# REACTIONS OF DIETHYLALUMINUM CYANIDE WITH ACYL PHOSPHONATES

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

BY

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

JANUARY 2010

Approval of the thesis:

**REACTIONS OF DIETHYLALUMINUM CYANIDE WITH ACYL PHOSPHONATES**

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## ABSTRACT

REACTIONS OF DIETHYLALUMINUM CYANIDE WITH ACYL PHOSPHONATES

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January 2010, 67 pages

This thesis includes reaction of diethylaluminum cyanide with acyl phosphonates. Cyanohidrin *O*-phosphates are synthesized from easily available acyl phosphonates and diethylaluminum cyanide. Synthesis of cross-benzoin product of acyl phosphonate, α-hydroxy phosphonate and tertiary carbinol are synthesized from the reaction of diethylaluminum cyanide with acyl phosphonates, representatively. Asymmetric syntheses of cyanohydrin and benzoin type reaction of acyl phoshonate are also investigated representatively.



**Keywords:** Diethylaluminum Cyanide, Cyanohidrin *O*-phosphate, α-Hydroxy Phosphonate, Tertiary Carbinol, Cross-Benzoin Reaction, Acyl Phosphonate

# ÖZ


DİETİLALÜMİNYUM SİYANÜRÜN AÇİL FOSFONATLAR İLE REAKSİYONLARI

Sevim, İlhan

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Ocak 2010, 67 sayfa

Bu tez dietilalüminyum siyanür ile açil fosfonatların reaksiyonlarını içermektedir. Açil fosfonatler ile dietilalüminyum siyanürün reaksiyonları sonucu siyanohidrin *O*-fosfatlar sentezlenmiştir. Açil fosfonatların çapraz benzoin ürünü, α-hidroksi fosfonat ve üçünü derece karbinol örnek sentezleri, açil fosfonatlar ve dietilalüminyum siyanür kullanılarak incelenmiştir. Siyanohidrin ve açil fosfonatın benzoin tipi örnek reaksiyonları asimetrik olarak incelenmiştir.



**Anahtar Kelimeler:** Dietilalüminyum Siyanür, Siyanohidrin *O*-Fosfat, α-Hidroksi Fosfonat, Üçünü Derece Karbinol, Çapraz Benzoin Reaksiyonu, Açil Fosfonat

To My Family,

**ACKNOWLEDGEMENTS**

I would like to express my sincere thanks to my supervisor Prof. Dr. Ayhan S. Demir not only for his guidance, support, encouragement, patience and for teaching us how to become a good scientist but also for listening and helping us in many ways.

I would like to thank to Dr. Mustafa Emrullahoğlu for his help.

I would like to thank to ASD Research Group members for their help and frienship.

I would like to thank to Meryem Seda Karayılan and Zehra Uzunoğlu for their kind help in our routine and special NMR analysis.

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# CHAPTER 1

# INTRODUCTION

Synthetic organic chemistry is an applied science as it includes the "design, analysis, and construction of works for practical purposes". Synthesizing a novel compound is a problem solving task in organic chemistry, where a synthesis is designed for a target molecule by selecting optimal reactions from optimal starting materials. Most of the complex compounds can have tens of reaction steps in a complex discipline that sequentially build the desired molecule. Designing and proving practically useful syntheses always requires conducting the actual synthesis in the laboratory.

In literature, there are several strategies to design a synthesis. E.J. Corey developed the modern method of "retrosynthesis", starting with the target molecule and splices it to pieces according to known reactions. The pieces, or the proposed precursors, receive the same treatment, until available and ideally inexpensive starting materials are reached. Then, the retrosynthesis is written in the opposite direction to give the synthesis. A "synthetic tree" can be constructed, because each compound and also each precursor has multiple syntheses.

Retrosynthetic (or antithetic) analysis is a systematic process for arriving at a solution for transforming the structure of a synthetic target molecule to a sequence of gradually simpler structures through a pathway which finally leads to simple or commercially available starting materials for a chemical synthesis. Converting the molecule to a synthetic precursor is achieved by the application of a transform, the exact reverse of a synthetic reaction, to a target structure. Each structure derived retrosyntheticaly from a target then itself becomes a target for further analysis. Repeating this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from

bottom to top corresponding to possible synthetic routes to the target molecule. Such trees, called ex-synthetic target trees since they grow out from the synthetic target, can be quite complex since a high degree of branching is possible at each node and since the vertical pathways can include many steps. This central fact implies the necessity for control or guidance in the generation of ex-synthetic target trees so as to avoid explosive branching and the proliferation of useless pathways [1].

In this perspective, there are different types of reactions to synthesize desired target molecules in literature. Recently, Demir et al. showed that reactions of acyl phosphonates offer practical solutions to synthesize desired starting compounds for many interesting molecules [2].

### 1.1 Reactivity Patterns In Organic Synthesis

#### 1.1.1 The Synthetic Problem

Great majority of reactions used in organic synthesis are polar in nature, i. e. nuclephilic or donor (**d**) and electrophilic or acceptor (**a**) sites are used to make and break bonds. Most of the target molecules in organic sytnthesis contain the heteroatoms nitrogen and oxygen as functional groups (amino, imino, hydroxyl, ether, carbonyl). These heteroatoms enforce an alternating acceptor and donor reactivity pattern upon the carbon skeleton, i. e. acceptor properties or attack by donors at carbons $C^{1, 3, 5,\cdots}$ , and donor properties or attack by acceptors at carbons $C^{2,4,6,\cdots}$ ; the heteroatom $X^0$ itself is a donor center $d^0$ [3].

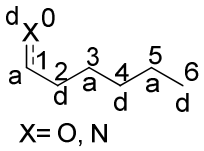



**Figure 1.** Reactivity Pattern in a Molecule

Since most organic reactions are polar in nature (i.e. a nucleophile attacks to electrophile), there is a synthetic limitation: only an odd number of carbons may be placed between functional groups;

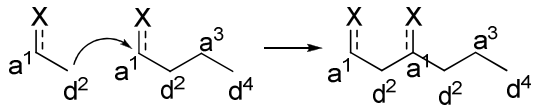



**Figure 2.** 1, 3 Disubstitution

Coupling of components with the same polarity are required to synthesize a molecule with even number of carbons in between functional groups.

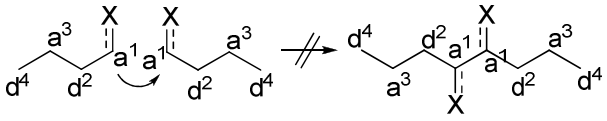



**Figure 3.** 1, 2 Disubstitution

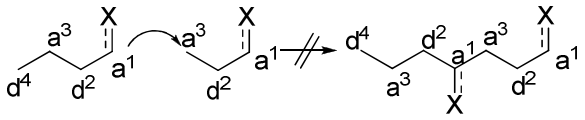



**Figure 4.** 1, 4 Disubstitution

Umpolung concept was introduced by D. Seebach (hence the German word umpolung for reversed polarity) and E.J. Corey to solve the problem [4]. Umpolung or polarity inversion in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group [3]. Classic umpolung applications can be found in Grignard reagents and in the benzoin condensation. Benzoin condensation will be mainly focused on in this part.

### 1.2 Acyl Phosphonates In Synthetic Organic Chemistry

#### 1.2.1 Benzoin Condensation

The **benzoin condensation** is a reaction between two aromatic aldehydes, particularly benzaldehyde. The reaction is catalyzed by a nucleophile such as the cyanide anion or an N-heterocyclic carbene. The reaction product is an aromatic acyloin with benzoin as the parent compound [5]. An early version of the reaction was developed in 1832 by Justus von Liebig and Friederich Woehler [6]. The catalytic version of the reaction was developed by Nikolay Zinin in the late 1830s [7], and the reaction mechanism for this organic reaction was proposed in 1903 by A. J. Lapworth [8].

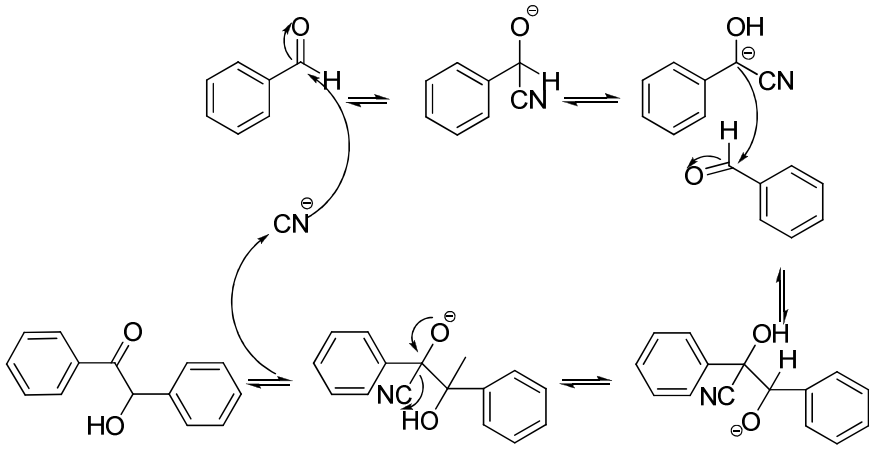



**Figure 5.** Benzoin Condensation Reaction Mechanism

In the first step in this reaction, the cyanide anion reacts with the aldehyde in a nucleophilic addition. Rearrangement of the intermediate results in polarity reversal of the carbonyl group, which then adds to the second carbonyl group in a second nucleophilic addition. Proton transfer and elimination of the cyanide ion affords benzoin as the product. This is a reversible reaction.

But this synthetic method has some drawbacks. When two different aldehydes are introduced to react, some limitations arise; relative thermodynamic stability of four products determine the result of the reaction because all of the steps in the classical benzoin condensation are reversible [9].

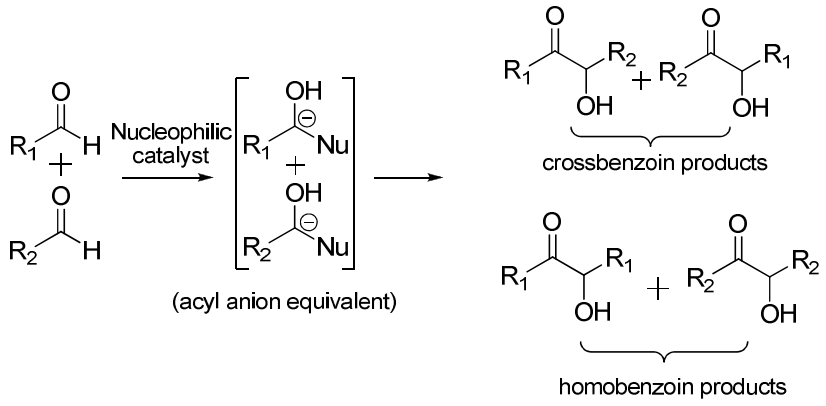



**Figure 6.** Cross Benzoin Reaction

At that point, it is very important to introduce a practical synthetic method to kinetically conrol the reaction and synthesize the desired product without any sideproducts. To solve this problem, chemists introduce the acyl anion equivalents to react with aldehydes to synthesize a variety of unsymmetrical benzoin derivatives. At this part, acyl silane chemistry will be discussed.

### 1.2.2 Acyl Silanes as Acyl Anion Precursors

In benzoin condensation the key step is generation of acyl anion equivalents via the reaction of an aldehyde with cyanide ion. In this context, generation of alternative methods to produce acyl anion equivalents may be achieved by controlled direct cross benzoin reactions. In literature there are some examples of this approach which contains in situ generation of (silyloxy)nitrile anions from acylsilanes by cyanide-promoted [1,2]-Brook rearrangement [10]. Johnson and his coworkers introduced this logic into cross benzoin condensation reactions and they get satisfactory results [9]. They described cross silyl benzoin addition reactions between acylsilanes **1** and aldehydes **2** catalyzed by metal cyanides. Unsymmetrical aryl-, heteroaryl-, and alkyl-substituted benzoin adducts can be generated in moderate to excellent yields with complete regiocontrol using potassium cyanide and a phase transfer catalyst as 18-crown-6.

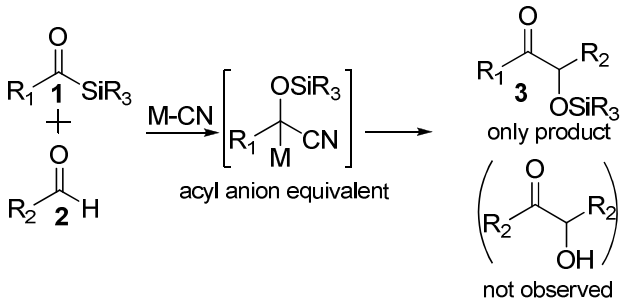



**Figure 7.** Cross Silyl Benzoin Additions Based on [1,2]-Brook Rearrangement

Proposed mechanism is introduced as in Figure 8.

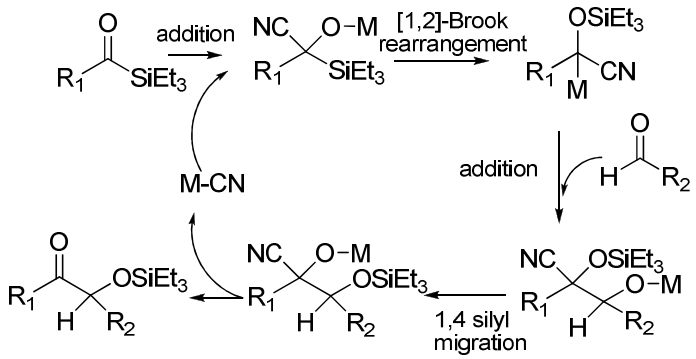



**Figure 8.** Proposed Mechanism for Cross Silyl Benzoin Addition

Johnson also expanded the scope of cross silyl benzoin reaction to enantioselective synthesis. Takeda proved that lithium diethyl phosphite reacts stoichiometrically with acylsilane to give carbanion after Brook rearrangement [11]. Zimmer also showed that the addition of (silyloxy)phosphanate anion to aldehydes can afford silyl benzoin products [12]. By using these informations, Johnson used metallophophite in Figure 9 and found moderate to high enantioselectivity (41-91 % ee).

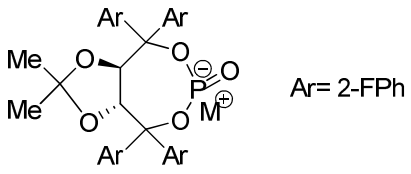



**Figure 9.** Metallophosphite

It must be stated that the cyanide catalyzed cross silyl benzoin reaction is good improvement on benzoin condensation reactions both in catalytic and asymmetric aspects. But the main drawback of cross silyl benzoin reaction is the availibilty of starting materials. Acyl silanes are expensive compounds because of their synthetic pathways. There are different types of reactions to synthesize acyl silanes. Generally used one is indicated in Figure 10. This synthetic pathway starts with protection of an aldehyde with propane-1,3-dithiol, generation of an acyl anion equivalent by taking proton with strong base n-BuLi, introducing $ClSiEt_3$ and hydrolysis.

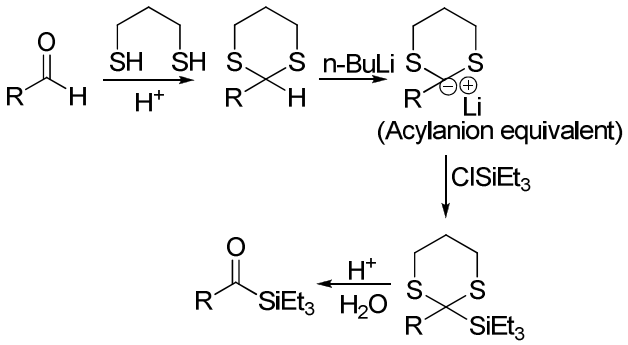



**Figure 10.** Synthesis of Acyl Silanes

So, it is obvious that this pathway has low atom economy and low overall yield due to reaction steps. Scientifically, this must be improved and chemists must introduce more practical way to get acyl anion equivalents in order to solve this problem. Recently, Demir and coworkers showed that acyl phosphonates are acyl anion precursors [2a].

### 1.2.3 Acyl Phosphonates as Acyl Anion Precursors

The Michaelis–Arbuzov reaction is the chemical reaction of a trialkyl phosphite and an alkyl halide to form a phosphonate. Application of this procedure to acyl chlorides give acyl phosphonates in multigram scales [13].(Figure 11.)

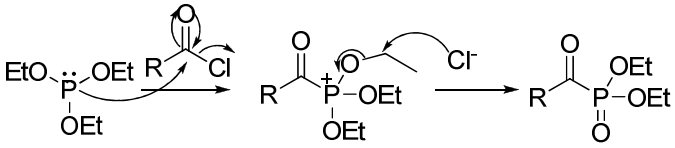



**Figure 11.** Synthesis of Acyl Phosphonates

Acyl phosphonates are easily accessible and stable compounds under unhydrous conditions. Phosphorus, like silicon, can migrate from carbon to oxygen and oxygen to carbon. Base catalyzed addition of dialkyl phosphites to acylphophonates and deprotonation of α-hydroxyphophonates include such phosphonate-phosphate rearrangements, which has same logic of 1,2-Brook rearrangementof acyl silanes [14]. Demir and his coworker's thougt that typical nucleophilic catalysis of benzoin might promote acylphosphonates to generate an appropriate concentration of the corresponding acyl anion equivalents that are sufficiently nucleophilic in order to participate in the reactions with electrophiles. At this point, it is important to note that Kurihara and co-workers showed the synthesis of cyanophosphate anions ( Figure 12) [15].

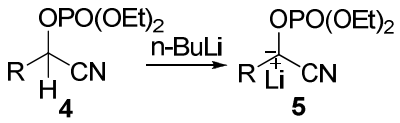



**Figure 12.** Access to Cyanophophate anion

Demir envisioned that it is possible to generate cyanophosphate anion as acyl anion precursors by considering phosphonate-phosphate rearrangement with using metalcyanides. Integrating all these informations, Demir's research group introduced a new method by using acylphophonate **6** as acyl anion precursor and aldehydes as electrophiles in the presence of cyanide catalyst to provide cross-benzoin product **12** (Figure 13).

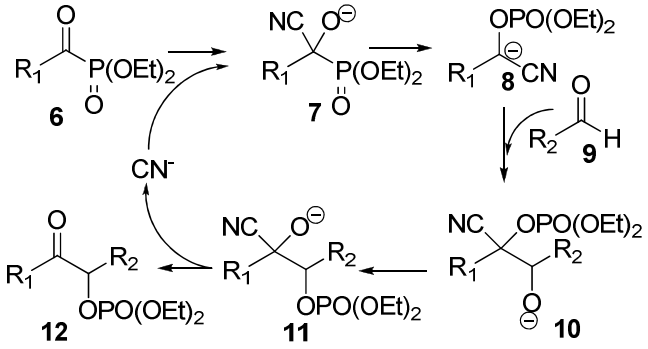



**Figure 13.** Mechanism of Cross-Benzoin Reaction via Cyanide Ion Promoted Generation of Acyl Anions from Acylphosphonates

They initially investigated the reaction of benzoylphosphonate with *p*-anisaldehyde catalyzed by 10% KCN in the presence of phase transfer catalysts ($Bu_4NBr$ or 18-crown-6) in various solvents and observed very slow or no conversion in many solvents at ambient temperature. Although heating provided varying degrees of conversions in different solvents, reaction in DMF provided a smooth and fast transformation into the desired product in 93% yield at ambient temperature without using a phase transfer catalyst. After investigating the scope of the reaction, they synthesized various aromatic-aromatic, aromatic-aliphatic and aliphatic aromatic cross benzoin products in good to excellent yields (64-94 %)[2a].

By showing acylphosphonates as acyl anion precursors in benzoin condensation, they carried out preliminary experiments to further study by extending the scope of this reaction. Thus, they examined the reaction of benzoylphosphonate with potent electrophile 2,2,2-trifluoroacetophenone **13**, which furnished the expected aldehyde-ketone coupling product **14** in 87% yield and later they investigated the conditions of this reaction and published this work[2g] (Figure 14). This was the first example in the literature for catalytic coupling of aldehydes with ketones.

