturated esters and described the first 1,3-DC reaction. (1888) [8].
- Huisgen established general application of 1,3-dipoles in organic synthesis (1960s) [6].

- Fukui [5^a], Woodward and Hoffmann developed conservation of orbital symmetry [5^{b, c}].
- Newest challenge: Control of stereochemistry.

1.1.1.1.1 1,3-Dipoles or Ylides

Firstly, Huisgen [6] defined the 1,3-dipoles also known as ylides. They are represented as “*a-b-c*” structure. On the structure, there are positive and negative charges distributed over three atoms. The atom “*a*” possesses an electron sextet, i.e. an incomplete valence shell combined with a positive formal charge and the atom “*c*” is the negatively charged center with an unshared electron pair. Moreover Pichon and co-workers [9] defined 1,3-dipole which is formed by 3 atoms with at least one heteroatom. This structure have 4π electrons with a zwitter ionic form where the positive charge is localized on the central atom and the negative charge is distributed on two terminal atoms according to octet stabilization structure.

1,3-Dipoles are divided into two main groups: the allyl anion type and propargyl/allenyl anion type [10].

1.1.1.1.1.1 Allyl Anion-Type Dipoles

The allyl anion-type dipoles are bent in geometry (*Figure 3*). These types of dipoles have four electrons which located in three parallel p_z orbitals and they are perpendicular to the plane of the dipole. The middle atom “*b*” can be nitrogen, oxygen and sulfur (*Figure 4*). There are two different structures for the allyl anion-type dipoles. In the octet-structure, two resonance forms in which three centers have an electron octet. The central atom “*b*” (N, O or S) carries a formal positive charge in all octet resonance forms. In the sextet-structure, two resonances form in which “*a*” or “*c*” has an electron sextet [11].

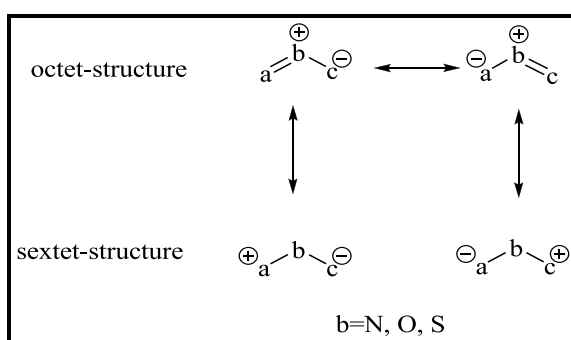


Figure 3. Allyl anion types dipoles

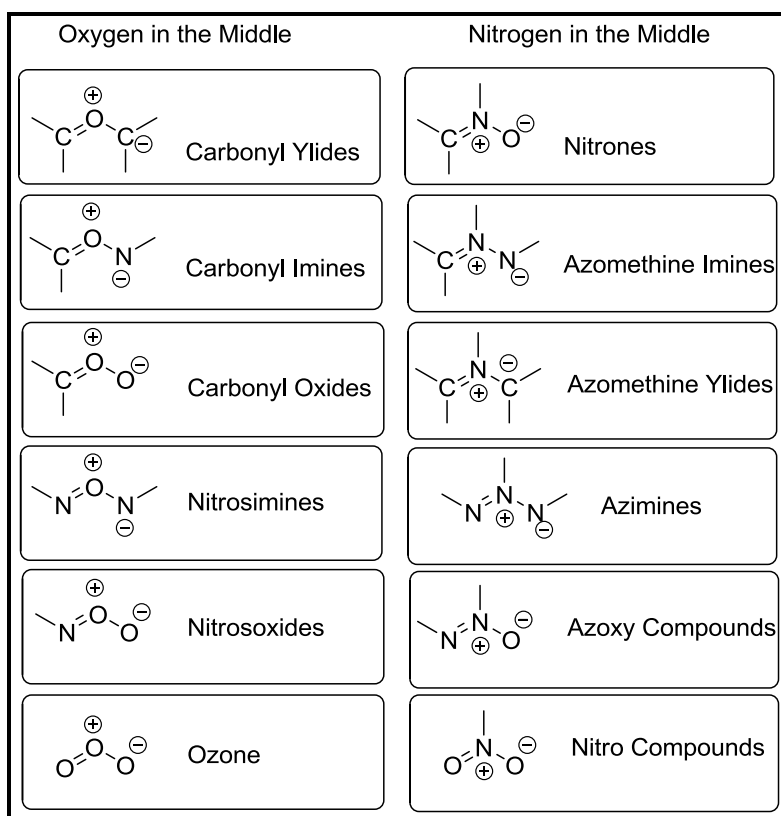


Figure 4. Allyl anion type of 1,3-dipoles

1.1.1.1.2 Propargyl/Allenyl Anion-Type Dipoles

The propargyl/allenyl anion type dipoles are linear in geometry (*Figure 5*). There is an extra π orbital located in the plane orthogonal to the allenyl anion type molecular orbital. In this type of 1,3-dipoles the central atom “*b*” only can be nitrogen (*Figure 5*). This nitrogen atom carries a formal positive charge in all octet resonance forms. Some examples to propargyl/allenyl anion type 1,3-dipoles are given in (*Figure 6*) [11].

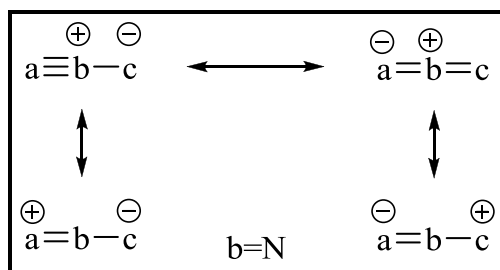


Figure 5. Propargyl/Allenyl anion-type dipoles

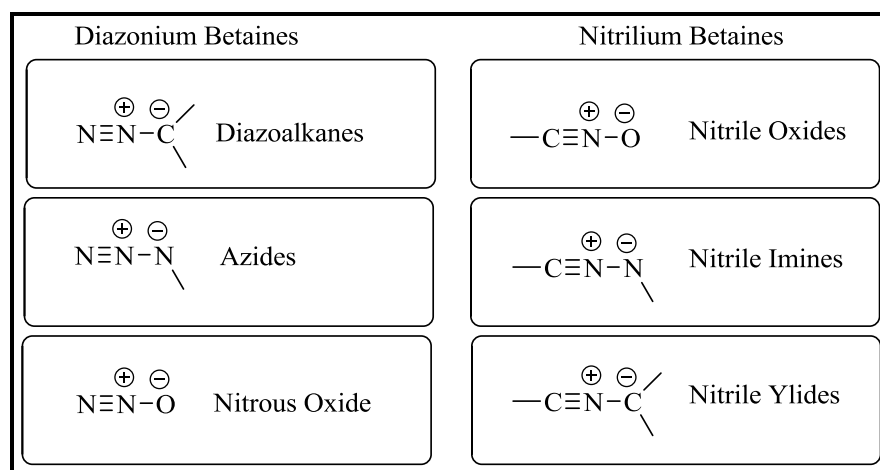


Figure 6. Propargyl/Allenyl anion-type of 1,3-dipoles

1.1.1.1.2 Dipolarophile

Dipolarophiles are 2π -electron systems and generally an alkene [12]. Dipolarophiles can react with 1,3-dipoles in a concerted manner to form heterocyclic rings [13]. There are different types of dipolarophiles as; α,β -unsaturated carbonyl compounds, ketones, allylic alcohols, allylic halides, alkynes, vinylic ethers, vinylic esters and imines (Figure 7) [14].

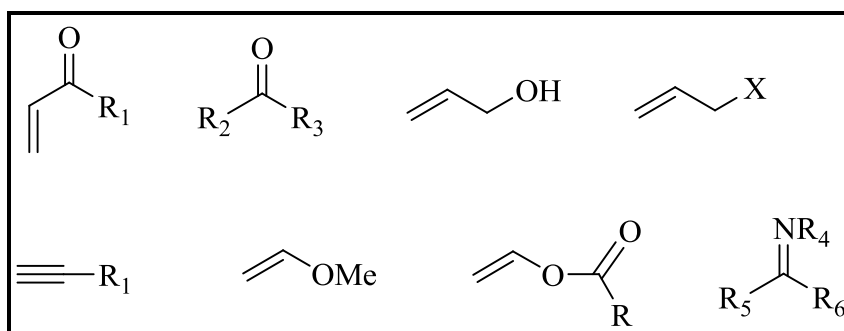


Figure 7. Dipolarophiles used in 1,3-DC reaction

1.1.1.1.3 Mechanistic Approach of 1,3-Dipolar Cycloaddition Reaction

There were two roads related to the reaction mechanism of 1,3-DC reaction in 1960s [15]. Huisgen and co-workers [6] were the first to offer a detailed clarification for the concerted mechanism of 1,3-dipolar cycloaddition reaction in 1960s (Figure 8). According to this mechanism, all the bonds were created at the same time, but not necessarily to the same extent at a particular time. Huisgen [6] also found that in the great majority of 1,3-cycloadditions, the solvent polarity does not influence the reaction rates, moderately and the

cycloadditions of 1,3-dipoles to alkene are stereospecifically suprafacial. The reaction needs small activation enthalpies and very negative activation entropies to undergo 1,3-dipolar cycloadditions. As a result, Huisgen's mechanistic studies have shown that 1,3-DC reactions take place in a concerted pathway on the strength of Woodward-Hoffmann rules.

On the other hand, Firestone [16] proposed that 1,3-DC reactions proceeded by stepwise reaction mechanism via a diradical intermediates for 1,3-DC reactions (*Figure 8*). But later Firestone realized that diradicals could not be ruled out in the mechanism. Therefore concerted mechanism was accepted by Firestone [15]. Because, *cis*- or *trans*-alkene as a dipolarophile can rotate around C-C bond by 180° in the diradical mechanism thus the stereospecificity of the reaction can be destroyed. The product can be a mixture of both the *cis* and *trans* isomers.

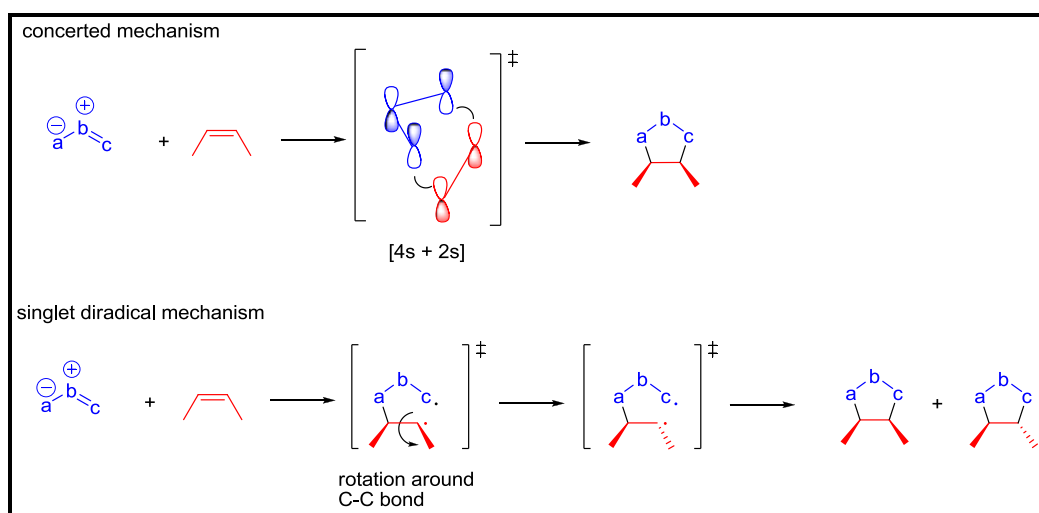


Figure 8. Mechanisms of 1,3-DC reaction

On the strength of Woodward-Hoffmann theory [17] three p_z orbitals of the 1,3-dipole and two p_z orbitals of the dipolarophile incorporated suprafacially. It means that, the stereochemistry of dipole and the dipolarophile are retained in the final product (*Figure 9*). As can be seen in *Figure 9*, *trans*-2-butene reacts with the hypothetical dipole to form *trans*-cycloadduct. Similarly, starting with the *cis*-alkene, one can get only the *cis*-cycloadduct.

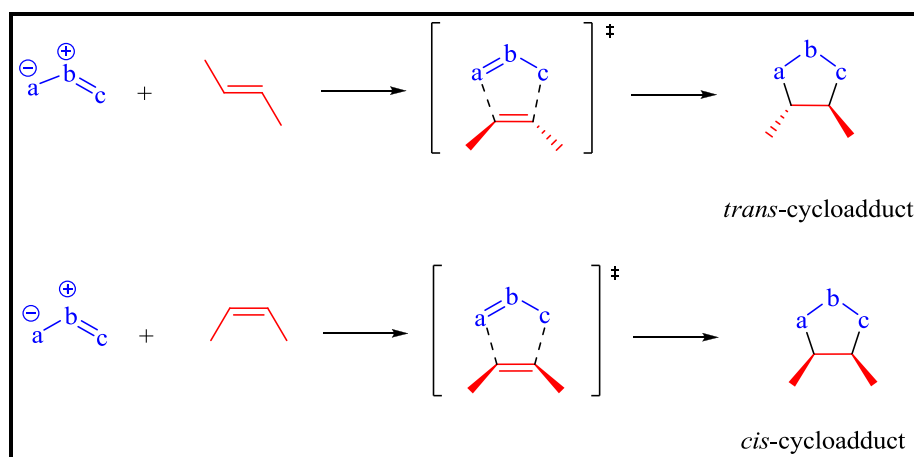


Figure 9. Stereochemistry of 1,3-DC reaction

The transition state of the concerted mechanism of 1,3-DC reaction is controlled by the frontier molecular orbitals (FMO) of dipole and dipolarophile. According to FMO theory, the $LUMO_{\text{dipole}}$ can interact with the $HOMO_{\text{dipolarophile}}$ and the $HOMO_{\text{dipole}}$ can interact with the $LUMO_{\text{dipolarophile}}$. In *Figure 10*, on the strength of relative FMO energies between the dipole and the dipolarophile, Sustman and co-workers have classified 1,3-DC reactions into three types [18].

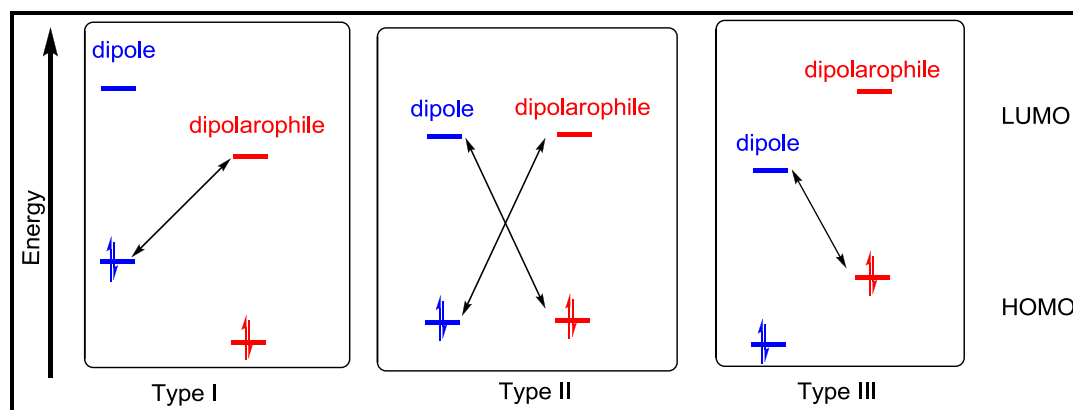


Figure 10. The classification of 1,3-DC reactions according to FMOs

- **In Type I**, the dominant FMOs interaction is in between the $HOMO_{\text{dipole}}-LUMO_{\text{alkene}}$. The reaction of azomethine ylide or azomethine imines can be given as an example [19].
- **In Type II**, $HOMO_{\text{dipole}}-LUMO_{\text{alkene}}$ or $HOMO_{\text{alkene}}-LUMO_{\text{dipole}}$ interactions are both important because of the similar FMO energies of the dipole and the alkene. The reaction of nitrile oxides and nitrones are classified as Type II [19].

- In Type III, the dominant FMO interaction is in between the $LUMO_{\text{dipole}}$ - $HOMO_{\text{alkene}}$. 1,3-DC reactions of ozone and nitrous oxide can be given as an example to Type III [19].

In addition, when electron-donating or electron-withdrawing groups are present on dipole and dipolarophile, the relative FMO energies can be altered. As a result the type of 1,3-DC reactions may change [20]. To illustrate, the reaction between methyl acrylate (dipolarophile) and *N*-methyl-*C*-phenylnitron (dipole) is controlled by the $HOMO_{\text{dipole}}$ - $LUMO_{\text{dipolarophile}}$ interaction (type I). On the other hand, the reaction between methyl vinyl ether (dipolarophile) and the same nitron is controlled by the $LUMO_{\text{dipole}}$ - $HOMO_{\text{dipolarophile}}$ interaction (type III). It was seen that, the substituents are very effective for the 1,3-DC reactions.

1.1.1.1.4 Similarity between the 1,3-DCR and Diels-Alder type reactions

The 1,3-DC reactions are very similar to well-known Diels-Alder reactions. They both are defined as a concerted reaction. Additionally, they both react in a $[\pi 4_s + \pi 2_s]$ -fashion. As shown in *Figure 11*, all the bonds are made or broken around a circle for each reaction and two new bonds are formed in a single transition state (*Figure 11*) [15].

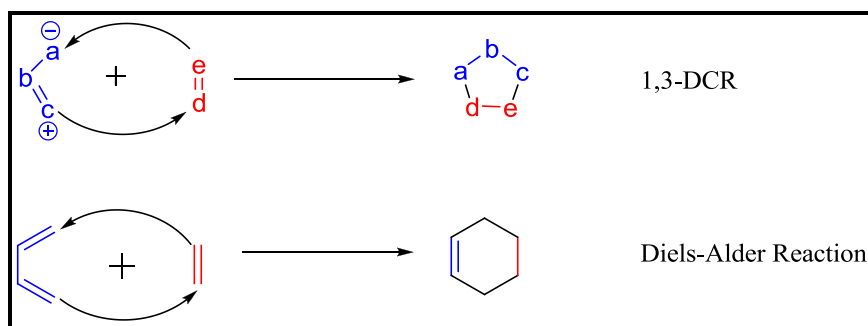


Figure 11. Similarity between 1,3-DCR and Diels-Alder Reaction

1.1.1.1.5 Azomethine Ylides and Their 1,3-Dipolar Cycloaddition Reactions

As shown in *Figure 12*, the structure of azomethine ylides is planar and they are allyl anion type 1,3-dipoles. In the general structure of azomethine ylides, there is one nitrogen atom in the center which is attached to two terminal sp^2 -hybridized-carbon atoms (*Figure 8*) [21]. Although there are examples to stable azomethine ylides in the literature [22], they are generally unstable and very reactive species. They have to be prepared *in situ*.

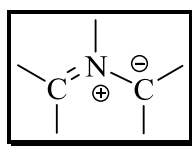
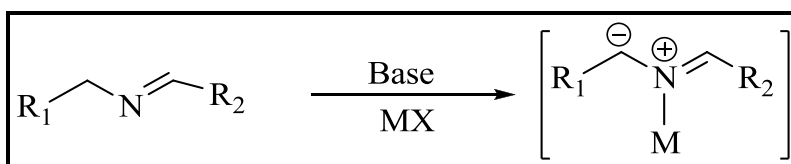
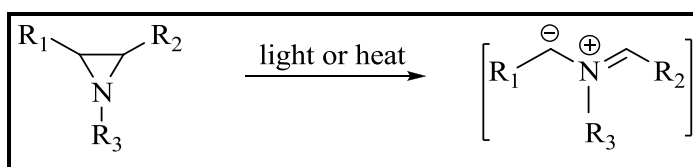


Figure 12. Azomethine ylides

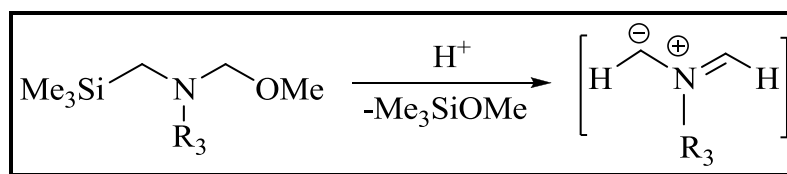
There are three main methods commonly used to generate azomethine ylides. These methods can be listed as proton abstraction from imine derivatives [23] (*Scheme 1*), photolysis or thermolysis of aziridines [24] (*Scheme 2*) and acid catalyzed decomposition of *N*-alkyl-*N*-methoxymethyl-*N*-(trimethylsilyl) methylamines [25] (*Scheme 3*).



Scheme 1. Proton abstraction from imine derivatives



Scheme 2. Photolysis or thermolysis of aziridines



Scheme 3. Decomposition of *N*-alkyl-*N*-methoxymethyl-*N*-(trimethylsilyl) methylamines

The cycloadditions of azomethine ylides with alkenes leads to the formation of five-membered heterocycles called as "Pyrrolidines" (*Figure 13*) [26]. As it can be seen in *Figure 13*, two C-C bonds and four chiral centers can be obtained in a single step.

Therefore, 1,3-DC reaction azomethine ylides is very important for complex pyrrolidine structure synthesis [27].

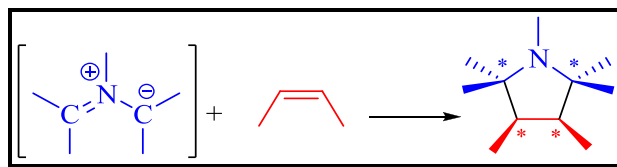


Figure 13. The cycloadditions of azomethine ylides with alkenes

Pyrrolidine ring system is a structural element of many natural products and drugs. Enantioselective construction of polysubstituted pyrrolidines by 1,3-dipolar cycloaddition of electron deficient dipolarophiles with azomethine ylides has been studied by a significant number of researchers using metal-catalysts [28] and organocatalysts [29].

1.1.1.1.6 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides

In recent years, methodologies for the catalytic asymmetric synthesis of enantiomerically pure pyrrolidine have been studied by organic groups significantly. As a result, azomethine ylides are one of the most used 1,3-dipoles. Nature has lots of example to pyrroline ring containing biologically active compounds. (*Figure 14*) [26].

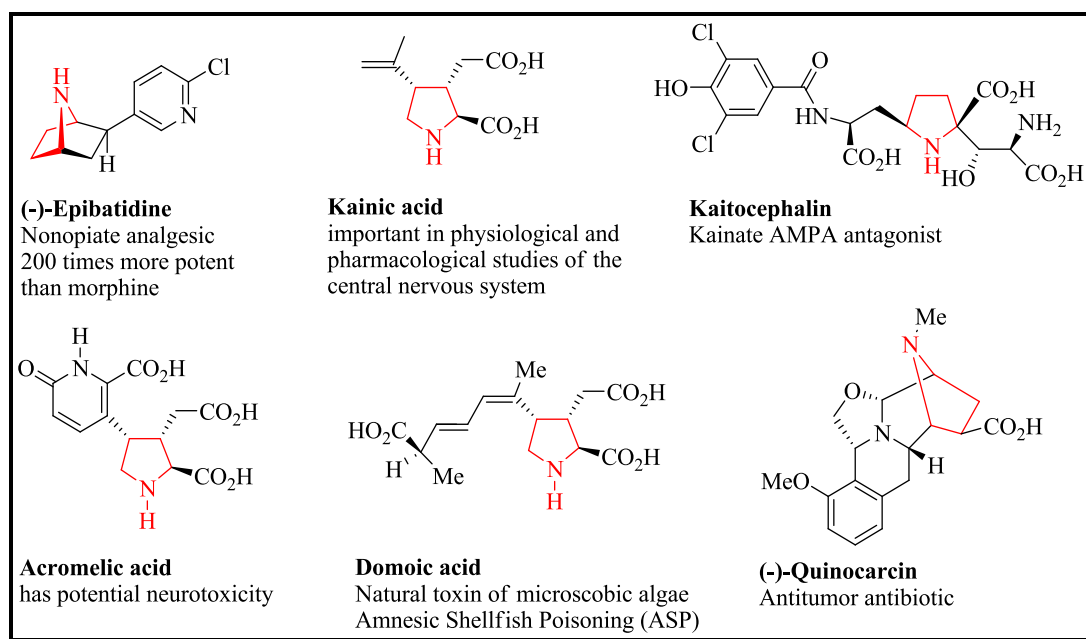


Figure 14. Examples of biologically active compounds containing pyrrolidine ring

In the literature, there are four common methods to obtain optically active 1,3-DC products:

1. Utilization of a chiral dipolarophile [30]
2. Utilization of a chiral dipole [31]
3. Utilization of chiral Lewis acid (LA) capable of complexing with both 1,3-dipole and dipolarophile [21]
4. Utilization an organocatalyst [32]

Our research group [33] and others [34] have studied metal-catalyzed asymmetric 1,3-DC reaction of azomethine ylides. In this methodology, dipole and dipolarophile both can coordinate to metal-ligand chiral catalyst to provide enantioselectivity (*Figure 15*) [33].

