SYNTHESIS OF CHIRAL AZIRIDINYL PHOSPHONATES, THEIR BIOLOGICAL ACTIVITIES AND ORGANOCATALYTIC EFFECT OF THEIR PHOSPHONIC ACID DERIVATIVES

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SYNTHESIS OF CHIRAL AZIRIDINYL PHOSPHONATES, THEIR BIOLOGICAL ACTIVITIES AND ORGANOCATALYTIC EFFECT OF THEIR PHOSPHONIC ACID DERIVATIVES

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ABSTRACT

SYNTHESIS OF CHIRAL AZIRIDINYL PHOSPHONATES, THEIR BIOLOGICAL ACTIVITIES AND ORGANOCATALYTIC EFFECT OF THEIR PHOSPHONIC ACID DERIVATIVES

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Aziridines are important three-membered heterocyclic ring systems in synthetic organic chemistry and medicinal chemistry. They can be used as the building blocks for the synthesis of amino acids, amino alcohols, pyrrolidines, pyrroles, lactams, and oxazoles. Aziridinyl phosphonates are attracting more attention in recent years. They are the precursors of α-amino phosphonates that find applications such as enzyme inhibitors and antibacterial agents. One of the methods for the synthesis of these compounds is the Gabriel–Cromwell reaction. In this thesis, it was planned to synthesize new chiral aziridinyl phosphonates using Gabriel-Cromwell reaction and evaluate their biological activities. In addition, it was also planned to convert them into their phosphonic acid derivatives to test their effect on enantioselectivity as organocatalyst for the synthesis of some organic compounds.

Key words: Aziridinyl phosphonates, phosphonic acids, organocatalysts, biological activity

ÖZ

KİRAL AZİRİDİNİL FOSFONATLARIN SENTEZİ, BİYOLOJİK AKTİVİTELERİ VE FOSFONİK ASİT TÜREVLERİNİN ORGANOKATALİTİK ETKİLERİ

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Aziridinler üçlü halkaya sahip sentetik organik kimya ve ilaç kimyası için önemli heterohalkalı bileşiklerdir. Bu bileşikler amino asitlerin, amino alkollerin pirolidinlerin, pirollerin, lactamların ve okzasollerin sentezi için önemli yapı taşlarıdır. Son yıllarda aziridinil fosfonatlar oldukça dikkat çekmeye başlamıştır. Bu bileşikler α-aminofosfonatların ana maddesisi olarak bazı enzimleri inhibe edebilmekte ve antibakteriyel özellik göstermektedir. Bu bileşiklerin sentezi için kullanılan yöntemlerden biri Gabriel-Cromwell tepkimesidir. Bu tezde kiral aziridinil fosfonatların Gabriel-Cromwell tepkimesiyle sentezi ve biyolojik aktivitelerinin ölçülmesi planlanmıştır. Bunlara ek olarak bu yapıların fosfonik asit türevlerine dönüştürülerek bazı organik tepkimelerde organokatalizör olarak enantiseçiciliğe etkilerinin araştırılması hedeflenmiştir.

Anahtar kelimeler: Aziridinil fosfonatlar, fosfonik asitler, organokatalizörler, biyolojik aktivite

To my lovely "Jojoshka"...

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TABLE OF CONTENT

LIST OF FIGURES

FIGURES

LIST OF SCHEMES

SCHEMES

LIST OF TABLES

TABLES

CHAPTER 1

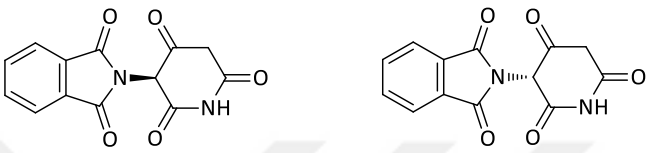
INTRODUCTION

1.1 Importance of chirality

The world is chiral.[1] Most of the organic compounds isolated from living cells are chiral, i.e. they have no symmetry element within the molecule. The chiral molecules can be found in their enantiomeric or diastereomeric forms, which are non-superimposable mirror images of each other, i.e. four different groups connected to the same carbon center have different alignment. Enantiomers have different properties not only in terms of rotating plane polarized light, but also in terms of biological activity, reactivity with chiral reagents, and even taste and smell. Depending on their absolute configurations, enantiomers can have different smell like limonene; one enantiomer smells like oranges and other like lemons. Enantiomers of phenylalanine taste as bitter and sweet, while those of carvone taste like spearmint and caraway.[1]

We can differentiate enantiomers through our receptors which are also chiral. This shows the importance of chirality and the absolute configurations of these compounds for the biological systems. Considering about the biological systems, enantiomers of the chiral molecules are also important for pharmaceutical industry. Since drugs should match the chiral receptors that we have in the body. In some cases, one enantiomer can be harmful, while the other enantiomer is useful. For instance, in the early 1960s, the drug for morning sickness for pregnant women, thalidomide seemed to cause defects in the limbs of the women who used that drug. The theory arisen that one enantiomer of

thalidomide was beneficial whereas the other caused birth defects.[2] Later it has been proved that *S*-isomer of thalidomide (**1**) shows teratogenic activity, and *R*-isomer of it (**2**) used as seductive[3] (Figure 1).



(*S*)-Thalidomide
1

(*R*)-Thalidomide
2

Figure 1. *Thalidomide enantiomers.*

This theory had brought all the pharmaceutical companies to a need of pure enantiomers of the drugs, which made asymmetric synthesis play a major role in pharmaceutical industry, biochemistry and organic chemistry.

1.2 Asymmetric synthesis

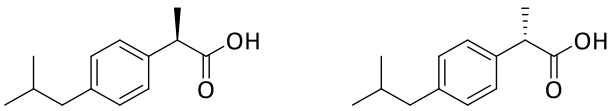
Asymmetric synthesis is a reaction or sequence of reactions that favors the formation of one configuration of one or more stereogenic centers over the other configuration.[1] So the aim of asymmetric synthesis is obvious: to produce relative or absolute configuration of one or more stereogenic centers.

In order to obtain pure enantiomer of a chiral compound, there are three ways to design the reactions (or sequence of reactions) to rich the target chiral molecule of optical purity: resolution, "chiral pool" synthesis, asymmetric induction.

1.2.1 Resolution

In this type of synthesis, a pro-chiral starting material is taken and after a reaction the formed racemic product, which is the formation of both enantiomers/diastereomers in equal amounts, is separated into its enantiomers/diastereomers by the purification techniques like chromatography. This makes the technique time consuming and like in the

case of ibuprophen (Figure 2), where *S*-isomer (**4**) is pain reliever and the *R*-isomer (**3**) is inactive, wasting half of the starting material.[3]



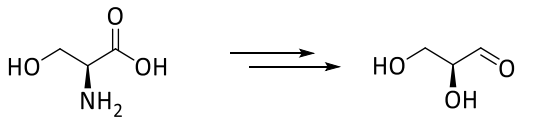
(*R*) Ibuprophen
3

(*S*) Ibuprophen
4

Figure 2. *Ibuprophen enantiomers.*

1.2.2 "Chiral pool" synthesis

In this type of synthesis, a chiral starting material is taken and used directly to synthesize the final product with no change of chirality of the starting stereogenic center. Here the term "chiral pool" is used for supplied enantiopure starting material. However, this type of synthesis is not convenient for industrial and pharmaceutical utilization, due to the lack of diversity of chiral starting materials, as well as the availability of the enantiomers of desire. However, there are still a large variety of natural chiral amino acids, carboxylic acids and monosaccharide that are used as the chiral pool for the target molecule with the same stereogenic center. For instance, L-serine (**5**), readily available amino acid, can be used as a starting material in a synthesis of L-glyceraldehyde (**6**), non-natural sugar (Scheme 1).



L-Serine
5

L-Glyceraldehyde
6

Scheme *1*. *Synthesis of L-glyceraldehyde from L-serine*.

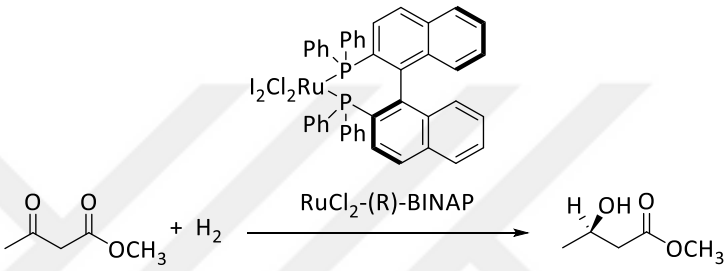
1.2.3 Asymmetric induction

Asymmetric induction is the main route for modern asymmetric synthesis, in which achiral molecule is transformed into a chiral product with a help of a chiral auxiliary or a catalyst. The energy difference for the formation of enantiomers or diastereomers favor some enantiomer or diastereomer over the other one. The purity of the product formed by this method was reasonably high; therefore, the chromatographic separation is not required, which makes this method to be major field of attention for academic, pharmaceutical and industrial studies.[1] For the past few decades, scientists have developed many different ways for asymmetric synthesis by the terms of induction. One of these methods would be using chiral solvents, i.e. dissolving the molecules in a chiral environment. This technique is very expensive, and therefore is not very useful.

One other method is to use chiral auxiliaries. In this method the target chiral molecule is formed by the covalent attachment of the pro-chiral starting material to a chiral auxiliary. The chiral auxiliary blocks one side of the molecules as a result the substrate attacks/adds from the other side. This leads to the formation of one enantiomer over the other one. Although this method is very powerful, the auxiliary has to be attached to the substrate at the beginning of the synthesis and removed from the product at the end of the synthesis. It adds two extra steps to the synthesis; if it is not recoverable, this technique may not be cost-efficient.[4]

The last but not the least way to synthesize enantiopure compound is using chiral catalyst, which is ideal solution for the limitations of the other methods. It requires catalytic amount of chiral material which makes it very cost-efficient and therefore more useful in industrial approach. In last decades, many chiral catalysts have been developed for many different types of reactions. Among the catalysts employed in asymmetric reactions, chiral metal complexes provide good enantioselectivity in a large range of the reactions.[5] Disadvantage of these catalysts is the limitation of metals by the drug companies. The best known industrial processes catalyzed by chiral metal-catalysts are asymmetric hydrogenation and epoxidation reactions. The most common example to

chiral metal complex catalysts is Noyori's BINAP-Ru (II) complex[2] that allows a very high enantiomeric excess, and works with a variety of functionalized olefins and ketones (Scheme 2). For this work, Noyori got a Noble Prize in 2001, which he shared with Shapless and Knowles.[6]



Scheme 2. *Stereoselective ketone reduction with Noyori's chiral metal complex.*

Other type of catalysts for asymmetric synthesis is biocatalysts. The enzymes are prepared from an organism and optimized by selective mutation or by evolutionary methods to interact in the reaction medium as in a living organism. Although it is a green method, the number of reactions catalyzed by enzymes is very limited. The third catalytic method is the use of organocatalysts. In organocatalysis, small and enantiomerically pure organic compounds are designed to mimic the enzyme activity. It has several advantages over other types of catalysis. Since they do not have transition metal in their structure it makes them very useful for the reactions that do not tolerate the metal, like in pharmaceutical area. Besides that, organocatalysts are robust, inexpensive, readily available and mostly do not require inert conditions, such as inert atmosphere, dry solvents, low temperature, etc.[7] For a different variety of reactions, many different organocatalysts have been synthesized by the scientists of all parts of the world. Common organocatalysts are shown in Figure 3. L-proline (**7**) is used for aldol type reactions by iminium ion or enamine pathways.[8] The D-Fructose derived ketone **8** can be used as oxygen source in the asymmetric epoxidation of a wide range of olefins with persulfate.[9]

Oxazolidinone **9** is a very powerful catalyst for Diels-Alder reaction of α,β-unsaturated aldehydes.[10] Quinine **10** is widely used as chiral base or a chiral nucleophilic catalyst.[11] Thiourea catalysts**11**, act like urea, and used in hydrocyanation of imines.[12]

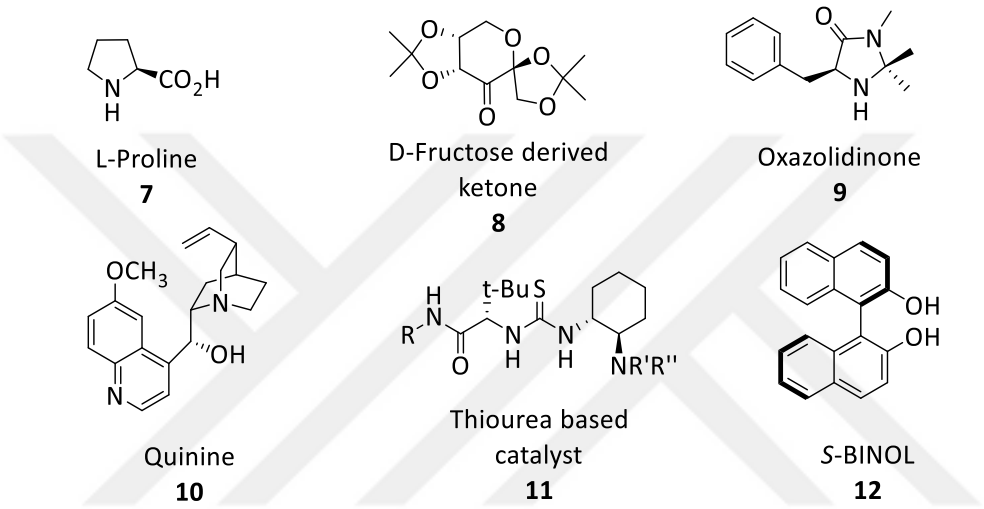
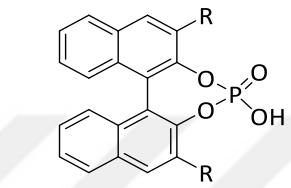


Figure 3. *Typical organocatalysts*

The BINOL **12**, different from all the other catalysts listed, has a C2 symmetry and expluatates its axial chirality to achieve very high enantioselectivity. But more importantly, it has arisen a whole new group of catalysts that have BINOL skeleton in the structure. Until 2004 the BINOL derivatives were used as metal complexes with high success, like Noyori's catalyst (Scheme 2). However, after Terada and Akiyama have independently prepared new metal free BINOL phosphoric acid **13**,[13,14] many attention was appealed to it, since it was one of the organocatalysts that activate the reaction via hydrogen bonding (Figure 4).

Brønsted acid, which are strong proton donors, have been proven to be very efficient in activating carbonyl compounds and imines.[15] Mechanistically, the LUMO of the electrophile is lowered due to the protonation, and therefore the reaction is activated

for nucleophile to react.[16] BINOL-derived phosphoric acid **13** has proven itself highly versatile for past decade. Due to its Brønsted acidity, it was able to perform a variety of asymmetric transformations with operational simplicity and mild conditions.[16]

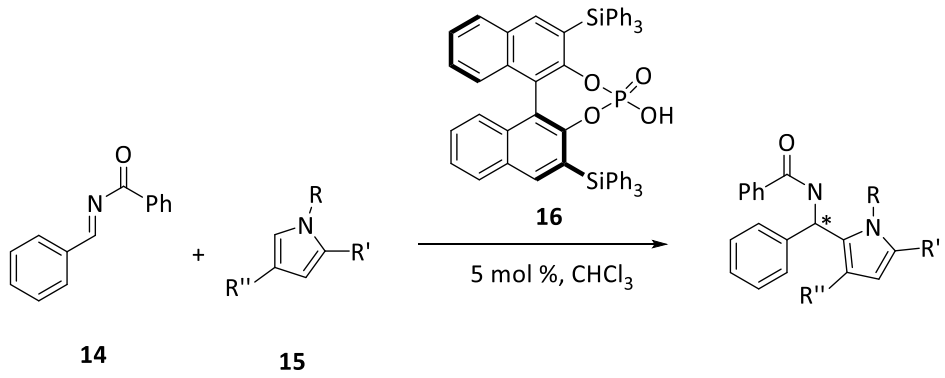


BINOL-derived phosphoric acid
13

Figure 4. *Structure of BINOL phosphoric acid.*

The BINOL phosphoric acid and its derivatives have been widely used in various Friedel-Crafts alkylation reactions providing products in good yields and stereoselectivities.[17,18] The asymmetric Friedel-Crafts alkylation reaction is very efficient reaction for synthesis of the optically pure compounds.[18] Particularly the Friedel-Crafts alkylation of indole and pyrrole derivatives with nitroalkenes and imines are the most powerful method for C-C bond formation, in preparation of natural and synthetic compounds with outstanding biological activities.[17,19]

Antilla and his coworkers has reported that Friedel-Crafts reaction of pyrrole derivatives **15** with acyl imines **14** showed excellent enantioselectivity up to 99% and yield up to 97%, with the help of phosphoric acid organocatalyst **16**[20] (Scheme 3).



Scheme 3. *Asymmetric Friedel-Crafts reaction of pyrrole with N-acyl imine.*

Inspired by the successive applications of the BINOL phosphoric acid, we decided to design new phosphonic acid based aziridinyl phosphonates organocatalysts and synthesize them in our group.

1.3 Aziridines

The reason why the aziridine was chosen as main part of the skeleton of the target chiral organocatalyst is due to its importance for living organisms. Aziridines are the smallest heterocyclic compounds having nitrogen (Figure 5).

Figure 5. *Structure of aziridine.*

Aziridines are important in organic chemistry due to the fact that they are building blocks of many biological important compounds such as miraziridine **17**, ficellomycin **18**, azinomycin B **19** and azicemicins A and B **20** (Figure 6).[21] This type of compounds have very essential biological activity. For instance, miraziridine **17** is the natural product isolated from the marine sponge. This molecule is very important for human organism since it has four different active sides and therefore function as four different inhibitors.[22]

The ficellomycin **18** is a promising new basic antibiotic which is expected to fight resistant strains of bacteria.[23] Similarly, azicemicins A and B **20** are new antimicrobial agents that show inhibition against gram-positive bacteria and mycobacteria.[24] The other complex natural compound Azinomycin B[25] **19** is a new antibiotic that shows antitumor activities (Figure 6).

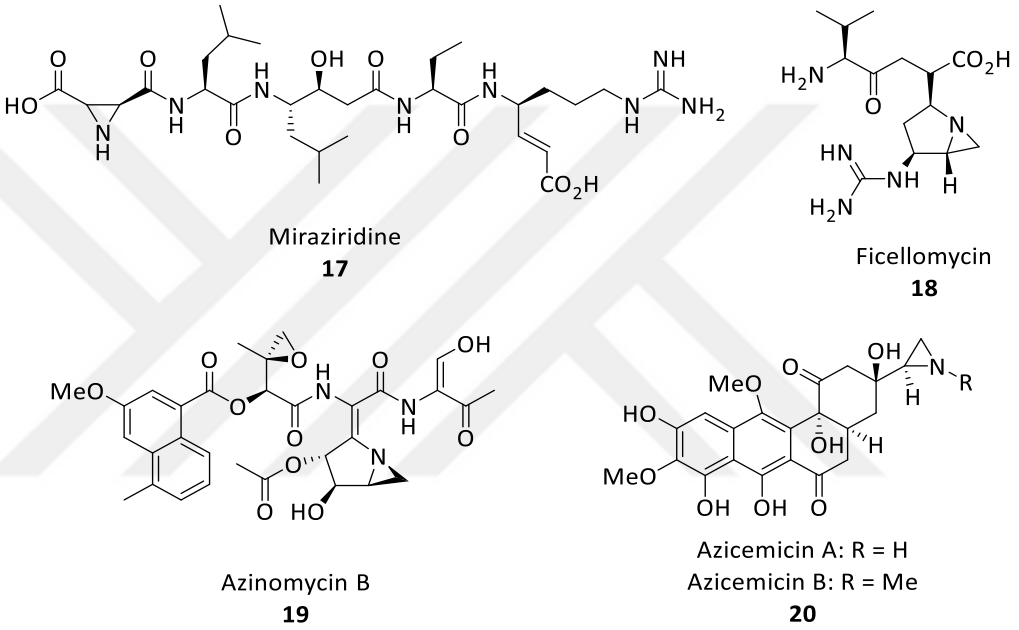
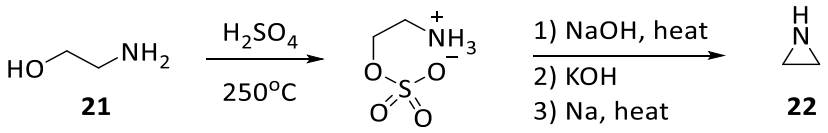


Figure 6. *Important natural products containing aziridine ring.*

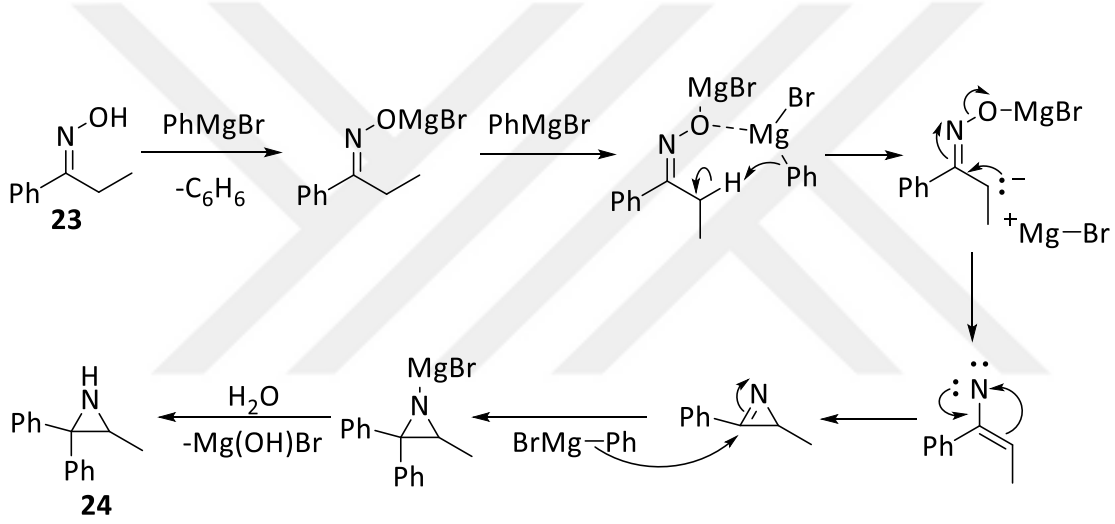
Besides, aziridines are also crucial precursors for the synthesis of more complex molecules. In the synthetic applications, the unique structure with ring strain energy of 26.8 kcal/mol is an advantage for nucleophilic attack by forming ring opened products or intermediates.[26] In various transformations, aziridines can demonstrate very rare chemical selectivity, regioselectivity or stereoselectivity.[27]

Within decades, different methods have been developed for the synthesis of aziridines. The oldest one is the Wenker's synthesis[28] which is the cyclization of an amino-alcohol **21** to aziridine **22** by using concentrated acid (Scheme 4).



