A NEW P-FAM-SILVER CATALYST FOR ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES

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ABSTRACT

A NEW P-FAM-SILVER CATALYST FOR ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES

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In this study new twelve phosphorus based chiral ligands were synthesized and characterized. Then the catalytic activity of these chiral ligands was tested with Cu(II) and Ag(I) salts in asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides. This method provides the synthesis of different pyrrolidine derivatives with up to four stereogenic centers. Pyrrolidine derivatives are found in the structure of many biologically active natural compounds and drugs. Therefore the asymmetric synthesis of these compounds is highly important and many groups are involved in this area. As the precursor of the azomethine ylides, *N*-benzyliden-glycinmethylester, *N*-(4-methoxy benzyliden)-glycinmethylester, *N*-(naphthalene-1-ylmethylene)-amino-acetic acid methyl ester, and *N*-(naphthalen-2-ylmethylene)-amino-acetic acid methyl ester were synthesized and used. As the dipolarophiles, methyl acrylate, dimethyl maleate and *N*-methyl maleimide were used. Using these imines and dipolarophiles with 6 mol % of one of the P-FAM chiral ligands in the presence of Ag(I) salt, pyrrolidine derivatives were synthesized in up to 95% yield and 89% enantioselectivity. Additionally, chiral ligand was recovered in more than 80% yield and reused without losing its activity.

Keywords: Chiral Catalysts, Asymmetric Synthesis, 1,3-Dipolar Cycloaddition Reactions, Azomethine Ylides, Pyrrolidine Derivatives.

ÖZ

AZOMETİN İLÜRLERİN ASİMETRİK 1,3-DİPOLAR HALKASAL KATILMA TEPKİMELERİ İÇİN YENİ BİR P-FAM-GÜMÜŞ KATALİZÖRÜ

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Bu çalışmada, oniki tane yeni fosforlu kiral ligand sentezlenmiş ve karakterize edilmiştir. Bu kiral ligandların Cu (II) ve Ag (I) tuzlarıyla birlikte azometin ilürlerin asimetrik 1,3-dipolar halkasal katılma tepkimelerinde katalitik aktiviteleri test edilmiştir. Bu yöntemle dört kiral merkeze sahip farklı pirolodin türevlerini sentezlemek mümkündür. Biyolojik aktiviteye sahip bir çok doğal ürün ve ilacın yapısında bulunan asimetrik pirolodinlerin sentezi çok önemlidir ve bir çok grup tarafından çalışılmaktadır. Azometin ilürlerin ön bileşeni iminler olarak *N*-benzyliden-glycinmethylester, *N*-(4-methoxybenzyliden)-glycinmethylester, *N*-(naphthalene-1-ylmethylene)-amino-acetic acid methyl ester ve *N*-(naphthalen-2-yl methylene)-amino-acetic acid methyl ester sentezlenip kullanılmıştır. Dipolarofiller olarak da methyl acrylate, dimethyl maleate and *N*-methyl maleimide seçilmiştir. Bu iminler ve dipolarofiller kiral ligandlardan bir tanesinden %6 mol oranında Ag (I) tuzu ile birlikte kullanılarak, farklı pirolodin türevleri %95'e varan verim ve %89'a varan enantioseçicilikle sentezlenmiştir. Ayrıca, kiral ligand %80'in üzerinde verimle geri kazanılıp aktivitesini kaybetmeden tekrar kullanılmıştır.

Anahtar kelimeler: Kiral Katalizör, Asimetrik Sentez, 1,3-Dipolar Halkasal Katılma Tepkimeleri, Azometin İlürler, Pirolidin Türevleri.

.

To my father and mother…

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TABLE OF CONTENTS

ABSTRACT……..iv
ÖZ……..vi
ACKNOWLEDGMENTS……....ix
TABLE OF CONTENTS……...x
LIST OF TABLES…….....xiv
LIST OF FIGURES……..xv
ABBREVIATIONS…….xxi

CHAPTERS
1.INTRODUCTION..... 1
1.1 Routes to enantiomerically pure compounds 1
1.1.1 Catalytic Asymmetric Cycloaddition Chemistry 1
1.1.1.1 1,3-Dipolar Cycloaddition Chemistry 2
1.1.1.1.1 1,3-Dipoles or Ylides 3
1.1.1.1.2 Dipolarophile..... 4
1.1.1.1.3 Mechanism of the 1,3-Dipolar Cycloaddition Reaction..... 5
1.1.1.1.4 Azomethine Ylides and Their 1,3-Dipolar Cycloaddition Reactions 8
1.1.1.1.5 Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides 10
1.2 Aim of the work 32

2.RESULTS AND DISCUSSION 34
2.1 The Synthesis of Chiral P-FAM Ligands..... 34
2.2 The Asymmetric 1,3-Dipolar Cycloaddition Reaction by Using Chiral P-FAM Ligands..... 37

2.2.1 Ligand Screening and Optimization of 1,3-Dipolar Cycloaddition Reaction 37
2.2.2 Enantioselective 1,3-Dipolar Cycloaddition Reaction of various aldimines and dipolarophiles 44

3.CONCLUSION 48

4.EXPERIMENTAL 49
4.1 General Consideration 49
4.1.1 General Procedures 49
4.1.2 Materials 50
4.1.3 Instrumentation 50
4.2 Synthesis and Characterization of Chiral Ligands 50
4.2.1 Synthesis and Characterization of Aziridines **160** and **161**. 50
4.2.2 Synthesis and Characterization of Tosylated Aziridines **162** 52
4.2.3 Synthesis and Characterization of phosphorus aziridino ketones **163** and **164** 53
4.2.4 Synthesis and Characterization of Chiral P-FAM Ligands **165** and **166** 55
4.2.4 Synthesis and Characterization of Chiral P-FAM Ligands **167** and **168** 56
4.2.5 Synthesis and Characterization of Tosylated Aziridine **169** 58
4.2.6 Synthesis and Characterization of phosphorus aziridino ketones **170** and **171** 59
4.2.7 Synthesis and Characterization of Chiral P-FAM Ligands **172** and **173** 60
4.2.8 Synthesis and Characterization of Chiral P-FAM Ligands **174** and **175** 62

4.3 General Procedure for the synthesis of α-iminoesters..... 64
4.4 General Procedure for Catalytic Asymmetric 1,3-DC Reaction ... 64
4.4.1 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate..... 65
4.4.2 (2*S*, 4*S*, 5*R*)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate 65
4.4.3 (2*R*, 4*R*, 5*S*)-4-^{t}Butyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate 66
4.4.4 (2*S*, 3*S*, 4*S*, 5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate..... 66
4.4.5 (1*S*, 2*R*, 4*S*, 5*R*)-Methyl octahydro-7-methyl-6,8-dioxo-4-phenyl 67
4.4.6 (2*S*, 4*S*, 5*R*)-Methyl 4-cyano-5-phenylpyrrolidine-2-carboxylate 68
4.4.7 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate 68
4.4.8 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(naphthalen-2-yl)pyrrolidine-2,4-dicarboxylate 69
4.4.9 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(naphthalen-1-yl)pyrrolidine-2,3,4-tricarboxylate 69
4.4.10 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(naphthalen-1-yl)pyrrolidine-2,4-dicarboxylate 70
4.4.11 (1*S*, 3*R*, 3*S*, 6*R*)-Methyl octahydro-5-methyl-3-(naphthalen-1-yl)-4,6-dioxopyrrolo[3,4-c]pyrrole-1-carboxylate..... 71
4.4.12 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate 71
4.4.13 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(4-chlorophenyl)pyrrolidine-2,4-dicarboxylate 72
4.4.14 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate 72

4.4.15 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylate 73

REFERENCES 74

APPENDIX A. NMR SPECTRUMS AND HPLC CHROMATOGRAMS OF COMPOUNDS 77

LIST OF TABLES

TABLES

Table 1 1,3-DC reactions of azomethine ylides with $Cu(OTf)_2$ 38

Table 2 1,3-DC reactions of azomethine ylides with AgOAc in THF 39

Table 3 1,3-DC reactions of azomethine ylides with AgOAc in DCM 40

Table 4 Optimization of the amounts of the reagents[a] 41

Table 5 1,3-DC reactions in different solvent[a] 42

Table 6 1, 3-DC reaction with different ligand to metal ratio..... 43

Table 7 1,3-DC reactions with different aldimines and dipolarophiles under optimized conditions[a] 45

LIST OF FIGURES

FIGURES

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

Figure 2 Examples of 1,3 dipoles. 4

Figure 3 Various dipolarophiles used in 1,3-DC reaction..... 4

Figure 4 Concerted and singlet diradical mechanisms of 1,3-DC reaction. 5

Figure 5 Similarity between 1,3-DC and Diels-Alder Reaction..... 6

Figure 6 Stereochemistry of 1,3-DC reaction. 6

Figure 7 The classification of 1,3-DC reactions on the basis of the FMOs. 7

Figure 8 The general structure of azomethine ylides. 8

Figure 9 Proton abstraction from imine derivatives..... 9

Figure 10 Photolysis or thermolysis of aziridines..... 9

Figure 11 Decomposition of N-alkyl-N-methoxymethyl-N (trimethylsilyl) methylamines 9

Figure 12 The cycloadditions of azomethine ylides **19** with alkenes **17**. 10

Figure 13 The retrosynthesis of 1,3-DC reactions..... 10

Figure 14 Examples of some biologically active compounds having pyrrolidine ring. 11

Figure 15 Formation of highly functionalized pyrrolidines using chiral catalyst. 12

Figure 16 1,3-DC reaction carried out by Grigg and co-workers. 13

Figure 17 1,3-DC reaction using chiral ligand **44** with AgOTf. 14

Figure 18 The chemical structures of chiral ligands **48-52**. 15

Figure 19 1,3-DC reaction using chiral catalyst **48**-$Ni(ClO_4)_2.6H_2O$..... 15

Figure 20 Chiral bisoxazoline ligands **57, 58,** and **59**. 16

Figure 21 1,3-DC reactions using chiral catalyst (*S*)-^{t}Bu-BOX-Zn(II). 16

Figure 22 The chemical structures of chiral FAM ligands **64-67**. 17

Figure 23 1,3-DC reactions using chiral catalyst **64**-$Zn(OTf)_2$. 17

Figure 24 The chemical structures of chiral ligands **72-77**. 18
Figure 25 1,3-DC reaction using **75a**- and **77**-$CuClO_4$. 19
Figure 26 Chiral phosphinooxazoline ligands **83, 84, 85a-f**. 20
Figure 27 1,3-DC reaction using chiral catalyst **85d**-$CuClO_4$. 20
Figure 28 The chemical structures of chiral ligands **89-91** 20
Figure 29 1,3-DC reaction using **89a**- and **89e**-$CuClO_4$ 21
Figure 30 The chemical structures of chial ligands **95-97** 21
Figure 31 1,3-DC reaction using chiral catalyst **95a**-$Cu(CH_3CN)_4ClO_4$. 22
Figure 32 The chemical structures of chiral ligand (R)-Fesulphos **102a-e** 23
Figure 33 1,3-DC reaction using chiral catalyst **102a**-$Cu(CH_3CN)_4ClO_4$. 23
Figure 34 Chiral phosphine ligands **106-111** 24
Figure 35 1,3-DC reaction using chiral catalyst **111b**-AgOAc. 24
Figure 36 The chemical structures of chiral phosphine **107**, and **115-119**. 25
Figure 37 1,3-DC reaction using chiral catalyst **119**-AgOAc. 25
Figure 38 The chemical structures of chiral P,N ligands **124** and **125**. 26
Figure 39 1,3-DC reaction using chiral catalyst **119**-AgOAc. 26
Figure 40 The chemical structures of chiral ligands **129**-**133** 27
Figure 41 1,3-DC reaction using chiral catalyst **132**-AgF. 28
Figure 42 The chemical structures of chiral BINAP ligands **106** and **137** 28
Figure 43 1,3-DC reaction using chiral catalyst **137**-$AgClO_4$. 29
Figure 44 1,3-DC reaction using chiral catalyst **145**-AgOAc. 29
Figure 45 1,3-DC reaction using **149a**- and **149b**-AgOAc. 30
Figure 46 Two different transition states **150a** and **150b**. 31
Figure 47 The chemical structures of chiral P,S ligands **151a**-**k**. 31
Figure 48 1,3-DC reaction using **151g**- and **151i**-AgOAc. 32
Figure 49 Synthesis of chiral aziridines **160** and **161** 35
Figure 50 Synthesis of chiral ligand **165**, **166**, **167** and **168**. 36
Figure 51 Synthesis of chiral ligand **172**, **173**, **174** and **175**. 37

Figure A.1 ^{1}H-NMR spectrum of compound **160** 77
Figure A.2 ^{13}C-NMR spectrum of compound **160** 77
Figure A.3 ^{1}H-NMR spectrum of compound **162** 78
Figure A.4 ^{13}C-NMR spectrum of compound **162** 78
Figure A.5 ^{1}H-NMR spectrum of compound **163** 79
Figure A.6 ^{13}C-NMR spectrum of compound **163** 79
Figure A.7 ^{31}P-NMR spectrum of compound **163** 80
Figure A.8 ^{1}H-NMR spectrum of compound **164** 80
Figure A.9 ^{13}C-NMR spectrum of compound **164** 81
Figure A.10 ^{31}P-NMR spectrum of compound **164** 81
Figure A.11 ^{1}H-NMR spectrum of compound **165** 82
Figure A.12 ^{13}C-NMR spectrum of compound **165** 82
Figure A.13 ^{31}P-NMR spectrum of compound **165** 83
Figure A.14 ^{1}H-NMR spectrum of compound **166** 83
Figure A.15 ^{13}C-NMR spectrum of compound **166** 84
Figure A.16 ^{31}P-NMR spectrum of compound **166** 84
Figure A.17 ^{1}H-NMR spectrum of compound **167** 85
Figure A. 18 ^{13}C-NMR spectrum of compound **167** 85
Figure A.19 ^{31}P-NMR spectrum of compound **167** 86
Figure A.20 ^{1}H-NMR spectrum of compound **168** 86
Figure A.21 ^{13}C-NMR spectrum of compound **168** 87
Figure A.22 ^{31}P-NMR spectrum of compound **168** 87
Figure A.23 ^{1}H-NMR spectrum of compound **161** 88
Figure A.24 ^{13}C-NMR spectrum of compound **161** 88
Figure A.25 ^{1}H-NMR spectrum of compound **169** 89
Figure A.26 ^{13}C-NMR spectrum of compound **169** 89
Figure A.27 ^{1}H-NMR spectrum of compound **170** 90
Figure A.28 ^{13}C-NMR spectrum of compound **170** 90
Figure A.29 ^{31}P-NMR spectrum of compound **170** 91

Figure A.30 ^{1}H-NMR spectrum of compound **171** 91
Figure A.31 ^{13}C-NMR spectrum of compound **171** 92
Figure A.32 ^{31}P-NMR spectrum of compound **171** 92
Figure A.33 ^{1}H-NMR spectrum of compound **172** 93
Figure A.34 ^{13}C-NMR spectrum of compound **172** 93
Figure A.35 ^{31}P-NMR spectrum of compound **172** 94
Figure A.36 ^{1}H-NMR spectrum of compound **173** 95
Figure A.37 ^{31}P-NMR spectrum of compound **173** 95
Figure A.38 ^{1}H-NMR spectrum of compound **174** 96
Figure A.39 ^{31}P-NMR spectrum of compound **174** 96
Figure A.40 ^{1}H-NMR spectrum of compound **175** 97
Figure A.41 ^{13}C-NMR spectrum of compound **175** 97
Figure A.42 ^{31}P-NMR spectrum of compound **175** 98
Figure A.43 ^{1}H-NMR spectrum of compound **178** 99
Figure A.44 ^{13}C-NMR spectrum of compound **178** 99
Figure A.45 ^{1}H-NMR spectrum of compound **179** 100
Figure A.46 ^{13}C-NMR spectrum of compound **179** 100
Figure A.47 ^{1}H-NMR spectrum of compound **180** 101
Figure A.48 ^{13}C-NMR spectrum of compound **180** 101
Figure A.49 ^{1}H-NMR spectrum of compound **181** 102
Figure A.50 ^{13}C-NMR spectrum of compound **181** 102
Figure A.51 ^{1}H-NMR spectrum of compound **182** 103
Figure A.52 ^{13}C-NMR spectrum of compound **182** 103
Figure A.53 ^{1}H-NMR spectrum of compound **183** 104
Figure A.54 ^{13}C-NMR spectrum of compound **183** 104
Figure A.55 ^{1}H-NMR spectrum of compound **184** 105
Figure A.56 ^{13}C-NMR spectrum of compound **184** 105
Figure A.57 ^{1}H-NMR spectrum of compound **185** 106
Figure A.58 ^{13}C-NMR spectrum of compound **185** 106

Figure A.59 ^{1}H-NMR spectrum of compound **186** 107
Figure A.60 ^{13}C-NMR spectrum of compound **186** 107
Figure A.61 ^{1}H-NMR spectrum of compound **187** 108
Figure A.62 ^{13}C-NMR spectrum of compound **187** 108
Figure A.63 ^{1}H-NMR spectrum of compound **188** 109
Figure A.64 ^{13}C-NMR spectrum of compound **188** 109
Figure A.65 ^{1}H-NMR spectrum of compound **189** 110
Figure A.66 ^{13}C-NMR spectrum of compound **189** 110
Figure A.67 ^{1}H-NMR spectrum of compound **190** 111
Figure A.68 ^{13}C-NMR spectrum of compound **190** 111
Figure A.69 ^{1}H-NMR spectrum of compound **191** 112
Figure A.70 ^{13}C-NMR spectrum of compound **191** 112
Figure A.71 ^{1}H-NMR spectrum of compound **192** 113
Figure A.72 ^{13}C-NMR spectrum of compound **192** 113
Figure A.73 HPLC Chromatogram of compound **178** 114
Figure A.74 HPLC Chromatogram of compound **179** 114
Figure A.75 HPLC Chromatogram of compound **180** 115
Figure A.76 HPLC Chromatogram of compound **181** 115
Figure A.77 HPLC Chromatogram of compound **182** 116
Figure A.78 HPLC Chromatogram of compound **183** 117
Figure A.79 HPLC Chromatogram of racemic **183** + ent-**183** 117
Figure A.80 HPLC Chromatogram of compound **184** 118
Figure A.81 HPLC Chromatogram of compound **185** 118
Figure A.82 HPLC Chromatogram of compound **186** 119
Figure A.83 HPLC Chromatogram of compound **187** 119
Figure A.84 HPLC Chromatogram of racemic **187** + ent-**187** 120
Figure A.85 HPLC Chromatogram of compound **188** 120
Figure A.86 HPLC Chromatogram of racemic **188** + ent-**188** 121
Figure A.87 HPLC Chromatogram of compound **189** 121

Figure A.88 HPLC Chromatogram of compound **190** 122
Figure A.89 HPLC Chromatogram of compound **191** 122
Figure A.90 HPLC Chromatogram of compound **192** 123
Figure A.91 HPLC Chromatogram of racemic **192** + ent-**192** 123

ABBREVIATIONS

Ar	: aryl (also argon)
Bn	: benzyl
BINAP	: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bu	: butyl
^{t}Bu	: tert-butyl
br	: broad singlet
^{o}C	:centigrade Celcius
δ	:chemical shift in parts per million downfield from tetramethylsilane
c	: concentration
J	: coupling constant
Cy	: cyclopentyl
de	: diastereomeric excess
DCE	: 1,2-dichloroethane
1,3-DC	: 1,3-Dipolar Cycloaddition
d	: doublet (spectral)
dt	: doublet of triplets (spectral)
dd	: doublet of doublet (spectral)
EWG	: Electron withdrawing group
ee	: enantiomeric excess
ΔE	: energy gap
Et	: ethyl
equiv	: equivalent
Fc	: ferrocenyl
FAM	: Ferrocenyl substituted Aziridinyl Methanol
FMO	: Frontier Molecular Orbitals
g	: gram(s)
Hz	: hertz

HOMO : Highest Occupied Molecular Orbital

HPLC : High Pressure Liquid Chromatography

h : hour(s)

HC : hydrocinchonine

IR : infrared

^{i}Pr : isopropyl

$KPPh_2$: potassium diphenylphosphide

LA : Lewis Acid

LUMO : Lowest Unoccupied Molecular Orbital

mp : melting point

MHz : megahertz

Me : methyl

mL : milliliter(s)

mmol : millimole(s)

min : minute(s)

m : multiplet (spectral)

nm : nanometer

NMR : Nuclear Magnetic Resonance

P-FAM : Phosphorous based Ferrocenyl substituted Aziridinyl Methanol

ppm : parts per million (in NMR)

Ph : phenyl

q : quartet (spectral)

R_f : retention factor (TLC)

t_R : retention time (in HPLC)

rt : room temperature

s : singlet (spectral)

THF : Tetrahydrofuran; solvent

TMS ; Tetramethylsilane, also Trimethylsilyl

TLC : Thin Layer Chromatography

Tf : Triflate (CF_3SO_2)

t : triplet (spectral)

UV : ultraviolet

CHAPTER 1

INTRODUCTION

1.1 Routes to enantiomerically pure compounds

Organic compounds, pharmaceuticals, agrochemicals, and other materials possessing useful biological activity, play an important part in modern life. Most of these organic compounds are chiral in other words mirror images of them are not superimposed. The enantiomers should be thought as two distinct compounds because they have different biological activity. To obtain enantiomerically pure compounds there are some methods: Resolution of racemates, starting from enantiomerically pure reagents, use of chiral auxiliaries, and chiral catalysts. In recent years, the last method is the most commonly studied one because small amount of the chiral catalytic mediator is enough to produce large amount of chiral product. Therefore this method provides economic and practical advantages.[1]

1.1.1 Catalytic Asymmetric Cycloaddition Chemistry

The construction of carbo- and heterocyclic compounds is important for the numerous total syntheses of complex molecules because of their broad and important biological activities. In addition to these, they are found in innumerable natural products and pharmaceuticals. Therefore these cyclic compounds, especially five- and six-membered N-heterocycles continue to attract considerable attention.[2] Moreover, cycloaddition reactions are very important in synthetic organic chemistry, since they have advantages of

synthetic efficiency and potentially high stereoselectivity for ring-containing structures.[3] Catalytic cycloaddition chemistry has attracted considerable interest so remarkable progress have been made in cycloaddition reaction. In the next section 1,3-DC (dipolar cycloaddition) reaction will be further explored for the scope of our studies.

1.1.1.1 1,3-Dipolar Cycloaddition Chemistry

The 1,3-DC reaction (4π +2π), one of the most efficient method for the preparation of five-membered heterocycles **3**, can be achieved by reaction of a 1,3-dipole or ylide **1**, with dipolarophile **2** (Figure 1). The 1,3-dipole is used as 4π electron component and dipolarophile is used as 2π electron component in 1,3-DC reaction.

Firstly Huisgen[4] indicated that cycloaddition of the type 3+2=5 leading to an uncharged 5-membered ring can be possible with the reactants having formal charges (Figure 1). Combination of such a 1,3-dipole with a multiple bond system d-e, termed the dipolarophile, is referred to as a 1,3-DC reaction (Figure 1).

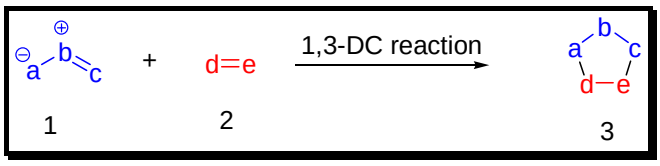


Figure 1 General representation of 1,3-DC reactions.

In organic chemistry, the 1,3-DC offers a remarkably wide range of utility in the synthesis of five-membered heterocycles.[4] Therefore 1,3-DC reaction has been reviewed recently.[5] The history of 1,3-dipoles goes back

to discovery of the diazoacetic ester. After Curtius[6] discovered this ester in 1883, Buchner[7] studied the reaction of diazoacetic ester with α,β-unsaturated esters. In 1888 Buchner described the first 1,3-DC reaction. After Huisgen[4] et al. formulated the general concept of 1,3-DC reaction, numerous cycloadditions involving different types of dipoles[8] have been described.

1.1.1.1.1 1,3-Dipoles or Ylides

Huisgen[4] defined the dipole (4π electron component) by using terms of "***a-b-c"*** as a 1,3-dipole. 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[9] and et al. defined 1,3-dipole which is formed by 3 atoms with at least one heteroatom. This compound have 4π electrons with a zwitterion 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 can be divided into two classes: those in which the three atoms comprising the 1,3-dipole are linear and those in which they are not. Examples of different types of dipoles are given in Figure 2.[10]

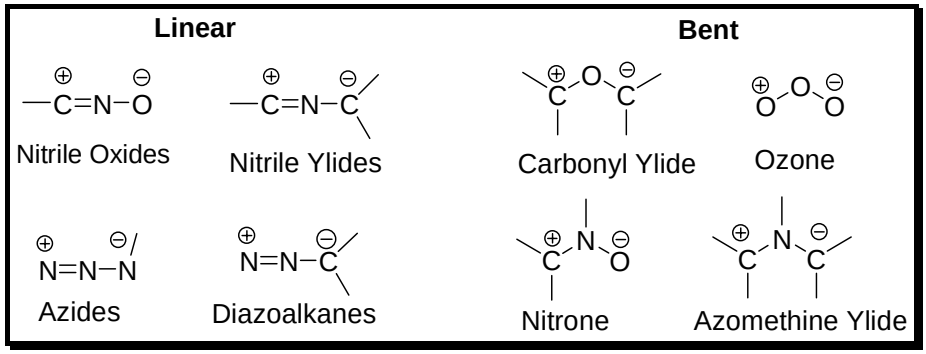


Figure 2 Examples of 1,3 dipoles.

1.1.1.1.2 Dipolarophile

Compound with 2π-electrons is generally an alkene and is named the dipolarophile in the 1,3-DC reaction. This specie reacts with 1,3-dipoles in a concerted manner in 1,3-DC reactions.[9] There are different dipolarophiles such as; α,β-unsaturated carbonyl compounds (**4**), ketones (**5**) allylic alcohols (**6**), allylic halides (**7**), alkynes (**8**), vinylic ethers (**9**), vinylic esters (**10**) and imines (**11**) (Figure 3).[11,10]

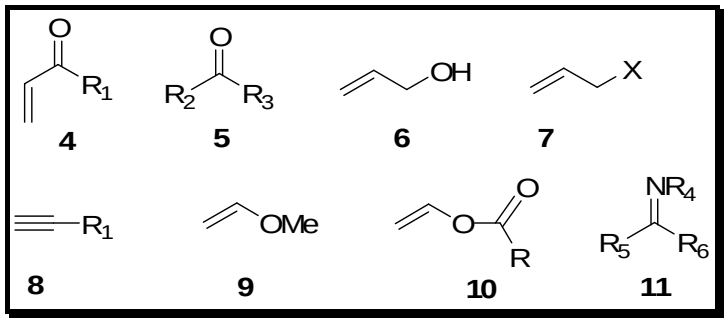


Figure 3 Various dipolarophiles used in 1,3-DC reaction.

1.1.1.1.3 Mechanism of the 1,3-Dipolar Cycloaddition Reaction

There were two approaches related to the reaction mechanism of 1,3-DC reaction in 1960s.[12] Huisgen[4] developed a detailed explanation for the concerted mechanism of this reaction (Figure 4). On the other hand, Firestone[13] claimed that 1,3-DC proceeded by stepwise reaction mechanism involving diradical intermediates for 1,3-DC reactions (Figure 4). Finally, Firestone agreed that the reaction was concerted because he could not rule out diradicalic mechanism on the basis of stereospecificity.[12]

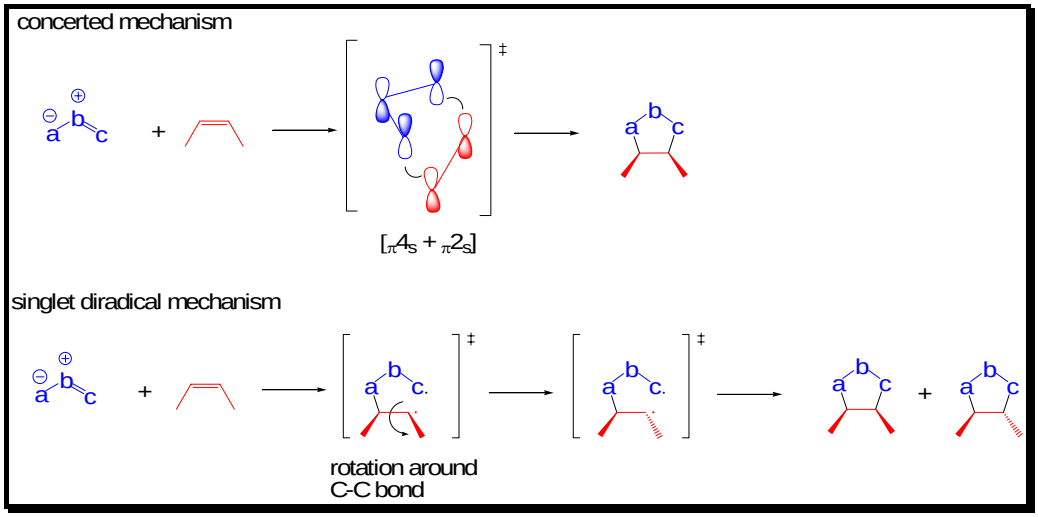


Figure 4 Concerted and singlet diradical mechanisms of 1,3-DC reaction.

Huisgen[4] found that cycloaddition of 1,3-dipoles to alkene are stereospecifically suprafacial, solvent polarity has little effect on reaction rates, and small activation enthalpies and large negative activation entropies. As a result, his mechanistic investigation have shown that 1,3-DC reaction take place in a concerted fashion in accordance with Woodward-Hoffmann rules.[14] They defined the concept of a concerted reaction, which is also named pericyclic reactions such as Diels-Alder, all

bonds are made or broken around a circle. Both Diels-Alder Reactions and 1,3-DC reactions take place in a concerted fashion, with partial formation of the two new bonds in the single transition state (Figure 5).[12]

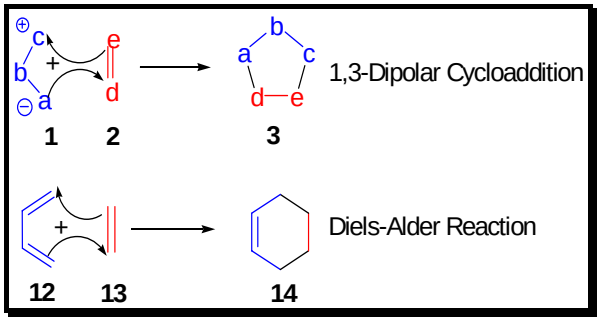


Figure 5 Similarity between 1,3-DC and Diels-Alder Reaction.

On the basis of Woodward-Hoffmann theory[14] three pz orbitals of the 1,3-dipole and two pz orbitals of the alkene combine suprafacially. Like Diels-Alder Reaction, 1,3-DC reaction proceeds with thermally allowed retains the configuration of the reactants. In other words, the stereochemistry of dipole and the dipolarophile are retained in the final product (Figure 6).

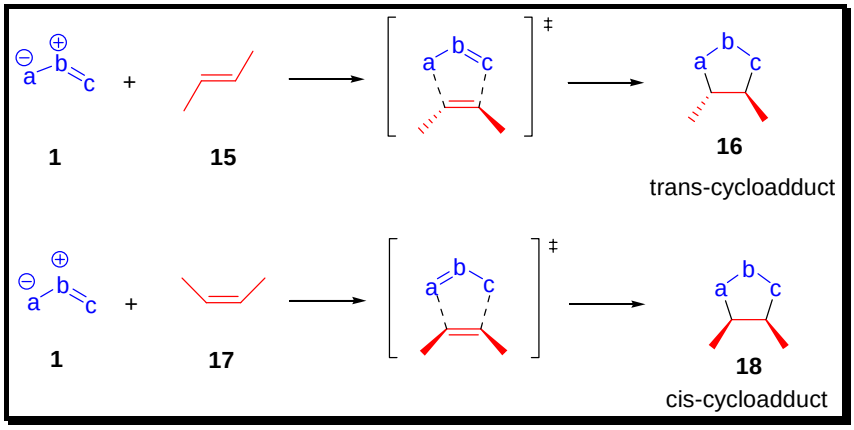


Figure 6 Stereochemistry of 1,3-DC reaction.

1,3-DC reaction model is based on the interactions of the HOMO's and LUMO's of both the dipolarophile and the 1,3-dipole according to the FMO theory.[15] The relative positions of HOMO and LUMO energies lead to three reactivity types in 1,3-DC reactions (Figure 7).[16]

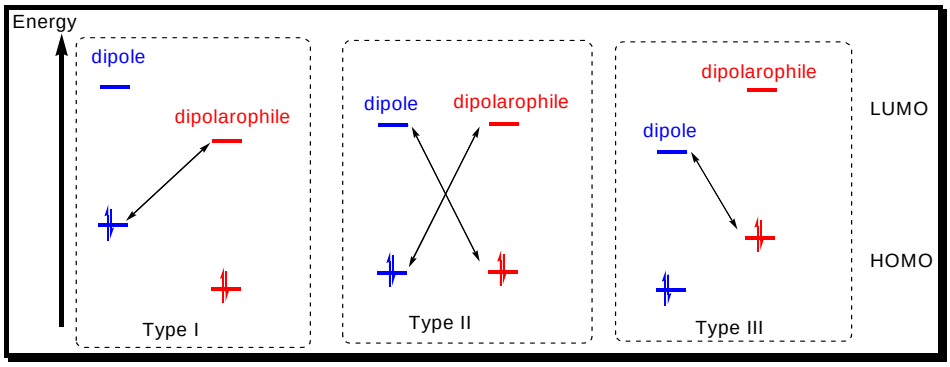


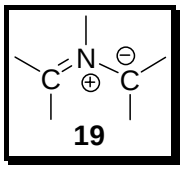
Figure 7 The classification of 1,3-DC reactions on the basis of the FMOs.

Type I $HOMO_{dipole}$-$LUMO_{alkene}$ controlled reactions such as azomethine ylides and azomethine imines. Type II $HOMO_{dipole}$-$LUMO_{alkene}$ or $HOMO_{alkene}$-$LUMO_{dipole}$ controlled additions such as nitrile oxides and nitrones. Type III $LUMO_{dipole}$-$HOMO_{alkene}$ controlled cycloadditions such as ozone and nitrous oxide.[16]

Electronic property of the substituent determines the reaction rates because the substituents influence the energy of the orbitals and change their relative separation.[15] Sustman and Trill[17] explained the effects of electron releasing and electron donating substituents for these three types of 1,3-DC reactions separately.

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

Azomethine ylides have planar structure and include one nitrogen atom attached to two terminal sp^2 carbon atoms (Figure 8).[18] Azomethine ylides are unstable species which have to be prepared in situ and trapped by almost any multiple C–C or C–X (X = heteroatom) bond.



19

Figure 8 The general structure of azomethine ylides.

A number of methods have been developed for the generation of azomethine ylides, such as thermolysis and photolysis of aziridines,[19] desilylation of various α-amino silane derivatives,[20] proton abstraction from imine derivatives of α-amino acids,[21] decarboxylative condensation of amino acids,[22] deprotonation of iminium salts,[23] and others.[24] There are three most commonly employed procedures; such as proton abstraction from imine derivatives **20** (Figure 9), photolysis or thermolysis of aziridines **22** (Figure 10) and acid catalyzed decomposition of N-alkyl-N-methoxymethyl-N (trimethylsilyl) methylamines **24** (Figure 11).[25]

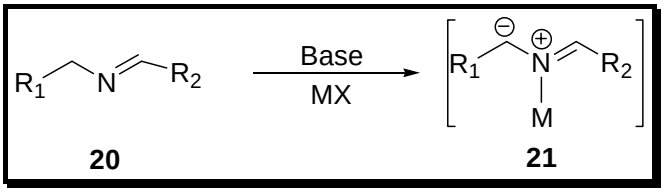


Figure 9 Proton abstraction from imine derivatives

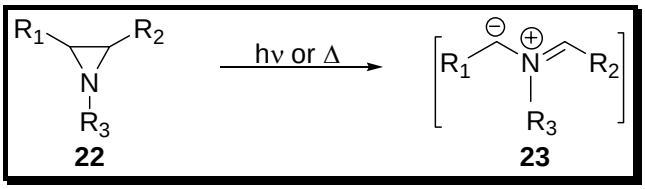


Figure 10 Photolysis or thermolysis of aziridines

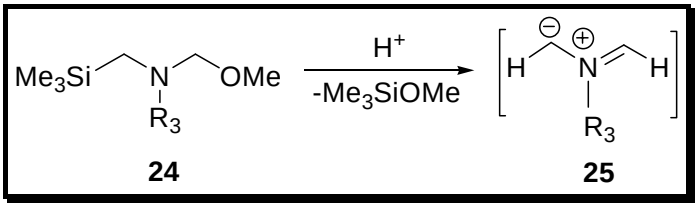


Figure 11 Decomposition of N-alkyl-N-methoxymethyl-N (trimethylsilyl) methylamines

The cycloadditions of unstable species of azomethine ylides **19** with alkenes **17** provide the synthesis of pyrrolidines (**26**) (Figure 12).[26] The 1,3-DC reaction is important for organic chemistry because it allows the formation of two bonds and up to four stereogenic centers in a single operation as shown in Figure 12.[27]

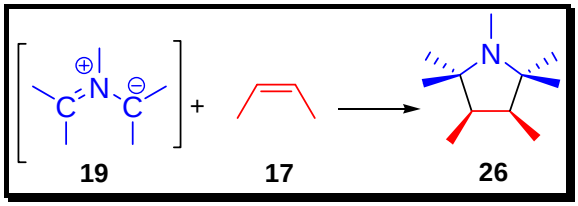


Figure 12 The cycloadditions of azomethine ylides **19** with alkenes **17**.

Synthesis of pyrrolidines is very important because the pyrrolidine substructure **26** (Figure 13) is a common motif in a wide range of biologically active compounds, especially alkaloids. An attractive synthetic approach to pyrrolidine-containing target molecules involves the construction of the C_2–C_3 and C_4–C_5 ring bonds via a [3+2] cycloaddition strategy. This approach calls for the use of a 4π electron azomethine ylide **19**, in a (4π +2π) cycloaddition with an alkene. Such a strategy has the advantage of synthetic efficiency and potentially high stereoselectivity.[28]

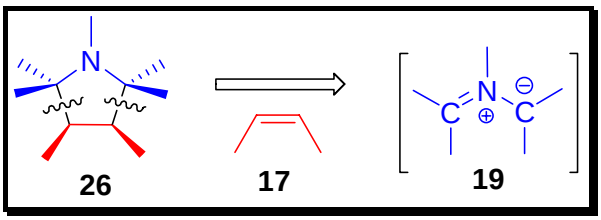


Figure 13 The retrosynthesis of 1,3-DC reactions.

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

In recent years, azomethine ylides have become one of the most investigated classes of 1,3-dipoles because their reaction with alkenes provide the synthesis of pyrrolidine rings. Substituted pyrrolidine rings

attract considerable attention due to their broad and important biological activities.[26] They are found in innumerable natural products and pharmaceutical compounds such as acromelic acid (**27**), cephalotoxine (**28**), cocaine (**29**), (+)-coccinine (**30**), lapidilectine B (**31**), lepadiformine (**32**), kainic acid (**33**) and quinocarcin (**34**) (Figure 14).[3]

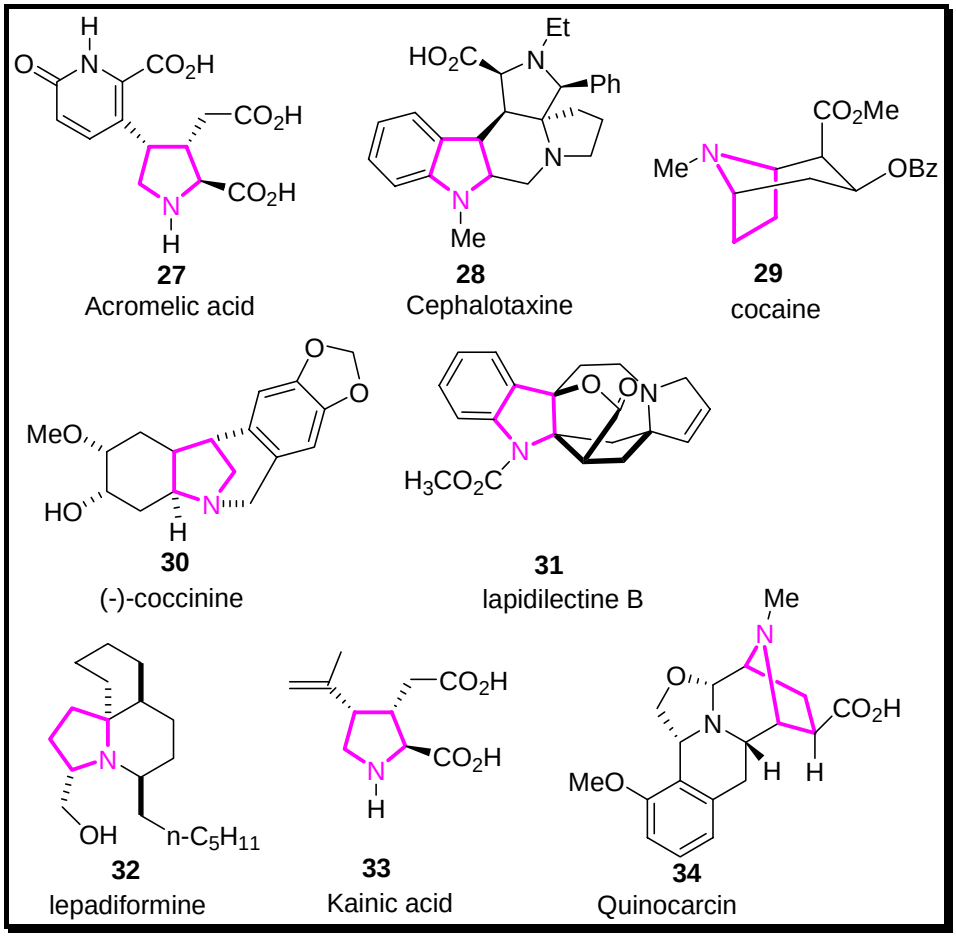


Figure 14 Examples of some biologically active compounds having pyrrolidine ring.

The development of new methods for the synthesis of pyrrolidines[29] is considerably important, particularly approaches leading to chiral derivatives of these ring skeletons.[30]

Three general approaches have emerged to directly provide optically active 1,3-DC products: 1-Utilization of a chiral, nonracemic dipolarophile or dipole,[31] 2-attachment of a chiral auxiliary to dipole[32] or the dipolarophile,[33] 3-utilization of chiral catalyst.[18,5] The latter approach has been investigated much frequently. Dipole or dipolarophile can coordinate to metal-ligand chiral catalyst to provide enantioselective reaction (Figure 15).[34-38]

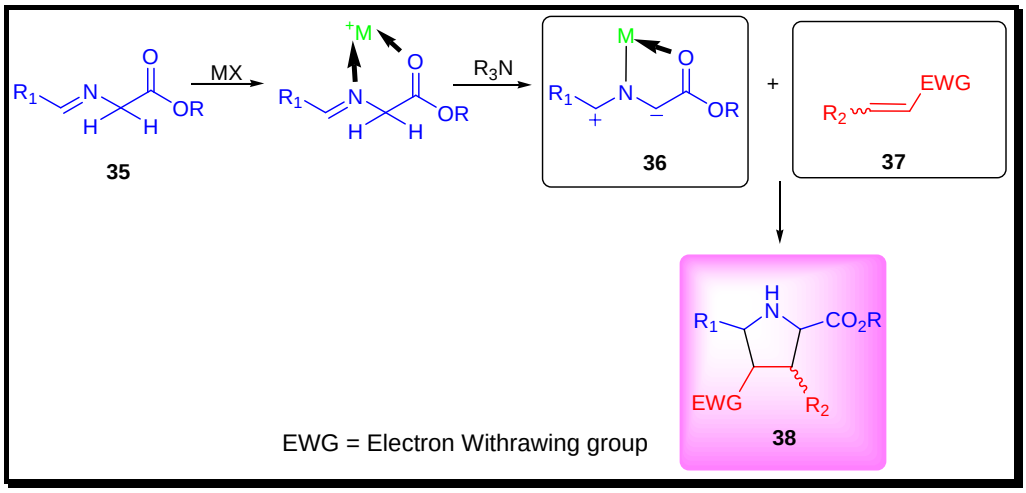


Figure 15 Formation of highly functionalized pyrrolidines using chiral catalyst.

Azomethine ylides **36** can be generated from imines by reaction with a base in the presence of a Lewis acid.[34a] Lewis acids form a complex as shown in Figure 16 with the imine. This complexation leads to a highly stereoselective cycloaddition reactions. On the other hand non-metalloazomethine ylides may undergo stereomutation processes. As a results less stereoselective cycloaddition reactions take place.[18]

1,3-DC reaction using Co(II),[35] Ni(II),[36] Zn(II),[34] Cu(II),[37] Cu(I),[37] Ag(I)[38] as the metal source have been reported.

First 1,3-DC reaction using a metal with a chiral ligand was reported by Grigg and co-workers.[35] They used stochiometric amount of $CoCl_2$ and $MnBr_2$ with chiral ligands **39a**, **39b**, and **39c**. Cycloadducts were obtained in high enantioselectivities with $CoCl_2$ (1 mol) and chiral ligand **39b** (2 mol) at room temperature (Figure 16). Using different imines with methyl acrylate (**41**), they obtained cycloadducts in 67-84% yields and in up to 96% ee's. They explained their results with the transition state complex **43** ($CoCl_2$ coordinates to chiral ligand **39b**) as shown in Figure 16. This complex shielded effectively one face of azomethine ylide to increase enanioselectivity.

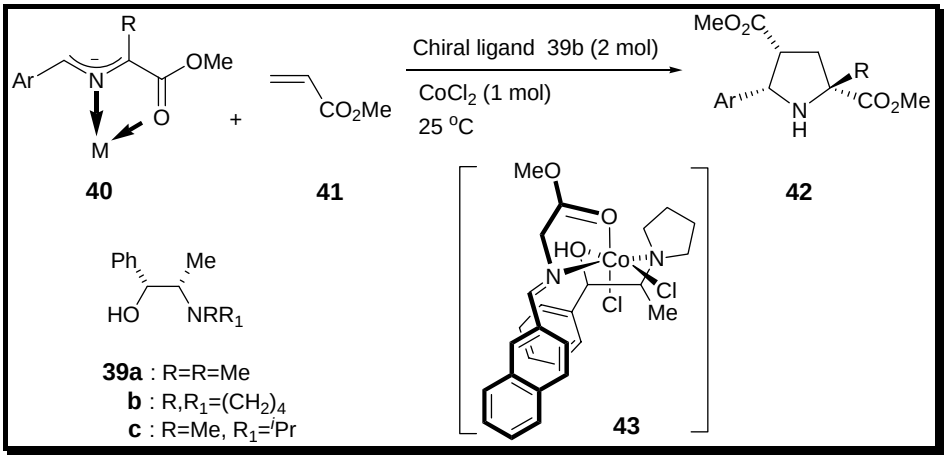


Figure 16 1,3-DC reaction carried out by Grigg and co-workers.

