ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

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ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

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ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

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ABSTRACT

ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

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Functionalized cyanophosphates are important starting materials for the synthesis of beta-lactam ring moiety of beta-lactam antibiotics. The cyanophosphates are synthesized starting from easily available acylphosphonate and ethylcyanoformate. Acylphosphonates are synthesized starting from acylchloride and trimethylphosphite. Addition of acylphoshonate to ethylcyanoformate furnishes the cyanophosphate with the quaternary center.

Keywords: catalytic reactions, acyl anion, umpolung, acylphosphonate, asymmetric synthesis, cinchona alkoloids, salen ligands, cyanohydrin.

ÖZ

AÇİL FOSFONATLARIN ETİLSİYANOFORMATA KATILIM REAKSİYONLARI

Barbaros Reis
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan S. Demir
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Fonksiyonlandırılmış siyanofosfatlar, beta-laktam antibiyotiklerinin beta-laktam halka kısmının sentezi için önemli başlangıç maddeleridir. Siyanofosfatlar kolaylıkla elde edilebilen açil fosfonat ve ethylsiyanoformattan başlanarak sentezlenmiştir. Açil fosfonatlar açil klorür ve trimetil fosfitten başlanarak sentezlenmiştir. Açil fosfonatın etilsiyanoformata katılımı kuarterner merkezli siyanoformatler vermiştir.

Anahtar kelimeler: katalitik reaksiyonlar, açil anyon, umpolung, açilfosfonat, asimetrik sentez, kinin alkaloitleri, salen ligandları, siyanohidrin.

To my mother,

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I would like to thank Ayhan S. Demir for introducing me to interesting and exciting chemistry world.

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CHAPTER 1

INTRODUCTION

The chemical synthesis of carbon-containing molecules has always been a major field of chemistry. Nonetheless, the area is still far from fully being developed. Although infinite number of carbon containing compounds may exist, a small part of it was synthesized and studied by the organic chemist. In addition, in last century a great effort by organic chemist resulted in an outstanding development in the area. Possible existence of infinite number of carbon containing molecules differing in number and types of constituent atoms, in size, in topology, in three dimensional arrangement, construction of specific molecules by a single chemical step is sometimes not possible even for relatively simple ones. For efficient synthesis, multistep reactions are usually required, each providing a specific transformation on the way to the target compound. If we think complexity of today's synthetic problems, chemists really need a rich pool of synthetic methodology to solve different problems with different requirements. Thus, development of new and more flexible synthetic methodology is the rate determining step of today's chemistry. As a result of importance of the field, organic chemist developed a wide range of bond forming and functional group interconversion reactions. However, the use of these methods in complex synthesis needs special attention and strategies. In the synthesis of any synthetic target, a systematic approach is required to circumvent the synthetic obstacles through out the synthetic design; that is possible by the perception of structural feature in reaction products and manipulation of the target structure in reverse synthetic sense. This method is known as retrosynthetic analysis [1]. Retrosynthetic analysis let chemist derive both simplified and accelerated pathways.

The path from complex to simple one requires using of good knowledge of how to manipulate or transform one molecule in to another one. The methods sought for particular transformation should be feasible in terms of purity of the product and efficiency of the efficiency of the reaction. Besides, cost of the process and environmental issues are also matter of attention for better methodology. Type and amount of solvents, reagents, substrates used in a reaction should be concerned while comparing alternative methodologies. Thus a methodology that is superior in terms of efficiency can be eliminated because of the materials employed in the process. In the light of these considerations, it is not surprising that there is an increasing interest in catalytic bond forming reactions. However, the discovery of catalytic methods for carbon-carbon bond formation, while creating functionality, remains a formidable challenge in the continuing development of efficient and reliable chemical processes. The apparent advantage of catalytic reactions is the operational simplicity and atom-economy, while stereocontrol over the newly created functionalities are additional benefits. So it is not unexpected that many reports appear everyday aiming the development of new methods that are either providing improved solutions to known methods or presenting new approaches.

Building blocks that have different functionality are important in synthesis since it is a very viable way to manipulate common building blocks in to a variety of different synthetic targets [2]. One of the most important building blocks in synthetic organic chemistry is cyanohydrins which are functionally dense molecules [3]. They contain both a hydroxyl or a protected hydroxyl group and a nitrile group which are sitting on the same carbon atom.

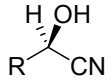

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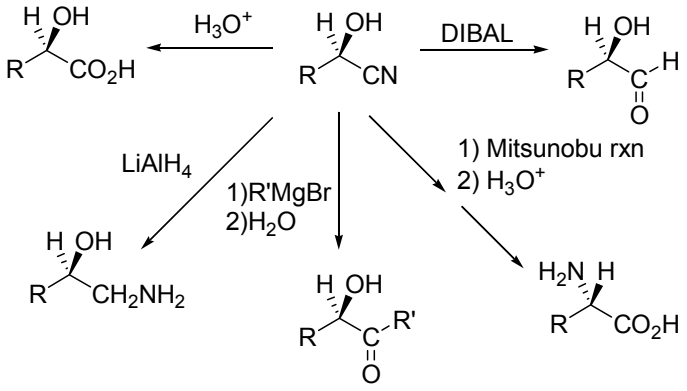
Figure 1. General structure of cyanohydrin

1.1 Cyanohydrins In the Organic Chemistry

Cyanohydrins are versatile building blocks in organic chemistry due to the readily transformable groups they contain. They can be transformed into different kinds of compounds such as β-amino-acids, α-hydroxy carbonyl compounds most of which are biologically active (Scheme 1) [4].



Scheme 1. Some of possible transformation from cyanohydrins

Cyanohydrins have also been used as starting materials in the synthesis of pharmaceuticals such as Diltiazem (**2**), a vasodilating agent with calcium channel blocking activity. In addition, cyanohydrins are found as a part of natural products such as the glucoside Amygdalin (**3**) and Fenvelerate (**4**), one of the pyrethroid classes of insecticides [5].

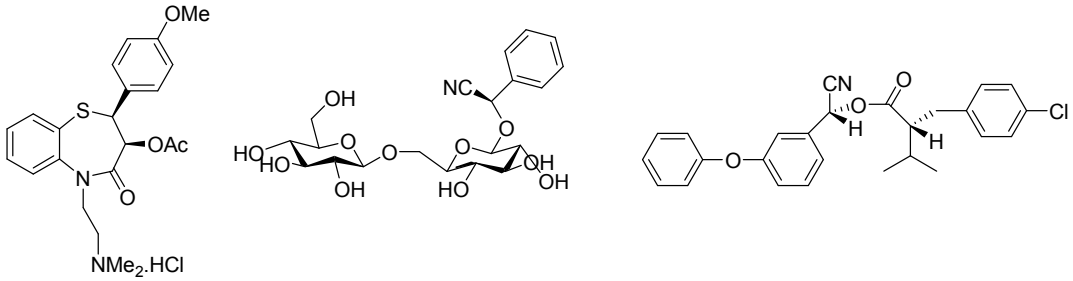
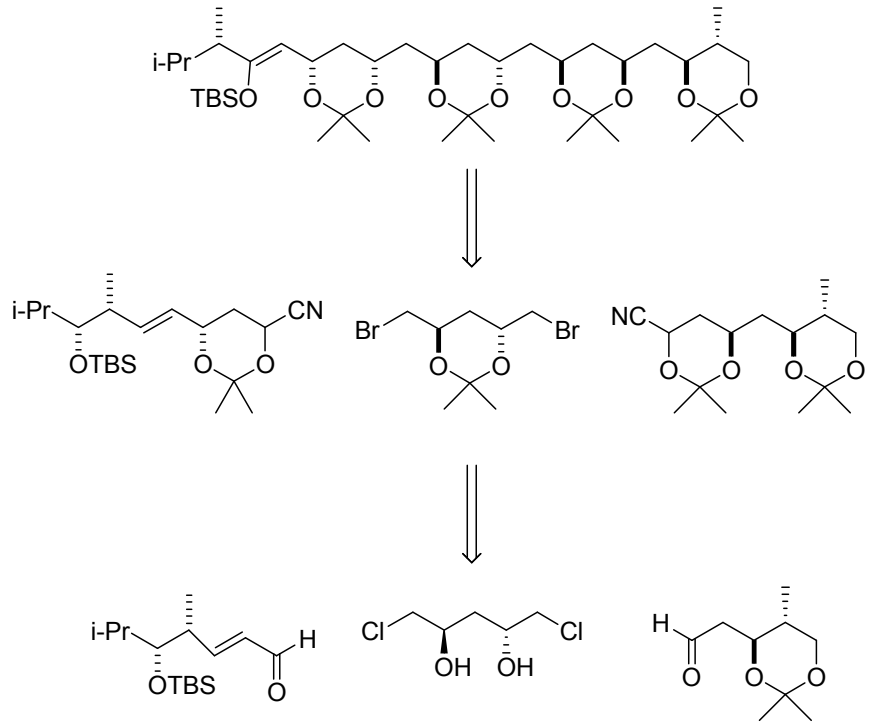


Figure 2. Structure of Diltiazem **(2)**, Amygdalin **(3)** and Fenvelerate **(4)**.

Cyanohydrin containing compounds are used in retrosynthetic analysis enabling a handful disconnection. One of them is Rychnovsky's Cyanohydrin Acetonide Alkylation [6] in which a ketone is masked as cyanohydrin that enables a disconnection between cyanohydrin and alkylating reagent. Cyanohydrins are well established as acyl anion equivalents in this type of strategies. However, cyanohydrin acetonides have several important advantages over simple cyanohydrins or dithianes as acylanion precursor. They alkylate to give the axial nitrile with high diastereoselectivity, rather than the mixtures commonly found with simple cyanohydrins. They are also easier to deprotonate than dithianes, the anions are excellent nucleophiles, and they can be deprotected under very mild conditions. These features make a cyanohydrin acetonide disconnection a very powerful strategy for convergent synthesis. Synthesis of roxaticin polyol is a good example from Rychnovsky's strategy (Scheme 2).



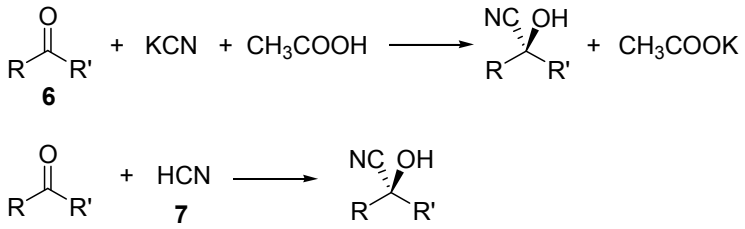
Scheme 2. Roxaticin Polyol Segment Retrosynthesis

1.2 Synthesis of cyanohydrins

Over billions years ago, at prebiotic earth, we are not certain about the composition of earth and condition on the surface, but the energy to drive chemical reactions would certainly have been present in the form of electric storms, volcanic activity, and ultraviolet radiation [7]. A basic laboratory simulation of primitive conditions on the earth involves heating water, methane, ammonia and hydrogen and supplying energy inform of an electric discharge or ultraviolet radiation; this yields several compounds including hydrogen cyanide, formaldehyde, amino acids, sugar precursor and nucleoside precursors. Even cyanide is toxic for higher organisms as a consequence of binding tightly to heme, it has a influence of cyanide on evolution. Cyanide is considered a fundamental precursor species for biomolecules such as nitrogen bases, most directly adenine which is a pentamer of hydrogen cyanide.

However, it is probable that much of the cyanide present in the early terrestrial hydrosphere and cryosphere was scavenged by ferrous ion to form ferrocyanide or by formaldehyde to form simplest of all cyanohydrins [8]. Hence, cyanide is not only one of the most important of the simplest molecules but also it is probably the source of more complex and biologically relevant molecules. And it is the probably the source of very first cyanohydrins in the nature.

First cyanohydrin laboratory synthesis was made by Urech in 1872 from a ketone, an alkali cyanide and acetic acid. This method is called as Urech cyanohydrin method [9]. Another method is direct addition of hydrogen cyanide to carbonyl compounds (scheme 3).

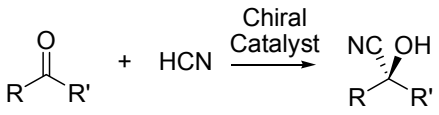


Scheme 3

A disadvantage of cyanohydrins which are directly synthesized by hydrogen cyanide (HCN) or acid+metal cyanide is their instability. They could be easily hydrolyzed in mild basic medium. To circumvent this problem, hydroxide part of cyanohydrin is generally protected [10]. Furthermore, this protection provides a chance to selective manipulation of the cyanohydrins in to valuable products. When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked [11]. A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. Because of reasons stated above,

finding out new methods for cyanohdrin synthesis that preferably accommodate new protection groups is a subject of current interest in synthetic organic chemistry.

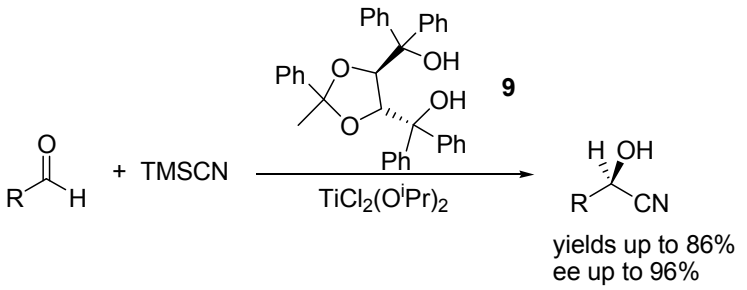
Although HCN addition to carbonyl compound is a successful way for a racemic cyanohydrin formation, a resolution step is needed for asymmetric synthesis (Scheme 4).



Scheme 4

One of the typical methods of forming tetrahedral carbon atoms selectively is to add cyanide ion carbonyl compunds. This type of approach is widely used in the construction of quarternary carbon centers, one of the biggest challenges in synthetic organic chemistry. Currently major attempts for asymmetric cyanohydrin synthesis are trimetylsilylcyanide (TMSCN) addition to carbonyl compound with chiral organometallic or pure organic catalyst. Organotitanium, organoaluminium, organoborane, organotin reagents are used as organometallic catalysts [12]. Nucleophilic organic molecules are also used as catalyst for asymmetric synthesis [13].

Narasaka et al. reported that a complex of the tartaric acid derivative **(9)** and dicholorodiisopropoxytitanium induced the asymmetric addition of trimetylsilylcyanide to aromatic aldehydes [14]. Optically active cyanohydrins were produced in good yields and good to excellent enantiomeric excess (Scheme 5).



Scheme 5

Shibasaki and co-workers showed that enantioselectivities in chiral Lewis acid catalyzed addition of TMSCN to aldehydes are sometimes enhanced by the addition of "promoters" such as Bu_3PO, CH_3POPh_2 and Ph_3PO [15]. These phosphine oxide activation effect led to the incorporation of phosphine oxide moitites into the catalytic Lewis acid structures as a Lewis acid-Lewis base pair for what have been described as "two center" catalysis. They designed a succesful catalyst based on phosphine containing binaphthol ligand and aluminium metal (Figure 2).

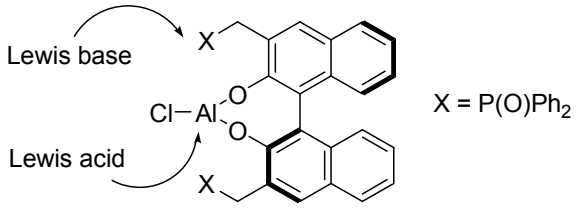
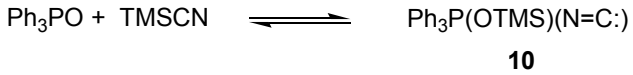


Figure 2. Bifunctional aluminium-Binol catalyst

The catalyst activates both subsrate aldehyde and TMSCN with dual activation. Aldehyde is activated by metal center and TMSCN is activated by phosphine oxygen. This dual interaction causes selective transfer of cyanide to aldehyde.

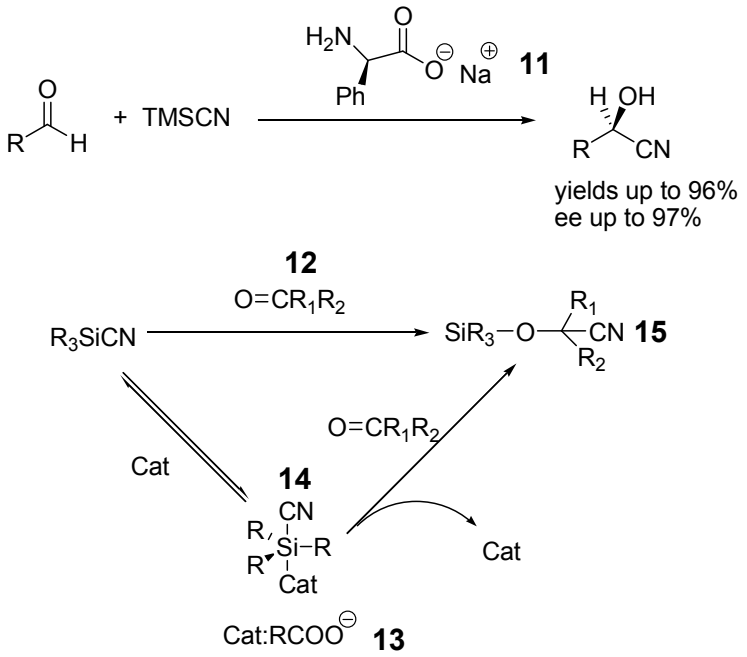
Later Corey and Ryu investigated the effect of phosphine oxide and proposed that a reaction between phosphine oxide and TMSCN as follows [16] (Scheme 6):



Scheme 6

They have supported their proposal with several NMR and IR experiments and identified **10** as a more reactive cyanosilylating reagent than the isomeric cyanide. They used oxazaborolidinium catalyst cooperative with phosphine oxide and TMSCN active complex.

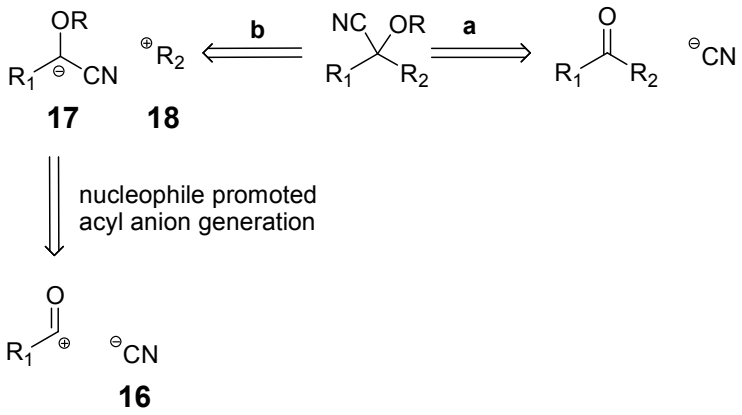
In the light of the activation of TMSCN by lewis bases, Feng's group used simple chiral amino acid alkali metal salt [17]. Nucleophilic substitution at silicon in R_3SiX compounds can be activated by nucleophiles which are good coordinating agents for Si, and proceeds via the formation of hypervalent silicon intermediates. Carboxylate ion and TMSCN formed an active cyanation intermediate, since nucleophilicity of the cyano group is enhanced by electron donation from the hypervalent silicon. This silicon intermediate readily reacts with carbonyl compound, followed by the immediate silylation to give the corresponding product (Scheme 7).



Scheme 7

1.3 Alternative approach for cyanohydrin formation

Typical method for cyanohydrin synthesis is the addition of a cyanide source, in various forms, to the corresponding carbonyl compounds in a single C-C bond forming step (Scheme 8, route a). Although this approach has been deeply investigated, another promising way would be a three component domino reaction utilizing a cyanide source, acyl anion precursor and an electrophile (Scheme 8, route b) [18]. In this way two sequential C-C bond formation takes place via a nucleophile (cyanide ion in this case) promoted acyl anion generation from an acyl anion precursor and its subsequent reaction with the electrophilic carbon center. This sequence of reaction has an obvious advantage over the traditional approach for the synthesis of cyanohydrins with quarternary carbon centers.



Scheme 8

The viability of an approach based on the use of acyl anions obviously depends on the availability of these valuable entities.

1.4 Chemistry of reactivity umpolung

Since most of the organic reactions are polar (Lewis acid-Lewis base), a prior knowledge of polarity of a given chemical entity provides a great advantage for the reaction design. In this way it is very easy to find out Lewis acid-Lewis base sites in a reagent and devise a plausible way to make a synthetic transformation on a subsrate. However, it is sometimes required the reverse the polarity of a given reaction site in a molecule from its natural reactivity to the opposite one and this approach gives an apparent synthetic design advantage. Changing polarity (reactivity) of molecule or a part of it is called umpolung [19].

The concept of umpolung can be summarized as follows (Figure 3):

1. The reactions most frequently used in organic synthesis are polar in nature, i.e nucleophilic or donor sites (d) and electrophilic or acceptor (a) sites are used to make and break bonds.

2. The large majority of target molecules of organic synthesis contain the heteroatoms nitrogen and oxygen as functional groups (amino, imino, hydroxyl, ether, carbonyl).

3. These heteroatoms impose an alternating acceptor and donor reactivity pattern through carbon skeleton. For example acceptor properties or attack by donors at carbons $C^{1,\ 3,\ 5...}$ and donor properties or attack by acceptors at carbons $C^{2,4,,6...;}$ the heteroatom X^{o} itself is a donor center.

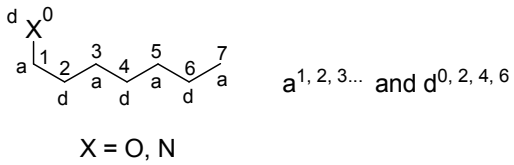


Figure 3. Heteroatom induced reactivity pattern

4. Synthetic limitation is the fact that combination of components with normal reactivity leads only to 1,3-, 1,5- ... disubstituted products (odd number of carbon atoms between the functional groups) (Figure 4)

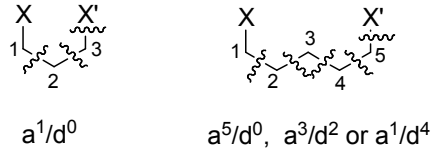
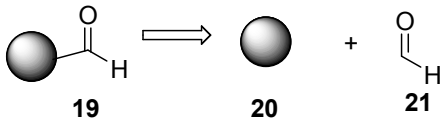


Figure 4. Retrosynthetic analysis of disubstituted products

5. According to the original proposition, synthons are "structural units within a molecule which are related to possible synthetic operations. Thus, the

molecule **(19)** is related with the substrate synthon **(20)** and the formyl synthon **(21)** (Scheme 9)**.**



Scheme 9. Possible synthons

6. An a^n- or d^n-synthon is, respectively, a synthon with an O- or N-heteroatom at C' and an acceptor or donor center at C^n (Fig. 5). An a^n- or d^n-synthon is an acceptor or donor heteroatom (O or N), respectively (Figure 5).