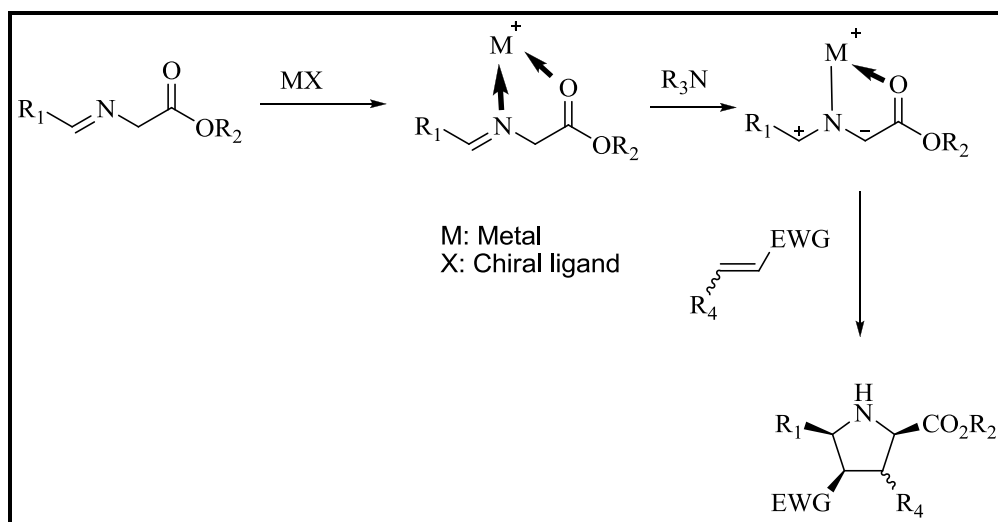


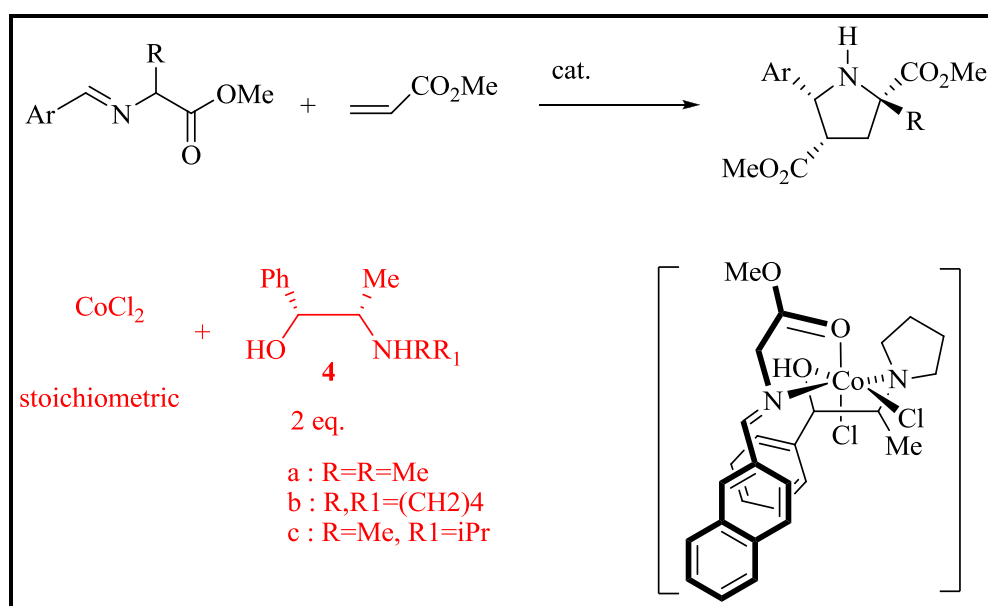
Figure 15. Pyrrolidine synthesis by using chiral metal catalyst

As it can be seen in *Figure 15*, the imine and Lewis acids form a complex in the first step, and then the azomethine ylides can be generated from imines in the reaction medium [36]. The complexation between the imine and Lewis acid are very critical because it provides a highly stereoselective cycloaddition reactions.

The FMO energy gap (ΔE) between the LUMO (or HOMO) and HOMO (or LUMO) may change when a catalyst was coordinated to the dipole or dipolarophile [36]. It means that, the energy gap (ΔE) gets narrow as result reaction goes faster.

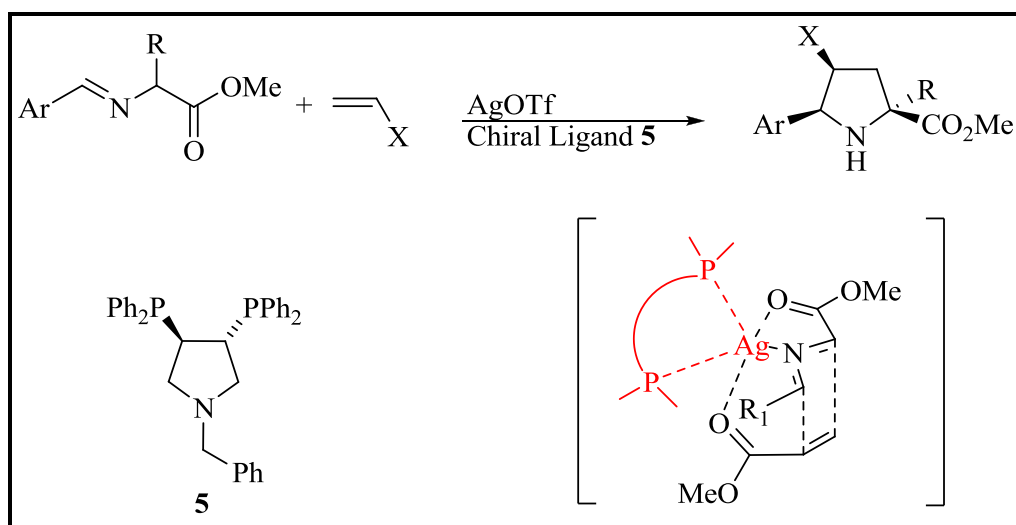
Literature examples to the use of different metal catalyst for 1,3-DC reactions of azomethine ylides can be listed as Co(II) [37], Ni(II) [38], Zn(II) [35], Cu(II) [39], Cu(I) [40], Ag(I) [33^b], Fe(II) [41].

The first chiral ligand controlled enantioselective cycloaddition reaction of azomethine ylides with alkenes was reported by Grigg and co-workers in 1991 [37]. They used ephedrine derivatives **4** as a chiral ligand with stoichiometric amount of CoCl_2 and MnBr_2 as metal sources. They synthesized cycloadducts in high enantioselectivities as 96% and good yields as 67-84% by using stoichiometric amount of CoCl_2 (1 mol) with excess chiral ligand (2 mol) at room temperature (*Scheme 4*). As shown in *Scheme 4*, they proposed a working model for the transition state. Although this study became a milestone to different groups in the literature, the use of 2 moles of ephedrine ligand was not actually catalytic amount.



Scheme 4. First asymmetric 1,3-DC reaction of azomethine ylides studied by Grigg and co-workers

Grigg and co-workers also used phosphorous based chiral ligand **5** with AgOTf as a metal source for 1,3-DC reaction (*Scheme 5*). Again the catalyst was used in stoichiometric amount. As a result of this study, they obtained pyrrolidines in 64-83% yields with 70% ee. The transition state proposed for this reaction is shown in *Scheme 5*.



Scheme 5. 1,3-DC reaction using chiral ligand **5** with AgOTf

1.1.1.1.6.1. AgOAc Catalyzed 1,3-DC Reactions of Azomethine Ylides in the Literature

Ag(I) based metal catalysts serve as excellent Lewis acids in the cycloaddition reactions of azomethine ylides. The advantage of silver salts can be listed as, the shorter reaction times and well-coordination with a chiral ligand. Moreover, the products can be isolated in very high yields and enantioselectivities.

In recent years, several chiral ligands are designed by organic groups [34] and used in catalytic asymmetric silver-catalyzed 1,3-DC reactions of azomethine ylides.

In the literature, the first study of catalytic phosphorous based chiral ligand-silver salt complexes was published by Zhang and co-workers in 2002 [42]. They used several bisphosphine chiral ligands [(*R*)-BINAP (**6**), (*R, R*)-Me-DuPhos (**7**), (*R, S, R, S*)-PennPhos (**8**), (*R, R, R, R*)-BICP (**9**), (*R, R*)-Trost ligand (**10**)] with silver acetate (Figure 16). As can be seen from Figure 16 enantioselectivity remained low (13-17%) with dimethyl maleate except for Trost ligand.

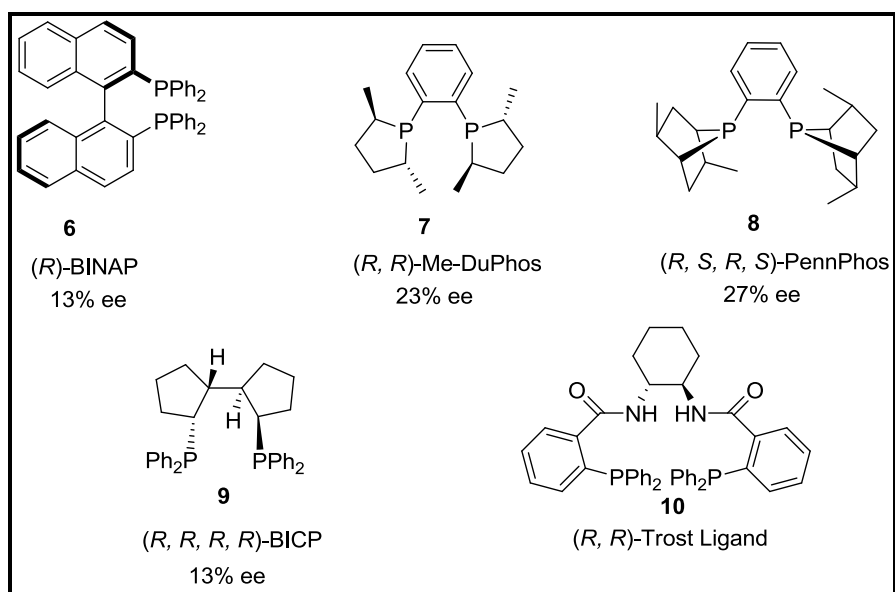
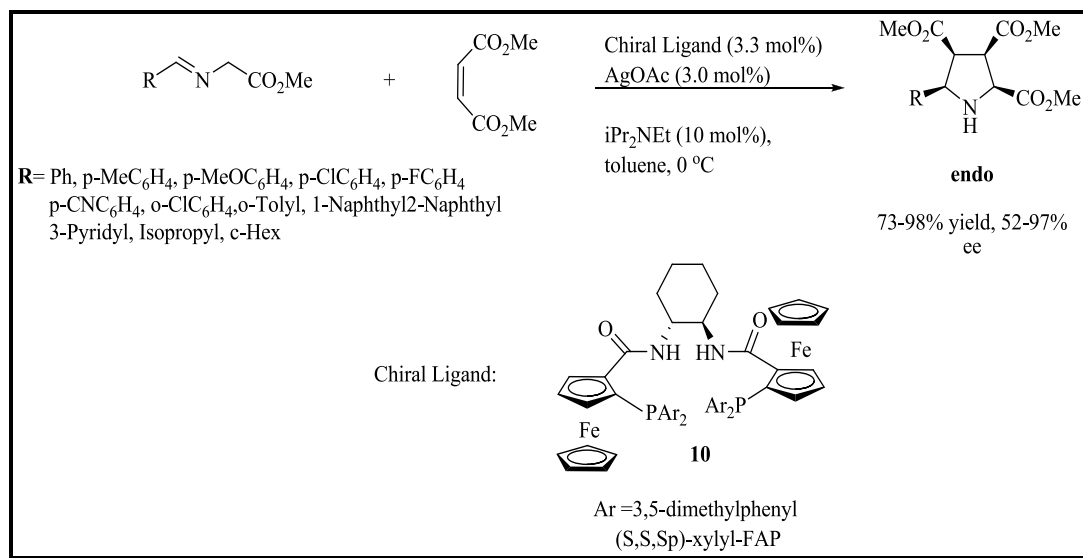


Figure 16. Chiral phosphine ligands used by Zhang and co-workers

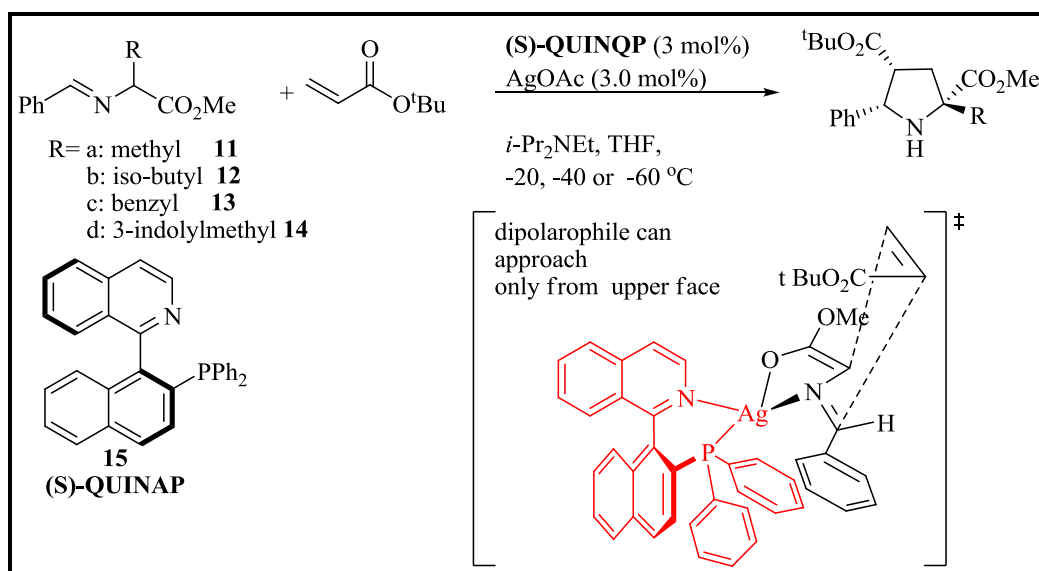
The Trost's ligand **10** gave the highest enantioselectivity (*Scheme 6*) compared to the other bisphosphine ligands. This can be explained by the more coordination sites of the Trost ligand where amide oxygens can also coordinate to silver metal. This may increase the rigidity of the transition state which increases the enantioselectivity.



Scheme 6. 1,3-DC reaction of azomethine ylides studied by Zhang and co-workers

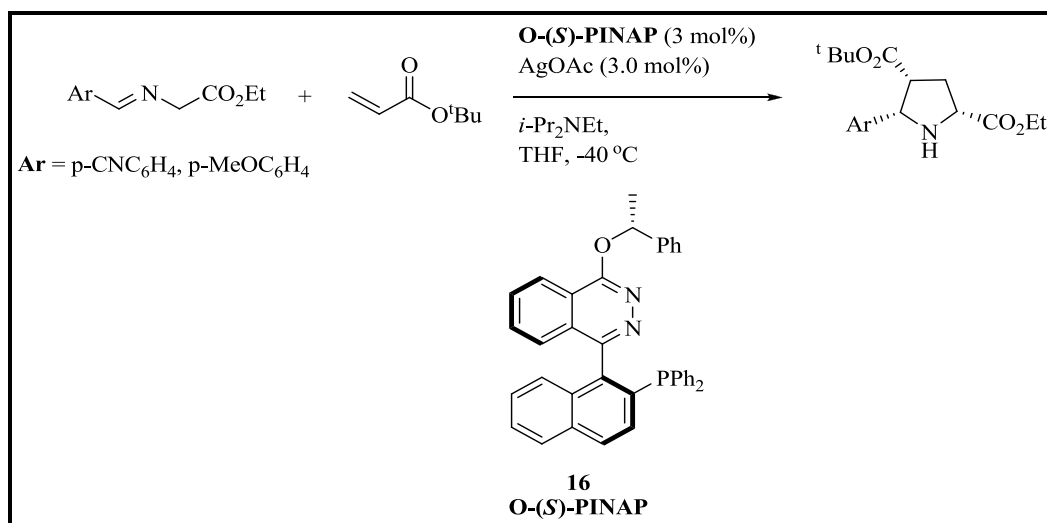
Schreiber and co-workers probed a new 1,3-DC reaction of azomethine ylides in 2003 [43]. They used α -iminoesters and acrylates to synthesize 3-substituted pyrrolidines in excellent yields and enantioselectivities (*Scheme 7*). This was the first generation of pyrrolidines which have quaternary centers at the 2-position. Schreiber and co-workers performed series of chiral mono-phosphines ligand and (*S*)-QUINAP (**15**) studies gave the highest

enantioselectivities. As the studies conducted on (*S*)-QUINAP (**15**) showed that, it forms a stable complex with silver acetate at the transition state. At first, the corresponding azomethine ylides are formed *in situ* by the deprotonation in the α -position by diisopropylethylamine. Then, bidentate complexation of chiral ligand and silver metal also coordinates to the imine nitrogen and the enolate oxygen (*Scheme 7*). By this catalyst system it was possible to form pyrrolidine derivatives in up to 98% yield and 80% ee.



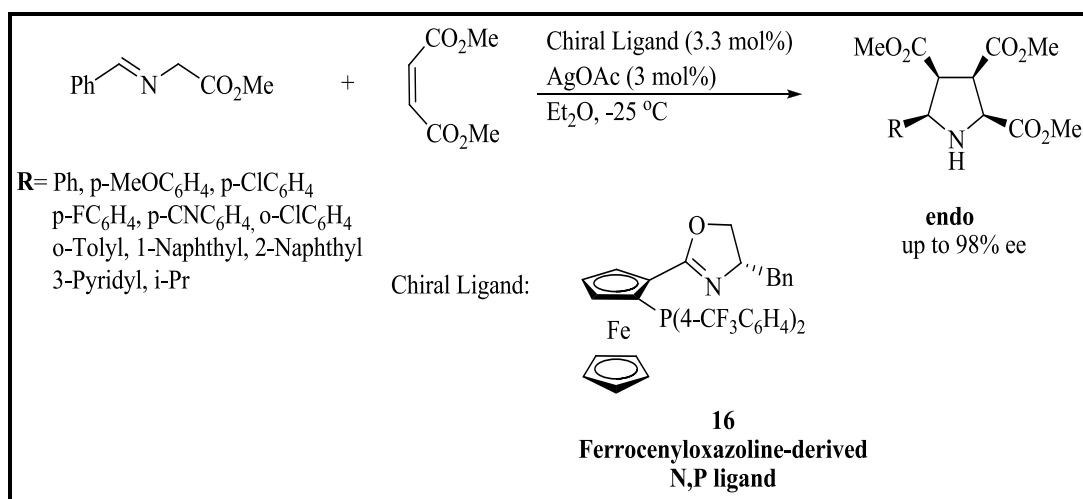
Scheme 7. 1,3-DC reaction of azomethine ylides studied by Schreiber and co-workers

Carreira and co-workers designed a new chiral ligand O-(*S*)-PINAP (**16**) in 2004 [44]. It is similar to (*S*)-QUINAP (**15**). By optimizing Schreiber's procedure and using 3 mol% catalyst it was possible to form pyrrolidines in similar yields and enantioselectivities as in the case of QUINAP catalyst (*Scheme 7*).



Scheme 8. 1,3-DC reaction of azomethine ylides studied by Carreira and co-workers

Zhou and co-workers synthesized chiral ferrocenyloxazoline derived *P,N*-ligand in 2005 (**16**) and used with silver acetate as shown in *Scheme 9* [45]. In this divergent study it was not necessary to use a base. It was claimed that acetate ion is serving as the base in deprotonating imino ester to form the azomethine ylide *in situ*. In this study, products were formed by *endo*-diastereoselectivity in up to 98% ee *Figure 17*.



Scheme 9. 1,3-DC reaction of azomethine ylides studied by Zhou and co-workers

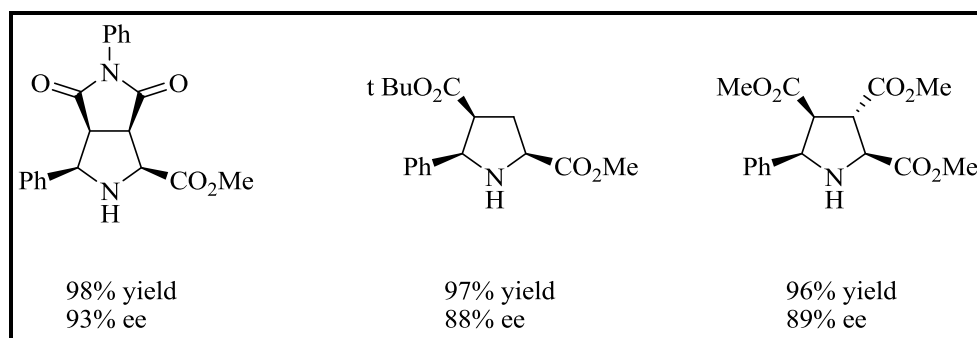


Figure 17. Pyrrolidine derivatives under optimized reaction conditions.

Dogan and co-workers synthesized new chiral phosphine oxide ligands **17**, **18**, **19**, **20**, **21**, **22** and tried for the 1,3-DC reactions of azomethine ylides in 2010 (*Figure 18*) [33]. They tested these chiral ligands by using silver acetate as the metal source. When the chiral ligands **17**, **18**, **19**, **20**, **21** were used, the cycloadduct was obtained in low yield and enantioselectivity. Higher yield and enantioselectivity were obtained with chiral ligand **22**.

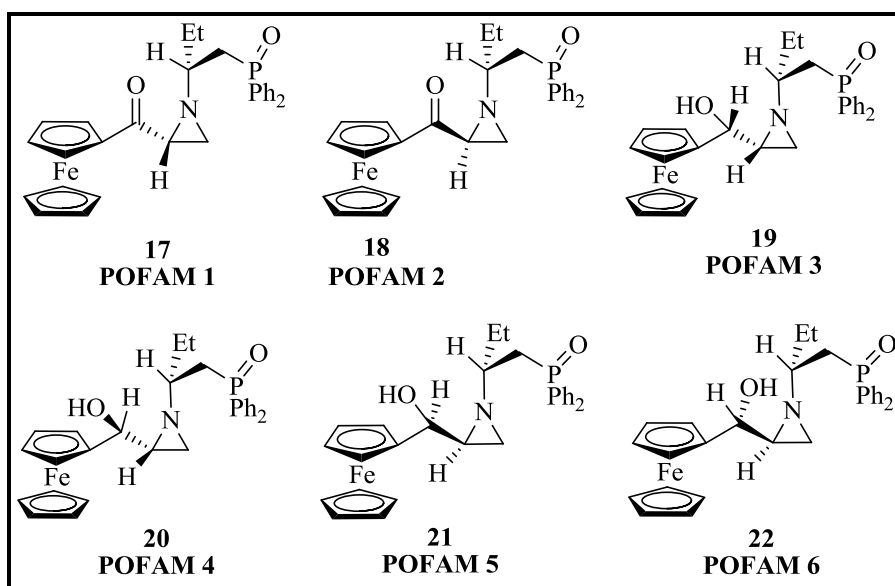
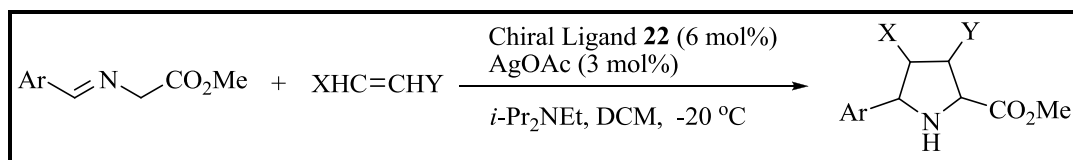


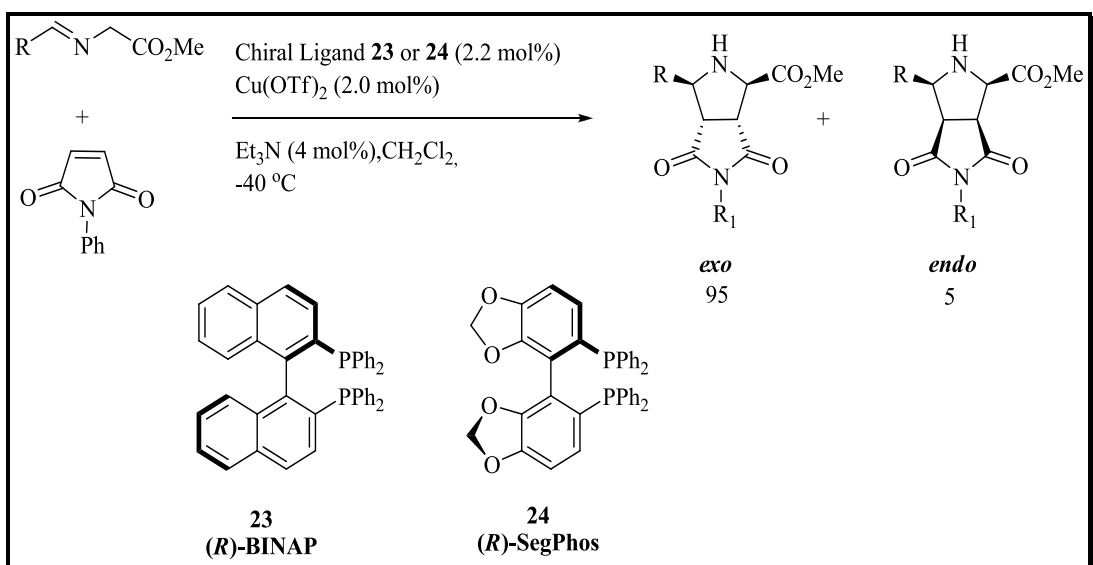
Figure 18. Chiral phosphine oxide ligands used by Dogan and co-workers

In the presence of 6 mol% of chiral ligand **22**, cycloadducts were formed in 33-99% yields and 15-77% ee's with *endo* selectivity.



Scheme 10. 1,3-DC reaction of azomethine ylides studied by Dogan and co-workers

Until now, the pyrrolidines were obtained in *endo* selectively from the cycloaddition reaction of azomethine ylides. Komatsu and co-workers reached the first example of an *exo*-selective cycloaddition reaction [46]. They used chiral bisphosphine ligands and $\text{Cu}(\text{OTf})_2$ as a metal source. $\text{Cu}(\text{OTf})_2$ forms a more stable complex with chiral bisphosphine ligands compared to silver sources. As a result of reaction proceed at $-40\text{ }^\circ\text{C}$; they obtained the *exo*-selective cycloaddition of *N*-benzylidene glycine methyl ester with *N*-phenylmaleimide. The ratio of *exolendo* was up to 95/5 in the case of *N*-phenylmaleimide (Scheme 11). They proposed a mechanism to explain this situation as shown in Figure 19. Among the ligands (*R*)-BINAP (**23**) and (*R*)-SegPhos (**24**) gave the highest enantioselectivities. Interestingly, when Komatsu and co-workers used dimethyl fumarate or fumaronitrile, they obtained *endo* instead of *exo* cycloadducts with these dipolarophiles. It means that, *exo/endo* selectivity depends on the dipolarophile.



Scheme 11. 1,3-DC reaction of azomethine ylides studied by Komatsu and co-workers

Komatsu et al. offered a mechanism for the *exo*-selectivity of the reaction (Figure 19). In this transition model, the azomethine ylide coordinates to the metal/ligand complex. Dipolarophile (*N*-Phenylmaleimide) approach this complex in an *exo*-mode rather than *endo*-mode which is sterically more hindered. Phenyl groups on the nitrogen and phosphorous repel each other in *endo* transition state therefore it is not favored.