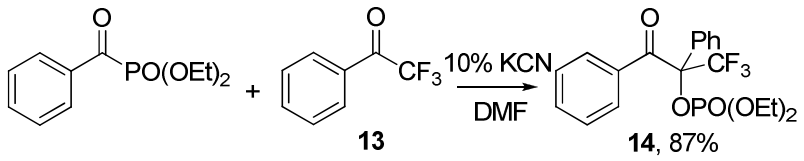



**Figure 14.** Reaction of Benzoylphosphonate With 2,2,2-Trifluoroacetophenone

As a result, Demir and coworkers showed that acylphosphonates are a new generation of potent acyl anion precursors that undergo nucleophile-promoted phosphonate-phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. Compared to laborious sythesis of acylsilanes, they are readily available on a multigram scale from the corresponding carboxylic acids or aldehydes, which offers an atom- and time-efficient access to acyl anions [2a].

### 1.3 Addition Reactions to Acyl Phophonates

#### 1.3.1 Sytnhesis of Cyanohidrin *O*-Phosphates

Carbon-carbon bond construction is very important in organic sythesis and acyl anion equivalents introduce a powerful alternative for this application. Cyanohidrins are very important intermediates in organic synthesis [16]. Hydrogen cyanide is generally used as cyanide source in cyanohidrin synthesis. But due to the reversible steps in this mechanism [17] (Figure 15), cyanohidrins are generally nonstable compounds under normal conditions.

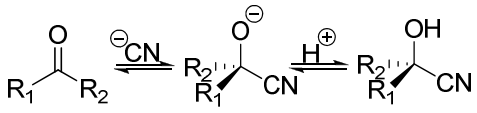



**Figure 15.** Cyanohidrin Synthesis

They can easily decompose to their starting aldehydes or ketones and produce toxic hydrogen cyanide gas. To solve this problem, *O*-protected cyanohidrins are required. So, classical *O*-protected cyanohidrin synthesis contains two steps; sythesizing cyonahidrin starting from aldehyde or ketone and protection. One-pot synthesis procedure is more advantageous than classical methods. There are different strategies for synthesis of cyanohidrin *O*-phosphates in literature [18]. But these strategies have complex and requires difficult available reagents. At that point, it is very important to introduce a more practical method which is starting from easily available compounds and mild conditions. Considering the phosphonate-phosphate rearrengement ability of acylphosphonates, they are acyl anion equivalents, when we look at the Figure 14, we see that compound **8** has carbanion and protonation of these carbanions give cyanohidrin *O*-phoshates in good yields [2c] (Figure 16).

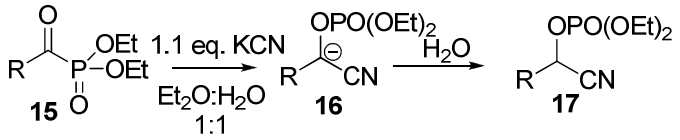



**Figure 16.** Protonation of Acyl Anion Equivalent Generated From Acyl Phosphonates

As shown in Figure 17, the protonation of **16** gives **17**, which is an aldehyde equivalent under the appropriate hydrolysis conditions. Therefore, this protonation strategy has the advantage of the direct reduction of carboxylic acids to aldehydes under aqueous conditions. The same transformation is known for the corresponding acylsilanes [19]. However, this is not a feasible approach because the synthesis of acylsilanes is laborious and generally obtained from aldehydes from which cyanohydrins are already available.

An interesting application of cyanohidrin *O*-phosphate has been shown in the literature. Reduction of cyanohidrin *O*-phosphate gives the corresponding β-amino alcohols, important intermediates in organic synthesis, in good yields (%88) (Figure 17)[20].

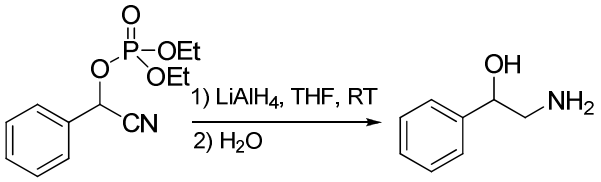



**Figure 17.** Reduction of Cyanohidrin *O*-Phosphate

### 1.3.2 Synthesis of Tertiary Carbinols

Acyl anion equivalents provide useful alternatives to traditional carbon-carbon bond forming reaction. Due to this ability of acyl phosphonates, Demir's research group showed another interesting application of acyl phosphonates [2e]. They have described new cyanation, phosphonate-phosphate rearrangement, *C*-acylation reactions of cyanophosphate anion with cyanoformate esters. With using phase-transfer catalyst, they synthesized protected tertiary carbinol products by cyanide-catalyzed reactions between acyl phosphonates and cyanoformates in good to excellent yields (74-95%). Ethyl cyanoformate is used as a cyanide source and electrophile. The scope of the reaction was investigated by using a number of benzoyl and acyl phosphonates along with ethyl cyanoformate (Figure 18).

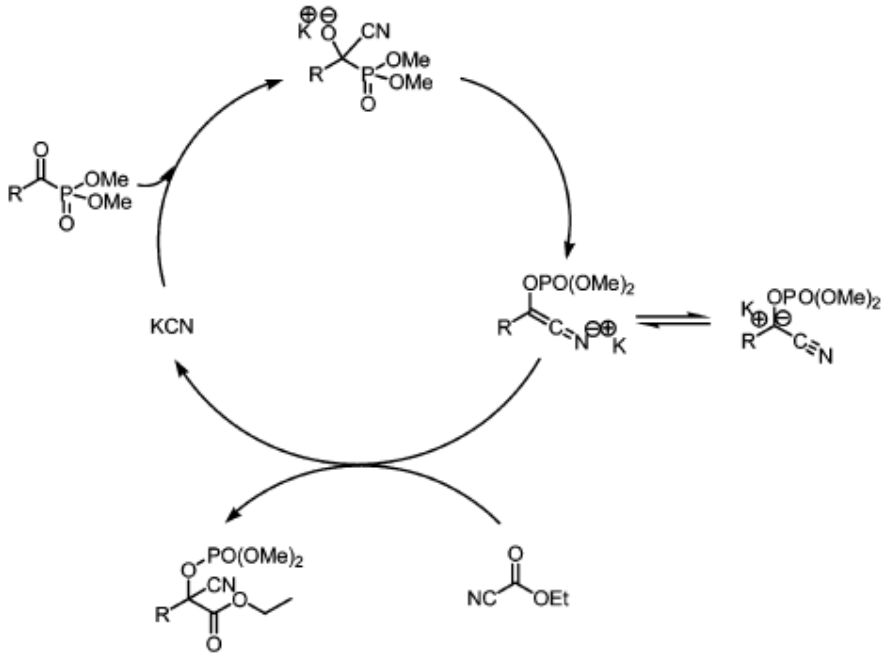



**Figure 18.** Proposed Meschanism of Carbinol Synthesis

Tertiary carbinols are useful compounds because they can be converted to many polyfunctionalized compounds. Demir's research group showed some of the intertesting applications of tertiary carbinols with satisfactory yields (Figure 19).

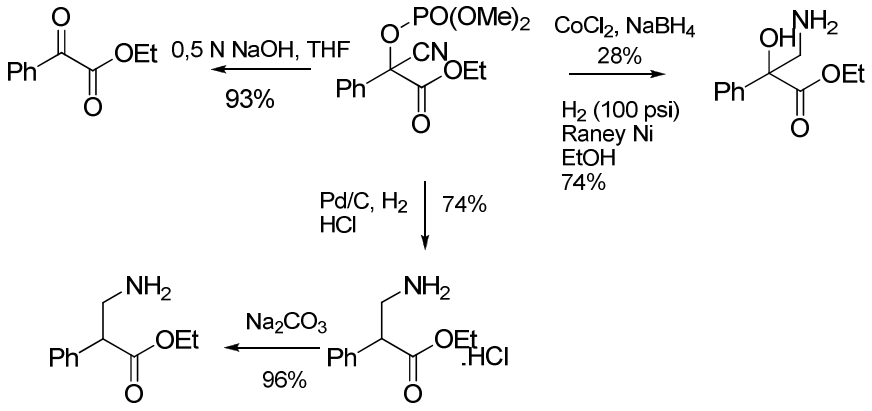



**Figure 19.** Representative Application of Tertiary Carbinol

### 1.3.3 Self Condensation Reaction of Acyl Phosphonates

As stated in part 1.2.3. acyl phosphonates are potential acyl anion equivalents. So, Göllü in his thesis showed that by generating these acyl anion equivalents in the presence of cyanide ion, it is possible to add one acyl phosphonate to another acyl phosphonate [21]. This self-condensation reactions of acylphosphonate would give tertiary α-hydroxy phosphonates. These compounds have importance in organic chemistry due to their biological activity. So it is important to find a practical way to synthesize them. The mechanism is similar to benzoin reaction of acylphosphonates with aldehydes (Figure 13).

Göllü found the optimum solvent for this reaction is DMF and best results were gained at 75 °C with 40% catalyst loading ( 62% yield) (Figure 20).

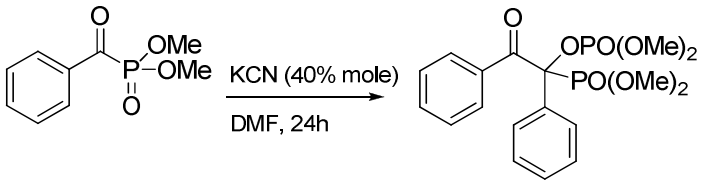



**Figure 20.** Self Condensation Reaction of Acyl Phosphonate

By this way, Göllü showed that it is possible to synthesize α-hydroxy phosphonates with generating their acyl anion equivalents in the presence of cyanide ion.

## 1.4 Acyl Phosphonates as Precursors for Biologically Active Compounds

### 1.4.1 α-Hydroxy Ketones

It is known in literature that cross-benzoin products of acyl phophonates are synthetic equivalents of α-hydroxy ketones. An aqueous amine solution can cleave the phophate ester and reveal the desired α-hydroxy ketone [22].

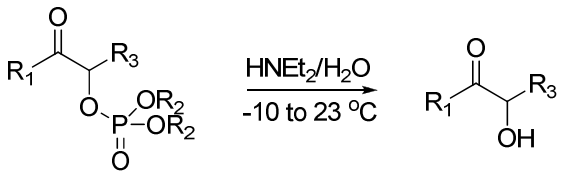



**Figure 21.** Deprotection of Keto Phosphates

α-hydroxy ketones are indispensable building blocks for asymmetric synthesis due to their versatile functional groups, which may be easily transformed to other functionalities, e.g., diols, halo or amino derivatives, and epoxides. Indeed, optically active α-hydroxy acids or ketones have been successfully utilized as starting materials for the asymmetric synthesis of a variety of biologically active molecules; a small selection is depicted in Figure 22 [23]. Clearly, the convenient and efficient synthesis of optically active α-hydroxy carbonyl compounds is of timely significance and in urgent demand. It is showed that acyl phophonates are useful precursors for α-hydroxy ketones. But in literature, asymmetric synthesis of additions of acylphophonates to aldehydes has not been introduced yet.

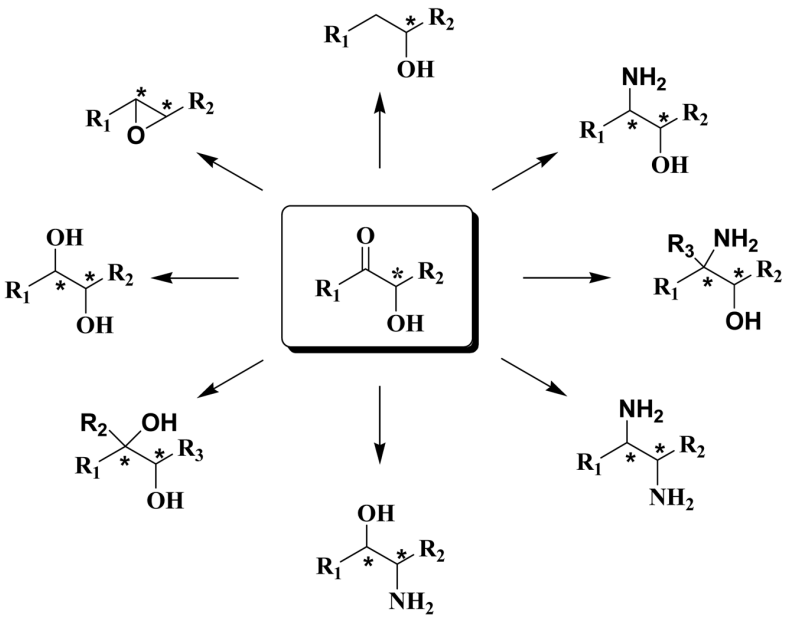


**Figure 22.** α-Hydroxy Ketones as Precursors for Several Biologically Active Compounds

### 1.4.2 α-Hydroxy Phosphonates

α-Hydroxy phosphonates are important precursors for some biologically acitive compounds because they can be converted to other α-oxyfunctionalized phosphonates such as α-amino, α-keto, α-halo and α-acetoxyphosphonates by synthetic ways. Many new types of C-P bond containing compounds have been found in hundreds of aquatic and terrestrial animals and microorganisms. Typical representatives of natural hydroxyphosphonic acids are phosphonothrixin and dihydroxyphosphonic acid (Figure 23) [24].

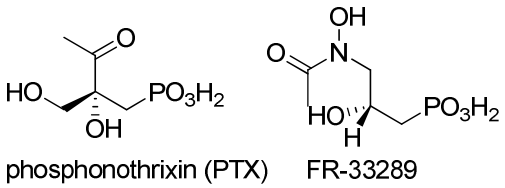



**Figure 23.** Naturally Occurring Hydroxyphosphonates

Zhao showed that acyl phosphonates give reaction with simple ketones to produce optically active α-hydroxy phosphonates by L-proline catalysis (Figure 24) [25].

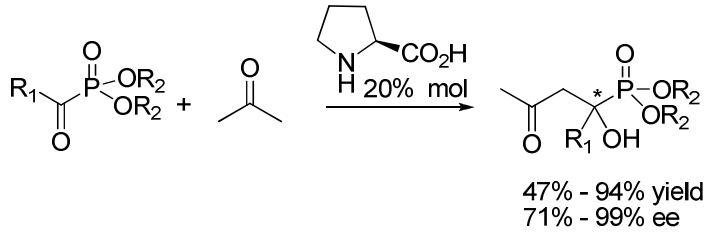



**Figure 24.** Synthesis of α-Hydroxy Phosphonates

It is also showed by Göllü that acyl phosphonates can undergo selfcondensation by cyanide ctalysis to produce tertiary α-hydroxy phosphonates [21].

### 1.4.3 Cyanohidrins

In section 1.3.1, it is showed that protected cyanohidrins (cyanohidrin *O*-phosphates) can easily be synthesized by using acyl phosphonates.

Cyanohidrins are useful intermediates in organic synthesis. Depending on the conditions used, acidic hydrolysis converts cyanohidrins to α-hydroxy acids or to α,β-unsaturated acids.

Cyanohidrins are easily decomposable molecules, and also in some reactions it is very important to avoid reactions of –OH group to get desired compounds. So it is very important to synthesize protected cyanohydrins.

O-Protection permits a wider range of reactions on the nitrile group and more extensive transformation [26].

To show an interesting application of cyanohidrins, it is suitable to give the Williams glycine template synthesis (Figure 25) [27].

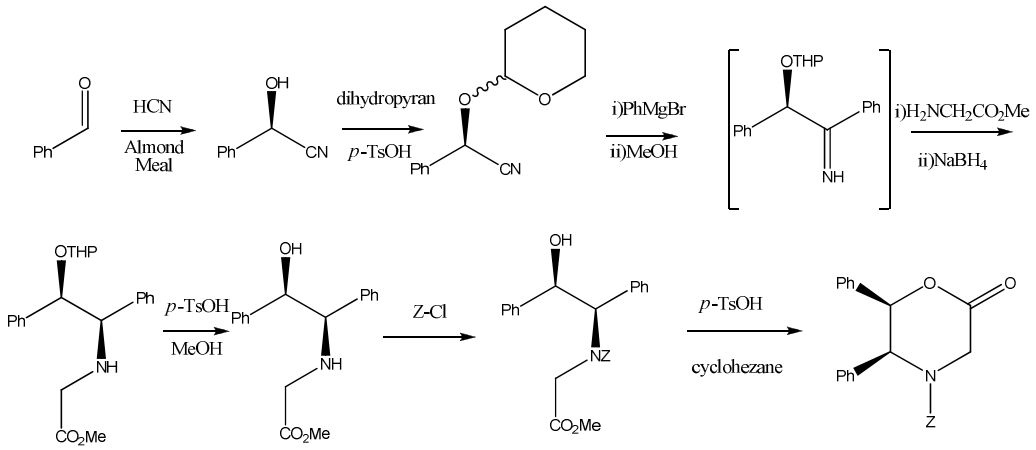



**Figure 25.** The Williams glycine template may be prepared from benzaldehyde in 48% overall yield.

The Williams glycine template enables the synthesis of unnatural amino acids.

## 1.5 Aim of the Work

Acyl phosphonates are easily available compounds in multigram scale. Due to their interesting applications, acylphosphonate chemistry has lots of advantages to synthesize interesting syhthetic targets. In the introduction part some of these applications are reviewed and all of these reactions require cyanide ion either catalytically or stoichiometrically. And cyanide salts are used in all of these reactions. Different metal cyanides have not been studied in acylphosphonate chemistry yet. Thus, we aimed to change the cyanide source by selecting commercially available $Et_2AlCN$ and to investigate its reactivity with acyl phosphonates. Furthermore, we aimed to investigate asymmetric reactions of acyl phosphonates with using chiral additives and $Et_2AlCN$.

# CHAPTER 2

# RESULTS AND DISCUSSION

## 2.1 Synthesis of Acyl Phosphonates

Acyl phosphonates are easily accessable compouns, reactions of acyl chlorides and trialkyl phosphites give acyl phosphonates in good yields [13]. In the first step of reaction trialkyl phosphite attacks to the carbonyl carbon of acyl chloride and produces unstable intermediate, following by the chlorine ion dealkylation gives resulting acyl phosphonate (Figure 26). This reaction is very exothermic. So, reaction generally performed at 0 °C in neat conditions. If an acyl chloride is solid, reaction is performed at room temperature or in organic solvents. The only side product of this reaction is alkyl chlorides.

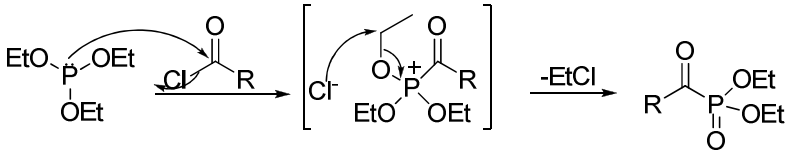



**Figure 26.** Synthesis of Acyl Phosphonates

Acylphosphonates can be synthesized in multigram quantities and very high yields from simple starting materials [13]. The reactions were carried out under inert atmosphere. Further purification of compounds is done with vacuum distillation. Their synthesis does not require any other special conditions or apparatus. Since they are sensitive to moisture, they should be stored under argon filled flasks to prevent decomposition or hydrolysis. Their synthesis from carboxylic acids is highly practical since there is vast amount of compounds in this oxidation states in nature. This also establishes a connection between acid oxidation state and acyl anion equivalents which generally obtained from aldehydes (Figure 27).

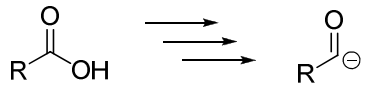


**Figure 27.** Connection Between Acid Oxidation State and Acyl Anion Equivalents

Figure 28 shows the representative structures of the acyl phosphonates used in this study.