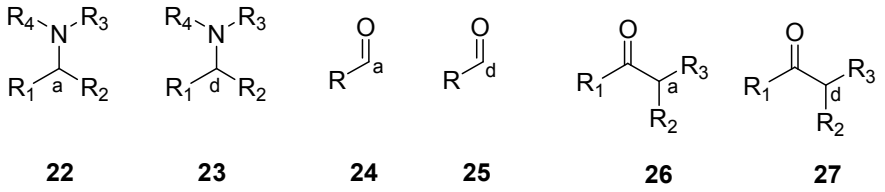
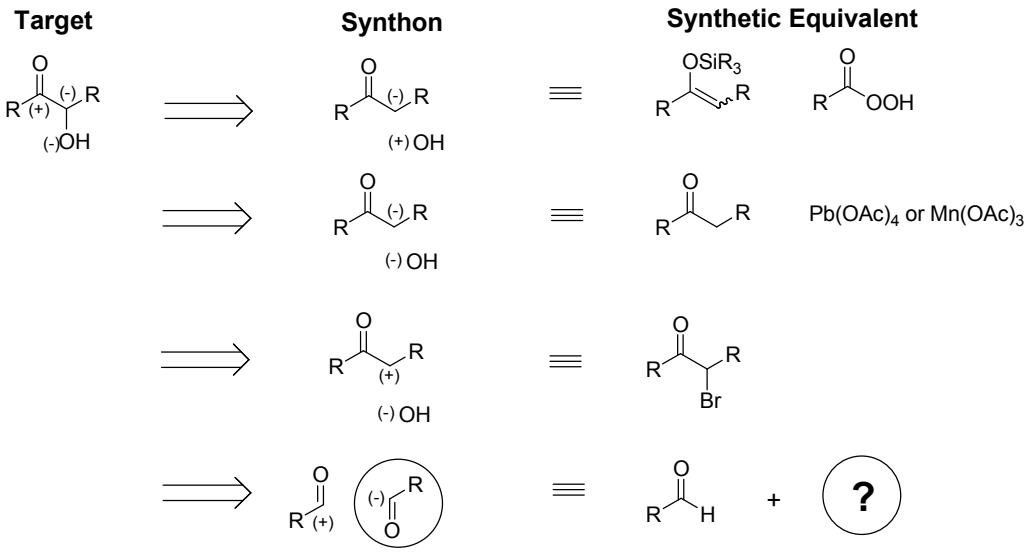


Figure 5. Donor and acceptor sides of some compounds.

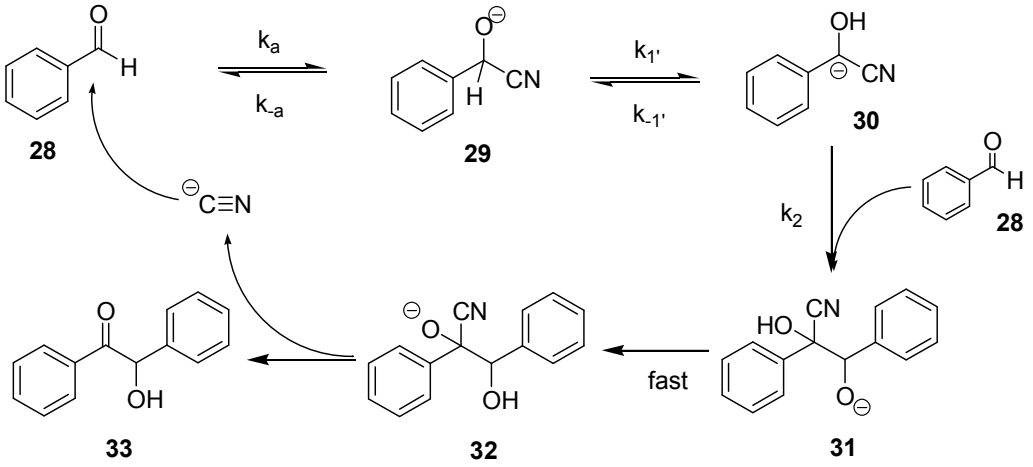
7. A reagent has normal reactivity if it corresponds to a synthon of general type (A) reactivity umpolung is present in a reagent in which a- and d-centers are reversed as compared to (A).

α-Hyroxy ketones are good examples to understand the importance of this approach and advantage of change of polarity (Scheme 10). If several disconnections has been made a variety of synthons is produced. Among these synthons, last one resulting from C-C central bond cleavage is probably the most interesting one since corresponding reverse polar coupling process will yield a carbon-carbon bond with an additional functional group. However such a process will only be possible after a certain transformation that will invert polarity of one of the carbonyl moieties.



Scheme 10

Over a century ago, Wohler and Liebig discovered classical benzoin reaction [20] and Labworth established mechanism for reaction at 1903 [21]. Lapworth proposed a carbanion intermediate which is critical part of the mechanism (Scheme 11). Reaction starts with addition of cyanide which is a very good nucleophile with linear cylindrical shape to a carbonyl compound to form cyanohydrin. Cyanide also helps the stabilization of the negative charge together with oxygen and phenyl group. At last it leaves to re-enter catalytic cycle. These properties make the cyanide a unique operator of this reaction.

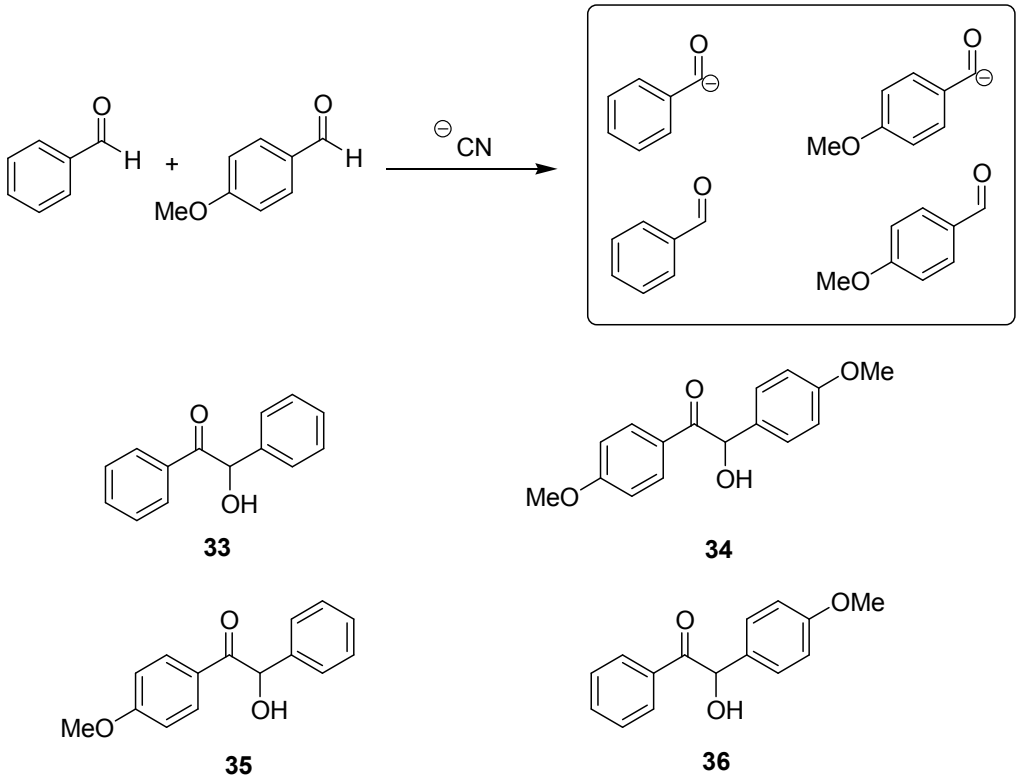


Scheme 11

The first step is quick addition of cyanide ion to benzaldehyde **28**. A new carbon-carbon bond is formed in exchange of a weaker CO π bond and favorable solvation of alkoxide **29** compared to cyanide ion is a plus in terms of energy considerations. Critical acyl anion equivalent **30** generation is the second step of the reaction. 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. Once the acyl anion was formed, it reacts with another mole of aldehyde and release the cyanide together with the benzoin **33** as shown in Scheme 11.

One drawback of benzoin condensation reaction is that it is almost impossible to selectively synthesize an unsymmetrically substituted benzoin derivative under classical conditions. There are several reasons for this behavior. First of all, it is obvious from the mechanism that the synthesis of a particular benzoin derivative requires the generation of an acyl anion equivalent followed by the addition to another aldehyde. In a mixture of two aldehydes in the presence of the cyanide ion, two different acyl anion equivalents will be formed in different ratios that depend on the rate constants of the preceding steps. Moreover there will be two acceptor aldehydes for each generated acyl anion equivalents. If it is hypothetically assumed

the same rate constant of each step for both aldehydes, then a statistical mixture of four products will be formed. At this point, reversibility of the benzoin condensation should also be accounted meaning that reaction provides a product distribution according to thermodynamic stabilities. As far as thermodynamic stability is concerned, benzoin isomers with phenyl ring accommodating electron-donating substituents adjacent to carbonyl group rather than hydroxyl group are more stable. This situation is exemplified in Scheme 12 that shows an experiment designed for the synthesis of benzoin **36**. In accord with the above discussion, this design will fail to give the desired product. Although it is hard to predict product distribution, it is safe to say that desired target will be formed as a minor component because it is thermodynamically less stable than its isomeric counterpart **35**.



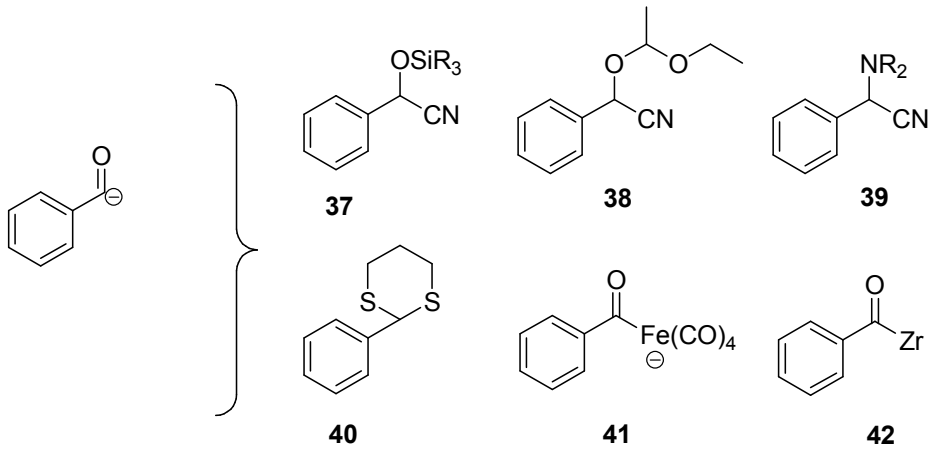
Scheme 12

Although benzoin condesantion is a highly useful reaction, it stems from major drawbacks mentioned above. However it inspired organic chemists to develop kinetically controlled acyl anion generation methods by which a variety of unsymmetrical benzoin derivatives can be synthesized. The potential of these intermediates have already gone beyond the synthesis of benzoin derivatives.

1.4 Method for generation of acylanion equivalents

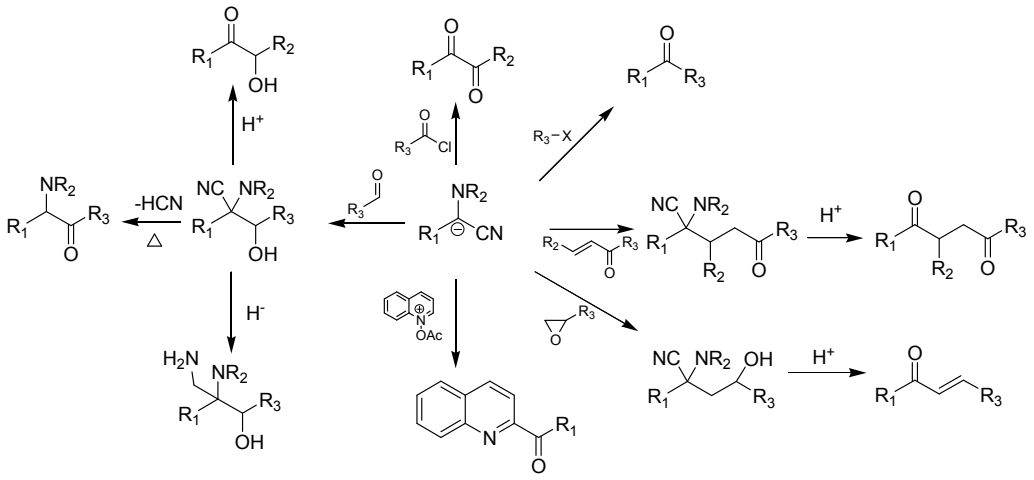
The main achievements of acyl anion chemistry were due to the synthetic chemist's efforts to find recourse in the conversion of aldehydes into nucleophilic carbanion centers. The obvious strategy was the controlled generation of an acyl anion equivalent that can be quenched with an electrophile in order to form the desired target. This approach allowed chemists to synthesize not only cross benzoin products but also variety of other valuable functionalities.

A variety of precursor has been developed for different needs with different availability, and capabilities. Generated carbanion is stabilized with functional groups which are on precursor. Considering the impact of benzoin condensation in the field, it is not surprising to find out that there are many reagents resembling the "active aldehydes intermediate" of benzoin condensation, e.g. **37**, **38** and **39**. Among these precursors developed, O-silyl-cyanohydrins **37**, α- amino nitriles **39** and (Corey-Seebach) dithianes **40** are most popular precursors [22] (Scheme 13).



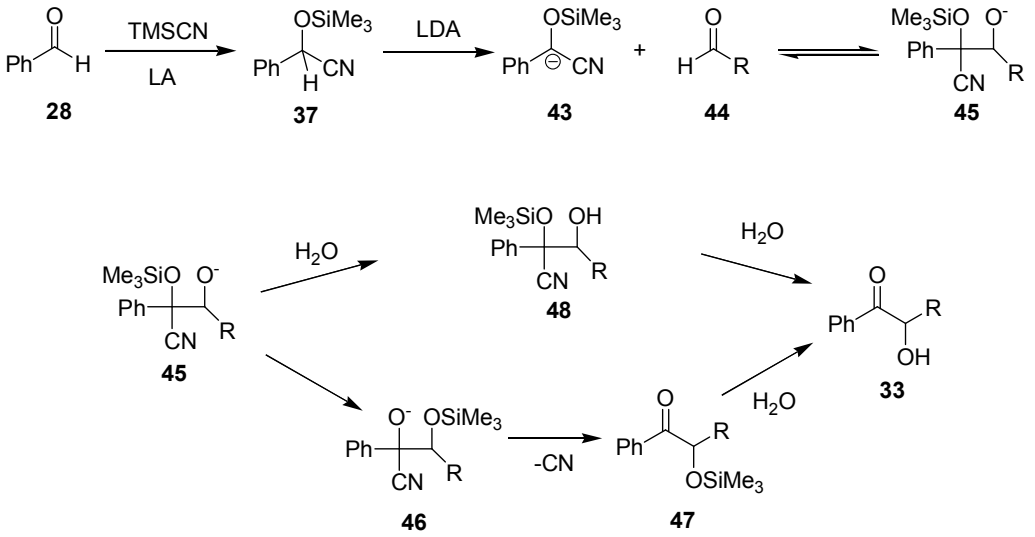
Scheme 13

These reagents offer a great flexibility in the design of unusual strategies for the synthesis of small or complex targets. For example, the synthetic potential of carbanions generated from α-amino nitriles **39** is shown in Scheme 14 [22h]. Since α-amino nitriles are easily accessible from the reaction of aldehydes with cyanide anion and a secondary amine, they are synthetically equivalent to acyl anions from which the corresponding acyl moiety can be regenerated at the end of the synthetic operation.



Scheme 14

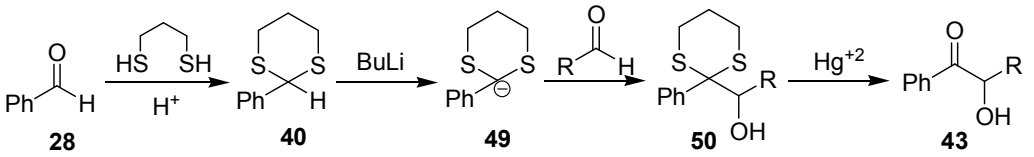
O-trimethylsilyl cyanohydrins were developed by Hünig [22a, b]. They can be thought as the protected form of the well-known carbanion intermediate of the benzoin condensation. Protection of oxygen ensures carbanion stability which would otherwise easily undergo retrocyanation to afford the corresponding aldehyde. According to Scheme 15, cyanohydrin silyl ethers **37** are easily obtained from the corresponding aldehydes in the presence of Lewis acid catalysts. Strong base (LDA) deprotonation of **37** at low temperature generates the corresponding acyl anion equivalent **43**, quenching with electrophile **44** affords the corresponding adduct **45** in a potentially reversible step. Adduct undergoes a 1,4 oxygen to oxygen silyl shift to afford the product **47** in O-TMS protected form that can be hydrolyzed to benzoin **49**. Protonation of **45** would lead to **48** that will eventually provide the desired benzoin upon hydrolysis. This protected cyanohydrin strategy is widely used for the synthesis of cross benzoins.



Scheme 15

Silyl protected cyanohydrin methodology has also been used in a complementary fashion that allow the synthesis of both isomer of a given benzoin from the same starting material.

Corey-Seebach dithiane [22c] addition is another widely used method in cross benzoin synthesis. In this approach, aldehyde **28** is converted into the corresponding dithiane **40** that can be deprotonated by BuLi to afford a stabilized carbanion **49**. **49** can be quenched subsequently with **44** to provide the protected benzoin product **50** (Scheme 16). Hydrolysis of the product affords the desired benzoin **43**. Although this method is widely used and proved to be superior over others for certain benzoin derivatives [22d], removal of the protection is generally problematic. Hydrolysis of the dithiane functionality is generally carried out by toxic Hg^{+2} salts to ensure irreversibility in favor of carbonyl regeneration. Alternative removal processes has been suggested and employed but the success of a specific method dramatically changes from one substrate to another.

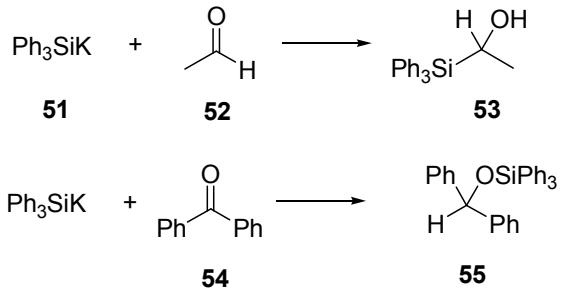


Scheme 16

Although strong base deprotonation of acyl anion precursors are routine means of cross benzoin synthesis, these methods suffer from major drawbacks. Above all, these methods are not atom and labor economic because of multiple protection and deprotection steps. Use of strong bases requires strict temperature control and moisture free reaction conditions. Considering the practical aspects of the cyanide umpolung processes, it is not unexpected to see chemists trying to find out better means of accessing acyl anion equivalents.

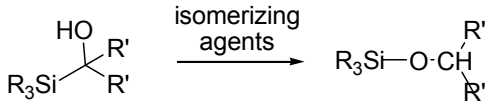
1.4.1 Acylsilanes as acylanion equivalent

The intramolecular 1,2-anionic migration of a silyl group from a carbon atom to an oxygen atom was originally recognized and studied by A. G. Brook in the late 1950s and early 1960's [23]. In the 1950's Gilm and co-worker's found that silylmetallic compounds such as triphenylsilylpotassium **(51)** add normally to aliphatic aldehydes or ketones to give the expected carbinols **(53)**, but with aromatic aldehydes or ketones (e.g., benzophenone) the isomeric alkoxysilanes **(55)** are formed instead [24]. It was not established whether this abnormal product arose from abnormal addition of the silylmetallic to the carbonyl group or whether it was the result of normal addition, followed by some kind of rearrangement (Scheme 17).



Scheme 17

Subsequent investigations revealed that all types of silylcarbinols rearrange, often fairly readily, when treated with small amounts of active metals, organometallic reagents, or bases such as pyridine, diethylamine, or triethylamine [25] (Scheme 18).



R:aryl, alkyl
R': aryl, alkyl, hydrogen
isomerizing agent: Na-K, NaH, RLi, Et_2NH, R_3N

Scheme 18

The reaction was first order in silylcarbinol, since the rates were doubled when the trace amounts of isomerizing agent were doubled, it was clear that the reaction was obeying pseudo-first-order kinetics overall.

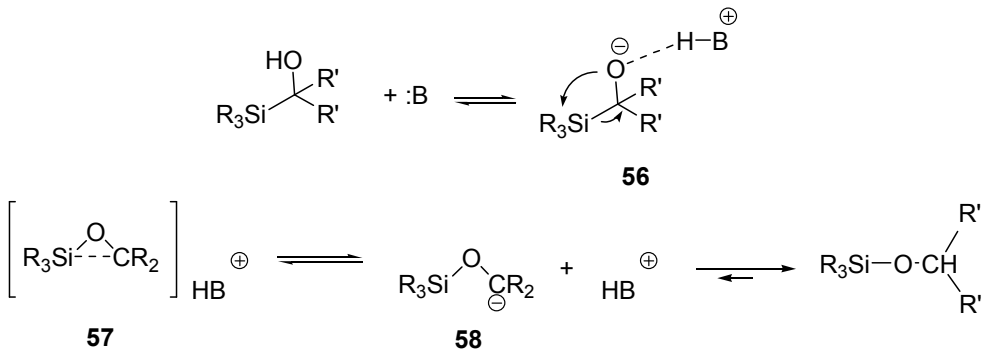
The rates are very sensitive to the nature of the group on the carbinol carbon. Carbinols bearing phenyl groups rearrange 103 times faster than when alkyl groups or hydrogen are substituted for phenyl. However, replacement of phenyl on silicon by methyl reduces the rates only by a factor of about 6 [26].

Kinetic studies showed that there is a very great sensitivity of the rearrangement to the substituents and specifically that considerable negative charge develops on the benzylic carbon during formation of the transition state, which was stabilized by electron-withdrawing and destabilized by electron-releasing substituents (Table 1) [27].

