SYNTHESIS AND REACTIONS OF ALPHA-KETO-BETA-HYDROXYPHOSPHONATES

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ABSTRACT

SYNTHESIS AND REACTIONS OF ALPHA-KETO-BETA-HYDROXYPHOSPONATES

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This thesis presents synthesis and different reactions of alpha-keto-beta-hydroxyphosphonates. Toward this aim, the hydroxyl functionality of alpha-hydroxycarboxylic acids were protected with alkyl or acyl groups and then formation of acid chloride followed by the reaction with trialkylphosphite furnished protected alpha-keto-beta-hydroxyphosponates. Nucleophilic addition reactions were applied to these compounds to obtain quaternary alcohols with phosphonate functionality. The addition reactions were tried with organocatalysts for the enantioselective formation of desired products.

Keywords: Acyl anion, acyl anion equivalent, ketophosphonates, chiral alpha-hydroxycarboxylic acids

ÖZ

ALFA-KETO-BETA-HİDROKSİFOSFONATLARIN SENTEZLERİ VE REAKSİYONLARI

Barış, Şehriban
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan Sıtkı Demir
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Ketofosfonat türevleri organik reaksiyonlarda önemli yapıtaşıdırlar ve biyolojik aktif ürünlerin de yapılarında bulunurlar. Bu çalışma alfa-keto-beta-hidroksifosfonatların sentezini ve farklı reaksiyonlarını sunmaktadır. Bu amaç doğrultusunda alfa-hidroksikarboksilik asitlerin hidroksi grubupları alkyl ya da açil gruplarıyla korunduktan sonra klor türevlerine çevrilmeleriyle elde edilen ara ürünler trialkilfosfonatlarla reaksiyona sokulmuş ve alfa-keto-beta-hidroksifosfonatlar elde edilmiştir. Bu ürünler değişik nükleofillerle reaksiyona sokularak fosfonat türevli kuaterner dioller elde edilmiştir. Ayrıca organokatalizörler kullanılarak farklı stereoseçicilikte hedef ürünler sentezlenmiştir.

Anahtar Kelimeler: Açil anyon, açil anyon eşleniği, ketofosfonat, kiral alfa-hidroksikarboksilik asit.

To My Family

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Finally, I would give huge thanks to my mother who has given me support through all my life

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LIST OF ABBREVIATIONS

AAE : Acyl anion equivalent

TPP: Thiamine pyrophosphate

TMSCN: Thrimethylsilycyanide

LDA: Diisopropyl amide

THF: Tetrahydro furan

KCN: Potassium cyanide

NHC: N-heterocyclic carbine

DMSO: Dimethyl sulfoxide

TEP: Thriethyl phosphate

TMP: Thrimethyl phosphite

DMS: Dimethyl sulfate

$SOCl_2$: Thionyl chloride

$Zn(OTf)_2$: Zinc thrifluoromethanesulfonate

TLC: Thin layer chromatography

DMBS: Borane dimethyl sulfide

$LiAlH_4$: Lithium tetrahyridoaluminate

K_2CO_3: Potassium carbonate

NaOAc: Sodium acetate

CHAPTER 1

INTRODUCTION

1.1 The Chemistry of Acyl Anion Equivalents and Precursor

Organic synthesis is the construction of organic molecules by using chemical processes. There exists 7 million organic compounds known, and most of them have been made by synthesis rather than being isolated from nature. There are many reasons to carry out synthesis of organic compounds, such as proving structure of a natural compound by 'putting it together' from simpler molecules and preparing compounds that are valuable to mankind e.g. pharmaceuticals, polymers, dyes etc. Two important types of reactions used in synthetic organic chemistry are carbon-carbon bond forming reactions and functional group reactions that is conversion of one functional group into another.

The carbon-carbon bond formation is an important concept for the construction of organic compounds because it is critical in the synthesis of complex organic molecules from smaller, simpler ones. In nature, a polarity difference between atoms assists making a bond to built bulky molecules. The uniqueness of carbon comes from the fact that it can bind to itself to built new compounds without needing a polarity difference. The result of this property is that chains are produced. It is known that carbon-carbon bond is very energetic and stable, for this reason generation of this bond is a challenging process but at the same time very essential in organic synthesis. The capacity to selectively form carbon-carbon bonds between organic fragments has been central to the development of synthetic organic

chemistry. Complex molecules held together largely by carbon-carbon bonds can be synthesized through careful planning and execution of a series of chemical reactions that build up the desired structure step by step. This approach is used, for example, in the chemical synthesis of natural product molecules for use in the pharmaceutical industry. The usual procedure for the formation of C-C bond is the stepwise creation of each individual bonds of the target molecule and this method has a wide range of application like the chemical synthesis of natural product molecules for use in the pharmaceutical industry. However, the number of generally useful and well tested reactions for effecting carbon-carbon bond formation is relatively small, compared with reactions used to modify functional groups. So, to solve this restriction problem some news are generated by modifying these classical and limited procedures [1]. The term called umpolung, the temporary reversal of the characteristic pattern of the normal reactivity of a functional group [2], is one of them.

The strategy umpolung was first introduced in 1962-1965 by Foling and Arens, Truce and Roberts, and Seebach and Corey [3]. In 1979, Seebach described a notation for the classification of the synthons that makes easier the determination of the synthetic equivalents in reactions. According to this notation, nucleophilic sites are donated as “d” for donor and electrophilic sites are donated as “a” for acceptor. The position of the acceptor and donor sites is then numbered starting from the point of attachment of the heteroatom. For example, charge affinity pattern and Seebach notation of a ketone is shown below together with plausible bond disconnections dictated by the polar reactivity of each carbon.

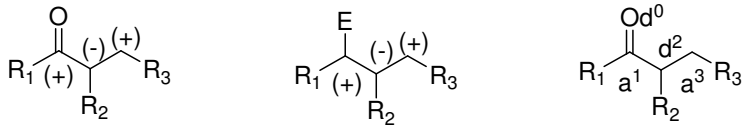


Figure 1 Charge Affinity Pattern / Seebach Notation of a Ketone

Disconnections shown in the Figure 1 are plausible ones derived from the natural charge affinity of a carbonyl compound (E function). An alternative approach would be inverting the inherent chemical reactivity that functional groups confer upon the organic molecule. Such an operation would enable to reverse the Lewis acid-base property of a given functionally activated carbon, adding new dimensions of flexibility to the design of complex molecules. Transformations which invert Lewis acid-base properties of a given carbon atoms are generally referred to as "charge affinity inversion" or more commonly "umpolung" [4].

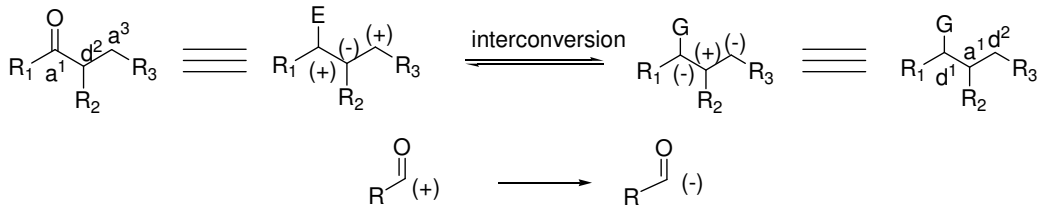


Figure 2 Charge Affinity Inversion

In order to understand the importance of umpolung, first of all it should recognized that reagents of opposite polarity for the introduction of a given fragment or synthon is desirable for developing simple routes for the synthesis of complex molecules [5]. Synthons are structural units within a molecule which are related to possible synthetic operations. For example, the molecule **1** is related with the substrate synthon **2** and the formyl synthon **3** [6] (Figure 3).

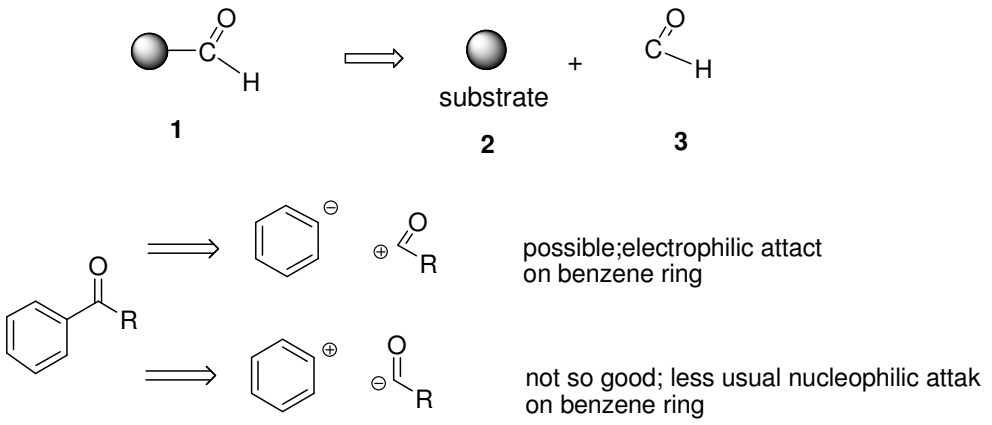


Figure 3 Synthons of a Molecule

Once the synthons were identified, it is necessary to determine the synthetic equivalents that are real reagents carrying out the function of a synthon. Figure 4 shows the corresponding synthons of the molecule in their natural charge affinities and ones having opposite polarity, converted by umpolung. Although these inverted species are conceptual formalities and are unlikely to exist in usable form, their structural equivalents of each exist and are used in C-C bond formation reactions.

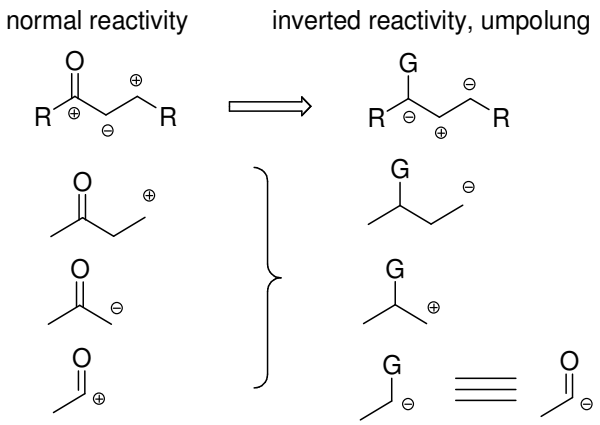


Figure 4 Reactivity Conversion by Umpolung

The interconvertion of the normally electrophilic carbonyl function with classes of functions that are capable of stabilizing adjacent carbanions (G function) would be capable of creating a synthetic equivalency between electrophilic carbonyl and unstable "carbonyl anion". Nucleophilic entities at the carbonyl center are generally named as masked "acyl anion" or "acyl anion equivalents (AAE)". By means of these synthons, new disconnections that are totally different from natural reactivity of the carbonyl group are possible during formation of new bonds. So ''acyl anion chemistry'' is a promising area in organic chemistry. Developments and further expectations in this area of synthetic organic chemistry will be mentioned in the following part of this chapter. Catalyzed reactions of acyl anion equivalents and benzoin synthesis via an acyl anion will be underlined as these reactions are the most important ones in this field.

1.1.1. Benzoin Condensation:

Considerable effort in the past few years has been devoted to the development and study of synthetic equivalents of acyl carbanions, in which nucleophilic reactivity is imparted to centers which ordinarily possess electrophilic characteristics [7] (Figure 5) and classical benzoin condensation reaction can be considered as the basis of acyl anion chemistry.

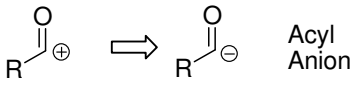
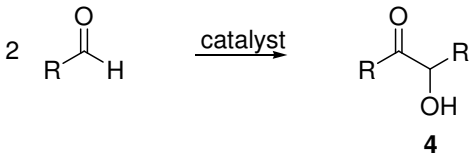


Figure 5 Acyl Anion

Benzoin condensation, a convenient and powerful method for the formation of C-C bonds, is the reaction of two moles of aromatic aldehyde to form an α-hydroxy ketone and it is the quintessential reaction of an acyl anion equivalent (Figure 6) [8]. Wöhler and Liebig accidentally discovered the benzoin condensation in 1832. Their research was focused on cyanohydrins the product of the addition reaction of cyanide to an aldehyde. Surprisingly they observed that when an aromatic aldehyde is used in the reaction, a new product formed which was an acyloin, α-hydroxy ketone **4**.



4

Figure6 Benzoin Condensation

In its traditional form, aromatic aldehydes could be coupled using only cyanide anion as a catalyst and the reaction mechanism for this organic reaction was proposed in 1903 by A. J. Lapworthand [9]. However, Ukai et al. found in 1943 that, as well as cyanide ions, the vitamin thiamin can be used as catalysts for the benzoin condensation [10]. The generation of an acyl anion equivalent in situ by the reaction of an aldehyde with a cyanide ion or a thiazolium ylide is the key step in the benzoin condensation, because of this reason, in the next section these two mechanisms will be explained in details.

1.1.2 Cyanide Ion Catalyzed Benzoin Condensation

The cyanide-catalyzed benzoin reaction is an expeditious route to α-hydroxy ketones (Figure 7). The reaction proceeds via a catalytically-generated nitrile anion that functions as an acyl anion equivalent [11].

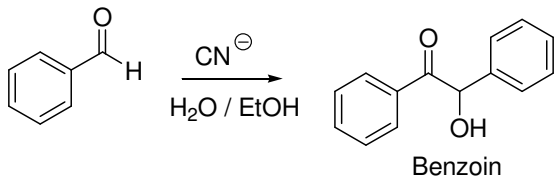


Figure 7 The Cyanide Catalyzed Benzoin Condensation

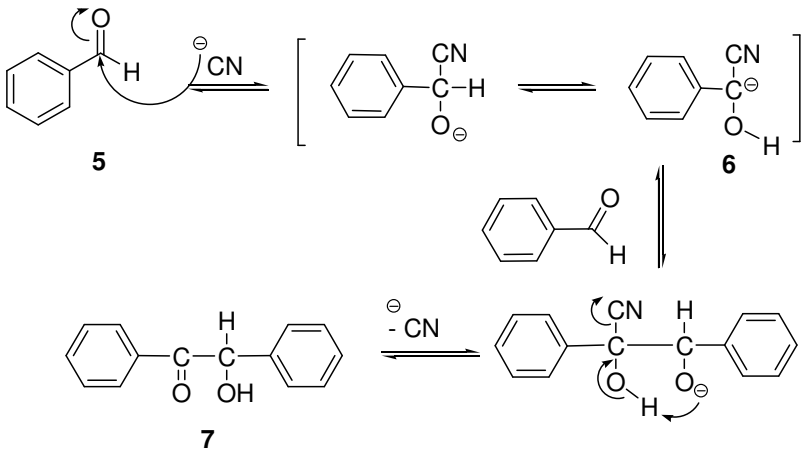


Figure 8 Mechanism of Cyanide Catlayzed Benzoin Condensation

In the mechanism (Figure 7), the first step is the reaction of cyanide ion with the benzaldehyde **5** in a nucleophilic addition. Umpolung reverses the polarity of the carbonyl group and the rearranged intermediate **6**, critical acyl anion equivalent generation, adds to the second carbonyl group in a second nucleophilic addition. Proton transfer (although exact nature of its formation is not known bimolecular proton transfer including solvent was favored over 1,2 shift of the proton from cyanohydrin carbon to oxygen) and elimination of the cyanide ion affords the benzoin **7** as shown in the Figure 8. This is a reversible reaction. In this reaction, both aldehydes have a different purpose; one aldehyde donates a proton and one aldehyde accepts a proton.

According to excepted mechanism of benzoin reaction, cyanide ion plays a critical role from the initial to the last step of the reaction. It serves three functions in this reaction; (1) it acts as a nucleophile, (2) it increases the acidity of α-hydrogen on the carbon atom because of its electron-withdrawing effect, (3) it acts as a leaving group after the condensation is completed [12]. These properties make the cyanide a unique operator of this reaction.

Although benzoin condensation provides an easy access to synthetically important α-hydroxyketones, there are some problems with this reaction. For example, if aromatic aldehydes with strong electron-donating or electron-withdrawing substituents are used in the reaction the yields are quite low. Another disadvantage of benzoin condensation reaction is selectively synthesizing of an unsymmetrically substituted benzoin derivative under classical conditions is nearly impossible. There are many reasons of this problem. First of all, as one can see from the reaction mechanism, attacking of the acyl anion equivalent to another aldehyde in the medium is responsible for the synthesis of a particular benzoin. So, when two different aldehydes are used, there will be two acceptor aldehydes for each generated acyl anion equivalents. If it is assumed that the rate constants of each step for two aldehydes are hypothetically same, then a statistical mixture of four products will be formed. In accord with the above discussion, this design will fail to give the desired product as the major one.

1.1.3 Thiamine Catalyzed Benzoin Condensation

Enzymes catalyze chemical reactions in living systems and perform its catalytic function by bringind reactants together in the spatial relationship necessary for a reaction to occur. In other words, en enzyme provides the structural active site for a biochemical reaction and they often require additional small molecules called coenzymes as cocatalysts. Much of the bond breaking and bond making in biochemical reactions involve coenzymes and many of coenzymes are synthesized from vitamins.

Thiamine in the form of its pyrophosphate, thiamine pyrophosphate **8** (TPP) is the coenzyme found in humans and other animals, and drived from vitamin B_1. TPP is required in a number of important biochemical reactions, including the decarboxylation of pyruvic acid to acetaldehyde, the conversion of pyruvic acid to

acetoin and the transketolase reaction; it is also involved in the oxidative decarboxylation of pyruvic acid to active acetate. These reactions all have one common feature in that they can be considered to involve the formationof an intermediate acyl carbanion, or some stabilized equivalent [13].

TPP have three distinctive units, namely, a pyrophosphate part, a thiazolium core and a pyrimidine unit (Figure 9). TPP mainly engaged in a variety of carbon-carbon bond forming reactions and each unit has a special role in enzymatic catalyses [14].

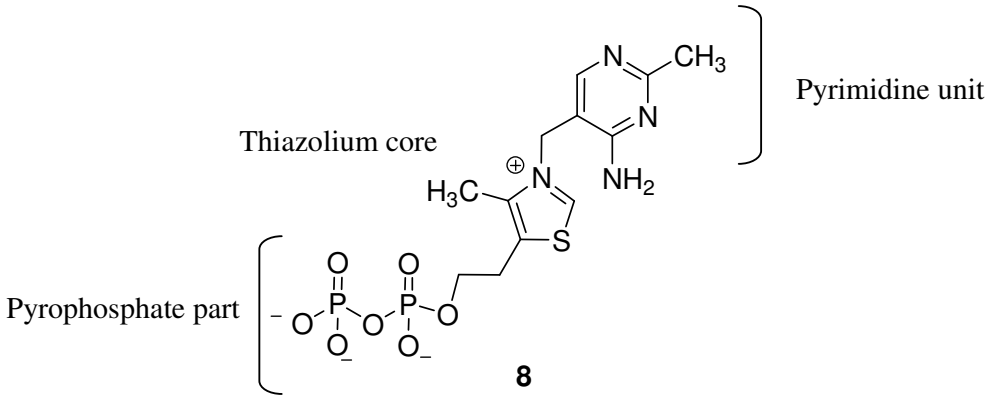


Figure 9 Thiamine Pyrophosphate

A number of biochemical reactions bear a close similarity to the benzoin condensation but they are not, obviously, catalyzed by the highly toxic cyanide ion [14]. Ukai et al. found in 1943 that, as well as cyanide ions, thiazolium salts can be used as catalysts for the benzoin condensation. Some years later, Mizuhara et al. showed that the catalytic activity of the natural thiamine is based on its thiazolium

unit as well [10]. Finally in 1958, Breslow presented a mechanism for the thiamin-catalyzed benzoin condensation, which was inspired by the mechanism for the corresponding cyanide-catalyzed transformation (Figure 10).

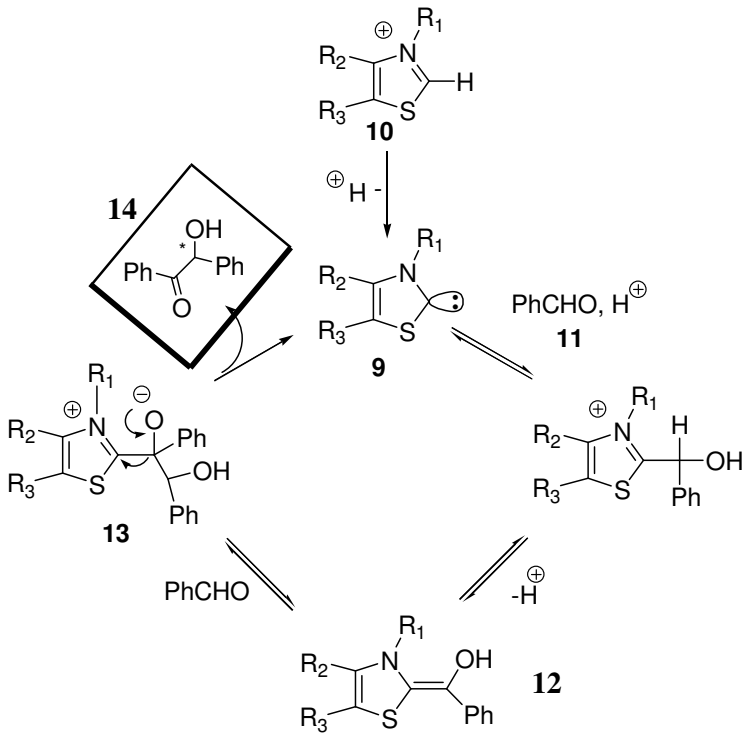


Figure 10 Mechanism of Thiamin Catalyzed Benzoin Condensation

Indeed, he based his mechanistic model for the thiazolium salt catalyzed benzoin condensation on Lapworth's work [10]. As shown in Figure 10, deprotonation of thiazolium salt **10** at its most acidic position generates the carbine **9**, the active catalyst. This resulting thiazol-2-ylidene makes a nucleophilic attack to the aldehyde 11 molecule to generate the resonance-stabilized enolamine **12**, the Breslow

intermediate, and it subsequently functions as the nucleophilic acylation reagent. After deprotonation, addition of this acyl carbanion equivalent to an electrophilic substrate such as a second aldehyde molecule yields the α-hydroxy ketone product **14** and the original carbene catalyst **9**.

The resonance-stabilized conjugate base of the thiazolium ion, thiamine, and the resonance-stabilized carbanion that it forms, are again the keys to the reaction. Like the cyanide ion, the thiazolium ion has just the right balance of nucleophilicity, ability to stabilize the intermediate anion, and good leaving group qualities [14].
Although thiazolium salts seemed to be promising catalyst precursors for benzoin-type condensation reactions, it is noteworthy that carbene catalysts have similar limitations to that of cyanide in the synthesis of cross benzoin adducts and they are not useful as cross benzoin catalysis.

1.1.4 Acylphosphonates As A New Acyl Anion Precursors

1.1.4.1 Bioactivity of Phosphonates and Phosphates

Historically, the first method for the generation of a carbon-phosphorus bond was described 103 years ago (1897) by Michaelis and Becker. It involved the nucleophilic phosphorylation of a saturated carbon by the salts of dialkylphosphites. One year later Michaelis and Kaehne discovered the nucleophilic phosphorylation of a saturated carbon by reaction of an ester of trivalent phosphorus with an alkyl halide. This latter reaction, the most useful transformation of this type, was explored in depth by Arbuzov and is now widely employed for the synthesis of phosphonates. Since 1949, the extensive literature on tire Michaelis-Arbuzov reaction has been summarised in several reviews. In addition to these two nucleophilic phosphorylation reactions, the addition of trivalent phosphorus to carbonyl groups, under thermal or basic conditions, the Abramovlo and Pudovik reactions, constitutes

two other important synthetic procedures for carbon-phosphorus bond formation. By way of contrast, the use of umpolung for generating carbon-phosphorus bonds has only been explored since 1975 [15].

In recent years, interest in phosphorous chemistry has expanded dramatically for a variety of reasons and organophosphorus compounds have found wide applications in chemistry, medicinal chemistry, and biology. They are, especially, important substrates in the study of biochemical processes, and tetracoordinate pentavalent phosphorus compounds are widely used as biologically active compounds. The key role of naturally occurring amino acids in the chemistry of life and as structural units in peptides, proteins, and enzymes has led to intense interest in the chemistry and biological activity of synthetic analogues. For a long time the so-called "phosphorus analogues" of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, or phosphinic acid group, as well as a phosphonate group, have attracted particular interest in the preparation of isosteric or bioisosteric analogues of numerous natural products. İsosteres are defined as groups or molecules which have chemical and physical similarities producing broadly similar biological properties [16]. For instance, β-aminophosphonic acids are isosteres of β -amino acids, so they occupy an important place and reveal diverse and interesting biological and biochemical properties: antibacterial agents, enzyme inhibitors, haptens for catalytic antibodies, or anti HIV agents.

Phosphonic acids and their phosphonate derivatives are common in the literature of organic chemistry where they are employed in three main synthetic operations; (i) sought for their potential contribution to biological activities, (ii) as transition state analogues in production of antibodies catalytic for a variety of reactions and (iii) to make carbon-carbon bond formation reactions.

Phosphonates are also important because of their roles in the preparation of catalytic antibodies. In a certain form, phosphonates are believed to present a shape and

charge distribution that mimics a high energy intermediate in acyl transfer reactions such as ester or amide hydrolysis [17]. So, they have also been extensively studied as transition state analogs to understand enzyme and drug activity mechanisms. In addition, being considered to be an isosteric replacement for the carboxyl group, they mimic the tetrahedral intermediate of reactions of carboxylic acid derivatives. (Figure 11)

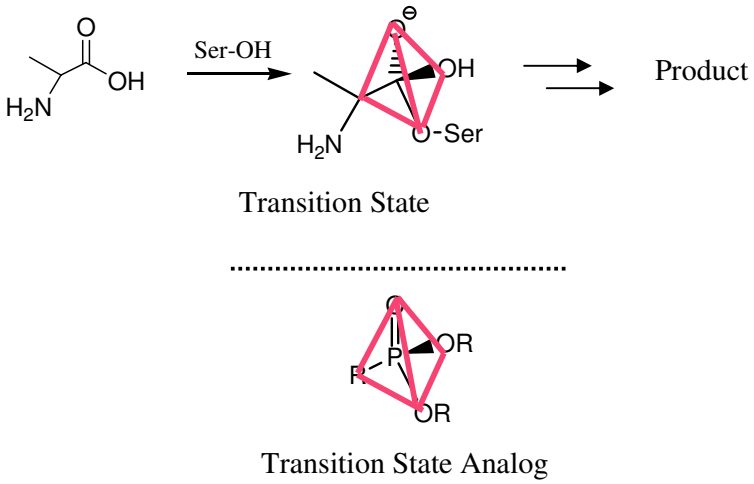


Figure 11 Transtion State Analogy of Phosphonates

Another application of phosphonates is one of the most important concept of the organic chemistry; carbon-carbon bond formation reactions. There are many routs to make C-C bond via phosphonates like Horner-Wadsworth-Emmons condensation, acylphosphonates, etc. However, since in this work acyl anion chemistry was followed, acylphosphonates will be discussed in details in the next section.

1.1.4.2 Acylphosphonates: Properties and Synthesis

Acylphosphonates (α-ketophosphonates) are a subdivision of phosphonate compounds. The adjacent phosphorus substituents and carbonyl functional groups in an acylphosphonate are the main reason that makes them interesting compounds in organic synthesis as a reagent or an intermediate [18]. They have been used, especially, as precursors to biologically active α-aminophosphonic acids and α-hydroxyphosphonic acids for years because of the reasons mentioned in the previous section.

The phosphorus substituents of an acylphosphonates, mainly, determine the chemical properties of the compound. However, in general, those are hybrid between the chemical properties of secondary amides and ketones. So, they can participate in many reactions and can be used in the preparation of other organophosphorus compounds. For example, the reduction of acylphosphonates gives the corresponding α-hydroxyphosphonates and treatment of them with a Wittig reagent affords the corresponding vinylphosphonates; the corresponding oximes and hydrazones can be obtained from the reactions of acylphosphonates with hydroxylamine and hydrazine; β,γ-unsaturated-acylphosphonate can be epoxidized and also undergo a very facile Diels-Alder cycloaddition both as diene and hetero-dienophile. Finally, the C-P bond in acylphosphonates is susceptible to facile cleavage under nucleophilic attack, for instance during acidic and basic hydrolysis, and therefore, α-ketophosphonates can be considered as synthetic equivalents to acid chlorides [19].

Acylphosphonates are available compounds and can be prepared in two classical methods. The first one is the Arbuzov reaction between the corresponding acylchloride and alkylphosphonites or alkylphosphites to produce an acyl phosphonate [20] (Figure 12). Reaction proceeds through formation of unstable

trialkoxyphosphonium intermediate **15** that is subsequently attacked by a halide anion leading to acylphosphonate.

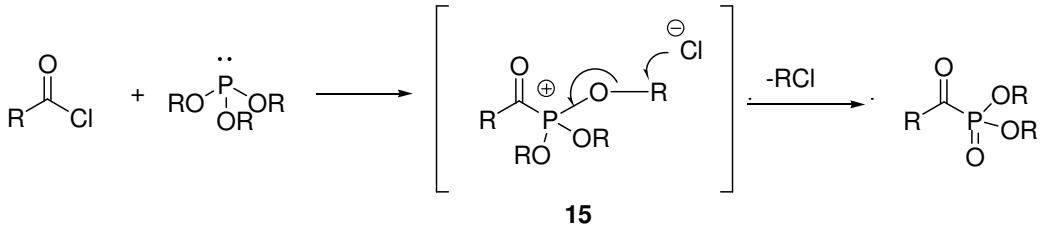


Figure 12 Acylphosphonate Synthesis via Arbuzov Reaction

Oxidation of the corresponding α-hydroxyphosphonates is an alternative method to the Arbuzov reaction for the synthesis of acylphosphonates (Figure 13). α-Hydroxyphosphonates are easily synthesized by addition of phosphorus nucleophiles to corresponding aldehyde. This method is also used often but limited range of substrates that can be employed is a problem [20].

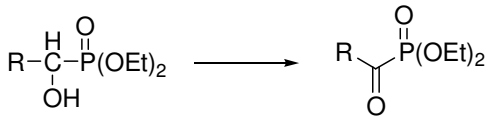


Figure 13 Acylphosphonate Synthesis via Hydroxyphosphonate Oxidation

For several years it has been known that the carbonyl of an acylphosphonate is activated towards attack by nucleophiles and that the carbon-phosphorus bond is easily cleaved. This property makes acylphosphonates potentially useful acylating agents and they undergo cyanide ion promoted phosphonate–phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates [21].

The phosphoryl group can migrate intramolecularly both from carbon to oxygen and oxygen to carbon under appropriate conditions. This rearrangement has a close analogy to the 1,2-Brook rearrangement of acylsilanes (Figure 14).

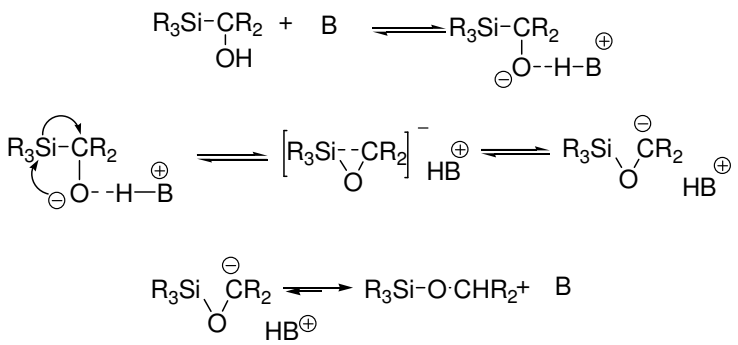


Figure 14 1,2-Brook Rearengeent of Acylsilanes

In this rearrangement, basic catalyst abstracts proton from the hydroxyl group, forming an alkoxide anion. This nucleophile intermolecularly attacks the silicon atom, passing through a transition state, in which significant silicon-oxygen bond formation and silicon-carbon bond breaking have occurred, placing negative charge on carbon which quickly abstracts a proton to form the resultant silyl ether [22].

The famous Perkow reaction is may be the most interesting reactions of phosphorous, since it shows phosphorous' ability to migrate. While there is not an exact mechanism explanation for the Perkow reaction, it is accepted that a trivalent-phosphorus ends up as a pentavalent-phosphorus through migration of phosphorus from carbon to oxygen. Although it is known that Perkow reaction competes with the classical Arbuzov reaction, when saturated α-halo ketones and aldehydes are used the Perkow product is the main one, forming a P-O bond rather than P-C bond because of phosphonate to phosphate rearrangement.

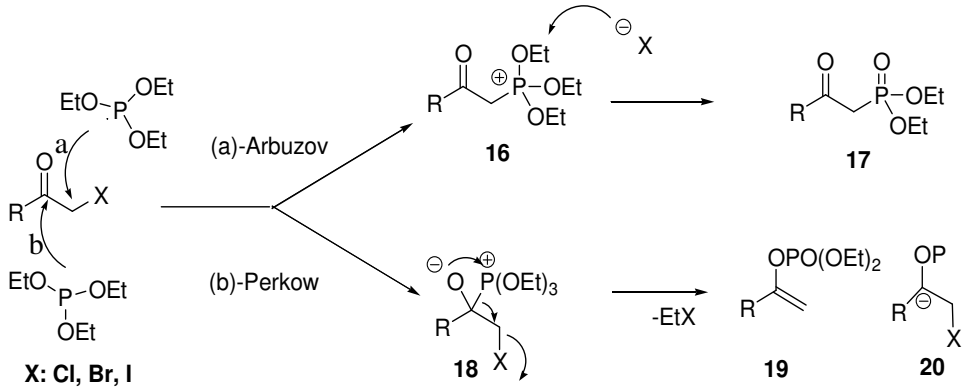


Figure 15 Mechanism of Perkow and Arbuzov Reactions

During the reaction, the α-halogen is displaced in a nucleophilic manner by phosphorous nucleophile. The phosphate ester salt is subject to keto-enol tautomerism and if the enol isomer is predominant the Perkow adduct is ғormed otherwise the keto form results in the Michaelis-Arbuzov adduct.

Intermediates like **19** are sometimes invoked and elimination of α-halogen generates an acyl anion equivalent. Putting a stabilizing group such as cyanide or phosphonate

instead of the carbon bearing one, the leaving group (EtX) would provide an opportunity to access to a new generation of acyl anion precursors.

There are many reactions that involve phosphonate to phosphate rearrangement, the migration of phosphorous from carbon to oxygen, in basic reaction conditions. However, alkali cyanide promoted rearrangement of acylphosphonates is not so common. Similar to other rearrangements, cyanide gives considerable stabilization to that provides leading protonation (Figure 16).

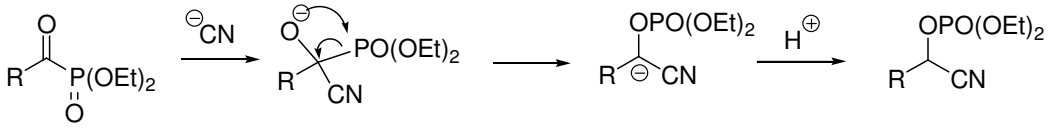


Figure 16 Phosphonate to Phosphate Rearrangement

Under the light of these reports, the cyanide promoted rearrangement of acylphosphonates in the presence of an electrophile was studied. In addition, acylphosphonates were used in the generation of acyl anion precursors.

1.2 Generation of Acyl Anion Equivalents

1.2.1 Stoichiometric methods:

By development in synthetic organic methodology, the formation and reaction of acyl anion nucleophiles have a great interest. They are used in many chemical operations to obtain new compounds. Especially, aldehyde umpolung reactions, in

which the electronics of aldehyde carbonyls are converted from an acceptor to a donor, are the main achievements of acyl anion chemistry. The generation of an acyl anion equivalent that can be reacted with an electrophile in order to form the desired target was the mainly preferred strategy for this conversion. By using this approach, chemists could synthesize variety of valuable functionalities.

In search for the design of umpoled reactive centers, a variety of precursors have been developed by synthetic chemists some of which are shown in Figure 17 . Among the most common acyl anion equivalents are, O-silyl-cyanohydrins **21**, α-amino nitriles **22**, (Corey-Seebach) dithianes **23**, alkyl vinyl ethers **24**, alkyl vinyl sulfides **25** and benzotriazole stabilized compounds **26** (Figure 17). They are masked carbonyl derivatives, which, after the reaction with an electrophile, have to be converted to the free carbonyl functionality by an extra deprotection step and will be discussed shortly.

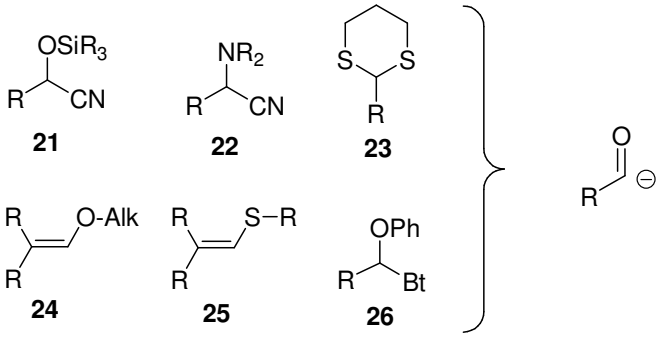


Figure 17 Common AAE

1.2.1.1 O-silyl-cyanohydrin Stabilized Acyl Anions

One of the most widely used methods for generation of acyl anion equivalents is *O*-trimethylsilyl-protected cyanohydrins. Hunig *et al.* reported that the condensation of aryl aldehydes with trimethylsilyl cyanide gives *O*-trimethylsilyl-protected cyanohydrins [23]. They can be thought as the protected form of the well-known carbanion intermediate of the benzoin condensation. Protection of oxygen provides considerable additional stabilization for the α-cyano carbanion which would otherwise easily undergo retrocyanation to give starting aldehyde.

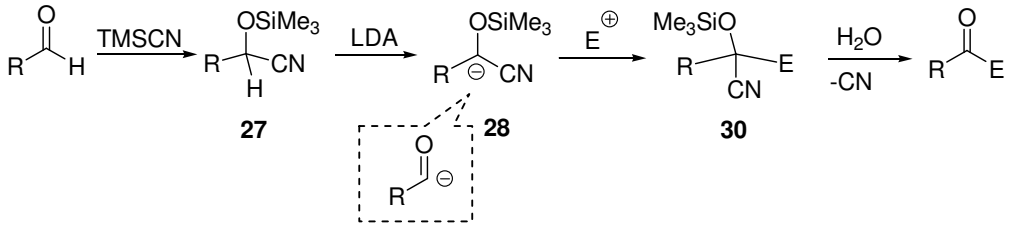


Figure 18 AAE Generation via *O*-trimethylsilyl-Protected Cyanohydrins

According to the mechanism, the reaction of an aldehyde with thrimethylsilylcyanide (TMSCN) gives cyanohydrin silyl ether **27**, which is deprotonated with a strong base like diisopropyl amide (LDA) to generate the corresponding acyl anion equivalent **28**. This carbanion subsequently reacts with an electrophile E such as an alkyl halide, aldehyde, or ketone to form the substituted derivatives (Figure 18). For instance, the synthesis of cross benzoin is an example for this protected cyanohydrin strategy. Of course this method also has some problems like using of expensive trimethylsilyl cyanide and need for special precautions due to the liberation of toxic HCN.

1.2.1.2 Amino Nitrile Stabilized Acyl Anion Equivalences

α-Amino nitriles are not only versatile intermediates in organic synthesis but also exhibit a valuable reactivity, which has been utilized in a broad range of synthetic applications (Figure 19). One mode of reactivity involves functional group interconversions of the nitrile group in which the original carbon atom connectivity is preserved. In historical terms, the hydrolysis of the nitrile group in order to generate α-amino acids, is perhaps the most important use of α-amino nitriles. A second extremely valuable use of α-amino nitriles is as stable precursors to iminium ions, whereby loss of cyanide anion under a variety of conditions generates an intermediate iminium species [24].

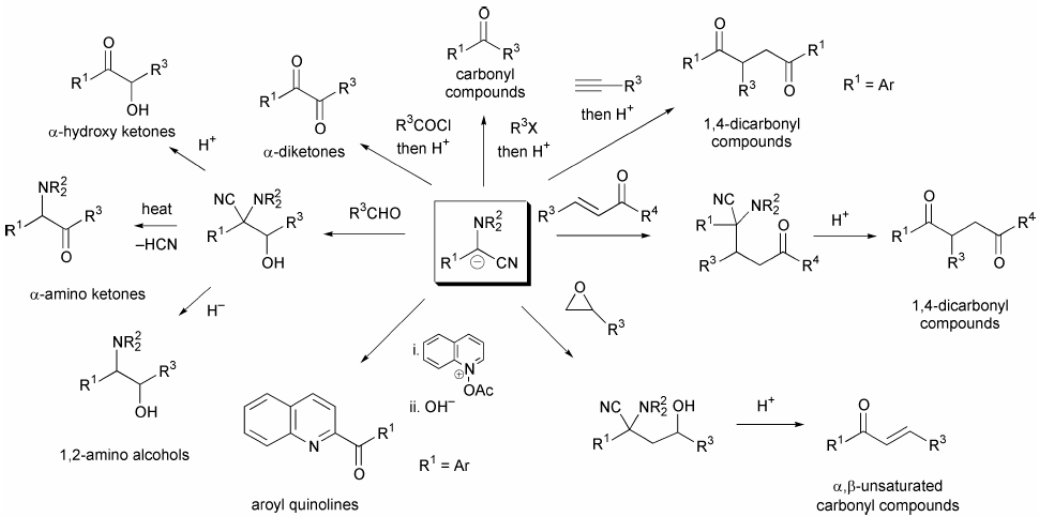


Figure 19 Use of Amino Nitrile Stabilized AAE in Organic Synthesis

A third mode of reactivity is complementary to that of the second in that it is formally a reversal in polarity (umpolung) at the α-carbon. When the α-amino nitrile bears an α-hydrogen it is possible to deprotonate at this position using strong bases. The carbanion **32** generated is capable of nucleophilic attack on a number of differing classes of electrophiles. This provides a new α-amino nitrile compound **33** which may in turn undergo any of the abovementioned transformations. For instance, hydrolysis of the resulting amino nitrile to the corresponding carbonyl compound **34** is overall a nucleophilic acylation, with the metallated α-amino nitrile acting as a masked acyl anion equivalent (Figure 20) [24].

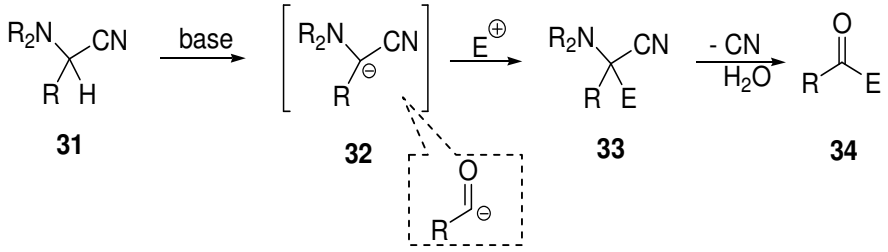


Figure 20 Generation of AAE from Amino Nitrile

1.2.1.3. 1,3-Dithiane Acyl Anion Equivalences

The concept of umpolung was accepted by the chemical community when Seebach introduced the term in 1974 to describe "dipole inversion" or inversion of reactivity. The obvious need for the term grew out of the pioneering work of Corey and Seebach on the design and applications of 1,3-dithianes, which are now well recognized as excellent strategic elements for the construction of complex natural and unnatural products (Figure 21) [25].

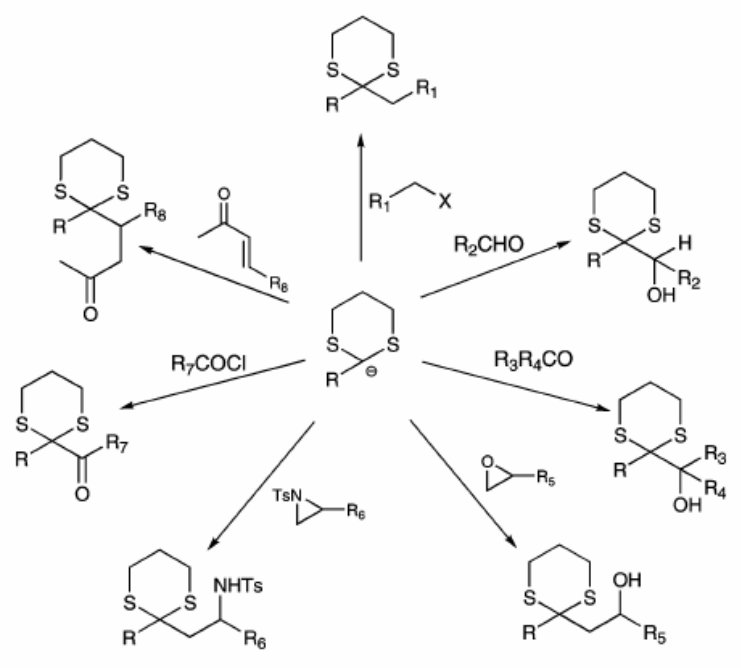


Figure 21 Reactions of AAE Generated from 1,3-Dithianes

1,3-Dithianes are accepted as excellent strategic elements for the construction of complex natural and unnatural products because they serve as convenient acyl anion equivalents. They are the most successful sulfur-stabilised acyl anion equivalents because of the effect of the sulfur atoms on adjacent carbanions by electron back-donation into vacant sulfur d-orbitals [26].

The 1,3-dithiane ring can be introduced in an organic molecule following two general approaches. The reaction of the anion of 1,3-dithiane with different electrophilic reagents is the method most commonly used and thioacetalisation of a carbonyl group, using Lewis or Brönsted acid catalysis, is the other methodology.When dithiane is used as an acyl anion equivalent, it must be

hydrolysed at some stage during a synthesis to reveal the carbonyl group which was originally masked [26].

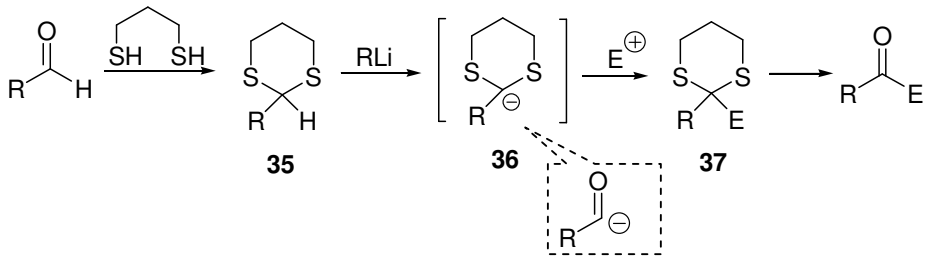


Figure 22 Generation of AAE from Dithianes

Aldehydes are easily converted in to the corresponding dithiane **35** which is deprotonated with alkyllithiums to give a stabilized carbanion **36**. This carbanion reacts with an electrophile followed by hydrolysis of the dithiane unit to provide the corresponding ketone. However, deprotection has often been extremely difficult to achieve, especially for complex and sensitive derivatives, and many procedures have therefore been developed and there is not a single method that can be generally applied.

1.2.1.4 Alkyl Vinyl Ether Stabilized Acyl Anion Equivalences

Alkyl vinyl ethers have been used as acyl anion equivalents [3]. By using *tert*-butyllithium, they are deprotonated and the carbanion is formed. The reactions of this carbanion with an electrophile yield intermediate, which can be hydrolyzed to the corresponding ketone by aqueous acid in the presence of mercury ion (Figure 23).

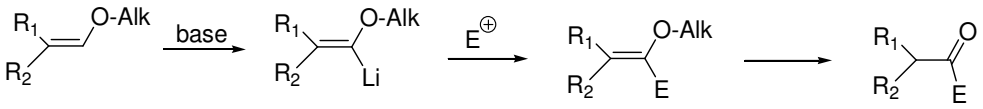


Figure 23 Generation of AAE from Alkyl Vinyl Ether

1.2.1.5 Vinyl Sulfide Stabilized Acyl Anion Equivalences

In a similar manner, vinyl sulfides have been used as acyl anion equivalents for the synthesis of corresponding ketones [3]. The reaction of the vinylanion intermediate with an electrophile gives masked ketones that can be hydrolyzed to ketones (Figure 24).

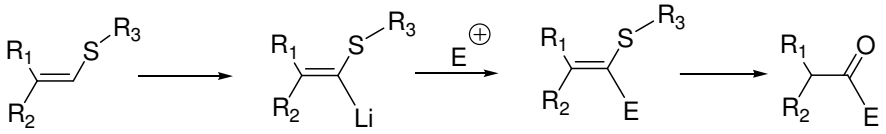


Figure 24 Generation of AAE from Vinyl Sulfides

1.2.1.6 Benzotriazole Stabilized Acyl Anion Equivalences

Benzotriazole is a versatile and reliable synthetic auxiliary for the synthesis of complex organic compounds, including classes difficult to prepare via other methods [27]. A variety of benzotriazole–stabilized acyl anion synthons has been developed (Figure 25) which are converted into acyl anion equivalents by treating with butyllithium.

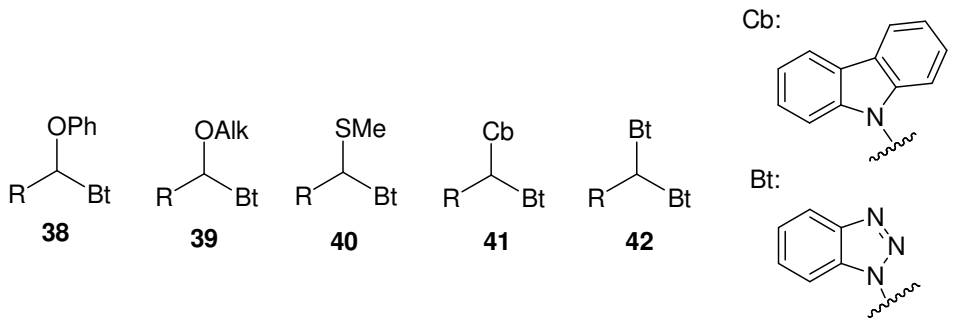


Figure 25 Benzotriazole Compounds

These synthons, obtained by deprotonation of **38**, **39**, **40**, **41** and **42** combine the stabilizing influence of a benzotriazolyl group and α-phenoxy-, α-alkoxy-, α-mercapto-, α-carbazolyl group, or a second α-benzotriazolyl group.

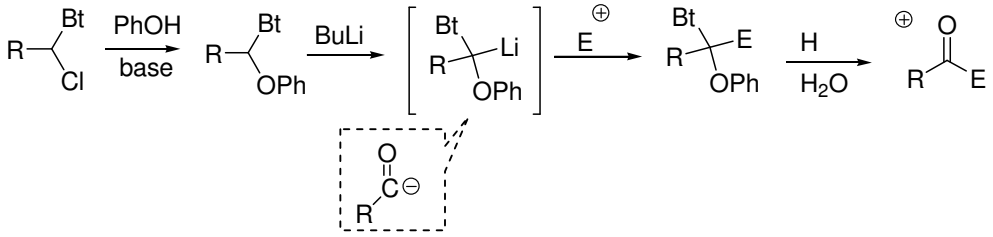


Figure 26 Generation of AEE from Benzotriazoles

Benzotriazole compounds can be deprotonated using butyllithium in THF at to give acyl anion equivalences, which react with a wide variety of electrophiles to give simple alkyl, α-hydroxyalkyl, and α-aminoalkyl masked ketones [3].

1.2.2 Catalytic Methods of Acyl Anion Generation

Recently impressive progress has been made in the catalytic generation of acyl anion equivalents, especially in the benzoin and Stetter reactions. As far as the cross-benzoin and intramolecular Stetter reactions are concerned, the use of acylsilanes as acyl anion precursors based on the nucleophile promoted Brook rearrangement is the most practical and selective method available [28]. Next sections present the current methodology, trends and developments in the catalytic generation of acyl anion equivalents. In catalytic methods for acyl anion generation, acylsilanes are mainly used. Thus it is more appropriate to consider these reagents under the catalyzed reactions category.

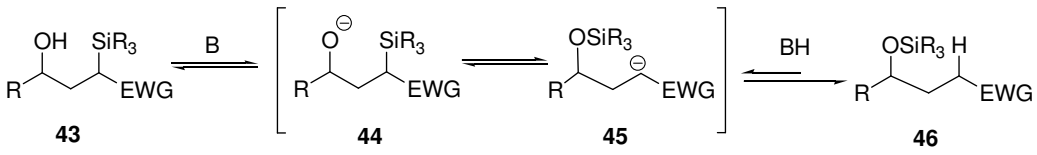


Figure 27 Nucleophile Promoted Brook Rearrangment

Brook rearrangement is an equilibrium process. (Figure 27). When trace amounth of base is used in a Brook rearrangement, relative stabilities of the silylcarbinol **43** and silanol **46** controls the position of the equilibrium. While the presence of an electron-withdrawing group enhances acidity, the strength of silicon-oxygen bond compared to carbon-silicon bond provides an extra driving force for complete conversion. However, under the influence of catalytic base, protonation of the B by the conjugate acid or starting silanol is rapid and irreversible that makes the method insufficient for carbon-carbon bond formation. Instead highly valuable tandem bond

formations are viable in the presence of excess strong base since the relative stabilities of the alkoxide **44** and carbanion **45** determine the position of equilibrium. In order to establish new carbon-carbon bonds, one should be able to trap the carbanion **45** by an electrophile. In this situation, the most important factors are the basicity of the carbanion and identity of the counterion [4]. In the presence of an electron withdrawing group, the silly migration is facilitated since it helps to stabilize the negative charge built up in the carbanionic intermediate. On the other hand, the counterion affects the alkoxide stability.

The 1,2-Brook rearrangement can be established in several ways; (i) treatment of α-silylcarbinol **47** with a base, (ii) reaction of an aldehyde or ketone with a silyllithium reagent or (iii) addition of a nucleophile to an acylsilane **49** (Figure 28).

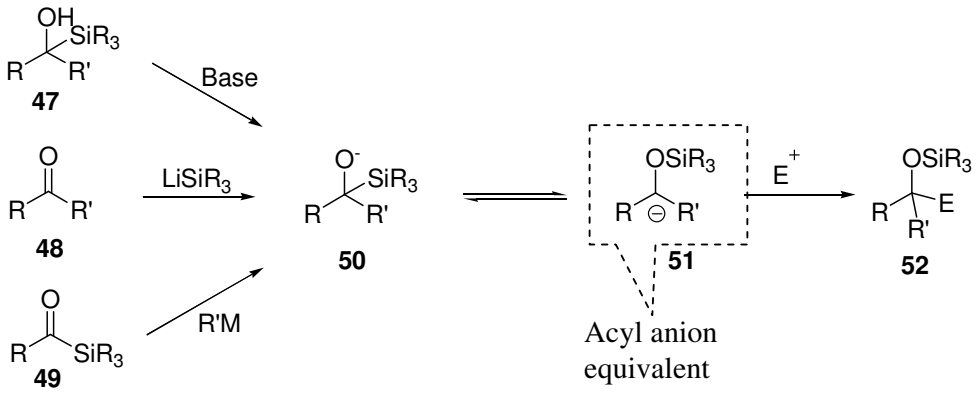


Figure 28 Different 1,2-Brook rearrangement methods used for the synthesis of acyl anion equivalents

1.2.2.1 Acylsilanes as Acyl Anion Precursors

Acylsilanes are valuable compounds in organic synthesis primarily due to their ability to access the Brook rearrangement manifold upon the addition of a strong nucleophile. The use of acylsilanes as acyl anion precursors typically involves the addition of highly charged, potentially toxic catalysts such as cyanide and fluoride anions. These approaches ensure significant charge density on the oxygen of the resulting tetrahedral intermediate to promote a 1,2-silyl group shift (Brook rearrangement) and render the acylsilane carbon nucleophilic[29].

Acylsilanes have been used to make a variety of tandem bond formation strategies and they are very useful entities providing acyl anion intermediates. It has been shown that carefully designed reactions could provide highly complex products as a result of one pot multiple bond forming steps. Addition of cyanoformate ester to acylsilanes is an example in which acylsilanes are used in an acylation reaction. For example, cyanide promoted Brook rearrangement of acylsilanes has been studied by many chemists since it provides the wellknown acyl anion intermediate widely used in the synthesis of acyloins. Takeda, Reich, and Degl'Innocenti have reported generation of carbanionic cyanohydrin derivatives via reactions of acylsilanes with

various $^{-}$CN sources [30]. Takeda [31] has shown that it is possible to catch the carbanion that is formed from the reaction of acylsilane and cyanide after a Brook rearrangement.

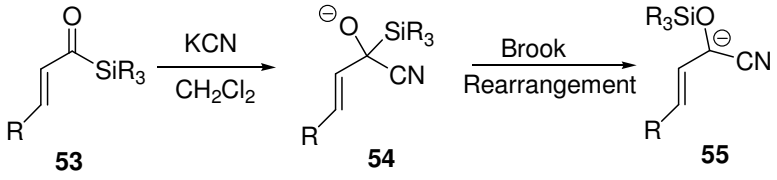


Figure 29 Cyanide Promoted Brook Rearrangement of Acylsilanes

In a similar reaction shown above, nucleophilic addition of metal cyanide to the acylsilanes generates cyanide ion **55** that undergo reactions with electrophiles which was shown by Johnson [30].

In this reaction (Figure 30), the addition of the metal cyanide to the acylsilane **56** generates a tetrahedral intermediate **57** which undergoes the Brook rearrangement. Then, acylation of the forming nitrile enolate **58** with a cyanoformate ester **59** which derives the carbanion, gives the desired product and regenerate the metal cyanide, completing the catalytic cycle.

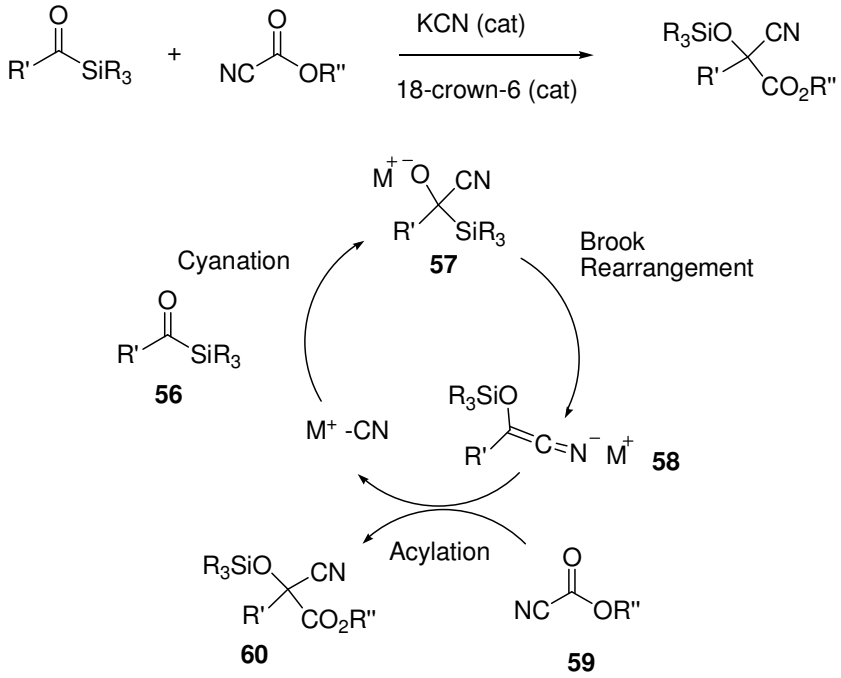


Figure 30 Mechanism of Metal-Cyanide Addition to Acylsilanes

Johnson [32] and coworkers also anticipated that with this system unsymmetrical α-silyloxy ketone products **61** could be prepared by trapping (silyloxy)nitrile anions with aldehydes (Figure 31).

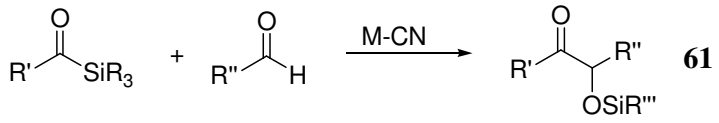


Figure 31 α-Silyloxy Ketone Synthesis via Metal-Cyanide Catalyst

In this reaction, KCN is in combination with 18-crown-6, and it is not only an effective reagent for cyanation of electrophilic subsubstrates but also an effective catalyst for initiation of the Brook rearrangement. According to the mechanism, aldehyde cyanation occurs and cyanide undergos nucleophilic addition to acylsilanes **62**, followed by [1,2]-Brook rearrangement to yield (silyloxy)-nitrile anion **63**, the acyl anion equivalent. The silyl group shuttles between two adjacent oxygen atoms in intermediates **64** and **65**, the latter of which reversibly releases the metal cyanide catalyst and leads to the desired product **61** (Figure 32).

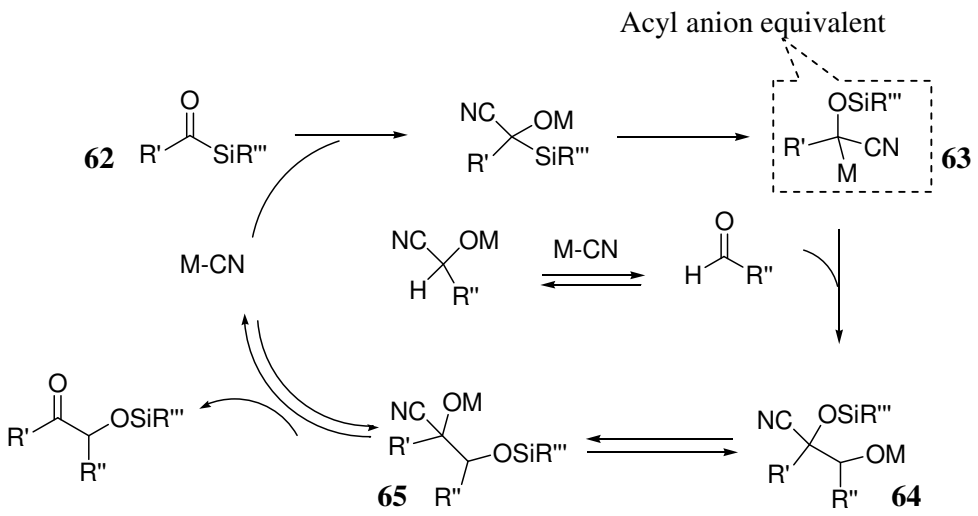


Figure 32 Mechanism for α-Silyloxy Ketone Synthesis via Metal-Cyanide Catalyst

The reactions of bis(acylsilanes) were also reported [33]. The rearrangement of **66** in the presence of cyanide ion provides **68** that intramolecularly reacts with the other acylsilane moiety to generate an intermediate, **69**, which may undergo [1,4]-O,O-silyl shift to provide **73** or a second 1,2-Brook rearrangement to furnish **71**. The release of cyanide from **70** or **72** in the last step of both reactions renders this process catalytic in nucleophile. This is quite interesting considering the possibility of designing reactions based on acyl anion equivalents that are catalytic in the promoting nucleophile (Figure 33).

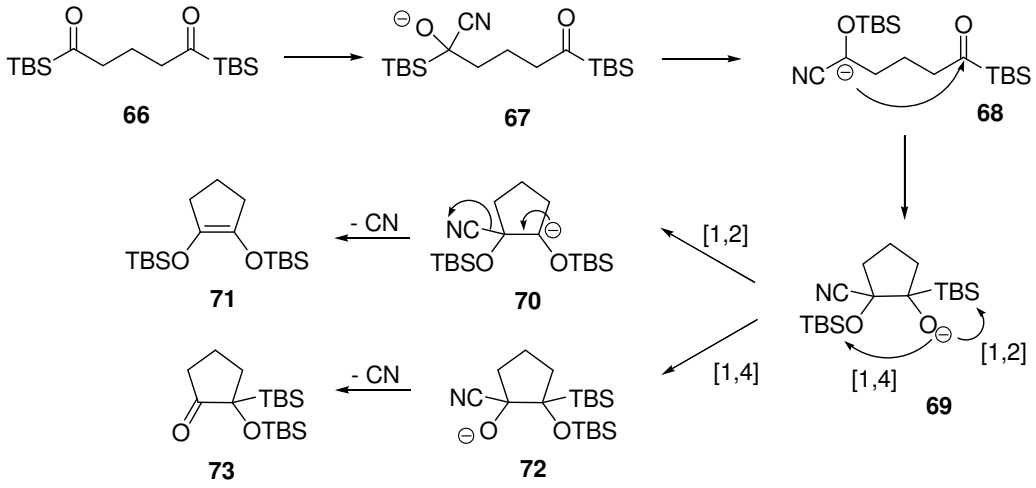


Figure 33 The rearrangement of bis(acylsilanes) in the presence of Cyanide Ion

Another strategy for the generation of carbonyl anion equivalents from acylsilanes is utilization of N-heterocyclic carbenes (NHCs) by Scheidt. They used the idea that NHC catalysis can be used to generate acyl anion equivalents from aldehydes, and applied this same approach to acylsilanes. Synthetically useful 1,4-diketones, **75**, and *N*-phosphinoyl-α-aminoketones, **74**, have been prepared in good to excellent yields via NHC-catalyzed additions of acylsilanes to the corresponding α,*β*-unsaturated systems and *N*-phosphinoylimines [34] (Figure34).

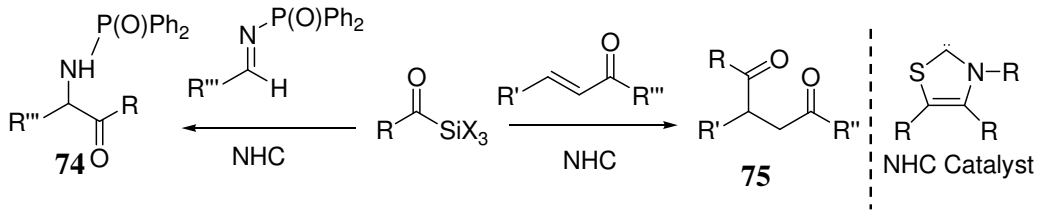


Figure 34 Generation of AAE from Acylsilanes by Using NHCs

During the course of the reaction, the N-heterocylic carben undergoes nucleophilic addition to an acylsilane and promote a 1,2-Brook rearrangement from carbon to oxygen, thus rendering the carbonyl carbon nucleophilic, an carbonyl anion equivalent (Figure 35).

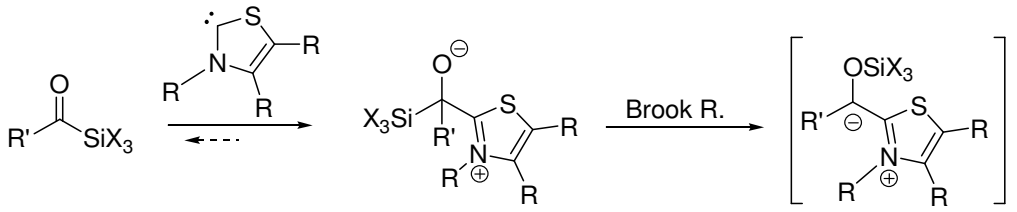
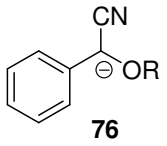


Figure 35 Synthesis of NHC derivatives via 1,2-Brook rearrangement

1.2.2.2 Cynanide Ion Catalyzed Benzil-Benzoin Reaarangement

The cyanide ion-catalyzed cleavage of benzils is used for the generation of various 'masked' acyl intermediates. The reaction of these intermediates with various aldehydes furnishes the corresponding esters of unsymmetrical benzoins (**77**) in very good yields. The cyanide ion-catalyzed condensation of aromatic aldehydes to the corresponding benzoins has great synthetic utility [35]. It is well known that in the classical benzoin condensation mechanism, cyanide ion catalyzed generation of acyl anion equivalent **76a** is the key step as mentioned before (Figure 36). To synthesize unsymmetrical benzoin is a bit problematic with traditional procedures in which thiazolium and its salt is used due to four possible benzoin products. Thus, the synthesis of a specific isomer, especially the more energetic one, is accomplished by condensation of an acceptor aldehyde with an acyl anion equivalent of type **76**.



R

76 a: H

76 b: Bz

Figure 36 Acyl Anion Equivalent

These intermediates may be reacted with various aromatic aldehydes to form the corresponding esters of unsymmetrical benzoins (**76**) in high yields (Figure 37). In other words, this method generally offers the simplest approach for certain benzoins and a variety of different benzoin derivatives can be synthesized in this way.

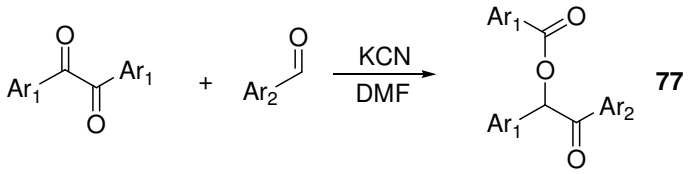


Figure 37 Route for the syntheses of unsymmetrical benzoyl benzoins

In 1923, Dakin and Harington showed that the cyanide ion catalyzes the cleavage of benzil to benzaldehyde and the ester of benzoic acid. Later, the mechanism and kinetics of the reaction were investigated by Kwart and Baevsky, demonstrating the intermediacy of **76b**. Trisler and Frye showed that **76b**, in aprotic solvent DMSO where it is highly nucleophilic, reacts with another molecule of benzil present in the reaction solution to form trans-α,α'-stilbendiol dibenzoate. This work showed that **76b** is a potent nucleophile and can react with an electrophile in the medium [35].

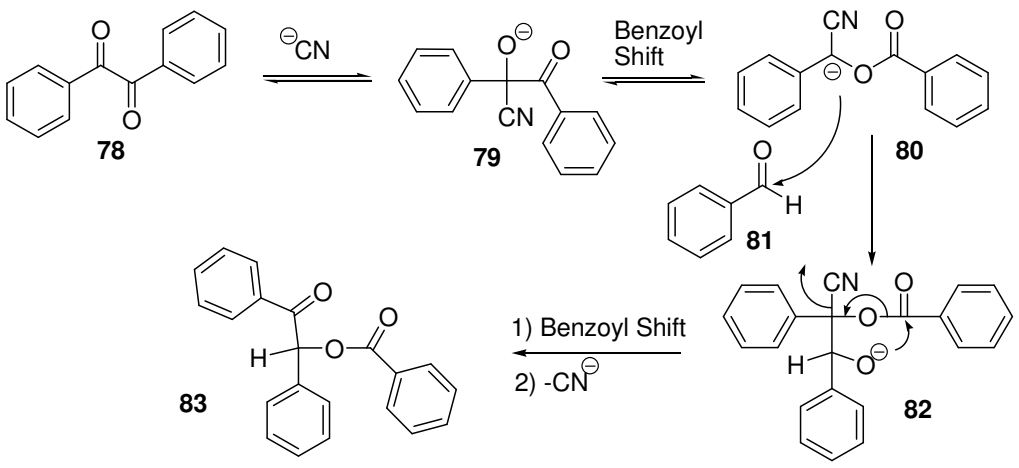


Figure 38 The Synthesis of *O*-benzoylated benzoin

In the synthesis of the *O*-benzoylated benzoin **83**, the benzil molecule **78** and an acceptor aldehyde, benzaldehyde **81**, are mixed in the presence of cyanide ion. During the course of the reaction, cyanide ion attacts to the benzil molecule. After the addition of the cyanide ion to the benzil molecule; a rearrangement takes place ending up with the *O*-benzoylated cyanohydrin **80**, which is very similar to the cyanohydrin formed in the conventional benzoin condensation. Besides its ability as a protecting group, the presence of the benzoyl group assists the formation and the stability of cyanohydrin. Once it is formed, *O*-benzoylated cyanohydrin can undergo a cleavage reaction in the presence of an acceptor aldehyde. When the reaction is carried out in a polar protic solvent, the intermediate **82** cleaves into benzaldehyde and the corresponding ester of benzoic acid, whereas in polar aprotic solvents, it rearranges to yield *O*-benzoylated benzoin **83** (Figure 38).

1.3. Amino Alcohols In Organic And Pharmaceutical Chemistry

Possessing both the properties of amines and alcohols, the 1,2-amino alcohol motif is rich in chemical and biological uses [36]. They are useful precursors of important non-racemic compounds such as drugs, amino acids, and chiral auxiliaries and ligands. As a result, the synthesis of new chiral amino alcohols is of great importance and the development of new efficient methods for their asymmetric synthesis is of high current interest.

Especially, 1,2-amino alcohol derivatives are useful precursors for syntheses of important non-racemic compounds. Possessing both the properties of amines and alcohols, the 1,2-amino alcohol motif is rich in biological and chemical uses. Thus, the development of new methods for general, facile and selective preparations of amino alcohols remains an important goal in synthetic organic chemistry. Many methods to synthesize amino alcohols and their derivatives, especially amino acids, have been developed. Among the numerous synthetic methods, there are only a few methods typically employed to prepare chiral amino alcohols. Nucleophilic cleavage of epoxides with nitrogen nucleophiles gives the amino alcohols. However, low regioselectivity can be problematic. Reduction of α-amino acid derivatives affords the amino alcohols. However, α-amino acids which are available as substrates are fairly limited. Although several methods have been developed for chiral 1,2-amino alcohols, including asymmetric aminohydroxylation and nucleophilic additions to imines, most methods have narrow scope [37].

The 1,2-amino alcohol unit has been found in a number of bioactive natural products such as alkaloids, amino sugars, enzyme inhibitors, and antibiotics [37]. They are important pharmacophores, a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity, present in inhibitors of aspartyl proteases, such as HIV protease inhibitors, in investigative inhibitors of β-amyloid peptide formation for the treatment of

Alzheimer's disease, in dopamine D_4 antagonists for the treatment of Parkinson's disease, and in aldose reductase inhibitors displaying anti-obesity and antidiabetic properties. The 1,2-amino alcohol motif has also been found to exhibit antidiabetic, anti-obesity, and antidepressant activities [36]. These structures are found as parts of more complex active substances or natural products such as anti-inflammatory VAP-1 inhibitor **84**, antihypotensive midodrine **85**, anti obesity **86** and antidepressant agents **87** in adrenoceptor agonists, and anti-HIV agent in the inhibition of HIV protease **88** (Figure 39).

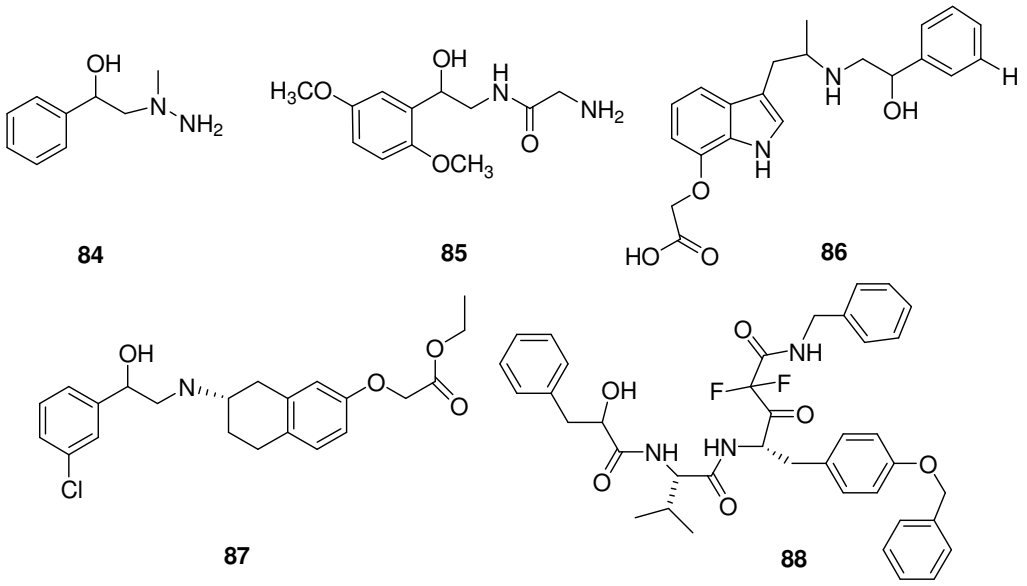


Figure 39 Some Important Compounds Having 1,2-Amino Alcohol Structure

In organic synthesis, optically active 1,2 amino alcohols are not only versatile chiral building blocks in asymmetric synthesis, but also important chiral ligands in asymmetric C–C bond formation. Thus, their design and synthesis is an area of

intense research. In addition, among various chiral ligands, such as diols, amino alcohols, amino thiols, and amino sulfides, 1,2-amino alcohols are the most popular ones due to their high efficiency in reactions [38].

1.4 Aim of the work:

In recent years, interest in phosphonate chemistry has expanded dramatically for a variety of reasons. Ketophosphonates are one of the most important classes of organophosphorus compounds and their functionalized derivatives are important building blocks in organic reactions since they are present in many biological active compounds. They are used as precursors to biologically active α-aminophosphonic acids and α- hydroxyphosphonic acids for years. The reactivity of acylphosphonates is particularly interesting. Considering these properties, in this study it was aimed to prepare acylphosphonates starting from the corresponding chiral α-hydroxycarboxylic acids for the further reactions with various nucleophiles to obtain quaternary alcohols and related compounds with phosphonate and phosphate functionalities.

CHAPTER 2

RESULTS AND DISCUSSION:

2.1 Perspective of the Work

The main objective of this study was to develop new functionalized acylphosphonates which would be reacted with different electrophiles to obtain new compounds like β-amino alcohols with phosphonate functionality. To achieve this idea, α-hydoxycarboxylic acids were used as starting materials. First of all, these hydroxyl functionalities of α-hydroxycarboxylic acids were protected with alkyl or acyl groups and then treated with acid chloride. The resultant acylchlorides reacted with trialkylphosphite and new protected α-keto-β-hydroxyphosponates were obtained. In the second part of the work, the synthesized acylphosphonates were converted to their acyl anion equivalents based on the nucleophile-promoted Brook rearrangement, and different reactions were performed based on this approach.

Acyl anion equivalents provide a powerful alternative to traditional carbon-carbon bond construction methods, and add new dimensions of flexibility to the design of synthetic targets. These useful entities have been obtained, traditionally, by functional group manipulation and stoichiometric strong base deprotonation of the corresponding carbonyl compounds [21]. Although there are many routes for the generation of acyl anion equivalents, they suffer some major drawbacks. Therefore acylphosphonates, which are easily available or accessible from simple starting materials, were proposed and investigated as a new generation of acyl anion precursor by Demir and coworkers [28].

The synthesis and properties of acylphosphonates were mentioned in the previous section, and in this study they were synthesized by using triethylphosphite (TEP), trimethylphosphite (TMP) and thionyl chloride ($SOCl_2$). For the synthesis of phosphonates, (S)-(+) mandelic acid **89** and (R)-(+)-2-(benzyloxy)propionic acid **91** were selected as starting carboxylic acids (Figure 40).

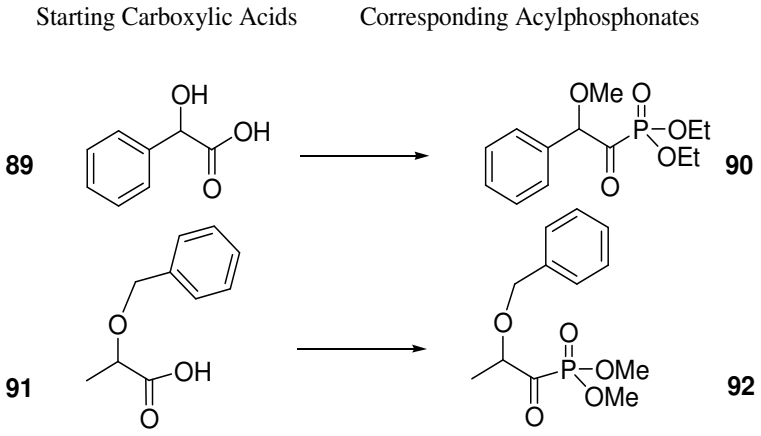


Figure 40 Acylphosphonate Products

During this study, firstly hydroxyl group of (S)-(+) mandelic acid on alpha position was converted into methoxy group by using DMS. There is only one procedure reported in the literature for this conversion and it was performed by a modification of Braun's method by adding (S)-(+)-mandelic acid to hot sodium hydroxide solution [39]. DMS was added to this solution, and the treatment of the reaction mixture with hot water and concentrated acid gave the product **89a** as solid. The product was identified by using NMR spectroscopy. Typical signal in identification of the product was the presence of $-OCH_3$ proton resonating at 3.50 ppm as singlet.

For the synthesis of the corresponding acylhalide, **89a** was treated with $SOCl_2$. The excess $SOCl_2$ was removed by vacuum and the product was used in the next step without any purification.

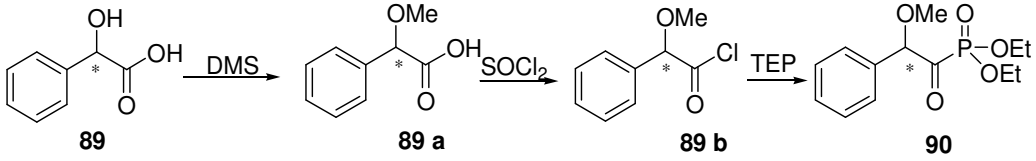


Figure 41 Synthesis of Diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate

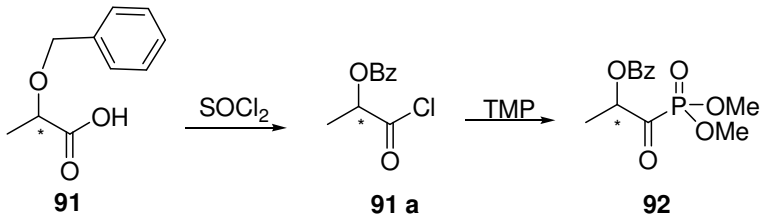


Figure 42 Synthesis of Dimethyl 2-(benzyloxy)-1-oxopropylphosphonate

The syntheses of acylphosphonates were achieved according to the literature procedures [40]. Compounds **89b** and **91a** were reacted with TEP but in the case of **91a,** lots of side products were observed. Therefore, TMP was used instead of TEP to obtain the corresponding acylphosphonate **92** (Figure 41 and 42). The phosphites were added dropwise to the reaction mediums in an ice-bath and under inert gas. The reactions were controlled by TLC and the excess phosphites were removed by vacuum distillation. Purification of the acylphosphonate **90** was carried out by using column chromatography (6:1, EtOAc-Hexane) and re-crystallization. However, the purification of **92** was problematic , and pure product could not be obtained.

2.2 Reactions of β-hydroxy-α-ketophosphonates:

The importance of acylphosphonates was discussed in previous sections. As mentioned, they are potent acyl anion precursors providing the corresponding acyl anion equivalents via nucleophile promoted phosphonate to phosphate rearrangement and they are used in the carbon-carbon bond formation reactions. By using this approach, after the generation of the corresponding acyl anion equivalents as reactive intermediates, different reactions were tried in the presence of different electrophiles. However, the expected acyl anion equivalent from dimethyl 2-(benzyloxy)-1-oxopropylphosphonate **92** could not be generated. As a result all the planned reactions with this acylphosphonate that will be mentioned in the next section were failed and in all cases no product could be obtained. The reason for this will be discussed later. Consequently, upon now all the reactions will be discussed on diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate **90**.

2.2.1 Generation and Protonation of The Acyl Anion Equivalent: Synthesis of Cyanohydrin *O*-Phosphate: 1-cyano-2-methoxy-2-phenylethyldiethylphosphate

The addition of cyanide to carbonyl compounds that is the synthesis of a cyanohydrin was reported in 1832 by Winkler [41]. Eighteen years later, Strecker [42] first reported the synthesis of amino nitriles by the three-component condensation reaction of a carbonyl compound, amine and cyanide, which bears his name. In the subsequent 170 years, both cyanohydrins and amino nitriles established themselves as key intermediates in organic synthesis, largely due to the wide variety of 1,2-bifunctional compounds into which they could readily be transformed [43] (Figure 43).

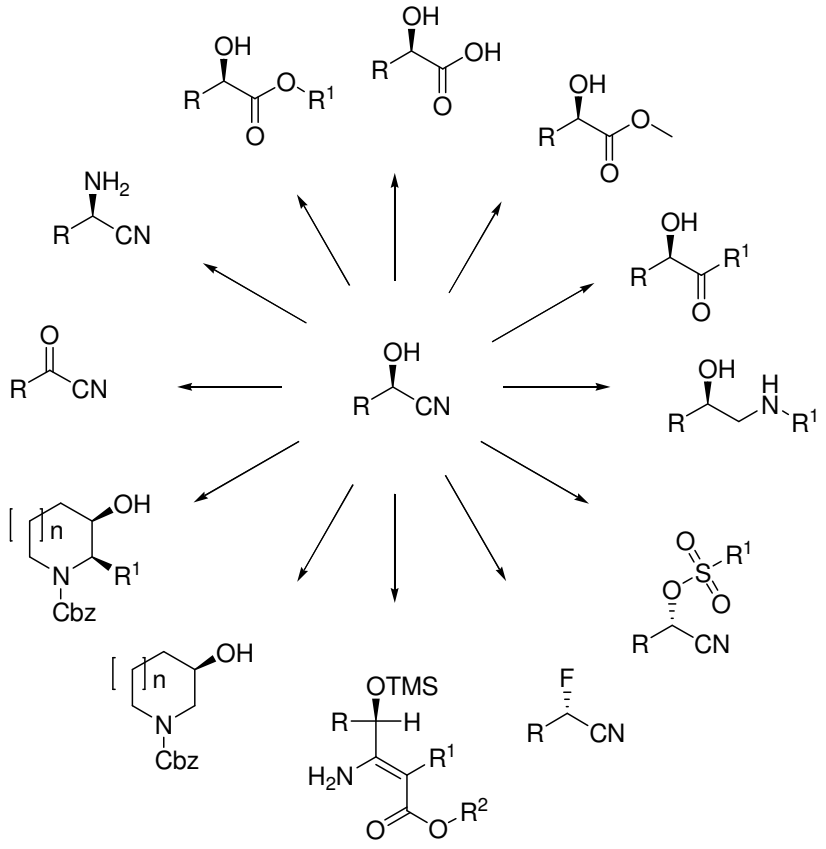


Figure 43 Some Synthetic Transformations of Cyanohydrins

TMS=trimethylsilyl, Cbz=benzyloxycarbonyl

Cyanohydrins are clear examples of unstable molecules and because of this reason they usually require immediate *O*-protection in order to ensure their configurational stability [44]. The direct enantioselective access to *O*-protected cyanohydrins from aldehydes and ketones is an important objective of current research. In accordance with this, Deng [45], Shibasaki [46], Nájera, Saá [47], and Belokon [48] studied syntheses of these *O*-protected cyanohydrins some of which were *O*-alkoxycarbonyl cyanohydrins, *O*-aroyl- or *O*-acyl-cyanohydrins, and cyanohydrin *O*-phosphates. Upon these protected cyanohydrins, cyanohydrin *O*-phosphates are interesting

building blocks for the synthesis of very important compounds, and a number of different strategies are known for the synthesis of cyanohydrin *O*-phosphonates. For instance, the synthesis of racemic cyanohydrin *O*-phosphates from ketones and aldehydes employing stoichiometric amount of lithium cyanide and diethyl chlorophosphate in combination with a sub-stoichiometric amount of lithium diisopropylamine, have been used in the presence of solvents [49]. However, these methods required considerable amount of the toxic lithium cyanide which is not commercially available any longer. Besides, there are some reports of catalytic asymmetric cyano-phosphorylation reaction by Nájera, Saá and co-workers. They reported the first enantioselective cyanophosphorylation of aldehydes catalyzed by the monometallic bifunctional system [50]. The system is derived from BINOL [51], which is the chiral part of the ligand, and it gives chirality unto the aluminum atom. The role of the metal atom is that it acts as a Lewis acid center to ligate, the aldehyde. The amino group in the systems works as a Lewis base to activate the nucleophile. Recently, Aoyama et al. [52] described the first catalytic method leading to the synthesis of various cyanohydrin-*O*-phosphonates using *N*-heterocyclic carbene as a nucleophilic catalyst in cyano-phosphorylation reactions. Finally, Shibasaki et al. described a highly enantioselective cyano-phosphorylation of aldehydes catalyzed by a rare earth-alkali metal-BINOL complex which is YLi_3tris(binaphthoxide) [53].

In view of the fact that the complexity and difficult availability of the reagents for the above mentioned methods, Demir [21] and coworkers developed simple, generally applicable methods for the synthesis of these important cyanohydrin *O*-phosphate compounds, in which protonation of acyl anion equivalents that are generated from acylphosphonates furnishes cyanohydrin *O*-phosphates. Knowing the outcomes of this study, the related cyanohydrin *O*-phosphate of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate **93** was synthesized.

For the synthesis of cyanohydrin *O*-phosphate **93**, an etheral solution of acylphophonate **90** was treated with KCN and water was added to the mixture. Product **93** was obtained as expected, in agreement with the mechanisms proposed in Figure 16. Considering previous works done by Demir's group [28], it was expected that the reaction would have been completed in a short time, however the reaction was very slow and only small amounts of product were observed after 48 hours. To get higher yield different solvent were tried, since the reaction between acylphophonate and KCN was a kind of two-phase reaction, it should have been influenced greatly by the solvents used. So, two different polar aprotic solvents, DMF and DMSO were used. In addition to this, some Lewis acids like yttrium trifluoromethanesulfonate, ytterbium trifluoromethanesulfonate, lanthanum trifluoromethanesulfonate and zinc trifluoromethanesulfonate were added as catalyst to the reaction medium. The reaction time and yield dramatically changed when the reaction was performed in the presence of zinc trifluoromethanesulfonate ($Zn(OTf)_2$) and DMF, in which KCN is highly soluble. This mixture provided higher the product in high yield (Figure 44).

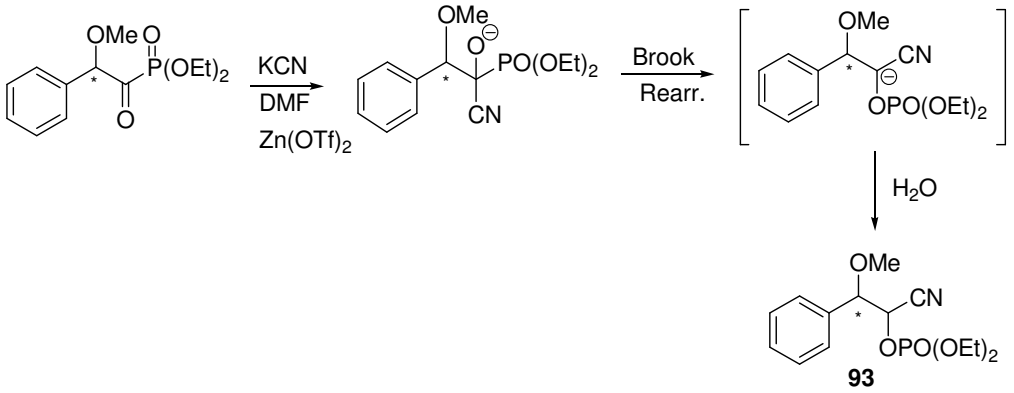


Figure 44 Synthesis of 1-cyano-2-methoxy-2-phenylethyldiethylphosphate

The role of the catalyst was that $Zn(OTf)_2$ increased the electrophilic character of the carbonyl group of the acylphosphonate by coordination of the Lewis acidic zinc with the lone pairs of the both oxygen atoms of carbon and phosphorous by making 1,2 chelation (Figure 45). This chelation also made the molecule conformationaly restricted for the nucleophilic attack of cyanide ion. As carbonyl was activated, attacking of the CN^- ion was easier and as a result, the reaction was completed in 2 hours. After extraction of the crude mixture with ethyl acetate, the product was purified with flash column chromatography and identified with NMR spectroscopy.

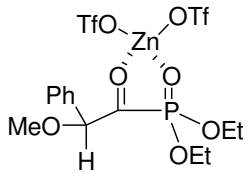
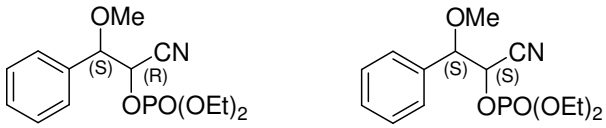


Figure 45 Coordination of compound **90** with $Zn(OTf)_2$

Under the normal reaction conditions, it appears that since the product has two stereocenters, two different stereoisomers are formed which are the diastereomers (1R,2S)-1-cyano-2-methoxy-2-phenylethyldiethylphosphate **94** and (1S,2S)-1-cyano-2-methoxy-2-phenylethyldiethylphosphate **95** (Figure 45). According to the NMR spectrum, the diastereomeric ratio was almost 1:1.



94 **95**

Figure 46 Diastereomers of 1-cyano-2-methoxy-2-phenylethyldiethylphosphate

Protonation of acyl anion equivalents generated from acylphosphonates has twofold potential. First, the protonation of these intermediates not only provides a practical nonhydride reduction of carboxylic acids but also provides products that can be used as synthons for a variety of targets. In addition to these, the product formed by protonation of the generated acyl anion equivalent is equivalent to an aldehyde under the appropriate hydrolysis conditions. In other words, by following this protonation strategy protected mandelic acid was directly converted to its corresponding aldehyde equivalent. Moreover, the protonation products, cyanohydrin phosphates, have been widely utilized as versatile intermediates for the synthesis of agricultural chemicals, nitriles, carbon anion synthons, α-hydroxycarboxylic acids, and methylene groups [54] (Figure 47).

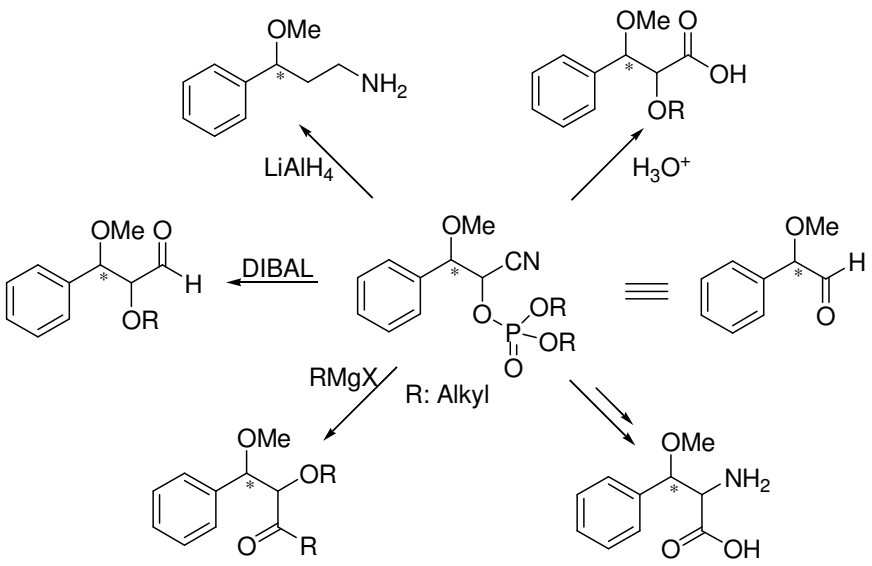


Figure 47 Possible Cyanohydrin Phosphate Transformations

2.2.2 Addition of TMSCN to diethyl 2-methoxy-1-oxo-2-phenylethyl -phosphonate

In the literature, it was reported that the reaction of acylphosphonates with TMSCN could only occur with a catalyst at a certain temperature. On the other hand, the uncatalyzed reactions of TMSCN with acylphosphonates were studied by our group before. Demir and coworkers attributed the enhanced reactivity of acylphophonates to the presence of phosphonate moiety that could interact with TMSCN through P=O and activates it to an intramolecular attack. According to that study, two separate experiments; benzaldehyde and a one to one mixture of benzaldehyde and benzoylphosphonate was reacted with 1 equiv of TMSCN. Although crude reaction mixtures were inspected for two possible products, **96** and **97,** it was observed that there were no traces of the product **97** in both reaction mixtures whereas **96** was the

single product in the latter reaction (Figure 48). As a result, it was concluded that the acylphosphonate did react with TMSCN without a catalyst.

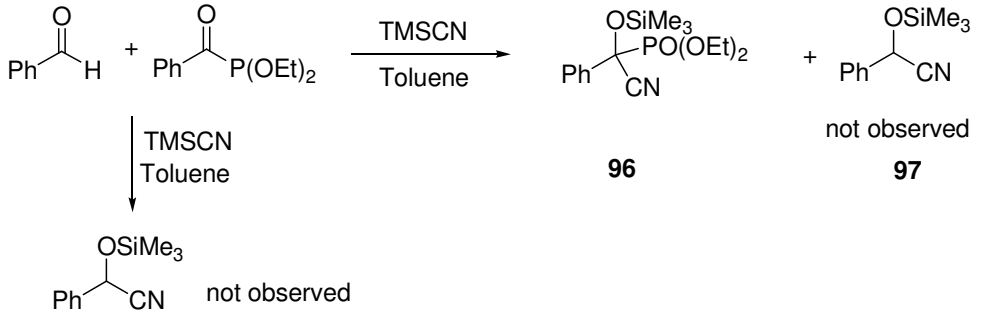


Figure 48 Uncatalyzed Reaction of Acylphophonates with TMSCN

So the uncatalyzed reaction of diethyl 2-methoxy-1-oxo-2-phenylethyl phosphonate with TMSCN was performed as the second experiment. To stirred solution of **90** in toluene, TMSCN was added dropwise under argon. It was expected that the reaction should have been completed in a short time when considering the previous work done by our group. However, there was no product formation after overnight stirring. The reaction was repeated with catalyst ($Zn(OTf)_2$) but again any product could be observed by TLC analysis.

2.2.3 Dimerization of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate

In this part of the work the dimerization of the diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate was aimed. The reaction of **90** with KCN generates the

acyl anion equivalent. Once this reactive intermediate was formed and rearranged, it could accept the second phosphonate molecule as an electrophile to form **98** (Figure 49). However, the result was not as expected. After the reaction was stirred for three days, by TLC monitoring, no product formation was observed. The reaction under the same conditions was repeated in the presence of $Zn(OTf)_2$. Yet, there was still no product formation, only starting material was recovered after work up.

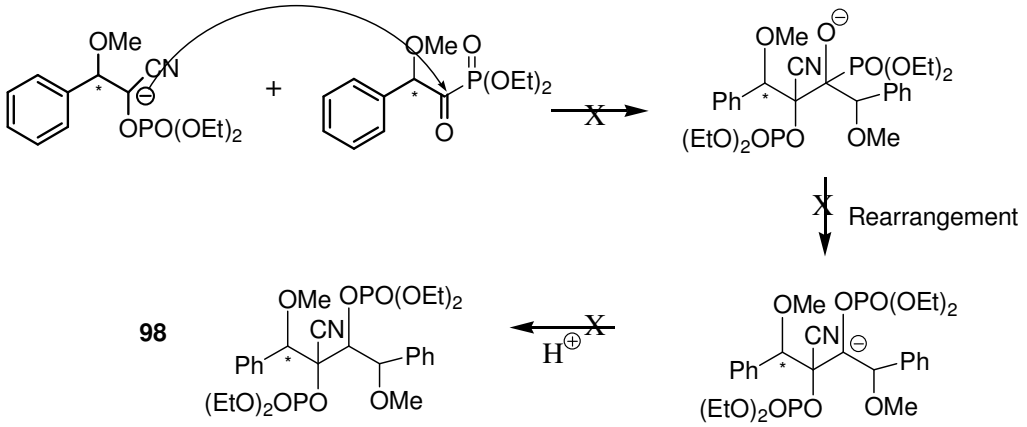


Figure 49 Dimerization Raction of diethyl 2-methoxy-1-oxo-2-phenyl ethyl phosphonate

2.2.4 Benzaldehyde Addition to diethyl 2-methoxy-1-oxo-2-phenylethyl-phosphonate

As it can be seen from Figure 50, attacking of the acyl anion equivalent intermediate to the benzaldehyde would give the intermediate **99** which would undergo 1,4-*O*,*O*-phosphate rearrangement to give the final product **101**. The acyl anion equivalent intermediate was generated in dry DMF as described previously. Freshly distilled

benzaldehyde was added to the mixture under argon. The reaction was stirred for 48 hours and monitored by TLC. However, no new product was formed. The reaction was repeated in the presence of catalyst $Zn(OTf)_2$ and the same result was obtained.

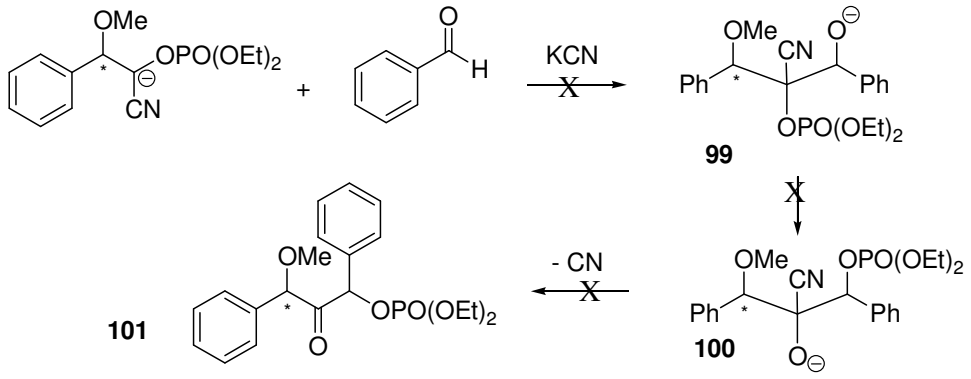


Figure 50 Reaction of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate with Benzaldehyde in the Precence of Cyanide Catalyst

2.2.5 Benzoylphosphonate Addition to diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate

In this reaction, contrary to other experiments, benzoylphosphonate **102** was used as the acyl anion equivalent source, while the acylphosphonate **90** was the electrophile. The generated acyl anion equivalent **103** was expected to attack to the carbonyl carbon of the acylphosphonate **90**. The final product **104** would have been produced after the migration of phosphoryl group. However, no product formation was observed after the reaction.

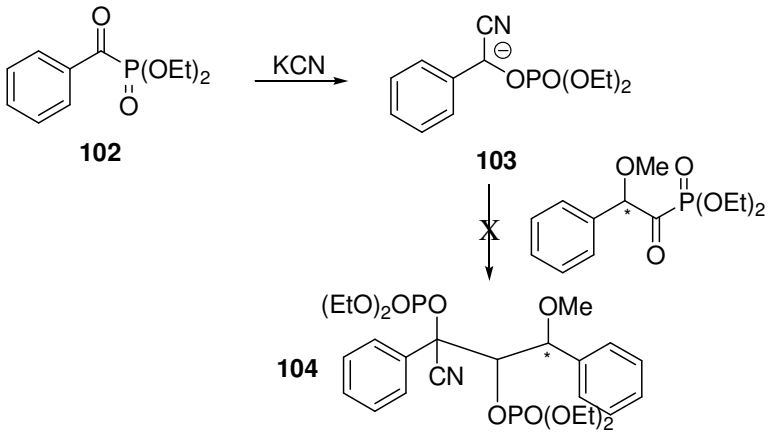


Figure 51 Benzoylphosphonate Addition to diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate

As mentioned before, all these experiments were performed by using corresponding phosphonate of (R)-(+)-2-(Benzyloxy)propionic acid as well. However, none of them gave any product. These negative results might be due to keto-enol tautomerism of acylphosphonates (Figure 52).

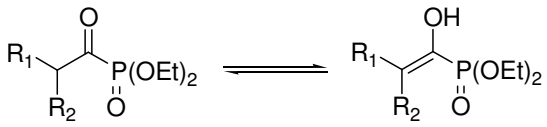


Figure 52 Keto-enol Tautomerism of Acylphosphonates

2.2.6 Reduction of 1-cyano-2-methoxy-2-phenylethyldiethylphosphate

Cyanohydrin phosphates are important intermediates for the synthesis of variety of compounds and they can be converted into many different reagents like primary amines. The reduction of 1-cyano-2-methoxy-2-phenylethyl diethyl phosphate **93** was tried by using $LiAlH_4$ and DMBS (Figure 53).

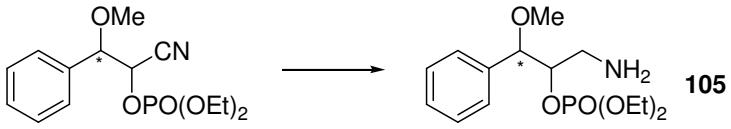


Figure 53 Reduction of 1-cyano-2-methoxy-2-phenylethyldiethylphosphate

During the course of the reaction, the nitrile reacts with $LiAlH_4$ followed by treatment of the reaction mixture with a dilute acid. Overall, the carbon-nitrogen triple bond is reduced to give a primary amine. The acylphosphonate dissolved in ether was added to the ether solution of $LiAlH_4$ and the reaction mixture was stirred overnight. After work up, no product formation was observed according to the NMR result. As an additional experiment, the mixture was refluxed for 2h, and again no product formation was observed. Borane dimethyl sulfide was also used for the reduction. Dimethylsulfide borane is a valuable reagent for the reduction of functional groups like nitrile. This complex is generally preferred because of its distinct stability and known to be very effective for the conversion of nitriles to amine [55].

The cyanohydrin *O*-phosphate in THF was refluxed and DMSB was added dropwise. The reaction was controlled via TLC. After work up, the crude product was purified by flash column chromatography and identified with NMR spectroscopy. Although a complete purification of the product could not be achieved the characteristic peaks in NMR spectrum were an evidence for the formation of the product **105** (Figure 54).

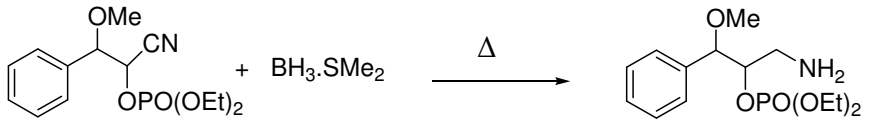


Figure 54 Reduction of 1-cyano-2-methoxy-2-phenylethyldiethylphosphate

2.2.7 Reduction of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate

Hydroxyphosphinic acids comprise an important class of compounds whose representatives are widely distributed in the nature. Some of these compounds possess interesting physiological properties being antibacterial, antiviral and anticancer preparations, antibiotics, ferment inhibitors, aminoacid mimetics and pesticides. Some of compounds are used in clinics for treating different diseases. Although existing methods allow ease preparation of racemic hydroxyphosphonates, synthesis of chiral compounds of this class remains a complicated synthetic challenge and commonly requires specific approach in a particular case [56] and most of the resent procedures require application of catalysts.

There are some routes for the asymmetric reduction of ketophosphonates such as use of borane or catecholborane in the presence of chiral oxazaborolydine catalysts, reduction with chiral chlorodiisopynacampheylboranes and enantioselective hydrogenation in the presence of chiral BINAP-ruthenium(II) catalyst [56]. Among these methods, the use of an oxazaborolidine formed by condensation of a chiral 1,2-amino alcohol with borane is one of the most successful methods of enantioselective ketone reduction [57].

The development of oxazaborolidines has been limited mainly by the availability of suitable chiral amino alcohols. Norephedrine and ephedrine are commercially available and relatively inexpensive in their two enantiomeric forms. Consequently, their derived oxazaborolidines have been widely investigated and reported as highly efficient chiral templates for the borane reduction of prochiral ketones. [58].

In this study, for the reduction of the acylphosphonate, oxazaborolidine that was derived from norephedrine **106** was used (Figure 55). As mentioned before, this catalyst should be prepared in reaction medium thus $BH_3.SMe_2$ was added to a mixture of norephedrine in anhydrous THF under argon gas. The mixture was left stirring for 8 hours for the complex **107** to form. Then acylphosphonate that was dissolved in THF was added dropwise to this mixture and it was stirred for 48 hours. The work up was performed with HCl and extracted with EtOAc. The main product was purified with flash column chromatography and identified with NMR. However, while the expected product was the α-hydroxyphosphonate **108**, it was concluded from NMR results that the product was the primary alcohol **109** in spite of the hydroxyphosphonate (Figure 56) which was not a valuable result since carboxylic acids can be directly reduced to the corresponding alcohols by using appropriate reagents. So, the resultant primary alcohol could be obtained directly from the starting carboxylic acid without doing all those transitional steps.

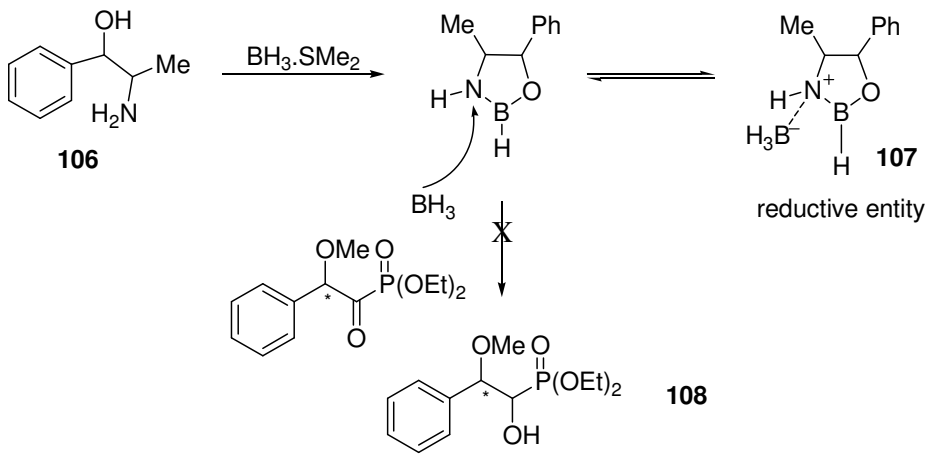


Figure 55 Reduction of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate in the Presence of Chiral Catalyst Oxazaborolidine

This unexpected result might arise from the idea that acylphosphonates have similar reactivity as acylhalides. When a hydride ion was released from borane, it might attack to the carbonyl of acylphosphonate and phosphonate moiety leaves the molecule resulting an aldehyde which was reduced to the corresponding alcohol by oxazaborolidine catalyst.

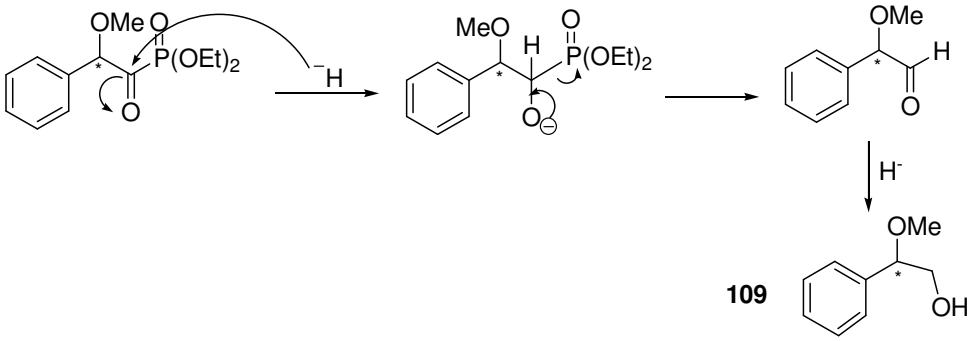


Figure 56 Reaction of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate with oxazaborolidine

2.2.8 $TMSCF_3$ Addition to diethyl 2-methoxy-1-oxo-2-phenylethyl -phosphonate

Organofluorine compounds have found rapidly increasing use in agrochemistry, pharmacy, and fluoropolymers. A number of antiviral, antitumor, and antifungal agents have been developed in which fluorine substitution has been a key to their biological activity [59].

Fluorine is often regarded as an isostere of hydrogen. The replacement of hydrogen by fluorine alters steric and electronic properties of the molecules, affecting the chemical and biological reactivity [59]. Especially trifluoromethyl group appears in many biologically active pharmaceutical and agrochemical compounds. Hence, the syntheses of trifluoromethylated synthons are very important for the introduction of the trifluoromethyl group, which often improves the biological activity and metabolic stability [60].

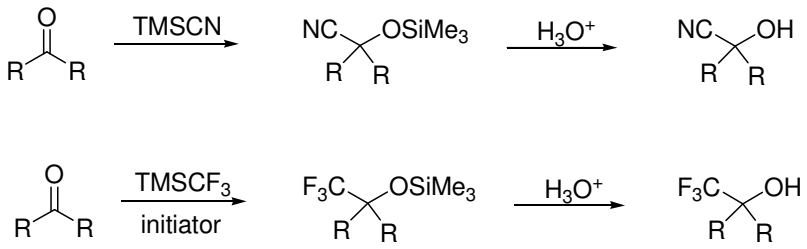


Figure 57 Reaction of carbonyl compounds with TMSCN and $TMSCF_3$

Over the years trimethylsilyl compounds substituted with electron-withdrawing substituents such as -CN, I, CI, Br, N_3, -NCO, -CNO, etc. have been used as synthetic reagents to attach these substitutents to electron-deficient centers. [61]. In

fact, the nucleophilic trifluoromethylation reactions of organic compounds via $TMSCF_3$ are very similar to this principle (Figure 57).

The trimethylation reaction of electrophiles with $TMSCF_3$ needs Lewis base as initiators. Among the Lewis base catalysts, oxygen-containing nucleophiles are more efficient due to the high bond strength as well as the kinetic lability of the silicon-oxygen bond. Therefore, oxygen-containing nucleophiles are suitable initiators or catalysts in $TMSCF_3$ chemistry.

$TMSCF_3$ and **90** were reacted in the presence of 20 mol % K_2CO_3 and NaOAc. The reactions were stirred at room temperature in DMF and controlled via TLC. While K_2CO_3 did not afford any product after prolonged reaction times, NaOAc afforded **110** after 48 hours in low yield (23%). The corresponding trifluoromethylated adduct **110** was isolated in pure form via flash column chromatography (3:1, EtOAc-Hexane) and idendified by NMR. (Figure 58)

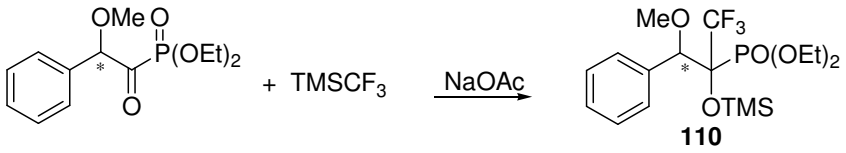


Figure 58 $TMSCF_3$ addition to Diethyl.2-methoxy-1-oxo-2-phenylethylphosphonate

CHAPTER 3

EXPERIMENTAL

3.1 The Synthesis of (S)-(+)Methoxyphenylacetic acid (89a) :

Sodium Acid Salt of α-Methoxyphenylacetic Acid: To a hot solution made by dissolving 17,41 g. (435 mmoles) of sodium hydroxide in 58mL of water, 5g. (33 mmoles) of α-mandelic acid was added. The reaction was carried out in a beaker to minimize the effect of foaming during the methylation. After cooling to 45-50^{0}C, 17,4mL (180 mmoles) of distilled dimethyl sulfate was added over a period of one and one-half to two hours, the reaction temperature remaining unchanged. After cooling to room temperature, the precipitate (mixture of normal sodium salts of mandelic and α-methoxyphenylacetic acids and inorganic salts) was filtered. It was dissolved in 20mL of hot distilled water and the sodium acid salt precipitated by adding concentrated hydrochloric acid to a pH of 3.1. The mixture was cooled to 20^{0}C and filtered. An additional precipitate was obtained by saturating the filtrate with adding sodium chloride to the filtrate. The combined materials were dissolved in 10 times their weight of boiling distilled water, filtered, cooled to 20^{0}C and the precipitate filtered. Additional sodium acid salt was recovered from the filtrate by adding a solution of sodium chloride, filtering, and recrystallizing from 10 times its weight of water.

α-Methoxyphenylacetic acid*:* 3 g. (1 mole) of the sodium acid salt of α-methoxyphenylacetic acid by treating a hot aqueous solution (530mL.) of it alternately with a total of 0,36 ml. of concentrated hydrochloric acid and more of the sodium acid salt. The addition of a large excess of hydrochloric acid to the hot solution was avoided. The oily α-methoxyphenylacetic acid which separated was extracted three times with ether from the cooled solution to which 3,5ml. more concentrated hydrochloric acid had been added, the ether extracts combined, washed once with a little water, dried, and the ethyl ether removed by vacuum distillation. (0,9g, 18 %) (White solid). $C_9H_{10}O_3$: 166,11 g/mole.

3.2 The Synthesis of 2-methoxy-2-phenylacetyl chloride (89b):

15mL Thionyl chloride was distilled directly into a flask containing 1,0 g α-methoxyphenylacetic acid (6 mmol). The resulting solution was aged at room temperature for 1 h, and the volatiles were removed *in vacuo*. The product was used in the next step without any prufication. (Yellow oil). $C_9H_9ClO_2$:184,6 g/mole

3.3 The Synthesis of Diethyl2-methoxy-1-oxo-2-phenylethylphosphonate (90):

1,9mL triethylphosphite (11mmol) was added dropwise onto the (S)-O-methylmandeloyl chloride (10 mmol) in an ice bath under an inert atmosphere. After completion of the addition, resulting mixture was stirred at room temperature for one night. Then, the excess of TEP was distilled off in evaporator and products were purified by using flash column chromatography. (EtOAc:Hexane, 6:1). (1,14 g, 83 %) (White solid). $C1_3H_{18}O_5P$: 285,3 g/mole

^{1}H-NMR (400 MHz,$CDCl_3$): δ ppm: d 1.30 (t, 3H),

d1.37 (t, 3H),

3.35 (s, 3H),

4.06–4.26 (m, 4H),

4.74 (s, 1H),

7.19–7.26 (m, 5H)

3.4 The Synthesis of 2-(benzyloxy)propanoyl chloride (91b) :

0,7mL of freshly distilled $SOCl_2$ (9mmol) and 500mg of (benzyloxy)propanoic acid (2,7mmol) was refluxed for one hour. The excess of $SOCl_2$ was evaporated by using evaporator and the product was used in the next step without any purification (Yellow oil). $C_{10}H_{11}ClO_2$: 198,6 g/mole.

3.5 The Synthesis of Dimethyl 2-(benzyloxy)-1-oxopropylphosphonate (92) :

0,1mL trimethylphosphite (1,1mmol) was added dropwise onto the 198mg 2-(benzyloxy)propanoyl chloride (1mmol) in an ice bath under an inert atmosphere. After completion of the addition, resulting mixture was stirred at room temperature for one night. Then, the excess of TMP was distilled off in evaporator and products were purified by using flash column chromatography. (EtOAc:Hexane:MeOH, 5:10:2). However, complete prufication could not be obtained (Yellow oil). $C_{12}H_{17}O_5P$: 272,1 g/mole.

3.6 The Synthesis of 1-cyano-2-methoxy-2-phenylethyl diethyl phosphate (93) :

94mg KCN (1,43mmol) was added to the mixture of diethyl 365mg of 2-methoxy-1-oxo-2-phenylethylphosphonate (1,3mmol) and $Zn(OTf)_2$ in 4mL DMF. After 15 min stirring 2 mL water was added to the mixture. After completion of the reaction, the mixture was diluted with water and ether. Organic phase was separated and dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by flash column chromatography (ether:petroleum ether, 5:2) (58,26 62%) (Yellow oil) $C_{14}H_{19}NO_5P$: 312,1 g/mole. $[\alpha]^{25}_D$= +11 ($CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): d 1.22–1.38 (m, 6H),

3.34 and 3.38 (2s, 3H),

3.77–4.19 (m, 4H),

4.47 (m, 1H),

4.96 and 5.12 (dd, 1H),

7.25–7.40 (m, 5H).

3.7 The Synthesis of 3-amino-1-methoxy-1-phenylpropan-2-yl diethyl phosphate (105) :

The flask charged with 3,64g of 1-cyano-2-methoxy-2-phenylethyl diethyl phosphate (1mmol) and 3mL of anhydrous THF and brought to reflux. Then 0,5mL of BMS (3mmol) was added dropwise over a period of 10 min. After 24h, the reaction mixture was cooled to room temperature and concentrated HCl was added until the reaction medium became acidic. The reaction was then heated under reflux for 0,5 hour. The clear solution was cooled to 0^0C and NaOH was added until the

reactiom medium became basic. The overall mixture was extracted with diethyl ether and dried over $MgSO_4$. The products were separated with flash column chromatography (EtOAc:Hexane, 1:1). (1,31g 36%) (Yellow oil). $C_{14}H_{23}NO_5P$: 316,1 g/mole

^{1}H-NMR (400 MHz, $CDCl_3$): d 1.11 (m, 3H),
d 1.32 (m, 3H),
2.65 (broad, 2H)
2.52 (dd, 1H),
2.73 (dd, 1H),
3.19 (s, 3H),
3.53 (td, 1H)
3.84-4.06 (m, 4H),
4.31 (m, 1H)
7.25–7.40 (m, 5H).

3.8 The Synthesis of diethyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-yloxy)trimethylsilane phosphonate (110) :

To a stirred solution of dry DMF and NaOAc (0,04mmol), the acylphosphonate (0,17mmol) dissolved in DMF was added. After 10 min stirring, $TMSCF_3$ (0,35 mmol) was added under argon. To increase yield more NaOAc was added after one day. Reaction monitored with TLC and stopped 2 days. The reaction mixture extracted with ether and the puroduct purified by flash column chromatography (EtOAc:Hexana, 3:1) (11,5 mg, 23%) $C_{17}H_{27}F_3O_5PSi$:427,4 g/ mole. $[\alpha]^{25}_D$= -82,7 ($CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): d 1.15–1.21 (m, 6H),

3.23 (s, 1H),

3.53 (s, 1H),

3.69–4.08(m, 4H),

4.52-4,57 (m, 1H),

7.25–7.40 (m, 5H).

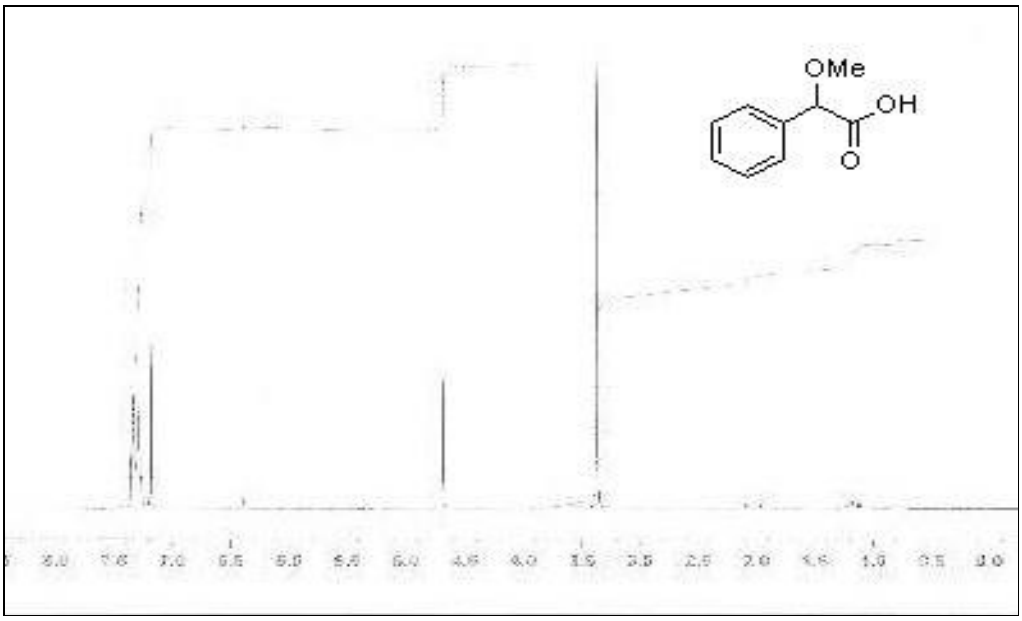


Figure 59. [1]H-NMR spectrum of (S)-(+)methoxyphenylacetic acid:

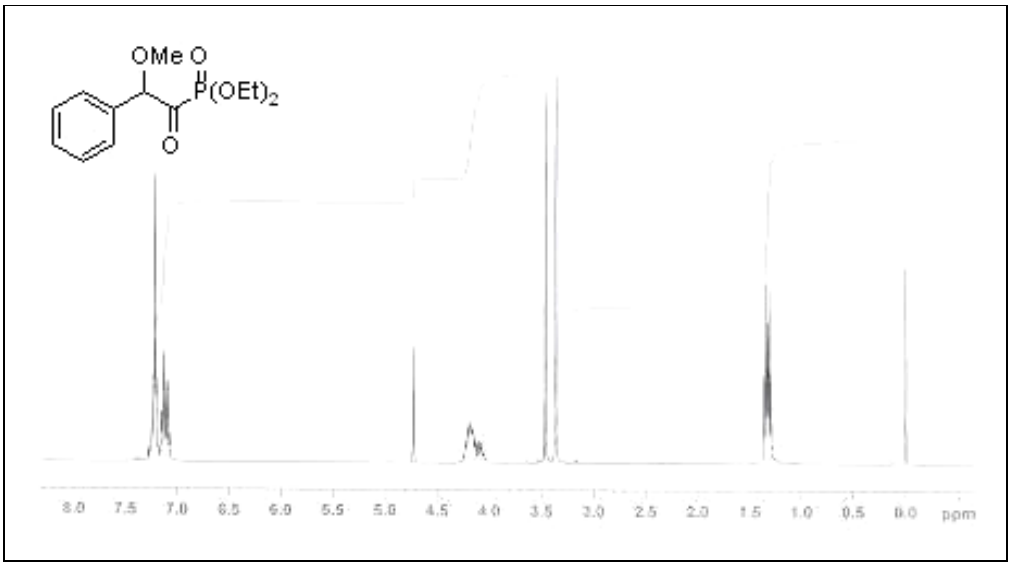


Figure 60. [1]H-NMR spectrum of diethyl.2-methoxy-1-oxo-2-phenylethyl-phosphonate

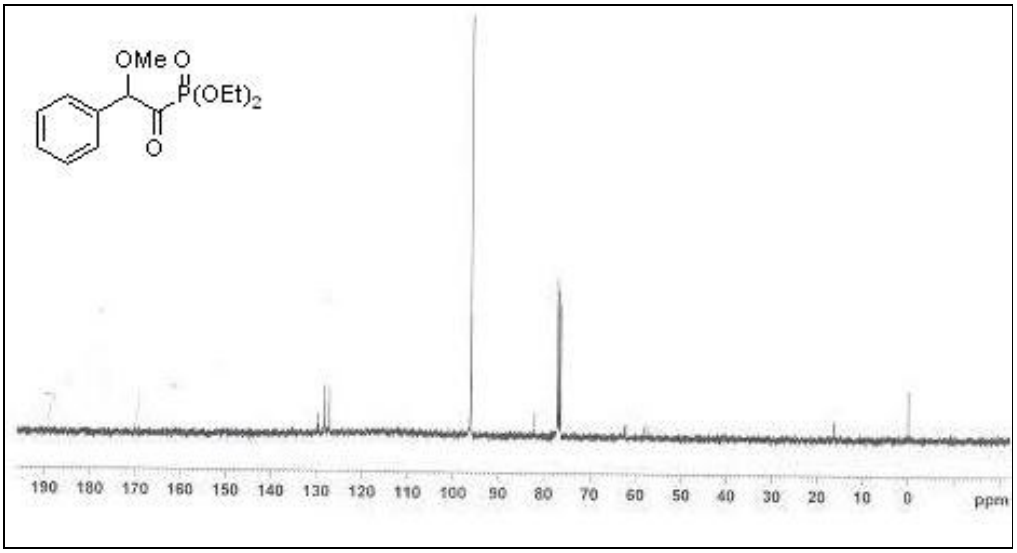


Figure 61 ^{13}C-NMR spectrum of diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate

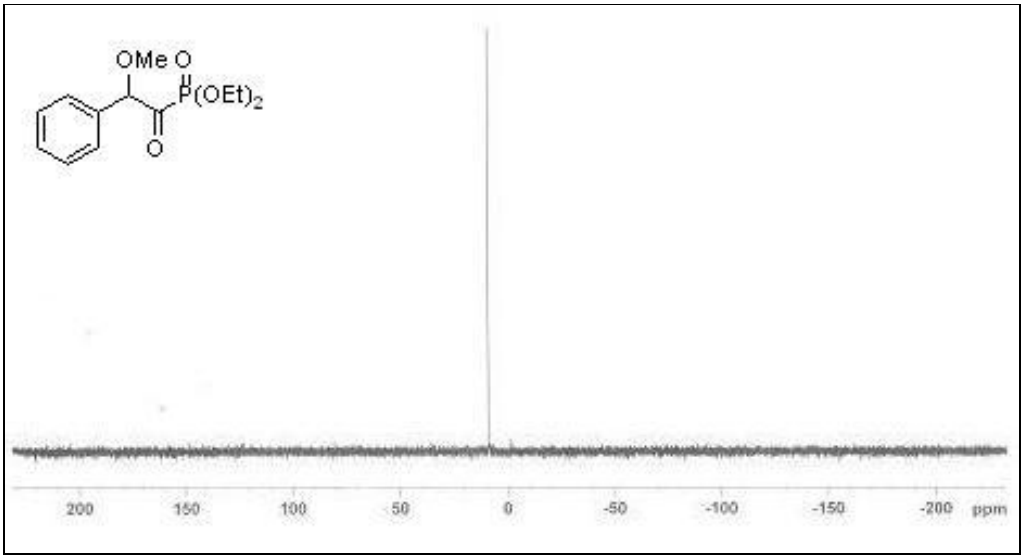


Figure 62 ^{31}P-NMR spectrum of diethyl 2-methoxy-1-oxo-2-phenylethyl-phosphonate

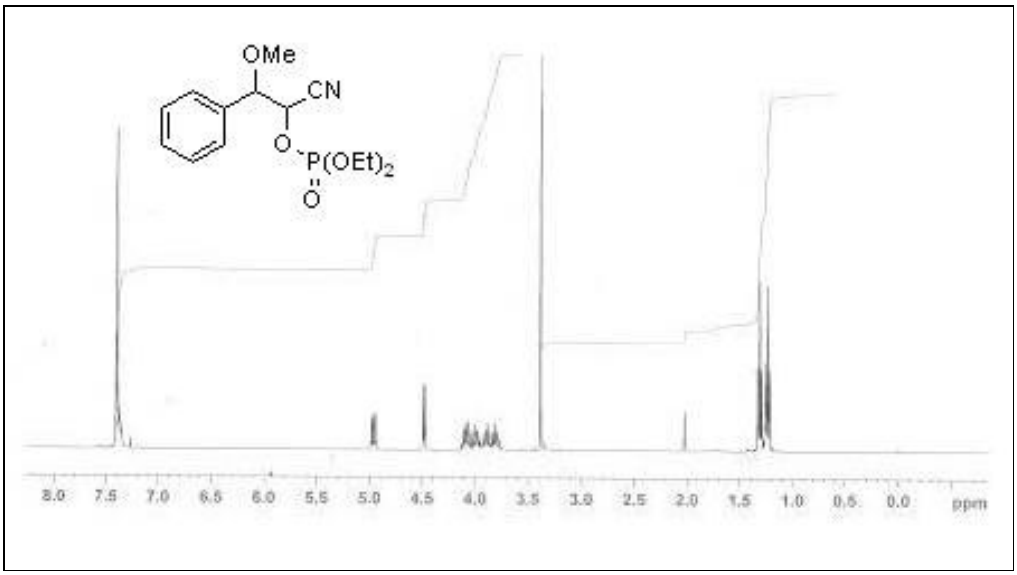


Figure 63 ^{1}H-NMR spectrum of 1-cyano-2-methoxy-2-phenylethyl diethyl phosphate

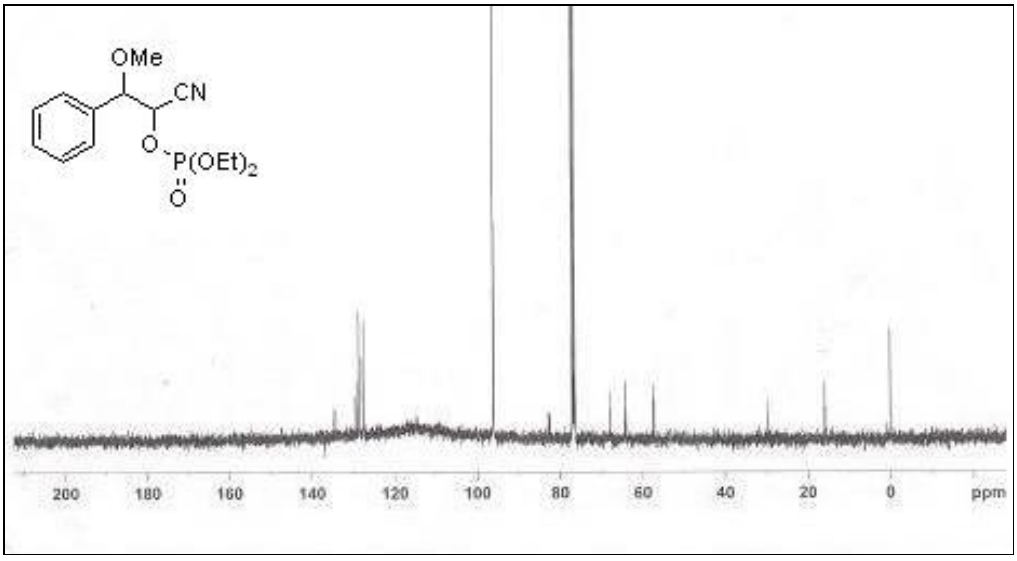


Figure 64 ^{13}C-NMR spectrum of 1-cyano-2-methoxy-2-phenylethyl diethyl phosphate

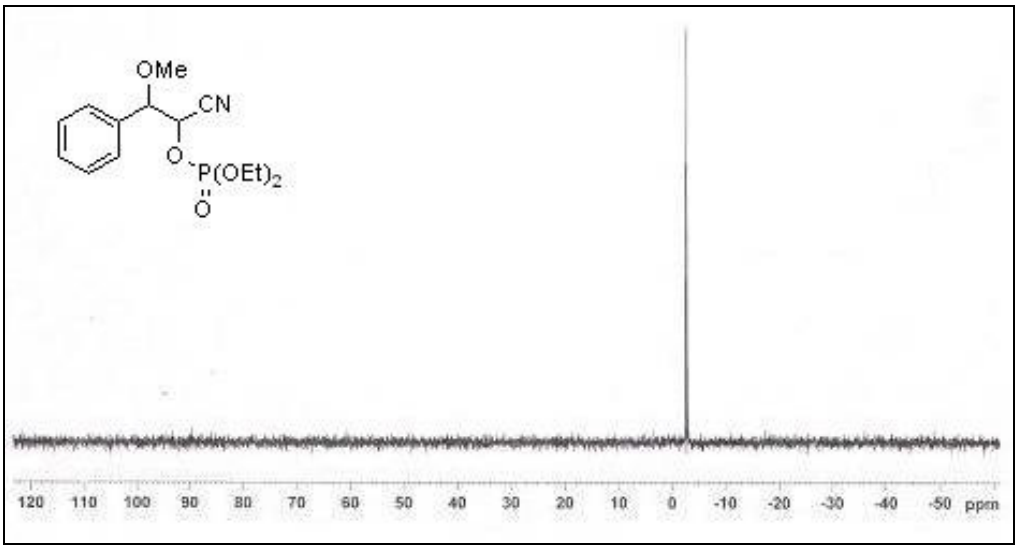


Figure 65 ^{31}P-NMR spectrum of 1-cyano-2-methoxy-2-phenylethyl diethyl phosphate

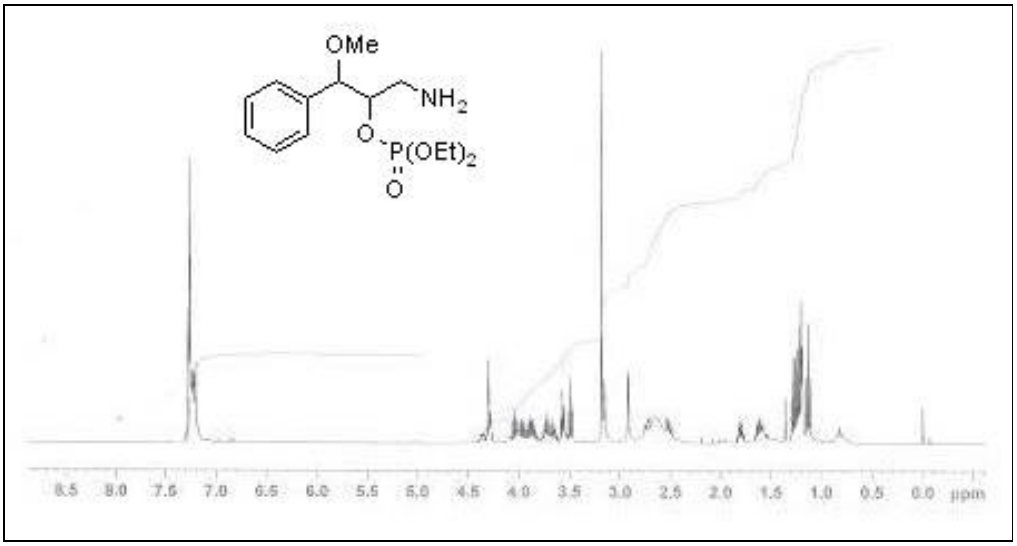


Figure 66 ^{1}H-NMR spectrum of 3-amino-1-methoxy-1-phenylpropan-2-yldiethyl phosphate

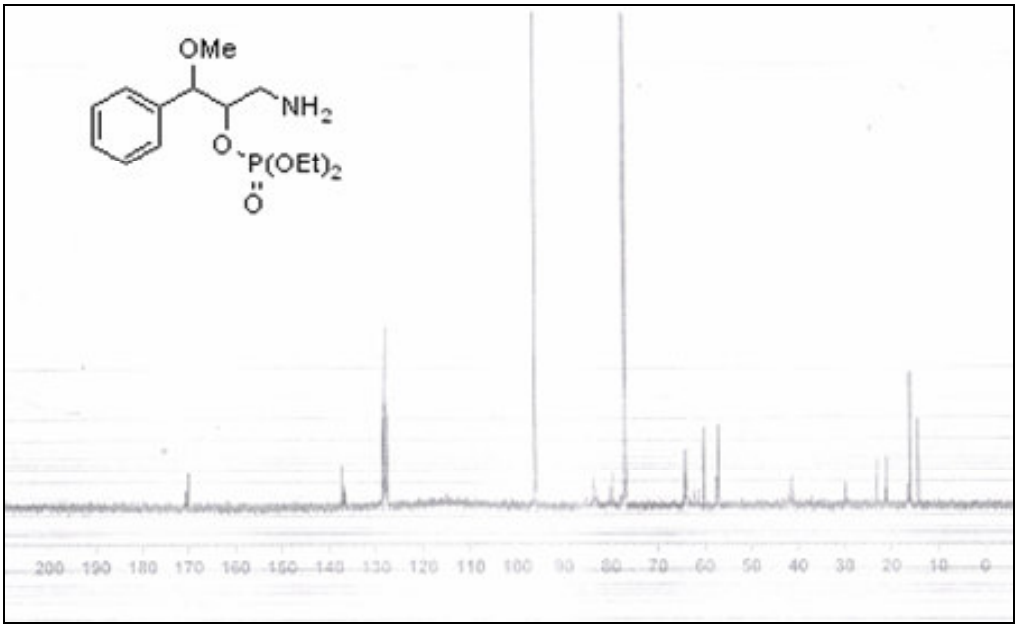


Figure 67 ^{13}C-NMR spectrum of 3-amino-1-methoxy-1-phenylpropan-2-yldiethyl phosphate

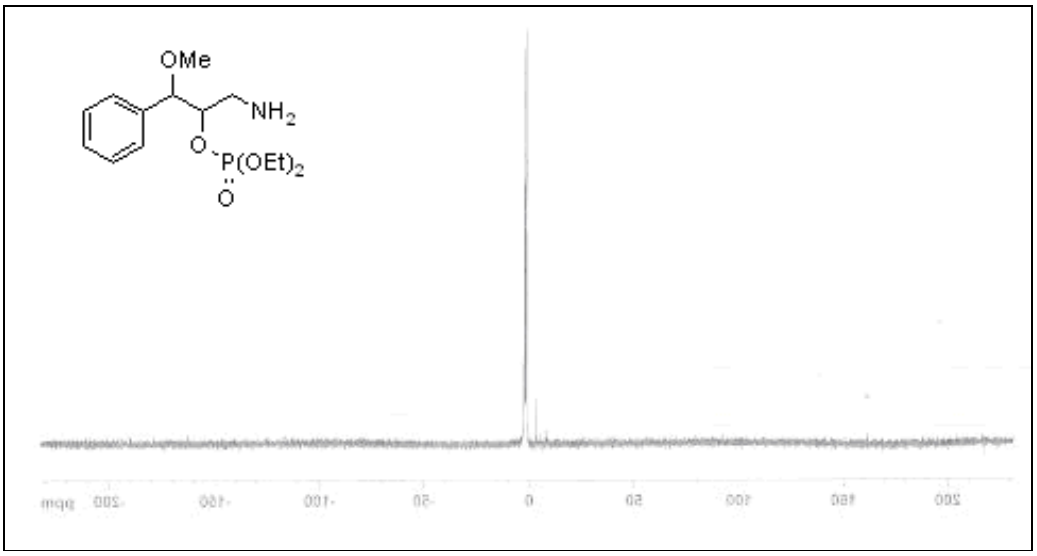


Figure 68. ^{31}P-NMR spectrum of 3-amino-1-methoxy-1-phenylpropan-2-yldiethyl phosphate

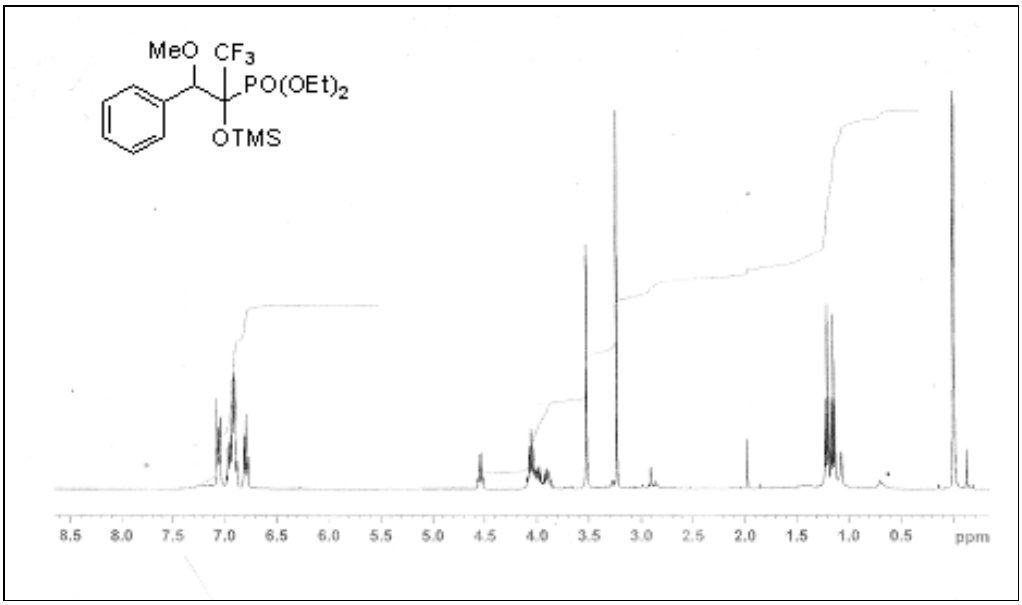


Figure 69 ^{1}H-NMR spectrum of diethyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-yloxy)trimethylsilane phosphonate

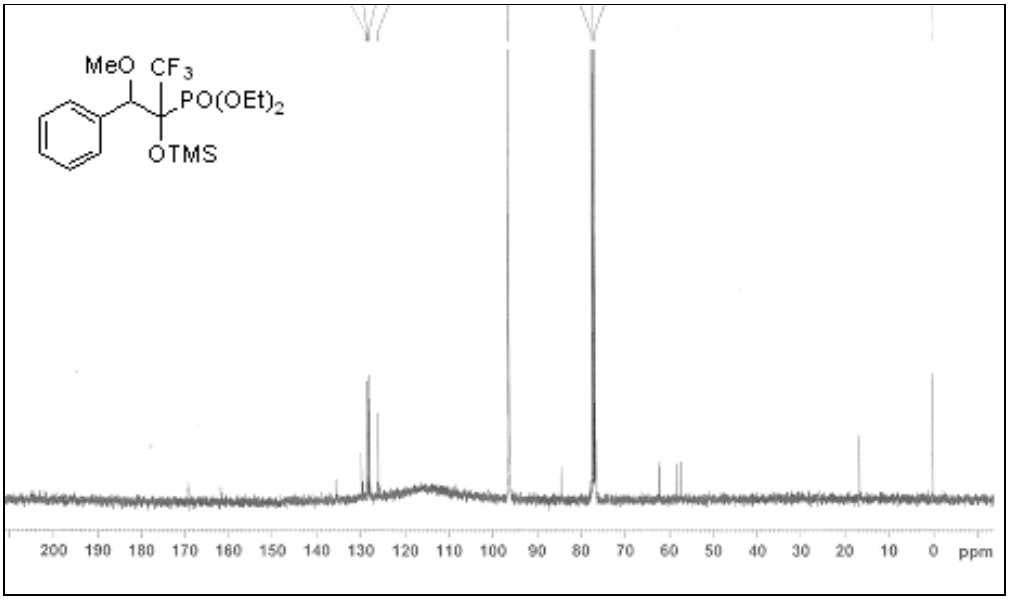


Figure 70 ^{13}C-NMR spectrum of diethyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-yloxy)trimethylsilane phosphonate

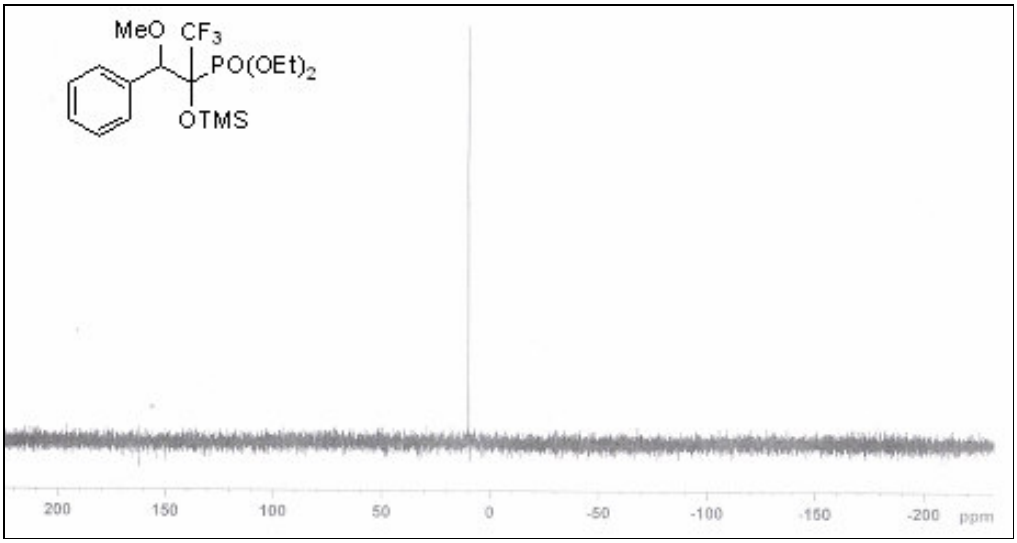


Figure 71 ^{31}P-NMR spectrum of diethyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-yloxy)trimethylsilane phosphonate

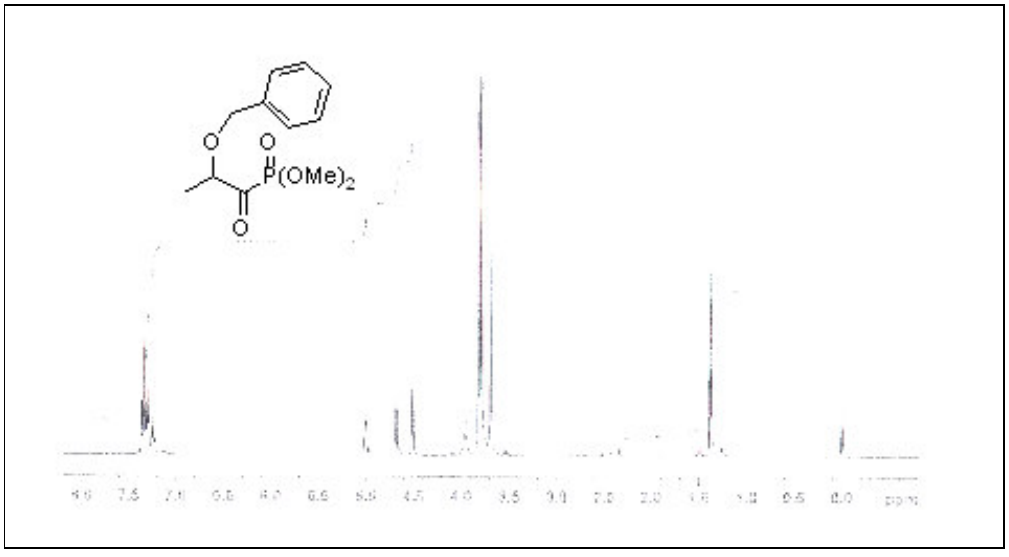


Figure 72 ^{1}H-NMR spectrum of dimethyl 2-(benzyloxy)-1-oxopropylphosphonate

CHAPTER 4

CONCLUSION

In this study, chiral mandelic acid and chiral benzyloxypropionic acid were used as the starting α-hydroxy ketones to synthesize corresponding functionalized new acylphosphonates which are diethyl2-methoxy-1-oxo-2-phenylethyl phosphonate **90** and dimethyl 2-benzyloxy-1-oxopropylphosphonate **92** respectively. According to the fact that acylphosphonates are a new generation of acyl anion precursors, it was tried to form corresponding acyl anions of these acylphosphonates as reactive intermediates for different reactions. Although previous studies have proven that protonation and reactions of acyl anion equivalents generated from acylphosphonates are possible, in the case of beta-functionalized acylphosphonates the circumstance is different and problematic. On the other hand, the acyl anion equivalent was generated via acylphosphonate **90** which has a β-functionality. The protonation of this acyl anion equivalent has provided a practical cyanohydrin synthesis compared with the literature. Furthermore, addition of $TMSCF_3$ to this functionalized acylphosphonate also provided trifluoromethylation**.**

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