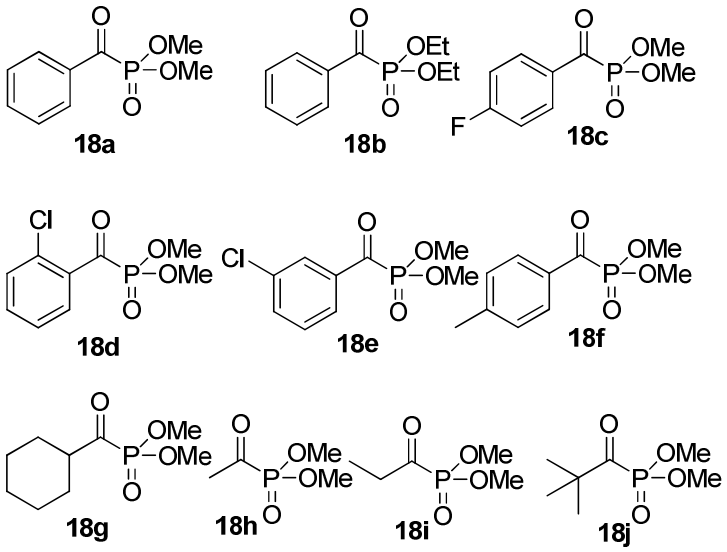



**Figure 28.** Acyl Phosphonates Used in This Study

## 2.2 Protected Cyanohidrin Formation via Acyl Phosphonate Chemistry

Cyanohidrins are very important synthetic intermediates [16] and are unstable molecules that require a suitable hydroxy-protecting group. This desirable protection can be performed in a two-step sequence, starting from the aldehyde or ketone, through the corresponding cyanohydrin, followed by *O*-protection. But one-pot procedure, starting from aldehydes or ketones, has become synthetically more advantageous. A number of different strategies are known for the synthesis of cyanohidrin *O*-phosphates [18]. Acyl phosphanates are precursors of acyl anion equivalents. In the presence of cyanide ion, nucleophilic acyl anion equivalent is generated [2a]. Using this strategy, Demir et al developed a practical synthesis of protected cyanohidrin formation. Cyanide ion promoted phosphonate-phosphate rearrangement of acyl phosphonates gives acyl anion equivalents as reactive intermediates. And protonation of these intermediates give cyanohidrin *O*-phosphates in good yields [2c]. This strategy is very practical, because acyl anion equivalents are higly reactive to proton. So, we first select this strategy to investigate reactions of $Et_2AlCN$ with acyl phosphonates.

$Et_2AlCN$ is commercially available as 1M solution in toluene. So we selected toluene as solvents in this study. We carried out this reaction with 1 mmol of acylphosphonate in 1 ml toluene by adding 1.2 ml of 1M $Et_2AlCN$ solution slowly at room temperature in 10 minutes. After hydrolysis with one drop of water, we monitored by TLC. This reaction is exothermic so we saw some decomposition products at TLC. Then we decided to perform reaction at 0 $^oC$ and we obtained good results monitoring by TLC. All of the reactions were carried out at 0 $^oC$.

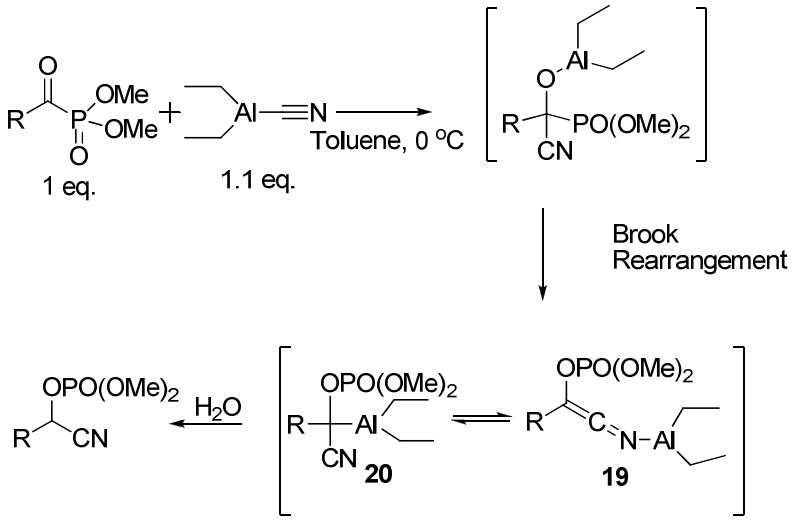
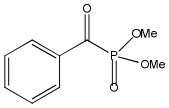
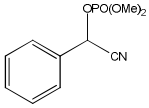
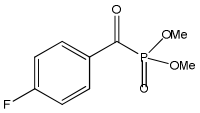
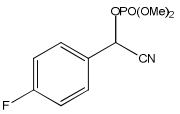
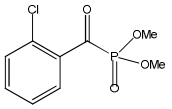
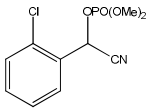
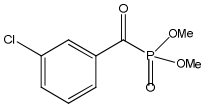
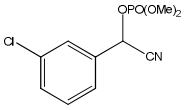
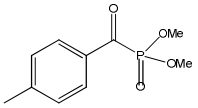
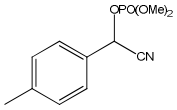
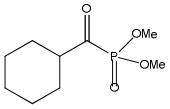
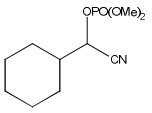
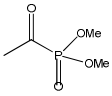
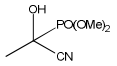
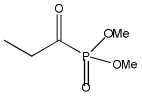
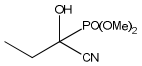
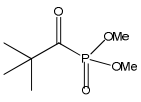
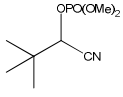



**Figure 29.** Protected Cyanohidrin Formation Using $Et_2AlCN$ and Acyl Phosphonate

In the first step of this reaction, cyanide addition to acylphosphonate occurs. After Brook rearrangement, the intermediates **19** or **20** occur, perhaps as equilibrating species. Hydrolysis of this intermediate gives *O*-protected cyanohidrin in good yields. We performed this reaction with different aliphatic and aromatic acyl phosphanets to investigate reactivity of $Et_2AlCN$ and obtained good results.

After taking NMR, the first identifier is –CN peak at $^{13}$C-NMR. Cyanide gives carbon peak around 116 ppm at $^{13}$C-NMR, this is good identification for cyanide addition. But to identify phosphonate- phosphate rearrangement we used both $^{1}$H and $^{31}$P-NMR. First of all phosphorus gives peak at positive part of the $^{31}$P-NMR for phosphonates, generally above 15 ppm, but in phosphates situation is different, it gives peak around zero or negative part of the spectrum. In $^{1}$H-NMR there are two specific identifiers for protected cyanohidrin formation. Firstly, the proton next to the cyanide group gives specifically a doublet at around 6 ppm. Secondly, –Me groups of -OPO(OMe)$_2$ in acyl phosphonates give only doublet between 3-4 ppm. But in the case of cyanohidrin *O*-phosphates these methyl groups give dublet of doublet between 3-4 ppm. This is good identification for phophate group migration from carbon to oxygen.

**Table 1.** Protected Cyanohidrins Synthesized in This Study

| Entry | Acylphosphonate | Product | Yield |
|---|---|---|---|
| 1 |  |  | 80% |
| 2 |  |  | 81% |
| 3 |  |  | 78% |
| 4 |  |  | 82% |
| 5 |  |  | 75% |
| 6 |  |  | 65% |
| 7 |  |  | 61% |
| 8 |  |  | 64% |
| 9 |  |  | 68% |

It must be stated that the reaction of acetyl and propionyl phosphonate (Entry 7and 8, Figure 30) with $Et_2AlCN$ is not the same as other phosphonates. We observed phosphonate-phosphate rearraengement at all of the acyl phosphonate reactions but we could not observed this rearrangement in the acetyl and propionyl phosphonate case. In phosphonates phosphorus gives peak around pozitive part of spectrum in $^{31}$P-NMR. But in cyanohidrin *O*-phosphates phosphorus gives peak around zero or negative part of the spectrum in $^{31}$P-NMR. We observed the carbon peak of -CN group at 118 ppm in $^{13}$C-NMR , then we detected phosphorus peak at 17.35 ppm. So, we conclude that phosphonate-phosphate rearrangement does not occur after cyanide addition. The possible reason of this behaviour could be the better stabilizer ability of aryl group for phosphonate-phosphate rearrangement with respect to methyl or ethyl group at the –R variable in acyl phosphonates.

The logical next step was the enatioselective synthesis of protected cyanohidrins by using coordination ability of $Et_2AlCN$ with chiral additives. Nakamura et al. performed enantioselective cyanation of imines with $Et_2AlCN$ [28].

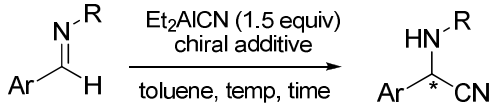



**Figure 30.** Enantioselective Cyanation of Imines

They used different chiral additives and found the best results with BINOL derivatives. The reaction gives moderate enantiomeric excess. So this was the logic for us to synthesize protected cyanohidrins asymmetrically.

We used (S)-BINOL and (+)-TADDOL as chiral additives (Figure 32).

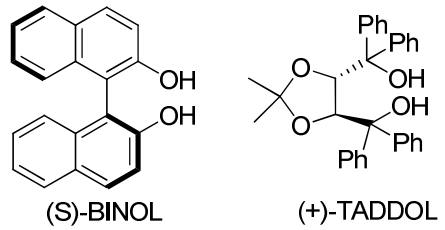



**Figure 32.** Chiral Additives

We first added 1.1 equivalent $Et_2AlCN$ to 1 equivalent chiral additive to form chiral complex at 0 °C for 30 minutes under argon atmosphere (Figure 33).

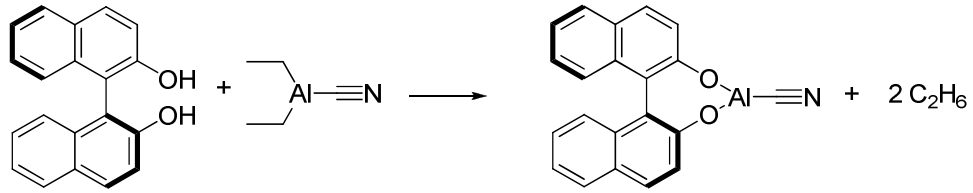



**Figure 33.** Propesed $Et_2AlCN$ (S)-BINOL Complex Formation

After addition of acyl phosphonate, reaction stirred at -78 °C for 3 hours and one drop of water added, dry ice bath is removed and reaction kept until reach the room temperature. After the work-up the crude sample was purified by flash column chromatography. We performed reaction at different temperatures (rt., 0 °C, -78 °C) and different time intervals. Even we saw little rotation at polarimetry we could not observed any enantiomeric excess in HPLC. There could be two different reason for this observation. First of all, we may have not been able to form chiral complex of $Et_2AlCN$ with chiral additive and cyanide addition could not occur enantioselectively as a result. Altervatively, protonation of organometallic intermediate during hydrolysis could not be performed selectiveley even we formed the chiral complex. To solve this problem we performed other reactions of $Et_2AlCN$ with acylphosphonates.

### 2.3 Benzoin Type Reaction of Acyl Phosphonates with $Et_2AlCN$

Cross-benzoin products of acyl phosphonates are synthetic equivalents of α-hydroxy ketones. It has been proved by Demir et al. that cyanide ion promoted benzoin type reactions of acyl phoshonates with aldehydes give keto phosphates in good yields [2a]. The reaction mechanism depicted at Figure 13 in previous section. By using this strategy we performed the reaction with $Et_2AlCN$. To a solution of 1 mmol acyl phosphonate in dry toluene, 10% mol of $Et_2AlCN$ and aldehyde added respectively under Argon atmosphere at room temperature. However, we could not observe any reaction.

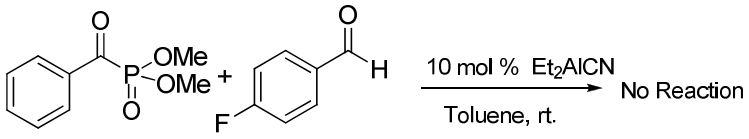



**Figure 33.** $Et_2AlCN$ Promoted Benzoin Type Reaction of Acyl Phosphonate

To understand the mechanism we changed the strategy and decided to use 1 equivalent of $Et_2AlCN$. To a solution of 1 mmol $Et_2AlCN$ in dry toluene acyl phosphonate and aldehyde added respectively under Argon atmosphere at room temperature. According to TLC, reaction completed in 15 minutes and gave interesting result (Figure 34).

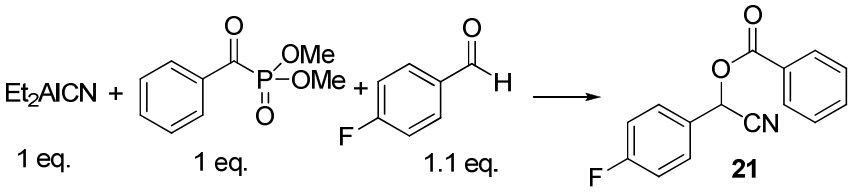



**Figure 34.** Protected Cyanohidrin Formation

The result was interesting, $Et_2AlCN$ prefered aldehyde for cyanation instead of acyl phosphonate. Most probably aldehyde cyanation occurs first and opened negative charge over oxygen attacks to the acyl phosphonate and removing the phosphate group reaction gives compound **21** with 72% yield (Figure 35)**.** This compound is again a protected cyanohidrin.

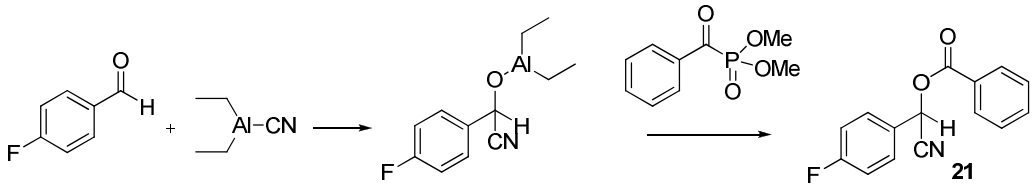



**Figure 35.** Proposed Mechanism

To investigate coordination ability of $Et_2AlCN$ with chiral additives, we decided to perform reaction with chiral additive. To a 0.5 mmol of (S)-BINOL, 0.6 mmol of $Et_2AlCN$ in 0.6 ml toluene added at 0 °C under Argon atmosphere and stirred for 30 minutes. 0.5 mmol of acyl phosphonate and 0.5 mmol of 4-fluorobenzaldehyde were added respectively and reaction stirred for 1 hours at 0 °C. By monitoring TLC, after completion of reaction the crude product was purified 68% yield. The analysis of the product by HPLC showed 50% ee. This shows us that we could performed $Et_2AlCN$ (S)-BINOL complex and cyanide addition occurs enantioselectively.

This raction also showed that we could not add acyl phosphonate and aldehyde at the same time to synthesize α-keto phosphates. So we changed the reaction strategy. To a 1 mmol $Et_2AlCN$ solution in dry toluene, 1 mmol of acyl phosphonate was added dropwise over a period of 1 hour at 0 °C under Argon atmosphere to synthesize compound **23**. The reaction stirred 1 hour additionally and 1.1 mmol of 4-fluorobenzaldehyde was added and stirred for 3 hours. After completion of reaction the product **27** was obtained in 38% yield (Figure 36).

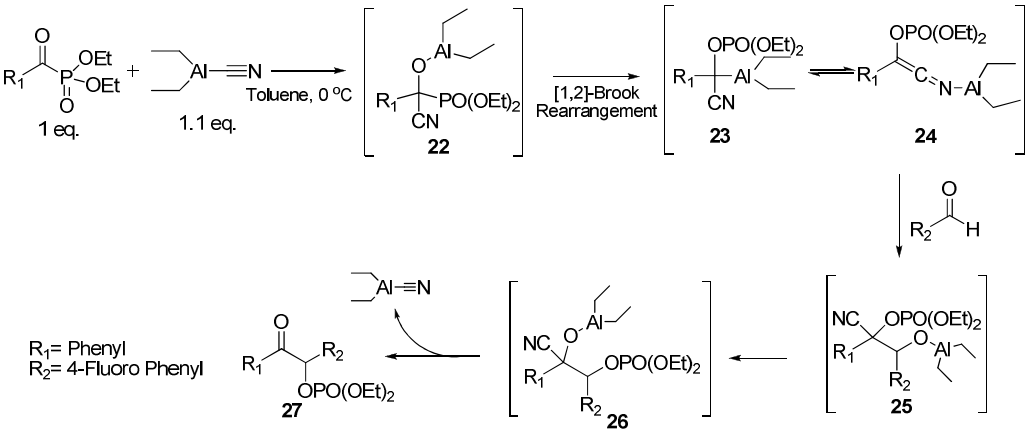



**Figure 36.** Benzoin Type Reaction of Acyl Phosphonate with Aldehyde

We also performed this reaction with chiral additive at 0 °C under Argon atmosphere for 5 hours, we again used $Et_2AlCN$ (S)-BINOL complex and obtained 32% yield and 16% ee at HPLC analysis.

## 2.4 Synthesis of α-Hydroxy Phosphonates

After we proposed the intermediates **19**, **20** (Figure 29), we thought that we could add acyl phosphonates to itself. So, we performed the reaction by using $Et_2AlCN$ as 0.5 equivalents (Figure 37).

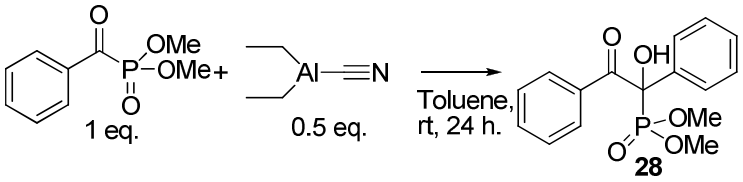



**Figure 37.** Synthesis of α-Hydroxy Phosphonate

To a 0.5 ml of $Et_2AlCN$ solution in toluene, acylphophonate was added at room temperature under argon atmosphere. Reaction stirred 24 hours at room temperature, after work up procedure and purification the compund **28** was obtained in 37% yield. We expected the product **29** (Figure38) instead of **28** but NMR data support that the compund is **28.** We thought that compound **29** was hydrolized during extraction as in Figure 22 due to the possible formation of $Et_2AlOH$.

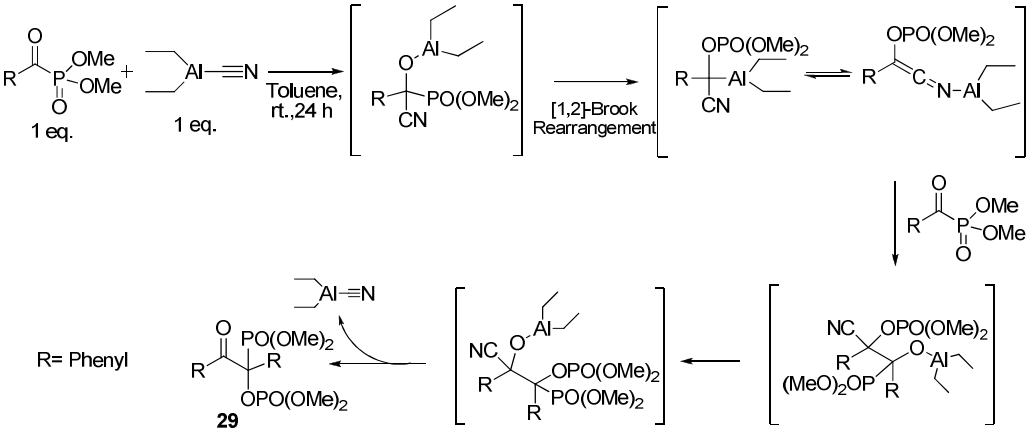



**Figure 38.** Proposed Mechanism of Self Condensation of Acyl Phosphonate

We proposed the formation of compound **28** as shown in Figure 38. To characterize the compound we used both $^{1}$H-NMR and $^{31}$P-NMR. The proton of –OH group in compound **28** gives dublet at 5.26 ppm at $^{1}$H-NMR spectrum. We used the reference 25 (Figure 24), which shows the addition of acetone to acyl phosphonate giving α-hydroxy phosphonates. At this reference the proton of –OH groups coupling is 19.0 Hz and in our compound coupling of proton is 21.8 Hz. And also in $^{31}$P-NMR phosphorus gives peak at 22.5 ppm, this show that phopspahte group bonded to carbon atom instead of oxygen atom.

We also tried reaction with different phosphonates but we could not get the same results. Further work is needed to improve the scope of this reaction.

### 2.5 Synthesis of Tertiary Carbinols

We also tried the reaction of acyl phosphonate with ethylcyanoformate to synthesize protected tertiary carbinols by using $Et_2AlCN$. To investigate the reaction we first used equal amount of $Et_2AlCN$ and acyl phosphonate (Figure 39).