Table 1. Rates of silyl-oxygen rearrangement

Carbinol	Rate, l. mol^{-1} sec^{-1}
Ph_3SiCPh_2OH	7.6
$Ph_3SiCMePhOH$	$6.7\ 10^{-3}$
$Ph_3SiCHPhOH$	$5.7\ 10^{-3}$
$Ph_3SiC(CH_2Ph)PhOH$	$1.1\ 10^{-1}$
Ph_3SiCMe_2OH	Too slow to measure
$MePh_2SiCPh_2OH$	1.2
$Me_2PhSiCPh_2OH$	$2\ 10^{-1}$
Me_3SiCPh_2OH	$3.3\ 10^{-2}$

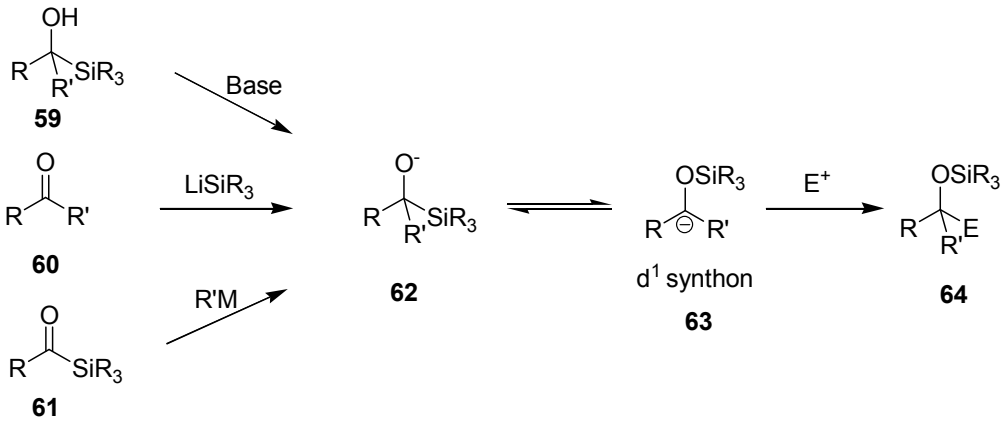
The kinetic data are satisfactorily explained by the mechanism shown in Scheme 19.



Scheme 19

The function of the basic catalyst is to remove the acidic carbinol proton, forming an α -oxyanion (**56)**. This ion subsequently attacks intramolecularly at silicon, passing through a transition state, **(57)** (or intermediate, by utilizing d orbitals; it has not been possible to differentiate between these possibilities), in which significant silicon-oxygen bond formation and silicon-carbon bond breaking have occurred, placing negative charge on carbon. This charge can be delocalized by electron-withdrawing substituents and the stabilized charge is protonated by protonated base. These kind of rearrangements in which oxygen-carbon or carbon-oxygen silyl migration takes place generally called as Brook rearrangements [28].

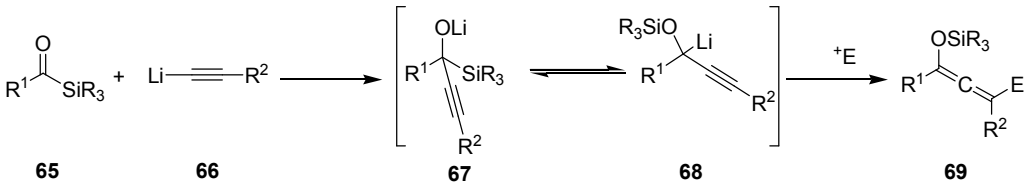
1,2-Brook rearrangement intermediates **63** react with electrophiles as carbon nucleophiles thus they can be classified as d^1 synthons. The 1,2-Brook rearrangement can be set up in several ways: most commonly an α-silylcarbinol **59** is treated with a base, when an aldehyde or ketone **60** is treated with a silyllithium reagent or when an acylsilane **61** is treated with a nucleophile. It is noteworthy that when nucleophilic addition to acylsilane is carried out with cyanide nucleophile, subsequent 1,2-Brook rearrangement affords the well-known deprotonated O-TMS cyanohydrin **43** of Hünig's method (Scheme 20).



Scheme 20

Among the possibilities mentioned above as strategies for inducing 1,2-Brook rearrangement as d^1 synthons, addition of nucleophiles to acylsilanes are highly promising. This approach can be used in a tandem carbon-carbon or carbon-heteroatom bond formation reaction because the critical silyl migration step is promoted by a bond formation at the carbonyl center that is followed by a second bond formation after the Brook rearrangement. In this respect use of acyl silanes have attracted increasing attendance.

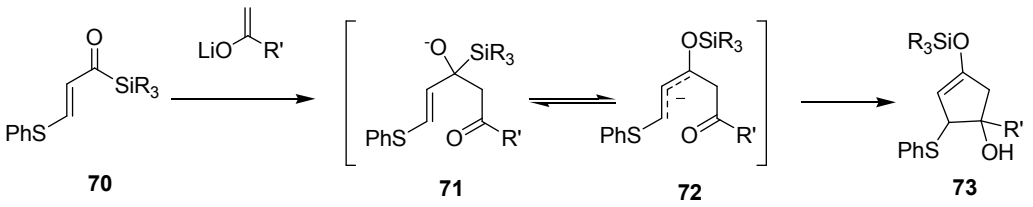
Acylsilanes have been utilized in a variety of tandem bond formation strategies and proved to be highly useful entities providing acyl anion intermediates [28]. It has been shown that carefully designed reactions could provide highly complex products as a result of one pot multiple bond forming steps. For example, Reich [29] had shown that addition of lithium acetylides **66** to acylsilanes **65** provide allenol silyl ethers. Reaction proceeds via addition of the alkynyl nucleophile to acylsilane followed by the Brook rearrangement forming a carbanion intermeadite **68** that reacts with an electrophile to provide the allenic product **69** (Scheme 21).



Scheme 21

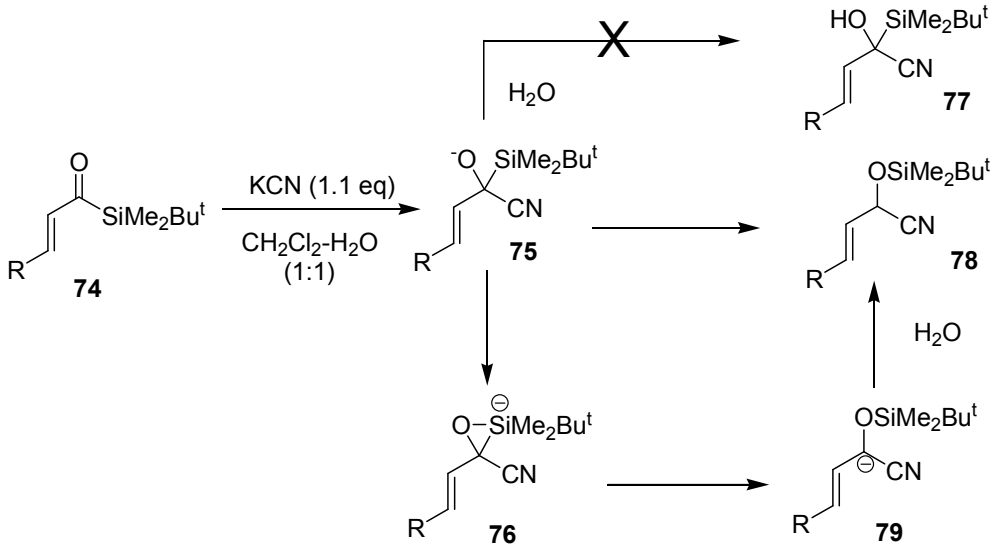
Takeda and co-workers [30] developed various transformations based on the Brook rearrangement of the acylsilanes. Among these interesting transformation, reactions of unsaturated acylsilanes bearing carbanion stabilizing group at β- position is intriguing. These substrates provide valuable homoenolates upon treatment with nucleophiles. Thus reaction of unsaturated acylsilane **70** with a lithium enolate

followed by a rearrangement affords the delocalized carbanion **72** that traps the present nucleophile intramolecularly as a homoenolate anion provided that there is a carbanion stabilizing group at the β-position. These two carbon-carbon bond forming processes provide valuable cyclopentanones **73** in the form of nucleophilic silylenol ethers (Scheme 22).



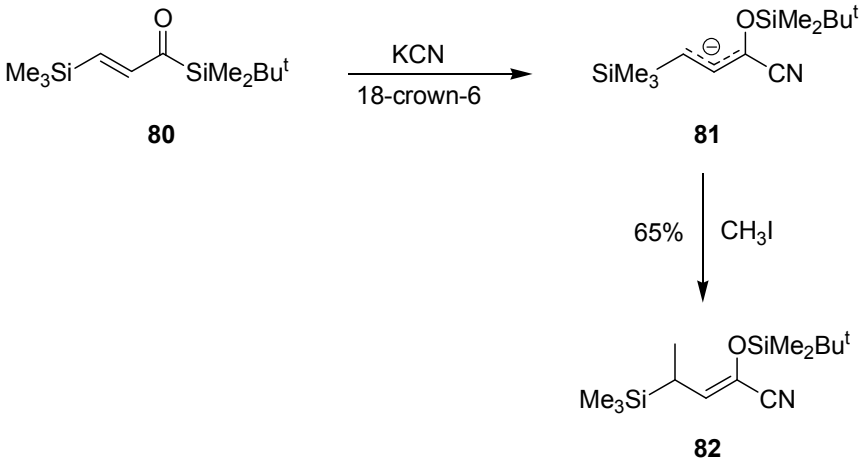
Scheme 22

Cyanide promoted Brook rearrangement of acylsilanes was first provided by Reich [31]. The use of cyanide nucleophile is quite interesting since it provides the well-known acyl anion intermediate widely used in the synthesis of acyloins. Takeda has shown that it possible to trap the carbanion **79** formed from acylsilane **74** and cyanide in aqueous media to provide the cyanohydrin product **78**. Interestingly, no product **77** arising from the O- protonation of **75** was observed. This was attributed to the faster intramolecular attack of the oxyanion on silicon compared to protonation of the oxyanion by the water. The possibility of a concerted process involving **76** was also invoked. This reaction was also shown to be useful in alkylation of the carbanion **79** in nonaqeous organic media (Scheme 23).



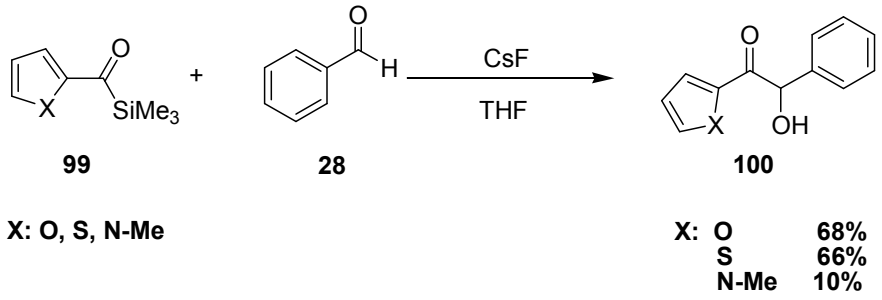
Scheme 23

In a similar reaction shown above, cyanide ion promoted Brook rearrangement of unsaturated acylsilanes **80** undergoes reactions with electrophiles as homoenolate **81** providing product type **82** [30] as shown in Scheme 24.



Scheme 24

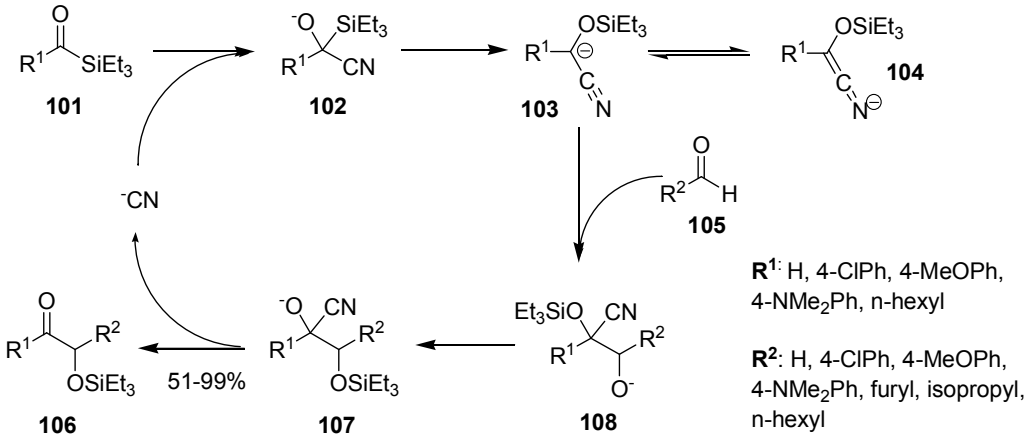
Synthesis of benzoins (or acyloins in general terms) requires the reaction of the carbanions of Brook rearrangement with carbonyl compounds as electrophiles. First example of this idea was reported by Degl'Innocenti in the fluoride catalyzed reaction of acylsilanes **99** with benzaldehyde to provide the expected benzoins **100** [33]. Yields were acceptable for furan and thiophene whereas pyrrole derivative proved to be a poor substrate. The utility of the reaction was also expanded to Michael addition and alkylation of the intermediate carbanions. This reaction was one of the first examples of a catalyzed reaction of acylsilanes with carbonyl reaction to provide acyloin products. Interestingly cyanide catalyzed Stetter version of this reaction was also reported by Degl'Innocenti (Scheme 25).



Scheme 25

Recently cyanide ion catalyzed reaction of acylsilanes **101** with aldehydes **105** in the presence of catalytic KCN and 18-crown-6 in Et_2O providing O-silyl protected benzoin adducts was reported [34]. The proposed mechanism of the reaction (Scheme 26) is very similar to that of the classical benzoin condensation catalyzed by cyanide. According to this mechanism, cyanide ion promoted Brook rearrangement of acylsilane **101** provides the acyl anion equivalent **103** in a usual manner. This is the very same intermediate obtained from the LDA deprotonation of O-silyl cyanohydrins. Considering the powerful carbanion stabilization provided by the nitrile, oxygen and the phenyl ring in case of aromatic acylsilanes (R^1=Ar), the formation of **104** is highly favored. Reaction with aldehyde and subsequent 1,4-silyl

migration affords alkoxide **107**. Retrocyanation leads to product α-silyloxy ketone **106** and release the cyanide needed to engage the rest of the acylsilane into the reaction. This reaction is completely regioselective and only provides the cross benzoin predicted by the mechanism. Yields range from good to excellent (66-95%) for reactions between aromatic acylsilanes and aromatic aldehydes.

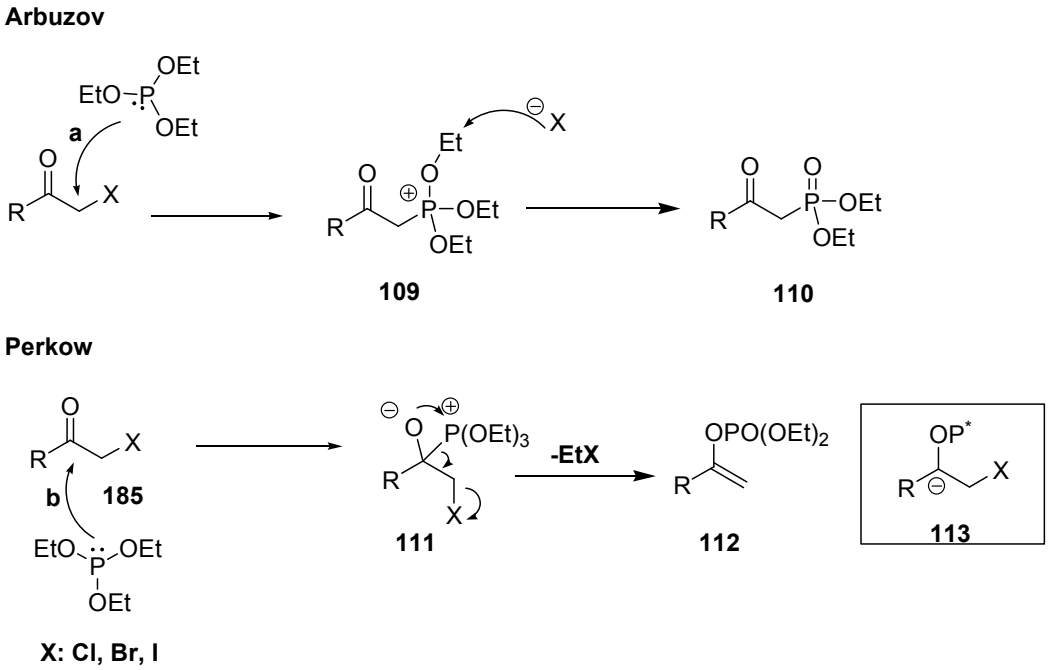


Scheme 26

1.4.2 Acyl phosphonates as an alternative acyl anion precursor

Phosphorus, like silicon, has the ability to migrate both from carbon to oxygen and oxygen to carbon under appropriate conditions [35].

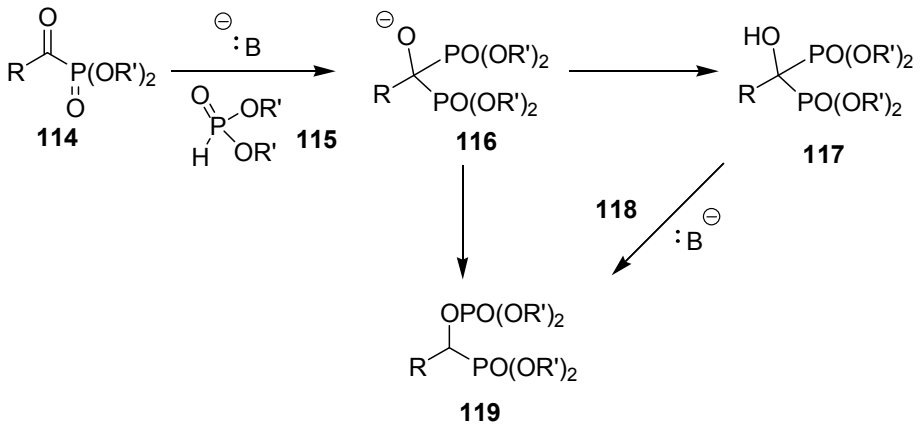
Probably the most intriguing example of migrating ability of phosphorus is the famous Perkow reaction [36]. Although its mechanism is not known exactly, it is generally accepted that a trivalent-phosphorus ends up as a pentavalent-phosphorus via a shift of phosphorus from carbon to oxygen. Perkow reaction is known to compete with the classical Arbuzov reaction and most of the time dominates the main reaction course. Mechanism of the Perkow reaction is generally depicted as shown in Scheme 27.



Scheme 27

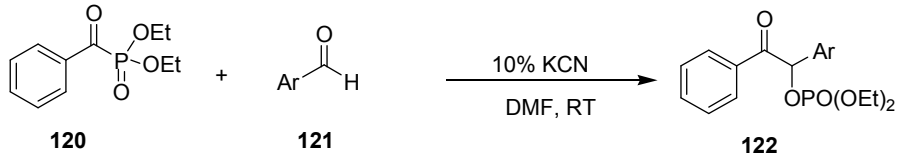
The mechanism of Perkow route involves the rearrangement of phosphorus from carbon to oxygen as in **111** resulting in enol ether **112**. Intermediates like **113** are sometimes invoked and it is actually an acyl anion equivalent eliminating a α-halogen group. It is obvious that putting a carbanion stabilizing group (like cyanide or phosphonate) instead of the carbon bearing the leaving group (CH_2X) would provide an opportunity to access to a new generation of acyl anion precursors.

Probably the most dominating examples of phosphonate-phosphate rearrangement were in the synthesis of controversial α-hydroxyalkylidenediphosphonate esters **117**. Synthesis of these compounds by the base catalyzed addition of dialkyl phosphites **115** to acyl phosphonate **114** were reported by McConnell and Coover [37] . Later it was shown that the product of this reaction was actually isomeric compound **119** having two different phosphorus atoms. [38] It is formed from rearrangement of intermediate **116** before protonation to **117**. It was also shown that isolated **117** rearranges to **119** under basic conditions (Scheme 28) [39].



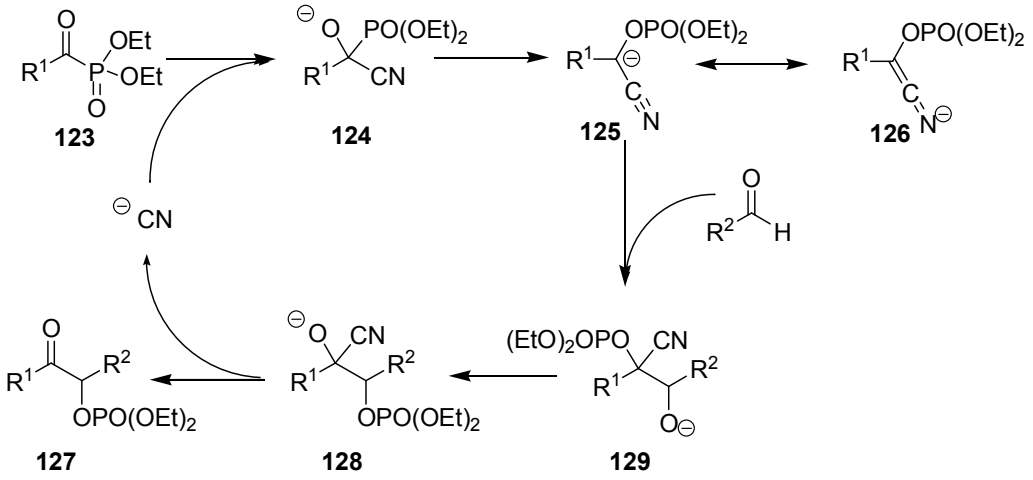
Scheme 28

Based on this knowledge, our group investigated acyl phosphonates as acylanion precursor in benzoin reaction [40]. Acyl phosphonates has shown their ability to generate acylanions via cyanide catalyst. Aromatic phosphonates reacts with aldehyde very efficiently to give benzoin derivatives (yields 86-94%) (Scheme 29).



Scheme 29

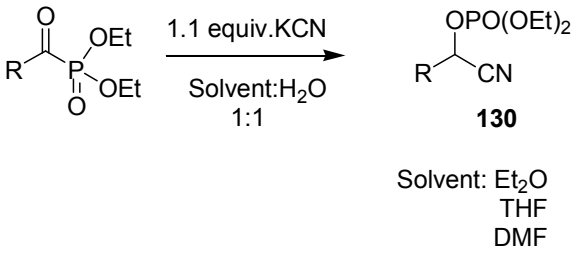
Reaction mechanism was similar to benzoin reaction with acylsilanes. Cyanide ion promoted rearrangement of **123** would provide the critical acyl anion equivalent **125**. Reaction of **125** with aldehyde afford the intermediate adduct **129** that undergoes a 1,4-O,O-phosphate migration leading to **128** that retrocyanates as usual to give the desired benzoin **127** and close the catalytic cycle (Scheme 30).



