# SYNTHESIS AND USE OF NEW PHOSPHINEOXY AZIRIDINYLPHOSPHONATES (POAP) AS ORGANOCATALYSTS IN ASYMMETRIC PHOSPHONYLATION OF ALDEHYDES

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**SYNTHESIS AND USE OF NEW PHOSPHINEOXY AZIRIDINYLPHOSPHONATES (POAP) AS ORGANOCATALYSTS IN ASYMMETRIC PHOSPHONYLATION OF ALDEHYDES**

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# ABSTRACT


**SYNTHESIS AND USE OF NEW PHOSPHINEOXY AZIRIDINYL PHOSPHONATES (POAP) AS ORGANOCATALYSTS IN ASYMMETRIC PHOSPHONYLATION OF ALDEHYDES**

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February 2012, 111 pages

A new phosphineoxy aziridiniyl phosphonates **POAP** were synthesized as potential organocatalysts and used for silicon based asymmetric Abramov-type phosphonylation of aldehydes with triethyl phosphite. Besides **POAP** organocatalyst, known chiral phosphineoxy ferrocenyl substituted aziridinyl methanol (**POFAM**) and aziridinyl phosphonates (**AP**) were also used for the same reaction. The product α-hydroxy phosphonates were obtained in good yields up to 99% but with poor enantioselectivities. Highest enantioselectivity (%34) was obtained with **POAP** organocatalyst. Optimization studies were done with different solvents, ligands, aldehydes, and concentrations.



Keywords: organocatalyst, silicon based, α-hydroxy phosphonates, asymmetric reaction, Abramov-type phosphonylation

# ÖZ

## YENİ FOSFİNOKSİ AZİRİDİNİL FOSFONATLARIN (POAP) SENTEZİ VE ALDEHİTLERİN ASİMETRİK FOSFORİLASYONUNDA ORGANOKATALİZÖR OLARAK KULLANILMASI

İşci, Muhammet

Yüksek lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Özdemir Doğan

Şubat 2012, 111 sayfa

Potansiyel bir organokatalizör olarak yeni fosfinoksi aziridinil fosfonat **POAP** sentezlendi ve silikon varlığında asimetrik Abramov-tipi aldehitlerin trietil fosfitle fosforlanması tepkimesinde kullanıldı. **POAP** organokatalizörlerinin yanı sıra bilinen kiral fosfinoksi ferrosenil sübstüte aziridinil metanol (**POFAM**) ve aziridinil fosfanatlar (**AP**) da aynı tepkime için kullanıldı. Ürün olarak α–hidroksi fosfonatlar % 99 a varan yüksek verimlerle elde edilmelerine rağmen enantioseçicilik düşük oldu. En yüksek enantioseçicilik % 34'le **POAP** organokatalizörüyle gerçekleşti. Optimizasyon çalışmaları değişik çözgenler, ligandlar, aldehitler ve derişimlerde yapıldı.

Anahtar kelimeler; organokatalizör, silikon tabanlı, asimetrik tepkime, Abramov-tipi fosforlama

***To my family…***

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Finally, I would like to express my love and respect to my family for their absolute belief in me.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ar | : aryl (also argon) |
| Bn | : benzyl |
| BINAPO | : 2,2'-Bis(Diphenylphosphinoxide)-1,1'-binaphthyl |
| br | : broad singlet |
| δ | : chemical shift in parts per million downfield from tetramethylsilane |
| *J* | : coupling constant |
| d | : doublet (spectral) |
| DCM | : Dichloromethane |
| dr | : diastereomeric ratio |
| dt | : doublet of triplets (spectral) |
| dd | : doublet of doublet (spectral) |
| ee | : enantiomeric excess |
| equiv | : equivalent |
| Fc | : ferrocenyl |
| FAM | : Ferrocenyl substituted Aziridinyl Methanol |
| HPLC | : High Pressure Liquid Chromatography |
| $KPPh_2$ | : Potassium diphenylphosphide |
| LA | : Lewis acid |

LB : Lewis base

mp : melting point

m : multiplet (spectral)

NMR : Nuclear Magnetic Resonance

PFAM : Phosphino Ferrocenyl Aziridinyl Methanol

POFAM : Phosphineoxy Ferrocenyl Aziridinyl Methanol

q : quartet (spectral)

$R_f$ : retention factor (TLC)

$t_R$ : retention time (in HPLC)

s : singlet (spectral)

THF : Tetrahydrofuran; solvent

TMS : Tetramethylsilane, also Trimethylsilyl

TLC : Thin Layer Chromatography

t : triplet (spectral)

# CHAPTER 1

# INTRODUCTION

## 1.1. Routes to enantiomerically pure compounds

The enantioselective synthesis of chemical compounds has been a significant study area for scientists for more than a century. Studies in the stereochemistry field, that subjected by Pasteur, Van't Hoff and Le Bell [1] as a pioneering work, have become a major topic of research nowadays [2]. Recognition of diastereomeric relationship leads to the synthesis and isolation of enantiomerically pure compounds [3]. Although one isomer of a compound called as eutomer possess the highest activity, other isomer, distomer, may exhibit less, different or even undesired activities [4]. For example, in the case of hypertensive agent the α-methyldopa only the L-enantiomer has the activity. Furthermore, enantiomers with the same potency or different activities exist. The D-enantiomer of propoxyphene is an analgesic, whereas the other enantiomer has antitussive properties and do not have an analgesic effect. To indicate the mirror image relationship of these compounds, Darvon® and Norvad® trade names have been given to those enantiomers shown in (*Figure 1)* below [5].

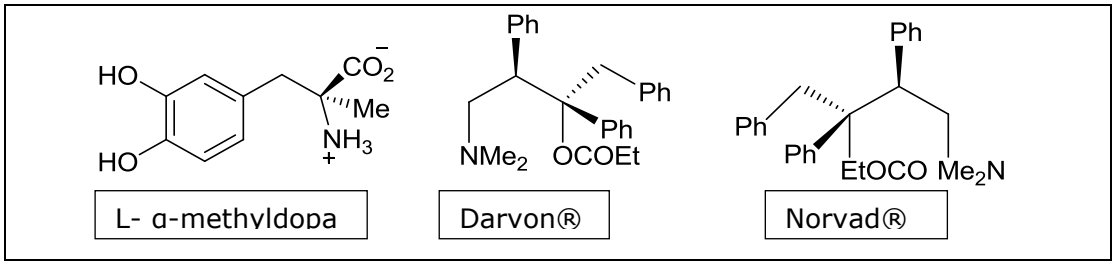
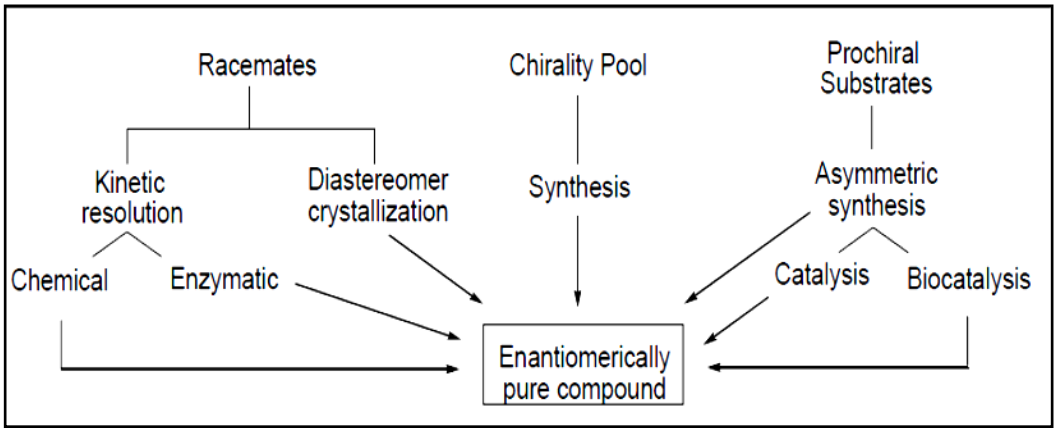



***Figure 1:*** *Some of the examples of enantiomers displaying different properties*

Due to the significant reasons mentioned above and increase in requirements of new bioactive compounds, the detailed research on effective synthesis of enantiomerically pure compounds is still active. For these purposes, three main routes are generally followed *(Scheme 1)*;

Resolution of racemic mixtures
Synthesis with compounds from the chirality pool
Asymmetric synthesis




***Scheme 1*** *Synthesis routes to enantiomerically pure compounds*

The route focused on the resolution of racemates by diastereomeric crystallization has been still followed in industry with a great importance, as opposed to the reported important developments in other routes for the synthesis of enantiomerically pure compounds [6]. Nevertheless, the

weakness of the former is that it provides low theoretical yield of one enantiomer by a maximum 50% under the conditions of recyclization of only corresponding enantiomer. In kinetic resolution, on the other hand, enantiomers of a racemic mixture differ in reaction rates with catalytic amounts of chiral compound [7]. By this route, many enzymes providing excellent kinetic resolutions were investigated.

In organic synthesis, chiral compounds from the nature (referred as "chirality pool") can either be utilized as starting materials for the synthesis of enantiomerically pure entities or used as enantioselective agents namely catalysts or ligands [8]. As most of the naturally occurring compounds are available in one enantiomeric form, many needed enantiomers have to be obtained synthetically. Although biochemical methods including use of enzymes, cell cultures and living microorganisms were thought to be only probable and powerful way for synthesis of enantiomerically pure compounds starting from prochiral precursors, they are usually specific for substrates. In contrast, there are various flexible stereoselective reactions complementing biological methods in organic synthesis, one of which is asymmetric reactions [9]. In asymmetric synthesis, chiral reagents or auxiliary functioning on heterotopic atoms faces or groups of substrate are used to create one configuration of one or more new stereogenic elements preferentially. Stereoselectivity depends on the chiral catalyst, reagent or auxiliary used in asymmetric reaction in major regardless of the presence of any stereogenic elements in the substrate [10]. Synthesis of optically active compounds is possible only by using chiral auxiliary either in stoichiometric or in catalytic amount. Products of stereoselective synthesis are formed as a result of diastereomeric transition states having different Gibbs free energy of activation. Synthesis will result in one selective enantiomer formation only if sufficient difference in Gibbs free energy of activation (≥ 3 kcal/mol) is provided.

### 1.1.1. Asymmetric Catalysis

Asymmetric catalysis including production of large amounts of enantiomerically enriched or ideally pure compounds from the small quantities of enantiomerically pure material, is the most potent and striking way of stereoselective synthesis. In this area, many different reactions in which chiral transition metal complexes prepared *in situ* and used as the catalysts, have been accounted with perfect enantiomeric excesses (ee's) > 95% [11,12]. Corresponding reactions are generally based on asymmetric reduction, asymmetric oxidation and asymmetric carbon-carbon bond formation, the latter of which has incredible synthetic efficacy. It should also be mentioned to present the importance and impact of asymmetric catalysis that in 2001, William S. Knowles, Ryoji Noyori, and K. Barry Sharpless were awarded the Nobel Prize in Chemistry for their contribution to the development of catalytic asymmetric synthesis.

*Figure 2* given below represents the working principle of a chiral catalyst. After Catalyst-Substrate complex formation reaction proceeds under control of chiral catalyst then finally modified substrate decomplexes from chiral catalyst and chiral catalyst starts another catalytic cycle. Chiral catalysts can be divided into three groups as follows;

Metal–Chiral ligand complexes
Biocatalysts
Organocatalysts

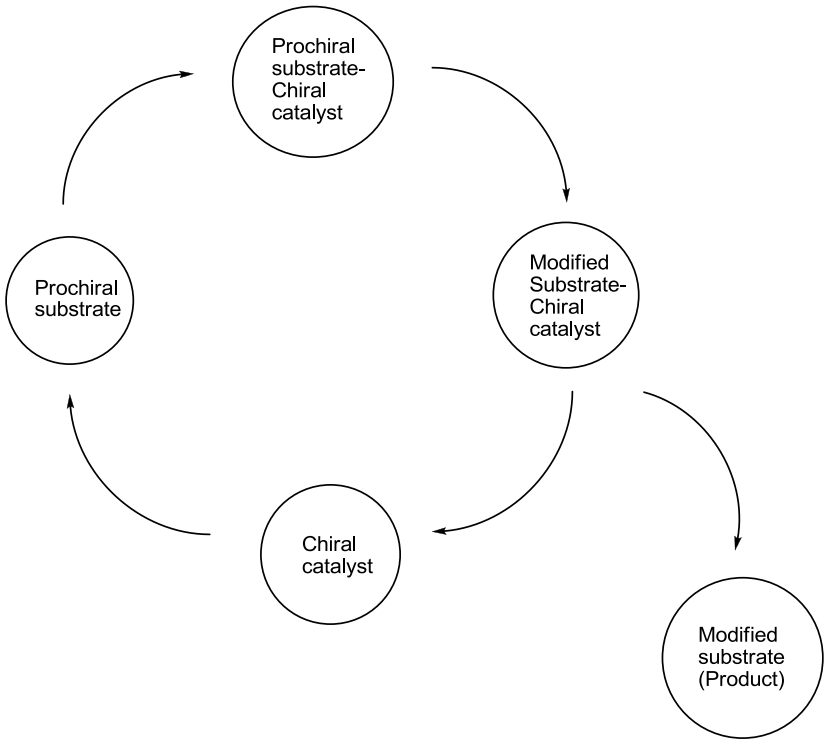



***Figure 2*** *Schematic representation of asymmetric catalysis*

### 1.1.1.1. Organocatalyst

An organocatalyst is an organic molecule that does not contain a metal which in substoichometric amounts accelerates a reaction. Carbon (C), hydrogen (H), nitrogen (N), oxygen (O), sulfur (S) and phosphorous (P) are the main elements that are found in such small organic compounds [13].

A system for the classification of organocatalysts which is based on the mechanism of catalysis, was introduced by List[14]. According to this system, there are the four categories for organocatalysts as Lewis Base, Lewis Acid, Bronsted Base, Bronsted Acid.

Figure representing the four groups is as follows (S: Substrate, P: Product, B: Base catalyst, A: Acid catalyst; *(Figure 3))*;

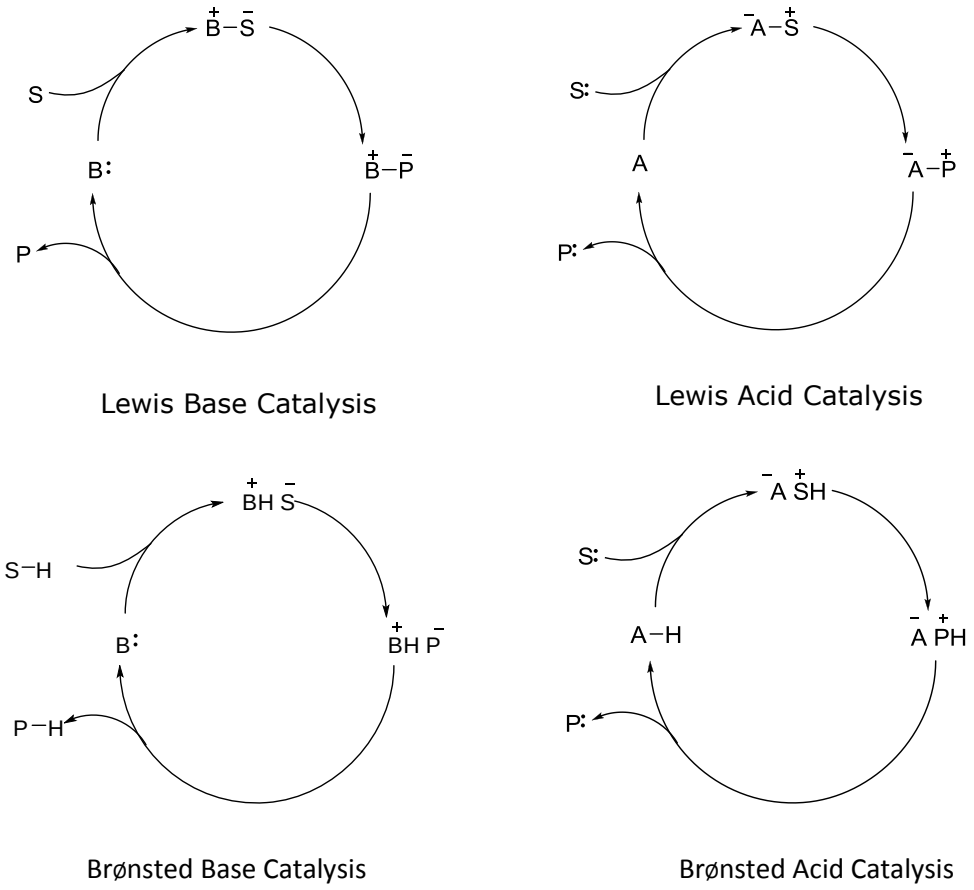


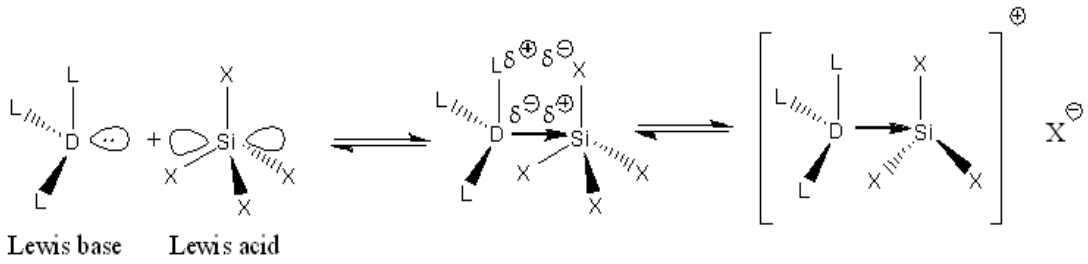

***Figure 3*** *Classification of organocatalysts according to mechanism of catalysis*

### 1.1.1.2. Hypervalent-Silicon Based Organocatalysts

Enamine and iminium catalysis are the mostly encountered as generic modes of activation in asymmetric organocatalysis [15]. Although most of the organocatalytic reactions proceed via formation of enamine and iminium catalysis or hydrogen bond formation between substrate and catalysts, substrate activation can be achieved also by combination of Lewis bases with silicon containing compounds which can form a Lewis acid center *in situ*.

Expansion capacity of valence shell orbitals of silicon atom makes the Lewis bases interaction possible with unoccupied orbitals of silicon atom. As a result of this interaction, the electron density of the most unstable

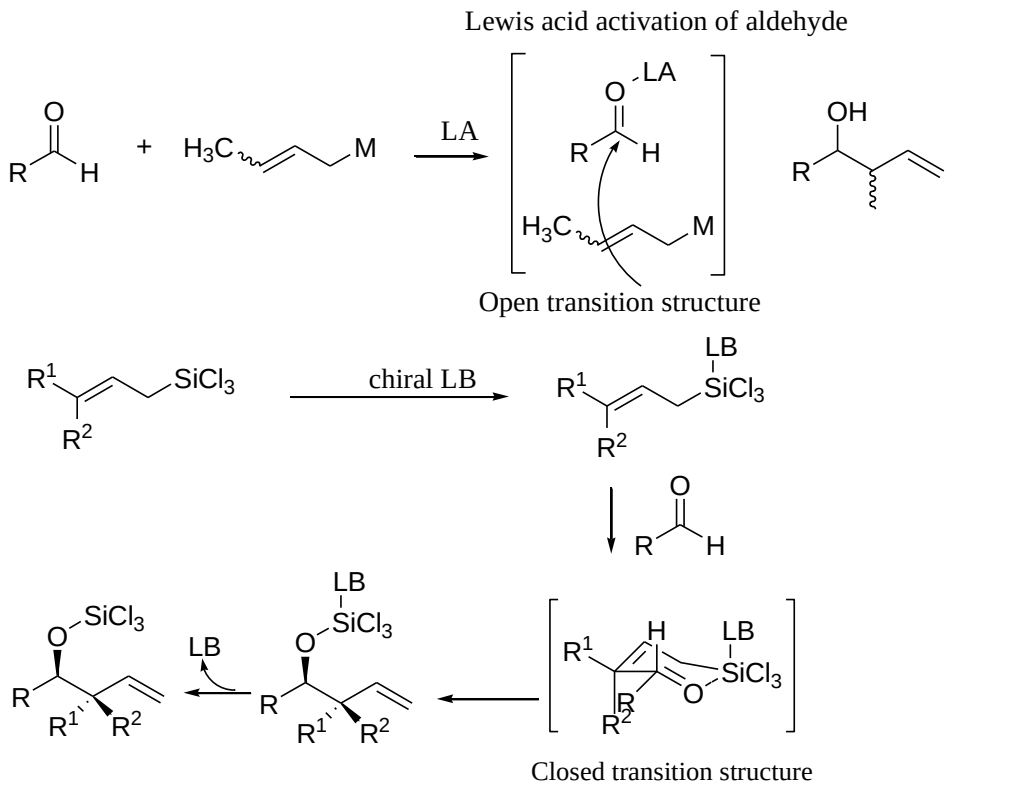
ligand on silicon atom increases. Upon the ionization or partially ionization of ligand, the formation of silicon complex occurs and it acts as a Lewis acid [16]. Free 3-d orbitals of silicon atom are responsible of many organic transformations *(Scheme 2)* [17, 18].




***Scheme 2*** *Lewis base Lewis acid pair*

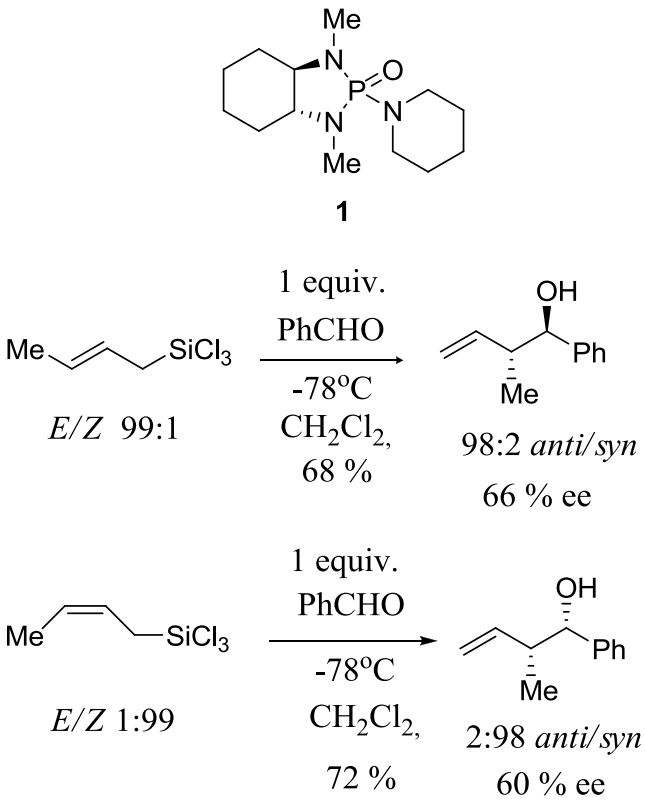
### 1.1.1.3. Lewis base catalyzed Silicon mediated asymmetric reactions

Enantioselective allylation of carbonyl compounds with corresponding allylating silicon agent leads to a homoallylic alcohol containing two consecutive chiral centers along a C-C bond as a product. Traditionally for this purpose, carbonyl center of electrophilic aldehyde is activated with a Lewis acid toward a nucleophilic attack of an allyl metal reagent [19]. Although high enantioselectivity was obtained, low diastereoselectivity was observed due to non-rigid transition structure. However, chiral Lewis base catalyzed allylation provides high degree diastereoselectivity and enantioselectivity due to dual mechanism of activation in which chiral Lewis base binds with silicon atom of nucleophile and interacts with aldehyde to activate carbonyl center *(Scheme 3)* [18b].



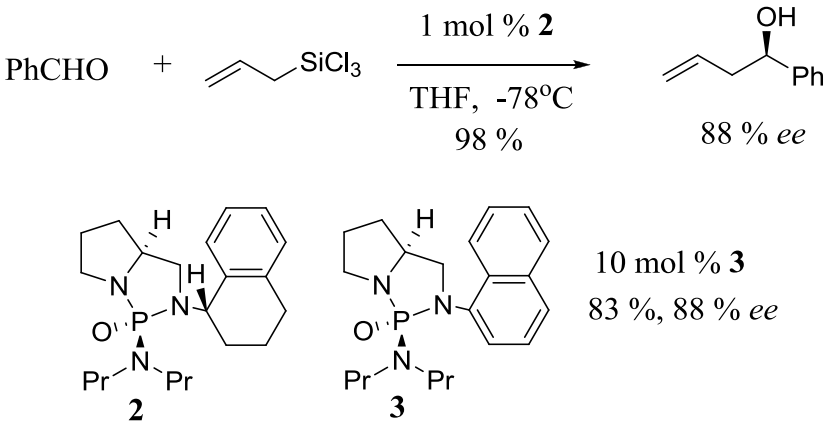

***Scheme 3*** *Chiral Lewis base catalyzed allylation reaction*

The first study for this reaction performed by Denmark and coworkers was in 1994*(Scheme 4)* [20]. To make allylation reaction selective, substoichometric amounts of phosphoramide *(R,R)* was used and a relationship between the geometry of allylsilane (*E/Z*) and diastereomeric ratio (*syn/anti*) of products was observed.



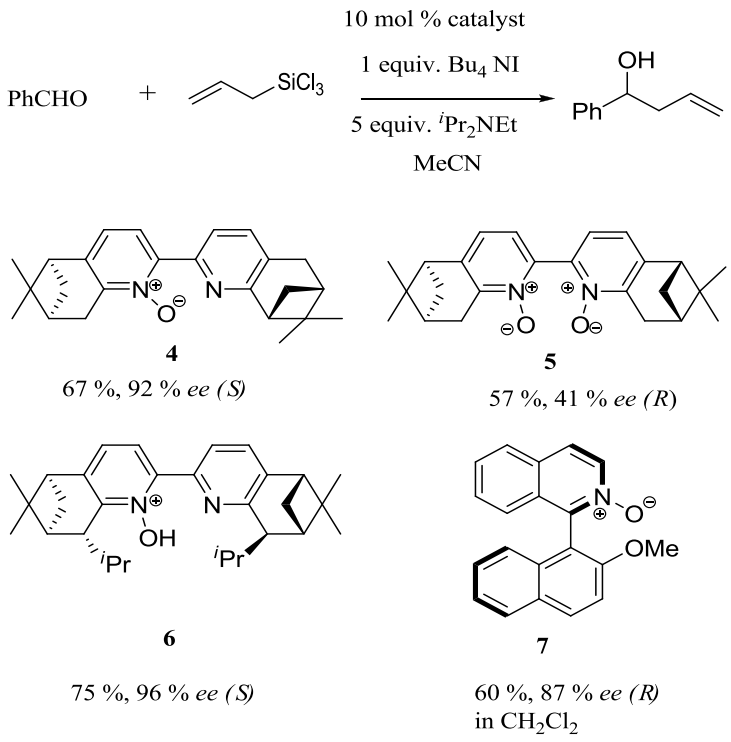

***Scheme 4*** *Lewis base* ***1*** *catalyzed allylation reaction*

Similar results were obtained by developing new chiral Lewis bases by different groups. Barret's group used stoichometric amount of 2-(2-pyridinyl)-2-oxazoline for this reaction [21]. Iseki and Kobeyashi [22] performed same reaction in 1996 by using proline based chiral HMPA derivatives. The amount of Catalyst **2** was decreased to 1% and excellent results were obtained. Regarding the catalyst loading, it considered to be the best catalyst for this reaction *(Scheme 5)* [23].



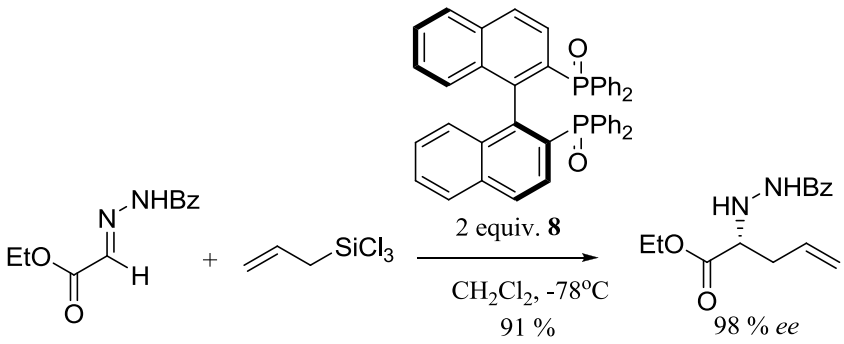

***Scheme 5*** *Lewis base* ***2*** *catalyzed allylation reaction*

Differently amine-*N*-oxide series was used as chiral Lewis base by Malkov and Kocovsky in enantioselective allylation reactions. The reaction and the chiral Lewis bases are given with corresponding yields and selectivities below *(Scheme 6)* [24-26].



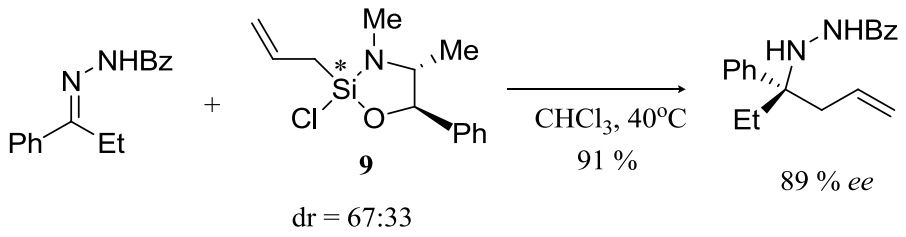

***Scheme 6*** *Enantioselective allylation reaction with axial chiral N-Oxides*

Next to aldehydes acylhydrazones were allylated and a chiral BINAP dioxide **8** was developed for the asymmetric allylation of N-acylhydrazones by Kobayashi and coworkers *(Scheme 7)* [27-28].



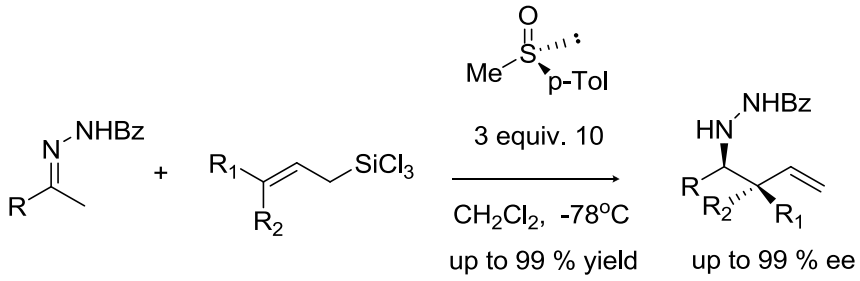

***Scheme 7*** *Allylation reaction with Lewis base* ***BINAPO***

Then, the synthesis of tertiary carbinamines was achieved via using allylic silane reagent in allylation of benzylhydrazone by Leighton [29] with high enantioselectivity in 24 h. This reaction is remarkable as it was performed by high enantioselectivities since the allylic silane reagent is a diastereomeric mixture. For this reaction, there may be two explanations for the surprising enantioselectivity [30]. By using 1,5 equiv. of reagent, only the major diastereomer allylates the benzylhydrazone and the minor one remains unreactive or the reaction proceeds through a hypervalent silicon intermediate which is prone to a pseudorotational process leading to epimerization of silicon stereocenter and makes the reaction proceed through only one diastereomer *(Scheme 8)*.



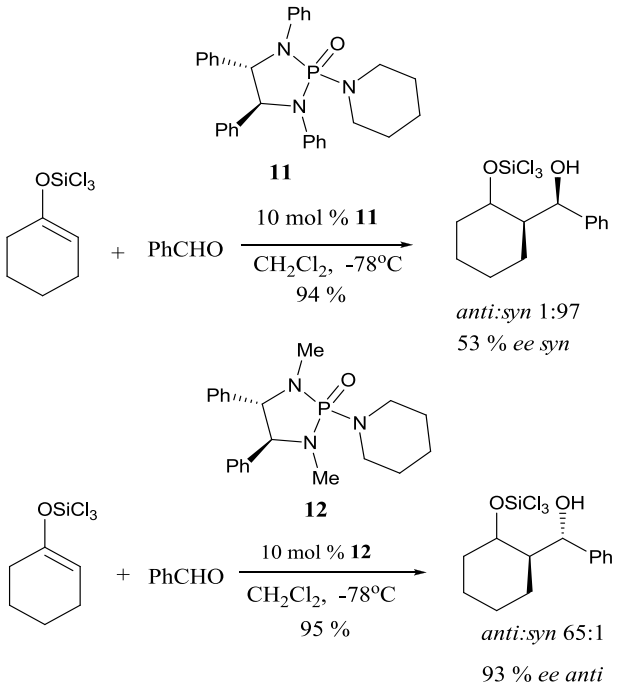

***Scheme 8*** *Asymmetric allylation with reagent* ***9***

Next to P(O) and N(O), there are a few examples where enantiopure sulfoxides were used in combination with silanes. Kobayashi and coworkers performed the allylation reaction with high yields and selectivities via using enantiopure sulfoxides *(Scheme 9)* [31].



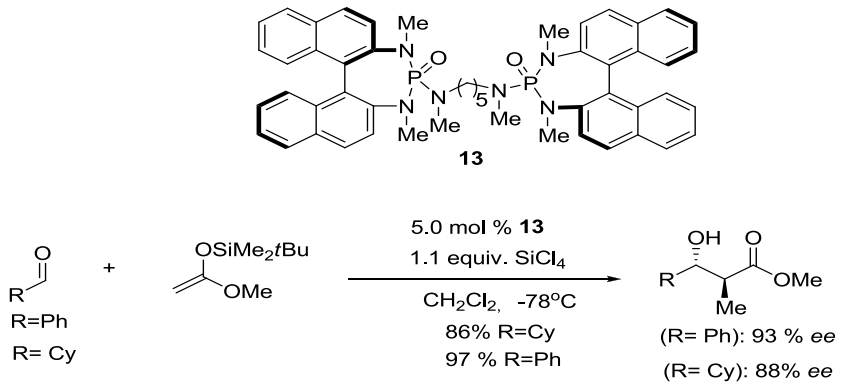

***Scheme 9*** *Asymmetric allylation reaction with sulfoxide* ***10***

After that, aldol reactions of sillylenolethers that catalyzed by Lewis bases have been researched as the structure and mode of action resembles similarities between sillylenol ethers (O-Si) and allylsilanes (C-Si). Using the chiral phosphoramide [32] as Lewis base asymmetric aldol reactions of trichlorosillyl enol ethers was performed first by Denmark with good diastereoselectivities and moderate to good enantioselectivities *(Scheme 10)*.



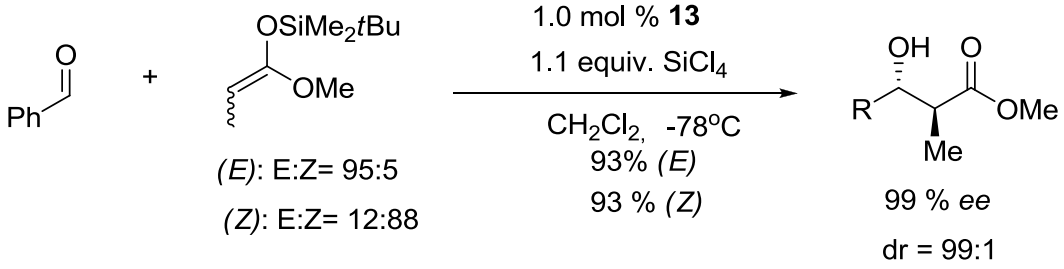

***Scheme 10*** *Lewis base catalyzed asymmetric aldol reaction*

Cross aldolization reaction of aromatic and aliphatic aldehydes performed with a sillyl ketene acetal [33] and good yield and high diastereo and enantioselectivities was obtained. For this reaction, stoichiometric amount of $SiCl_4$ and catalytic amount of chiral Lewis base **13** were employed. Required Lewis acid species to make the reaction selective formed *in situ (Scheme 11)*.




**Scheme 11** Asymmetric cross aldolization

Later, same aldol products were obtained with good enantioselectivities for the reaction of benzaldehyde and *E* and *Z* configurated sillyl ketene acetals [33]. It was found that diastereo and enantioselectivity was not affected by the double bond geometry of sillyl ketene acetal due to acyclic transition state for the asymmetric reaction *(Scheme 12)*.

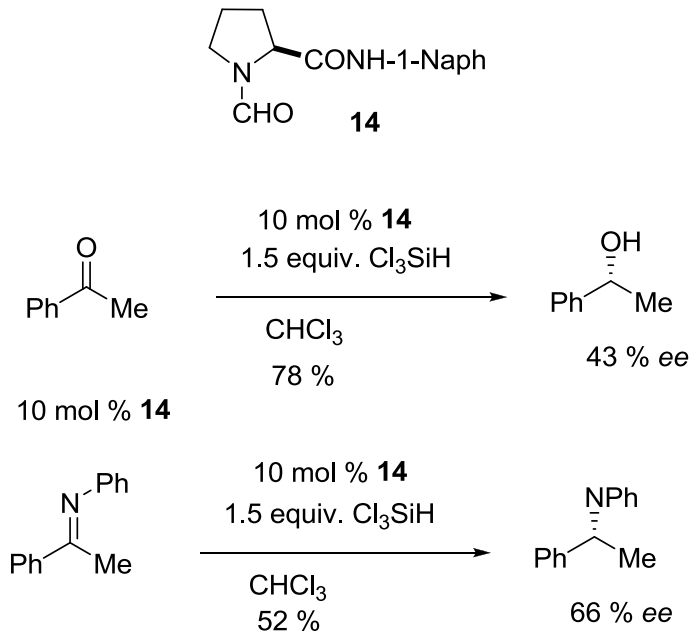



***Scheme 12*** *Cross aldolization with trisubstituted sillyl ketene acetals*

Catalytic amounts of chiral phosphoramides **13** (1 mol %) also catalyzes the asymmetric aldol reactions of aromatic aldehydes with sillyl ethers [34], vinyloguous silicon enolates [35] and even with isocyanates [36] in the presence of catalytic amounts of $SiCl_4$ with good yields and high enantioselectivities.