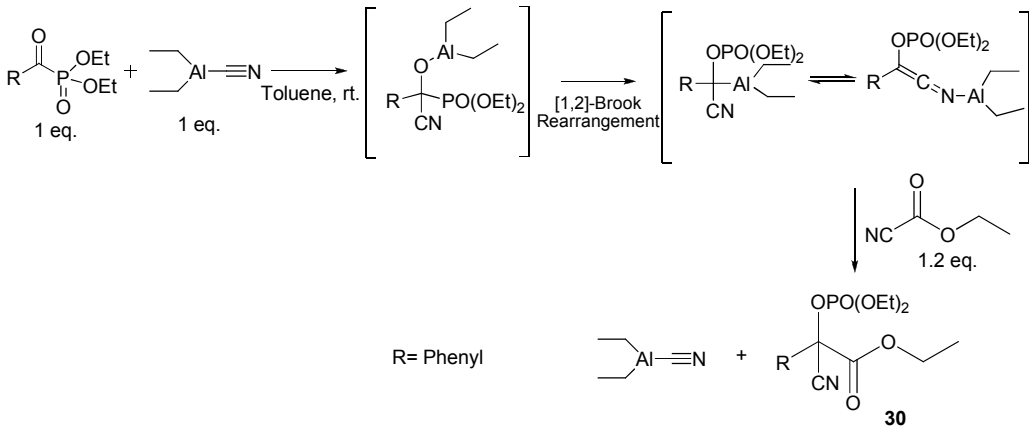



**Figure 39.** Proposed Mechanism of Tertiary Carbinol Formation

To a solution of 1mmol $Et_2AlCN$ in 1 ml toluene, 1.5 mmol of ethyl cyanoformate and 1 mmol of acyl phosphonate was added respectively at room temperature under argon atmosphere. Monitoring by TLC showed that reaction was completed in 15 minutes. After purification, product **30** was obtained in 70% yield. We also tried reaction by using 30% of $Et_2AlCN$ in 1 ml toluene for 6 hours under Argon atmosphere and we could get good result. Both catalytic and asymmetric reactions of this type are still under investigation.

# CHAPTER 3

# EXPERIMENTAL

## 3.1 Materials and Methods

$^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 400 MHz with Bruker Ultrashield Superconducting 400 MHz, with $Me_4Si$ as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively, relative to $CHCl_3$ ($^{1}H$: δ=7.26) and $CDCl_3$ ($^{13}C$: δ=77.0) as an internal standart. All reactions were analyzed by TLC on silica gel 60 $F_{254}$. TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm) or appropriate organic stains. Column chromatography was performed on silica gel 60 (70-230 mesh). Enantiomeric excesses of all the products were determined by Thermo Finnigan Surveyor HPLC device using appropriate optically active columns.

## 3.2 Preparation of Acylphosphonates

Acylphosphosphonates **18a-j** were synthesized according to literature procedures. Briefly 1 equiv. of neat triethylphosphite was added drop wise onto the neat acylchloride in a water bath under a positive inert atmosphere. After completion of the addition, resulting mixture was stirred at room temperature for 60 min. The products were purified by vacuum distillation [13].

### 3.3 Synthesis of Cyanohidrin *O*-phosphates

To a 1 mmol of acyl phosphonate in 1 ml toluene, 1.2 mmol of $Et_2AlCN$ ( 1M solution in toluene) is added slowly at 0 °C. After a few minutes, one drop of water is added. Monitoring by TLC, reaction is completed in 10 minutes. After completion of reaction, mixture is diluted with 10 ml of EtOAc and water. Organic phase is separated and aqueuos phase is extracted with 10 ml of EtOAc three times. Combined organic phase is dried over $MgSO_4$. Organic phase is concentrated under reduced pressure. Crude product is purified by flash column chromatography on silica gel with EtOAc:Hexane.

**Cyano(phenyl)methyl dimethyl phosphate:** colorless oil $^1$H NMR (400 MHz, $CDCl_3$) δ 3.58 (d, *J*=11.4Hz, 3H); 3.79 (d, *J*=11.4Hz, 3H); 5.99 (d, *J*=8.7Hz, 1H); 7.36-7.42 (m, 3H); 7.46-7.52 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 54.6 (d, *J*=5.9Hz); 54.8 (d, *J*=6.0Hz); 66.7 (d, *J*=4.4Hz); 115.9 (d, *J*=6.1Hz); 127.6; 129.3; 130.6; 132.4 (d, *J*=5.2Hz); $^{31}$P NMR ($CDCl_3$) δ 0.28.

**Cyano(4-fluorophenyl)methyl dimethyl phosphate:** colorless oil $^1$H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, *J*=11.4Hz, 3H); 3.80 (d, *J*=11.4Hz, 3H); 5.99 (d, *J*=8.7Hz, 1H); 7.06-7.12 (m, 2H); 7.48-7.54 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 54.6 (d, *J*= 6.2Hz); 54.9 (d, *J*=6.1Hz); 66.0 (d, *J*=4.2Hz); 116.5 (d, *J*=22.1Hz); 129.8 (d, *J*=8.8Hz); 162.7, 165.2; $^{31}$P NMR ($CDCl_3$) δ 0.23.

**(2-chlorophenyl)(cyano)methyl dimethyl phosphate:** colorless oil $^1$H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, *J*=11.4Hz, 3H); 3.81 (d, *J*=11.4Hz, 3H); 6.30 (d, *J*=8.7Hz, 1H); 7.30-7.45 (m, 3H); 7.64-7.68 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 54.9 (t); 63.8 (d, *J*=4.5Hz); 115.2 (d, *J*=4.2Hz); 127.7; 129.1; 130.3; 131.8; 133.1 $^{31}$P NMR ($CDCl_3$) δ -0.06.

**(3-chlorophenyl)(cyano)methyl dimethyl phosphate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.64 (d, *J*=11.4Hz, 3H); 3.82 (d, *J*=11.4Hz, 3H); 5.97 (d, *J*=8.8Hz, 1H); 7.32-7.41 (m, 3H); 7.49 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 55.1 (d, *J*=6.1Hz); 55.3 (d, *J*=6.3Hz); 66.1 (d, *J*=4.4Hz); 115.7 (d, *J*=5.7Hz); 125.8; 127.9; 130.9; 131.2; 134.5 (d, *J*=5.6Hz); 135.7 $^{31}$P NMR ($CDCl_3$) δ 0.20.

**Cyano(p-tolyl)methyl dimethyl phosphate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H); 3.57 (d, *J*=11.4Hz, 3H); 3.78 (d, *J*=11.4Hz, 3H); 5.95 (d, *J*=8.6Hz, 1H); 7.19 (d, *J*=7.9Hz, 2H); 7.38 (d, *J*=8.2Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.3; 54.7 (d, *J*=6.0Hz); 54.9 (d, *J*=6.1Hz); 66.7 (d, *J*=4.6Hz); 116.1 (d, *J*=6.4Hz); 127.6; 129.4 (d, *J*=5.0Hz); 130.0; 141.0; $^{31}$P NMR ($CDCl_3$) δ 0.17.

**Cyano(cyclohexyl)methyl dimethyl phosphate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.05-1.30 (m, 5H); 1.60-1.90 (m, 6H); 3.75-3.80 (q, 6H); 4.72-4.76 (q, 1H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 25.5 (d, *J*=4.1Hz) 26.0; 27.8; 28.1; 29.2; 41.8 (d, *J*=5.6Hz); 55.1 (d, *J*=6.2Hz); 69.9 (d, *J*=6.2Hz); 116.3 (d, *J*=3.4Hz); $^{31}$P NMR ($CDCl_3$) δ 0.51.

**Dimethyl 1-cyano-1-hydroxyethylphosphonate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.69 (d, *J*=14.8Hz, 3H); 3.87 (d, *J*=10.7Hz, 6H); 6.54 (b, 1H) $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 23.1; 55.1 (d, *J*=7.4Hz); 55.5 (d, *J*=6.9Hz); 65.6; 118.0 (d, *J*=6.6Hz); $^{31}$P NMR ($CDCl_3$) δ 17.27.

**Dimethyl 1-cyano-1-hydroxypropylphosphonate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, 3H); 1.85-2.05 (m, 2H); 3.84-3.90 (m, 6H); 6.20-6.35 (b, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 7.82 (d, *J*=9.4Hz); 28.9; 55.4 (d, *J*=7.4Hz); 55.5 (d, *J*=7.1Hz); 70.3; 117.3 (d, *J*=5.8Hz); $^{31}$P NMR ($CDCl_3$) δ 16.3.

**1-cyano-2,2-dimethylpropyl dimethyl phosphate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H); 3.75-3.82 (q, 6H); 4.58 (d, *J*=8.2Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 24.8; 35.7 (d, *J*=6.0Hz); 55.7 (d, *J*=5.9Hz); 73.6 (d, *J*=6.9Hz); 115.8 $^{31}$P NMR ($CDCl_3$) δ 0.68.

### 3.4 Synthesis of Cyano(4-fluorophenyl)methyl Benzoate

To a 1 mmol $Et_2AlCN$ in 1 ml toluene, 1 mmol benzoyl phosphonate and 1.1 mmol 4-fluorobenzaldehayde are added respectively at room temperature under argon atmosphere. By monitoring TLC, reaction is completed in 15 minutes. After completion of reaction, mixture is diluted with 10 ml of EtOAc and water. Organic phase is separated and aqueuos phase is extracted with 10 ml of EtOAc three times. Combined organic phase is dried over $MgSO_4$. Organic phase is concentrated under reduced pressure. Crude product is purified by flash column chromatography on silica gel with EtOAc:Hexane. The product is obtained as %72 yield.

For the asymmetric synthesis; to a 0.5 mmol of (S)-BINOL, 0.6 mmol of $Et_2AlCN$ in 0.6 ml toluene is added at 0 °C under argon atmosphere and stirred for 30 minutes. 0.5 mmol of acyl phosphonate and 0.5 mmol of 4-fluorobenzaldehyde are added respectively and reaction is stirred for 1 hours at 0 °C. After completion of reaction product is purified and found 68% yield with 50% ee at HPLC analysis.

**Cyano(4-fluorophenyl)methyl benzoate:** colorless oil $^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H); 7.16 (t, 2H); 7.46 (t, 2H); 7.58-7.65 (m, 3H); 8.03-8.07 (q, 2H) $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 62.7; 116.0; 116.4; 116.6; 128.0; 128.7; 130.1; 134.2; 162.6; 164.5; 165.1. HPLC; ChiralPack-AS column; 90:10 n-Hexanes: isopropanol; 1 ml/min flowrate; 233nm; 9.7 min; 11.9 min.

### 3.5 Synthesis of Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate

To a 1 mmol $Et_2AlCN$ solution in dry toluene, 1 mmol of acyl phosphonate is added dropwise over a period of 1 hour at 0 $^{o}$C under Argon atmosphere. The reaction is stirred 1 hour additionally and 1.1 mmol of 4-fluorobenzaldehyde is added and stirred 3 hours. Mixture is diluted with 10 ml of EtOAc and water. Organic phase is separated and aqueuos phase is extracted with 10 ml of EtOAc three times. Combined organic phase is dried over $MgSO_4$. Organic phase is concentrated under reduced pressure. Crude product is purified by flash column chromatography on silica gel with EtOAc:Hexane. The product is obtained as 38% yield.

For the asymmetric synthesis; to a 0.5 mmol of (S)-BINOL, 0.6 mmol of $Et_2AlCN$ in 0.6 ml toluene is added at 0 $^{o}$C under argon atmosphere and stirred for 30 minutes. The same procedure for unsymmetrical one is applied after this part with 0.5 mmol of acyl phosphonate and 0.6 mmol of 4-fluorobenzaldehyde. The product is obtained as 32% yield and %16 ee at HPLC analysis.

**Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate:** colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, 3H); 1.25 (t, 3H); 3.80-3.90 (m, 2H); 4.0-4.20 (m, 2H), 6.54 (1H, d, *J*=8.0 Hz); 6.95-7.0 (m, 2H); 7.32- 7.47 (m, 5H); 7-85 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 15.8 (d, *J*=6.7 Hz); 16.0 (d, *J*=6.9 Hz); 64 (d, *J*=6.2 Hz); 64.3 (d, *J*=6.0 Hz); 78.1 (d, *J*=4.7 Hz); 116.1 (d, *J*=22.0 Hz); 128.7, 128.9, 139.0 (d, *J*=8.6 Hz); 163.2 (d, *J*=249 Hz); 193.5 (d, *J*=5.0 Hz); $^{31}$P NMR (CDCl3) δ -2.33. HPLC; ChiralPack-AD column; 95:5 n-Hexanes: isopropanol; 1 ml/min flowrate; 250nm; 33.9 min; 52.1 min.

### 3.6 Synthesis of Dimethyl 1-hydroxy-2-oxo-1,2-diphenylethylphosphonate

To a 0.5 mmol of $Et_2AlCN$ solution in 1ml toluene, 1 mmol of acylphophonate is added at room temperature under argon atmosphere. Reaction turned 24 hours at room temperature. Mixture is diluted with 10 ml of EtOAc and water. Organic phase is separated and aqueuos phase is extracted with 10 ml of EtOAc three times. Combined organic phase is dried over $MgSO_4$. Organic phase is concentrated under reduced pressure. Crude product is purified by flash column chromatography on silica gel with EtOAc:Hexane. The product is obtained as 37% yield.

**Dimethyl 1-hydroxy-2-oxo-1,2-diphenylethylphosphonate:** colorless oil $^1$H NMR (400 MHz, $CDCl_3$) δ 3.62 (d, *J*=10.9Hz, 3H); 3.70 (d, *J*=10.9Hz, 3H); 5.26 (d, *J*=21.8Hz, 1H); 7.20-7.50 (m, 8H); 7.87 (d, *J*=7.2Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3/CCl_4$) δ 51.6 (d, *J*=10.2Hz); 51.9 (d, *J*=6.6Hz); 53.0; 126.1 (d, *J*=3.0Hz); 126.7; 127.1; 127.6; 127.7; 129.4 (d, *J*=9.3Hz); 131.5; 134.4 (d, *J*=6.1Hz); 191.4 (d, *J*=5.2Hz); $^{31}$P NMR ($CDCl_3$) δ 22.5.

### 3.7 Synthesis of Ethyl 2-cyano-2-(diethoxyphosphoryloxy)-2-phenylacetate

To a 1 mmol of $Et_2AlCN$ in 1 ml dry toluene, 1.5 mmol of ethyl cyanoformate and 1 mmol of acyl phosphonate were added respectively at room temperature under argon atmosphere. By monitoring TLC, reaction was completed in 15 minutes. Mixture is diluted with 10 ml of EtOAc and water. Organic phase is separated and aqueuos phase is extracted with 10 ml of EtOAc three times. Combined organic phase is dried over $MgSO_4$. Organic phase is concentrated under reduced pressure. Crude product is purified by flash column chromatography on silica gel with EtOAc:Hexane. The product is obtained as 70% yield.

**Ethyl 2-cyano-2-(diethoxyphosphoryloxy)-2-phenylacetate:** $^1$H NMR (400 MHz, $CDCl_3$,) δ: 1.21 (t, 3H), 1.28 (t, 3H), 1.34 (t, 3H), 4.10-4.30 (m, 6H), 7.34 7.41(m, 3H), 7.60-7.65 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 12.7, 14.9 (d, *J*=7.3 Hz), 15.0 (d, *J*=7.5 Hz), 63.1, 63.8 (d, *J*=6.1 Hz), 64.1 (d, *J*=6.0 Hz), 75.6, 114.3, 124.6, 128.0, 129.5, 131.9 (d, *J*=9.4 Hz), 163.4; $^{31}$P NMR ($CDCl_3$) δ: -4.60.

# CHAPTER 4

# CONCLUSION

In this study we have investigated the reactivity of $Et_2AlCN$ toward acyl phosphonates. Acyl phosphonates are known in synthetic organic chemistry as potential acyl anion equivalents and they have wide variety of useful reactions to synthesize potentially important molecules. Almost all of the reactions of acyl phosphonates in acyl anion chemistry, KCN is used either catalytically or stoichiometrically. Because of its ionic character, it is almost impossible to perform asymmetric reactions of acyl phosphonates. So, it must be studied the reactions of acyl phosphonates with different metal cyanides. This has not been done in literature yet. We have chosen $Et_2AlCN$ because of its ease of availability and cost with respect to other metal cyanides to start. We have investigated its reactivity in acyl phosphonate chemistry. We first synthesized protected cyanohidrins, and investigated benzoin type condensation of acyl phosphonates with using $Et_2AlCN$. Then we also performed self condensation reaction of acyl phosphonate and synthesis of tertiary carbinol representatively with using $Et_2AlCN$. We also used $Et_2AlCN$'s ability of coordination with chiral additives. By this way we have investigated some of asymmetric reactions of acyl phosphonates representatively.

It must be stated that some of the reactions in this study are only representative ones. Further study of $Et_2AlCN$ with acyl phosphonates is under investigation to be improved.

This sdudy shows that metal cyanides have potential to investigate asymmetric reactions in acyl phosphonate chemistry.