Scheme 30

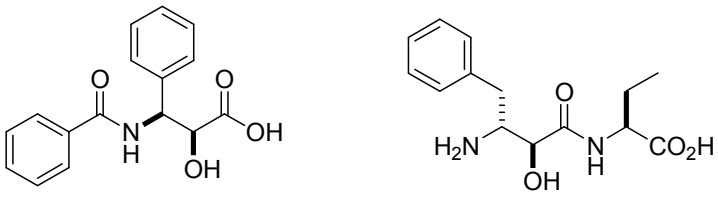
Aliphatic substrates were used as both as acceptor and donor parts. These subsrates were problematic due to their enolizable nature. While acceptor site was aliphatic, yields were so low. When cyanide source was changed from KCN to TMSCN+CsF, yields increased to good levels (yields 75-87%). In case of aliphatic donors reaction was still not effective and this problem tackled by using high catalyst load and carrying out reaction in refluxing toluene (yields 64-87%).

After the benzoin reaction, acyl phosphonates as acyl anion precursor were tested with a simpler electrophile, proton [41]. Reaction followed the same mechanism; generated acyl anion was protonated by water. In this reaction, reaction efficiency was sensitive to co-solvent which used together with water. Starting from aromatic and aliphatic phoshonates, cyanophoshonates were effectively synthesized with good to excellent yields (67-95%) (Scheme 31).



Scheme 31

In this way reduction of carboxylic acid was accomplished via protonation of acyl anion equivalents generated from acyl phosphonates without use of moisture free condition and reagents like DIBAL. Furthermore, some target molecules can be reached easily starting from amino acids without racemization. Two selected examples are the side chain of taxol **(131)**, an anti- cancer drug and bestatin, an anti-viral drug **(132)** (Scheme 32).



131

phenylisoserine

132

bestatin

Scheme 32

1.5 Aim of work

In recent years, synthesis of cyanohydrins both in racemic form and enantiopure form has taken a great deal of attention. The most abundant strategy for the synthesis of these useful entities is the addition of the cyanide anion to the appropriate carbonyl compound. This strategy allows the construction of a C-C bond but it has an apparent drawback of being limited to the use of a carbonyl compound. However cyanide anion promoted generation of an acyl anion equivalent that in turns react with a carbon centered electrophile in a tandem reaction, during which two C-C bonds are formed sequentially, would provide a great advantage. Within the frame of this aim, we studied the reactions between acylphosphonates and ethylcyanoformate catalyzed by the cyanide anion.

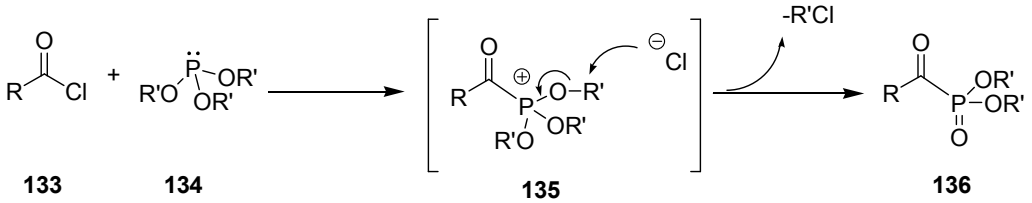
CHAPTER 2

RESULTS AND DISCUSSION

The main objective of this study was to test acyl phosphonates as acyl anion equivalents in tandem reactions and develop a new method for the acylation of acyl anion intermediates. We investigated the scope and limitations of this potentially useful approach for synthesizing functionalized cyanohydrins that may be starting materials for synthesis of β-lactam derivatives.

2.1 Synthesis of Acyl Phosphonates

Acyl phosphonates are easily available compounds. The most direct access to these compounds is the well-known Arbuzov reaction between acylchlorides **133** and trialkylphosphites **134** which proceeds via formation of an unstable intermediate **135** that eventually leads to acyl phosphonate **136** [42, 46]. It is generally carried out by mixing neat reactants at or below room temperature. The reaction can also be carried out in a proper organic solution. This reaction is highly efficient and clean in terms of product purity considering that the main side products are the gaseous alkyl chlorides (Scheme 33).



Scheme 33

Acyl phosphonates **136** are all obtained by the Arbuzov reaction depicted as in Scheme 33. Throughout this study we utilized variety of aliphatic and aromatic acyl chlorides in this particular transformation and found that it proceeds without any complications. All crude aromatic and aliphatic acyl phosphonates were obtained in near quantitave yields and, most of the time, they were pure enough to use directly. However, they were routinely purified with vacuum distillation to ensure the purity. Briefly, acyl phosphonates are easily available in high yields and purity from commercially available precursors with a simple single step reaction. Both aliphatic and aromatic substrates are tolerated in a similar fashion. And, contrary to some reports and expectations, acyl phosphonate**136** are stable enough to store in sealed flasks for months without decomposition. These practical aspects provide an appearent advantage for acyl phosphonates as acyl anion precursors. The acyl phosphonates, synthesized in this study, are summarized in Table 2.

Table 2. Some of the acyl phosphonates synthesized in this study.

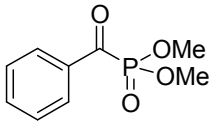
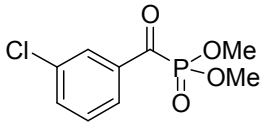
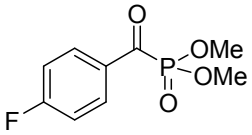
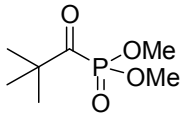
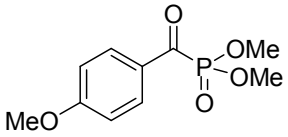
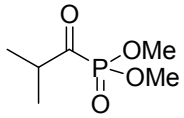
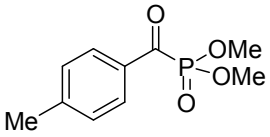
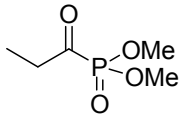
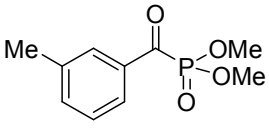
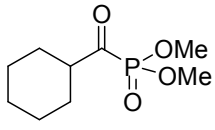
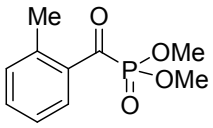
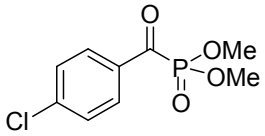
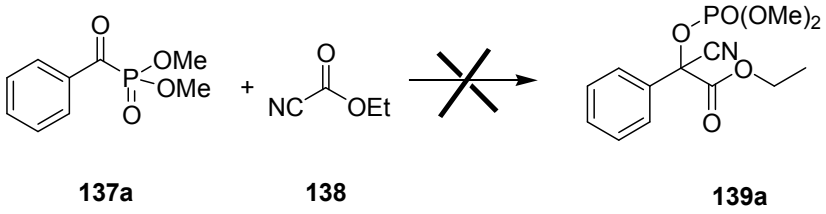
Entry	**Acyl phosphonate**	Entry	**Acyl phosphonate**
1		7	
2		8	
3		9	
4		10	
5		11	

Table 2. (cont.)

6		12	

2.2 C-acylation reactions of acyl anion intermediates generated via phosphonate-phosphate rearrangement

We proposed that acyl anion intermediates can be acylated to provide quarternary cyanohydrin type products as depicted in scheme 34. This type of reaction required the identification of an appropriate acyl anion precursor and a reactive acyl compound as an electrophile. While there are vast choices for electrophilic counterpart, other reacting partner, namely acyl anion equivalents, are seldom in the literature. We developed acyl phosphonates as acyl anion equivalents that generate the expected acyl anion equivalents in the presence of cyanide. Ethylcyanoformate **138** was chosen as the acylation agent due to the presence of cyanide as a leaving group in the molecule. This would provide a constant presence of cyanide anion in the reaction mixture throughout of the reaction. We tested the reaction with **137a** as donor and ethylcyanoformate as acyl electrophile [47] (Scheme 34).



137a **138** **139a**

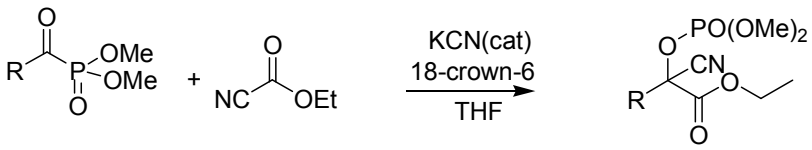
Scheme 34

Firstly, simple mixing the reaction partners **137a** and **138** did not provide any products in a variety of solvents. Considering the absence of an initiator to generate the very first acyl anion equivalents necessary for reaction to proceed, addition of catalytic amount of KCN was successful but severely limited. Addition of KCN was

helpful promoting the reaction in relatively polar solution, like DMF, and almost ineffective in typical organic solvents. We speculated the low solubility of KCN in typical solvents could be the reason and decided to use phase transfer catalysis to increase the solubility of KCN. The use of crown ethers, such as 18-crown-6 is typical and it is widely used as a phase transfer catalyst. Its effectiveness in organic transformations reactions utilizing KCN is well documented by studies of Evans [48]. In fact addition of catalytic amount of 18-crown-6 to the reaction mixture together with KCN boosted the reaction in a variety of solvents. Therefore we examined the reaction in different organic solvents in the presence of catalytic KCN and crown ether. All reactions were complete in 15-20 min regardless of the solvent. However, identity of the solvent was important on the efficiency of the reaction as summarized in table 2. Among the solvents tested, THF was best in terms of yield and product purity (Scheme 35, Table 3). Typical side product of this reaction was found to be the protonation of the critical acyl anion equivalent and the extend of the formation of this side product was varying from solvent to solvent. The possible reasons for these side products were thought to be the presence of water in the solvents and/or the possible presence of HCN in the ethylcyanoformate. The presence of HCN in ethylcyanoformate could be observed by ^{13}C-NMR and its possible presence in the reagent should be taken into account when utilizing this reagent.

Table 3. Results of solvent screening

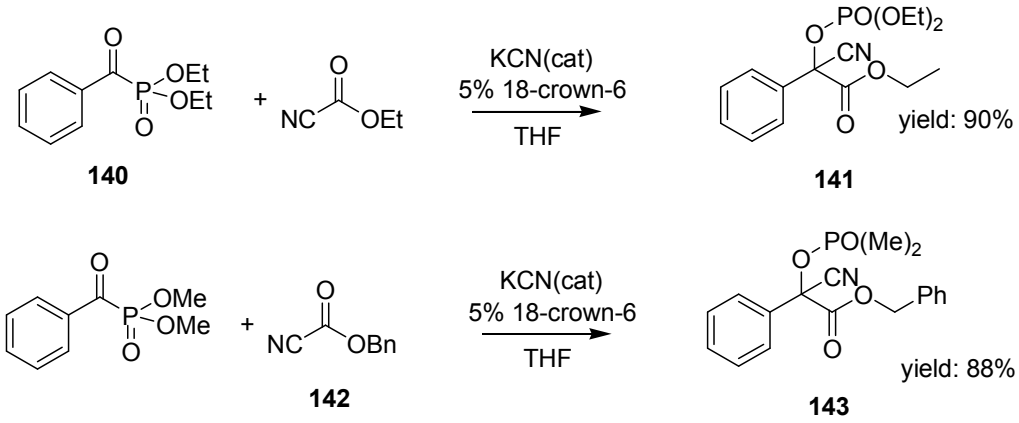
Entry	Solvent	Yield
1	Et_2O	75
2	THF	91
3	Toluene	88
4	DMF	82
6	$CHCl_3$	68
7	CH_3CN	79



Scheme 35

After some experimentation, we found that 5% 18-crown-6 and catalytic KCN just enough to start the reaction in 0.5 M solution of substrates in THF was provided best results.

After determining the optimum reaction conditions, we tested impact of both phosphonate ester and cyanoformate ester on the reaction efficiency. First we changed donor **137a** to benzoyl phosphonate ethyl ester **(140)**. We observed no deteriotitaion in yields and purity of product. Second benzylcyanoformate **(142)** was used as acceptor against **(137a)** and again the reaction proceeded with a similar efficiency (Scheme 36).

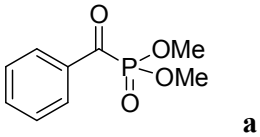
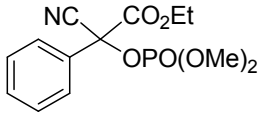
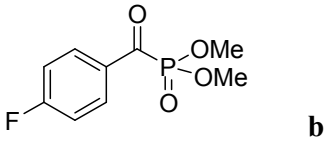
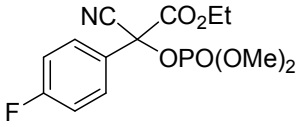
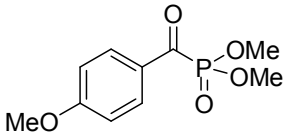
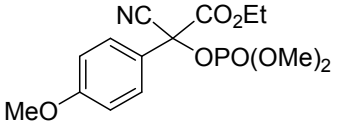
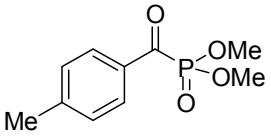
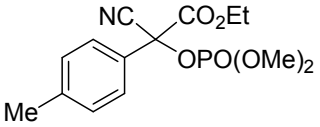
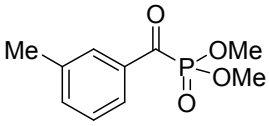
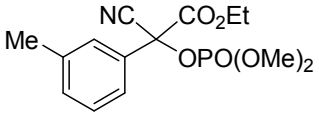
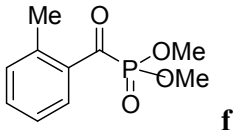
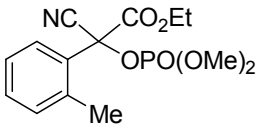
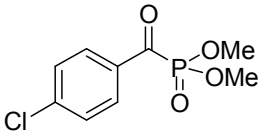
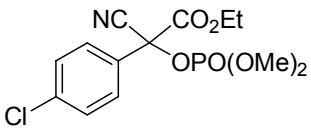


Scheme 36

After that the scope of the developed reaction was tested with a selection of acyl phosphonates in electronic and steric properties to shed light on the factors effecting the reaction. For this purpose, we used aromatic acyl phosphonates with different groups on different positions and aliphatic acyl phosphonates as summarized in Table 4. In general, reaction provided the expected products with very good yields regardless of the sterics and electronics of the acylanion equivalents. Aromatic acyl phosphonates with electron-withdrawing and electron-donating groups substituted on various positions were better in terms of reaction efficiency and product purity than

aliphatics. In fact, reactions with aromatic acyl phosphonates provided crude products that were pure enough for most of the purposes (entries 1, 2, 3, 4, 5, 7; NMR spectra of these products were provided in the Appendix A). This aspect adds a practical dimensionality to this synthesis strategy. When products were contaminated with side products, they were easily purified with column chromatography to provide analytically pure products.

Table 4. Yields and products of reaction between acyl phosphonates and ethylcyanoformate

Entry	**Acyl phosphonate**	**Product**	Yield (%)
1	 **a**	 **a**	91
2	 **b**	 **b**	86
3	 **c**	 **c**	88
4	 **d**	 **d**	95
5	 **e**	 **e**	90
6	 **f**	 **f**	90
7	 **g**	 **g**	90

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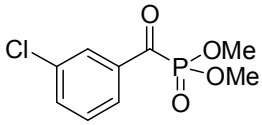
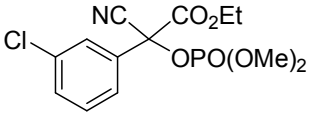
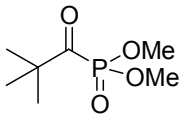
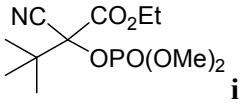
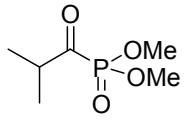
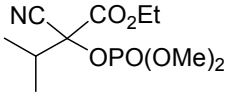
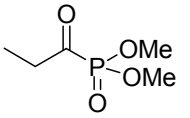
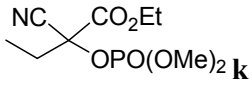
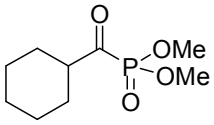
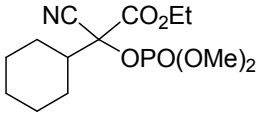
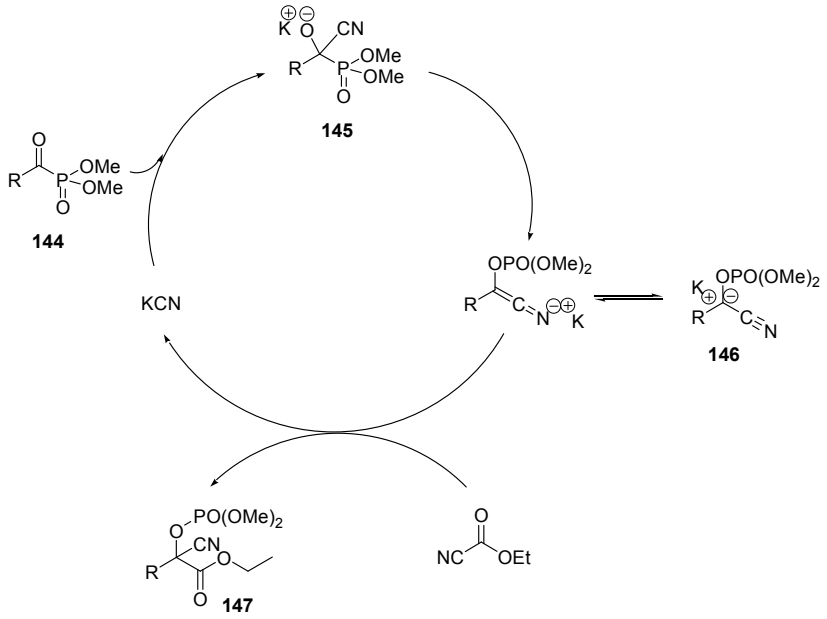
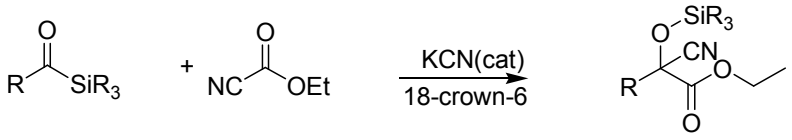
8	 **h**	 **h**	90
9	 **i**	 **i**	87
10	 **j**	 **j**	75
11	 **k**	 **k**	69
12	 **l**	 **l**	90

Mechanism of the reaction is similar to mechanism of the benzoin synthesis from acyl phosphonates. The reaction is initiated by KCN which is solubilized by 18-crown-6 and addition of cyanide to phosphonate **(144)** produces **145**. **145** rearranges to **146** which is stabilized by oxygen, cyanide and phenyl groups. That intermediate attacks to ethylcyanoformate to furnish **147** with releasing a cyanide anion entering the catalytic cycle (Scheme 37).



Scheme 37

At 2002, Johnson et. al. performed similar reaction with acylsilanes and ethylcyanoformate [49]. They used ether and toluene as solvent and same catalytic system, KCN-18-crown-6-ether. Although results were good, they suffered from the low reactivity and inefficiency of several substrates. They solved the problems with using high catalyst load and high amount of acceptor with slow addition of acylsilane and in some cases high temperature with high catalyst load was necessary (Scheme 38).



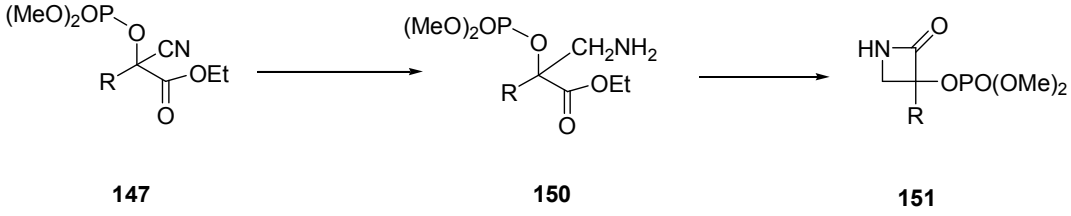
Scheme 38

- They used 60% of 18-crown-6, 4-6 equivalent cyanoformate and slow addition of acylsilane for aliphatic examples

- High temperature, high catalyst load, 4-6 equivalent cyanoformate for aromatic examples with deactivating groups (4-OMe and 4-NMe_2).

Comprasion of these two results, from acyl phosphonates and acylsilanes, shows that acyl phosphonates produces much more effectively acylanion intermediate in a large spectrum of solvents in acylation reaction. Beside, if we compare synthesis of acyl phosphonates and acyl silanes, acyl phosphonates are superior due to its simple and single step preparation.

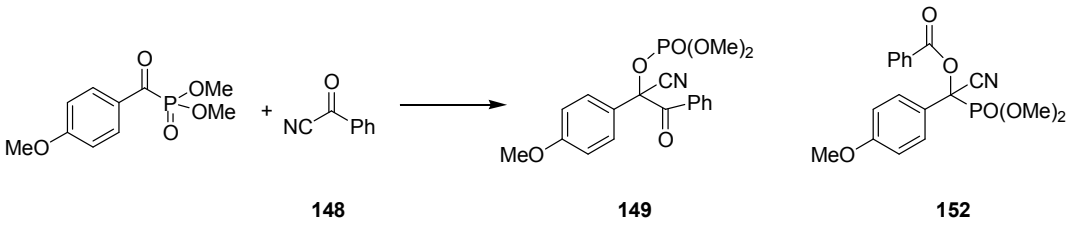
147 could be potential precursor of β-lactams which are biologically important compounds. Possible route to β-lactams can start with reduction of nitrile of **147,** which gives **150** and lactamization of it produces **151**. Silyl derivative of **147** was converted with same route to β-Lactam by Johnson with 70% yield (Scheme 39).