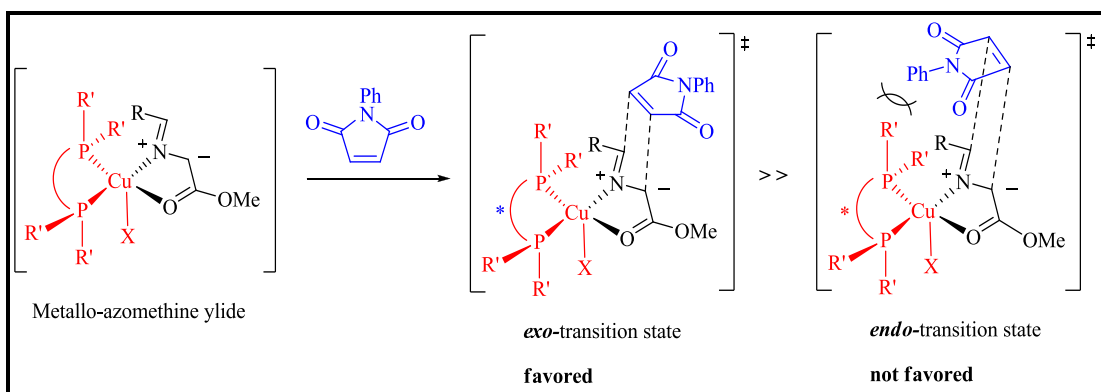


Figure 19. Transition state for *exo* selectivity

1.2 Aim of work

Given the structural novelty and the potential biological activity of pyrrolidines, it is very important to synthesize these compounds in enantiomerically pure forms by efficient and economical methodologies. For this purpose, various procedures had been developed in the literature. Different chiral catalysts have been used for the synthesis of these compounds by 1,3-DC reactions of azomethine ylides with dipolarophiles. There is no study in the literature reporting one-pot 1,3-DC reaction of azomethine ylides for the metal catalyzed catalytic asymmetric synthesis of pyrrolidines. In previous studies, work done by our group and other groups, first the imines were synthesized from glycine methyl ester and aromatic aldehydes then the cycloaddition reactions were carried out in total of two steps. However, in this study, we aimed to develop a more practical method for the synthesis of pyrrolidines by a one-pot 1,3-DC reaction. Our group previously synthesized phosphorous based phosphino ferrocenyl aziridiny methanol (**PFAM** and **POFAM**) chiral ligands and reported their activity for 1,3-DC reaction of azomethine ylides. In this thesis the performance of same chiral ligands for the one-pot 1,3-DC reaction of azomethine ylides were planned to be tested. By doing so we aimed to develop a new practical method which saves up time and consumables. In short pyrrolidine derivatives were intended to be synthesized in a one-pot reaction.

CHAPTER 2

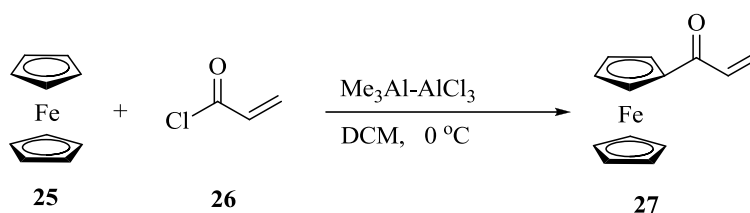
RESULTS AND DISCUSSION

2.1 The Synthesis of Chiral P-FAM Ligands

In order to test the performance of **PFAM** and **POFAM** series of chiral ligands for one-pot 1,3-DC reactions of azomethine ylides, they were synthesized as reported previously [33].

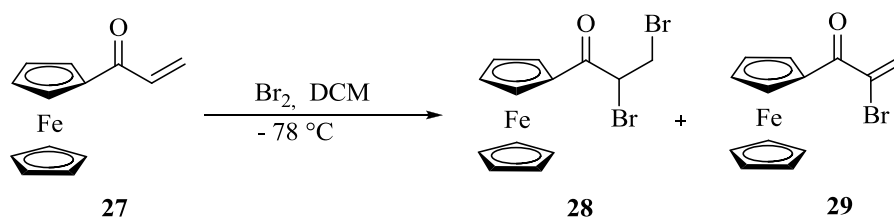
2.1.1 Synthesis of Aziridines

Ferrocene **25** and acryloyl chloride **26** were mixed in the presence of $\text{Me}_3\text{Al}-\text{AlCl}_3$ to form acryloyl ferrocene in 99% yield. The crude product was reasonable pure so it was used for the next step without purification (*Scheme 13*) [33^b].



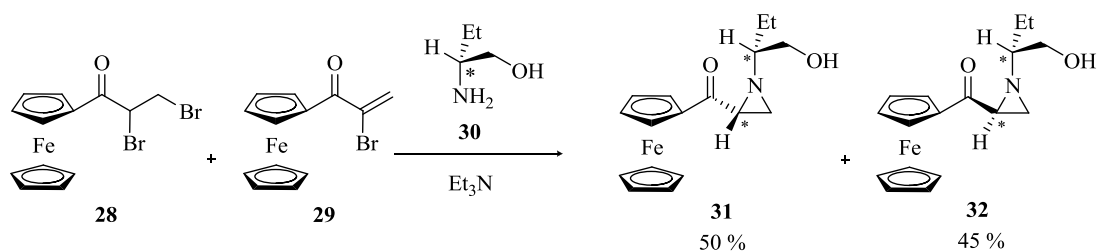
Scheme 12. Synthesis of acryloyl ferrocene from ferrocene and acryloyl chloride

Bromination of acryloyl ferrocene **27** in DCM at $-78\text{ }^\circ\text{C}$ provided dibromo compound **28** in excellent yield (>95%) with minor amount of mono-bromo compound **29** (*Scheme 13*). In the literature, bromination of acryloyl ferrocene reported to be problematic due to salt formation and bromination of ferrocene rings [47]. By this method, it is possible to run this reaction on a gram scale.



Scheme 13. Bromination of acryloyl ferrocene

In order to form aziridines, the mixture of dibromide **28** and α -bromo compound **29** were stirred first with triethylamine then the chiral amino alcohol was added (*Scheme 14*).

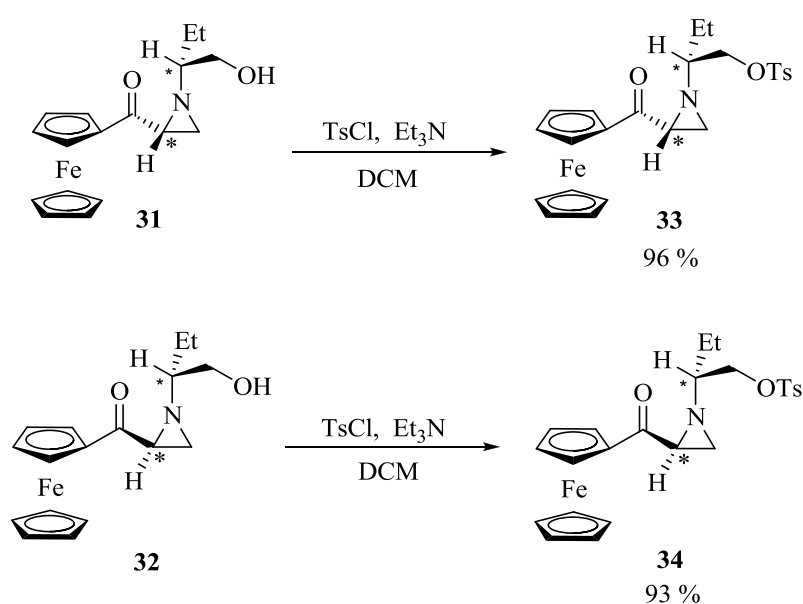


Scheme 14. Aziridination reaction with Gabriel-Cromwell reaction

From this reaction diastereomeric mixture of aziridines **31** and **32** were obtained in 50% and 45% yields, respectively after flash column chromatography (*Scheme 14*). This reaction is also known as Gabriel-Cromwell reaction [48].

2.1.2 Synthesis of Tosylated Aziridines

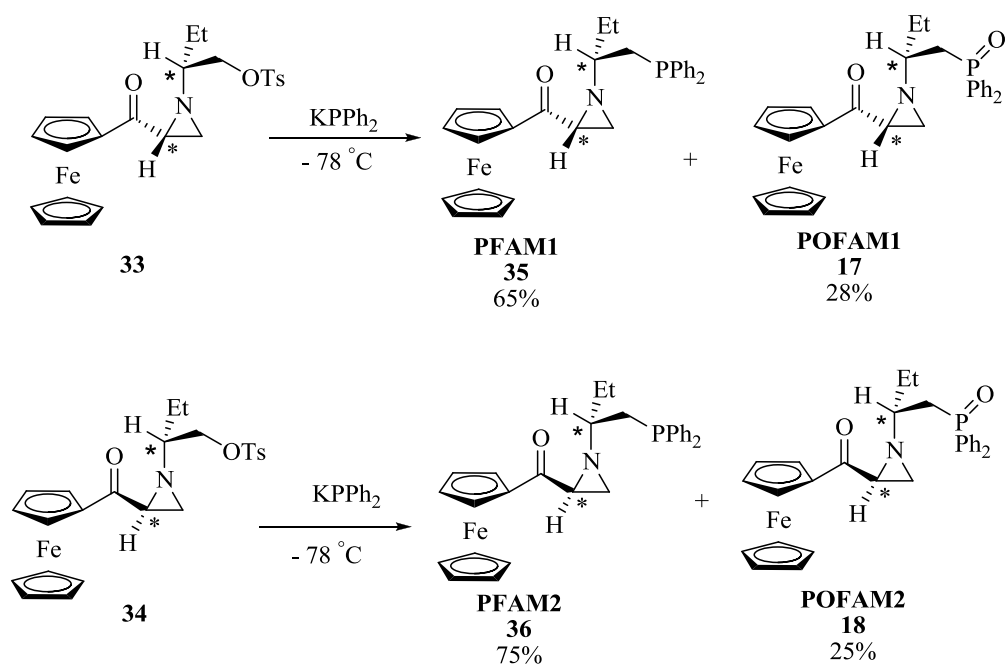
In order to introduce phosphorous group to aziridinyl ketones it was necessary to convert hydroxyl group into better leaving group tosylate. This was achieved easily by reacting aziridinyl ketones **31** and **32** individually with tosyl chloride (*Scheme 15*). From these reactions tosylated aziridinyl ketones **33** and **34** were obtained in 96% and 93% yields, respectively.



Scheme 15. Tosylation of aziridinyl ketones

2.1.3 Phosphorylation of tosylated aziridinyl ketones

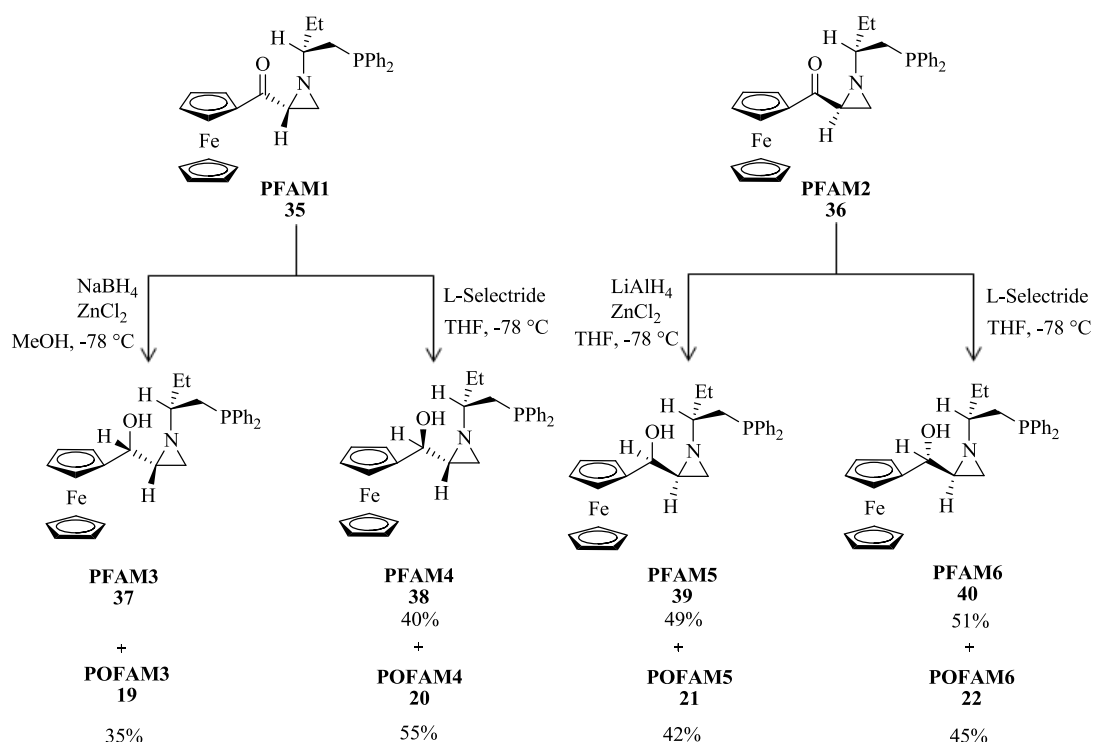
Reaction of ketones **33** and **34** with potassium diphenylphosphide, using the procedure reported by Williams and co-workers [49], yielded phosphino aziridinyl ketones **35** and **36** in 65% and 75% yields with their oxidized forms **17** (28%) and **18** (25%) respectively (*Scheme 16*).



Scheme 16. Synthesis of phosphino aziridinyl ketones

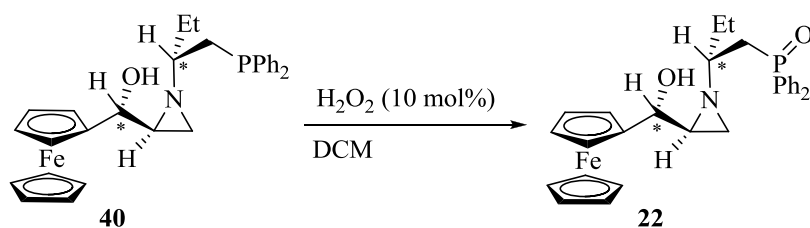
2.1.4 Reduction of phosphorylated aziridinyl ketones

The final step for completion of ligand synthesis was the reduction of keto groups to alcohols. To achieve that, the procedure reported by Yun and co-workers was used [50]. Absolute configurations of chiral **PFAM** ligands were based on an analogy with our previously synthesized **FAM** ligands [33^a]. The **PFAM** series are highly sensitive to oxidation therefore it is important to keep them away from the air.



Scheme17. Synthesis of phosphino and phosphineoxy aziridiny methanol ligands

On the other hand, since **POFAM** series performed well in the reactions, it was necessary to fully convert **PFAM** ligands into their oxidized forms. This was easily accomplished by using hydrogen peroxide (*Scheme 18*).



Scheme18. Synthesis of phosphineoxy aziridiny methanol ligands

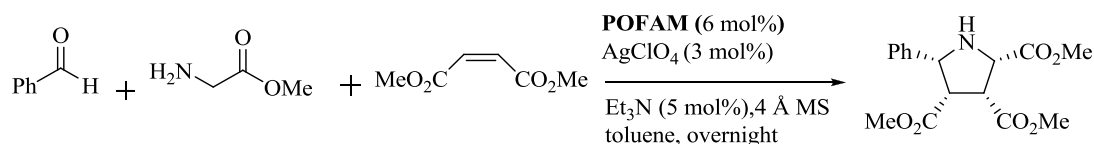
2.2 The Asymmetric One-pot 1,3-Dipolar Cycloaddition Reaction by Using Chiral POFAM Ligands

After the synthesis of **POFAM** ligands, their performance were tested for asymmetric one-pot 1,3-DC reaction as a catalyst with silver metal. Various chiral ligands and metal salts were performed for 1,3-DC reaction by different research groups in the literature [34]. Among the metal salts, silver salts have advantages compare to the other transition metal salts. Because silver coordinates well with phosphine oxy groups [45]. Therefore, we started to test the performance of **POFAM** ligands with silver salts in one-pot 1,3-DCR type reaction.

2.2.1 Ligand screening studies of asymmetric one-pot 1,3-dipolar cycloaddition reaction

In screening the ligands, we have followed literature procedure [51] and run the reactions with benzaldehyde, glycine methyl ester, and dimethyl maleate. Although total of twelve phosphorous based chiral ligands were synthesized, previous studies in our group showed that **PFAM** ligands (**37**, **38**, **39** and **40**) were not effective in 1,3-DC reactions of azomethine ylides. We speculate that phosphine oxide coordinates metal more strongly than phosphine group thus provides a more rigid system. Therefore we focused on **POFAM** series (**17**, **18**, **19**, **20**, **21**, and **22**). The results of ligand screening studies are summarized in (*Table 1*). As can be seen from this table **POFAM6** ligand gave the product in highest enantioselectivity (30%) than the others. As a result **POFAM6** was selected as the ligand and used in further optimization studies.

Table 1. Ligand screening studies

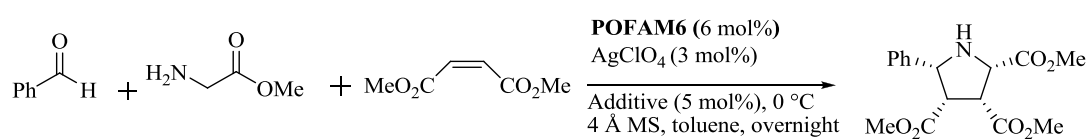


Entry	Ligand structures	Chiral ligand	Yield (%)	ee (%)
1		POFAM 1 (<i>R, R</i>)	20	5
2		POFAM 2 (<i>S, R</i>)	75	10
3		POFAM 3 (<i>R, R, R</i>)	n.d	n.d
4		POFAM 4 (<i>S, R, R</i>)	80	7
5		POFAM 5 (<i>S, S, R</i>)	25	27
6		POFAM 6 (<i>R, S, R</i>)	58	30

2.2.2 Additive screening studies

Next optimization study was to determine the effect of additives. As mentioned previously, Zhou [45] and co-workers didn't use additives when AgOAc was used as the metal salt. They reasoned that acetate ion coming from AgOAc is serving for this purpose by removing the proton of aldimine thus forming the azomethine ylide *in situ*. Since we run the experiments with AgClO₄ and AgOAc it was important to see the effect of additives on the reaction. Therefore three additives DIPEA, TEA, and TMEDA were tried. The results of these studies were reported in *Table 2*. Among the additives DIPEA was found to be better than the others. As a result it was decided to be the additive of the reaction.

Table 2. Additive screening studies

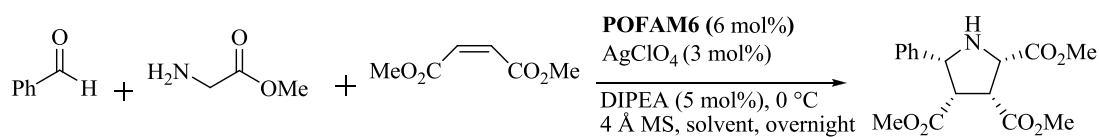


Entry	Additive	Yield (%)	ee (%)
1	none	37	30
2 ^a	none	47	29
3	DIPEA	58	33
4	TEA	58	30
5	TMEDA	30	20

^a Performed with AgOAc

2.2.3 Solvent screening studies

After determining the ligand and additives, it was also necessary to see the effect of solvents. As the solvent, toluene, CH₃CN, DCM, 1,2-DCE and DMSO were used. The results of solvent effects were summarized in *Table 3*. As can be seen from this table the highest enantioselectivity was obtained in DCM (*entry 2*). According to the kinetic studies performed by Huisgen, the solvent polarity has little effect on reaction rates of 1,3-DC reactions. Moreover, in nonpolar solvents as toluene, there is a solubility problem that can be seen easily by the cloudy reaction mixture. Furthermore, when the metal source is less soluble, non-metalloazomethine ylides may leave to reach stereomutation processes. As a result less stereoselective cycloaddition can take place. In DCM, the reaction medium was homogenous throughout the reaction. The product was obtained in 53% yield and 50% ee. From these studies DCM was chosen as the solvent for this reaction.

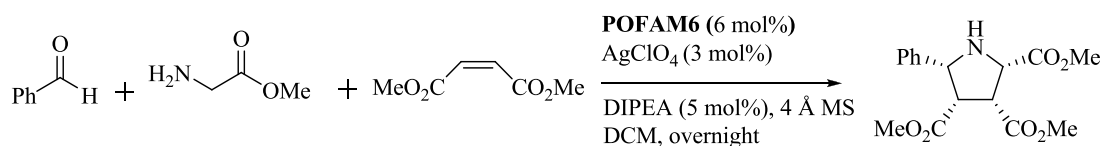
Table 3. Solvents screening studies

Entry	Solvent	Yield (%)	ee (%)
1	CH ₃ CN	57	34
2	DCM	53	50
3	1,2-DCE	60	31
4	Toluene	58	33
5	DMSO	n.d	n.d

2.2.4 Temperature and concentration screening studies

After deciding on solvent as DCM, base as DIPEA and chiral ligand as **POFAM6**, the temperature and concentration screenings were also conducted. When the reaction was carried out at room temperature, product was obtained in higher yield as expected but in lower ee (*Table 4, entry 1*). When the temperature was decreased to -20 °C, the product was obtained in lower yield with no enantioselectivity (*Table 4, entry 3*). Lower yield at low temperature can be expected but lower enantioselectivity was rather unexpected. We speculate that at low temperature complexation between reactants and chiral catalyst is not effective or taking place at all. As a result cycloaddition is taking place without control of the catalyst. From these studies 0 °C found to be the optimum temperature for this reaction.

As summarized in *Table 4*, the concentration effect was also investigated. For this purpose reaction was carried at 0.94M, 0.56M and 0.1M. From these studies 0.56M was found to be the optimum concentration for asymmetric one-pot 1,3-DC reaction.

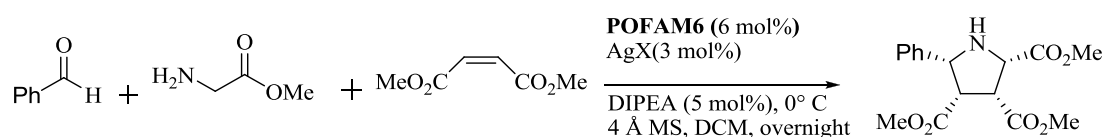
Table 4. Temperature and concentration screening studies

Entry	Temperature (°C)	Molarity (M)	Yield (%)	ee (%)
1	rt	0.94	63	23
2	0	0.94	53	50
3	-20	0.94	29	rac
4	0	0.56	52	55
5	0	0.1	63	27

2.2.5 Silver salt screening studies

Under the optimized reaction conditions specified so far it was also interesting to see the effect of different silver salts on the reaction. For this purpose reactions were performed with AgOAc, AgOTf, and AgClO₄. The results of these studies are summarized in *Table 5*. Since it is known that the complexation is taking place between metal, chiral ligand and substrates, the type of the silver salt and its amount can be crucial for this reaction. As can be seen from *Table 5*, AgClO₄ and AgOTf gave similar yield and ee (*entries 1 and 2*). In trying hydrated form of silver perchlorate (AgClO₄·H₂O), the product was obtained in highest yield (67%) (*entry 3*) but in lower ee (43%). By replacing silver salt with AgOAc, the product was obtained in highest enantioselectivity (74%) with 53% yield (*entry 4*).

Table 5. Silver salt screening studies



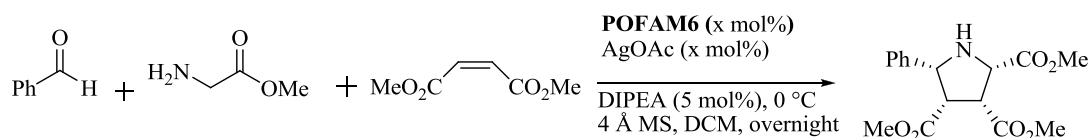
Entry	Silver salt	Silver salt (mol %)	POFAM6 (mol %)	Yield (%)	ee (%)
1	AgClO ₄	3	6	52	55
2	AgOTf	3	6	50	55
3	AgClO ₄ ·H ₂ O	3	6	67	43
4	AgOAc	3	6	53	74

2.2.6 Optimization studies at different AgOAc-ligand ratio

The amount of ligand and metal is very significant for metal catalyzed asymmetric reactions. Firstly, lowest possible amounts are valuable and preferable for the catalytic reactions. Secondly, during catalyst preparation by mixing metal and ligand, reaction medium must be homogeneous. Therefore metal-ligand ratio is crucial. For this purpose, using the previously optimized conditions (*Scheme 20*), the experiments were performed by using different ligand to metal ratio. The results of these studies are summarized in *Table 6*. It is also possible that if some metals left uncomplexed with the ligand, they may catalyze the background reaction (reaction leading to the racemic product formation).

First, the amount of AgOAc was decreased to 1.5 mol % which yielded the product in same yield as 3 mol % metal salt but in lower ee (*entry 2*). Second, the ligand was increased to 10 mol % and the metal was increased to 2.5 mol %. Under these conditions yield was increased to 86% but ee was decreased to 51% (*entry 3*). Finally, the use of 5 mol % AgOAc and 10 mol % ligand (*entry 4*) provided the product in low yield (50%) and ee (50%). From these results, it was decided to stay at 6 mol % ligand and 3 mol % metals (*entry 1*).

Table 6. Different AgOAc-ligand ratio studies



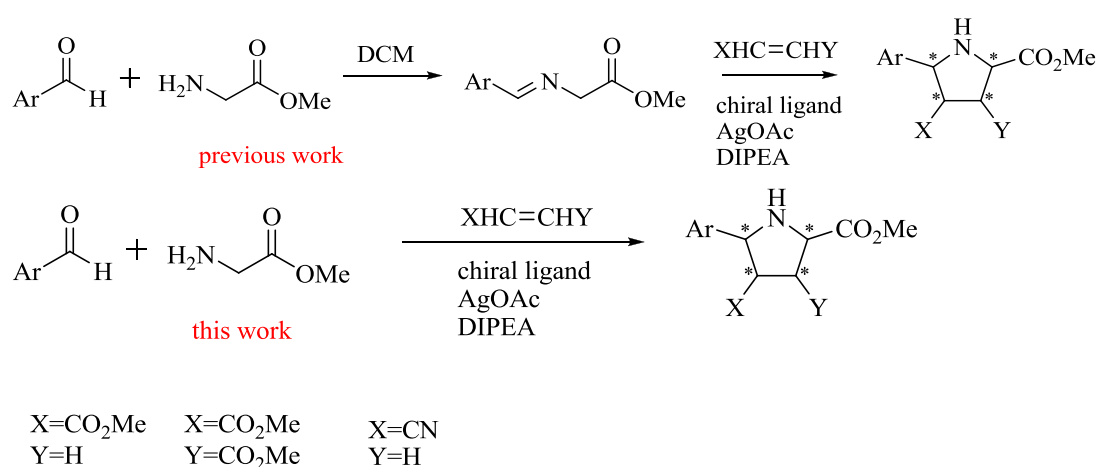
Entry	POFAM6 (mol %)	AgOAc (mol %)	Yield (%)	ee (%)
1	6	3	53	74
2	6	1,5	58	47
3	10	2,5	86	51
4	10	5	50	50

From all these optimization studies, it was decided that benzaldehyde (1 eq.), glycine methyl ester (1,3 eq.), dimethyl maleate (3 eq.), chiral ligand **POFAM6** (6 mol %), AgOAc (3 mol %), DIPEA (5 mol %), DCM as the solvent, and 0 °C as the reaction temperature needed to be used for asymmetric one-pot 1,3-DC reactions of azomethine ylides. After determining the optimum conditions, we decided to test the effect of this catalyst on different aldehydes and dipolarophiles to show the applicability.