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## APPENDIX

## NMR AND HPLC DATA

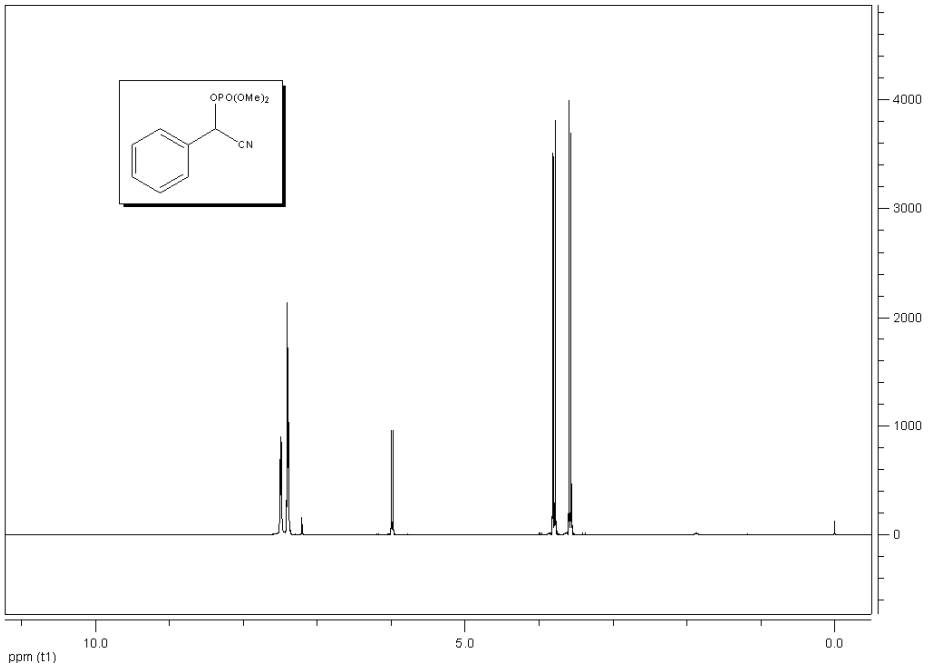


**Figure A.1** $^{1}$H-NMR Spectrum of Cyano(phenyl)methyl dimethyl phosphate

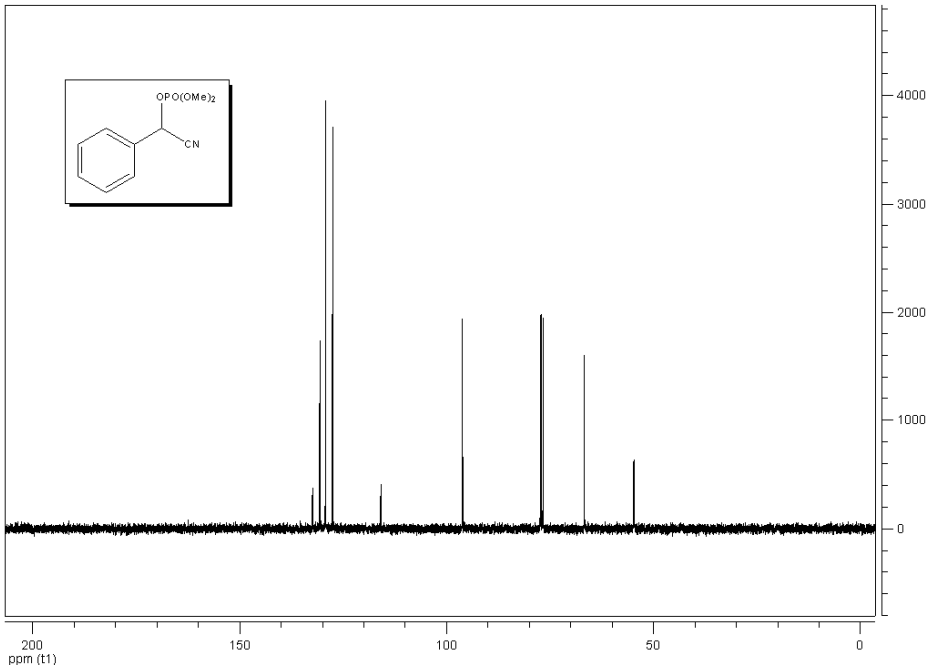


**Figure A.2** $^{13}$C-NMR Spectrum of Cyano(phenyl)methyl dimethyl phosphate

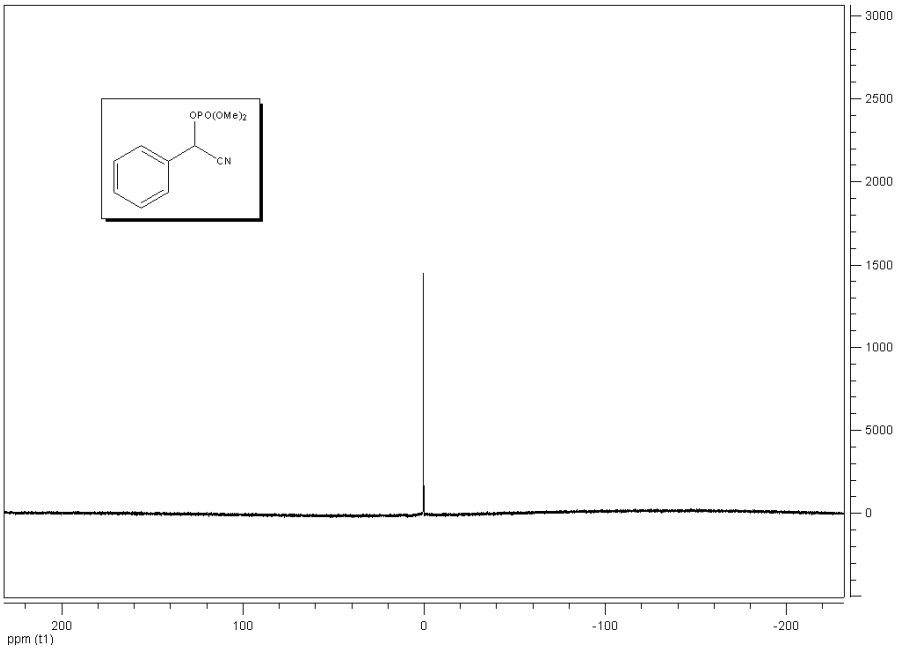


**Figure A.3** $^{31}$P-NMR Spectrum of Cyano(phenyl)methyl dimethyl phosphate

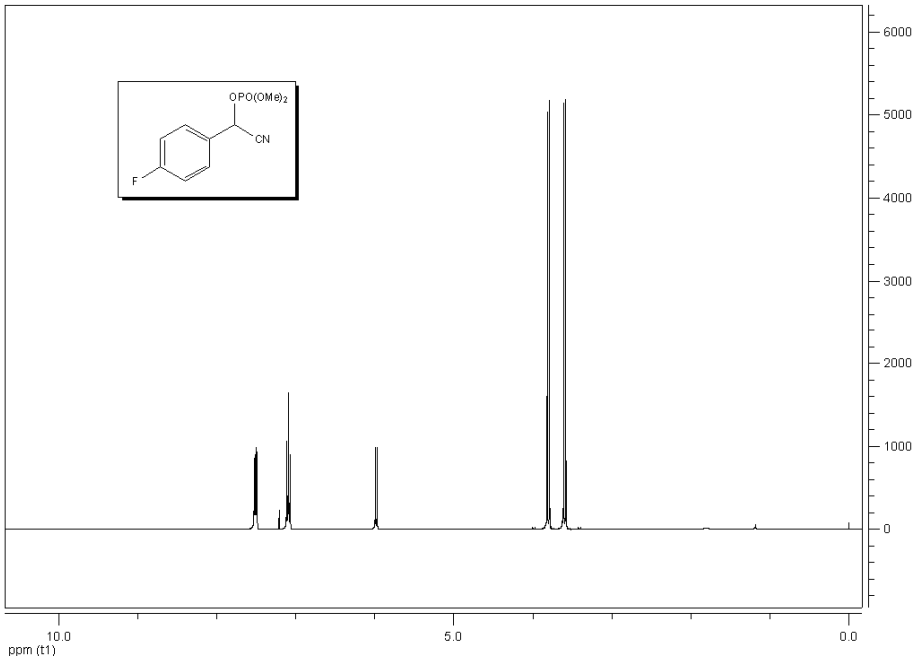


**Figure A.4** $^{1}$H-NMR Spectrum of Cyano(4-fluorophenyl)methyl dimethyl phosphate

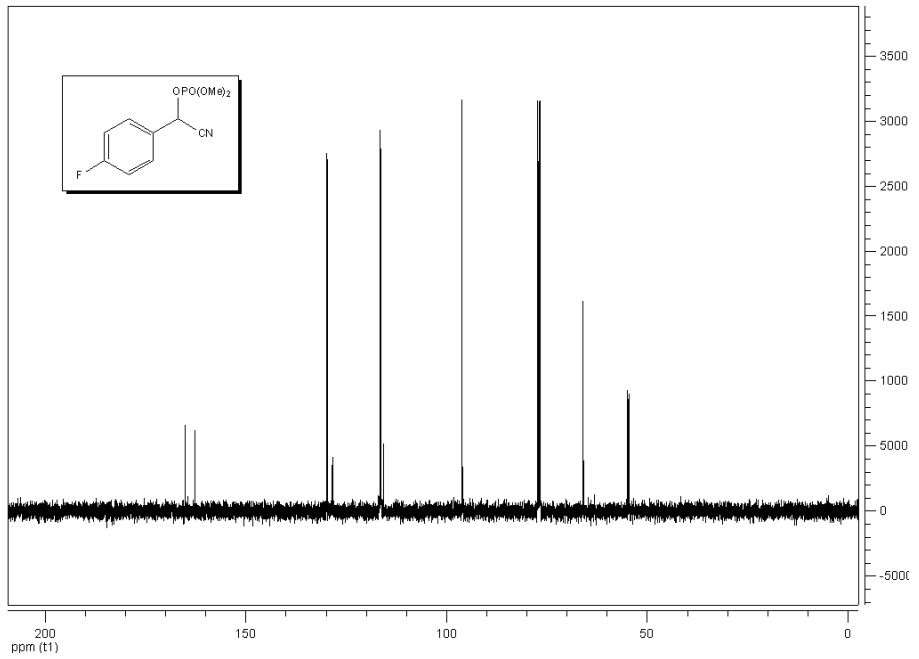


**Figure A.5** $^{13}$C-NMR Spectrum of Cyano(4-fluorophenyl)methyl dimethyl phosphate

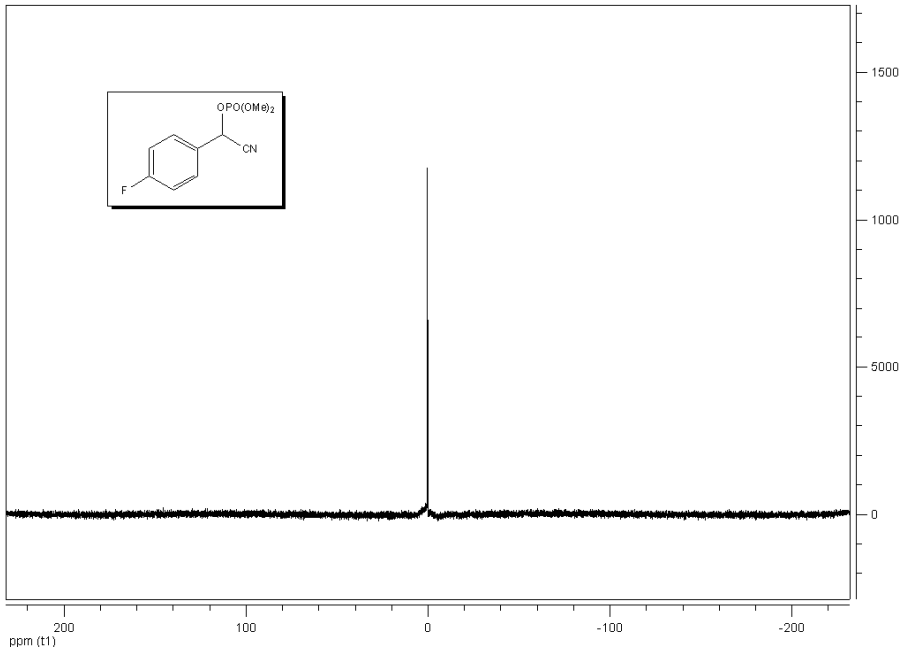


**Figure A.6** $^{31}$P-NMR Spectrum of Cyano(4-fluorophenyl)methyl dimethyl phosphate

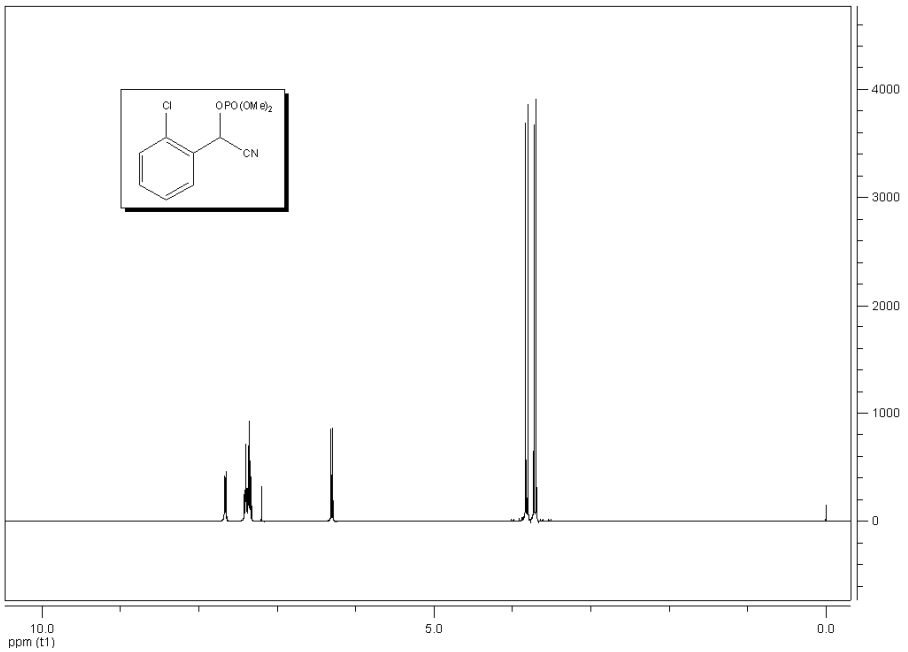


**Figure A.7** $^{1}$H-NMR Spectrum of (2-chlorophenyl)(cyano)methyl dimethyl phosphate

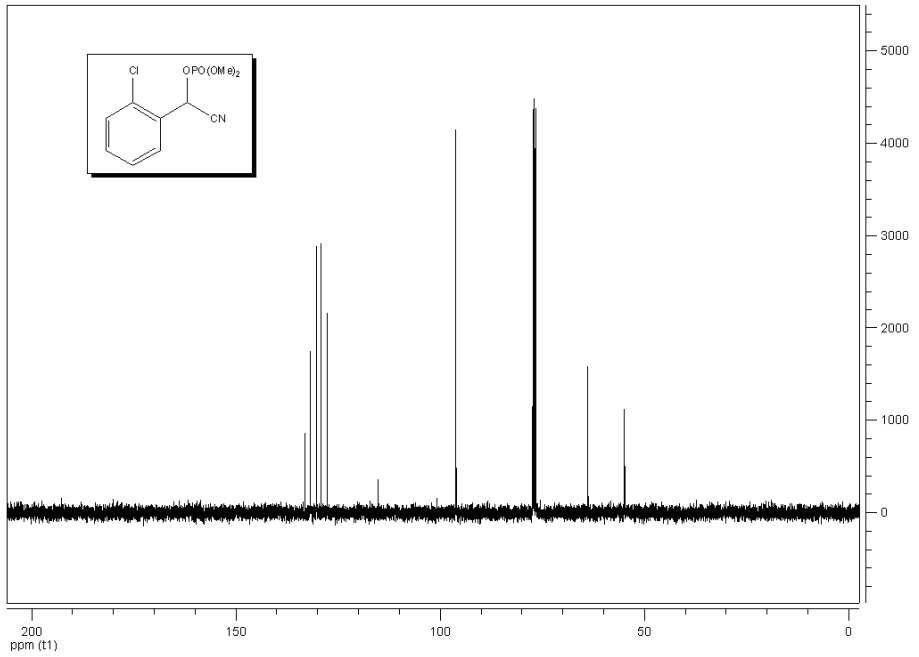


**Figure A.8** $^{13}$C-NMR Spectrum of (2-chlorophenyl)(cyano)methyl dimethyl phosphate

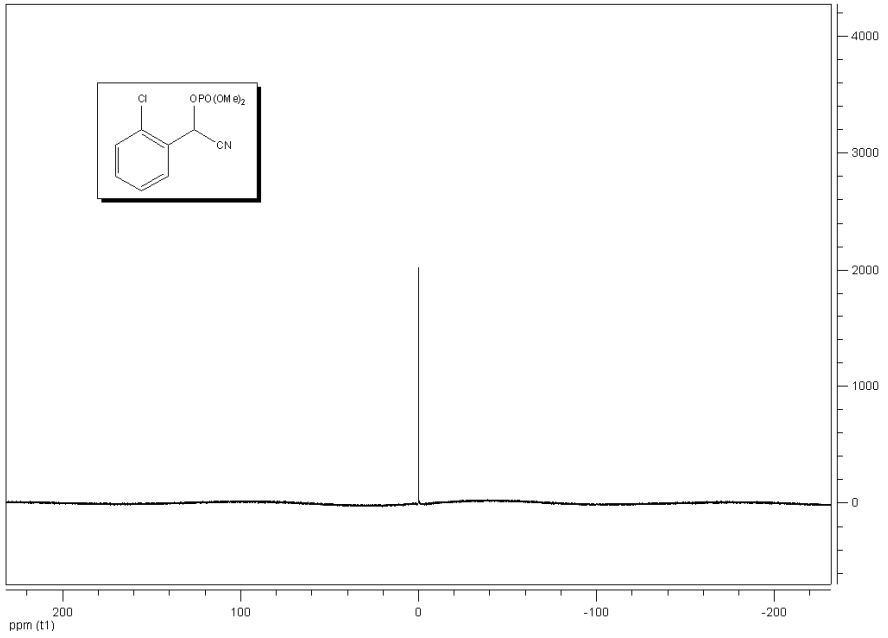


**Figure A.9** $^{31}$P-NMR Spectrum of (2-chlorophenyl)(cyano)methyl dimethyl phosphate

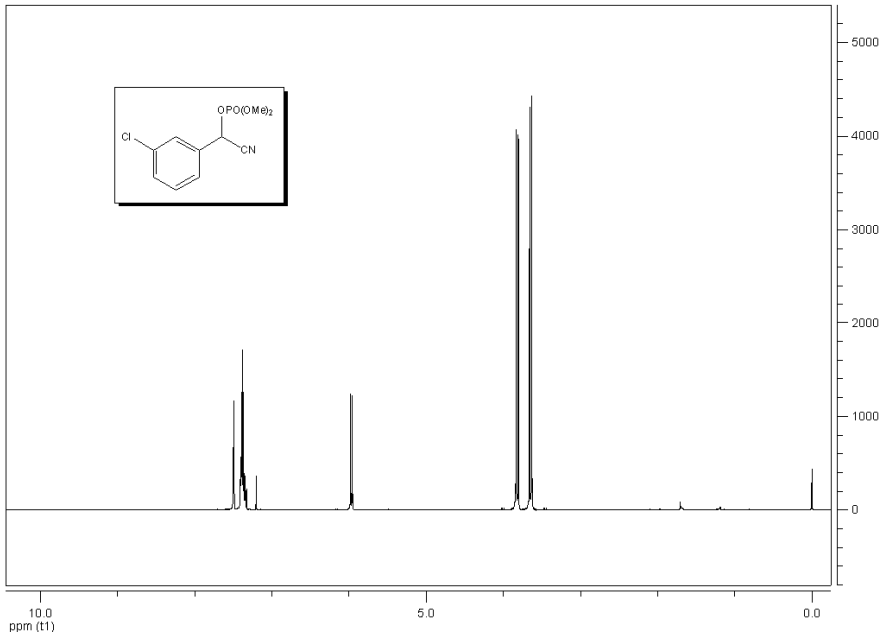


**Figure A.10** $^{1}$H-NMR Spectrum of (3-chlorophenyl)(cyano)methyl dimethyl phosphate

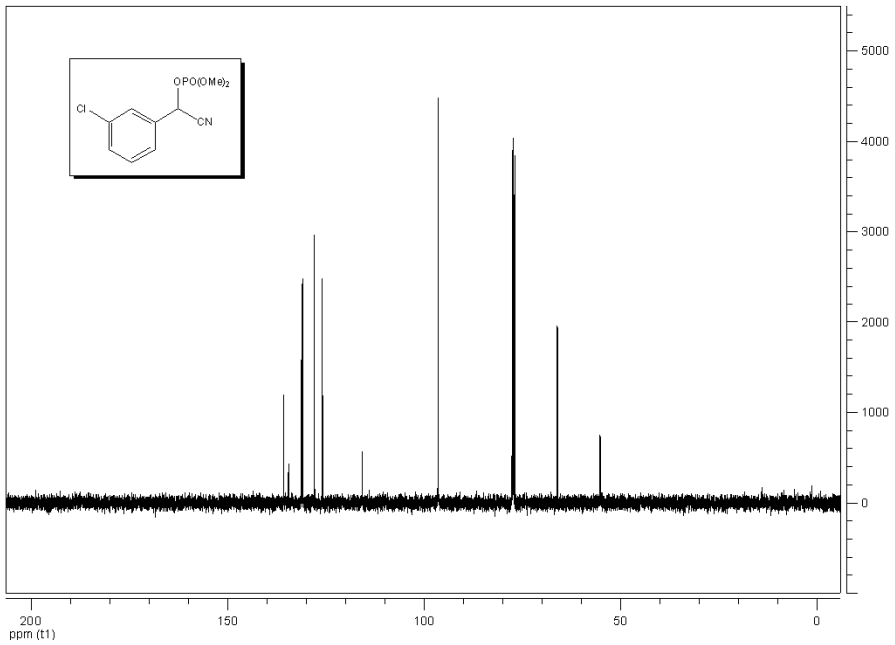