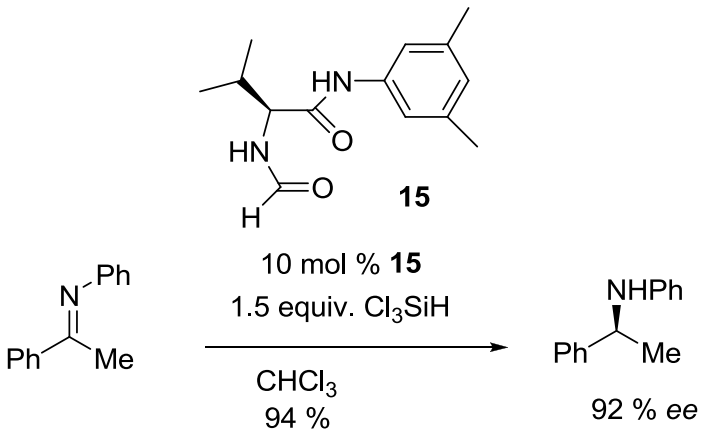
Different from phosphoramides, Denmark reported that the axially chiral N-oxides promoted the asymmetric aldol reaction of trichlorosillyl enol ethers with ketones [37]. Not only Denmark but also Hashimato reported an aldol reaction with another axially chiral N- oxide (3 mol %) with good yields and enantioselectivities [38].

Next, Matsumura and coworkers reported the reduction of ketones and imines via the usage of trichlorosilane as reductant and N-formylpyrolidyne derivatives as ligand *(Scheme 13)* [39, 40].



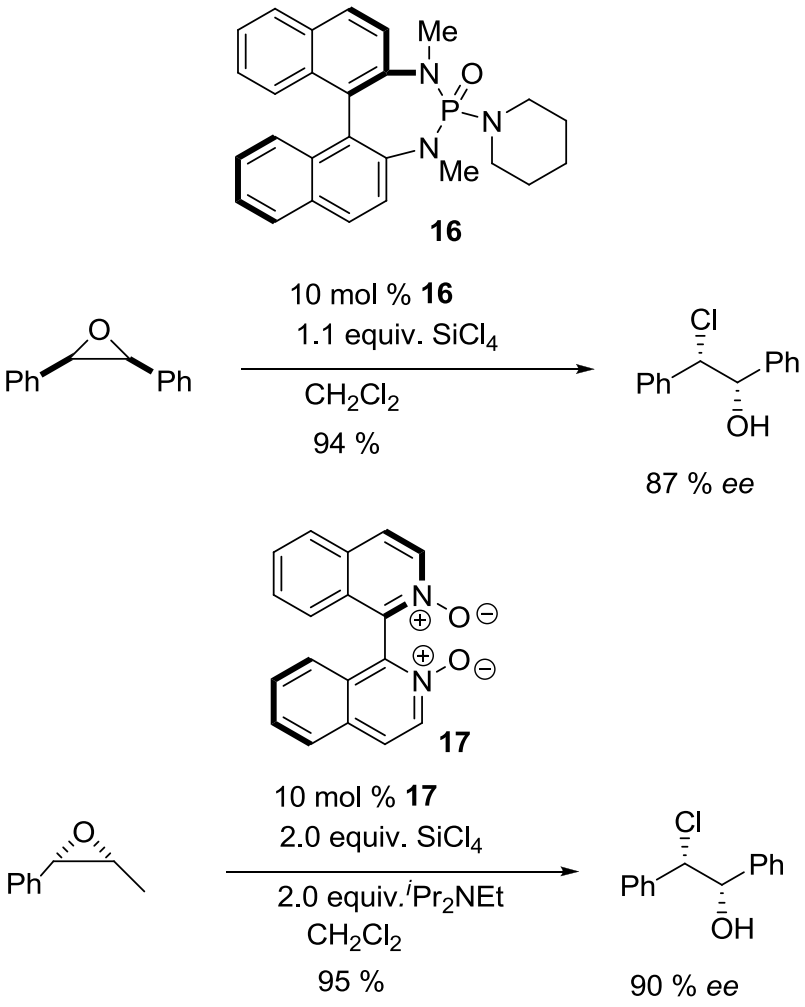

***Scheme 13*** *Reduction of ketones and imines*

Later, enantioselective reduction of imines was performed by Malkov and Kocovsky in which they used N-methyl L-valine derivative and high yields and enantioselectivities were observed *(Scheme 14)* [41].



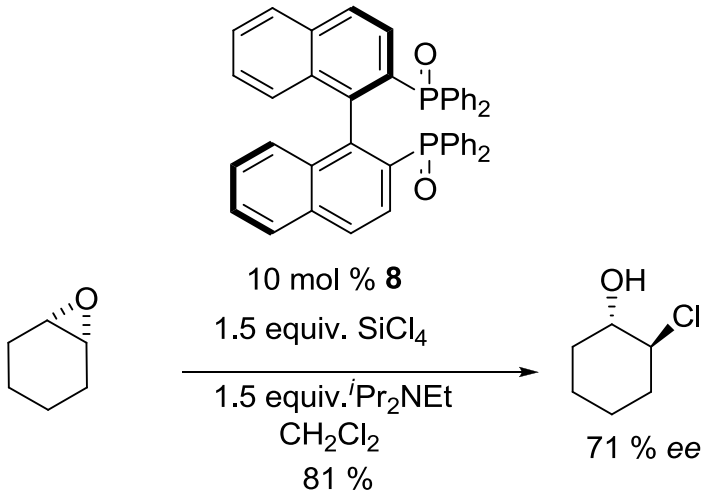

***Scheme 14*** *Reduction of imines with catalyst* ***15***

Some of the reactions given above presented the use of $SiCl_4$ for the *in situ* preparation of a Lewis acid catalyst with a Lewis base for the aldol reactions, it is also possible to perform ring opening reactions of epoxides which yields chlorinated alcohols via the usage of this compound as a reagent. Enantioselective ring opening reaction of *meso*-epoxides in the presence of $SiCl_4$ was performed by Denmark with *N*-phosphoramides [42a]. Same reactions are promoted also via the usage of *N*-oxides as catalyst by Hashimato at 2002 *(Scheme 15)* [43].



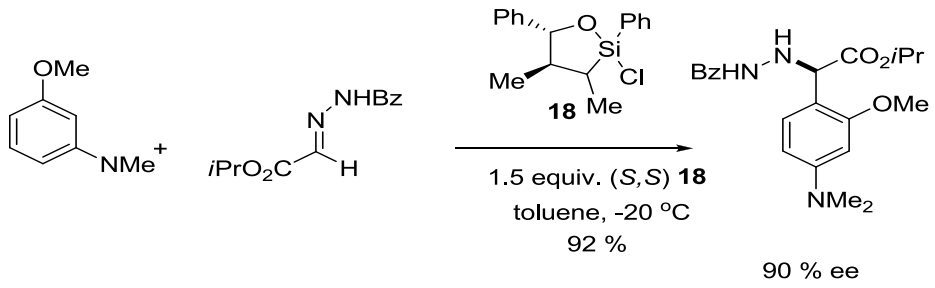

***Scheme 15*** *Asymmetric epoxide ring opening reaction*

In 2005, cyclohexane oxide treated for the ring opening reaction and to make this reaction asymmetric **BINAPO** was used as a catalyst by Hashimato [44]. Corresponding product chlorohydrine was isolated with high yields and enantioselectivities *(Scheme 16)*.



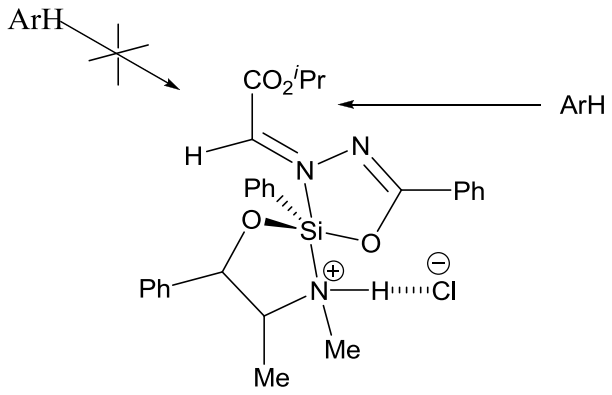

***Scheme 16*** *Epoxide ring opening catalyzed with Lewis base* ***8***

Leighton *et al*. depicted a mechanism for asymmetric Friedel-Crafts alkylation using the *strained silacycle* reagents. Preparation of chiral silane Lewis acid in situ from (*S,S* or *R,R*) pseudoephedrine and $PhSiCl_3$ in bulk and in a single step and use of this *strained silacycle* reagents in asymmetric Friedel-Crafts alkylation with benzoyl hydrozones then which can be recycled at good yield during the work-up extended the application of this strained reagents. The best example was given below which was achieved with 92% yield and 90% ee in 48 h *(Scheme 17)* [45].




***Scheme 17*** *Enantioselective Friedel- Crafts alkylation*

Although the catalyst was used in 1.5 equiv., it provided good results with heteroarenes for the alkylation reactions. This result can be explained by the model given below in the scheme. As the phenyl group on the silicon blocks the back (*re*) face, the arene approaches from the front (*si)* face *(Scheme 18).*




***Scheme 18*** *Proposed mechanism for enantioselective Friedel- Crafts alkylation*

### 1.1.1.3.1. Abramov-Type Asymmetric phosphonylation of aldehydes

Coordination of chiral Lewis bases with weakly acidic $SiCl_4$ enables the asymmetric ring-opening of epoxides [42] or addition of allyl/proparglytin [46], enoxysilanes [33, 35, 47], isocyanides [36, 48], or sillyl ketene

imines [49] as nucleophiles to aldehydes or ketones. While the studies for further development of chiral Lewis base-catalyzed asymmetric reactions have been still continuing [43, 50], it was envisioned that a chiral Lewis base LB*-$SiCl_4$ complex could activate prochiral aldehydes and promotes enantioselective attack of trialkyl phosphites to yield trichlorosilylated α-hydroxy phosphonates after Arbuzov-type liberation of the corresponding alkyl chloride. Although a few successful examples of metal catalyzed Pudovik-type asymmetric reactions performed with dialkyl phosphites for phosphonylation of aldehydes [51, 52], enantioselective Abramov-type reaction [53] of aldehydes with trialkyl phosphites has recently been achieved by Nakajima and coworkers in 2008 as an alternative to Pudovik-type dialkylphosphite addition to aldehydes *(Figure 4)* [54].

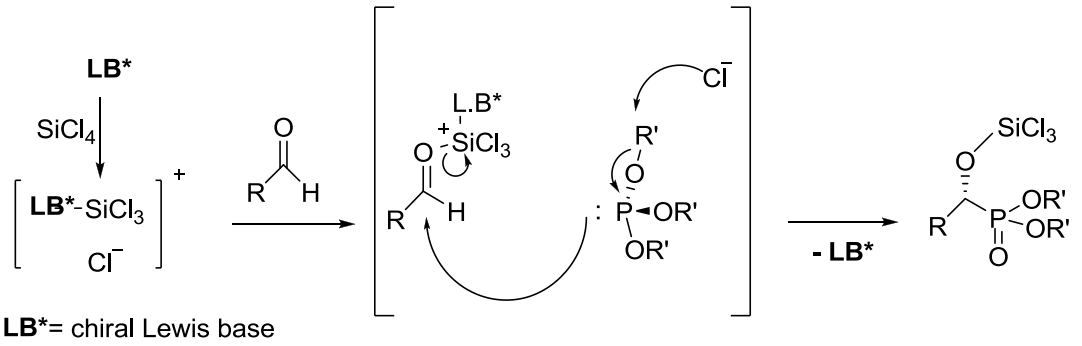
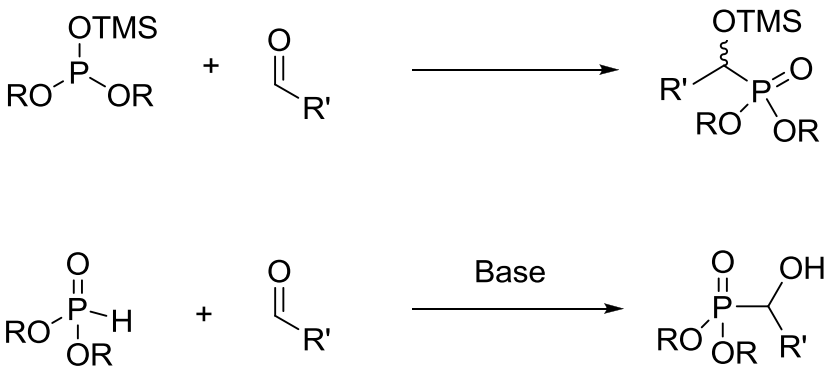


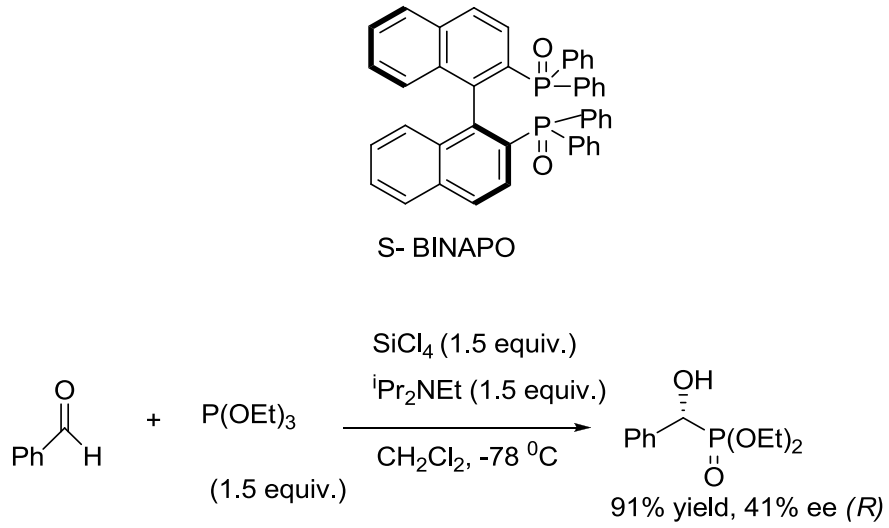

***Figure 4*** *Assumed reaction mechanism of asymmetric Abramov-type phosphonylation*

α-hydroxy phosphonates can be synthesized by Abramov and Pudovik reactions. Both reactions employ similar mechanisms in which attack of nucleophilic phosphorous compound to carbonyl center of aldehyde occurs. While fully esterified trialkyl phosphites are employed in Abramov reactions, dialkyl phosphites are used in Pudovik reactions. Schematic representation of Pudovik and Abramov reactions are given below.




***Scheme 19*** *Representation of Abramov and Pudovik reactions*

Asymmetric phosphonylation of aldehydes performed with BINAP dioxide (**BINAPO**) due to its effectiveness in asymmetric aldol reactions [50d, e], allylations [50b, e] and epoxide ring opening reactions *(Scheme 19)* [50c].




***Scheme 20*** *Asymmetric Abramov-type phosphonylation of aldeydes with trialkyl phosphites catalyzed by* ***BINAPO****.*

Asymmetric Abramov reaction was also performed with the chiral Lewis bases shown in the *Figure 5*. According to study carried out by Nakajima and coworkers triarylphosphine oxides showed higher activities than the alkylarylphosphine oxides and bisquinoline *N-N'*-dioxides *(Figure 5)* [54].

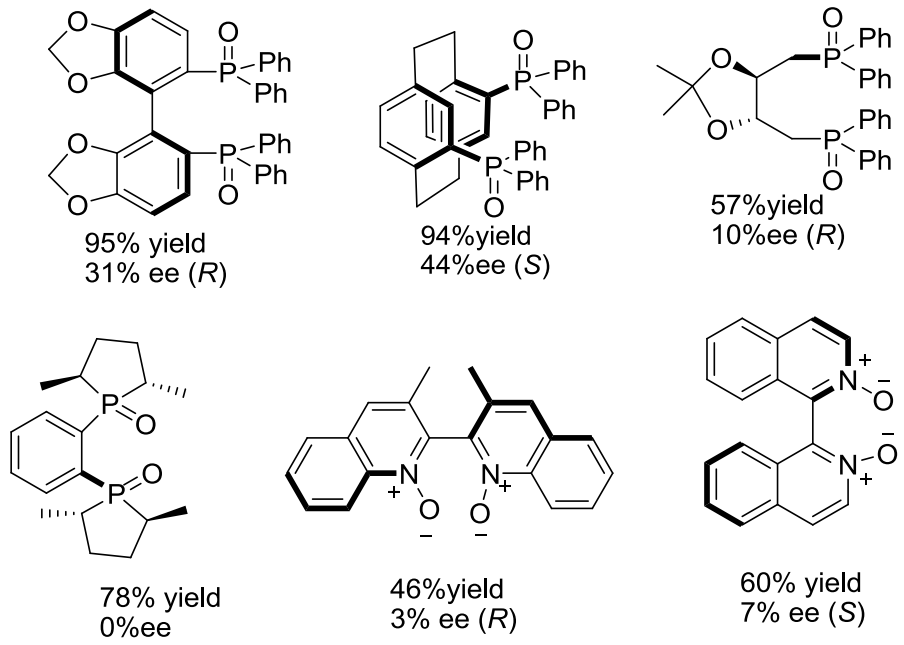



***Figure 5*** *Some examples of chiral Lewis bases used as chiral ligands in enantioselective phosphonylation of aldehydes with trialkyl phosphites*

Finally, Pudovik-type phosphonylation reactions with dialkyl phosphites also catalyzed by $SiCl_4$ and **BINAPO** chiral Lewis base complex but relatively inferior results were obtained with respect to Abramov-type phosphonylation reaction with trialkyl phosphites by the same group [54].

## 1.2. Aim of work

In the literature chiral compounds possessing Lewis base character, especially the phosphine oxide group containing ones, were subjected to asymmetric reactions such as ring-opening of epoxides, asymmetric aldol reactions and addition of several nucleophiles including allyl/proparglytin, enoxysilanes, isocyanides or sillyl ketene imines to aldehydes or ketones. All the reactions mentioned above can be achieved by hypervalent-silicon based organocatalysts. Desire to develope new chiral Lewis bases to improve silicon based asymmetric reactions or applying the existing ones to a new asymmetric reaction was the main reason of this work.

More specifically in this study enantioselective phosphonylation of aldehydes with triethyl phosphites to obtain optically active α-hydroxy phosphonates were carried out. As α-hydroxy phosphonates are an attractive class of biologically active compounds and their biologic activity generally depends on the absolute configuration, their asymmetric synthesis has been focused by our research group. Furthermore, this study would enable us to observe catalytic activity of our existing (**POFAM** and **AP**) and newly synthesized (**POAP**) chiral Lewis bases for asymmetric Abramov-type phosphonylation reactions.

# CHAPTER 2

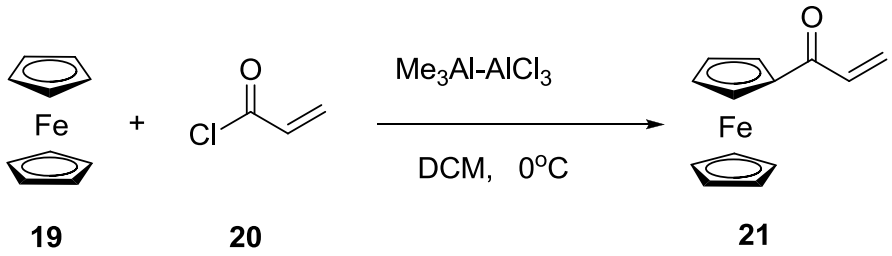
# RESULTS AND DISCUSSION

## 2.1 The synthesis of PFAM and POFAM ligands

Phosphineoxy counterpart of the **PFAM** ligand, **POFAM**, was required as chiral Lewis base for the asymmetric Abramov-type phosphonylation of aldehydes with trialkyl phosphites. Chiral phosphineoxy ferrocenyl substituted aziridinyl methanol, **POFAM**, was synthesized by previously used method published by our group [55].

### 2.1.1 Synthesis of acryloyl ferrocene

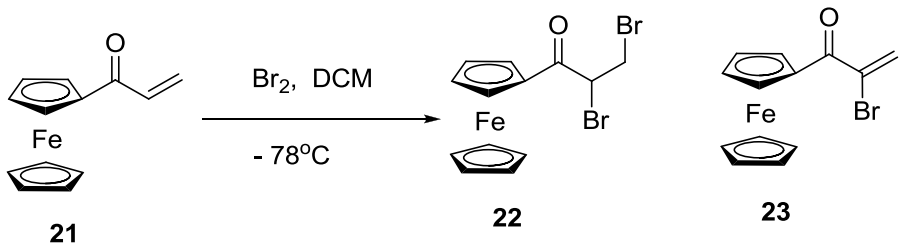
Firstly, synthesis of acryloyl ferrocene was achieved by reacting ferrocene and acryloyl chloride in the presence $AlMe_3$-$AlCl_3$ Lewis acids. This method developed by our group provides a yield greater than 95 % *(Scheme 20)*. Extraction is adequate to remove reaction residues, no need for further purification [56].




***Scheme 20*** *Synthesis of acryloyl ferrocene*

## 2.1.2 Bromination of acryloyl ferrocene

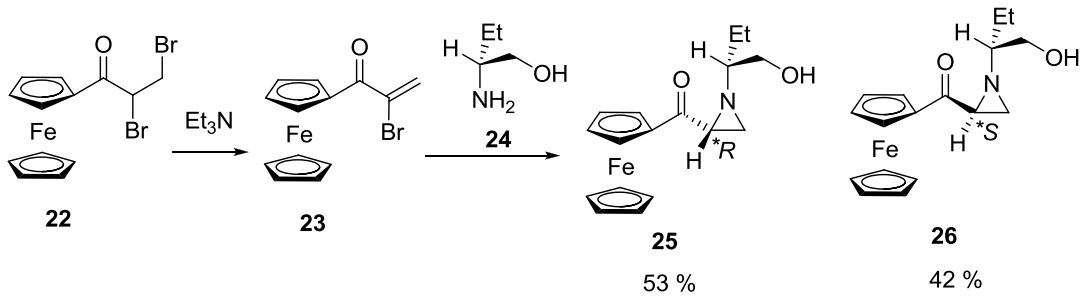
Next step in the synthesis of **PFAM** and **POFAM** ligands was the bromination of olefinic unit. This step was easily achieved by addition of bromine in DCM to acryloyl ferrocene at -78 °C [57] *(Scheme 21)*.




***Scheme 21*** *Bromination of acryloyl ferrocene*

## 2.1.3 Formation and aziridination of monobromo ferrocenyl alkene compound

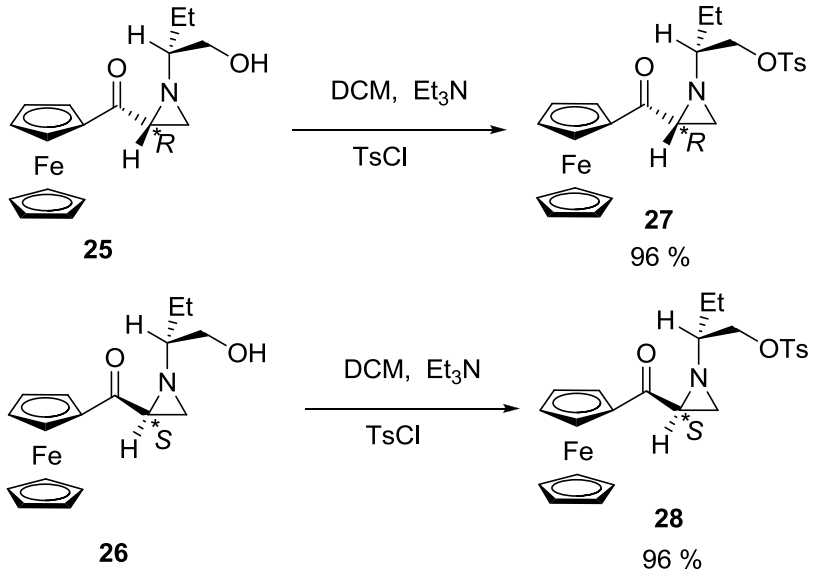
As for the aziridination step, it was necessary to have α-bromoacryloyl ferrocene. This was accomplished by treating **22** with $Et_3N$. It is worth noting that dibromo compound **22** is always isolated with some monobromo compound **23**. Next step in the synthesis was the aziridination which was achieved by Gabriel-Cromwell [58] reaction by using (*R*)-(-)-2 amino-1-butanol. From this step aziridines were obtained in 95 % total yield as a diastereomeric mixture (53 % and 42 %). Thanks to colorful appearance of ferrocenyl aziridines, they were easily separated by flash column (EtOAc + 2% $NEt_3$) without UV visualization (*Scheme 22*).




***Scheme 22*** *Aziridine formation from dibromo compound* ***22***

## 2.1.4 Tosylation of aziridinyl ketones

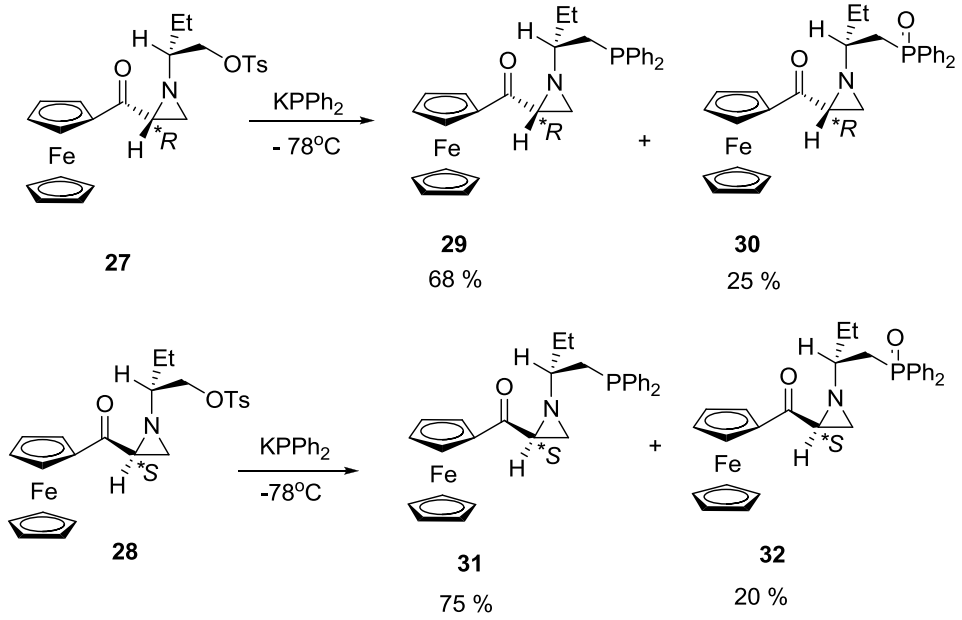
In order to convert the hydroxy group into a good leaving group for phosphorylation, both aziridines **25** and **26** were tosylated separately by standard procedure in 96% yield *(Scheme 23).*




***Scheme 23*** *Tosylation of aziridinyl ketones*

## 2.1.5 Phosphonylation of tosylates 27 and 28

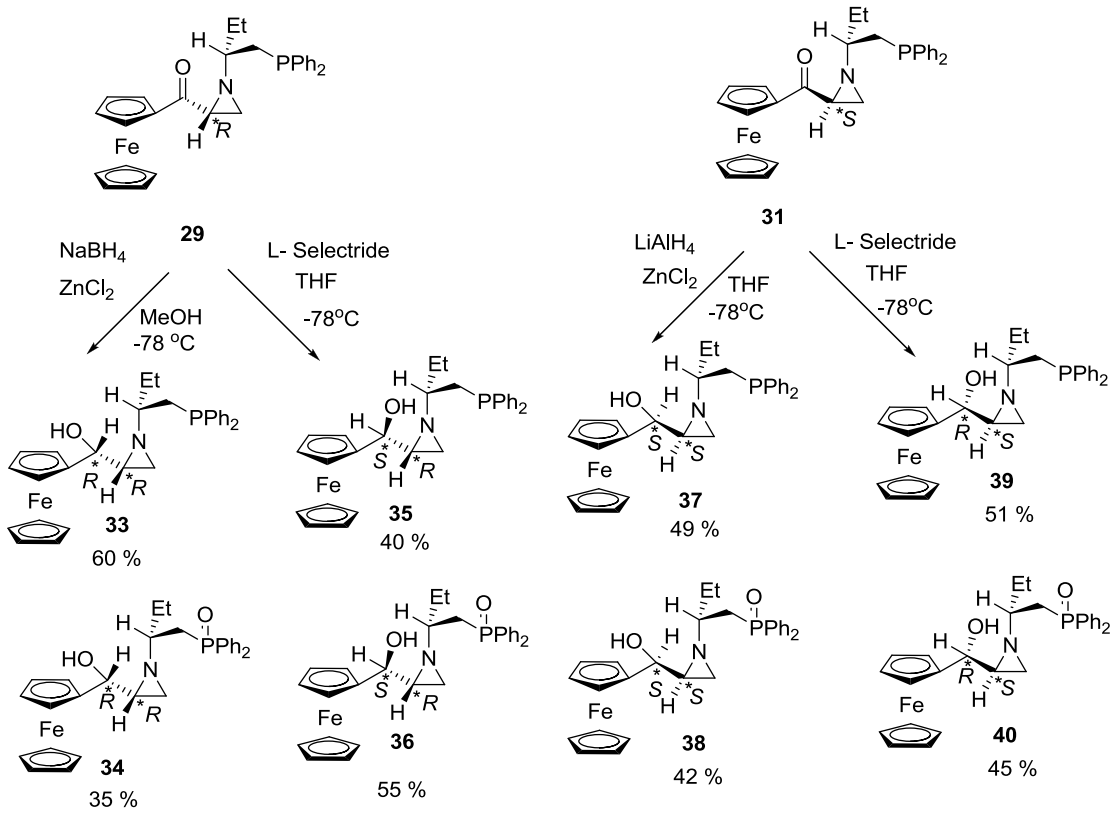
Application of the procedure published by Williams and coworkers [59] was used for phosphonylation of tosylates **27** and **28**. Treatment of tosylate **27** with potassium diphenylphosphine at -78 °C gave desired product **29** in 93 % total yield with its oxidized form **30**. Using the same procedure, **31** and **32** were obtained in 95 % total yield *(Scheme 24)*.




***Scheme 24*** *Phosphonylation of tosylates **27** and **28**.*

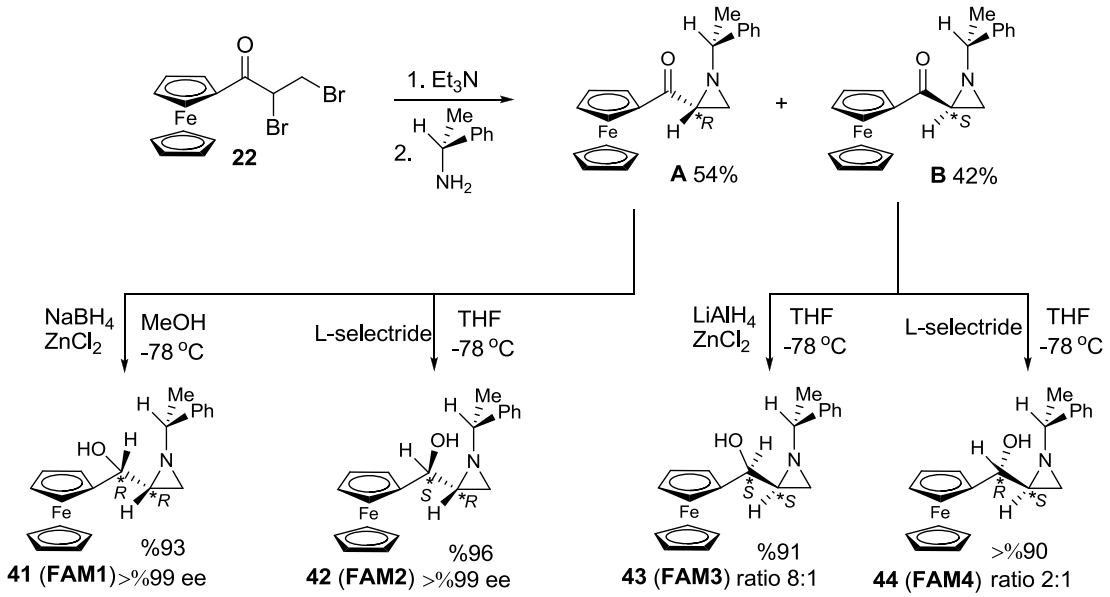
## 2.1.6 Reduction of phosphonylated aziridinyl ketones

Final step for the synthesis of **PFAM** and **POFAM** compounds were the reduction of keto group. This was achieved by the procedure developed by Yun and his coworkers [60] *(Scheme 25)*. As can be seen from *Scheme 25*, **PFAM** ligands were formed with their oxidized forms.




***Scheme 25*** *Reduction of phosphonylated aziridinyl ketones*

Configurational assignments of these compounds were made by analogy to similar compounds (**FAM** ligands) synthesized in our group under the same reaction conditions [56] *(Scheme 26)*. The absolute stereochemistry of **FAM** ligands was determined by X-ray analysis. In assigning stereochemistry of the **PFAM** ligands, we used the following observations; first, aziridinyl ketone **25** has a higher $R_f$ value than aziridinyl ketone **26**. In the **FAM** *(Scheme 26)* series (*R,R*)-ketone **A** has a higher $R_f$ value than (*R*,*S*)-ketone **B**. Second, the aziridinyl ketone **29** was reduced to its alcohol under Luche conditions ($NaBH_4$-$ZnCl_2$) but in order to reduce ketone **31** more powerful $LiAlH_4$-$ZnCl_2$ had to be used. The same observation was made during the reduction of (*R*,*R*)-ketone **A** to **FAM1** (achieved by $NaBH_4$-$ZnCl_2$) and (*R*,*S*)-ketone **B** to **FAM3** (achieved by $LiAlH_4$-$ZnCl_2$).




***Scheme 26*** *Synthesis of* ***FAM*** *compounds*

## 2.3 Synthesis of aziridinyl phosphonates

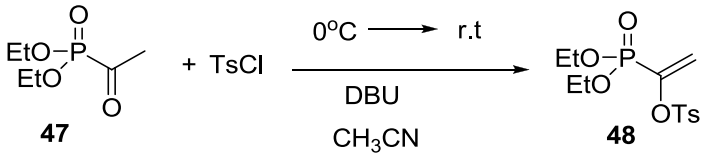
Synthesis of aziridinyl phosphonates can be achieved by Gabriel-Cromwell reaction from two different starting materials;

α-tosylatedvinyl phosphonate **48** and

1,2-dibromoethyl phosphonate **50**

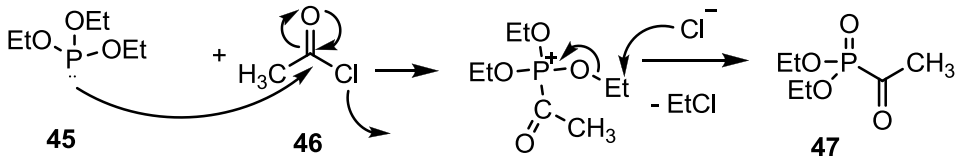
### 2.3.1 Synthesis of α-tosylatedvinyl phosphonate

Acetyl phosphonate was treated with tosyl chloride in the presence of DBU as a nonnucleophilic base in acetonitrile to obtain α-tosylatedvinyl phosphonate **48** with yields up to 87 % *(Scheme 27)*.




***Scheme 27*** *Synthesis of α-tosylated vinyl phosphonate* ***48***

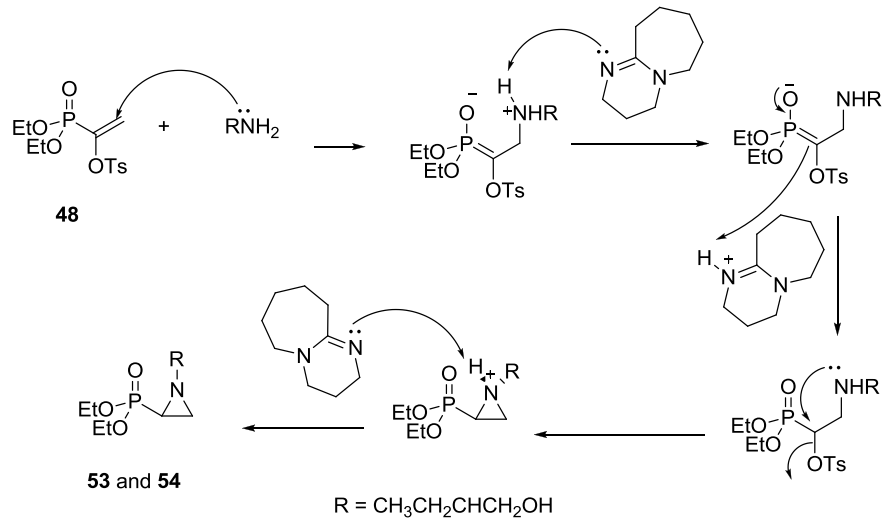
The starting material **47** can be synthesized with Michaelis-Arbuzov reaction by refluxing acetyl chloride with triethyl phosphite under inert atmosphere. It can be isolated in high purity and yields after vacuum distillation. This reaction starts with the addition of $P(OEt)_3$ to carbonyl center of acetyl chloride. Liberated chloride anion attacks to the alkyl group and forms acetyl phosphonate *(Scheme 28)*.