Same group[5] also synthesized phosphorous based chiral ligand **44** and used with AgOTf as a chiral catalyst for 1,3-DC reaction (Figure 17). Using this catalyst system pyrrolidine derivatives were obtained in 64-83% yields with 70% ee. The transition state complex **47** proposed for this reaction is shown in Figure 17.

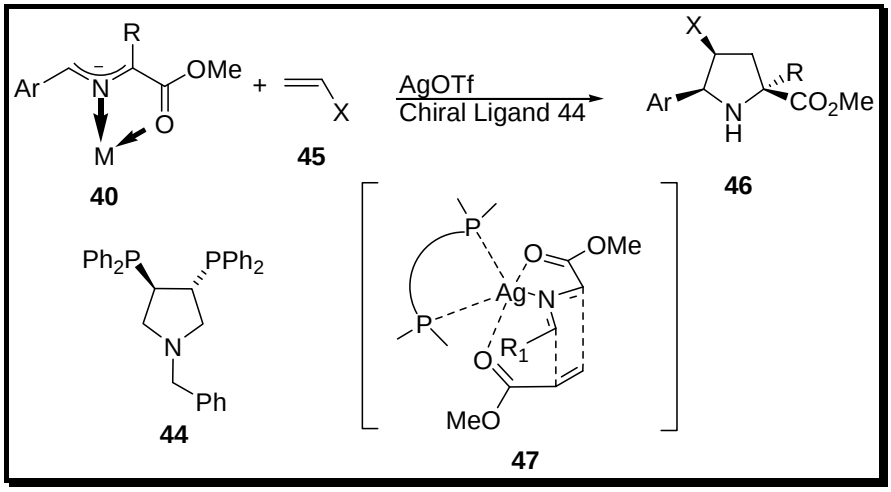


Figure 17 1,3-DC reaction using chiral ligand **44** with AgOTf.

Shi[36] and coworkers developed chiral binapththalenediimine (BINIM)-ligands **48, 49, 50, 51,** and **52** (Figure 18). They have screened these ligands with different metal salts CH_3CO_2Ag, $Cu(CH_3CN)_4ClO_4$, $Mg(ClO_4)$, $Zn(OTf)_2$ and $Ni(ClO_4)_2{\cdot}6H_2O$. From this study ligand **48** and $Ni(ClO_4)_2{\cdot}6H_2O$ was found to be the most effective.

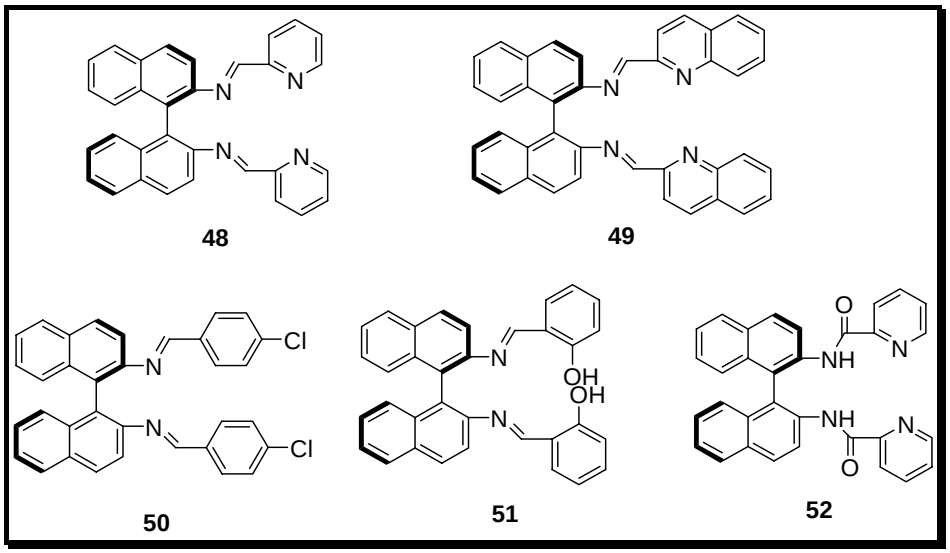


Figure 18 The chemical structures of chiral ligands **48-52**.

Different imines and several N-arylmaleimides were used to show the generality of this catalyst system for enantioselective 1,3-DC reaction. All reactions proceeded smoothly to give corresponding cycloadducts with *endo* selectivity (substituent on the dipolarophile and azomethine ylide nitrogen are on the same side) in 52-92% yields and 72-95% ee's. The possible transition state proposed for this catalyst system involves the *endo* approach of N-phenylmaleimide to hexacoordinated Ni(II) complex (**56**) as illustrated in Figure 19.

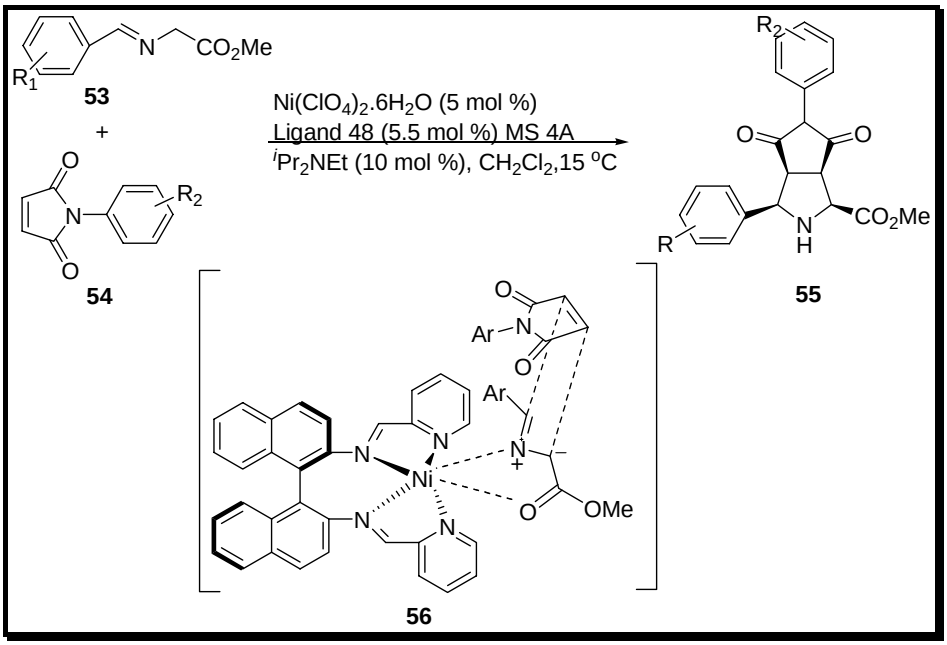


Figure 19 1,3-DC reaction using chiral catalyst **48**-$Ni(ClO_4)_2.6H_2O$.

Jorgensen[34a] and co-workers used chiral bisoxazoline ligands **57, 58,** and **59** with $Zn(OTf)_2$ and $Cu(OTf)_2$ as the metal sources for 1,3-DC reactions of azomethine ylides (Figure 20). The use of $Cu(OTf)_2$ with chiral bisoxazoline ligands **57, 58,** and **59** gave high conversion only with ligand

57 but the selectivity was very low. However, higher enantioselectivity and yield were obtained by using the chiral ligand **57** with $Zn(OTf)_2$.

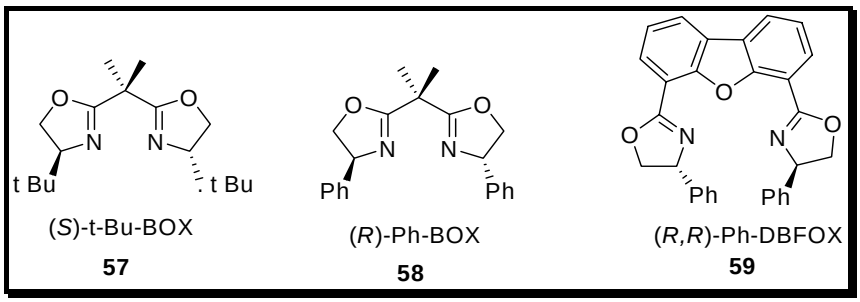


Figure 20 Chiral bisoxazoline ligands **57**, **58**, and **59**.

This catalyst system (chiral ligand **57**-$Zn(OTf)_2$ gave cycloadducts in 76-95% yields with 61-94% enantioselectivities. To explain the *diastereo*- and *enantio*-selectivity, they proposed the transition state complex **63** in which the cycloaddition took place by *endo* approach (Figure 21).

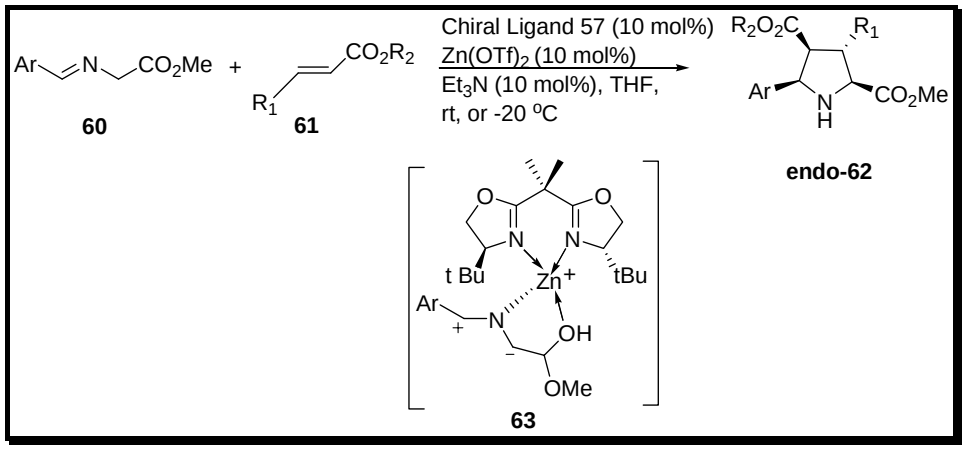


Figure 21 1,3-DC reactions using chiral catalyst (*S*)-^{t}Bu-BOX-Zn(II).

Dogan[34c] and coworkers used FAM (Ferrocenyl substituted Aziridinyl Methanol) chiral ligands **64, 65, 66,** and **67** for 1,3-DC reactions of

azomethine ylides (Figure 22). The catalytic performance of the chiral ligands **64, 65, 66,** and **67** were tested by using $Zn(OTf)_2$ as the metal source. When the chiral ligands **65, 66,** and **67** were used, the cycloadduct was obtained in reasonable yield but low enantioselectivity. Higher yield and enantioselectivity were obtained with chiral ligand **64**.

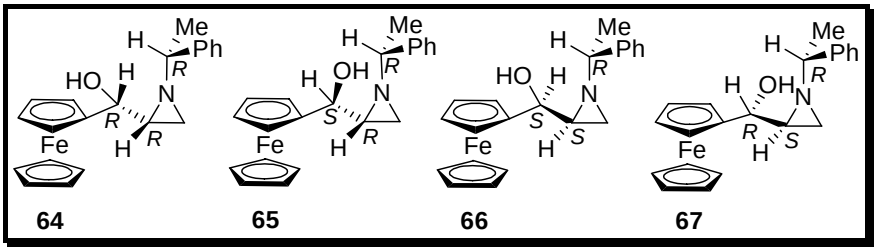


Figure 22 The chemical structures of chiral FAM ligands **64-67**.

Using this catalyst system, cycloadducts were obtained in 63-93% yield and 36-95% ee with *endo* selectivity. This diastereoselectivity was explained by pre-transition state **71** shown in Figure 23.

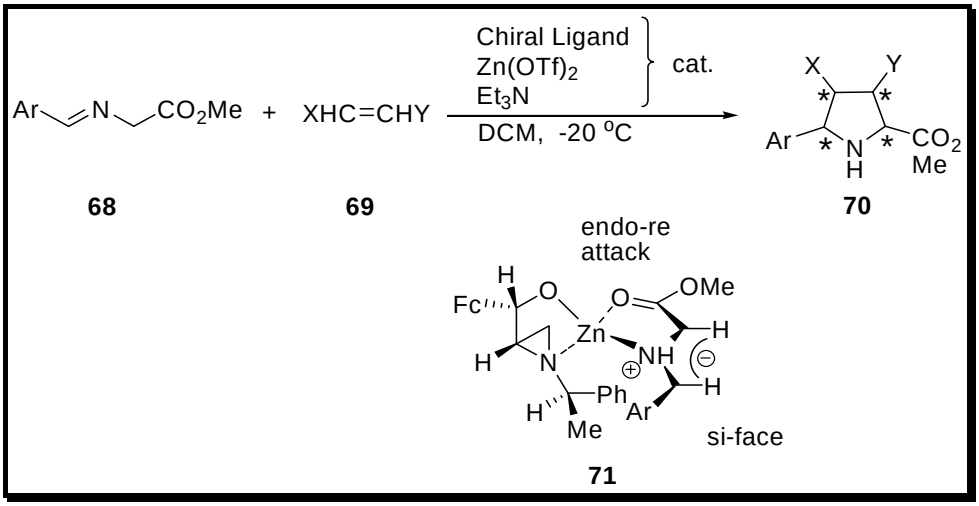


Figure 23 1,3-DC reactions using chiral catalyst **64**-$Zn(OTf)_2$.

Komatsu[37a] and co-workers used phosphorous based chiral ligands (*R*,*R*)-CHIRALPHOS (**72**), (*S*,*S*)-BDPP (**73**), (*R*,*R*)-DIOP (**74**), (*R*)-BINAP (**75a**), (*R*)-Tol-BINAP (**75b**), (*R*)-H8-BINAP (**76**), and (*R*)-SEGPHOS (**77**) for 1,3-DC raction of azomethine ylides (Figure 24).

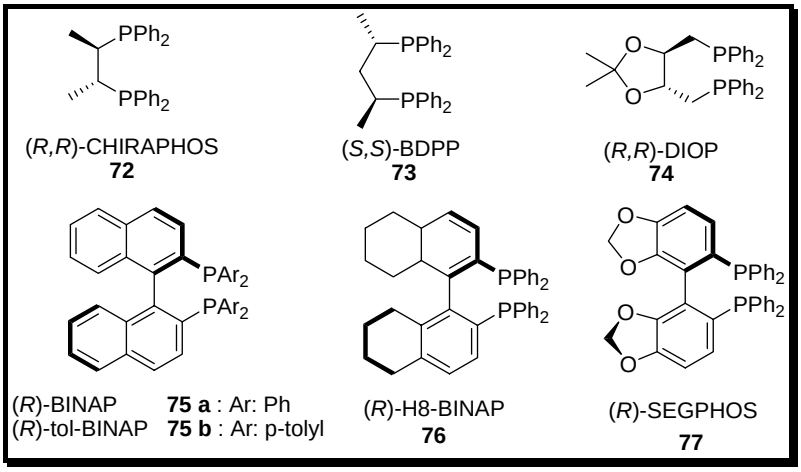


Figure 24 The chemical structures of chiral ligands **72-77**.

The catalytic performance of these chiral ligands **72**, **73**, **74**, **75**, **76**, and **77** were tested by using $Cu(OTf)_2$ as the metal source. The Cu(II) salt with (*R*)-BINAP **75a** gave the products in moderate yields (57-83%) with 55-82% ee's and highest *exo/endo* ratio. When (*R*)-SEGPHOS **77** was used with the same metal the products were obtained in 54-94% yields with 62-92% ee's.

Komatsu and co-workers explained the *exo* selectivity (substituent on the dipolarophile and azomethine ylide nitrogen are on the opposite sides) of the reaction by offering the transition model **81** (Figure 25). The metal/ligand coordinated azomethine ylide reacted with the dipolarophile

(N-Phenylmaleimide) in *exo* mode rather than *endo* one due to a steric repulsion in *endo* transition state.

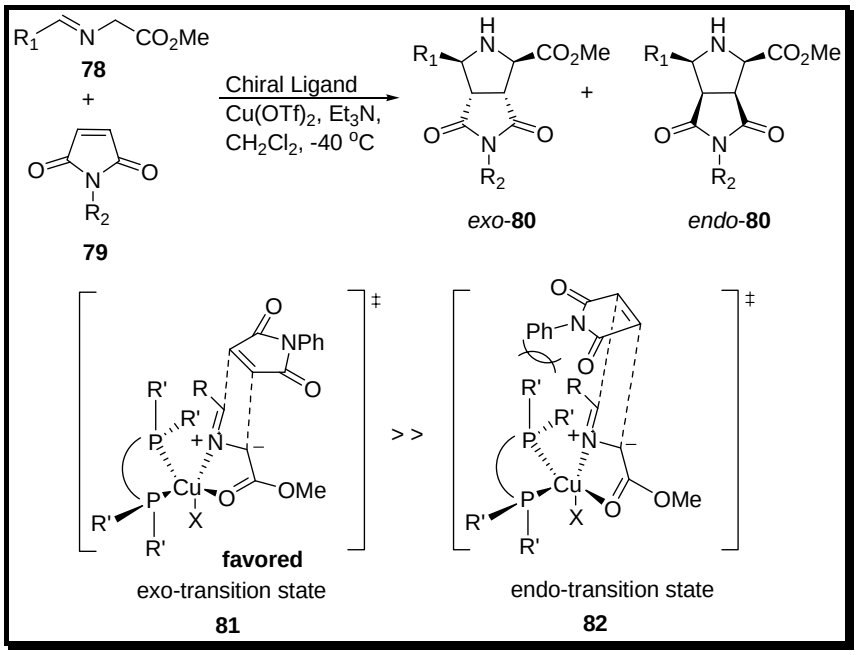


Figure 25 1,3-DC reaction using **75a**- and **77**-$CuClO_4$.

Zhang[37b] and co-workers examined chiral ligands **83, 84,** and **85a-f** (Figure 26) with CuOAc salt for the enantioselective 1,3-DC azomethine ylides with acrylates at 0 °C. Among these chiral ligands, **85d-**Cu combination gave the cycloadducts in high ee's with moderate yields.

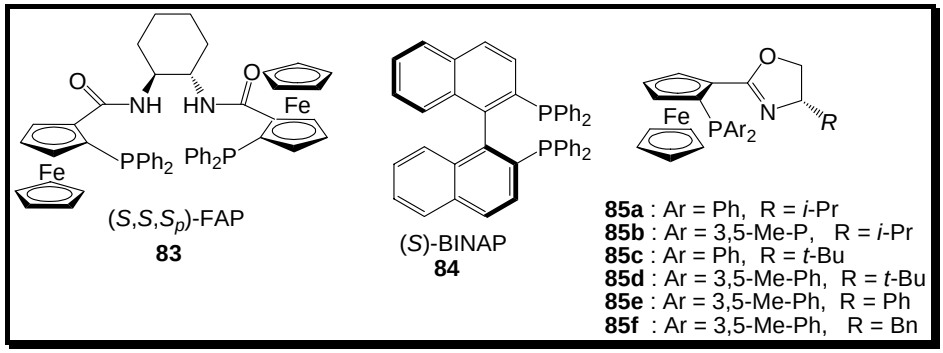


Figure 26 Chiral phosphinooxazoline ligands **83**, **84**, **85a-f**.

When **85d**-$CuClO_4$ catalyst system was used at -25 ^oC the *exo* cycloadducts were obtained in 61-87% yields with excellent enantioselectivities 89-98% (Figure 27).

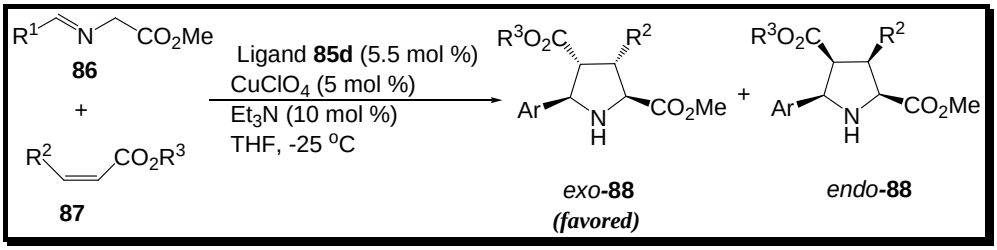


Figure 27 1,3-DC reaction using chiral catalyst **85d**-$CuClO_4$.

Hou[37c] et al. used chiral catalysts obtained from P-, N-ferrocene ligands **89a-e, 90, 91a**,**b** and $CuClO_4$ for 1,3-DC reactions of azomethine ylides with nitroalkenes (Figure 28).

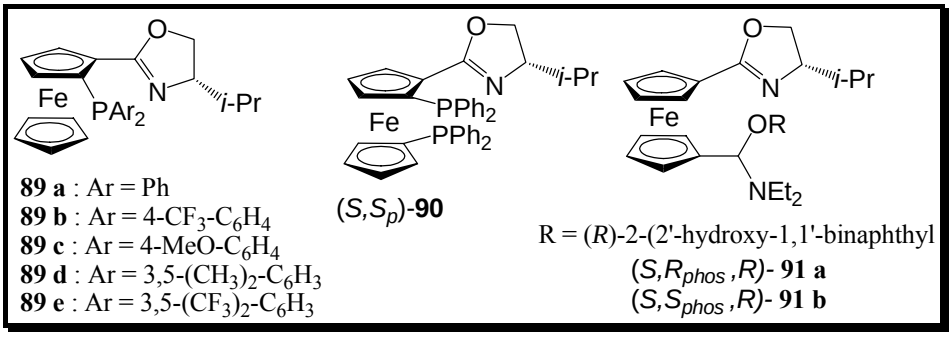


Figure 28 The chemical structures of chiral ligands **89-91**

When ligand **89a**-$CClO_4$ was used as the catalyst with different imino esters **92** and nitroalkanes **93** for 1,3-DC reactions (Figure 29), *exo* diastereomers were obtained in 70-97% yields with the 92-98% ee. The ratio of *exo*/*endo* ranged from 88:12 to 92:8. In the case of catalyst **89a**-$CuClO_4$, however, *endo* diastereomers were obtained in 71-98% yields and 84-97% ee's. The ratio of *endo* to *exo* ranged from 70:30 to 94:6.

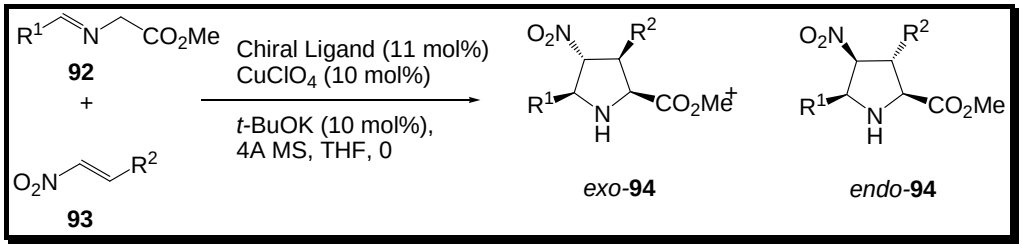


Figure 29 1,3-DC reaction using **89a**- and **89e**-$CuClO_4$

In another study, Shi[37d] and coworkers used thiophosphoramide ligands **95a-d, 96** and diphenylselenophoramide ligand (**97**) as chiral catalysts with different metal salts, $Cu(CH_3CN)_4ClO_4$, AgOAc, AgOTf, $Cu(OTf)_2$ and $Zn(OTf)_2$ for 1,3-DC reactions of azomethine ylides (Figure 30).

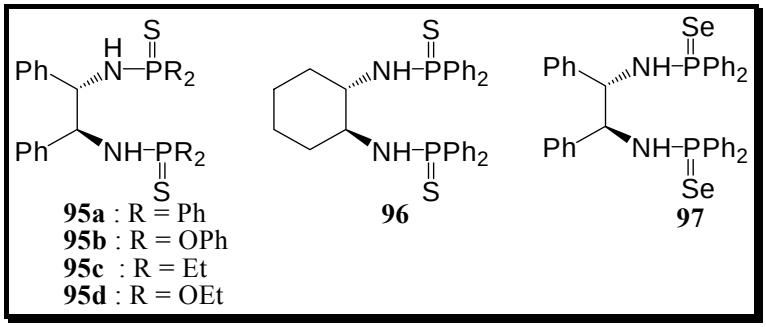


Figure 30 The chemical structures of chial ligands **95-97**

The chiral ligand **95a** was found to be the most effective one when used with $Cu(CH_3CN)_4ClO_4$ as a catalyst for 1,3-DC reaction of azomethine ylides. With this catalyst system *endo* cycloadducts were obtained in 60-89% yields with moderate enantioselectivities 26-79%. Enantioselectivity of the reaction was explained by the transition state model shown in Figure 31.

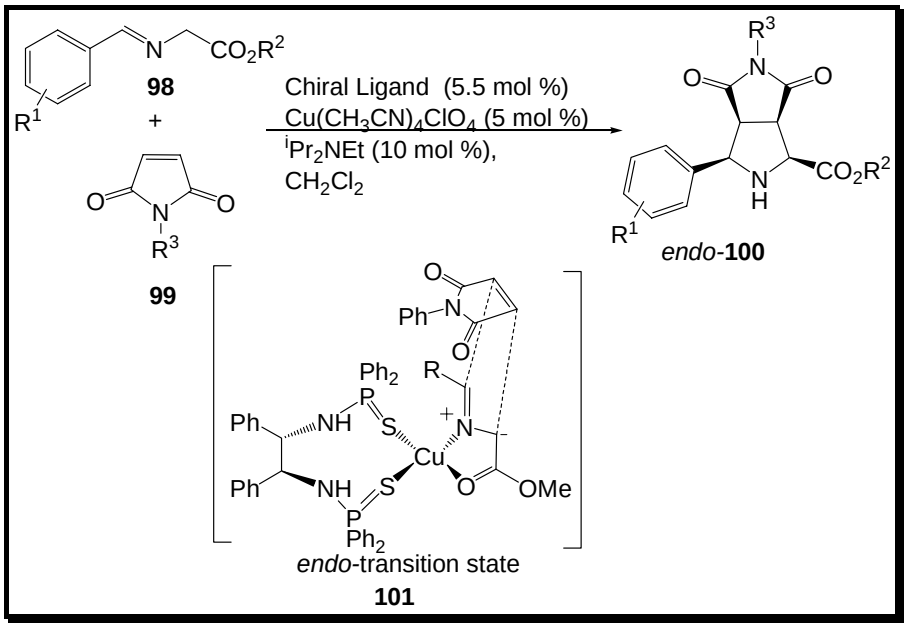


Figure 31 1,3-DC reaction using chiral catalyst **95a**-$Cu(CH_3CN)_4ClO_4$.

In a different study by Carretero[37e,f] and coworkers chiral Fesulphos ligands **102a-e** were used with Cu(I) and Ag(I) as catalysts for 1,3-DC reaction of azomtehine ylides (Figure 32).

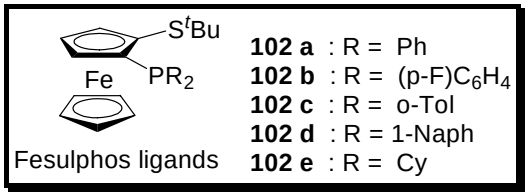
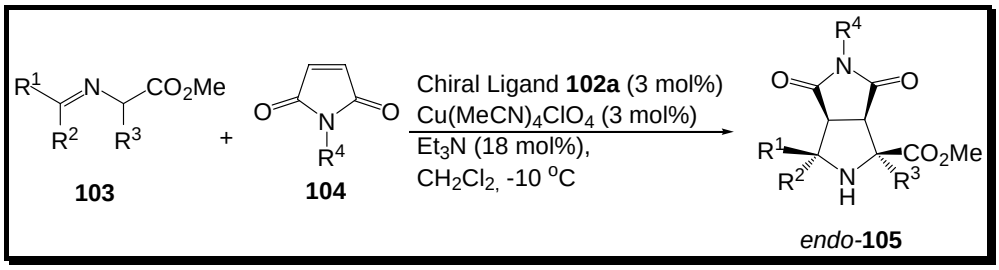


Figure 32 The chemical structures of chiral ligand (R)-Fesulphos **102 a-e**

Fesulphos ligand **102a** showed the best performance as a catalyst with copper(I) in 1,3-DC reaction of azomtehine ylides (Figure 33). Different dipolarophiles and imines were screened to synthesize pyrrolidines in 63-97% yield with 76-99% ee's. These experiments showed that the reactions were highly dipolarophile dependent, it was necessary to optimize the reaction conditions with respect to dipolarophile (symmetric or antisymmetric).



103 **104** *endo*-**105**

Figure 33 1,3-DC reaction using chiral catalyst **102a**-Cu$(CH_3CN)_4ClO_4$.

In the study of Zhang[38a] and co-workers, chiral phosphine ligands **106-111** were used with Ag as a catalyst for asymmetric 1,3-DC reaction of azomethine ylides (Figure 34).

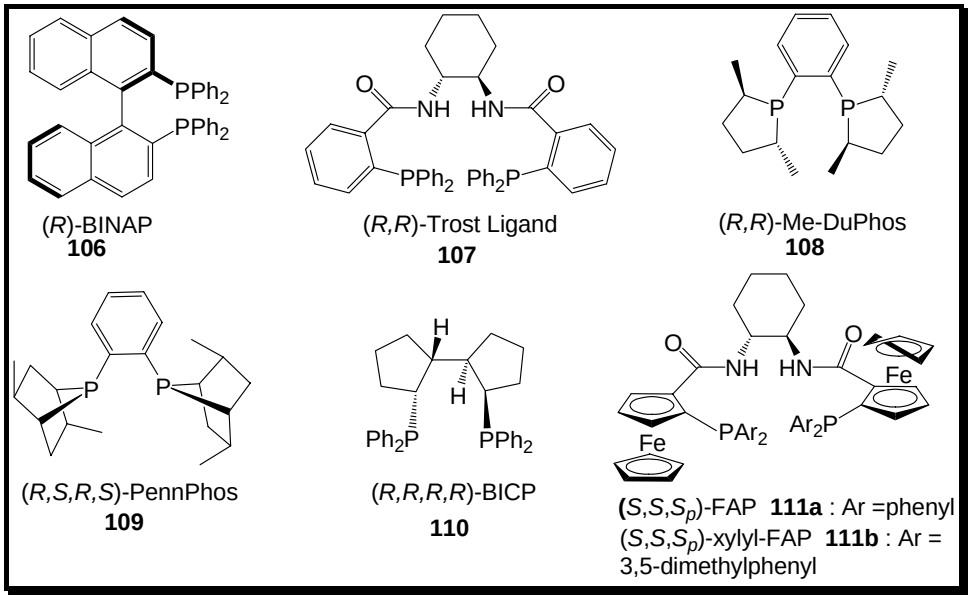


Figure 34 Chiral phosphine ligands **106-111**

Using **111b-**AgOAc catalyst system only *endo* cycloadducts were obtained in 73-98% and 52-97% ee's Figure 35.

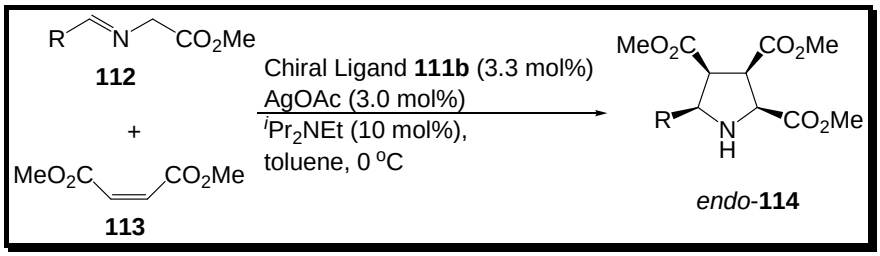


Figure 35 1,3-DC reaction using chiral catalyst **111b**-AgOAc.

Schreiber[38b] and co-workers used commercially available chiral phosphine ligands **107**, and **115-119** with AgOAc for 1,3-DC reaction of azomethine ylides (Figure 36).

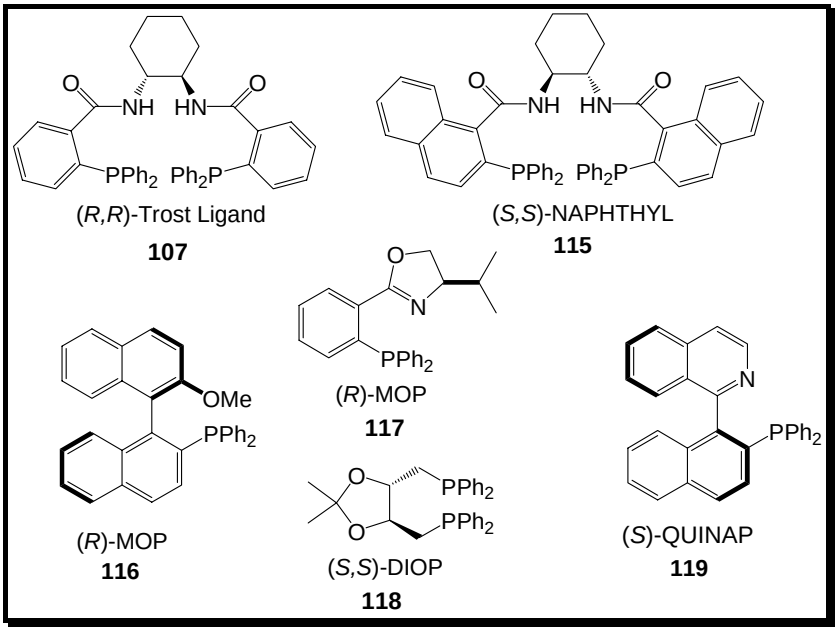


Figure 36 The chemical structures of chiral phosphine **107**, and **115-119**.

The P,N-ligand (*S*)-QUINAP **119** worked the best as a catalyst with Ag(I) to form pyrolidines in 47-95% yield with 60-96% ee's. By this catalyst system *endo* product formation was dominant. To explain this selectivity they proposed a transition sate complex **123** as shown Figure 37.

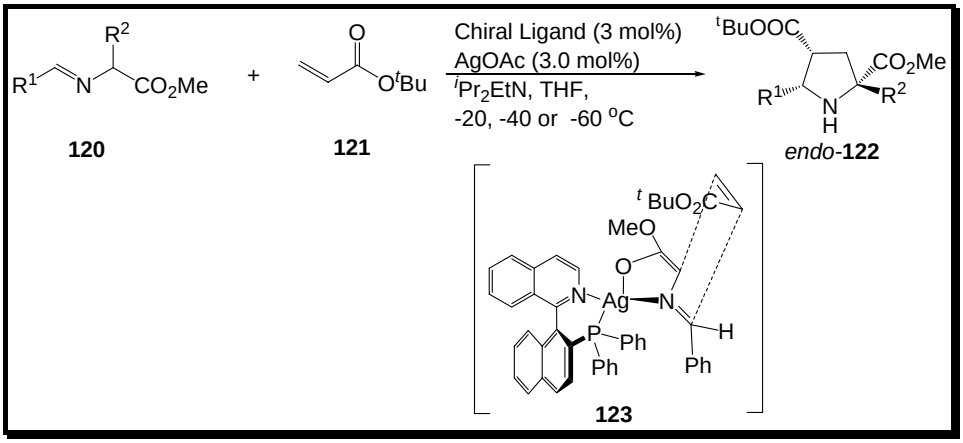


Figure 37 1,3-DC reaction using chiral catalyst **119**-AgOAc.

Carreira[38c] and co-worker developed a new P,N-ligands (PINAP) **124** and **125** (Figure 38) that are structurally similar to commercially available QUINAP **119** (Figure 36). They used these ligands with Ag(I) for 1,3-DC reaction of azomethine ylides.

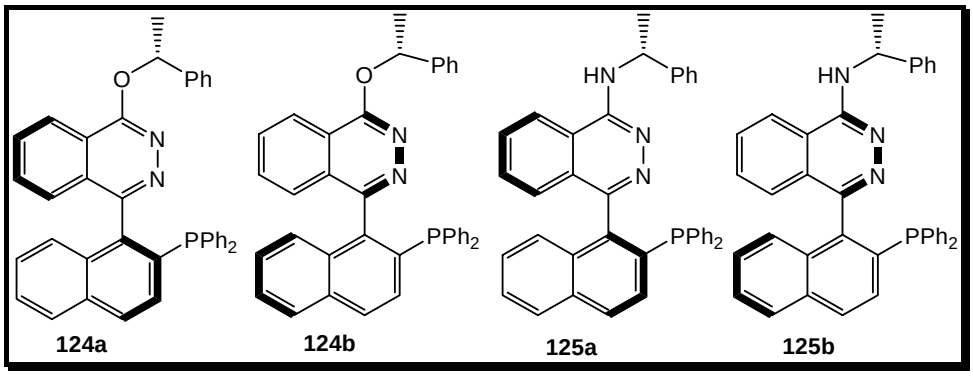
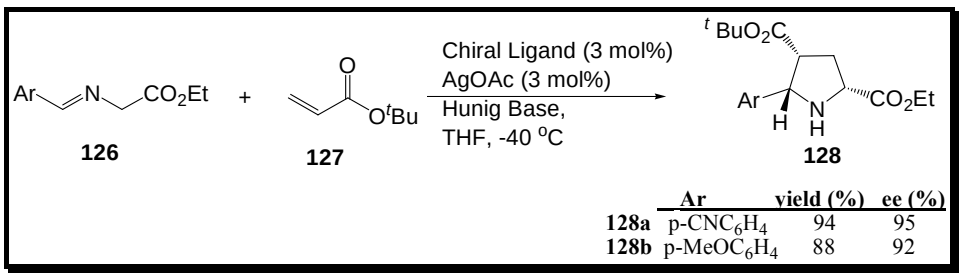


Figure 38 The chemical structures of chiral P,N ligands **124** and **125**.

Chiral PINAP ligand **124a** gave cycloadducts in 88-94% yields with 92-95% ee's Figure 39.



	Ar	yield (%)	ee (%)
128a	p-CNC_6H_4	94	95
128b	p-$MeOC_6H_4$	88	92

Figure 39 1,3-DC reaction using chiral catalyst **119-**AgOAc.

In 2005, Jorgensen[38d] and co-workers screened Cinchona alkoloids **129-133** (Figure 40) as chiral bases for 1,3-DC reaction with different Lewis acids LiBr, $ZnCl_2$, $AgNO_3$, AgF, and AgCl.

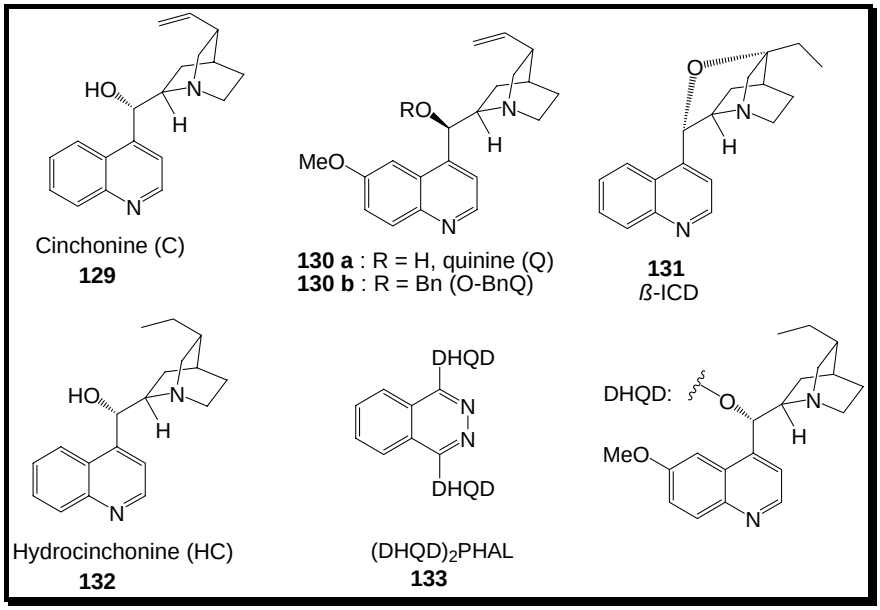


Figure 40 The chemical structures of chiral ligands **129-133**

In this study they didn't use another source of a base because cinchona alkaloid acts as the chiral base. **HC-132** showed better catalytic activity with AgF for 1,3-DC reaction of azomethine ylides. With this catalyst, *endo* pyrrolidine derivatives were obtained in 80-97% yields with 61-70% ee's (Figure 41). It was not necessary to take specific precautions such as inert atmosphere and dry solvents etc.

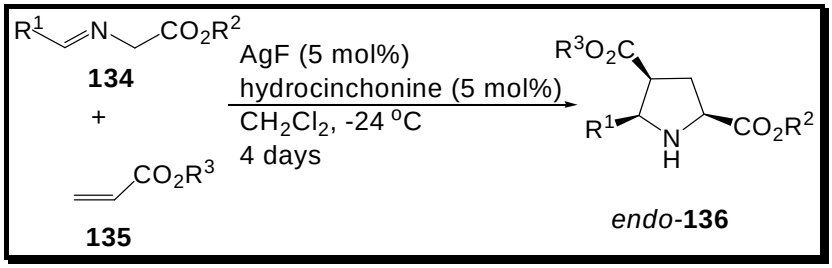


Figure 41 1,3-DC reaction using chiral catalyst **132**-AgF.

Sansano[38e] and coworkers used (*R*)-BINAP **106**, and (*S*)-BINAP **137** with different silver salts AgOAc, AgOTf, AgF, $AgClO_4$ and $AgClO_4 \cdot H_2O$ for 1,3-DC reaction of azomethine ylides and maleimides (Figure 42). The highest diastereo- and enantioselectivities were observed by using (*S*)-BINAP 1**37** with AgOAc and $AgClO_4$, but they used last one because the catalytic complex (*S*)-BINAP-$AgClO_4$ ***S*-141** could be separated almost quantitavely.

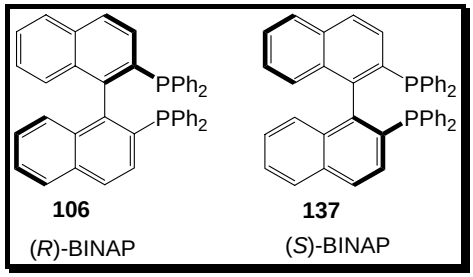


Figure 42 The chemical structures of chiral BINAP ligands **106** and **137**

This catalyst gave cycloadducts in 64-99% yields and 82-90% ee's with *endo* selectivity (Figure 43). The transition state complex ***S*-141** was proposed for the selectivity of the reaction.

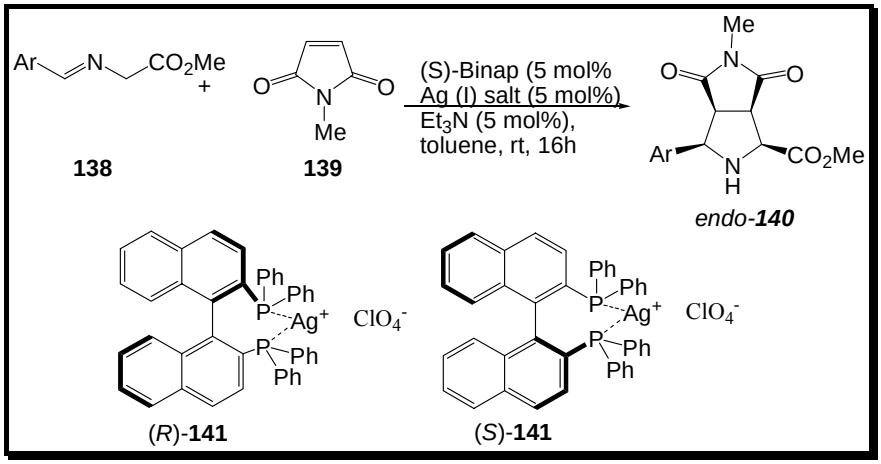


Figure 43 1,3-DC reaction using chiral catalyst **137**-$AgClO_4$.

Another catalyst system was developed by Zhou[38f] and co-workers. They used N,P-ligand **145** with AgOAc as a catalyst for 1,3-DC reaction of azomethine ylide (Figure 44). Cycloadducts were obtained in 85-99% yields with 88-98% ee's. With this catalyst system, it was not necessary to use a different base to remove α-proton of imine because AgOAc was playing a bifunctional role for this reaction.

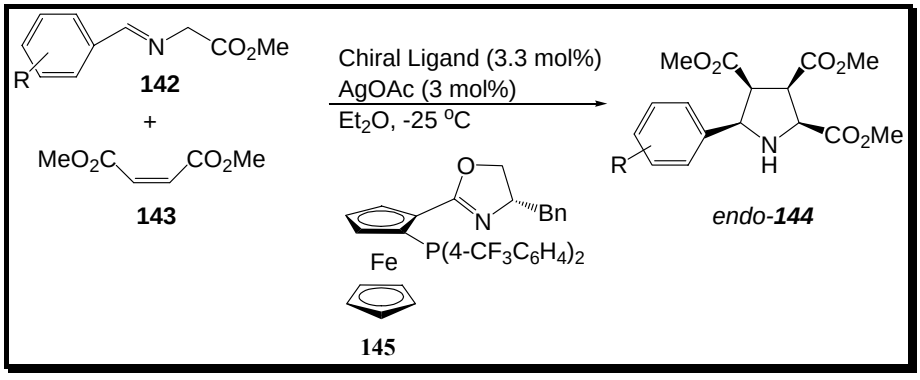


Figure 44 1,3-DC reaction using chiral catalyst **145**-AgOAc.

Same group also synthesized chiral ligands **149a** and **149b** Figure 45.[38g]

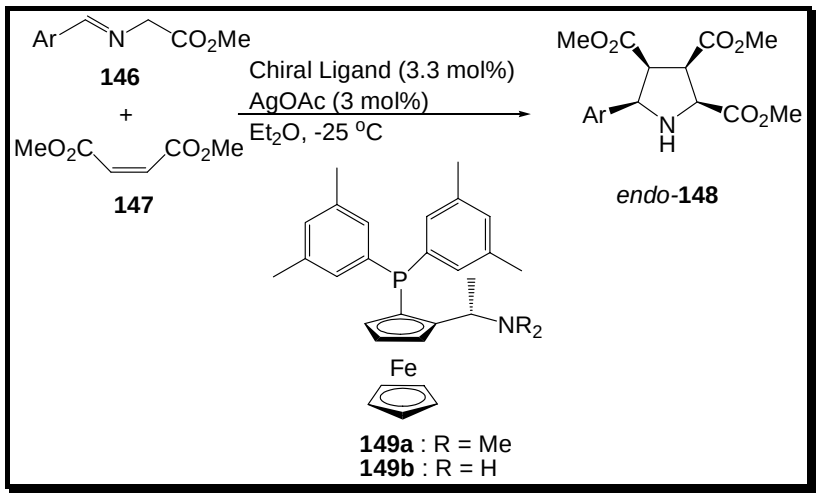


Figure 45 1,3-DC reaction using **149a**- and **149b**-AgOAc.

Both of the catalyst obtained from these ligands showed *endo* approach of dipolarophile but from opposite sides of the azomethine ylides (opposite facial selectivity) as shown in Figure 46. In the case of complex **150b**, hydrogen bonding was taking place between both carbonyl oxygens and NH_2 group of the ligand. As a result the dipolarophile approached from upper face during cycloaddition. But in the case of complex **150a** hydrogen bonding was not possible and the upper face of the azomethine ylide was blocked by methyl groups of the ligand. Therefore diporophile approached from the lower face of azomethine ylide during cycloaddition. With this catalyst system cycloadducts were obtained in 90-98% yield and with 36-97% ee's.