**Figure A.11** $^{13}$C-NMR Spectrum of (3-chlorophenyl)(cyano)methyl dimethyl phosphate

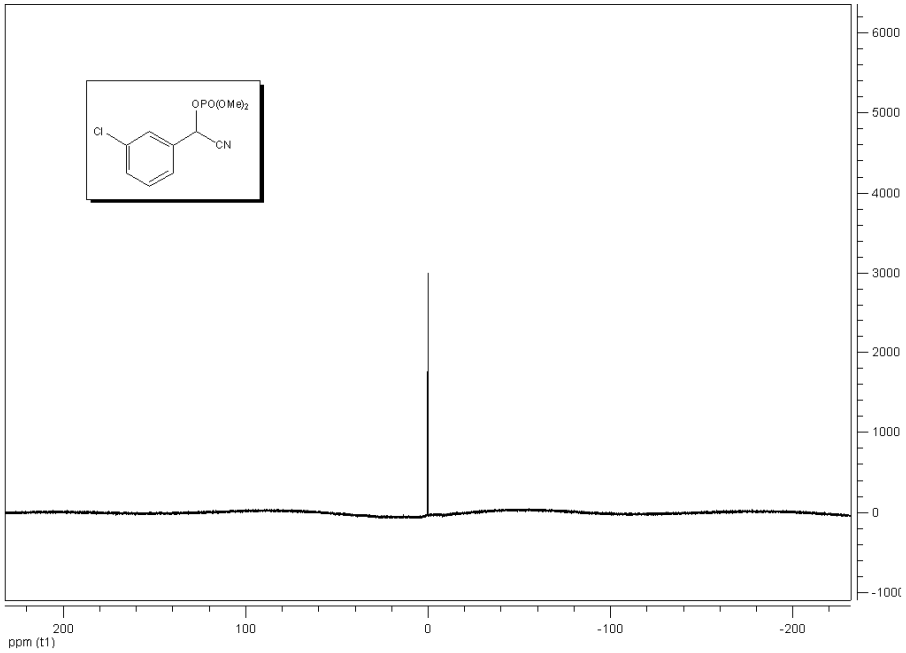


**Figure A.12** $^{31}$P-NMR Spectrum of (3-chlorophenyl)(cyano)methyl dimethyl phosphate

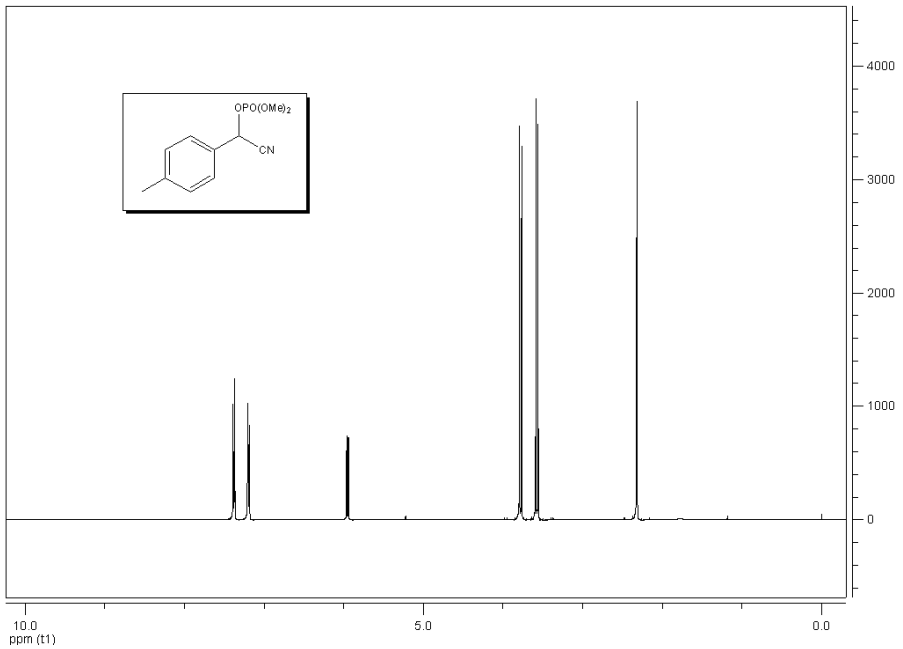


**Figure A.13** $^{1}$H-NMR Spectrum of Cyano(p-tolyl)methyl dimethyl phosphate

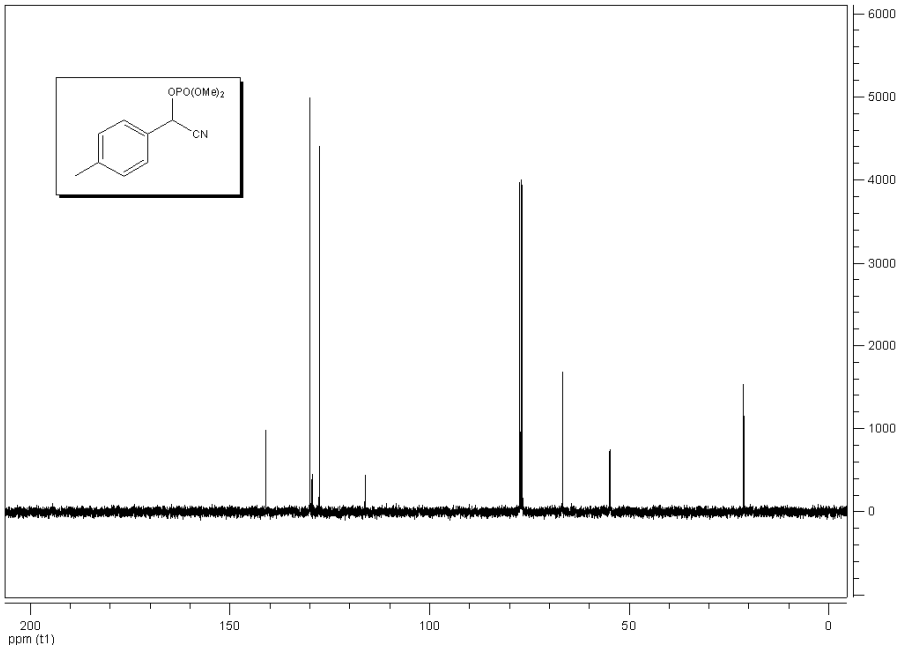


**Figure A.14** $^{13}$C-NMR Spectrum of Cyano(p-tolyl)methyl dimethyl phosphate

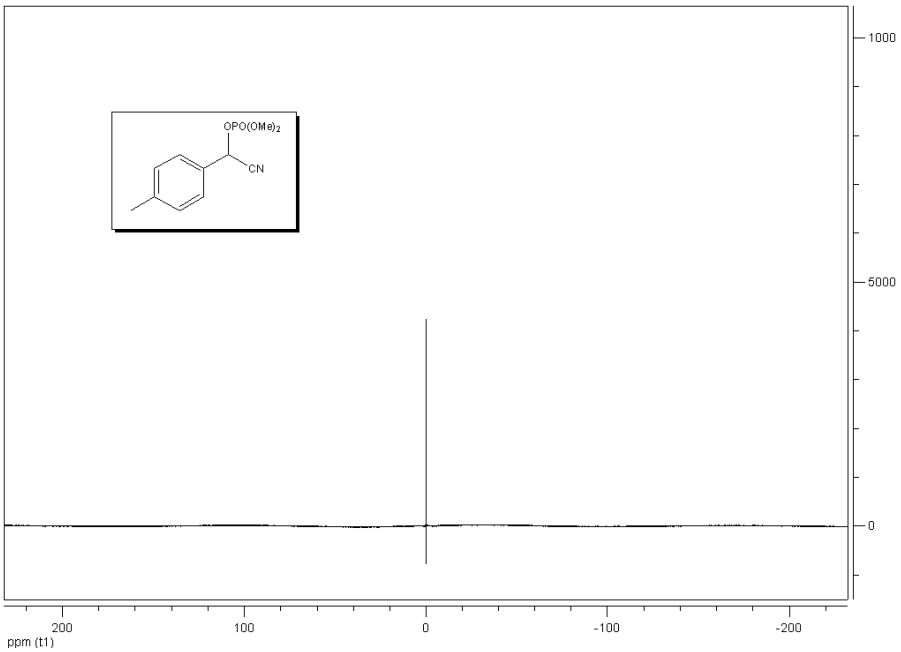


**Figure A.15** $^{31}$P-NMR Spectrum of Cyano(p-tolyl)methyl dimethyl phosphate

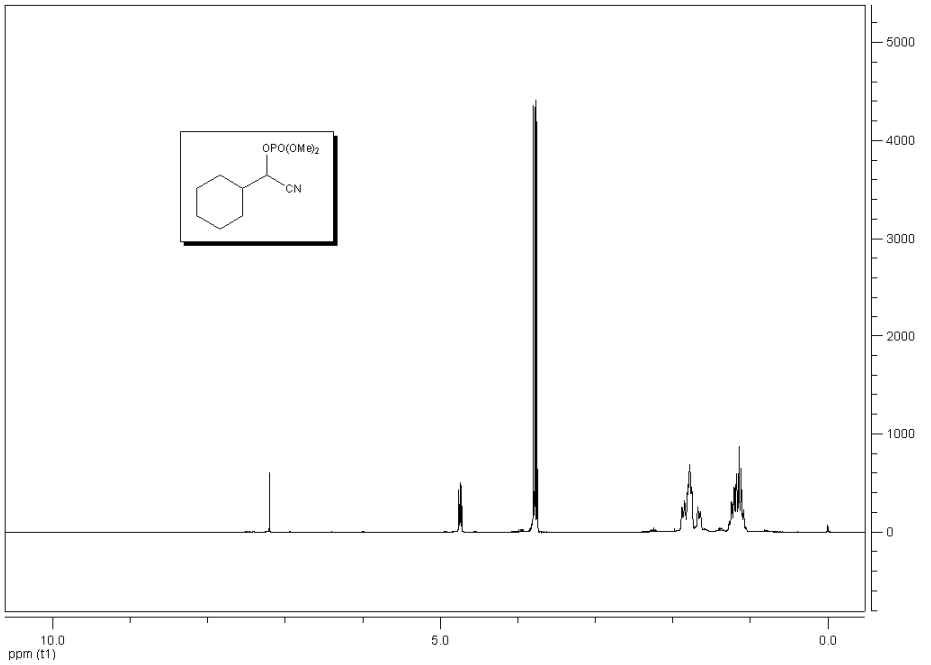


**Figure A.16** $^{1}$H-NMR Spectrum of Cyano(cyclohexyl)methyl dimethyl phosphate

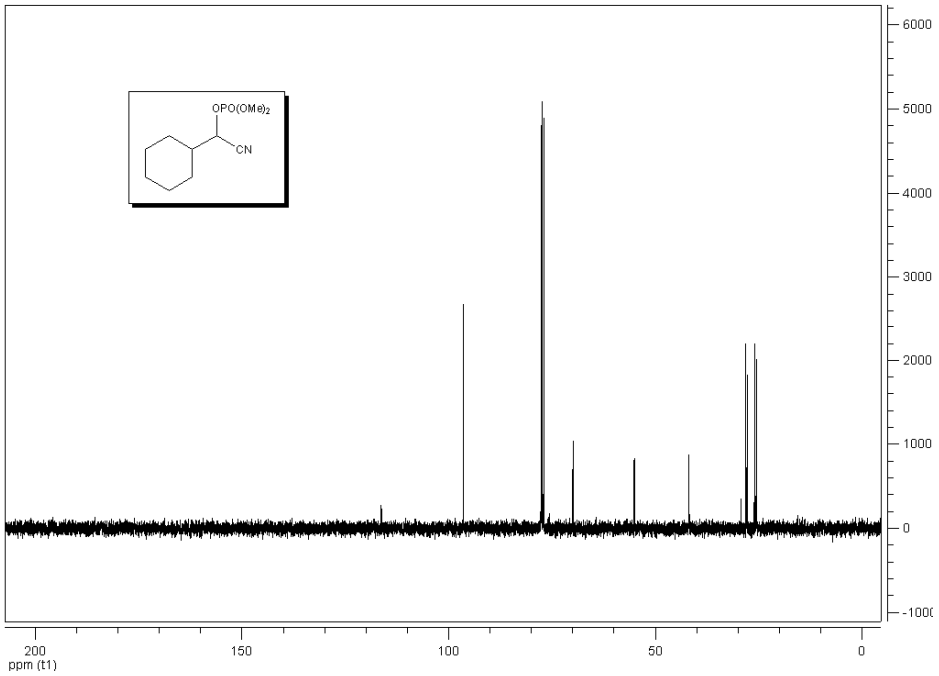


**Figure A.17** $^{13}$C-NMR Spectrum of Cyano(cyclohexyl)methyl dimethyl phosphate

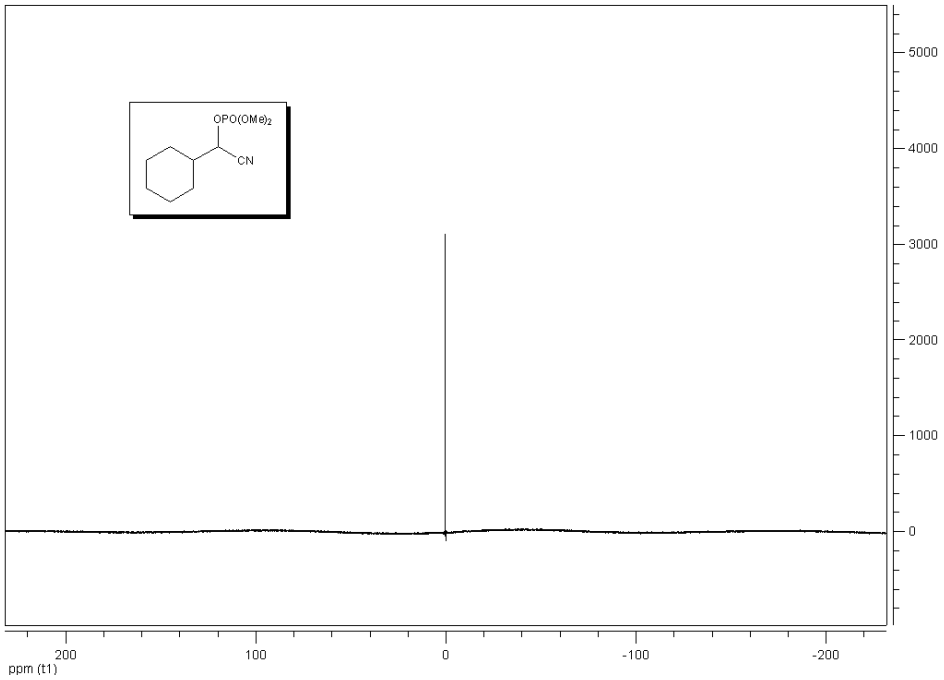


**Figure A.18** $^{31}$P-NMR Spectrum of Cyano(cyclohexyl)methyl dimethyl phosphate

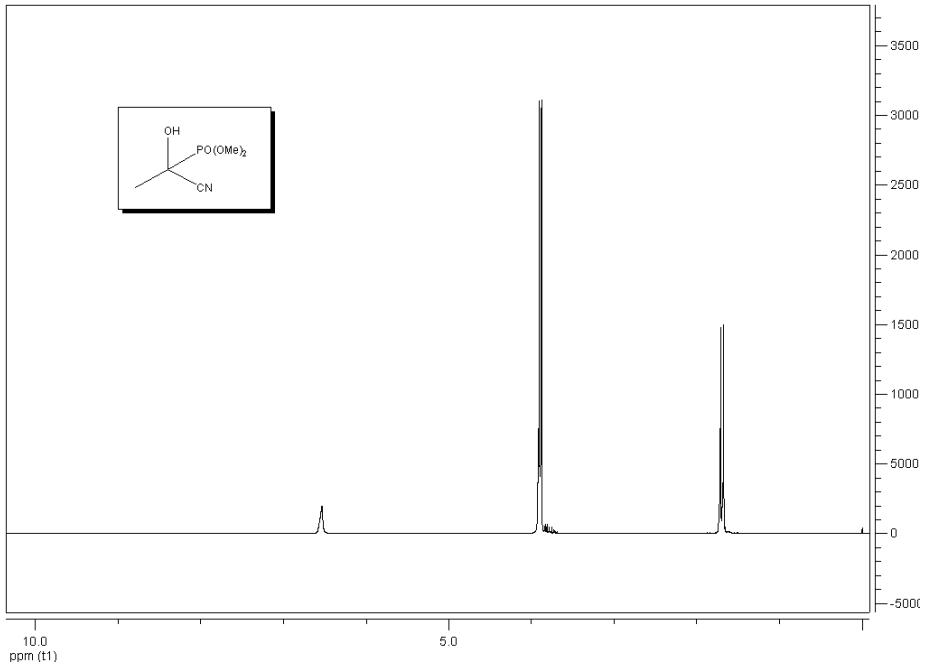


**Figure A.19** $^{1}$H-NMR Spectrum of Dimethyl 1-cyano-1-hydroxyethylphosphonate

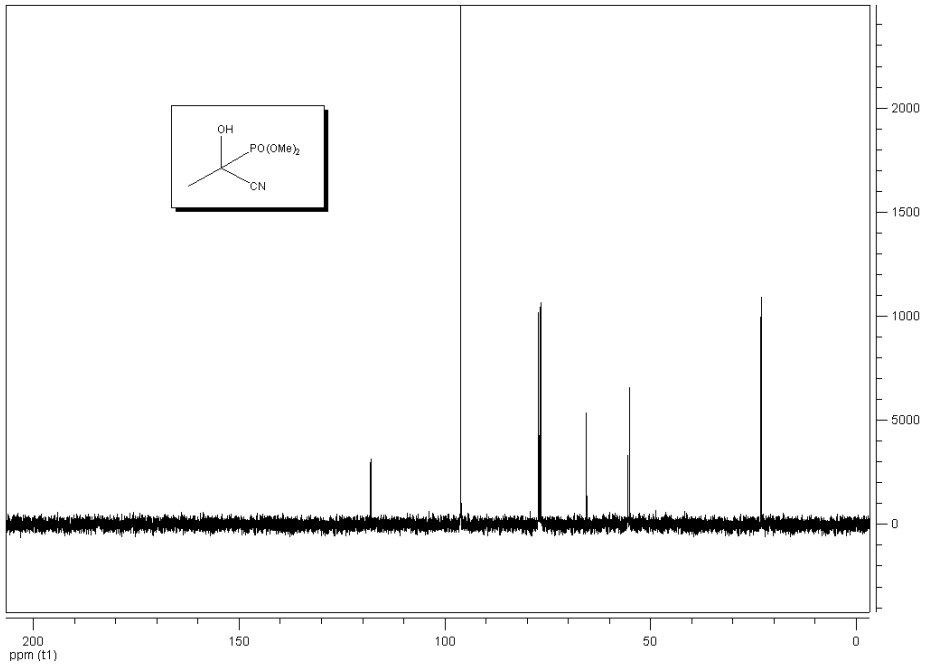


**Figure A.20** $^{13}$C-NMR Spectrum of Dimethyl 1-cyano-1-hydroxyethylphosphonate

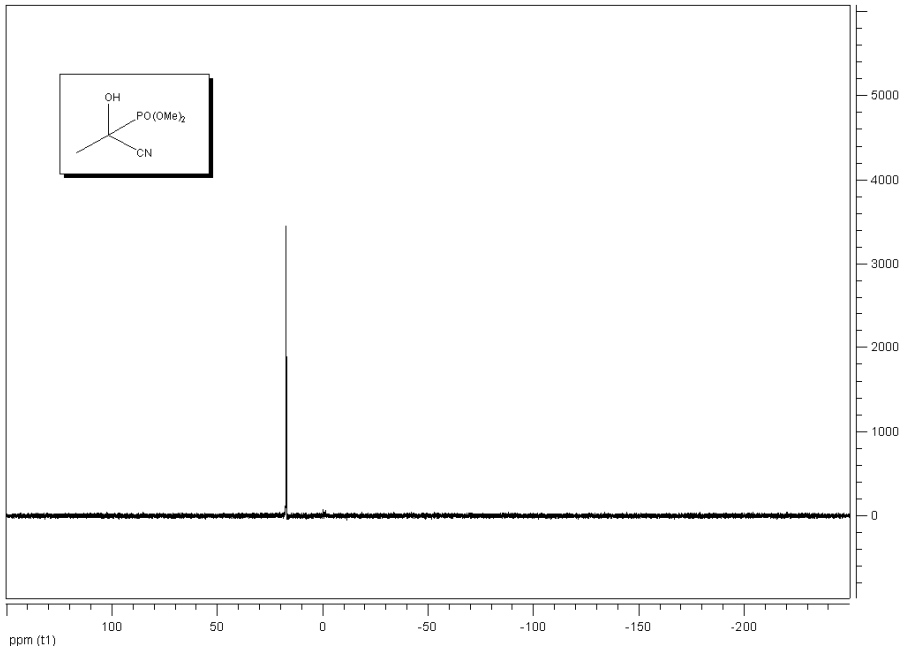


**Figure A.21** $^{31}$P-NMR Spectrum of Dimethyl 1-cyano-1-hydroxyethylphosphonate

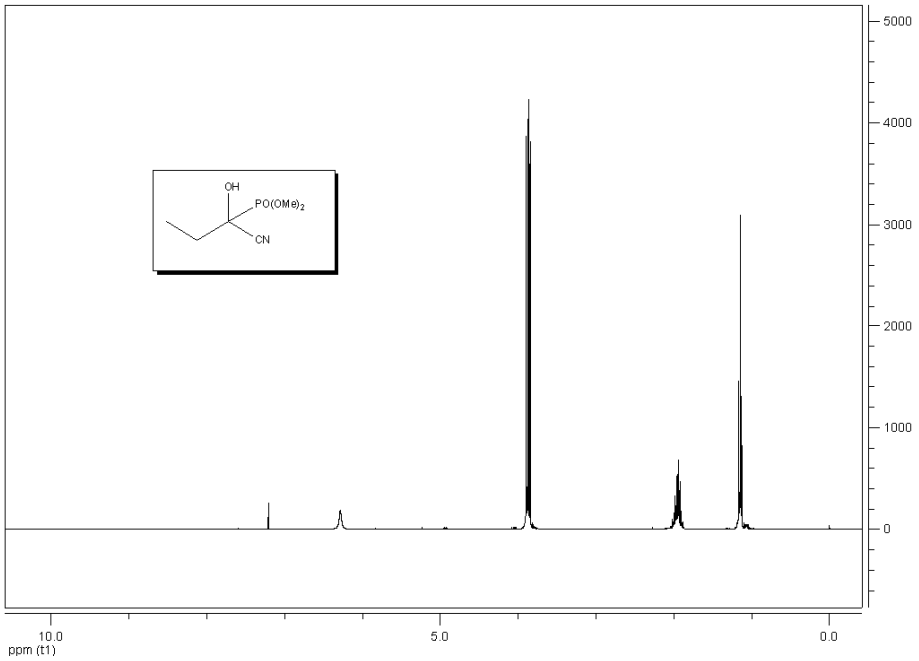