***Scheme 28*** *Synthesis of acetyl phosphonate by Michaelis-Arbuzov reaction*

### 2.3.1.1 Synthesis of aziridinyl phosphonates 53 and 54 from α-tosylatedvinyl phosphonate 48

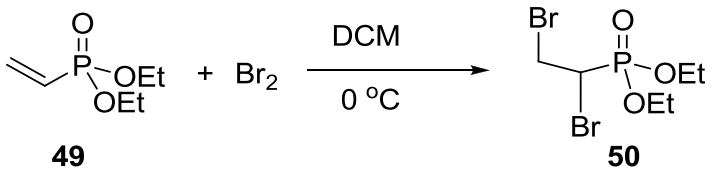
Aziridine-2-phosphonates can be synthesized by treating the α-tosylatedvinyl phosphonate **48** with primary amines in the presence of DBU in $CH_3CN$. The proposed mechanism is shown in *(Scheme 29)*. Firstly, conjugate addition of primary amines takes place. Then, α-protonation is achieved. Finally, $S_N2$ displacement of tosylate forms aziridine ring.




***Scheme 29*** *Synthesis of aziridinyl phosphonates from α-tosylated vinyl phosphonate*

## 2.3.2 Synthesis of 1,2-dibromoethyl phosphonate

Bromination of commercially available diethyl vinyl phosphonate at 0 $^{o}$C yielded 1,2-dibromoethyl phosphonate quantitatively. Completion of reaction can be monitored with TLC. Filtration of reaction mixture through a short plug of silica provides 1,2-dibromoethyl phosphonate in high purity (*Scheme 30*).

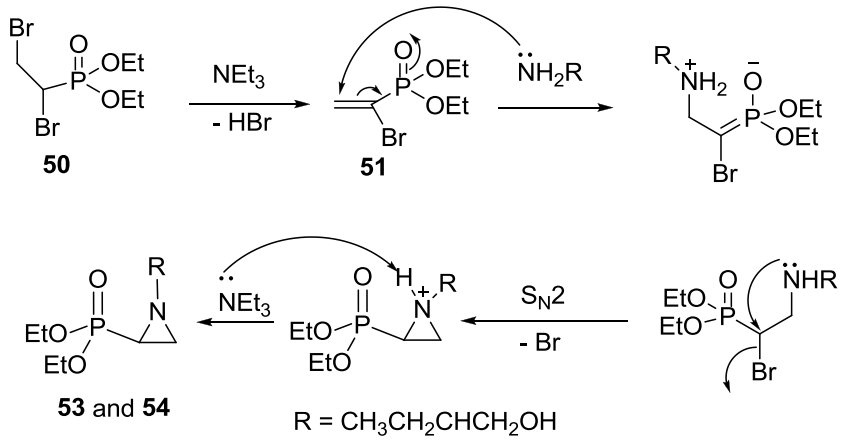



***Scheme 30*** *Bromination of diethyl vinyl phosphonate*

### 2.3.2.1 Synthesis of aziridinyl phosphonate from 1,2-dibromoethyl phosphonate 50

Synthesis of aziridinyl phosphonates can easily be carried out starting from 1,2-dibromoethyl phosphonate which can be converted easily to desired monobromo compound in situ with $Et_3N$. Then, reaction proceeds

through Gabriel-Cromwell reaction. Firstly, conjugate addition of primary amine takes place. Then α-protonation is achieved. Finally, aziridine ring formation by $S_N2$ displacement of bromide completes the product formation *(Scheme 31)*.




***Scheme 31*** *Aziridine formation from dibromophosphonate* ***50****.*

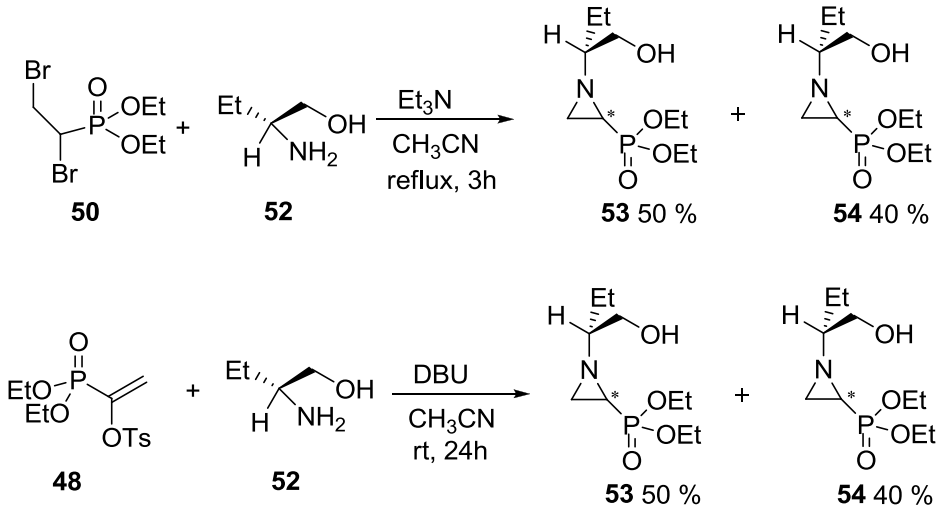
## 2.4 Synthesis of phosphineoxy aziridinyl phosphonates (POAP)

Literature examples showed that diphosphineoxy organocatalysts serve better for Abramov-type asymmetric phosphonylation of aldehydes. Therefore, **POAP** having two phosphorous units (phosphineoxy-phosphonate) was designed and synthesized as a new organocatalyst.

### 2.4.1 Synthesis of (1-(1-hydroxybutan-2-yl) aziridin-2-yl phosphonate

For the synthesis of **POAP**, aziridinyl phosphonates **53** and **54** were synthesized first by using Gabriel-Cromwell reaction as described previously. Reaction of 1,2-dibromoethyl phosphonate **50** or α-tosyl vinyl

phosphonate **48** with (*R*)-(-)-2-amino-1-butanol formed diastereomers **53** and **54** in 50 % and 40 % yields respectively *(Scheme 32)*.




***Scheme 32*** *Synthesis of (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate*

## 2.4.2 Comparison of two methods

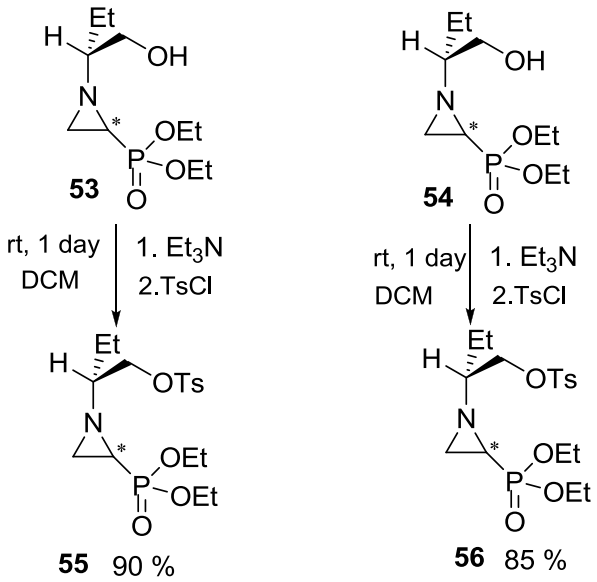
Although α-tosylatedvinyl phosphonate can be synthesized in good yields and can be prepared easily in the laboratory, it requires longer reaction times for both preparation of itself and aziridination reactions. On the other hand, commercially available diethyl vinyl phosphonate can be brominated easily in quantitative yield and provides better yields of aziridinyl phosphonates *(Table 1)*.

***Table 1*** *Comparison of two starting materials for aziridination reaction*

| | **Aziridines from α-tosylatedvinyl phosphonate** | **Aziridines from 1,2-dibromoethyl phosphonate** |
|---|---|---|
| ***(R)*-(-)-2 amino-1-butanol** (equiv.) | 3.0 | 3.0 |
| **Base** (equiv.) | 1.0 (DBU) | 1.2 ($NEt_3$) |
| **Molarity** (solvent) | 1.0 ($CH_3CN$) | 0.55 ($CH_3CN$) |
| **Time** (h) | 24 | 3 |
| **Yield** (%) | 78.2 | 90.9 |

### 2.4.1.1 Synthesis of tosylated aziridinyl phosphonates

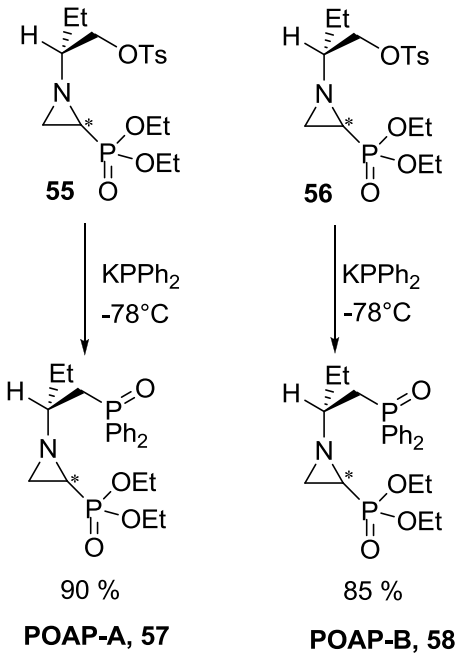
In order to introduce second phosphorous group to aziridines **53** and **54**, it was necessary to convert hydroxy group into a good leaving group. For this reason hydroxy group of the aziridines **53** and **54** was converted to its tosylate derivative by treatment of alcohol with tosyl chloride in the presence of $NEt_3$ with 90 % and 85 % yields respectively *(Scheme 33)*.




***Scheme 33*** *Tosylation of (1-(1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate*

### 2.4.1.1.1 Synthesis of phosphineoxy aziridinyl phosphonates (POAP)

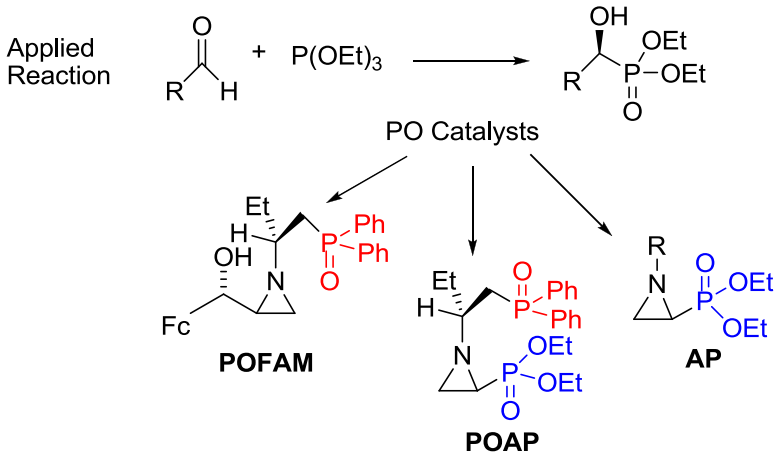
Final step for synthesis of chiral Lewis base **POAP** was the diphenylphosphide addition to tosylated aziridinyl phosphonate. This was achieved by the reaction of **55** or **56** with potassium diphenylphosphide at -78 $^{o}$C. Reaction was completed in about 4h as judged by TLC. Crude reaction mixture was extracted with $NH_4Cl$. Organic layer was dried and concentrated. $^{1}$H NMR of the reaction mixture showed that crude product was a mixture of phosphine compound and its phosphineoxy form. Therefore without purification reaction mixture was treated with $H_2O_2$ to oxidize phosphine group into its phosphineoxy. After removing excess $H_2O_2$ with saturated solution of $Na_2S_2O_3$ crude product was purified by flash column chromotography (2/1: hexane/acetone + 2 % $NEt_3$) to give **POAP**-**A, 57,** in 90 % yield and **POAP**-**B, 58,** in 85 % yield *(Scheme 34)*.




***Scheme 34*** *Synthesis of phosphineoxy aziridinyl phosphonates (**POAP**)*

## 2.5 Asymmetric trials

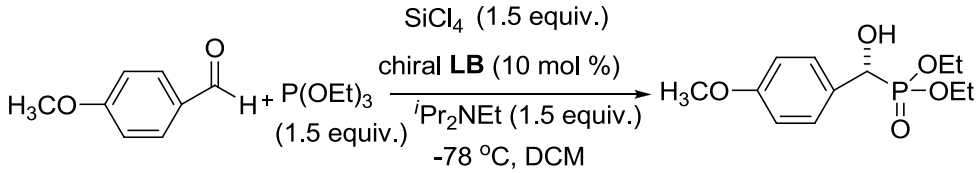
Chiral Lewis bases can be used in several types of reactions as mentioned in the introduction part. After the synthesis of **POAPs** next step was to test the performance of these compounds for the Abramov-type asymmetric phosphonylation reaction of aldehydes with triethyl phosphite. Besides the newly synthesized **POAP** organocatalysts, initially known phosphineoxy ferrocenyl substituted aziridinyl methanols (**POFAM**) and aziridinyl phosphonates (**AP**) were also experimented for the same reaction as potential organocatalysts *(Scheme 35)*.




***Scheme 35*** *Representation of chiral Lewis bases and applied reaction*

### 2.5.1 Catalyst screening studies for asymmetric phosphonylation of aldehydes

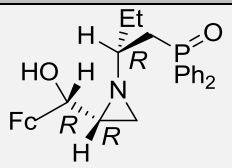
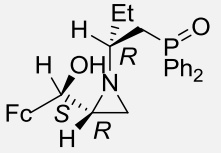
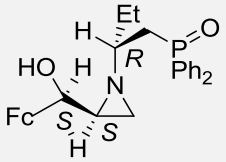
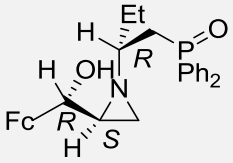
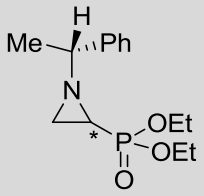
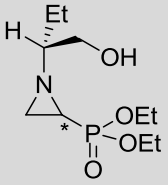
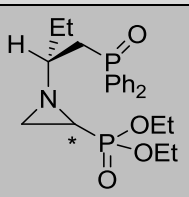
All chiral Lewis bases were tested in asymmetric Abramov-type phosphonylation of anisaldehyde using triethyl phosphite at -78 °C in the presence of $SiCl_4$. Addition of $SiCl_4$ was critical, it must be done slowly otherwise the reaction takes place rapidly with low or no enantioselectivity observed in the reaction (*Scheme 36*).




***Scheme 36*** *Asymmetric triethyl phosphite addition to anisaldehyde*

The results of ligand screening studies are summarized in *Table 2*. First studies were carried out with **POFAM** chiral Lewis bases. This catalyst series gave the product in acceptable to good yields but low enantioselectivities *(Table 2, entries 1-4)*. In the case of **AP** catalysts again yields were good but the reaction was almost non-selective. For the ligand screening studies **POAP** catalysts were tried lastly. There are two diastereomers of **POAP** catalysts one with (*R,R*) configurations and the other with (*R,S*) configurations at the stereogenic centers. Absolute stereochemistry of these compounds was not determined yet. One of the diastereomer is solid so we will try to obtain single crystal for x-ray analysis. Arbitrarily one of the diastereomer was called as **POAP-A, 57,** and the other as **POAP-B, 58**. In terms of the results of these catalysts, **POAP-A** gave the product in very good yield (91%) and low ee (34%). In the case of **POAP-B**, product was obtained in acceptable yield but as a racemic mixture. Although the enantioselectivities are not high, this is typical for this reaction. Highest enantioselectivity reported in the literature for this reaction is around 40%. Another point for the ligand screening studies is that while **POFAM** and **AP** catalysts formed the product with (*R*) configuration, **POAP-A** catalyst formed the product with (*S*) configuration *(Table 2)*.

***Table 2*** *Ligand screening studies*

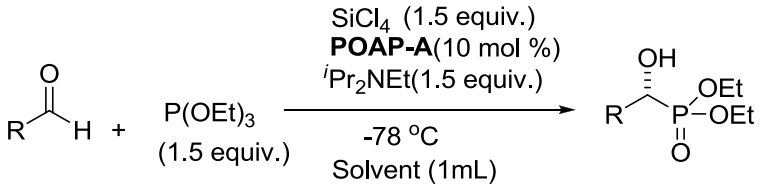
| Entry | Structure of chiral LB | Name of chiral LB | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  | **POFAM3** (*R,R,R*) | 84 | 10 *(R)* |
| 2 |  | **POFAM4** (*S,R,R*) | 85 | 5 *(R)* |
| 3 |  | **POFAM5** (*S,S,R*) | 55 | 7 *(R)* |
| 4 |  | **POFAM6** (*R,S,R*) | 74 | 11 *(R)* |
| 5 |  | **APPE-A** | 73 | 2 *(R)* |
| 6 | | **APPE-B** | 71 | 5 *(R)* |
| 7 |  | **APOH-A** | 70 | 4 *(R)* |
| 8 | | **APOH-B** | 80 | 5 *(R)* |
| 9 |  | **POAP-A** | **91** | **34 *(S)*** |
| 10 | | **POAP-B** | 70 | 2 *(S)* |
| 11 | - | **-** | 72 | - |

## 2.5.2 Solvent and aldehyde screening

After determining the catalyst giving highest enantioselectivity, reaction was carried out in different solvents. As the solvents toluene, THF, and acetonitrile were used instead of DCM *(Table 3, entries 1-4)*. Among the solvents toluene formed the product in highest yield. Enantioselectivity on the other hand remained low (13-19%). In DCM product was formed in very good yield and highest enantioselectivity therefore aldehyde screening studies were carried out in this solvent *(Table 3, entry 4)*.

Benzaldehyde, cinnemaldehyde and ferrocenecarbaldehyde were also used under the same reaction conditions *(Table 3, entries 5-7)*. As can be seen from the table all the aldehydes formed the product in very good yields (90-98%) and similar enantioselectivities (28-29%).

***Table 3*** *Solvent and aldehyde screening*




| Entry | R | Solvent | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | *p*-$MeOC_6H_4$ | Toluene | 98 | 13 *(S)* |
| 2 | *p*-$MeOC_6H_4$ | THF | 77 | 14 *(S)* |
| 3 | *p*-$MeOC_6H_4$ | Acetonitrile at -45 °C | 71 | 19 *(S)* |
| 4 | *p*-$MeOC_6H_4$ | DCM | 91 | 34 *(S)* |
| 5 | Ph | DCM | 98 | 27 *(S)* |
| 6 | *(E)*-PhCH=CH | DCM | 99 | 29 *(S)* |
| 7 | Ferrocenyl | DCM | 90 | 28 |

### 2.5.3 Concentration and reaction time studies

Optimization studies were continued by changing concentration and time for $SiCl_4$ addition *(Table 4, entries 1-8)*. Lowering $SiCl_4$ addition time from 2h to 1h reduced the yield but didn't affect the enantioselectivity. First of all in the time column first number corresponds to the time for $SiCl_4$ addition and the second one is the time of stirring after addition. Comparing the 1$^{st}$ and 3$^{rd}$ entry, decreasing the $SiCl_4$ addition time to 1 h from 2 h decreased the yield from 93 % to 66 % but didn't change enantioselectivity significantly. When the amount of $SiCl_4$ decreased from 1.5 to 1.1 equivalent (Table 4, entry and 2), yield and ee remained almost the same. Small changes in the reaction concentration (Table 4, entries 1, 4, and 5) had very small effect on the yield and ee. More dilution slowed down the reaction and reduced the yield (Table 4, entry 7) however; it can be compensated by extending the time (Table 4, entry 8). Increasing the amount of chiral catalyst from 10 to 20 mol % reduced the yield without affecting the enantioselectivity (Table 4, entry 6).

For the **POFAM** catalyzed reactions, although reducing the amount of $(EtO)_3P$ didn't affect the yield and selectivity significantly (Table 4, entry 11), low amount of $SiCl_4$ reduced the yield without affecting the selectivity (Table 4, entry 12-14). At low concentration product was formed in low yield but with higher ee (Table 4, entries 10, 13, and 14).

***Table 4*** *Concentration and reaction time studies for* ***POAP*** *and* ***POFAM*** *ligands*

| **Entry** | **$P(OEt)_3$** (equiv.) | **$^{i}Pr_2NEt$** (equiv.) | **$SiCl_4$** (equiv.) | **POAP-A** (mol %) | **DCM** (mL) | **Time** (h) | **Yield** (%) | **ee** (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.1 | 1.5 | 1.5 | 10 | 2 | 2+1 | 93 | 29 *(S)* |
| 2 | 1.1 | 1.5 | 1.1 | 10 | 2 | 2+1 | 91 | 27 *(S)* |
| 3 | 1.5 | 1.5 | 1.5 | 10 | 2 | 1+1 | 66 | 30 *(S)* |
| 4 | 1.5 | 1.5 | 1.5 | 10 | 1.5 | 2+1 | 93 | 32 *(S)* |
| 5 | 1.5 | 1.5 | 1.5 | 10 | 1.0 | 2+1 | 91 | 34 *(S)* |
| 6 | 1.5 | 1.5 | 1.5 | 20 | 1.0 | 2+1 | 80 | 33 *(S)* |
| 7 | 1.5 | 1.5 | 1.5 | 10 | 6 | 2+1 | 66 | 23 *(S)* |
| 8 | 1.5 | 1.5 | 1.5 | 10 | 6 | 3+12 | 99 | 22 *(S)* |
| | | | | **POFAM** (mol %) | | | | |
| 9 | 1.5 | 1.5 | 1.5 | 10 | 2 | 2+1 | 99 | 10 *(R)* |
| 10 | 1.5 | 1.5 | 1.5 | 10 | 10 | 2+1 | 84 | 18 *(R)* |
| 11 | 1.05 | 1.5 | 1.5 | 10 | 2 | 2+1 | 94 | 11 *(R)* |
| 12 | 1.05 | 1.5 | 1.05 | 10 | 10 | 2+1 | 65 | 12 *(R)* |
| 13 | 1.05 | 1.05 | 1.05 | 10 | 10 | 4+1 | 60 | 20 *(R)* |
| 14 | 1.05 | 5.0 | 1.05 | 10 | 10 | 2+1 | 50 | 18 *(R)* |

# CHAPTER 3

# CONCLUSION

In this work, a new chiral phosphineoxy aziridinyl phosphonates (**57, 58**) were synthesized with high yields. These compounds can be regarded as third generation of our previously synthesized aziridine based ligands. As these new compounds contain phosphineoxy and phosphonate groups they can serve as chiral Lewis bases for enantioselective Abramov-type reaction of aldehydes with triethyl phosphites. The results of newly synthesized **POAP** organocatalysts showed that the product is forming in high yields but in low ee (highest 34%). Although different reaction conditions were applied (solvent screening, concentration screening, time of $SiCl_4$ addition, amounts of reactants etc.), enantioselectivity could not be increased. We observed that the product formation is taking place both by involvement and without involvement (background reaction) of organocatalyst.

Besides **POAP** Lewis bases previously known aziridinyl phosphonates (**AP**) and phosphineoxy aziridinyl methanols (**POFAM**) were also tried as Lewis bases for the same reaction. In both series α-hydroxy phosphonates were obtained in acceptable to good yields but very low enantioselectivities.

# CHAPTER 4

# EXPERIMENTAL

## 4.1. General Procedure

All asymmetric reactions were performed under inert atmosphere in previously heated and vacuumed glasswares. Solvents, reagents and catalysts were dried, purified and stored as stated in standard procedures prior to use.

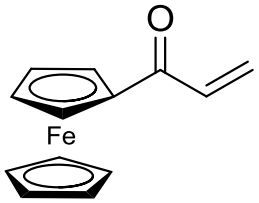
Product formation and reagent purity monitored by TLC analysis using silica coated plates (250μm Silica Gel 60 $F_{254}$ plates). TLC plates monitored by UV-light at 254 nm and ninhydrin and phosphomolibdic acid solutions assistance. Work-up studies of reaction mixtures accompanied with extraction method when the need arises before the flash column chromatography. E. Merck Silica Gel 60 (particle size: 0.040- 0.063 mm, 230-400 mesh ASTM) applied in column as a stationary phase. After analysis product solutions were vacuumed under reduced pressure by using rotary evaporator and stored in vials. Enantiomeric excess of addition products were determined by HPLC analysis using DAICEL Chiralpak AS-H Column eluting with hexane-$^{i}$PrOH solvent mixture with 1mL/min flow rate. UV detection was done by scanning at 254 nm. Detection of retention times were found previously by separating racemic mixtures and racemic compounds for those analyses were prepared in the absence of chiral ligands.

$^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra were reported on a Brucker spectrospin Avance DPX-400 Ultra shield instrument at 400 MHz, 100 MHz and 162

MHz respectively relative to TMS for $^{1}H$ and $^{13}C$ NMR and $H_3PO_4$ for $^{31}P$ NMR. NMR samples were prepared in 1:1 $CDCl_3$-$CCl_4$ solution.

Rudolph Research Analytical Autopol III Polarimeter was used to measure optical rotations. Measurements was done in 1 dm cell and reported as $[\alpha]^{25}_{D}$ (c in 10mg/ 1 mL solvent).

## 4.2. Synthesis and Characterization of Acryloyl Ferrocene

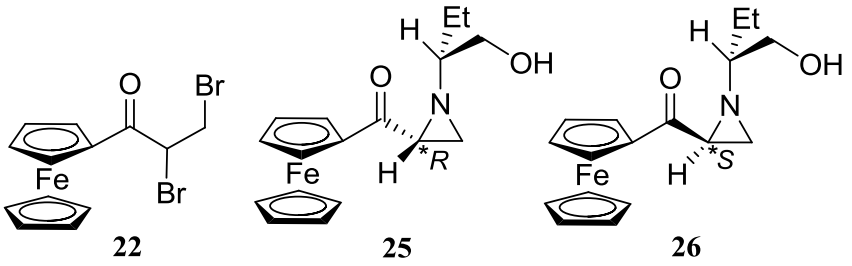



**21**

Ferrocene (4.0 g, 21.5 mmol) in 250 mL double-necked balloon was dissolved in 72.0 mL $CH_2Cl_2$ under inert atmosphere and cooled to 0 $^{o}$C. Acryloyl chloride (2.1 mL, 25.8 mmol) was added slowly to the stirred solution of ferrocene. In different 50 mL double-necked balloon, $AlCl_3$ (2.9 g, 21.50 mmol) was dissolved in 20.0 mL $CH_2Cl_2$ under inert atmosphere and cooled to 0 $^{o}$C. $Me_3Al$ was added to the solution of $AlCl_3$ followed by 10 minutes mixing. Then, dropwise addition of obtained Lewis acid mixture to the solution of ferrocene and acryloyl chloride was performed during 45-60 minutes in regular time intervals. Reaction progress was checked by TLC and after ensuring the completeness of reaction, reaction was completed by hydrolysis with saturated $NH_4Cl$ solution. Organic phase was extracted by distilled EtOAc (3x15mL). Separated organic phase was dried over $NH_4Cl$ and concentrated to give crude dark orange solid powder product **21** with 99 % yield. $R_f$ = 0.61, 3:1 Hexane- EtOAc; $^{1}H$-NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, J= 17.0 & 10.2 Hz, 1H), 6.44 (d, J= 16.8 Hz, 1H), 5.71 (d,*j*= 10 Hz,1H), 4.81 (s, 2H, Fc), 4.54 (s, 2H, Fc), 4.17 (s, 5H, Fc); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 72.67 ($C_q$, Fc), 72.39(CH,

Fc), 70.03 (CH,5C, Fc), 69.89 (CH, Fc), 69.73 (CH, Fc), 69.23 (CH, Fc), 126.02 ($CH_2CH$), 132.65 (CH).

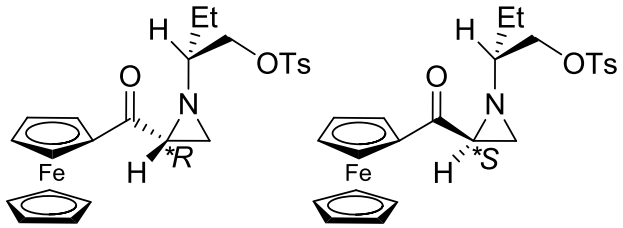
## 4.2.1. Synthesis of Aziridino Ketones 25 and 26




Dissolved acryloyl ferrocene in 83.5 mL $CH_2Cl_2$ in 150 mL double-necked balloon was cooled to -78 °C. $Br_2$ (0.42 mL, 8.35 mmol) dissolved in 14.0 mL $CH_2Cl_2$ and cooled to -78 °C was poured into acryloyl ferrocene solution rapidly. Reaction progress was checked by TLC and reaction was completed in 5 minutes. Then crude mixture was directly filtered through a short column of silica gelby $CHCl_3$ as eluent. After evaporation of solvent, crude product of 2-dibromopronionylferrocene **22** (3.4 g) was obtained with 95% yield. To a stirred solution of 2-dibromopronionylferrocene (3.4 g, 8.50 mmol) in 85.0 mL $CH_2Cl_2$, $Et_3N$ (2.0 mL, 14.45 mmol) was added at RT. After 1 h of stirring, complete conversion of 2-dibromopronionylferrocene to α-bromoacryloylferrocene, *R*-(-)-2-amino-1-butanol (1.6 mL, 17.0 mmol) was added and reaction was stirred overnight at RT. Reaction mixture was concentrated by rotary evaporation. The aziridino ketone **25** (52 % yield, light orange solid) and **26 (**41 % yield, orange solid) were separated by performing flash column chromatography on silica gel (EtOAc + 2% $Et_3N$). **25:** $R_f$ = 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 4.92 (s, 1H, Fc), 4.84 (s, 1H, Fc), 4.51 (s, 2H, Fc), 4.21 (s, 5H, Fc), 3.75 (br, 2H), 2.68 (br, 1H), 2.32 (s, 1H), 2.23 (br, 1H, OH) 1.66 (m, 4H), 0.98 (t, *J* = 7.2 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. **26:** $R_f$ = 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), 1.79 (br, 1H), 1.67 (m, 1H), 1.57 (m, 1H), 1.45 (br, 1H), 0.93 (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 Aziridino Ketones 27 and 28




**27** **28**

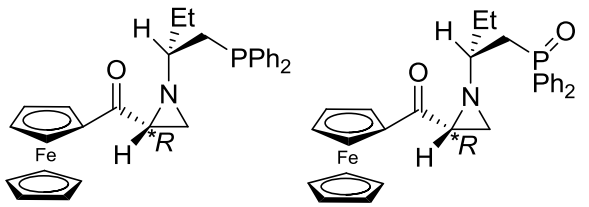
### 4.2.2.1. Synthesis and Characterization of Tosylated Aziridino Ketones 27 from Aziridine 25

Aziridine **25** (2.0 g) was dissolved in $CH_2Cl_2$ (12.2 mL) at room temperature and $Et_3N$ (1.3 mL, 9.17 mmol) was added to the solution. After addition of p-toluenesulfonylchloride (1.8 g, 9.17 mmol) to stirred solution of Aziridine **25** and $Et_3N$, reaction mixture was stirred overnight up to observation of no starting material in TLC. Then, reaction was hydrolyzed with $H_2O$, and extracted by $CH_2Cl_2$ (3x10 mL). Then organic phase was treated with $Na_2SO_4$ to remove aqueous phase residuals of extraction and concentrated by rotary evaporation. Purification of crude mixture was done with flash column on silica gel (1:2 Hexane-EtOAc). Pure orange solid product **27** (2.86 g) was obtained by 97 % yield. $R_f$ = 0.47, 1:2 Hexane-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 & 10.1 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), 2.30 (s, 1H), 1.86 (m, 1H), 1.70 (d, *J* = 6.4, 1H), 1.61 (m, 2H), 0.98 (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.

### 4.2.2.2. Synthesis and Characterization of Tosylated Aziridino Ketones 28 from Aziridine 26

$Et_3N$ (1.1 mL, 7.70 mmol) was added to the dissolved aziridino ketone **26** (1.7 g) in $CH_2Cl_2$ (0.5 M). Then, p-toluenesulfonylchloride (1.5 g, 7.70 mmol) was added to the stirred solution. Reaction was proceeded overnight up to total conversion of starting material to product **28** checked by TLC. Reaction was completed with $H_2O$, following by the extraction by $CH_2Cl_2$ (10 mL) three times. Organic phase was dried by using $Na_2SO_4$ and solvent removed by rotary evaporation. Then, flash column chromatography purification was performed on silica gel by 1:2 Hexane-EtOAc as eluent to obtain pure orange oily product **28** (2.35 g) by 95 % yield. $R_f$ = 0.67, 1:2 Hexane-EtOAc; $[\alpha]_D^{21.7}$ = +95.7 (*c* 0.98, DCM); $^1$H-NMR (400 MHz, $CDCl_3$), 7.80 (d, *J* = 8.15 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), 1.59 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) _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).

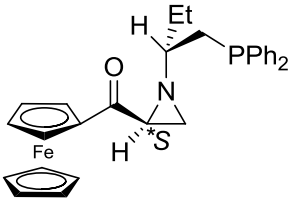
### 4.2.2.3. Synthesis and Characterization of Phosphino Aziridines 29 & 30 and Phosphineoxy aziridines 31 & 32



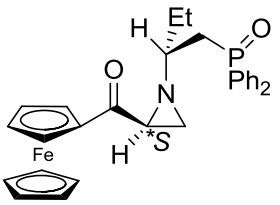

**29**




**30**




**31**




**32**

### 4.2.2.4. Synthesis and Characterization of Phosphino Aziridine 29 and Phosphineoxy aziridine 30

Solution of tosylated aziridino ketone **27** (1.0 g, 2.07 mmol) in THF (6.7 mL, dried over Na-benzophenone) was cooled to -78 $^{o}$C. Potassium diphenylphosphide (4.7 mL in 0.5 M THF) was added dropwise through 60 minutes and reaction was stirred during 1h. After 1h, TLC showed the complete conversion of starting material to products **29** and **30**. Crude mixture was purified by flash column chromatography on silica (5:1 Hexane-EtOAc) under inert atmosphere. After concentration by rotary evaporation, pure air sensitive orange oil phosphino aziridine **29** (0.8 g) and its oxidized form, red oily phosphineoxy aziridine **30** (0.2 g) were obtained by 77 % and 19 % yields, separately. It is possible to obtain oxidized product **30** by exposing the product **29** to air. **29**: $R_f$ = 0.70, 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). **30**: $R_f$ = 0.14, 1:1 hexanes: EtOAc after treatment of $Et_3N$ for TLC ; $^1H$-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), 2.95 (dd, $J$ = 2.8 and 3.1 Hz, 1H), 2.51 (m, 2H), 2.31 (s, 1H), 2.04 (m, 1H), 1.81 (d, $J$ = 6.1, 1H), 1.61 (m, 1H), 1.53 (m, 1H), 0.82 (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.

### 4.2.2.5. Synthesis and Characterization of Phosphino Aziridine 31 and Phosphineoxy aziridine 32

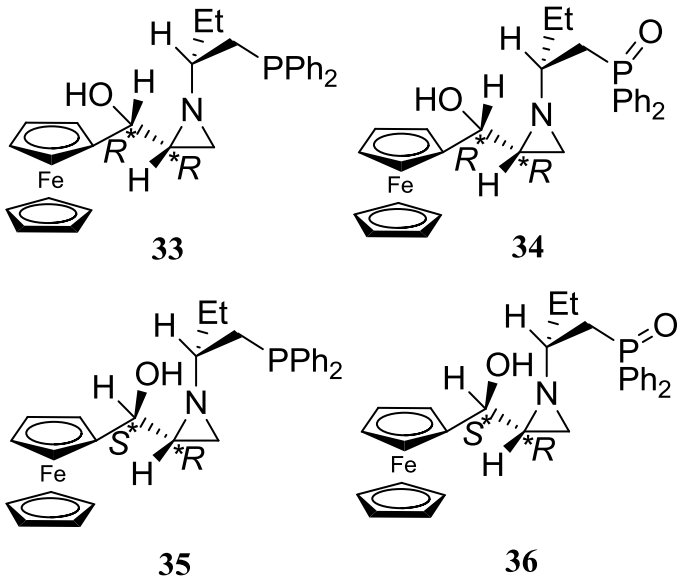
Dissolved tosylated aziridino ketone **28** ( 1.5 g, 3.12 mmol) in THF (8.8 mL, dried over Na-benzophenone) was cooled to -78 $^oC$, followed by the dropwise addition of potassium diphenylphosphide (7.0 mL in 0.5 M THF) in 75 minutes. Reaction was stirred during 1h as a result of which TLC showed the complete conversion of starting material to products **31** and **32**. Crude mixture was purified by flash column chromatography on silica (5:1 Hexane-EtOAc) under inert atmosphere. After concentration by

rotary evaporation, pure air sensitive orange solid phosphino aziridine **31** (1.2 g, 76% yield) and its oxidized form, red solid phosphineoxy aziridine **32** (0.3 g, 20% yield) were obtained. It is possible to obtain oxidized product **32** quantitatively by exposing the product **31** to air. **31**: $R_f$ =0.72, 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. **32**: $R_f$ = 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.