Scheme 39

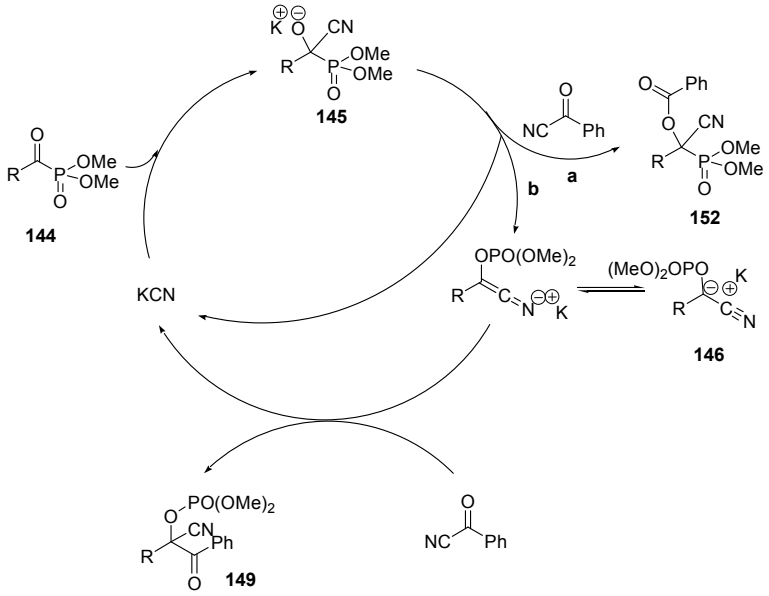
Next, we turned our attention to other acceptors for acylation. We used benzoyl cyanide **(148)** with **137c** in order to develop a general acylation reaction with broad acceptor and donor spectrum**.** Under similar reaction conditions, conversion of acyl phosphonate was observed with TLC within short time. But product was not the expected one, namely C-acylation **149,** but O-acylation **152**. These isomeric products can be easily differentiated with ^{13}C- and ^{31}P-NMR. **149**, which contains phosphate group, resonances between -1 and -2 ppm in ^{31}P-NMR, whereas in **152**, phosphonate

resonances between 10 and 15 ppm [50]. And also **152** contains an ester group that is also a key for differentiation (Scheme 40).



Scheme 40

Mechanism starts like Scheme 36 but after formation **145,** rearrangement can not occur and reaction follows the route **a** instead of **b**, thus **145** is trapped by **148** to afford **152** (Scheme 41).



Scheme 41

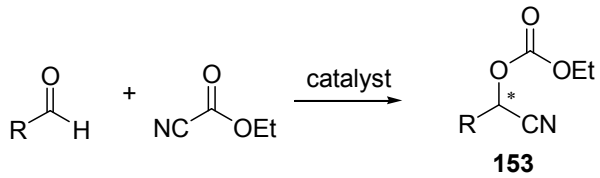
In order to force the reaction to follow the route **b**, we designed several reaction. We tested influence of concentration, temperature and slow addition of acyl phosphonate

to outcome of reaction. Even decreasing the temperature and slow addition of the acyl phosphonate did not affect to outcome, dilution of the reaction medium resulted in a mixture of products **149** and **152** with changing proportions. Further experiments showed that synthesizing **152** was not eligible via this method. Because the ratio of these isomers was not reproducible and isolation of the product was problematic.

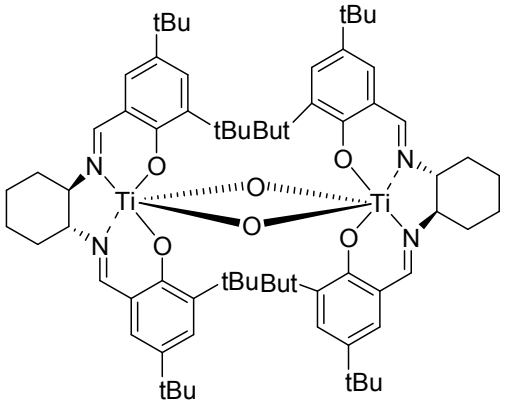
2.3 Enantioselective addition to ethylcyanoformate

There is currently a significant interest in asymmetric cyanohydrin synthesis due to the synthetic versatility of chiral cyanohydrins and their utility as chiral starting materials for natural product synthesis. A range of catalyst classes are available for this reaction. However, most of these methods require the use of either hydrogen cyanide or trimethyl silyl cyanide as cyanide source [51]. Both of these reagents are volatile and hence hazardous, and trimethylsilyl cyanide is also too expensive for commercial use. Cyanoformate esters are also known to react with aldehyde and ketones, leading directly to cyanohydrin carbonates [52]. Syntheses of cyanohydrin carbonates are important due to stability of O-protecting groups.

Feng [53], North [54], Moberg [55], has shown enantipure cyanohydrin carbonates could be synthesized by reacting an aldehyde with ethylcyanoformate in the presence of the salen-titanium bimetallic catalyst (**154**) (Scheme 42).



153



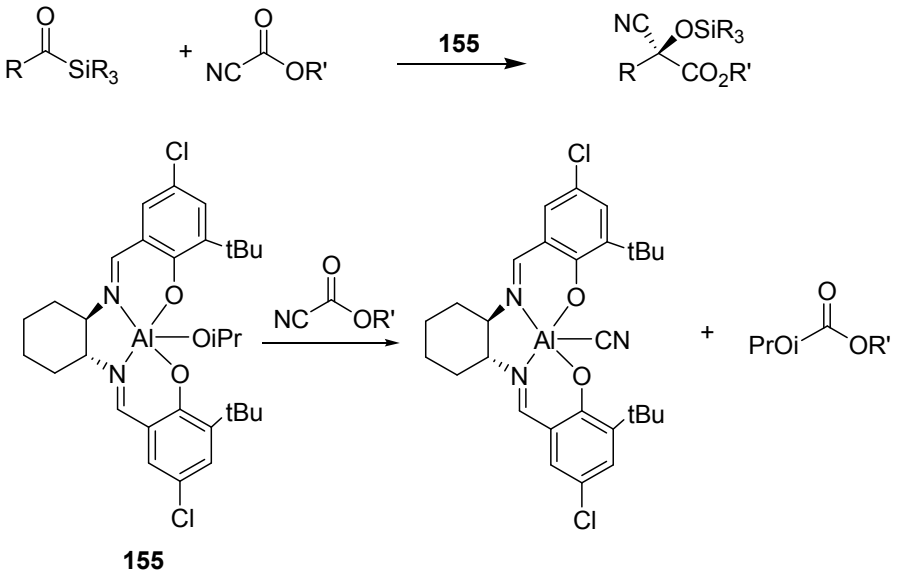
catalyst

154

Scheme 42

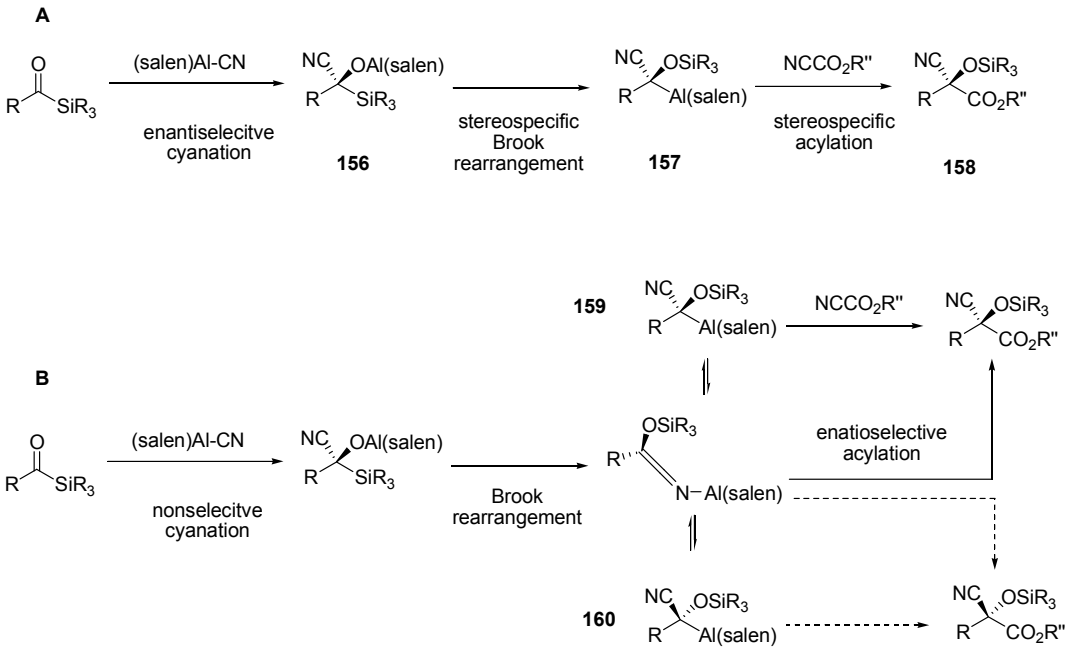
North's group has reported asymmetric addition of ethylcyanoformate to aldehyde in 2003. They tested reaction with benzaldehyde and **154** as catalyst. Initially, they reputed that the reaction proceeds at -73^0C with 1 mol % of **154** give to 94% enantiomeric excess. They tested both aromatic and aliphatic aldehydes and results were good to excellent (76-95 % ee).

In 2004, Johnson's group has accomplished enantioselective C-acylation reaction with acylsilane and ethylcyanoformate with salen-aluminum catalyst [56] (Scheme 43).



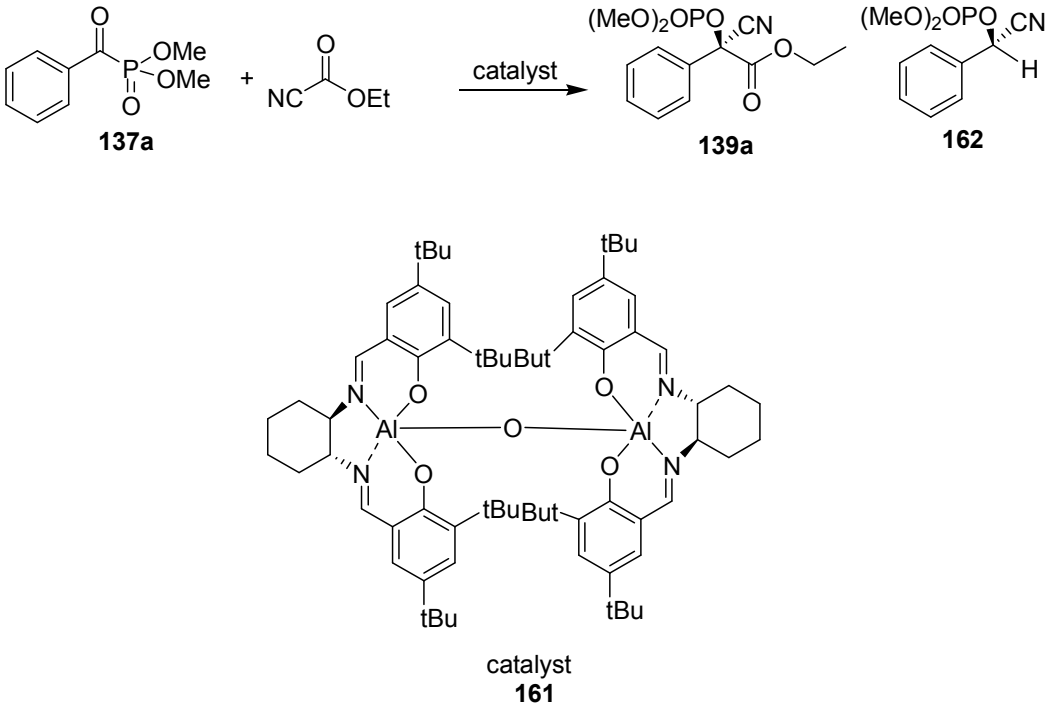
Scheme 43

They found via NMR studies the evidence of the formation of (salen)Al-CN complex. They also indicated an equilibrium between diasteromeric species **159** and **160** (Scheme 44). However, mechanism of chirality transfer is problematic though they proposed some possible mechanisms. First, enantioselective cyanation **(156)** is followed by stereospecific 1-2 Brook rearrangement and organoaluminum **(157)** is acylated sterospecifically (Scheme 44, route A). Second, acylsilanes may undergo nonselective cyanation and/or Brook rearrangement to afford interconverting organoaluminum diastereomers **(159 and 160)** that undergo acylation at different rates (Scheme 44, route B).



Scheme 44

Combining these precedents, we wished to acylate acylanion intermediate stereoselectively generated from acyl phosphonate. First, we tested bimetallic-salen titanium **(154)** and alimunium catalysts **(161)** (Scheme 45).



Scheme 45

Both catalysts were used with two equivalents of ethyl cyanoformate in toluene at room temperature. Reaction with catalyst **154** led to consumption of benzoyl phosphonate **(137a)** in 12 hours. We also verified formation of product **139a** with almost an equal amount of product **162** which was formed by protonation of acyl anion intermediate by NMR spectroscopy. Then we removed the catalyst from crude mixture by filtering reaction mixture through a pad of silica with CH_2Cl_2 which gave only mixture of **139a** and **162**. Unfortunately, reaction with **161** gave no conversion even after four days. And we decided to use of KCN as co-catalyst to initiate reaction since the compatibility of KCN has been shown previously with similar catalyst system [57]. Therefore, reaction was completed after several hours and reaction was purified explained previously. Again reaction resulted in almost equal amount of mixture of **139a** and **162**. Enatiomeric excess (ee) of both of these reactions and consequent ones determined without further purification. ee values were determined with HPLC with columns with chiral stationary phase (flow rate: 1, AD-H column, 20 min. and 21 min. for product **139a** and at the same condition 34 min. and 36 min.

for product **162**). While catalyst 154 conclude in **139a** with 20% ee and **162** 6% ee, catalyst **161** gave racemic mixture of both products.

After these results, we screened some solvents, which were CH_2Cl_2, THF and $CHCl_3$, with **154**; they resulted in 10%, 53% and 13% e.e respectively. According to these results, we choose THF as solvent for further experiments. We also investigated DABCO and DMAP as co-catalyst which may initiate reaction with attacking to cyanoformate and release a cyanide anion. These reactions were resulted in nearly racemic mixtures. Reactions generally suffered from reproducibility and several reactions resulted in ee values varying from 25 and 53 % ee.

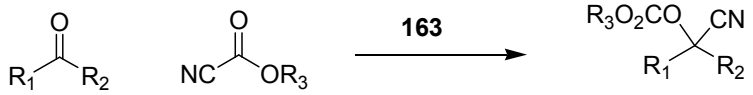
Although it is very speculative at this point, **154** can act as bifunctional catalyst as two metal centers activate both acyl phosphonate and ethylcyanoformate which is in accord with the previous reports related to O-carboxyl cyanohydrin formation starting with aldehyde and ethylcyanoformate. Besides that, ethyl cyanoformate contains trace amount of HCN that may take a role in reaction and could also be the source of **162.** But we should keep in mind that in our racemic reactions, some of our crude products were analytically pure without any contamination with **162**.

These results show us that acyl anion addition to ethyl cyanoformate is suitable to render it stereoselective. But reaction needs more investigation and further optimization. This can be accomplished by changing the reaction conditions while still using **154** or identifiying a better catalyts system.

2.4 Enantioselective protonation

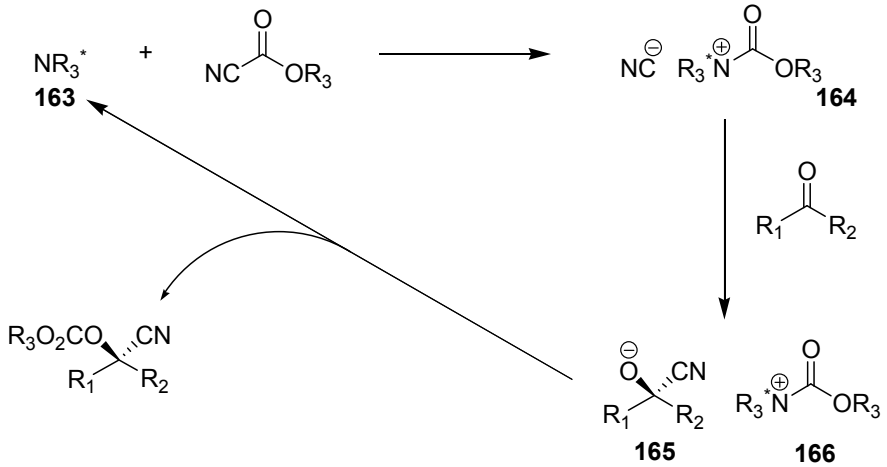
Protonation acyl anion intermediates are valuable reactions which gives some opportunities by means of providing a newer and flexible route to different kind of product and biological important compounds. In light of these, we tried to make this reaction in an enantioselectivity fashion.

Deng's group has reported that chiral amines can catalyze O-carbonyl cyanohydrin formation with using acyl cyanide as cyanide source [58]. They used dimeric cinchona alkoloids-$(DHQD)_2AQN$ (**163**) as catalyst (Scheme 46).



Scheme 46

Reaction proceeds through formation of quartenary amines (**164**) with catalyst (**163**) and acyl cyanide with releasing of cyanide ion. Free cyanide attacks to carbonyl group to form corresponding alkoxide (**165**) and that alkoxide attack chiral quarternary amine (**166**) for acylation (Scheme 47).



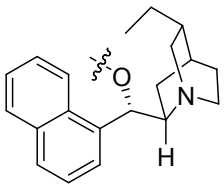
Scheme 47

Firstly, we thought that cinchona alkoloids can be used for carbonyl acylation, according to Deng's studies. We tested first quinidine (**167**) as catalyst in dry $CHCl_3$, CH_2Cl_2, Toluene and THF and benzoyl phosphonate (**137a**) and ethyl cyanoformate as subsrates under argon atmosphere. **137a** was consumed, except in toluene, after 12 hours which was determined by TLC analysis but ^{1}H-NMR analysis showed the

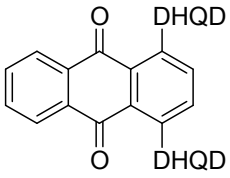
formation of **162** instead of **139a**. HPLC analysis showed that the products were not racemic even though the extend of enantioselectivity was poor (Table 5, Scheme 48).

Table 5. Results of solvent screening

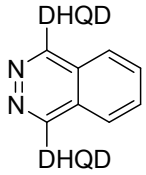
Entry	Solvent	ee(%)
1	$CHCl_3$	23
2	CH_2Cl_2	14
3	THF	12
4	Toluene	n.d



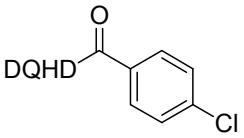
DHQD



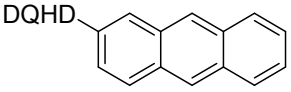
$(DHQD)_2$AQN-163



$(DHQD)_2$PHAL-169



168

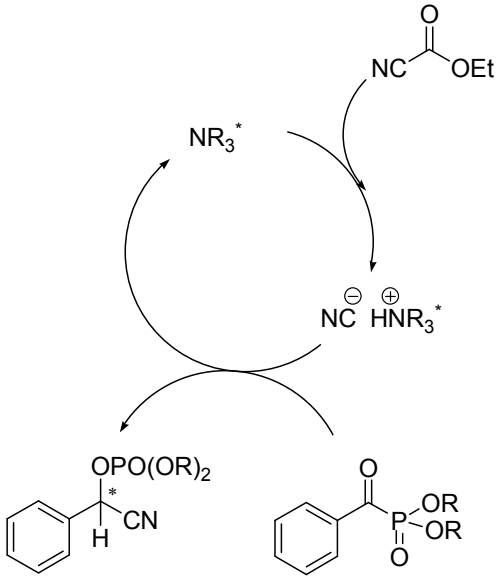


170

Scheme 48

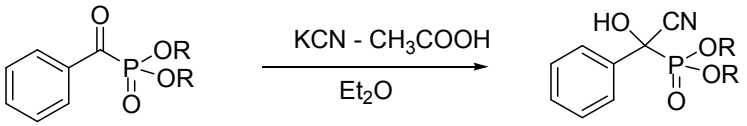
When we repeated reactions carefully under dry reaction conditions, we still couldn't observe any **139a**. We investigated effect of hydroxyl group on catalyst on outcome and we used O-protected catalysts; hydroquinide-4-chloro-benzoate (**168**), (DHQD) PHAL (**169**), hydroquinidine-4-phenanthryl ether (**170**). But product was again **162**. And then we reduced temperature to -40^0C, which could effect outcome of reaction and also amount of enantio-selectivity. Reduced temperature did not changed product but ee was increased to 40 %.

It is known that ethylcyanoformate contains varying amounts of HCN which can be confirmed by the signals at 135 ppm in ^{13}C-NMR. This HCN was silent in our racemic C-acylation reactions and we were able to obtain analytically pure products. However the behavior of the reaction is different in the presence of the amines used as the source of chirality. It could be speculated that these chiral amines behave as a catalyst for HCN delivery via formation of ammonium cyanide species that delivers cyanide to acyl phosphonate and in return act as a source of proton for the critical acyl anion equivalent. The extend of the formation of protonation product could be understood if it is assumed that chiral amine also catalyses the hydrolysis of the ethylcyanoformate. In this respect, the source of water is the chiral amine itself that are known to be hygroscopic. Therefore this reaction system represent a situation of enantioselective HCN delivery system and the transfer of chirality is probably occur thorough an enantioselective protonation of the acyl anion equivalent (Scheme 49).



Scheme 48

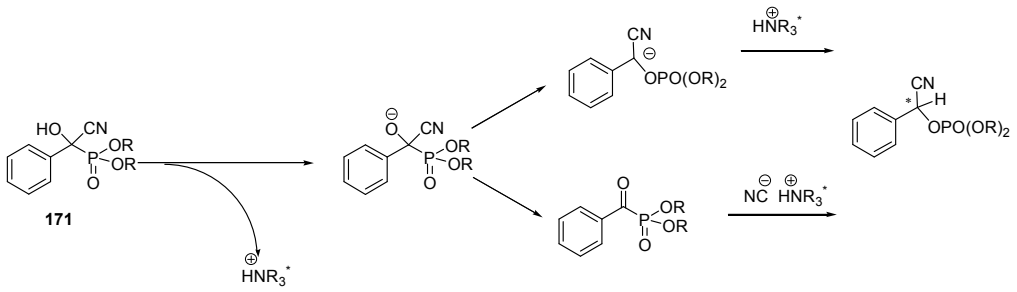
In order to shed light on these possibilities, we synthesized the corresponding cyanohydrin of acyl phosphonate by adding KCN and acetic acid to the wet ethereal solution of the acyl phosphonate (Scheme 50).



171

Scheme 50

This cyanohydrin formation proceeds with quantitative conversion to the expected cyanohydrin product **171**. When this cyanohydrin product **171** was treated with the chiral amine **168**, it quantitavely forms the protonation product. This product was formed via deprotonation of the hydroxyl group that can rearrange and protonated at the nucleophilic carbon. It is also possible that cyanohydrin product undergoes a retrocyanation to form an ammonium cyanide intermediate that can deliver HCN (Scheme 51).



Scheme 51

These findings simply showed us the potential of these chrial amines as a HCN delivery system and also shed light on the formation of protonated product in the attempted C-acylation reactions.

We used the combination of an acid and KCN as an equivalent of HCN. We investigated different acids and they gave different result in terms of absolute configuration and enantio-induction of the products. Different absolute configuration was indicated by negative sign in table 6. There was no linear relationship between strength of acid and amount of selectivity and absolute configuration of the products. It could be proposed that those acids are involved in the transition state as counter ions and therefore has decisive effect on the outcome of the reaction.

Table. 6 Results of acid screening

Entry	Acid	ee(%)
1	TFA	13
2	Camphor sulfonic Acid	9
3	p-toluene sulfonic acid	(-)17
4	Acetic Acid	(-) 23
5	Benzoic Acid	16
6	Phenol	(-) 15

Hereafter, stereoselective protonation acyl anion intermediate with chiral amines is a promising reaction. Considering the very little number of successful enantioselective protonations, it can be clearly stated that enantioselective protonations are challenging reactions. Therefore our efforts through the understanding the nature of this reaction and optimization to its full potential is underway.

CHAPTER 3

EXPERIMENTAL

THF was freshly distilled from sodium-benzophenone. Purification of products was carried out by automatic flash column chromatography. Analytical thin layer chromatography was performed on aluminium sheets precoted with silica gel 60F254. Visualization was accomplished with UV light and anisaldehyde or 2,4-dinitrophenylhydrazine followed by heating. ^{1}H-NMR spectra are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Acyl phosphonates were prepared according to well established procedures and purified by vacuum distillation. All acyl phosphonates were stored in flasks under nitrogen and they were stable at least for months. KCN was dried under vacuum at 100 °C. 18-crown-6 was recrystallized from acetonitrile and dried under vacuum at ambient temperature.

3.1 General Procedure for addition acyl phosphonates to ethylcyanoformate:

An oven dried Schlenk flask with a magnetic stir bar was charged with 0.5 mmol of acylphosphonate. Subsequently, 1 mL of dry THF, 0.6 mmol of ethyl cyanoformate, 0.025 mmol of 18-crown-6, and a tip of spatula of KCN was added under argon. The reaction was monitored by TLC (completed within 15-20 min.). After the completion of the reaction, the reaction was extracted with ether and brine three times. The organic phases were combined and concentrated under reduced vacuum. If needed, the crude

product was purified with automatic flash column chromatography using ether-petroleum ether as eluent.

(Ethoxycarbonyl)(cyano)(phenyl)methyl dimethyl phosphate(139a): Yield 142 mg (91%) yellow liq.; IR (Neat) : ν =2963, 1769, 1255, 1042 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, *J*=7.3 Hz), 3.79 (3H, d, *J*=11.5 Hz), 3.88 (3H, d, *J*=11.5 Hz), 4.20-4.30 (2H, m), 7.37-7.41 (3H, m), 7.62-7.64 (2H,m); ^{13}C NMR ($CDCl_3$) δ 12.6, 54.0 (d, *J*=5.5 Hz), 54.3 (d, *J*= 5.5 Hz), 63.3, 76.7 (d, *J*= 6.3 Hz), 115.3, 124.6, 128.0, 129.6, 131.6 (d, *J*= 9.6 Hz), 163.3 (d, *J*=2.3 Hz); ^{31}P NMR ($CDCl_3$) δ –1.64 ppm .

(Ethoxycarbonyl)(cyano)(4-fluorophenyl)methyl dimethyl phosphate(139b): Yield 142 mg (86%) yellow liq.; IR (Neat) : ν = 2964, 1769, 1252, 1040 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, *J*=6.3 Hz), 3.79 (3H, d, *J*=11.7 Hz), 3.88 (3H, d, *J*=11.7 Hz), 4.20-4.31 (2H, m), 7.05-7.11 (2H, m), 7.60-7.65 (2H,m) ^{13}C NMR ($CDCl_3$) δ 13.6, 55.0 (d, *J*=6.0 Hz), 55.3 (d, *J*=6.0 Hz), 64.4, 76.1 (d, *J*=6.1 Hz), 115.2, 116.2 (d, *J*=22.4 Hz), 127.9 (d, *J*= 8.8 Hz), 128.6 (d, *J*=67 Hz), 163.4 (d, *J*=150.6 Hz), 165.1; ^{31}P NMR ($CDCl_3$) δ –1.64 ppm .

(Ethoxycarbonyl)(cyano)(4-methoxyphenyl)methyl dimethyl phosphate(139c): Yield 151 mg (88%) yellow liq.; IR (Neat) : ν = 2962, 1761, 1511, 1257, 1046 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, *J*=6.7 Hz), 3.76 (3H, s), 3.77 (3H, d, *J*=11.5 Hz), 3.86 (3H, d, *J*=11.5 Hz), 4.19-4.30 (2H, m), 6.88 (2H, d, *J*= 8.5 Hz), 7.54 (2H,d, *J*= 9.1); ^{13}C NMR ($CDCl_3$) δ 12.7, 53.9 (d, *J*= 6.6 Hz), 54.2 (d, *J*=6.6 Hz), 54.4, 63.2, 75.5 (d, *J*=6.7 Hz), 113.4, 114.4, 123.4 (d, *J*= 9.4 Hz), 126.3, 160.3, 163.4 ; ^{31}P NMR ($CDCl_3$) δ –2.29 ppm .

(Ethoxycarbonyl)(cyano)(4-methylphenyl)methyl dimethyl phosphate(139d): Yield 155 mg (95%) yellow liq.; IR (Neat) : ν = 2962, 1766, 1451, 1282, 1037 s cm-1.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.23 (3H, t, *J*=7.0 Hz), 2.32 (3H, s), 3.77 (3H, d, *J*=11.7 Hz), 3.87 (3H, d, *J*=11.6 Hz), 4.16-4.35 (2H, m), 7.17 (2H, d, *J*=8.1 Hz), 7.49

(2H, d, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 13.7, 21.2, 54.8 (d, *J*=6 Hz), 55.1 (d, *J*=6 Hz), 64.0, 76.5 (d, *J*=6.7 Hz), 115.3, 125.7, 129.7, 137.2, 140.7, 164.3; ^{31}P NMR (CDCl3) δ: -1.90 ppm.

(Ethoxycarbonyl)(cyano)(3-methylphenyl)methyl dimethyl phosphate(139e): Yield 147 mg (90%) yellow liq.; IR (Neat) : ν = 3435, 1764, 1257, 1048 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, *J*= 7.1 Hz), 2.32 (3H, s), 3.78 (3H, d, *J*=11.6 Hz), 3.87 (3H, d, *J*=11.6 Hz), 4.17-4.33 (2H, m), 7.18-7.20 (1H, m), 7.24-7.29 (1H, m), 7.40-7.41 (2H, m); ^{13}C NMR ($CDCl_3$) δ 13.6, 21.4, 54.9 (d, *J*= 6.0 Hz), 55.3 (d, *J*= 6.0 Hz), 64.2, 76.7, 115.5, 122.7, 126.1, 128.9, 131.3, 132.6 (d, *J*= 9.2 Hz), 139.1, 164.3; ^{31}P NMR ($CDCl_3$) δ –2.20 ppm

(Ethoxycarbonyl)(cyano)(2-methylphenyl)methyl dimethyl phosphate(139f): Yield 147 mg (90%) yellow liq.; IR (Neat) : ν = 2962, 1767, 1283, 1034 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, *J*= 7.6 Hz), 2.46 (3H, s), 3.74 (3H, d, *J*=11.0 Hz), 3.82 (3H, d, *J*=11.0 Hz), 4.27-4.39 (2H, m), 7.15-7.24 (2H, m), 7.26-7.31 (1H, m), 7.52 (1H, d, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.1, 54.9 (d, *J*= 5.3 Hz), 55.1 (d, *J*= 6.1 Hz), 64.3, 77.2 (d, *J*=6.9 Hz), 115.0, 126.4, 127.5, 130.5, 130.6, 132.8, 137.1, 164.0; ^{31}P NMR ($CDCl_3$) δ –2.60 ppm .

(Ethoxycarbonyl)(cyano)(4-chlorophenyl)methyl dimethyl phosphate(139g): Yield 156 mg (90%) yellow liq.; IR (Neat) : ν = 2960, 1761, 1279, 1037 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, *J*=7.3 Hz), 3.83 (3H, d, *J*=11.9 Hz), 3.88 (3H, d, *J*=11.7 Hz), 4.24-4.34 (2H, m), 7.37 (2H, d, *J*= 8.6 Hz), 7.57 (2H,d, *J*= 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 55.0 (d, *J*=5.9 Hz), 55.3 (d, *J*= 6.0 Hz), 64.5, 76.1 (d, *J*= 6.2 Hz), 115.0, 127.1, 129.3, 131.2 (d, *J*= 9.4 Hz), 136.9, 163.9; ^{31}P NMR ($CDCl_3$) δ –2.10 ppm.

(Ethoxycarbonyl)(cyano)(3-chlorophenyl)methyl dimethyl phosphate(139h): Yield 156 mg (90%) yellow liq.; IR (Neat) : ν = 2962, 1765, 1275,

1035 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, *J*=7.1 Hz), 3.81 (3H, d, *J*=11.6 Hz), 3.90 (3H, d, *J*=11.6 Hz), 4.23-4.35 (2H, m), 7.32-7.40 (2H, m), 7.52-7.54 (1H, m), 7.60-7.63 (1H, m); ^{13}C NMR ($CDCl_3$) δ 13.7, 55.1 (d, *J*= 6.0 Hz), 55.4 (d, *J*= 6.1 Hz), 64.6, 76.2, 115.0, 123.9, 125.9, 126.8, 130.3, 130.8, 134.6 (d, *J*= 9.3 Hz), 135.2, 152.2, 163.9; ^{31}P NMR ($CDCl_3$) δ –2.10 ppm .

1-(Ethoxycarbonyl)-1-cyano-2,2-dimethylpropyl dimethyl phosphate(139i): Yield 127 mg (87%) colorless liq.; IR (Neat) : ν = 3435, 2962, 1756, 1259, 1045, 800 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.11 (9H, s), 1.31 (3H, t, *J*= 6.7 Hz), 3.79 (3H, d, *J*=8.4 Hz), 3.82 (3H, d, *J*=8.4 Hz), 4.29-4.34 (2H, m), 6.88 (2H, d, *J*= 8.5 Hz), 7.54 (2H,d, *J*= 9.1); ^{13}C NMR ($CDCl_3$) δ 12.9, 23.8, 39.2 (d, *J*= 8), 53.8 (d, *J*= 5.7 Hz), 54.0 (d, *J*= 5.7 Hz), 62.5, 81.3 (d, *J*=8.3 Hz), 114.3, 163.0 ; ^{31}P NMR ($CDCl_3$) δ –0.96 ppm .

1-(Ethoxycarbonyl)-1-cyano-2-methylpropyldimethyl phosphate(139*j*): Yield 105 mg (75%) colorless liq.; IR (Neat) : ν = 2955, 1752, 1451, 1030, 810 s cm-1.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.05 (d, *J*=6.8 Hz, 3H); 1.09 (d, *J*=6.7 Hz, 3H); 1.33 (t, *J*=7.1 Hz, 3H); 2.30 (m, 1H); 3.78 (s, 3H); 3.81 (s, 3H); 4.31 (dq, J_1=1.8 Hz, J_2= 7.1 Hz, 2H) ^{13}C NMR ($CDCl_3$) δ: 13.9; 16.6; 16.7; 37.3 (d, *J*=9 Hz); 54.9 (d, *J*=6 Hz); 55.0 (d, *J*=6 Hz) ; 63.7; 80.1 (d, *J*=8 Hz); 114.6; 164.9 ^{31}P NMR (CDCl3) δ: -1.44 ppm.

1-(ethoxycarbonyl)-1-cyanopropyl dimethyl phosphate(139k): Yield 98 mg (74%) colorless liq.; IR (Neat) : ν = 2968, 1756, 1028, 803 s cm-1.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.08 (3H, t, *J*=7.4 Hz), 1.31 (3H, t, *J*=7.1), 2.08-2.15 (2H,m) 3.78(3H, d, *J*=4.3 Hz) 3.81(3H, d, *J*=4.3 Hz), 4.28-4.33(2H, m) ^{13}C NMR ($CDCl_3$) δ: 7.0; 13.0; 31.6; 31.8; 54.4 (d, *J*=6 Hz); 54.7 (d, *J*=6 Hz) ; 62.9; 75.5 (d, *J*=7.6 Hz); 114.3; 164.0 ^{31}P NMR (CDCl3) δ: -2.18 ppm.

(Ethoxycarbonyl)(cyano)(cyclohexyl)methyl dimethyl phosphate(139l): Yield 144 mg (90%) colorless liq.; IR (Neat) : ν = 2962, 1759, 1450, 1261, 1026, 801 s cm-1.; ^{1}H NMR ($CDCl_3$) δ 1.06-1.33 (8H, m), 1.62-1.87 (5H, m), 1.96-2.02 (1H, m), 3.78 (3H, d, *J*=5.4 Hz), 3.81 (3H, d, *J*=5.4 Hz), 4.27-4.34 (2H, m); ^{13}C NMR ($CDCl_3$)

δ 13.9, 25.4 (d, *J*=9.3 Hz), 26.7 (d, *J*=11.8), 30.3, 46.0 (d, *J*= 8.2), 54.8 (d, *J*= 5.4 Hz), 55.0 (d, *J*=5.9 Hz), 63.6, 79.6, (d, *J*= 8 Hz), 114.8, 164.8; ^{31}P NMR ($CDCl_3$) δ –1.64 ppm.

(Ethoxycarbonyl)(cyano)(phenyl)methyl diethyl phosphate(141): Yield 153 mg (90%) yellow liq.; IR (Neat) : ν = 2985, 1767, 1259, 1024 s cm-1.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (3H, t, *J*=7.2 Hz), 1.28 (3H, t, *J*=7.0), 1.34 (3H, t, *J*=7.2 Hz), 4.10-4.30 (6H,m), 7.34-7.41(3H, m), 7.60-7.65 (2H,m); ^{13}C NMR ($CDCl_3$) δ: 12.7, 14.9 (d, *J*=7.3 Hz), 15.0 (d, *J*=7.5 Hz), 63.1, 63.8 (d, *J*=6.1 Hz), 64.1 (d, *J*=6.0 Hz), 75.6, 114.3, 124.6, 128.0, 129.5, 131.9 (d, *J*=9.4 Hz), 163.4
^{31}P NMR (CDCl3) δ: -4.60 ppm.

((Benzyloxy)carbonyl)(cyano)(phenyl)methyl dimethyl phosphate(143): Yield 165 mg (88%) yellow liq.; IR (Neat) : ν = 2961, 1770, 1453, 1282, 1041 s cm-1.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.76 (3H, d, *J*=11.6 Hz), 3.80 (3H, d, *J*=11.6 Hz), 5.18 (1H, d, *J*=12.2 Hz), 5.22 (1H, d, *J*=12.2 Hz), 7.12-7.19 (2H, m), 7.20-7.25 (3H, m), 7.30-7.40 (3H, m), 7.55-7.60(2H,m), ^{13}C NMR ($CDCl_3$) δ: 55.0(d, *J*=6.0 Hz), 55.3(d, *J*=5.9 Hz), 69.5, 115.2, 125.7, 128.1, 128.6, 128.7, 129.1, 130.6, 132.4, 132.5, 133.9, 164.1; ^{31}P NMR (CDCl3) δ: -2.20 ppm.

3.2 General Procedure for enantioselective addition acyl phosphonates to ethylcyanoformate:

A flame dried schlenk was charged with 0.01 mmol catalyst, 0.1 mmol benzoyl phosphonate and then 0.5 mL dried THF was added under argon atmosphere. After stirring mixture 10 minutes, 0.2 mmol ethylcyanoformate was added via syringe. Reaction was controlled with TLC. Reaction filtered through a pad of silica with CH_2Cl_2. Corresponding mixture was concentrated with vacuum.

3.3 General Procedure for racemic protonation of acyl anion equvialent:

KCN (0.55 mmol) was added to the solution of 0.5 mmol acylphosphonate in 2 mL diethyl ether (or appropriate solvent). After 5 min stirring 1 mL water was added to the mixture. After completion of the reaction (<15 min) (if solvent DME or THF reaction time is 1–2 h), the mixture was diluted with 5 mL ether and 5 mL water. Organic phase was separated and dried with MgSO4 and evaporated under reduced pressure. The products are purified by using flash column chromatography (EtOAC–hexane).

Cyano(phenyl)methyl diethyl phosphate: yellow liq.; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, dt, *J*=1.1, 7.1 Hz), 1.40 (3H, dt, *J*=1.1, 7.1 Hz), 3.93-4.02 (2H,m), 4.13-4.21 (2H, m), 6.07 (1H, d, *J*=8.8 Hz), 7.45-7.51 (3H, m), 7.54-7.60 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, *J*=6.9 Hz), 16,0 (d, *J*=6.9 Hz), 64.7 (d, J=6.1 Hz), 64.9(d, *J*=6.0 Hz), 66.5 (d, *J*=4.7 Hz), 116.2, 127.5 , 129.3, 130.6, 132.5 (d, *J*=5.1 Hz); ^{31}P NMR ($CDCl_3$) δ -2.20.

3.3 General procedure for enantioselective protonation of acyl anion equvialent:

A oven dried schlenk was charged with catalyst (%30) and dried solvent (1 mL). After that, acyl phosphonates (0.5 mmol) and ethylcyanoformate was added via syringe under argon. Reaction was controlled with TLC. Corresponding mixture was extracted with EtOAc and 1 N HCl.

CHAPTER 4

CONCLUSION

This study can be divided in two parts. First one is C-acylation of acyl anion equivalent generated from acyl phosphonates which leads functionalized cyanohydrin derivatives. Second part is the development of enantioselective addition to ethylcyanoformate and protonation of acyl anion intermediate.

Acyl phosphonates were found so effective for carbonyl acylation in terms of yields, purity of product and reaction times. If we compare the reaction with similar ones, it is superior because of reaction conditions, catalyst load for most of the subsrates, especially aliphatic and deactivated aromatic examples. But reaction suffers type of acceptor used in the reaction. When acyl cyanide was used apart from cyanoformate, O-acylation was dominating product over C-acylation.

Enantioselective acyl anion reactions were promising after a limited test reaction for both of addition to ethylcyanoformate and protonation. Bimetallic salen-titanium catalyst was a promising catalyst for addition to ethylcyanoformate. But this reaction should be optimized, with may be by changing temperature, concentration, additive, catalyst type. Cinchona alkoloids were used as organocatalysts for protonation reaction and they showed interesting results that should be studied further.

In conclusion, acyl phosphonates were tested as acyl anion precursor for a tandem reaction and they proved their better efficiency and reactivity than acylsilanes. And also acyl phosphonates are readily susceptible to stereoselective reaction.

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APPENDIX A

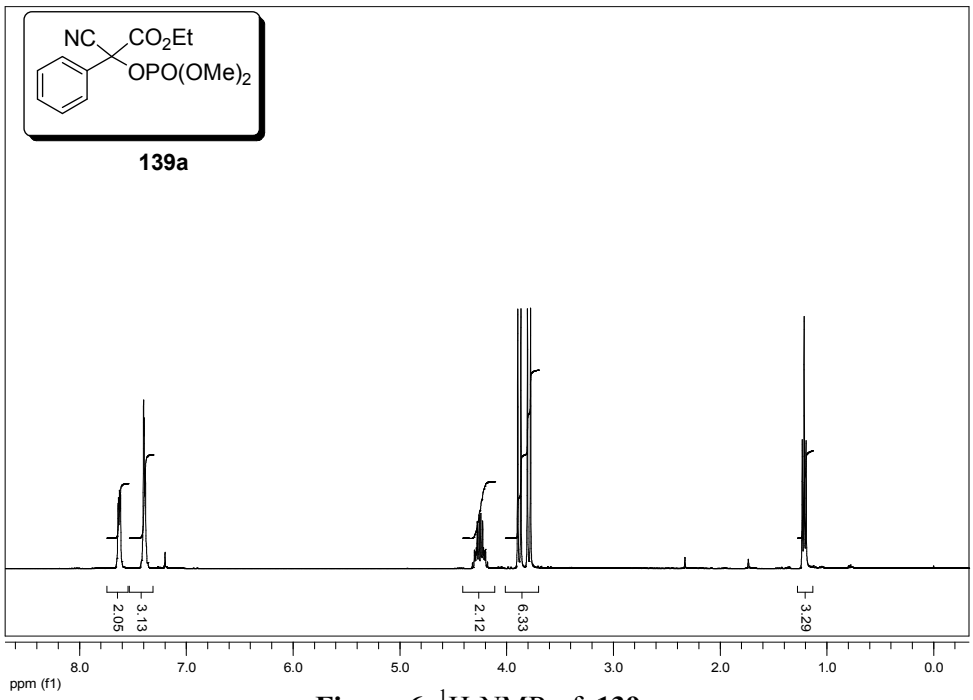

Figure 6. ^{1}H-NMR of **139a**

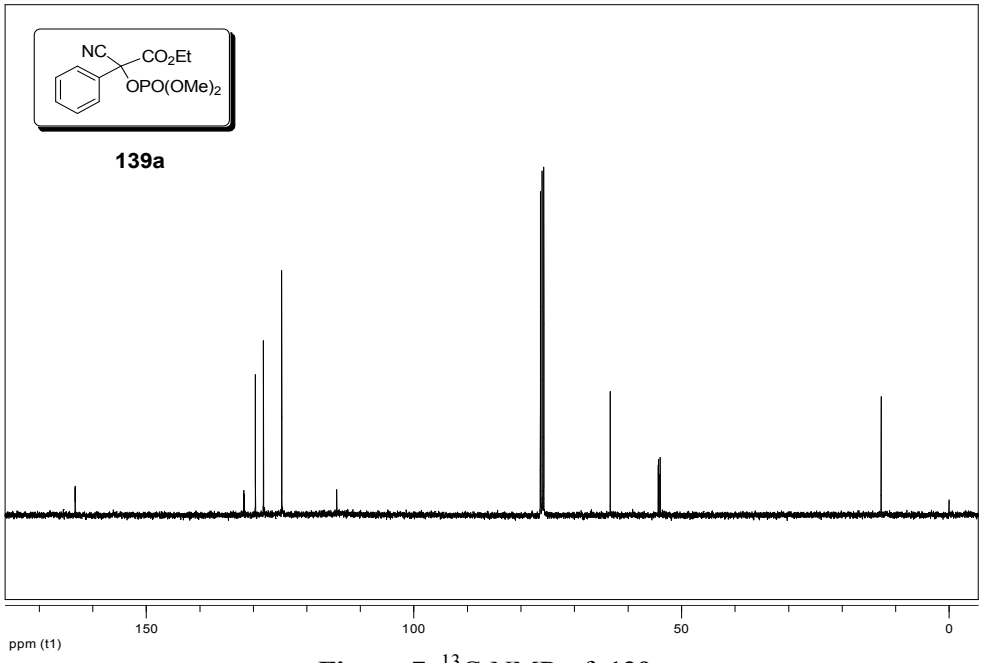

Figure 7. ^{13}C-NMR of **139a**

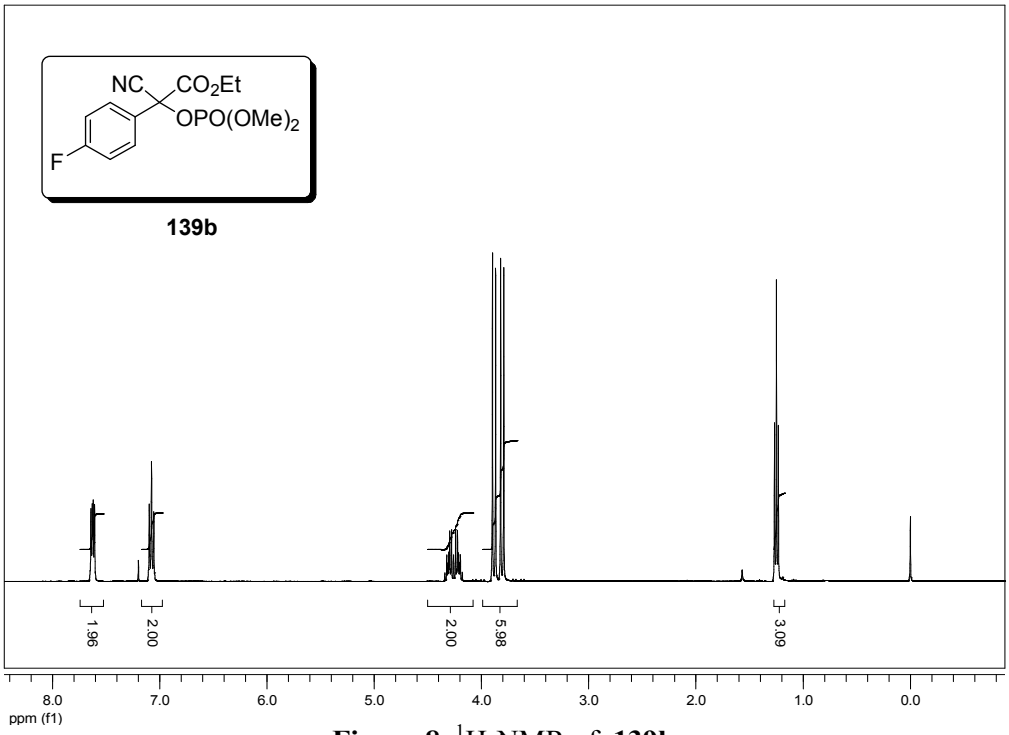

Figure 8. ^{1}H-NMR of **139b**

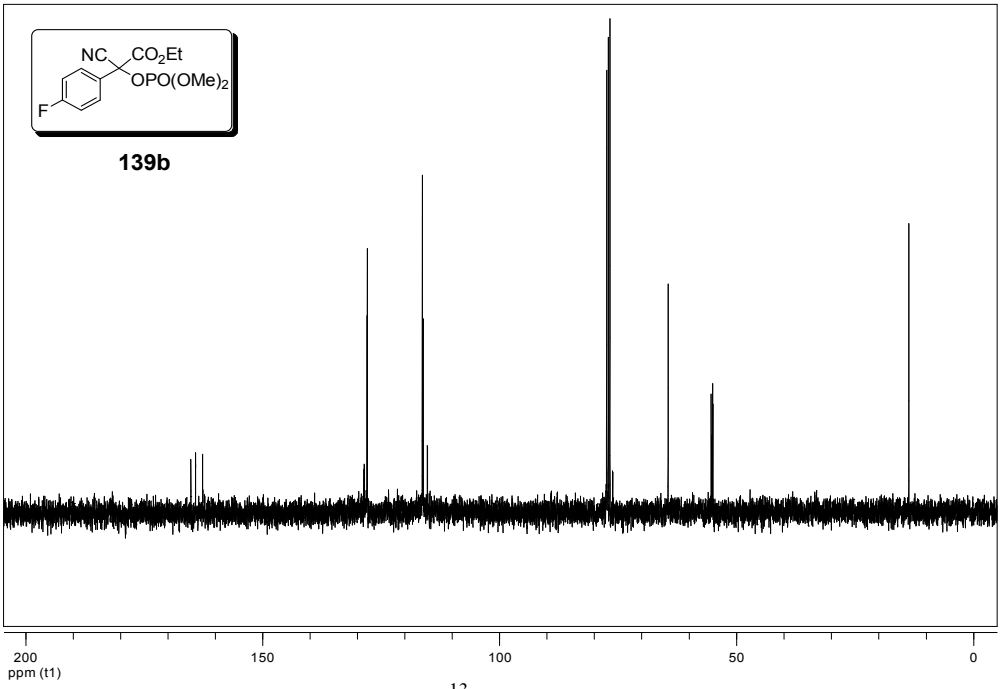

Figure 9. ^{13}C-NMR of **139b**

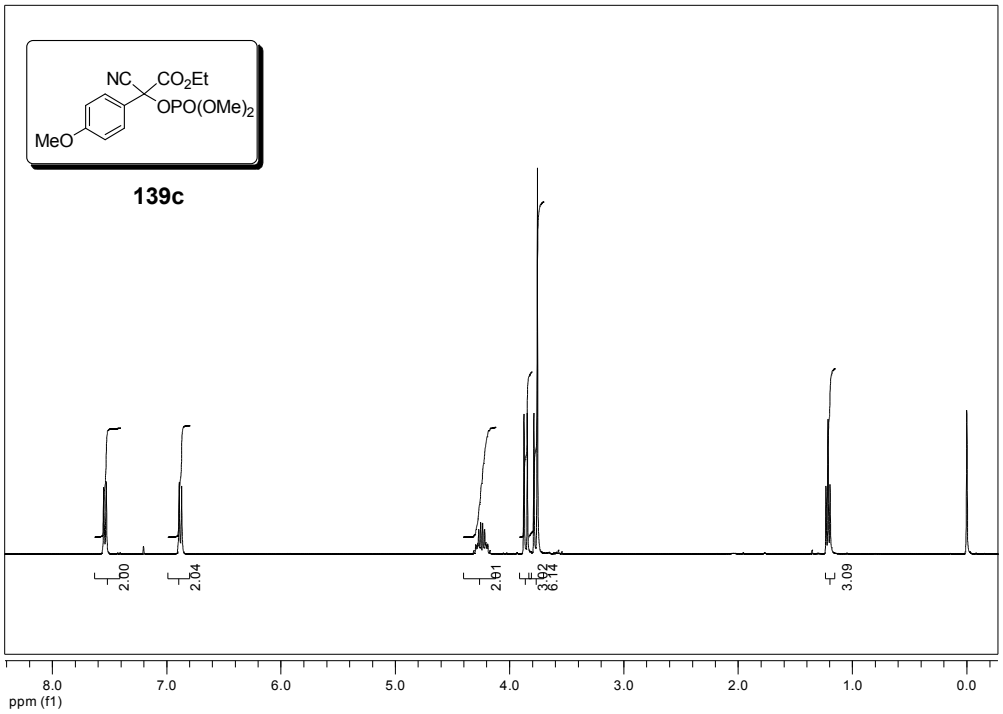

Figure 10. ^{1}H-NMR of **139c**

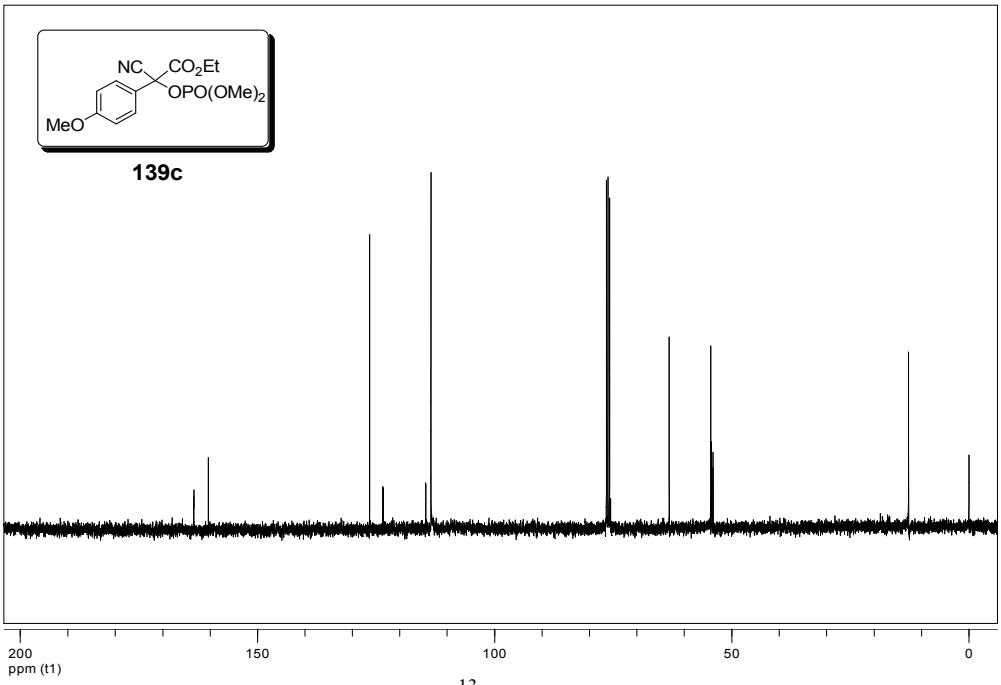

Figure 11. ^{13}C-NMR of **139c**

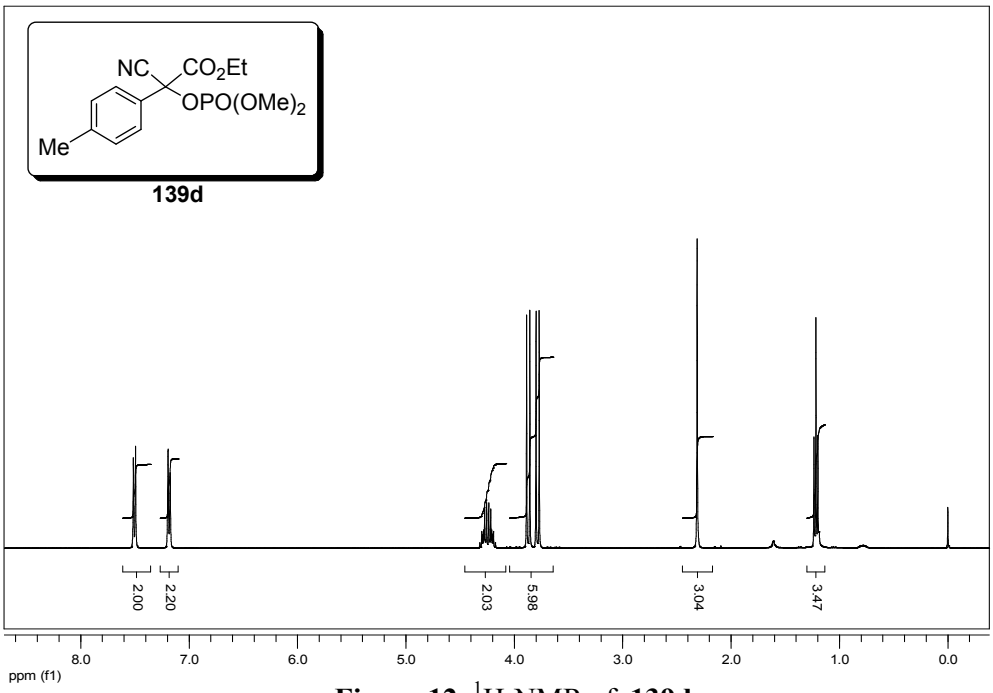

Figure 12. ^{1}H-NMR of **139d**

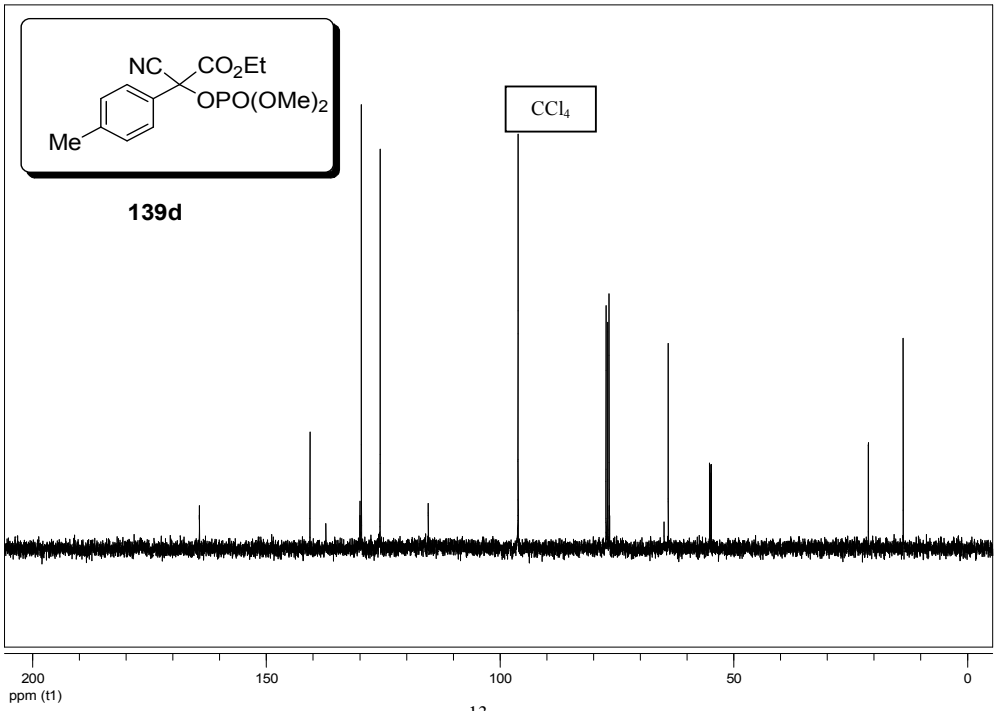

Figure 13. ^{13}C-NMR of **139d**

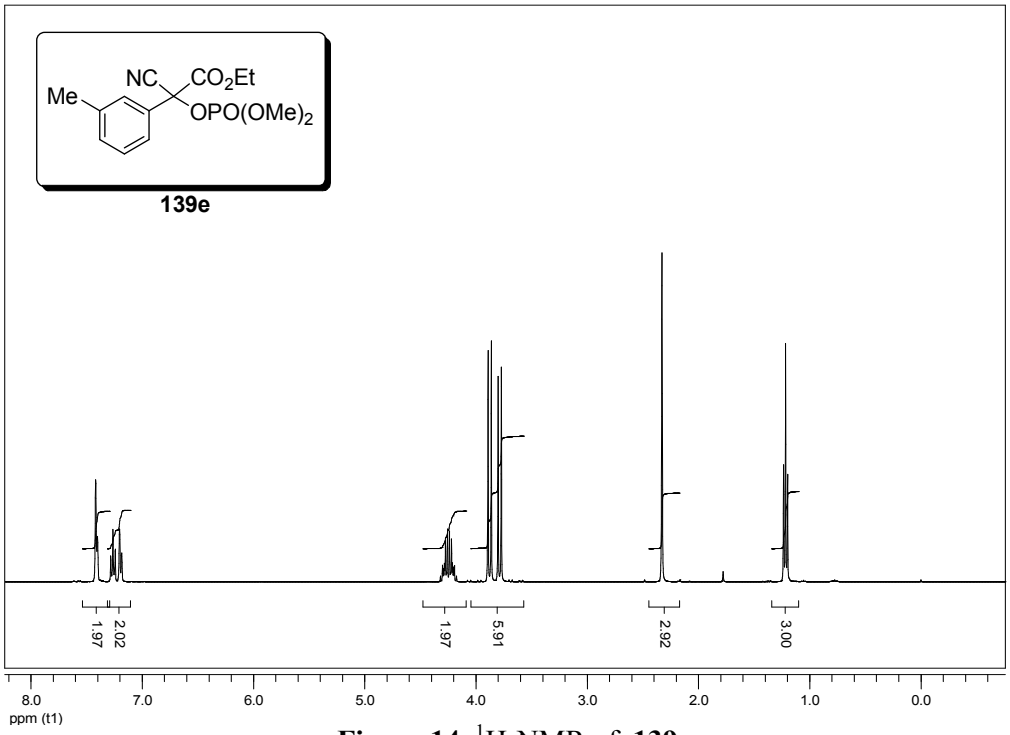

Figure 14. ^{1}H-NMR of **139e**

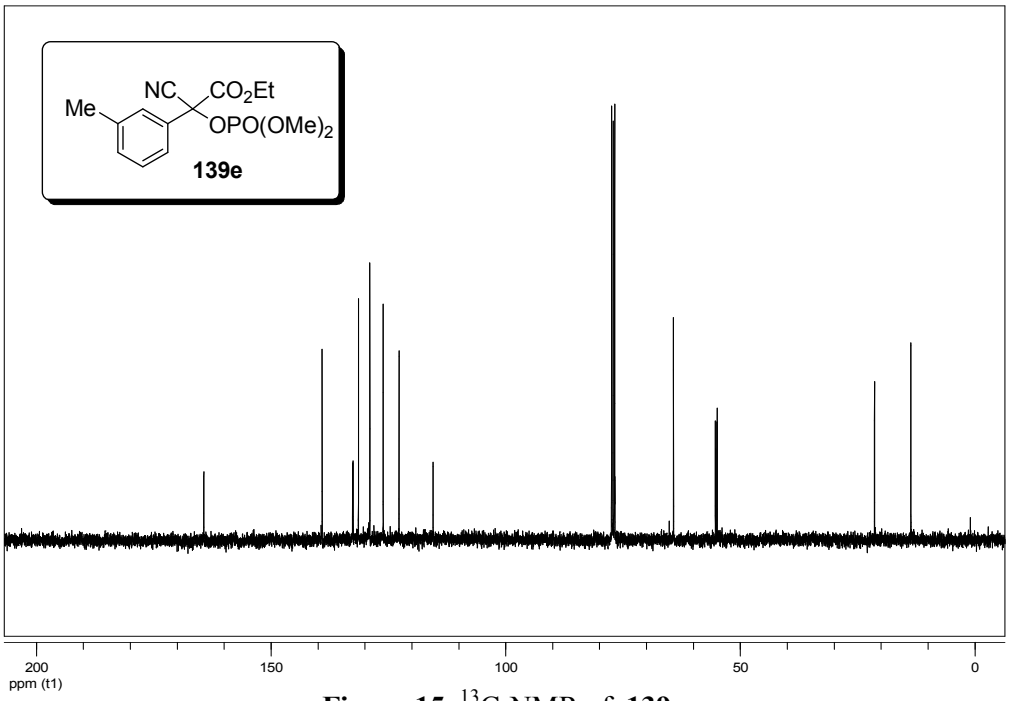

Figure 15. ^{13}C-NMR of **139e**