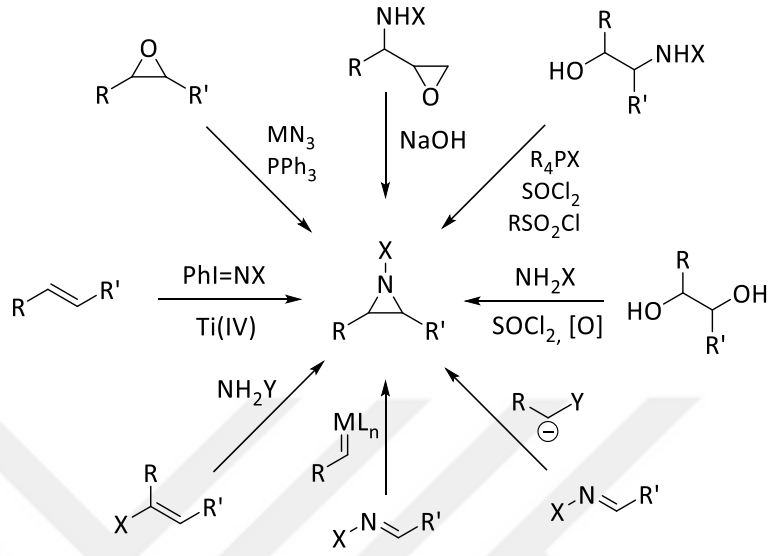
***Scheme* 4.** *Wenker's synthesis of aziridines*

Another method is the Hoch-Campbell synthesis,[29] which converts oxime **23** to aziridine **24** by Grignard reagents (Scheme 5).



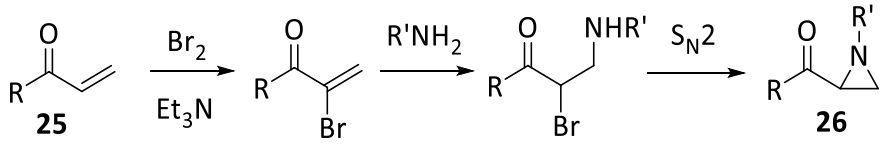
Scheme 5. *Hoch-Campbell synthesis.*

Some other methods for aziridine synthesis are from the epoxides using azides of different metals, from amino-epoxides using bases. It is also possible to prepare different derivatives of aziridines from amino alcohols and diols using thionyl chloride. Furthermore, three membered ring with nitrogen atom can be formed from imines, using different ligands or nucleophiles, and by addition of nitrogen to alkenes. The summary of the traditional ways of aziridine synthesis is shown in Scheme 6.[27,30]



Scheme 6. *Synthesis of aziridine derivatives.*

Aziridines can also be prepared from α,β-unsaturated carbonyl compounds **25** by using the modified Gabriel-Crowmell reaction.[31] First α,β-unsaturated carbonyl compound is treated with molecular bromine then dibromo-carbonyl compound undergoes HBr elimination with the help of triethylamine. Followed by addition of primary amine S_N2 reaction leads to ring closure to produce aziridine **26** (Scheme 7).



Scheme 7*. Gabriel-Crowmell reaction to form aziridines.*

1.4 Aim of the work

Aziridine based compounds have appealed interest for many years due to their easy transformations into various compounds. Biologically important compounds having aziridine ring have also been reported in literature. Our group have synthesized and measured the biological activities of racemic aziridinyl phosphonates against bacteria. In this thesis, we aimed to synthesize enantiopure derivatives of aziridinyl phosphonates and investigate biological activities against bacteria and fungus. In doing so, we wanted to find out whether there is a significant difference in biological activities of the enantiomers. We also aimed to study their potential as organocatalysts by converting them into their phosphonic acid derivatives.

For the synthesis of aziridinyl phosphonates, we used the same method developed by our group which starts from α-tosylated vinyl phosphonate and chiral primary amines. This method can also be called as modified Gabriel-Cromwell reaction. For the conversion of these compounds into their phosphonic acid forms, we planned to use simple basic hydrolysis.

CHAPTER 2

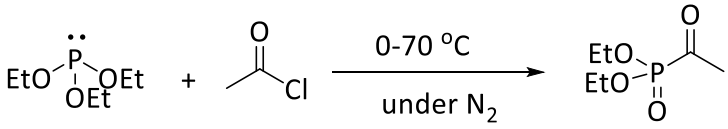
RESULTS AND DISCUSSION

2.1 Synthesis of aziridinyl phosphonates

In this study, aziridines were synthesized by the modified Gabriel-Crowmell reaction that has been developed by our group.[32] This synthesis starts with Michael-Arbuzov reaction of nucleophilic phosphite and electrophilic acetyl halide. The product of this reaction, acetyl phosphonate, can easily be converted to α-tosylated vinyl phosphonate. Tosylate group serves as a good leaving group during aziridine formation step where bromide is used in original Gabriel-Crowmell reaction.

2.1.1 Michael-Arbuzov reaction

The Michael-Arbuzov reaction was carried out between triethyl phosphite (**27**) and acetyl chloride (**28**) under inert atmosphere at 0°C. The product, acetylphosphonate **29** was obtained in 87% yield after distillation (Scheme 8).

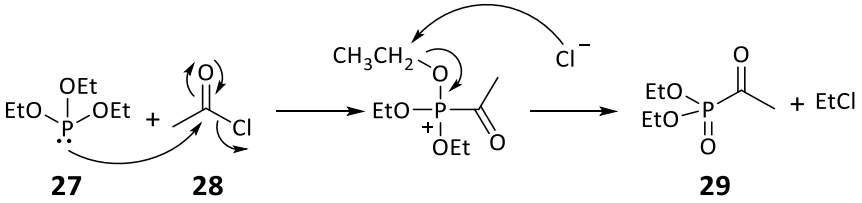


27 **28** **29**

Scheme 8*. Synthesis of acetylphosphonate.*

Michael-Arbuzov reaction is taking place as shown in Scheme 9. The reaction starts with nucleophilic attack of triethylphosphite (**27**) to carbonyl carbon of acetyl

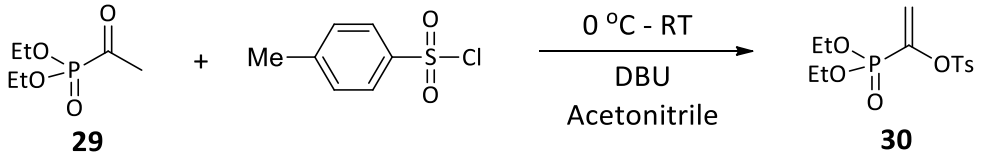
chloride (**28**). Elimination of chloride leads to the formation of acetyl phosphonate after the formation of ethyl chloride as the side product.



Scheme 9. *Mechanism of Michael-Arbuzov reaction.*

2.1.2 Synthesis of α-tosylated vinyl phosphonate

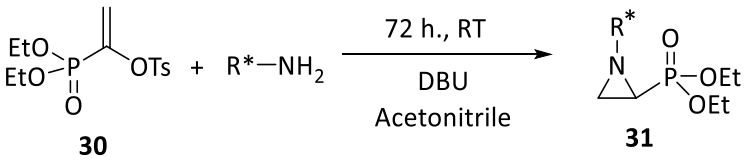
For the synthesis of α-tosylated vinyl phosphonate **30**, acetylphosphonate **29** was treated with *p*-toluenesulfonyl chloride in the presence of DBU in acetonitrile as shown in Scheme 10.



Scheme 10*. Synthesis of α-tosylated vinyl phosphonate.*

2.1.3 Synthesis of aziridinyl phosphonate derivatives

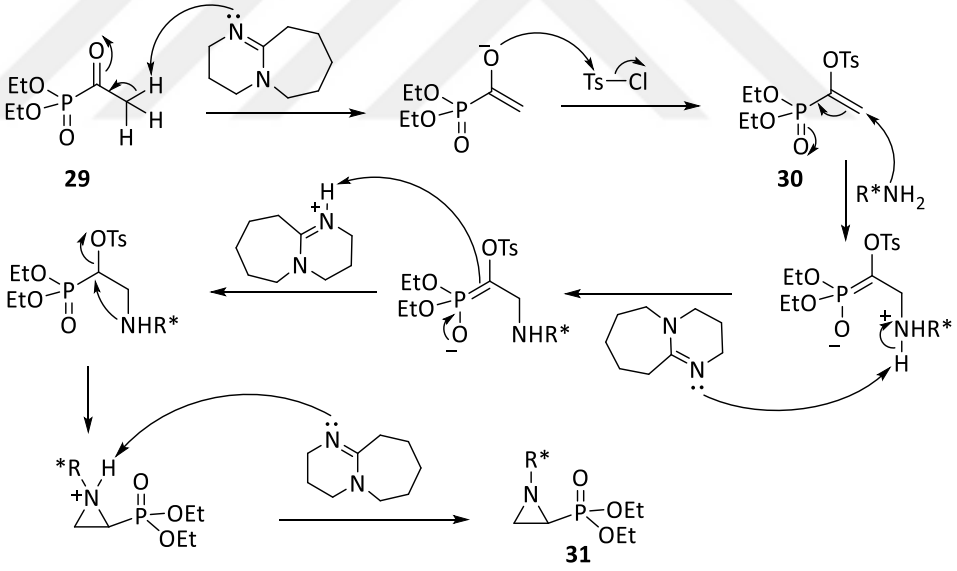
Aziridinyl phosphonates were synthesized by the reaction of α-tosylated vinyl phosphonate **30** with chiral amines in the presence of DBU in acetonitrile (Scheme 11).



Scheme 11*. Synthesis of aziridine phosphonates.*

The aziridine phosphonates **31** have two stereogenic centers: one with fixed configuration originated from chiral amine, the other one is a newly formed stereogenic center on the aziridine ring.

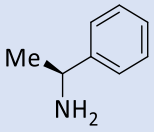
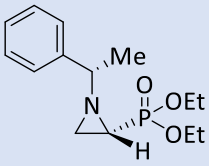
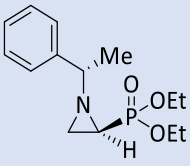
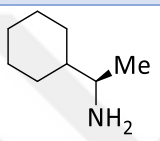
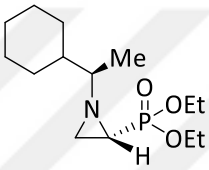
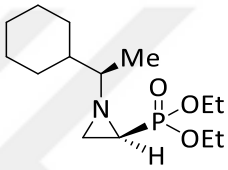
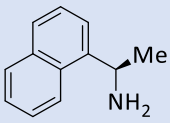
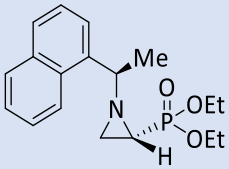
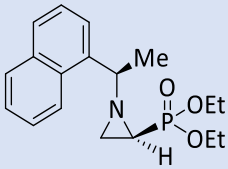
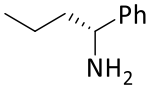
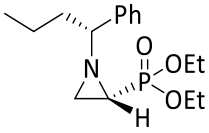
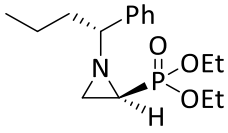
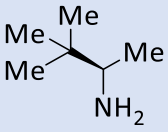
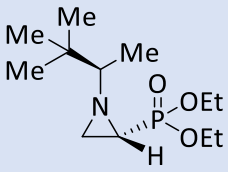
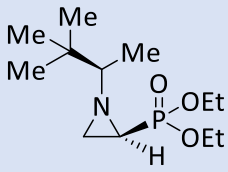
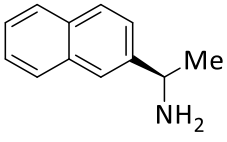
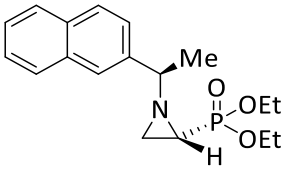
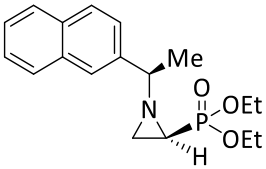
The mechanism of this reaction is believed to be taking place as shown in Scheme 12. According to this mechanism, DBU takes the α-proton of acetyl phosphonate to form an enolate as an intermediate. Then, the reaction of this enolate with *p*-toluenesulfonyl chloride (TsCl) leads to the formation of α-tosylated vinyl phosphonate **30**. The next step is the 1,4-addition of the primary amine to α-tosylated vinyl phosphonate **30** and then protonation at α-position. Finally S_N2 attack of the nitrogen by displacement of the tosylate group leads to the aziridine ring formation.



***Scheme 12**. Mechanism of modified Gabriel-Crowmell reaction.*

Since our purpose in this thesis was the enantioselective synthesis of a series of aziridinyl phosphonates, we, therefore, repeated this reaction with different chiral amines. The chiral amines and the obtained aziridinyl phosphonates from these amines were listed in Table 1.[33]

Table 1. *Aziridine phosphonate derivatives.*

Entry	Chiral amines (R*-NH_2)	Aziridinyl phosphonates[a]	
1	 **32**	 **33a,** 49%	 **33b,** 33%
2	 **34**	 **35a,** 30%	 **35b,** 35%
3	 **36**	 **37a**, 31%	 **37b,** 36%
4	 **38**	 **39a**, 29%	 **39b**, 33%
5	 **40**	 **41a**, 20%	 **41b**, 35%
6	 **42**	 **43a**, 23%	 **43b**, 29%

[a]Isolated yield

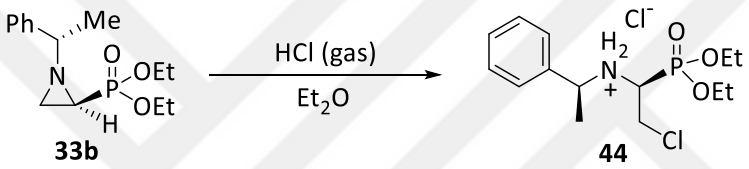
As can be seen from Table 1, reaction of (*S*)-phenylethylamine (**32**) provided a diastereomeric mixture of aziridinyl phosphonates **33a** and **33b** in 82% isolated total yield. These compounds were easily separated and purified by flash-column chromatography using silica gel. Characterizations of these compounds were done by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Besides other data, ^{1}H NMR signals of aziridine protons at around 1.0-2.5 ppm are very characteristic for these compounds (Appendix A, Figures 11 and 12).

In the case of (*R*)-1-cyclohexylethan-1-amine (**34**), aziridinyl phosphonates **35a** and **35b** were obtained in 65% isolated total yield. Purification and characterization were done as in previous case. As the third chiral amine, we used (*R*)-1-naphthylethylamine (**36**) which yielded aziridinyl phosphonates **39a** and **39b** in 67% total isolated yield. Aziridinyl phosphonates **39a** and **39b** were obtained by using the chiral amine (*R*)-1-phenylbutylamine (**38**) in 62% total isolated yield. Another commercially available chiral amine for the synthesis of *tert*-butyl substituted aziridinyl phosphonates was (*R*)-3,3-dimethylbutan-2-amine (**40**) which formed **41a** and **41b** in total of 55% isolated yield. In the characterization of these compounds, besides typical aziridine signals a sharp singlet corresponding to nine-protons of the *tert*-butyl group was observed at around 1 ppm on the ^{1}H NMR. The synthesis of final aziridinyl phosphonates **43a** and **43b** of Table 1 was accomplished by employing (*R*)-1-naphthylethylamine (**42**). In this case, the products were obtained in 52% total isolated yield. In the ^{1}H NMR of these compounds besides the expected aziridine, ethoxy and methyl signals naphthylene protons were observed in aromatic region.

Although the diastereoselectiviy of these reactions were quite low, this was not important for our purpose. Because we wanted to test the biological activity and organocatalytic activity of as many stereoisomers as possible. Diastereoselectivity was measured from crude reaction product by ^{1}H NMR and also from isolated yield, the numbers were very close.

2.1.4 Determination of absolute configuration of the aziridinyl phosphonates

In order to assign the configuration of new stereogenic center at aziridine ring, aziridinyl phosphonate **33b** was dissolved in ether and HCl gas (generated by drop wise addition of HCl over sulfuric acid) was bubbled into this solution until a cloudy mixture was formed. The cloudy mixture became clear by the precipitation of white solids of compound **44** (Scheme 13). Recrystallization of the white solids from hexane:ethyl acetate provided crystals for x-ray analysis.



33b **44**

Scheme 13*. Aziridine ring opening of compound* ***33b*** *by HCl gas.*

Besides all the other data ^{1}H, ^{13}C, ^{31}P NMR, IR and Mass (see the experimental part), the structure of compound **44** was assigned unambiguously by single crystal x-ray analysis (Figure 7).

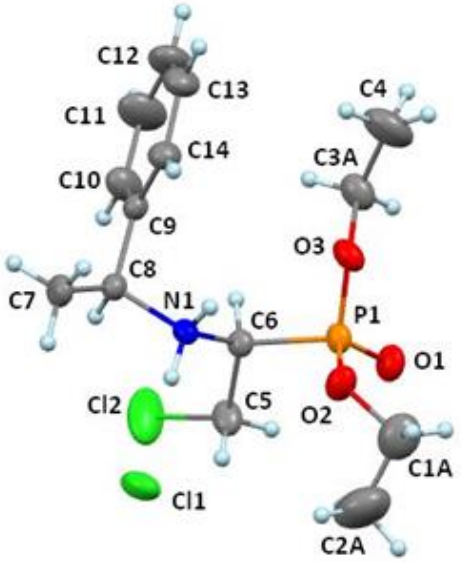


Figure 7. *X-ray structure of the compound* ***44****.*

In the ^{1}H NMR spectrum of compound **44**, positively charged nitrogen splitted aromatic protons into two, *ortho*-protons were shifted more downfield than *meta*- and *para*-protons as expected. A similar effect of nitrogen was also seen for the benzylic proton which appeared as a quartet at ~5 ppm. Diastereotopic protons appeared as multiplets one at ~4.5 ppm and the other one at ~4.0 ppm. Chirality center at α-position created slight difference between two ethoxy groups. As a result, "O$\underline{CH_2}CH_3$" protons appeared as two different multiplets at ~4.2-4.4 ppm and methyl protons appeared as triplets at ~1.45 and 1.40 ppm. Proton at α-position was seen at 3.7 ppm as a dt due to phosphorous and diastereotopic protons (Figure 8).

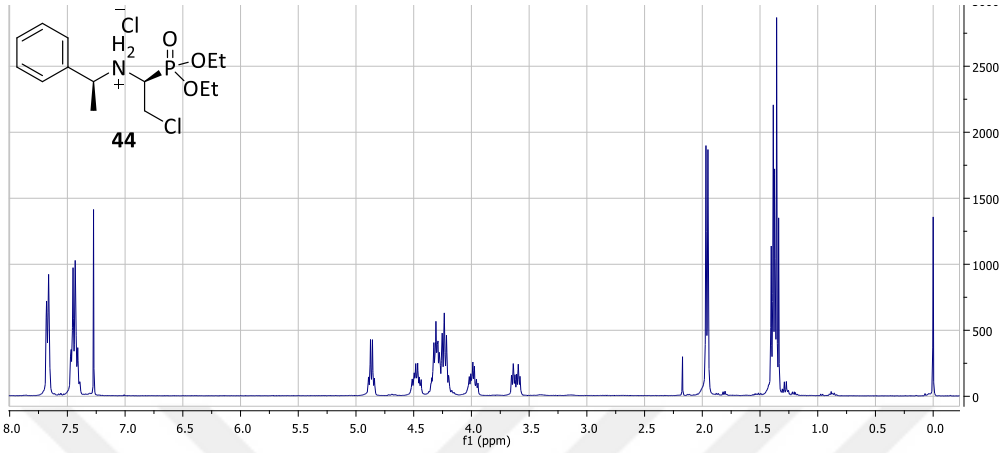


Figure 8. *^{1}H NMR spectrum of compounds **44**.*

X-ray analysis of compound **44** provided the absolute configuration of compound **33b** and its diastereomer **33a**. For the other phosphonate esters, we made analogy based on the splitting patterns of the methyl protons of the ethoxy groups. In all of the first isomers of aziridinyl phosphonates (**33a**, **35a**, **37a**, **39a**, **41a**, and **43a**), methyl protons of ethoxy groups appeared as a triplet for 6H with a same chemical shift value. On the other hand, in the second isomers of aziridinyl phosphonates except **35b** (**33b**, **37b**, **39b**, **41b**, and **43b**), same protons appeared as two different triplets for each methyl groups.

2.1.5 The biological activity tests of the synthesized aziridine phosphonates

After synthesizing the aziridinyl phosphonates in enantiomerically pure forms, their biological activities were studied against several bacteria and a fungus using dilution method which determines Minimum Inhibition Concentration (MIC). The MIC values obtained for aziridinyl phosphonates **33a**, **33b**, **35a**, **35b**, **37a**, **37b**, **41a**, **41b**, **43a**, **43b**are listed in Table 2 along with the reference antibiotics.

Escherichia coli ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Bacillus subtilis* ATCC 6633 and *Candida albican*s ATCC 10231 were taken from Mueller-Hinton Broth (Difco) after 24 hours of incubation. In order to measure the MIC values of the aziridinyl phosphonates in

antibacterial and antifungal assays listed above, aziridinyl phosphonates were dissolved in DMSO at the concentration of 200 µg/ml. Each aziridinyl phosphate was tested in duplicates for each of the bacteria and fungi. As the reference for the activity, sultamicillin, ampicillin, fluconazole and ciprofloxacin antibiotics were used.

Table 2. *Biological activity results of aziridinyl phosphonates.*

	MIC values (µg/ml)				
Compounds	***S.aureus*** **ATCC 25923**	***E. coli*** **ATCC 25922**	***P.aeruginosa*** **ATCC 27853**	***B.subtilis*** **ATCC 6633**	***C.albicans*** **ATCC 10231**
33a	≥100	100	100	100	100
33b	≥100	100	100	100	100
35a	≥100	100	100	100	100
35b	≥100	100	≥100	100	12.5
37a	≥100	100	≥100	100	100
37b	≥100	100	≥100	100	100
41a	≥100	100	≥100	100	100
41b	≥100	100	≥100	100	50
43a	≥100	100	≥100	100	100
43b	≥100	100	≥100	100	100
Sultamicillin	0.78	-	-	0.78	-
Ampicillin	1.56	-	-	50	-
Fluconazole	-	-	-	-	0.78
Ciprofloxacin	0.19	0.09	-	0.09	-

As it can be seen from the table, all of the compounds have showed low antibacterial activity against *Escherichia coli* ATCC 25922 and *Bacillus subtilis* ATCC 6633. The activity of aziridinyl phosphonates against *Staphylococcus aureus* ATCC 25923 is almost insignificant. The phosphonates **33a**, **33b** and **35a** displayed low activity

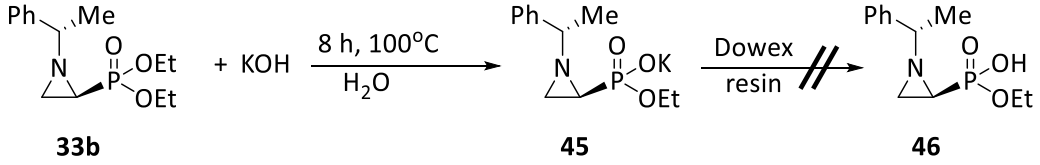
against *Pseudomonas aeruginosa* ATCC 27853, while other phosphonates did not show antibacterial activity against these bacteria. In terms of antifungal activity, phosphonates **35b** and **41b** showed reasonable activity against *Candida albican*s ATCC 10231, the others did not show activity against this fungus. The Minimum Inhibition Values for **35b** is12.5 µg/ml and for **41b** is 50 µg/ml.

After studying biological activities of synthesized aziridinyl phosphonates, we also wanted to find out their organocatalytic effect for the enantioselective synthesis of organic compounds. For this purpose, it was necessary to convert them into their phosphonic acid derivatives.

2.2 Synthesis of aziridinyl phosphonic acids

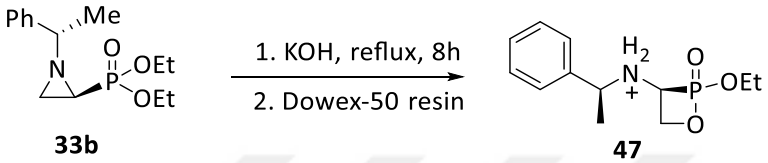
2.2.1 Hydrolysis using potassium hydroxide

In order to convert aziridinyl phosphonates into their aziridinyl phosphonic acid forms, we started from compound **33b**. Treatment of this compound with KOH in water at reflux temperature for 8h formed the desired potassium salt **45**. In order to convert the salt into acid form, it was passed through a small column filled with strongly acidic ion-exchange resin Dowex-50 which exchanges K^+ with H^+. After removing water by freeze-dry, white solids were submitted for NMR analysis and it was observed that the desired product **46** was not formed (Scheme 14).



***Scheme 14**. Attempted synthesis of aziridine phosphonic acid **46**.*

Unfortunately, all our attempts in obtaining crystals of the hydrolysis product failed. Based on ^{1}H, ^{13}C, ^{31}P NMR, IR and Mass data (see the experimental part) we proposed the following structure for the hydrolysis product **47** (Scheme 15).



***Scheme 15**. Proposed structure of hydrolysis product **47**.*

In the ^{1}H NMR spectrum characteristic signals of aziridine protons at around 1.0-2.5 ppm were not seen. As in compound **44**, positively charged nitrogen splits the aromatic protons into two and the benzylic proton was shifted to ~5 ppm. The diastereotopic protons appeared at ~4.7 and ~4.2 ppm as multiplets. The α-proton was seen at ~3.2 ppm as ddd due to diastereotopic protons and phosphorous. The "O$\underline{CH_2}CH_3$" protons appeared at ~3.8 ppm as a multiplet and "$OCH_2\underline{CH_3}$" protons resonated at around 1.2 ppm as a triplet (Figure 9).

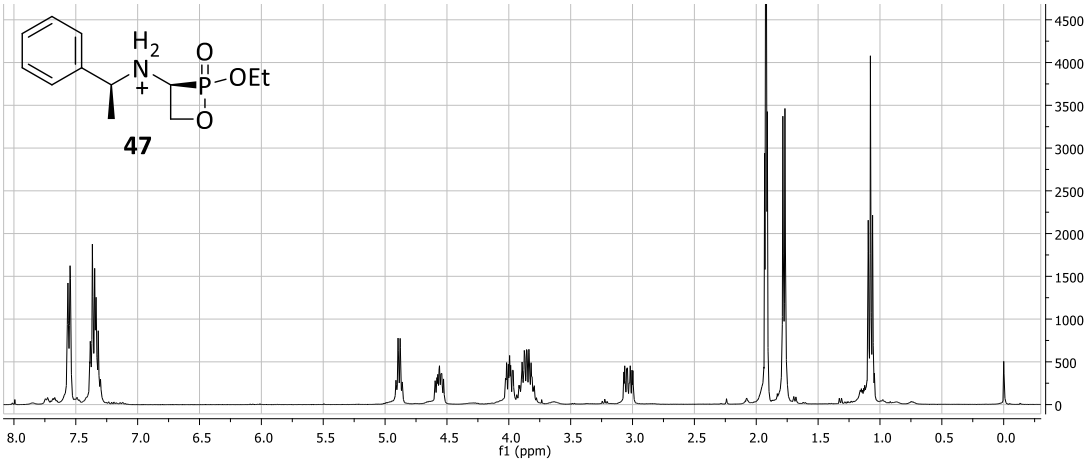
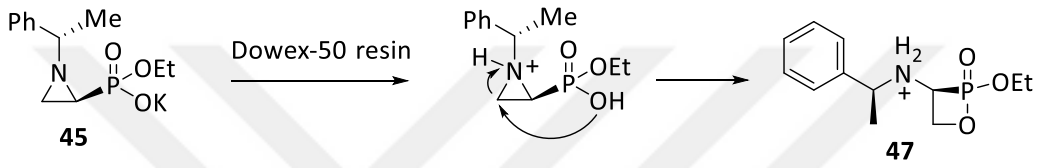


***Figure 9**.* ^{1}H NMR spectrum of compounds **47**.

For the formation of compound **47**, following reaction mechanism was proposed (Scheme 16). According to this mechanism, aziridine nitrogen and oxygen gets protonated from strongly acidic resin first. Then protonated aziridine ring gets opened easily by the attack of OH group on the phosphorous. As a result, oxaphosphetane 2-oxide structure **47** was formed (Scheme 16).

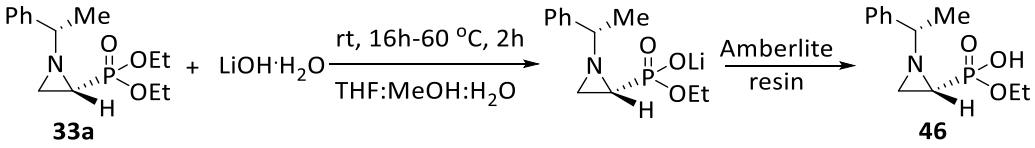


Scheme 16. *Proposed mechanism for the formation of* ***47****.*

After concluding that the aziridine ring could not survive strongly acidic resin, it was decided to change the resin to a weakly acidic one. In doing so hydrolysis conditions were also changed from KOH to LiOH in a mixed solvent system (THF/MeOH/H_2O).This procedure eliminated freeze-dry step as well.

2.2.2 Hydrolysis using lithium hydroxide

After an unsuccessful result with KOH hydrolysis, we tried the same reaction with less basic LiOH. Performing the reaction at room temperature for 16hours, then heating at 60 ^oC for 2hours provided corresponding Li-salt. Treatment of this salt with a weakly acidic resin yielded desired phosphonic acid **46** in 80% without a need for further purification (Scheme 17).



Scheme 17. *Hydrolysis of* ***33a*** *with lithium hydroxide.*

All the data ^{1}H, ^{13}C, ^{31}P NMR, IR and Mass (see the experimental part) were in agreement with the structure of compound **46**. As can be seen from Figure 9, one of the ethoxy groups on the starting material **33a** disappeared. All three protons of the aziridine ring appeared at expected region ~1.9-1.7 ppm as multiplets.

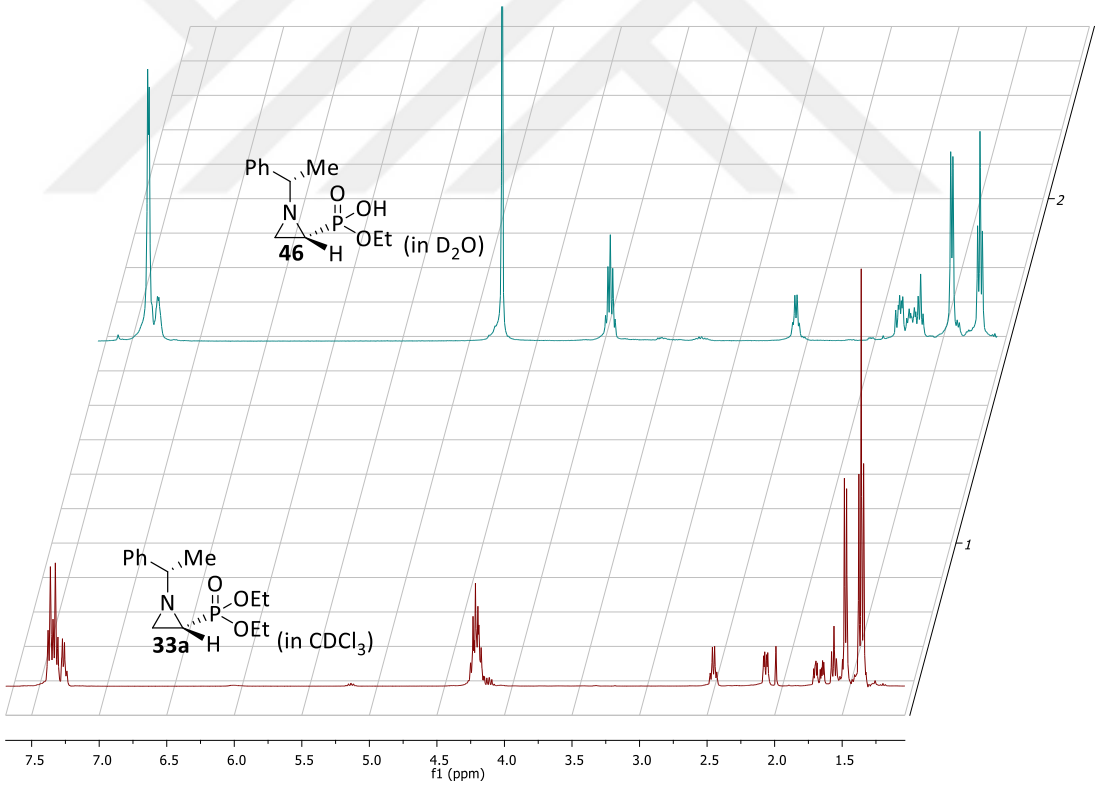


Figure 10. *^{1}H NMR spectra of compounds* ***33a*** *and* ***45****.*

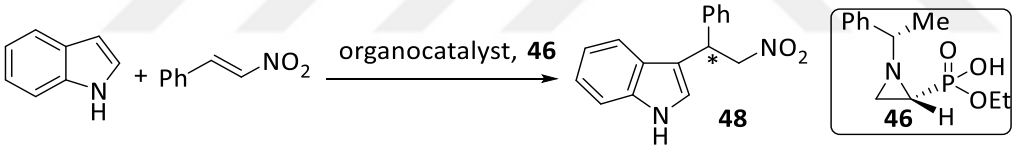
After the synthesis of phosphonic acid **46**, we wanted to test its organocatalytic effect on the organic reactions.

2.3 Organocatalytic effect of the aziridinyl phosphonic acid

2.3.1 Organocatalytic indole addition to nitrostyrene

We have chosen organocatalytic indole addition to nitrostyrene as the first examples because BINOL phosphoric acids have already been tried successfully for this reaction by Akiyama group.[34] By adapting the procedure published by Akiyama group, different reaction conditions were tried, the results of these studies were summarized in Table 3. Since our purpose was to see the enantioselectivity first, we didn't calculate the yield for most of the cases. The crude reaction mixture was applied to a quick column and the isolated product was injected to the chiral HPLC.

***Table 3**. Indole addition to nitrostyrene.*



Entry	Organocat. (46) (mol%)	Reaction conditions	Yield (%)	Solvent (con. in M)	ee[a] (%)
1	-	24 h, rt	44	DCM (0.25)	racemic
2	10	168 h, rt	ND	Benzene:DCE (0.2)	5.0
3	10	5 h, rt	5	DCM (0.25)	8.0
4	10	24 h, rt	ND	Toluene (0.25)	racemic
5	10	24 h, rt	ND	DCE (0.25)	racemic
6	5	24 h, rt	ND	DCM (0. 25)	7.0
7	20	24 h, rt	ND	DCM (0. 25)	racemic
8	10	24 h, rt	ND	DCM (0.125)	racemic
9	10	24 h, -35°C	ND	DCM (0.25)	racemic

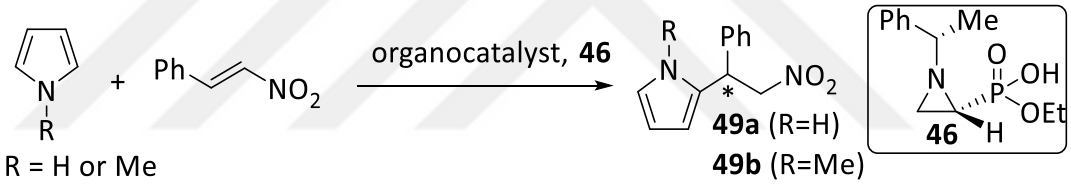
[a]Determined by chiral HPLC. ND: not determined.

As can be seen from Table 3, we have changed catalyst loading, reaction temperature, reaction time, solvent, and concentration. Unfortunately all these changes did not affect the enantioselectivity of the reaction, the product was formed as a racemic mixture as in entry 1 where no organocatalyst was used.

2.3.2 Organocatalytic pyrrole addition to nitrostyrene

After disappointing results of the previous reaction, we wanted to repeat the same reaction with pyrrole. The results of pyrrole addition to nitrostyrene were summarized in Table 4.

***Table 4**. Pyrrole addition to nitrostyrene.*



Entry	R-group	Organocat. (46) (mol %)	Reaction time (h)	Yield (%)	Solvent	ee[a] (%)
1	H	-	72	ND	DCM	racemic
2	Me	-	72	ND	DCM	racemic
3	H	10	24	ND	DCM	racemic
4	Me	10	24	ND	DCM	4
5	H	10	40	ND	DCE	2
6	Me	10	40	ND	DCE	racemic
7	H	10	72	ND	toluene	3
8	Me	10	72	ND	toluene	racemic

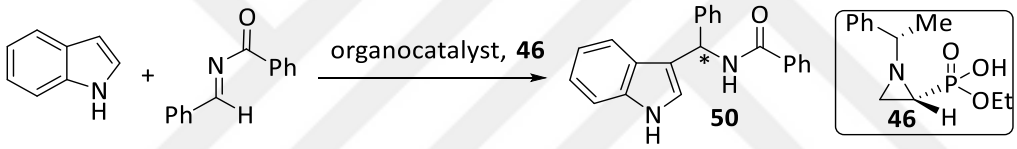
[a]Determined by chiral HPLC. ND: not determined. In all the cases reactions were carried out at RT with 0.25M concentration.

Although we tried different reaction conditions as in previous case, the reaction showed either no selectivity or very low enantioselectivity. Without trying further optimizations, we wanted to try the effect of our phosphonic acid on the Friedel-Crafts reactions of imines.

2.3.3 Reaction of indole with *N*-benzoyl imine

After disappointing results, we wanted to try indole addition to benzoyl imine. This reaction was also studied in the literature by Antilla group using phosphoric acid organocatalysts.[14]

Table 5. *Indole addition to N-benzoyl imine*.



Entry	Organocat. (46) (mol %)	Reaction conditions	Yield (%)	Solvent (con. in M)	ee[a] (%)
1	-	rt, overnight	36	DCM (0.13)	racemic
2	10	rt, 30 min	ND	DCM (0.13)	14
3	10	-35°C, 30 min	ND	DCM (0.13)	9
4	10	-35°C,60 min	ND	Toluene(0.13)	racemic
5	10	rt, 60 min	87	DCM (0.05)	racemic

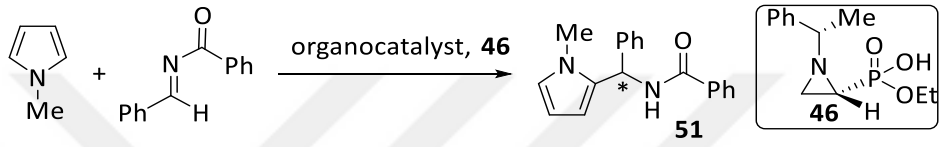
[a]Determined by chiral HPLC. ND: not determined.

As in the previous reactions, different reaction conditions were tried by adopting the literature procedure. The results of these studies were summarized in Table 5. Although not many conditions were tried, results of initial experiments were not promising. Therefore, we decided not to study this reaction further.

2.3.4 Reaction of *N*-methylpyrrole with *N*-benzoyl imine

We also tested the catalytic effect of our phosphonic acid for the same reaction by using *N*-methylpyrrole instead of indole with *N*-benzoyl imine. The results of these reactions were summarized in Table 6.

Table 6. *N-methylpyrrole addition to N-benzoyl imine.*



Entry	Organocat. (46) (mol %)	Reaction conditions	Yield (%)	Solvent (con. in M)	ee[a] (%)
1	-	rt, overnight	ND	toluene (0.25)	racemic
2	10	rt, 30 min	ND	DCM (0.25)	5
3	10	rt, 30 min	ND	DCM (0.13)	2
4	10	-35°C, 24 h	ND	DCM (0.25)	racemic
5	10	-78°C, 24 h	ND	DCM (0.25)	8

[a]Determined by chiral HPLC. ND: not determined.

The results of these experiments were also not promising, either no selectivity or very low enantioselectivity was measured. Therefore, no further optimizations were done.

CHAPTER 3

CONCLUSION

The enantioselective synthesis of chiral aziridinyl phosphonates by the modified Gabriel-Crowmell method was achieved successfully. Biological activity tests for these compounds were done by dilution method against some bacteria and a fungus. The results of these tests showed that all these compounds have low activity against bacteria. On the other hand, two of the aziridinyl phosphonates showed acceptable activity against the fungus tested in these studies.

One of the aziridinyl phosphonates was converted into its phosphonic acid derivative and tested for its organocatalytic effect. As the test reactions, indole and pyrrole additions to nitrostyrene and *N*-benzoyl imine were carried out under different reaction conditions. In all of four reactions, either no selectivity or very low enantioselectivity was observed.

Modification of phosphonic acid structure and the tests of the synthesized phosphonic acid for some other reactions will be studied in our group.

CHAPTER 4

EXPERIMENTAL

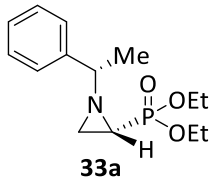
4.1 General

All chiral amines are commercially available and were used as received from Sigma–Aldrich, unless otherwise stated. Column chromatography was performed using 230–400-mesh silica gel. ^{1}H, ^{13}C, and ^{31}P NMR spectra were reported on a Brucker Avance DPX-400 instrument at 400, 100, and 162 MHz, respectively relative to TMS for ^{1}H and ^{13}C NMR and H_3PO_4 for ^{31}P NMR. Peak multiplicity (abbreviations are as follows: s as singlet; d as doublet; t as triplet; q as quartet; m as multiplet; br as broad) and coupling constants in Hertz integrated number of protons. Optical rotations were measured on a Rudolph Research Analytical Autopol III Polarimeter. An Agilent 6224 TOF-LC/MS instrument120 was used for mass analyses. IR spectra were obtained by Bruker Platinum ATR-IR instruments and are reported in cm^{-1}. X-ray diffraction data of amino phosphonate salt **44** were collected with an Agilent XCalibur X-ray diffractometer with EOS CCD detector using Mo-Ka radiation (graphite crystal monochromator k = 0.7107 Å) at the room temperature.

Phosphomolybdic acid in ethanol and ninhydrin was used for TLC dye. The relative portions of solvents are in volume:volume ratio used in column chromatography as eluent.

4.2 Synthesis and characterization of aziridinyl phosphonates

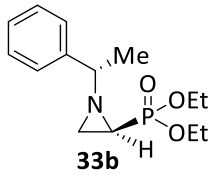
4.2.1 Synthesis and characterization of the compounds **33a** and **33b**[26]



33a

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**30)**, (3.619 g, 10.8 mmol) and L-α-methylbenzyl amine (**32**) (2.68 mL, 21.6 mmol, 2.0 equiv.) in dry acetonitrile was stirred at room temperature. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (1.78 mL, 11.9 mmol, 1.1 equiv.) was added slowly drop-by-drop and the resulting mixture was stirred at room temperature for 72 hours.

The crude product was purified by silica gel chromatography (EtOAc, Rf = 0.38) to yield Diethyl ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**33a**) (1.49 g, 5.3 mmol, 49 % yield) as a colorless oil. Colorless oil, $[\alpha]_D^{20}$ = -45 (*c*=0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.26 (m, 5H), 4.25-4.17 (m, 4H, -O$\underline{CH_2}$$CH_3$), 2.47 (q, *J* = 6.5 Hz, 1H, -CHPh), 2.08 (dd, *J* = 8.9, 3.4 Hz, 1H), 1.67 (ddd, *J* = 19.4, 6.8, 3.6 Hz, 1H), 1.57 (t, *J* = 7.1 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H, -CH_3), 1.37 (t, *J* = 7.1 Hz, -OCH$_2$$\underline{CH_3}$, 6H). ^{13}C NMR: 143.79 (Ph), 128.28 (Ph), 127.14 (Ph), 126.58 (Ph), 70.97 (d, *J* = 7.1 Hz, CHPh), 62.41 (d, *J* = 6.5 Hz, CH_2OP), 62.19 (d, *J* = 6.3 Hz, CH_2OP), 32.59 (d, J_{P-C} = 218.6 Hz, CHP), 31.53 (d, *J* = 5.2 Hz, CH_2N), 23.54 (CH_3CH), 16.52 (d, J_{P-C} = 5.7 Hz, CH_3CH_2), 16.46 (d, J_{P-C} = 5.8 Hz, CH_3CH_2).^{31}P NMR: 22.76. IR (neat, cm^{-1}) 3060, 2978, 2929, 2906, 1245, 1021, 961. HRMS-EI (m/z): calculated for $C_{14}H_{21}NO_3PNa$ (M+Na$^+$): 306.1235; found: 306.1237.

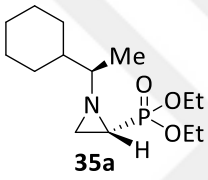


33b

Diethyl ((S)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**33b**) was purified by silica gel chromatography (EtOAc, R_f=0.14) to yield (1.0 g, 3.56 mmol, 33 % yield) as a colorless oil, $[\alpha]_D^{20}$ = -16 (*c*=0.66, CH_2Cl_2).^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.26, m, 5H), 3.96-3.70 (m, 4H, -O$\underline{CH_2}$$CH_3$), 2.43 (q, *J* = 6.5 Hz, 1H, -CHPh), 2.31 (dd, *J* = 9.1, 2.8 Hz, 1H), 1.73 (t, *J* = 7.0 Hz, 1H), 1.57 (ddd, *J* = 19.1, 6.9, 3.6 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H, -CH_3),

1.19 (t, J = 7.0 Hz, -OCH$_2$CH$_3$, 3H), 1.10 (t, J = 7.0 Hz, -OCH$_2$CH$_3$, 3H). ^{13}C NMR:143.21 (Ph), 128.23 (Ph), 127.34 (Ph), 127.13 (Ph), 71.42 (d, J = 6.9 Hz, CH$_3$CH), 62.14 (d, J = 6.2 Hz, CH$_2$CH$_3$), 61.48 (d, J = 6.0 Hz, CH$_2$CH$_3$), 31.97 (d, J= 5.2 Hz, CH$_2$N), 31.28 (d, $J_{P\text{-}C}$ = 216.4 Hz, CHP), 22.93 (CH$_3$CH), 16.30 (CH$_3$CH$_2$), 16.23 (CH$_3$CH$_2$). ^{31}P NMR: 21.49. IR (neat, cm^{-1}) 3060, 2978, 2929, 2906, 1246, 1022, 954. HRMS-EI (m/z): calculated for $C_{14}H_{21}NO_3PNa$ (M+Na$^+$): 306.1235; found: 306.1225.

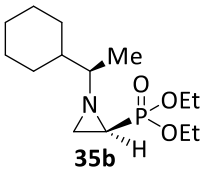
4.2.2 Synthesis and characterization of the compounds **35a** and **35b**



35a

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**30)**, (1.7 g, 5.1 mmol) and (*R*)-1-cyclohexylethan-1-amine (**34**) (0.9 mL, 6.1 mmol, 1.2 equiv.) in acetonitrile was stirred at room temperature. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.91 mL, 6.1 mmol, 1.2 equiv.) was added slowly drop-by-drop and the resulting mixture was stirred at room temperature for 72 hours.