## 4.2.3. Synthesis and Characterization of Chiral PFAM Ligands

### 4.2.3.1. Synthesis and Characterization of Chiral PFAM Ligands from Phosphino Aziridine 29




#### 4.2.3.1.1. Synthesis and Characterization of Chiral PFAM Ligands (*R,R,R*) 33 and 34

Solution of compound **29** (0.5 g, 1.00 mmol) in dry MeOH (0.1 M) was cooled to -78 $^{o}$C, followed by the addition of $ZnCl_2$ (0.2 g, 1.5 mmol) to the stirred solution. After 1 h stirring, $NaBH_4$ (0.11 g, 3.00 mmol) was added, followed by additional 4 h stirring at -78 $^{o}$C. When the TLC

showed the completeness of reaction, reaction mixture was hydrolyzed by $H_2O$ (10 mL) and extraction done with $CH_2Cl_2$ (3 x 10 mL). The organic phase was dried over $Na_2SO_4$ and concentrated. Isolation of product **33** was performed by applying flash column chromatography method on silica (5:1 Hexane-EtOAc) under inert atmosphere. Pure air sensitive pale yellow oil product **33** and its oxidized form, yellow oily product **34** were obtained by 62 % and 34 % yields, separately. **33:** $R_f$ = 0.51, 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). **34:** $R_f$ = 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),

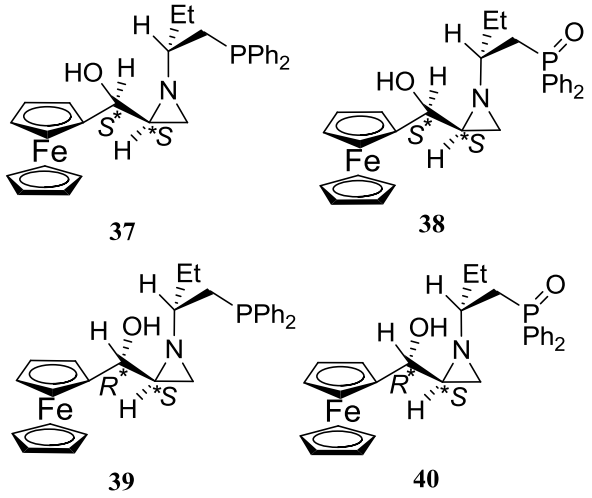
63.21 (CH, Fc), 44.35 (CH, aziridine), 34.97-32.67 ($CH_2$, $CH_2$-P), 21.68 ($CH_2$, aziridine), 16.17 ($CH_2$), 9.96 ($CH_3$); $^{31}$P NMR (161.97 MHz, $CDCl_3$) δ 28.27.

#### 4.2.3.1.2. Synthesis and Characterization of Chiral PFAM Ligands (*S,R,R*) 35 and 36

Dissolved compound of **29** (0.5 g, 1.0 mmol) in THF (7.6 mL, dried over Na-benzophenone) was cooled to -78 $^{o}$C, followed by the dropwise addition of L-Selectride (1.5 mL in 1M THF solution) over 60 minutes. Reaction mixture was stirred during 8 h as a result of which TLC showed the total conversion of starting material to product. After hydrolysis of reaction with 10 % NaOH (10 mL) extraction was performed 3 times with EtOAc (15 mL). Organic phase of extraction was dried over $Na_2SO_4$ and solvent was removed by rotary evaporation. Isolation of product was performed with flash column packed with silica (3:1 hexanes-EtOAc) under inert atmosphere. After solvent removal, pure compound **35** (0.21 g, 42 % yield) as pale yellow oil and its oxidized form compound **36** (0.27 g, 52 % yield) as yellow oily product were obtained. When pure compound **35** was exposed to air, it was oxidized quantitatively to **36**. **35:** $R_f$ = 0.6451:1 Hexane: 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* = 6.4 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). **36:** $R_f$ = 0.18, 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), 3.90 (d, *J* = 6.0 Hz, 1H), 2.55 (m, 1H), 2.37 (m, 1H), 1.70 (br, 1H), 1.55 (m, 2H), 1.29 (d, *J* = 7.1 Hz, 2H), 1.20 (s, 1H), 0.81 (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.

### 4.2.3.2. Synthesis and Characterization of Chiral PFAM Ligands from Phosphino Aziridine 31




#### 4.2.3.2.1. Synthesis and Characterization of Chiral PFAM and POFAM ligands (*S,S,R*) 37 and 38

Solution of compound **31** (0.7 g, 1.41 mmol) in THF (14.6 mL, dried over Na-benzophenone) was cooled to -78 °C, followed by the addition of $ZnCl_2$ (0.3 g, 2.11 mmol) to the solution. After 1 h $LiAlH_4$ (0.1 g, 2.88 mmol) was added followed by additional 4 hour stirring as a result of which TLC showed that no starting material was left. Reaction mixture was hydrolyzed with $H_2O$ (10 mL) and extraction was performed 3 times

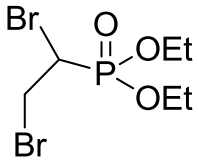
by using EtOAc (10 mL). Collected organic layers were dried over $Na_2SO_4$ and solvent was removed by rotary evaporation. Compound **37** was isolated by flash column chromatography method on silica (3:1 hexanes-EtOAc) under inert atmosphere. After concentration, pure pale yellow oily product **37** and its oxidized form, yellow oil product **38** were obtained by 50 % and 41 % yields. When pure compound **37** was exposed to air, it was oxidized to **38**. **37:** $R_f$ = 0.40, 1:1 Hexane: 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* = 7.3 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). **38:** $R_f$ = 0.15, 1:1 Hexane: 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.

#### 4.2.3.2.2. Synthesis and Characterization of Chiral PFAM Ligands (*R,S,R*) 39 and 40

Dissolved compound of **31** (0.5 g, 1.0 mmol) in THF (7.1 mL, dried over Na-benzophenone) was cooled to -78 $^{o}$C, followed by the dropwise addition of L-Selectride (1.5 mL in 1M THF solution) over 60 minutes. Reaction mixture was stirred during 8 h as a result of which TLC showed the total conversion of starting material to product. Reaction was hydrolyzed with 10% NaOH (10 mL) and extracted by EtOAc (15 mL) three times. The seperated organic phase was dried over $Na_2SO_4$ and concentrated. Crude products were seperated by flash column chromatography method on silica (3:1 hexanes-EtOAc) under inert atmosphere. After concentration, pure **39** (0.26 g, 51 % yield) was obtained as pale yellow oil and its oxidized form **40** (0.23 g, 45 % yield), yellow oily product. When pure compound **39** was exposed to air, it was oxidized quantitatively to **40**. **39**: $R_f$ = 0.44, 1:1 Hexane: 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* = 7.3 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). **40**: $R_f$ = 0.20, 1:1 Hexane: 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* = 7.3 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

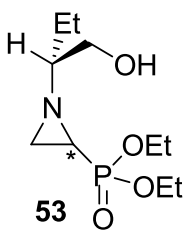
## 4.3. Synthesis of diethyl 1,2 dibromoethyl phosphonate



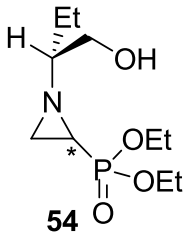

**50**

Diethylvinylphosphonate (2.0 mL, 12.43 mmol) was dissolved in DCM (0.1 M, 125.0 mL) and cooled to 0°C. Then $Br_2$ solution (16.16 mmol in 24 mL DCM) was introduced into the reaction flask. After 4h, consumption of all starting material was observed by performing TLC control of reaction mixture. Then the mixture was concentrated and flash column chromatography was performed by using short plug of silica (EtOAc) to afford diethyl 1,2-dibromoethylphosphonate as a light yellow oily liquid (4.0 gr, 99% yield). $R_f$=0.74 ( EtOAc); $^1$H NMR δ 4.18 (m, 4H), 3.96 (m, 2H), 3.55 (m, 1H), 1.34 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR δ 64.10 (d, $J$ = 7.1 Hz, $CH_2CH_3$), 63.75 (d, $J$ = 6.8 Hz, $CH_2CH_3$), 41.92 (d, $J_{P-C}$ = 151.1 Hz), 31.74 ($CH_2Br$), 16.39 ($CH_3CH_2$), 16.31 ($CH_3CH_2$); $^{31}$P NMR δ 15.29.

## 4.3.1. Aziridination of dibromoethylphosphonate



**53**



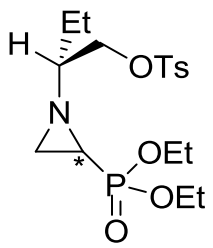
**54**

Diethyl 1,2-dibromoethylphosphonate (4.00 gr, 12.43 mmol) was dissolved in acetonitrile (25 mL, 0.5M). Then $Et_3N$ (2.1 mL, 15 mmol) was syringed into this solution at room temperature and reaction mixture became bulky due to formation of white solids. After addition of *R*-(-)-2-amino-1-butanol (3 mL, 37.3 mmol) white solids were disappeared. Then, the reaction was proceeded throughout 3 h at 80-85 °C. After 3 h, TLC control of reaction was performed and solvent was removed by rotary evaporation.

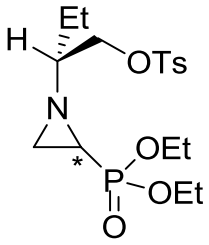
Flash column chromatography was carried out with silica and EtOAc and compound **53** was isolated with 46 % yield as slightly yellow oil. $R_f$=0.30; $[\alpha]_{21}$= -62 (*c*, 0.10, $CH_2Cl_2$); $^1$H NMR δ 4.11 (m, 4H), 3.60 (m, 2H), 3.29 (s, 1H), 2.02 (dd, *J* = 8.8, 3.5 Hz, 1H), 1.69 (ddd, *J* = 20.5 & 6.7 & 3.5 Hz, 1H), 1.54 (t, *J* = 7.2 Hz, 1H), 1.45 (m, 2H), 1.34 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR δ 72.49 (d, *J* = 6.9 Hz, $CHCH_2OH$), 65.49 ($CH_2OH$), 62.98 (d, *J* = 5.9 Hz, $CH_2CH_3$), 61.98 (d, *J* = 6.5 Hz, $CH_2CH_3$), 31.08 (d, $J_{P\text{-}C}$ = 217.2 Hz), 30.01 (d, *J* = 6.0 Hz, $CH_2N$), 24.72 ($CH_2CHN$), 16.40 (d, *J* = 2.9 Hz, $CH_3CH_2O$), 16.29 (d, *J* = 2.1 Hz, $CH_3CH_2O$), 10.51 ($CH_3CH_2CH$); $^{31}$P NMR δ 23.83; IR (neat, $cm^{-1}$) 3396, 2981, 2924, 2881, 1232, 1018, 964, 797. HRMS-EI (m/z): calcd. for $C_{10}H_{23}NO_4P$ ($M^+H^+$): 252.1363; found: 252.1359.

The other diastereomer compound **54** was obtained with 42 % yield as slightly yellow oil. R*f* =0.21 $[\alpha]_{21}$= +37 (*c*, 0.10, $CH_2Cl_2$); $^1$H NMR δ 4.08 (m, 4H), 3.62 (m, 2H), 2.41 (s, 1H), 2.11 (dd, *J* = 9.2 & 3.7 Hz, 1H), 1.71 (t, *J* = 7.2 Hz, 1H), 1.60 (m, 1H), 1.49 (m, 2H), 1.34 (m, 1H), 1.32–1.29 (m, 3H), 1.26 (m, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR δ 72.84 (d, *J* = 6.6 Hz, $CHCH_2OH$), 63.84 ($CH_2OH$), 62.53 (d, *J* = 6.5 Hz, $CH_2O$), 61.90 (d, *J* = 6.4 Hz, $CH_2O$), 31.35 ($CH_2N$), 29.75 (d, $J_{P\text{-}C}$ = 220.1 Hz), 24.15 ($CH_2CHN$), 16.44 (d, $J_{P\text{-}C}$ = 6.0 Hz, $CH_3CH_2$), 16.40 (d, $J_{P\text{-}C}$ = 6.2 Hz, $CH_3CH_2$), 10.25 ($CH_3CH_2CH$); $^{31}$P NMR δ 22.87; IR (neat, $cm^{-1}$) 3392, 2985, 2924, 2885, 1231, 1018, 966, 781; HRMS-EI (m/z): calcd. for $C_{10}H_{23}NO_4P$ ($M^+H^+$): 252.1363; found: 252.1354.

## 4.3.2. Tosylation of Diethyl (1-(1-hydroxybutan-2-yl) aziridin-2-yl)




**55**




**56**

### 4.3.2.1. Tosylated aziridinyl phosphonate 55

Compound **53** (2 mmol, 502 mg) was dissolved in 3 mL DCM (0.6 M). $Et_3N$ (3 mmol, 0.42 mL) was syringed into this stirring solution. Then *p*-toluenesulfonylchloride (4 mmol 762 mg) was put into this solution at room temperature. After 1 day, TLC control of the reaction was done and almost consumption of starting material was observed. Extraction was carried out with distilled water (10 mL) and DCM (10 mL x 2). The extract was dried over $Na_2SO_4$ and filtered. After removal of solvent from crude mixture under reduced pressure crude tosylated compound was

obtained as pale yellow viscous liquid. Further purification was achieved by performing flash column chromatography with silica and EtOAc.

2-(2-(diethoxyphosphoryl) aziridin-1-yl) butyl 4-methylbenzenesulfonate **55** was isolated with 90% yield (730mg, 1.802 mmol) as a light yellow oil. ; R*f* =0.41, EtOAc, $[\alpha]_{25}$= -12.5 (*c*, 0.5, $CH_2Cl_2$); $^1$H NMR δ 7.80 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 4.10 (m, 4H), 4.07 (m, 2H), 2.46 (s, 3H), 2.15 (dd, *J* = 5.4 & 1.8 Hz, 1H), 2.03 (d, *J* = 4.4 Hz, 1H), 1.67 (ddd, *J* = 18.4 & 6.8 & 4 Hz, 1H),1.61(t, *J* = 2.4 Hz, 1H) 1.58 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.92 (t,*J* = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.4 ($C_q$, ArC-S), 133.2 ($C_q$, ArC-$CH_3$), 129.7 (CH, 2C, Ph), 127.9 (CH, 2C, Ph), 71.2 ($CH_2$-OTs), 69.8 (CH), 62.4 ($OCH_2CH_3$), 31.91 ($CH_2CH_3$), 30.67 (CH, aziridine), 24.94 ($CH_2$ aziridine), 21.63 ($CH_3$, Ts),16.44 ($OCH_2CH_3$), 9.89 ($CH_3$); $^{31}$P NMR δ 22.31; IR (neat, $cm^{-1}$) 2978, 1358, 1247, 1175, 1022, 962, 812, 787,664

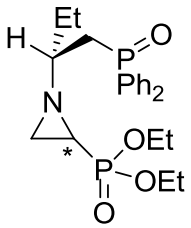
### 4.3.2.2. Tosylated aziridinyl phosphonate 56

Compound **54** (1.2 mmol, 302 mg) was dissolved in 1.8 mL DCM (0.6 M) at room temperature and $Et_3N$ (1.8 mmol, 0.26 mL) addition was done. Then, *p*-toluenesulfonylchloride (2.4 mmol 459 mg) was transferred into the reaction medium at room temperature. After 1 day, TLC controls of reaction was not monitored anymore formation product. Extraction was performed two times with DCM (10 mL) and distilled water (10 mL) as aqueous phase. $Na_2SO_4$ was used as drying agent. After filtration and solvent removal, the crude mixture was obtained as a pale yellow viscous liquid and further purification was obtained by performing flash column chromatography with silica and EtOAc.

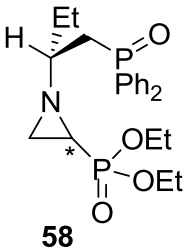
2-(2-(diethoxyphosphoryl) aziridin-1-yl) butyl 4-methylbenzenesulfonate **56** was isolated with 85 % yield (414 mg, 1.023 mmol ) as a light yellow oil. ; R*f* =0.57, EtOAc, $[\alpha]_{25}$= +44 (*c*, 2.4, $CH_2Cl_2$); $^1$H NMR δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.35 (d,*J* = 8 Hz, 2H), 4.08 (m, 4H), 4.05 (m, 2H), 2.46 (s, 3H), 2.06 (dd, *J* = 8.9 & 4.0 Hz, 1H), 1.75 (t, *J* = 7.2 Hz, 1H), 1.62 ( d, *J* = 2.4 Hz, 1H),1.58 (m, 2H), 1.49 (ddd, *J* = 18.0 & 6.7 & 4.1 Hz,

1H), 1.31 (t, $J$ = 7.1 Hz, 3H), 1.30 (t, $J$ = 7.1 Hz, 3H), 0.92 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.7 ($C_q$, ArC-S), 133.2 ($C_q$, ArC-$CH_3$), 129.8 (CH, 2C, Ph), 127.8 (CH, 2C, Ph), 71.8 ($CH_2$-OTs), 69.7 (CH), 62.4 ($OCH_2CH_3$), 31.15 (CH, aziridine), 28.74 ($CH_2CH_3$), 24.69 ($CH_2$ aziridine), 21.60 ($CH_3$, Ts),16.36 ($OCH_2CH_3$), 9.67 ($CH_3$); $^{31}$P NMR δ 22.70; IR (neat, $cm^{-1}$) 2980, 1357, 1245, 1175, 1022, 959, 812, 787, 665

## 4.3.3. Phosphinylation of tosylated aziridines




57




58

### 4.3.3.1. Synthesis of phosphineoxy aziridiniyl phosphonate 57

Tosylated compound **55** (3.7mmol, 1.498mg) was dissolved in 9 ml dry THF (0.20 M). Then, potassium diphenylphosphide (8.88 mL, from 0.5 M THF solution) was introduced into the reaction solution slowly over 45 min at -78 °C. After 4 hours, TLC controls monitored consumption of starting material. Then addition of saturated $NH_4Cl$ solution (25 mL) and extraction with DCM (25ml × 2) were performed. After the solvent removal under reduced pressure, crude product was obtained. Crude product treated with $H_2O_2$ (30% aq, 1.74 ml, 18.5 mmol, 5.0 equiv.) in acetone (120 mL). After 1h of stirring, the reaction was quenched with saturated solution of $Na_2S_2O_3$ (4mL). The crude product was then extracted with DCM (25mL×2) and combined organic phases were collected and concentrated under reduced pressure. For further

purification flash column chromatography was done with silica gel, 2:1 hexane-acetone + 2% $Et_3N$ eluent mixture.

Diethyl 1-(1-diphenylphosphoryl) butan-2-yl) aziridin-2-ylphosphonate **57** was isolated with 90 % yield (1.446 mg, 3.33 mmol) as a light yellow oil; $R_f$=0.26 2:1 hexane-acetone + 2% $Et_3N$, $[\alpha]_{25}$= -8.2 (*c*, 0.3, $CH_2Cl_2$); $^1$H NMR δ 7.77 (m, 4H), 7.49 (m, 6H), 4.13 (m, 4H), 2.70 (m, 1H), 2.57 (m, 1H), 2.14 (dd, $J$ = 9.6 & 3.6 Hz, 1H),1.67 (m, 1H),1.38 (m, 1H), 1.33 (m, 1H), 1.31 (t, $J$ = 7.2 Hz, 3H), 1.30 (t, $J$ = 7.0 Hz, 3H), 0.90 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 134.04 ($C_q$, ArC-P), 133.75 ($C_q$, ArC-P), 131.65 (CH, 2C, Ph), 130.89 (CH, Ph), 130.80 (CH, Ph), 130.70 (CH, Ph), 130.61 (CH, Ph), 128.69 (CH, Ph), 128.63 (CH, Ph), 128.57 (CH, Ph),128.51(CH, Ph),65.6 (CH), 62.47 ($OCH_2CH_3$), 61.99 ($OCH_2CH_3$), 35.07 (CH, aziridine), 34.34-33.60 ($CH_2$, $CH_2$-P), 31.03 ($CH_2$, aziridine), 28.92 ($CH_2CH_3$), (16.45 ($OCH_2CH_3$), 9.70 ($CH_3$); $^{31}$P NMR δ 23.19 ($P(O)(OEt)_2$), 28.54 ($P(O)Ph_2$); IR (neat, $cm^{-1}$) 2987, 2921, 2875, 1452, 1260, 1171, 1020, 739, 713. HRMS-EI (m/z): calcd. for $C_{22}H_{32}NO_4P_2$ ($M^+H^+$): 436.1807; found: 436.1811.

### 4.3.3.2. Synthesis of phosphineoxy aziridiniyl phosphonate 58

Tosylated product **58** (3.0 mmol, 1.214 mg) was dissolved in 8 mL THF (0.20 M).Then potassium diphenylphosphide (7.2 mL from 0.5 M THF solution) was syringed into the reaction solution slowly over 45 min at -78 $^o$C. After 4 hours, TLC controls monitored consumption of starting material. Then addition of saturated $NH_4Cl$ solution (20 mL) and extraction with DCM (20ml × 2) were performed. After the solvent removal under reduced pressure, crude product was obtained. Crude product treated with $H_2O_2$ (30% aq, 1.41 mL, 15.0 mmol, 5.0 equiv.) in acetone (100 mL). After 1h of stirring, the reaction was quenched with saturated solution of $Na_2S_2O_3$ (3.2 mL). The crude product was then extracted with DCM (20mL×2) and combined organic phases were

collected and concentrated under reduced pressure. For further purification flash column chromatography was done with silica gel and 2:1 hexane-acetone + 2% $Et_3N$ eluent mixture.

Diethyl 1-(1-diphenylphosphoryl) butan-2-yl) aziridin-2-ylphosphonate **58** was isolated with 85 % yield (1.106 g, 2.55 mmol) as a white solid; $R_f$=0.20 TLC, 2:1 hexane-acetone + 2% $Et_3N$, $[\alpha]_{25}$= +6.0 (*c*, 1.0, $CH_2Cl_2$); $^1$H NMR δ 7.82 (ddd, $J$ = 11.5 & 8.0 & 1.6, 2H), 7.70 (ddd, $J$ = 11.5 & 8.0 & 1.6 2H),7.47 (m, 6H), 4.06 (m, 4H), 2.57 (m, 2H),1.89 (p, $J$ =5.2 Hz,1H) ,1.65 (m, 2H), 1.61 (m, 2H), 1.53 (ddd, $J$ = 19.1 &6.7 & 3.8 Hz, 1H), 1.29 (t, $J$ = 7.2 Hz, 3H), 1.27 (t, $J$ = 7.2 Hz, 3H), 0.94 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 131.66 ($C_q$, ArC-P,2C),130.78 (CH, 2C, Ph), 130.38 (CH, Ph,2C), 128.66(CH, Ph,3C), 128.55 (CH, Ph, 3C), 62.16 (CH), 62.10 ($OCH_2CH_3$), 32.0 (CH, aziridine), 31.86 ($CH_2$, $CH_2$-P), 28.37 ($CH_2$, aziridine), 25.20 ($CH_2CH_3$), (16.41 ($OCH_2CH_3$), 9.13 ($CH_3$); $^{31}$P NMR δ 22.90 ($P(O)(OEt)_2$), 28.34 ($P(O)Ph_2$); IR (neat, $cm^{-1}$) 2978, 2911, 2863, 1454, 1270, 1161, 1023, 749, 723. HRMS-EI (m/z): calcd. for $C_{22}H_{32}NO_4P_2$ ($M^+H^+$): 436.1807; found: 436.1810.

## 4.4. Asymmetric Trials

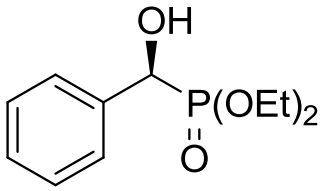
### 4.4.1. General procedure for asymmetric triethyl phosphite addition to aldehydes

A solution of aldehyde (0.5 mmol), $^i$$Pr_2NEt$ (130µL, 0.75 mmol), and chiral Lewis base (10 mmol %) in 1mL DCM was prepared at -78 °C and on this solution $P(OEt)_3$ (130µL, 0.75 mmol) was added under inert atmosphere. Then, another solution of $SiCl_4$ (86 µL, 0.75 mmol) in 2 mL DCM was prepared and introduced slowly to previously prepared aldehyde solution over 2 h. After addition of all $SiCl_4$ Lewis acid, TLC control (2/1: hexane/acetone) was performed and formation of

corresponding α-hydroxy phosphonate and almost completion of reaction was observed.

Then, hydrolysis of reaction mixture was done by adding distilled water (2mL), saturated $NaHCO_3$ (5 mL) and EtOAc (5 mL). After 1 h stirring, the reaction mixture filtered through a celite pad. Extraction was performed 3 times with EtOAc (5 mL). Organic phase washed with brine and the resulting mixture dried over $MgSO_4$.After filtration, solvent of reaction mixture was removed under reduced pressure. Then, flash column chromatography was performed on silica gel and elution was done with 2/1 hexane -acetone solution. Finally, product was obtained and HPLC analysis of product was carried out by using Chiralcel AS-H column at room temperature.

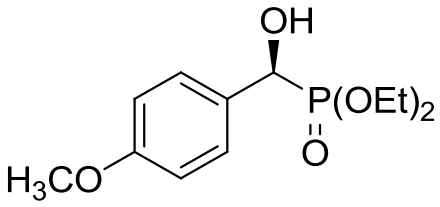
### 4.4.1.1. (*S*)-diethyl hydroxyl(phenyl)methylphosphonate




**59**

TLC: $R_f$ = 0.40 (Hexane/Acetone = 1/1, stained blue with phosphomolybdic acid / EtOH); $[\alpha]_D^{25}$ = -10.1 (c 1.0, $CHCl_3$) for 28 % ee (S). [lit. 54$[\alpha]_D^{20}$ + 19.1 (c 1.0, $CHCl_3$) for 53 % ee (*R*)]; $^1$H NMR ($CDCl_3$/ $CCl_4$): δ 1.22 (t,3H, $J$=7.0 Hz), 1.28 (t, 3H, $J$=7.0 Hz), 4.14 (br, s, 1H), 4.04 (m, 4H), 4.98 (dd, 1H, $J$=10.5 & 5.1 Hz, 7.32 (m, 3H), 7.46 (m,2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.41 ($CH_3$), 62.97 ($OCH_2CH_3$), 71.49 (CHOH), 127.05 (Ph,2C), 128.0 (Cq, Ph), 128.2 (Ph,2C); $^{31}$P NMR ($CDCl_3$/ $CCl_4$): δ 21.55; IR (neat, $cm^{-1}$) 3250, 2991, 2097, 1448, 1224, 1045, 1019, 959, 700; HPLC (Daicel Chiralpak AS-H, flow rate: 1.0 mL/ min, hexane/ $^i$PrOH=4/1, UV detection at 254 nm):$t_R$=17.0 min (*R*, minor), 22.0 min (*S*, major).

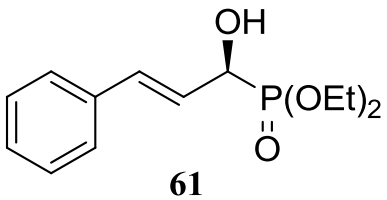
### 4.4.1.2.(*S*)-diethylhydroxy(4-methoxyphenyl)methylphosphonate



**60**

TLC: $R_f$ =0.31 (Hexane/Acetone = 1/1, stained blue with phosphomolybdic acid / EtOH); $[\alpha]_D^{25}$ = -12.0 (c 1.0, $CHCl_3$) for 28 % ee (S). [lit.54 $[\alpha]_D^{20}$ + 29.8 (c 1.49, $CHCl_3$) for 74 % ee (*R*)]; $^1$H NMR ($CDCl_3$/$CCl_4$): δ 1.22 (t,3H, *J*=7.2 Hz), 1.29 (t, 3H, *J*=7.2 Hz), 3.80 (s, 3H), 4.01 (m, 4H), 4.15 (m, 1H), 4.91 (dd, 1H, *J*=9.8 & 5.4 Hz), 6.86 (d, *J* = 8.8 Hz, 2H), 7.39 (dd, 8.6 & 2.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.41 ($CH_3$), 53.04 (CHOH), 55.0 ($OCH_3$), 62.68 ($OCH_2CH_3$), 113.64 Ph,2C), 128.0 (Cq, Ph), 128.82 (Ph,2C), 159.33 (Cq, Ph); $^{31}$P NMR ($CDCl_3$/ $CCl_4$): δ 21.83; IR (neat, $cm^{-1}$) 3244, 2963, 1510, 1223, 1196, 1169, 1057, 961, 795; HPLC (Daicel Chiralpak AS-H, flow rate: 1.0 mL/ min, hexane/ $^i$PrOH=4/1, UV detection at 254 nm):$t_R$=21.0 min (*R*, minor), 34.0 min (*S*, major)

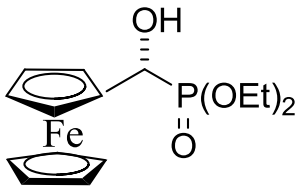
### 4.4.1.3. *E*-(*S*)-diethyl 1-hydroxy-3-phenylallylphosphonate



**61**

TLC: R*f* =0.34 (Hexane/Acetone=1/1, stained blue with phosphomolybdicacid/ EtOH); $[a]_D^{25}$= - 6.0. (c 1.0, $CHCl_3$) for 28 % ee (*S*). [lit. 54 $[a]_D^{20}$ + 4.7 (c 0.59, $CHCl_3$) for 41 % ee (*R*)]; mp: 99.0–99.5 °C; $^1$H NMR ($CDCl_3$): δ 1.34 (t, *J*= 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H),3.15 (m, 1H), 4.19 (m, 4H), 4.63 (m, 1H), 6.29 (dt, *J*= 15.6 & 5.6 Hz, 1H ), 6.76 (ddd, *J*=16.0 & 5.0 & 1.4 Hz, 1H), 7.24 (m, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H); $^{31}$P NMR ($CDCl_3$): δ 21.52; IR (neat, $cm^{-1}$) 3247, 2981, 1223, 1016, 980, 756, 729 ;HPLC (Daicel Chiralpak AS-H, flow rate: 1.0 mL/ min, hexane/ $^i$PrOH= 9/1, UV detection at 254 nm): $t_R$=17.6 min (*R*, minor), 44.4 min (*S*, major).

### 4.4.1.4. Diethyl hydroxy(ferrocenyl)methylphosphonate




**62**

TLC: $R_f$=0.42 (Hexane/Acetone=2/1, yellow oily product; $[a]_D^{25}$= + 3.5 (c 1.0, $CHCl_3$) for 28 % ee; $^1H$ NMR ($CDCl_3$): δ 1.20 (t, *J*= 6.9 Hz, 3H), 1.25 (t, *J*= 6.9 Hz, 3H), 3.43 (br, 1H), 3.95 (m, 4H), 4.10 (s, Fc, 2H),4.15 (s, Fc, 5H), 4.21 (s, Fc, 1H),4.35 (s, Fc, 1H), 4.50 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 14.08 ($CH_3$), 63.52 (CHOH), 63.72 ($OCH_2CH_3$),65.34 (Fc,CH), 65.52 (Fc, CH), 65.71 (Fc, CH), 65,76 (Fc, CH), 66.35 (Fc,5C), 83.42 (Fc, Cq) $^{31}P$ NMR ($CDCl_3$): δ 21.04; IR (neat, $cm^{-1}$) 3288, 2981, 1221, 1002, 960, 809 HPLC (Daicel Chiralpak AS-H, flow rate: 1.0 mL/min, hexane/ iPrOH= 4/1, UV detection at 254 nm): $t_R$=24.0 min. (major ), 65.0 min.(minor).

## 4.4.2. Preparation of racemic products of triethyl phosphite addition to aldehydes

To compare the asymmetric results, racemic forms of α-hydroxyphosphonates were prepared. Same reaction procedure with general procedure for asymmetric triethyl phosphite addition to aldehydes was applied but chiral Lewis base did not used for reaction.