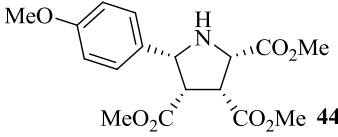
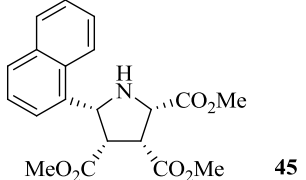
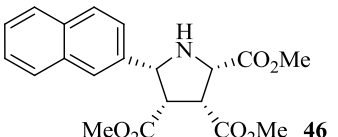
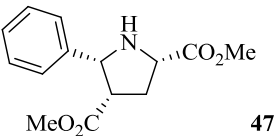
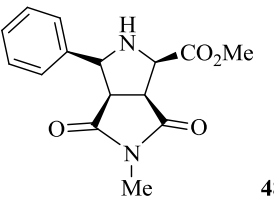
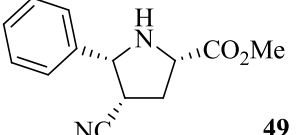
2.3.1 Enantioselective asymmetric one-pot 1,3-Dipolar Cycloaddition Reaction of various aldehyde and dipolarophiles

In order to show the applicability of the catalyst on the one-pot reaction five different aldehydes (benzaldehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-methoxyaldehyde, 2-naphthaldehyde, 1-naphthaldehyde) were used to form azomethine ylides *in situ* and reacted with electron deficient dipolarophiles (dimethyl maleate, methyl acrylate, *N*-methylmaleimide and acrylonitrile). The results of these studies were summarized and compared with the results obtained previously in our group in *Table 7*.

Table 7. Results of this work and previous work



Entry	Structure	Previous work (starts from imine)		This work (cascade)	
		Yield (%)	ee (%)	Yield (%)	ee (%)
1	 41	95	70	53	74
2	 42	20	60	60	86
3	 43	35	28	45	40

4	 <chem>COC(=O)C1CC(N1)C2=CC=C(C=C2)OC</chem> 44	42	74	55	72
5	 <chem>COC(=O)C1CC(N1)C2=CC=C3C=CC=CC23</chem> 45	70	74	42	55
6	 <chem>COC(=O)C1CC(N1)C2=CC=C3C=CC=CC23</chem> 46	93	89	50	65
7	 <chem>COC(=O)C1CC(N1)C2=CC=CC=C2</chem> 47	87	70	72	45
8	 <chem>COC(=O)C1CC(N1C2=CC=CC=C2)C3=CC(=O)N(C)C3=O</chem> 48	99	30	99	41
9	 <chem>COC(=O)C1CC(N1)C2=CC=CC=C2C#N</chem> 49	93	70	92	75

As can be seen from *Table 7*, derivatization studies were carried out under optimum conditions. Firstly, the cycloaddition product **41** was obtained from benzaldehyde and dimethyl maleate proceeded with lower yield and higher enantioselectivity (53 % yield and 74 % ee) as compared to the previous work (*entry 1*). Then, we have investigated the effect of both electron donating and withdrawing substituents on the aromatic ring. For this purpose, *p*-chloro-, *p*-bromo- and *p*-methoxybenzaldehydes were reacted with the initially used dipolarophile (*entries 2-4*). In all these cases products were formed in high yields as compared to previous work and also in high enantioselectivities except for the *p*-anisidine case (*entries 2-4*). In the case of sterically more hindered naphthaldehydes, it was seen that reactions carried out by isolated imines (previous work) formed the pyrrolidines in better yields and enantioselectivities than one-pot reaction (this work) (*entries 5 and 6*). In the case of different dipolarophiles (methyl acrylate, *N*-methylmaleimide, and acrylonitrile) except methyl acrylate, products were formed in same yields with better enantioselectivities by the use of one-pot reaction (*entries 7-9*). In general except three cases (*entries 5-7*) one-pot reaction formed pyrrolidines in better enantioselectivities than two step reaction.

CHAPTER 3

CONCLUSION

In recent years one-pot reactions have been studied significantly by different groups. This reaction provides complex molecules from very simple starting materials in a single step. For that reason it is considered as atom economical reaction and “green chemistry”. Asymmetric version of this reaction is also being studied by organic groups for the synthesis of complex chiral compounds. In this respect, we have studied metal catalyzed one-pot reaction of azomethine ylides with electron deficient dipolarophiles using chiral ligands with silver metal.

Chiral ligands were synthesized by using reported procedures and standard optimization studies (ligand screening, metal salt screening, additive screening, solvent screening, temperature, and concentration screening) were performed to form pyrrolidines in high yields and enantioselectivities. Derivatization studies using various kinds of aldehydes and electron deficient dipolarophile were also conducted. The yields of the products varied between 42-99% and the enantioselectivities varied between 40-86%. In general one-pot reaction formed pyrrolidines with similar or higher yields but better enantioselectivities than two step reaction.

To conclude, pyrrolidines were obtained in reasonable yields and enantioselectivities by using one-pot reaction which is more efficient, practical, and green.

CHAPTER 4

EXPERIMENTAL

4.1 General Consideration

4.1.1 General Procedures

All reactions were carried out in flame-dried glassware under reduced pressure and then filled with argon to obtain inert atmosphere. Light and moisture-sensitive AgOAc salts stored in desiccators and wrapped with aluminum foil. Ligands were purified by flash column chromatography on silica gel and TLC analyses were performed on triethylamine (5 mol %). Cycloaddition products were also purified by flash column chromatography on silica gel (E. Merck Silica Gel 60, particle size: 0.040- 0.063 mm, 230-400 mesh ASTM). TLC analyses were performed on 250 μm Silica Gel 60 F₂₅₄ plates and visualized by UV or ninhydrin in butanol as the coloring agent. Enantiomeric excess (ee) was determined by chiral HPLC. Racemic compounds were prepared by using silver (I) acetate in the absence of chiral ligand.

4.1.2 Materials

Dichloromethane (DCM), 1,2-dichloroethane (DCE) and acetonitrile (CH₃CN) were distilled and dried over calcium hydride prior to use. Toluene was dried over sodium and stored under nitrogen. Reagent grade dimethyl sulfoxide (DMSO) was used directly. Tetramethylethylenediamine (TMEDA) was distilled over sodium under vacuum and stored over potassium hydroxide pellets under inert atmosphere. *N,N*-diisopropylethylamine (DIPEA) was distilled under reduced pressure and stored over molecular sieves. Triethylamine (Et₃N) and diisopropylethylamine (ⁱPr₂NEt) were distilled and kept over NaOH pellets under nitrogen. Liquid dipolarophiles and aldehydes were distilled by using micro distillation and kept under inert atmosphere. Molecular sieves (4 Å) were activated at 110 °C in the oven.

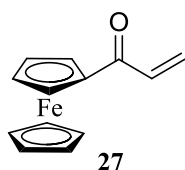
4.1.3 Instrumentation

Enantiomeric excess values of cycloadducts were determined by chiral HPLC. Retention times were consistent with the literature and also confirmed by the analysis of the racemic products. ¹H- and ¹³C-NMR spectra were reported on a Bruker spectropin Avance DPX-400 Ultra shield instrument at 400 and 100 MHz respectively. ¹H-NMR data are reported as chemical shifts (δ , ppm) relative to tetramethylsilane (δ 0.00) with multiplicity (s= singlet, br= broad singlet, d= doublet, dd= doublet of doublet, ddd=doublets of doublets of doublet, dq= doublet of quartet, t= triplet, q= quartet, dt= doublet of triplet, p= pentet, sx= sextet, m= multiplet), coupling constant (Hz) and integration. NMR samples were prepared in CDCl₃. Optical rotations were measured by Rudolph Research Analytical Autopol III Polarimeter in 1 dm cell with an average of 5 measurements, each with an integration time of 15 s and

reported as $[\alpha]_D^{30}$ (c in 2.5 mg/mL solvent). For overnight reactions performed at 0°C, reaction flask was placed in an isopropanol bath cooled by cryostat (HAAKE EK90).

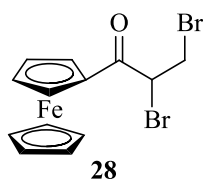
4.2 Synthesis and Characterization of Chiral Ligands

4.2.1 Synthesis of acryloyl ferrocene



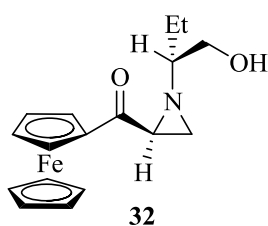
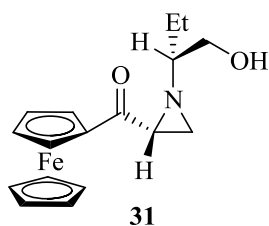
Acryloyl ferrocene **27** was synthesized by following the literature procedure [33]. $^1\text{H-NMR}$ (400 MHz) δ 6.80 (dd, $J = 17.0$ Hz, $J = 10.3$ Hz, 1H), 6.42 (d, $J = 16.6$ Hz, 1H), 5.70 (d, $J = 10.0$ Hz, 1H), 4.80 (s, 2H), 4.55 (s, 2H), 4.16 (s, 5H).

4.2.2 Bromination of acryloyl ferrocene



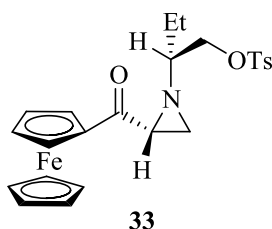
Dibromo compound **28** was synthesized by following the procedure given in the literature [33]. $^1\text{H-NMR}$ (400 MHz) δ 4.79 (s, 1H), 4.68 (s, 1H), 4.61 (s, 1H), 4.34 (s, 5H), 4.23 (m, 1H), 3.76 (dd, $J = 9.8$ Hz, $J = 3.8$ Hz, 1H).

4.2.3 Synthesis of aziridinyl ketones



The aziridinyl ketones **31** and **32** were synthesized by following the procedure given in the literature [33]. **31**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 4.91 (s, 1H, Fc), 4.86 (s, 1H, Fc), 4.53 (s, 2H, Fc), 4.22 (s, 5H, Fc), 3.75 (br, 2H), 2.67 (br, 1H), 2.30 (s, 1H), 2.22 (br, 1H, OH) 1.77-1.54 (m, 4H), 0.98 (t, $J = 7.3$ Hz, 3H, CH_3); **32**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 4.82 (d, $J = 12.97$ Hz, 2H, Fc), 4.46 (s, 2H, Fc), 4.13 (s, 5H, Fc), 3.68 (br, 2H), 2.49 (br, 1H), 2.26 (s, 1H), 2.14 (br, 1H, OH), 1.80 (br, 1H), 1.69 (m, 1H), 1.59 (m, 1H), 1.47 (br, 1H), 0.95 (t, $J = 7.25$ Hz, 3H).

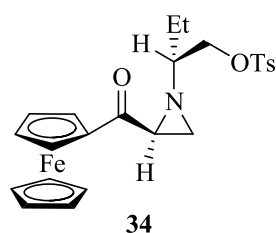
4.2.4 Synthesis of tosylated aziridinyl ketone **33**



3H, CH₃).

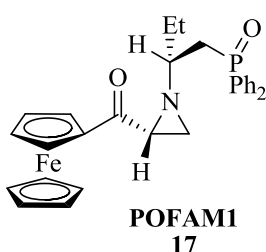
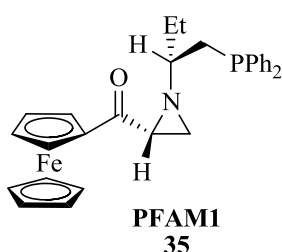
Hydroxy ketone **31** was tosylated to form **33** by the literature procedure [33]. ¹H-NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 8.1 Hz, 2H, Ph), 7.22 (d, *J* = 8.0 Hz, 2H, Ph), 5.02 (s, 1H, Fc), 4.87 (s, 1H, Fc), 4.56 (s, 2H, Fc), 4.20 (s, 5H, Fc), 4.14 (dd, *J* = 3.8 Hz, *J* = 10.2 Hz, 1H), 3.98 (dd, *J* = 7.7 Hz, *J* = 10.0 Hz, 1H), 2.82 (q, *J* = 3.1 Hz, 1H), 2.39 (s, 3H, CH₃, Ts), 2.32 (s, 1H), 1.87 (m, 1H), 1.71 (d, *J* = 6.5 Hz, 1H), 1.61 (m, 2H), 0.99 (t, *J* = 7.5 Hz,

4.2.5 Synthesis of tosylated aziridinylo ketone **34**



Hydroxy ketone **32** was tosylated to form **34** by the literature procedure [33]. ¹H-NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.1 Hz, 2H, Ph), 7.35 (d, *J* = 7.6 Hz, 2H, Ph), 4.86 (s, 2H, Fc), 4.51 (s, 2H, Fc), 4.17 (s, 5H, ferrocene), 4.11 (d, *J* = 5.7 Hz, 2H, CH₂-OTs), 2.51 (dd, *J* = 3.0 Hz, *J* = 6.4 Hz, 1H), 2.45 (s, 3H, CH₃, Ts), 2.22 (s, 1H), 1.91 (d, *J* = 6.6 Hz, 1H), 1.83 (pentet, *J* = 5.7 Hz, 1H), 1.62 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H).

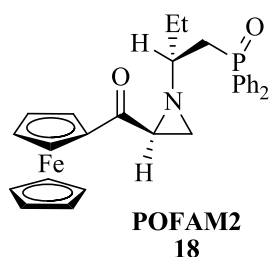
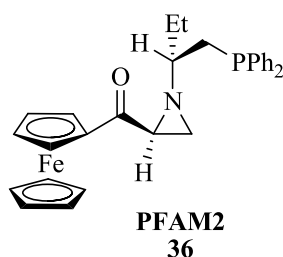
4.2.6 Synthesis of phosphino aziridine **35** and phosphineoxy aziridine **17**



The phosphino aziridine **35** and its oxidized form **17** were synthesized from compound **33** by following the procedure given in the literature [33]. **35**: ¹H-NMR (400 MHz, CDCl₃) δ 7.34 (m, 4H, Ph), 7.23 (m, 6H, Ph), 4.77 (s, 2H, Fc), 4.43 (s, 2H, Fc), 4.08 (s, 5H,

Fc), 2.32 (t, *J* = 7.5 Hz, 2H), 2.27 (d, *J* = 7.1 Hz, 1H), 1.74 (sx, *J* = 7.2 Hz, 2H), 1.65 (d, *J* = 6.6 Hz, 1H of CH₂ aziridine), 1.38 (sx, *J* = 5.8 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H, CH₃). **17**: ¹H-NMR (400 MHz, CDCl₃) δ 7.65 (m, 4H, Ph), 7.39 (m, 4H, Ph), 7.28 (m, 2H, Ph), 5.00 (s, 1H, Fc), 4.77 (s, 1H, Fc), 4.41 (s, 2H, Fc), 4.05 (s, 5H, Fc), 2.96 (dd, *J* = 2.9 Hz, *J* = 3.2 Hz, 1H), 2.52 (m, 2H), 2.32 (s, 1H), 2.05 (m, 1H), 1.82 (d, *J* = 6.2 Hz, 1H), 1.62 (m, 1H), 1.54 (m, 1H), 0.81 (t, *J* = 7.4 Hz, 3H, CH₃).

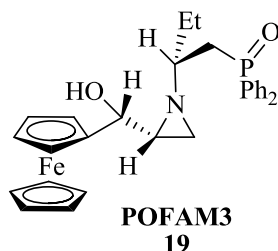
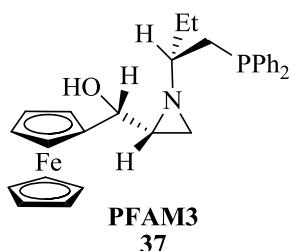
4.2.7 Synthesis of phosphino aziridine **36** and phosphineoxy aziridine **18**



Phosphino aziridine **36** and its oxidized form **18** were synthesized from compound **34** by following the procedure given in the literature [33]. **36**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.45 (m, 4H, Ph), 7.34 (m, 6H, Ph), 4.84 (s, 2H, Fc), 4.50 (s, 2H, Fc), 4.19

(s, 5H, Fc), 2.44 (m, 3H), 2.19 (s, 1H), 1.81 (p, $J = 7.2$ Hz, 2H), 1.61 (d, $J = 6.7$ Hz, 1H), 1.51 (sx, $J = 6.3$ Hz, 1H), 1.01 (t, $J = 7.4$ Hz, 3H, CH_3); **18**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.86 (m, 2H, Ph), 7.75 (m, 2H, Ph), 7.50 (m, 6H, Ph), 4.82 (s, 2H, Fc), 4.51 (s, 2H, Fc), 4.17 (s, 5H, Fc), 2.67 (m, 2H), 2.60 (dd, $J = 2.7$ Hz, $J = 6.3$ Hz, 1H), 2.15 (septet, $J = 5.5$ Hz, 1H), 1.90 (s, 1H), 1.83 (d, $J = 6.7$ Hz, 1H), 1.69 (p, $J = 7.3$ Hz, 2H), 0.94 (t, $J = 7.4$ Hz, 3H).

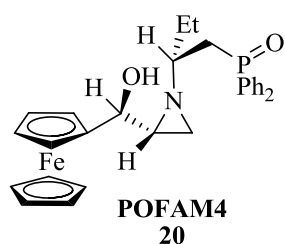
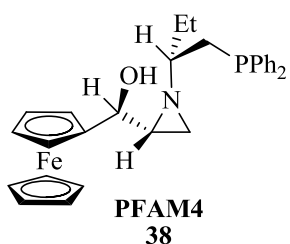
4.2.8 Synthesis of phosphine and phosphine oxy ferrocenyl aziridinyl methanol (*R, R*) **37** and **19**



Phosphino ferrocenyl aziridinyl methanol **37** and its oxidized form **19** were synthesized from compound **35** by following the procedure given in the literature [40]. **37**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.34 - 7.23 (m, 10H, Ph), 4.29 (d, $J = 4.3$ Hz, 1H, Fc), 4.19 (s, 1H,

Fc), 4.16 (s, 1H, Fc), 4.11 (s, 5H, Fc), 4.08 (s, 1H, Fc), 2.46 (br, 1H, OH), 2.09 (ddd, $J = 7.7$ Hz, $J = 6.3$ Hz and $J = 5.1$ Hz, 2H), 1.81 (d, $J = 3.3$ Hz, 1H), 1.66 (sx, $J = 6.2$ Hz, 1H), 1.59 (sx, $J = 7.1$ Hz, 1H), 1.53 (m, 1H), 1.33 (sx, $J = 7.5$ Hz, 1H), 1.23 (d, $J = 6.4$ Hz, 1H), 0.89 (t, $J = 7.4$ Hz, 3H, CH_3); **19**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.57 (q, $J = 7.4$ Hz, 4H, Ph), 7.43-7.37 (m, 6H, Ph), 4.23 (s, 1H, Fc), 4.18 (s, 1H, Fc), 4.14 (s, 5H, Fc), 4.11 (s, 2H, Fc), 3.97 (s, 1H), 2.50 (br, 1H), 2.32-2.13 (m, 2H), 1.81 (s, 1H), 1.66 (m, 1H), 1.33 (d, $J = 6.3$ Hz, 2H), 1.23 (d, $J = 6.2$ Hz, 1H), 1.19 (s, 1H), 0.84 (t, $J = 7.4$ Hz, 3H, CH_3).

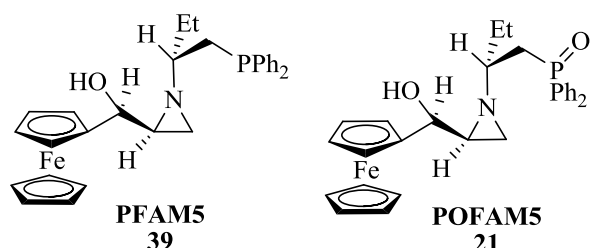
4.2.9 Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols (*S, R*) **38** and **20**



The phosphino aziridine **38** and its oxidized form **20** were synthesized from compound **35** by following the procedure given in the literature [33]. **38**: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.34 (m, 4H, Ph), 7.25 (m, 6H, Ph), 4.23 (s, 1H, Fc), 4.12 (s, 5H, Fc), 4.10 (s, 2H, Fc), 4.08 (s, 1H, Fc), 4.06 (s, 1H), 2.20

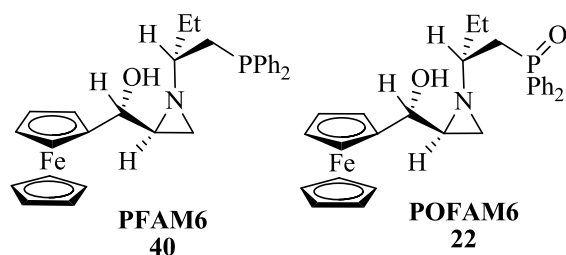
(m, 2H), 1.72 (d, $J = 3.2$ Hz, 1H), 1.59 (m, 1H), 1.52 (p, $J = 7.3$ Hz, 1H), 1.40 (q, $J = 6.0$ Hz, 1H), 1.27 (d, $J = 6.5$ Hz, 1H), 1.19 (m, 1H), 0.88 (t, $J = 7.3$ Hz, 3H, CH₃); **20**: ¹H-NMR (400 MHz, CDCl₃) δ 7.64 (dd, $J = 10.7$ Hz, $J = 4.7$ Hz, 4H, Ph), 7.41 (m, 6H, Ph), 4.24 (s, 1H, Fc), 4.17 (s, 5H, Fc), 4.13 (s, 1H, Fc), 4.07 (s, 2H, Fc), 3.91 (d, $J = 6.0$ Hz, 1H), 2.56 (m, 1H), 2.38 (m, 1H), 1.71 (br, 1H), 1.55 (m, 2H), 1.30 (d, $J = 7.1$ Hz, 2H), 1.19 (s, 1H), 0.80 (t, $J = 7.0$ Hz, 3H, CH₃).

4.2.10 Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols (*S*, *S*, *R*) **39** and **21**



The phosphino aziridine **39** and its oxidized form **21** were synthesized from compound **36** by following the procedure given in the literature [33]. **39**: ¹H-NMR (400 MHz, CDCl₃) δ 7.35 (m, 4H, Ph), 7.23 (m, 6H, Ph), 4.39 (s, 1H, Fc), 4.12 (s, 1H, Fc), 4.08 (s, 5H, Fc), 4.05 (s, 2H, Fc), 4.05 (s, 1H), 2.57 (s, 1H), 2.26 (d, $J = 6.4$ Hz, 2H), 1.60 (m, 4H), 1.44 (sx, $J = 6.1$ Hz, 1H), 1.09 (d, $J = 6.2$ Hz, 1H), 0.86 (t, $J = 7.4$ Hz, 3H, CH₃). **21**: ¹H-NMR (400 MHz, CDCl₃) δ 7.75 (dd, $J = 10.5$ Hz, $J = 3.5$ Hz, 2H, Ph), 7.67 (dd, $J = 10.3$ Hz, $J = 3.6$ Hz, 2H, Ph), 7.40 (m, 6H, Ph), 4.48 (s, 1H, Fc), 4.17 (s, 1H, Fc), 4.11 (s, 1H, Fc), 4.08 (s, 5H, Fc), 4.05 (s, 1H, Fc), 4.03 (s, 1H), 2.54 (m, 2H), 1.98 (p, $J = 5.4$ Hz, 2H), 1.78 (br, 1H), 1.54 (m, 2H), 1.23 (d, $J = 6.2$ Hz, 1H), 1.05 (d, $J = 6.0$ Hz, 1H), 0.80 (t, $J = 7.4$ Hz, 3H, CH₃).

4.2.11 Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols (*R*, *S*, *R*) **40** and **22**



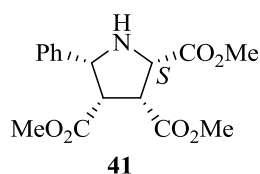
The phosphino aziridine **40** and its oxidized form **22** were synthesized from **36** by following the procedure given in the literature [33]. **40**: ¹H-NMR (400 MHz, CDCl₃) δ 7.37 (s, 4H, Ph), 7.23 (s, 6H, Ph), 4.15 (s, 1H, Fc), 4.09 (s, 5H, Fc), 4.05 (s, 3H, Fc), 3.93 (d, $J = 5.1$ Hz, 1H), 2.29 (m, 3H), 1.57 (t, $J = 7.3$ Hz, 2H), 1.54 (s,

2H), 1.32 (m, 1H), 1.18 (d, $J = 6.0$ Hz, 1H), 0.87 (t, $J = 7.4$ Hz, 3H, CH₃); **22**: ¹H-NMR (400 MHz, CDCl₃) δ 7.82 (dd, $J = 7.4$ Hz, $J = 3.3$ Hz, 2H, Ph), 7.73 (dd, $J = 7.0$ Hz, $J = 3.3$ Hz, 2H, Ph), 7.46 (ddd, $J = 7.6$ Hz, $J = 8.5$ Hz and $J = 3.7$ Hz, 6H, Ph), 4.22 (s, 1H, Fc), 4.15 (s, 5H, Fc), 4.10 (s, 3H, Fc), 3.93 (d, $J = 5.8$ Hz, 1H), 2.65 (br, 1H, OH), 2.56 (q, $J = 5.9$ Hz, 2H, CH₂-P), 1.97 (p, $J = 6.8$ Hz, 1H), 1.71 (ddd, $J = 3.7$ Hz, $J = 2.6$ Hz and $J = 3.4$ Hz, 1H, aziridine), 1.50 (p, $J = 7.1$ Hz, 2H), 1.45 (d, $J = 6.6$ Hz, 1H, aziridine), 1.31 (d, $J = 3.4$ Hz, 1H, aziridine), 0.89 (t, $J = 7.4$ Hz, 3H, CH₃).

4.4 Representative General Procedure for Asymmetric One-pot 1,3-DC Reaction

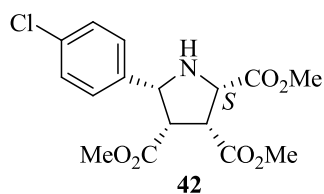
In a 10 mL vacuumed and flame-dried schlenk tube filled with nitrogen, AgOAc (5 mg, 0.028 mmol), **POFAM6** ligand (29 mg, 0.056 mmol) and 4 Å molecular sieves (200 mg) were added. Then freshly distilled DCM (0, 56 M, 1.7 ml) was added and the resulting mixture was stirred at room temperature for 1 hour. At the end of this period, the reaction mixture was cooled to 0 °C by using cryostat. To this mixture was added benzaldehyde (100 mg, 0.94 mmol), glycine methyl ester (136 µl, 1.60 mmol), dry ⁱPr₂NEt (8.20 µl, 0.047 mmol), and dimethyl maleate (353 µl, 2.82 mmol) respectively. The reaction mixture was stirred at 0 °C for about 24-30h and monitored by TLC. Then, the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel using Hexane/EtOAc 3:1 as the eluent.