**Figure A.22** $^{1}$H-NMR Spectrum of Dimethyl 1-cyano-1-hydroxypropylphosphonate

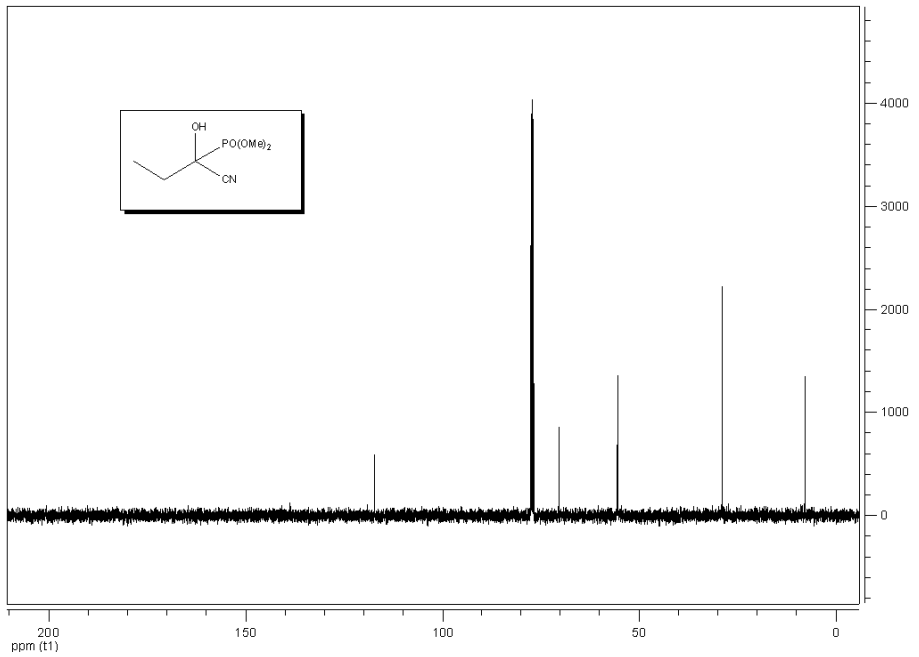


**Figure A.23** $^{13}$C-NMR Spectrum of Dimethyl 1-cyano-1-hydroxypropylphosphonate

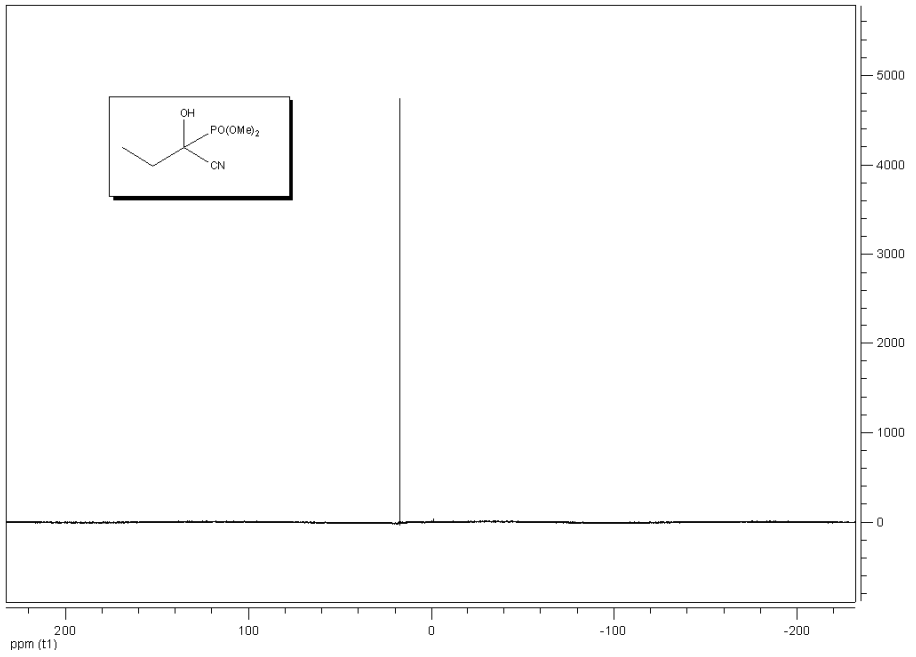


**Figure A.24** $^{31}$P-NMR Spectrum of Dimethyl 1-cyano-1-hydroxypropylphosphonate

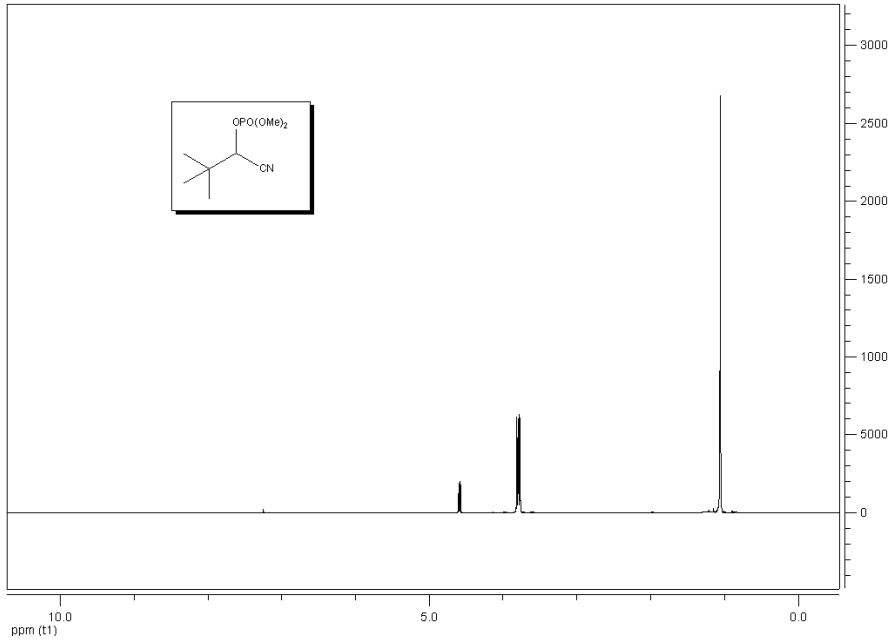


**Figure A.25** $^{1}$H-NMR Spectrum of 1-cyano-2,2-dimethylpropyl dimethyl phosphate

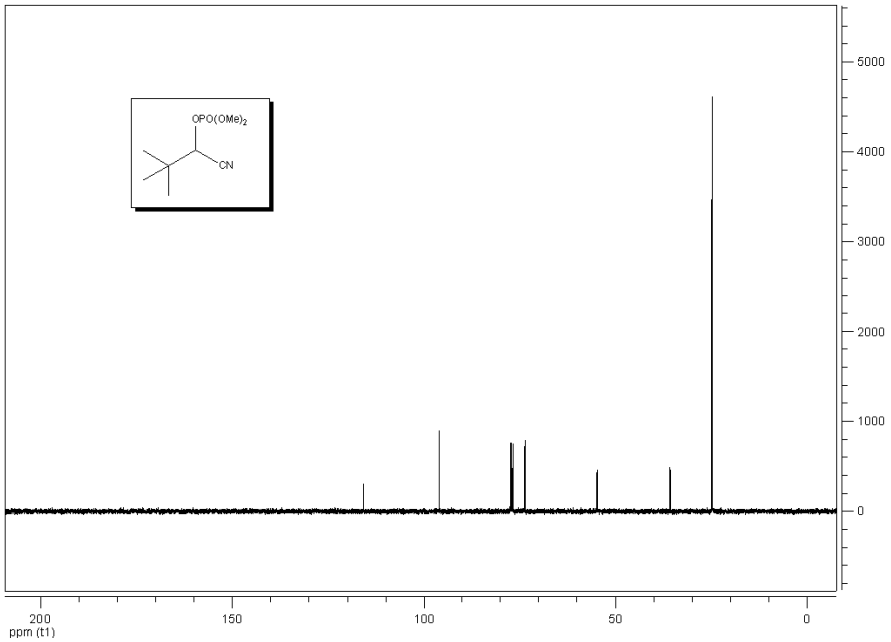


**Figure A.26** $^{13}$C-NMR Spectrum of 1-cyano-2,2-dimethylpropyl dimethyl phosphate

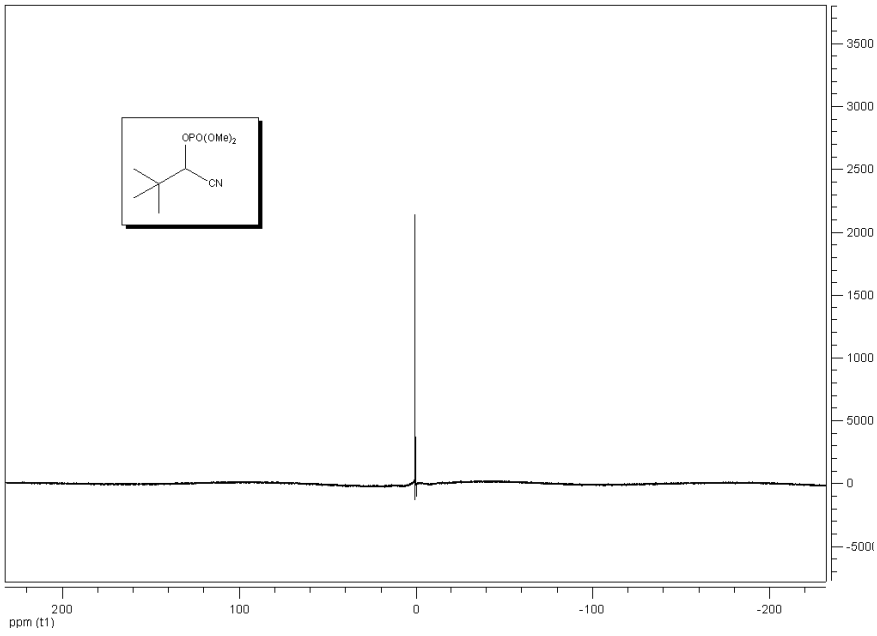


**Figure A.27** $^{31}$P-NMR Spectrum of 1-cyano-2,2-dimethylpropyl dimethyl phosphate

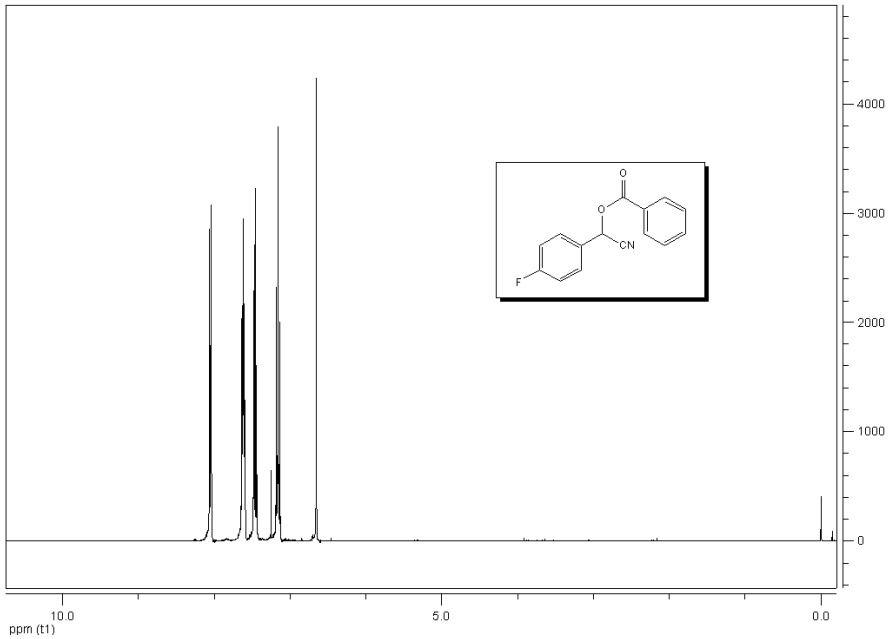


**Figure A.28** $^{1}$H-NMR Spectrum of Cyano(4-fluorophenyl)methyl benzoate

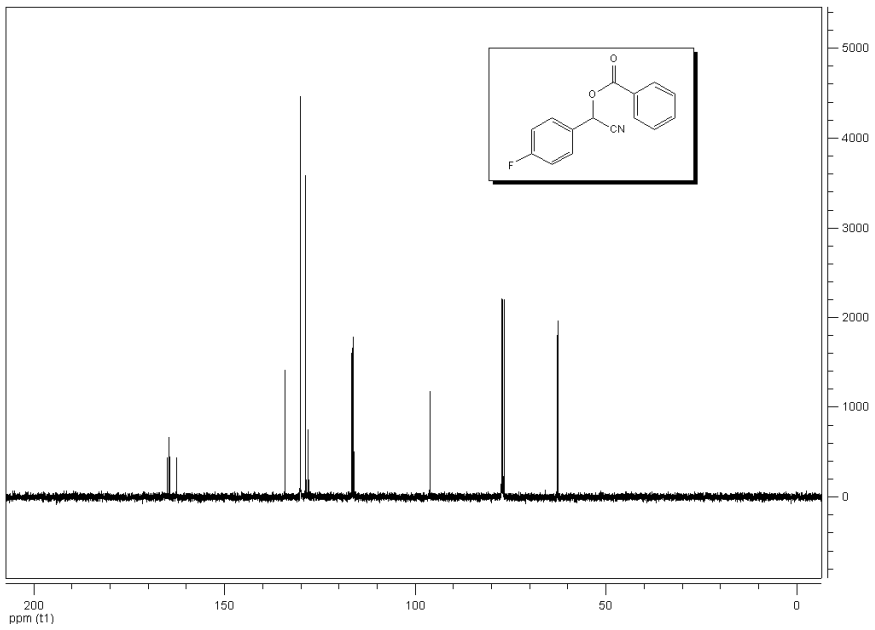


**Figure A.29** $^{13}$C-NMR Spectrum of Cyano(4-fluorophenyl)methyl benzoate

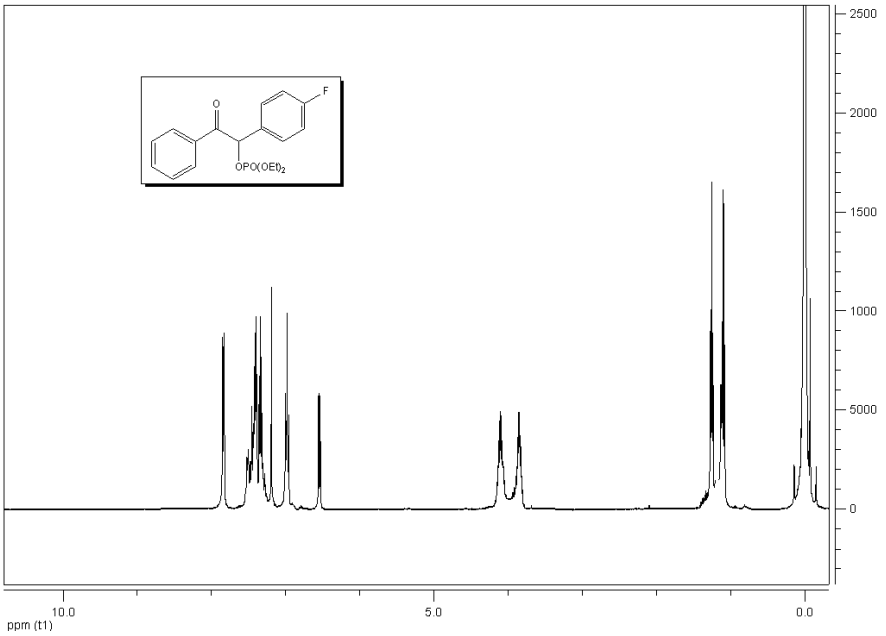


**Figure A.30** $^{1}$H-NMR Spectrum of Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate

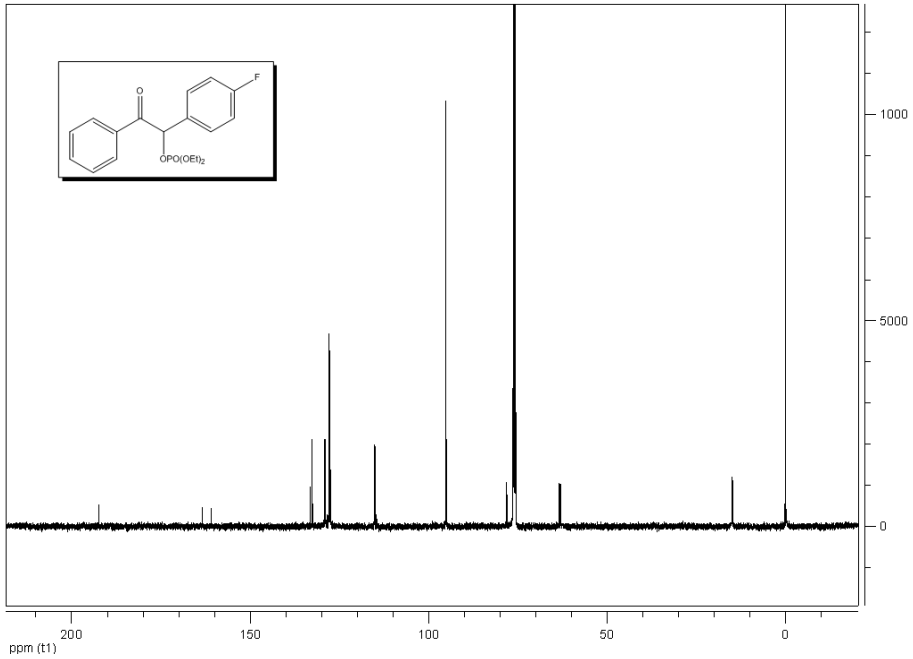


**Figure A.31** $^{13}$C-NMR Spectrum of Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate

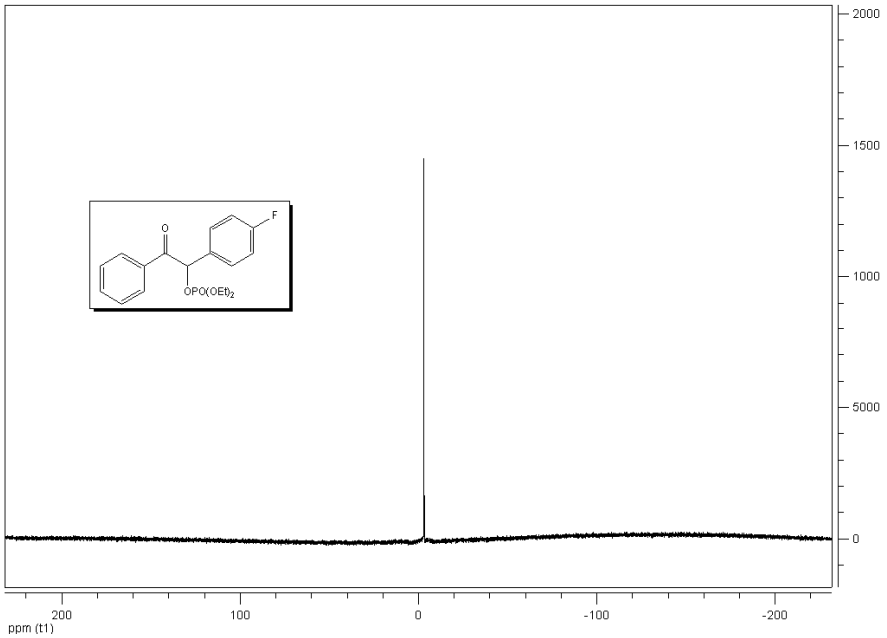