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# APPENDIX A

NMR SPECTRA and HPLC CHROMATOGRAMS

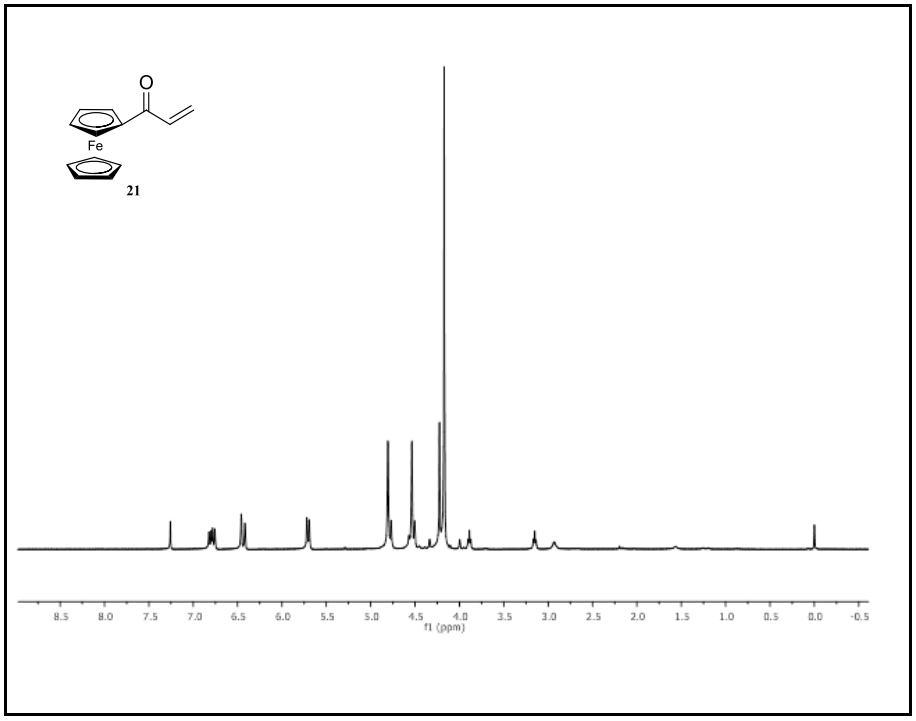



***Figure A.1*** *$^{1}$H-NMR spectrum of compound* ***21***

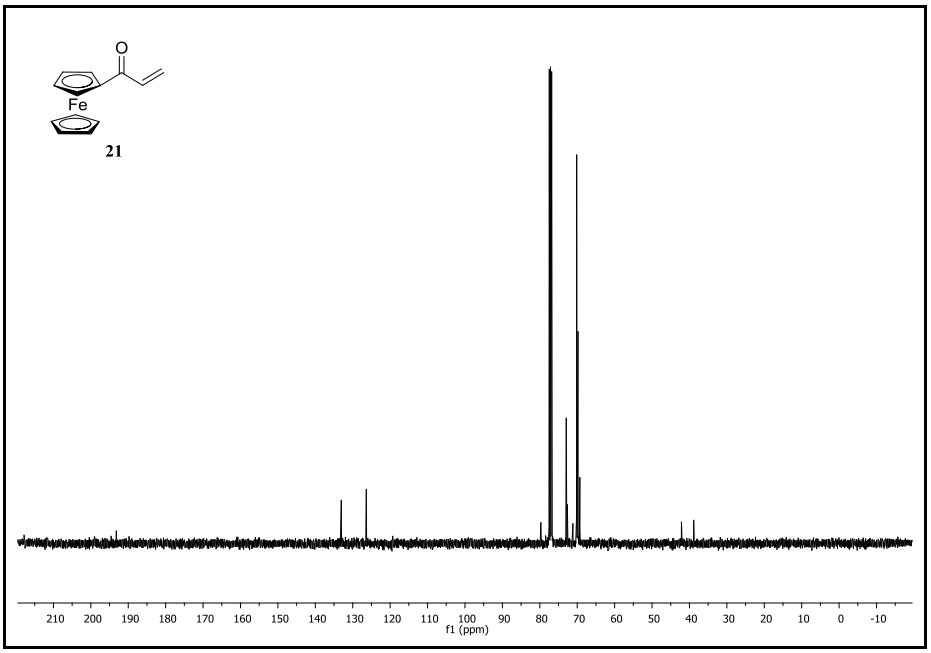



***Figure A.2*** *$^{13}$C-NMR spectrum of compound* ***21***

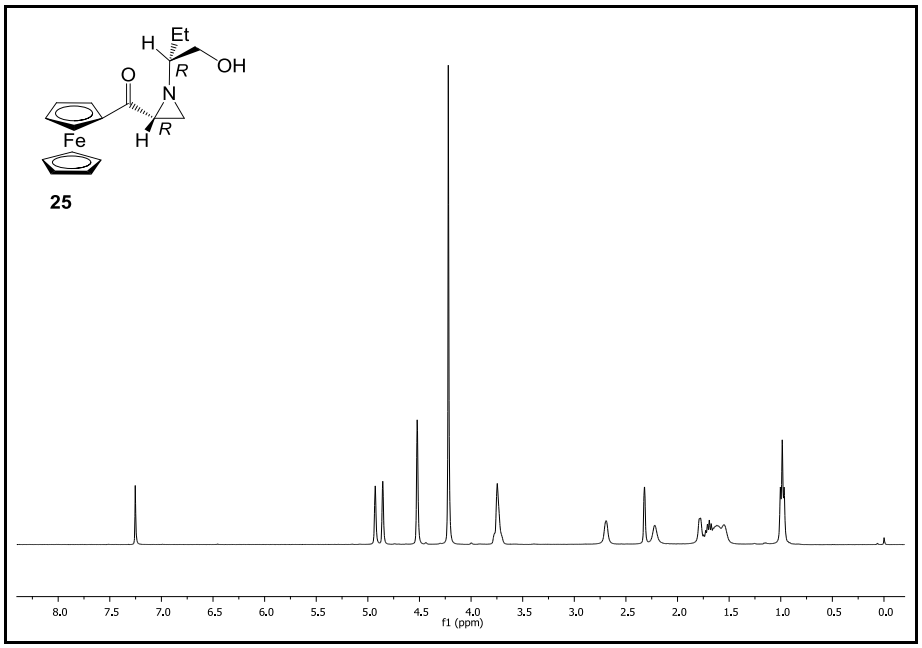



***Figure A.3*** *$^{1}$H-NMR spectrum of compound* ***25***

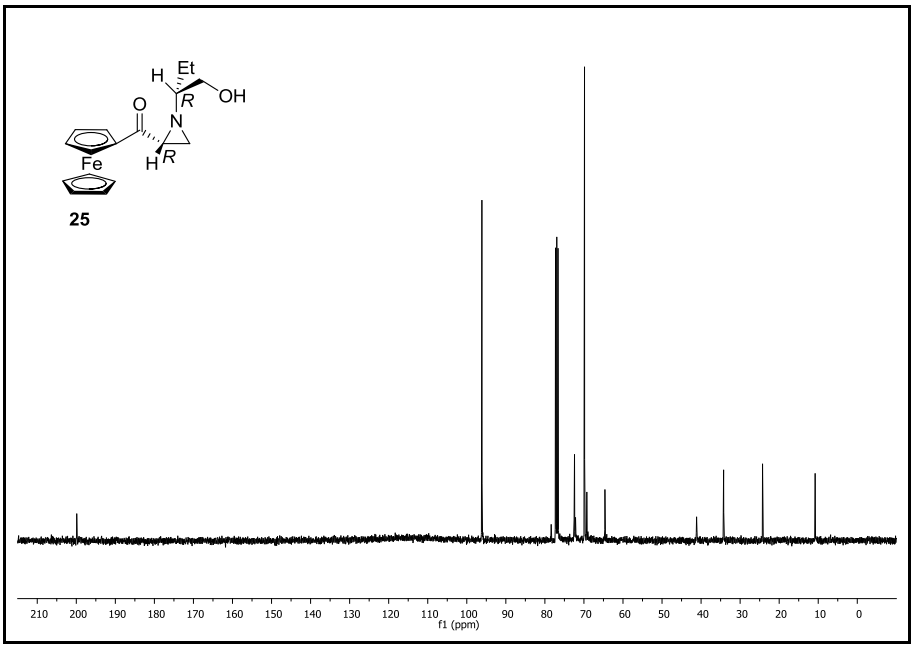



***Figure A.4*** *$^{13}$C-NMR spectrum of compound* ***25***

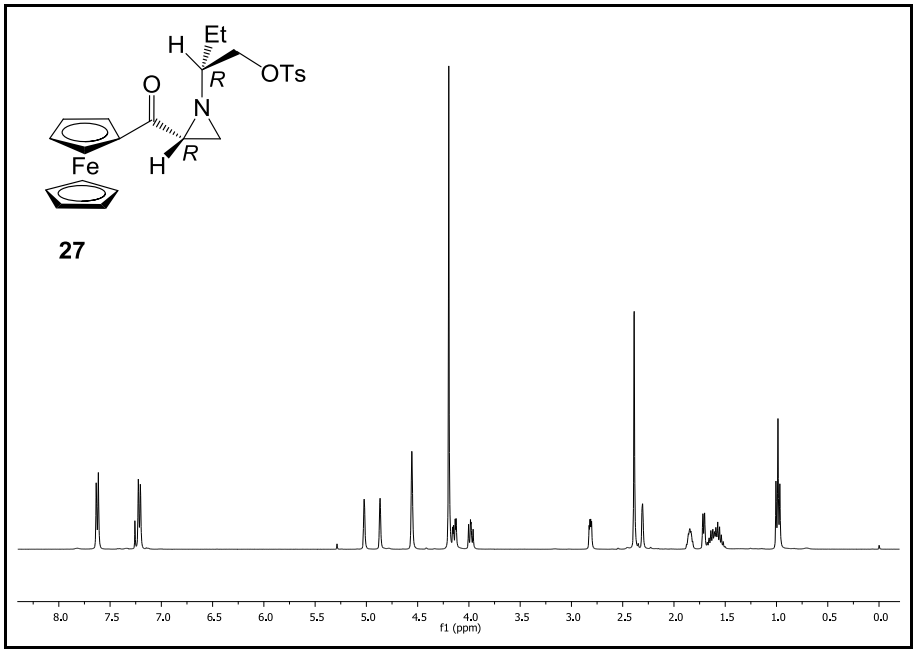



***Figure A.5*** *$^{1}$H-NMR spectrum of compound* ***27***

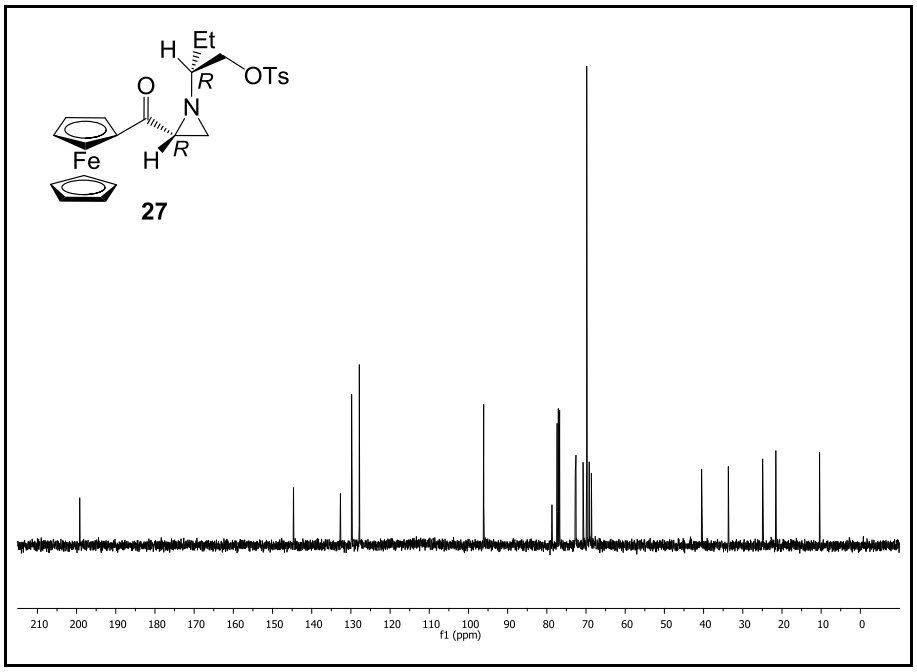



***Figure A.6*** *$^{13}$C-NMR spectrum of compound* ***27***

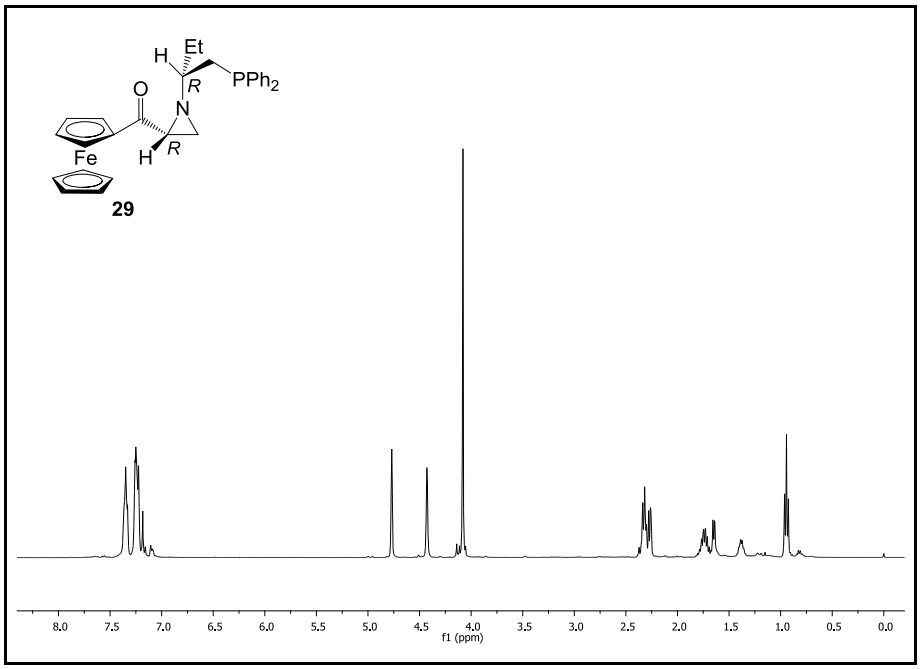



***Figure A.7*** *$^{1}$H-NMR spectrum of compound* ***29***

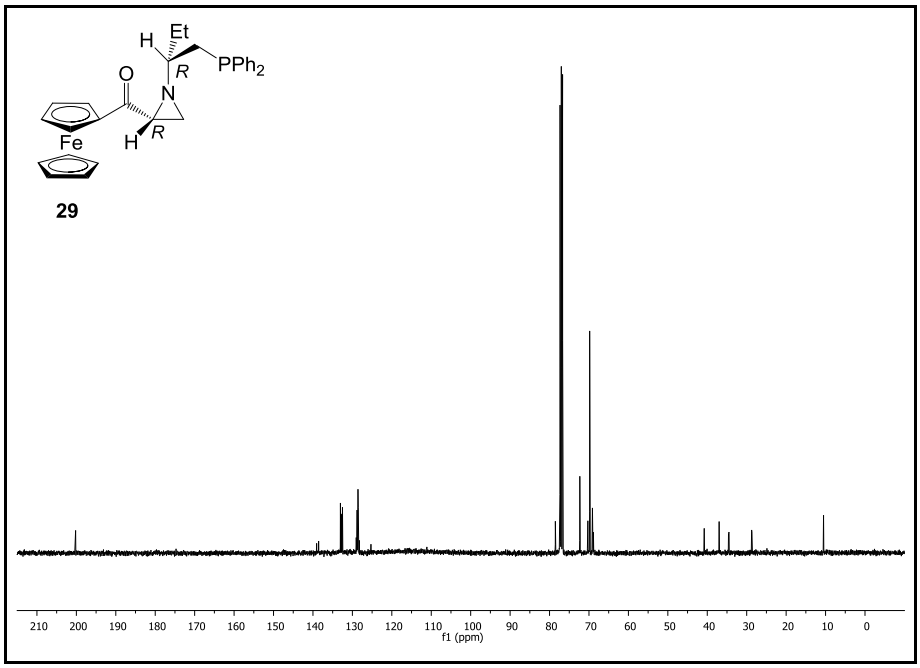



***Figure A.8*** *$^{13}$C-NMR spectrum of compound* ***29***

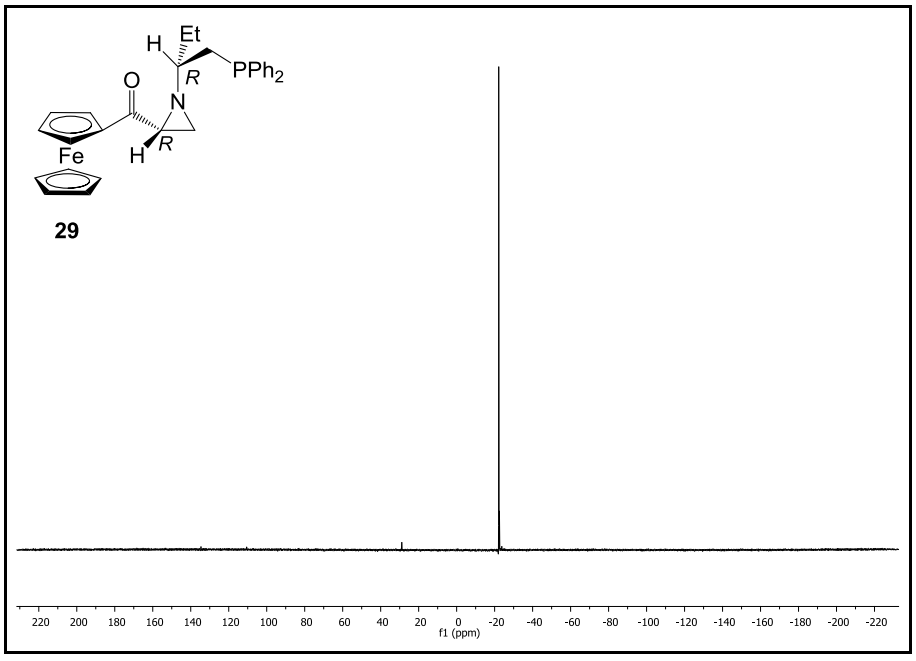



***Figure A.9*** *$^{31}$P-NMR spectrum of compound* ***29***

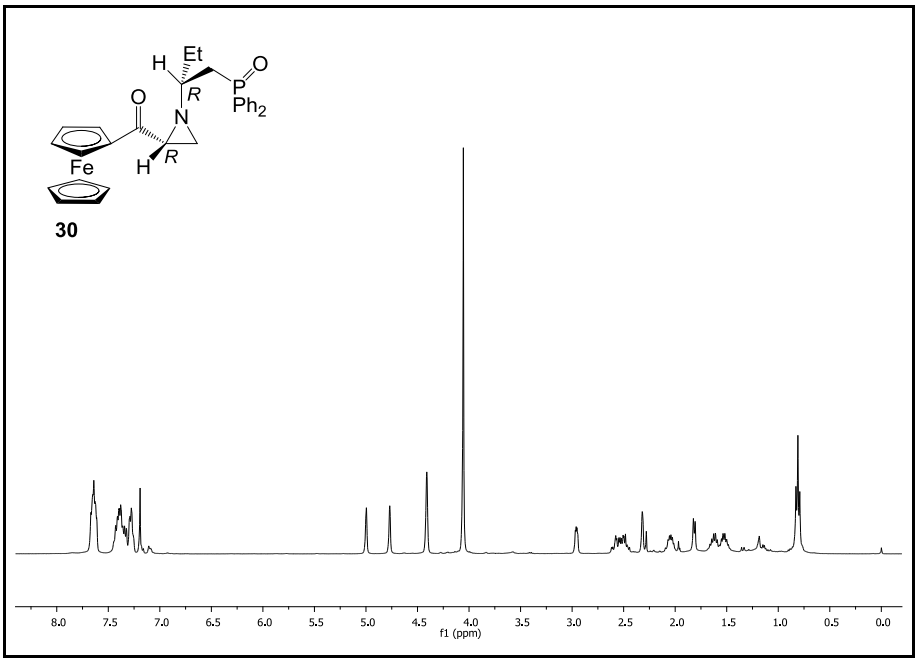



***Figure A.10*** *$^{1}$H-NMR spectrum of compound* ***30***

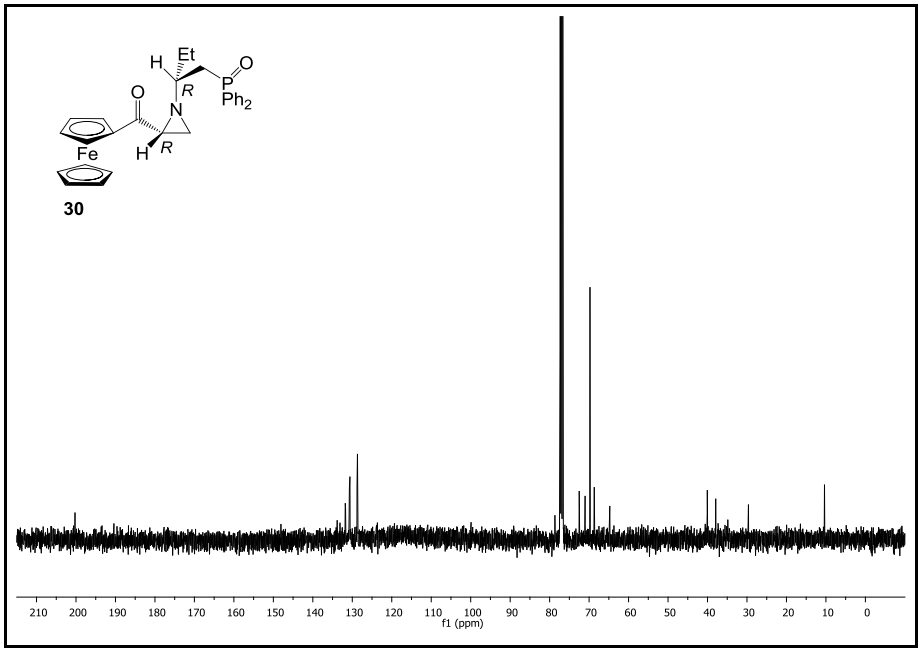



**Figure A.11** $^{13}$C-NMR spectrum of compound **30**

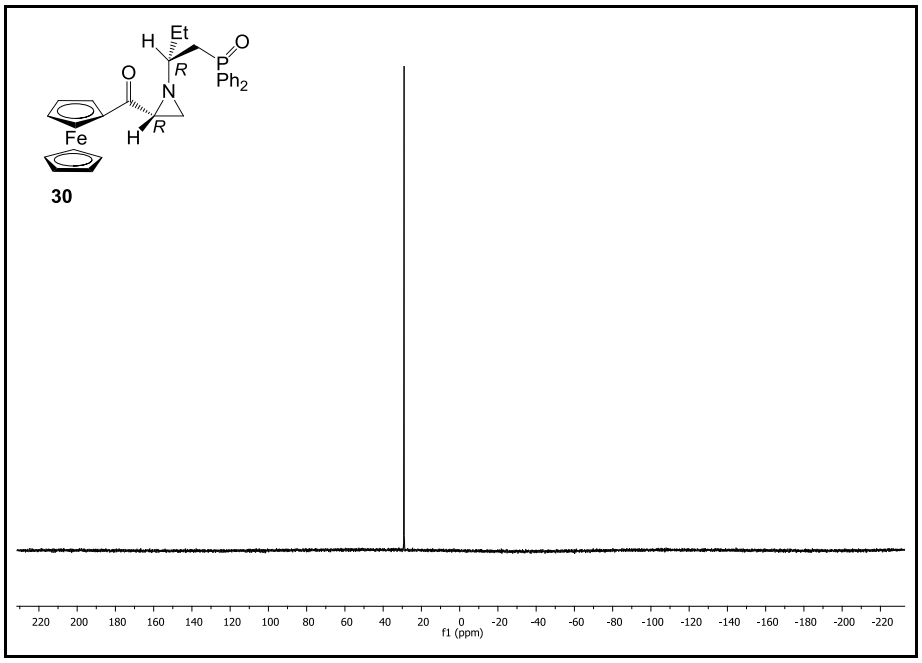



***Figure A.12*** *$^{31}$P-NMR spectrum of compound 30*

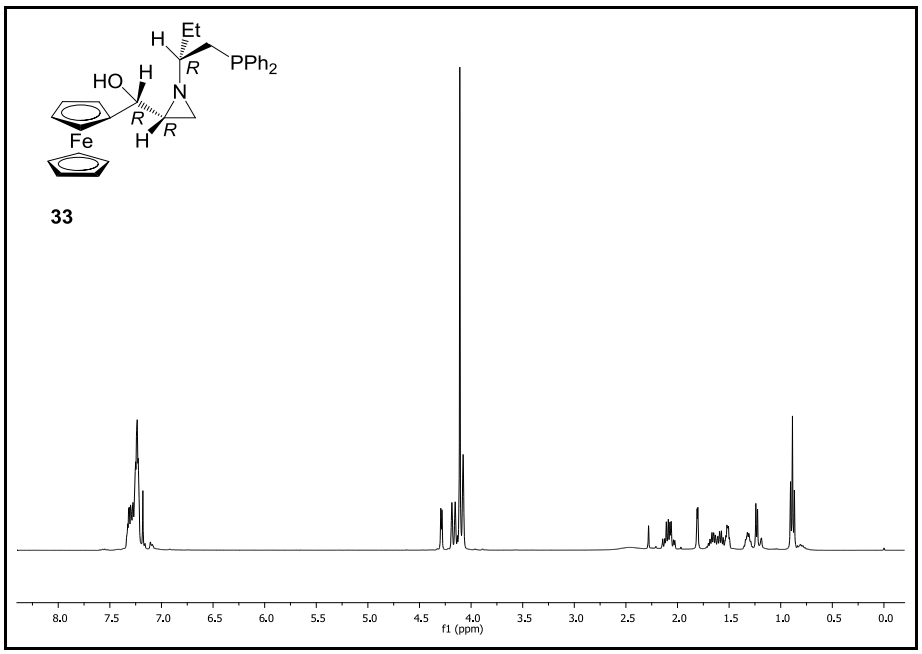



***Figure A.13*** *$^{1}$H-NMR spectrum of compound **33***

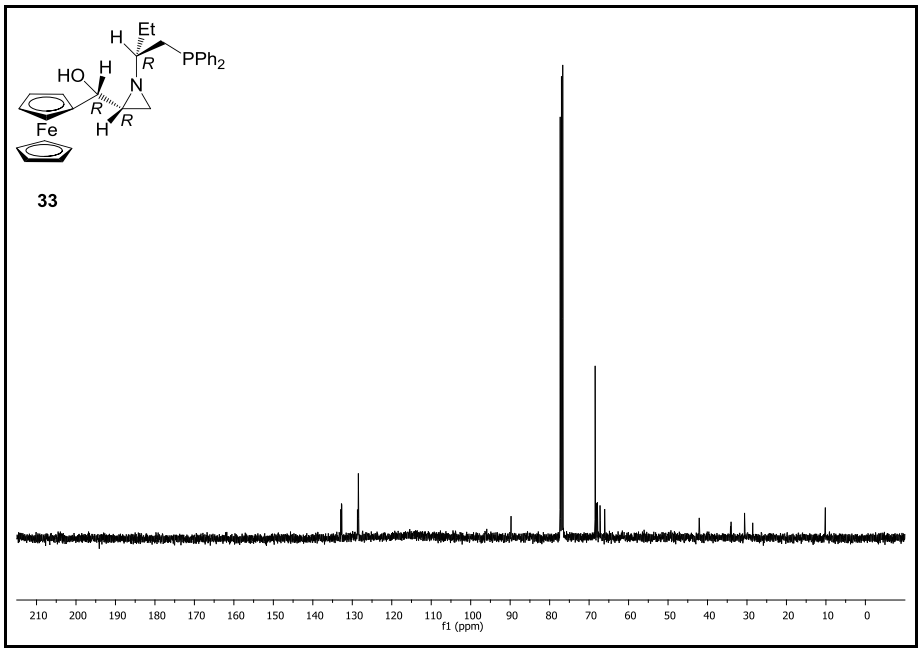



***Figure A.14*** *$^{13}$C-NMR spectrum of compound* ***33***

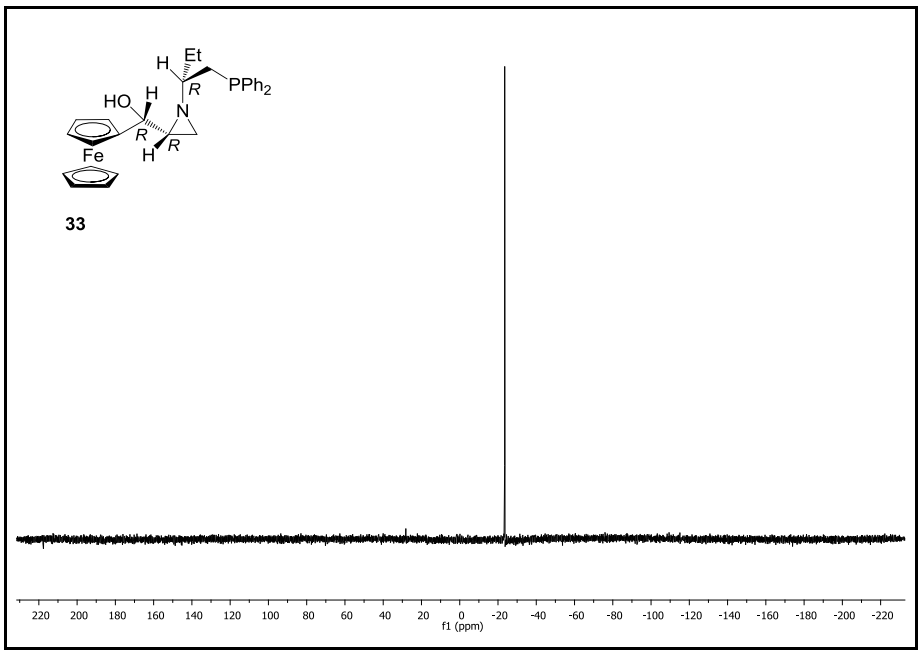



***Figure A.15*** *$^{31}$P-NMR spectrum of compound* ***33***

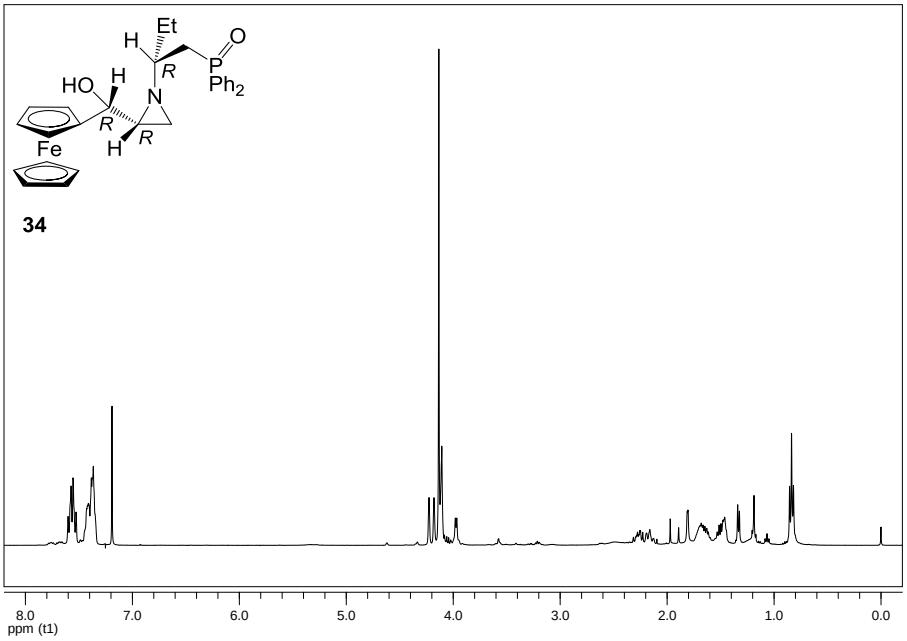



***Figure A.16*** *$^{1}$H-NMR spectrum of compound* ***34***

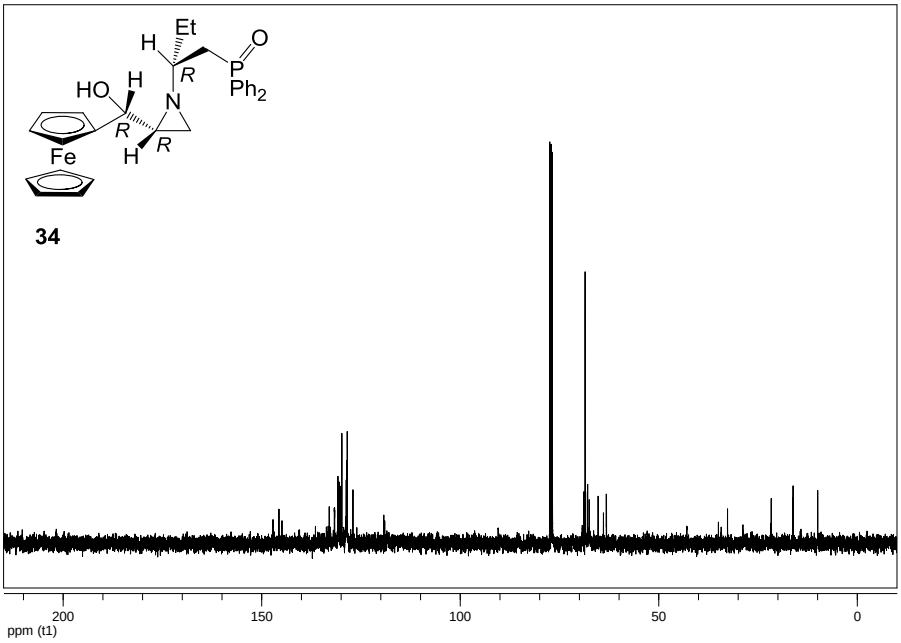



***Figure A.17*** *$^{13}$C-NMR spectrum of compound* ***34***

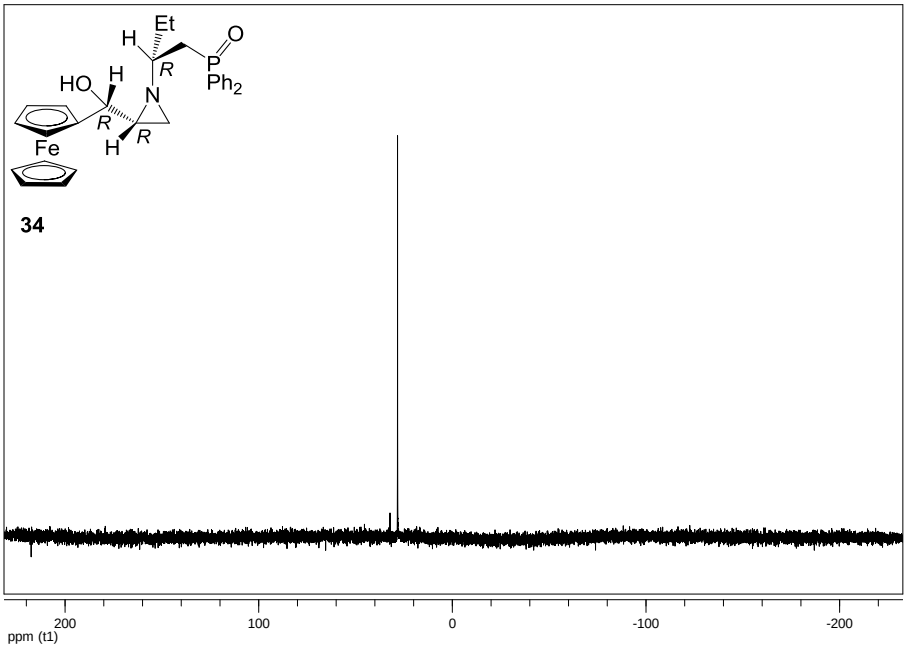



***Figure A.18*** *$^{31}$P-NMR spectrum of compound* ***34***

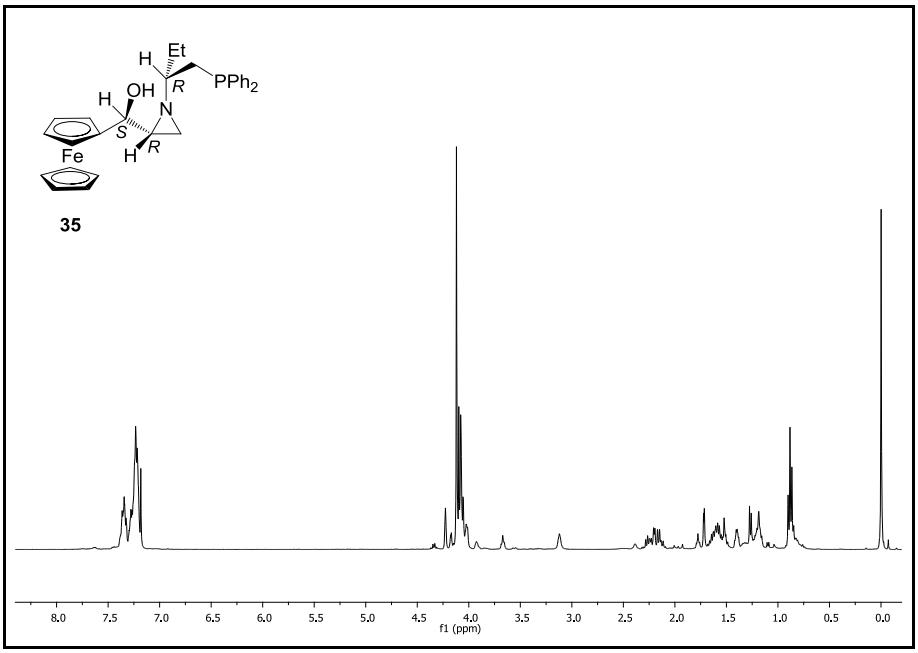



***Figure A.19*** *$^{1}$H-NMR spectrum of compound* ***35***

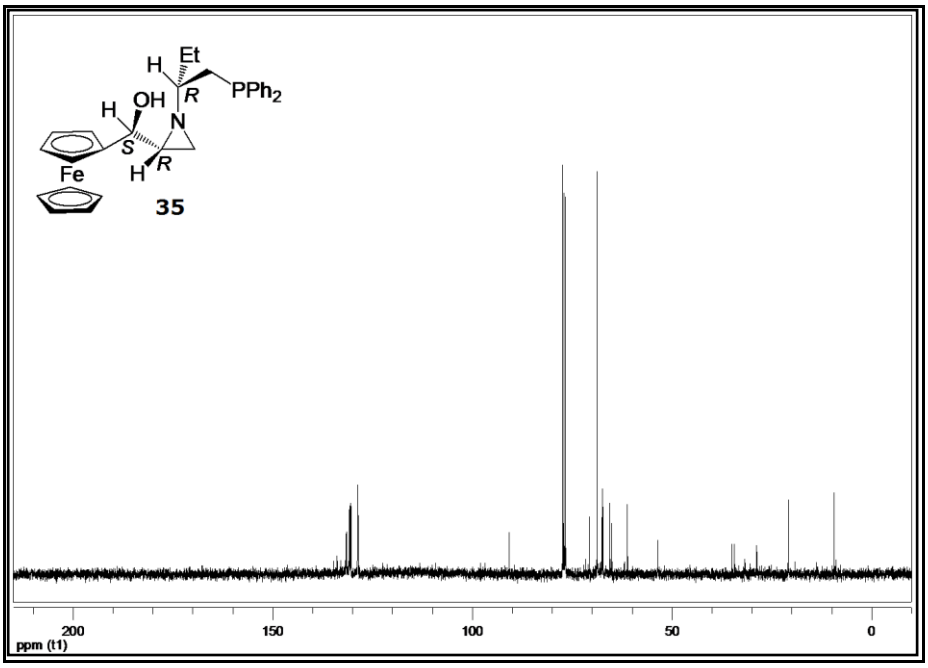



***Figure A. 20*** *$^{13}$C-NMR spectrum of compound* ***35***

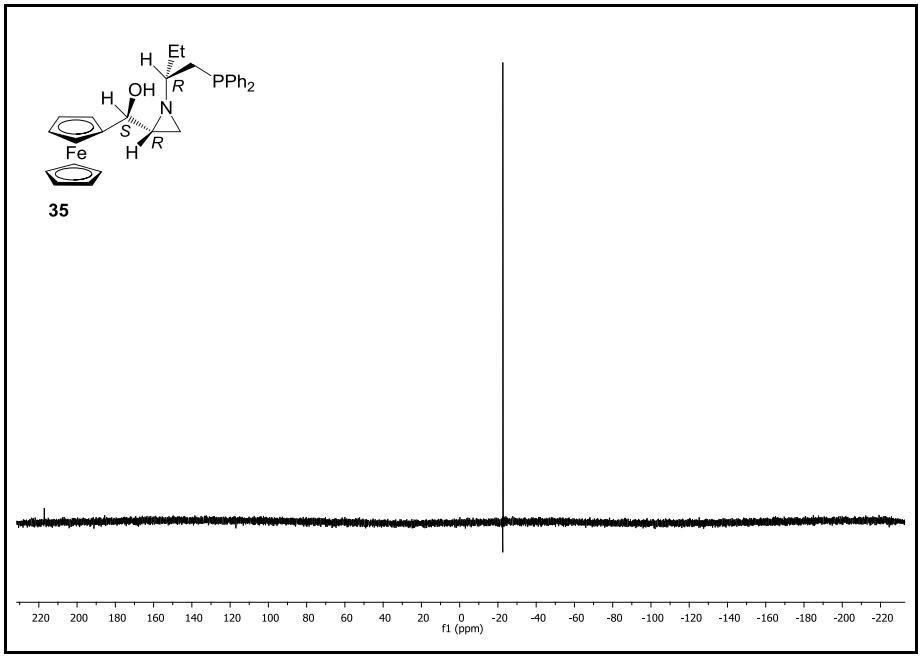



***Figure A.21*** *$^{31}$P-NMR spectrum of compound* ***35***

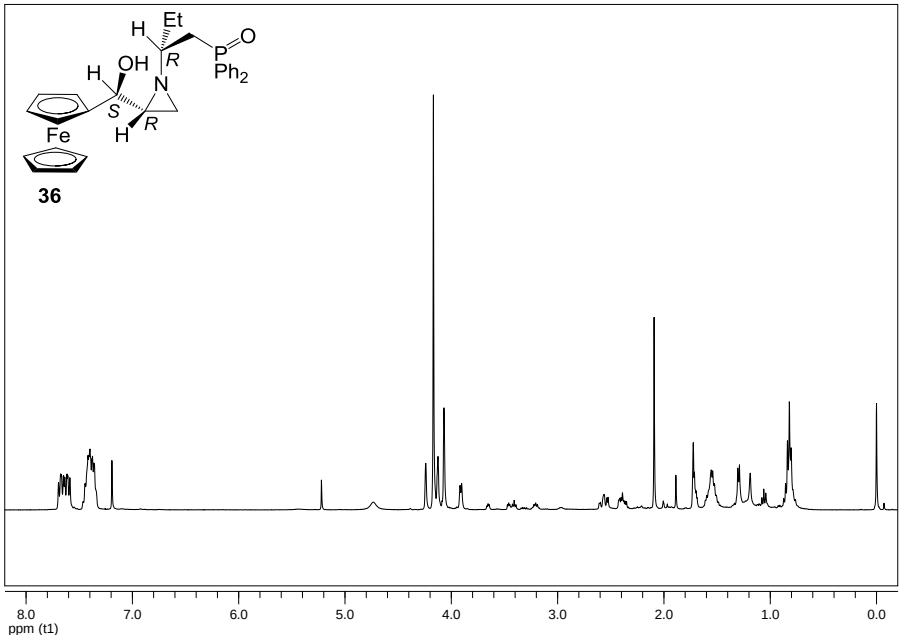



***Figure A.22*** *$^{1}$H-NMR spectrum of compound* ***36***

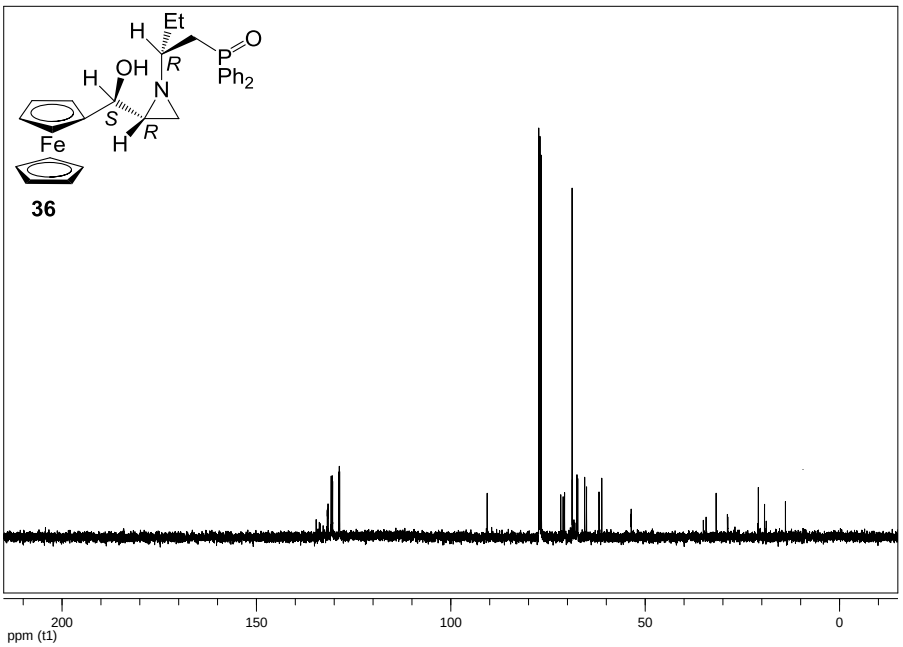



***Figure A.23*** *$^{13}$C-NMR spectrum of compound* ***36***

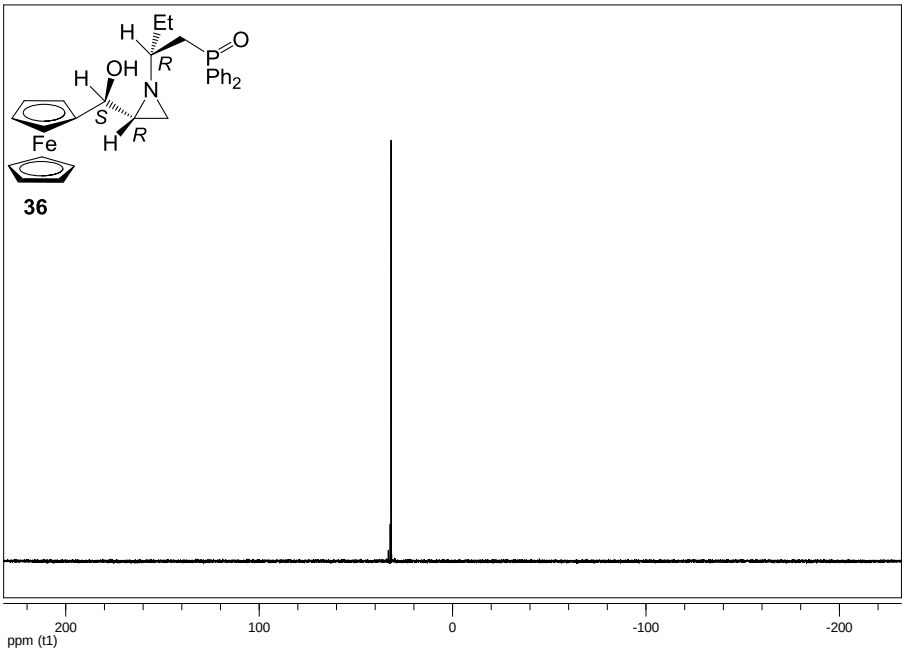