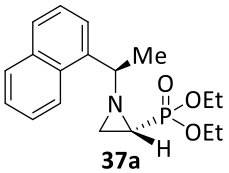
The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.35) to yield Diethyl ((R)-1-((R)-1-cyclohexylethyl)aziridin-2-yl)phosphonate (**35a**) (0.44 g, 1.53 mmol, 30 % yield) as a colorless oil, $[\alpha]_D^{21}$ = +38.1 (c=1.0, CHCl$_3$).^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.19-4.09 (m, 4H, -OCH$_2$CH$_3$), 2.15 (dd, J = 3.5, 8.9 Hz, 1H), 1.82-1.65 (m, 5H), 1.61 (t, J = 6.9 Hz, 1H), 1.50-1.46 (m, 1H), 1.41 (ddd, J = 3.6, 6.7, 20.3 Hz, 1H), 1.33 (t, J = 7.0 Hz, 6H, -OCH$_2$CH$_3$), 1.28-1.11 (m, 4H), 1.09 (d, J = 5.0 Hz, 3H, -CH$_3$), 1.06-0.94 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 71.3 (d, J_{C-P} = 6.5 Hz, -CHCyclo), 62.6 (d, J_{C-P} = 6.5 Hz, -OCH$_2$CH$_3$), 62.1 (d, J_{C-P} = 6.4 Hz, -OCH$_2$CH$_3$), 43.8, 33.4 (d, J_{C-P} = 5.5 Hz), 29.8 (d, J_{C-P}= 219.3 Hz, -CHPO(OEt)$_2$), 30.9, 30.1, 28.8, 26.5, 26.4, 17.1, 16.4 (t, J_{C-P} = 5.9 Hz, -OCH$_2$CH$_3$, 2C). ^{31}P NMR (CDCl$_3$, 161 MHz): δ 24.1. IR (cm^{-1}): 2980, 2924, 2852, 1245, 1023, 964, 749. HRMS-EI (m/z): calculated for $C_{14}H_{28}NO_3P$ [M+H]: 290.1885 and found: 290.1885.



35b

Diethyl ((S)-1-((R)-1-cyclohexylethyl)aziridin-2-yl)phosphonate (**35b**) was purified by silica gel chromatography (EtOAc, R_f = 0.22) to yield (0.51g, 1.78 mmol, 35 % yield) as a colorless oil. $[\alpha]_D^{21}$ = -21.6 (*c*=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.20-4.10 (m, 4H, -O<u>CH</u>$_2$CH$_3$), 2.10 (dd, *J* = 3.2, 9.0 Hz, 1H), 1.93-1.86 (m, 1H), 1.79-1.71 (m, 2H), 1.70-1.65 (m, 1H), 1.59-1.54 (m, 2H), 1.53-1.47 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 6H, -OCH$_2$<u>CH</u>$_3$), 1.28-1.07 (m, 6H), 1.05 (d, *J* = 6.3 Hz, 3H, -CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 71.3 (d, J_{C-P} = 7.0, -<u>CH</u>Cyclo), 62.0 (d, J_{C-P} = 5.0 Hz, -O<u>CH</u>$_2$CH$_3$), 61.6 (d, J_{C-P} = 6.2 Hz, -O<u>CH</u>$_2$CH$_3$), 42.6, 31.9 (d, J_{C-P}= 219.0 Hz, -<u>CH</u>PO(OEt)$_2$), 30.4, 29.8, 27.0, 26.5, 26.4, 26.2, 16.2 (d, J_{C-P} = 6.1 Hz, -OCH$_2$<u>CH</u>$_3$), 16.1 (d, J_{C-P} = 6.4 Hz, -OCH$_2$<u>CH</u>$_3$), 15.5 (-CH$_3$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.7. IR (cm^{-1}): 2979, 2923, 2852, 1244, 1022, 960, 780. HRMS-EI (*m*/*z*): calculated for $C_{14}H_{28}NO_3P$ [M+H]: 290.1885 and found: 290.1889.

4.2.3 Synthesis and characterization of the compounds **37a** and **37b**

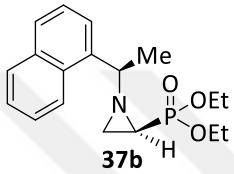


37a

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**30)**, (1.3 g, 3.9 mmol) and (R)-1-(naphthalen-1-yl)ethan-1-amine (**36**)(0.75 mL, 4.68 mmol, 1.2 equiv.) was stirred at room temperature. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.7 mL, 4.68 mmol, 1.2 equiv.) was added slowly drop-by-drop and the resulting mixture was stirred at room temperature for 72 hours.

The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.51) to yield Diethyl ((R)-1-((R)-1-(naphthalen-1-yl)ethyl)aziridin-2-yl)phosphonate (**37a**) (0.4 g, 1.2 mmol, 31 % yield) as a colorless oil. $[\alpha]_D^{21}$ = +70.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 5.5 Hz, 1H), 7.91- 7.85 (m, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.50-7.45 (m, 3H), 4.29-4.20 (m, 4H, -O<u>CH</u>$_2$CH$_3$), 3.21 (q, *J* = 6.4 Hz, 1H), 2.15 (dd, *J* = 3.5, 9.0 Hz, 1H), 1.82 (ddd, *J* = 3.6, 6.8, 19.5 Hz, 1H), 1.62 (d, *J* = 6.5 Hz, 3H, -CH$_3$), 1.54 (t, *J* = 7.1 Hz, 1H), 1.40 (t, *J* = 7.0 Hz, -OCH$_2$<u>CH</u>$_3$, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.7, 133.6, 130.4, 128.8, 127.4, 125.7, 125.6, 125.2, 123.9, 122.9, 77.2 (-

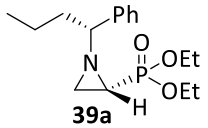
CHNaphtyl), 62.6 (d, J_{C-P}= 6.5 Hz, -O$\underline{CH_2}CH_3$), 62.3 (d, J_{C-P}= 6.2 Hz, -O$\underline{CH_2}CH_3$), 32.8 (d, J_{C-P}= 218.0 Hz, -$\underline{CH}PO(OEt)_2$), 31.7 (d, J_{C-P}= 5.3 Hz, -$\underline{CH_2}N$), 22.9 (-CH_3), 16.40 (d, J_{C-P}= 5.9 Hz, -$OCH_2\underline{CH_3}$), 16.36 (d, J_{C-P}= 5.9 Hz, -$OCH_2\underline{CH_3}$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.1. IR (cm^{-1}): 2983, 1242, 1022, 965, 747. HRMS-EI (*m*/*z*): calculated for $C_{18}H_{24}NO_3P$ [M+H]: 334.1572 and found: 334.1572.



37b

Diethyl ((S)-1-((R)-1-(naphthalen-1-yl)ethyl)aziridin-2-yl)phosphonate (**37b**) was purified by silica gel chromatography (EtOAc, R_f = 0.29) to yield (0.47 mg, 1.4 mmol, 36 % yield) as a colorless oil. $[\alpha]_D^{21}$ = +15.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (bs, 1H), 7.87-7.85 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.50-7.45 (m, 3H), 3.99-3.84 (m, 4H, O$\underline{CH_2}CH_3$), 3.19 (bs, 1H), 2.41 (dd, *J* = 3.6, 9.1 Hz, 1H), 1.84 (t, *J* = 7.0 Hz, 1H), 1.62 (d, *J* = 6.5 Hz, -CH_3, 3H), 1.55 (ddd, *J* = 3.6, 6.9, 19.3Hz, 1H), 1.16 (t, *J* = 7.0 Hz, -$OCH_2\underline{CH_3}$, 3H), 1.08 (t, *J* = 7.2 Hz, -$OCH_2\underline{CH_3}$, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.1, 133.8, 130.7, 128.9, 127.7, 125.7, 125.5, 125.3, 124.8, 123.3, 77.2 (-$\underline{CH}$Naphtyl), 62.3 (d, J_{C-P}= 6.5 Hz, -O$\underline{CH_2}CH_3$), 61.8 (d, J_{C-P}= 6.1 Hz, -O$\underline{CH_2}CH_3$), 31.6 (d, J_{C-P}= 216.4 Hz, -$\underline{CH}PO(OEt)_2$), 32.3 (d, J_{C-P}= 5.1 Hz, -$\underline{CH_2}N$), 22.8 (-CH_3), 16.2 (d, J_{C-P}= 6.4 Hz, 2C, -$OCH_2\underline{CH_3}$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 22.9. IR (cm^{-1}) 2981, 1243, 1023, 951, 777, 748. HRMS-EI (*m*/*z*): calculated for $C_{18}H_{24}NO_3P$ [M+H]: 334.1572 and found: 334.1578.

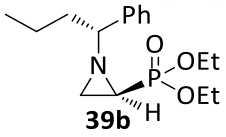
4.2.4 Synthesis and characterization of the compounds **39a** and **39b**



39a

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**30)**, (3.2 g, 9.57 mmol) and *R*-1-phenylbutyl amine (**38**) (1.83 mL, 11.5 mmol, 1.2 equiv.) was stirred at room temperature. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (1.7 mL, 11.5 mmol, 1.2 equiv.) was added slowly drop-by-drop and the resulting mixture was stirred at room temperature for 72 hours.

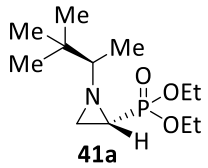
The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.46) to yield Diethyl ((R)-1-((R)-1-phenylbutyl)aziridin-2-yl)phosphonate (**39a**) (0.863 g, 2.8 mmol, 29% yield) as a colorless oil. $[\alpha]_D^{18}$ = +34.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.23 (m, 4H), 7.19-7.17 (m, 1H), 4.17-4.08 (m, 4H, -O<u>CH</u>$_2$CH$_3$), 2.21 (dd, *J* = 4.8, 8.1 Hz, 1H), 1.91 (dd, *J* = 3.4, 8.9 Hz, 1H), 1.85-1.69 (m, 2H), 1.63 (ddd, *J* = 3.6, 6.8, 19.8 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 6H, -OCH$_2$<u>CH</u>$_3$), 1.18-1.09 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H, -CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.5, 128.1 (2xCH), 127.5 (2xCH), 127.2, 75.9 (d, *J* = 7.2 Hz, -<u>CH</u>Ph), 62.6 (d, *J* = 6.6 Hz, -O<u>CH</u>$_2$CH$_3$), 62.4 (d, *J* = 6.2 Hz, -O<u>CH</u>$_2$CH$_3$), 39.5, 33.2 (d, J_{C-P}= 217.7 Hz, -<u>CH</u>PO(OEt)$_2$), 30.9 (d, *J* = 5.5 Hz), 18.8, 16.44 (d, J_{C-P}= 5.9 Hz, -OCH$_2$<u>CH</u>$_3$), 16.40 (d, J_{C-P}= 5.9 Hz, -OCH$_2$<u>CH</u>$_3$), 14.0. ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.1. IR (cm^{-1}): 2958, 2931, 1244, 1021, 962, 735, 700. HRMS-EI (*m*/*z*): calculated for $C_{16}H_{26}NO_3P$ [M+H]: 312.1728 and found: 312.1732.



39b

Diethyl ((S)-1-((R)-1-phenylbutyl)aziridin-2-yl)phosphonate (**39b**) was purified by silica gel chromatography (EtOAc, R_f = 0.29) to yield (0.982 g, 0,32 mmol, 33 % yield) as a colorless oil. $[\alpha]_D^{17}$ = +5.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.24 (m, 5H), 3.93-3.69 (m, 4H, -O<u>CH</u>$_2$CH$_3$), 2.32 (dd, *J* = 4.1, 9.1 Hz, 1H), 2.25 (t, *J* = 6.8 Hz, 1H), 1.90-1.84 (m, 2H), 1.76 (t, *J* = 6.8 Hz 1H), 1.51 (ddd, *J* = 3.7, 6.9, 19.3 Hz, 1H), 1.30-1.21 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H, -OCH$_2$<u>CH</u>$_3$), 1.10 (t, *J* = 7.0 Hz, 3H, -OCH$_2$<u>CH</u>$_3$), 0.86 (t, *J* = 7.3 Hz, 3H, -CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.1, 128.2 (2xCH), 127.9 (2xCH), 127.4, 76.5 (d, *J* = 6.6 Hz, -<u>CH</u>Ph), 62.4 (d, *J* = 6.3 Hz, -O<u>CH</u>$_2$CH$_3$), 61.7 (d, *J* = 6.0 Hz, -O<u>CH</u>$_2$CH$_3$), 39.3, 33.0 (d, *J* = 5.2 Hz), 30.3 (d, J_{C-P}= 215.6 Hz, -<u>CH</u>PO(OEt)$_2$), 29.7, 19.4, 16.2 (d, J_{C-P}= 6.2 Hz, -OCH$_2$<u>CH</u>$_3$, 2C), 14.0. ^{31}P NMR ($CDCl_3$, 161 MHz): δ 23.0. IR (cm^{-1}): 2958, 2931, 1246, 1022, 961, 735, 700. HRMS-EI (*m*/*z*): calculated for $C_{16}H_{26}NO_3P$ [M+H]: 312.1728 and found: 312.1732.

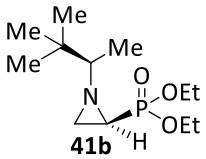
4.2.5 Synthesis and characterization of the compound **41a** and **41b**



41a

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**30)**, (0.6 g, 1.79 mmol) and *R*-3,3-dimethyl-2-butyl amine (**40**) (0.29 mL, 2.15 mmol, 1.2 equiv.) was stirred at room temperature. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (0.27 mL, 2.15 mmol, 1.2 equiv.) was added slowly drop-by-drop and the resulting mixture was stirred at room temperature for 72 hours.

The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.41) to yield Diethyl ((R)-1-((R)-3,3-dimethylbutan-2-yl)aziridin-2-yl)phosphonate (**41a**) (94.7 mg, 0.36 mmol, 20% yield) as a colorless oil. $[\alpha]_D^{34}$ = +29.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11-4.05 (m, 4H, -O<u>C</u>H$_2$CH$_3$), 2.12 (dd, *J* = 3.5, 8.9 Hz, 1H), 1.57 (t, *J* = 6.8 Hz, 1H), 1.36 (ddd, *J* = 3.5, 6.5, 20.8 Hz 1H), 1.24 (t, *J* = 7.0 Hz, 6H, -OCH$_2$<u>C</u>H$_3$), 1.07 (t, *J* = 6.6 Hz, 1H), 0.99 (d, *J* = 6.4 Hz, 3H, -<u>C</u>H$_3$), 0.87 (s, 9H, -C(<u>C</u>H$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 74.2 (d, J_{C-P}= 6.3 Hz, -<u>C</u>Ht-butyl), 62.5 (d, J_{C-P}= 6.5 Hz, -O<u>C</u>H$_2$CH$_3$), 62.2 (d, J_{C-P}= 6.2 Hz, -O<u>C</u>H$_2$CH$_3$), 35.6 (d, J_{C-P}= 5.7 Hz, -<u>C</u>H$_2$N), 35.1 (-<u>C</u>(CH$_3$)$_3$), 28.6 (d, J_{C-P}= 219.9 Hz, -<u>C</u>HPO(OEt)$_2$), 26.8 (-C(<u>C</u>H$_3$)$_3$), 16.3 (t, J_{C-P}= 5.6 Hz, 2C, -OCH$_2$<u>C</u>H$_3$), 15.5 (-<u>C</u>H$_3$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 24.1. IR (cm^{-1}): 2976, 1245, 1032, 964, 751, 544. HRMS-EI (*m*/*z*): calculated for $C_{12}H_{26}NO_3P$ [M+H]: 264.1728 and found: 264.1736.

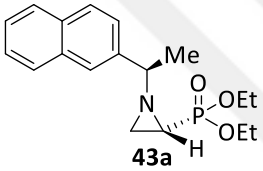


41b

Diethyl ((S)-1-((R)-3,3-dimethylbutan-2-yl)aziridin-2-yl)phosphonate (**41b**) was purified by silica gel chromatography (EtOAc, R_f = 0.35) to yield (165.7 mg, 0.63 mmol, 35 % yield) as colorless oil. $[\alpha]_D^{34}$ = -132.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): 4.19-4.11 (m, 4H, -O<u>C</u>H$_2$CH$_3$), 2.01 (dd, *J* = 3.2, 9.5 Hz, 1H), 1.73 (ddd, *J* = 3.4, 6.8, 20.9 Hz, 1H), 1.44 (t, *J* = 7.1 Hz, 1H), 1.34 (t, *J* = 7.0 Hz, 3H, -OCH$_2$<u>C</u>H$_3$), 1.33 (t, *J* = 7.0 Hz, 3H, -OCH$_2$<u>C</u>H$_3$), 1.17 (q, *J* = 6.3 Hz, 1H), 1.05 (d, *J* = 6.5 Hz, 3H, -CH$_3$), 0.99 (s, 9H, -C(<u>C</u>H$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 74.5 (d, J_{C-P}= 7.1 Hz, -<u>C</u>Ht-butyl), 62.2 (d, J_{C-P}= 6.3 Hz, -

O$\underline{CH_2}$$CH_3$), 62.1 (d, J_{C-P}= 6.6 Hz, -O$\underline{CH_2}$$CH_3$), 34.9 (d, J_{C-P}= 217.0 Hz, $\underline{CH}$PO(OEt)$_2$), 34.8 (-$\underline{C}$(CH_3)$_3$), 28.6 (d, J_{C-P}= 5.5 Hz, -$\underline{CH_2}$N), 26.9 (-C($\underline{CH_3}$)$_3$, 3C), 16.3 (t, J_{C-P}= 5.8 Hz, -OCH$_2$$\underline{CH_3}$, 2C), 15.8 (-$\underline{CH_3}$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 19.2. IR (cm^{-1}): 2976, 1243, 1022, 960, 772, 543. HRMS-EI (*m*/*z*): calculated for $C_{12}H_{26}NO_3P$ [M+H]: 264.1728 and found: 264.1732.

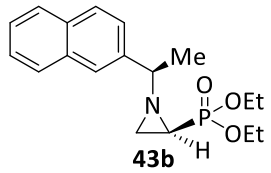
4.2.6 Synthesis and characterization of the compounds **43a** and **43b**



43a

A mixture of 1-(diethoxyphosphoryl)vinyl 4-methylbenzenesulfonate (**30**), (4.13 g, 12.4 mmol) and *R*-1-(2-naphtyl)ethyl amine (**42**) (2.54 g, 14.8 mmol, 1.2 equiv.) was stirred at room temperature. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (2.21 mL, 14.8 mmol, 1.2 equiv.) was added drop-by-drop and the resulting mixture was stirred at room temperature for 72 hours.

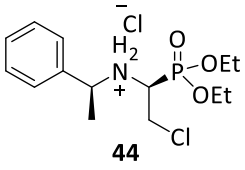
The crude product was purified by silica gel chromatography (EtOAc, R_f = 0.38) to yield Diethyl ((R)-1-((R)-1-(naphthalen-2-yl)ethyl)aziridin-2-yl)phosphonate (**43a**) (1.2 g, 3.6 mmol, 29% yield) as a colorless oil. $[\alpha]_D^{34}$ = +51.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.05 (m, 4H), 7.50 (dd, *J* = 1.4, 8.6 Hz, 1H), 7.48-7.45 (m, 2H), 4.28-4.19 (m, 4H, -O$\underline{CH_2}$$CH_3$), 2.61 (q, *J* = 6.4Hz, 1H), 2.11 (dd, *J* = 3.5, 9.0 Hz, 1H), 1.74 (ddd, *J* = 3.6, 6.8, 19.3 Hz, 1H), 1.62 (t, *J* = 7.2 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, -CH_3, 3H), 1.39 (t, *J* = 7.1 Hz, 6H, -OCH$_2$$\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.1, 133.1, 132.6, 127.8, 127.6, 127.4, 125.8, 125.5, 125.0, 124.9, 70.8 (d, J_{C-P}= 7.0 Hz, -$\underline{CH}$Naphtyl), 62.6 (d, J_{C-P}= 6.5 Hz, -O$\underline{CH_2}$$CH_3$), 62.2 (d, J_{C-P}= 6.3 Hz, -O$\underline{CH_2}$$CH_3$), 32.4 (d, J_{C-P}= 217.7 Hz, 2C, -$\underline{CH}$PO(OEt)$_2$), 31.4 (d, J_{C-P}= 5.3 Hz, -$\underline{CH_2}$N), 23.2 (-CH_3), 16.3 (d, J_{C-P}= 6.0 Hz, -OCH$_2$$\underline{CH_3}$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 22.8. IR (cm^{-1}): 2978, 1240, 1020, 964, 943, 748, 537, 478. HRMS-EI (*m*/*z*): calculated for $C_{18}H_{24}NO_3P$ [M+H]: 334.1572 and found: 334.1580.



43b

Diethyl ((S)-1-((R)-1-(naphthalen-2-yl)ethyl)aziridin-2-yl)phosphonate (**43b**) was purified by silica gel chromatography (EtOAc, R_f = 0.23) to yield (1.6 g, 0.48 mmol, 39 % yield) as a yellow oil. $[\alpha]_D^{34}$ = +55.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68-7.65 (m, 4H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.33-7.27 (m, 2H), 3.81-3.62 (m, 3H, -O$\underline{CH_2}CH_3$), 3.58-3.48 (m, 1H, -O$\underline{CH_2}CH_3$), 2.38 (q, *J* = 6.2 Hz, 1H), 2.20 (dd, *J* = 2.6, 9.1 Hz, 1H), 1.60 (t, *J* = 7.0 Hz, 1H), 1.45 (ddd, *J* = 3.6, 6.8, 19.1 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, -CH_3, 3H), 0.96 (t, *J* = 7.1 Hz, 3H, -$OCH_2\underline{CH_3}$), 0.77 (t, *J* = 7.0 Hz, 3H, -$OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.3, 132.7, 132.4, 127.4, 127.2, 127.0, 125.4, 125.4, 125.1, 124.8, 70.7 (d, J_{C-P}= 6.9 Hz, -$\underline{CH}$Naphtyl), 61.7 (d, J_{C-P}= 6.3 Hz, -O$\underline{CH_2}CH_3$), 61.1 (d, J_{C-P}= 6.1 Hz, -O$\underline{CH_2}CH_3$), 31.5 (d, J_{C-P}= 5.1 Hz, -$\underline{CH_2}$N), 30.7 (d, J_{C-P}= 215.5 Hz, -$\underline{CH}PO(OEt)_2$), 22.3 (-CH_3), 15.6 (d, J_{C-P}= 6.3 Hz, -$OCH_2\underline{CH_3}$), 15.4 (d, J_{C-P}= 6.2 Hz, -$OCH_2\underline{CH_3}$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 22.8. IR (cm^{-1}): 2980, 1244, 1023, 962, 789, 745, 531, 478. HRMS-EI (*m*/*z*): calculated for $C_{18}H_{24}NO_3P$ [M+H]: 334.1572 and found: 334.1582.