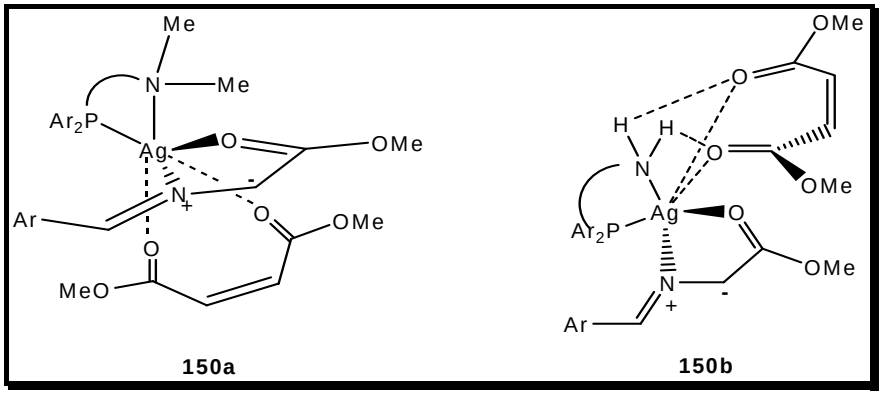
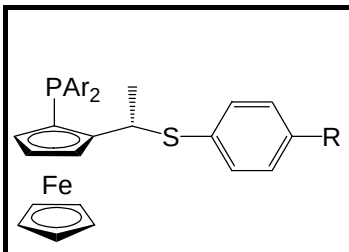


Figure 46 Two different transition states **150a** and **150b**.

Zhou and Zeng[38h] also synthesized P,S-chiral ligands **151a-k** (Figure 47) and used them with AgOAc for asymmetric 1,3-DC reaction of azomethine ylides.



(*S*,*Rp*) **151a** : Ar = Ph, R = H
(*S*,*Rp*) **151b** : Ar = Ph, R = Cl
(*S*,*Rp*) **151c** : Ar = Ph, R = OMe
(*S*,*Rp*) **151d** : Ar = Ph, R = Me
(*S*,*Rp*) **151e** : Ar = 4-$MeOC_6H_4$, R = OMe
(*S*,*Rp*) **151f** : Ar = 3,5-$Me_2C_6H_3$, R = OMe
(*S*,*Rp*) **151g** : Ar = 3,5-$(CF_3)_2C_6H_3$, R = OMe
(*S*,*Rp*) **151h** : Ar = 4-$CF_3C_6H_4$, R = OMe
(*S*,*Rp*) **151i** : Ar = 4-$CF_3C_6H_4$, R = Cl
(*S*,*Rp*) **151k** : Ar = 4-$CF_3C_6H_4$, R = CF_3

Figure 47 The chemical structures of chiral P,S ligands **151a-k**.

Ligand screening and optimization studies showed that catalyst system **151g**-AgOAc was the best for 1,3-DC reaction of azomethine ylides with N-phenylmaleimide Figure 48a. Only *endo* cycloadducts were obtained in 95-98% yields with 86-93% ee's. In the case of dimethyl maleate, catalyst system **151i**-AgOAc found to be the best by giving the products in 86-96%

yields with 84-89% ee's. Again only *endo* cycloadducts were obtained Figure 48b.

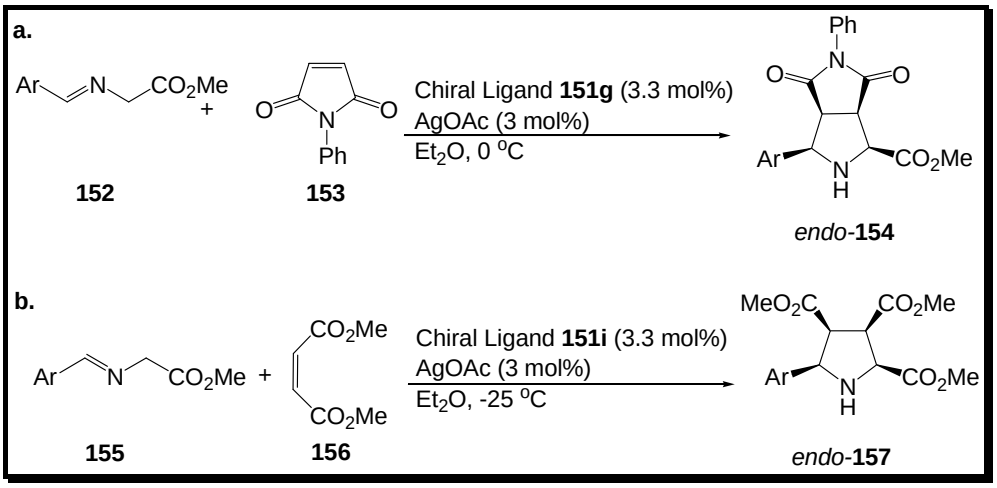


Figure 48 1,3-DC reaction using **151g**- and **151i**-AgOAc.

1.2 Aim of the work

Our group previously synthesized ferrocenyl substituted aziridinyl methanols (FAM) and used them as chiral catalysts for different types of asymmetric reactions. The use of these ligands with $Zn(OTf)_2$ in asymmetric 1,3-DC reactions of azomethine ylides gave pyrrolidines with ee's up to 95%.[34c] Asymmetric diethylzinc addition to enones gave β-ethylated ketones in up to 82%.[39] Asymmetric diethylzinc addition to aldehydes gave secondary alcohols with ee's up to 96%.[40] Asymmetric alkynylzinc addition to aldehydes gave propargylic alcohols in up to 96% ee.[41] Finally the use of FAM ligands as a catalyst with zinc in nitroaldol (Henry) reaction gave the desired products in up to 92% ee.[42] In this study we aimed to synthesize phosphorous derivatives of FAM ligands (P-FAM). It is known in literature that ligands having phosphorous group work much better as a catalyst with cupper and silver metals for 1,3-DC reactions of

azomethine ylides. Also, compared to amino alcohol ligands, phosphorous based ligands are used in smaller quantities. For these reasons we planned to synthesize P-FAM ligands and use them as a catalyst with cupper and silver metals for the enantioselective synthesis of pyrrolidine derivatives by employing 1,3-DC reactions of azomethine ylides. Pyrrolidine derivatives are found in the structure of many natural products and pharmaceuticals. Therefore the asymmetric synthesis of these compounds attracts the attention of many groups worldwide. Different chiral catalysts have been used for the synthesis of these compounds by 1,3-DC reactions of azomethine ylides with dipolarophiles. In general, the catalysts are either dipolarophile dependent, or require complicated synthesis and difficult purifications, or have to be used in higher amounts to reach good yields and enantioselectivites. Therefore it is necessary to develop a more efficient catalyst system which is more selective, dipolarophile independent and doesn't require a complicated synthesis.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 The Synthesis of Chiral P-FAM Ligands

We started our studies with the synthesis of P-FAM ligands. For the synthesis of these ligands we followed the steps used for the syntheis of FAM ligands. First step of the synthesis is the reaction of ferrocene with acryloyl chloride. Our group developed a good method for this reaction which gives acryloyl ferrocene in 85-90% yield.[43] The next step in the synthesis of the chiral P-FAM ligands is bromination of acryloyl ferrocene. Our group also developed a nice protocol for this reaction which gives dibromo compound **159** in about 95% yield. Previous literature studies for the direct bromination of acryloyl ferrocene all failed because ferrocene ring also gets brominated and the reaction gives a complicated mixture of products. In the following step, dibromo compound was treated first with Et_3N followed by addition of (*R*)-2-amino-1-butanol. This reaction is also known as Gabriel-Cromwell reaction.[44] The ketones **160** and **161** obtained from this reaction were easily separated from each other and purified by flash column chromatography in 53% and 42% yields respectively Figure 49.

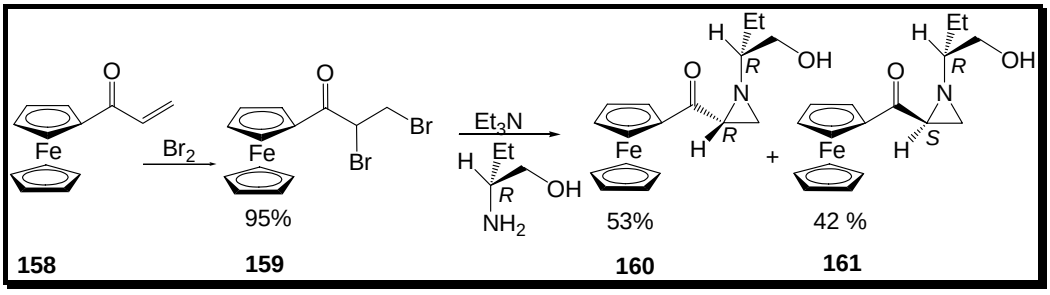


Figure 49 Synthesis of chiral aziridines **160** and **161**

In the third step, the compound **160** was tosylated with tosyl chloride by overnight stirring at room temperature to yield product **162** in 96% yield Figure 50. In the next step, the compound **162** was treated with potassium diphenyl phosphide at -78 ^{o}C by using the procedure published by Williams and co-workers.[45] This reaction gave **163** and its oxidized form **164** in 68% and 25% yields, respectively (Figure 50). To complete the synthesis of the chiral ligand, carbonyl group of ketone **163** was reduced by using $NaBH_4$+$ZnCl_2$ to give alcohol **165** in 60% yield and its oxidized form **166** in 35% yield as the only stereoisomer. Reduction of the same ketone by L-selectride at -78 ^{o}C gave alcohol **167** in 40% yield and its oxidized form **168** in 55% yield with opposite stereochemistry at alcohol center. This alcohol was also obtained as the only stereoisomer (Figure 50). The procedure used for the reduction of ketones was developed by Korean group.[46] Both of the ligands were isolated as yellow colored oil.

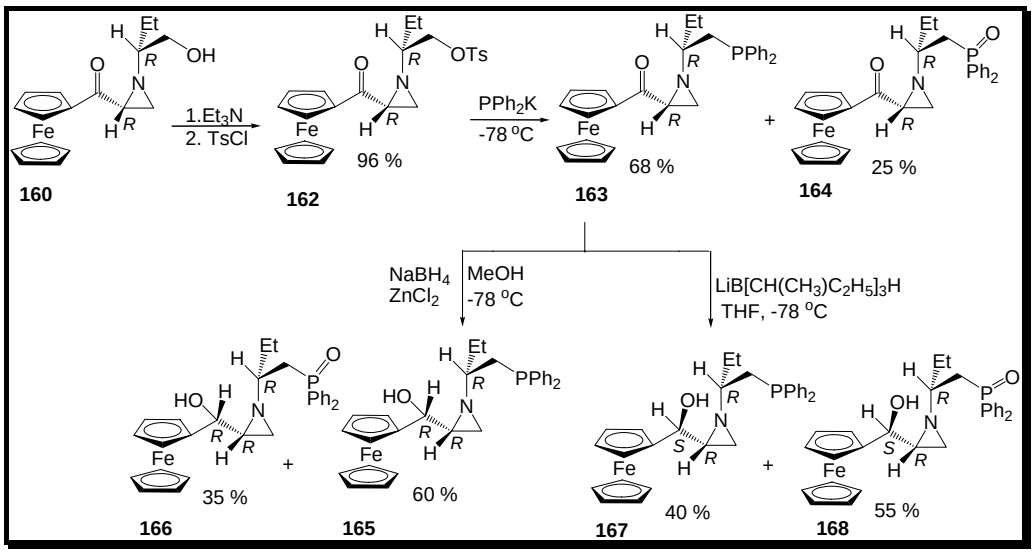


Figure 50 Synthesis of chiral ligand **165, 166, 167** and **168**.

In order to convert ketone **161** to the ligand, we followed the same synthetic pathway. Tosylation of compound **161** gave compound **169** in 96% yield Figure 51. Phosphorylation step yielded phospho ketone **170** and its oxidized form **171** in 75% and 20% yields respectively Figure 51. Stereocontrolled reduction of the compound **170** with $NaBH_4$+$ZnCl_2$ didn't take place even with excess amount of $NaBH_4$, starting material was recovered. Therefore, the reduction step was carried out by using more powerful reducing agent $LiAlH_4$. From this reduction alcohol **172** and its oxidized form **173** were obtained in 49% and 42% yields respectively Figure 51. They were both yellow in color and oily. When L-Selectride was used as the reducing agent, chiral ligand **174** and its oxidized form **175** were isolated in 51% and 45% yields respectively Figure 51. Chiral ligand **174** was yellow oil and its oxidized form **175** was yellow solid (mp 39-40 ^{o}C).

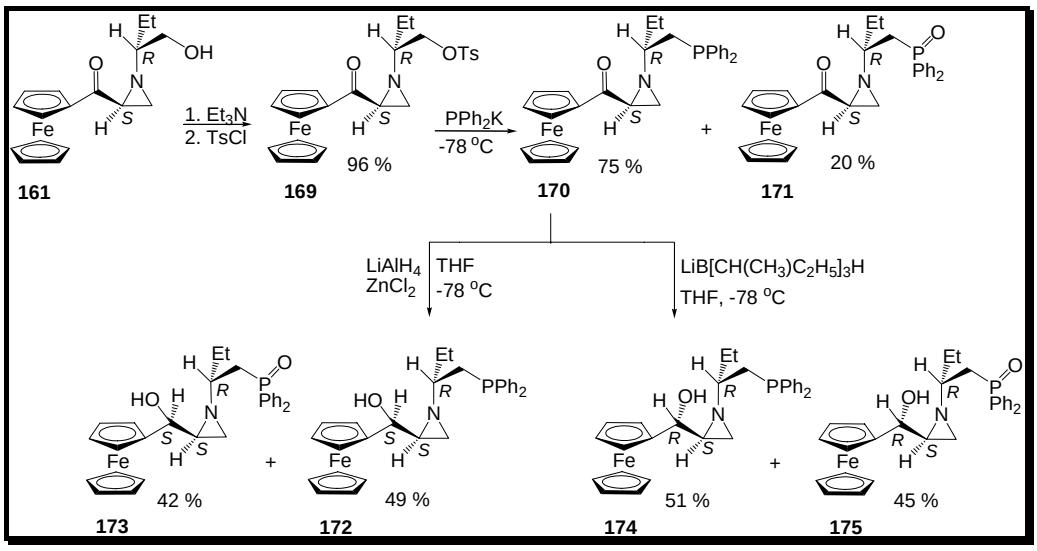


Figure 51 Synthesis of chiral ligand **172, 173, 174** and **175**.

The configurations of the P-FAM ligands were assigned by analogy with the configuration of FAM ligands which were determined by X-ray analysis.

2.2 The Asymmetric 1,3-Dipolar Cycloaddition Reaction by Using Chiral P-FAM Ligands

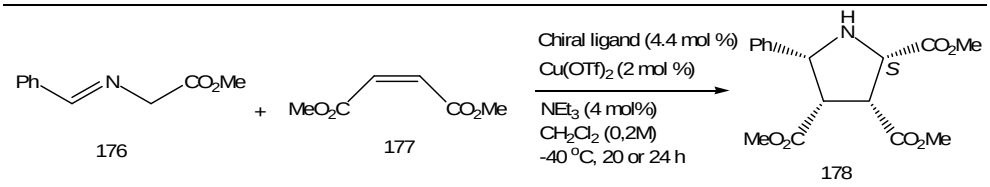
2.2.1 Ligand Screening and Optimization of 1,3-Dipolar Cycloaddition Reaction

After the synthesis of P-FAM chiral ligands and their oxidized forms (total of twelve new potential chiral ligands), they were tried for 1,3-DC reaction as a catalyst with copper and silver metals.

Firstly, the efficiency of the ligands with Cu(II) in 1,3-DC reaction was tested by adapting the literature procedure reported by Komatsu and coworkers.[37a] 1,3-DC reactions of azomethine ylides (1 eq.) with dimethyl maleate (1.1 eq.) in the presence of 4.4 mol % of chiral ligand **171**, 2 mol % $Cu(OTf)_2$ and 4 mol % Et_3N gave the cycloadduct **178** in 98% yield

with very low ee (Table 1, entry 8) at -40 ^{o}C. Under the same conditions, the other ligands **163-168**, **170,** and **172-175** also gave the cycloadduct **178** in low yield and very low enantioselectivity (Table 1).

Table 1 1,3-DC reactions of azomethine ylides with $Cu(OTf)_2$



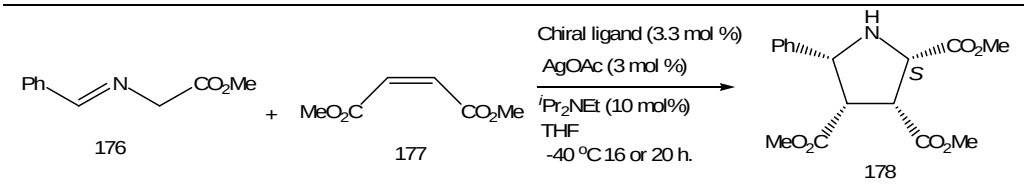
Entry	chiral ligand	Aldimine	dipolarophile	yield[a] (%)	ee[b] (%)
1	**163**	176	177	-	-
2	**164**	”	”	20	5
3	**165**	”	”	25	6
4	**166**	”	”	-	-
5	**167**	”	”	75	0
6	**168**	”	”	15	10
7	**170**	”	”	5	0
8	**171**	”	”	98	5
9	**172**	”	”	5	3
10	**173**	”	”	35	7
11	**174**	”	”	-	-
12	**175**	”	”	-	-

[a] Isolated Yield. [b] Determined by HPLC using a Chiralpak AS column.

Next, the efficiency of the ligands in 1,3-DC reaction was tested with a different metal salt (AgOAc) by using the literature procedure.[38c] 1,3-DC reactions of azomethine ylides (1 eq.) with dimethyl maleate (1.15 eq.) was performed in the presence of 3.3 mol % of chiral ligand**,** 3 mol % AgOAc

and 10 mol % $^{i}Pr_2NEt$ in THF at -40 ^{o}C (Table 2). Under these reaction conditions, all the ligands gave the expected cycloadduct in high yield (except chiral ligands **163** and **165)** but very low ee (Table 2).

Table 2 1,3-DC reactions of azomethine ylides with AgOAc in THF



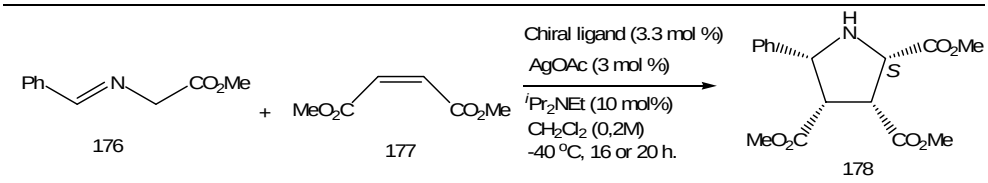
Entry	Chiral ligand	Aldimine	dipolarophile	yield[a] (%)	ee[b] (%)
1	**163**	176	177	37	5
2	**164**	”	”	90	1
3	**165**	”	”	10	4
4	**166**	”	”	80	5
5	**170**	”	”	94	4
6	**171**	”	”	62	1
7	**172**	”	”	80	4
8	**173**	”	”	67	22
9	**175**	”	”	98	21

[a] Isolated Yield. [b] Determined by HPLC using a Chiralpak AS column.

After the unsatisfactory results we decided to change the solvent to DCM (dichloromethane) because reaction medium became cloudy, as the reaction proceeded in THF. This was due to lower solubility of the product in THF. Due to the inhomogenity of the reaction medium, the results were unreliable. In DCM, the reaction medium was homogenous throughout the reaction and the results were more promising. Therefore we screened all

the chiral P-FAM ligands by using DCM as the solvent. The results of these studies are summarized in Table 3.

Table 3 1,3-DC reactions of azomethine ylides with AgOAc in DCM



Entry	chiral ligand	Aldimine	dipolarophile	yield[a] (%)	ee[b] (%)
1	**165**	176	177	-	-
2	**166**	”	”	-	-
3	**167**	”	”	19	0
4	**168**	”	”	80	7
5	**170**	”	”	90	3
6	**171**	”	”	75	10
7	**172**	”	”	5	46
8	**173**	”	”	25	46
9	**174**	”	”	-	-
10	**175**	”	”	30	65
11 [c]	**175**	”		93	61

[a]Isolated Yield. [b]Determined by HPLC using a Chiralpak AS column. [c]Reaction was conducted at -20 °C.

In DCM reaction was slower compared to THF but enantioselectivity was higher. Ligand screening studies under optimized conditions showed that cycloadduct **178** could be obtained in higher yield with the chiral ligands **168**, **170**, **171**, and **175** (Table 3, entries 4, 5, 6, and 11). But only chiral ligand **175** gave the product in acceptable ee. To reach higher yield with this ligand, it was necessary to increase the reaction temperature to -20 °C (entries 10 and 11).

After determining the metal salt, chiral ligand, solvent, and the temperature we investigated the amount of all the reagents necessary for the highest yield and ee of the product. The parameters we changed did not show significant effect on the yield and ee of the product (Table 4, entries 1-6). Therefore we decided to stay with the conditions used for entry 1.

Table 4 Optimization of the amounts of the reagents[a]

Entry	Ligand **175** (mol %)	AgOAc (mol %)	dipolarophile **177** (equiv)	$^{i}Pr_2NEt$ (mol %)	yield[b] (%)	ee[c] (%)
1	3.3	3	1.15	10	93	61
2[d]	3.3	3	1.15	10	75	59
3	3.3	3	1.15	***5***	80	58
4	3.3	3	***1***	10	87	54
5	3.3	***1.5***	1.15	10	80	55
6	***6.6***	3	1.15	10	99	59
7	3.3	1.5	1.15	-	72	50
8	3.3	3	1.15	-	76	50
9	6.6	3	1.15	-	52	60

[a]Imine (1 equiv), -20 ^{o}C, DCM, 0.2M. [b]Isolated Yield. [c]Determined by HPLC using a Chiralpak AS column. [d]Reaction was performed at 0.1M.

We also decided to investigate the effect of the base, because Zhou[38f,g,h] and coworkers claimed that when AgOAc was used as the Lewis acid, it was not necessary to use amine which deprotonates the aldimine. They reasoned that OAc ion coming from AgOAc is basic enough to remove the proton of aldimine to generate azomethine ylide. In our case this was not exactly true, the yield and the ee was low without using amine (Table 4, entries 7-9).

Initially we have found that DCM was a better solvent than THF, but we didn't search for the other solvents. Also when THF was used as the solvent reaction temperature was -40 ^{o}C. Therefore we decided to try other

solvents including THF at -20 ^{o}C. The results of these studies were summarized in Table 5. As can be seen from this table cylcoadduct was obtained in more than 90% yield in all the solvents except acetonitrile. Product formation was faster in the case of toluene and THF. However the highest ee was obtained in DCM. In all the solvents there was still a solubility problem of the catalyst (chiral ligand+AgOAc). During the preparation of the catalyst the reaction mixture was slightly cloudy.

Table 5 1,3-DC reactions in different solvent[a]

Entry	solvent	aldimine	dipolarophile	yield[b] (%)	ee[c] (%)
1[d]	**DCM**	176	177	93	61
2[d]	**DCE**	”	”	91	57
3[d]	**THF**	”	”	98	21
4[d]	**Toluene**	”	”	96	42
5[e]	**CH_3CN**	”	”	83	34

[a]Imine (1 equiv), dimethyl maleate (1.15 eq.), chiral ligand **175** (3.3 mol %)**,** AgOAc (3 mol %), $^{i}Pr_2NEt$ (10 mol %), -20 ^{o}C, 0.2M. [b]Isolated Yield. [c]Determined by HPLC using a Chiralpak AS column. [d]Reaction time 16h. [e]Reaction time 22h.

In order to obtain homogenous mixture during catalyst preparation we decided to investigate appropriate ligand to metal ratio. We thought that some of the AgOAc remain uncomplexed with the ligand therefore the reaction mixture was not homogenous. And also, besides the chiral catalyst which leads to the enantioselective product formation, uncomplexed AgOAc was catalyzing the background reaction by forming the product as a racemic mixture. We believed that due to the background reaction, higher ee can not be obtained. In order to test this hypothesis, first we carried out a background reaction using 3 mol % AgOAc under previous reaction conditions except using the chiral ligand. From this reaction the

cycloadduct was isolated in high yield as a racemic mixture. It was also observed that the reaction mixture was slightly cloudy during the reaction. This experiment proved our hypothesis and it was necessary to modify ligand to metal ratio in order to get homogenous reaction mixture.

The experiments carried out by using different ligand to metal ratio are summarized in Table 6. As can be seen from this table by changing ligand to metal ratio from 1:1 to 2:1, the yield increased by 5% and the ee decreased by 4% (Table 6, entries 1 and 2). This was not a significant change. Therefore we decided to increase ligand to metal ratio to 4:1. By keeping this ratio but increasing the amounts of both the ligand and metal, highest yield and ee was reached by using 6 mol % chiral ligand with 1.5 mol % metal (Table 6, entry 7). It is important to note that at this ligand:metal ratio reaction medium was homogenous.

Table 6 1, 3-DC reaction with different ligand to metal ratio

Entry	Ligand **175** (mol %)	AgOAc (mol %)	Aldimine **176** (equiv)	dipolarophile **177** (equiv)	yield[a] (%)	ee[b] (%)
1[c]	3.3	3	1	1.15	75	59
2[c]	3.3	1.5	1	1.15	80	55
3[d]	2	0.5	1	1.15	6	67
4[d]	4	1	1	1.15	40	65
5[e]	6	1.5	1	1.15	65	70
6[e]	8	2	1	1.15	75	70
7[f]	6	1.5	1	1.5	95	70

[a]Isolated Yield. [b] Determined by HPLC using a Chiralpak AS column. [c]Taken from Table 4. [d]Reaction was conducted at -20 ^{o}C at 0.2M for 40h. [c,e]Reaction was conducted at -20 ^{o}C at 0.2 for 20h. [f]Reaction was conducted at -20 ^{o}C at 0.2M for 30h.

From all these studies 1.5 mol % of chiral ligand **175**, 6 mol % of AgOAc, 1.5 equiv of dipolarophile, 10 mol % of $^{i}Pr_2NEt$, DCM as the solvent, -20

^{o}C as the reaction temperature, and 30h as the reaction time were determined to be the optimum conditions for 1,3-DC reactions of azomethine ylides. After determining the optimum conditions, we decided to use different aldimines and dipolarophiles to see whether our catalyst can give the cycloadducts derived from these starting materials in high yields and ee's.

2.2.2 Enantioselective 1,3-Dipolar Cycloaddition Reaction of various aldimines and dipolarophiles

In order to show the applicability of the new catalyst system [chiral ligand **175-**Ag(I)], 1,3-DC reactions with various azomethine ylides and dipolarophiles were carried under the optimized conditions (6 mol % of chiral ligand **175,** 1.5 mol % AgOAc and 10 mol % $^{i}Pr_2NEt$ in DCM at -20 ^{o}C). Five different aldimines $ArCH{=}NCH_2CO_2Me$ (Ar = phenyl, 2-naphthyl, 1-naphthyl, *p*-chlorophenhyl and *p*-methoxyphenyl) were used as the precursors of azomethine ylides with electron deficient dipolarophiles (dimethyl maleate, dimethyl fumarate, methyl acrylate, *tert*-butyl acrylate and N-methylmaleimide). The results of these studies were summarized in (Table 7).

Table 7 1,3-DC reactions with different aldimines and dipolarophiles under optimized conditions[a]

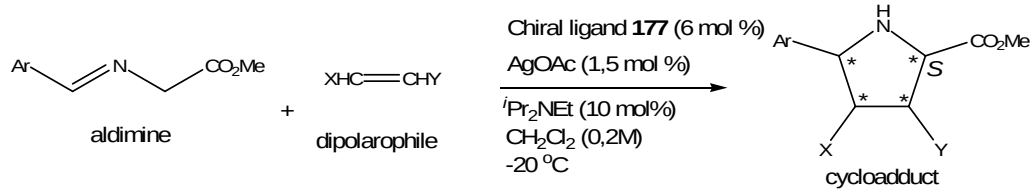


Table 7 (Continued)

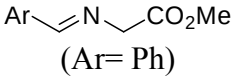
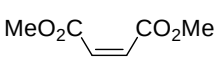
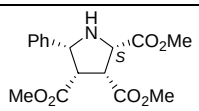
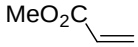
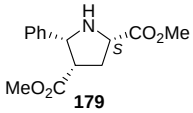
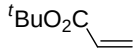
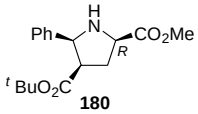
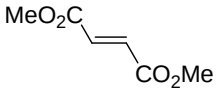
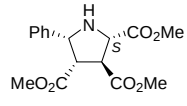
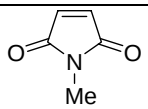
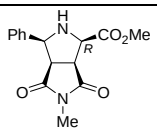
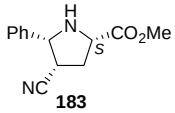
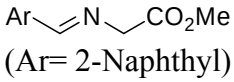
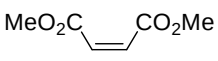
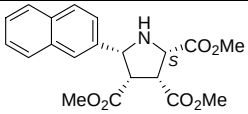
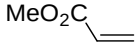
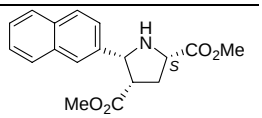
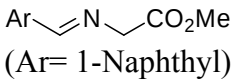
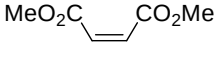
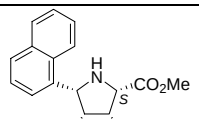
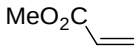
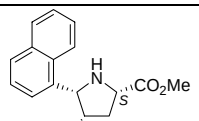
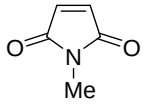
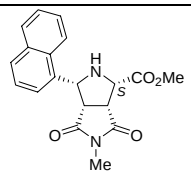
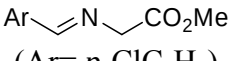
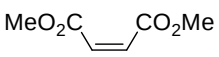
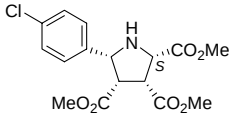
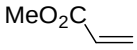
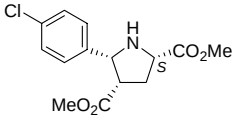
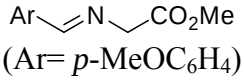
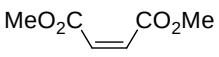
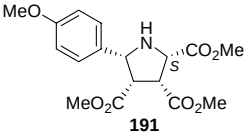
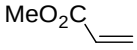
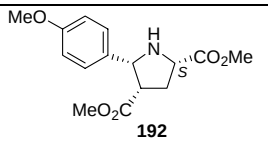
Entry	aldimine	dipolarophile	yield[b] (%)	ee[c] (%)	Cycloadduct
1[d]	 (Ar= Ph)		95	70	 **178**
2[d]	”		87	70	 **179**
3[d]	”		75	20	 **180**
4[d]	”		90	15	 **181**
5[d]	”		99	30	 **182**
6[e]	”		93	70	 **183**
7[e]	 (Ar= 2-Naphthyl)		70	74	 **184**
8[e]	”		75	74	 **185**
9[d]	 (Ar= 1-Naphthyl)		93	89	 **186**
10[f]	”		97	76	 **187**

Table 7 (Continued)

11 [d]	”		96	47	 **188**
12 [g]	 (Ar= *p*-ClC_6H_4)		20	60	 **189**
13 [g]	”		15	32	 **190**
14 [h]	 (Ar= *p*-$MeOC_6H_4$)		42	74	 **191**
15 [h]	”		33	77	 **192**

[a]Imine (1 eq.), dipolarophile (1.5 eq.), chiral ligand **177** (6 mol %), AgOAc (1.5 mol %), $^{i}Pr_2NEt$ (10 mol %), DCM, -20 ^{o}C. [b]Isolated Yield. [c]Determined by HPLC using a Chiralpak AS or Daicel Chiralcel OD column. [d]Reaction time 30h. [e]Reaction time 48h. [f]Reaction time 18h. [g]Reaction time 96h. [h]Reaction time 72h.

As can be seen from Table 7, cycloaddition reactions carried out with aldimine obtained from bezaldehyde and glycine methyl ester proceeded with high yields (75-99%). Enantioselectivity, however, was not very high. Dipolarophiles; dimethyl maleate, methyl acrylate and acrylonitrile were more selective by giving the product in 70% ee (Table 7, entries 1, 2 and 6) than *tert*-butyl acrylate, dimethyl fumarate and N-methylmaleimide (Table 7, entries 3-5). When the aldimine obtained from 2-naphthaldehyde was reacted with dimethyl maleate and methyl acrylate the cycloadducts were obtained in good yields and ee’s (Table 7, entries 7 and 8). Best results were obtained when the aldimine obtained from 1-naphthaldehyde was

reacted with dimethyl maleate (93% yield and 89% ee, entry 9). Methyl acrylate also gave good results with the same aldimine (97% yield and 76% ee, entry 10). N-methylmaleimide was also used with this aldimine to give the product in 96% yield and 47% ee (entry 11).

We have also investigated the effect of electron donating and withdrawing substituents on the aromatic ring of aldimine. For this purpose aldimines obtained from p-chlorobenzaldehyde and p-methoxybenzaldehyde were reacted with the initially used dipolarophiles (entries 12-15). With both aldimines, although the yields were low, the ee's were similar to the aldimine obtained from benzaldehyde except for methyl acrylate (entry 13).

From these results it can be said that enantioselectivity of the 1,3-DC reaction can be increased with aldimines having bulky aromatic units like naphthyl group. Effect of the substituent on the aromatic ring of aldimine was not so significant for the enantioselectivity of the reaction. We have also observed that the reaction was highly dipolarophile dependent which was also reported in previous studies. Interestingly cycloaddition reaction with tert-butyl acrylate (bulky substitiuent) gave the cycloadduct with lowest enantioselectivity (Table 7, entry 3) we do not have a good explanation for this result. Absolute configurations of all the products except cycloadducts **183, 187, 188** and **192** in Table 8 were determined by comparing the specific optical rotation values reported in the literature. Absolute configurations of cycloadducts **183, 187, 188** and **192** were determined by the analogy with the structurally related compounds characterized by X-ray crystallography in the literature. In all the cases, single cycloaddition product was obtained with (*S*)-configuration (except cycloadducts **182** and **184**) on the second position. Based on the stereochemistry of the products it can be said that the cycloaddition reaction took place by *endo* diastereoselectivity. Enantioselectivities of the products were determined by chiral HPLC.

CHAPTER 3

CONCLUSION

We have synthesized 12 new phosphorous based chiral P-FAM ligands which can be regarded as the second generation of our previously synthesized FAM ligands. These P-FAM ligands were used as a catalyst with a metal in 1,3-DC reactions of azomethine ylides with electron deficient dipolarophiles. We used cupper and silver salts as the metal sources but silver gave better results than cupper. Among the chiral ligands P-FAM **175** was found to be the most effective in terms of yield and enantioselectivity of the 1,3-DC reaction of azomethine ylides. As the source of azomethine ylides, five different aldimines were used. From these aldimines, bulky substituted ones (1-naphtyl and 2-naphtyl) gave the cycloadducts in better ee's than the others. It was also found out that 1,3-DC reaction of azomethine ylides was highly dipolarophile dependent. Dimethyl maleate gave the highest ee (89%) with 1-naphtyladimine. It is also worth mentioning that the chiral ligand can be recovered in more than 80% yield and used without losing its activity.

CHAPTER 4

EXPERIMENTAL

4.1 General Consideration

4.1.1 General Procedures

All reactions were performed in flame-dried glassware under an atmosphere of argon. Air and moisture-sensitive liquids and solutions were transferred via syringe. Ligands, which contained phosphorus group, were purified by dry neutral alumina under an atmosphere of argon. TLC analyses were performed on triethylamine deactivated Silica Gel. Chiral P-FAM (Phoshorus Ferrocenyl substituted Aziridinyl Methanol) ligands **163, 164, 165, 166, 167, 168, 170, 171, 172, 173, 174, 175** were benzene-azeotroped and dissolved in dry DCM before transferring into the reaction flask. Commercial AgOAc was weighted out in a glove box and added to a round-bottomed flask equipped with a side arm. Cycloaddition products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh ASTM). TLC analyses were performed on 250 μm Silica Gel 60 F254 plates and visualized by quenching of the UV fluorescence at 254 nm. Enantiomeric excess (ee) was determined by chiral HPLC analysis using a chiral stationary phase (Chiralpak AS or Daicel Chiralcel OD column) with 1 mL/min flow rate, eluting with *i*-PrOH-hexanes, and using UV detection at 210 nm. Racemic compounds were prepared by using silver(I) acetate in the absence of chiral ligand.

4.1.2 Materials

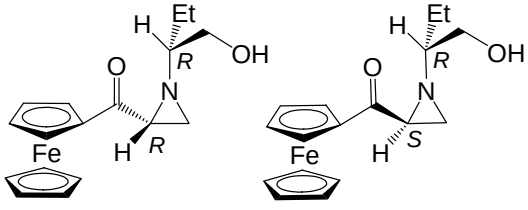
Solvents were dried with standard procedures and degassed with N_2. Dichloromethane (DCM) was dried and distilled over calcium hydride prior to use. Liquid dipolarophiles were distilled and kept under Ar prior to use. Stock solutions of the solid N-methyl maleimide and solid dimethyl fumarate in dry DCM were transferred *via* syringe. Et_3N and $^{i}Pr_2NEt$ was distilled and kept over NaOH pellets under Ar.

4.1.3 Instrumentation

All melting points were taken in open-end capillary tubes and are uncorrected. IR spectra are reported in reciprocal centimeters (cm^{-1}). Unless indicated otherwise, ^{1}H-NMR and ^{13}C-NMR samples were prepared in 1:1 $CDCl_3$-CCl_4 and recorded at 400 MHz and 100 MHz, respectively. ^{1}H-NMR data are reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ 0.00), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet), coupling constant (Hz) and integration. Proton decoupled ^{13}C-NMR and ^{31}P-NMR data are reported as chemical shifts. Optical rotations were measured in a 1dm cell using a Rudolph Research Analytical Autopol III, automatic polarimeter with an average of 5 measurements, each with an integration time of 15 s. Infrared spectra were recorded on a Varian-1000 FT-IR spectrometer.

4.2 Synthesis and Characterization of Chiral Ligands

4.2.1 Synthesis and Characterization of Aziridines 160 and 161

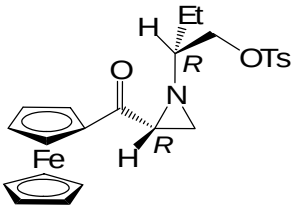


160 **161**

Acryloyl ferrocene **158** (3.5 g, 14.56 mmol) was dissolved in DCM (0.1 M) and cooled to -78 °C. Br_2 (33.86 mmol in 29 mL DCM) was added to this solution. After five minutes the reaction was judged to be complete by TLC. The crude mixture was directly filtered through a silica gel by using $CHCl_3$ as an eluent. After evaporation of the solvent pure 1,2-dibromopronionylferrocene **159** (5.9 g, 95% yield) was obtained. Et_3N (1.18 mL, 8.5 mmol) was added to a stirred solution of this material (2.0 g, 5 mmol) in DCM (0.1 M) at room temperature. After 1 hour stirring, R-(-)-2-amino-1-butanol (0.96 mL, 10 mmol) was added to this stirred. Then the reaction mixture was stirred at room temperature overnight. Solvent was removed by rotary evaporation and the crude residue was purified by flash column chromatograpy using silica gel (EtOAc + %2 Et_3N). Aziridines **160** (53% yield, light orange solid) and **161** (42%, orange solid) were obtained. **160**: R_f = 0.40, EtOAc + %2 Et_3N; mp: 117-119 °C; $[\alpha]_D^{21.7}$ = -112.5 (*c* 0.5, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 1H, Fc), 4.85 (s, 1H, Fc), 4.52 (s, 2H, Fc), 4.22 (s, 5H, Fc), 3.76 (br, 2H), 2.69 (br, 1H), 2.31 (s, 1H), 2.22 (br, 1H, OH) 1.77-1.54 (m, 4H), 0.99 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.89 (C=O), 78.40 (C_q, Fc) 72.50 (CH, Fc), 72.43 (CH, Fc), 72.16 (CH, Fc), 69.94 (CH, Fc), 69.86 (CH, 5C, Fc), 69.27 (CH), 64.63 (CH_2-OH), 41.15 (CH, aziridine), 34.24 (CH_2, aziridine), 24.27 (CH_2), 10.80 (CH_3); IR (neat) cm^{-1} 3433 (O-H), 3120 (stretching, C-H, Fc), 2935 (C-H, aziridine), 1651 (C=O), 1462 (C-H), 1260 (C-N), 1100 (C-O), 825 (bending, C-H, Fc). Anal. Calcd. for $C_{17}H_{21}FeNO_2$: C, 62.40; H, 6.47; N, 4.28; found C, 63.58; H, 6.83; N, 4.39. **161**: R_f = 0.21, EtOAc + %2 Et_3N; mp: 76-78 °C; $[\alpha]_D^{21.7}$ = + 93.6 (*c* 0.47, DCM) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.82 (d, *J* = 12.97 Hz, 2H, Fc), 4.46 (s, 2H, Fc), 4.14 (s, 5H, Fc), 3.68 (br, 2H), 2.49 (br, 1H), 2.26 (s, 1H), 2.14 (br, 1H, OH), 1.81 (br, 1H), 1.68 (m, 1H), 1.58 (m, 1H), 1.46 (br, 1H), 0.94 (t, *J* = 7.25 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.79 (C=O), 78.41 (C_q, Fc), 72.44 (CH, 2C, Fc), 72.40 (CH, Fc), 69.86 (CH, 5C, Fc), 69.76 (CH, Fc), 69.38 (CH), 63.89 (CH_2-OH), 39.96 (CH, aziridine), 35.88 (CH_2,

aziridine), 24.28 (CH_2), 10.62 (CH_3); IR (neat) cm^{-1} 3423 (O-H), 3120 (stretching, C-H, Fc), 2924 (C-H, aziridine), 1658 (C=O), 1462 (C-H), 1258 (C-N), 1120 (C-O), 824 (bending, C-H, Fc). Anal. Calcd. for $C_{17}H_{21}FeNO_2$: C, 62.40; H, 6.47; N, 4.28; found C, 62.24; H, 6.73; N, 4.25.

4.2.2 Synthesis and Characterization of Tosylated Aziridines 162

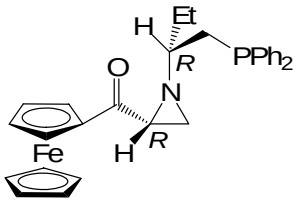


162

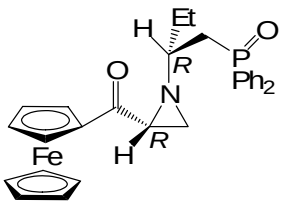
Et_3N (0.43 mL, 3.06 mmol) was added to a stirred solution of aziridine **160** (666 mg, 2.04 mmol) in DCM (0.5 M) at room temperature. To this stirred solution was added p-toluenesulfonylchloride (580 mg, 3.05 mmol). Then the reaction mixture was stirred at room temperature overnight at which point TLC showed no starting material. To the reaction flask, water (10 mL) was added and then extracted with DCM (10 mL x 2 times). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give crude **162**. The crude mixture was purified by flash column chromatography on silica gel eluting with 1:2 hexane-EtOAc to afford pure **162** as an orange solid (936 mg) in 96% yield. R_f = 0.46, 1:2 hexanes-EtOAc; mp: 103-104°C; $[\alpha]_D^{21.7}$ = -138.9 (*c* 1.0, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) 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 & 10.2 Hz, 1H), 3.98 (dd, *J* = 7.7 & 10.0 Hz, 1H), 2.82 (q, *J* = 3.1 Hz, 1H), 2.39 (s, 3H, CH_3, Ts), 2.31 (s, 1H), 1.85 (m, 1H), 1.71 (d, *J* = 6.5, 1H), 1.61 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.20 (C=O), 144.65 (C_q, ArC-S), 132.67 (C_q, ArC-CH_3),

129.82 (CH, 2C, Ph), 127.86 (CH, 2C, Ph), 78.71 (C_q, Fc), 72.76 (CH, Fc), 72.68 (CH, Fc), 72.58 (CH, Fc), 70.76 (CH, Fc), 69.83 (CH, 5C, Fc), 69.19 (CH), 68.65 (CH_2-OTs), 40.52 (CH, aziridine), 33.69 (CH_2, aziridine), 24.94 (CH_2), 21.58 (CH_3, Ts), 10.42 (CH_3); IR (neat) cm^{-1} 3120 (stretching, C-H, Fc), 2969 (C-H, aziridine), 1645 (C=O), 1455 (C-H), 1357 and 1182 (Ph-SO_2-OCH_2), 1261 (C-N), 1150 (C-O), 869 and 790 (C-H, Ph), 822 (bending, C-H, Fc). Anal. Calcd. for $C_{24}H_{27}FeNO_4S$: C, 59.88; H, 5.65; N, 2.91; S, 6.66; found C, 60.54; H, 5.88; N, 2.92; S, 6.66.

4.2.3 Synthesis and Characterization of phosphorus aziridino ketones 163 and 164



163

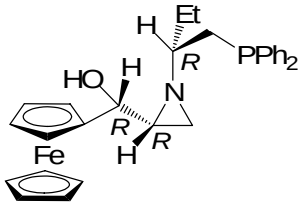


164

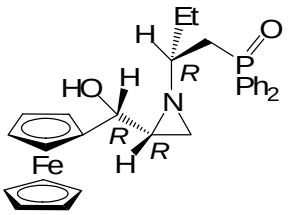
Compound **162** (450 mg, 0,93 mmol) was dissolved in THF (3 mL, distilled over Na-benzophenone and degassed) in a reaction flask. The flask was cooled to -78 ^oC and potassium diphenylphosphide (2.1 mL, from 0.5 M THF solution) was added slowly over 30 min. After stirring about 1 hour TLC showed no starting material. The crude mixture was filtered through a short plug of basic alumina using 5:1 hexanes-EtOAc as an eluent under N_2. After evaporation of the solvent, pure **163** (348 mg, 75% yield) was obtained (it is an air sensitive orange oil) together with its oxidized form **164** (20% yield, red oily product). When pure **163** was exposed to air, it was oxidized completely to **164**. **163**: R_f = 0.73, 1:1 hexanes: EtOAc after treatment of Et_3N for TLC; ^{1}H-NMR (400 MHz, $CDCl_3$) 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 (sextet, J = 7.2 Hz, 2H), 1.65 (d, J = 6.6 Hz, 1H of CH_2 aziridine), 1.38 (sextet, , J = 5.8 Hz 1H), 0.94 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.19 (C=O), 139.08-138.94 (C_q, ArC-P), 138.57-138.45 (C_q, ArC-P), 133.04 (CH, Ph), 132.86 (CH, Ph), 132.71 (CH, Ph), 132.52 (CH, Ph), 128.82 (CH, Ph), 128.62 (CH, Ph), 128.59 (CH, Ph), 128.56 (CH, Ph), 128.51 (CH, Ph), 128.30 (CH, Ph), 78.53 (C_q, Fc), 72.3 (CH, Fc), 70.30 (CH, Fc), 69.83 (CH, 5C, Fc), 69.13 (CH), 69.05 (CH, Fc), 68.89 (CH, Fc), 40.81 (CH, aziridine), 37.01 (CH_2, aziridine), 34.63-34.49 (CH_2-P), 28.70 (CH_2), 10.53 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ -21.53; IR (neat) cm^{-1} 3051 (stretching, C-H, Fc), 2967 (C-H, aziridine), 1665 (C=O), 1457 (C-H), 1255 (C-N), 913, 745 and 697 (C-H, Ph), 823 (bending, C-H, Fc). **164**: R_f = 0.12, 1:1 hexanes: EtOAc after treatment of Et_3N for TLC ; ^{1}H-NMR (400 MHz, $CDCl_3$) 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 and 3.2 Hz, 1H), 2.52 (m, 2H), 2.32 (s, 1H), 2.05 (m, 1H), 1.82 (d, J = 6.2, 1H), 1.62 (m, 1H), 1.54 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.26 (C=O), 131.79 (C_q, ArC-P), 130.73 (C_q, ArC-P), 130.60 (CH, Ph), 128.80 (CH, Ph), 128.70 (CH, Ph), 128.59 (CH, Ph), 78.67 (C_q, Fc), 72.51 (CH, Fc), 71.03 (CH, Fc), 69.79 (CH, 5C, Fc), 68.70 (CH), 64.78 (CH, Fc), 40.06 (CH, aziridine), 37.94 (CH_2, aziridine), 29.64 (CH_2-P), 28.70 (CH_2), 10.37 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 29.07.