4.4.1 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**41**)



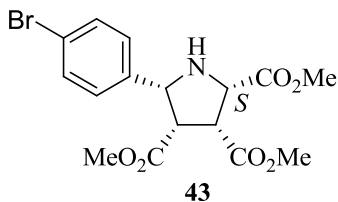
Following the general procedure cyloadduct **41** was obtained in 53 % yield (88.0 mg, 0.25 mmol) as a white crystalline solid. $R_f = 0.29$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +46.3$ (c 1.4, DCM) for 74% ee (*S*). Lit.^{33 b} $[\alpha]_D^{25} +61.9$ (c 1.44, DCM) for 90% ee (*S*); ¹H-NMR (400 MHz, CDCl₃) δ 7.32-7.28 (m, 4H, Ph), 7.25 (m, 1H, Ph), 4.44 (d, $J = 6.8$ Hz, 1H, H-5), 4.10 (d, $J = 8.9$ Hz, 1H, H-2), 3.80 (s, 3H, 2- CO₂Me), 3.68 (s, 3H, 3- CO₂Me), 3.66 (t, $J = 8.7$ Hz, 1H, H-3), 3.52 (t, $J = 7.2$ Hz, 1H, H-4), 3.22 (s, 3H, 4-CO₂Me); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 7:3, flow 1.0 mL min⁻¹, $t_R = \square 7.7$ min (*S*, major), 16.1 min (*R*, minor).

4.4.2 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(4-chlorophenyl) pyrrolidine-2,3,4-tricarboxylate (**42**)



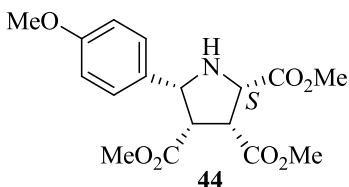
Following the general procedure cyloadduct **42** was obtained in 60 % yield (109.0 mg, 0.28 mmol) as a yellow oil. $R_f = 0.32$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +40.0$ (c 1.06, DCM) for 86% ee (*S*). Lit.⁴⁵ $[\alpha]_D^{20} +62.7$ (c 1.0, DCM) for 98% ee (*S*); ¹H-NMR (400 MHz, CDCl₃) δ 7.28 (s, 4H), 4.40 (br, 1H), 4.09 (d, $J = 8.6$ Hz, 1H), 3.67 (s, 3H), 3.65 (t, $J = 8.6$ Hz, 1H), 3.63 (s, 3H), 3.50 (t, $J = 7.0$ Hz, 1H), 3.28 (s, 3H); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 9:1, flow 1.0 mL min⁻¹, $t_R = \square 38.4$ min (*S*, major), 63.7 min (*R*, minor).

4.4.3 (2*S*,3*R*,4*S*,5*R*)-trimethyl 5-(4-bromophenyl)pyrrolidine-2,3,4-tricarboxylate (**43**)



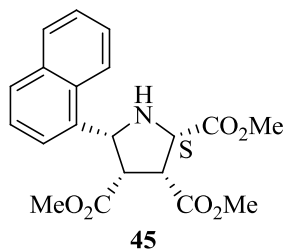
Following the general procedure cycloadduct **43** was obtained in 45 % yield (84.0 mg, 0.21 mmol) as a white crystalline solid. $R_f = 0.35$, hexane/EtOAc 1:1; $[\alpha]_D^{30} +33.7$ (c 1.06, DCM) for 40% ee (*S*). Lit.⁵² $[\alpha]_D^{23} -47.2$ (c 0.8, DCM) for 94% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.45–7.33 (m, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 4.37 (t, $J = 7.6$ Hz, 1H), 4.08 (s, 1H), 3.74 (s, 3H), 3.65 (dd, $J = 8.2, 4.2$ Hz, 1H), 3.63 (s, 3H), 3.53–3.46 (m, 1H), 3.22 (s, 3H); HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 5:5, flow 1.0 mL min⁻¹, $t_R = \square$ 8.7 min (*S*, major), 13.0 min (*R*, minor).

4.4.4 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (**44**)



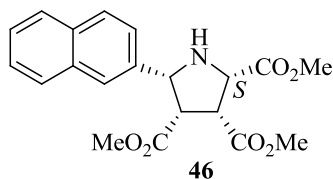
Following the general procedure cycloadduct **44** was obtained in 55 % yields (90.0 mg, 0.26 mmol) as a white crystalline solid. $R_f = 0.23$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +37.8$ (c 1.01, DCM) for 72% ee (*S*). Lit.^{33b} $[\alpha]_D^{25} +72.6$ (c 0.74, DCM) for 95% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.23 (d, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 4.39 (d, $J = 6.9$ Hz, 1H), 4.08 (d, $J = 8.8$ Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.61 (t, $J = 8.3$ Hz, 1H), 3.47 (t, $J = 7.5$ Hz, 1H), 3.26 (s, 3H); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 7:3, flow 1.0 mL min⁻¹, $t_R = \square$ 11.6 min (*S*, major), 21.4 min (*R*, minor).

4.4.5 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(naphthalen-1-yl)pyrrolidine-2,3,4-tricarboxylate (**45**)



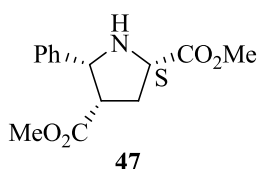
Following the general procedure cycloadduct **45** was obtained in 42 % yields (73.2 mg, 0.20 mmol) as a white crystalline solid. $R_f = 0.34$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +200.4$ (c 1.3, DCM) for 55% ee (*S*). Lit.⁴² $[\alpha]_D^{25} +199.8$ (c 1.12, DCM) for 85% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.86 (d, $J = 8.2$ Hz; 1H), 7.77 (d, $J = 7.4$ Hz; 1H), 7.68 (d, $J = 8.2$ Hz; 1H), 7.52 (d, $J = 7.2$ Hz; 1H), 7.46–7.36 (m, 3H), 5.09 (d, $J = 5.0$ Hz; 1H), 4.12 (d, $J = 8.5$ Hz; 1H), 3.78 (s, 3H), 3.74 (t, $J = 7.2$ Hz; 2H), 3.59 (s, 3H), 2.87 (s, 3H); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 5:5, flow 1.0 mL min⁻¹, $t_R = \square$ 10.7 min (*S*, major), 22.4 min (*R*, minor).

4.4.6 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (46)



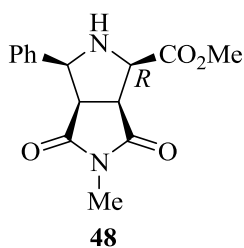
Following the general procedure cyloadduct **46** was obtained in 50 % yields (87.0 mg, 0.24 mmol) as a white crystalline solid. $R_f = 0.33$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +42.8$ (c 1.3, DCM) for 65% ee (*S*). Lit.⁴² $[\alpha]_D^{25} +46.4$ (c 1.12, DCM) for 97% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.82-7.76 (m, 4H), 7.47-7.40 (m, 3H), 4.59 (d, $J = 6.3$ Hz; 1H), 4.16 (d, $J = 8.9$ Hz; 1H), 3.83 (s, 3H), 3.72 (t, $J = 8.2$ Hz; 1H), 3.69 (s, 3H), 3.62 (t, $J = 6.9$ Hz; 1H), 3.48 (br, 1H, NH), 3.15 (s, 3H); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 5:5, flow 1.0 mL min^{-1} , $t_R = \square$ 12.8 min (*S*, major), 22.8 min (*R*, minor).

4.4.7 (2*S*, 4*S*, 5*R*)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate (47)



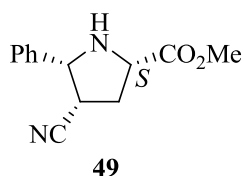
Following the general procedure cyloadduct **47** was obtained in 72 % yields (73.2 mg, 0.20 mmol) as a colorless oil. $R_f = 0.40$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +25.2$ (c 1.3, DCM) for 45% ee (*S*). Lit.^{33b} $[\alpha]_D^{25} +20.9$ (c 0.46, DCM) for 46% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.22 (d, $J = 4.2$ Hz, 4H, Ph), 7.21 (dt, $J = 8.4$ and 4.4 Hz, 1H, Ph), 4.43 (d, $J = 7.8$ Hz, 1H, H-5), 3.86 (t, $J = 8.1$ Hz, 1H, H-2), 3.75 (s, 3H, 2-CO₂Me), 3.20 (q, $J = 7.1$ Hz, 1H, H-4), 3.13 (s, 3H, 4-CO₂Me), 2.59 (br, 1H, NH), 2.32 (t, $J = 7.3$ Hz, 2H, H-3); HPLC: Chiralpak OD column, UV detection at 254 nm, eluent: hexane/2-propanol 9:1, flow 1.0 mL min^{-1} , $t_R = \square$ 15.9 min (*S*, major), 37.0 min (*R*, minor).

4.4.8 (1*S*, 2*R*, 4*S*, 5*R*)-Methyl octahydro-7-methyl-6,8-dioxo-4-phenyl-3,7-diazabicyclo [3.3.0]pyrrole-2-carboxylate (48)



Following the general procedure cyloadduct **48** was obtained in 99 % yields (134.0 mg, 0.47 mmol) as a white crystalline solid. $R_f = 0.31$, hexane/EtOAc 1:1; $[\alpha]_D^{28} -34.0$ (c 1.5, DCM) for 41% ee (*S*). Lit.^{33b} $[\alpha]_D^{25} -61.9$ (c 1.24, DCM) for 70% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.31-7.25 (m, 5H, Ph) 4.47 (t, $J = 6.0$ Hz, 1H, H-2), 4.00 (t, $J = 5.9$ Hz, 1H, H-4), 3.87 (s, 3H, 2-CO₂Me), 3.51 (t, $J = 7.4$ Hz, 1H, H-1), 3.52 (t, $J = 8.1$ Hz, 1H, H-5), 2.86 (s, 3H, NMe) 2.36 (br, 1H, N-H); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 1:4, flow 1.0 mL min^{-1} , $t_R = \square$ 6.8 min (*R*, minor), 15.4 min (*S*, major).

4.4.9 (2*S*, 4*S*, 5*R*)-Methyl 4-cyano-5-phenylpyrrolidine-2-carboxylate (**49**)



Following the general procedure cycloadduct **49** was obtained in 92 % yields (99.50 mg, 0.43 mmol) as a yellow oil. $R_f = 0.31$, hexane/EtOAc 1:1; $[\alpha]_D^{28} +37.0$ (c 1.3, DCM) for 75% ee (*S*). Lit.^{33b} $[\alpha]_D^{25} +20.9$ (c 0.46, DCM) for 46% ee (*S*); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.43-7.34 (m, 5H, Ph), 4.38 (d, $J = 6.3$ Hz, 1H, H-5), 3.94 (t, $J = 7.4$ Hz, 1H, H-2), 3.83 (s, 3H, 2- CO_2Me), 3.24 (q, $J = 5.8$ Hz, 1H, H-4), 2.64 (br, 1H, NH), 2.47-2.61 (m, 2H, H-3); HPLC: Chiralpak AS column, UV detection at 254 nm, eluent: hexane/2-propanol 5:5, flow 1.0 mL min^{-1} , $t_R = 10.3$ min (*S*, major), 44.0 min (*R*, minor).

4.5 General procedure for racemic cycloaddition reactions

To a suspension of glycine methyl ester hydrochloride (1.1 equiv) and magnesium sulfate (2.0 equiv) in DCM was added triethylamine (1.1 equiv). This solution was stirred at room temperature for 1h. The corresponding aldehyde (1.0 equiv) was added and the reaction mixture was stirred at room temperature overnight. Magnesium sulfate was removed by filtration and the filtrate was washed once with H_2O . The aqueous phase was extracted once with DCM and the combined organic layers were washed with brine. The organic phase was dried over MgSO_4 , filtered and concentrated to get the imines.

In a 10 mL flame-dried reactor purged with nitrogen, dry AgOAc (3 mol %), imine (0.1 g), DCM (2.0 mL), dry $^i\text{Pr}_2\text{NEt}$ (10 mol %), dipolarophile (1.1 equiv.) were added respectively. The resulting homogeneous mixture was stirred at room temperature overnight. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel by eluting with Hexanes/EtOAc 3:1.

REFERENCES

1. Procter, G. *Asymmetric Synthesis*; Oxford University Press: New York, **1996**, 1,12.
2. Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.
3. Pearson, W. H. *Pure Appl. Chem.* **2002**, 74, 1339.
4. (a) Cheng, Y.; Huang, Z.-T.; Wang, M.-X. *Curr. Org. Chem.* **2004**, 8, 325. (b) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, 37, 580. (c) Pearson, W. H.; Stoy, P. *Synlett.* **2003**, 903. (d) *Pharmaceuticals*, Vol. 1–4 (Ed.: J. L. McGuire), Wiley-VCH, Weinheim, **2000**.
5. (a) Fukui, K. *Acc. Chem. Res.* **1971**, 4, 57. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, **1970**. (c) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, 87, 395.
6. Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, 2, 565.
7. Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, 16, 2230.
8. Buchner, E. *Ber. Dtsch. Chem. Ges.* **1888**, 21, 2637.
9. Pichon, M. Figadere, B., *Tetrahedron: Asymmetry* **1996**, 7, 927.
10. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; 5 ed.; John Wiley & Sons, Inc.: New York, **2001**.
11. Huisgen, R. *J. Org. Chem.* **1976**, 41, 403.
12. Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, 58, 9477.
13. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, 96, 223.
14. Atkinson, R. S. *Stereoselective Synthesis*, Wiley and Sons: England, **1995**, 173, 231.
15. Houk, K. N.; Gonzales, J.; Li, Y. *Acc. Chem. Res.* **1995**, 28, 81.
16. Firestone, R. A., *J. Org. Chem.* **1968**, 33, 2285.
17. Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, 87, 395.
18. Sustmann, R. *Tetrahedron Lett.* **1971**, 12, 2717.
19. Sustmann, R. *Pure Appl. Chem.* **1974**, 40, 569.
20. Sustman, R., Trill, H. *Angew. Chem. Int. Ed.* **1972**, 11, 839.
21. Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, 16, 2047.
22. (a) Grigg, R.; Malone, J. F.; Mongkolaussavaratana, T.; Thianpatanagul, S. *Tetrahedron* **1989**, 45, 3849. (b) Fleury, J. P.; Schoeni, J. P.; Clerin, D.; Fritz, H. *Helv. Chim. Acta* **1975**, 58, 2018. (c) Seidl, H.; Huisgen, R.; Knorr, R. *Chem. Ber.* **1969**, 102, 904.
23. (a) Huisgen, R.; Grashey, R. *Tetrahedron Lett.* **1963**, 4, 1441. (b) Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1983**, 24, 3427.

24. (a) Huisgen, R.; Scheer, W.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397. (b) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753. (c) Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 4. (d) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979.
25. (a) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941. (b) Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 644. (c) Wee, A. G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1363. (d) Komatsu, M.; Okada, H.; Yokoi, S.; Minakata, S. *Tetrahedron Lett.* **2003**, *44*, 1603.
26. Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
27. Grigg, R.; Malone, J. F.; Mongkolaussavaratana, T.; Thianpatanagul, S. *Tetrahedron* **1989**, *45*, 3849.
28. Han, M. L.; Wang, D. Y.; Zeng, P. W.; Zheng, Z.; Hub, X.-P. *Tetrahedron: Asymmetry* **2012**, *23*, 306.
29. He, L.; Chen, X. H.; Wang, D. N.; Luo, S. W.; Zhang, W. Q.; Yu, J.; Ren, L.; Gong, L. *Z. J. Am. Chem. Soc.* **2011**, *133*, 13504.
30. Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527.
31. Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 4.
32. Chen, X. H.; Zhang, W. Q.; Gong L. *Z. J. Am. Chem. Soc.* **2008**, *130*, 5652.
33. (a) Doğan, Ö.; Koyuncu, H.; Garner, P.; Bulut, A.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *21*, 4687. (b) Eröksüz, S.; Doğan, Ö.; Garner, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2535.
34. (a) Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (b) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431. (f) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569. (g) Carbrera, S.; Gomez, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (h) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043. (i) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241. (j) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (k) Llamas, T.; Arrayas, R. G.; and Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795. (l) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem.* **2002**, *114*, 4410.; *Angew. Chem. Int. Ed.* **2002**, *41*, 4236. (m) Zeng W.; Zhou Y.-G. *Tetrahedron Lett.* **2007**, *48*, 4619.
35. Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem.* **2002**, *114*, 4410.
36. Zeng W.; Zhou Y. G. *Tetrahedron Lett.* **2007**, *48*, 4619.

37. (a) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.
38. Shi, J., Zhao, M., Lei, Z., Shi, M., *J. Org. Chem.*, **2008**, *73*, 305.
39. Shi, M., Shi, J., *Tetrahedron: Asymmetry*, **2007**, *18*, 645.
40. Carbrera, S.; Gomez, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394.
41. Wu, H.; Wang, B.; Liu, H.; Wang, L. *Tetrahedron* **2011**, *67*, 1210.
42. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.
43. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.
44. Knopf, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.
45. Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055.
46. Oderaotshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043.
47. See Liu, W.; Xie, T.; Liang, Y.; Liu, W.; Ma, Y. *J. Organomet. Chem.* **2001**, *627*, 93.
48. Nagel, D. L.; Woller, P. B.; Cromwell G. *J. Org. Chem.* **1971**, *36*, 3911.
49. (a) Dawson, G. J.; Frost, C.G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (b) Williams, J. M. J. *Synlett* **1996**, 705.
50. Yun, J. M.; Sim, T. B.; Hahm, H. S.; Lee, W. K. *J. Org. Chem.* **2003**, *68*, 7675.
51. He, L.; Chen, X. H.; Wang, D. N.; Luo, S. W.; Zhang, W. Q.; Yu, J.; Ren, L.; Gong, L. *Z. J. Am. Chem. Soc.* **2011**, *133*, 13504.
52. Yu, S. B.; Hua, X. P.; Deng, J.; Wang, D. Y.; Duan Z. C.; Zheng Z. *Tetrahedron: Asymmetry* **2009**, *20*, 621.

APPENDIX A

NMR SPECTRA AND HPLC CHROMATOGRAMS OF COMPOUNDS

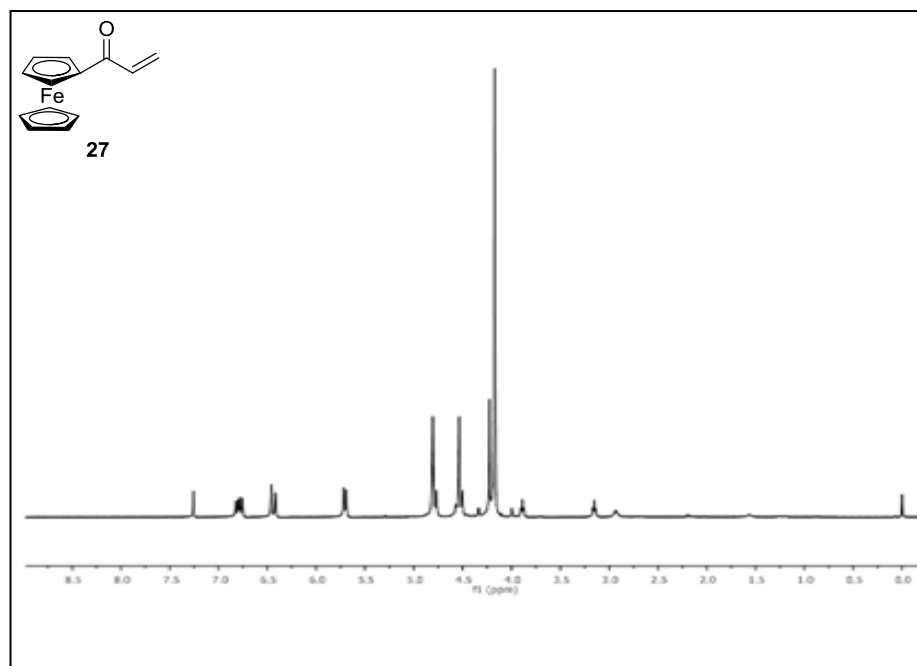


Figure A. 1 $^1\text{H-NMR}$ spectrum of compound 27

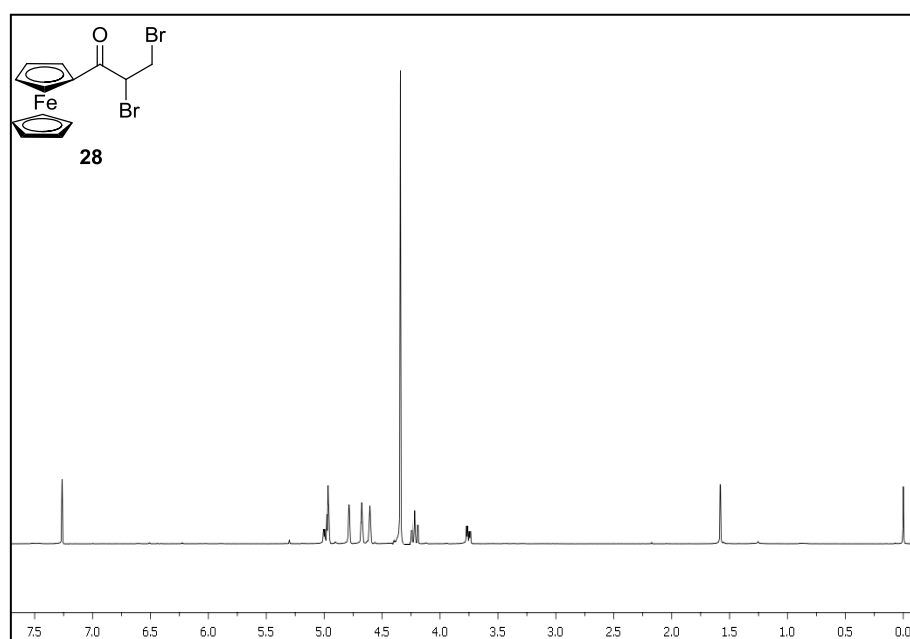


Figure A. 2 $^1\text{H-NMR}$ spectrum of compound 28

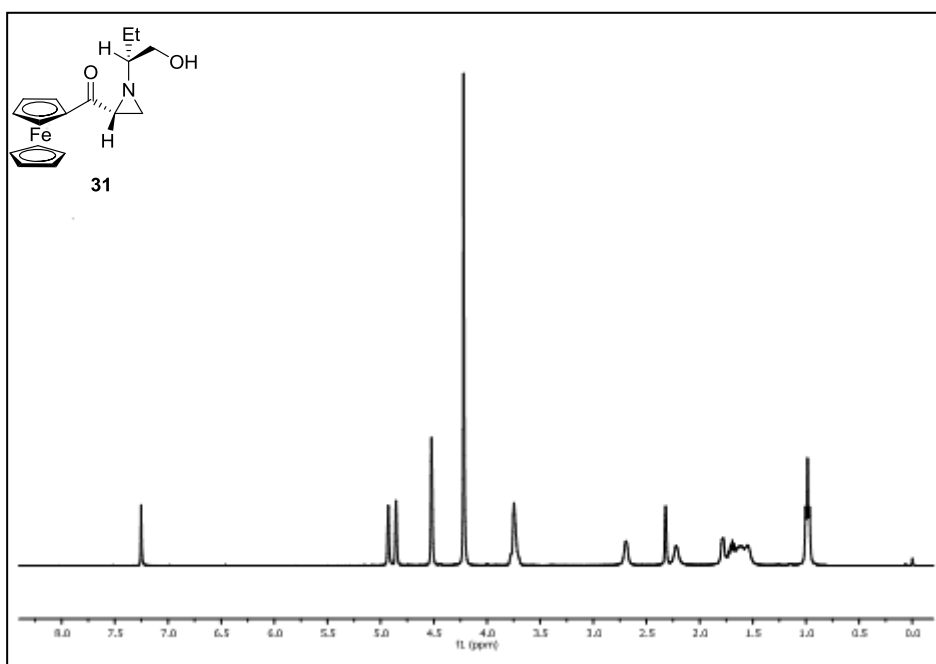


Figure A. 3 $^1\text{H-NMR}$ spectrum of compound **31**

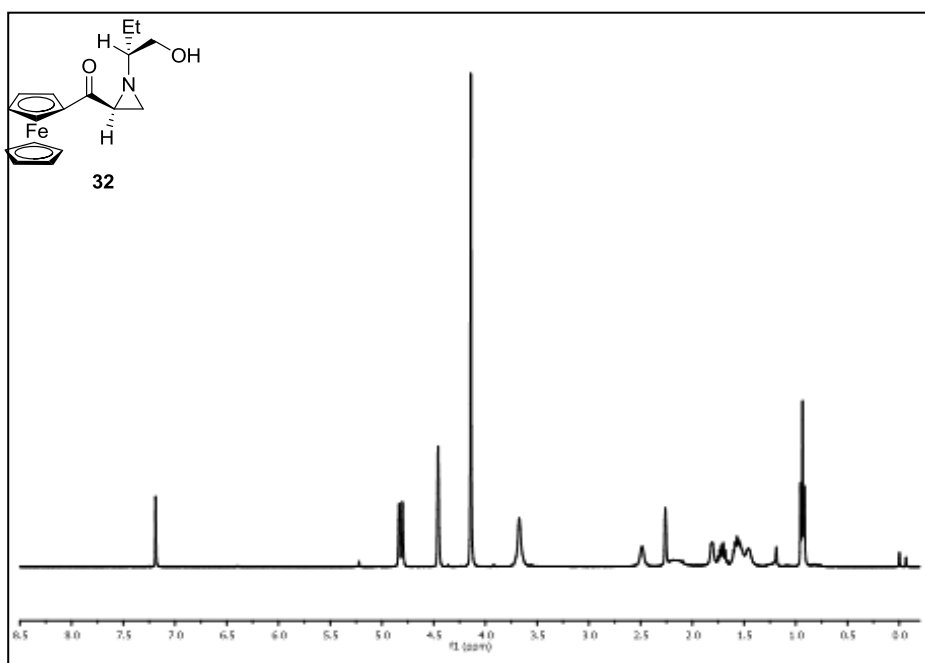


Figure A. 4 $^1\text{H-NMR}$ spectrum of compound **32**

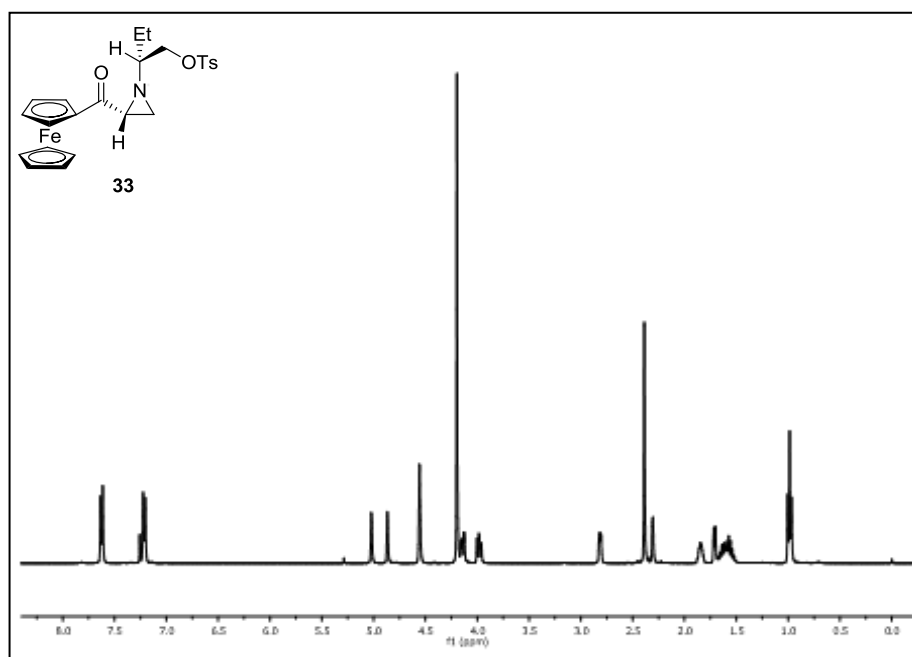


Figure A. 5 ¹H-NMR spectrum of compound 33

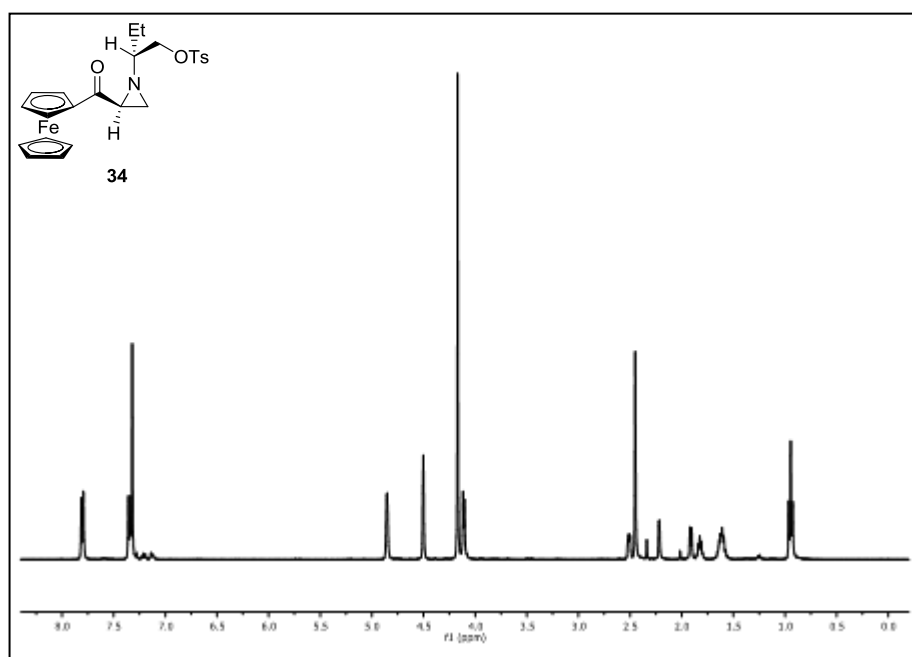


Figure A. 6 ¹H-NMR spectrum of compound 34

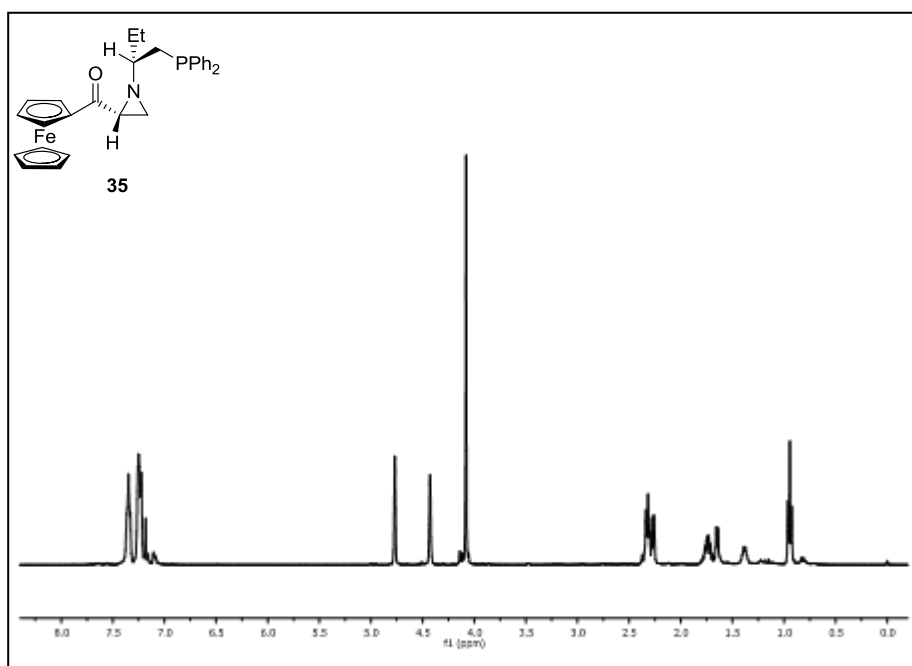


Figure A. 7 ¹H-NMR spectrum of compound 35

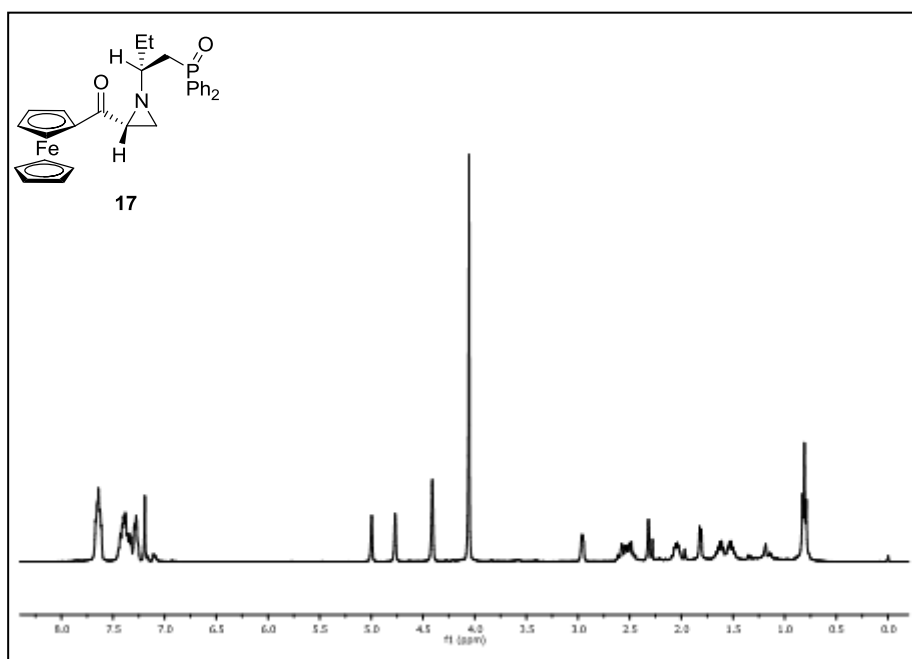


Figure A. 8 ¹H-NMR spectrum of compound 17

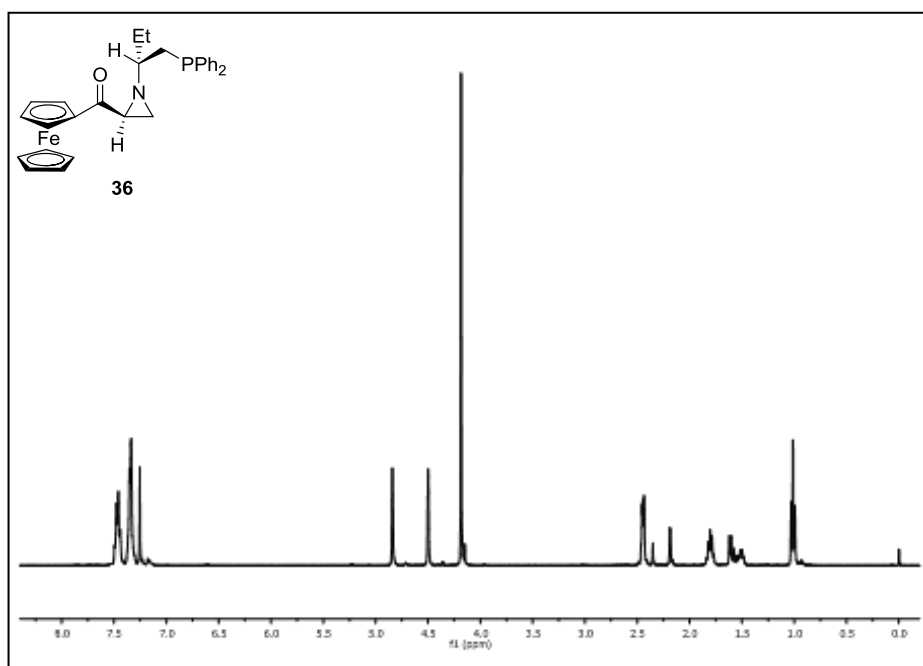


Figure A. 9 ¹H-NMR spectrum of compound **36**

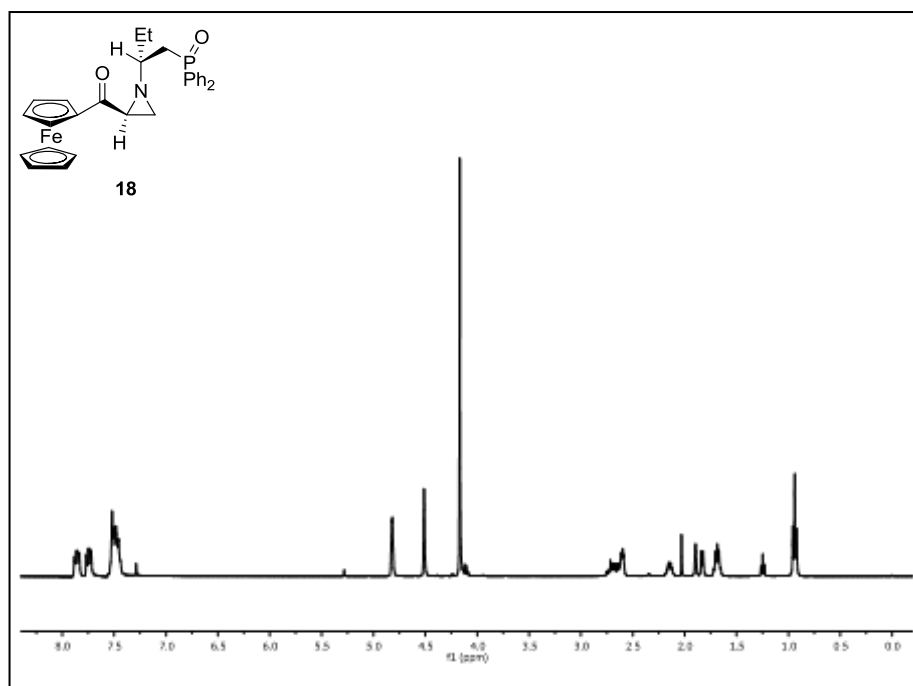


Figure A. 10 ¹H-NMR spectrum of compound **18**

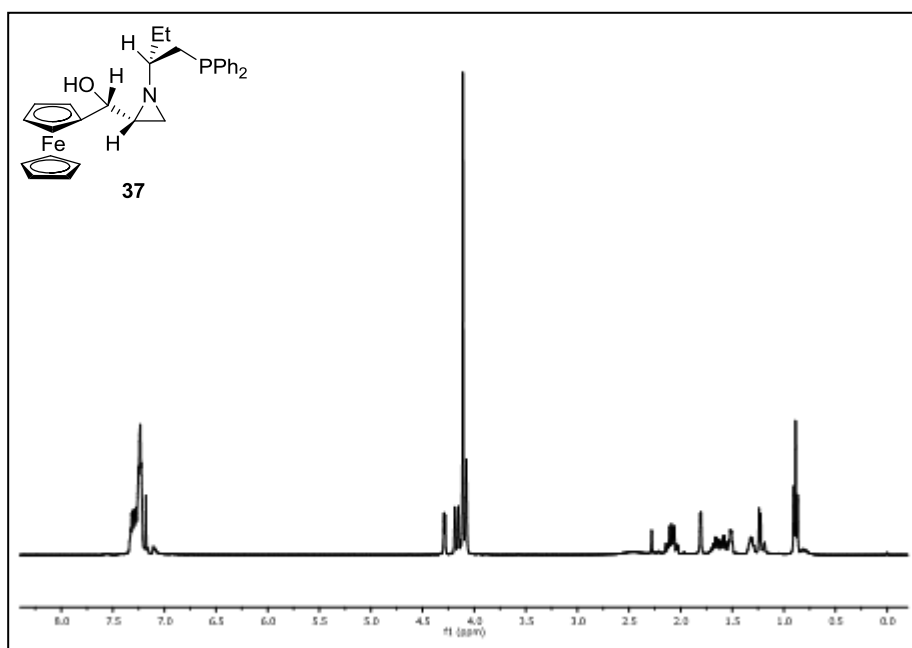


Figure A. 11 ^1H -NMR spectrum of compound **37**

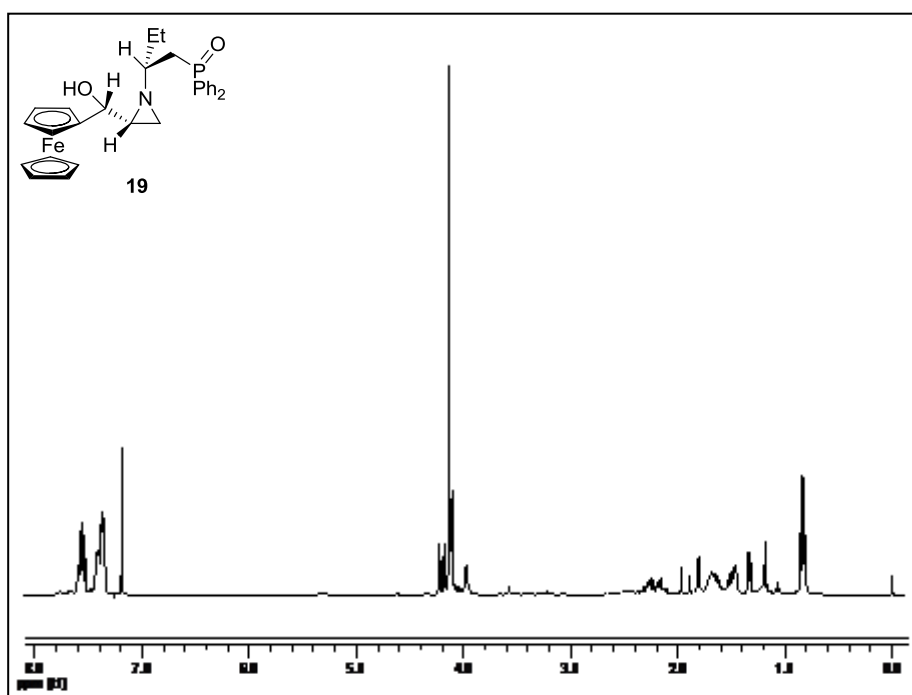


Figure A. 12 ^1H -NMR spectrum of compound **19**

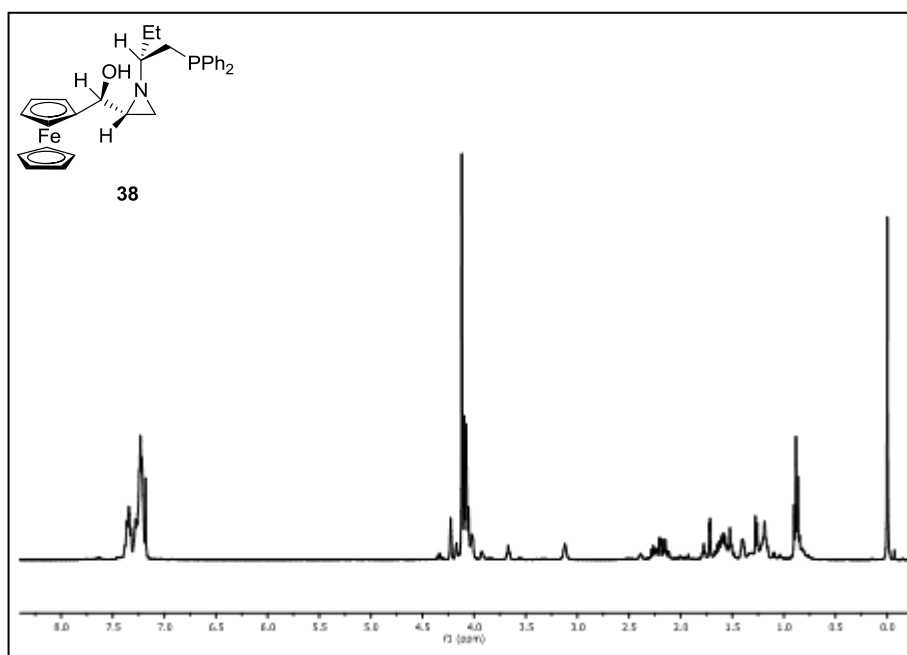


Figure A. 13 $^1\text{H-NMR}$ spectrum of compound **38**

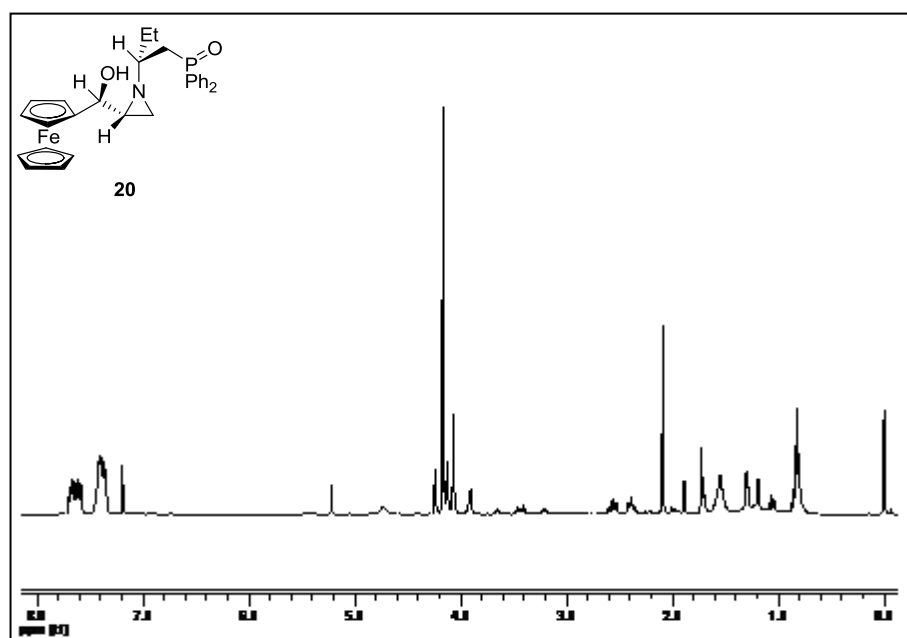


Figure A. 14 $^1\text{H-NMR}$ spectrum of compound **20**

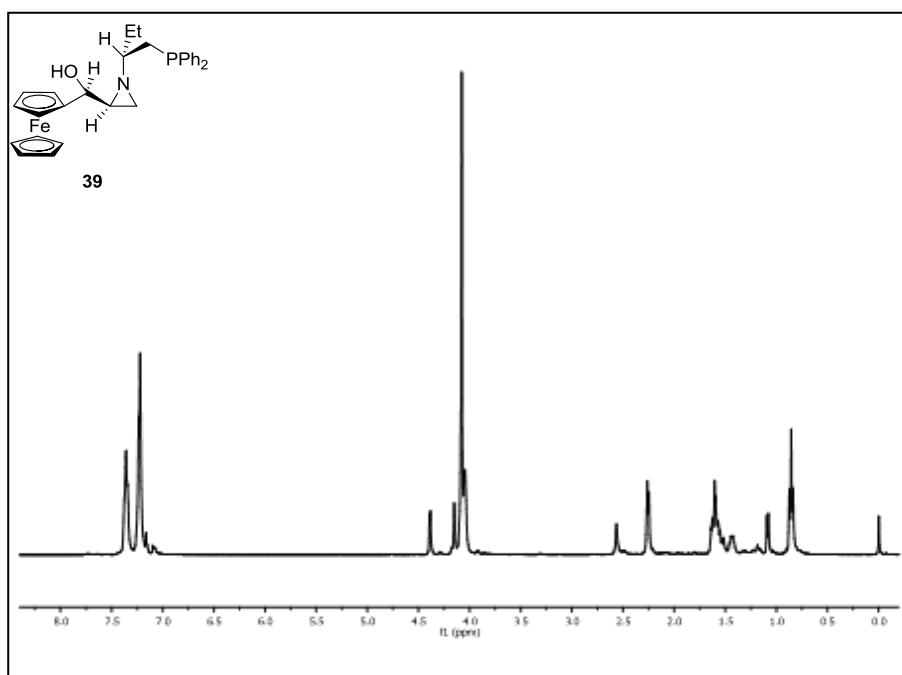


Figure A. 15 ¹H-NMR spectrum of compound **39**

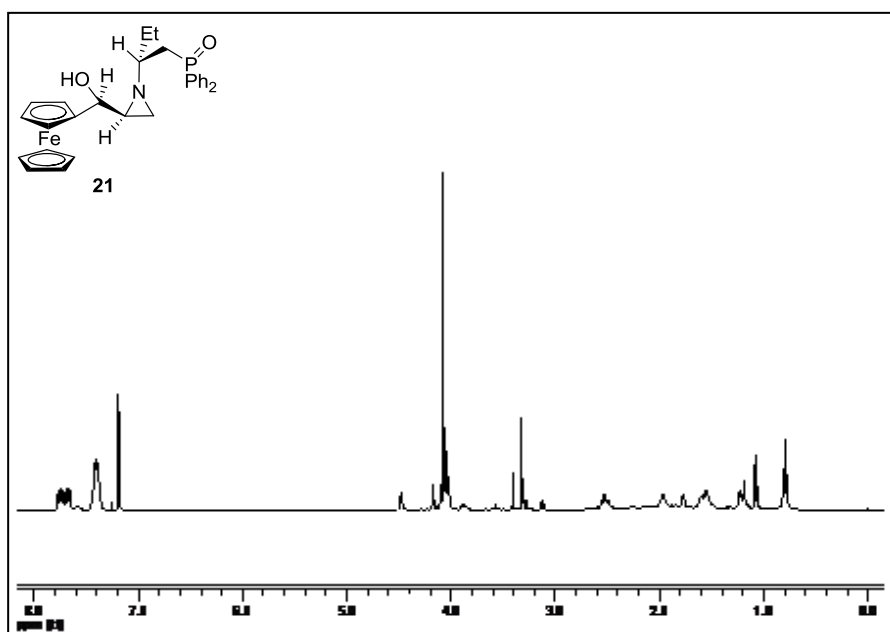


Figure A. 16 ¹H-NMR spectrum of compound **21**

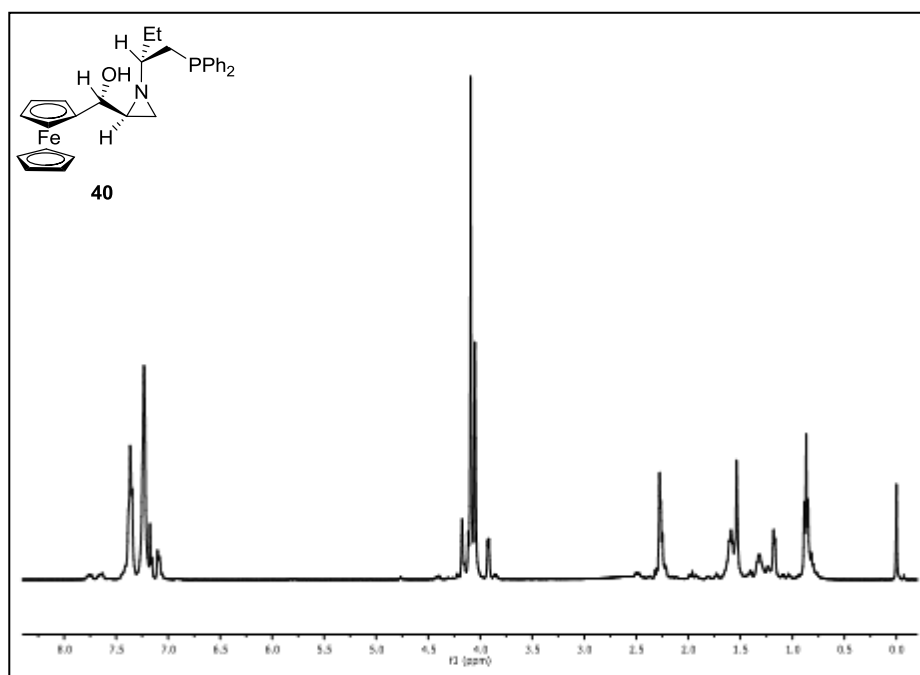


Figure A. 17 ¹H-NMR spectrum of compound 40

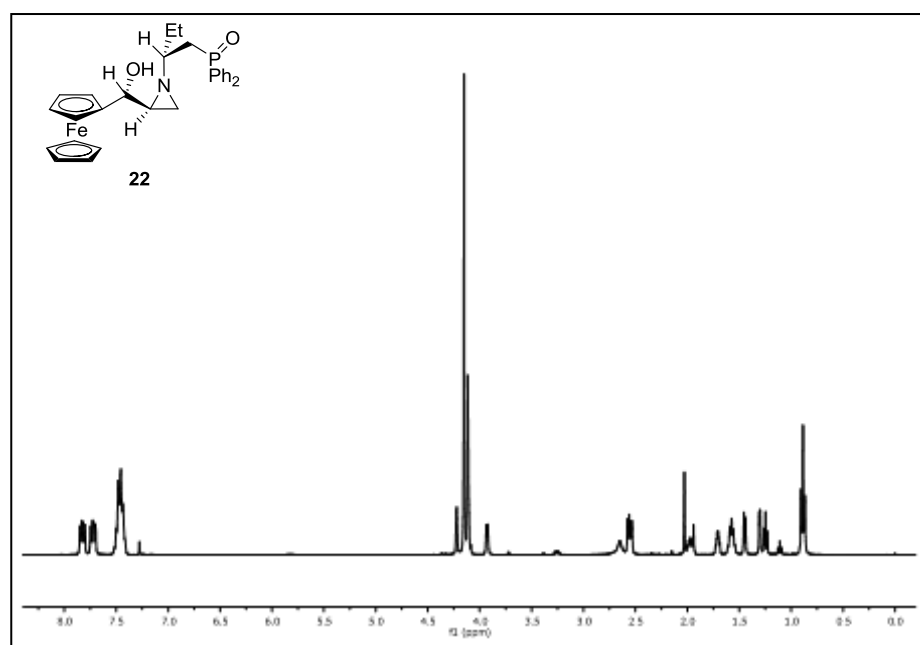


Figure A. 18 ¹H-NMR spectrum of compound 22

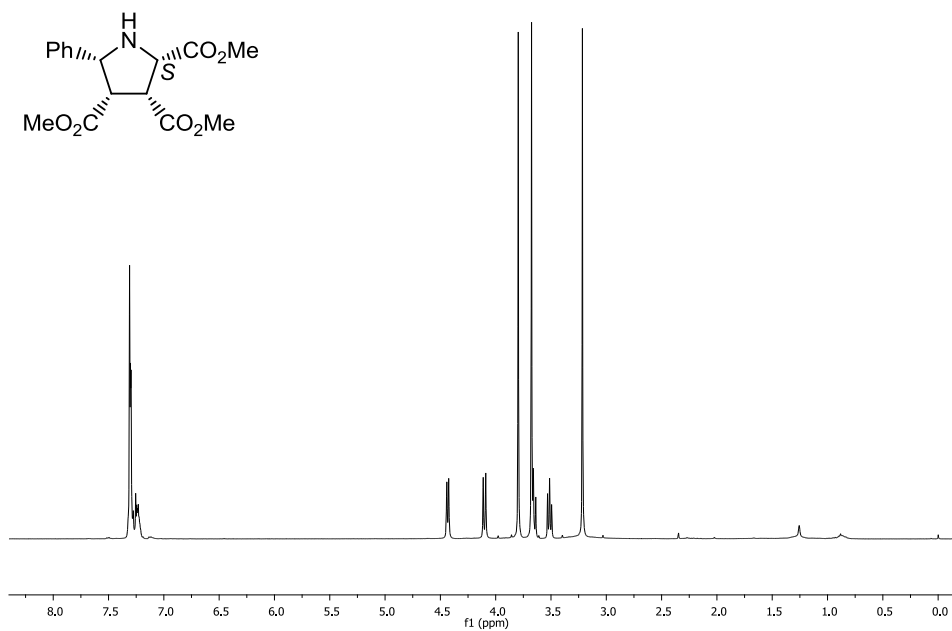


Figure A. 19 ¹H-NMR spectrum of compound **41**

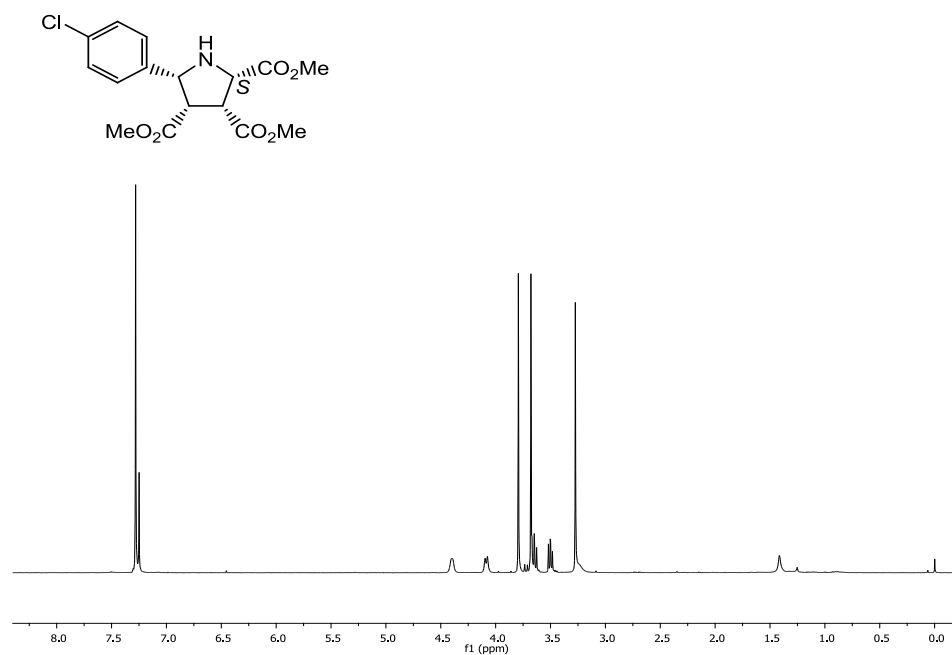


Figure A. 20 ¹H-NMR spectrum of compound **42**

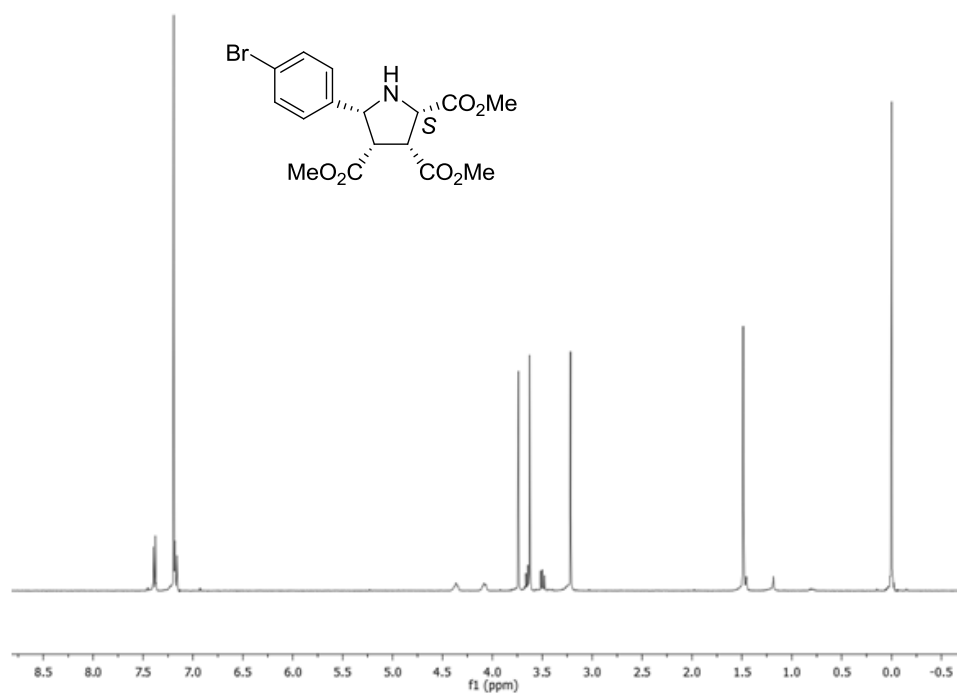


Figure A.21 ¹H-NMR spectrum of compound **43**

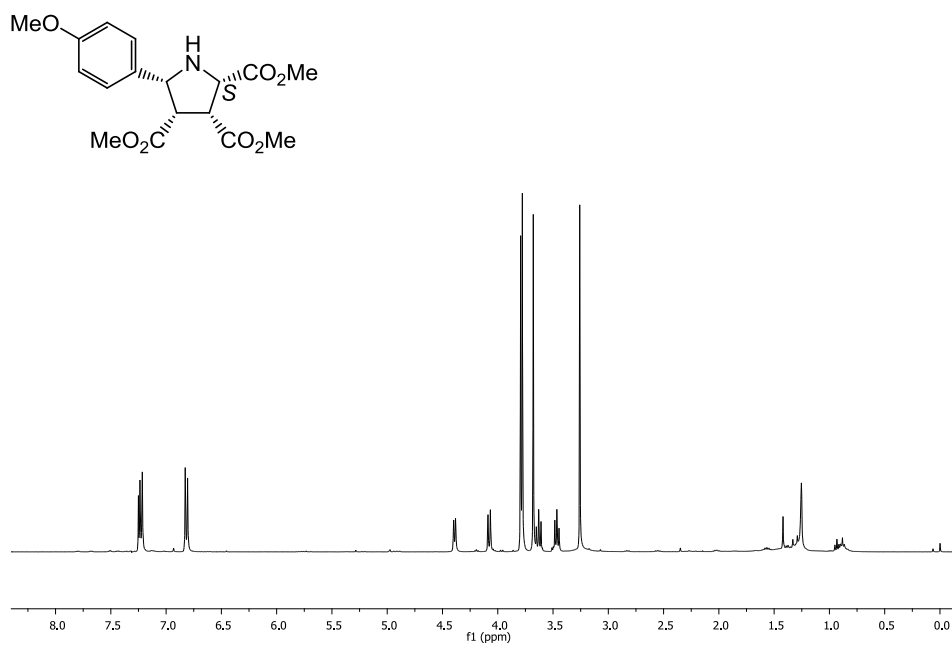


Figure A. 22 ¹H-NMR spectrum of compound **44**

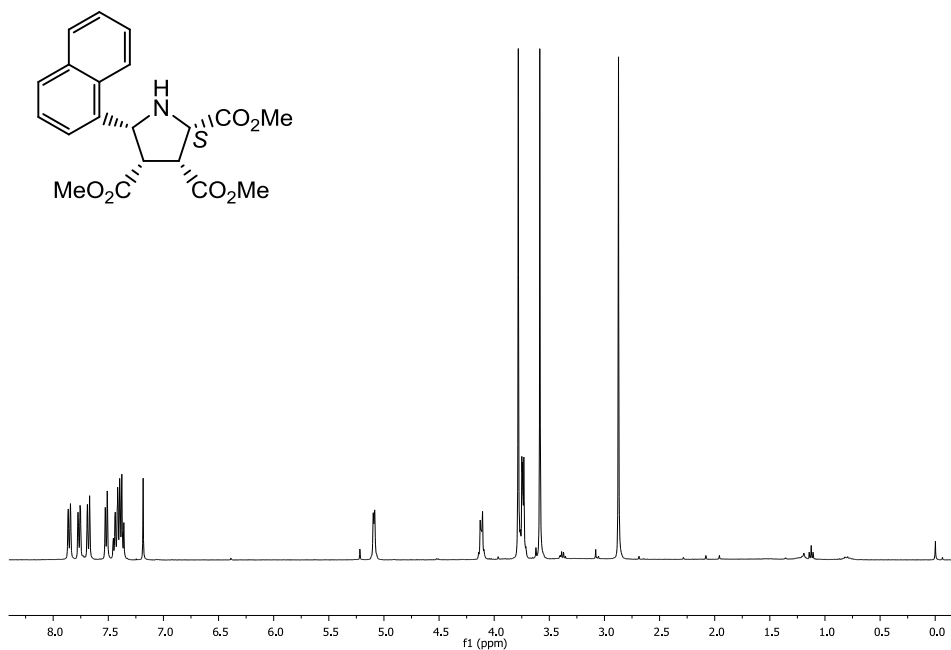


Figure A.23 ¹H-NMR spectrum of compound **45**

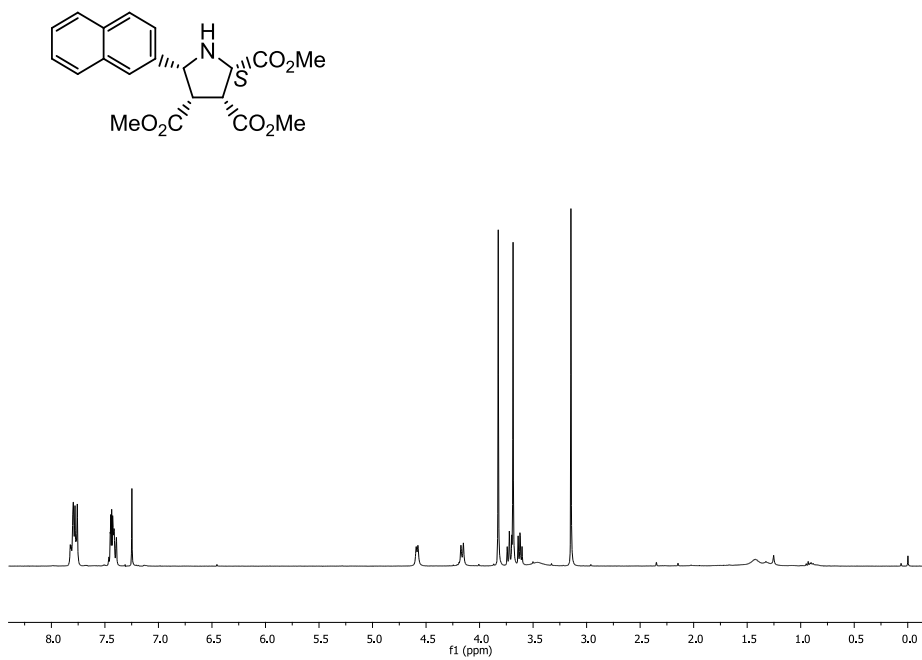


Figure A.24 ¹H-NMR spectrum of compound **46**

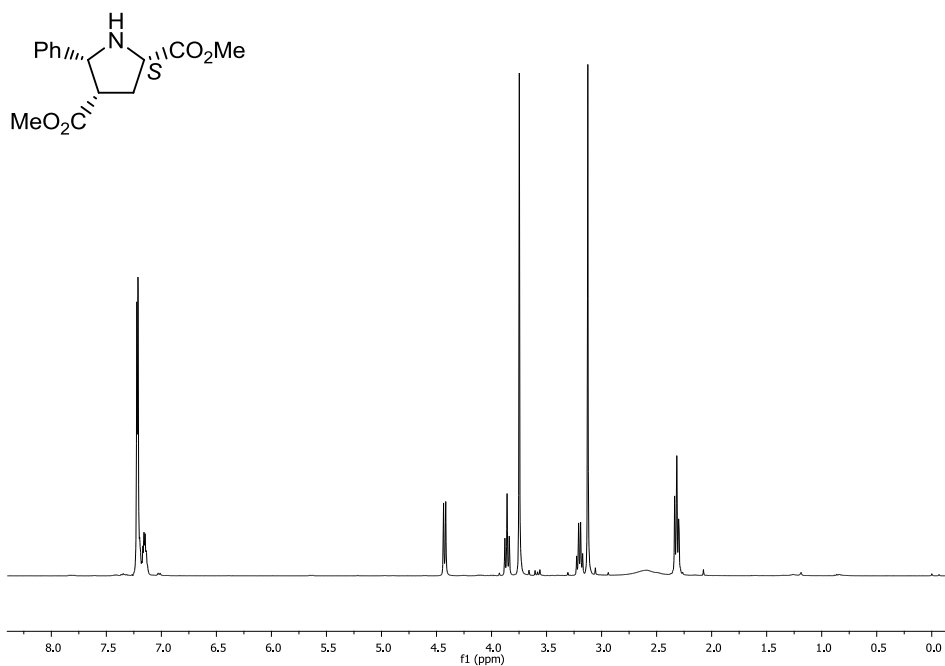


Figure A.1 ¹H-NMR spectrum of compound 47

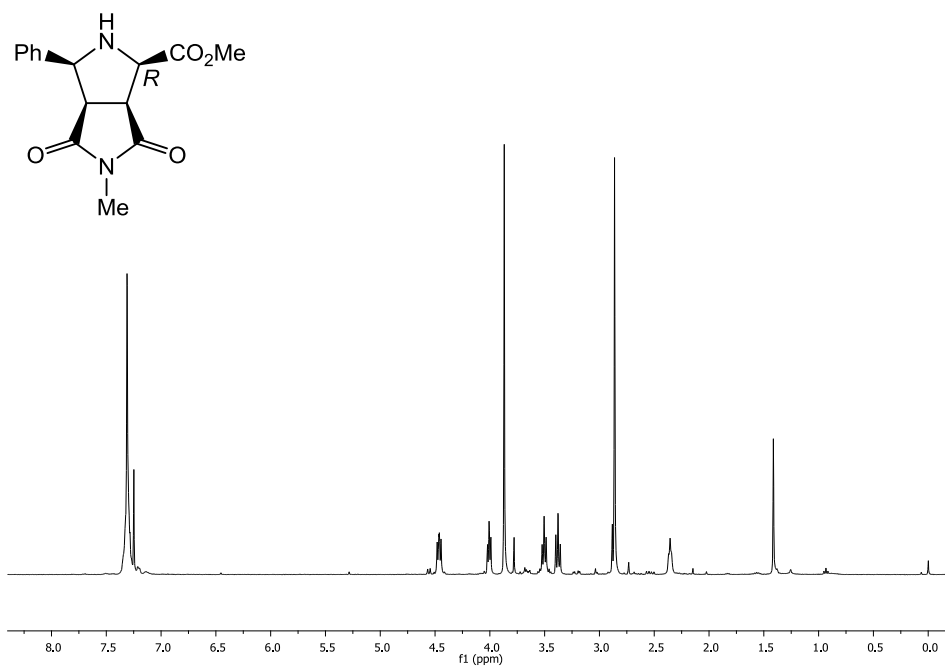


Figure A.26 ¹H-NMR spectrum of compound 48

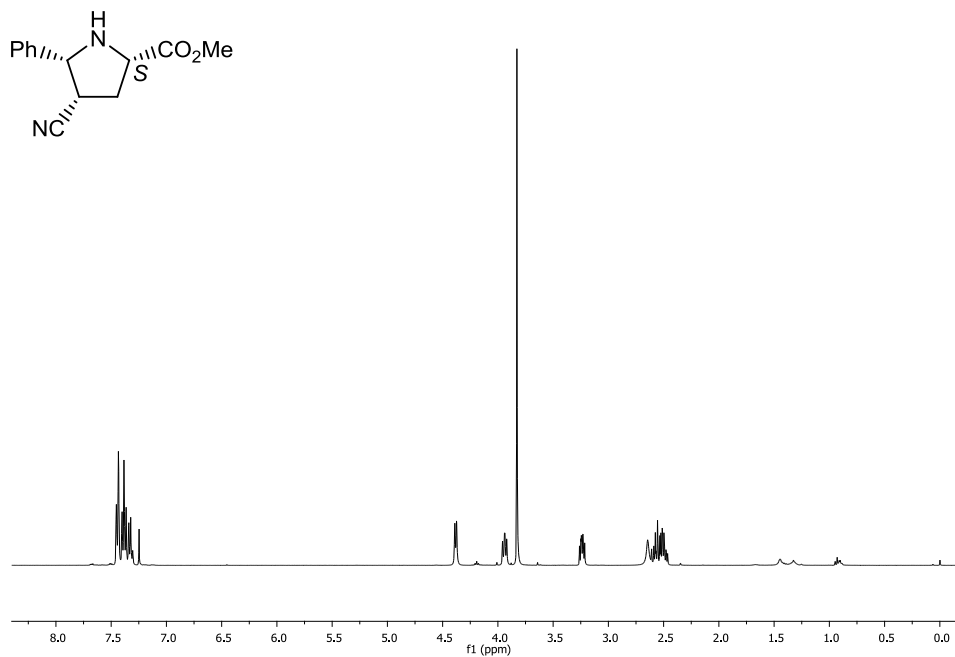
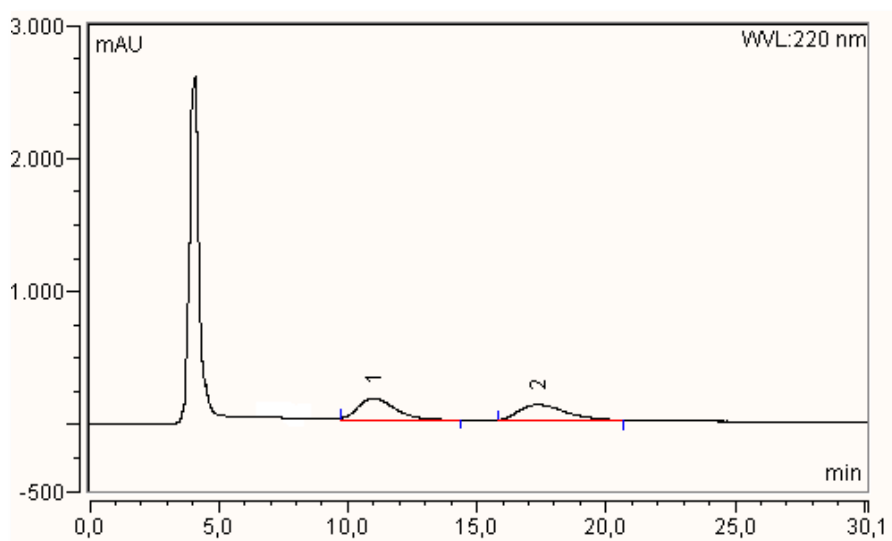
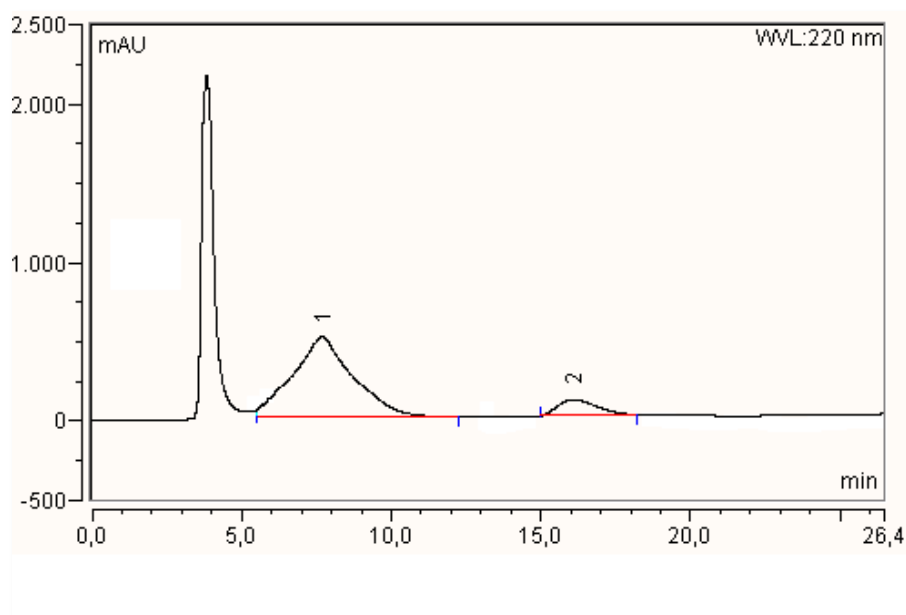


Figure A. 27 ¹H-NMR spectrum of compound **49**



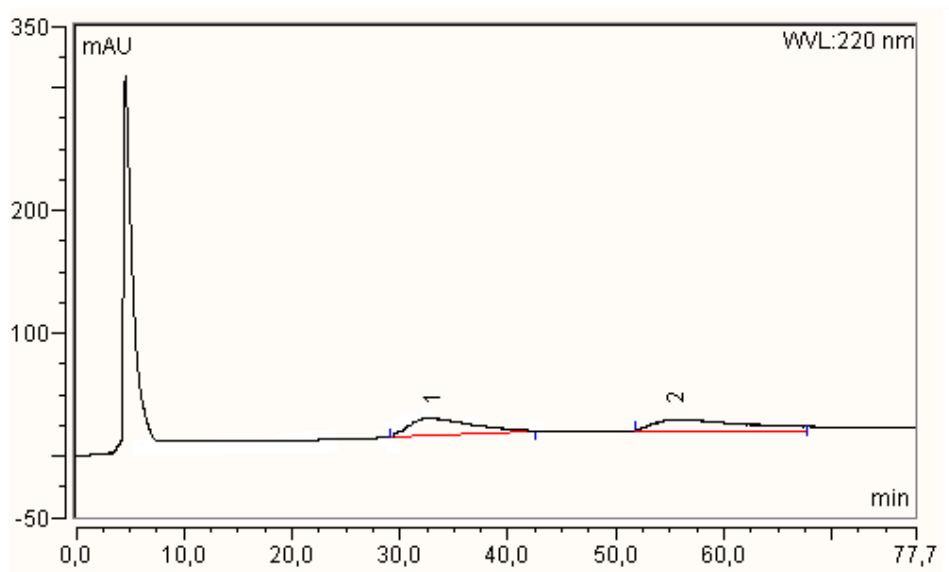
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	10,982	160,586	53,29
2	17,354	116,130	46,71

Figure A. 28 HPLC chromatogram of compound (±)-41



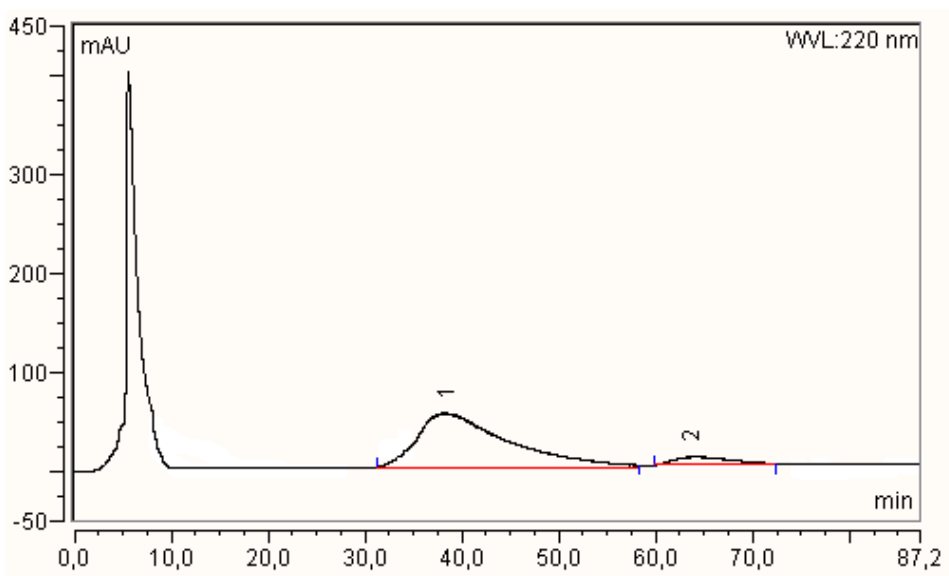
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	7,681	509,998	86,93
2	16,088	100,969	13,07

Figure A. 29 HPLC chromatogram of compound 41



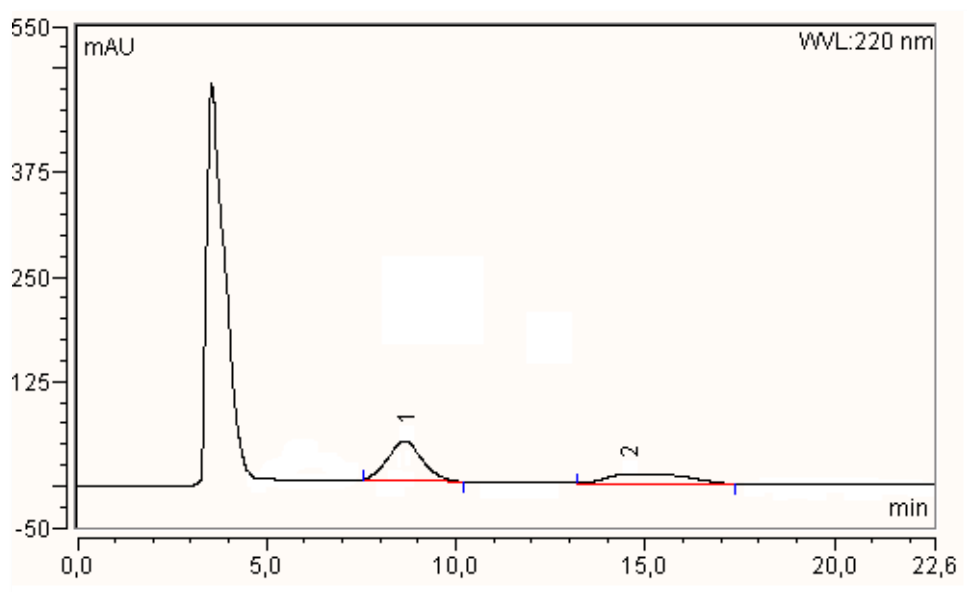
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	32,936	13,787	50,33
2	55,492	9,324	49,67

Figure A. 30 HPLC chromatogram of compound (±)-42



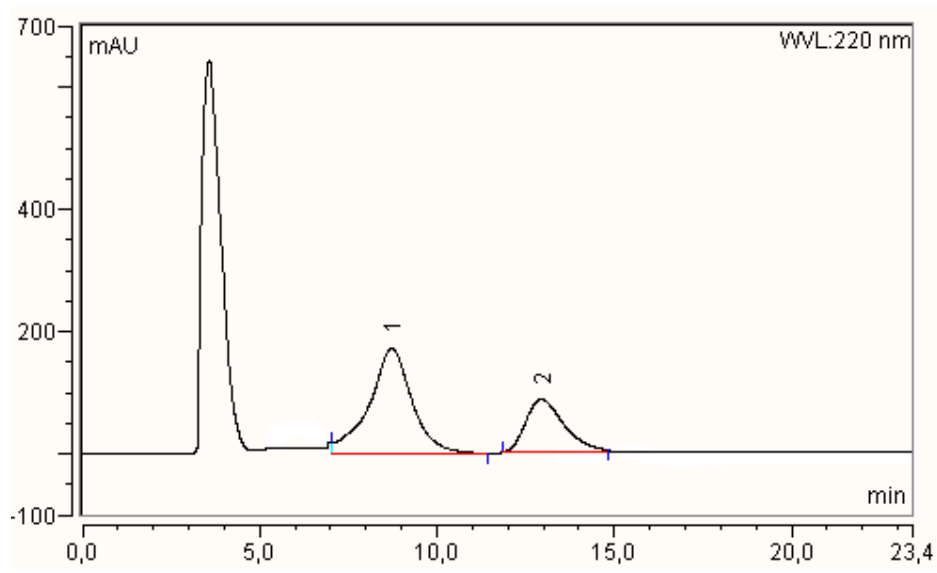
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	38,355	54,798	93,09
2	63,659	7,036	6,91

Figure A. 21 HPLC chromatogram of compound 42



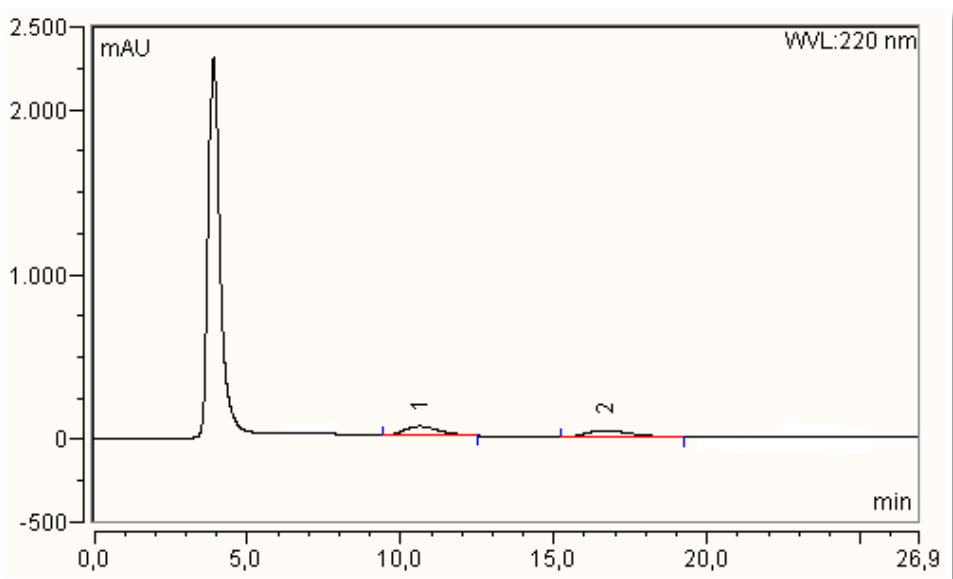
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	8,657	47,093	50,13
2	14,573	13,004	49,87

Figure A. 22 HPLC chromatogram of compound (±)-**43**



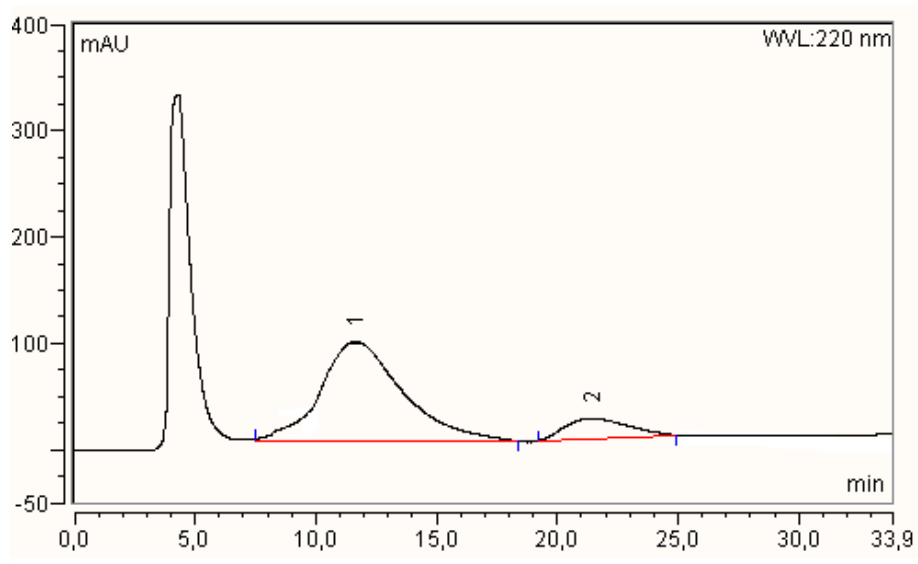
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	8,721	172,411	69,51
2	12,977	85,222	30,49

Figure A. 23 HPLC chromatogram of compound **43**



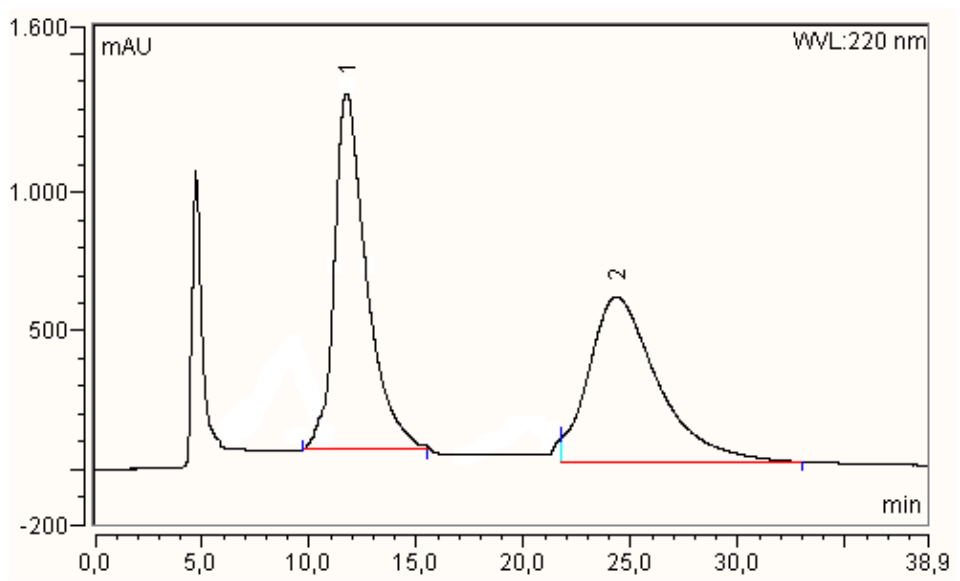
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	10,591	56,769	50,64
2	16,670	42,567	49,36

Figure A. 24 HPLC chromatogram of compound (±)-44



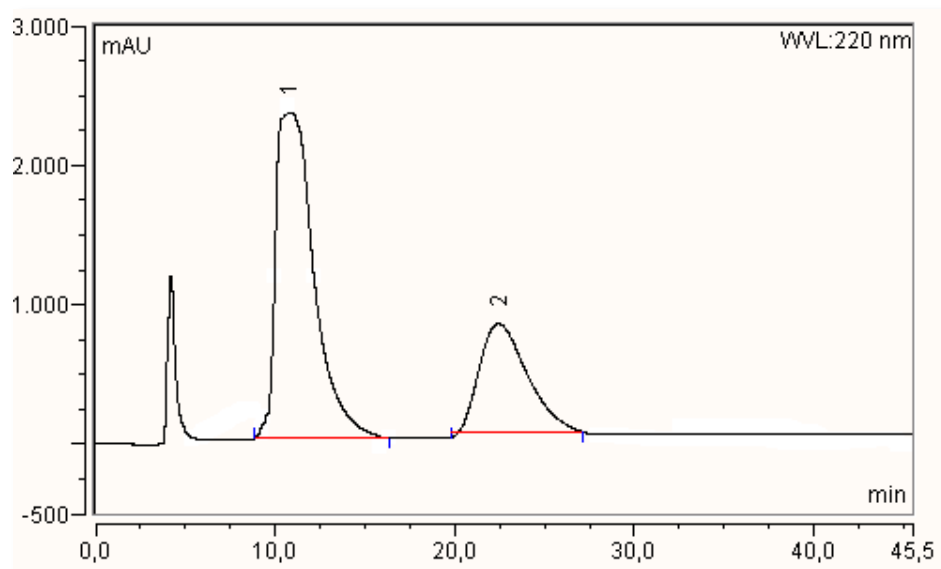
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	11,638	94,000	86,27
2	21,398	19,333	13,73

Figure A. 24 HPLC chromatogram of compound 44



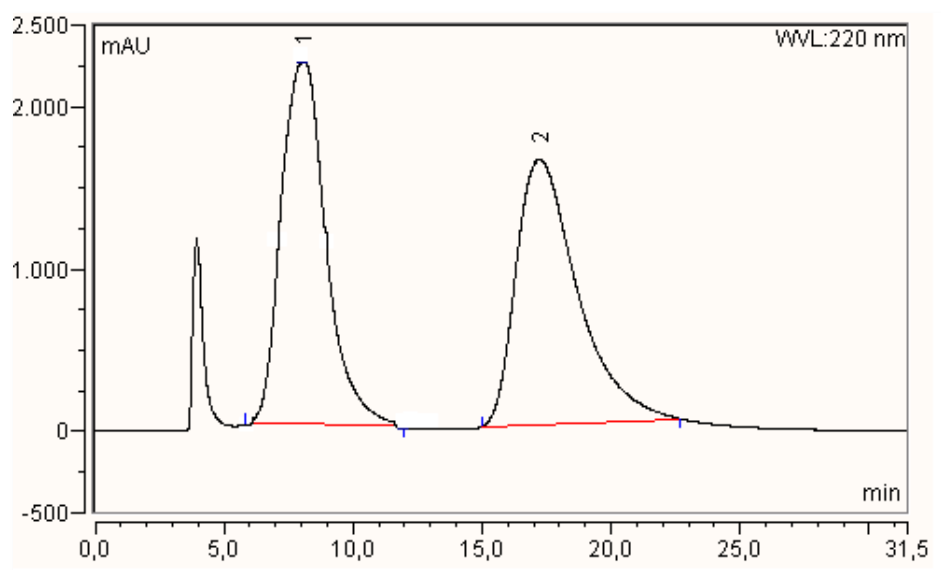
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	11,726	1299,656	49,68
2	24,340	595,628	50,32

Figure A. 25 HPLC chromatogram of compound (±)-45



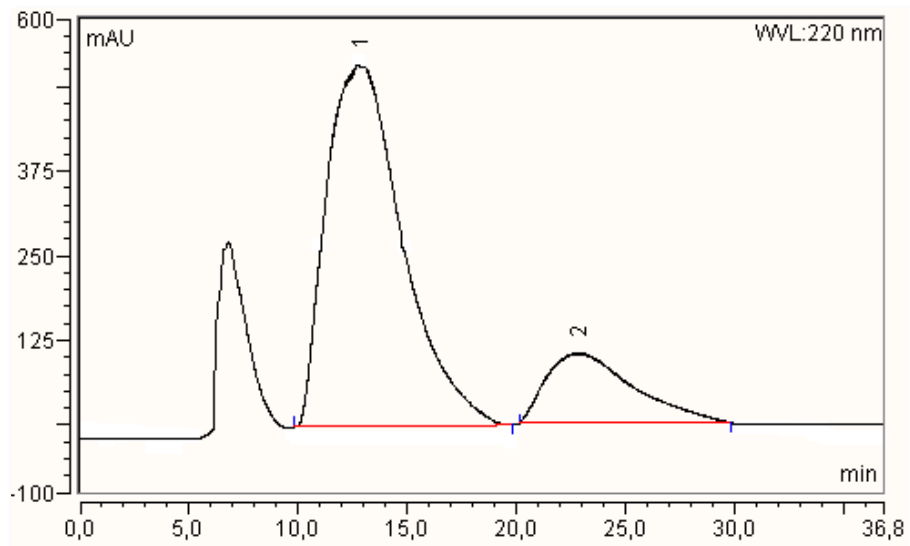
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	10,688	2347,912	75,27
2	22,410	587,395	19,73

Figure A. 26 HPLC chromatogram of compound 45



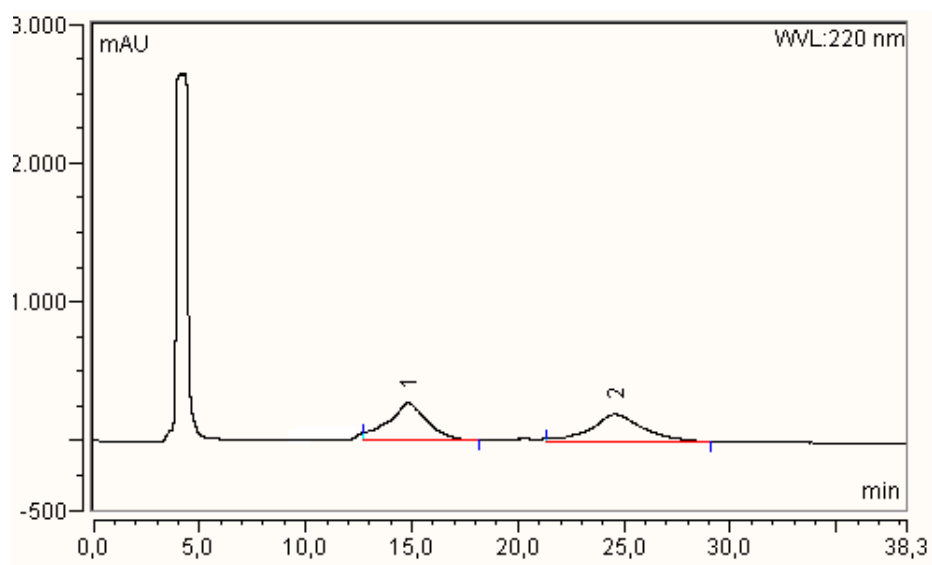
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	8,037	2251,114	49,81
2	17,257	1640,471	50,19

Figure A. 27 HPLC chromatogram of compound (±)-46



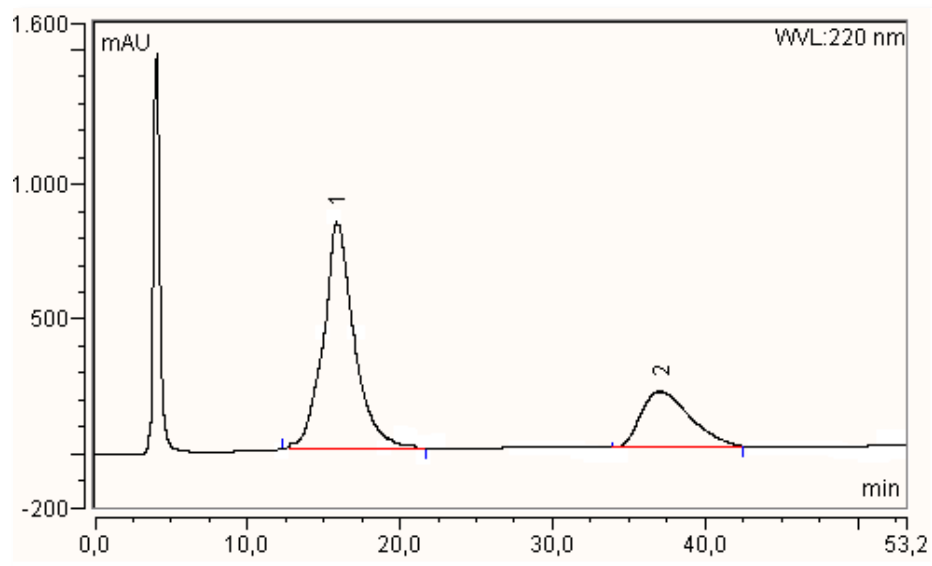
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	12,845	544,732	82,67
2	22,822	104,344	17,33

Figure A. 28 HPLC chromatogram of compound 46



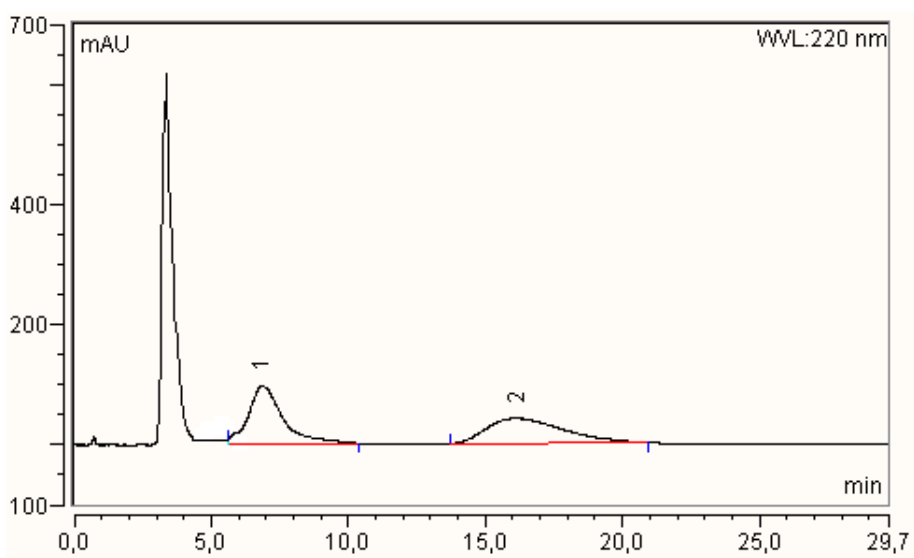
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	14,807	269,516	50,38
2	24,555	196,518	49,62

Figure A. 29 HPLC chromatogram of compound (±)-47



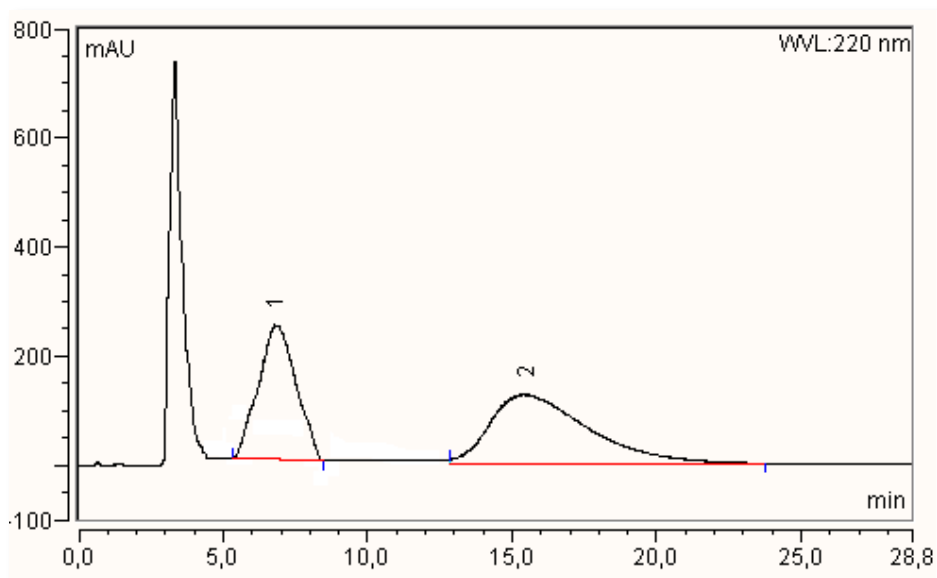
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	15,882	849,316	72,66
2	37,054	204,548	27,34

Figure A. 30 HPLC chromatogram of compound 47



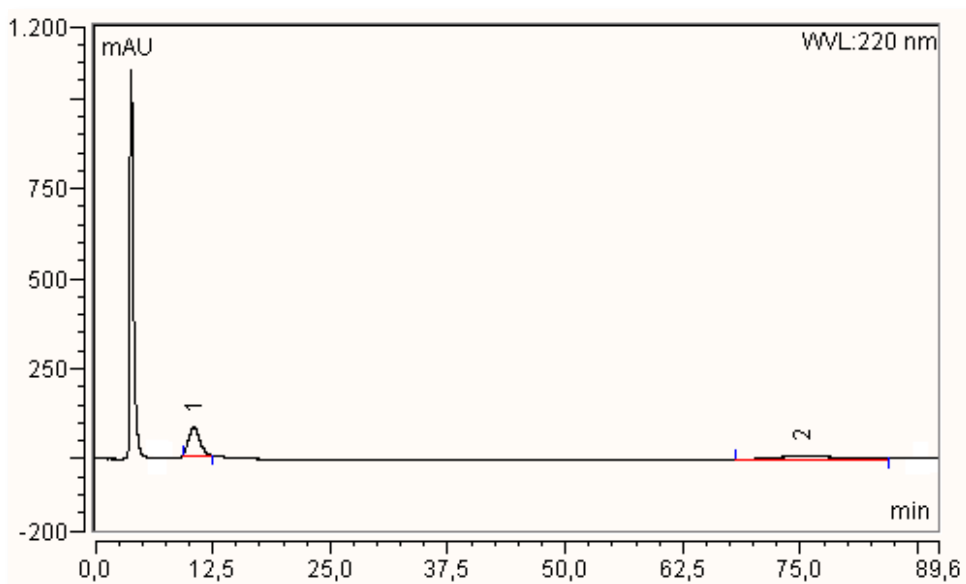
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	6,794	95,726	49,95
2	16,083	42,425	50,05

Figure A. 31 HPLC chromatogram of compound (±)-48



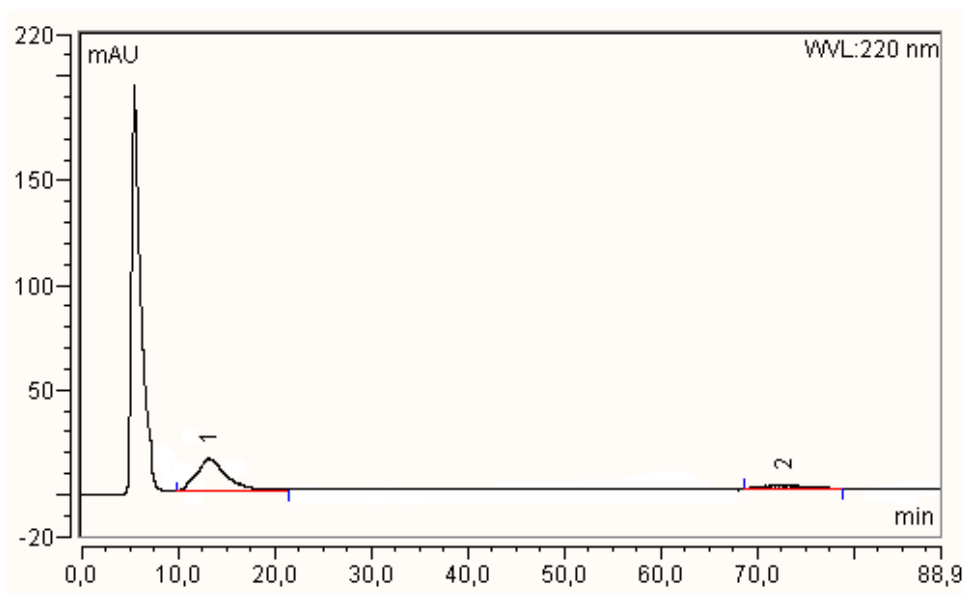
No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	6,780	184,742	29,23
2	15,448	128,051	70,77

Figure A. 32 HPLC chromatogram of compound 48



No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	10,504	77,832	52,52
2	75,152	9,864	47,48

Figure A. 32 HPLC chromatogram of compound (±)-49



No	Ret. Time (min)	Height (mAU)	Rel. Area (%)
1	12,157	16,547	87,65
2	72,611	1,587	12,35

Figure A. 33 HPLC chromatogram of compound 49