4.2.7 Synthesis and characterization of the compound **44**

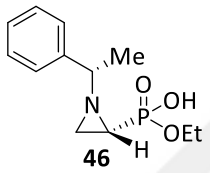


44

Diethyl ((S)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**33b**) was dissolved in dry diethyl ether (6 ml) at room temperature. HCl gas, generated by drop wise addition of HCl (37%, 2 ml) over sulfuric acid (98%, 2 ml), was passed through the solution for 15 minutes where an oily layer was formed. Then, the reaction flask was dipped into an ice bath and scratched with a glass rod to obtain compound **44** as a white solid. The solvent was then evaporated and the white solid was recrystallized from hexane-ethyl acetate (1:1) for x-ray analysis. The product **44** was obtained as white crystals (84% yield), mp: 119.4 ^oC. $[\alpha]_D^{22}$ = -16 (*c* = 1.0, $CHCl_3$), R_f = 0.67 (EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 6.9 Hz, 2H), 7.56-7.33 (m, 3H), 4.87 (q, *J* = 6.8 Hz, 1H, -$\underline{CH}$Ph), 4.47 (td, *J* = 6.7, 12.2 Hz, 1H, -$\underline{CH_2}$Cl), 4.43-4.13 (m, 4H, -O$\underline{CH_2}CH_3$), 3.98 (td, *J* = 6.4, 12.4 Hz, 1H, -

$\underline{CH_2}Cl$), 3.62 (dt, J = 5.9, 17.5 Hz, 1H, -$\underline{CH}P(OEt)_2$), 1.96 (d, J = 6.8 Hz, 3H, -CH_3), 1.38 (t, J = 7.0 Hz, 3H, -$OCH_2\underline{CH_3}$), 1.36 (t, J = 7.0 Hz, 3H, -$OCH_2\underline{CH_3}$).^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.0, 129.7, 129.3 (2XCH), 128.6 (2XCH), 64.7 (d, J_{C-P}= 6.8 Hz, -$O\underline{CH_2}CH_3$), 64.3 (d, J_{C-P}= 6.9 Hz, -$O\underline{CH_2}CH_3$), 60.3 (d, J_{C-P}= 4.4 Hz, -CH_2Cl), 54.4 (d, J_{C-P}= 149.9 Hz, -$\underline{CH}PO(OEt)_2$), 39.4 -$\underline{CH}$Ph), 20.3 (-CH_3), 16.4 (d, J_{C-P}= 5.7 Hz, -$OCH_2\underline{CH_3}$), 16.3 (d, J_{C-P}= 5.7 Hz, -$OCH_2\underline{CH_3}$). ^{31}P NMR ($CDCl_3$, 161 MHz): δ 16.7. IR (cm^{-1}): 3064, 2981, 2187, 2125, 2013, 1248, 1224, 993, 703. HRMS-EI (m/z): calculated for $C_{14}H_{24}Cl_2NO_3P$ [M^+]: 355.0871 and found: 355.0866.

4.2.8 Synthesis and characterization of the compound **46**

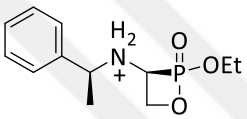


46

Diethyl ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**33a**)(0.400 g, 1.56 mmol) was dissolved in THF (3 ml). In a separate beaker LiOH.H_2O (0.300g, 7.8 mmol, 5 equiv.) was sonicated in 1:1 ratio of Water**:** Methanol (10 mL), which was subsequently added to the reaction flask at 0^{o}C. The ice bath was removed to run this reaction at room temperature for 16 hours, since no change was seen then temperature was raised up to 60^{o}C for 2 hrs. TLC showed no starting material. The reaction mixture was concentrated under reduced pressure. And Amberlite IR-120 H^+ (0.400 g) was added to the mixture with Methanol (5 mL). After 30 minutes stirring at room temperature, the resin was filtered and the filtrate was concentrated again. The product was re-dissolved in acetone (10 mL) and filtered to get rid of the excess of lithium hydroxide. The solvent was dried *in vacuo*, and product, ethyl hydrogen ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**46**) (320 mg, 1.25 mmol, 80% yield), was isolated as yellow solid. mp:124.7^{o}C.$[\alpha]_D^{12.3}$ = -39.7 (c = 1.0, MeOH), R_f = 0.25 ($CHCl_3$: MeOH (5:1)). ^{1}H NMR (400 MHz, D_2O) δ 7.62 – 6.90 (m, 5H, -Ph), 4.03 – 3.69 (m, 2H, -$O\underline{CH_2}CH_3$), 2.66 – 2.40 (m, 1H, -$\underline{CH}$Ph), 1.85 – 1.52 (m, 3H, -$\underline{CH_2}NCH$-), 1.37 (d, J = 6.6 Hz, 3H, -$CH\underline{CH_3}$), 1.16 (t, J = 7.1 Hz, 3H, -$OCH_2\underline{CH_3}$). ^{13}C NMR (101 MHz, D_2O) δ 143.20 (s), 128.68 (s), 127.61 (s), 126.90 (s), 69.68 (d, J_{C-P} = 5.8 Hz, -$\underline{CH}$Ph), 61.38 (d, J_{C-P} = 4.9 Hz, -$O\underline{CH_2}CH_3$),

34.36 (d, J_{C-P} = 198.5 Hz, -CHPO(OEt)$_2$), 30.66 (d, J_{C-P} = 2.7 Hz, -CH$_2$-N), 21.25 (s, -CHCH$_3$), 16.08 (d, J_{C-P} = 5.3 Hz, -CH$_2$CH$_3$).^{31}P NMR (D$_2$O, 161 MHz): δ 19,28.IR (ATR techniques, cm^{-1}): 2000-3000 (weak and broad), 2981, 1207, 1162, 1031, 1008, 950, 700, 680, 563, 525. HRMS-EI (*m*/*z*): calculated for $C_{12}H_{18}NO_3P$ [M+H]: 256.10 and found: 256.11.

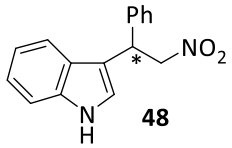
4.2.9 Synthesis and characterization of the compound **47**



47

To a solution of Diethyl ((S)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**33b**) (600 mg, 2.12 mmol, 1 equiv.) in water (2.0 ml) was added KOH (589 mg, 10.5 mmol, 5.0 equiv.). The resulting reaction mixture was refluxed for about 8hours until disappearance of aziridinyl phosphonate indicated by TLC ($CHCl_3$: MeOH (5:1)). The crude product was filtrated through the pre-activated Dowex (activated by 1M HCl then passed water until pH 5-6). After removing of water by using freeze dryer the product, ethyl ((S)-2-chloro-1-(((S)-1-phenylethyl)-l4-azanyl)ethyl)phosphonate (**47**) (341 mg, 1.34 mmol, 63% yield), was obtained as white solid, $[\alpha]_D^{34.2}$ = -12.9 (*c* = 1.0, MeOH), R_f = 0.37 ($CHCl_3$: MeOH (5:1)). ^{1}H NMR (*d*-acetone, 400 MHz): δ 7.55 (d, *J* = 7.0 Hz, 2H), 7.38-7.30 (m, 3H), 4.89 (q, *J* = 6.7 Hz, 1H), 4.60-4.53 (m, 1H), 3.99 (ddd, *J* = 3.0, 8.6, 12.8 Hz, 1H), 3.94-3.78 (m, 2H, -OCH$_2$CH$_3$), 3.03 (ddd, *J* = 2.9, 8.7, 17.7 Hz), 1.78 (d, *J* = 6.8 Hz, 3H, -CH$_3$), 1.09 (t, *J* = 7.0 Hz, 3H, -OCH$_2$CH$_3$). ^{13}C NMR (*d*-acetone, 100 MHz): δ 138.4, 131.13, 131.10, 130.1, 64.2 (d, J_{C-P}= 6.4 Hz, -OCH$_2$CH$_3$),62.1 (d, J_{C-P} = 7.2 Hz, -CHPh), 56.4 (d, J_{C-P} = 140.0 Hz, -CHPO(OH)(OEt)), 42.8 (d, J_{C-P} = 3.4 Hz, -CH$_2$ aziridine), 22.2 (-CH$_3$), 17.7 (d, J_{C-P} = 5.5 Hz, -OCH$_2$CH$_3$). ^{31}P NMR (D$_2$O, 161 MHz): δ 6.21. IR (ATR techniques, cm^{-1}): 2000-2800 (weak and broad), 2981, 1203, 1031, 949, 763, 699, 518. HRMS-EI (*m*/*z*): calculated for $C_{12}H_{18}NO_3P$ [M-H]: 254.0946 and found: 254.0953.

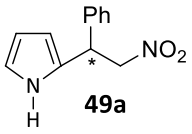
4.2.10 Representative procedure for the compound **48**



48

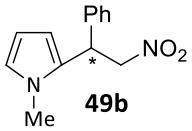
Data are identical with those reported in the literature.[34] To a solution of activated powder MS 3Å (20.3 mg), ethyl hydrogen ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**46**) (5.1 mg, 0.02 mmol, 0.1 equiv.) and nitrostyrene (60 mg, 0.4 mmol, 2 equiv.) in dichloromethane (0.5 mL) was added indole (26.3 mg, 0.2 mmol, 1 equiv.) at room temperature. After being stirred at the temperature for 24 hours, the reaction mixture was poured on silica gel column and purified by column chromatography (Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ =8.09 (brs, 1 H), 7.44 (d, 1 H, J=7.9 Hz), 7.37-7.18 (m, 7 H), 7.09-7.03 (m, 2 H), 5.19 (t, 1 H, J=8.0 Hz), 5.07 (dd, 1 H, J=12.5, 7.5 Hz), 4.94 (dd, 1 H, J=12.5, 8.2 Hz). The enantiomeric excess of the product **48**was determined by chiral HPLC analysis on a Daicel Chiralpak AD-H column, 254 nm, 90:10 Hexane: iso-Propanol, flow rate = 0.75 ml/min, t_1= 30 min, t_2= 33 min (Appendix A, Figure 30).

4.2.11 Representative procedure compounds **49a** and **49b**



49a

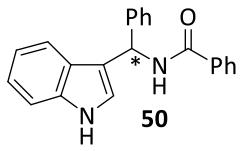
Data are identical with those reported in the literature.[35] To a solution of activated powder MS 3Å (20.3 mg), ethyl hydrogen ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate(**46**) (5.1 mg, 0.02 mmol, 0.1 equiv.) and nitrostyrene (140 mg, 0.14 mmol, 2 equiv.) in dichloromethane (0.5 mL) was added pyrrole (100 mg, 0.7 mmol, 1 equiv.) at room temperature. After being stirred at the temperature for 72 hours, the reaction mixture was poured on silica gel column and purified by column chromatography (Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77-4.97 (m, 3H), 6.07 (s, 1H), 6.15 (s, 1H), 6.66 (s, 1H), 7.20-7.37 (m, 5H), 7.85 (brs, 1H). The enantiomeric excess of the product **49** was determined by chiral HPLC analysis on a Daicel Chiralpak OD-H column, 254 nm, 80:20 Hexane: iso-Propanol, flow rate = 1.0 ml/min, t_1= 9 min, t_2= 11 min (Appendix A, Figure 31).



49b

Data are identical with those reported in the literature.[35] To a solution of activated powder MS 3Å (20.3 mg), ethyl hydrogen ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate(**46**) (5.1 mg, 0.02 mmol, 0.1 equiv.) and nitrostyrene (160 mg, 0.14 mmol, 2 equiv.) in dichloromethane (0.5 mL) was added *N*-methylpyrrole (100 mg, 0.7 mmol, 1 equiv.) at room temperature. After being stirred at the temperature for 72 hours, the reaction mixture was poured on silica gel column and purified by column chromatography (Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (s, 3H), 452-4.76 (m, 3H), 6.01-6.06 (m, 2H), 6.43 (s, 1H), 7.07-7.21 (m, 5H). The enantiomeric excess of the product **49** was determined by chiral HPLC analysis on a Daicel Chiralpak AS-H column, 254 nm, 99:1 Hexane: iso-Propanol, flow rate = 0.75 ml/min, t_1= 20 min, t_2= 22 min (Appendix A, Figure 32).

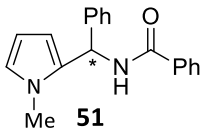
4.2.12 Representative procedure compound **50**



50

Data are identical with those reported in the literature.[18] To a solution of activated powder MS 3Å (20.3 mg), ethyl hydrogen ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate (**46**) (5.1 mg, 0.02 mmol, 0.1 equiv.) and *N*-Benzoyl imine (83.3 mg, 0.4 mmol, 2 equiv.) in dichloromethane (0.5 mL) was added indole (26.3 mg, 0.2 mmol, 1 equiv.) at room temperature. After being stirred at the temperature for 1 hour, the reaction mixture was poured on silica gel column and purified by column chromatography (Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (s, 1H), 6.05 (t, J = 3.0 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 6.65 (m, 2H), 6.8-8.0 (m, 14H). The enantiomeric excess of the product **50** was determined by chiral HPLC analysis on a Daicel Chiralpak OD-H column, 85:15 Hexane: iso-Propanol, 254 nm, flow rate = 1 ml/min, t_1= 13 min, t_2= 17 min (Appendix A, Figure 33).

4.2.13 Representative procedure compound **51**



51

Data are identical with those reported in the literature.[20] To a solution of activated powder MS 3Å (20.3 mg), ethyl hydrogen ((R)-1-((S)-1-phenylethyl)aziridin-2-yl)phosphonate(**46**)(6.1 mg, 0.024 mmol, 0.1 equiv.) and *N*-benzoyl imine(50 mg, 0.24 mmol, 1 equiv.) in dichloromethane (0.5 mL) was added N-methylpyrrole(39 mg, 0.48 mmol, 2 equiv.) at room temperature. After being stirred at the temperature for 30 minutes, the reaction mixture was poured on silica gel column and purified by column chromatography (Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (s, 3H), 5.80 (s, 1H), 6.05 (t, J = 3.0 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 6.65 (m, 2H), 7.27-7.55 (m, 8H), 7.80 (d, J = 7.3 Hz, 2H). The enantiomeric excess of the product **51** was determined by chiral HPLC analysis on a Daicel Chiralpak OD-H column, 98:2 Hexane – iso-Propanol, 254nm, flow rate= 1 ml/min, t_1= 22 min, t_2= 26 min (Appendix A, Figure 34).

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APPENDIX A

NMR SPECTRA

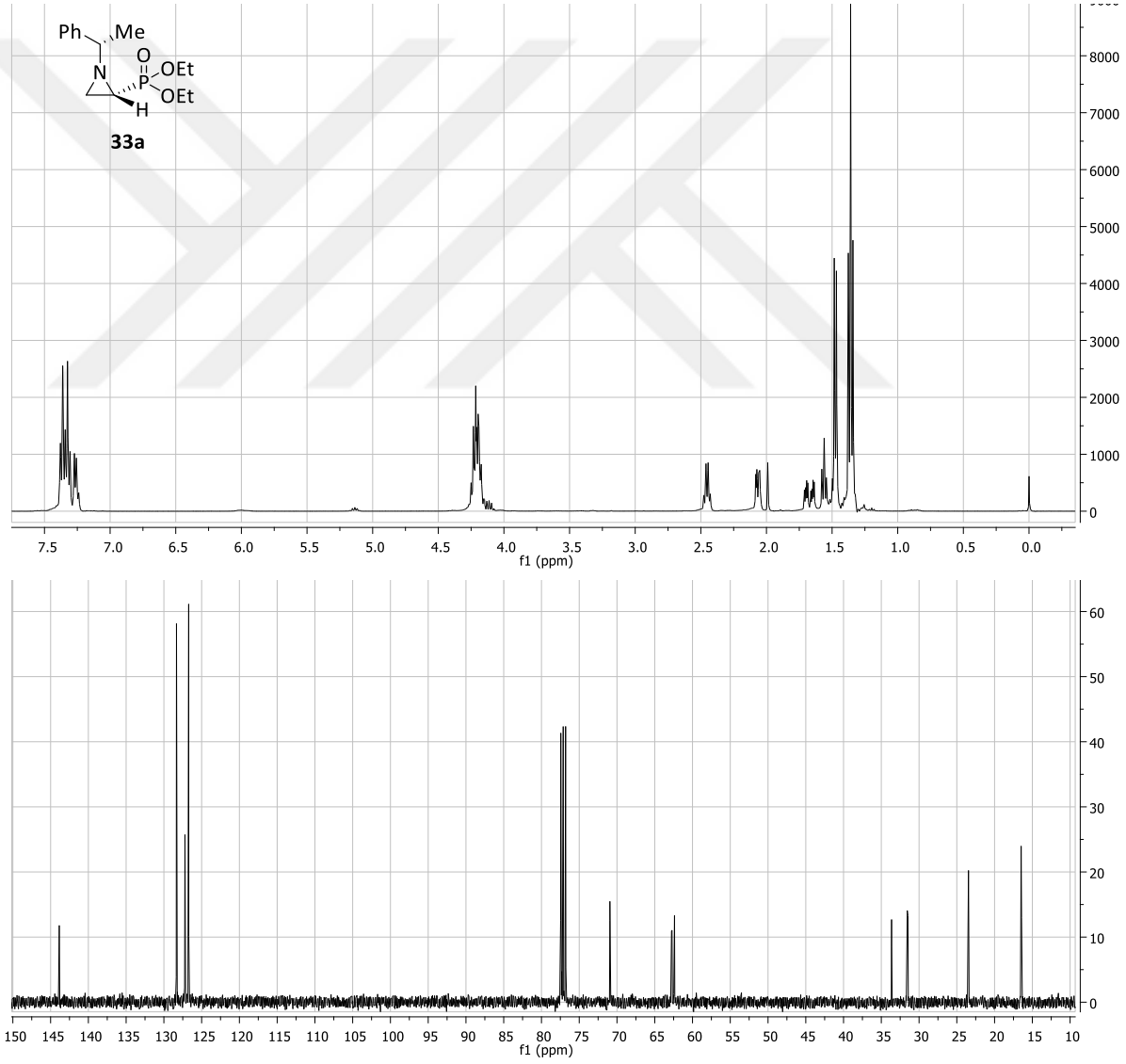


Figure 11. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***33a.***

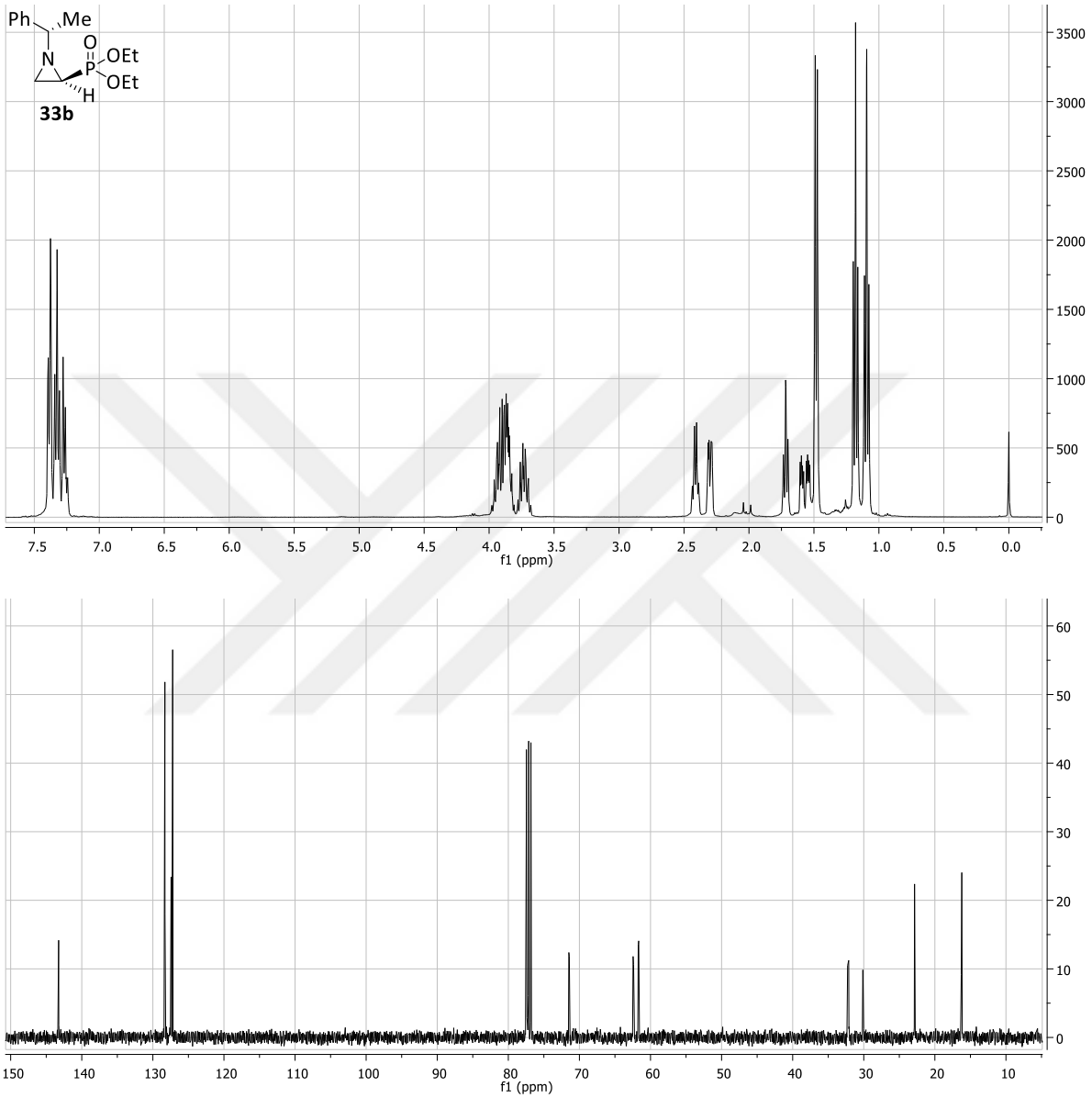


Figure 12**. ^{1}H, ^{13}C and ^{31}P NMR spectra of compound **33b.