***Figure A.24*** *$^{31}$P-NMR spectrum of compound* ***36***

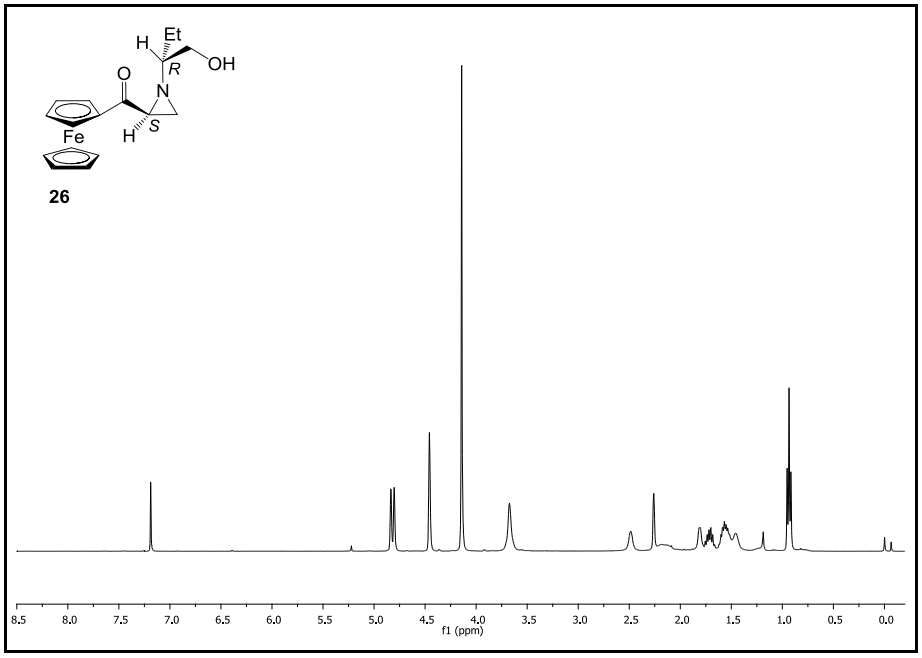



***Figure A.25*** *$^{1}$H-NMR spectrum of compound* ***26***

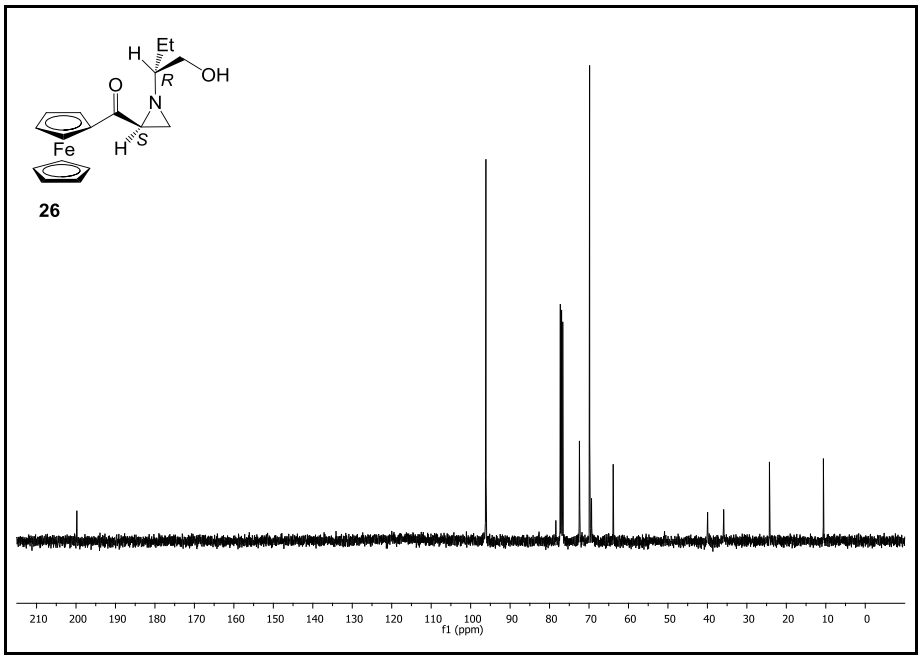



***Figure A.26*** *$^{13}$C-NMR spectrum of compound* ***26***

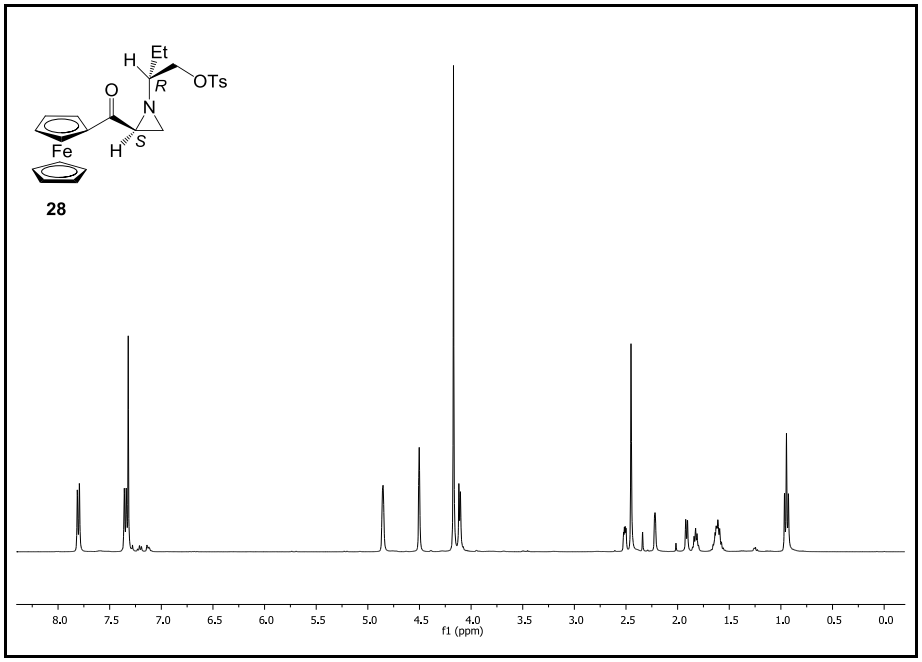



***Figure A.27*** *$^{1}$H-NMR spectrum of compound* ***28***

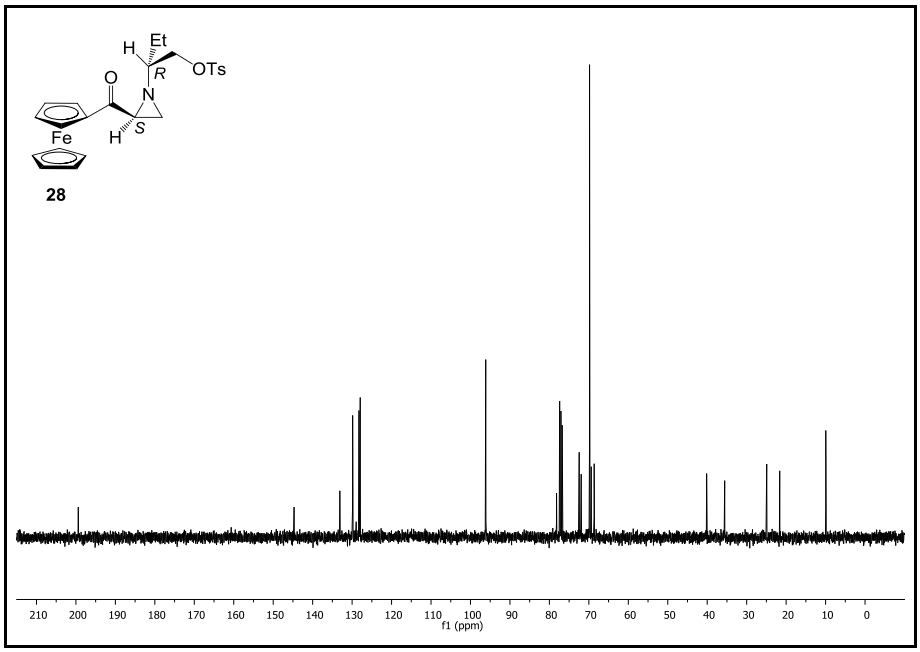



***Figure A.28*** *$^{13}$C-NMR spectrum of compound* ***28***

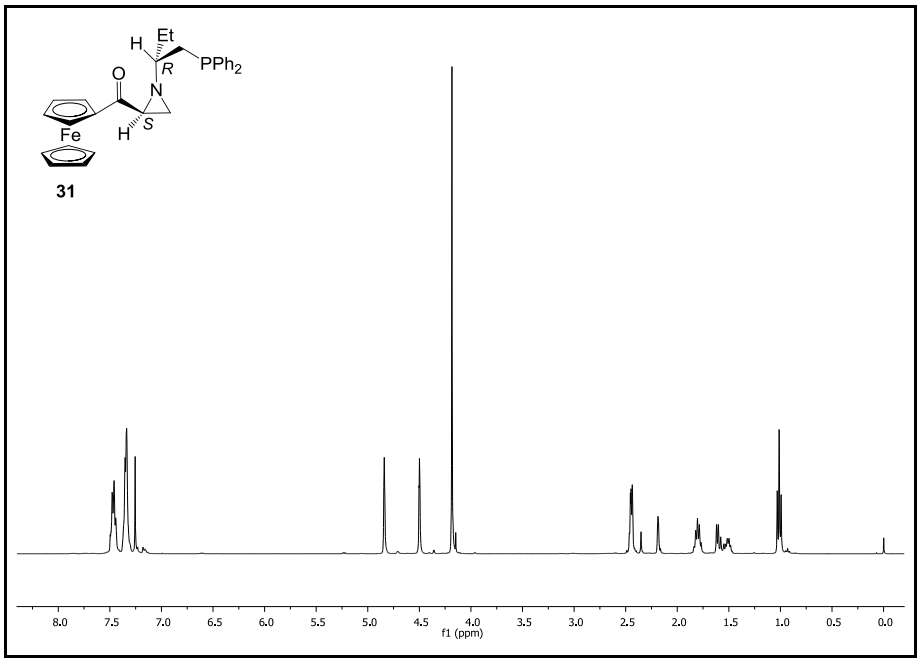



***Figure A.29*** *$^{1}$H-NMR spectrum of compound* ***31***

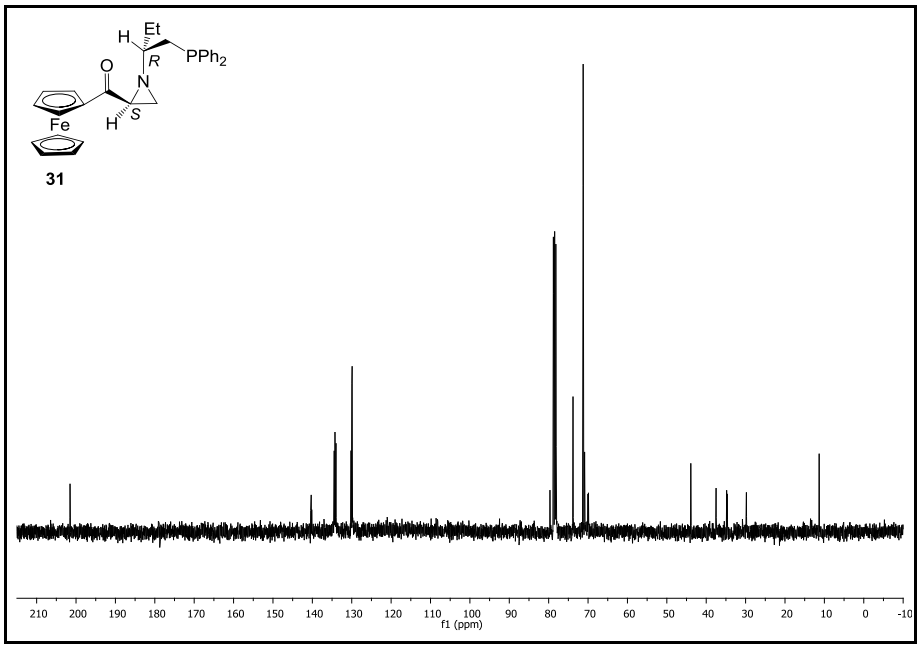



***Figure A.30*** *$^{13}$C-NMR spectrum of compound* ***31***

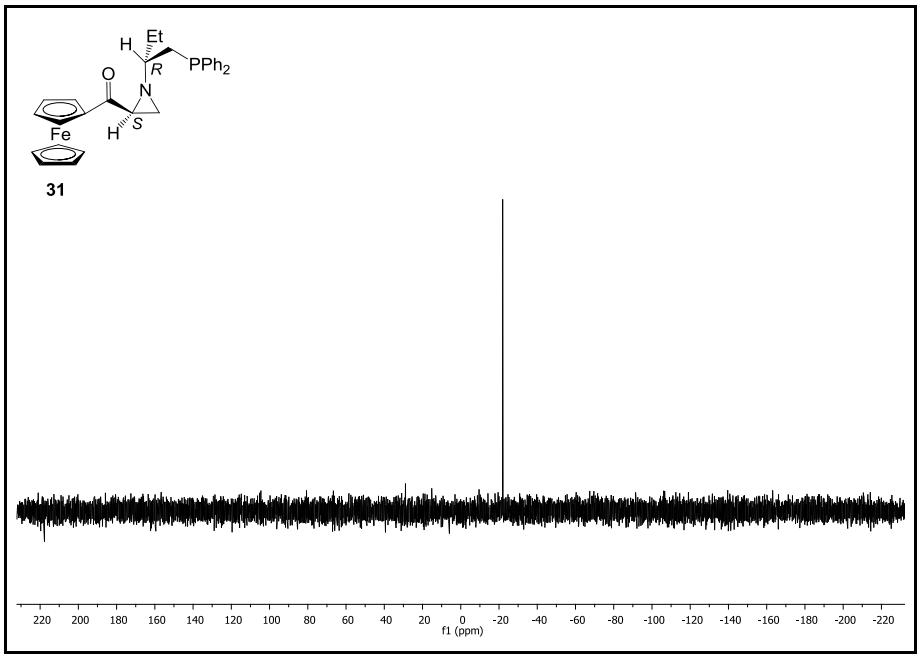



***Figure A.31*** *$^{31}$P-NMR spectrum of compound* ***31***

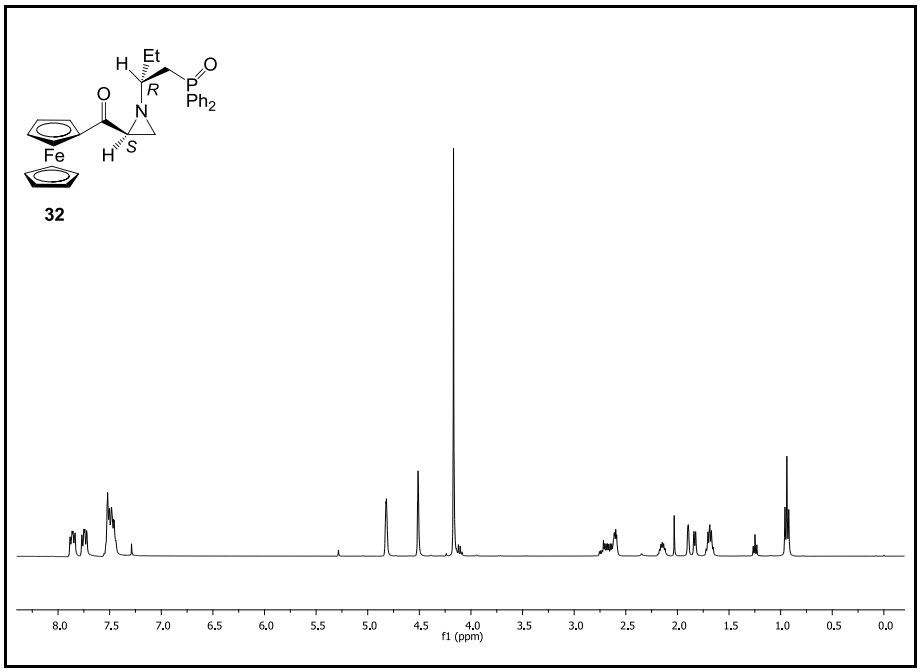



***Figure A.32*** *$^{1}$H-NMR spectrum of compound* ***32***

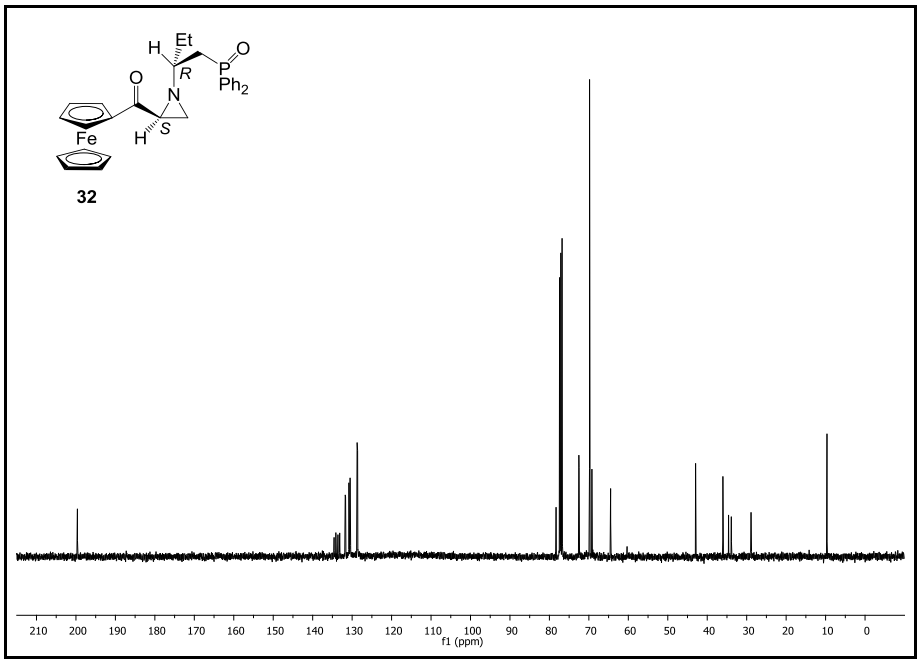



***Figure A.33*** *$^{13}$C-NMR spectrum of compound* ***32***

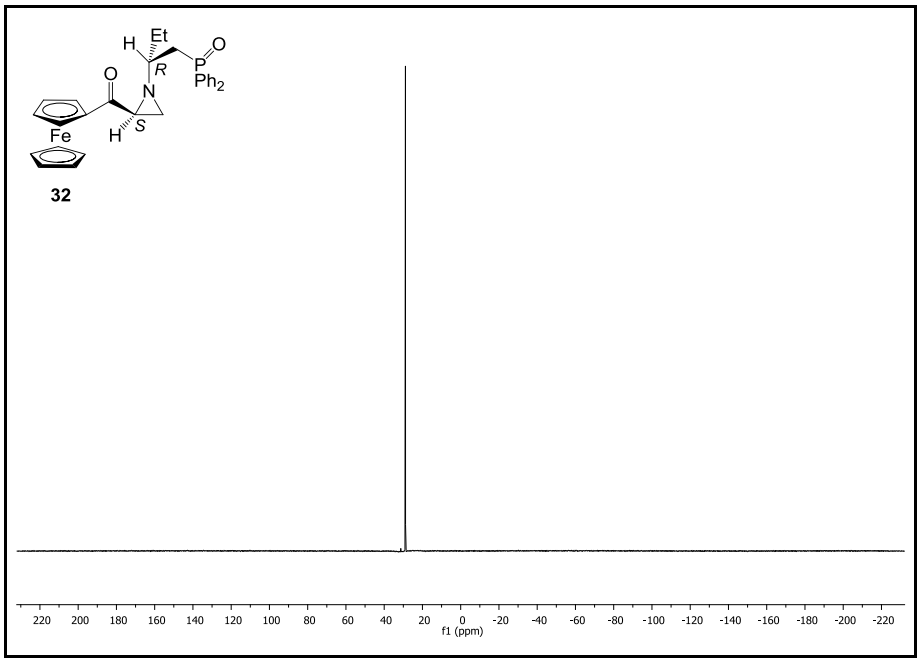



***Figure A.34*** *$^{31}$P-NMR spectrum of compound* ***32***

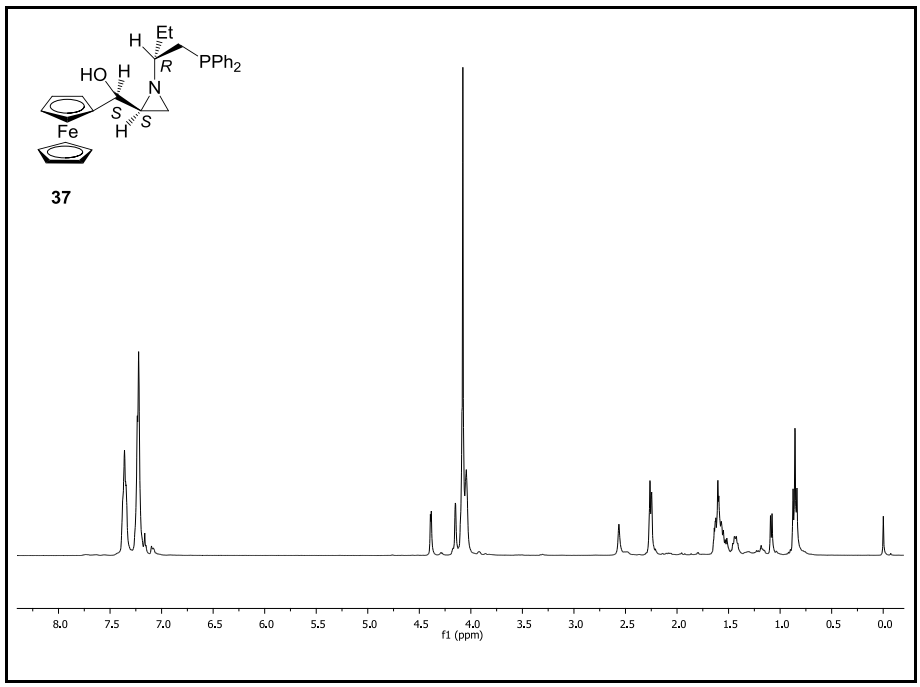



***Figure A.35*** *$^{1}$H-NMR spectrum of compound* ***37***

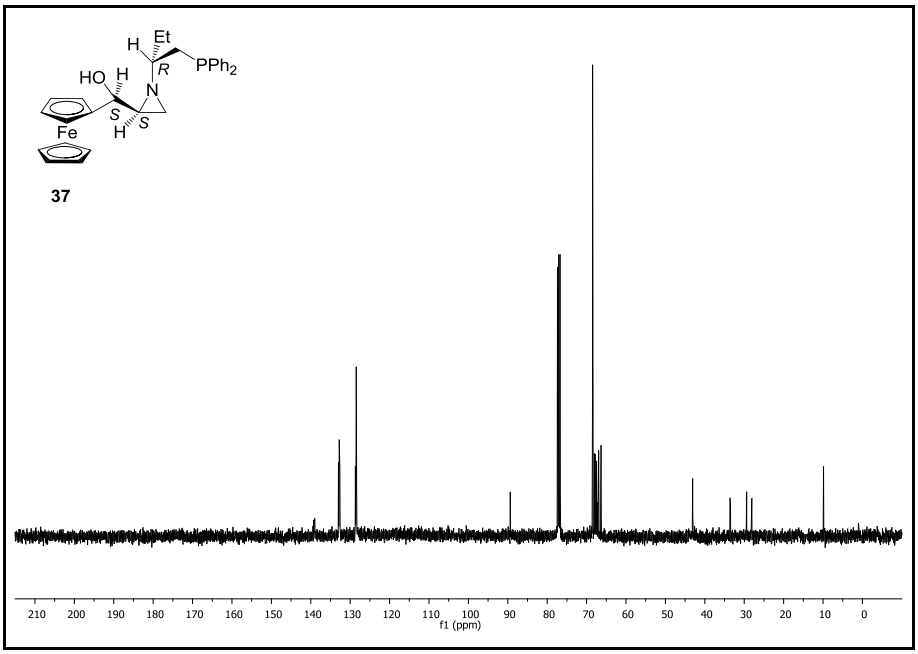



***Figure A.36*** *$^{13}$C-NMR spectrum of compound* ***37***

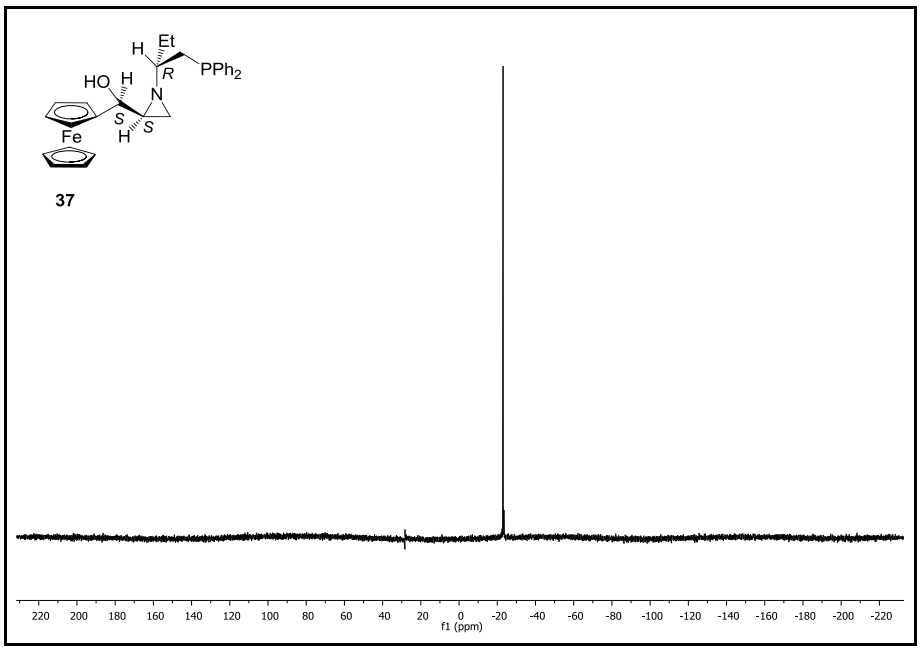



***Figure A.37*** *$^{31}$P-NMR spectrum of compound* ***37***

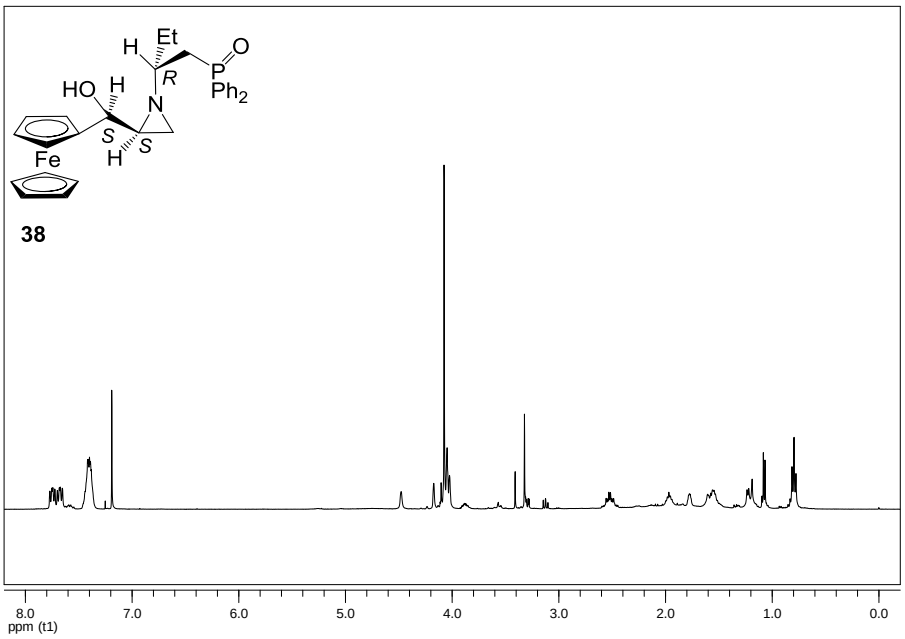



***Figure A.38*** *[1]H-NMR spectrum of compound* ***38***

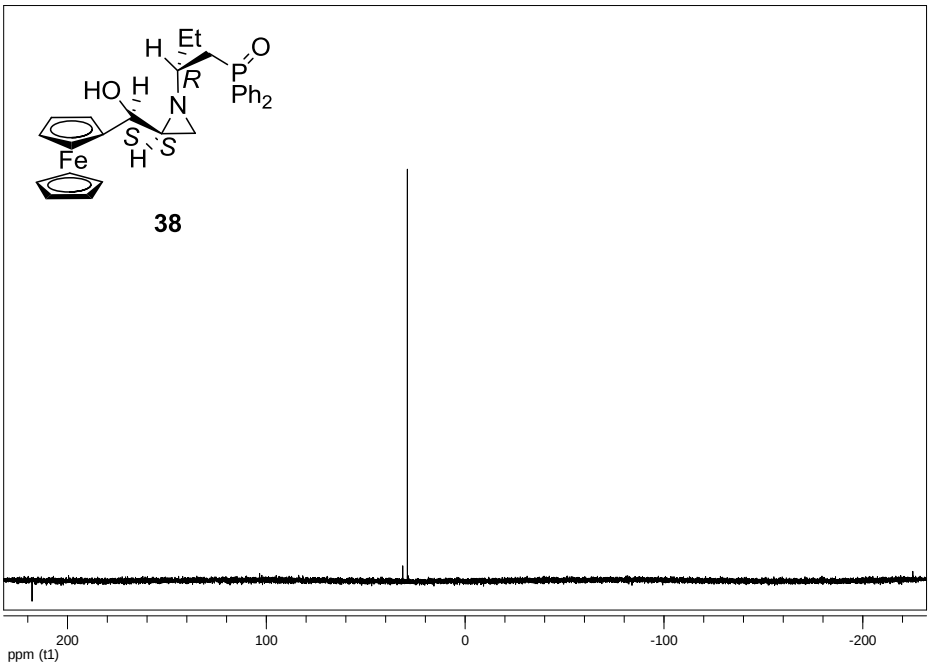



***Figure A.39*** *[31]P-NMR spectrum of compound* ***38***

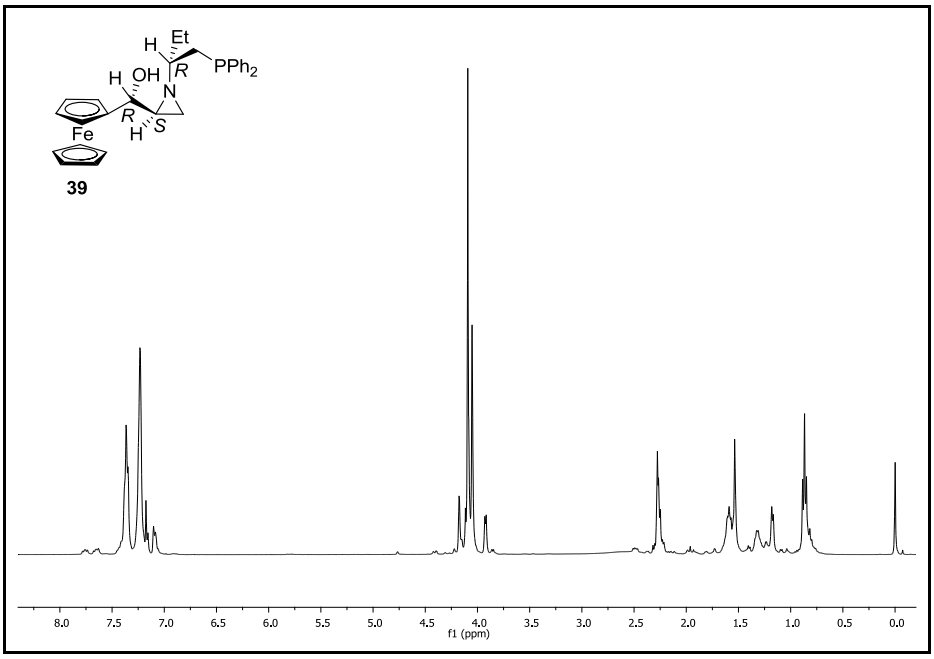



***Figure A.40*** *$^{1}$H-NMR spectrum of compound* ***39***

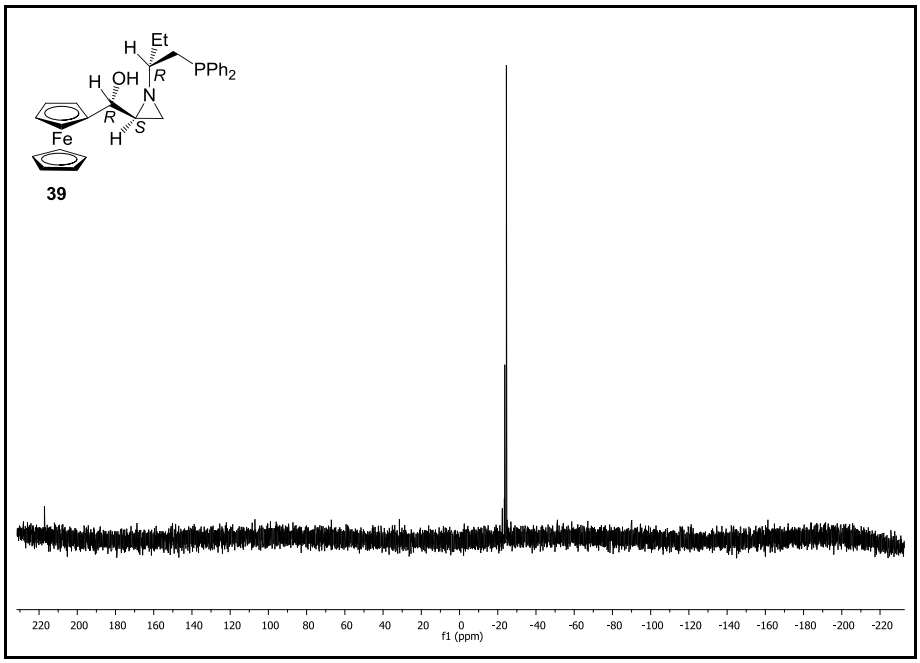



***Figure A.41*** *$^{31}$P-NMR spectrum of compound* ***39***

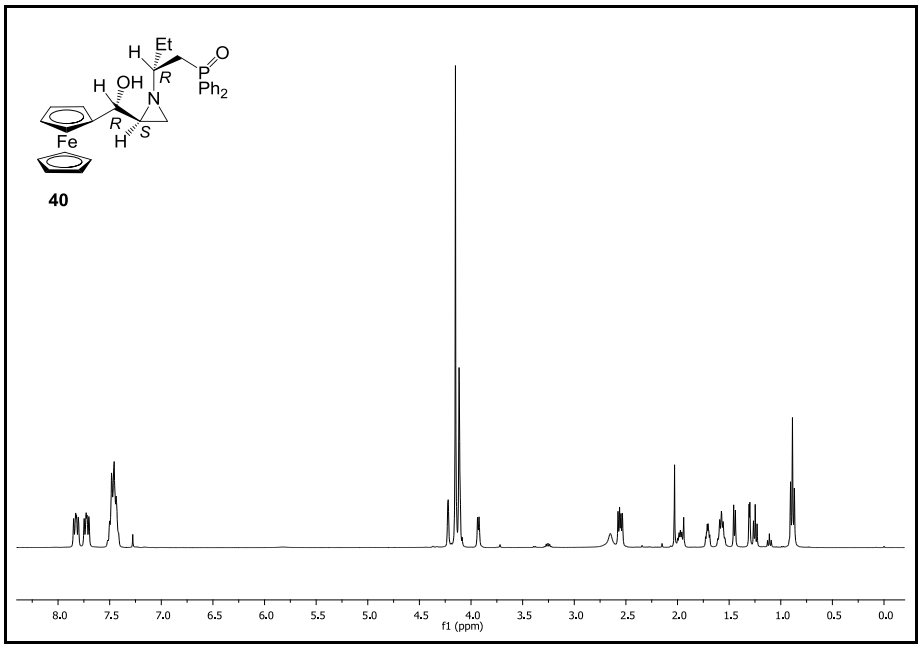



***Figure A.42*** *$^{1}$H-NMR spectrum of compound* ***40***

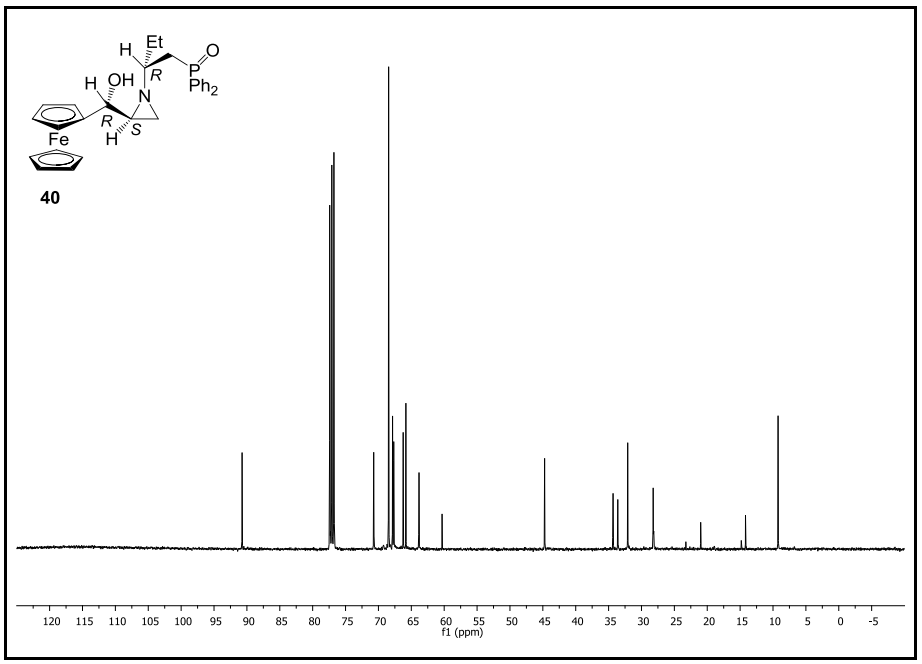



***Figure A.43*** *$^{13}$C-NMR spectrum of compound* ***40***

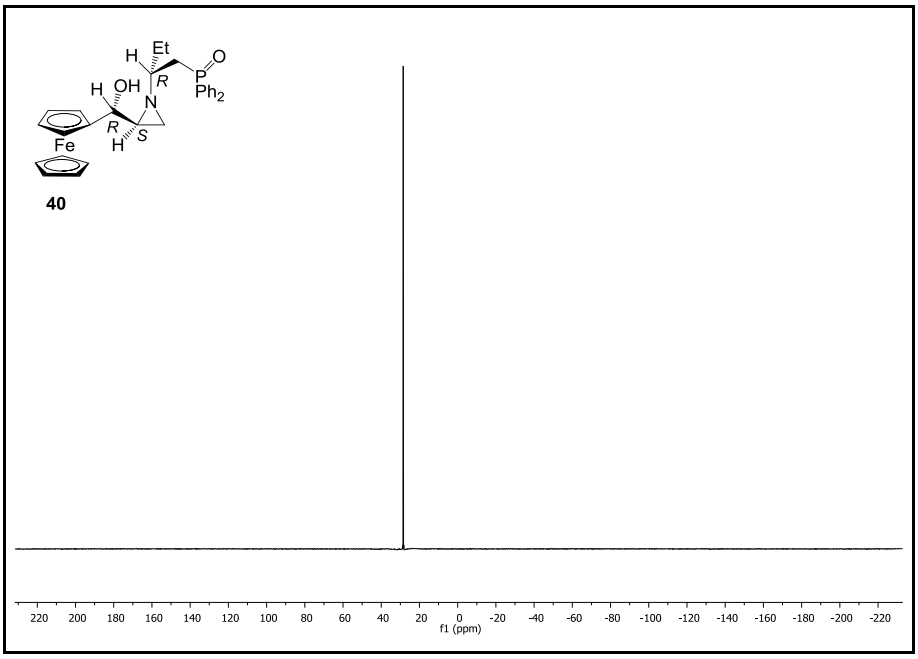



***Figure A.44*** *$^{31}$P-NMR spectrum of compound* ***40***

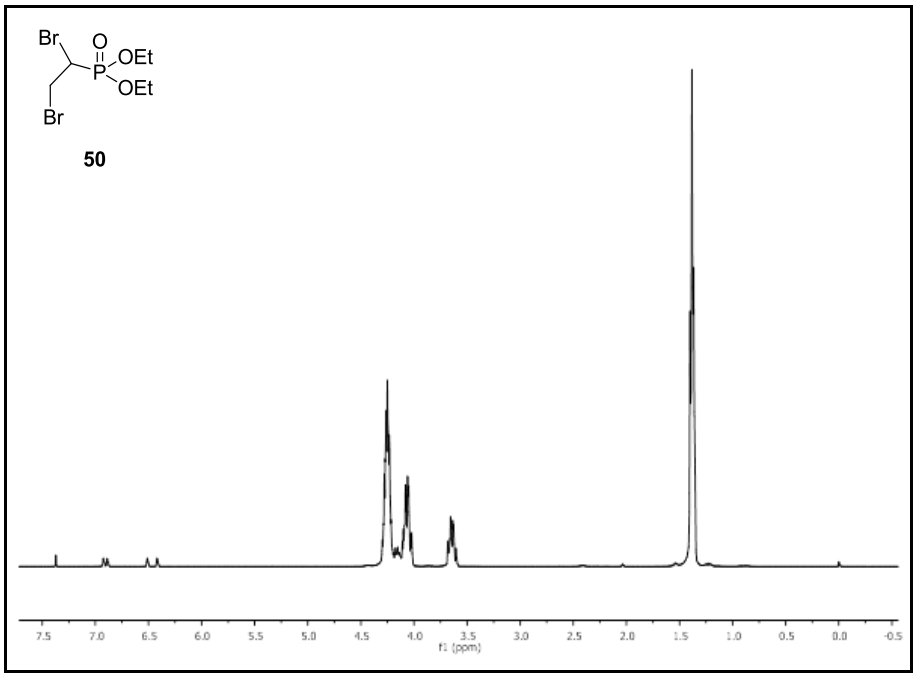



***Figure A.45*** *$^{1}$H-NMR spectrum of compound* ***50***

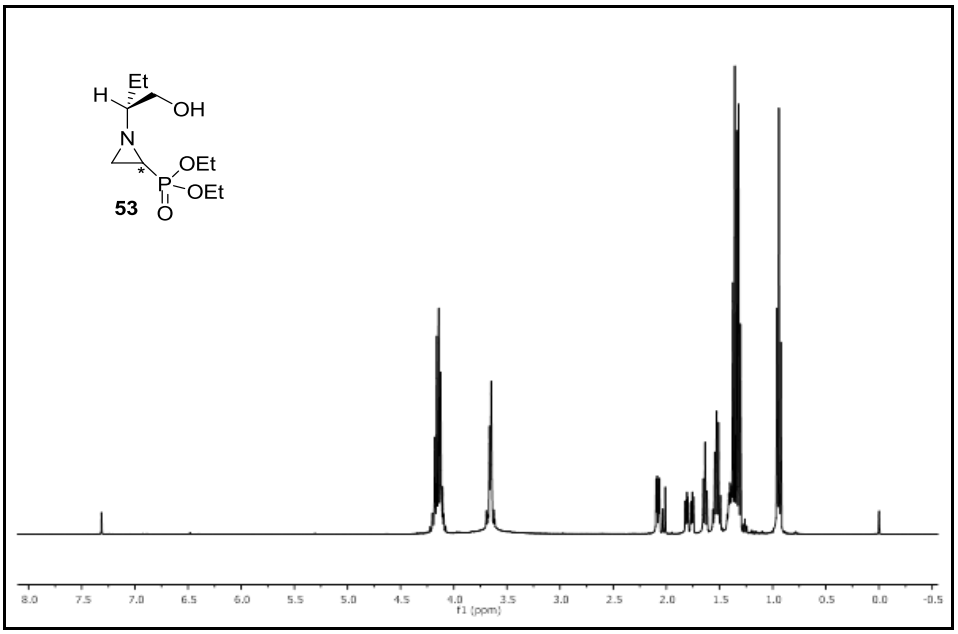



***Figure A.46*** *$^{1}$H-NMR spectrum of compound* ***53***

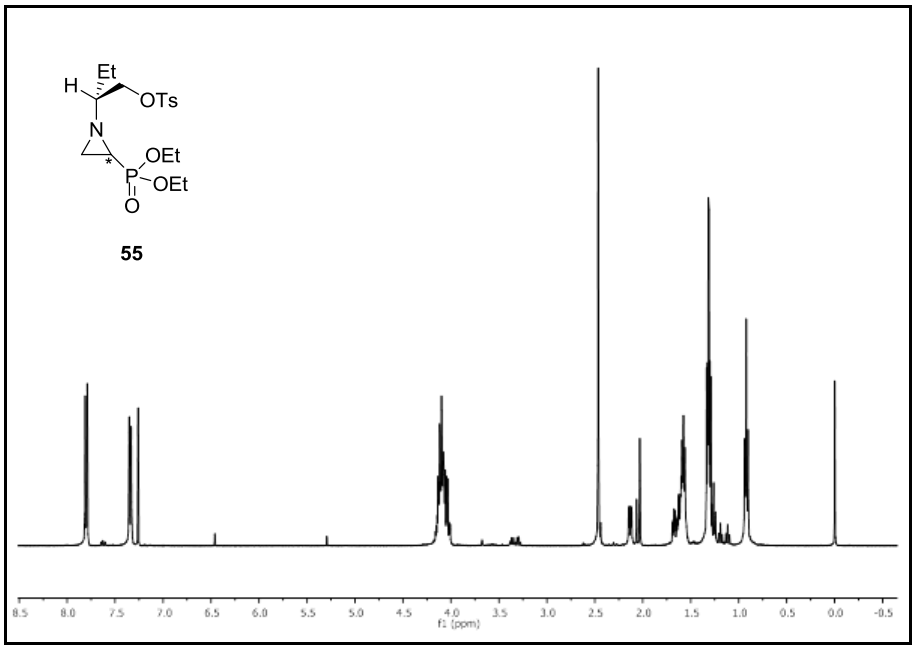



***Figure A.47*** *$^{1}$H-NMR spectrum of compound* ***55***

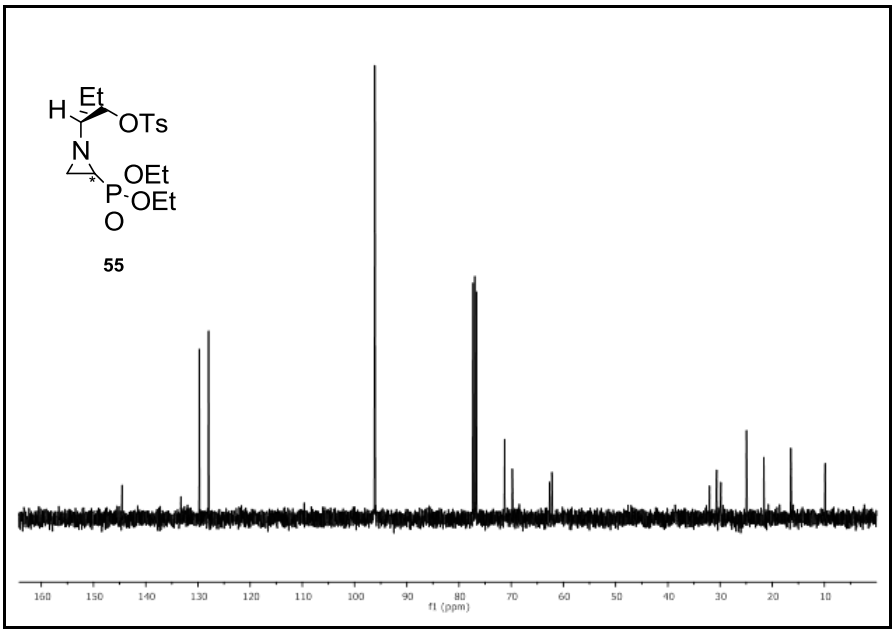



***Figure A.48*** *$^{13}$C-NMR spectrum of compound* ***55***

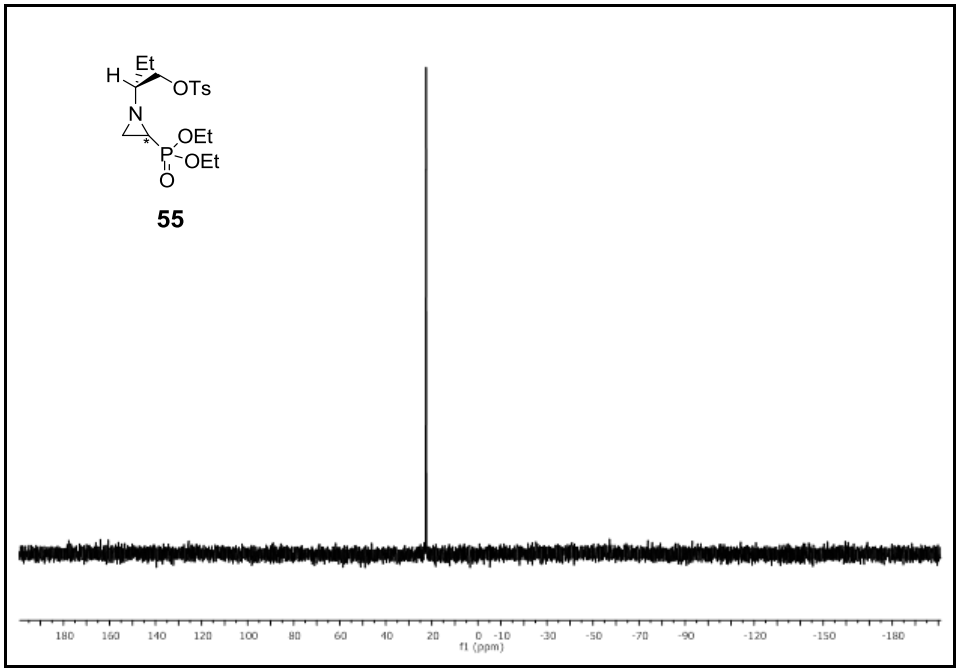