4.2.4 Synthesis and Characterization of Chiral P-FAM Ligands 165 and 166



165

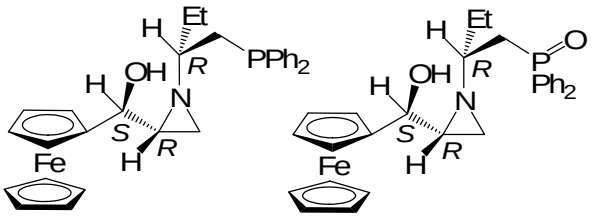


166

Compound **163** (155 mg, 0.313 mmol) was dissolved in MeOH (0.1 M, degassed) and cooled to -78 °C. $ZnCl_2$ (64 mg, 0.470 mmol) was added to this stirred solution. After 1 hour $NaBH_4$ (23.7 mg, 0.626 mmol) was added and stirring continued at -78 °C for 4 hours. At that time TLC analysis showed that the reaction was completed. The reaction mixture was partitioned between DCM (2 x 10 mL) and water (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give crude **165**. Purification by column chromatography under N_2 on a short plug of basic alumina with 5:1 hexanes-EtOAc gave pure **165** in 60% yield as an air sensitive pale yellow oil and oxidized form **166** (35% yield, yellow oily product). When pure compound **165** was exposed to air, it was converted to oxidized form **166** quantitatively. **165**: R_f = 0.52, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC; ^{1}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, 6.3 and 5.1 Hz, 2H), 1.81 (d, *J* = 3.3, 1H), 1.66 (sextet, *J* = 6.2 Hz, 1H), 1.59 (sextet, *J* = 7.1 Hz, 1H), 1.53 (m, 1H), 1.33 (sextet, *J* = 7.5 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.11-138.97 (C_q, ArC-P), 138.82-138.69 (C_q, ArC-P), 132.94 (CH, Ph), 132.86 (CH, Ph), 132.75 (CH, Ph), 132.66 (CH, Ph), 128.70 (CH, Ph), 128.60 (CH, Ph), 128.47 (CH, 2C, Ph), 128.40 (CH, 2C, Ph), 89.78 (C_q, Fc), 68.47 (CH, 5C, Fc), 68.09 (CH, Fc), 67.91 (CH,

Fc), 67.24 (CH, Fc), 67.16 (CH, Fc), 67.02, 66.07, 42.11 (CH, aziridine), 34.18-34.4 (CH_2-P), 30.63 (CH_2, aziridine), 28.63 (CH_2), 10.16 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ -23.49; IR (neat) cm^{-1} 3396 (O-H), 3071 (stretching, C-H, Fc), 2964 (C-H, aziridine), 1480 (C-H), 1260 (C-N), 815 (bending, C-H, Fc), 742 and 697 (bending, C-H, Ph). **166**: R_f = 0.15, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC; ^{1}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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.98-131.64 (C_q, ArC-P), 130.79-130.70 (C_q, ArC-P), 130.58 (CH, Ph), 130.49 (CH, Ph), 130.22 (CH, 2C, Ph), 129.80 (CH, Ph), 128.70 (CH, Ph), 128.60 (CH, Ph), 128.49 (CH, Ph), 127.01 (CH, 2C, Ph), 90.05 (C_q, Fc), 68.87 (CH-OH), 68.54 (CH, 5C, Fc), 67.97 (CH, Fc), 67.90 (CH, Fc), 67.49 (CH, Fc), 65.27 (CH, Fc), 63.93 (CH, Fc), 63.21 (CH, Fc), 44.35 (CH, aziridine), 34.97-32.67 (CH_2, CH_2-P), 21.68 (CH_2, aziridine), 16.17 (CH_2), 9.96 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 28.27.

4.2.4 Synthesis and Characterization of Chiral P-FAM Ligands 167 and 168

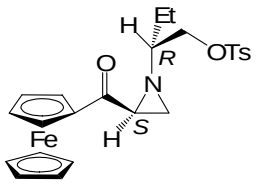


167 **168**

Compound **163** (163 mg, 33 mmol) was dissolved in THF (2.5 mL, distilled over Na-benzophenone and degassed) in a reaction flask. The

flask was cooled to -78 ^{o}C and L-Selectride (0.5 mL, from 1M THF solution) was added slowly over 30 min. After stirring about eight hours TLC showed no starting material. To the reaction flask was added 10% NaOH (10 mL) and EtOAc (15 mL) then the two layers were separated. The aqueous layer was extracted one more time with EtOAc (15 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by a short plug of basic alumina using 3:1 hexanes-EtOAc as an eluent under N_2. After evaporation of the solvent, pure **167** (65 mg, 40% yield) was obtained as an air sensitive pale yellow oil and its oxidized form **168** (55% yield, yellow oily product). When pure compound **167** was exposed to air, it was oxidized quantitatively to **168**. **167**: R_f = 0.64, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC; ^{1}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, 1H), 1.59 (m, 1H), 1.52 (pentet, *J* = 7.3, 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, CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ -24.42; IR (neat) cm^{-1} 3340 (O-H), 3093 (stretching, C-H, Fc), 2960 (C-H, aziridine), 1438 (C-H), 1241 (C-N), 817 (bending, C-H, Fc), 737 and 697 (bending, C-H, Ph). **168**: R_f = 0.17, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* =10.7 and 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, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.81-133.62 (C_q, ArC-P), 131.73-131.57 (C_q, ArC-P), 130.76 (CH, Ph), 130.67 (CH, Ph), 130.49 (CH, Ph), 130.39 (CH, Ph), 128.78 (CH, Ph), 128.70 (CH, Ph), 128.67 (CH, 2C, Ph), 128.58 (CH, 2C, Ph), 90.63 (C_q, Fc), 68.78 (CH-OH), 68.70 (CH, Fc), 68.32 (CH, Fc), 68.22 (CH, 5C, Fc), 67.42 (CH, Fc), 67.33 (CH, Fc), 65.55 (CH), 35.03-34.31 (CH_2, CH_2-P), 31.73 (CH, aziridine), 28.83 (CH_2, aziridine), 20.98 (CH_2), 18.85 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 30.79.

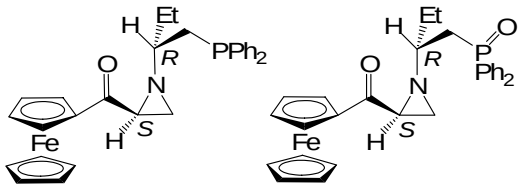
4.2.5 Synthesis and Characterization of Tosylated Aziridine 169



169

Et_3N (0.585 mL, 4.22 mmol) was added to a stirred solution of aziridine **161** (920 mg, 2.81 mmol) in DCM (0.5 M) at room temperature. To this stirred solution was added p-toluenesulfonylchloride (802.13 mg, 4.22 mmol). Then the reaction mixture was stirred at room temperature overnight at which point TLC showed that no starting material was left. To the reaction flask water (15 mL) was added and then extracted with DCM (15 mL). The aqueous layer was extracted one more time with DCM (15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give crude **169**. Purification by flash column chromatography on silica gel eluting with 1:1 hexane-EtOAc gave pure compound **169** (1.3 g, orange oily product) in 96% yield. R_f = 0.68, 1:2 hexanes-EtOAc; $[\alpha]_D^{21.7}$ = 95.7 (*c* 0.98, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H, Ph), 7.35 (d, *J* = 7.6 Hz, 2H, Ph), 4.86 (s, 2H, ferrocene), 4.51 (s, 2H, ferrocene), 4.17 (s, 5H, ferrocene), 4.11 (d, *J* = 5.7 Hz, 2H, CH_2-OTs), 2.51 (dd, *J* = 3.0 & 6.4 Hz, 1H), 2.45 (s, 3H, CH_3, 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.40 (C=O), 144.72 (C_q, ArC-S), 133.12 (CH, Ph), 129.87 (CH, Ph), 128.97 (C_q, ArC-CH_3), 128.27 (CH, Ph), 127.95 (CH, Ph), 78.20 (C_q, Fc), 72.48 (CH, Fc), 72.45 (CH, Fc), 71.95 (CH, Fc), 69.83 (CH, 5C Fc), 69.77 (CH, Fc), 69.40 (CH), 68.66 (CH_2-OTs), 40.15 (CH, aziridine), 35.58 (CH_2 aziridine), 24.93 (CH_2), 21.64 (CH_3, Ts), 9.96 (CH_3); IR (neat) cm^{-1} 2925 (C-H, aziridine), 1657 (C=O), 1460 (C-H), 1360 and 1177 (Ph-SO_2-OCH_2), 1259 (C-N), 1100 (C-O), 840 (C-H, Ph), 820 (bending, C-H, Fc).

4.2.6 Synthesis and Characterization of phosphorus aziridino ketones 170 and 171

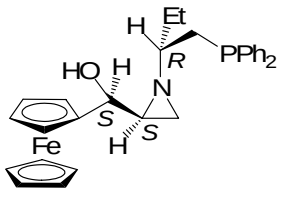


170 **171**

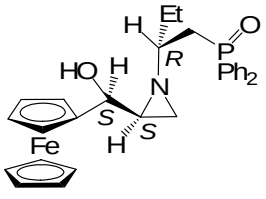
Compound **169** (856 mg, 1.78 mmol) was dissolved in THF (5 mL, distilled over Na-benzophenone and degassed) in a reaction flask. The flask was cooled to -78 ^{o}C and potassium diphenylphosphide (4 mL, from 0.5 M THF solution) was added slowly over 30 min. After stirring about 1 hour TLC showed no starting material. The crude mixture was purified through a short plug of basic alumina using 5:1 hexanes-EtOAc as an eluent under N_2. After evaporation of the solvent pure **170** (661 mg, 75% yield) was obtained as an air sensitive orange solid with its oxidized form **171** (20% yield, red solid). When pure compound **170** was exposed to air, it turned into oxidized form **171** quantitatively. **170**: R_f =0.73, 1:1 hexanes: EtOAc after treatment of Et_3N for TLC ; mp: 145-146°C; $[\alpha]_D^{21.7}$ = 45.9 (*c* 1, DCM); ^{1}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 (pentet, *J* = 7.2 Hz, 2H), 1.61 (d, *J* = 6.7 Hz, 1H), 1.51 (sextet, *J* = 6.3, 1H), 1.01 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.53 (C=O), 140.42-140.29 (C_q, ArC-P), 140.29-140.16 (C_q, ArC-P), 134.46 (CH, Ph), 134.26 (CH, Ph), 134.20 (CH, Ph), 134.00 (CH, Ph), 130.19 (CH, Ph), 130.04 (CH, 2C, Ph), 129.97 (CH, 2C, Ph), 129.91 (CH, Ph), 79.69 (C_q, Fc), 73.83 (CH, 2C, Fc), 71.25 (CH, 5C, Fc), 70.88 (CH, Fc), 70.05 (CH, Fc) 69.91 (CH) , 43.92 (CH, aziridine), 37.51 (CH_2, aziridine), 34.82-34.67 (CH_2-P), 29.88 (CH_2), 11.34 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ -21.90; IR (neat) cm^{-1} 3067 (stretching, C-H, Fc), 2964 (C-H, aziridine), 1656 (C=O), 1453 (C-H), 1254 (C-N), 853, 746 and

700 (C-H, Ph), 822 (bending, C-H, Fc). Anal. Calcd. for $C_{29}H_{30}FeNOP$: C, 70.31; H, 6.10; N, 2.83; found C, 70.12; H, 6.08; N, 2.74. **171**: R_f = 0,35 EtOAc after treatment of Et_3N for TLC ; decomposes after 160°C; $[\alpha]_D^{21.7}$ = 75.8 (*c* 1, DCM) ; ^{1}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 & 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 (pentet, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.63 (C=0), 134.58-134.14 (C_q, ArC-P), 133.60-133.16 (C_q, ArC-P), 131.76 (CH, Ph), 131.67 (CH, Ph), 130.82 (CH, Ph), 130.73 (CH, Ph), 130.52 (CH, Ph), 130.43 (CH, Ph), 128.77 (CH, Ph), 128.74 (CH, Ph), 128.66 (CH, Ph), 128.62 (CH, Ph), 78.31 (C_q, Fc), 72.54 (CH, Fc), 72.50 (CH, Fc), 69.83 (CH, 5C, Fc), 69.24 (CH, Fc), 64.50 (CH, Fc), 60.32 (CH) 42.96 (CH, aziridine), 36.04 (CH_2, aziridine), 34.61-33.90 (CH_2-P), 28.91 (CH_2), 9.66 (CH_2); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 28.90; IR (neat) cm^{-1} 3070 (stretching, C-H, Fc), 2977 (C-H, aziridine), 1655 (C=O), 1448 (C-H), 1255 (C-N), 1204 (P=O), 831, 760 and 712 (C-H, Ph), 820 (bending, C-H, Fc). Anal. Calcd. for $C_{29}H_{30}FeNO_2P$: C, 68.11; H, 5.91; N, 2.74; found C, 68.26; H, 6.13; N, 2.72.

4.2.7 Synthesis and Characterization of Chiral P-FAM Ligands 172 and 173



172



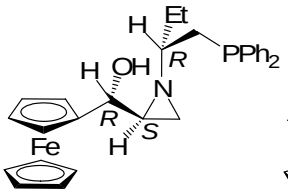
173

Compound **170** (171.8 mg, 0.347 mmol) was dissolved in THF (3.6 mL, distilled over Na-benzophenone and degassed) in a reaction flask (25 mL).

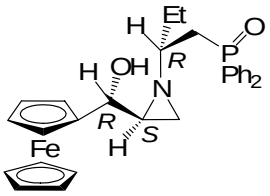
Reaction flask was then cooled to -78 ^{o}C and $ZnCl_2$ (71 mg, 0.52 mmol) was added and the reaction mixture was stirred for 1 h at this temperature. Then $LiAlH_4$ (27 mg, 0.71 mmol) was added and stirring continued for about 4 hour at which point TLC showed that no starting material was left. The contents of the reaction flask was hydrolyzed with 10 mL distilled water and then extracted with EtOAc (10 mL). The aqueous layer was extracted one more time with EtOAc (10 mL). Then, the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Then, crude **172** was purified through a short plug of basic alumina using 3:1 hexanes-EtOAc as an eluent under N_2 gas. After evaporation of the solvent pure **172** (84 mg, 49% yield) was obtained as an air sensitive pale yellow oil as well as oxidized form **173** (42% Yield**,** yellow oily product). When pure **172** was exposed to air, it was converted to oxidized form **173** quantitatively. **172**: R_f = 0.40, 1:1 hexanes: EtOAc after treatment of Et_3N for TLC ; ^{1}H-NMR (400 MHz, $CDCl_3$) 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 (sextet, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 6.2 Hz, 1H), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.29-139.20 (C_q, ArC-P), 139.07-138.98 (C_q, ArC-P), 132.97 (CH, Ph), 132.82 (CH, Ph), 132.78 (CH, Ph), 132.63 (CH, Ph), 128.68 (CH, Ph), 128.53 (CH, Ph), 128.47 (CH, 2C, Ph), 128.40 (CH, 2C, Ph), 89.39 (C_q, Fc), 68.49 (CH, 5C, Fc), 68.05 (CH, Fc), 67.82 (CH, Fc), 67.48 (CH, Fc), 66.95 (CH, Fc), 67.34, 43.09 (CH, aziridine), 33.63-33.49 (CH_2-P), 29.40 (CH_2, aziridine), 28.16 (CH_2), 9.89 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ -23.00; IR (neat) cm^{-1} 3420 (O-H), 3071 (stretching, C-H, Fc), 2962 (C-H, aziridine), 1460 (C-H), 1260 (C-N), 818 (bending, C-H, Fc), 741 and 697 (bending, C-H, Ph). **173**: R_f = 0.14, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* =10.5 and 3.5 Hz, 2H, Ph), 7.67 (dd, *J* =10.3 and 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

(pentet, 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, CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 29.40.

4.2.8 Synthesis and Characterization of Chiral P-FAM Ligands 174 and 175



174



175

Compound **170** (422.5 mg, 0.85 mmol) was dissolved in THF (6 mL, distilled over Na-benzophenone and degassed) in a reaction flask. The flask was cooled to -78 ^{o}C and L-Selectride (1.275 mL, from 1M THF solution) was added slowly over 30 min. After stirring about 6 hours TLC showed no starting material. To the reaction flask was added 10% NaOH aqueous solution (10 mL) followed by EtOAc (15 mL) and the two layers were separated. The aqueous layer was extracted one more time with EtOAc (15 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by a short plug of basic alumina using 3:1 hexanes-EtOAc as an eluent under N_2 gas. After evaporation of the solvent pure **174** (216 mg, 51% yield) was obtained as an air sensitive pale yellow oil as well as oxidized form **175** (45% Yield, yellow solid). When pure compound **174** was exposed to air, it was converted to oxidized form **175** quantitatively. **174**: R_f = 0.45, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC; ^{1}H-NMR (400 MHz, $CDCl_3$) 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, CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ -22.4; IR (neat) cm^{-1} 3364 (O-H), 3056 (stretching, C-H, Fc), 2958 (C-H, aziridine), 1459 (C-H), 1262 (C-N), 816 (bending, C-H, Fc), 742 and 697 (bending, C-H, Ph). **175**: R_f = 0.19, 1:1 hexanes: EtOAc after treatment with Et_3N for TLC; mp: 39-40°C; $[\alpha]_D^{21.7}$ = +12.2 (*c* 1, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* =7.4 and 3.3 Hz, 2H, Ph), 7.73 (dd, *J* =7.0 and 3.3 Hz, 2H, Ph), 7.46 (ddd, *J* =7.6, 8.5 and 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, CH_2-P), 1.97 (pentet, *J* = 6.8 Hz, 1H), 1.71 (ddd, *J* = 3.7, 2.6 and 3.4 Hz, 1H, aziridine), 1.50 (pentet, *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, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.76-134.27 (C_q, ArC-P), 133.78-133.28 (C_q, ArC-P), 131.62 (CH, Ph), 131.55 (CH, Ph), 130.86 (CH, Ph), 130.76 (CH, Ph), 130.54 (CH, Ph), 130.45 (CH, Ph), 128.65 (CH, Ph), 128.62 (CH, Ph), 128.54 (CH, Ph), 128.51 (CH, Ph), 90.74 (C_q, Fc), 70.72 (CH-OH), 68.46 (CH, 5C, Fc), 67.86 (CH, Fc), 67.69 (CH, Fc), 66.25 (CH, Fc), 65.84 (CH, Fc), 63.84 (CH), 44.75 (CH, aziridine), 34.33-33.62 (CH_2, CH_2-P), 32.11 (CH_2, aziridine), 28.20 (CH_2), 9.24 (CH_3); ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 28.53; IR (neat) cm^{-1} 3396 (O-H), 3093 (stretching, C-H, Fc), 2963 (C-H, aziridine), 1446 (C-H), 1274 (C-N), 1178 (P=O), 816 (bending, C-H, Fc), 742 and 716 (bending, C-H, Ph). Anal. Calcd. for $C_{29}H_{32}FeNO_2P$: C, 67.85; H, 6.28; N, 2.73; found C, 69.5; H, 6.99; N, 2.62.

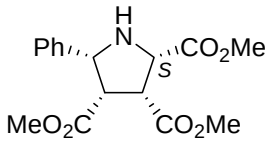
4.3 General Procedure for the synthesis of α-iminoesters

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 stirred at room temperature overnight. The 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 evaporated. The imines showed satisfactory purity as determined by ^1H NMR spectroscopy and were used without further purification.

4.4 General Procedure for Catalytic Asymmetric 1,3-DC Reaction

Dry AgOAc (1.5 mol %) was weighed in a glove bag into a pre-dried reaction flask under Ar. The reaction flask was then connected to a vacuum line and heated with a heat gun for 10-15 min. Benzene-azeotroped chiral ligand (6 mol %) dissolved in freshly distilled DCM (5 mL per mmole of imine) was added to the reaction flask at rt. The homogeneous mixture was stirred at this temperature for about 1 h and then cooled to -20 ^oC. To this mixture was added sequentially, the imine (1 equiv), dry $^iPr_2NEt$ (10 mol %) and the dipolarophile (1.5 equiv). The resulting mixture was stirred at -20 ^oC under Ar atmosphere, at which point the solvent was removed under reduced pressure and the crude product was isolated by flash column chromatography on silica gel. The reaction can be performed on up to 100 mg of imine.

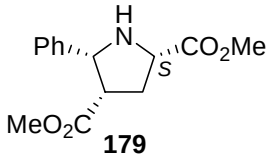
4.4.1 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate



178

70% Ee as determined by HPLC, Chiralpak AS column+ guard column, 70:30 hexanes-*i*-PrOH, t_R(major) = 10.9 min, t_R(minor) = 25.8 min; $[\alpha]_D^{30}$ = +48.8 (*c* 1.39, DCM) ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 4H, Ph), 7.24 (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- CO_2Me), 3.68 (s, 3H, 3- CO_2Me), 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-CO_2Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7 170.5, 170.4, 137.2, 128.2 (2xC), 127.6, 126.7 (2xC), 65.4, 62.1, 52.4, 52.1, 51.8, 51.1, 51.0.

4.4.2 (2*S*, 4*S*, 5*R*)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate

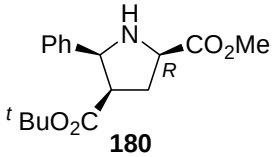


179

70% Ee as determined by HPLC, Chiralcel OD column, 90:10 hexanes-*i*-PrOH, t_R(major) = 16.1 and t_R(minor) = 35.3 min; $[\alpha]_D^{30}$ = +23.6 (*c* 1.61, DCM); ^{1}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- CO_2Me), 3.20 (q, *J* = 7.1 Hz, 1H, H-4), 3.13 (s, 3H, 4-CO_2Me), 2.59 (br, 1H, NH), 2.32 (t, *J* = 7.3 Hz, 2H, H-3); ^{13}C-NMR (100

MHz, $CDCl_3$) δ 173.4, 172.6, 139.2, 128.1 (2xC), 127.5, 126.8 (2xC), 65.9, 59.9, 52.1, 51.0, 49.7, 33.3.

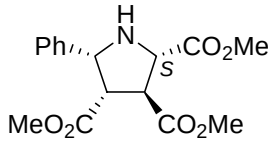
4.4.3 (2*R*, 4*R*, 5*S*)-4-^{t}Butyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate



180

20% Ee as determined by HPLC, Chiralpak AS + guard column, 95:5 hexanes-*i*-PrOH, t_R(minor) = 10.2 min, t_R(major) = 17.8 min; $[\alpha]_D^{30}$ = -4.4 (*c* 1.14, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.3 Hz, 2H, Ph) 7.29 (t, *J* = 7.8 Hz, 2H, Ph), 7.21 (t, *J* = 7.1 Hz, 1H, Ph), 4.43 (d, *J* = 7.8 Hz, 1H, H-5), 3.89 (t, *J* = 8.3 Hz, 1H, H-2), 3.81 (s, 3H, 2-CO_2Me), 3.22 (q, *J* = 7.8 Hz, 1H, H-4), 2.77 (br, 1H, NH), 2.44-2.37 (m, 1H, H-3), 2.33 -2.27 (m, 1H, H-3), 1.01 (s, 9H, *t*-Bu); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3, 171.4, 139.4, 128.0 (2xC), 127.3 (2xC), 127.2, 80.2, 65.6, 59.8, 52.0, 50.1, 34.1, 27.5 (9xC).

4.4.4 (2*S*, 3*S*, 4*S*, 5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate

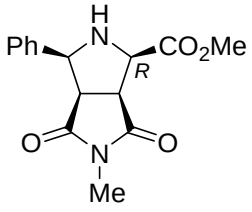


181

15% Ee as determined by HPLC, Chiralcel OD column, 90:10 hexanes-*i*-PrOH, t_R(major) = 32.4 min, t_R(minor) = 59.6 min; $[\alpha]_D^{30}$ = +3.0 (*c* 1.25

g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.21 (m, 5H, Ph), 4.62 (t, *J* = 8.0 Hz, 1H, H-5), 4.14 (t, *J* = 7,2 Hz, 1H, H-2), 3.84 (s, 3H, 2-CO_2Me), 3.77 (s, 3H, 3- CO_2Me), 3.60 (dd, *J* = 1.4 and 7.3 Hz, 1H, H-3), 3.53 (dd, *J* = 2.2 and 7.0 Hz, 1H, H-4), 3.19 (s, 3H, 4-CO_2Me), 2.73 (br, 1H, N-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3, 171.7, 171.3, 138.2, 128.2 (2xC), 127.8, 126.9 (2xC), 65.5, 63.3, 53.8, 52.4, 52.3, 51.4, 50.1.

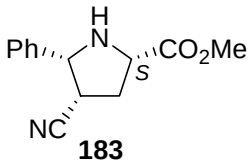
4.4.5 (1*S*, 2*R*, 4*S*, 5*R*)-Methyl octahydro-7-methyl-6,8-dioxo-4-phenyl -3,7-diazabicyclo[3.3.0]pyrrole-2-carboxylate



182

30% Ee as determined by HPLC, Chiralpak AS column + guard column, 4:1 *i*-PrOH-hexanes, t_R(minor) = 7.9 min, t_R(major) = 22.1 min; $[\alpha]_D^{30}$ = -34.3 (*c* 1.51, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H, Ph), 7.25 (m, 1H, 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-CO_2Me), 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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.5 175.1, 170.3, 138.6, 128.3, 128.0 (2xC), 127.3 (2xC), 62.8, 60.9, 51.4, 49.0, 47.8, 24.3.

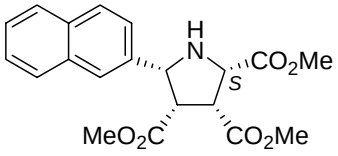
4.4.6 (2*S*, 4*S*, 5*R*)-Methyl 4-cyano-5-phenylpyrrolidine-2-carboxylate



183

70% Ee as determined by HPLC, Chiralcel AS column+ guard column, 50:50 hexanes-*i*-PrOH, t_R(major) = 10.3 and t_R(minor) = 44 min; $[\alpha]_D^{30}$ = +36.9 (*c* 1.40, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.3 Hz, 2H, Ph), 7.39 (t, *J* = 7.7 Hz, 2H, Ph), 7.34 (d, *J* = 4.7 Hz, 1H, 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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.6, 137.7, 128.6 (2xC), 128.5, 127.0 (2xC), 118.8, 64.8, 58.6, 52.4, 35.9, 34.2.

4.4.7 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate

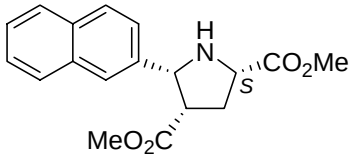


184

74% Ee as determined by HPLC, Chiralpak AS column+ guard column, 50:50 hexanes-*i*-PrOH, t_R(major) = 10.9 min, t_R(minor) = 23.6 min; $[\alpha]_D^{30}$ = +40.8 (*c* 1.23 g/100mL, DCM); ^{1}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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.3,

134.6, 133.2, 132.8, 128.1, 127.9, 127.5, 126.1, 126.0, 125.6, 124.8, 65.6, 62.1, 61.8, 52.4, 52.3, 51.9, 51.2.

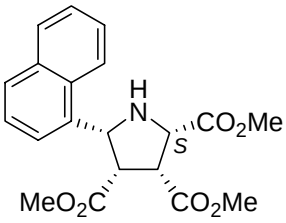
4.4.8 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(naphthalen-2-yl)pyrrolidine-2,4-dicarboxylate



185

74% Ee as determined by HPLC, Chiralpak AS column+ guard column, 85:15 hexanes-*i*-PrOH, t_R(major) = 15 min, t_R(minor) = 31.4 min; $[\alpha]_D^{30}$ = +23.6 (*c* 1.37 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81-7.74 (m, 4H), 7.43-7.37 (m, 3H), 4.65 (d, *J* = 7.7 Hz; 1H), 3.98 (t, *J* = 8.2 Hz; 1H), 3.84 (s, 3H), 3.36 (q, *J* = 6.7 Hz; 1H), 3.10 (s, 3H), 2.50-2.39 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 172.6, 136.6, 133.2, 132.9, 128.0, 127.7, 127.5, 126.0, 125.8, 125.5, 125.1, 66.0, 59.9, 52.1, 51.1, 49.6, 33.4.

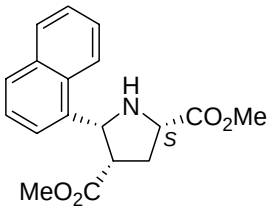
4.4.9 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(naphthalen-1-yl)pyrrolidine-2,3,4-tricarboxylate



186

89% Ee as determined by HPLC, Chiralpak AS column+ guard column, 50:50 hexanes-*i*-PrOH, t_R(major) = 20.4 min, t_R(minor) = 39.9 min; $[\alpha]_D^{30}$ = +210.5 (*c* 1.40 g/100mL, DCM); ^{1}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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 170.1, 133.5, 132.5, 131.1, 128.9, 128.2, 126.1, 125.4, 125.1, 123.3, 122.6, 61.4, 61.3, 57.7, 52.2, 51.9, 51.1, 50.9.

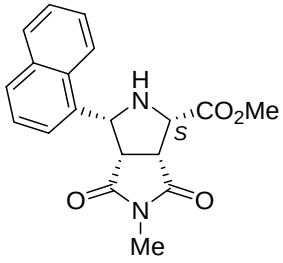
4.4.10 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(naphthalen-1-yl)pyrrolidine-2,4-dicarboxylate



187

76% Ee as determined by HPLC, Chiralpak AS column+ guard column, 90:10 hexanes-*i*-PrOH, t_R(major) = 26.0 min, t_R(minor) = 61.5 min; $[\alpha]_D^{30}$ = +144.1 (*c* 1.26 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz; 1H), 7.82 (d, *J* = 7.7 Hz; 1H), 7.73 (d, *J* = 8.2 Hz; 1H), 7.63 (d, *J* = 7.2 Hz; 1H), 7.51-7.41 (m, 3H), 5.25 (d, *J* = 7.5 Hz; 1H), 4.02 (t, *J* = 8.2 Hz; 1H), 3.84 (s, 3H), 3.50 (t, *J* = 7.4 Hz; 1H), 2.84 (s, 3H), 2.54-2.44 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3, 172.6, 134.5, 133.4, 131.2, 128.8, 127.9, 125.9, 125.3, 125.1, 123.0, 122.8, 61.6, 59.4, 52.0, 50.7, 48.6, 33.3.

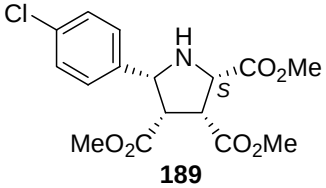
4.4.11 (1*S*, 3*R*, 3*S*, 6*R*)-Methyl octahydro-5-methyl-3-(naphthalen-1-yl)-4,6-dioxopyrrolo[3,4-c]pyrrole-1-carboxylate



188

47% Ee as determined by HPLC, Chiralpak AS column+ guard column, 4:1 *i*-PrOH-hexanes,, t_R(minor) = 9.1 min, t_R(major) = 53.2 min; $[\alpha]_D^{30}$ = +72.2 (*c* 1.32 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz; 1H), 7.89 (d, *J* = 7.8 Hz; 1H), 7.79 (d, *J* = 8.1 Hz; 1H), 7.67 (d, *J* = 7.1 Hz; 1H), 7.57-7.48 (m, 2H), 7.41 (d, *J* = 7.7 Hz; 1H), 5.05 (dd, *J* = 8.2 and 3.6 Hz; 1H), 4.05 (dd, *J* = 6.6 and 2.1 Hz; 1H), 3.64 (t, *J* = 7.9 Hz; 1H), 3.55 (t, *J* = 7.1 Hz; 1H), 2.75 (s, 3H), 2.32 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.0, 174.2, 170.3, 133.4, 133.1, 131.2, 129.2, 128.5, 126.4, 125.7, 125.4, 123.3, 122.3, 61.3, 59.8, 52.3, 48.1, 48.0, 24.9.

4.4.12 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate

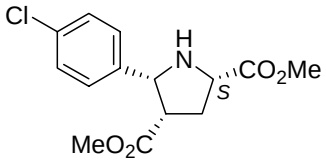


189

60% Ee as determined by HPLC, Chiralpak AS column+ guard column 90:10 hexanes-*i*-PrOH, t_R(major) = 32.4 min, t_R(minor) = 55.5 min; $[\alpha]_D^{30}$ = +38.9 (*c*

1.06 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) 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), 3.50 (t, *J* = 7.0 Hz, 1H), 3.28 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.9, 170.8 170.7, 135.8, 133.6, 128.5 (2xC), 128.2 (2xC), 64.7, 62.2, 52.5, 52.3, 52.2, 51.5, 50.9, 29.7.

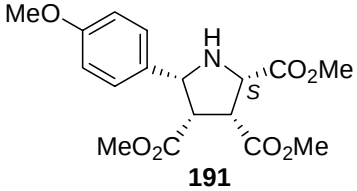
4.4.13 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(4-chlorophenyl)pyrrolidine-2,4-dicarboxylate



190

32% Ee as determined by HPLC, Chiralpak AS column+ guard column 95:5 hexanes-*i*-PrOH, t_R(major) = 26.1 min, t_R(minor) = 59.7 min; $[\alpha]_D^{30}$ = +9.0 (*c* 0.90 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 4H), 4.41 (d, *J* = 7.8 Hz, 1H), 3.85 (t, *J* = 8.1 Hz, 1H), 3.75 (s, 3H), 3.21 (t, *J* = 7.2 Hz, 1H), 3.19 (s, 3H), 2.60 (br, 1H, NH), 2.31 (t, *J* = 7.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3, 172.3, 138.0, 133.4, 128.3, 65.1, 59.7, 52.1, 51.2, 49.5, 33.1.

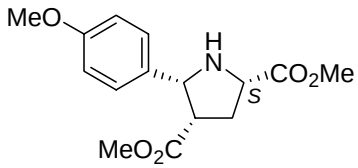
4.4.14 (2*S*, 3*R*, 4*S*, 5*R*)-Trimethyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate



191

74% Ee as determined by HPLC, Chiralpak AS column+ guard column 70:30 hexanes-*i*-PrOH, t_R(major) = 15.3 min, t_R(minor) = 29.6 min; $[\alpha]_D^{30}$ = +41.4 (*c* 1.01 g/100mL, DCM); ^{1}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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 170.0, 158.6, 128.7, 127.4 (2xC), 113.1 (2xC), 64.5, 61.7, 54.5, 52.0, 51.7, 51.4, 50.7, 50.4.

4.4.15 (2*S*, 4*S*, 5*R*)-Dimethyl 5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylate



192

77% Ee as determined by HPLC, Chiralpak AS column+ guard column 95:5 hexanes-*i*-PrOH, t_R(major) = 39.8 min, t_R(minor) = 66.3 min; $[\alpha]_D^{30}$ = +42.9 (*c* 1.34 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.45 (d, *J* = 7.8 Hz, 1H), 3.90 (t, *J* = 8.2 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.24 (s, 3H), 2.67 (br, 1H, NH), 2.35 (t, *J* = 5.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.0, 172.2, 158.5, 130.8, 127.4, 113.0, 64.9, 59.3, 54.5, 51.5, 50.6, 49.2, 32.8.

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APPENDIX A

NMR SPECTRUMS AND HPLC CHROMATOGRAMS OF COMPOUNDS

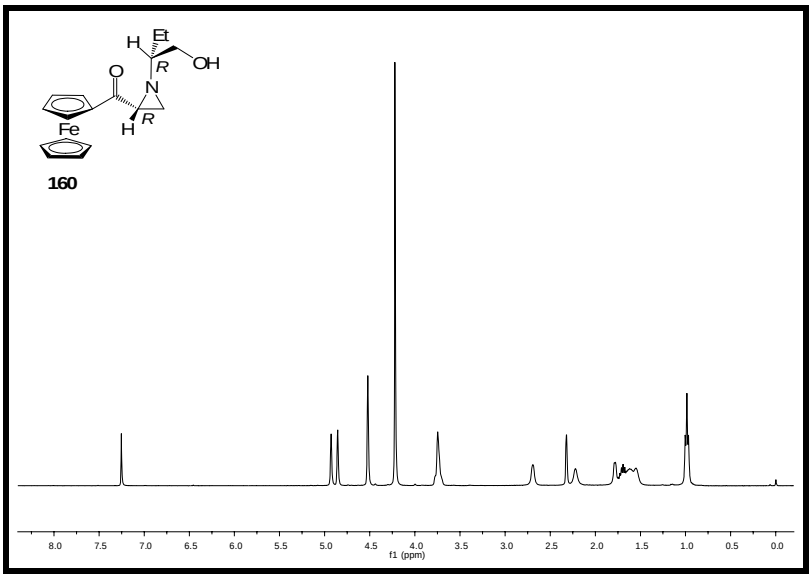


Figure A.1 ^{1}H-NMR spectrum of compound **160**

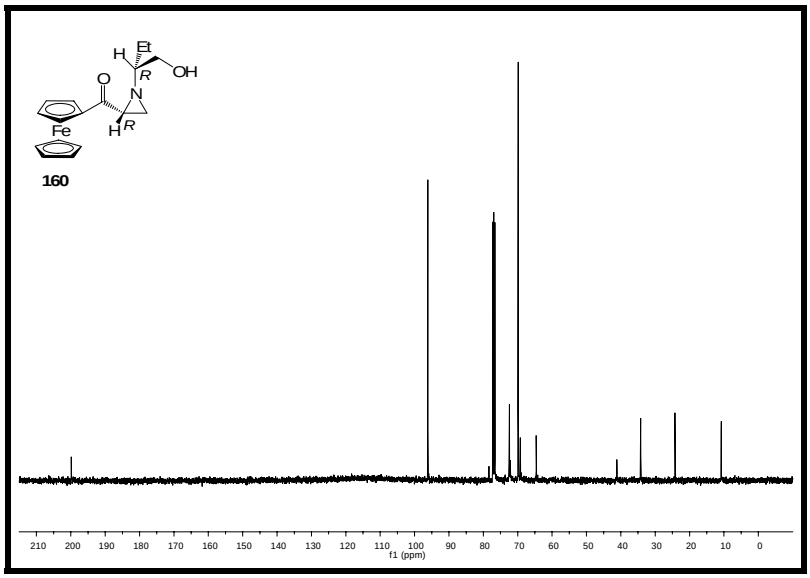


Figure A.2 ^{13}C-NMR spectrum of compound **160**

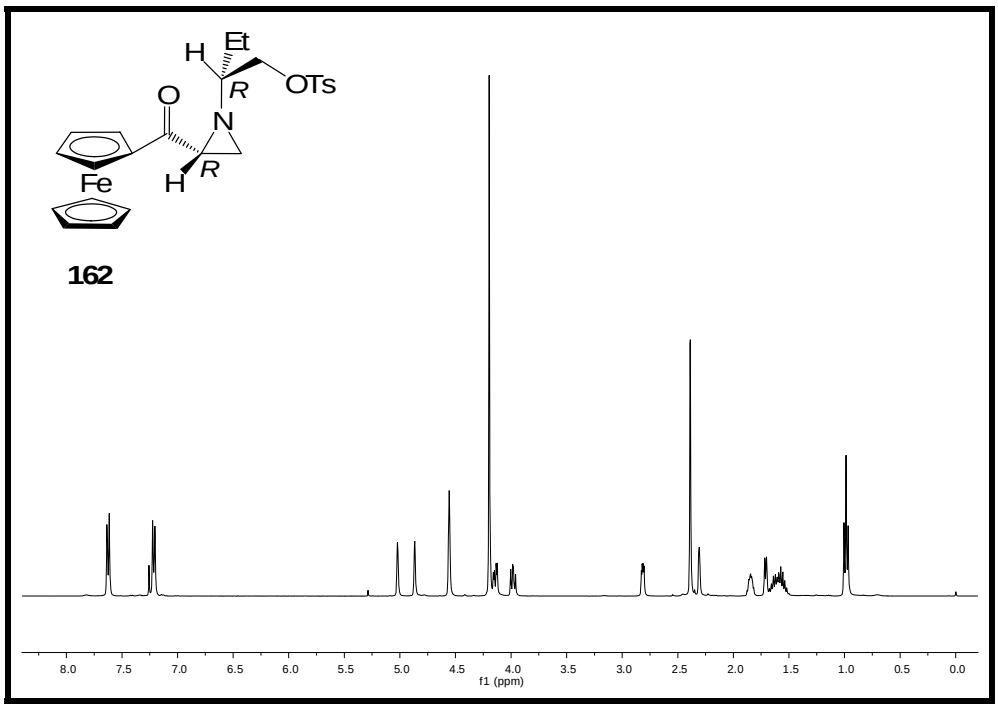


Figure A.3 ^{1}H-NMR spectrum of compound **162**

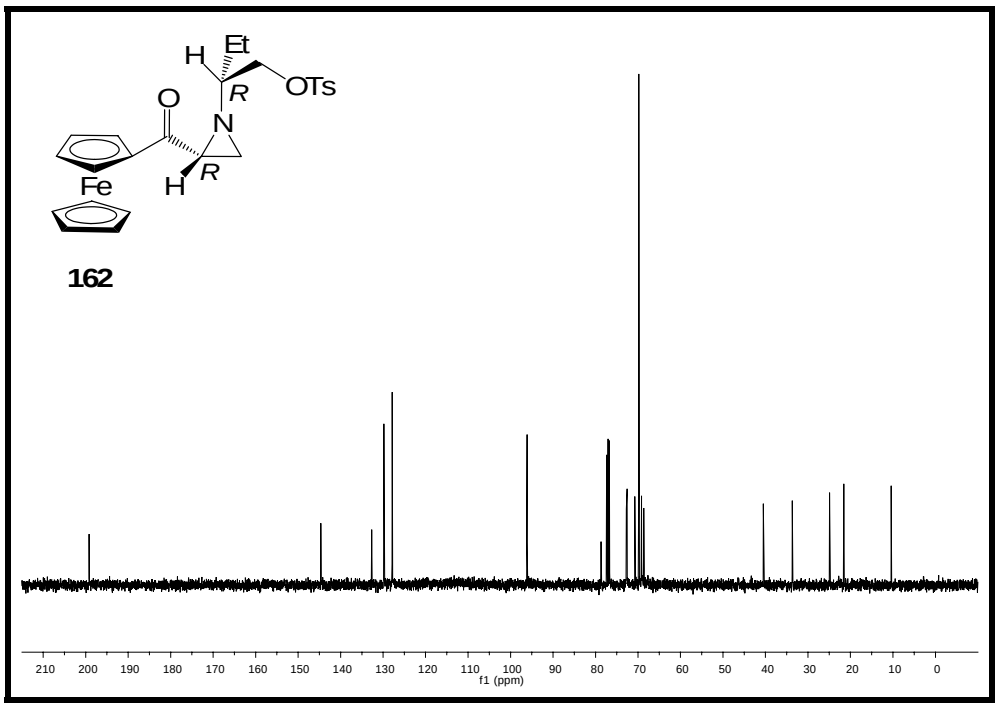


Figure A.4 ^{13}C-NMR spectrum of compound **162**

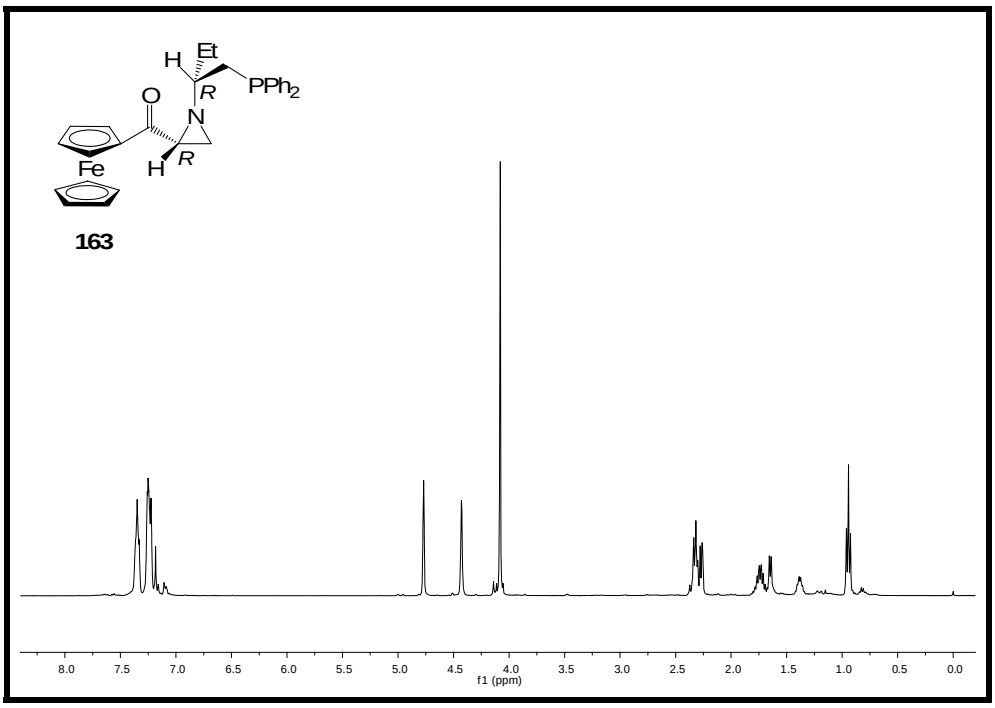


Figure A.5 ^{1}H-NMR spectrum of compound **163**

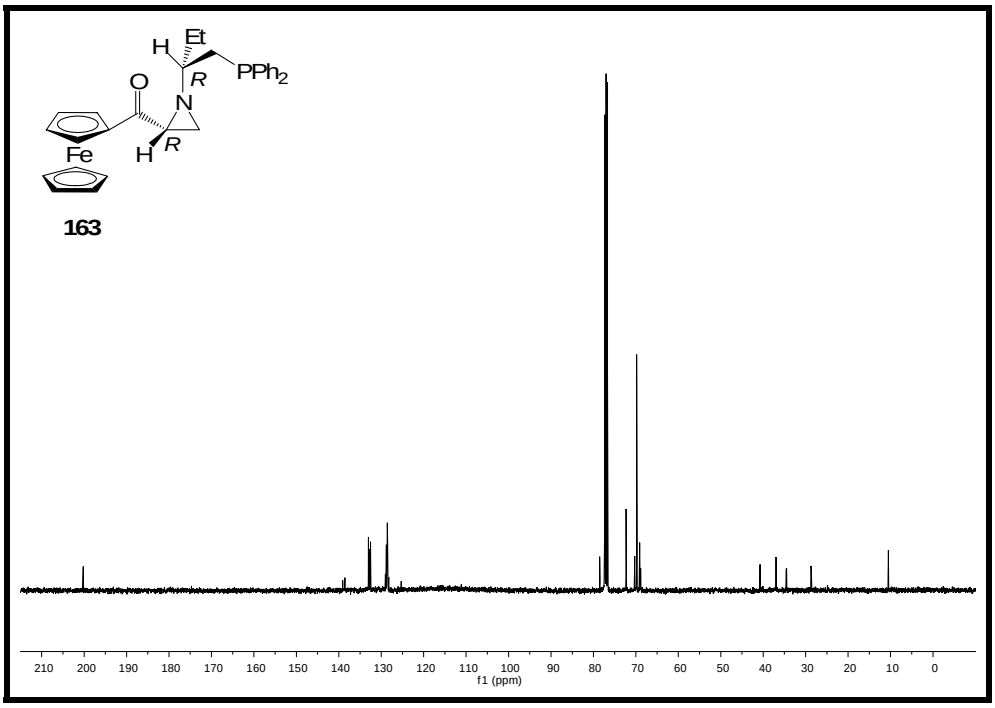


Figure A.6 ^{13}C-NMR spectrum of compound **163**

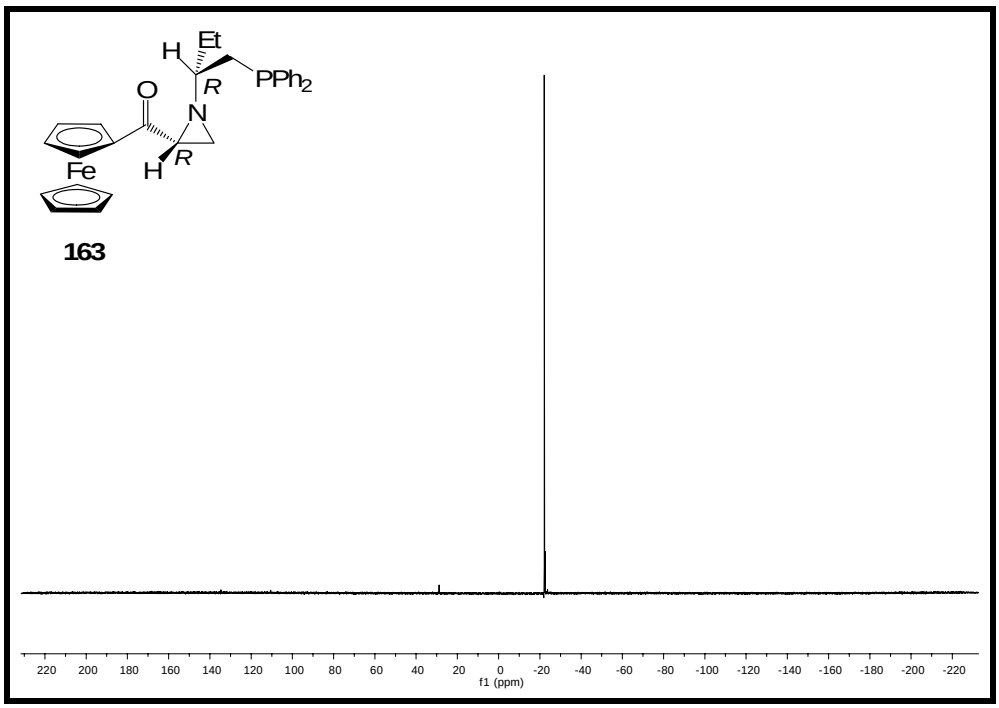


Figure A.7 ^{31}P-NMR spectrum of compound **163**

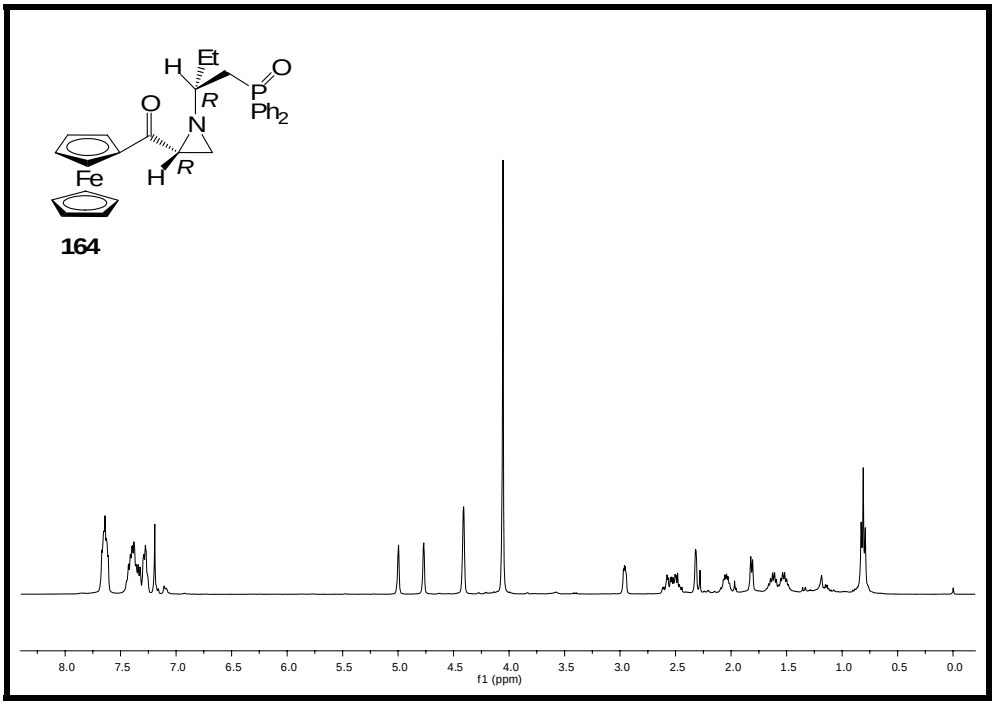


Figure A.8 ^{1}H-NMR spectrum of compound **164**

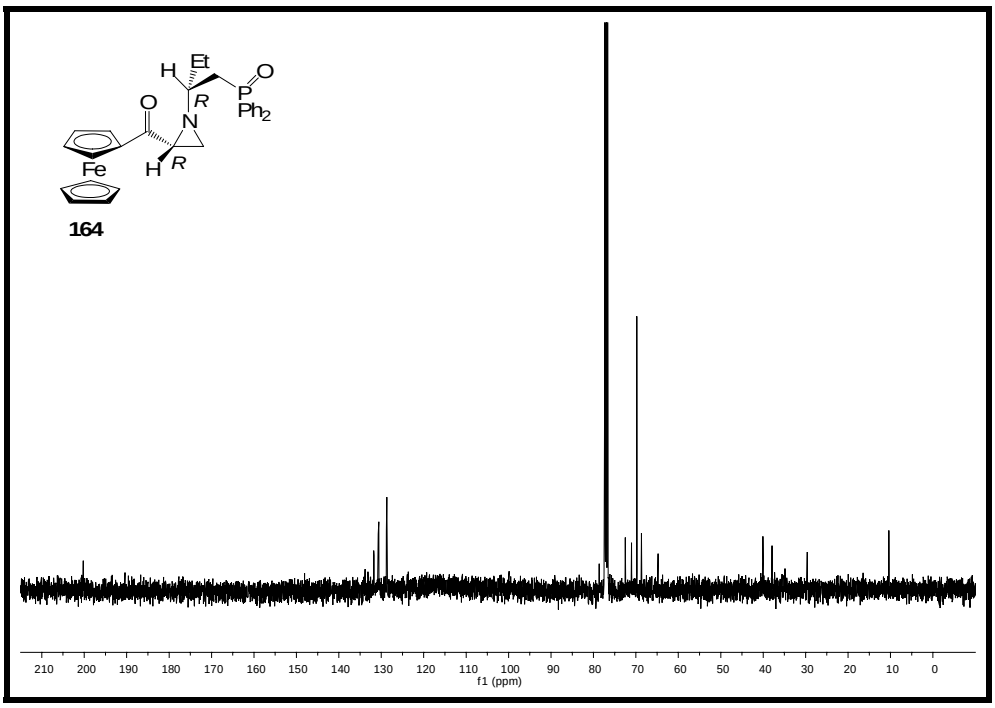


Figure A.9 ^{13}C-NMR spectrum of compound **164**

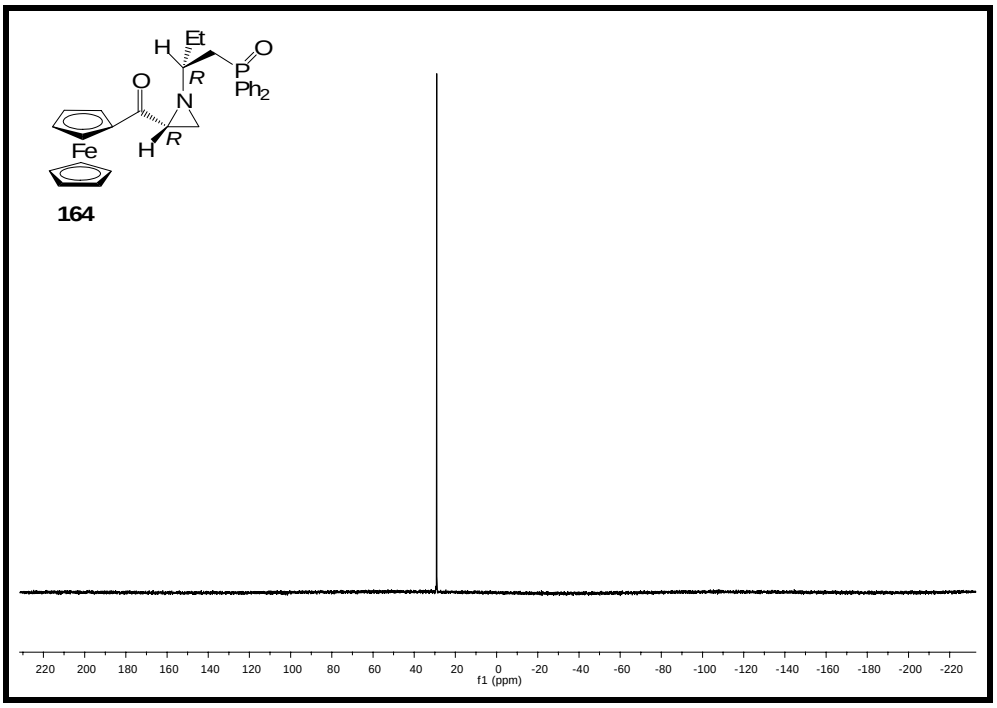


Figure A.10 ^{31}P-NMR spectrum of compound **164**

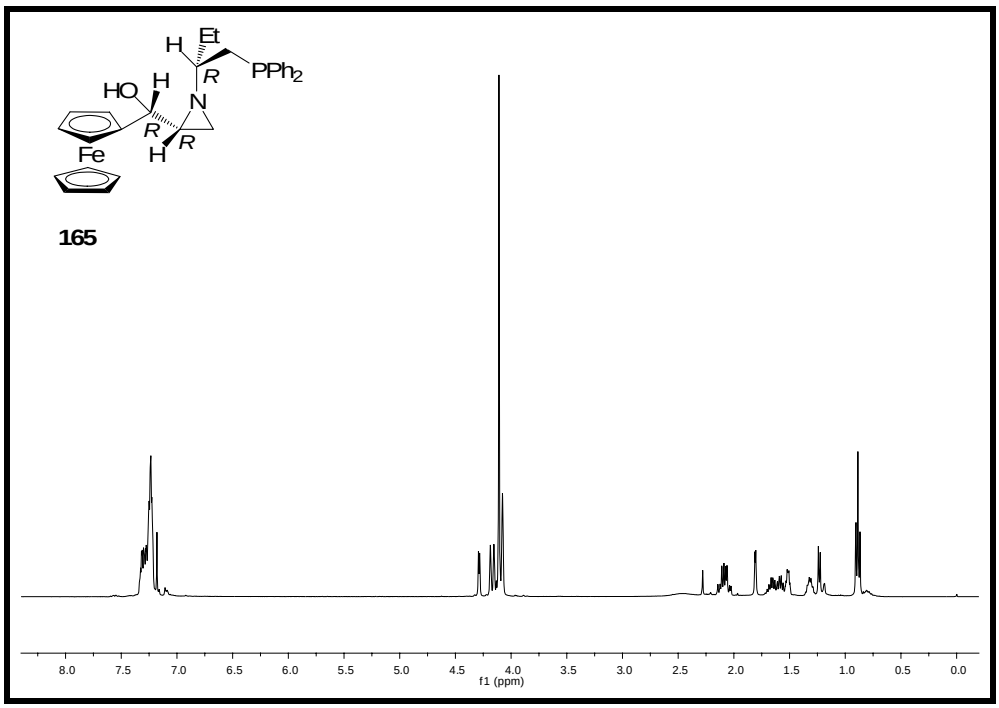


Figure A.11 ^{1}H-NMR spectrum of compound **165**

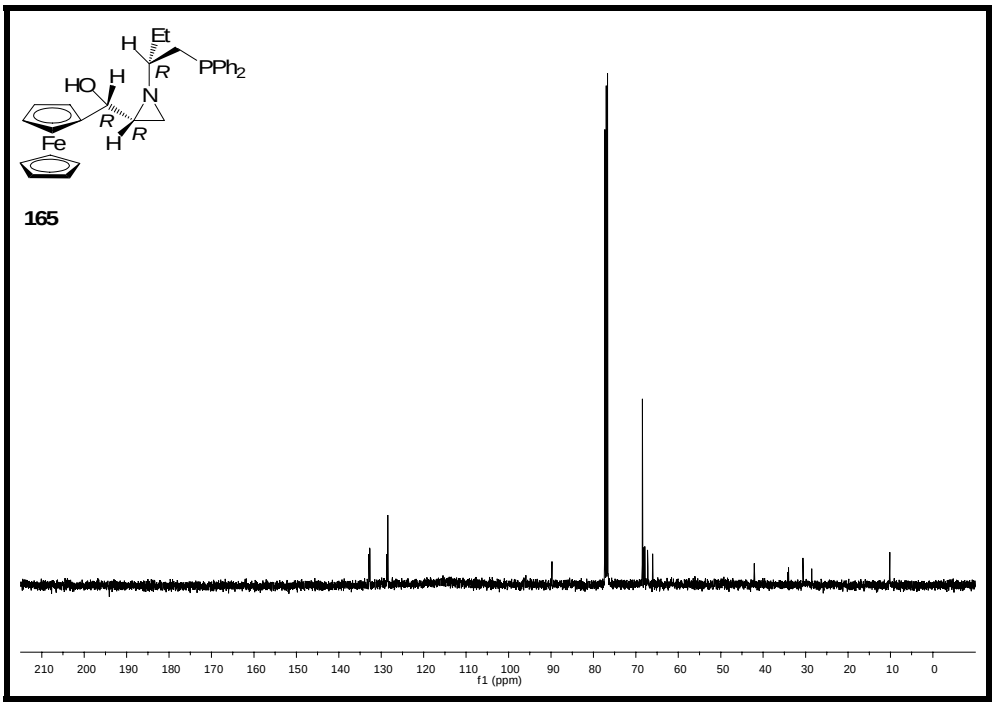


Figure A.12 ^{13}C-NMR spectrum of compound **165**

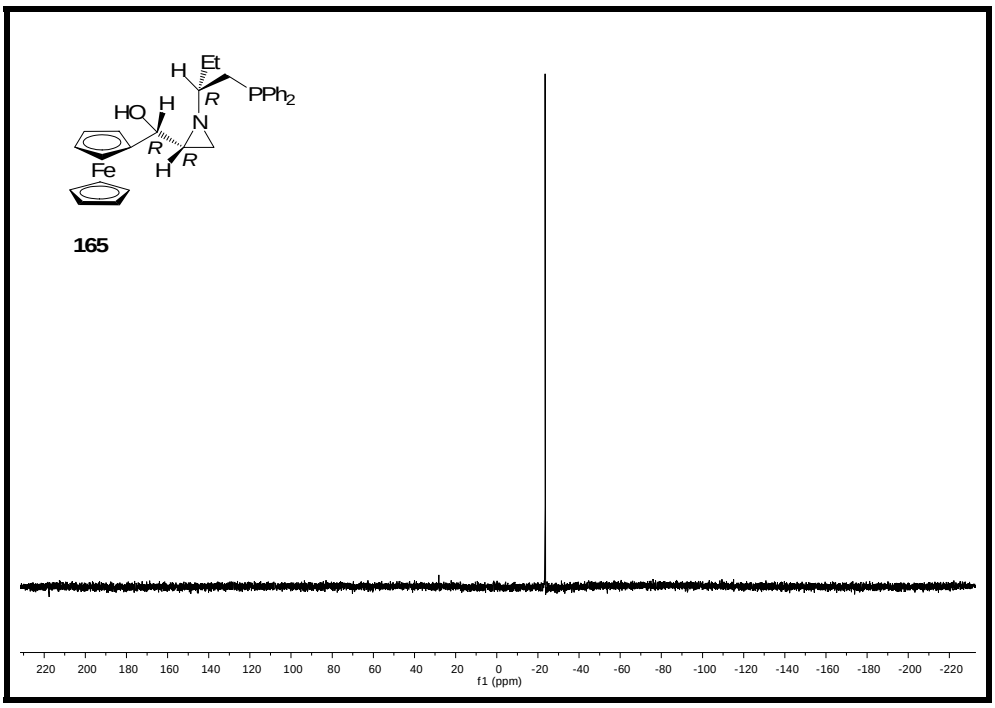


Figure A.13 ^{31}P-NMR spectrum of compound **165**

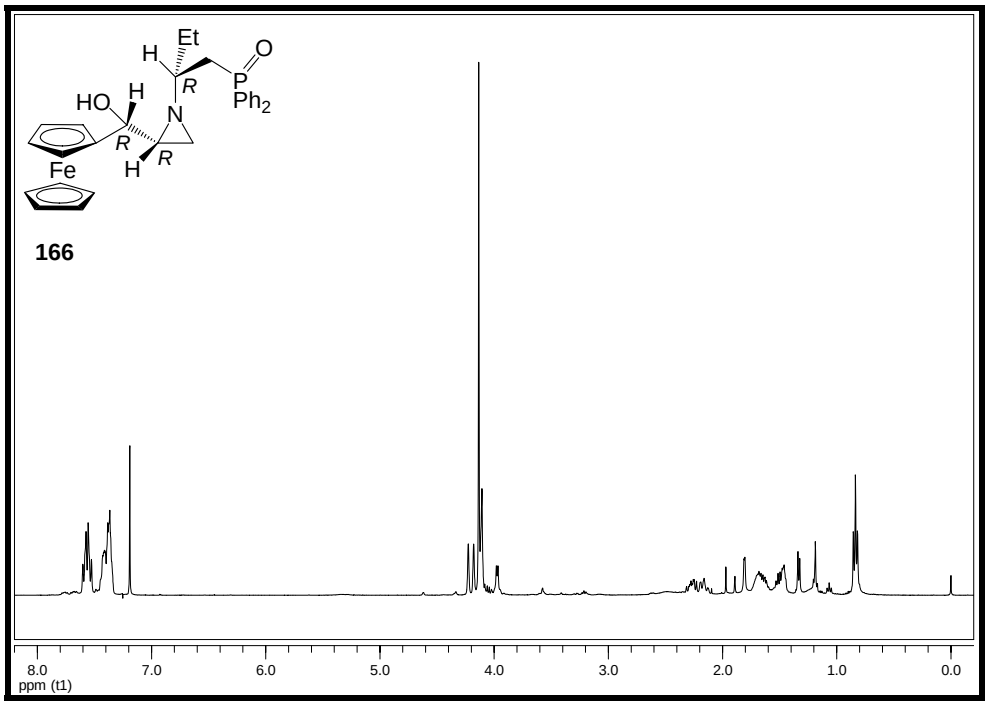


Figure A.14 ^{1}H-NMR spectrum of compound **166**

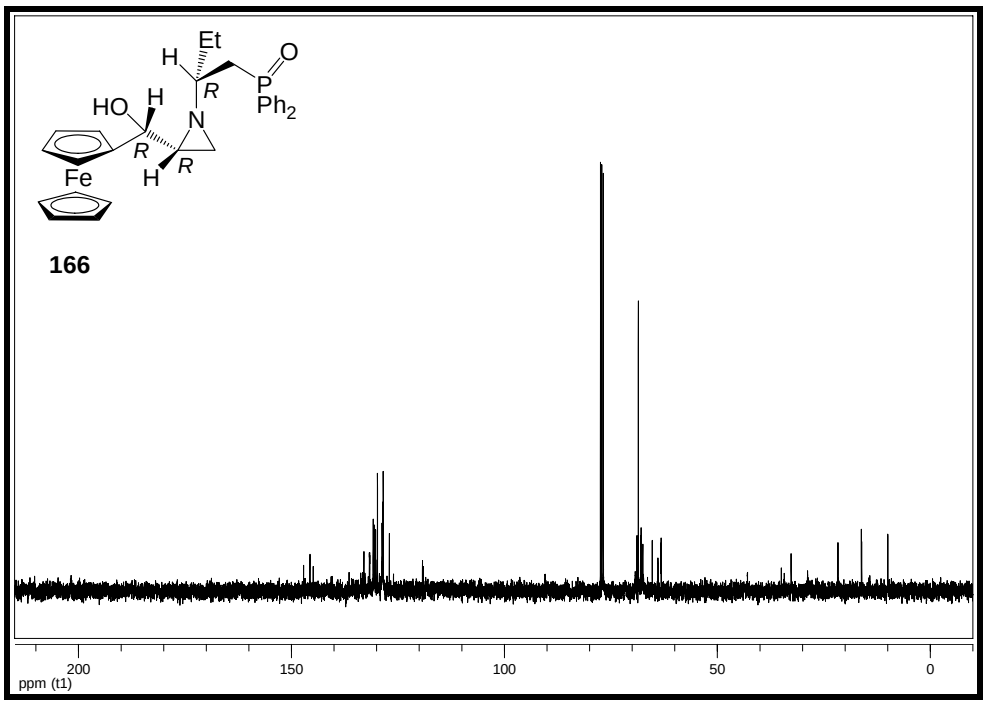


Figure A.15 ^{13}C-NMR spectrum of compound **166**

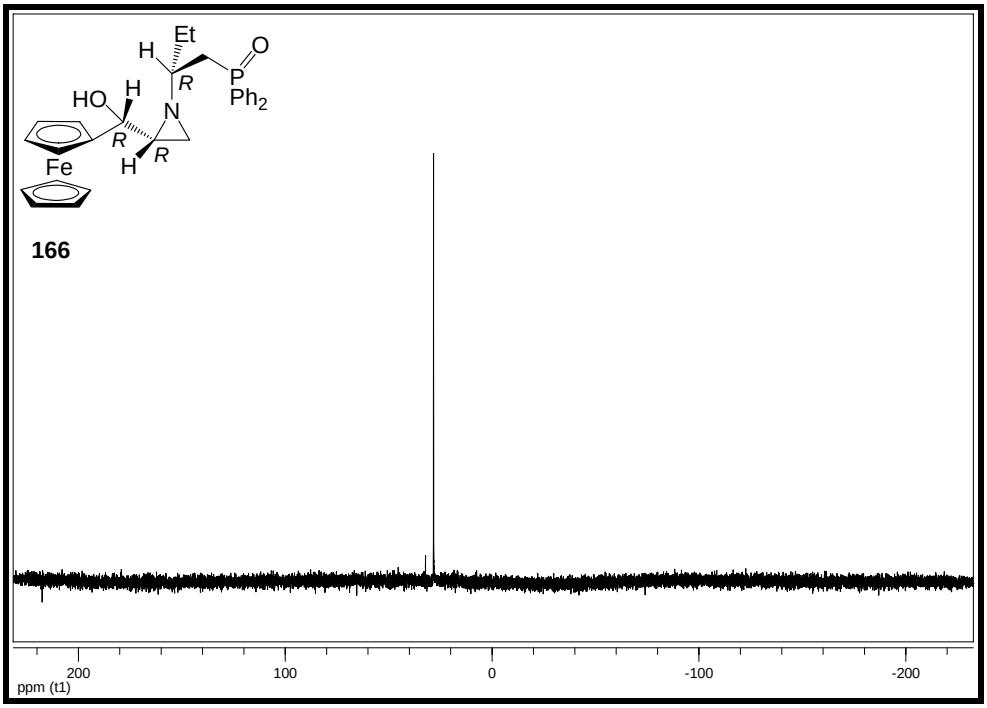


Figure A.16 ^{31}P-NMR spectrum of compound **166**

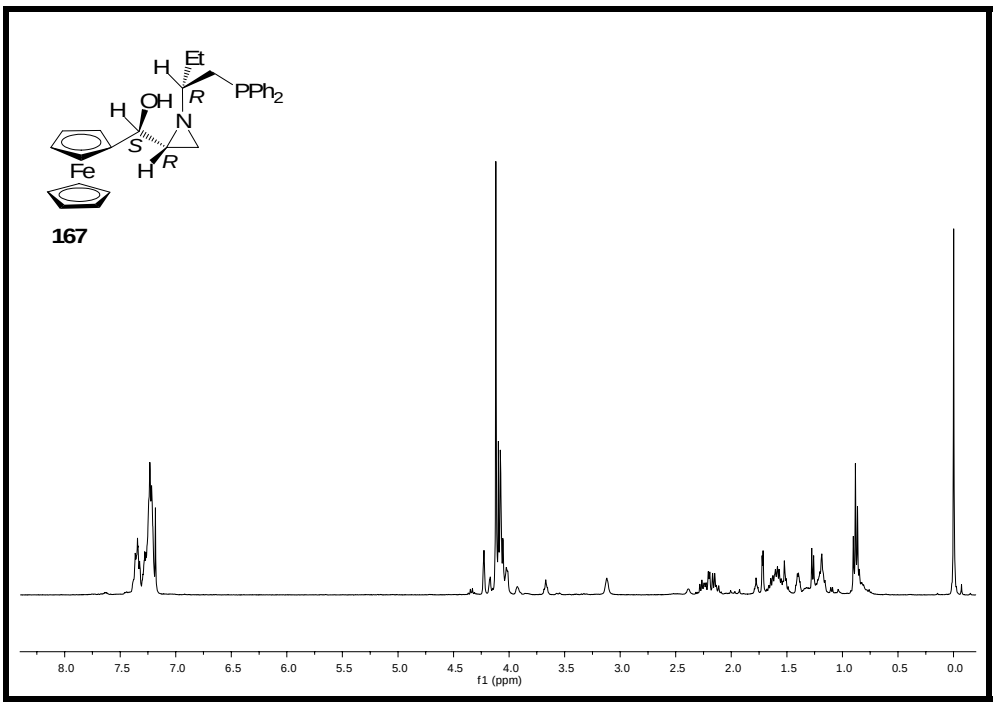


Figure A.17 ^{1}H-NMR spectrum of compound **167**

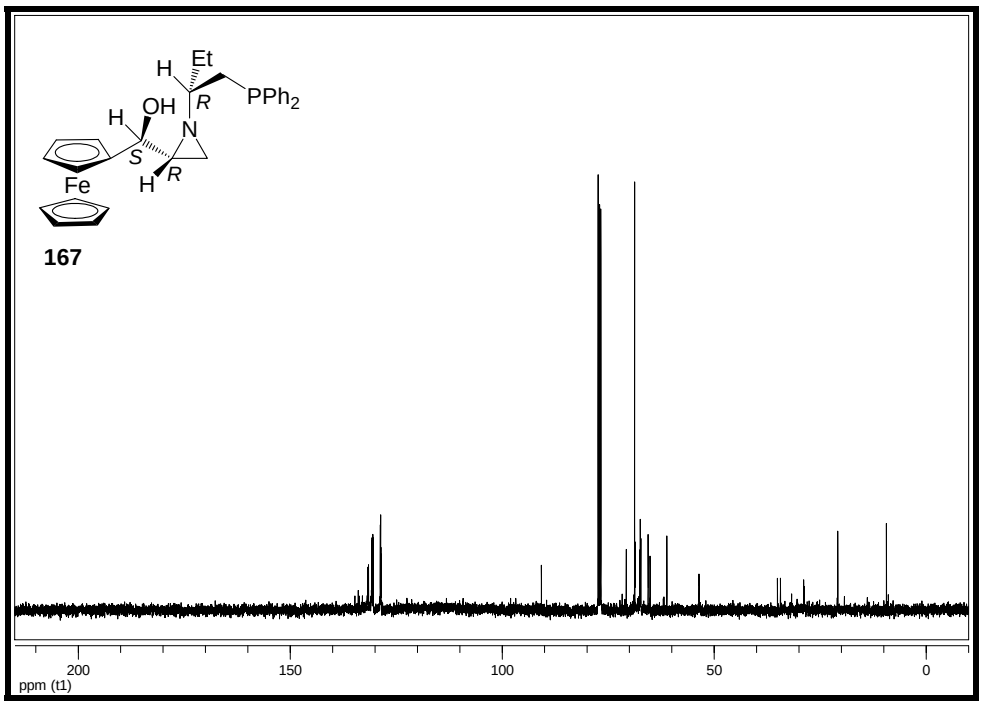


Figure A. 18 ^{13}C-NMR spectrum of compound **167**

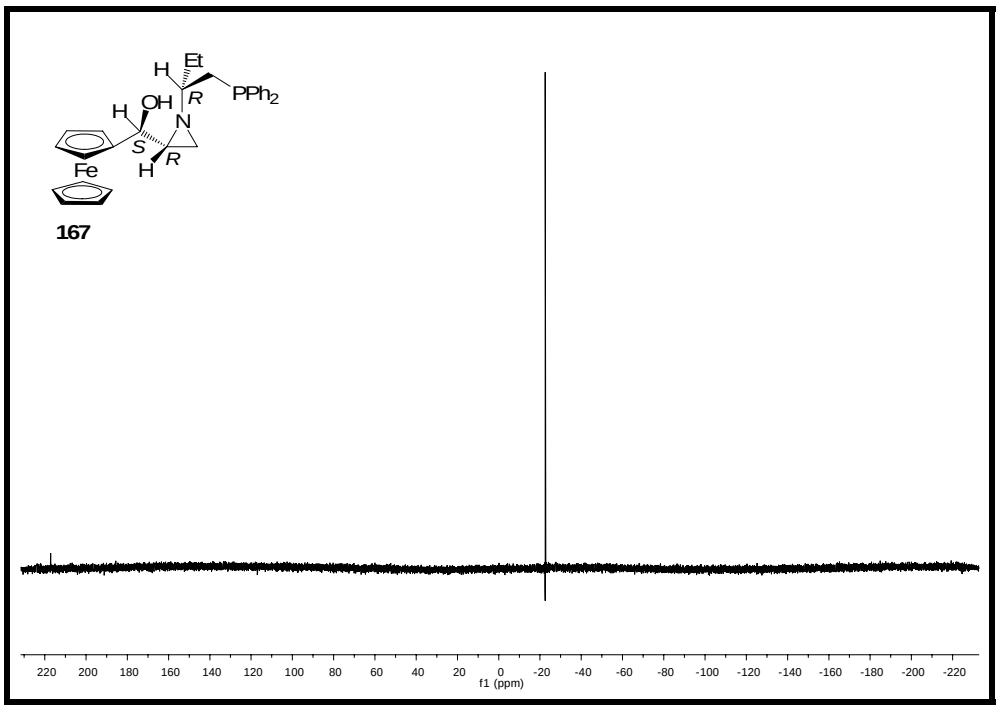


Figure A.19 ^{31}P-NMR spectrum of compound **167**

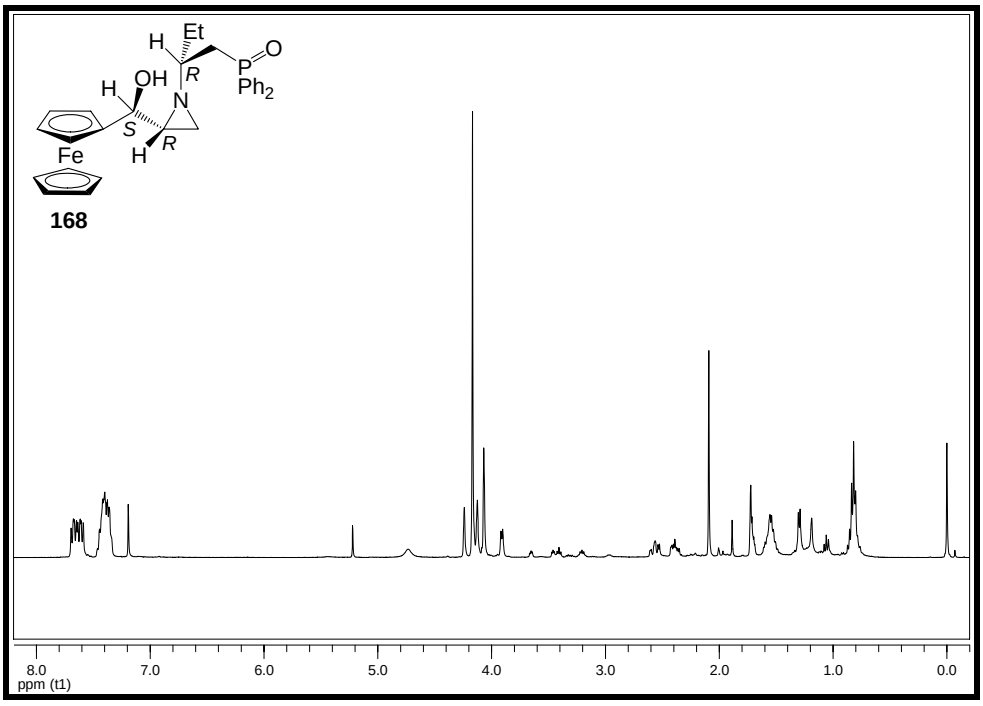


Figure A.20 ^{1}H-NMR spectrum of compound **168**

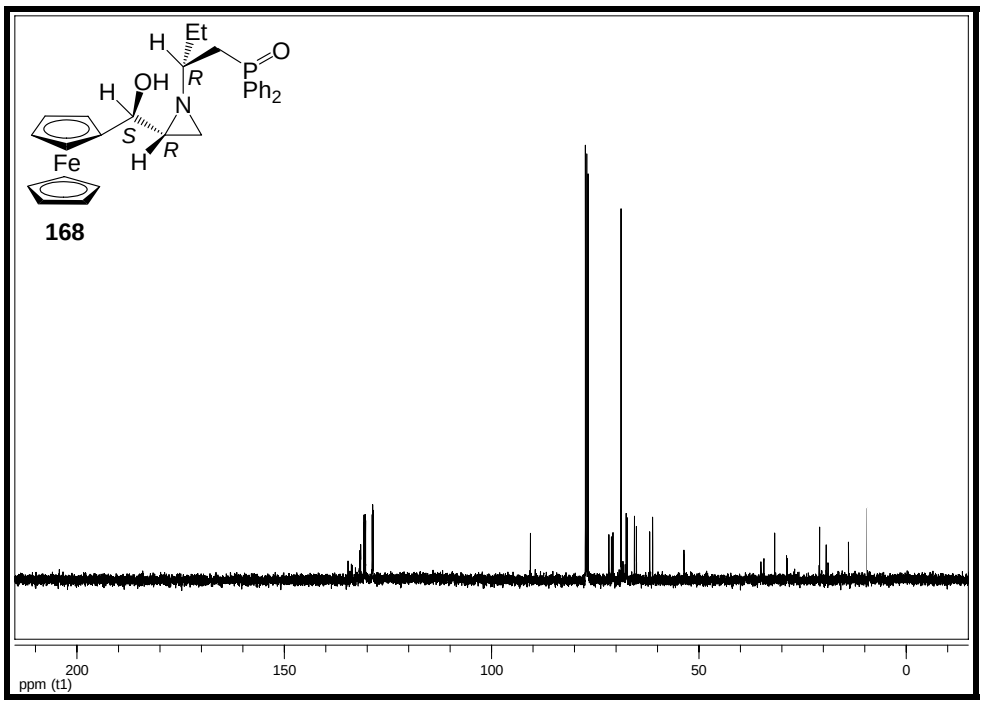


Figure A.21 ^{13}C-NMR spectrum of compound **168**

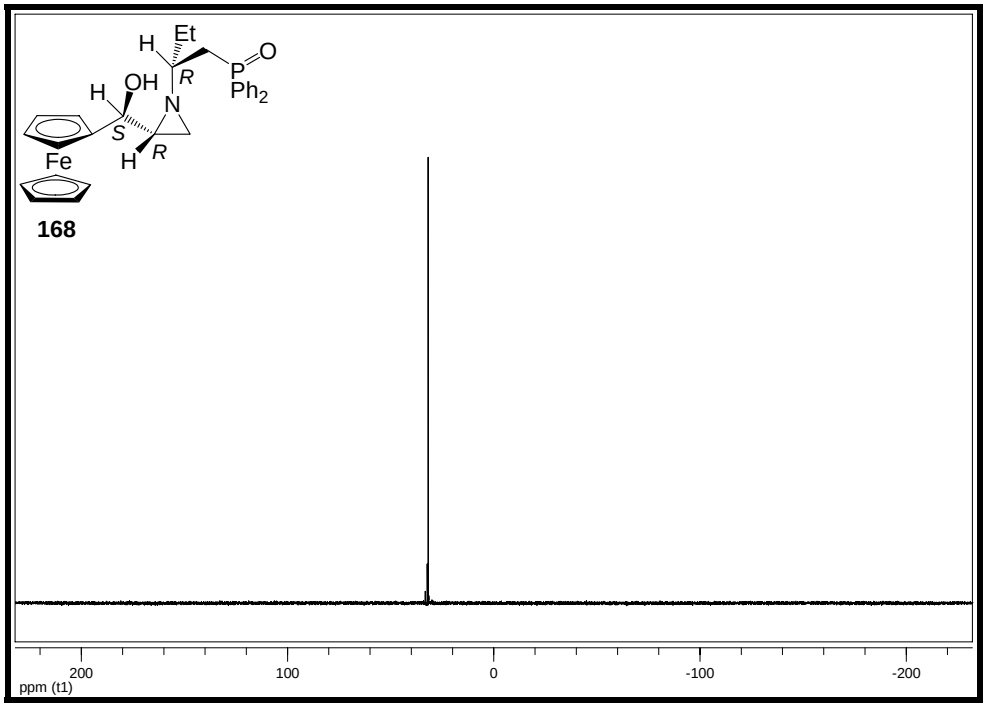


Figure A.22 ^{31}P-NMR spectrum of compound **168**

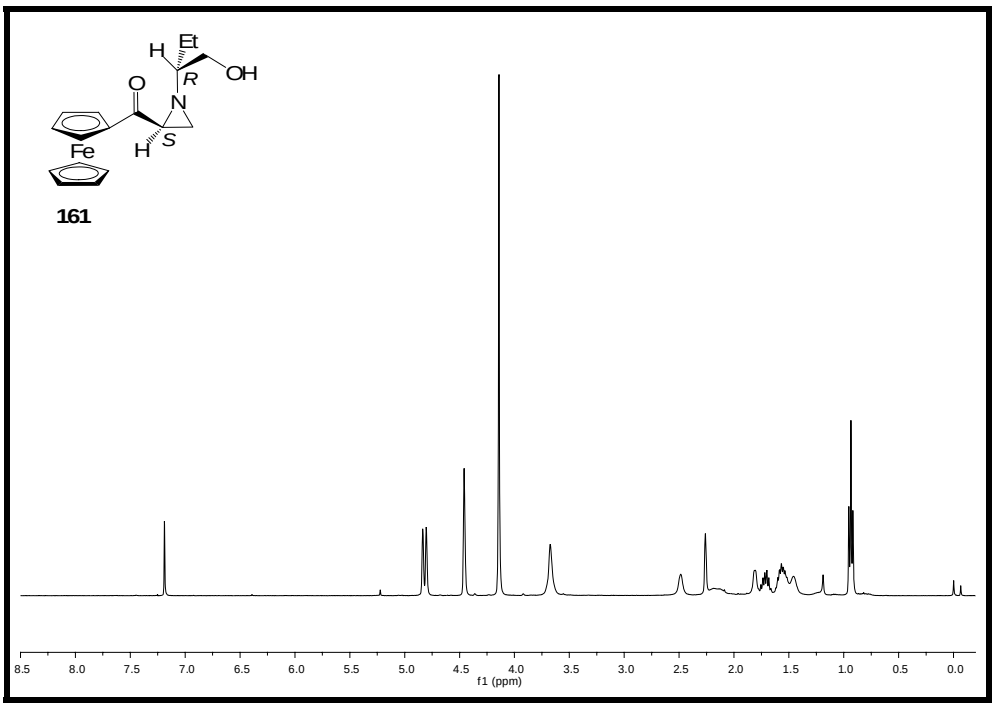


Figure A.23 ^{1}H-NMR spectrum of compound **161**

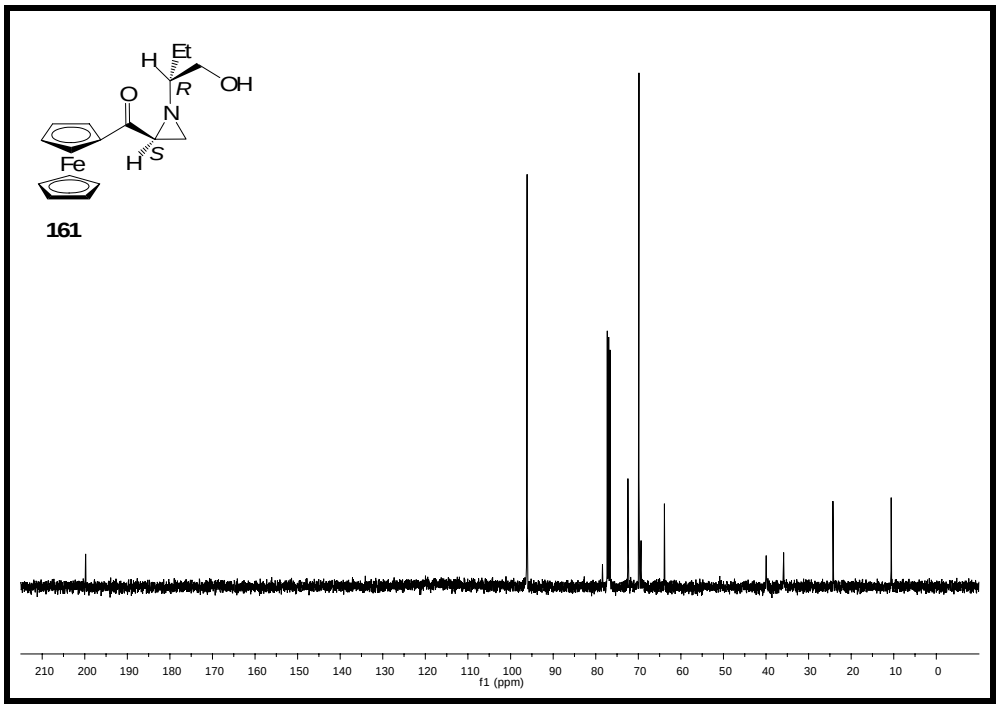


Figure A.24 ^{13}C-NMR spectrum of compound **161**

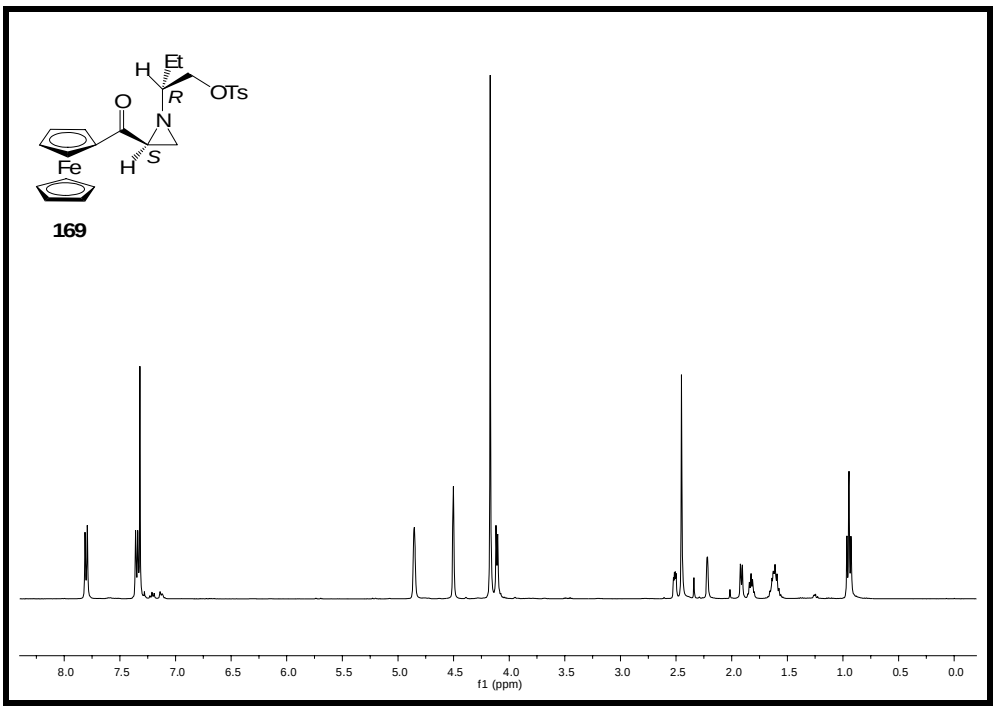


Figure A.25 ^{1}H-NMR spectrum of compound **169**

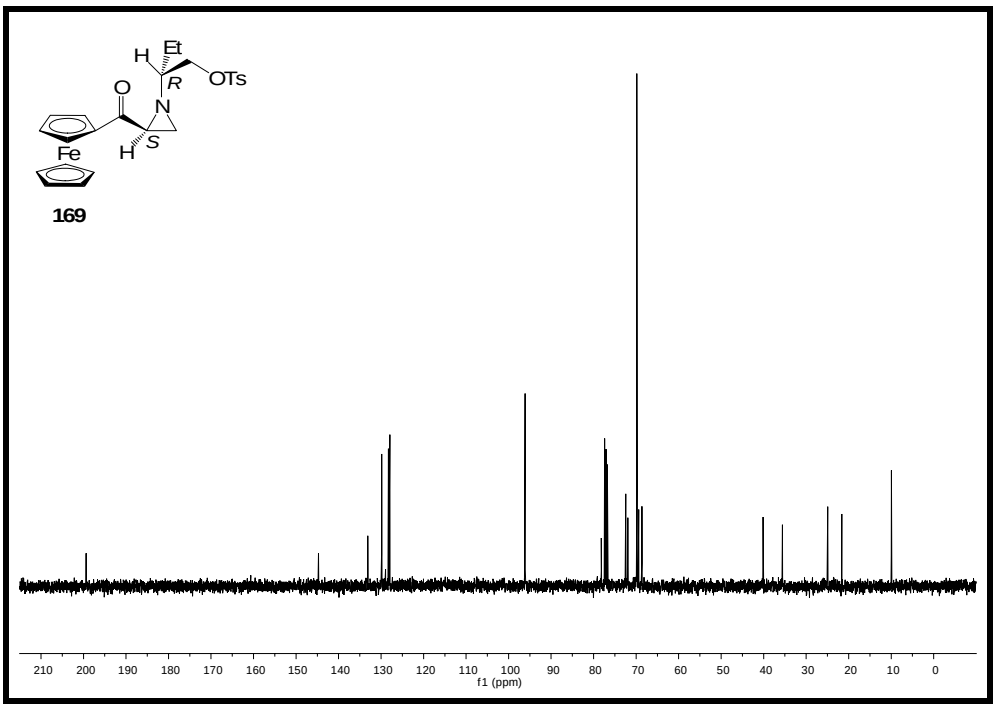


Figure A.26 ^{13}C-NMR spectrum of compound **169**

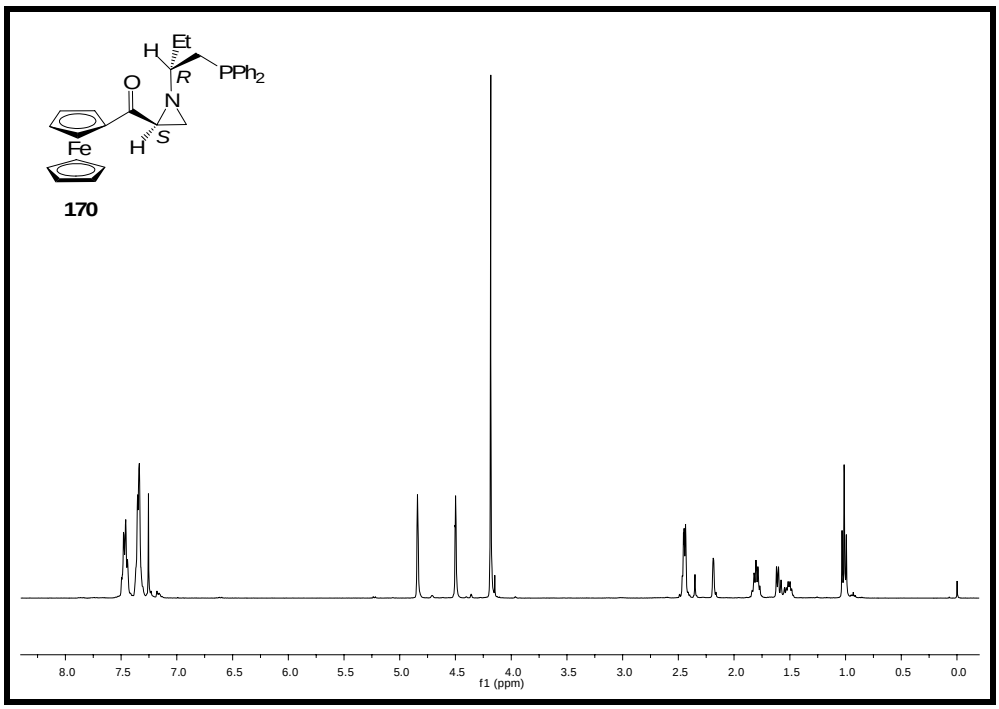


Figure A.27 ^{1}H-NMR spectrum of compound **170**

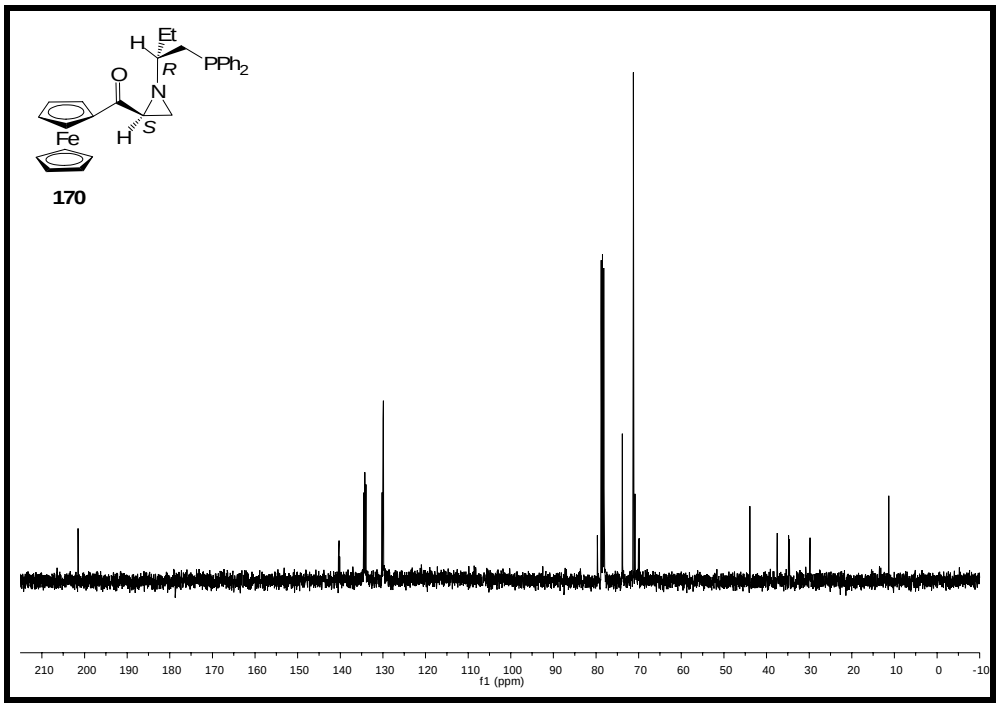


Figure A.28 ^{13}C-NMR spectrum of compound **170**

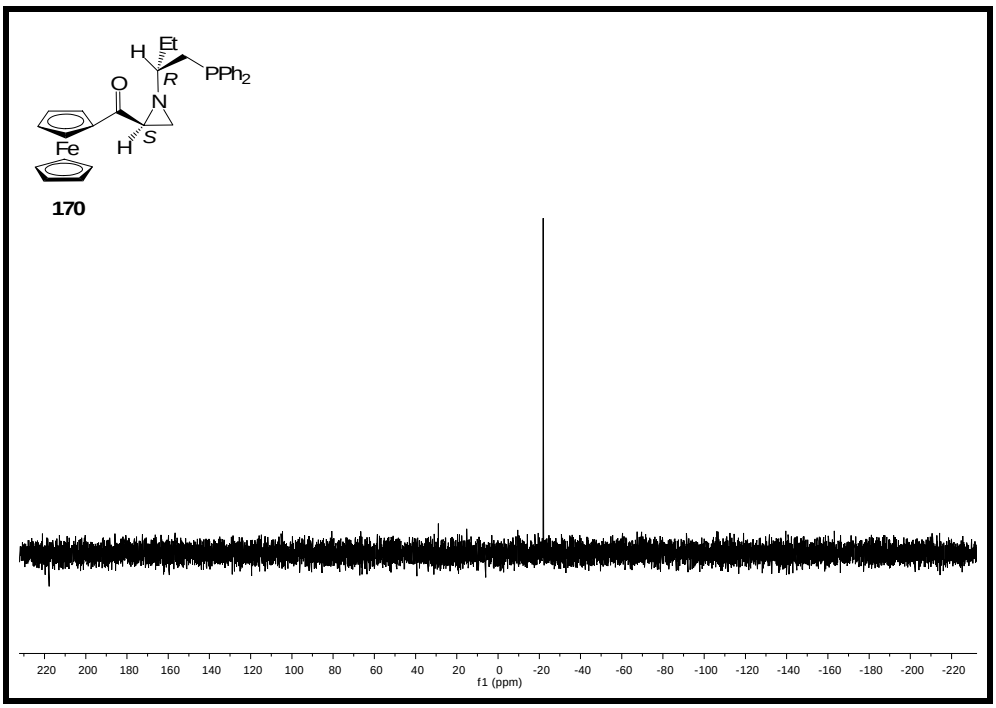


Figure A.29 ^{31}P-NMR spectrum of compound **170**

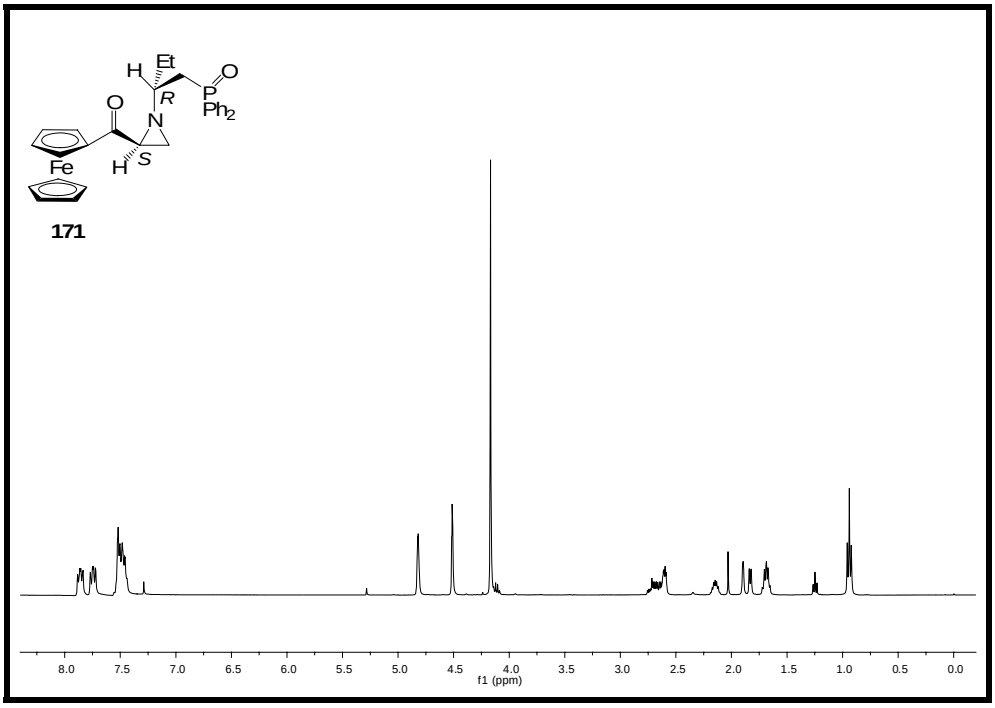


Figure A.30 ^{1}H-NMR spectrum of compound **171**

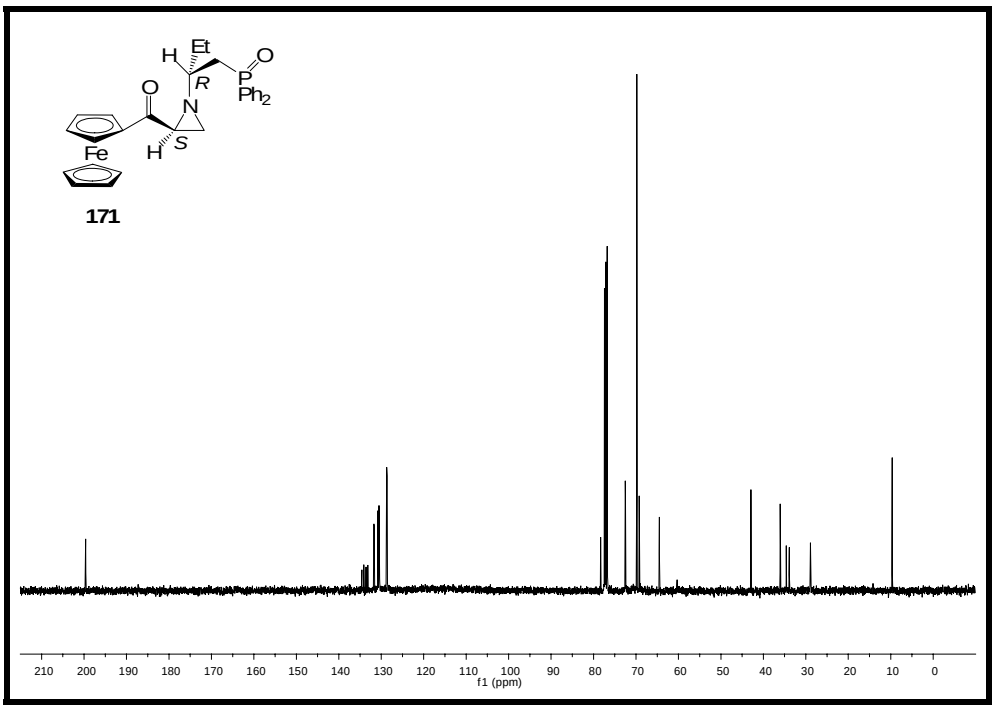


Figure A.31 ^{13}C-NMR spectrum of compound **171**

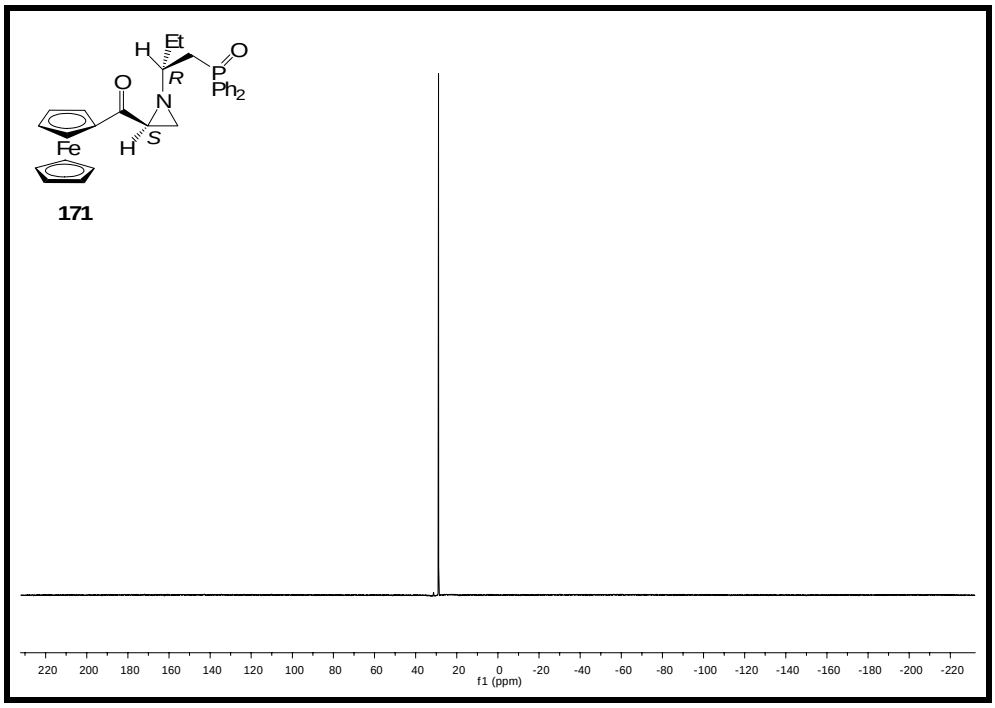


Figure A.32 ^{31}P-NMR spectrum of compound **171**

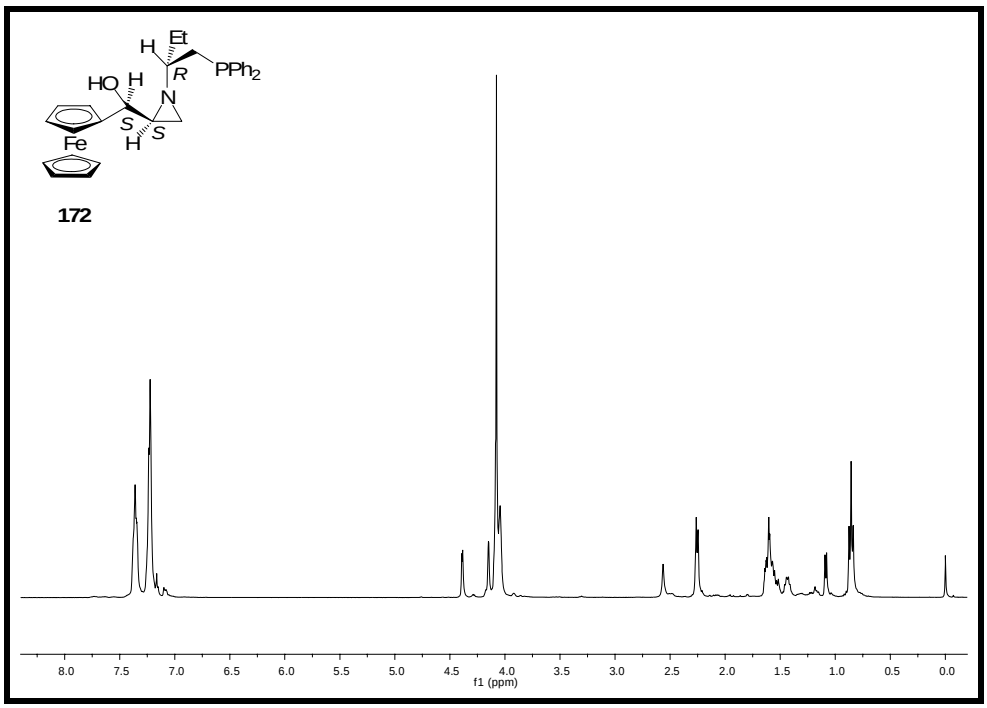


Figure A.33 ^{1}H-NMR spectrum of compound **172**

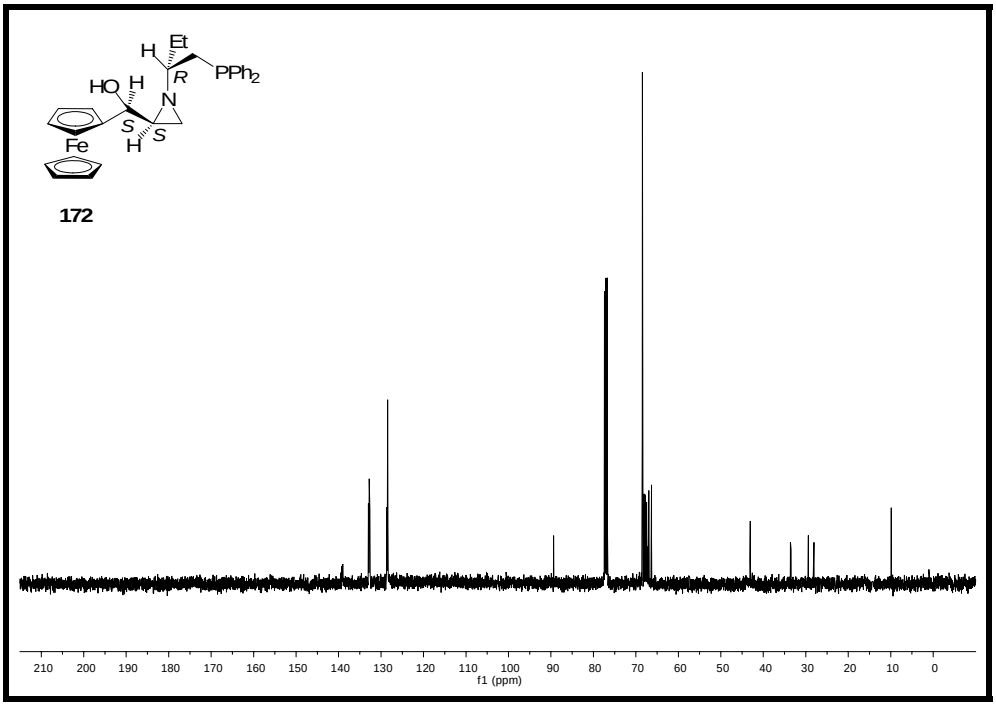


Figure A.34 ^{13}C-NMR spectrum of compound **172**

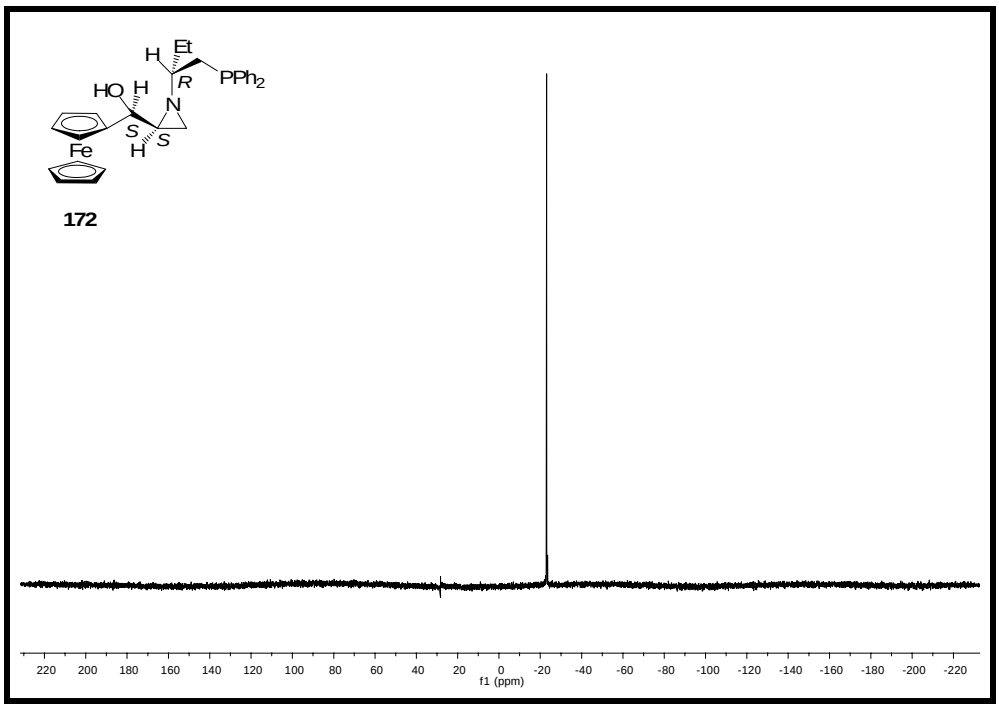


Figure A.35 ^{31}P-NMR spectrum of compound **172**

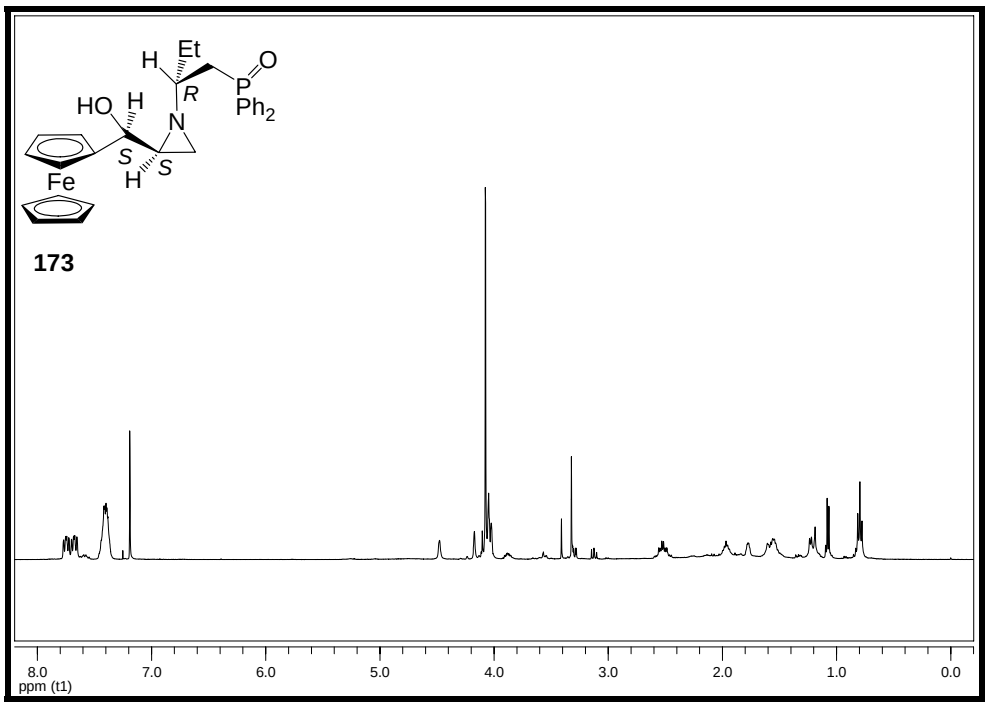


Figure A.36 ^{1}H-NMR spectrum of compound **173**

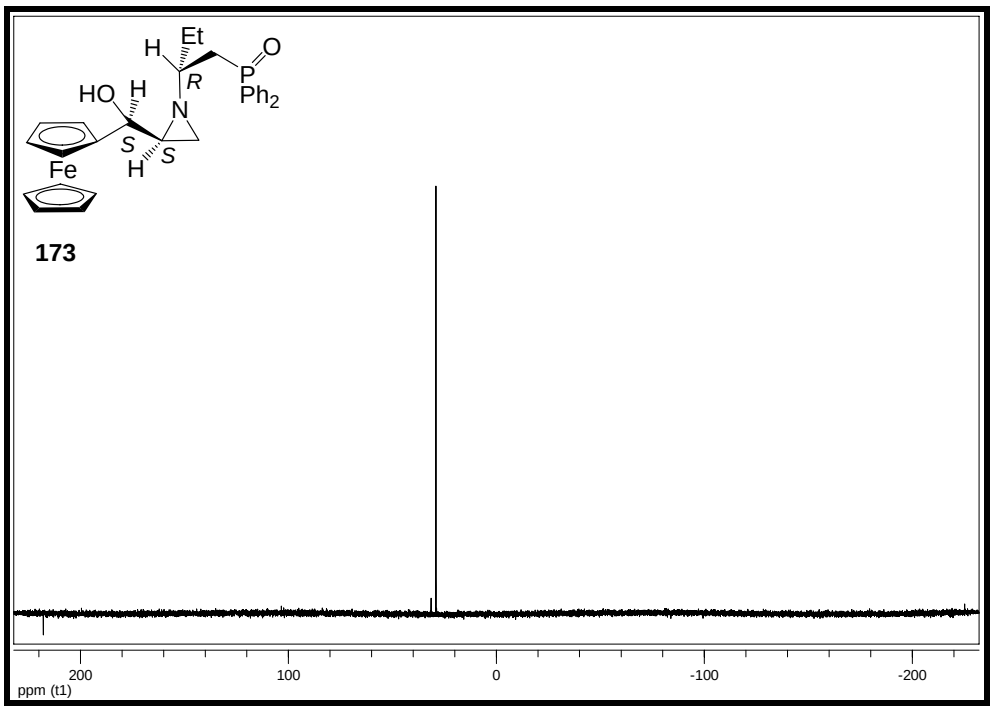


Figure A.37 ^{31}P-NMR spectrum of compound **173**

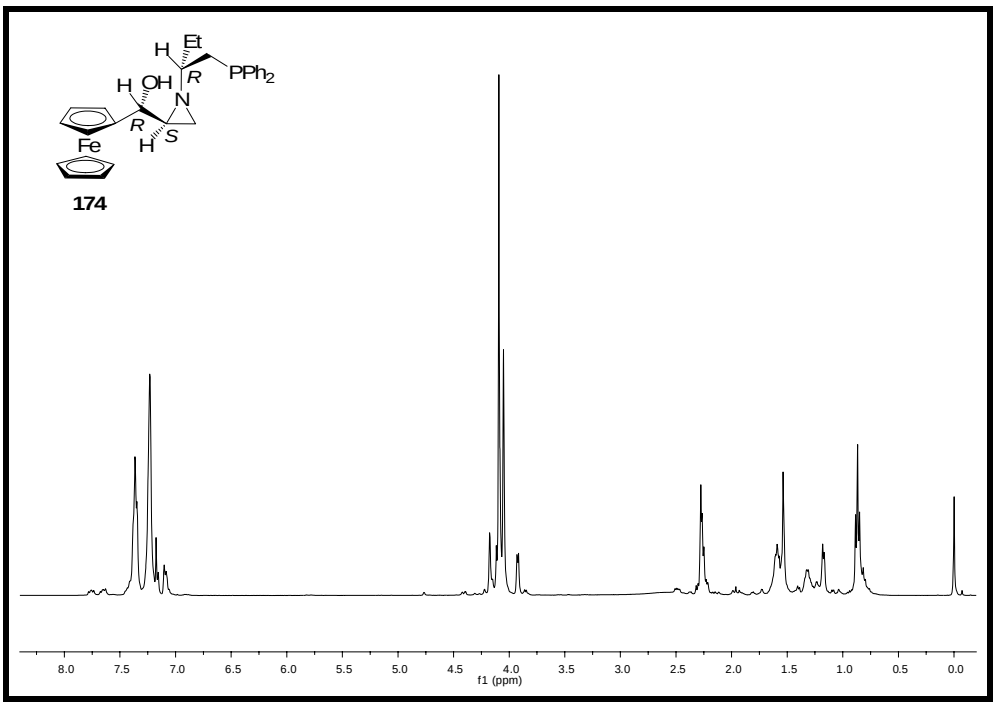


Figure A.38 ^{1}H-NMR spectrum of compound **174**

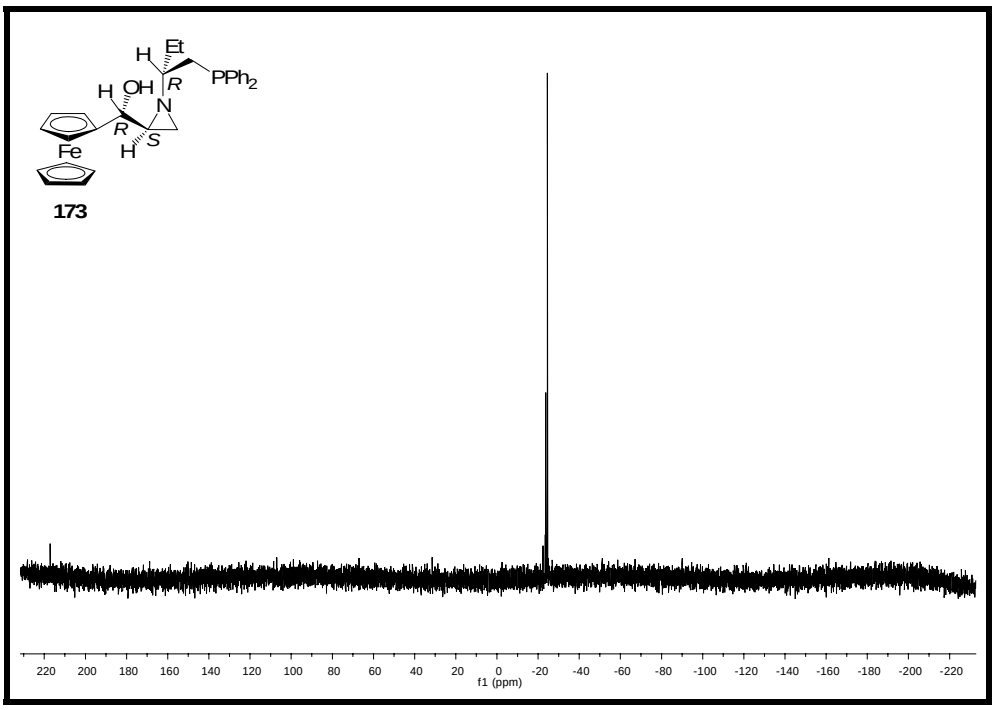


Figure A.39 ^{31}P-NMR spectrum of compound **174**

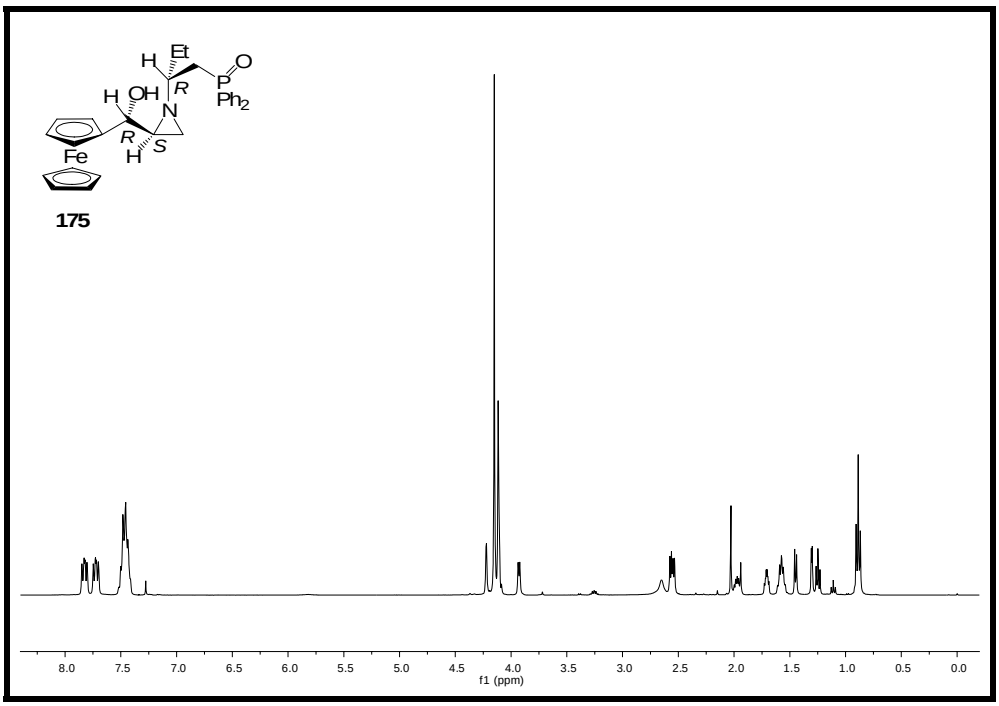


Figure A.40 ^{1}H-NMR spectrum of compound **175**

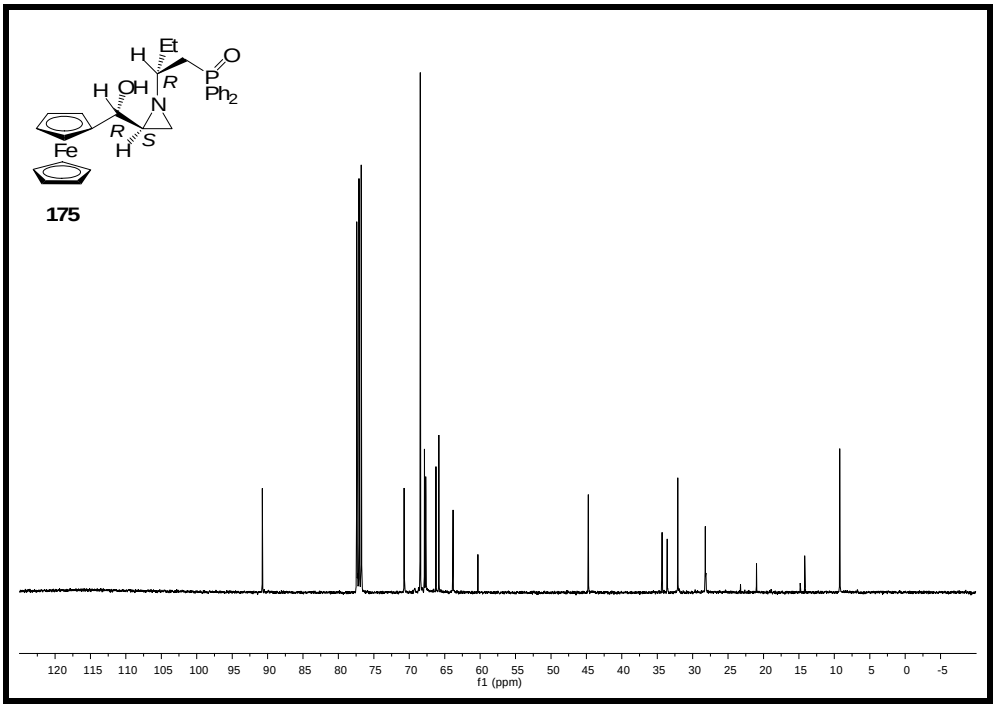


Figure A.41 ^{13}C-NMR spectrum of compound **175**

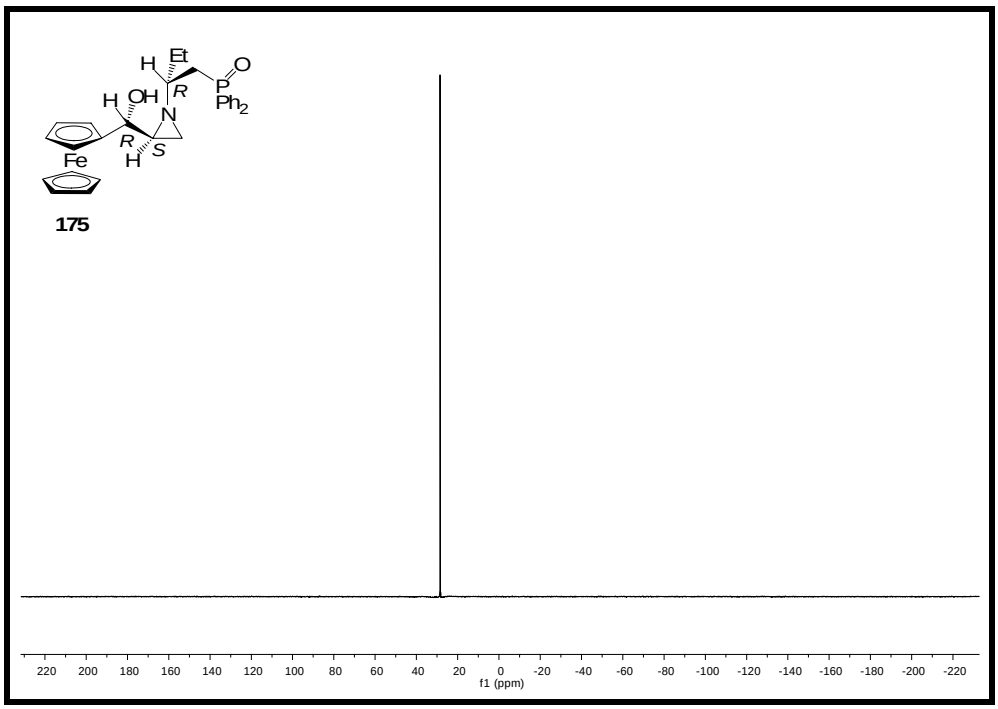


Figure A.42 ^{31}P-NMR spectrum of compound **175**

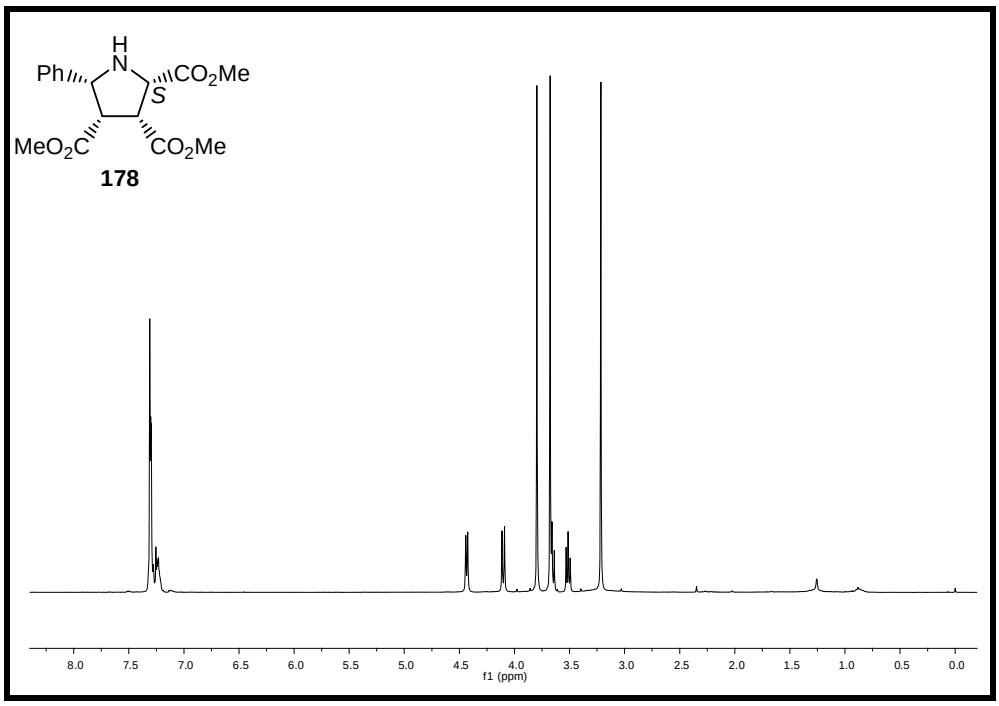


Figure A.43 ^{1}H-NMR spectrum of compound **178**

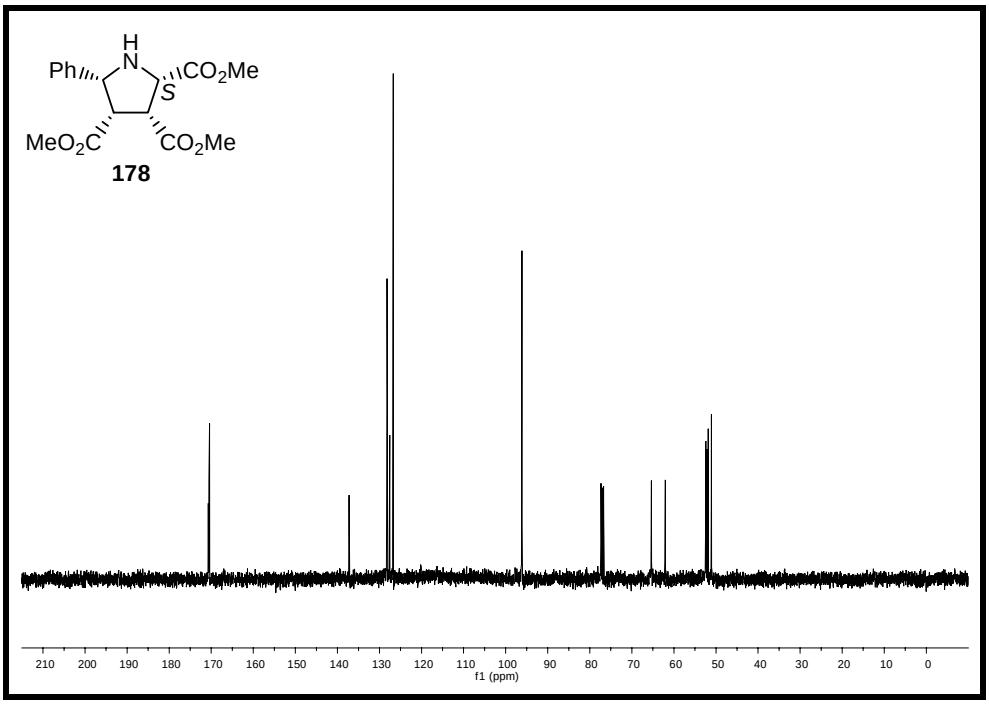


Figure A.44 ^{13}C-NMR spectrum of compound **178**

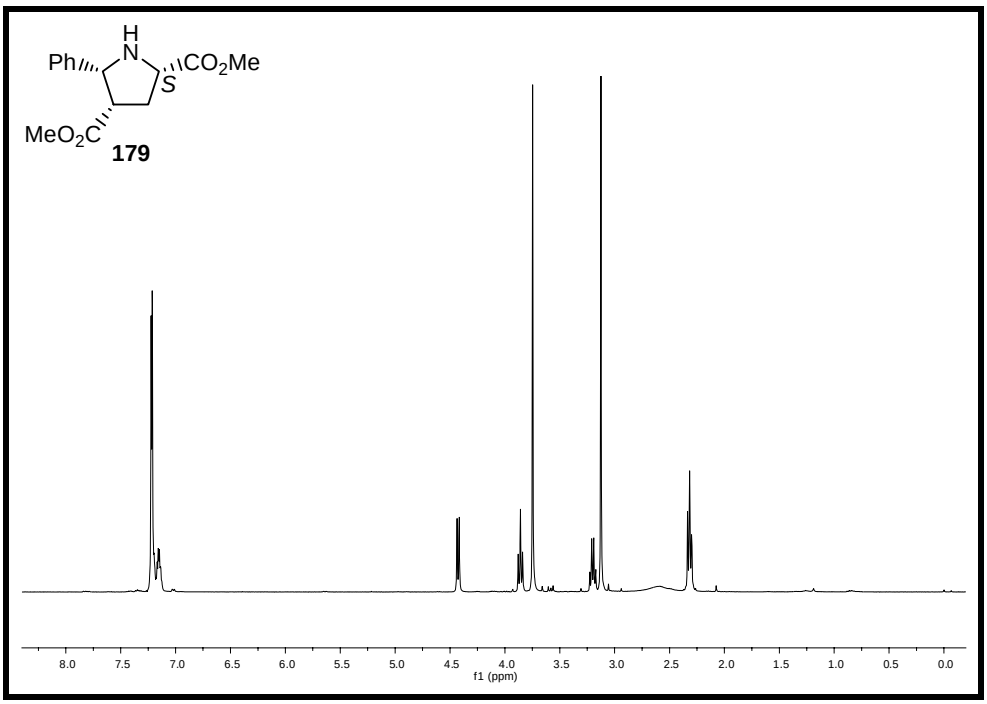


Figure A.45 ^{1}H-NMR spectrum of compound **179**

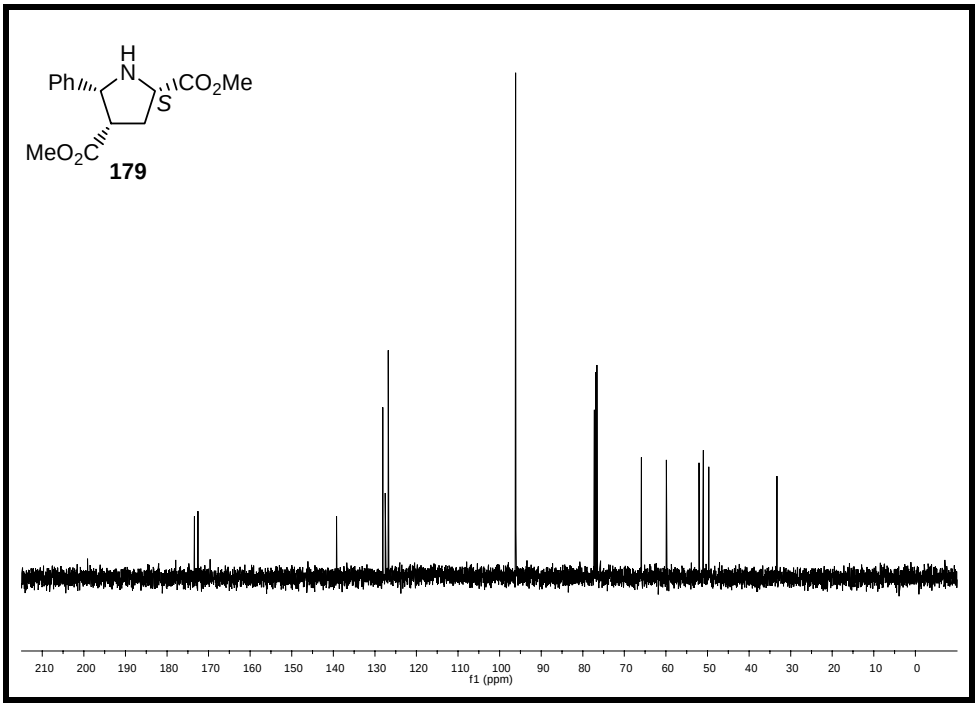


Figure A.46 ^{13}C-NMR spectrum of compound **179**

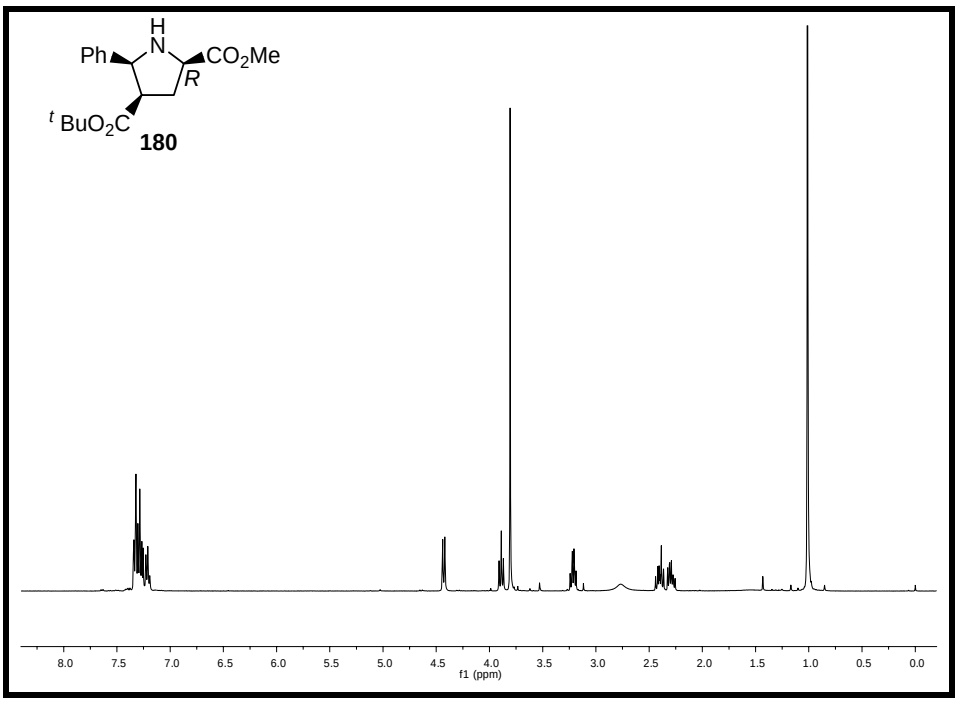


Figure A.47 ^{1}H-NMR spectrum of compound **180**

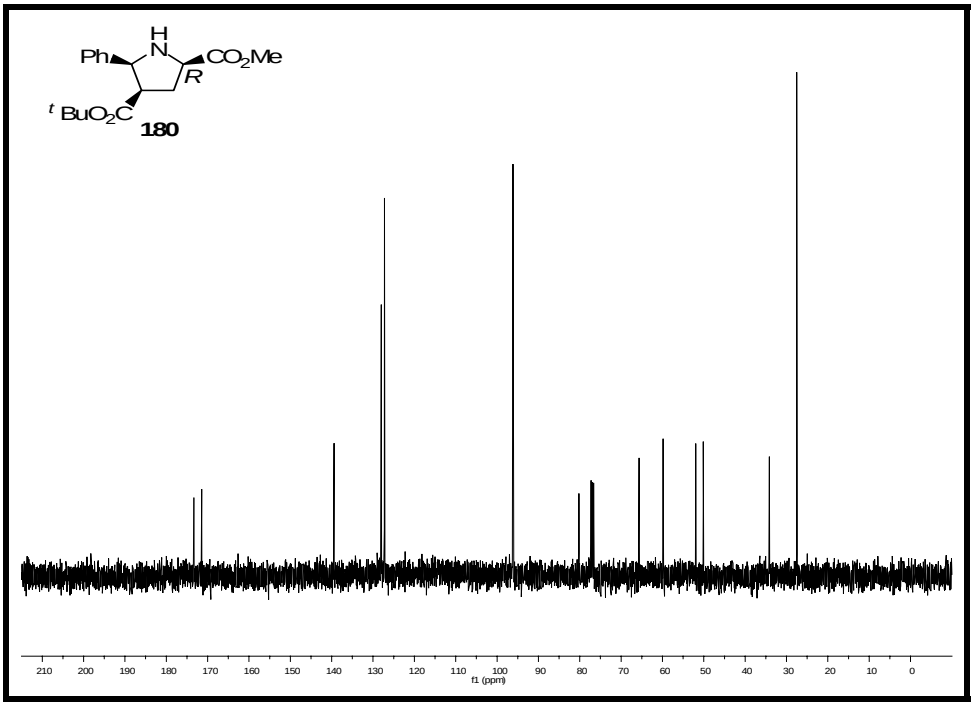


Figure A.48 ^{13}C-NMR spectrum of compound **180**

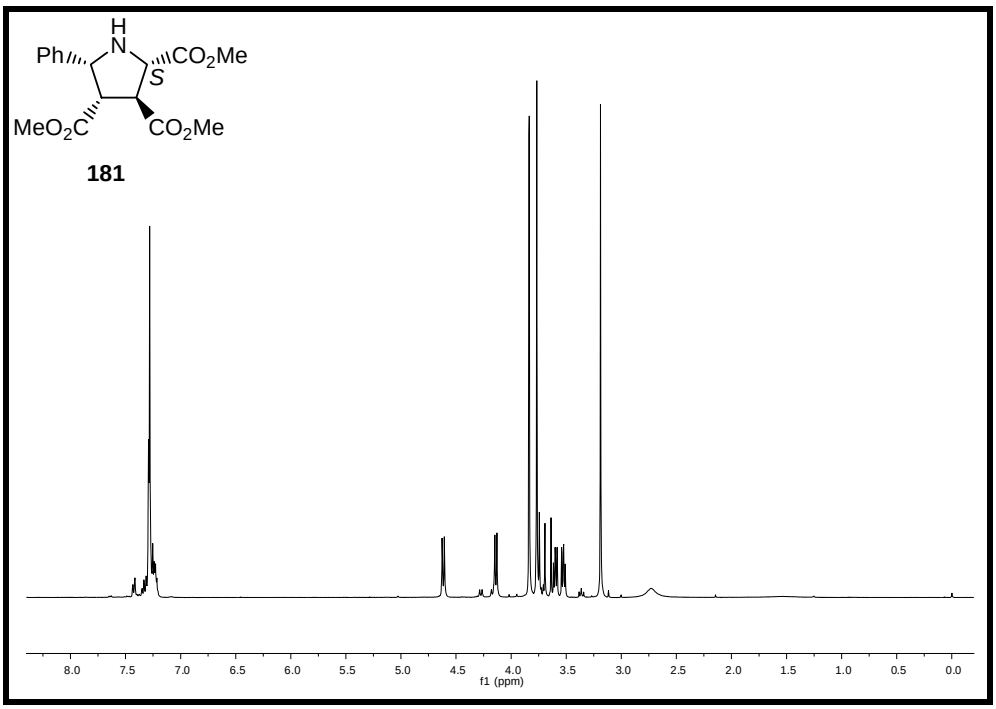


Figure A.49 ^{1}H-NMR spectrum of compound **181**

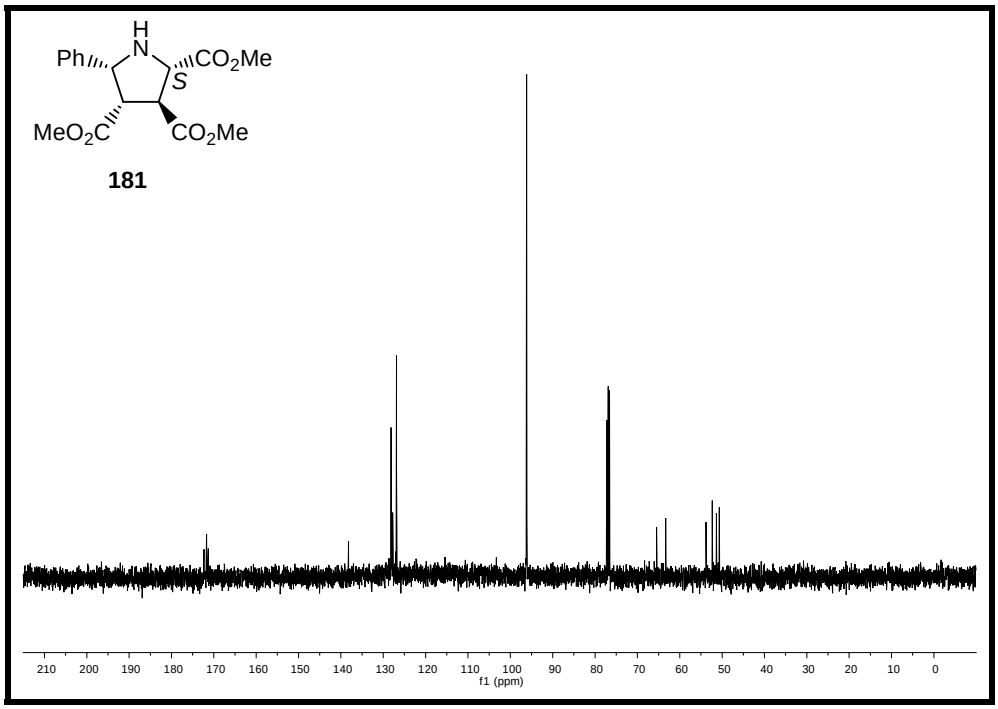


Figure A.50 ^{13}C-NMR spectrum of compound **181**

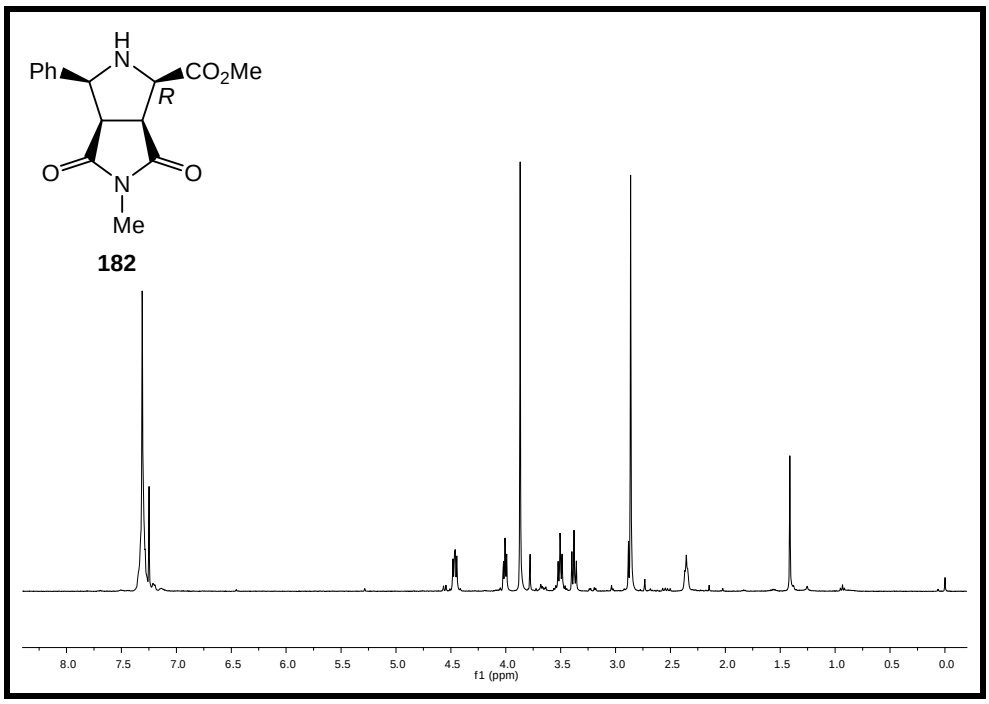


Figure A.51 ^{1}H-NMR spectrum of compound **182**

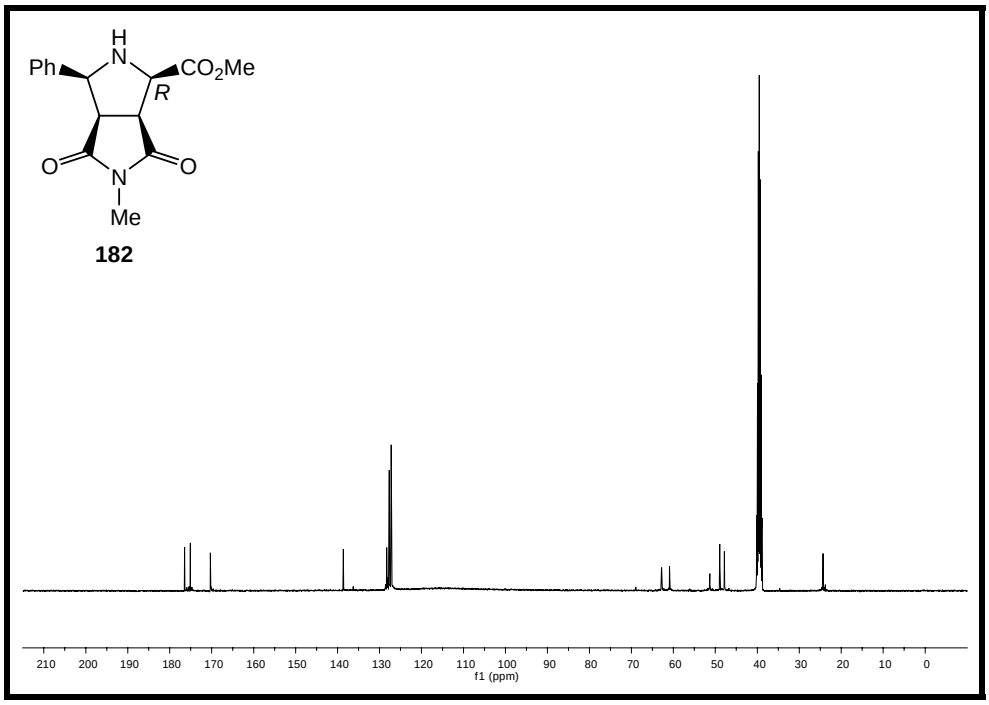


Figure A.52 ^{13}C-NMR spectrum of compound **182**

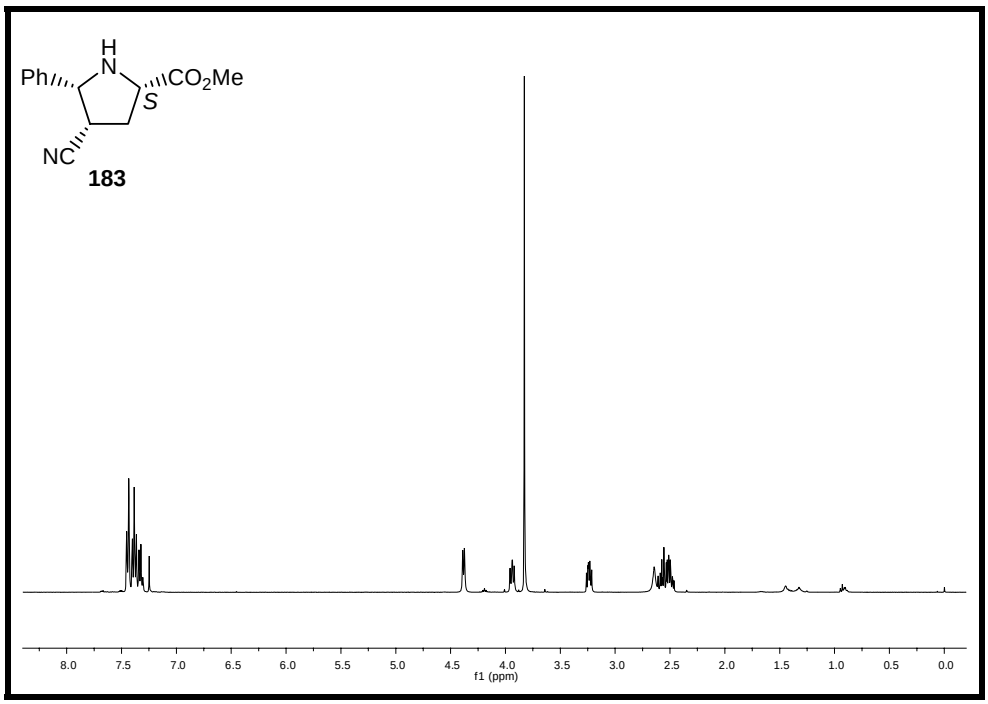


Figure A.53 ^{1}H-NMR spectrum of compound **183**

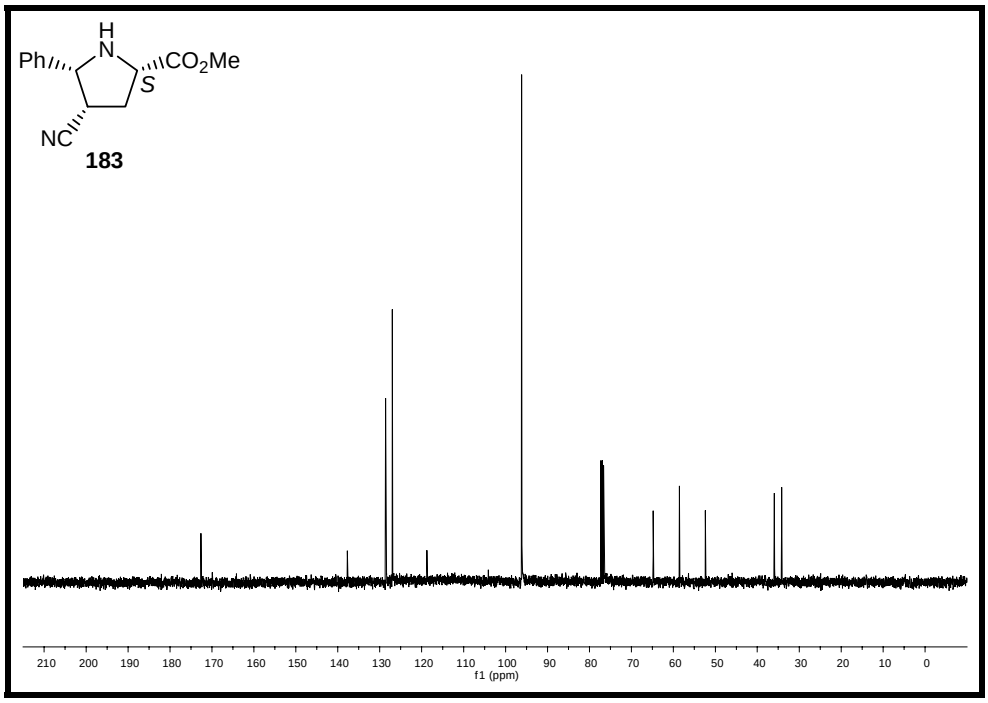


Figure A.54 ^{13}C-NMR spectrum of compound **183**

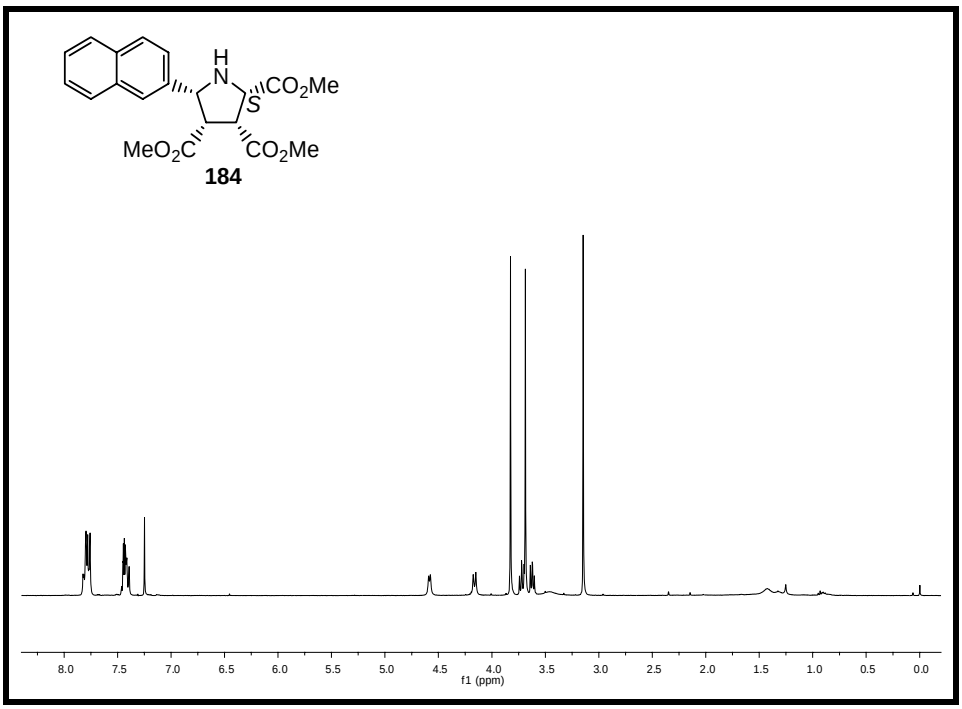


Figure A.55 ^{1}H-NMR spectrum of compound **184**

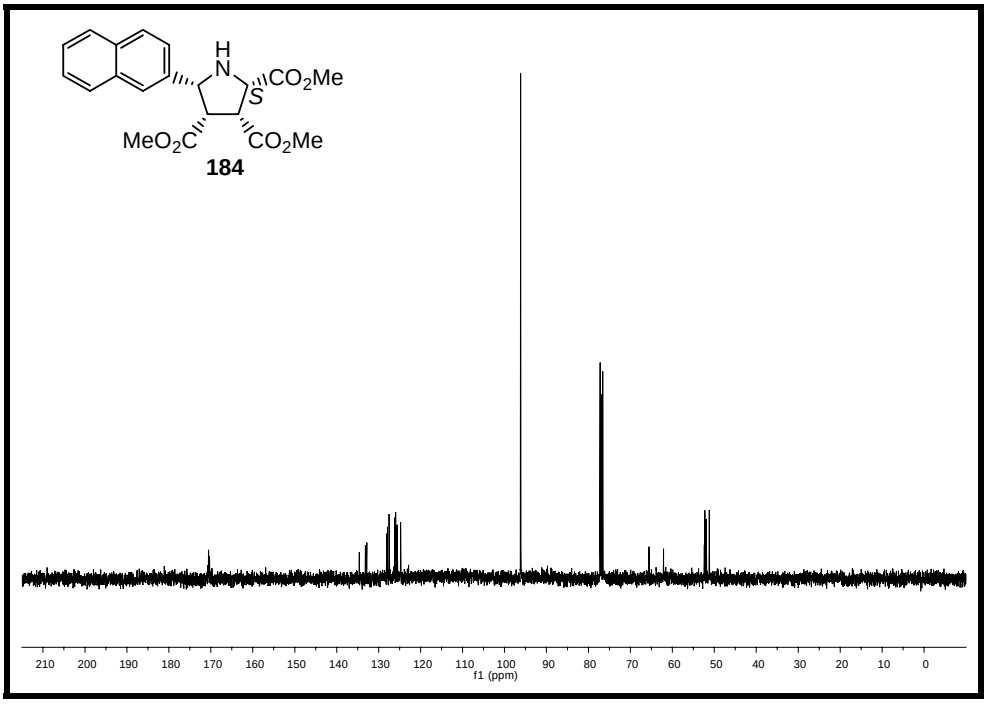


Figure A.56 ^{13}C-NMR spectrum of compound **184**

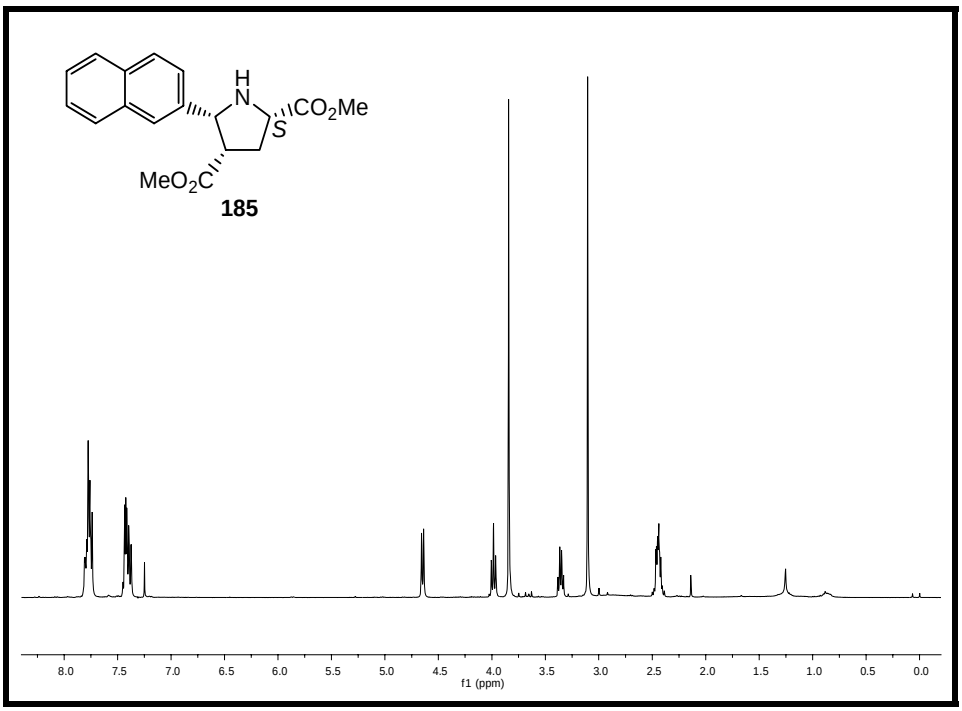


Figure A.57 ^{1}H-NMR spectrum of compound **185**

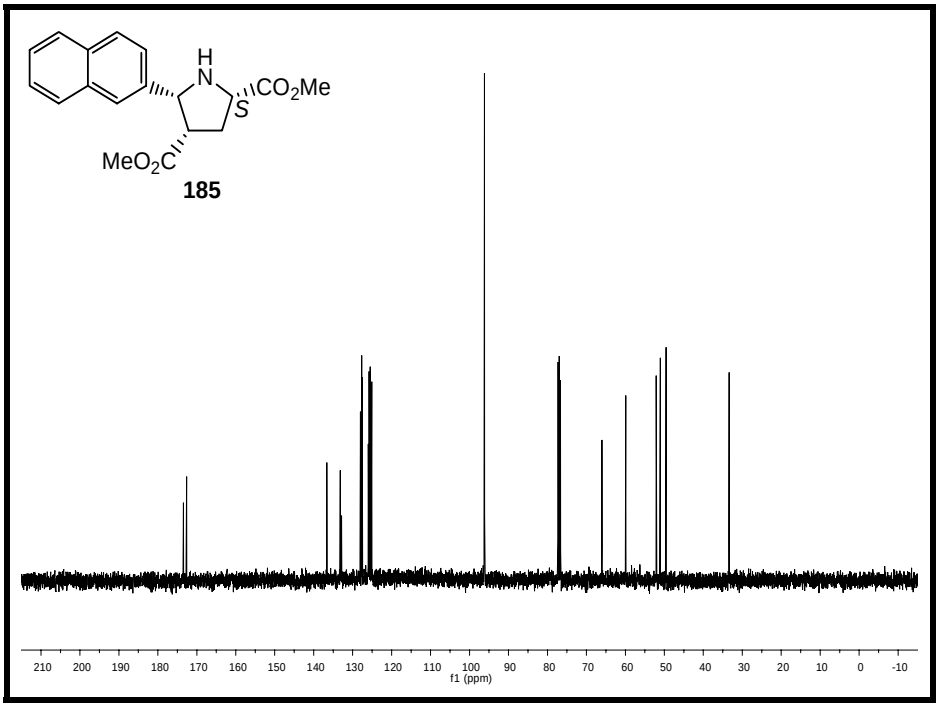


Figure A.58 ^{13}C-NMR spectrum of compound **185**

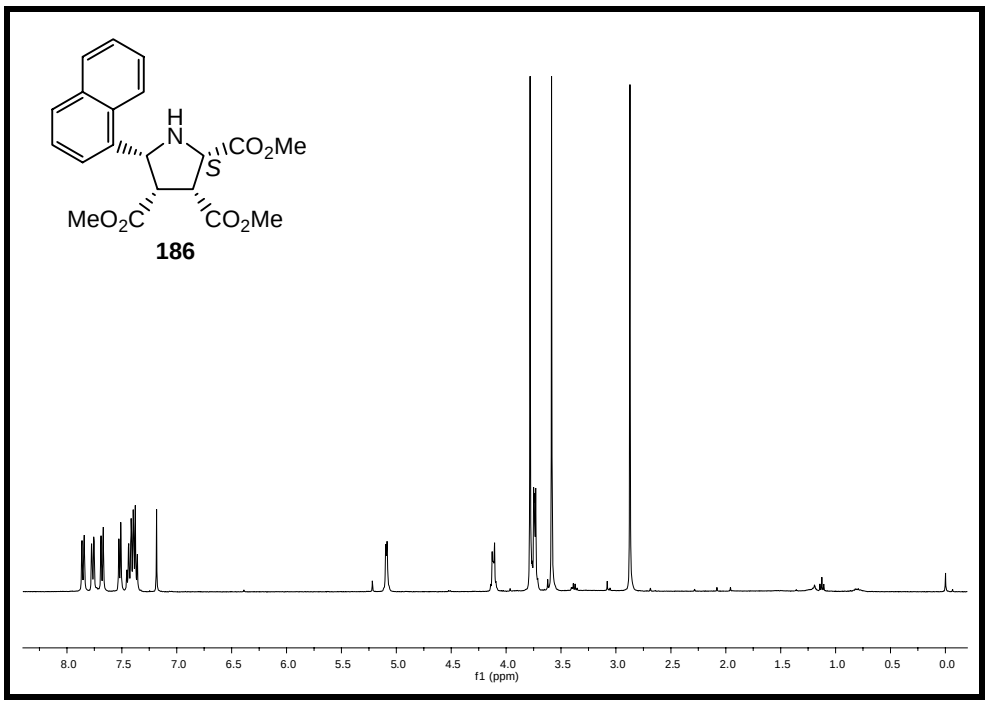


Figure A.59 ^{1}H-NMR spectrum of compound **186**

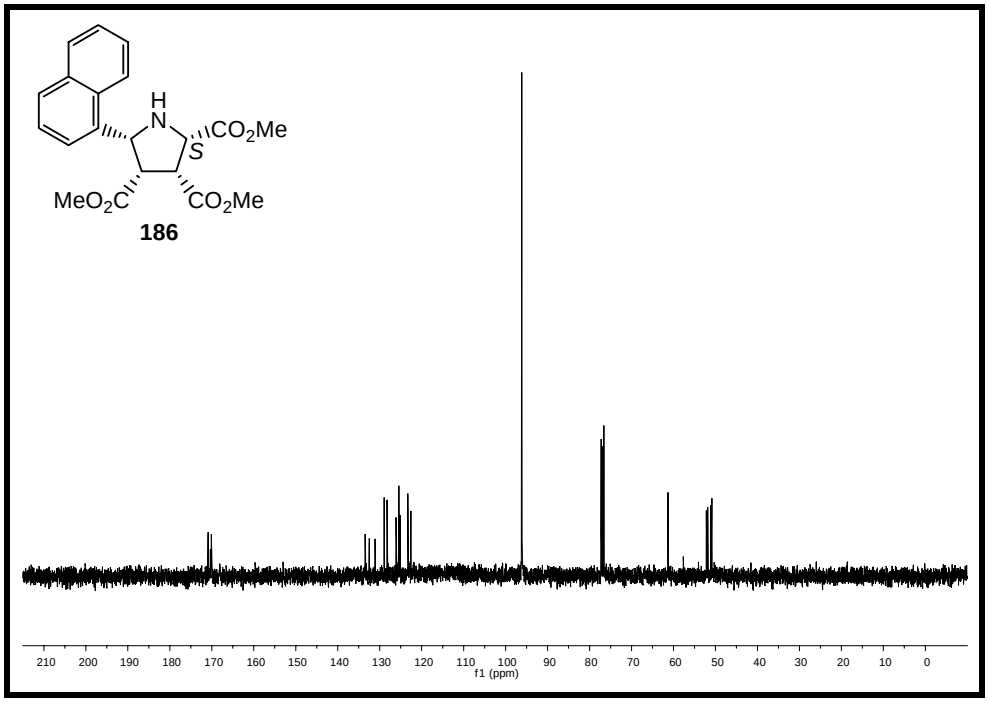


Figure A.60 ^{13}C-NMR spectrum of compound **186**

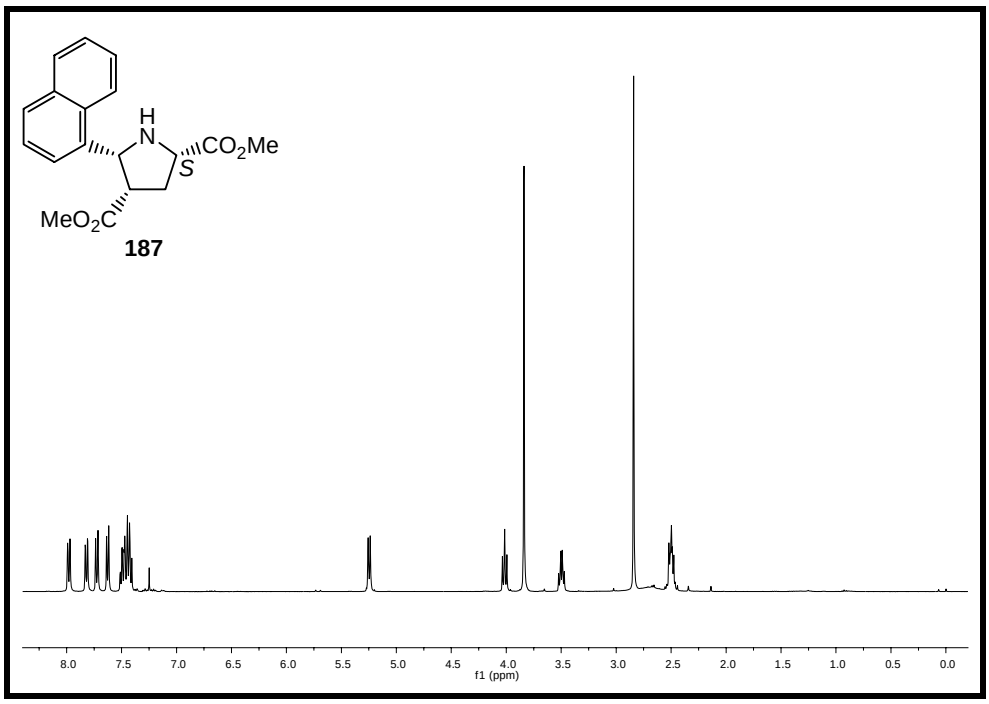


Figure A.61 ^{1}H-NMR spectrum of compound **187**

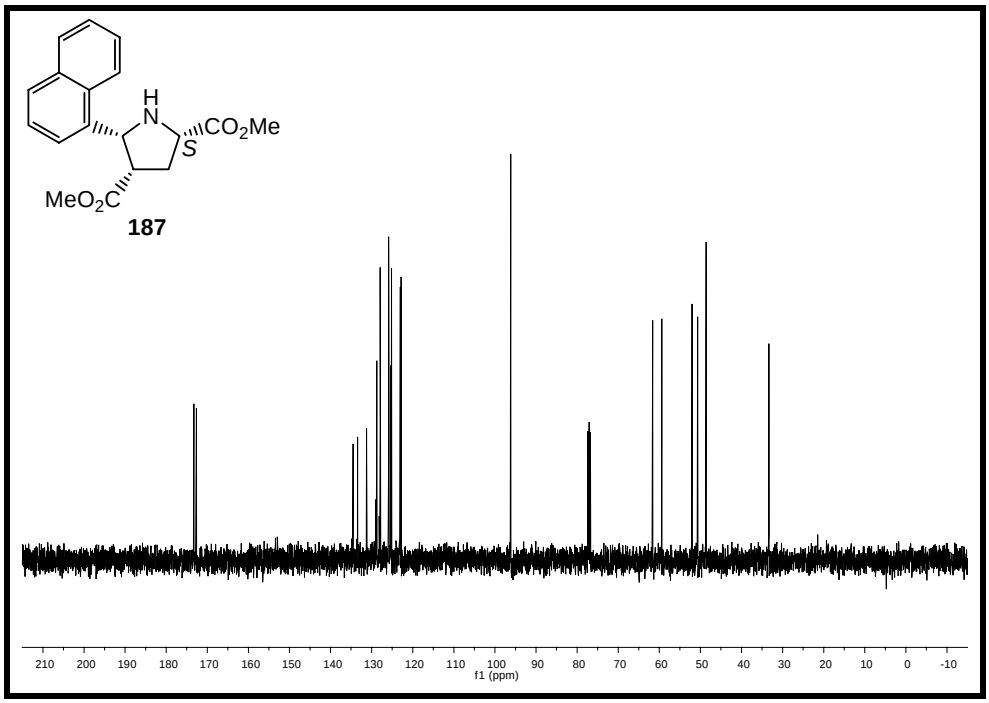


Figure A.62 ^{13}C-NMR spectrum of compound **187**

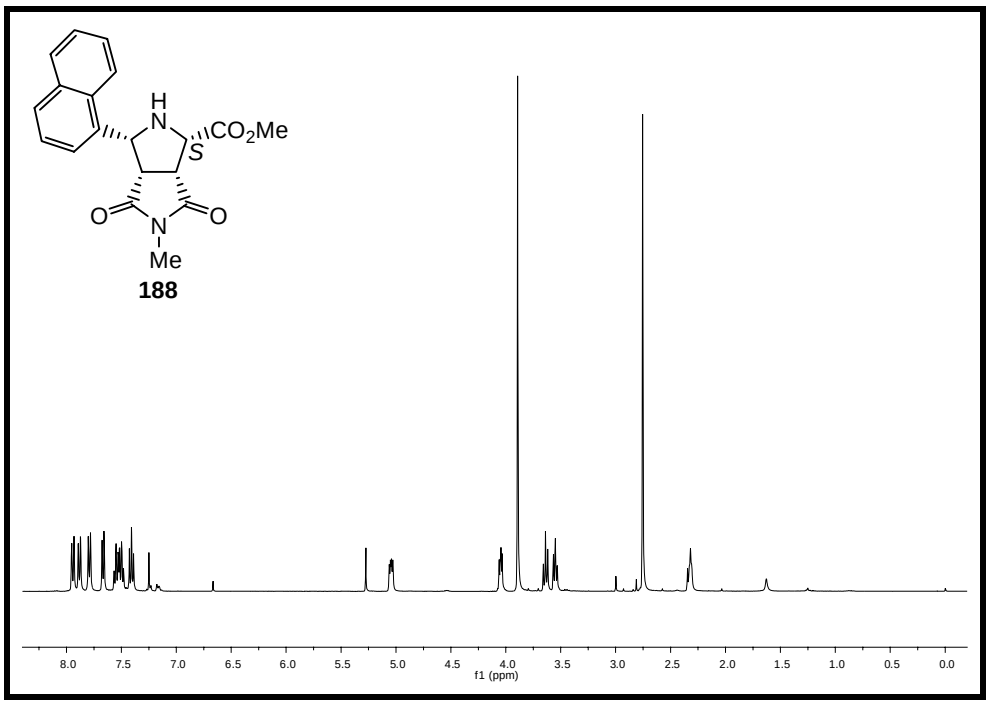


Figure A.63 ^{1}H-NMR spectrum of compound **188**