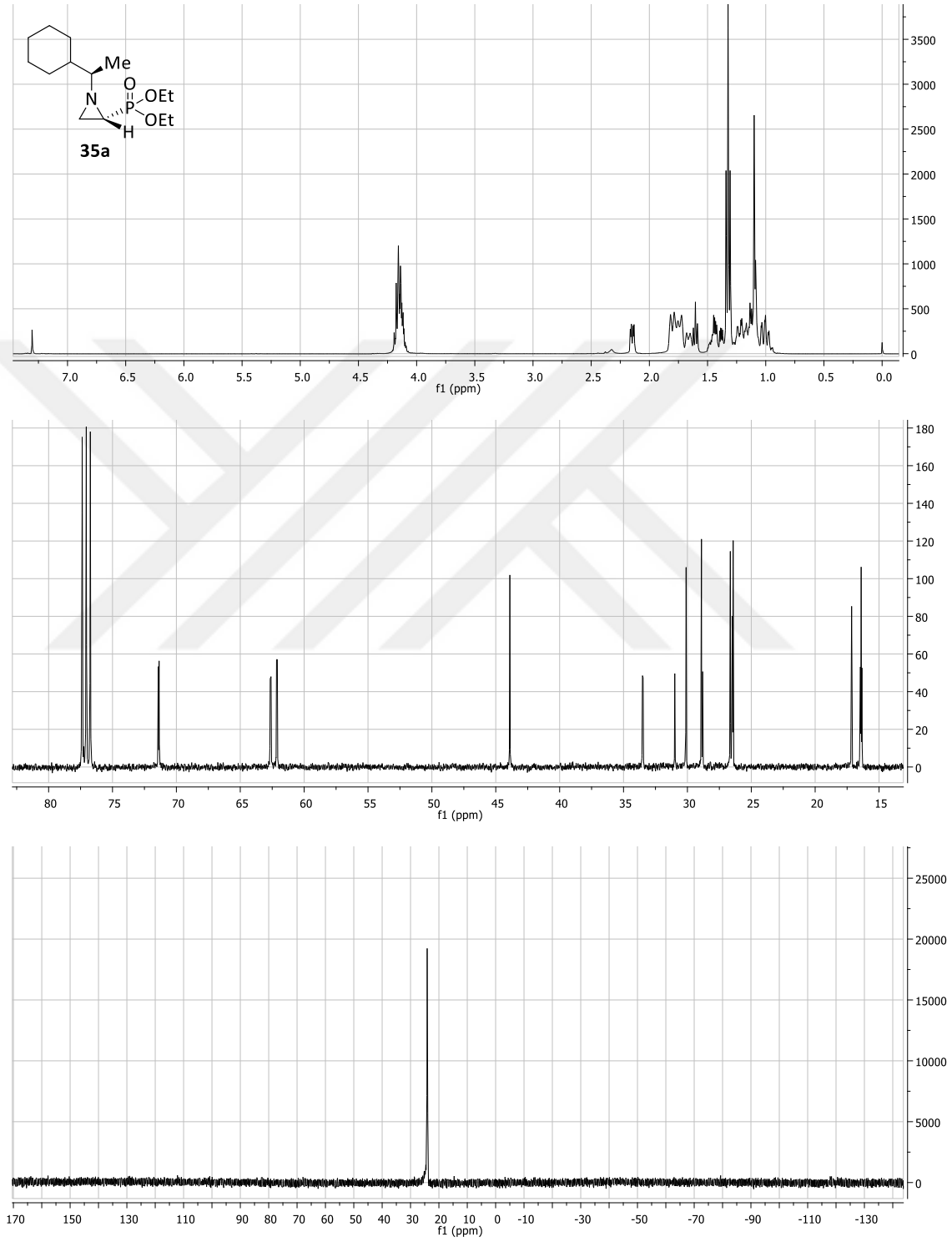


Figure 13. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***35a.***

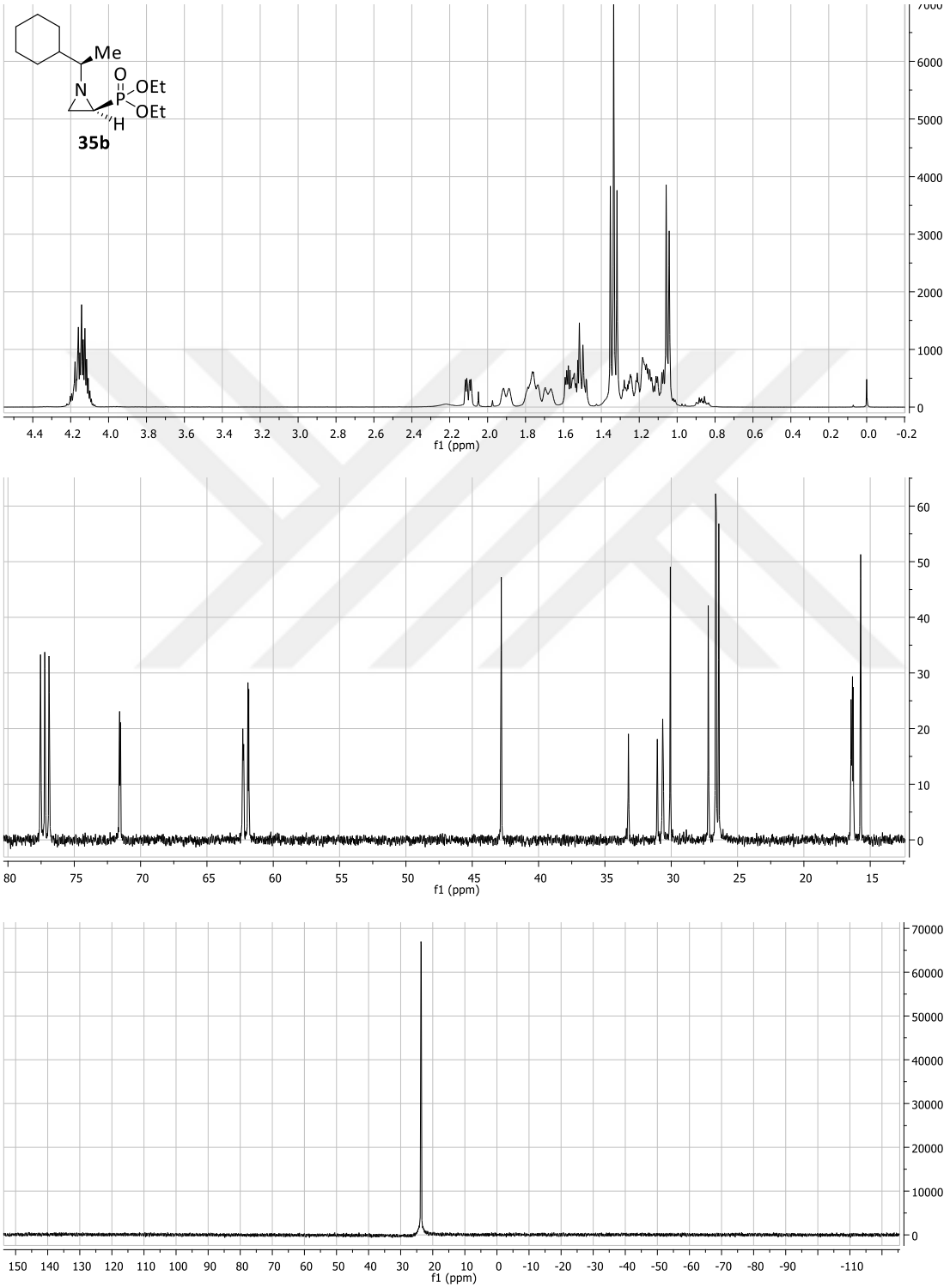


Figure 14. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***35b.***

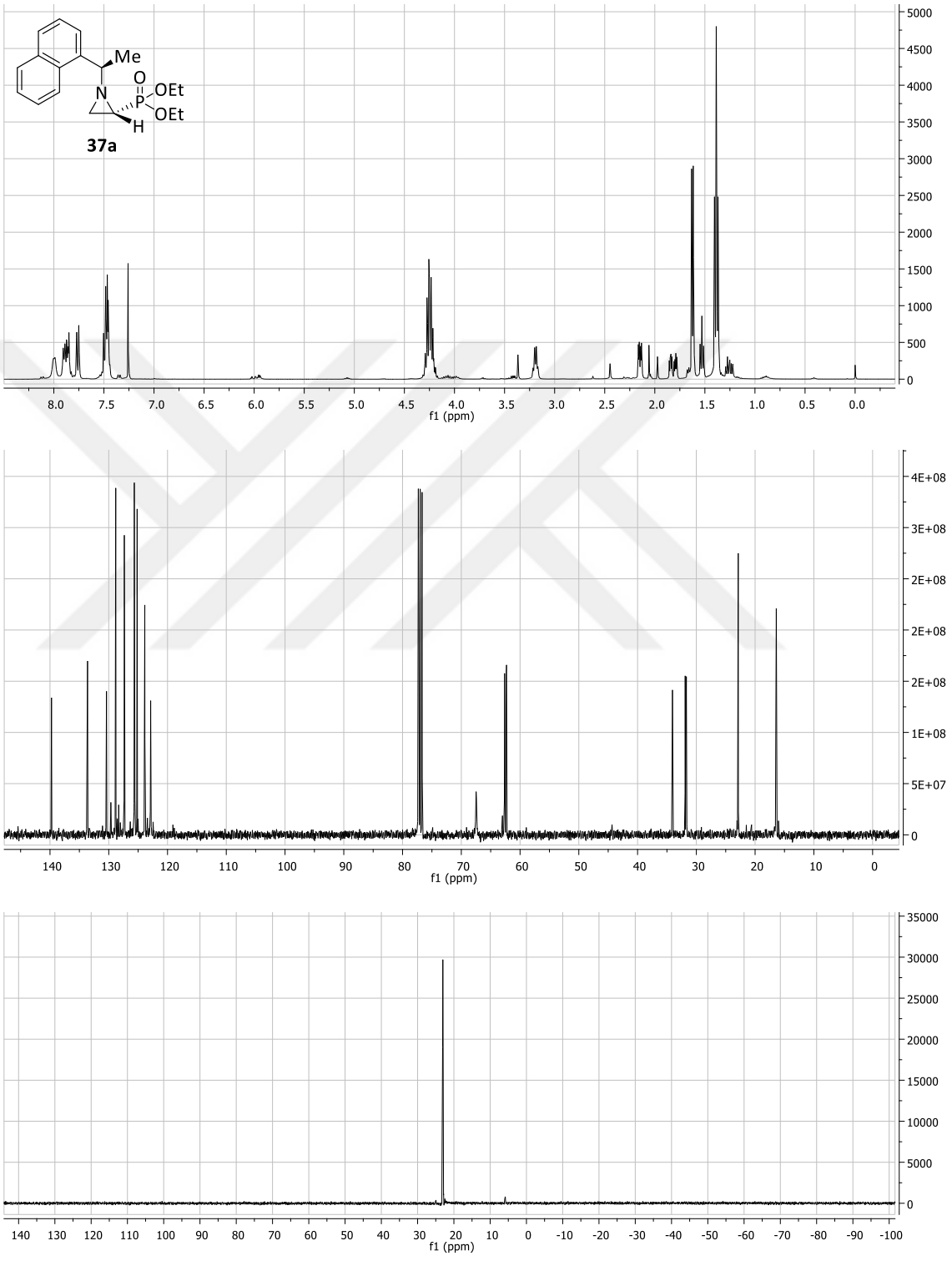


Figure 15. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***37a.***

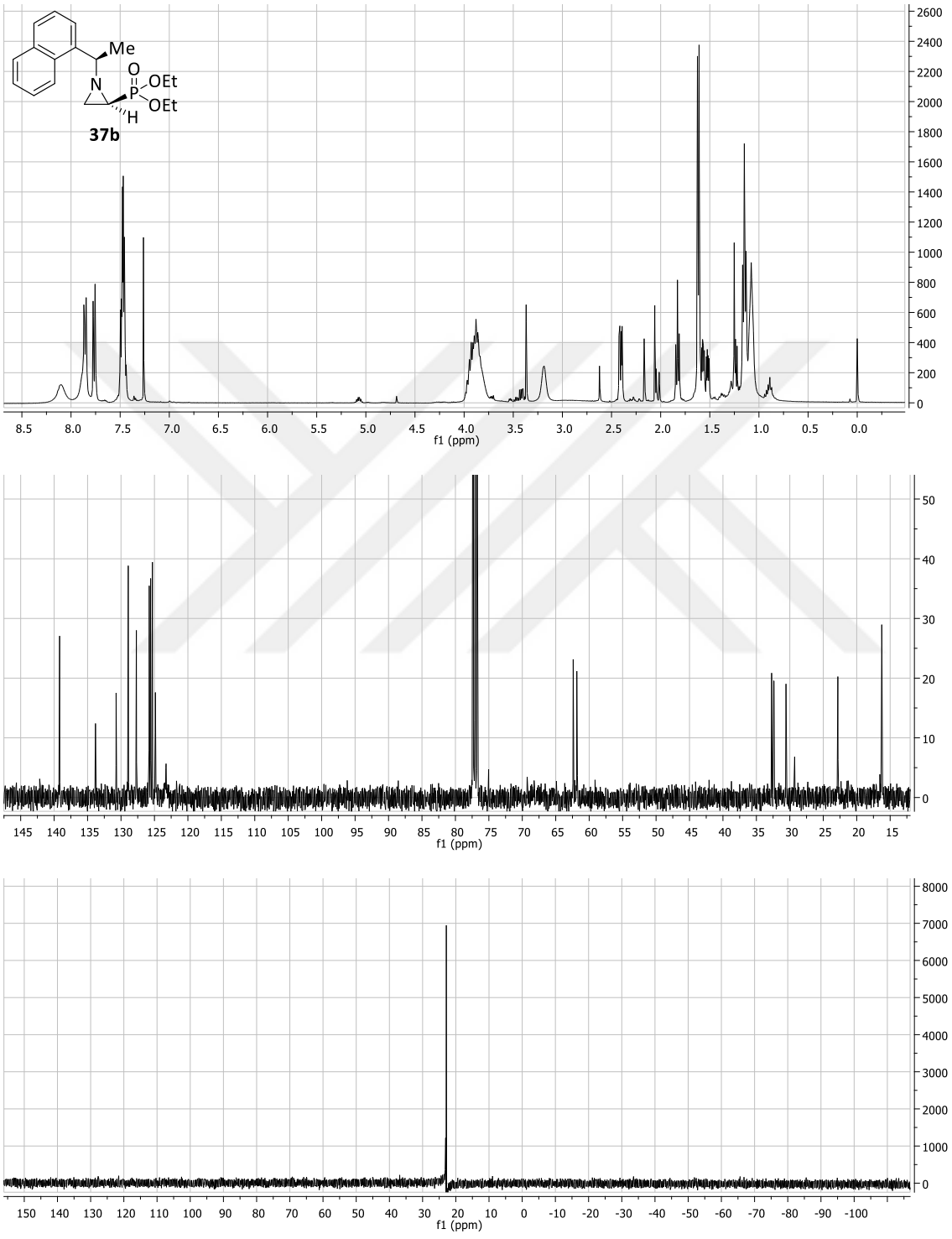


Figure 16. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***37b.***

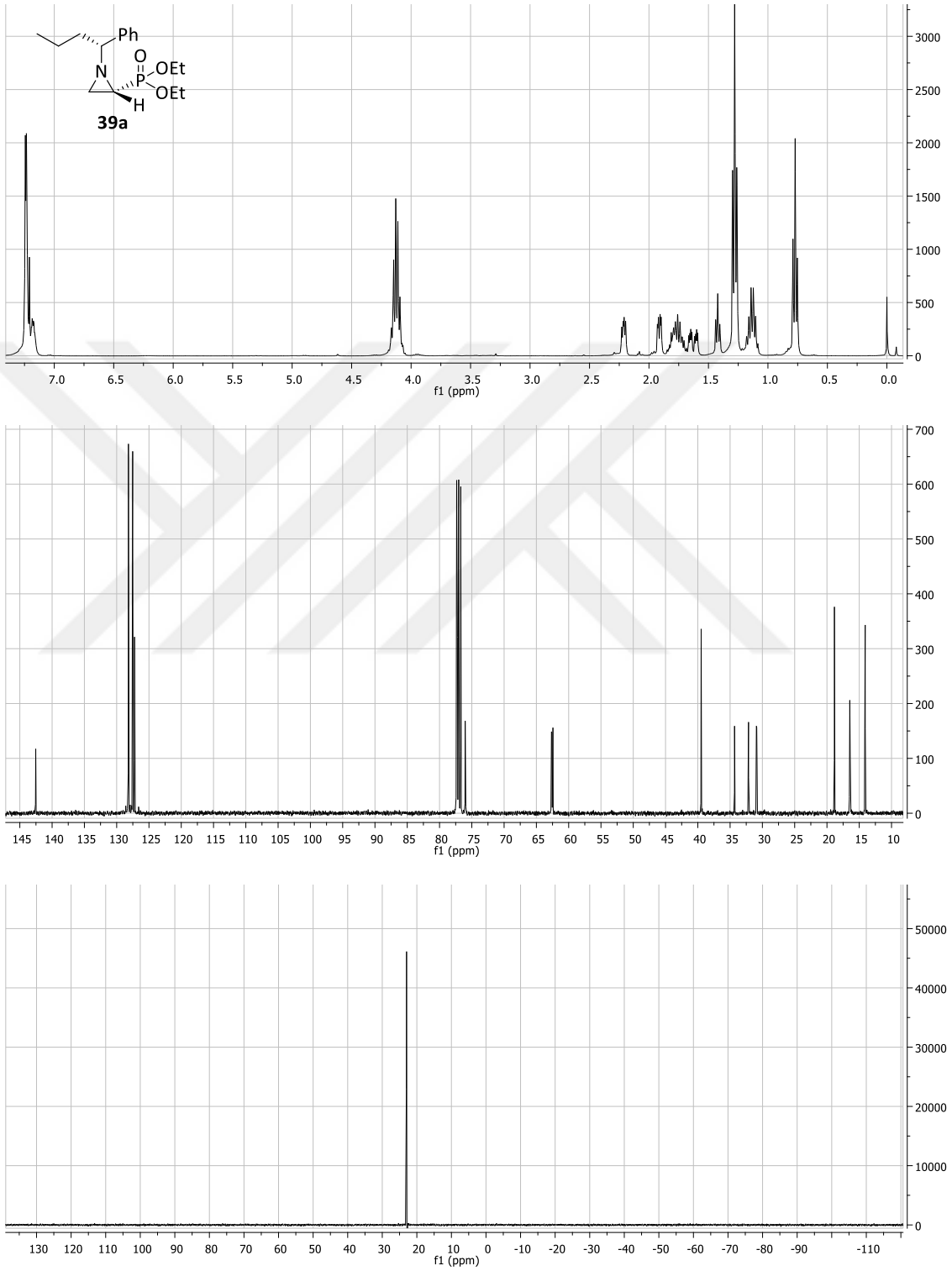


Figure 17. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***39a.***

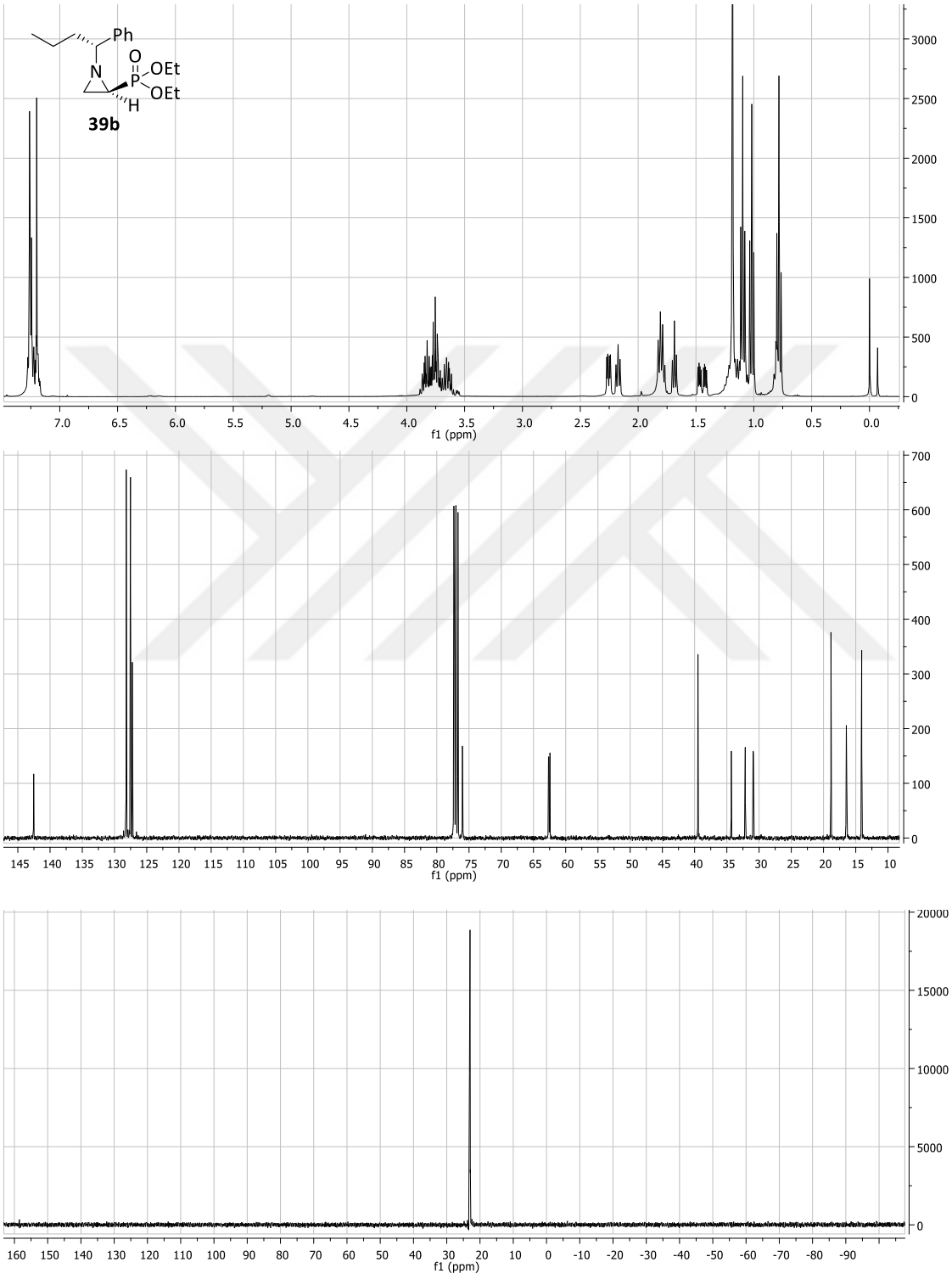


Figure 18. ^{1}H, ^{13}C and ^{31}P NMR spectra of compound **39b.**

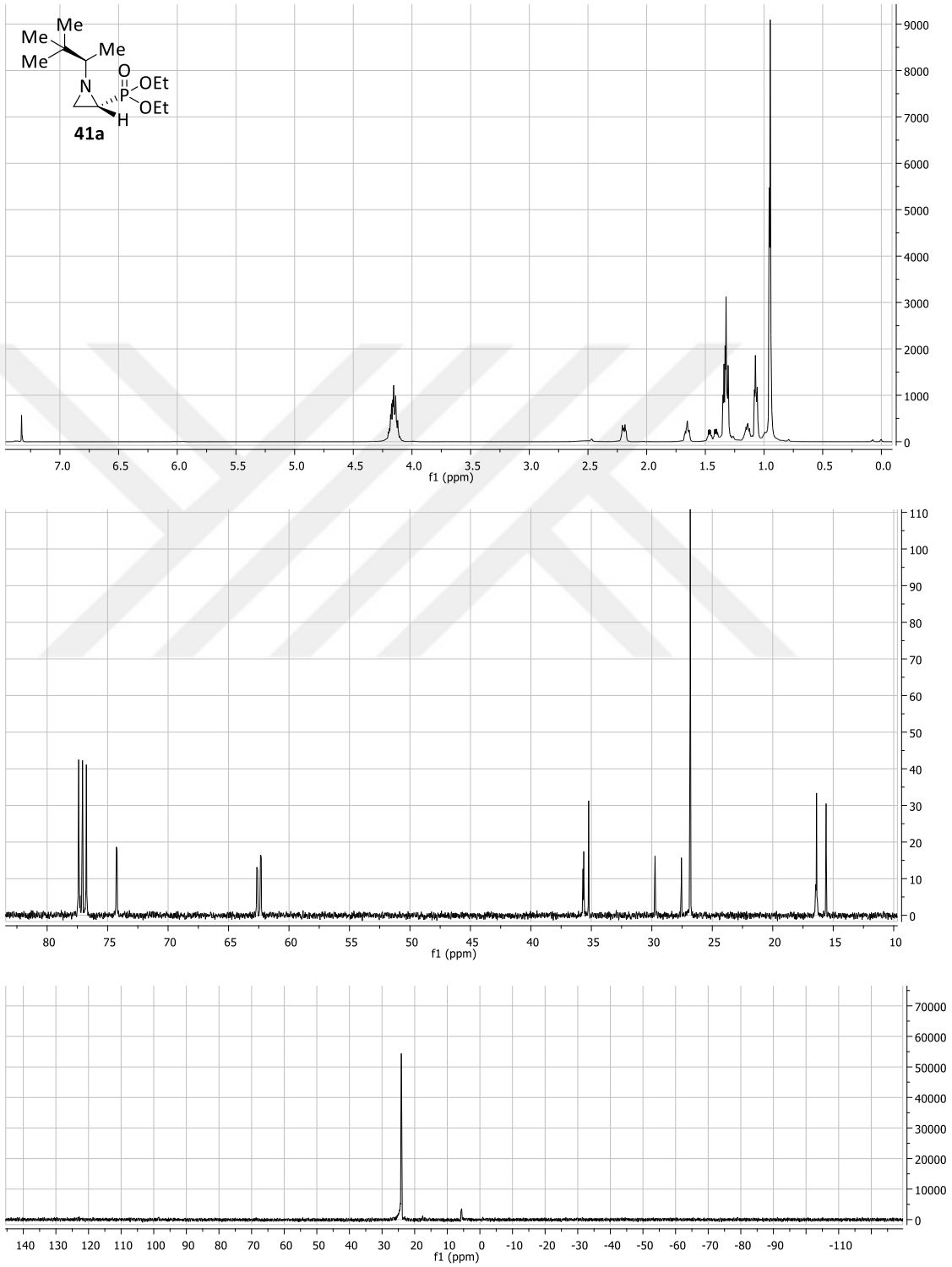


Figure 19**. ^{1}H, ^{13}C and ^{31}P NMR spectra of compound **41a.

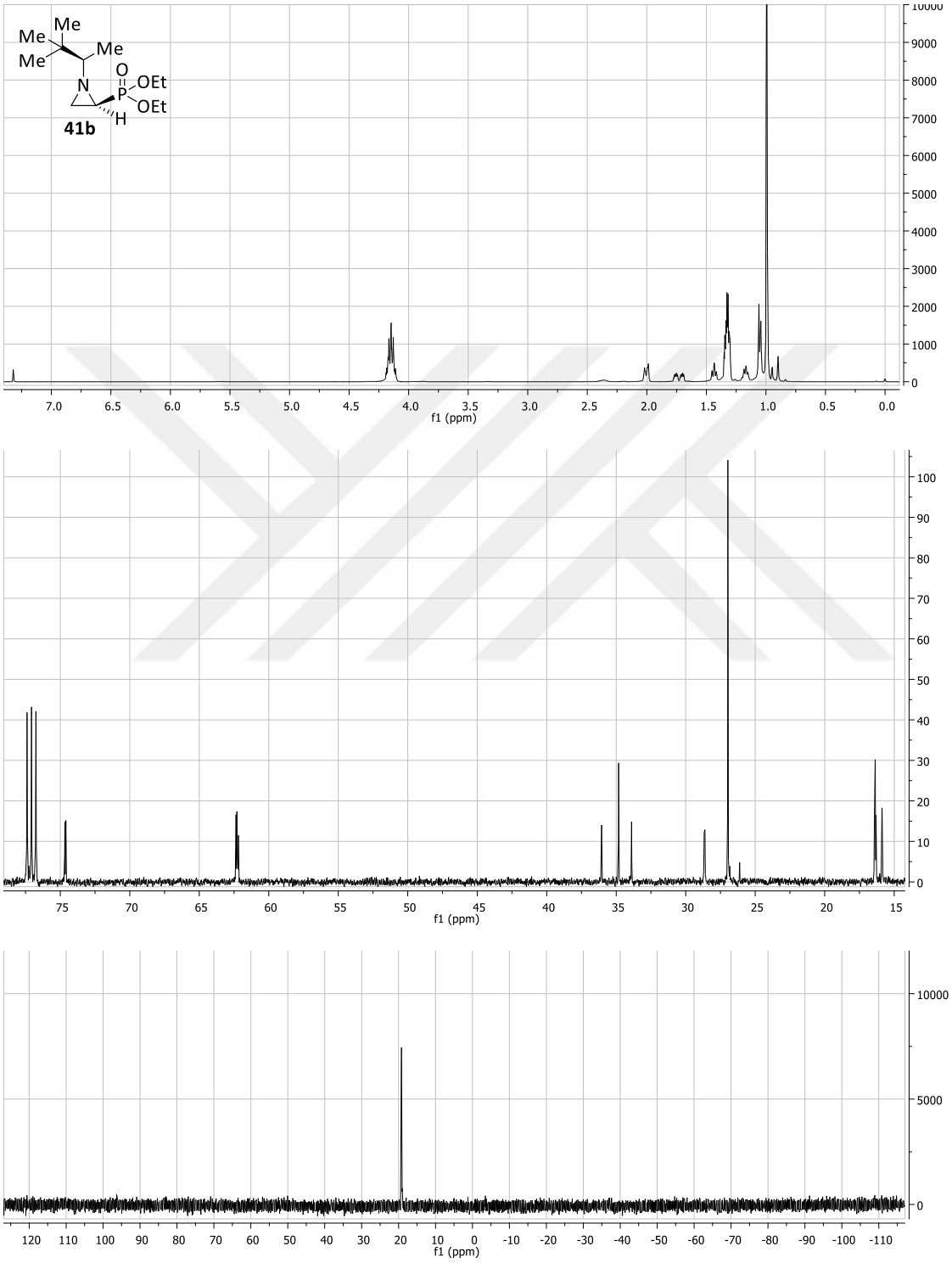


Figure 20**. [1]H, [13]C and [31]P NMR spectra of compound **41b.