***Figure A.49*** *$^{31}$P-NMR spectrum of compound* ***55***

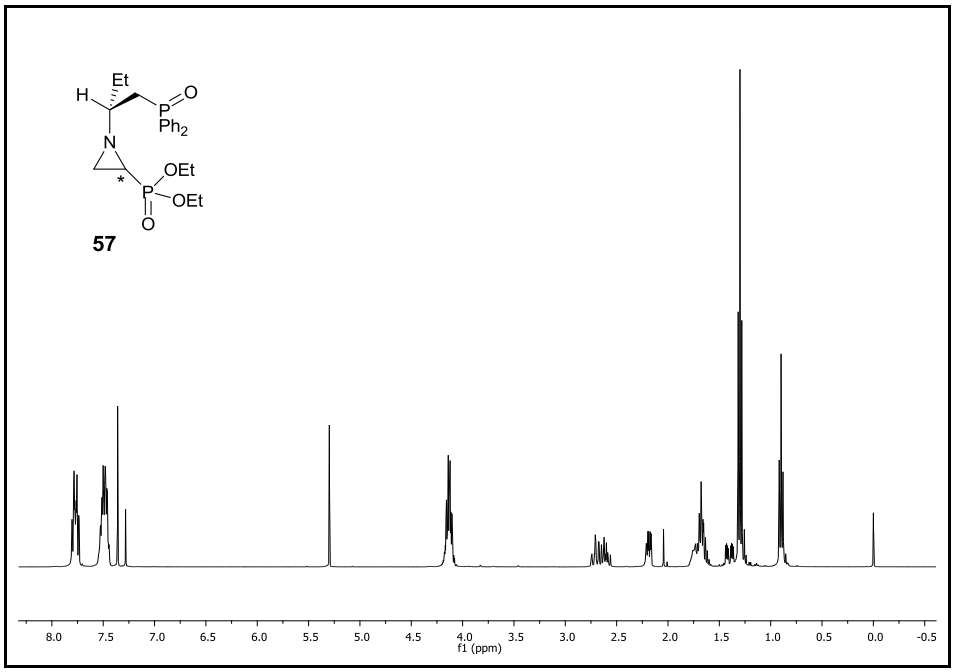



***Figure A.50*** *$^{1}$H-NMR spectrum of compound* ***57***

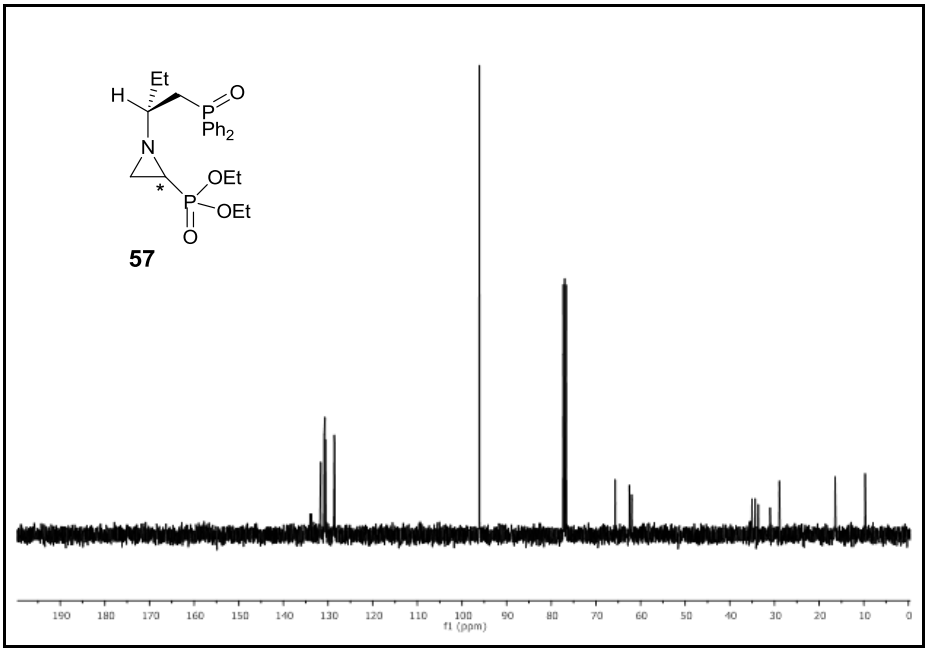



***Figure A.51*** *$^{13}$C-NMR spectrum of compound* ***57***

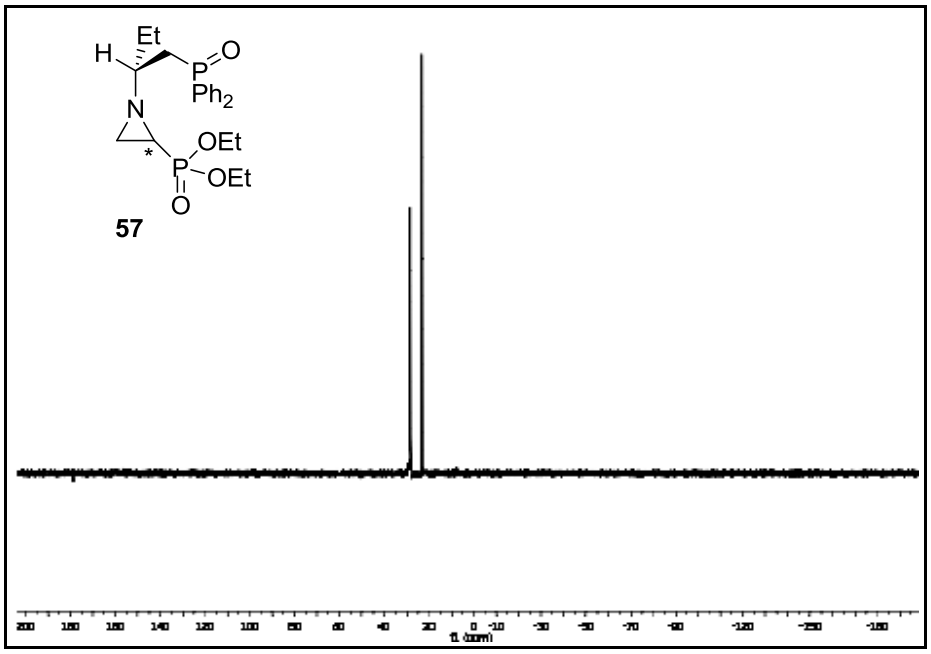



***Figure A.52*** *$^{31}$P-NMR spectrum of compound* ***57***

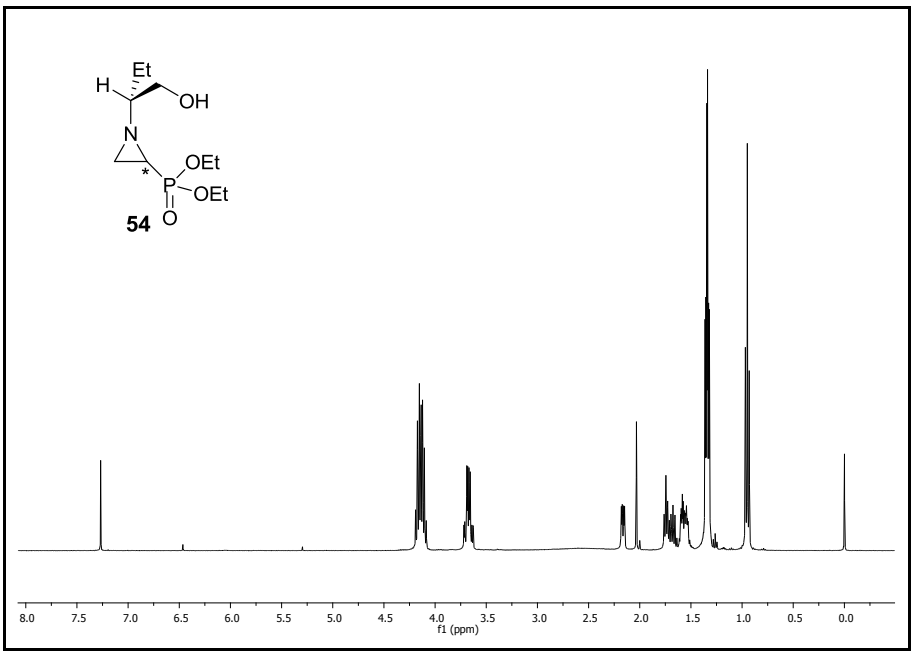



***Figure A.53*** *$^{1}$H-NMR spectrum of compound* ***54***

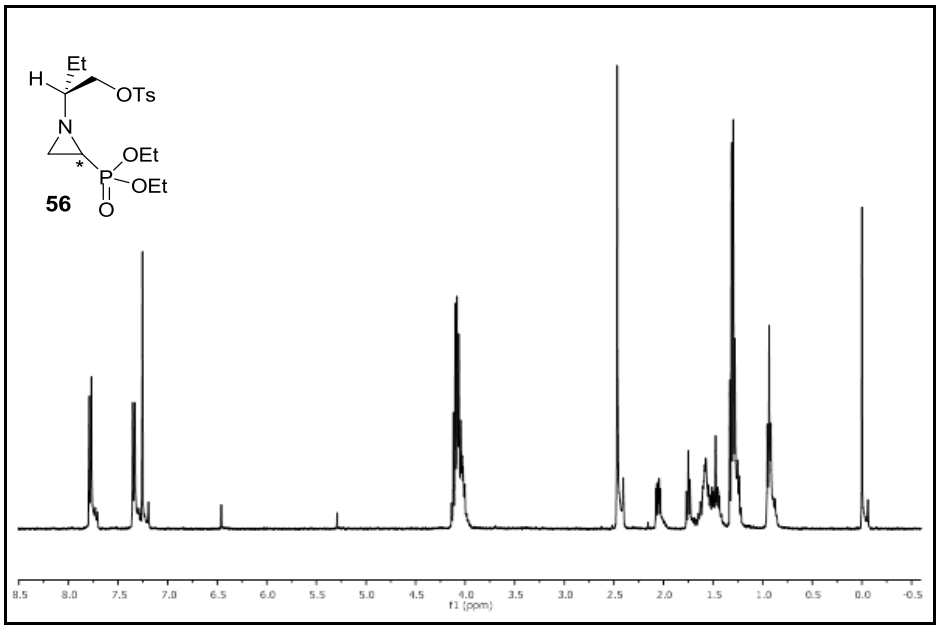



***Figure A.54*** *$^{1}$H-NMR spectrum of compound* ***56***

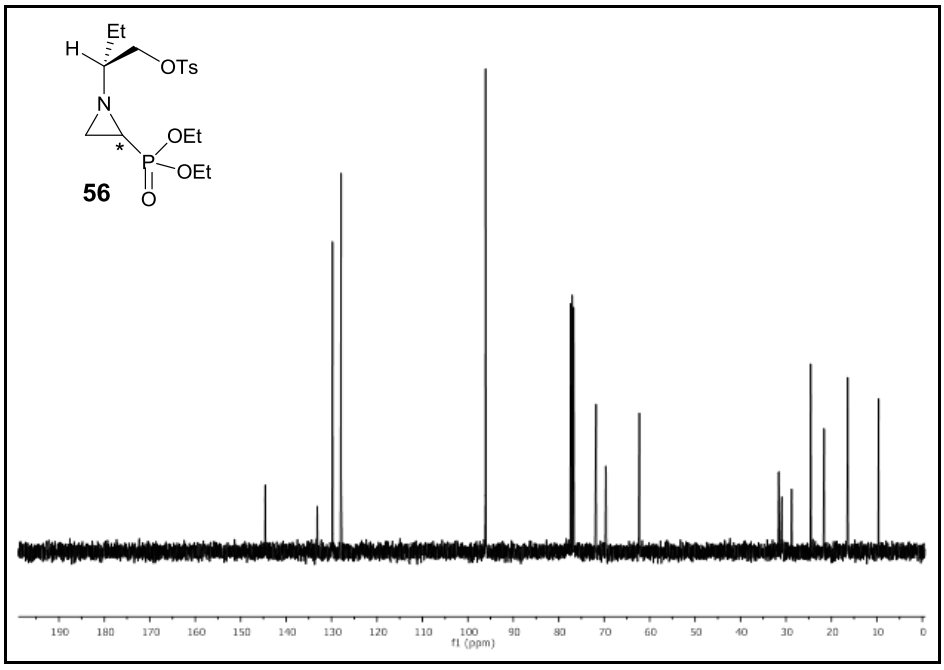



***Figure A.55*** *$^{13}$C-NMR spectrum of compound* ***56***

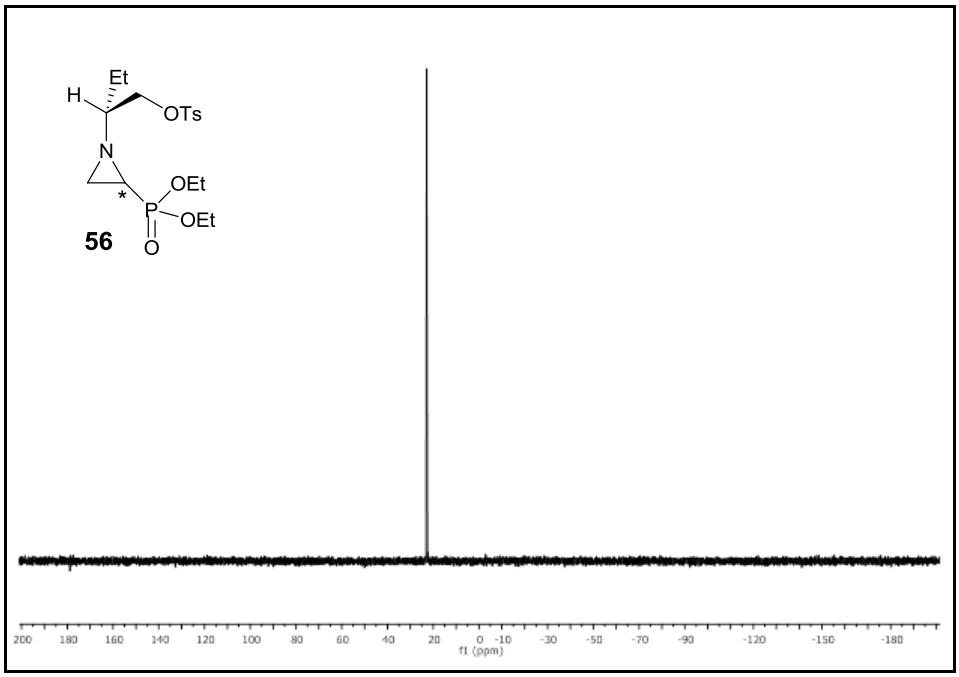



***Figure A.56*** *$^{31}$P-NMR spectrum of compound* ***56***

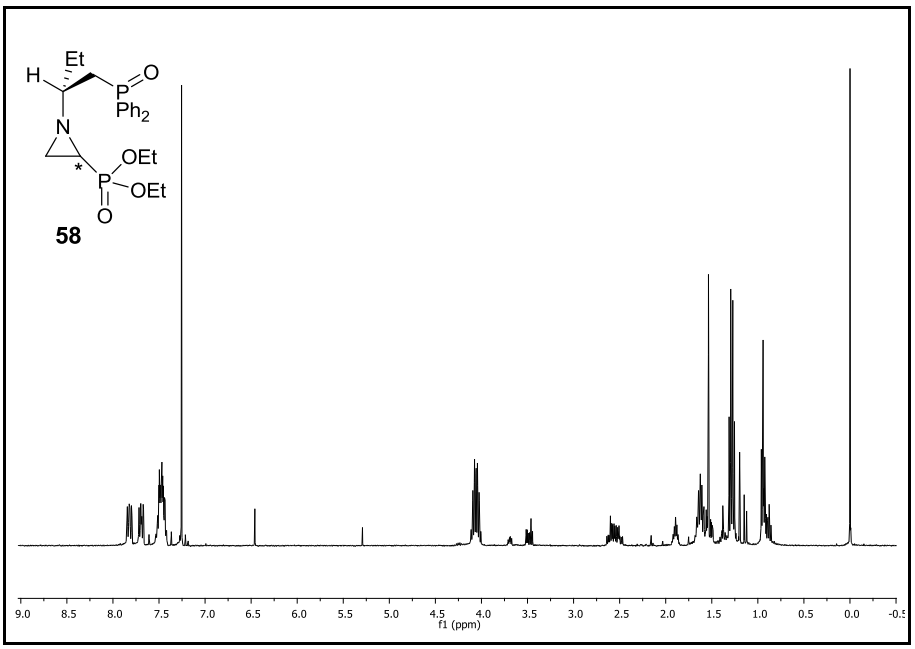



***Figure A.57*** *$^{1}$H-NMR spectrum of compound* ***58***

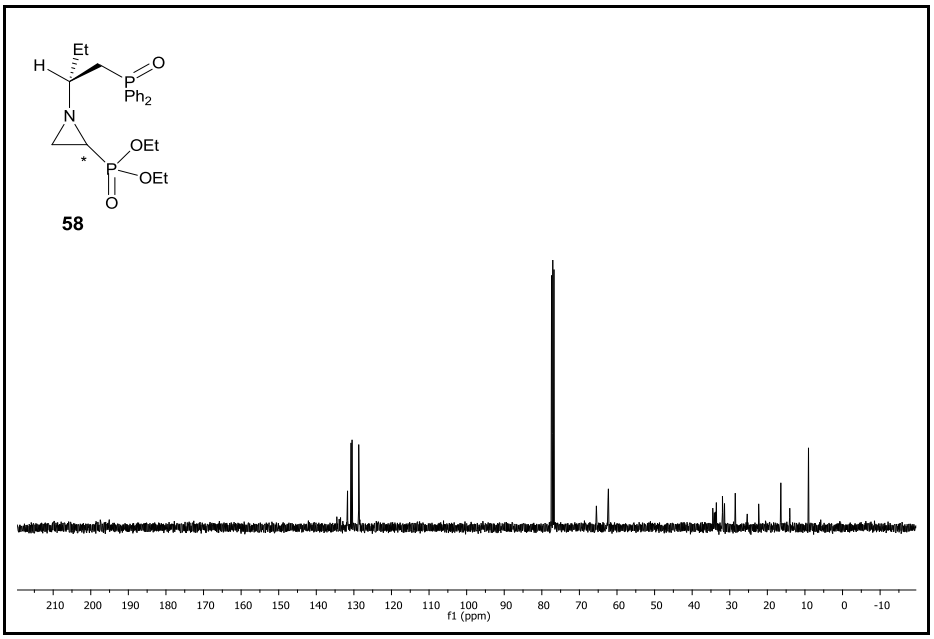



***Figure A.58*** *$^{13}$C-NMR spectrum of compound* ***58***

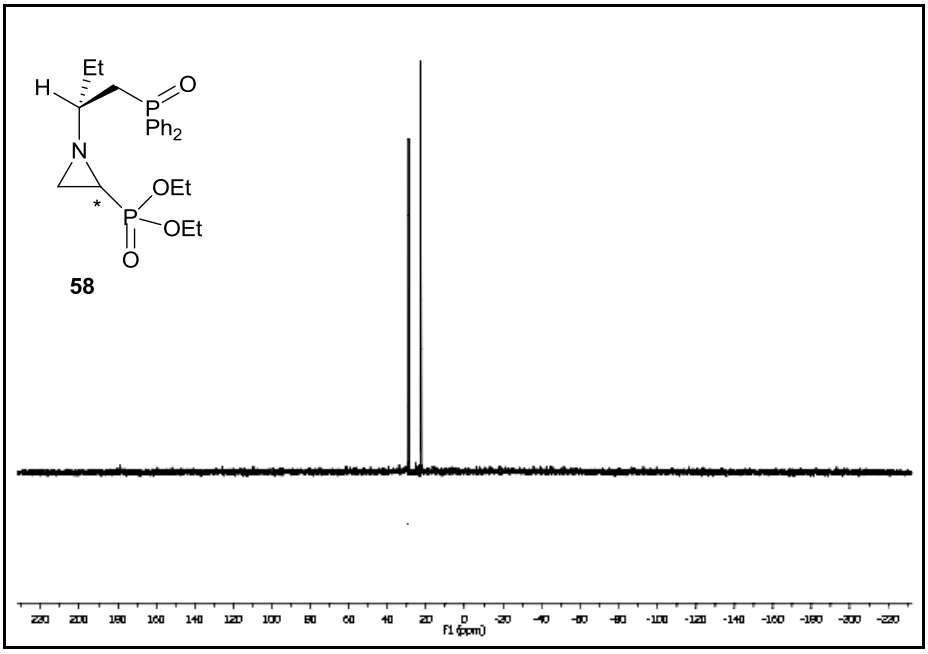



***Figure A.59*** *$^{31}$P-NMR spectrum of compound* ***58***

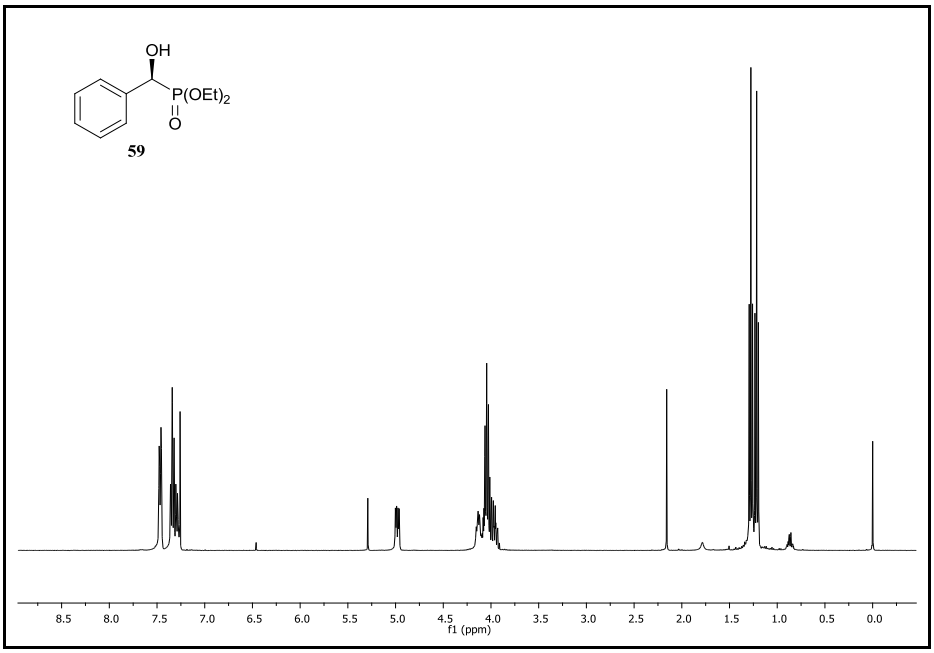



***Figure A.60*** *$^{1}$H-NMR spectrum of compound* ***59***

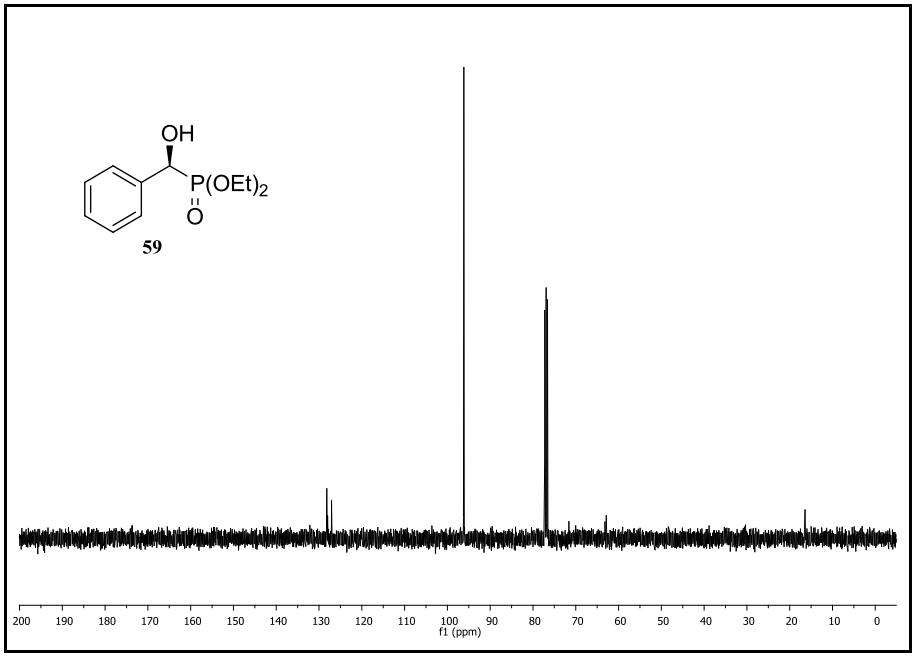



***Figure A.61*** *$^{13}$C-NMR spectrum of compound* ***59***

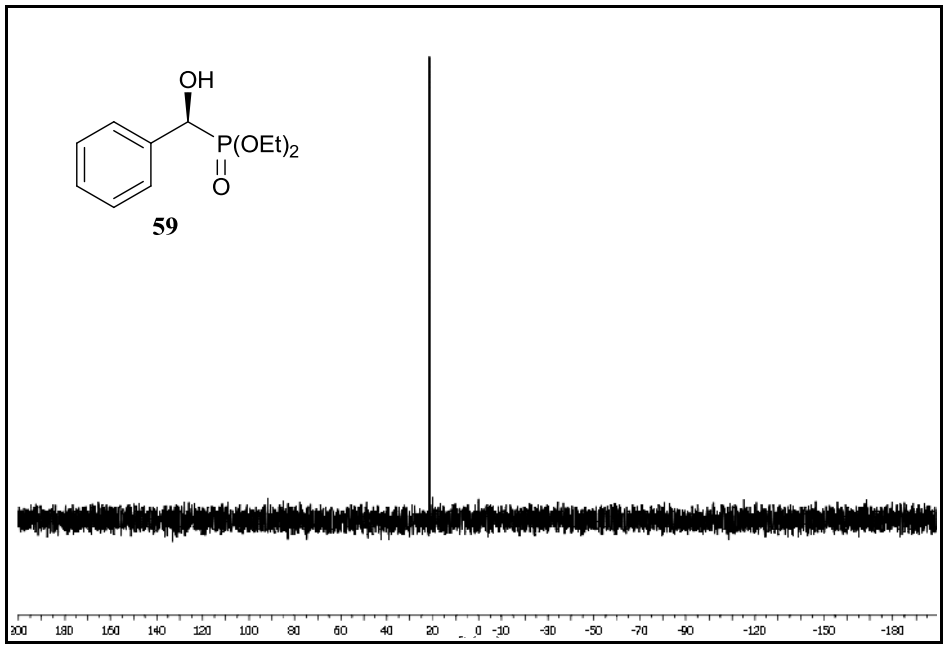



***Figure A.62*** *$^{31}$P-NMR spectrum of compound* ***59***

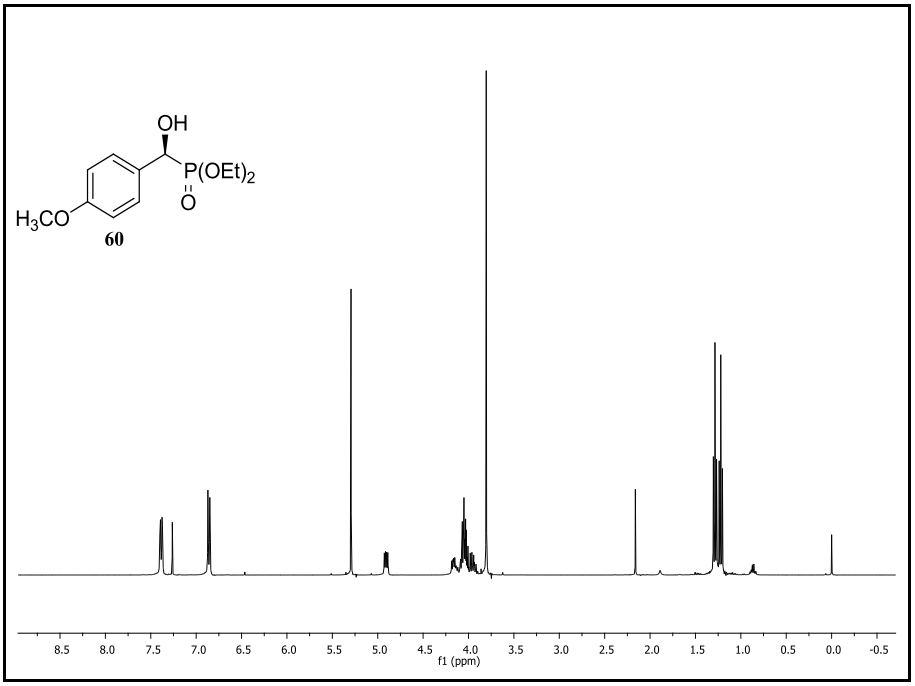



***Figure A.63*** *$^{1}$H-NMR spectrum of compound* ***60***

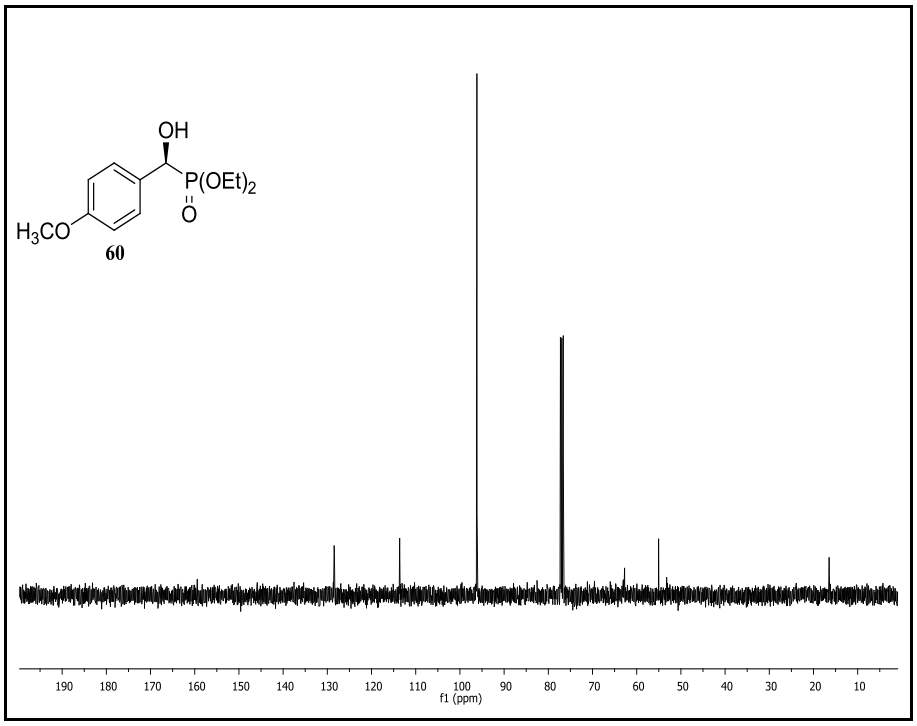



***Figure A.64*** *$^{13}$C-NMR spectrum of compound* ***60***

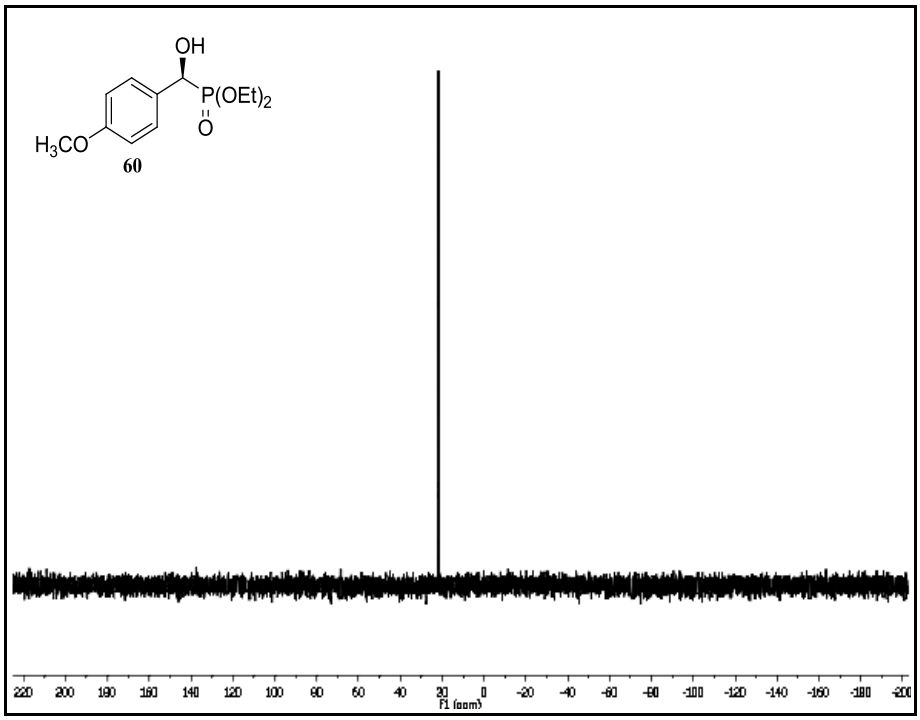



***Figure A.65*** *$^{31}$P-NMR spectrum of compound* ***60***

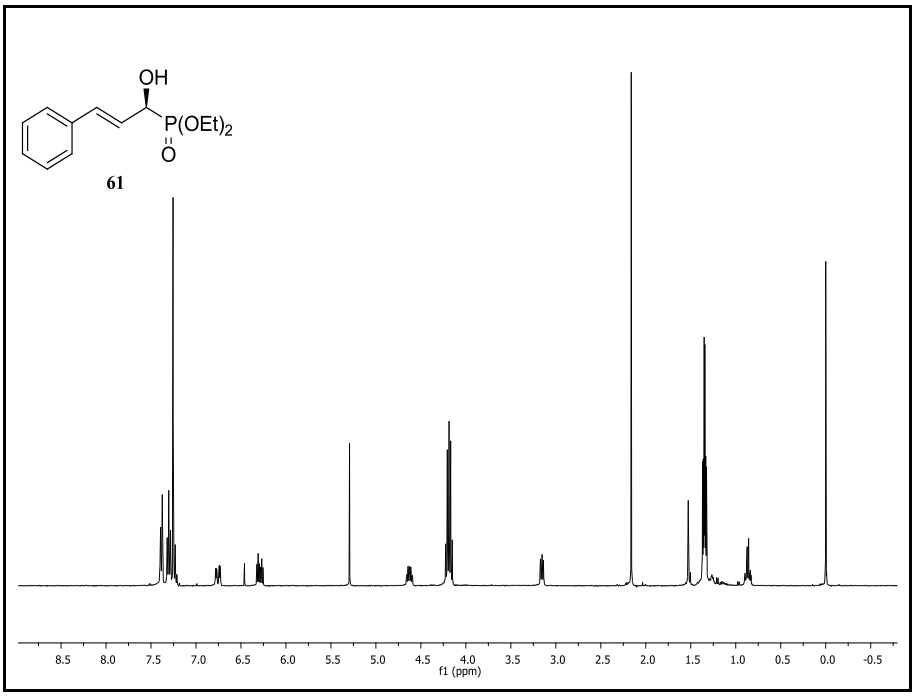



***Figure A.66*** *$^{1}$H-NMR spectrum of compound* ***61***

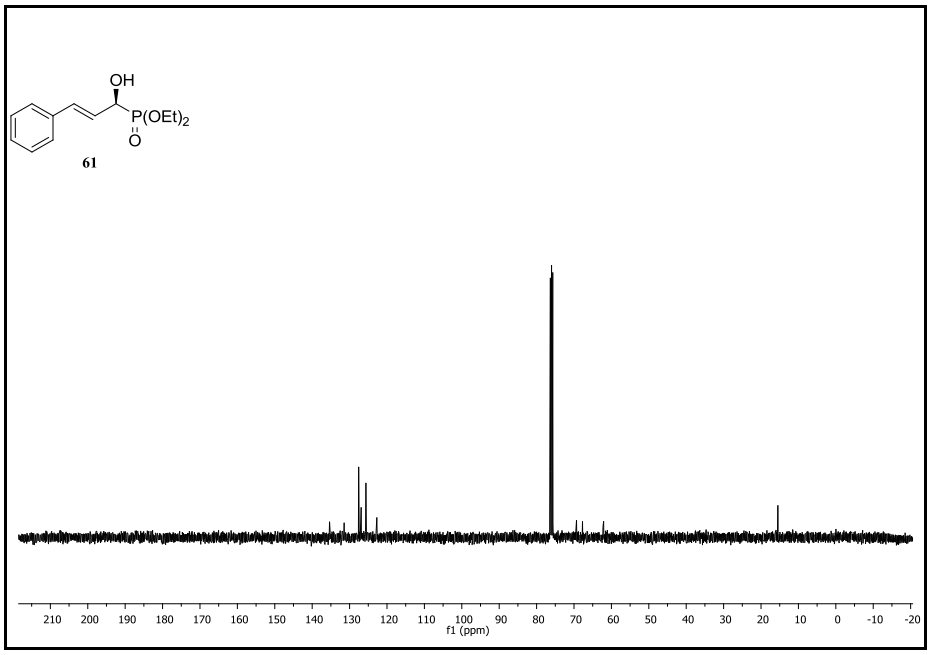



***Figure A.67*** *$^{13}$C-NMR spectrum of compound* ***61***

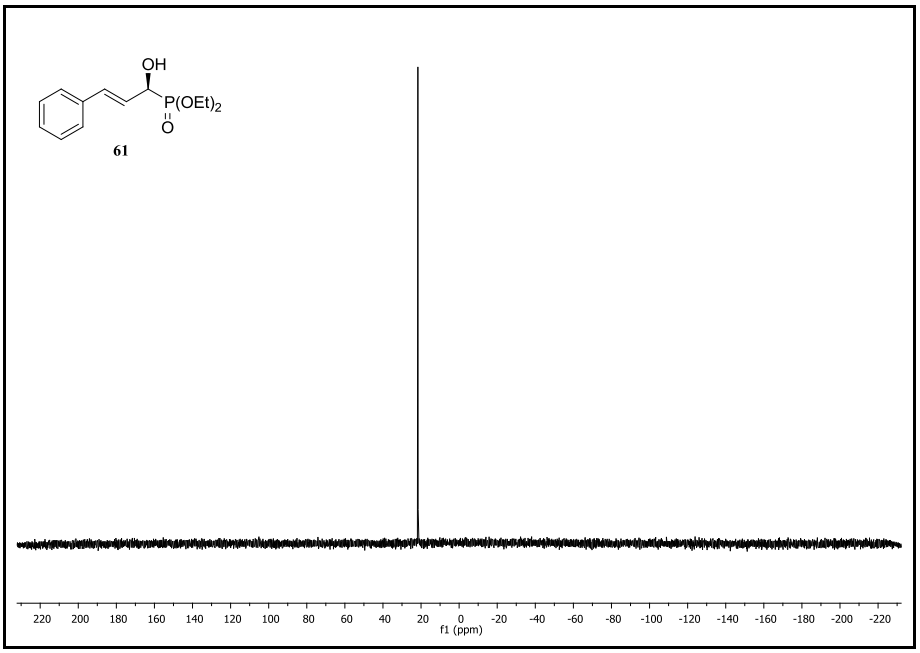



***Figure A.68*** *$^{31}$P-NMR spectrum of compound* ***61***

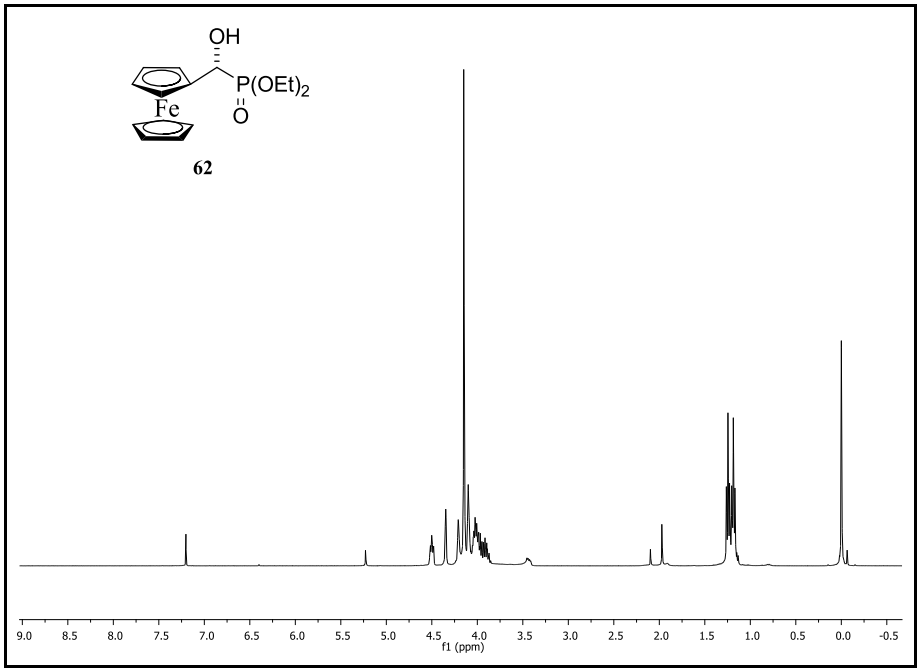



***Figure A.69*** *$^{1}$H-NMR spectrum of compound* ***62***

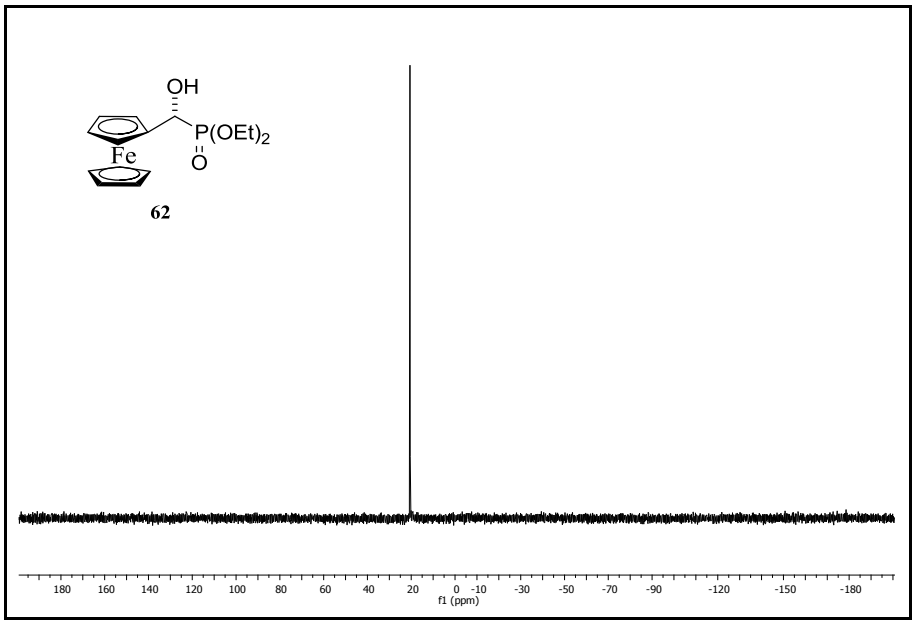
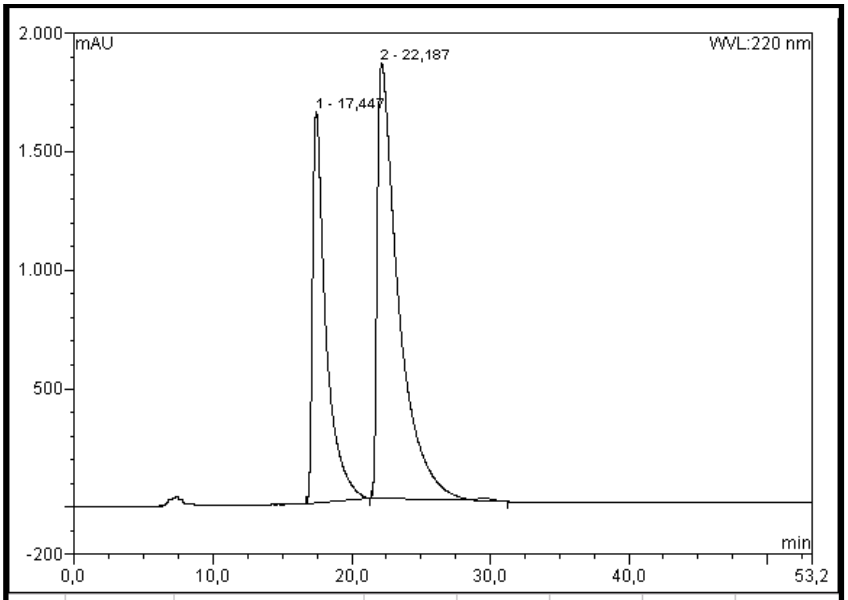
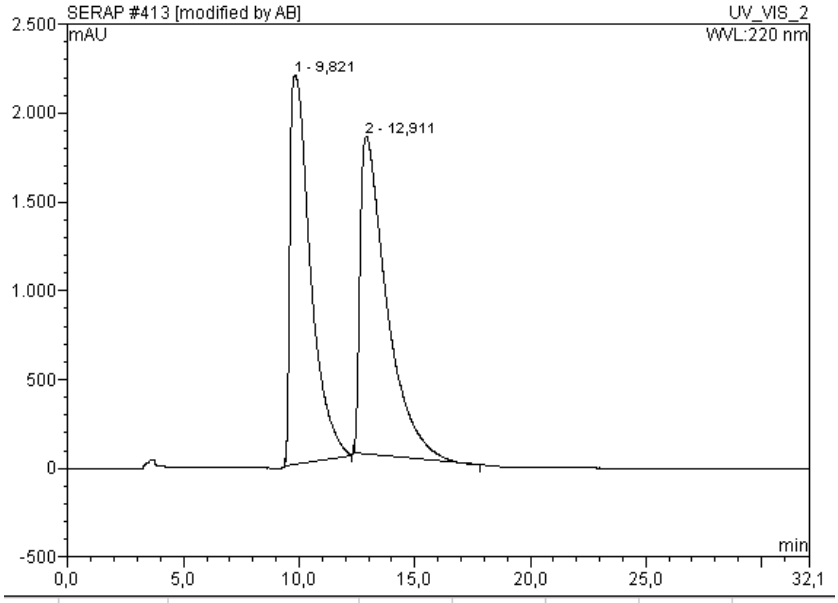



***Figure A.70*** *$^{31}$P-NMR spectrum of compound* ***62***



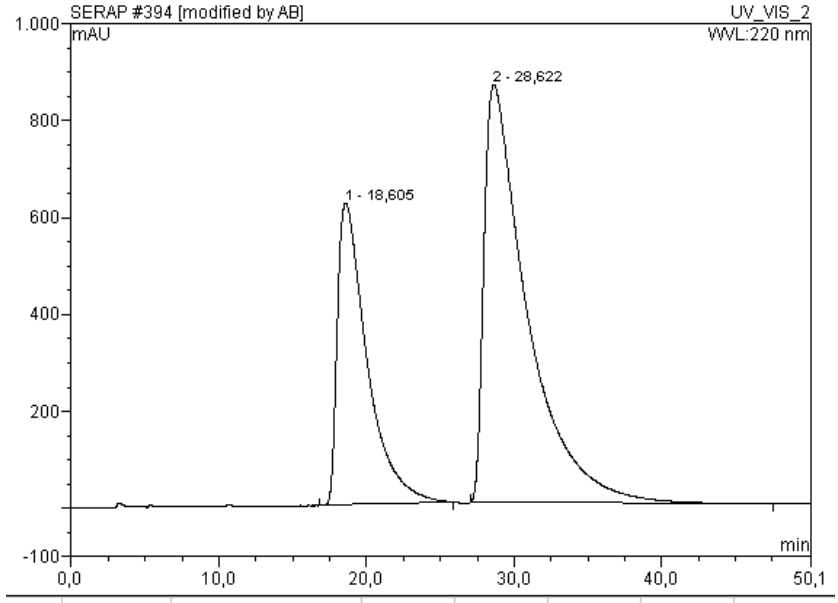

| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 17,45 | n.a. | 1653,693 | 1865,206 | 36,35 | n.a. | BMB* |