**Figure A.32** $^{31}$P-NMR Spectrum of Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate

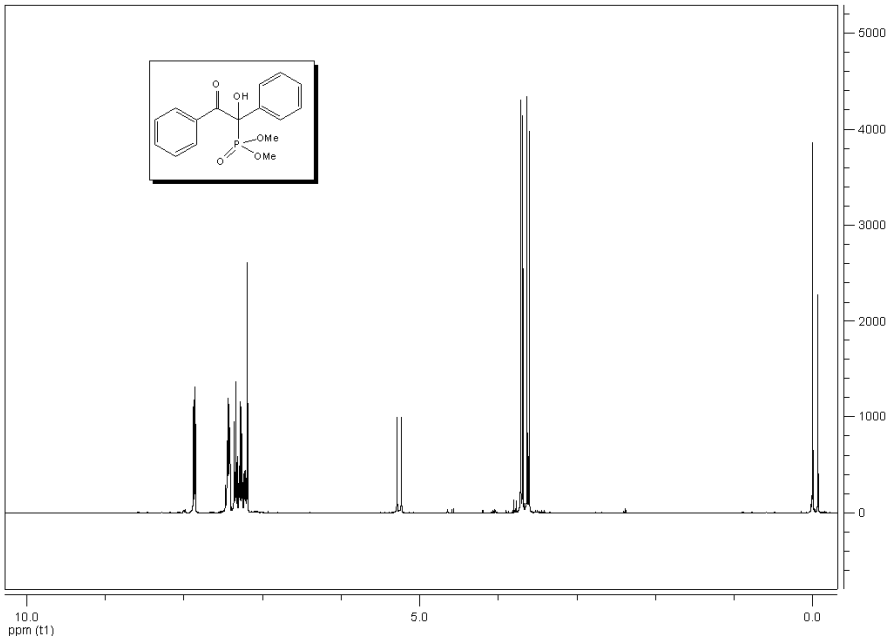


**Figure A.33** $^{1}$H-NMR Spectrum of Dimethyl 1-hydroxy-2-oxo-1,2-diphenylethylphosphonate

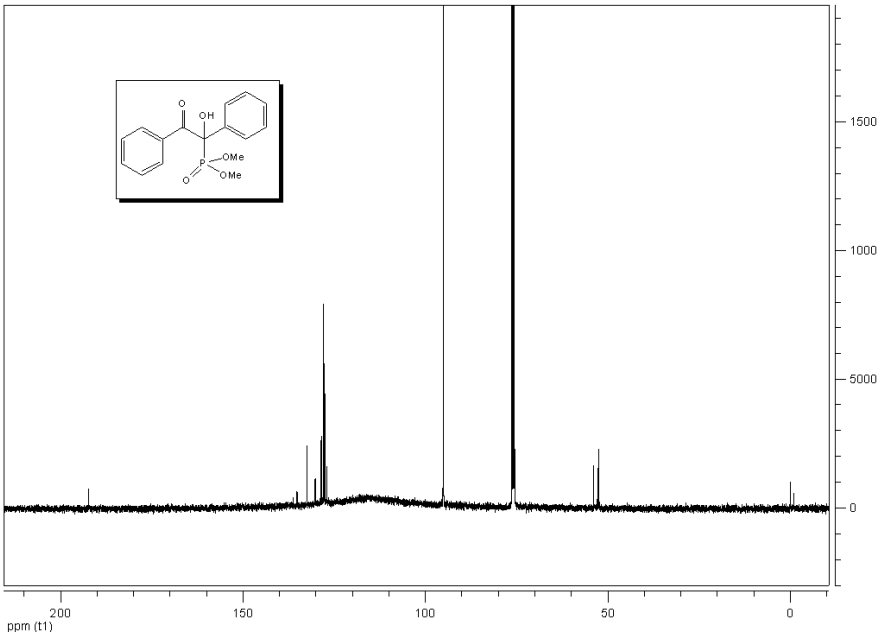


**Figure A.34** $^{13}$C-NMR Spectrum of Dimethyl 1-hydroxy-2-oxo-1,2-diphenylethylphosphonate

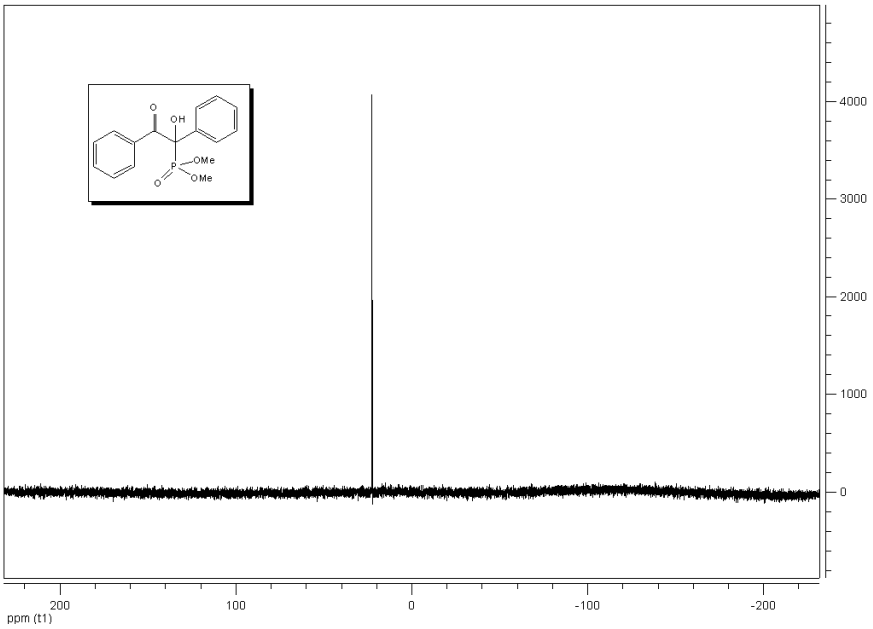


**Figure A.35** $^{31}$P-NMR Spectrum of Dimethyl 1-hydroxy-2-oxo-1,2-diphenylethylphosphonate

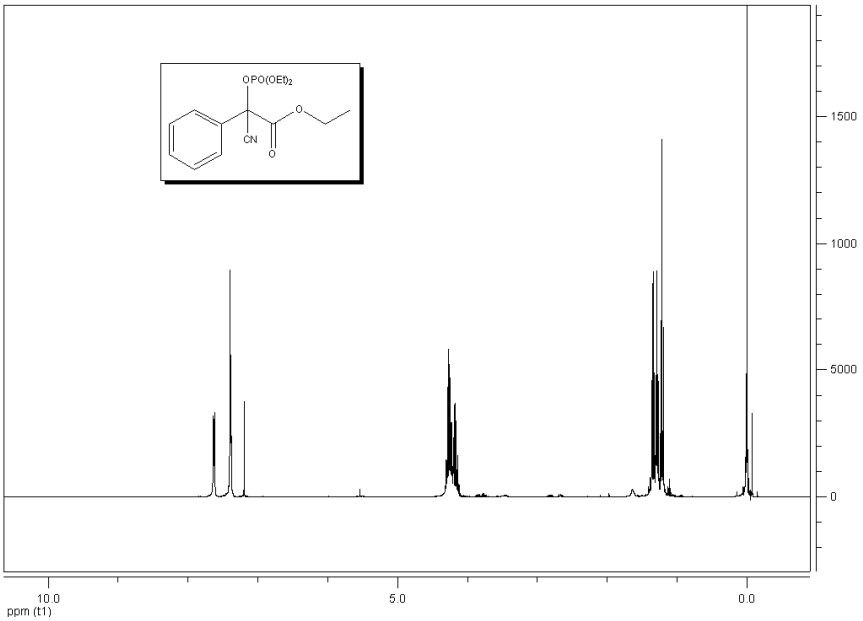


**Figure A.36** $^{1}$H-NMR Spectrum of Ethyl 2-cyano-2-(diethoxyphosphoryloxy)-2-phenylacetate

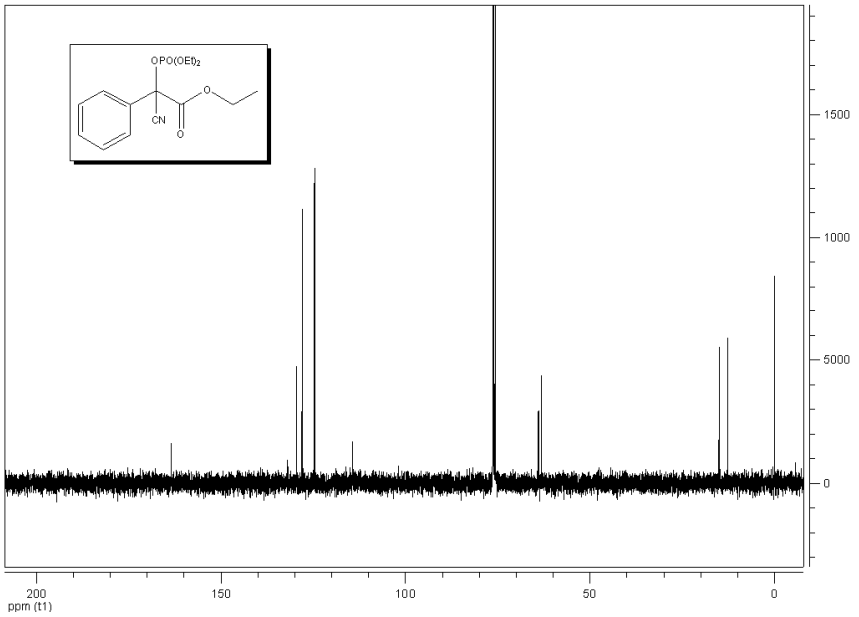


**Figure A.37** $^{13}$C-NMR Spectrum of Ethyl 2-cyano-2-(diethoxyphosphoryloxy)-2-phenylacetate

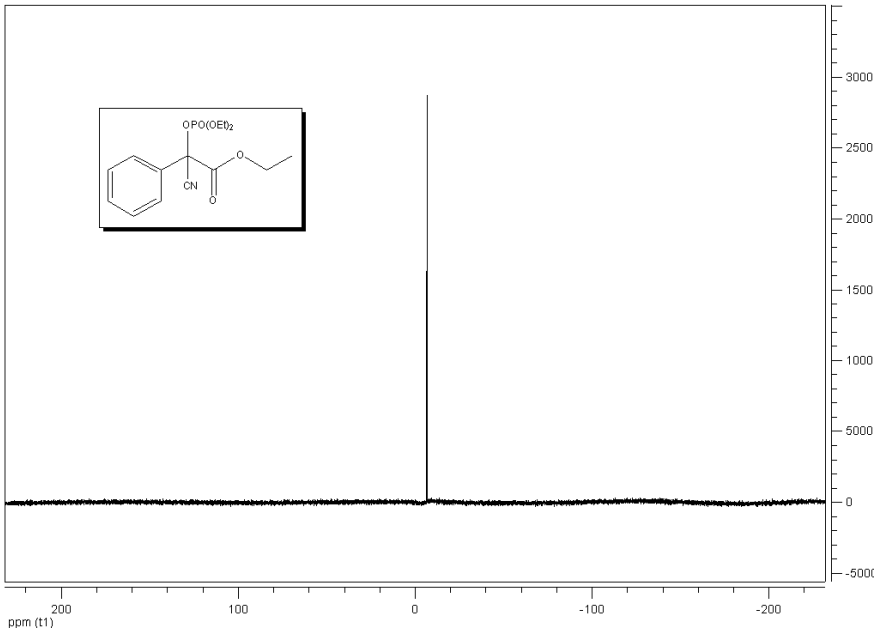


**Figure A.38** $^{31}$P-NMR Spectrum of Ethyl 2-cyano-2-(diethoxyphosphoryloxy)-2-phenylacetate

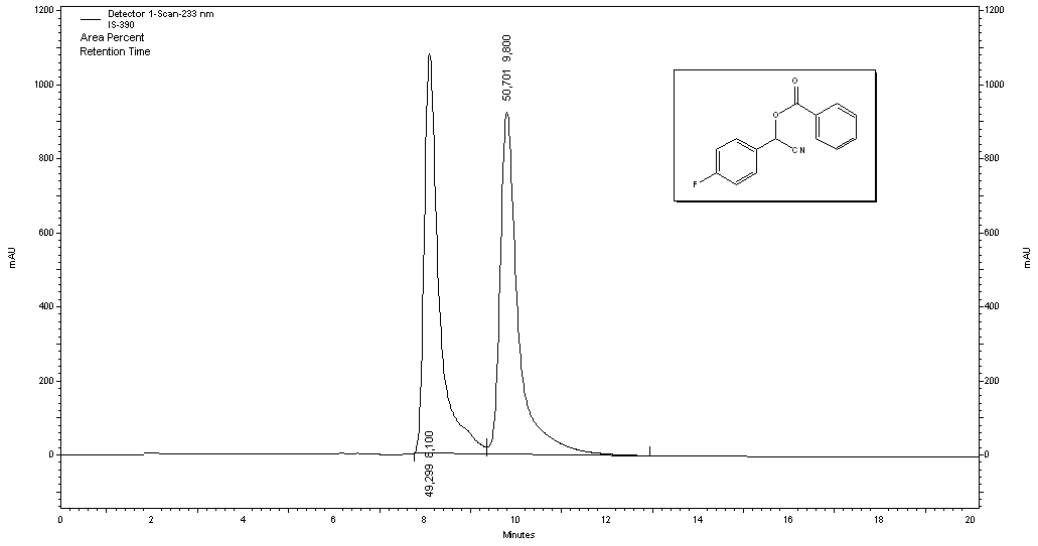


**Figure A.39** HPLC Spectrum of Racemic Cyano(4-fluorophenyl)methyl benzoate

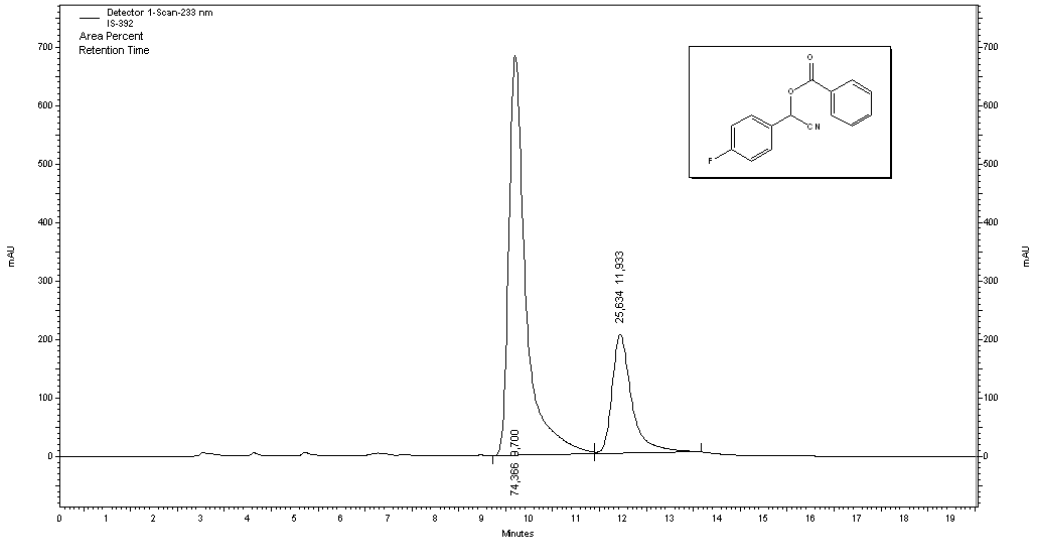


**Figure A.40** HPLC Spectrum of Asymmetric Cyano(4-fluorophenyl)methyl benzoate

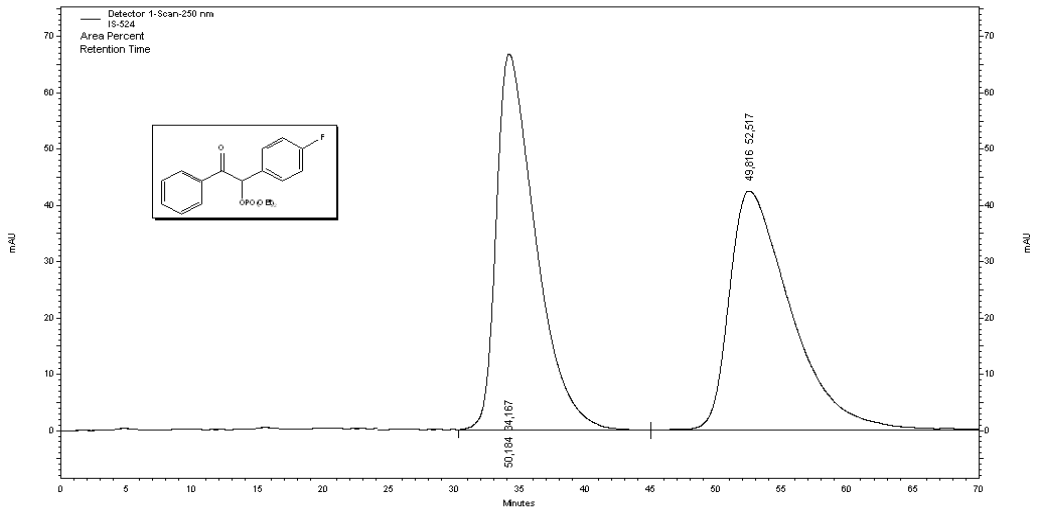


**Figure A.41** HPLC Spectrum of Racemic Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate

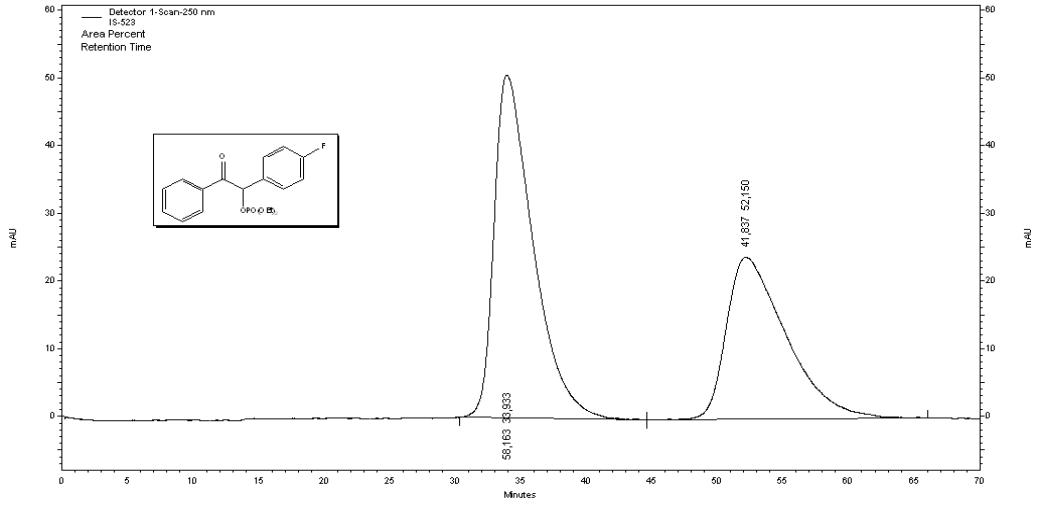


**Figure A.42** HPLC Spectrum of Asymmetric Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate