SELF CONDENSATION REACTION OF ALPHA-KETOPHOSPHONATES

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SELF CONDENSATION REACTION OF ALPHA-KETOPHOSPHONATES

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Approval of the thesis:

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ABSTRACT

SELF CONDENSATION REACTION OF

α-KETOPHOSPHONATES

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This thesis presents synthesis of tertiary α-hydroxy phosphonate derivatives. α-Ketophosphonates is known that they are both acyl anion precursors and electrophiles. In this work, α-ketophosphonates were used as both acyl anion precursors and electrophiles in the presence of catalytic amount of KCN. α-Ketophosphonates underwent benzoin-type condensation reaction.

Keywords: benzoin, catalytic, acyl anion, acyl anion equivalent, α-hydroxy phosphonate, acylphosphonate

ÖZ

α-KETOFOSFONATLARIN
KENDİ KENDİLERİNE KATILMALARI

Göllü, Mehmet

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Eylül 2007, 58 sayfa

Bu çalışma üçüncül α-hidroksi fosfonatların sentezini sunmaktadır. α-Ketofosfonatların hem açil anyon eşdeğeri hem de elektrofil oldukları bilinmektedir. Bu çalışmada, α-ketofosfonatlar hem açil anyon öncülü hem de elektrofil olarak kullanılmıştır. α-Ketofosfonatlar benzoin tipi reaksiyon vermişlerdir.

Anahtar sözcükler: benzoin, katalitik, açil anyon, açil anyon eşdeğri, α-hidroksi fosfonat, açil fosfonat

To My Parents

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CHAPTER 1

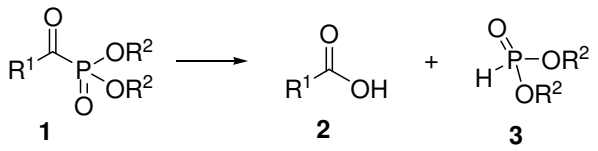
INTRODUCTION

1.1 Acylphosphonates in Organic Chemistry

In the organophosphorus chemistry, phosphonates are interesting compounds. They show biological activity. Within this class of compounds, the α-ketophosphonates have an important part. The reason why α-ketophosphonates are interesting compounds is the adjacent phosphorous and carbonyl groups. The electron with-drawing phosphonate group enhances the electrophilicty of carbonyl group. α-Ketophosphonates are a hybrid of wide range of carbonyl compounds of varying oxidation states. It is possible to derive hydrazones, imines and oximes from the carbonyl function; to reduce α-ketophosphonates to the corresponding α-hydroxyphosphonates, or to use them as acylating reagents.

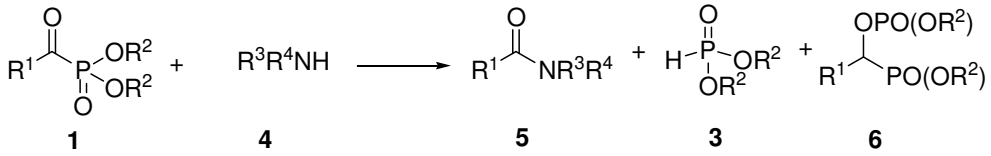
1.1.1 Reactions with Amine Nucleophiles

Phosphorus-carbon (P-C) bonds are quite stable and can not be cleaved easily under the usual conditions [1]. Hence, the use of organophosphorus compounds as synthetic reagents is lacking. However, acylphosphonates are in general unstable. C-P bond in acylphosphonates can be cleaved by moisture in air to give carboxylic acids and phosphites (Scheme 1).



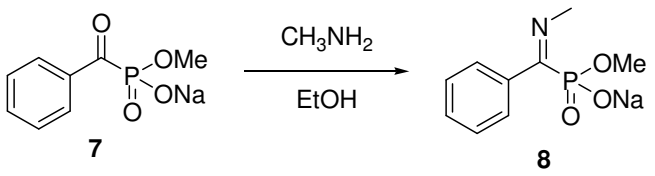
Scheme 1 Hydrolysis of acyl phosphonates

In the light of this information, Sekine et al. reported acylation of amines by means of α-ketophosphonates (Scheme 2) [2]. The reactions of diethyl benzoylphosphonate with aliphatic and aromatic amines carried out in dry ether. Whereas aliphatic amines give corresponding amides in good yields, aromatic (aniline) and 2-amino pyridine do not undergo this reaction. The reactivity of the amines for the acylation is almost parallel to basicity of amines. Three products are isolated from the reaction. Two of them are major products, the corresponding amide and the ethyl phosphite. The third one is a side product, α-(phosphory1oxy)benzylphosphonate **6**. This product is formed by addition of diethyl phosphite to diethyl benzoylphosphonate followed by rearrangement of phosphorus from carbon to oxygen.



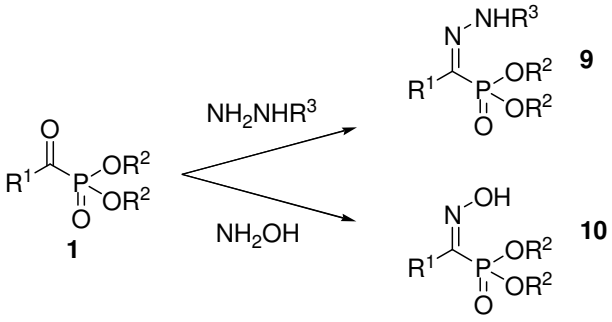
Scheme 2 Acylation of amines

On the other hand, P-C bond in mono sodium salts of acylphosphonates is stable to nucleophilic cleavage and mono sodium salts of acylphosphonates form imines with amines (Scheme 3) [3].



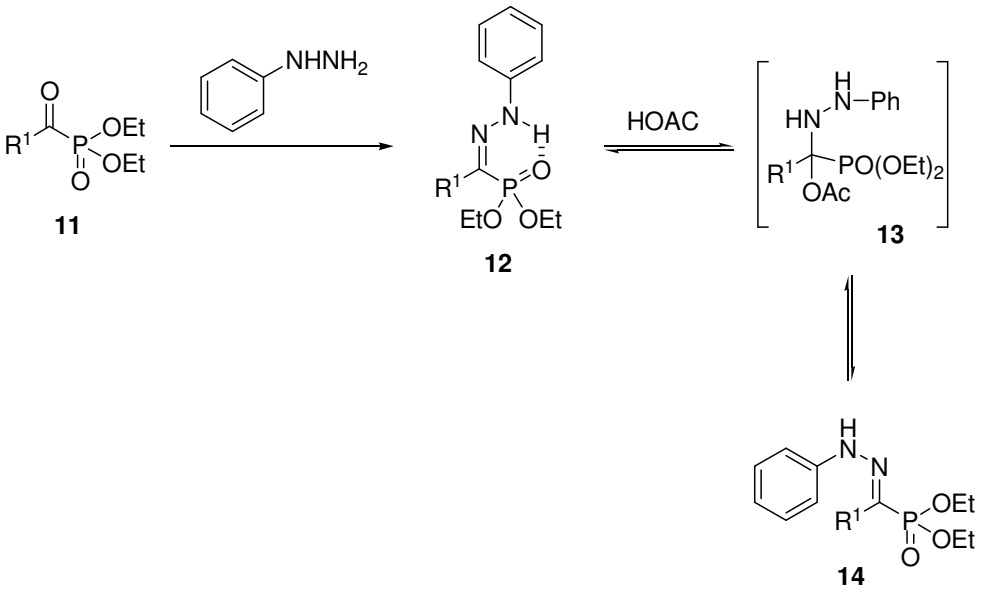
Scheme 3 Imine formation of mono sodium salt of benzoyl phosphonate

While amines react with acylphosphonates to give amides, the reactions of acylphosphonates with hydroxyl amine and substituted hydrazines give oximes and hydrazones, respectively (Scheme 4) [4].



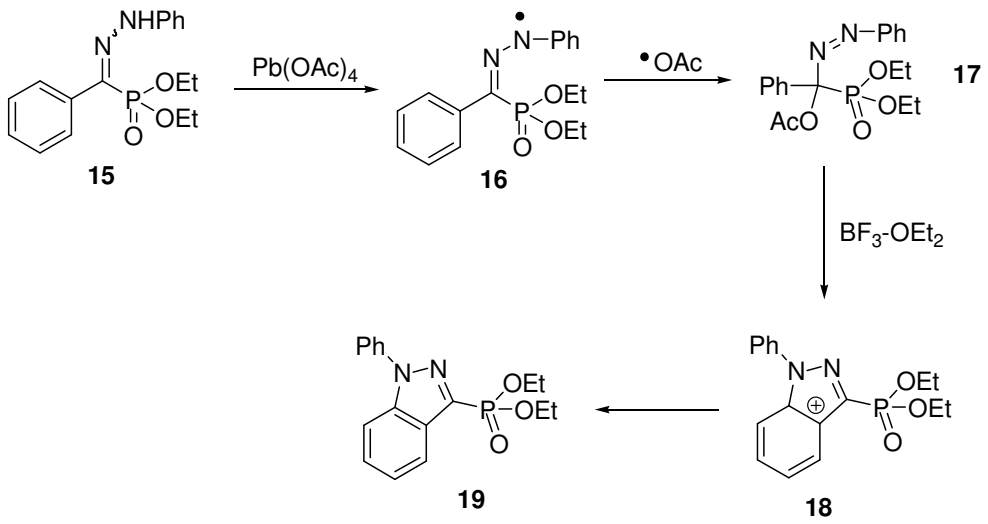
Scheme 4 Reaction of acyl phosphonates with hydrazines and hydroxyl amines

Acyl phosphonates form hydrazones with phenylhydrazines in good yields. Hydrazones from acylphosphonates can be in both the configurational isomers, ***Z*** and ***E***. ***Z*** isomer **12** is stabilized by intramolecular H-bonding whereas ***E*** isomer **14** lacks such stabilization. However, it is less sterically hindred. The formed hydrazone from the reaction between acylphosphonates and phenylhydrazine is in ***Z*** form. It isomerizes to ***E*** configuration in boiling acetic acid (Scheme 5).



Scheme 5 Synthesis and isomerization of Z isomer

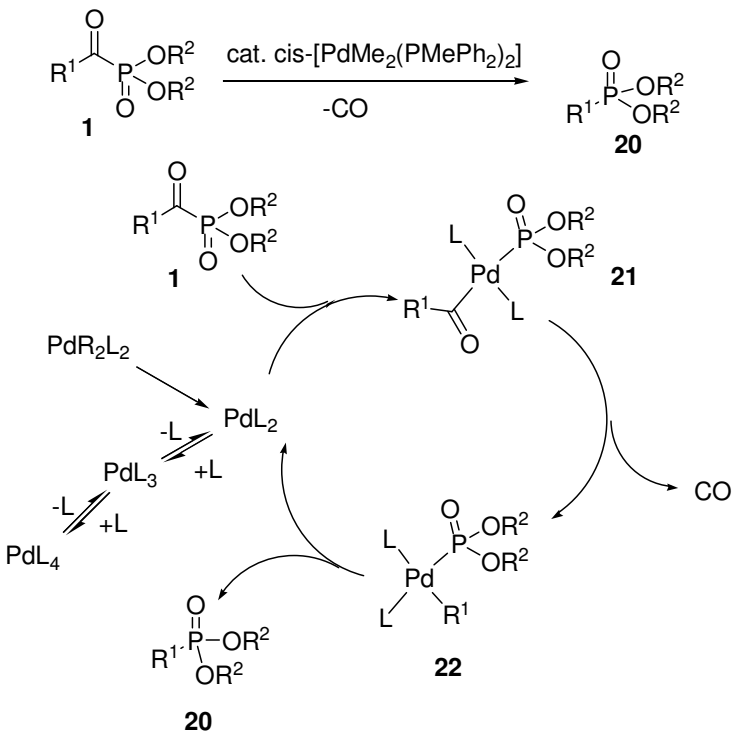
In this work, Kaushik et al. reported oxidation of phenyl hydrazones and the cyclizaton of oxidation products with BF_3:OEt_2 that leads to 1-phenyl indazole derivatives (Scheme 6). Oxidation is carried out with lead tetraacetate in benzene. The oxidation product is azoacetates. Phenyl hydrazones are oxidized to azoacetates while (2,4-dinitrophenyl)hydrazones do not undergo oxidation. Cyclization of azoacetates with BF_3:OEt_2 in boiling temperature produces 1-phenyl indazole derivatives **19**.



Scheme 6 1-Phenyl indazole synthesis

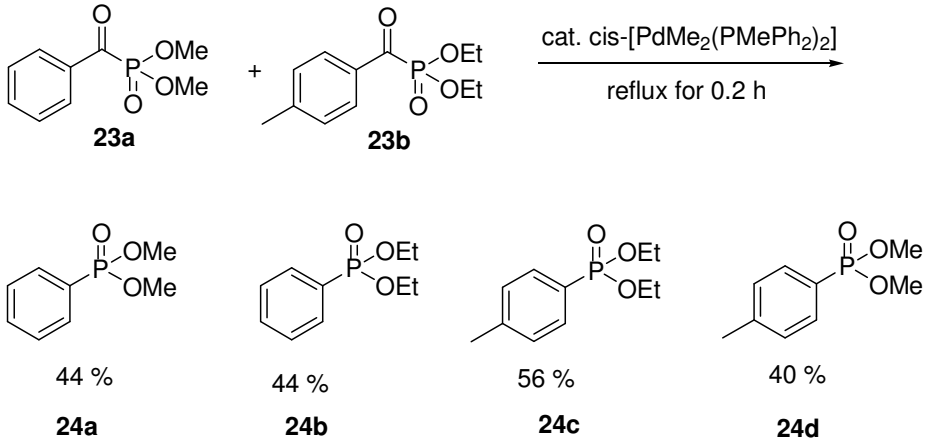
1.1.2 Decarbonylation of α-Ketophosphonates

In 1989, Nakazawa et al. reported decarbonylation of α-ketophosphonates to give corresponding aryl- and alkyl-phosphonates (Scheme 7) [5]. The decarbonylation reaction is catalyzed by Pd-complexes in toluene in reflux conditions. The catalytic cycle is started by oxidative addition of α-ketophosphonates to PdL_2 at P-C bond to give intermediate **21**. Decarbonylation of **21** produces **22**. The reductive elimination of **22** yields aryl- or alkyl-phosphonates and PdL_2 reenters to catalytic cycle.



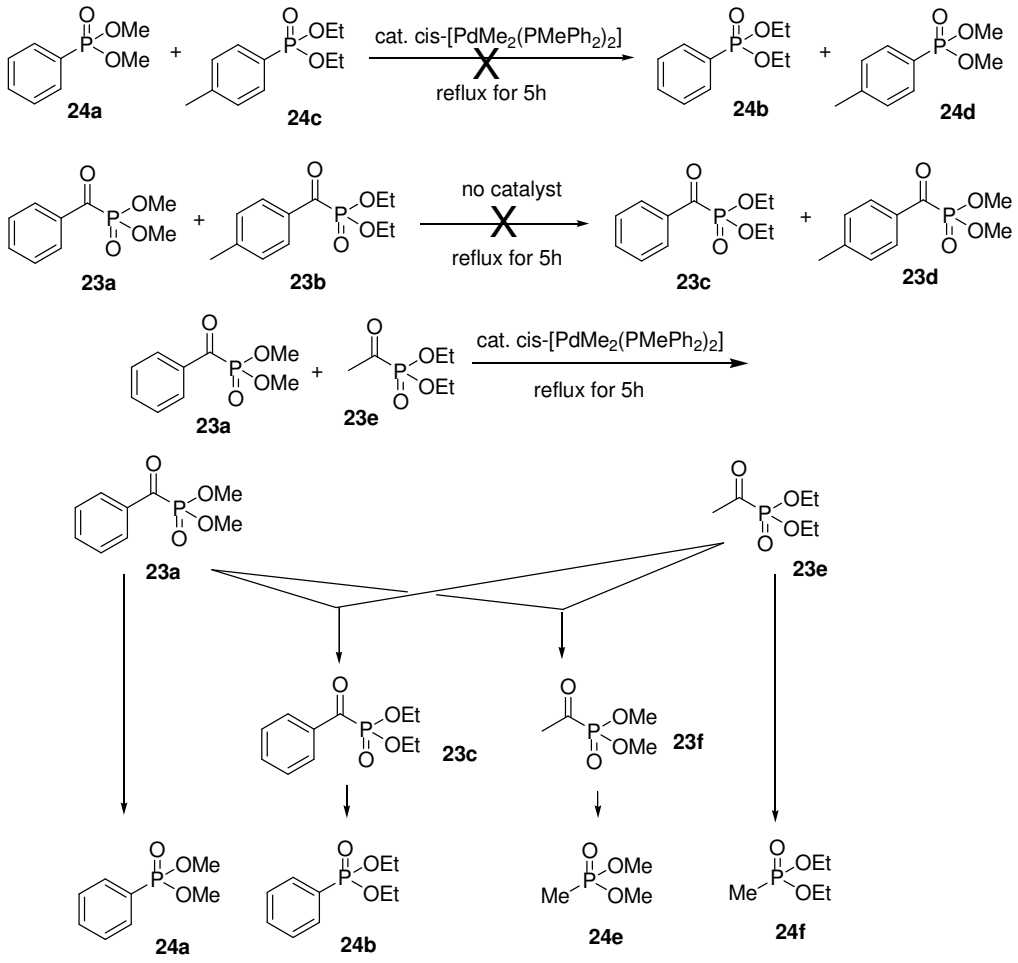
Scheme 7 Decarbonylation of acyl phosphonates

In a crossover experiment including (Ph)C(O)P(O)(OMe)$_2$ **23a** and (p-MeC$_6$H$_4$)C(O)P(O)(OEt)$_2$ **23b** four products are isolated in almost equal amounts (Scheme 8).



Scheme 8 Crossover decarbonylation

After several crossover experiments (Scheme 9), it is concluded that prior to decarbonylation, a metathesis reaction occurs between two α-ketophosphonates [6]. After the crossover experiment involving $MeC(O)P(O)(OEt)_2$ **23e** and $(Ph)C(O)P(O)(OMe)_2$ **23a**, $MeC(O)P(O)(OMe)_2$ **23f** is detected from the reaction mixture. This is evidence of the metathesis reaction. $PhC(O)P(O)(OEt)_2$ **23c** is not formed because decarbonylation rate of aroylphosphonates are greater than that of aliphatic phosphonates. But, its decarbonylation product **24b** is detected (Scheme 9).

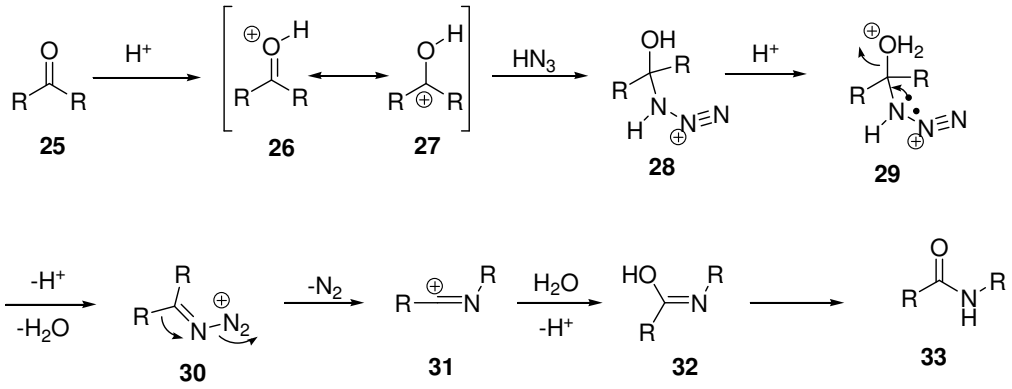


Scheme 9 Several crossover experiments on decarbonylation

1.1.3 Schmidt Reaction of α-Ketophosphonates

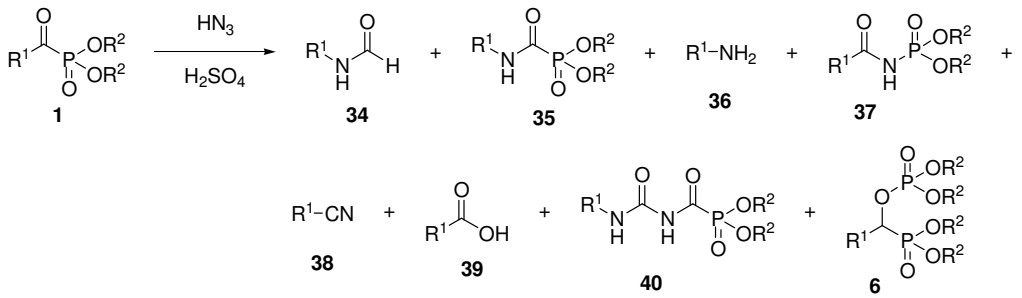
In 1994, Sprecher et al. reported Scmidt reaction of dialkyl acyl phosphonates (Scheme 11) [7]. Schmidt reaction is the acid-catalysed reaction of hydrogen azide with electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes. After a rearrangement and extrusion of N_2, amines, nitriles, amides or imines are produced.

In the reaction with ketone, azide attacks to carbonyl group to give the azidohydrine intermediate. After the elimination of water, the formed intermediate rearranges and water adds and tautomerization gives the amide (Scheme 10).



Scheme 10 Schmidt reaction of a ketone

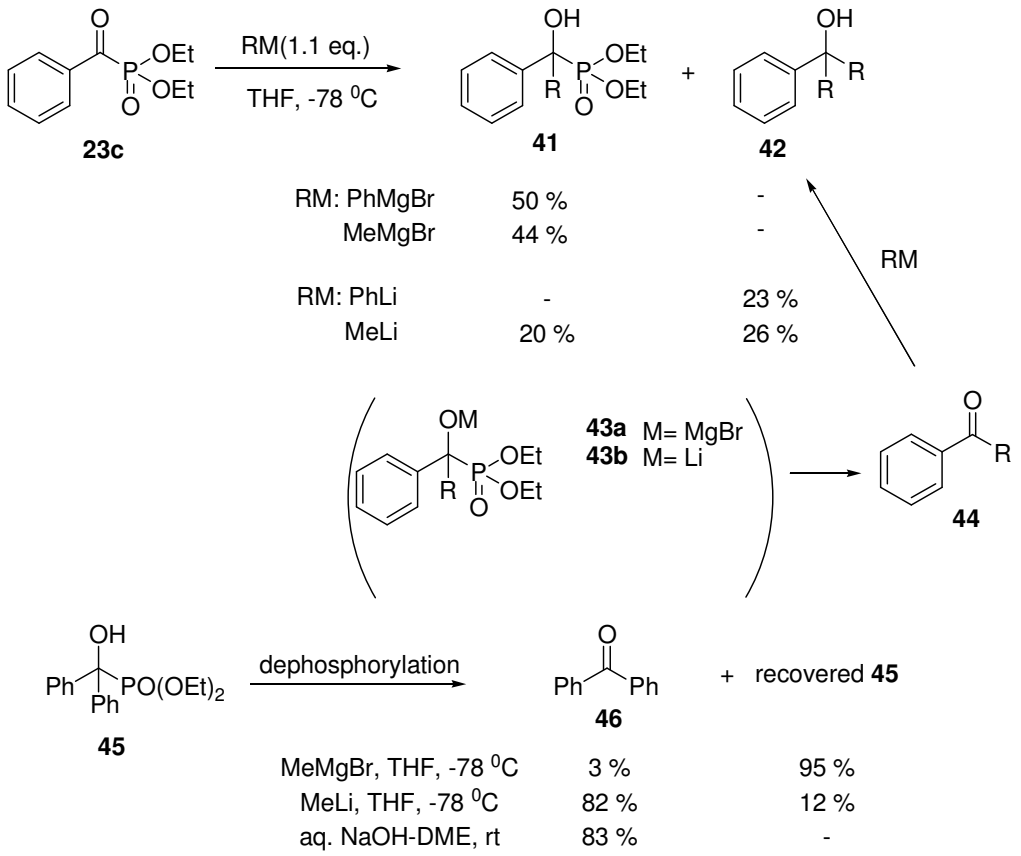
Reaction of hydrogen azide with α-ketophosphonates in conc. H_2SO_4 at 0 ^oC gives eight kinds of products (Scheme 11). Product distribution depends on both R^1 and R^2. According to nature of R^1 and R^2, yields of products change and in some cases they are not formed.



Scheme 11 Schmidt reaction of acyl phosphonates

1.1.4 Reactions of α-ketophosphonates with Grignard and Organolithium Reagents

Reactions of acylphosphonates with Grignard and organolithium reagents give corresponding α-hydroxy phosphonates and ketones [8]. The reactions are carried out in THF at -78 ^{o}C. Grignard reagents give corresponding α-hydroxy phosphonates whereas organolithium reagents produce corresponding ketones. The difference is explained by the intermediates **43a** and **43b**. The **43b** is more unstable than **43a** and rapidly decomposes to ketone. These ketone reacts rapidly with excess organolithium reagents to yield quarternery alcohols. This consideration is confirmed by treatment of α-hydroxy phosphonate with MeMgBr, MeLi and aq. NaOH-DME (Scheme 12).

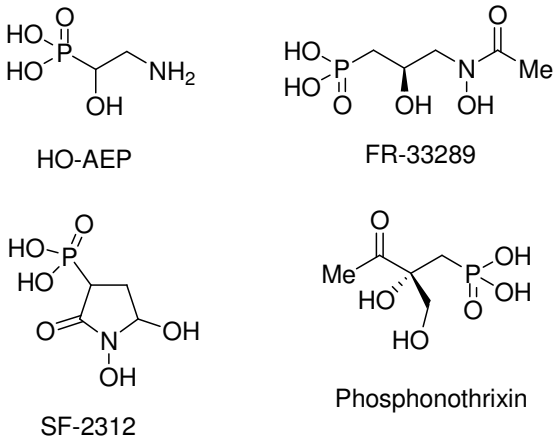


Scheme 12 Reactions of α-ketophosphonates with Grignard and Organolithium Reagents

1.2 α-Hydroxy Phosphonates

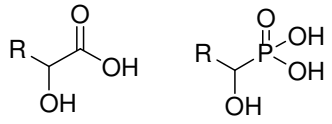
Hydroxy phosphonic acids have an important area in chemistry and biology due to their biological activities. Some of hydroxy phosphonic acids exists in nature. The first natural organophosphorus compounds having C-P bond were discovered by Horiguchi and Kandatsu in living organisms in 1959 [9]. 1-Hydroxy-2-aminoethylphosphonic acid (HO-AEP), 3-(N-acetyl-N-hydroxyamino)-2-hydroxypropylphosphonic acid (FR-33289), 1,5-dihydroxy-2-oxopyrrolidin-3-ylphosphonic acid (SF-2312), phosphonothrixin are well-known natural hydroxy

phosphonic acids (Scheme 13) [10]. Many of these compounds have biological activities such as antibacterial, antiviral and antitumour agents, antibiotics, enzyme inhibitors, amino acid mimetics and pesticides [11].



Scheme 13 Some natural hydroxy phosphonic acids

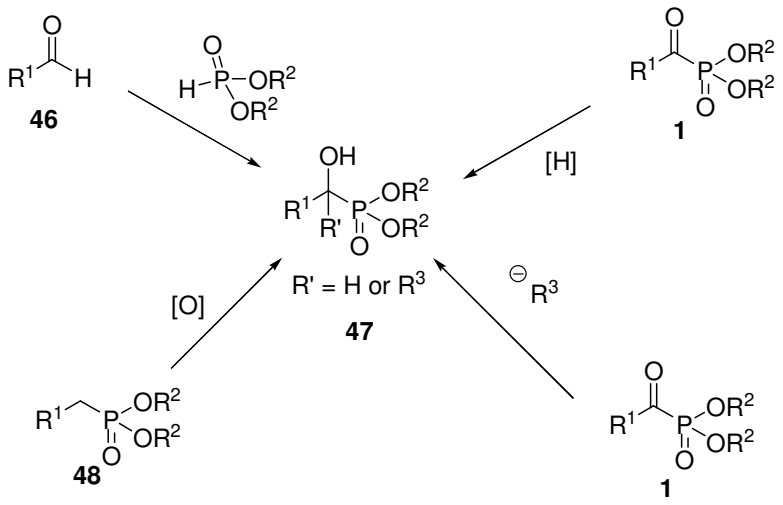
Hydroxy phosphonates resembles structurally to biologically important phoshate with P-O bond. α-Hydroxy phosphonic acids are structural analogs of α-hydroxy acids (Scheme 14). These two properties make hydroxy phosphonates important molecules. α-Hydroxy phosphonic acids can inhibite activities of enzymes or receprors with which corresponding natural α-hydroxy acids interact [12].



Scheme 14 Structural anology between α-hydroxy carboxylic and phosphonic acids

Due to their biological properties, there are a great effort to synthesize α-hydroxy phosphononates in last decade [13]. There are a variety of methods to get α-hydroxy phosphononates. We can divide these methods into main four parts: 1) Phospho-

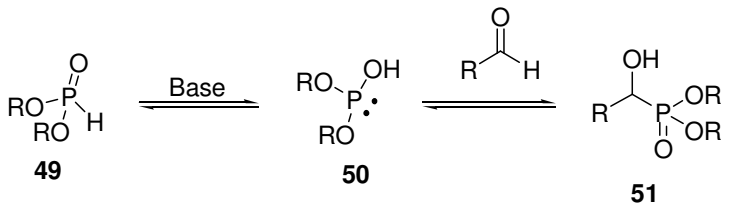
aldol condensation; 2) The reduction of keto phosphonates; 3) Oxidation of alkylphosphonates; 4) Addition of carbon nucleophiles to carbonyl group of acyl phosphonates (Scheme 15).



Scheme 15 General methods for synthesizing α-hydroxy phosphonates

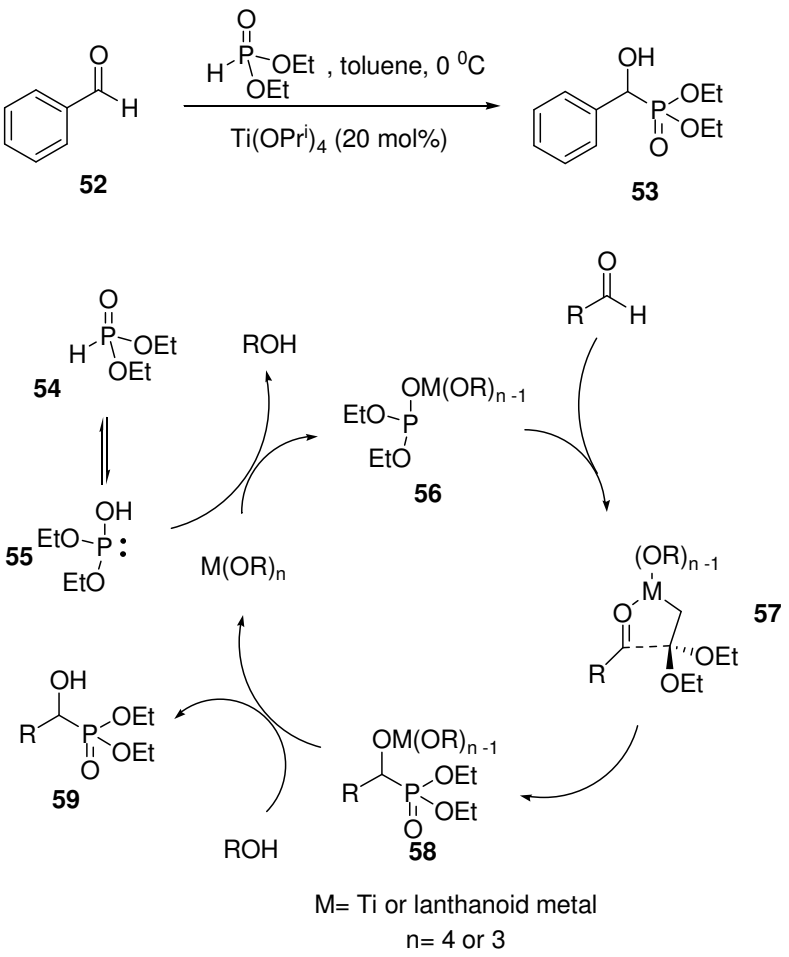
1.2.1 Phospho-aldol condensation

Phospho-aldol reaction is the reaction of aldehydes with dialkyl phosphite to give α-hydroxy phosphonates [14]. Dialkyl phosphites exists in two tautomeric forms. In the presence of a base, predominant tautomer **49** shifts to nucleophilic tautomer **50**. This tautomer is more nucleophilic towards to electrophiles. The main contribution to new C-P bond formation in Pudovik reaction becomes from the second tautomer (Scheme 16).



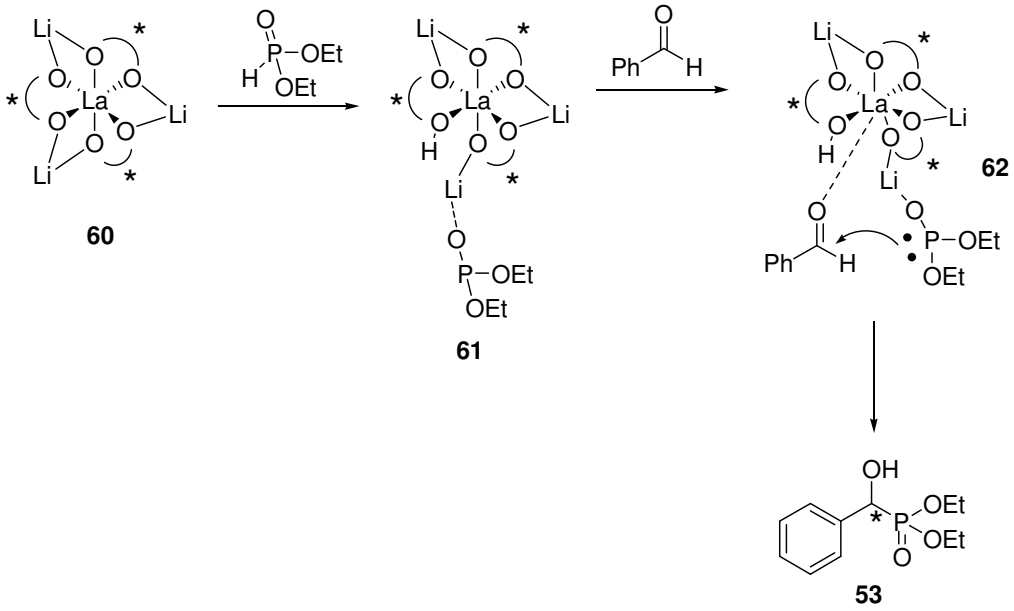
Scheme 16 Phospho-aldol reaction

Suitable activation of the phosphites by means of bases leads to phospho-aldol reaction. Shibuya and coworkers reported that lanthanoid and titanium alkoxides catalyze the phospho-aldol reaction (Scheme 17) [15]. It is known that lanthanoid and titanium alkoxides are weak bases. Alkoxides give ligand-exchange reaction with phosphites. Aldehyde carbonyl cordinates to metal in the organometallic phosphorus species. By this, a dual activation occurs. After that, phosphorus adds to aldehyde to give corresponding α-hydroxy phosphonates.



Scheme 17 Titanium alkoxide catalyzed phospho-aldol reaction

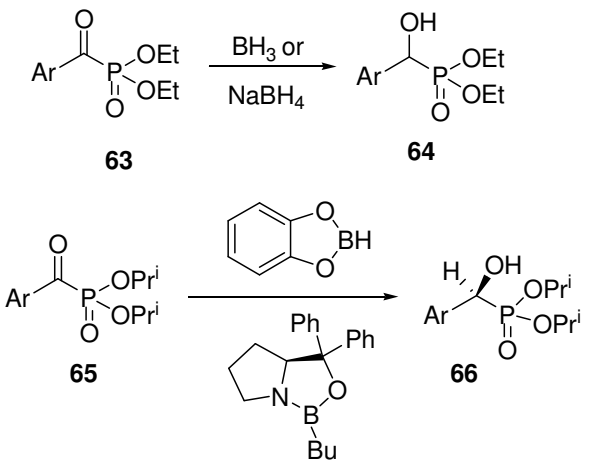
In the same work, Shibuya et al. performed the same reaction with chiral titanium and lanthanoid alkoxides based on (Scheme 18). Titanium and lanthanoid alkoxides are modified by tartarate and binaphtol derivatives, respectively. Enantioselectivity for the reactions depends on the electron density of aromatic ring. Electron rich aldehydes, *p*-anisaldehyde and *p*-tolualdehyde, give the enantioselectivities of 82 and 58% ee, respectively. On the other hand, neutral, benzaldehyde, and electron deficient aldehydes, *p*-chlorobenzaldehyde, proceeds with low enantioselectivities of 20 and 17%, respectively. Possible mechanism of La-Li-(*R*)-BINOL catalyzed reaction is shown in scheme 18.



Scheme 18 Enantioselective phospho-aldol reaction

1.2.2 Reduction of α-Ketophosphonates

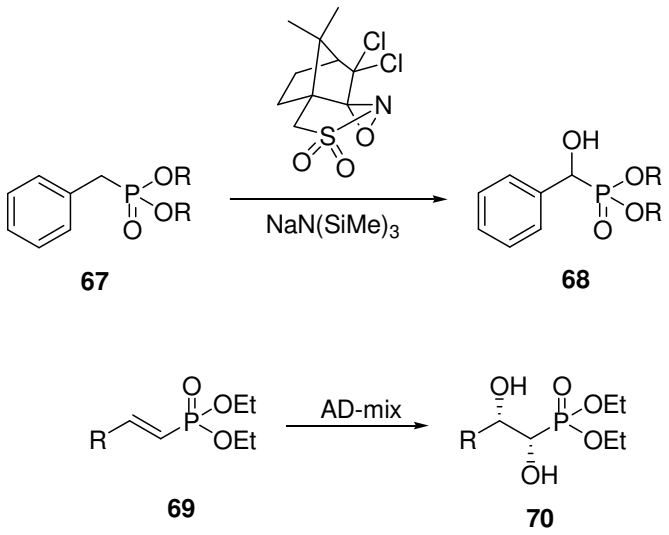
Reduction of α-ketophosphonates is a convienent method to access α-hydroxy phosphonates. The reduction can be performed by BH_3 or $NaBH_4$ (Scheme 19) [16, 17]. α-Hydroxy phosphonates are synthesized enantioselectively with chiral boran catalysis (Scheme 19) [18]. Borane or catecholborane controlled by (S)-oxazaborolidines reduces diisopropyl α-ketophosphonates to (S)-1-hydroxy benzylphosphonates with 53-83% enantiomeric excess.



Scheme 19 Synthesis of α-hydroxy phosphonates via reduction

1.2.3 Oxidation of Alkyl and Vinyl-phosphonates

Oxidation of alkyl and vinyl phosphonates a usefull method for synthesizing of α-hydroxy phosphonates (Scheme 20). Oxidation of benzyl phosphonates with oxaziridines give the corresponding α-hydroxy phosphonates [19]. Oxidation of vinylphosphonates with AD-mix-α or AD-mix-β produces α,β-dihydroxy phosphonates with high enantioselectivities [20]. The highest enantiomeric excess is obtained from β-aryl vinyl phosphonates.

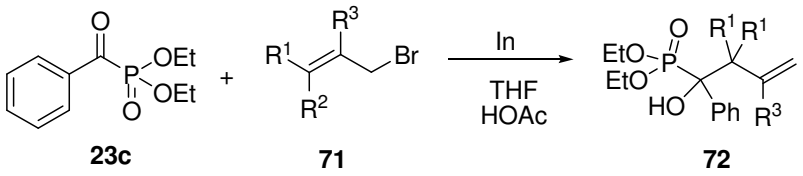


Scheme 20 Synthesis of α-hydroxy phosphonates via oxidation

1.2.4 Addition of Carbon Nucleophiles to α-Ketophosphonates

Phosphonate group in the α-ketophosphonates has electron withdrawing properties and enhances the electrophilicty of carbonyl group. By addition of suitable carbon nucleophiles to carbonyl group, quarternery α-hydroxy phosphonates are obtained. Hard nucleophiles like organolithium compunds cause cleavage of P-C bond [8].

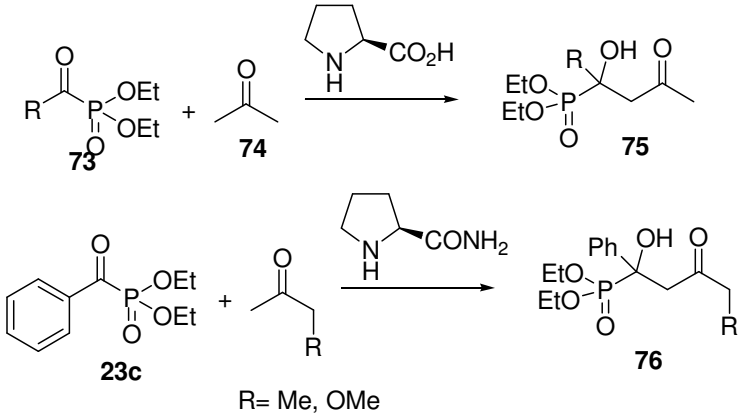
Wiemer et al. reported allylic addition to α-ketophosphonates by means of allylic bromide in the presence of indium metal (Scheme 21) [21]. The reaction is carried out in THF in the presence of acetic acid. The target compounds are obtained in excellent yields in these conditions. The scope of the reaction is quite wide. The method works with both aliphatic and aromatic phosphonates. Also, the reaction proceeds with crowded allyl bromides with high level of yields.



23c **71** **72**

Scheme 21 Allylation of acyl phosphonates

Another method to get quarternery α-hydroxy phosphonates is aldol condensation of α-ketophosphonates with acetone catalyzed by L-proline (Scheme 22) [22]. L-proline and proline based organocatalysts have attracted great attention since 2001 [23]. In aldol reaction catalyzed by organocatalyst, while donors can be ketone or aldehydes, acceptors are mainly aldehydes. In their work, Samanta et al. take α-ketophosphonates as acceptor and aceton as donor. Highest yields and enantioselectivities are obtained in neat conditions. Both aliphatic and aromatic α-ketophosphonates undergo the reaction with moderate to high yields and with high enetioselectivities. 2-Butanone and methoxyacetone participate in this reaction when L-prolinamide is used as the catalyst. The reaction is regioselective: one regioisomer is formed.



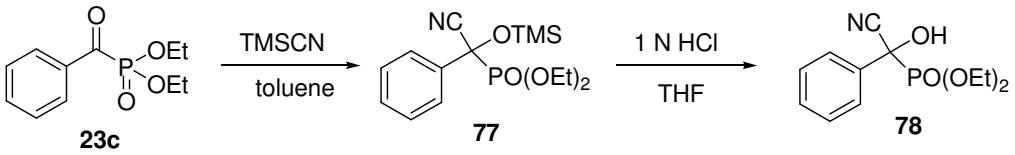
73 **74** **75**

23c **76**

R= Me, OMe

Scheme 22 Aldol condensation of acyl phosphonates

Also, our group described a new method for synthesizing α-hydroxyphosphonates [24]. The reaction of acyl phosphonates with trimethylsilyl cyanide give the trimethylsilyloxycyanophosphonates (Scheme 23). The reaction proceeds quantatively without any catalyst in various solvents. The protected product can be hydrolyzed to α-hydroxyphosphonates with 1 N HCl.

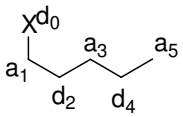


Scheme 23 TMSCN addition to acyl phosphonates

1.3 Polarity Synthons and Umpolung Reactivity

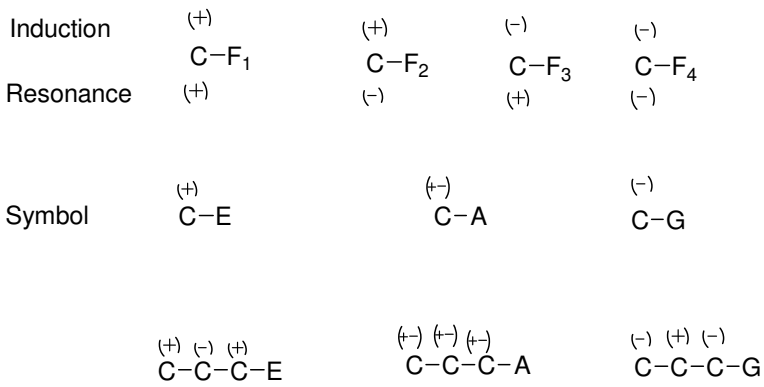
Most of organic reactions producing C-C bonds are polar: a negative carbon atom of one reagent combines with a positive carbon atom of another reagent. These negative and positive polarities are called donor synthones and acceptor synthones, respectively [25].They are resulted from functional groups.

Most of the target molecules in organic synthesis contain heteroatoms as functional groups. These heteroatoms impose charge affinity patterns trough carbon skeleton. Heteroatoms in organic compounds (N, O, S and halogens) are more electronegative than carbon atom. A carbon atom attached to one of these atoms is charged positively and it is an acceptor. Next carbon aton is negatively charged and it is a donor. Polarity synthons are numbered according to relative positions to functional group (Scheme 24).



Scheme 24 Polarity synthones of a carbon skeleton

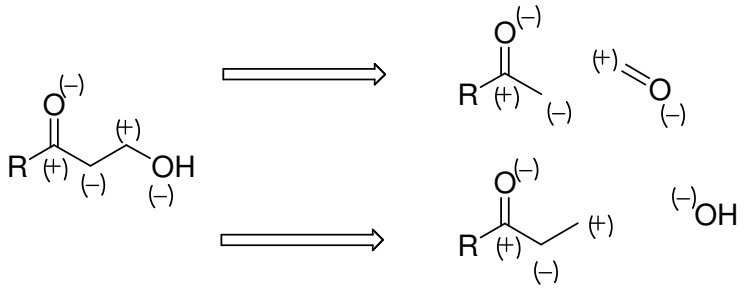
It is possible to generalize the polarity synthones-functional group relationships [26]. Functional groups (FG) interact inductively or mesomerically with the carbon atom to which they are bounded. Inductive and mesomeric interactions are independent so the total reactivity of FG can be divided to four classes. According to this classification, FGs can act as electrophilic, nucleophilic or amphilic. These functions and their charge affinity patternscan be seen in Scheme 25.



Scheme 25 Generalization of the polarity synthones-functional group relationships

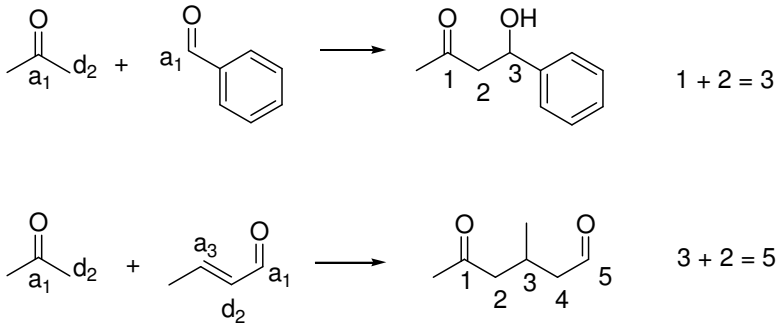
Common E functions are =O, -OR, =NR, $=NR_2$, and halogens. Common G functions are organometallic, orgasilicon and organoboran reagents. A functions are usually more complex FGs composed of polyatomic assemblages of nitrogen, oxygen or their heavier relatives P, S, As or Se. A very common A function is $–NO_2$ that can act as both an electrophile and nucleophile at the point of attachment depending on the reaction conditions.

In retrosynthetic analysis, the target molecule can be disconnected by using polarity synthons to get starting materials via polar coupling process. Hydroxy ketone is a good example to understand this process (Scheme 26).



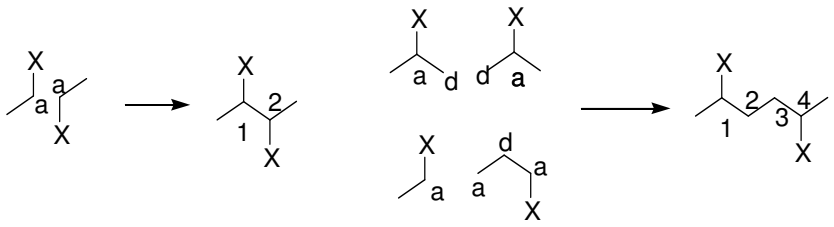
Scheme 26 Retrosynthetic analysis of a β-hydroxy ketone

In normal polarity synthons, as a cosequence and a limitation, after the formation of new C-C bond, the distance between functional groups in new compound is determined by the sum of numbers of acceptor and donor synthons (Scheme 27) [25b].



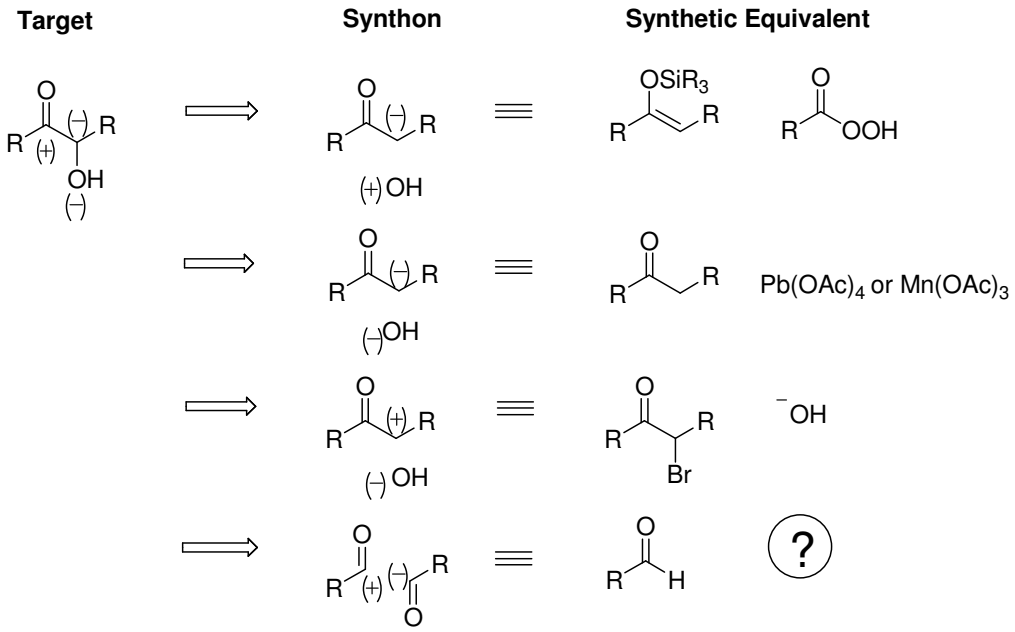
Scheme 27 Formation of odd bifunctional products

Normal reactivity patterns does not give 1,2-, 1,4-, ..., 1,2n- bifunctional products. To get such a product, we couple two carbon atoms with same reactivity (Scheme 28).



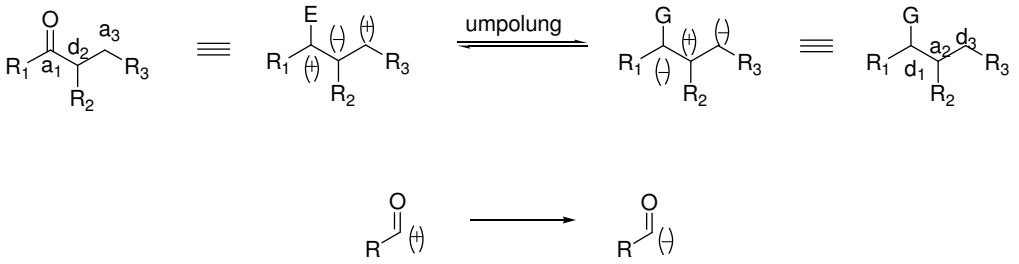
Scheme 28 Formation of even bifunctional products

It is obvious that one of the reactivity of the carbon atom should be changed. It gives flexibilty to synthesise of 1.2n-bifunctional groups containing target molecules. The importance of the changing of the polarity of one reagent can be understood by examining α-hydroxy ketones. Several disconnections produce a variety of synthones (Scheme 29). Last synthones are only avaliable after proper synthetic operations on the carbonyl component. Among these synthons, the last one is the most interesting one because it requires a inversion of the charge affinity pattern of one of the carbonyl groups after a certain transformation.



Scheme 29 Possible disconnections of α-hydroxy ketones

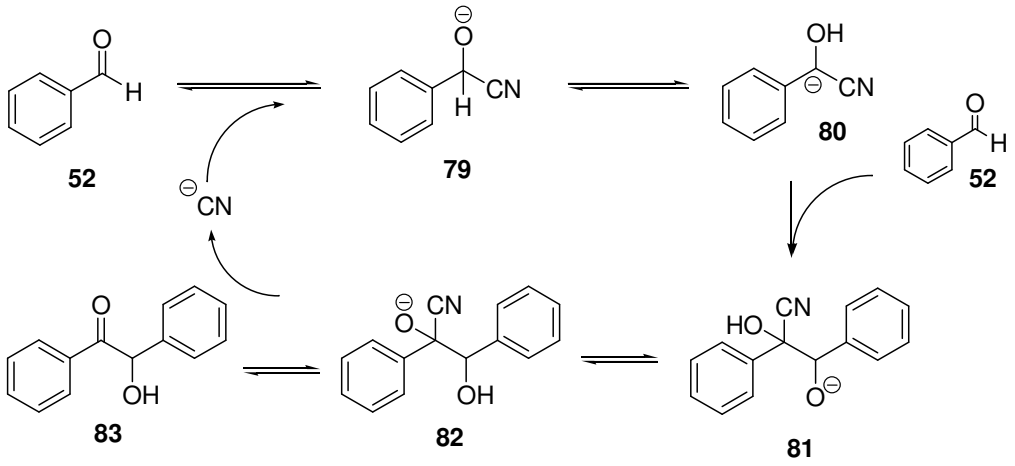
The inversion of charge affinity patterns is called *umpolung*. Synthetic operations that convert electrophilic carbonyl functions to carbanion stablizing G functions can establish an equilibrium between electrophilic carbonyl (a1) and unstable "carbonyl anion" (d1) (Scheme 30).



Scheme 30 Umpolung reactivity

1.3.1 Cyanide Ion Catalyzed Benzoin Condensation

Liebig and Wöhler discovered clssical benzoin condensation reaction more than a century ago [27]. The mechanism of the reaction was established by Lapworth in 1903. In the excepted mechanism, cyanide ion has a key role. First, it is a good nucleophile with cylindrical shape and attacks to aldehyde to form cyanohydrine. Second, it stabilizes adjusent carbanion. Finally, it is leaving group and at the last step, it reenters to catalytic cycle (Scheme 31).



Scheme 31 Mechanism of classical benzoin condensation

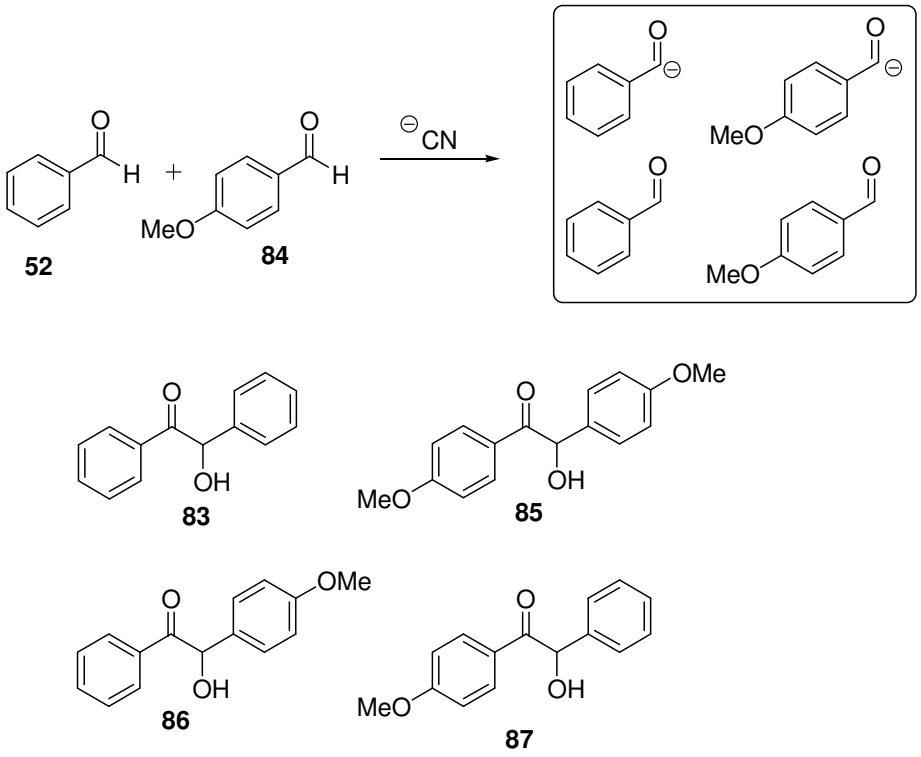
Schowen [28] reinvestigated the mechanism of the benzoin reaction and obtained information about kinetics of every single step. The initial step is addition of cyanide ion to benzaldehyde to form a new C-C bond wihch is stronger than C=O π-bond. Furthermore, solvation of alkoxide compared to solvation of cyanide ion is more favorable in terms of energy consideration. Second step is formation of critical acyl anion equivalent. Although how it form is not exactly known, it is assumed that bimolecular hydrogen transfer between alkoxide and solvent molecule is favored over 1,2-H shift. Then, acyl anion equivalent attacks to another benzaldehyde and at the last step, cyanide ion is released to catalytic cycle to produce benzoin.

Benzoin condensation is a useful method for synthesizing α-hydroxy ketones. However, it has several drawbacks. First, its scope is limited to aromatic aldehydes. It does not work with aliphatic aldehydes. Aromatic aldehydes with strong elelctron-donating and electron-withdrawing substituents do not give considerable yields under the classical conditins. The reason is reversibility of each single step in the mechanism of benzoin reaction.

The most important drawback of the benzoin reaction is selective synthesis of unsymmetrically substituted benzoin derivatives are nearly impossible. There exists several reasons. Firstly, generation of acyl anion equivalent is required for the

reaction. It is obvious that two different acyl anion equivalent will be generated from the mixture of two differen aldehydes in the benzoin conditions. The ratios of these acyl anion equivalents depends on rates of proceding steps. Furthermore, there will exist two different acceptor aldehydes for both acyl anion equivalents. If we assume that rate constants of all steps for both aldehydes are the same, there will be four products in equal amounts.

Product distribution does not only depend on kinetics of reaction steps. Benzoin reaction is a reversable process. According to this, product distribution depends on thermodynamic stabilities of products. The most stable product will be dominant. Benzoin isomers with aromatic rings substituted with electron-donating groups on the carbonyl sides are more stable than on the hydroxyl group side. If we desire to synthesize benzoin **86**, we should mix benzaldehyde and 4-methoxy benzaldehyde. It is hard to predict product ratios. But, it can be said easily the desired benzoin will be minor component since isomeric benzoin **87** is thermodynamically more stable (Scheme 32).



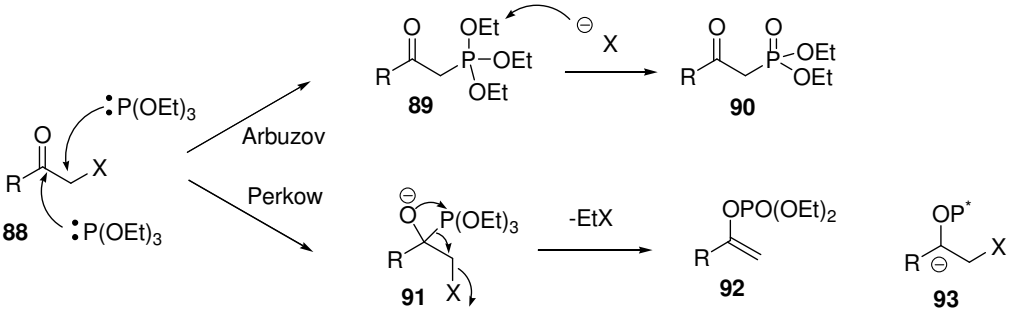
Scheme 32 Possible benzoin products of two aldehydes

To overcome drawback of the benzoin reaction mentioned above, chemists have developed a variety of methods to generate acyl anion equivalent controlling kinetically.

1.3.2 Umpolung Reactions with Phosphonates

Phosphorous has the ability of migration both from carbon to oxygen and from oxygen to carbon [29].

A well-known example of migrating ability of phosphorous is Perkow reaction [30]. Although its mechanism is not known exactly, it is generally accepted that a trivalent-phosphorus ends up as a pentavalent-phosphorus via a shift of phosphorus from carbon to oxygen. Perkow reaction competes with the classical Arbuzov reaction and mostly dominates the main reaction course. Mechanism of Perkow reaction is generally represented as in Scheme 33.

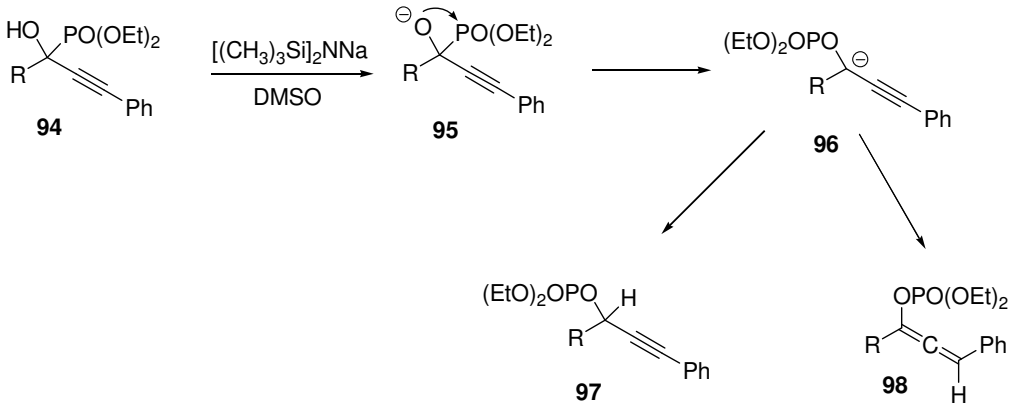


Scheme 33 Mechanisms of Perkow and Arbuzov reactions

The route of Perkow reaction inludes the rearrangement of phosphorous from carbon to oxygen yielding enol ether by elimination of X. Also, one can claim that mechanism of the Perkow reaction goes on an intermediate like **93**. Intermediate **93** is actually an acyl anion equivalent eliminating X. It is obvious that replacing

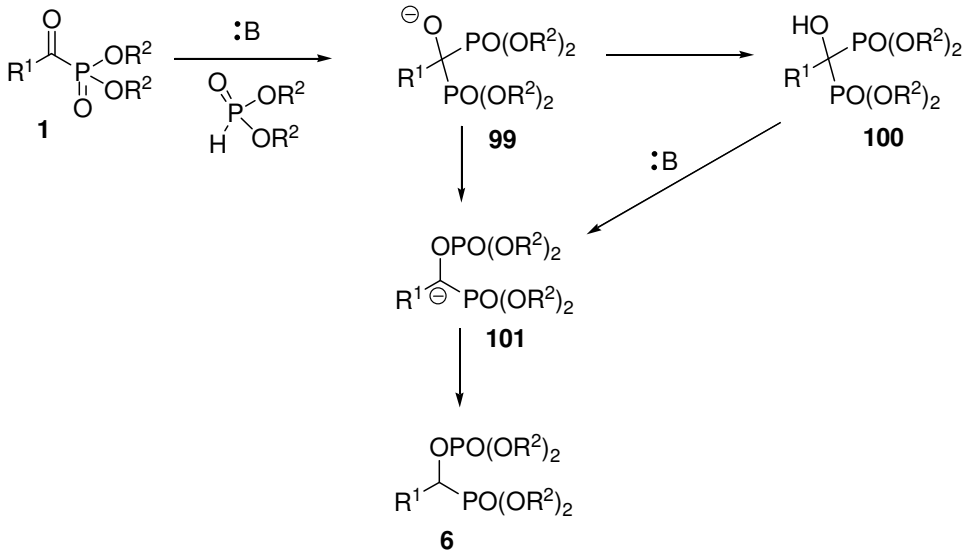
carbon bearing the leaving group with a carbanion stabilizing group like cyanide or phosphonate can provide a new generation of acyl anion precursors.

Base promoted migration of phosphorus from carbon to oxygen has been reported many times. Deprotonation of α-hydroxyphosphonate **94** leads such a rearrangement resulting in a d1 synthon **96** [31]. Protonation of **96** mainly occurs at the γ- position giving **98**. Same reaction sequence provides a mixture of **98** and **97** in methoxide/methanol (Scheme 34). This example shows the tendency of alkoxides of type **95** undergoing phosphonate-phosphate rearrangement.



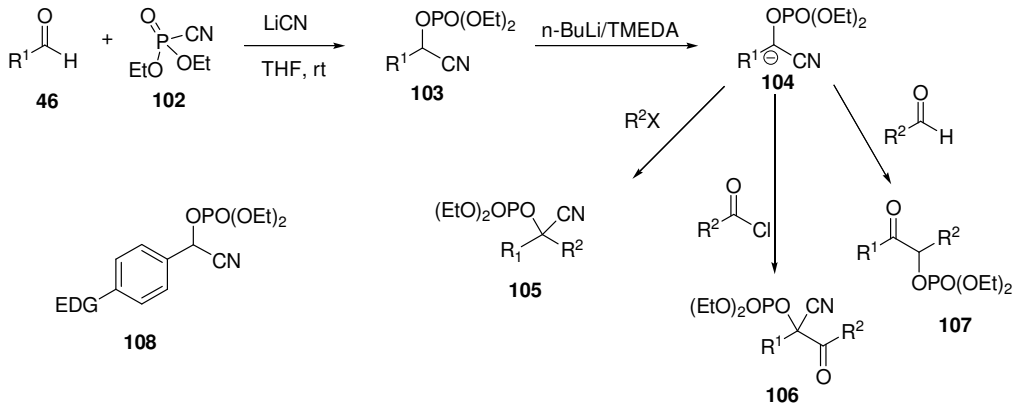
Scheme 34 Phosphonate to phosphate rearrangement

Another example of phosphonate-phosphate rearrangement is in the synthesis of α-hydroxyalkylidenediphosphonate esters **100** (Scheme 34). Synthesis of these compounds by the addition of dialkyl phosphites to acylphosphonates **1** under basic conditions were reported by McConnell and Coover [32]. Later it was shown that the product of this reaction was actually isomeric compound **6** [33]. It is formed from rearrangement of intermediate **99** to intermediate **100** before protonation to **100**. It was also shown that isolated **100** rearranges to **6** under basic conditions via the same intermediate **101**.



Scheme 34 Base promoted migration of phosphorous from carbon to oxygen

Kurihara et al. reported the use of derivatives of **103** as acyl anion precursors (Scheme 36) [34]. The cyanophosphates **103** were prepared by the reaction of aldehydes **46** with diethylphosphorocyanidate **102** and LiCN. Deprotonation of **103** to **104** and subsequent reaction with various electrophiles including alkylhalides, acylhalides and aldehydes yielded alkylated **105**, acylated **106** and acyloins **107** type products, respectively. Aliphatic derivatives of **103** were failed to give any product and only starting materials were recovered. Moreover electron donating group substituted **108** were reported to be unstable, thus, it was not useful for the generation of corresponding **104**.

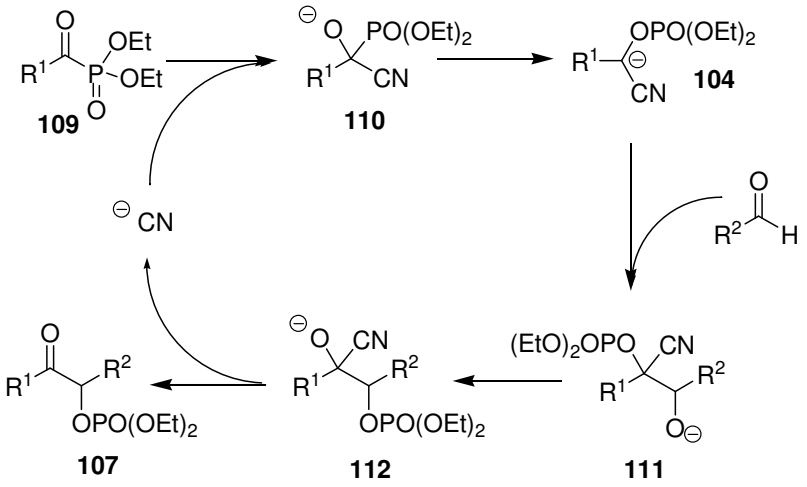


Scheme 36 Phosphate protected cyanohydrines as acyl anion precursors

1.3.3 Benzoylphosphonates as Acyl Anion Equivalent

In hand of these infornations, our group introduced acylphosphonates as new generation of acyl anion precursor in benzoin reaction [35]. Cyanide promoted rearrangement from phosphonate to phosphate give the corrosponding acyl anion equivalent. These acyl anion equivalents react with variaty of aldehydes to yield cross benzoin adducts. With this method, to synthesize a variety of aromatic-aromatic, aromatic-aliphatic, and aliphatic-aromatic acyloins is possible.

The mechanism is similar to classical benzoin reaction. The acyl anion equivalent is generated by the migration of phosphorous from carbon to oxygen after the addition of cyanide ion to carbony group. Reaction of this acyl anion equivalent with an aldehyde give the intermediate **111**. Retrocyanates following the 1-4 migration of phosphorous from O to O yields the benzoin adduct and close the catalytic cycle (Scheme 37).



Scheme 37 Mechanism of benzoin reaction of acyl phosphonates

The scope of the reaction for the synthesis of aromatic-aromatic benzoins are quite wide. The reaction runs with both electron rich and electron deficient aromatics in both acceptor and donor sides with good to excellent yields. Electron-rich 4-MeO-benzoylphosphonate reacts very slowly under the usual reaction conditions. Increasing the catalyst load from 10% KCN to 30% KCN results in a smooth transformation giving benzoin adducts in very good yields.

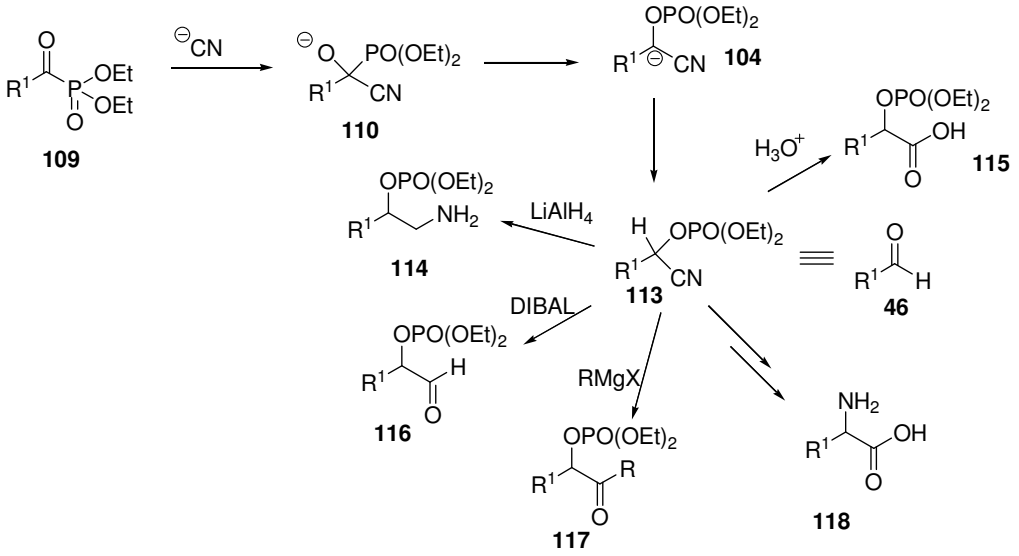
Reactions of aliphatic donors and acceptors with aromatic aldehydes and phosphonates, respectively, give acyloins. Due to their enolizable characters, the yields are low in the the same conditions as in aromatic-aromatic benzoins. The use of CsF (20%) and TMSCN (30%) instead of KCN increased the yields to good levels in the reactions between benzoylphosphonates and aliphatic aldehydes (cyclohexancarboxaldehdye and benzyloxyacetaldehyde).

In the case of reactions between aliphatic acylphosphonates and aromatic aldehydes, use of both KCN and CsF + TMSCN failed to give high yields. The use of 30% KCN and 30% 18-crown-6 in refluxing toluene provided better yields.

Compared to results reported by Kurihara et al., this method is superior. In Kurihara's work, aliphatic and elecrton rich aromatics failed to give corresponding benzoin products. However, cyanid catalyzed benzoin reactions of

acylphosphonates with aldehydes work with electron rich donors and both of aliphatic donors and acceptors.

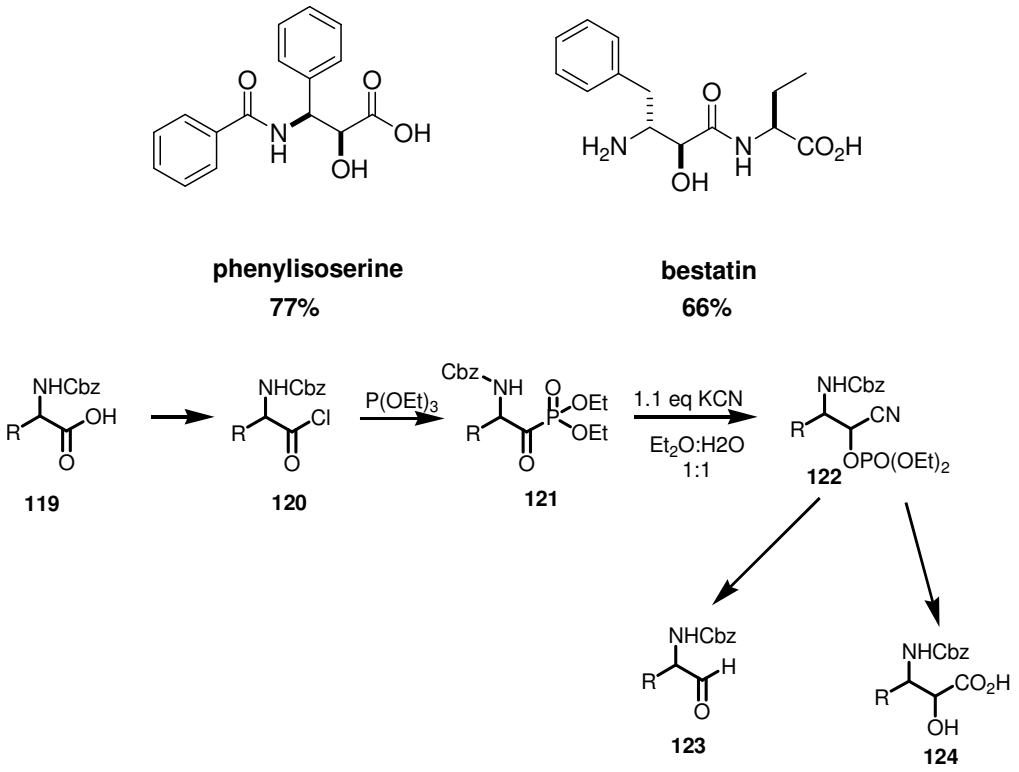
Protonation of acyl anion equivalent generated from acylphosphonates give valuable intermediates [36]. The main product is hydroxy protected cyanohydrines. From cyanohydrines, a variety of compounds can be syntesized (Scheme 38).



Scheme 38 Protonation of acyl anion equivalent and some transformations of the product

Acylphosphonates are easily synthesized from carboxylic acids and the protonation products lead to a common intermediate for the synthesis of α-amino aldehydes, α-hydroxy-β-amino acids, and diols.

α-Amino aldehydes and α-hydroxy-β-amino acids are highly important compounds. The latter can be found in the structures of Taxol's side chain, N-benzoyl-phenylisoserine, bestatin, and amprenavir. α-Amino aldehydes and α-hydroxy-β-amino acids can be synthesized from starting α-amino acids via protonation of acylanion equivalents generated from corrosponding acylphosphonates of α-amino acids (Scheme 39).



Scheme 39 Synthesis of some valuable compounds from α-amino acids

This method also provides reduction of carboxylic acids to aldehydes. The intermediate from protonation of acyl anion equivalents is equivalent to aldehyde under hydrolysis conditions. Usually, carboxylic acids are reducud to aldehydes via corrosponding esters or amides with DIBAL under water free conditions. This protonation strategy provides the direct reduction of carboxylic acids to aldehydes under aqueous conditions.

1.4 Aim of the Work

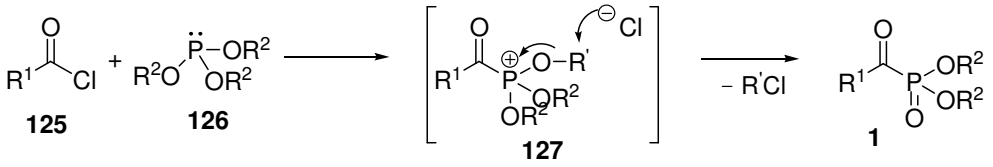
α-Hydroxy phosphonic acid derivatives are biologically very important molecules. They can act as enzyme inhibitors, antibacterial, antiviral and antitumour agents, antibiotics, and anti-HIV. Due to these great properties, many efforts are attempted to synthesize α-hydroxy phosphonates. Most of the methods give secondary α-hydroxy phosphonates. Few examples exist for tertiary α-hydroxy phosphonates. Thus, we aimed to synthesize tertiary α-hydroxy phosphonate from simple starting metarials.

CHAPTER 2

RESULTS AND DISCUSSION

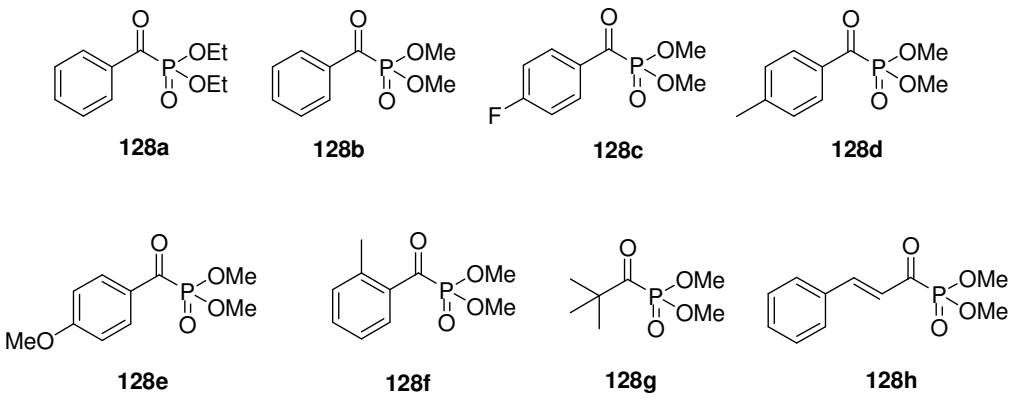
2.1 Synthesis of Acyl phosphonates

Acyl phosphonates are easily accessable compounds. The most convienent way to get these compounds is the well-known Arbuzov reaction between acyl chlorides and trialkylphosphites [37, 38]. Reaction proceeds via formation of unstable intermediate **127** that eventually leads to acylphosphonate (Scheme 40). Reaction is very exothermic. So, it is generally carried out at 0 ^{o}C in neat conditions. Once one of the reactants is solid, it is carried out at room temperature or in organic solvents. Alkyl chloride is the only side product.



Scheme 40 Synthesis of acyl phosphonates

These compounds were synthesized via classical Arbuzov route according to literature procedures. Purification was done by vacuum distillation. Product of type **128h** was problematics (Scheme 41). The Arbuzov reaction only gives low yields with considerable amount of side products. The reason is the activated olefin functionality that is susceptible to Michael type addition of triethylphosphite. An alternative high yield route to these compounds is oxidation of the corresponding α-hydroxyphosphonates [39]. α-Hydroxyphosphonates are easily synthesized by addition of phosphorus nucleophiles to corresponding aldehydes.



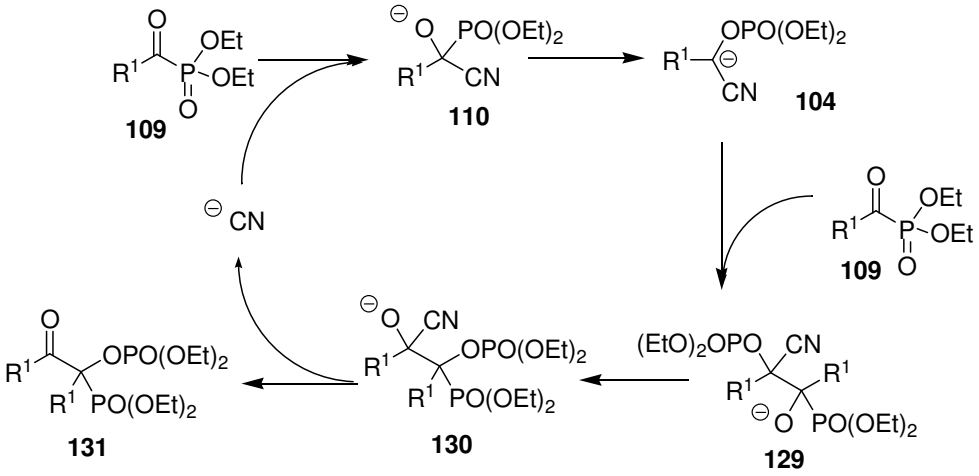
Scheme 41 Acyl phosphonates used in this study

Acylphosphonates can be synthesized in multigram quantities and very high yields from simple starting materials [37, 38]. The reactions were carried out under inert atmosphere. Their synthesis does not require any other special conditions or apparatus. Since they are sensitive to moisture, they should be stored under argon filled flasks to prevent decomposition or hydrolysis. Moreover, they can be handled on benchtop without a special precaution and even their TLC sample solutions are hydrolysed slowly. Their synthesis from carboxylic acids is highly interesting since there is vast amount of compounds in this oxidation states in nature. This also establishes a connection between acid oxidation state and acyl anion equivalents which generally obtained from aldehydes. At last phosphonate moiety in acylphosphonates provides a useful platform for fine tuning of their reactivity.

2.2 Cyanide Ion Catalyzed Self Condensations of Acylphosphonates

Acylphosphonates are precursor of acyl anion equivalents. In the presence of cyanide ion, nucleophilic acyl anion equivalent is generated [35]. At the same time, acylphosphonates are electrophiles [8, 21, 22]. Phosphonate group increases the reactivity of carbonyl group. Then, we proposed the idea of adding of acyl anion equivalent generated from acylphosphonate to another acylphosphonate in the

presence of cyanide. This self-condensation reactions of acylphosphonate would give tertiary α-hydroxy phosphonates. The mechanism is similar to benzoin reaction of acylphosphonates with aldehydes. First, cyanide promoted generation of acyl anion equivalent would ocur. Then, this anion would attack to another mole of acylphosphonate and sunsequent 1,4-migration of phosphate would provide the intermediate **130**. While cyanide is released to catalytic cycle, the target molecule would be formed (Scheme 42).



Scheme 42 Mechanism of self condensation of acyl phosphonates

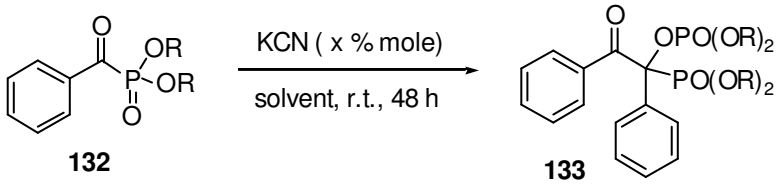
We started to investigate the reaction with diethyl benzoylphosphonate. The benzoin reaction of acylphosphonates gave best results in DMF. Hence, we carried out the reaction in this solvent with 1 mmole of diethyl benzoylphosphonate and 10 mol % of KCN at room temperature. The reaction proceeded smoothly. We monitored the reaction by TLC analysis and we terminate the reaction after two days. After work-up and purification processes, we obtained the target compound in 40 % yield.

We characterized our title compound by NMR analyses. In the ^{31}P-NMR, there are two signals. The signal at -5.58 belongs to phosphate group [O-PO(OEt)$_2$] whereas the other peak belongs to phosphonate group [C-PO(OEt)$_2$]. The existence of the

carbonyl group is observed by ^{13}C-NMR. It gives signal at 192,9 ppm. From the ^{1}H-NMR, there are two aromatic rings(two 2H and two 3H). There are four ethoxy group in the ^{1}H-NMR. Methylen groups of the ethoxy gives multiplet instead of quartet because it is splitted by P atoms. Also, they are diastereotopic protons. One of the ethoxy group gives signals at higher field compered to other three ethoxy groups. Probably, it is forced to over the aromatic ring and due to shilding effects it is shifted higher fields.

To test solvent effect, we performed the reaction in THF. We used 18-crown-6 as phase tarnsfer catalyst (PTC) due to low solubility of KCN. In THF, the reaction took place at longer time and the isolated yield was much lower. Then, we turned to DMF for further optimization.

To draw the yield to acceptable levels, we increased the catalyst loading to 30 mol %. A slight increase was observed. Then, we used dimethyl benzoylphosphonate which is stericially less hindred than diethyl benzoylphosphonate. Dimethyl benzoylphosphonate was found to be more efficient. However, yield was stil low (Table 1).



132 **133**

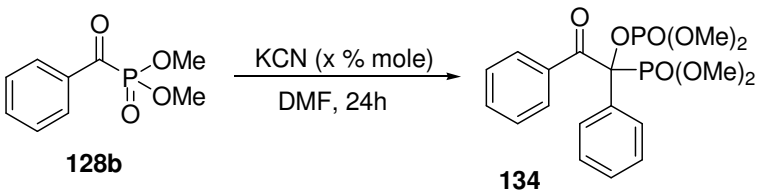
Table 1

entry	R	solvent	X % mole of KCN	yield
1	Et	DMF	20	40
2	Et	THF*	20	25
3	Et	DMF	40	42
4	Me	DMF	20	46

*18-crown was used as PTC.

The low yield is caused by steric hindrance at the reaction center. Both the acyl anion equivalent and the acceptor acyl phosphonates are stericially hindred because of crowded phosphate and phosphonate groups. This effect increases the activation energy of the reaction.

Next, we examined the effect of temperature on the reaction (Table 2). At higher temperatures, we can defeat the high activation energy caused by steric effects. To rise the temperature from room temperature to 40 ^{o}C increased the yield. Also, rising temperature shortened the reaction time. The reaction time is reduced to 24h. Then, we increased the temperature to 75 ^{o}C. A slight increase in yield was observed. When we used 40 mole % of KCN, yield rised to 62 %.



128b **134**

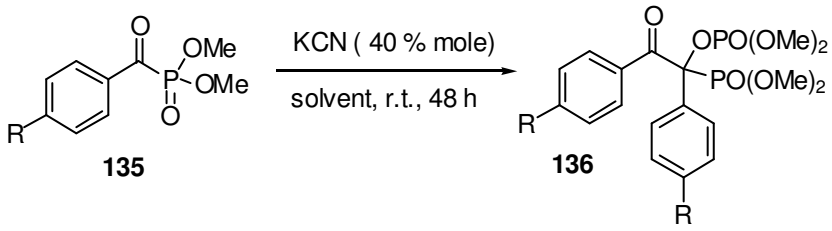
Table 2

entry	T (^{o}C)	x % mole of KCN	yield
1	rt	20	46
2	40	20	52
3	75	20	55
4	75	40	62

In long reaction time, α-(phosphoryloxy)benzylphosphonate was observed as side product. Reducing reaction time by increasing temperature diminshed the production of α-(phosphoryloxy)benzylphosphonate.

Next, we examined the scope of the reaction with substituted benzoylphosphonate. Para substituted benzoylphosphonates underwent the reaction. Whereas 4-

methoxybenzoylphosphonate was good substrate for this reaction, 4-fluorobenzoylphosphonate gave low yield. Also, 4-methylbenzoylphosphonate proceeded the reaction. 2-methylbenzoylphosphonate gave α-(phosphoryloxy)benzylphosphonate as dominant product. This was probably resulted from steric effects. Ortho substituted substrates are stericially more hindrance.

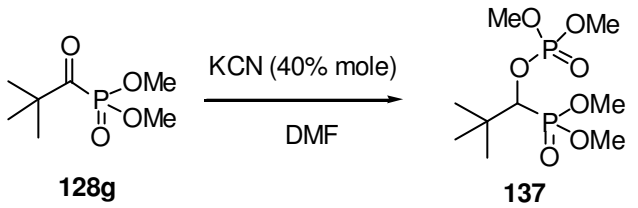


135 **136**

Table 3

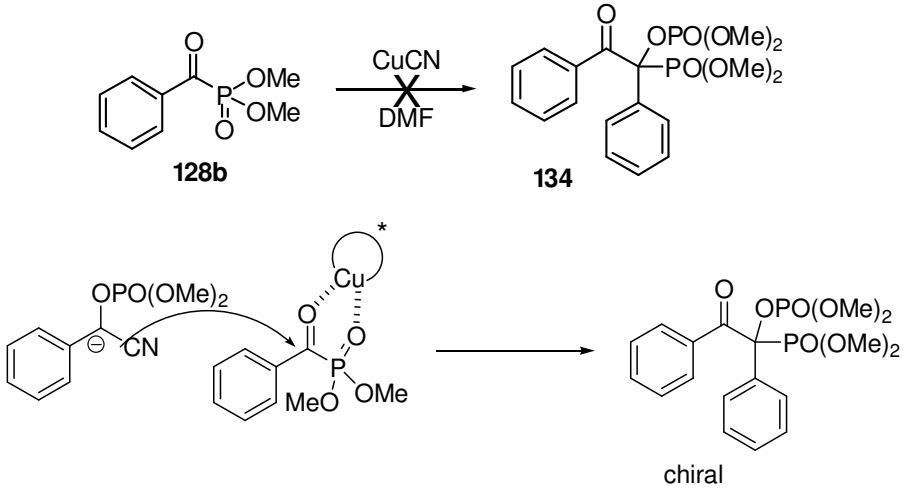
entry	R	yield
1	OMe	40
2	F	25
3	Me	42

We also examined aliphatic phosphonates. We selected dimethyl 2,2-dimethyl-propanoylphosphonate due to its non-enolazible character. Enolizable aliphatic phosphonates can give protonation product[36] as main product. Enolizable substrates have acidic protons. However, the only observed product was α-(phosphoryloxy)benzylphosphonate (Scheme 43). Aliphatic phosphonates are less reactive than aromatic phosphonates. Before the title compound was formed, the side product was produced.



Scheme 43 Reaction of dimethyl 2,2-dimethyl-propanoylphosphonate

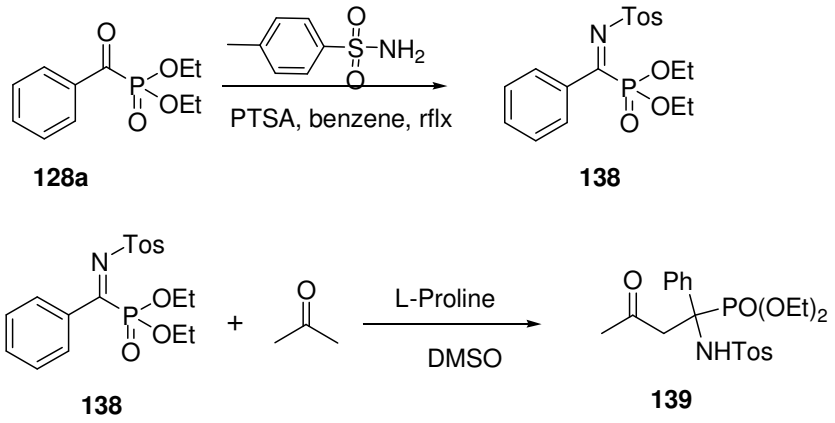
There are many reports about using chiral Cu-complexes as catalysts in asymmetric synthesis [40]. Hence, we used CuCN as catalyst. Our proposel was based on if CuCN catalyze the reaction we could use chiral ligands together with CuCN for enantioselective self-condensation reaction. Unfortunately, CuCN did not catalyze the reaction (Scheme 44). Starting metarial was almost recovered. The main reason why CuCN did not catalyze the reaction is CuCN is not dissolved in DMF.



Scheme 44 CuCN catalyzed reaction and proposed mechanism for chiral version

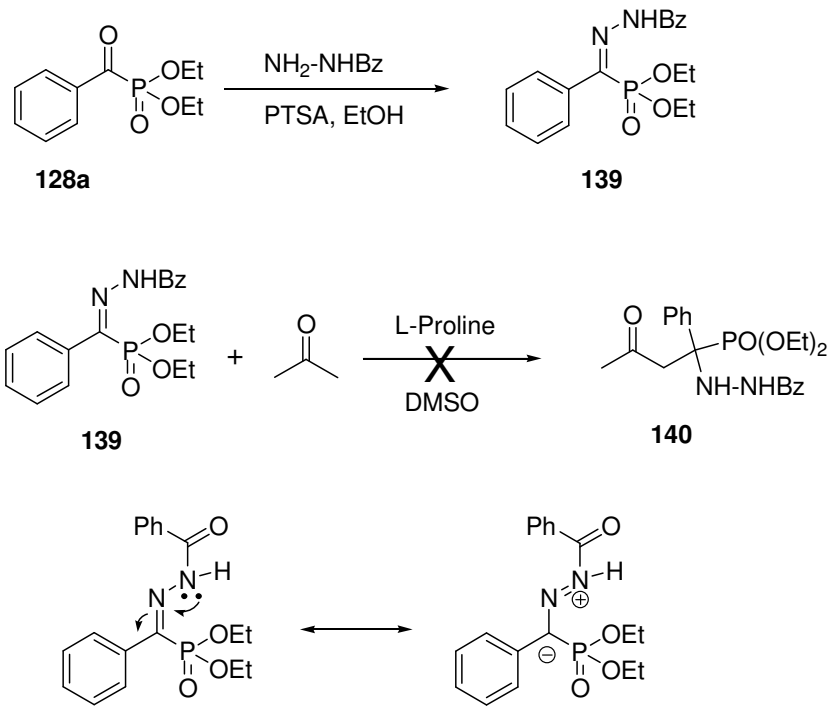
We also tried to synthesize α-amino phosphonate via proline catalyzed Mannich-type reaction (Scheme 45). Our initial attempts were focused on synthesis of N-tosyl imines derived from acyl phosphonates. We carried out reactions with diethyl benzoylphosphonates and p-toluenesulfonamide in the catalytic amount of PTSA in

benzene in reflux conditions. However, any reaction was not observed. To carry out reaction at higher temperature, we used toluene as solvent. Unfortunately, no reaction was observed. P-toluenesulfonamide is a weak nucleophile because nitrogen is attached to a strong electron withdrawing group. Also, there is a steric hindrance. These two reasons may cause the reaction did not proceed.



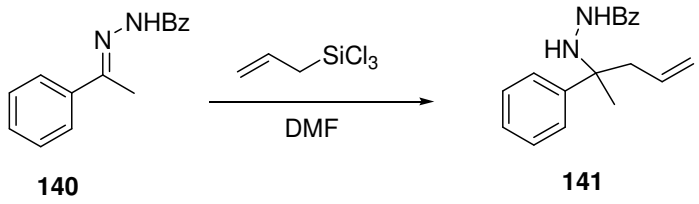
Scheme 45 Proposed pathway for α-amino phosphonate synthesis

From literature, it is known that acyl phosphonates can form hydrazones with substituted hydrazines [4]. The reaction of diethyl benzoyl phosphonate with N-benzoyl hydrazine gave the corresponding hydrazone. We carried out a reaction with 1 mmole of this hydrazine and 4 mmlole of acetone in DMSO in the presence of 20% mole of L-proline. However, the desired reaction did not proceed. To change solvent did not affect the reactivity. The reason is low reactivity of hydrazones. Resonance of the structure of the hydrazone explains this low reactivity (Scheme 46).



Scheme 46 Synthesis of N-benzoyl hydrazone of benzoyl phosphonate

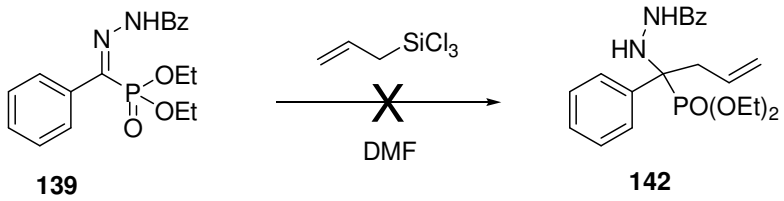
Allyl trichlorosilanes can be added to hydrazones in DMF (Scheme 47) [41]. DMF ccordinates to silicon atom and forms an intermediate with pentavalent silicon. This intermediate is very reactive to electrophiles.



Scheme 47 Allylation of ketone derived hydrazone

Then, we performed a reaction consisting 1 mmole of acyl phosphonate and 1.2 mmole of allyl trichlorosilane in DMF (Scheme 48). Acyl phosphonate was dissolved in DMF and allyl trichlorosilane was added dropwise. In the ^{1}H-NMR

spectra, typical signals of ethoxy groups of acyl phosphonates were not observed. The C-P bond was broken in the reaction medium.



139 **142**

Scheme 48 Reaction for allylation of benzoyl phosphonate derived hydrazone

CHAPTER 3

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts d are reported in ppm relative to C*H*Cl3 (1H: δ = 7.26) and *C*DCl3 (13C: δ = 77.0) as an internal standard; coupling constnats are reported in Hz. Column chromatography was conducted on silica gel 60 (mesh size 40-63 um). TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm).

3.1 Preparation of Acylphosphonates

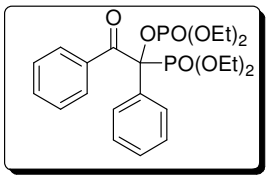
Acylphosphosphonates **128a-g** were synthesized according to literature procedures. Briefly 1 equiv. of neat triethylphosphite was added drop wise onto the neat acylchloride in a water bath under a positive inert atmosphere. After completion of the addition, resulting mixture was stirred at room temperature for 60 min. The products were purified by vacuum distillation.

3.2 General Procedure for Synthesis of α-hydroxyphosphonates

3.2.1 Synthesis of 1-(ethoxyphosphono)-2-oxo-1,2-diphenylethyl diethyl phosphate

13 mg of KCN was dried at 100°C under vacuum for 3 h and dissolved in dry DMF (1 ml). Then, 1 mmole (242 mg) of diethyl benzoylphosphonate was added. The reaction mixture was stirred for 2 days. The reaction was diluted with Et_2O and brine solution was added. The aquous phase was extracted wirh Et_2O three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced

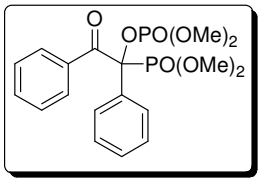
pressure. The crude mixture was purifed by flash column chromatography on silica gel with EtOAc as eluent. 97 mg of product was obtained.



1-(ethoxyphosphono)-2-oxo-1,2-diphenylethyl diethyl phosphate: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J*= 7.0 Hz, 3H); 1.17 (t, *J*= 7.0 Hz, 3H); 1.19-1.26 (m, 6H); 3.50-3.66 (m, 2H); 3.93-4.22 (m, 6H); 7.13-7.19 (m, 3H); 7.25-7.35 (m, 3H); 7.50 (d, *J*= 7.2 Hz); 7.58 (d, *J*= 7.6 Hz); ^{31}P NMR ($CDCl_3$) -5.58; 12.64.

3.2.2 Synthesis of 1-(methoxyphosphono)-2-oxo-1,2-diphenylethyl dimethyl phosphate

13 mg of KCN was dried at 100°C under vacuum for 3 h and dissolved in dry DMF (1 ml). Then, 1 mmole (214 mg) of dimethyl benzoylphosphonate was added. The reaction mixture was stirred for 2 days. The reaction was diluted with Et_2O and brine solution was added. The aquous phase was extracted wirh Et_2O three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purifed by flash column chromatography on silica gel with EtOAc as eluent. 98 mg of product was obtained.

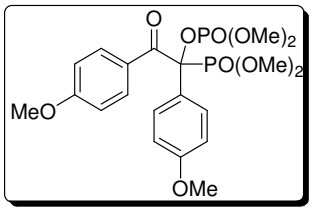


1-(methoxyphosphono)-2-oxo-1,2-diphenylethyl dimethyl phosphate: ^{1}H NMR ($CDCl_3$) δ 3.29 (d, *J*=11.5Hz, 3H); 3.67 (d, *J*=10.8Hz, 3H); 3.73 (d, *J*=11.6Hz, 3H); 3.79 (d, *J*=10.9Hz, 3H); 7.16-7.20 (m, 3H); 7.30-7.36 (m, 3H); 7.52 (d, *J*=7.2Hz, 2H); 7.61 (d, *J*=7.8Hz, 2H).

3.2.3 Synthesis of 1-(methoxyphosphono)-1,2-bis(4-methoxyphenyl)-2-oxoethyl dimethyl phosphate

26 mg of KCN was dried at 100°C under vacuum for 3 h and dissolved in dry DMF (1 ml). Then, 1 mmole (244 mg) of dimethyl p-methoxybenzoylphosphonate was

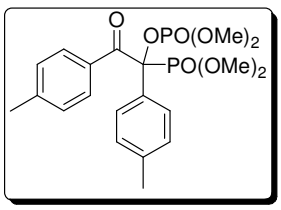
added. The reaction mixture was stirred for 2 days. The reaction was diluted with Et_2O and brine solution was added. The aquous phase was extracted wirh Et_2O three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purifed by flash column chromatography on silica gel with EtOAc as eluent. 98 mg of product was obtained



1-(methoxyphosphono)-1,2-bis(4-methoxyphenyl)-2-oxoethyl dimethyl phosphate: ^{1}H NMR ($CDCl_3$) δ 3.40 (d, *J*=11.5Hz, 3H); 3.68 (d, *J*=10.7Hz, 3H); 3.71 (s, 3H); 3.72 (d, *J*=11.1Hz, 3H); 3.73 (s, 3H); 3.77 (d, *J*=10.,9Hz, 3H); 6.68 (d, *J*=8.9Hz, 2H); 6.83 (d, *J*=8.8Hz, 2H); 7.41 (dd, J_1=2.2Hz, J_2=8.9Hz, 2H); 7.66 (d, *J*=8.9Hz, 2H); ^{13}C NMR ($CDCl_3$) 53.1 (d, *J*=7.4Hz); 53.3 (d, *J*=6.0Hz); 53.8 (d, *J*=7.3Hz); 54.1 (d, *J*=6.1Hz); 54.2; 54.3; 112.3; 113.0; 125.1; 125.8 (d, *J*=6.2Hz); 126.8 (d, *J*=4.2 Hz); 132.0; 159.0 (d, *J*=2.8Hz); 162.2; 190.6; ^{31}P NMR ($CDCl_3$) 15,9; -2,86.

3.2.4 Synthesis of 1-(methoxyphosphono)-2-oxo-1,2-dip-tolylethyl dimethyl phosphate

26 mg of KCN was dried at 100°C under vacuum for 3 h and dissolved in dry DMF (1 ml). Then, 1 mmole (228 mg) of dimethyl p-methylbenzoylphosphonate was added. The reaction mixture was stirred for 2 days. The reaction was diluted with Et_2O and brine solution was added. The aquous phase was extracted wirh Et_2O three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purifed by flash column chromatography on silica gel with EtOAc as eluent. 96 mg of product was obtained.

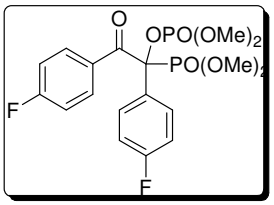


1-(methoxyphosphono)-2-oxo-1,2-dip-tolylethyl dimethyl phosphate: ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H); 2.27 (s, 3H); 3.36 (d, *J*=11.5Hz, 3H); 3.67 (d, *J*=10.8Hz, 3H); 3,72 (d, *J*=11.6Hz, 3H); 3.77 (d, *J*=10.9Hz, 3H); 6.99 (d, *J*=8.1Hz, 2H); 7.12 (d, *J*=8.0Hz, 2H); 7.37 (d,

J=8.2Hz, 2H); 7.54 (d, *J*=8.2Hz, 2H); ^{13}C NMR ($CDCl_3$) 20.15; 20.60; 53.13 (d, *J*=7Hz); 53.29 (d, *J*=6Hz); 53.85 (d, *J*=6.5Hz); 54.08 (d, *J*=6.2Hz); 59.34; 125.14; 125.18; 126.8; 127.00; 127.67; 128.29; 128.32; 129.65, 130.52; 130.60; 191.79; ^{31}P NMR ($CDCl_3$) -3.35; 15.69.

3.2.5 Synthesis of 1-(methoxyphosphono)-1,2-bis(4-fluorophenyl)-2-oxoethyl dimethyl phosphate

26 mg of KCN was dried at 100°C under vacuum for 3 h and dissolved in dry DMF (1 ml). Then, 1 mmole (232 mg) of dimethyl p-fluorobenzoylphosphonate was added. The reaction mixture was stirred for 2 days. The reaction was diluted with Et_2O and brine solution was added. The aquous phase was extracted wirh Et_2O three times. Collected organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purifed by flash column chromatography on silica gel with EtOAc as eluent. 58 mg of product was obtained

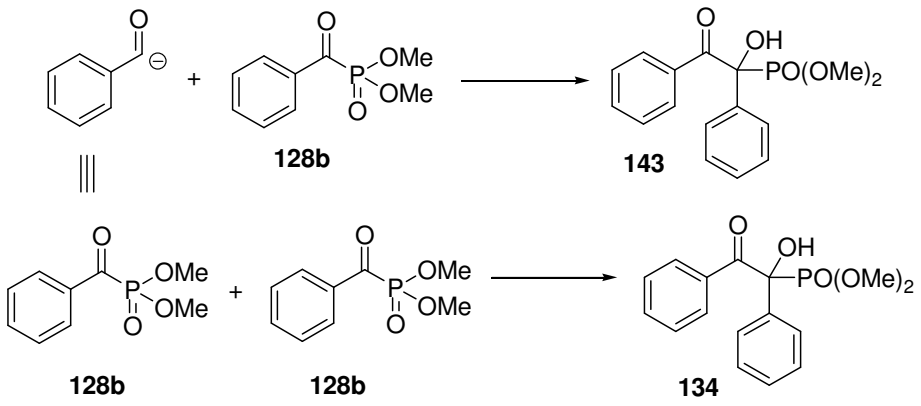


1-(methoxyphosphono)-1,2-bis(4-fluorophenyl)-2-oxoethyl dimethyl phosphate: ^{1}H NMR ($CDCl_3$) δ 3.38 (d, *J*=11.5Hz, 3H); 3.68 (d, *J*=10.8Hz, 3H); 3,75 (d, *J*=11.6Hz, 3H); 3.80 (d, *J*=10.9Hz, 3H); 6.89 (d, *J*=8.6Hz, 2H); 7.03 (d, *J*=8.5Hz, 2H); 7.47-7.51 (m, 2H); 7.66 (dd, J_1=8.7Hz, J_2=5.5Hz, 2H); ^{13}C NMR ($CDCl_3$) 54.31 (d, *J*= 6 Hz); 55.23 (*J*= 6.2 Hz); 60.45; 115.18; 115.40; 115.78; 115.98; 128.31; 130.26; 133.16; 133.25; 191.44; ^{31}P NMR ($CDCl_3$) -3.15; 15.02.

CHAPTER 4

CONCLUSION

We have developed a new method for synthesis of α-hydroxyphosphonates . This method provides quarternery α-hydroxyphosphonates. This method works well with aromatic aldehydes. Substrates with electron donating groups gave higher yileds than substrates with electron withdrawing groups. However, aliphatic phosphonates did not proceed this reaction. Moreover, attempts for enantioselective version of this reaction was failed. Chiral version and reactions with aliphatic phosphonates are under investigation.



Scheme 49 Self condensation of dimethyl benzoyl phosphonate

We proposed that Mannich type reaction of imines of acyl phosphonates could give α-amino phosphonates. However, our attempts for synthesizing N-tosyl imines derived from acyl phosphonates were failed. Then, we synthesized N-benzoyl hydrazone from acyl phosphonates. Allylic addition to hydrazone of acyl phosphonates were performed but reaction gave complex mixture in which typical NMR peaks of phosphonate were not observed.

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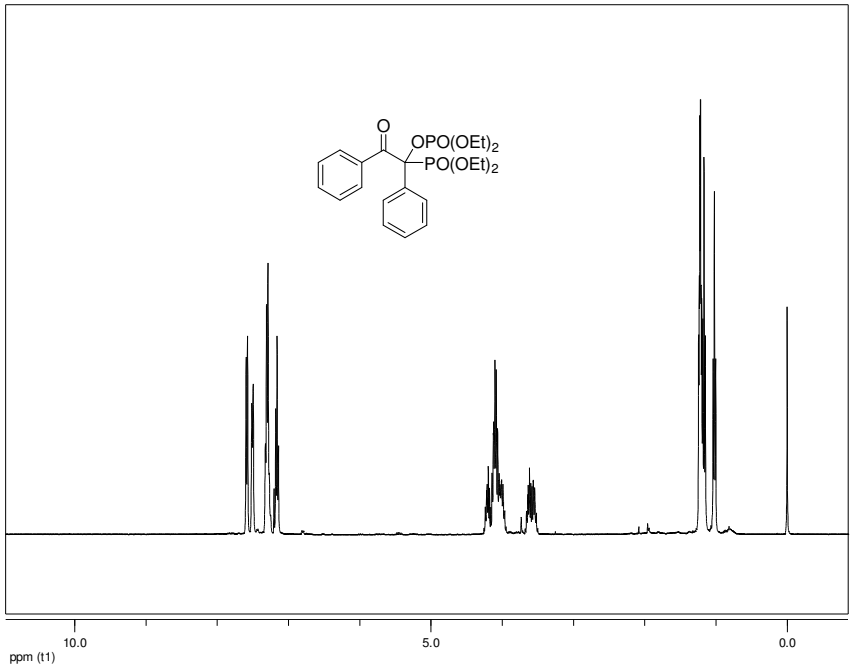
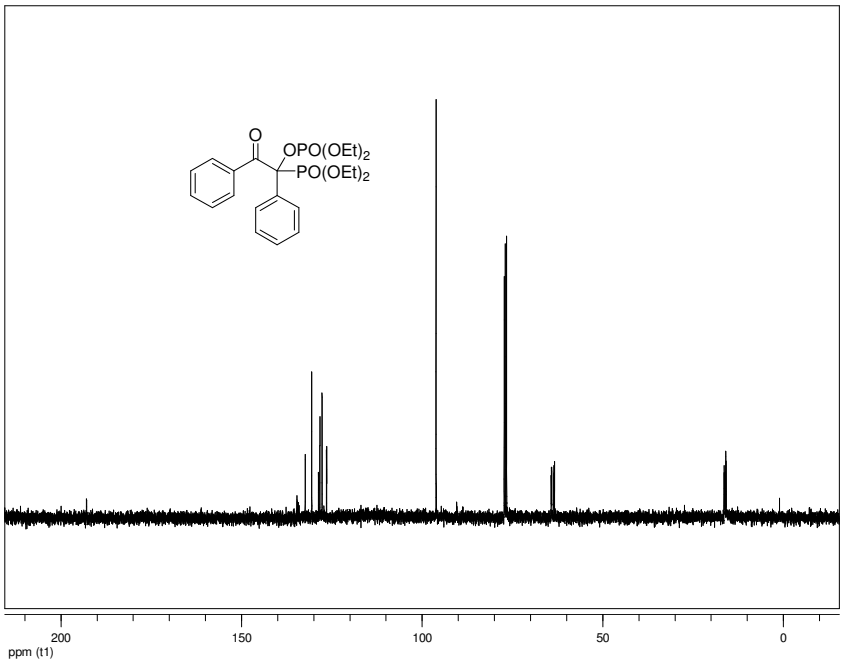
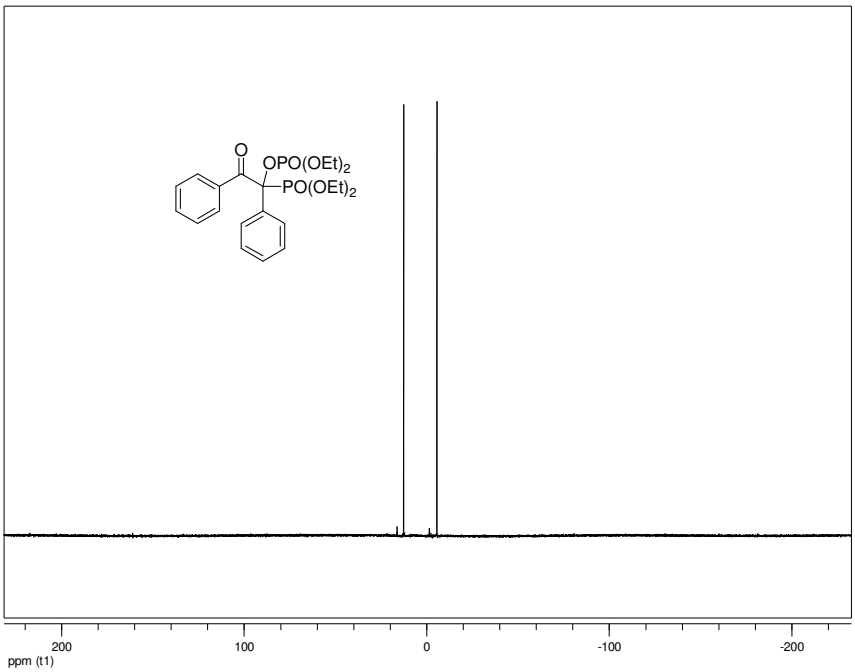
APPENDIX



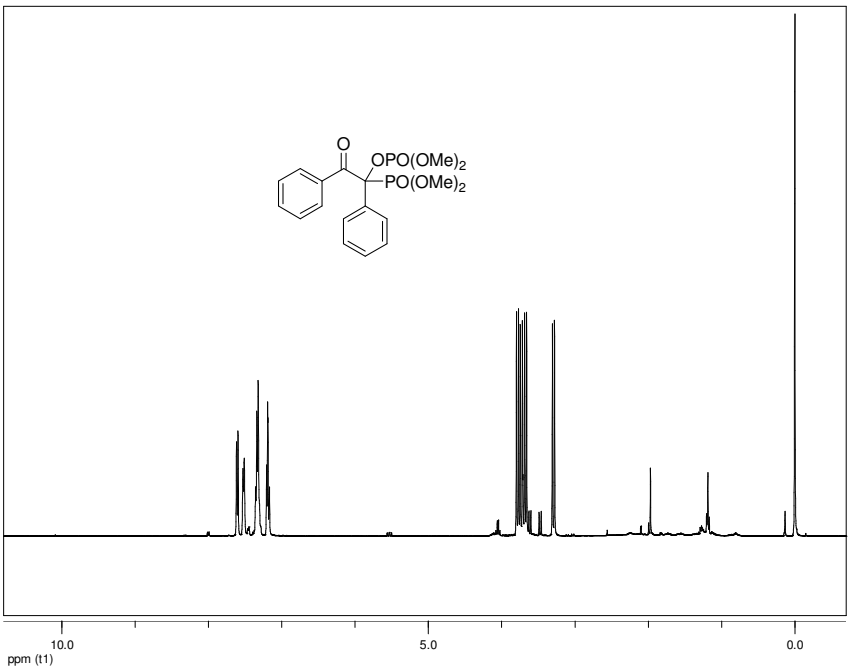
Scheme 50 ^{1}H-NMR of 1-(ethoxyphosphono)-2-oxo-1,2-diphenylethyl diethyl phosphate



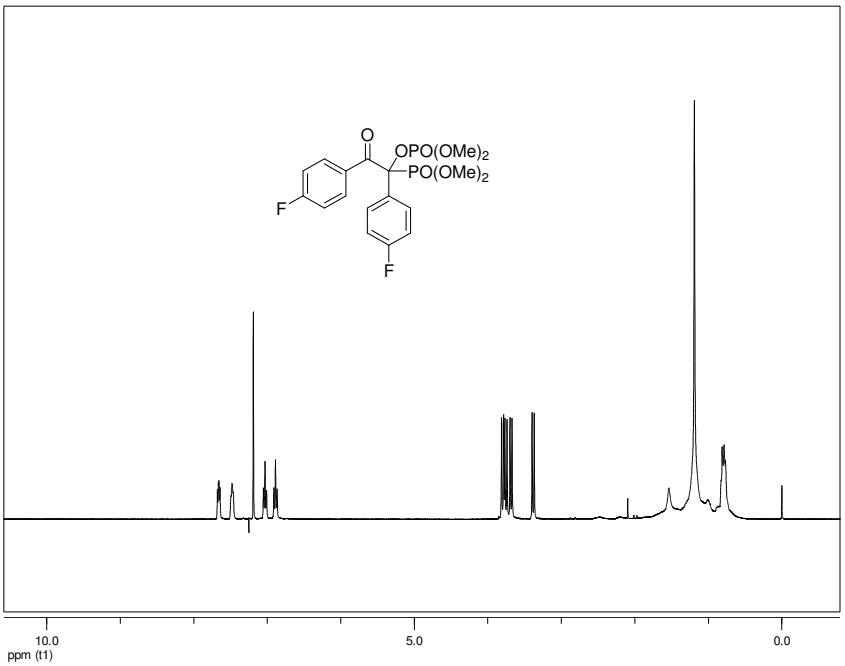
Scheme 51 ^{13}C-NMR of 1-(ethoxyphosphono)-2-oxo-1,2-diphenylethyl diethyl phosphate



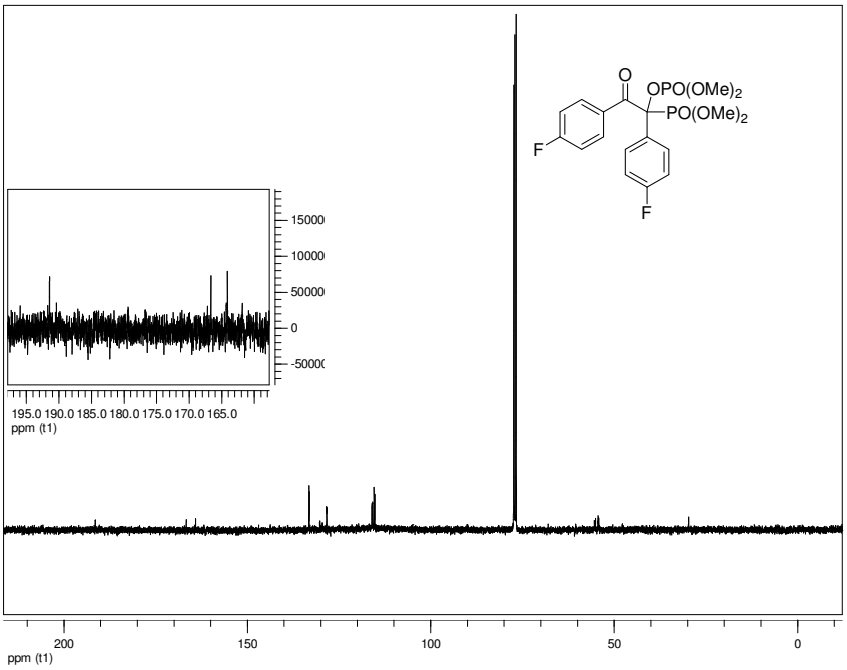
Scheme 52 ^{31}P-NMR of 1-(ethoxyphosphono)-2-oxo-1,2-diphenylethyl diethyl phosphate



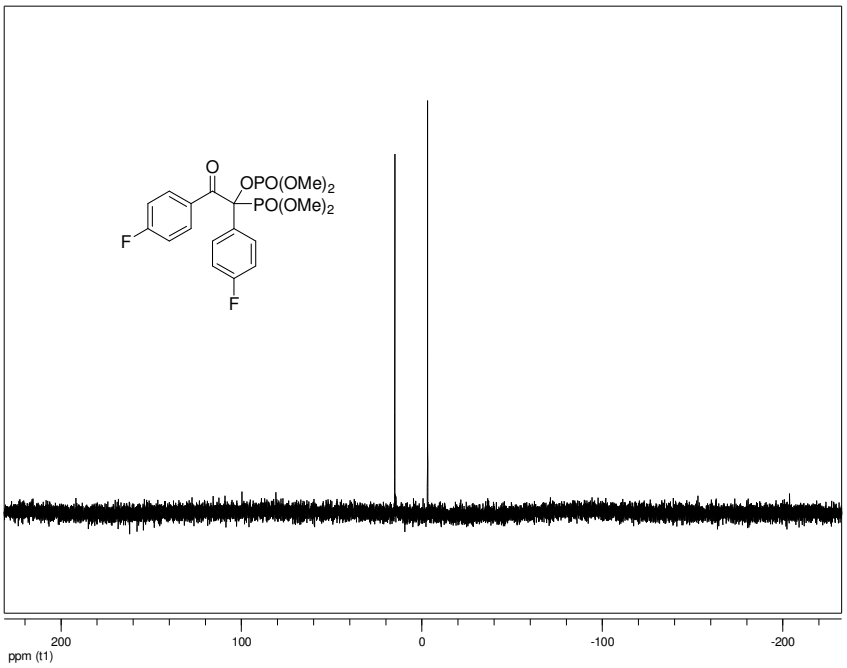
Scheme 53 ^{1}H-NMR of 1-(methoxyphosphono)-2-oxo-1,2-diphenylethyl dimethyl phosphate



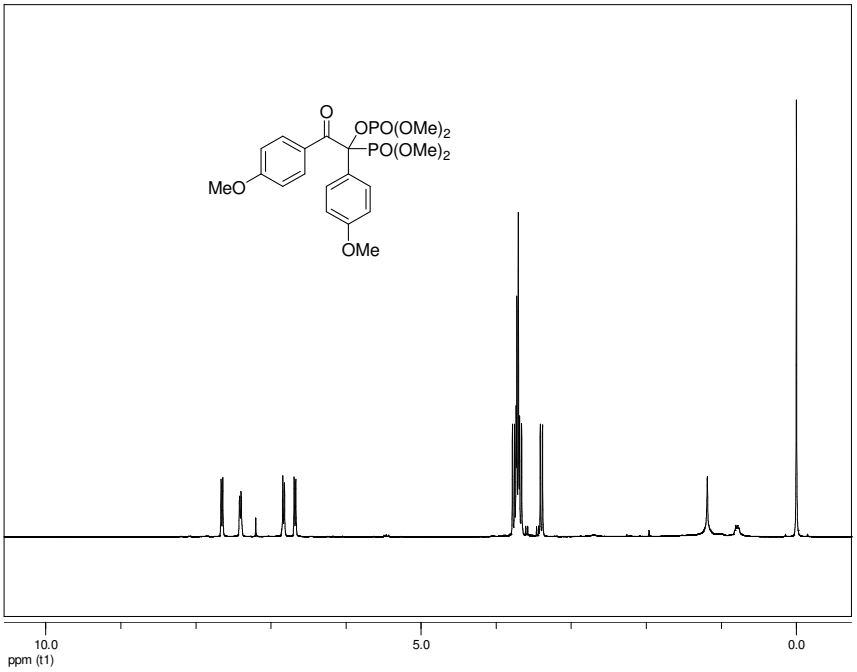
Scheme 54 ^{1}H-NMR of 1-(methoxyphosphono)-1,2-bis(4-fluorophenyl)-2-oxoethyl dimethyl phosphate



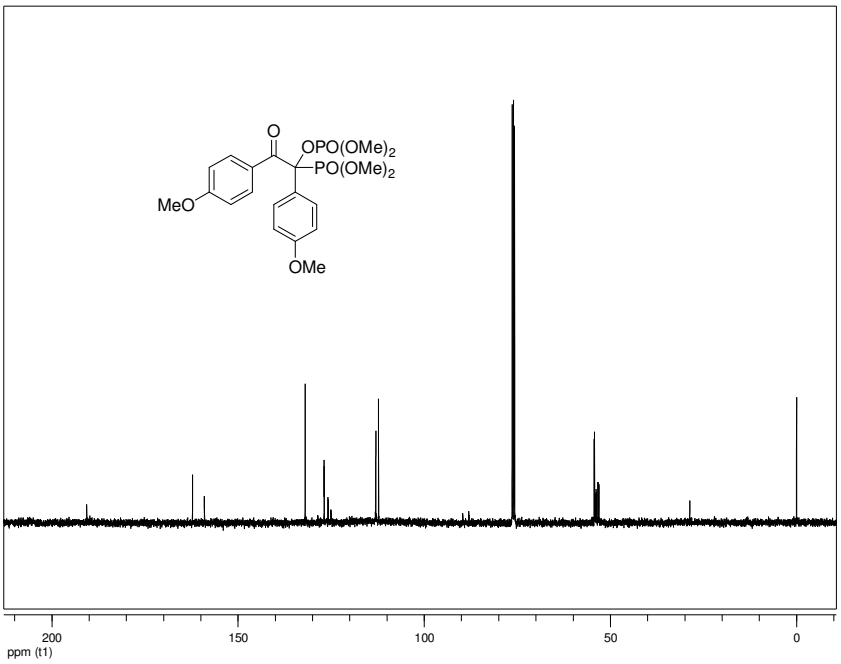
Scheme 55 ^{13}C-NMR of 1-(methoxyphosphono)-1,2-bis(4-fluorophenyl)-2-oxoethyl dimethyl phosphate



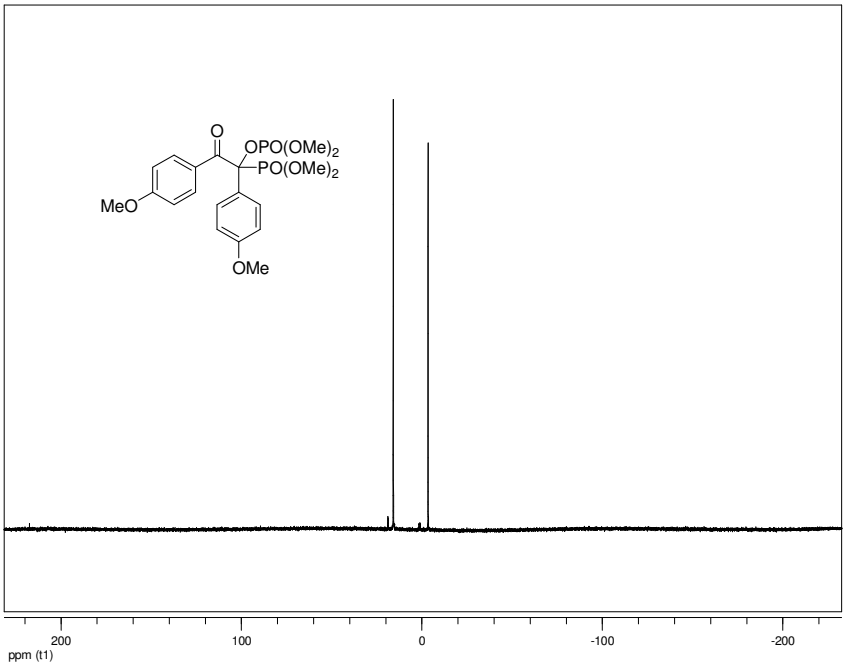
Scheme 56 ^{31}P-NMR of 1-(methoxyphosphono)-1,2-bis(4-fluorophenyl)-2-oxoethyl dimethyl phosphate



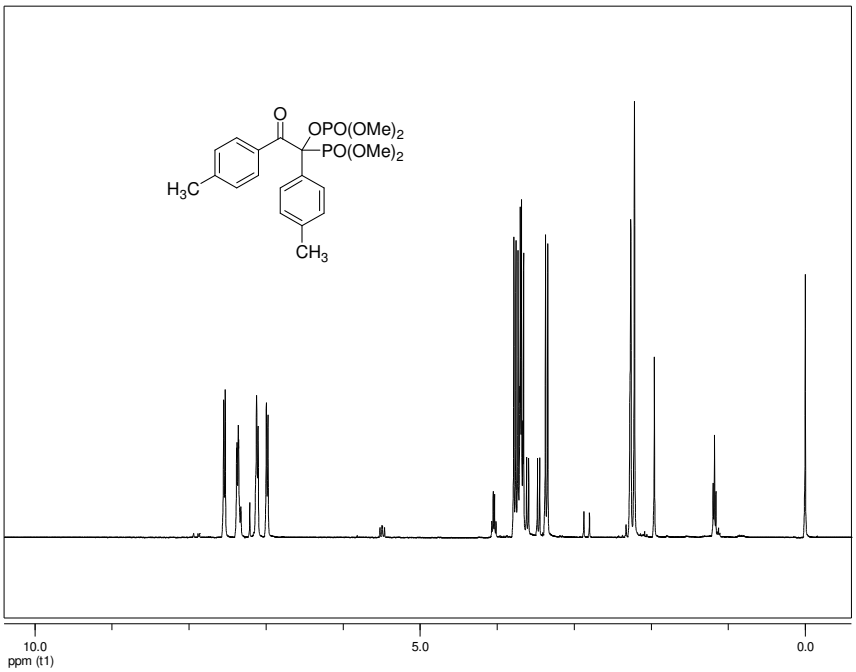
Scheme 57 ^{1}H-NMR of 1-(methoxyphosphono)-1,2-bis(4-methoxyphenyl)-2-oxoethyl dimethyl phosphate



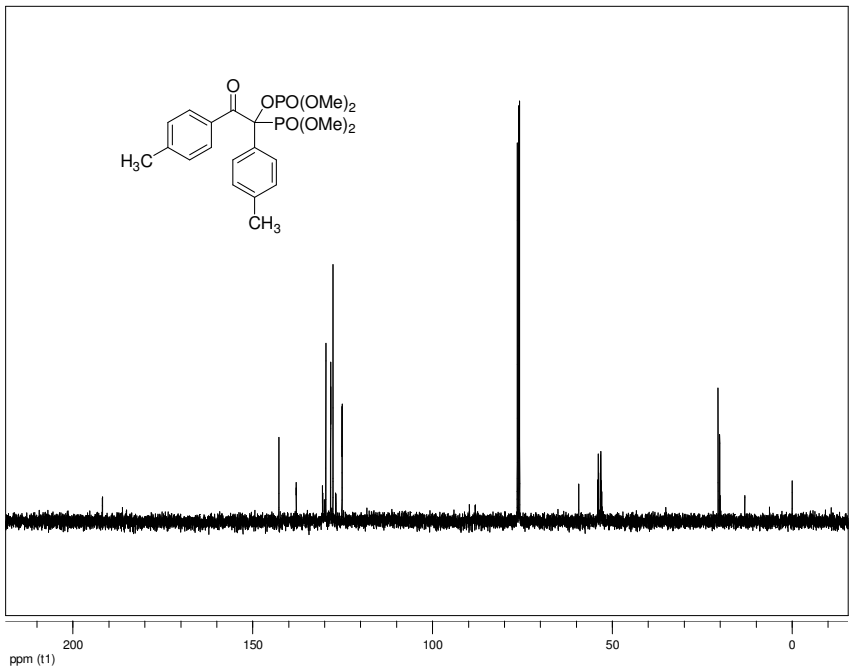
Scheme 58 ^{13}C-NMR of 1-(methoxyphosphono)-1,2-bis(4-methoxyphenyl)-2-oxoethyl dimethyl phosphate



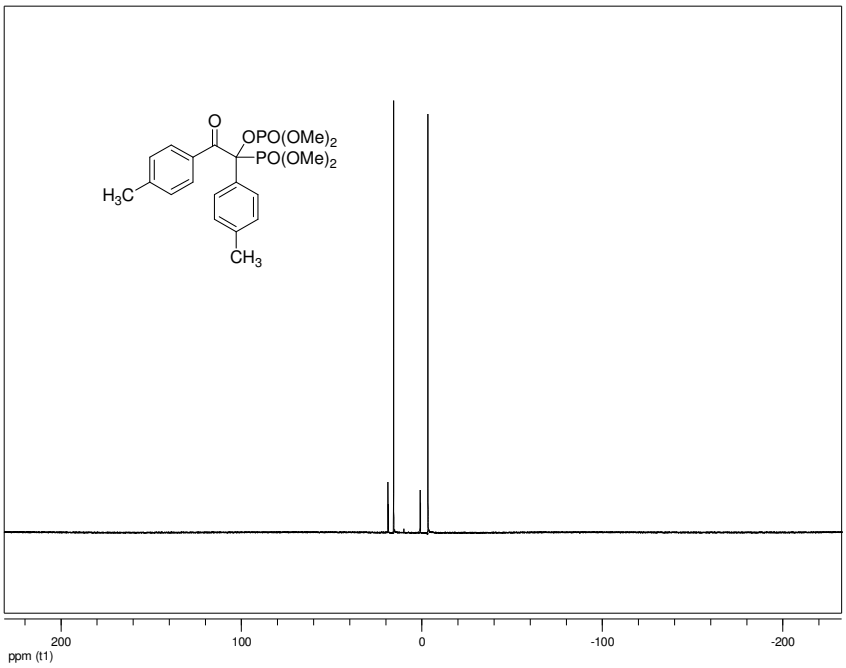
Scheme 59 ^{31}P-NMR of 1-(methoxyphosphono)-1,2-bis(4-methoxyphenyl)-2-oxoethyl dimethyl phosphate



Scheme 60 ^{1}H-NMR of 1-(methoxyphosphono)-2-oxo-1,2-dip-tolylethyl dimethyl phosphate



Scheme 60 ^{13}C-NMR of 1-(methoxyphosphono)-2-oxo-1,2-dip-tolylethyl dimethyl phosphate



Scheme 61 ^{31}P-NMR of 1-(methoxyphosphono)-2-oxo-1,2-dip-tolylethyl dimethyl phosphate