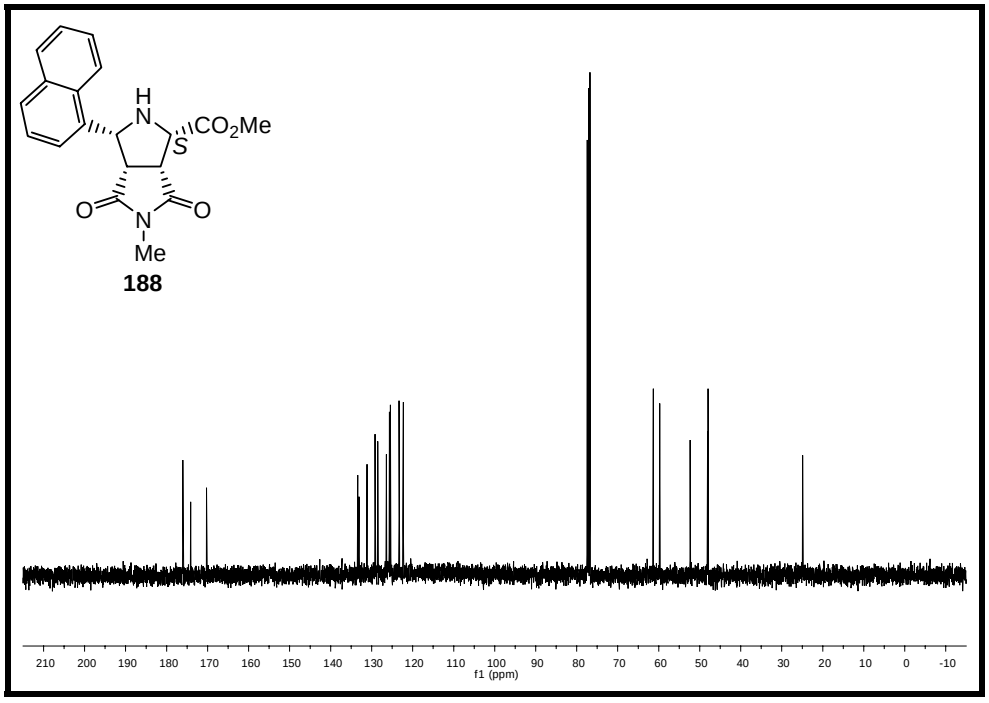


Figure A.64 ^{13}C-NMR spectrum of compound **188**

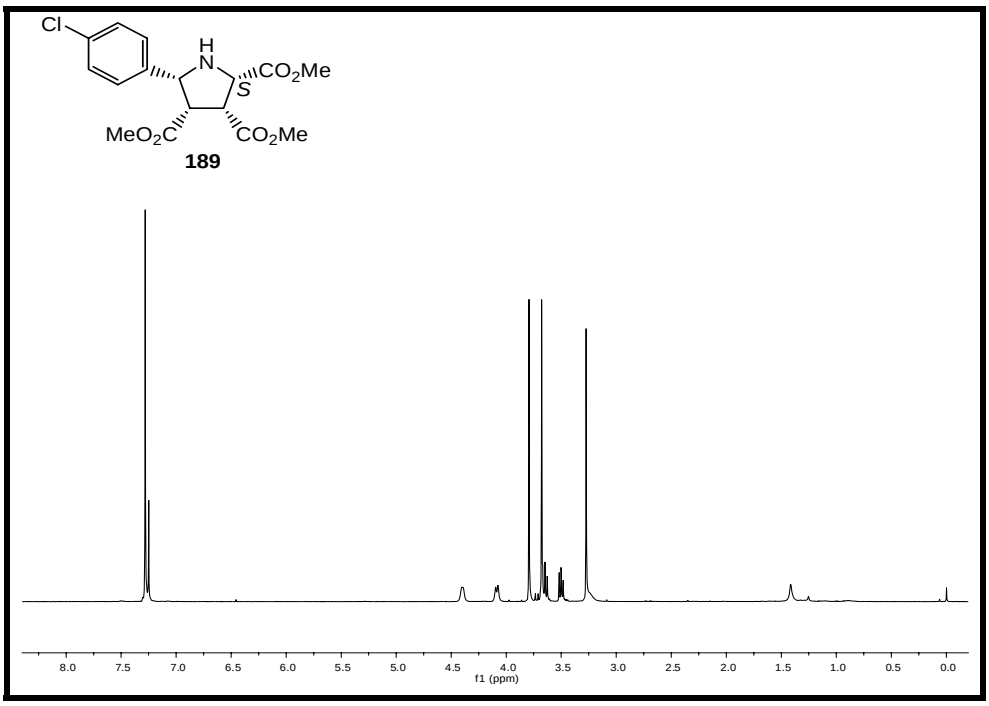


Figure A.65 ^{1}H-NMR spectrum of compound **189**

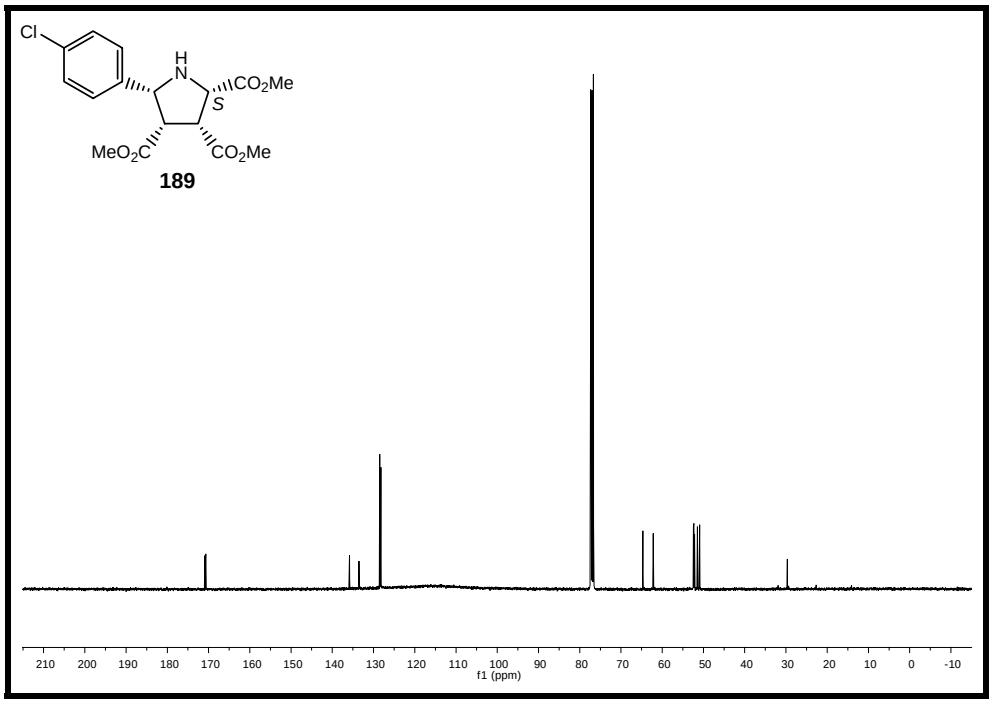


Figure A.66 ^{13}C-NMR spectrum of compound **189**

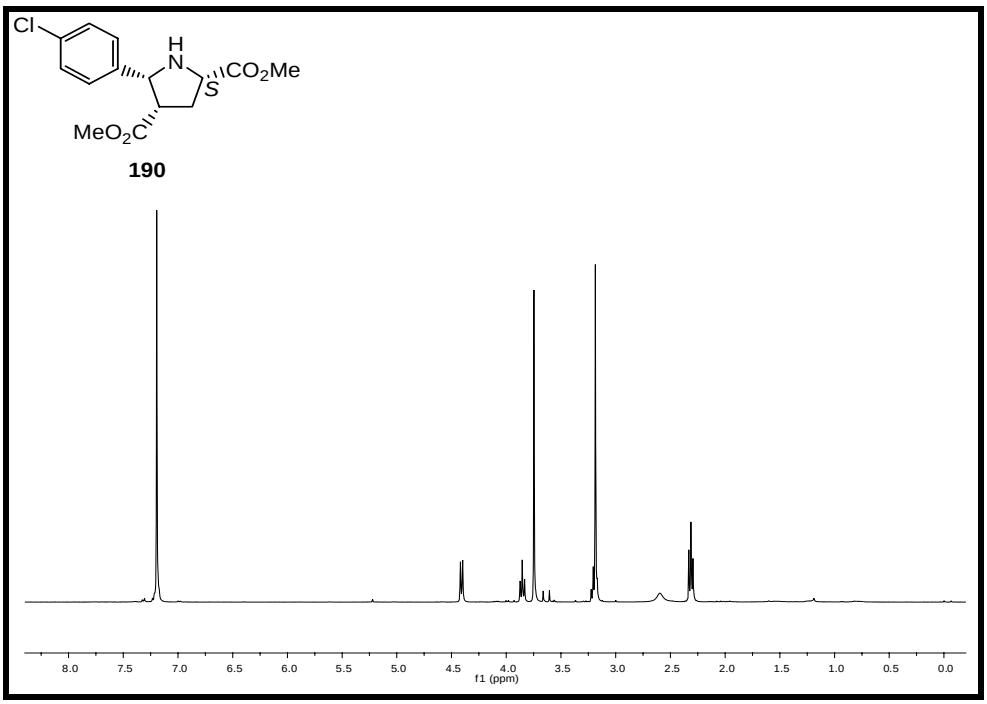


Figure A.67 ^{1}H-NMR spectrum of compound **190**

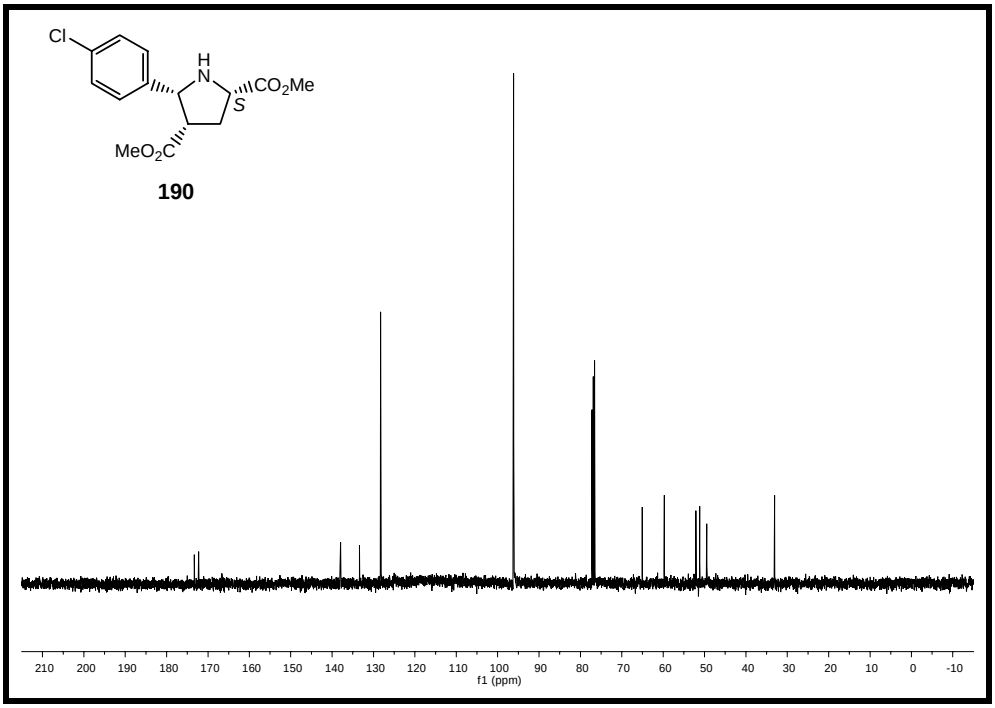


Figure A.68 ^{13}C-NMR spectrum of compound **190**

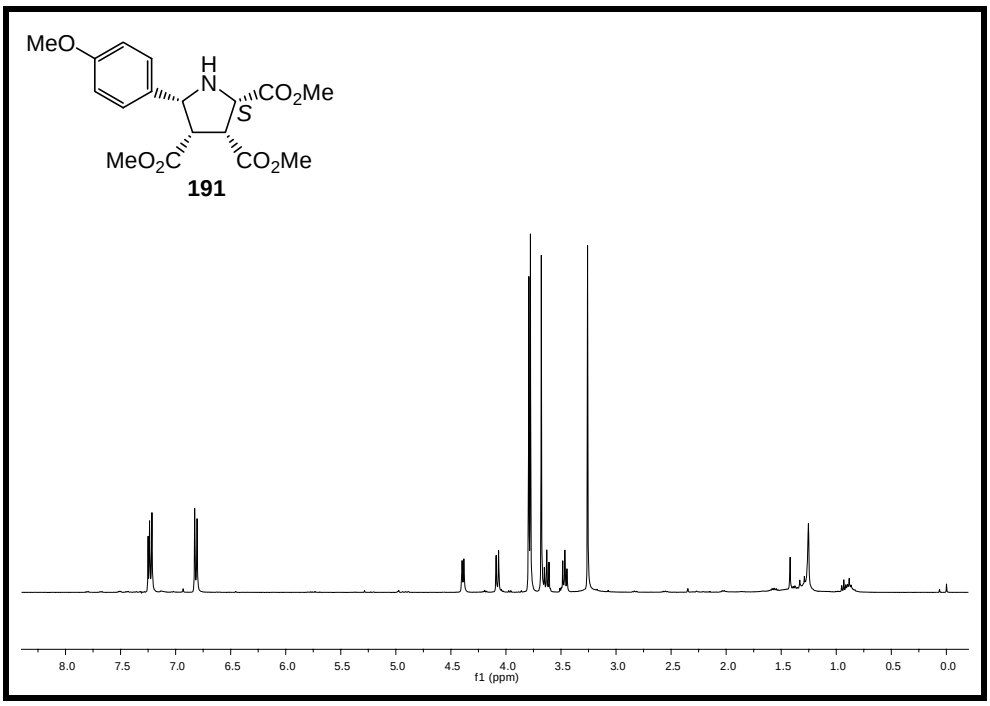


Figure A.69 ^{1}H-NMR spectrum of compound **191**

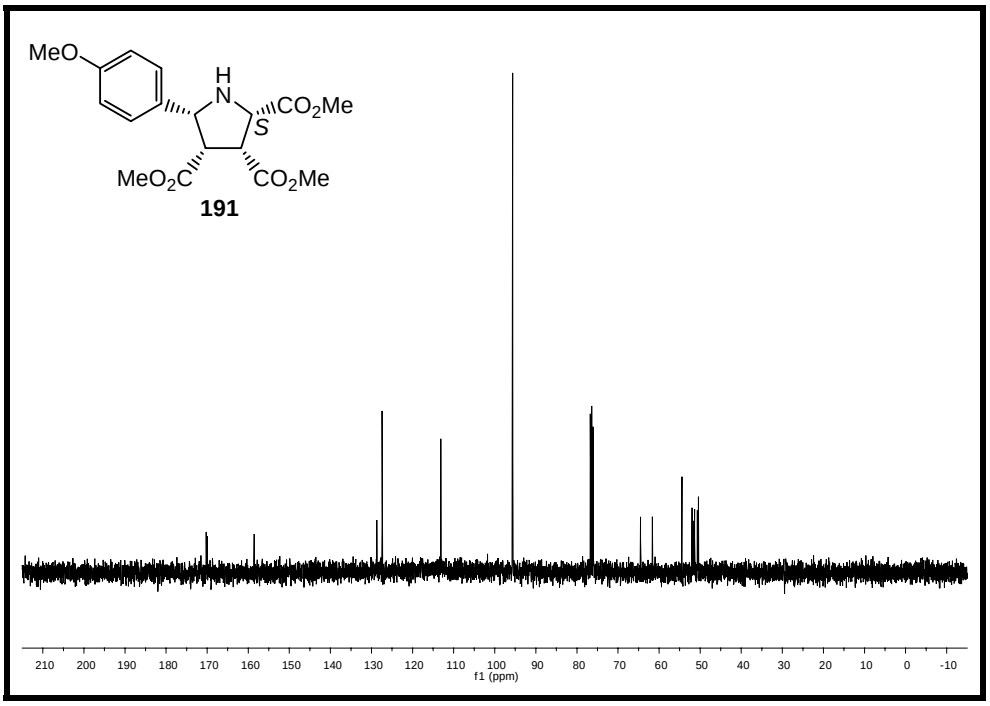


Figure A.70 ^{13}C-NMR spectrum of compound **191**

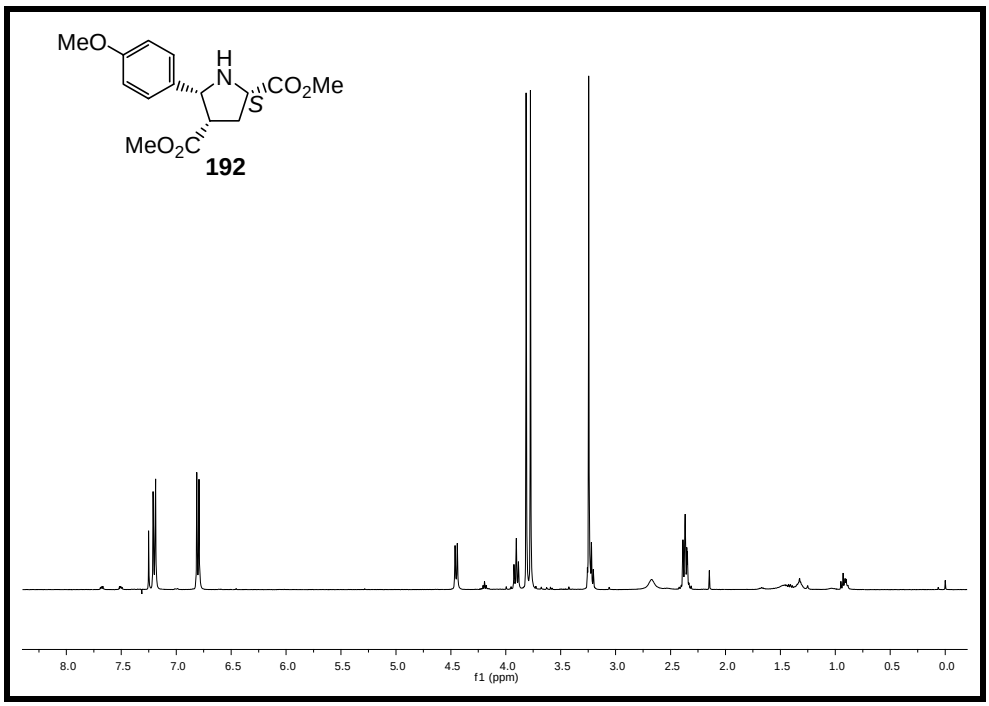


Figure A.71 ^{1}H-NMR spectrum of compound **192**

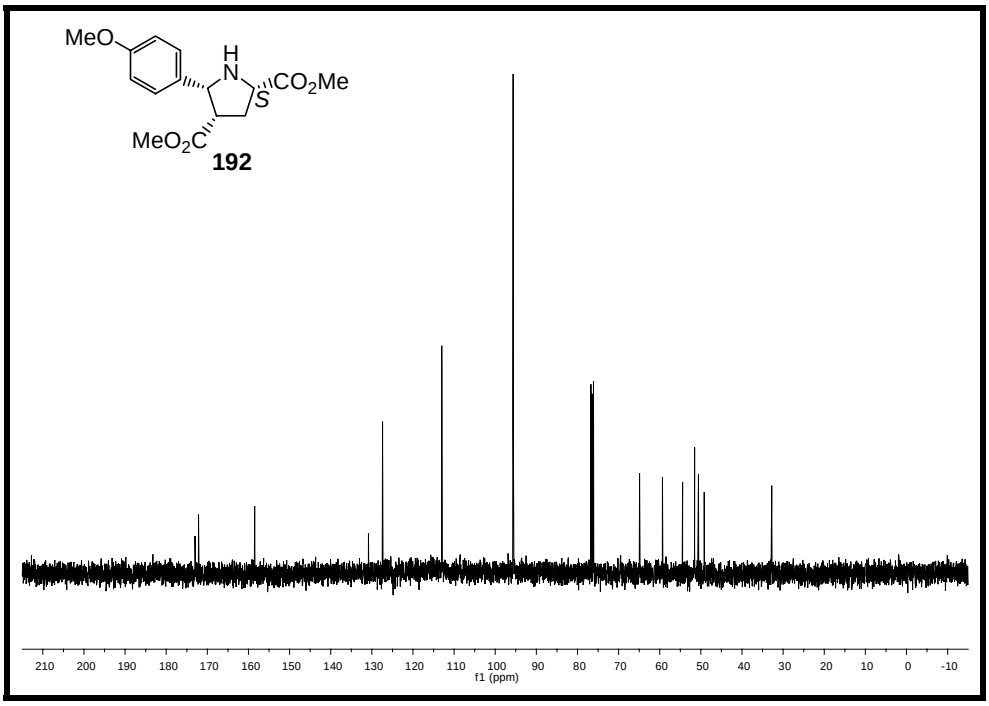
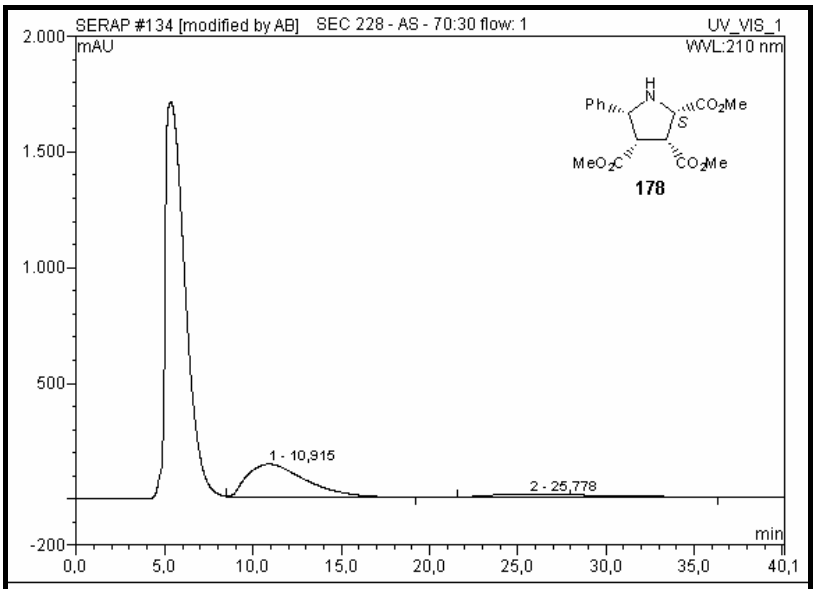
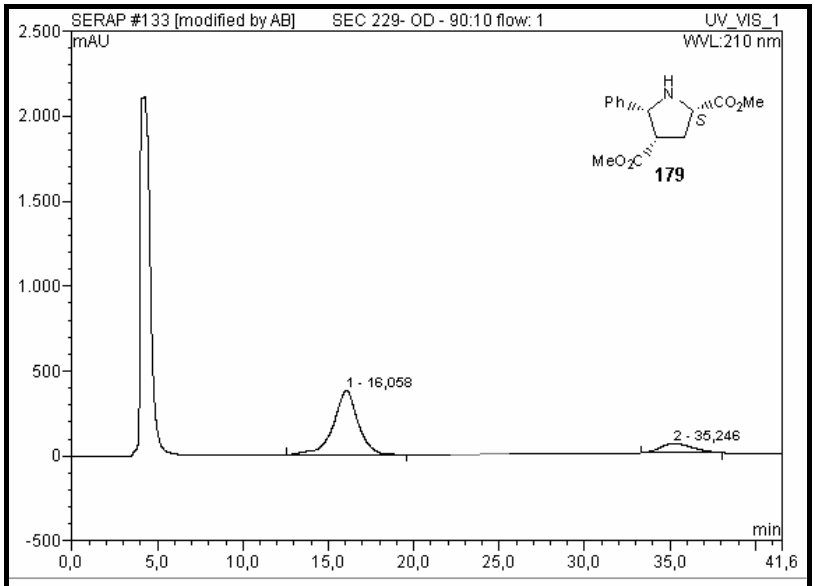


Figure A.72 ^{13}C-NMR spectrum of compound **192**



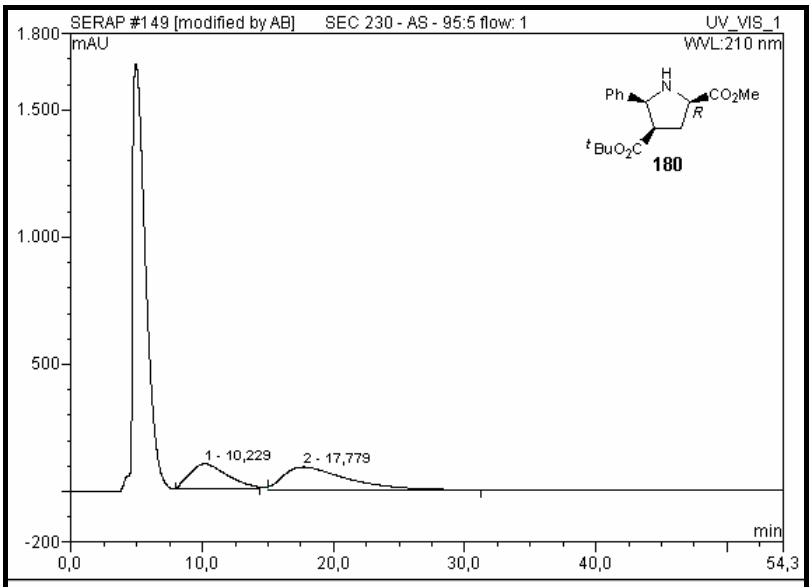
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	10,92	n.a.	144,323	559,210	85,00	n.a.	MB*
2	25,78	n.a.	12,713	98,723	15,00	n.a.	BMB*
Total:			157,036	657,933	100,00	0,000	

Figure A.73 HPLC Chromatogram of compound **178**



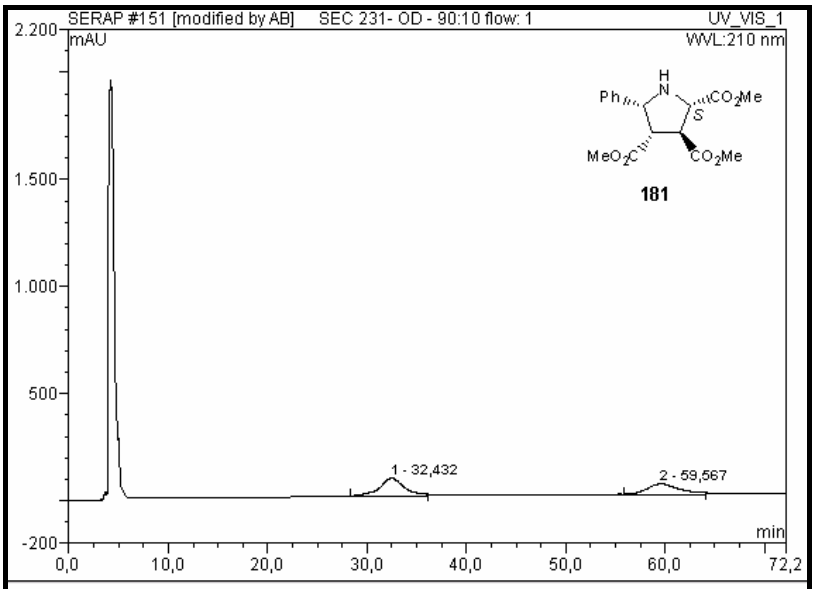
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	16,06	n.a.	380,347	635,451	85,05	n.a.	BM *
2	35,25	n.a.	54,332	120,610	14,95	n.a.	BMB*
Total:			434,679	756,062	100,00	0,000	

Figure A.74 HPLC Chromatogram of compound **179**



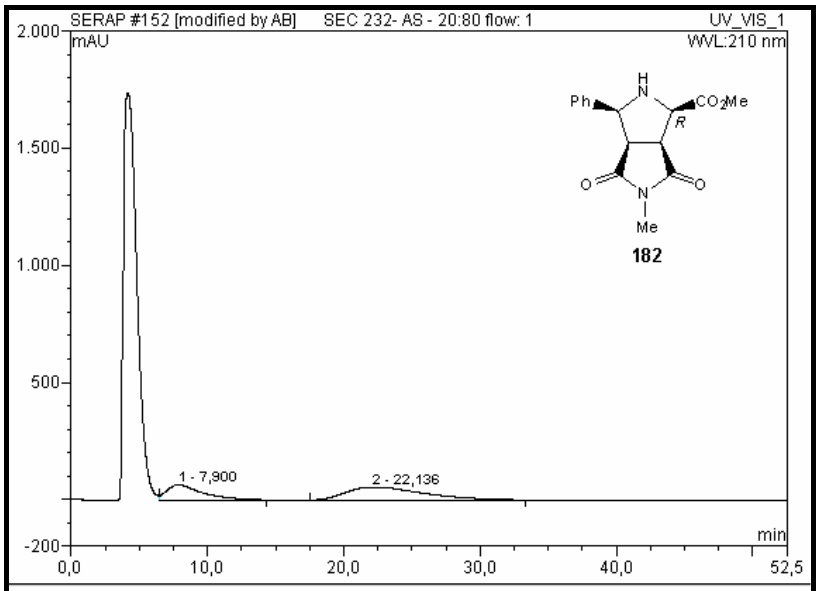
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	10,23	n.a.	98,621	332,237	39,94	n.a.	BM *
2	17,78	n.a.	89,890	499,529	60,06	n.a.	MB*
Total:			188,511	831,766	100,00	0,000	

Figure A.75 HPLC Chromatogram of compound **180**



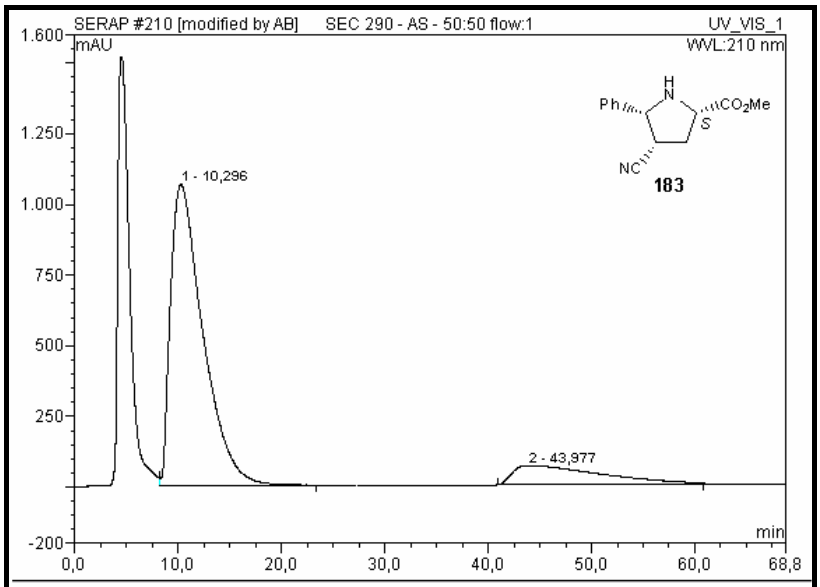
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	32,43	n.a.	82,373	236,997	57,42	n.a.	BM *
2	59,57	n.a.	47,984	175,730	42,58	n.a.	BM *
Total:			130,357	412,727	100,00	0,000	

Figure A.76 HPLC Chromatogram of compound **181**



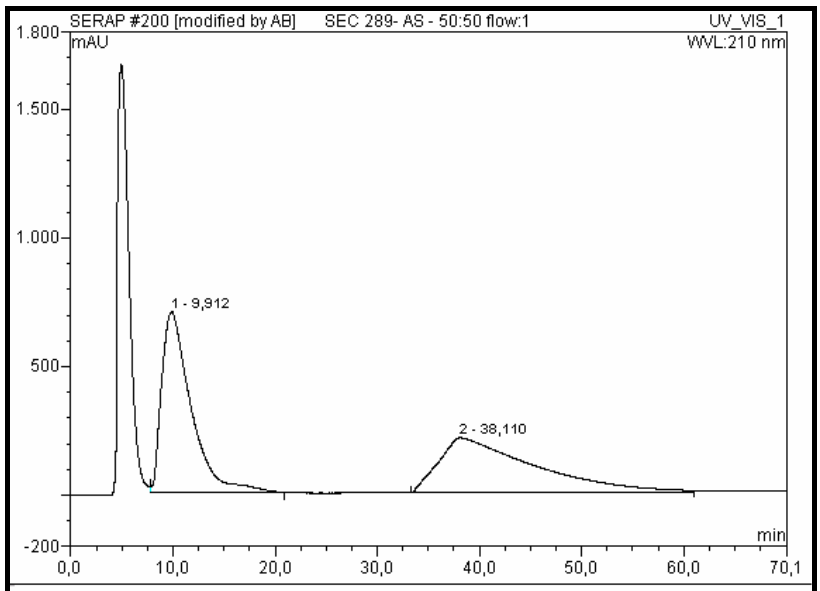
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	7,90	n.a.	65,193	197,372	35,17	n.a.	MB*
2	22,14	n.a.	55,705	363,822	64,83	n.a.	BMB*
Total:			120,898	561,193	100,00	0,000	

Figure A.77 HPLC Chromatogram of compound **182**



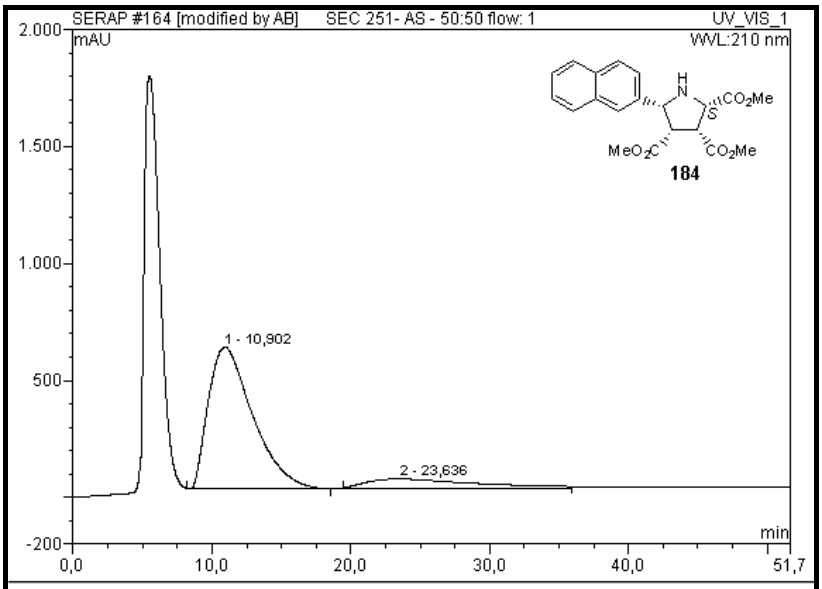
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	10,30	n.a.	1063,103	3851,135	84,94	n.a.	MB*
2	43,98	n.a.	67,775	682,600	15,06	n.a.	BM *
Total:			1130,878	4533,735	100,00	0,000	

Figure A.78 HPLC Chromatogram of compound **183**



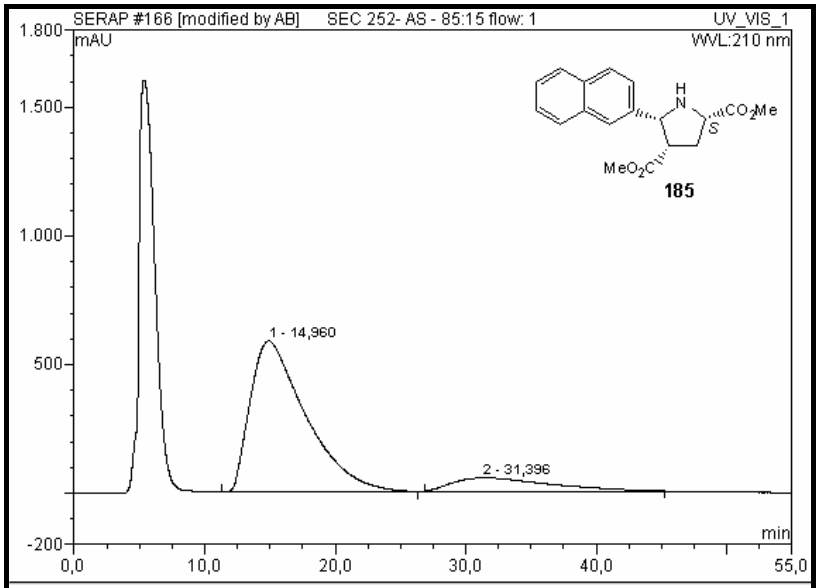
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	9,91	n.a.	700,705	2340,487	50,23	n.a.	MB*
2	38,11	n.a.	213,859	2318,914	49,77	n.a.	BM *
Total:			914,564	4659,401	100,00	0,000	

Figure A.79 HPLC Chromatogram of racemic **183** + **ent-183**



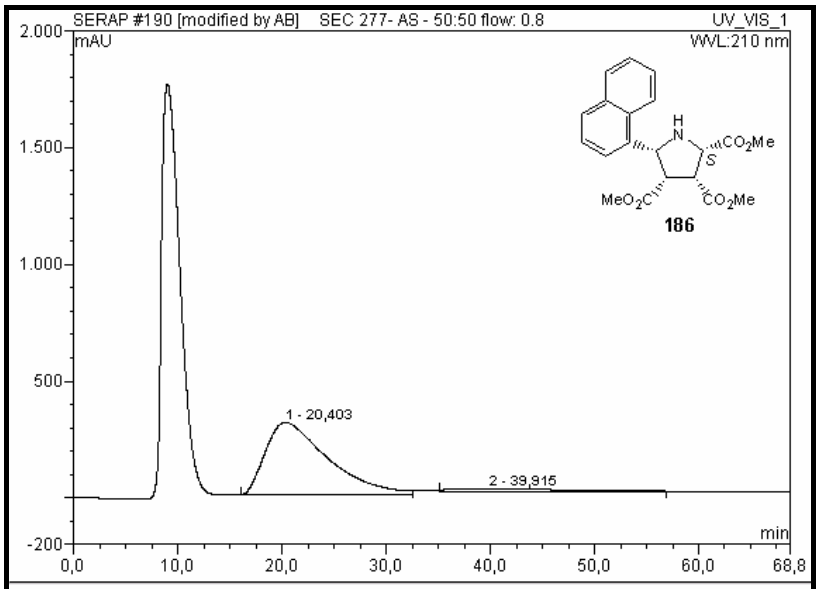
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	10,90	n.a.	606,931	2252,596	86,98	n.a.	MB*
2	23,64	n.a.	38,137	337,081	13,02	n.a.	BM *