| 2 | 22,19 | n.a. | 1832,637 | 3265,433 | 63,65 | n.a. | BMB* |
| Total: | | | 3486,329 | 5130,639 | 100,00 | 0,000 | |

***Figure A.71*** *HPLC Chromatogram of compound* ***59***



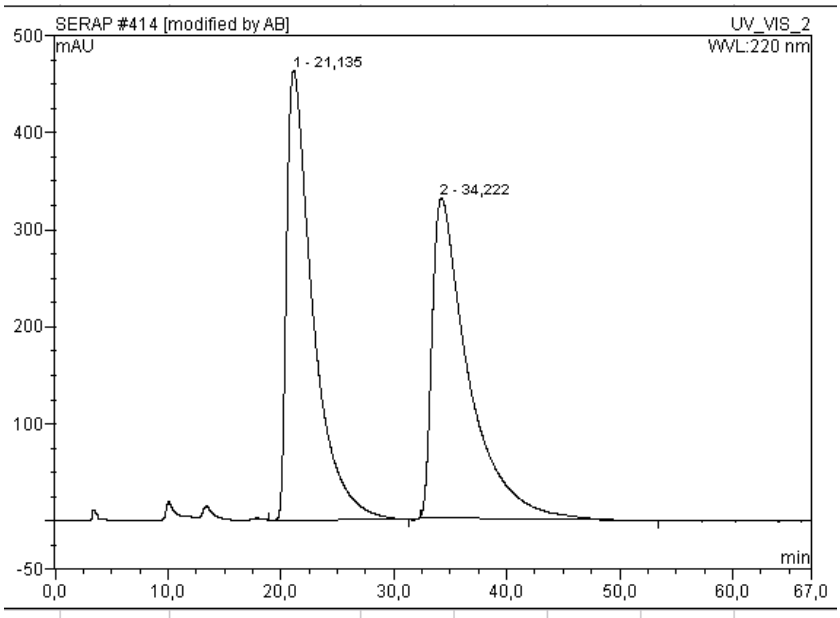

| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 9,82 | n.a. | 2188,255 | 2246,286 | 48,60 | n.a. | BMB* |
| 2 | 12,91 | n.a. | 1788,255 | 2375,751 | 51,40 | n.a. | BMB* |
| Total: | | | 3976,510 | 4622,038 | 100,00 | 0,000 | |

***Figure A.72*** *HPLC Chromatogram of racemic compound* ***59***



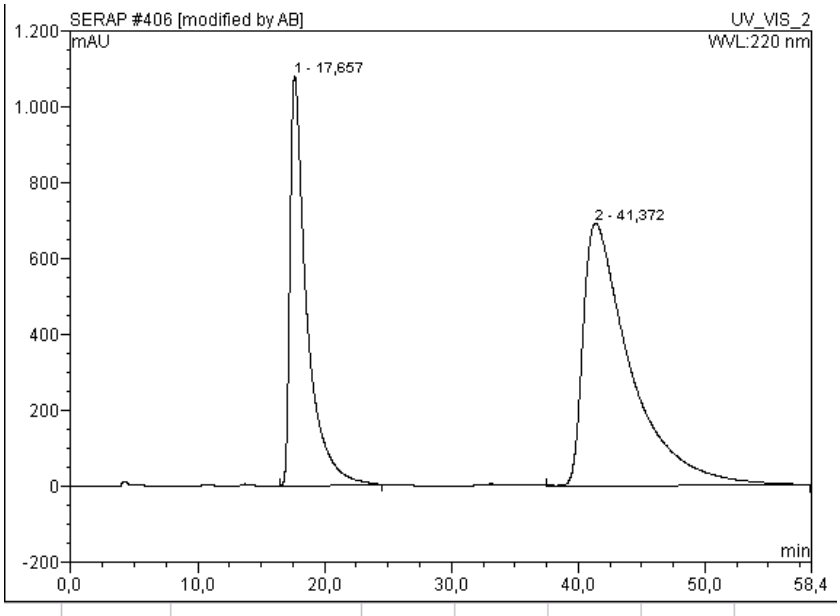

| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 18,61 | n.a. | 623,328 | 1454,951 | 33,25 | n.a. | BMB* |
| 2 | 28,62 | n.a. | 861,817 | 2920,820 | 66,75 | n.a. | BMB* |
| Total: | | | 1485,145 | 4375,772 | 100,00 | 0,000 | |

***Figure A.73*** *HPLC Chromatogram of compound* ***60***



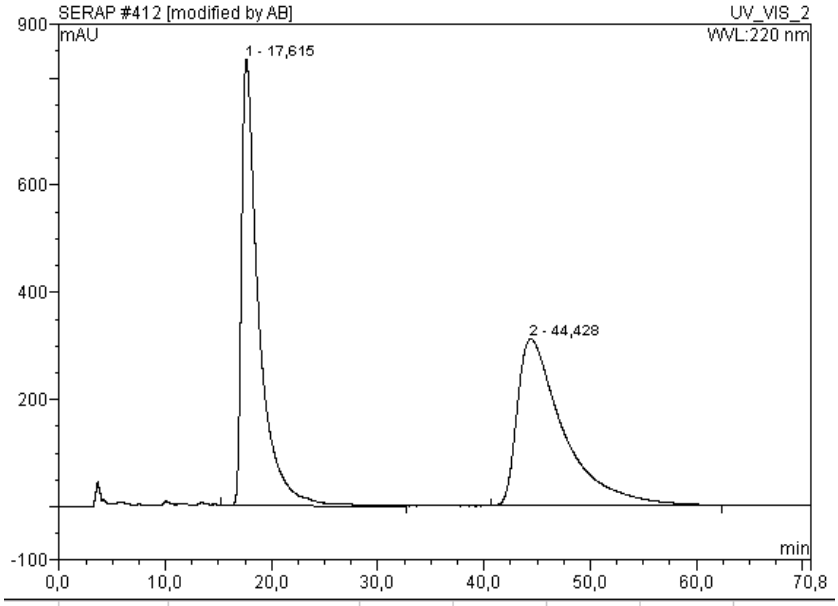

| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 21,13 | n.a. | 463,091 | 1240,970 | 50,35 | n.a. | BMB* |
| 2 | 34,22 | n.a. | 329,812 | 1223,719 | 49,65 | n.a. | BMB* |
| **Total:** | | | 792,902 | 2464,689 | 100,00 | 0,000 | |

***Figure A.74*** *HPLC Chromatogram of racemic compound* ***60***



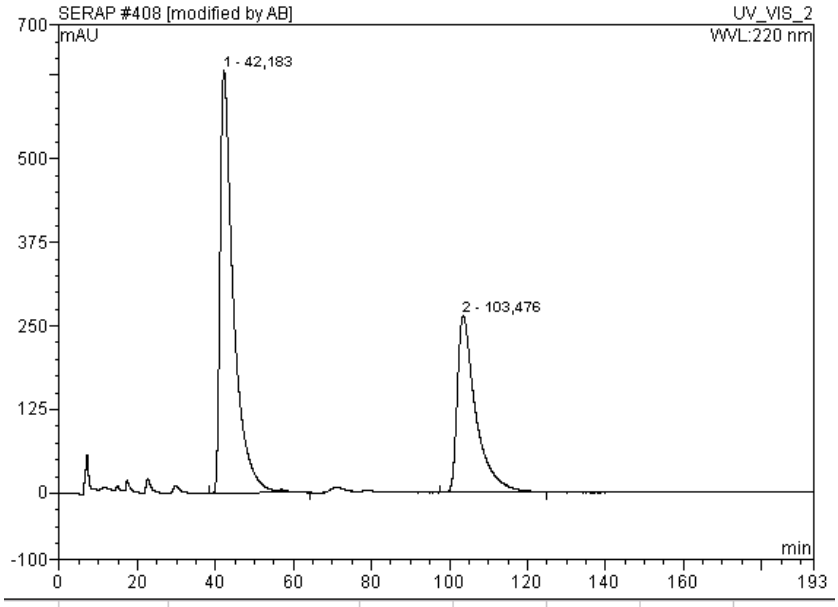

| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 17,66 | n.a. | 1078,199 | 1643,605 | 35,63 | n.a. | BMB* |
| 2 | 41,37 | n.a. | 690,223 | 2968,959 | 64,37 | n.a. | BMB* |
| **Total:** | | | 1768,422 | 4612,564 | 100,00 | 0,000 | |

***Figure A.75*** *HPLC Chromatogram of compound* ***61***



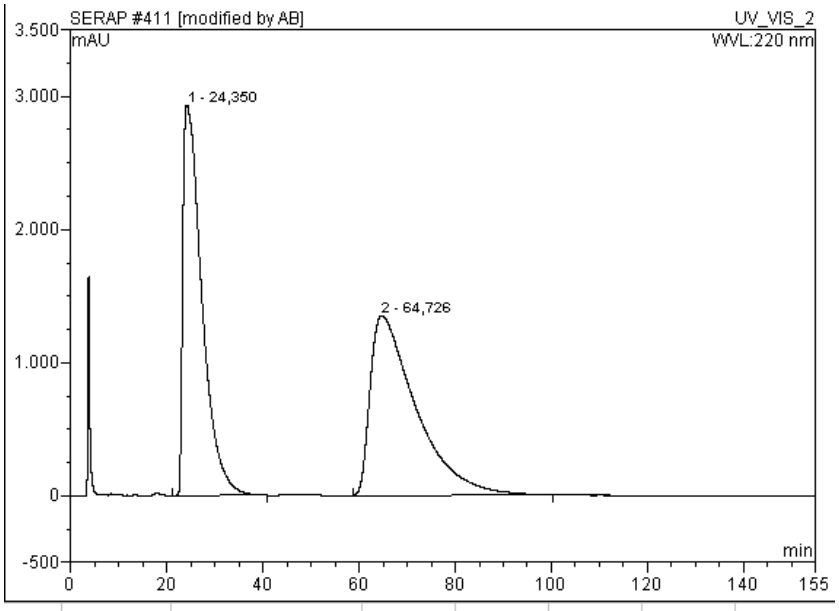

| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 17,62 | n.a. | 831,671 | 1557,041 | 49,85 | n.a. | BMB* |
| 2 | 44,43 | n.a. | 310,906 | 1566,529 | 50,15 | n.a. | BMB* |
| **Total:** | | | 1142,578 | 3123,570 | 100,00 | 0,000 | |

***Figure A.76*** *HPLC Chromatogram of racemic compound* ***61***




| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 42,18 | n.a. | 632,431 | 2519,534 | 63,49 | n.a. | BMB* |
| 2 | 103,48 | n.a. | 264,085 | 1448,936 | 36,51 | n.a. | BMB* |
| **Total:** | | | 896,516 | 3968,470 | 100,00 | 0,000 | |

***Figure A.77*** *HPLC Chromatogram of compound* ***62***




| No. | Ret.Time | Peak Name | Height | Area | Rel.Area | Amount | Type |
|---|---|---|---|---|---|---|---|
| | min | | mAU | mAU*min | % | | |
| 1 | 24,35 | n.a. | 2925,768 | ########## | 47,50 | n.a. | BMB* |
| 2 | 64,73 | n.a. | 1349,123 | ########## | 52,50 | n.a. | BMB* |
| **Total:** | | | 4274,891 | ########## | 100,00 | 0,000 | |

***Figure A.78*** *HPLC Chromatogram of racemic compound* ***62***