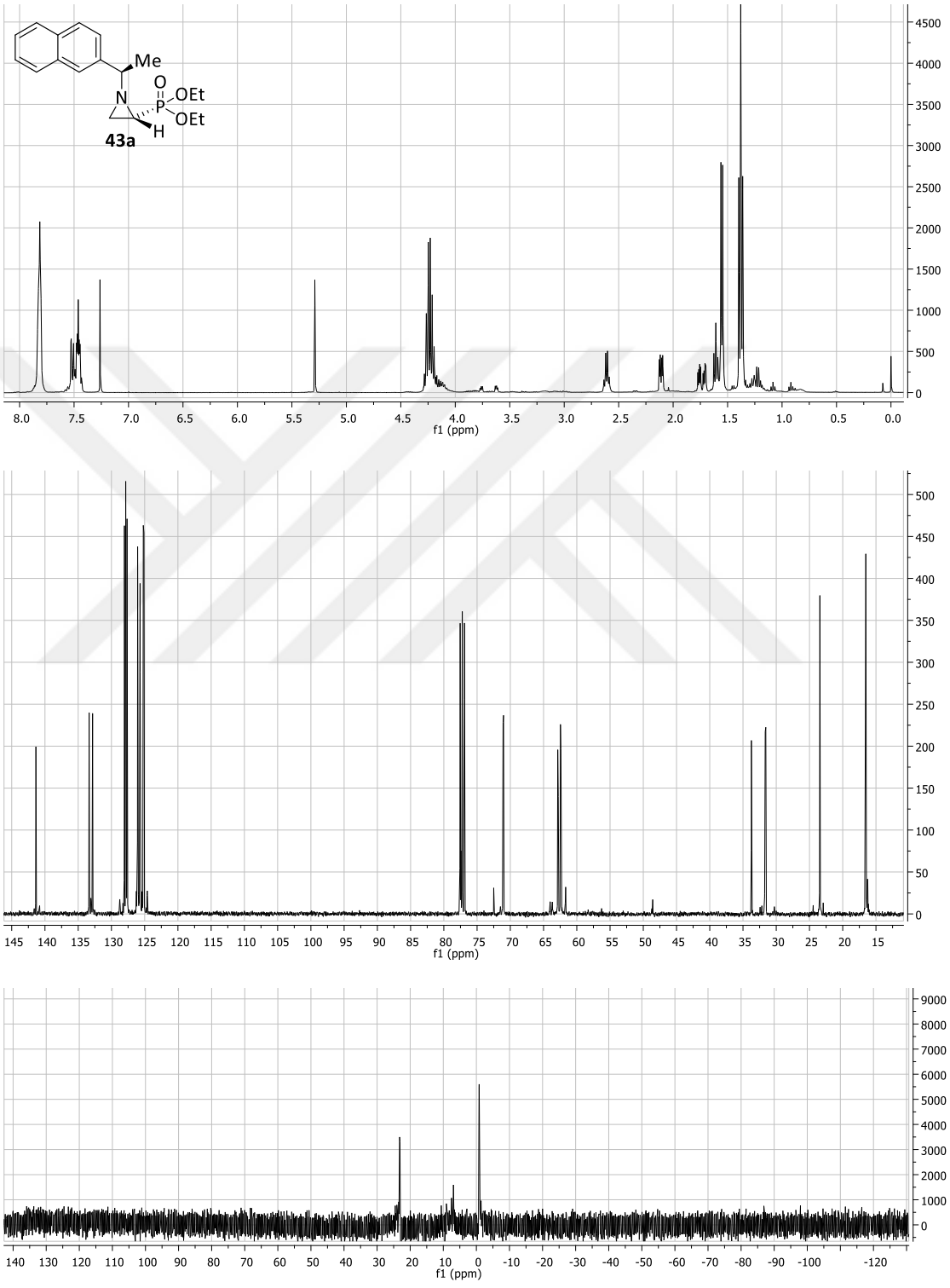


Figure 21. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***43a.***

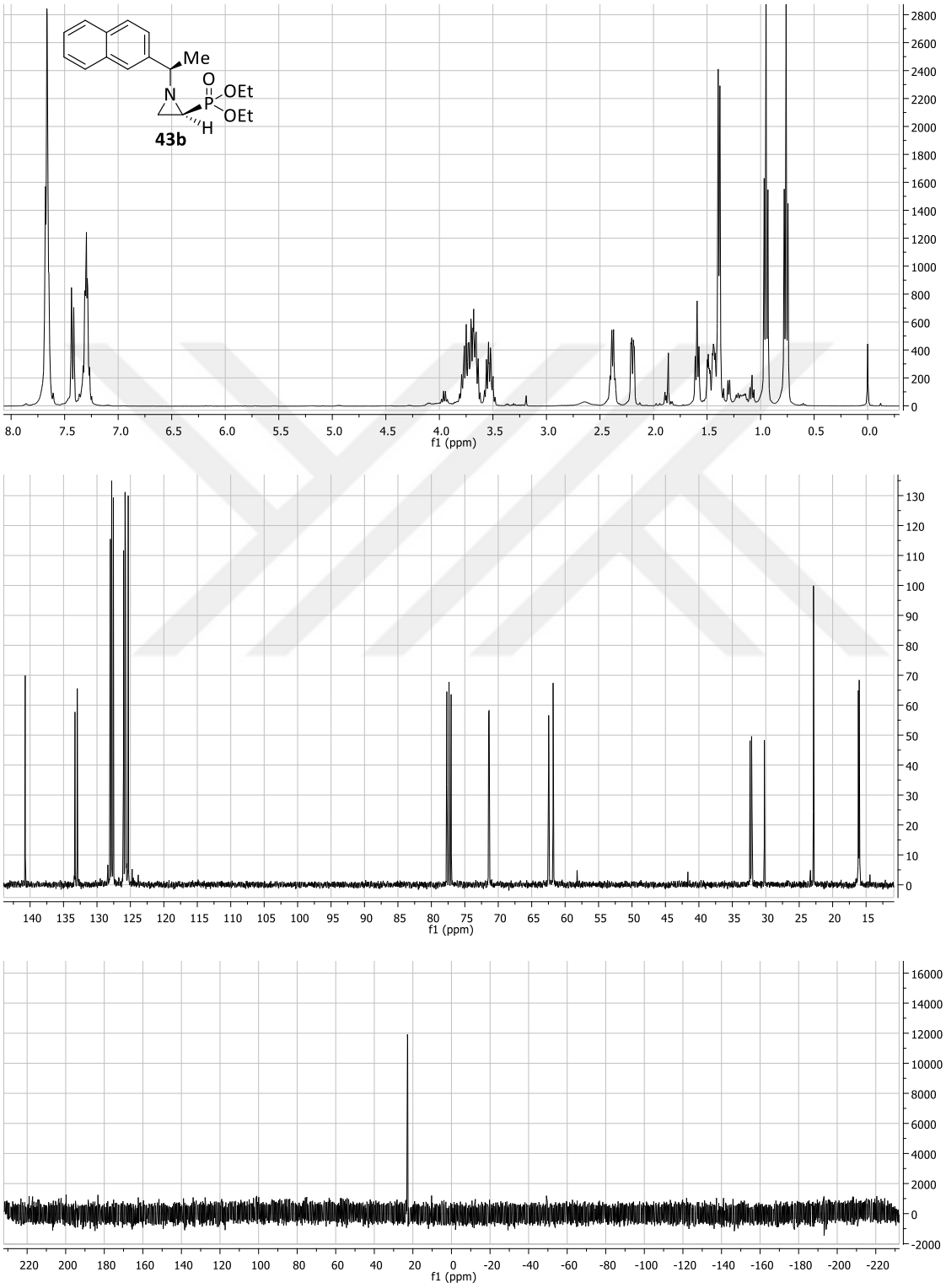


Figure 22. *^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***43b.***

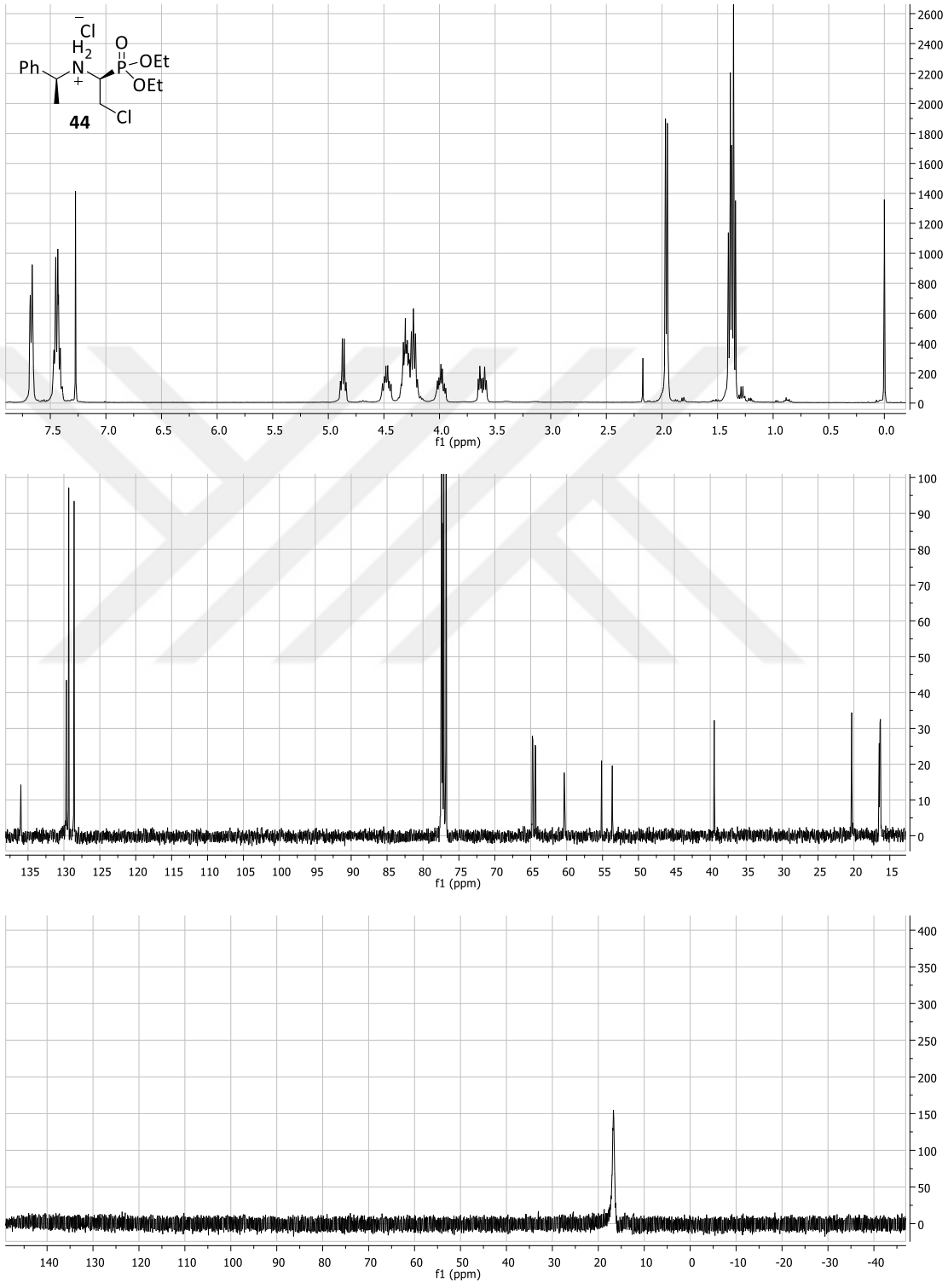


Figure 23*. [1]H, [13]C and [31]P NMR spectra of compound* ***44.***

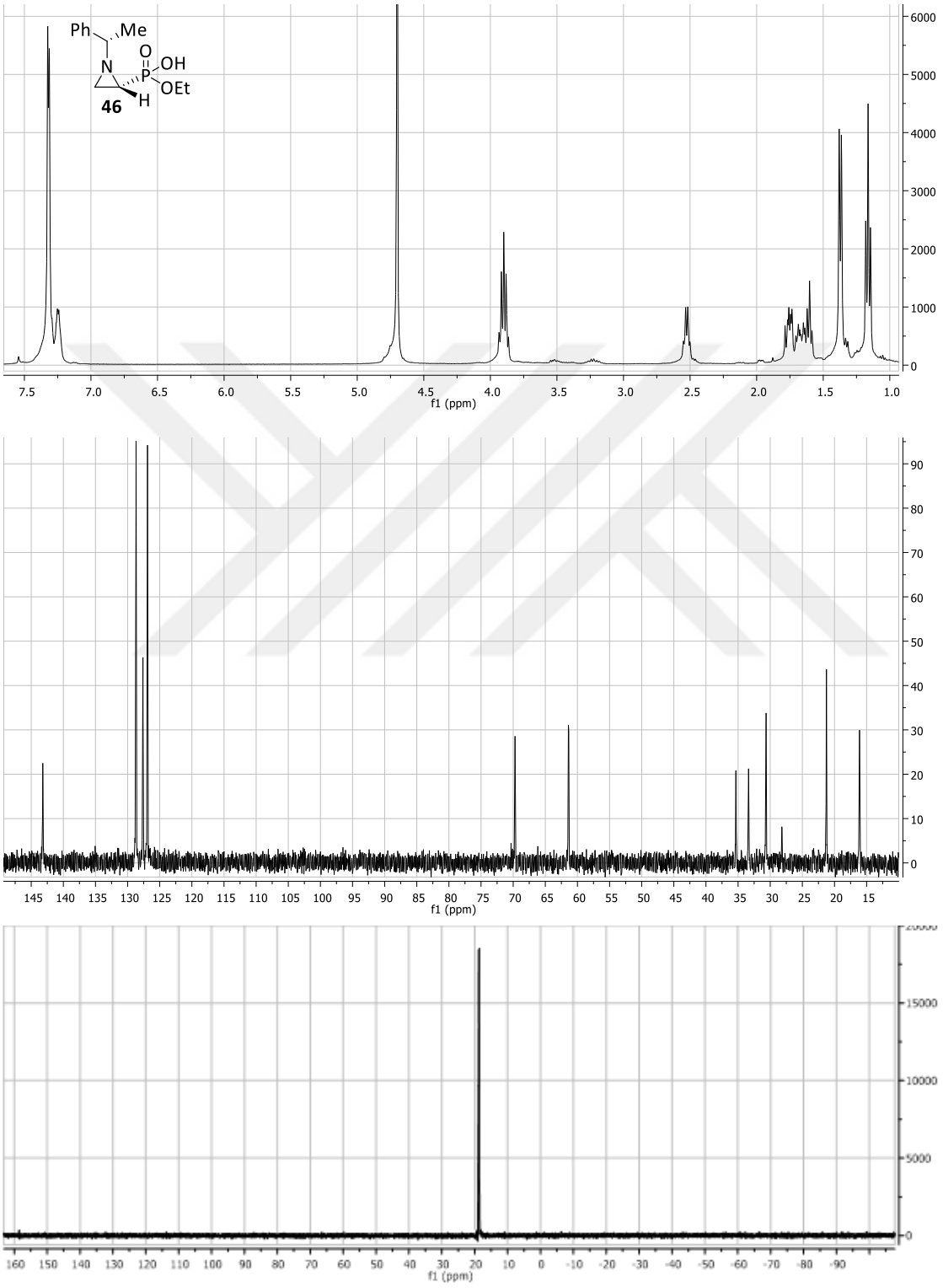


Figure 24*. ^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***46.***

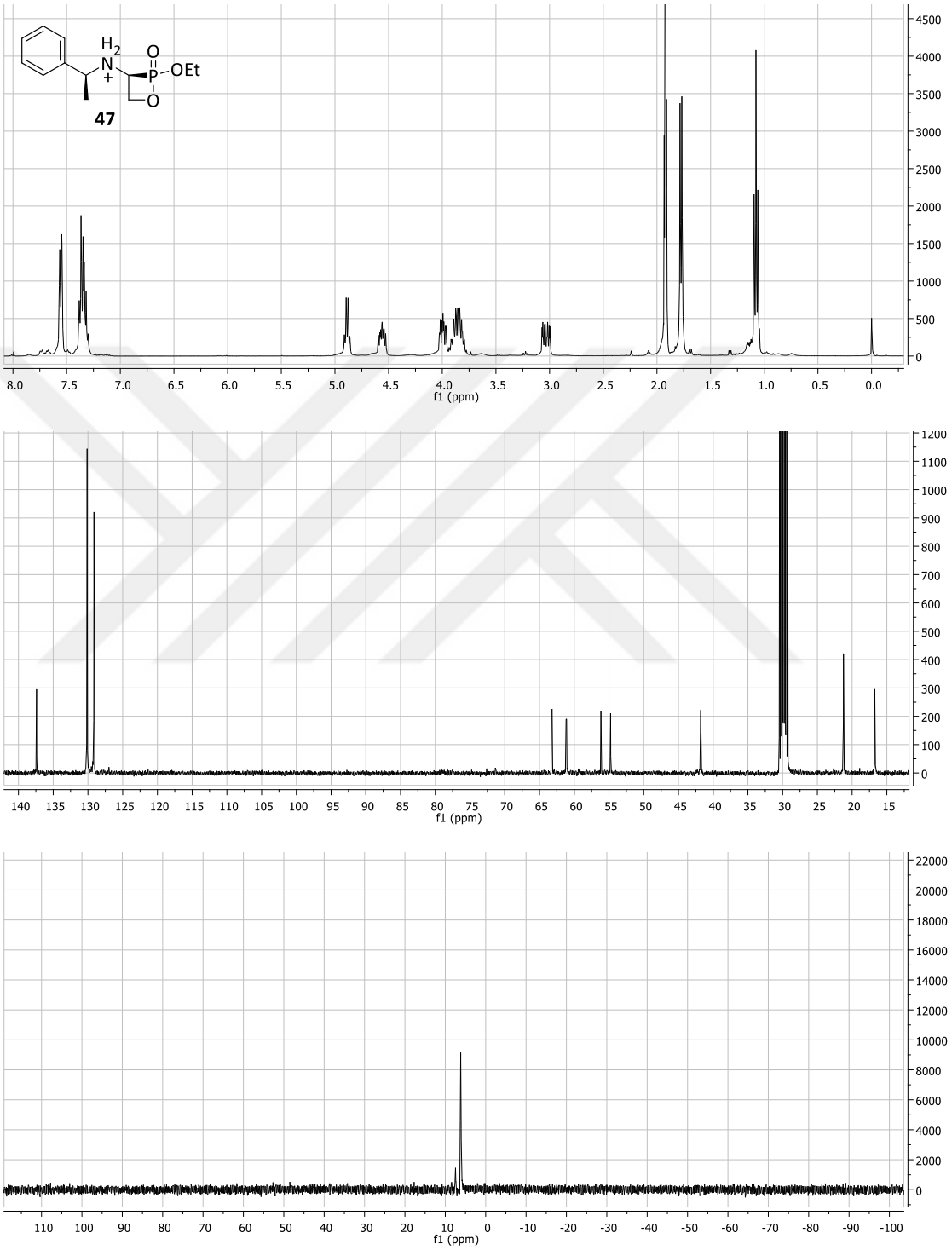


Figure 25*. ^{1}H, ^{13}C and ^{31}P NMR spectra of compound* ***47.***

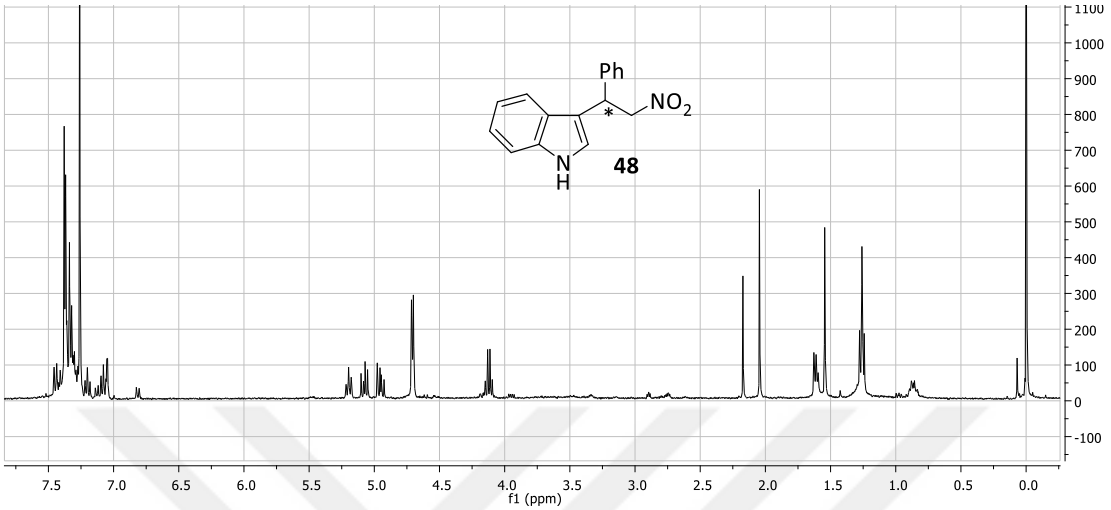


Figure 26*. [1]H NMR spectra of compound* ***48.***

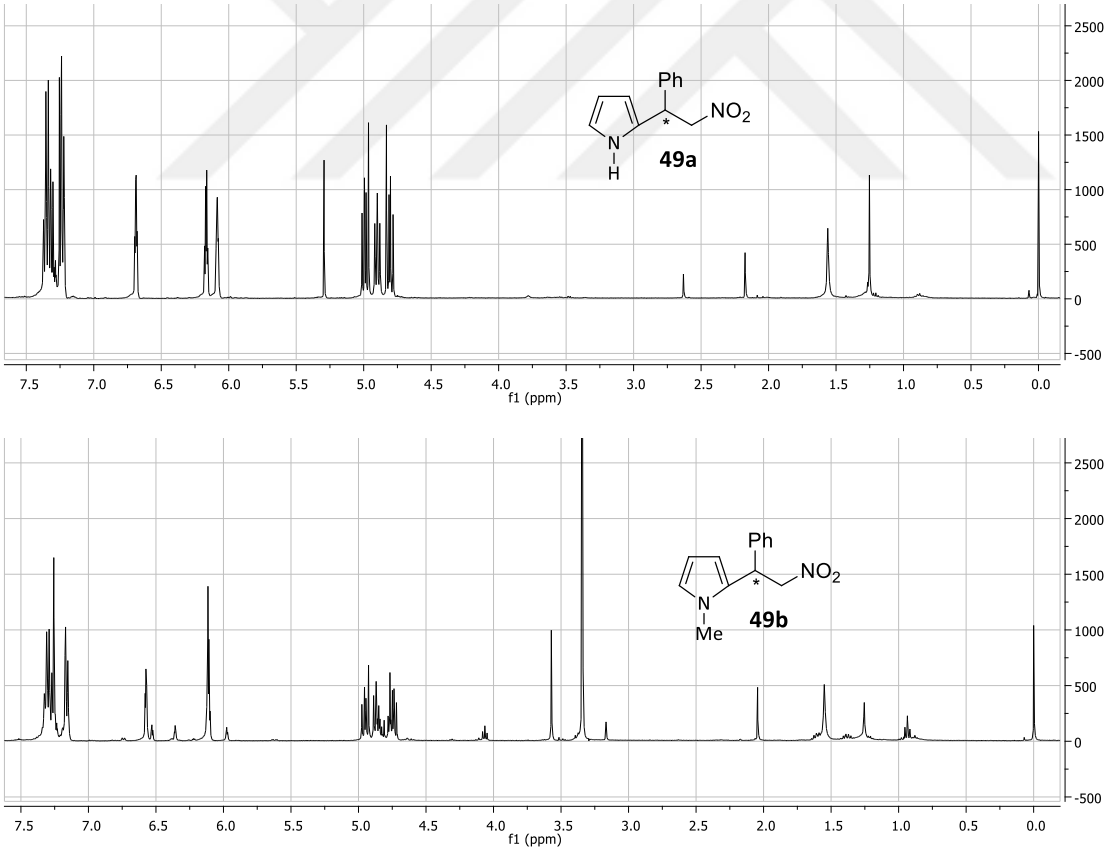


Figure 27*. [1]H NMR spectra of compounds* ***49a*** *and* ***49b.***

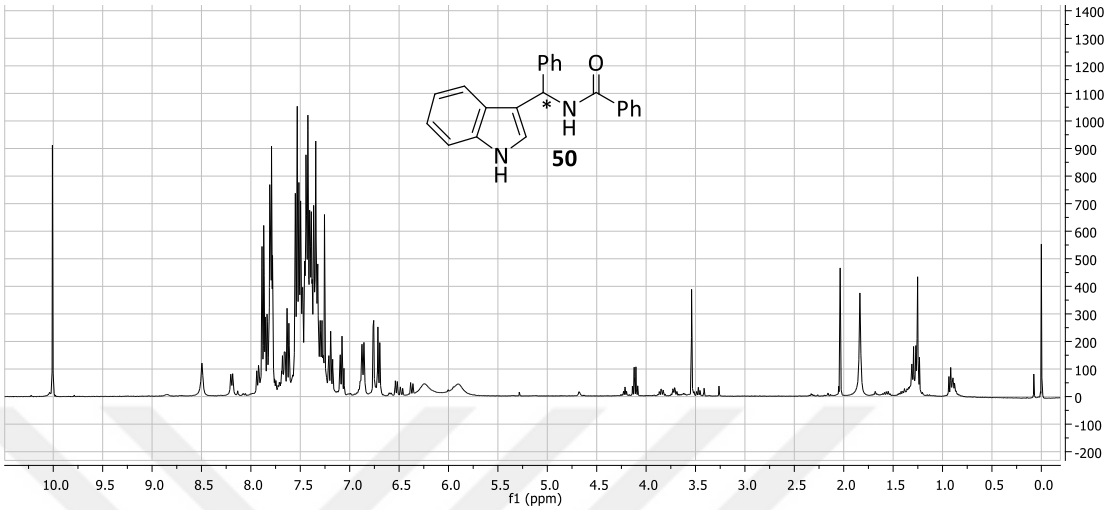


Figure 28**. [1]H NMR spectra of compound **50.

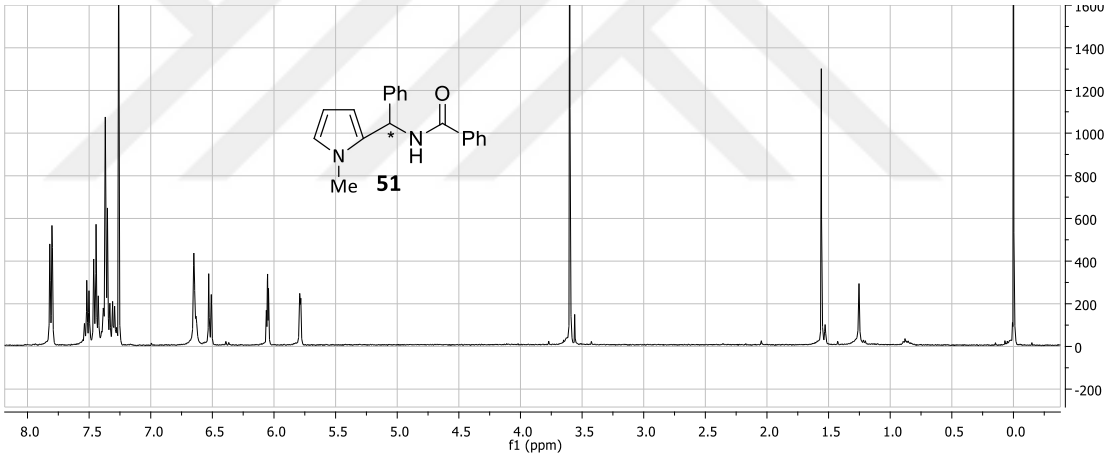
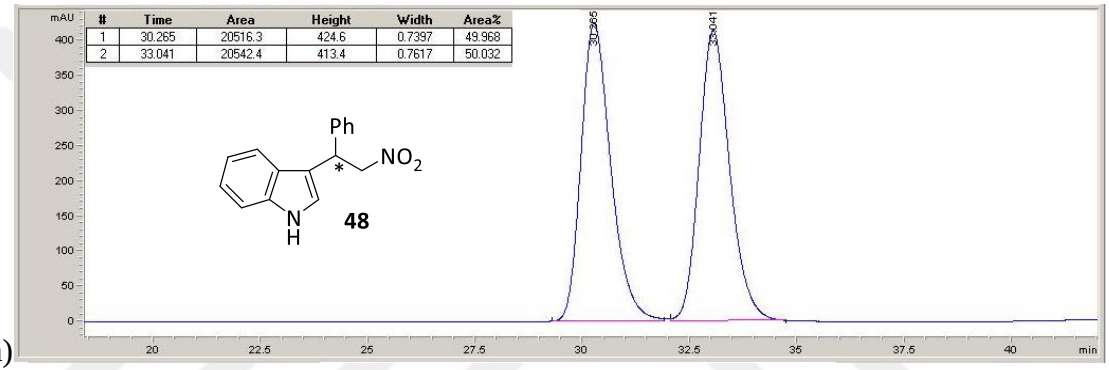


Figure 29**. [1]H NMR spectra of compound **51.

APPENDIX B

HPLC CHROMATOGRAPHY

a)



b)

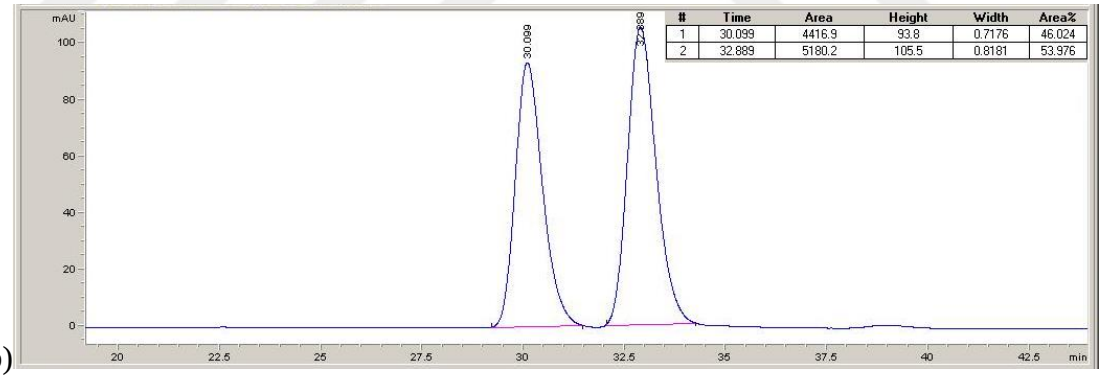
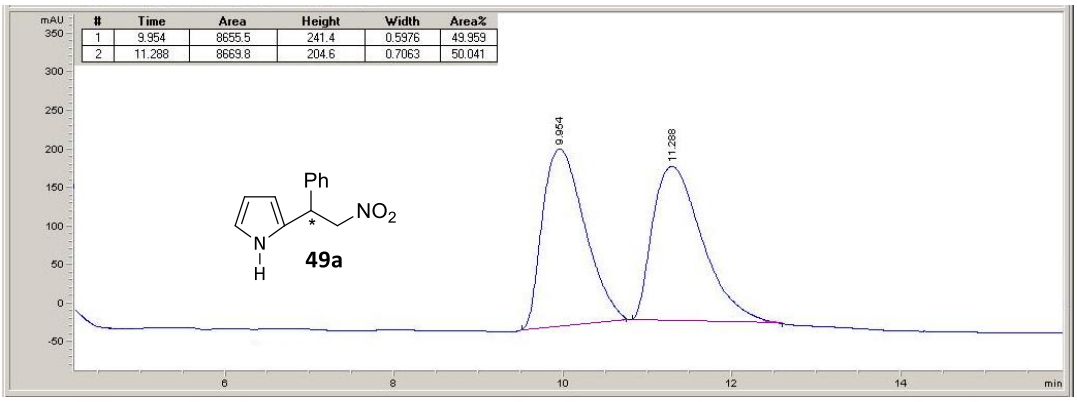


***Figure 30**. HPLC of the compound **48**, a) racemic, b) 8% ee.*

a)



b)

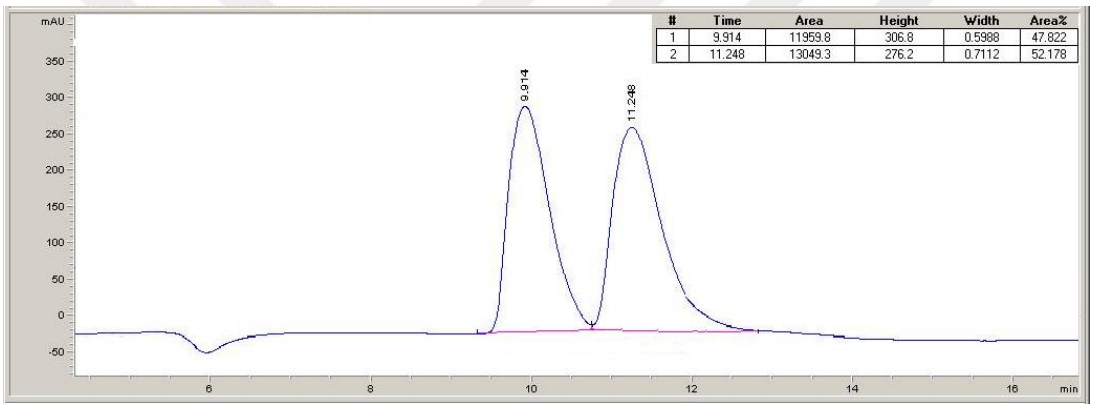
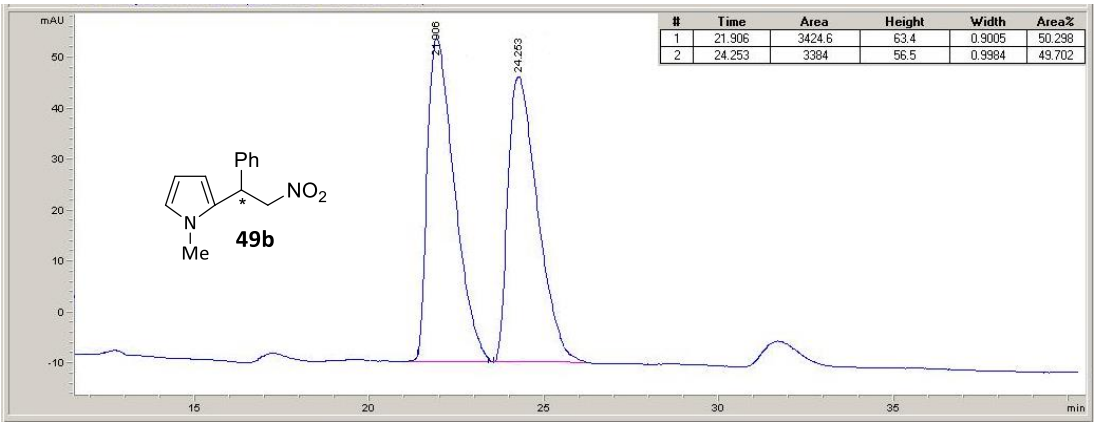


Figure 31. *HPLC of the compound* ***49a****, a) racemic, b) 4% ee.*

a)



b)

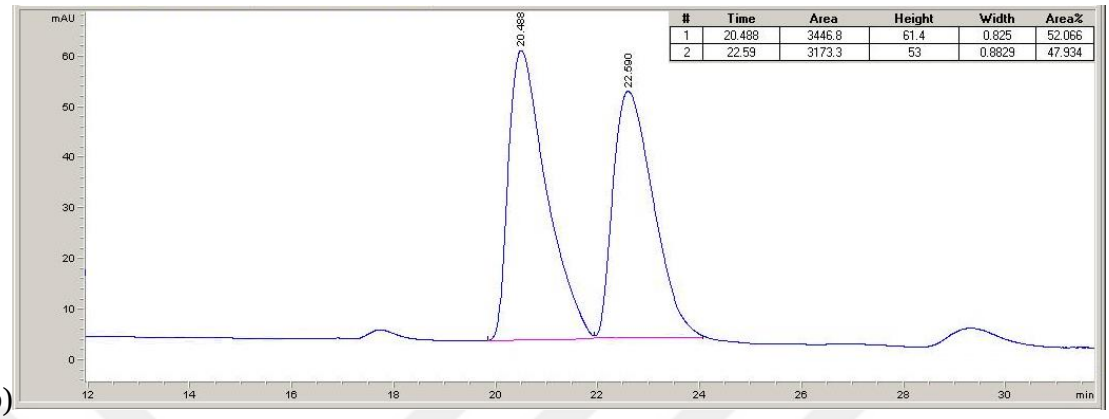
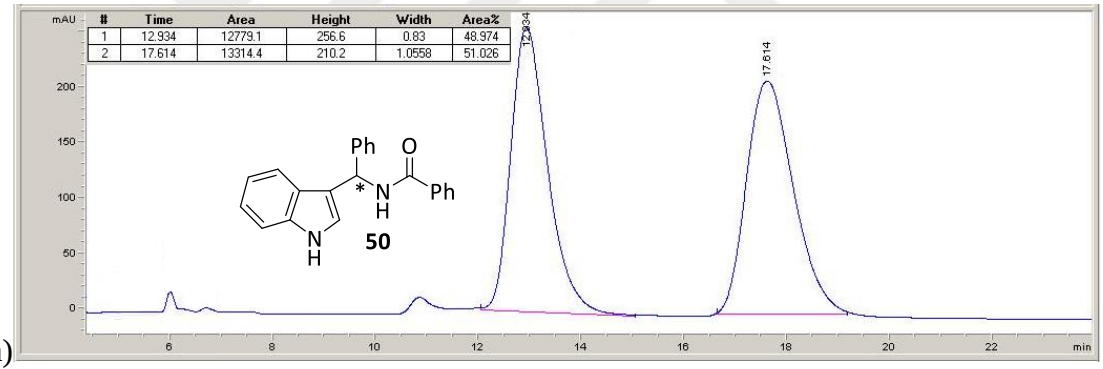


***Figure 32**. HPLC of the compound **49b**, a) racemic, b) 4% ee.*

a)



b)

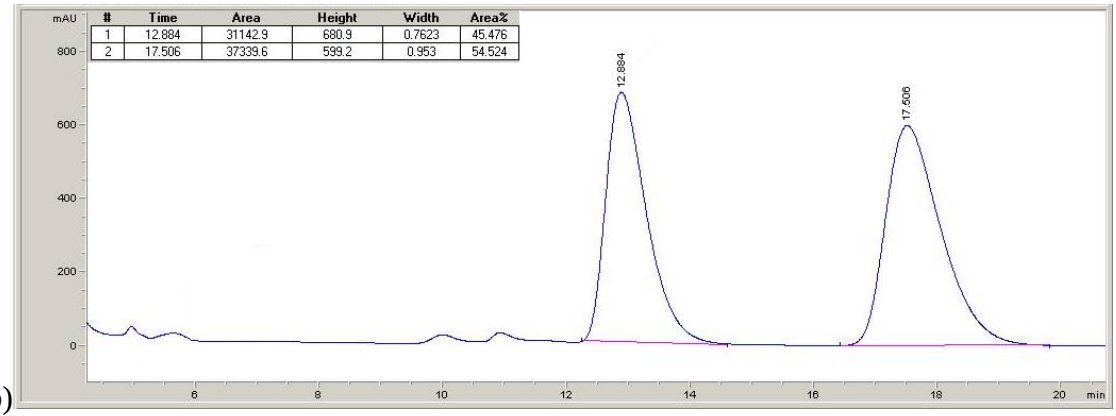
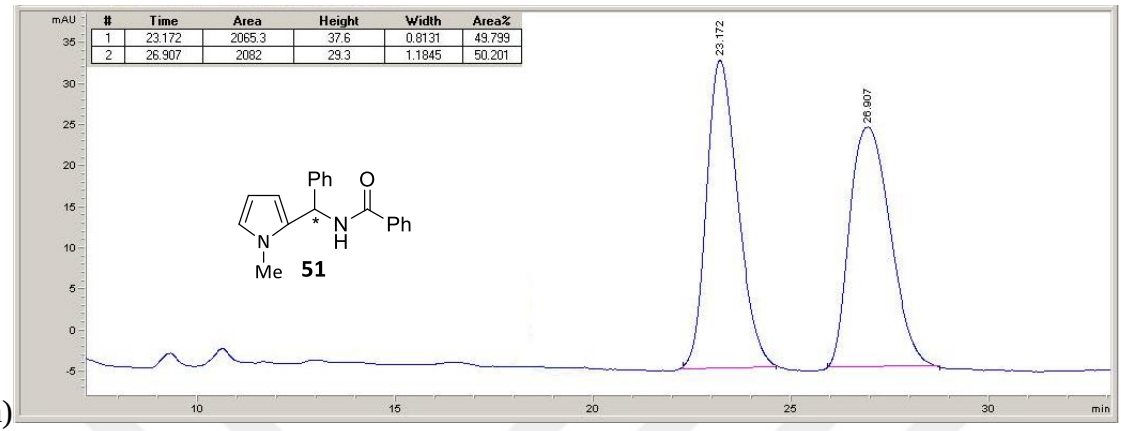


***Figure 33**. HPLC of the compound **50**, a) racemic, b) 9% ee.*

a)



b)

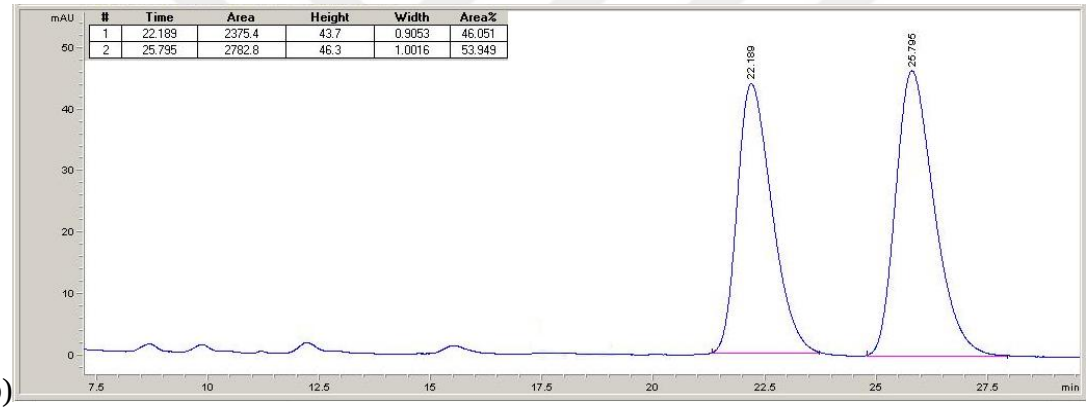


Figure 34*. HPLC of the compound* ***51****, a) racemic, b) 8% ee.*