Total:			645,068	2589,677	100,00	0,000	

Figure A.80 HPLC Chromatogram of compound **184**



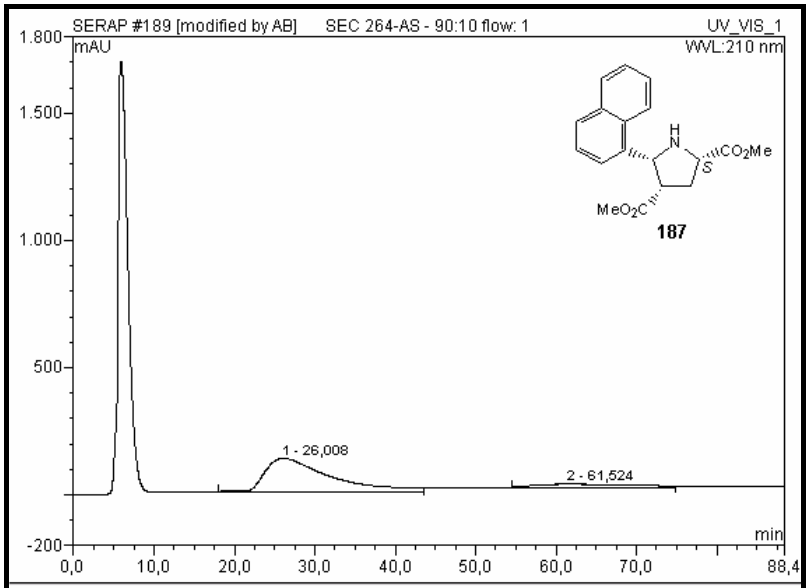
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	14,96	n.a.	584,849	2875,971	86,72	n.a.	BMB*
2	31,40	n.a.	51,615	440,314	13,28	n.a.	MB*
Total:			636,464	3316,286	100,00	0,000	

Figure A.81 HPLC Chromatogram of compound **185**



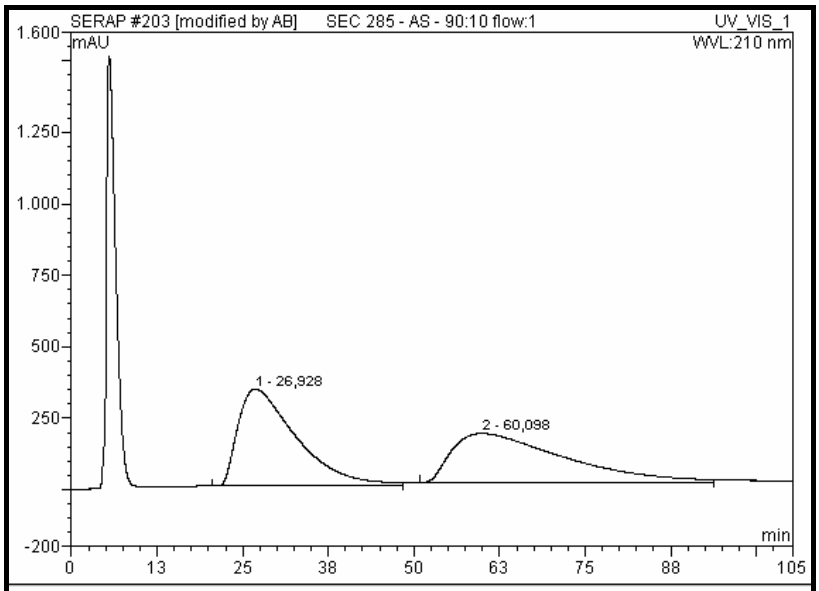
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	20,40	n.a.	308,592	2128,028	94,43	n.a.	BM *
2	39,91	n.a.	11,062	125,554	5,57	n.a.	MB*
Total:			319,654	2253,581	100,00	0,000	

Figure A.82 HPLC Chromatogram of compound **186**



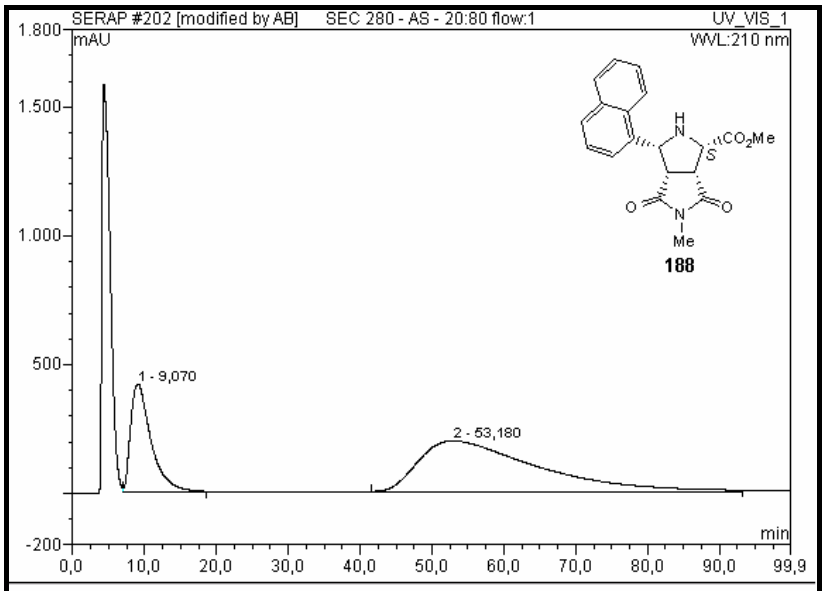
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	26,01	n.a.	129,447	1189,248	87,78	n.a.	BM *
2	61,52	n.a.	11,982	165,587	12,22	n.a.	BM *
Total:			141,429	1354,835	100,00	0,000	

Figure A.83 HPLC Chromatogram of compound **187**



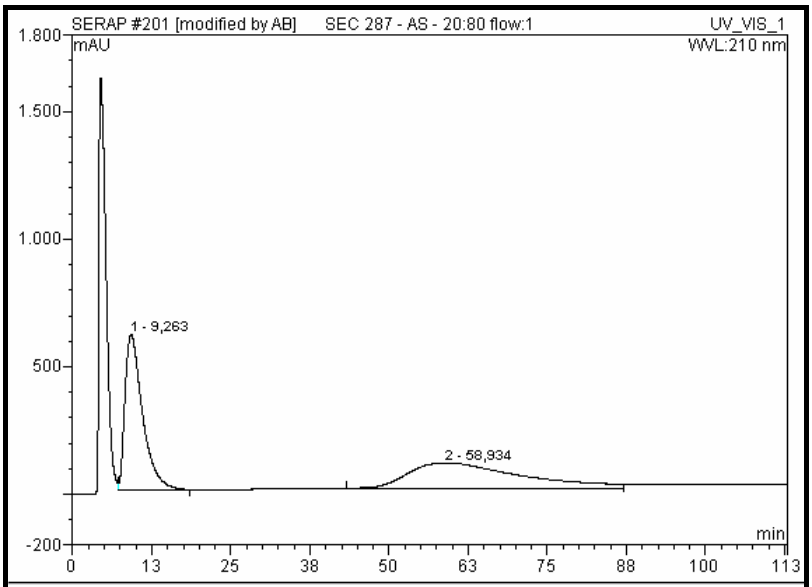
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	26,93	n.a.	338,599	3354,914	50,38	n.a.	BM *
2	60,10	n.a.	172,668	3304,497	49,62	n.a.	BM *
Total:			511,267	6659,411	100,00	0,000	

Figure A.84 HPLC Chromatogram of racemic **187** + **ent-187**



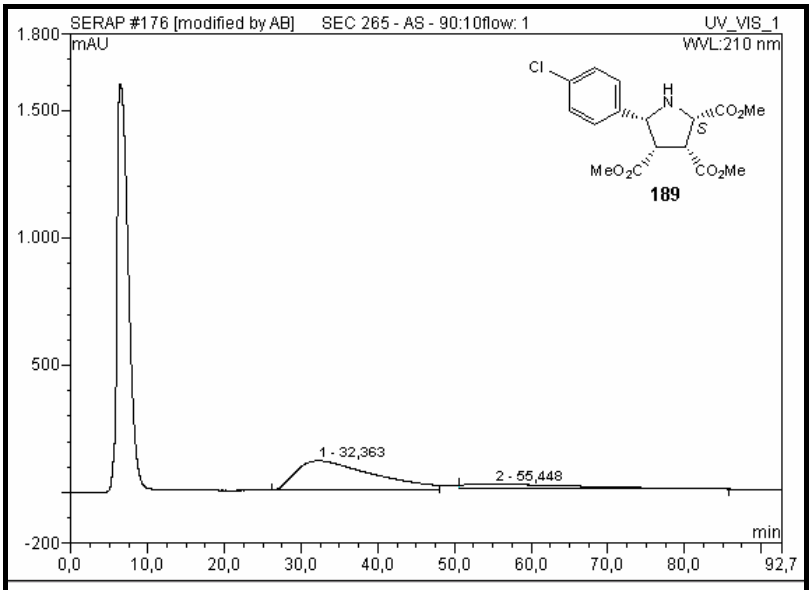
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	9,07	n.a.	417,597	1364,416	26,73	n.a.	MB*
2	53,18	n.a.	196,104	3739,179	73,27	n.a.	BM *
Total:			613,700	5103,595	100,00	0,000	

Figure A.85 HPLC Chromatogram of compound **188**



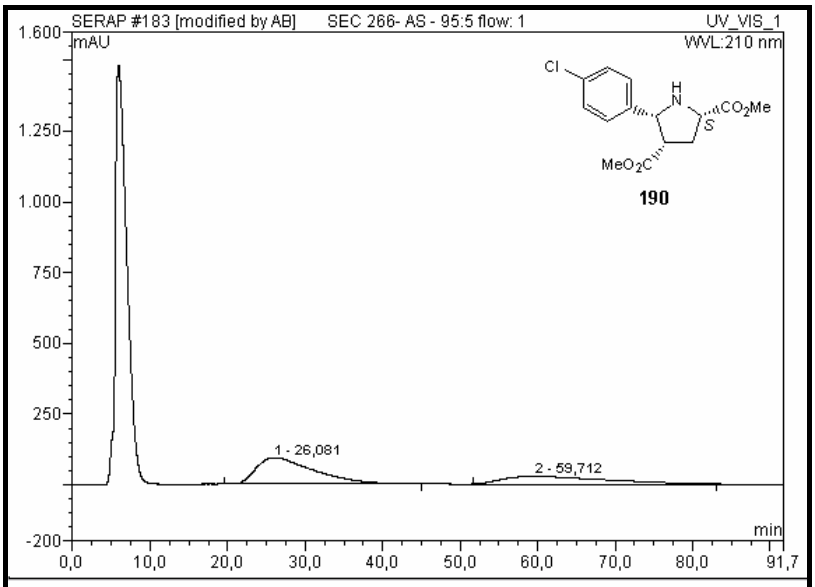
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	9,26	n.a.	608,841	1954,368	49,24	n.a.	MB*
2	58,93	n.a.	99,568	2014,833	50,76	n.a.	BM *
Total:			708,409	3969,201	100,00	0,000	

Figure A.86 HPLC Chromatogram of racemic **188** + **ent-188**



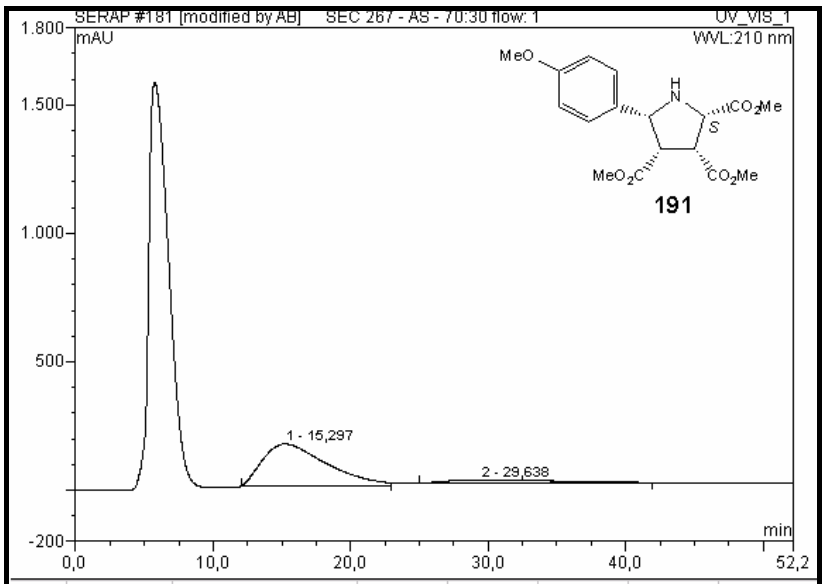
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	32,36	n.a.	114,799	1352,195	79,90	n.a.	BM *
2	55,45	n.a.	18,323	340,097	20,10	n.a.	MB*
Total:			133,122	1692,292	100,00	0,000	

Figure A.87 HPLC Chromatogram of compound **189**



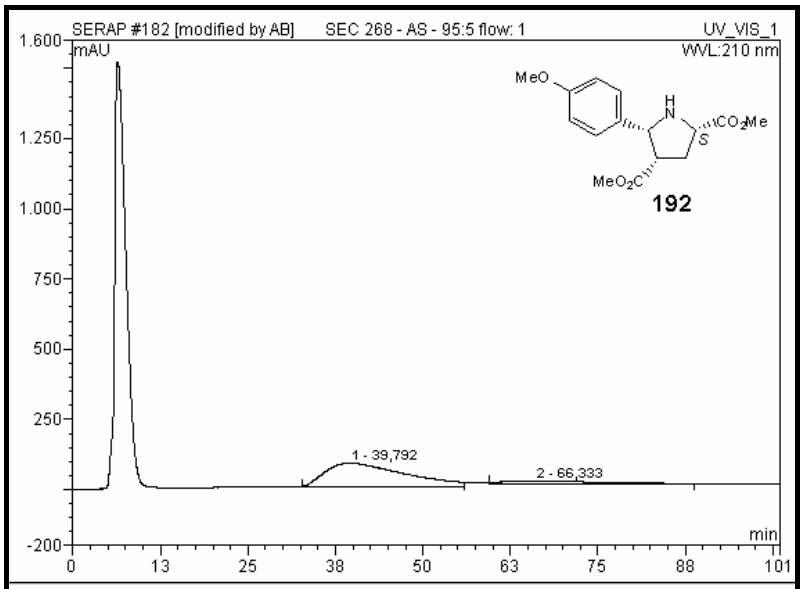
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	26,08	n.a.	93,322	801,882	66,13	n.a.	BM *
2	59,71	n.a.	27,058	410,668	33,87	n.a.	BMB*
Total:			120,381	1212,550	100,00	0,000	

Figure A.88 HPLC Chromatogram of compound **190**



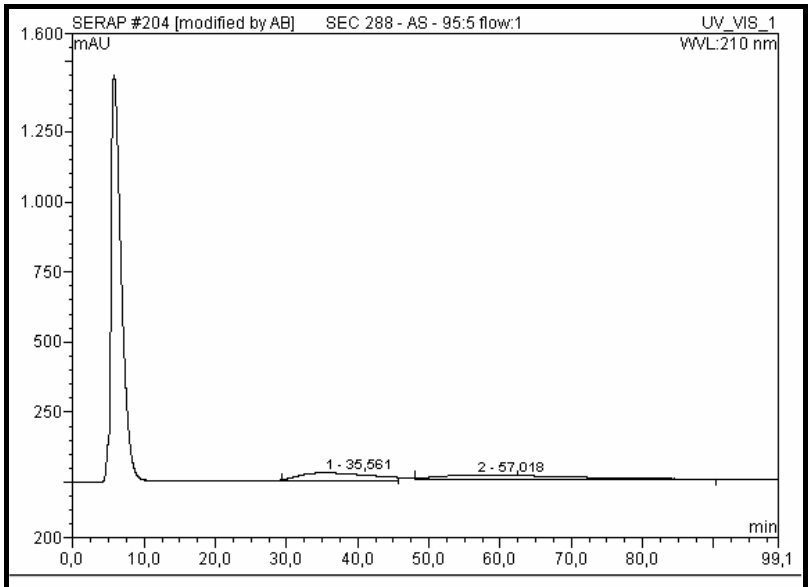
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	15,30	n.a.	163,919	887,101	86,85	n.a.	BM *
2	29,64	n.a.	12,615	134,328	13,15	n.a.	BM *
Total:			176,534	1021,429	100,00	0,000	

Figure A.89 HPLC Chromatogram of compound **191**



No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	39,79	n.a.	83,247	1089,708	88,26	n.a.	BM *
2	66,33	n.a.	8,907	144,970	11,74	n.a.	MB*
Total:			92,154	1234,678	100,00	0,000	

Figure A.90 HPLC Chromatogram of compound **192**



No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	35,56	n.a.	25,759	289,472	49,66	n.a.	BM *
2	57,02	n.a.	14,936	293,394	50,34	n.a.	MB*
Total:			40,695	582,865	100,00	0,000	

Figure A.91 HPLC Chromatogram of racemic **192** + **ent-192**