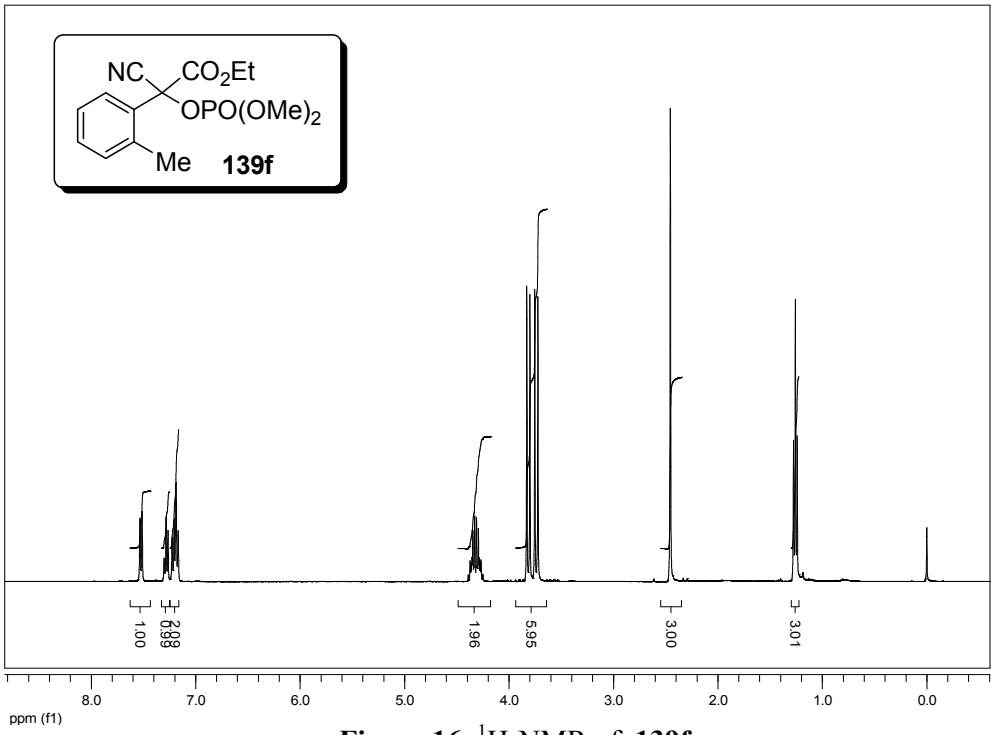

Figure 16. ^{1}H-NMR of **139f**

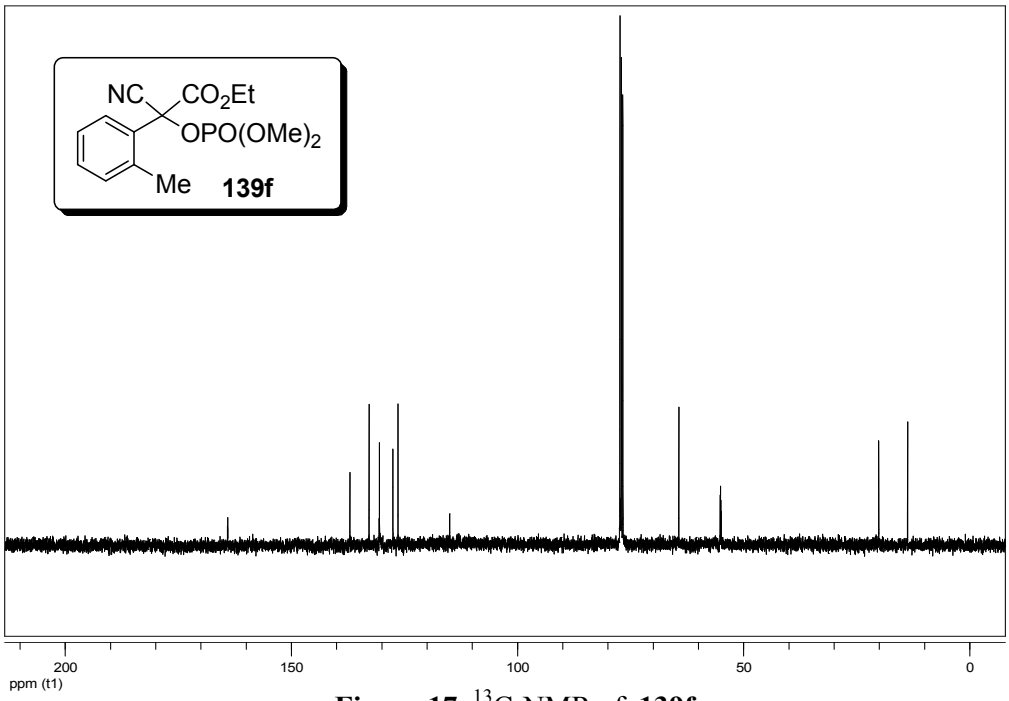

Figure 17. ^{13}C-NMR of **139f**

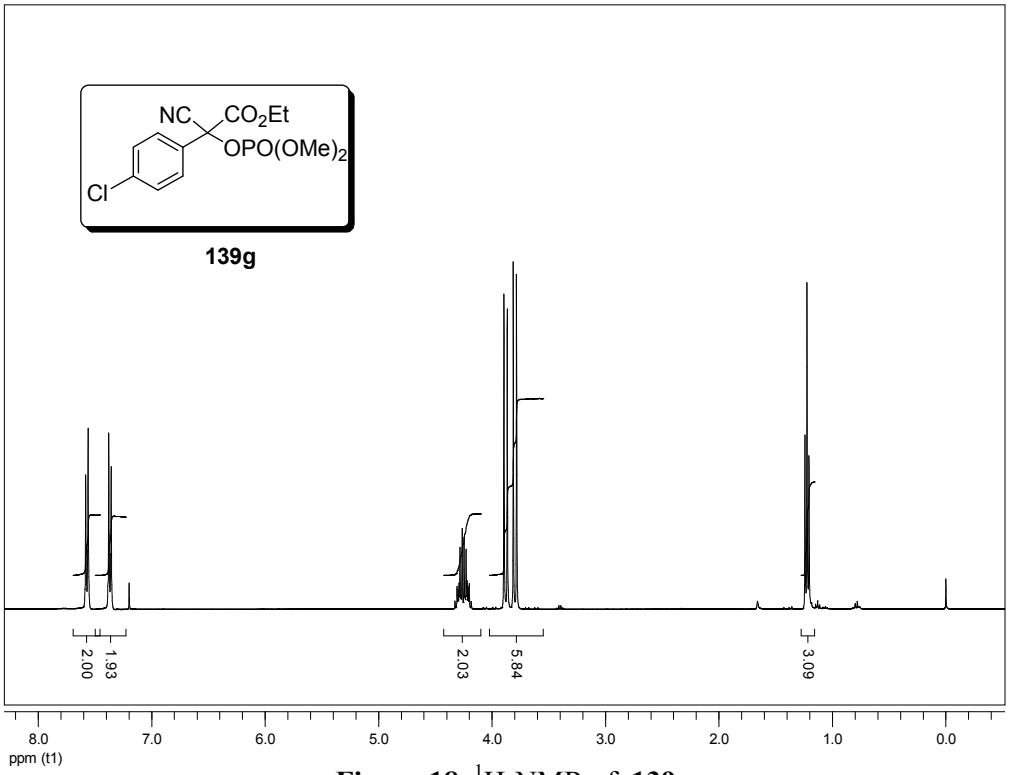

Figure 18. ^{1}H-NMR of **139g**

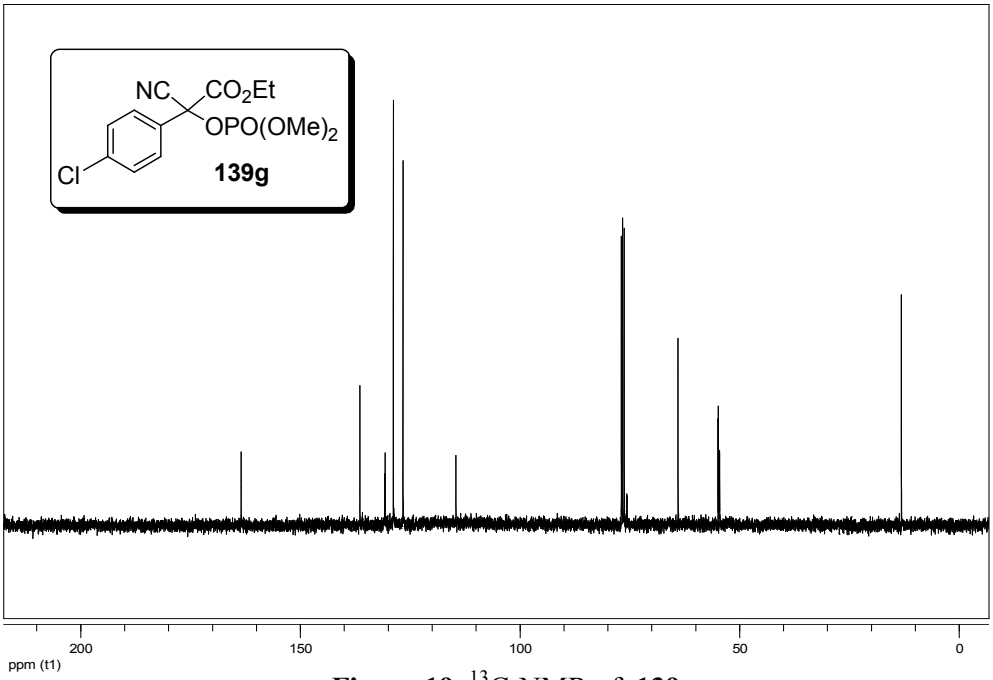

Figure 19. ^{13}C-NMR of **139g**

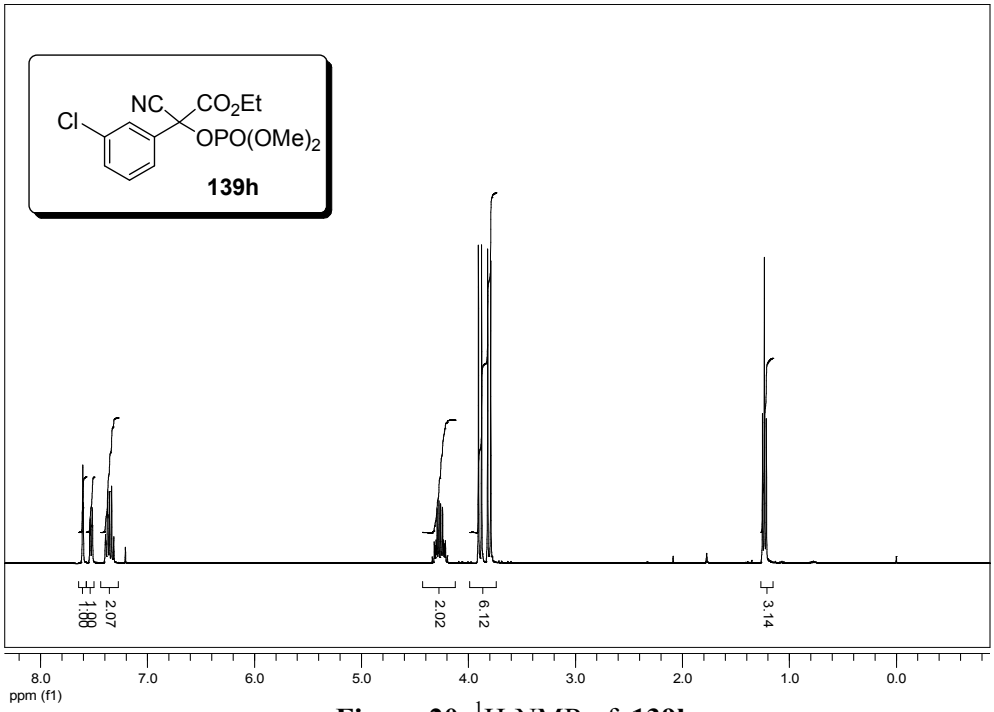

Figure 20. ^{1}H-NMR of **139h**

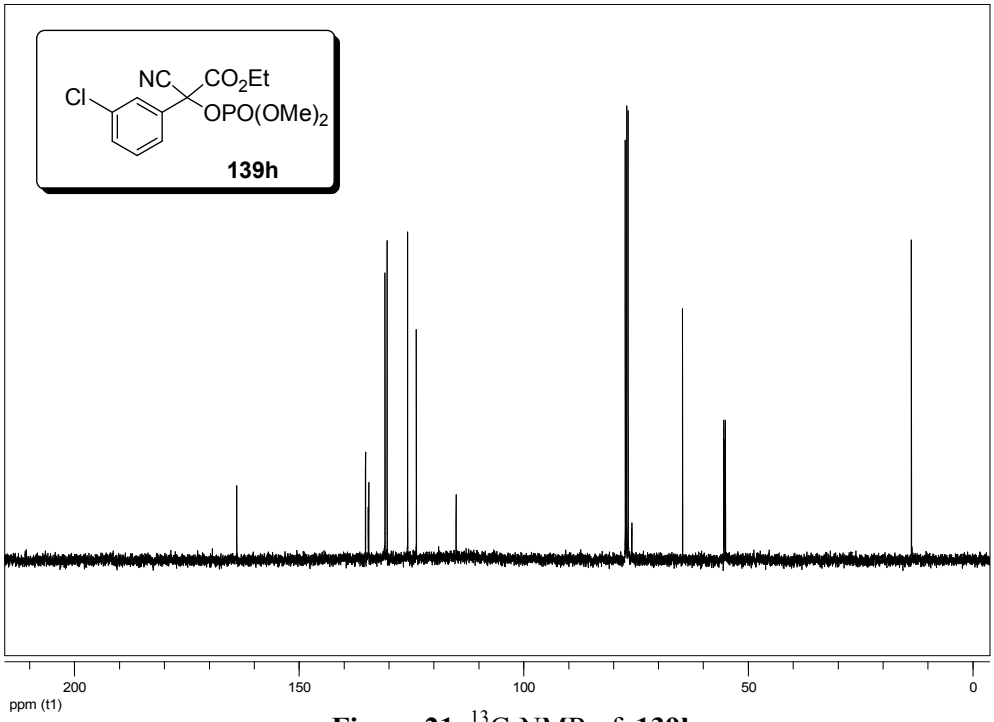

Figure 21. ^{13}C-NMR of **139h**

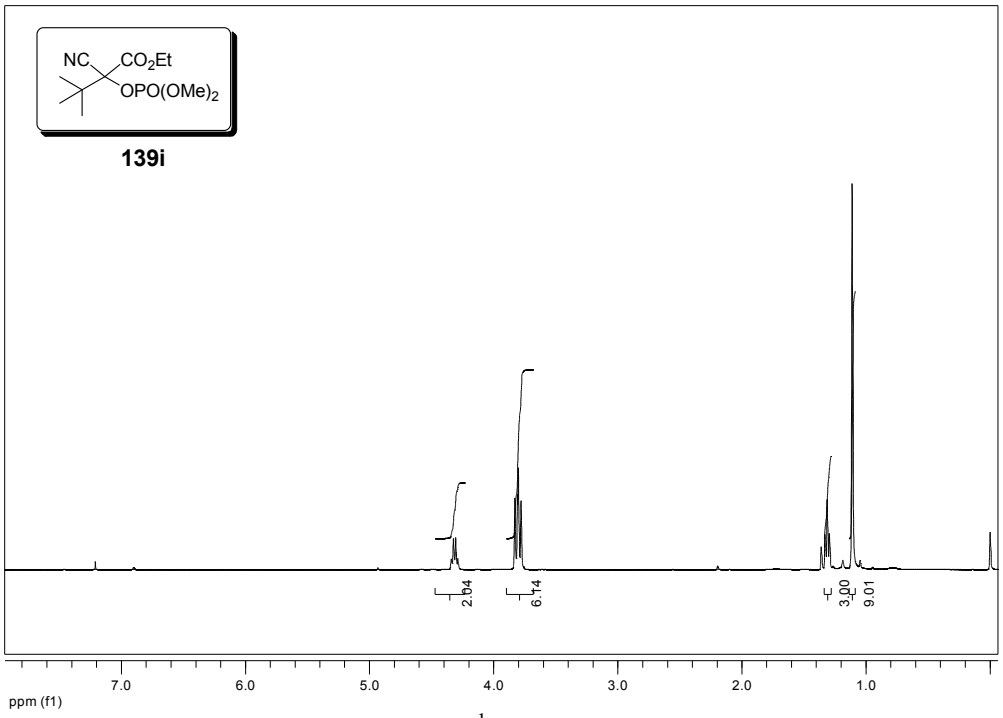

Figure 21. ^{1}H-NMR of **139i**

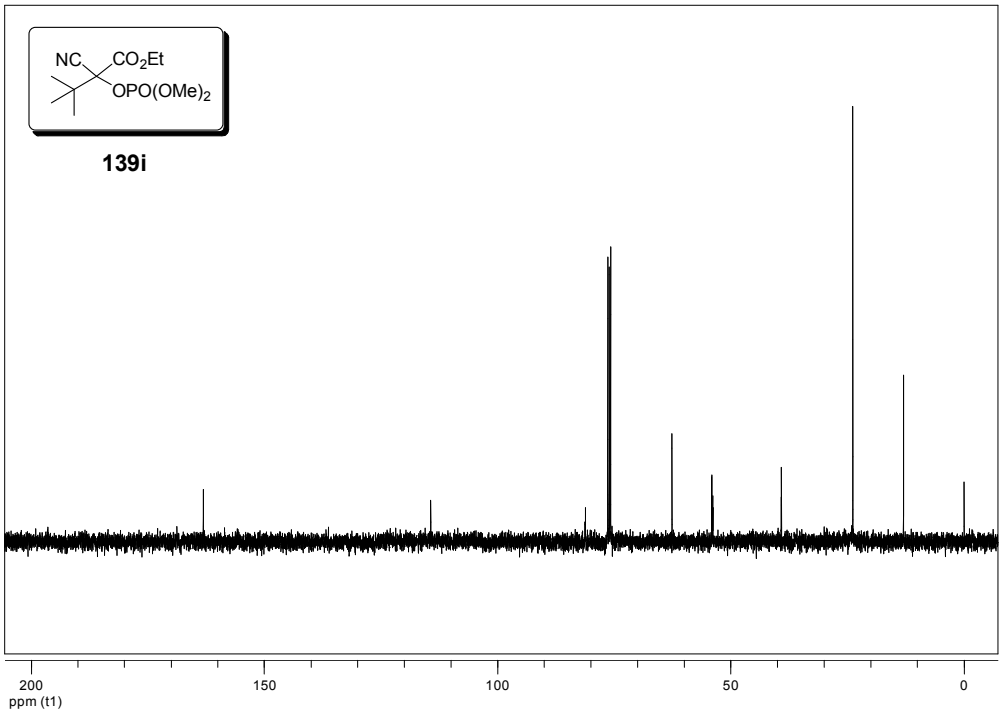

Figure 22. ^{13}C-NMR of **139i**

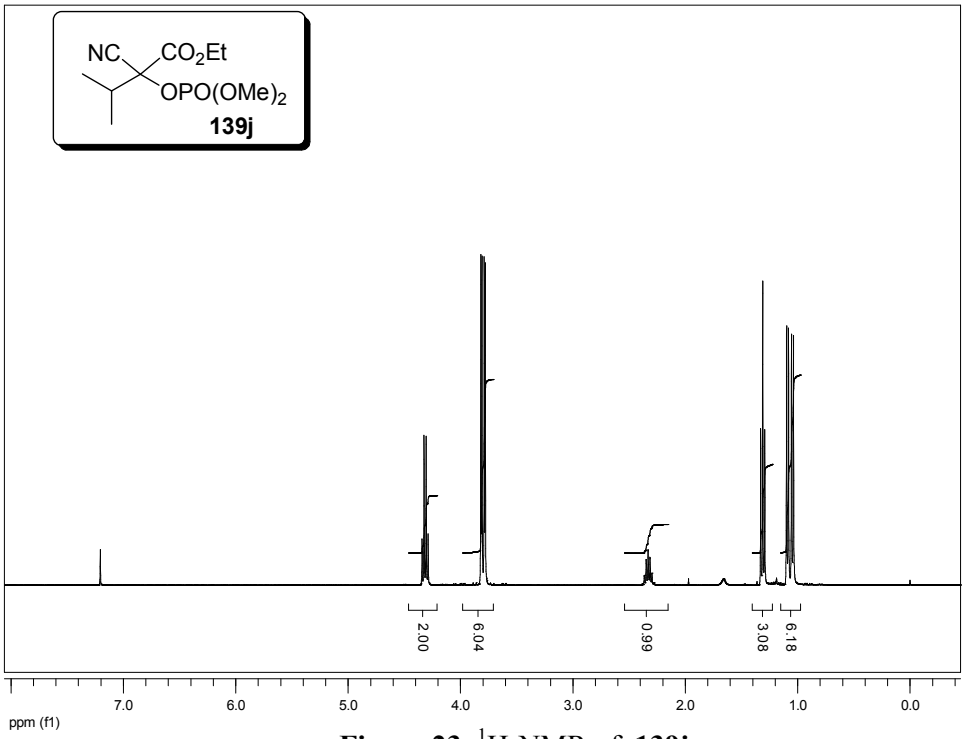

Figure 23. ^{1}H-NMR of **139j**

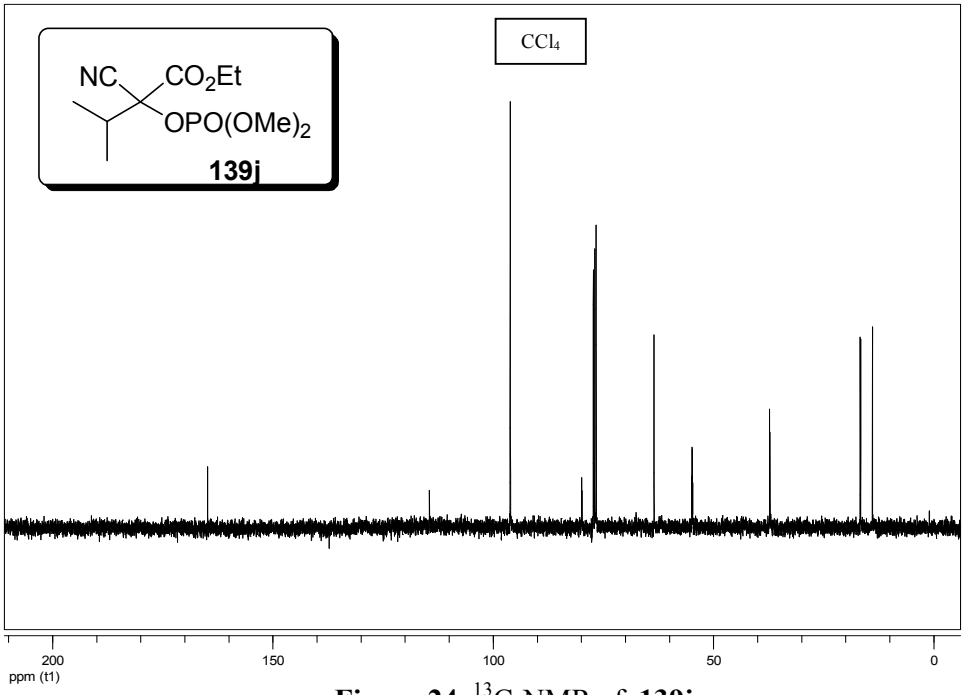

Figure 24. ^{13}C-NMR of **139j**

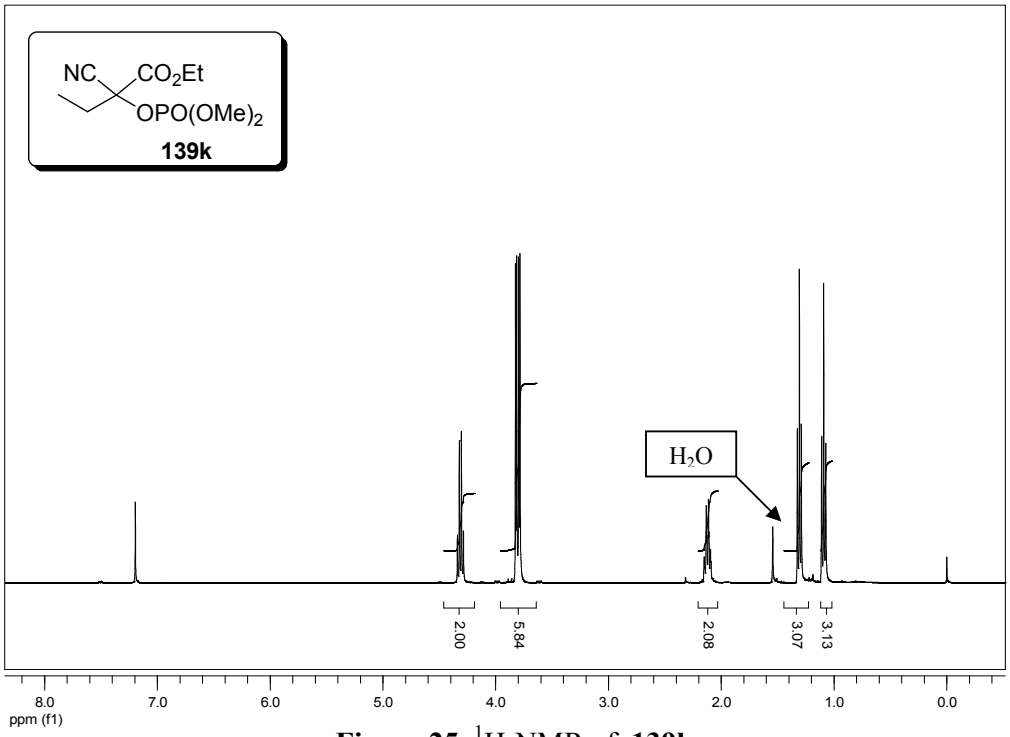

Figure 25. ^{1}H-NMR of **139k**

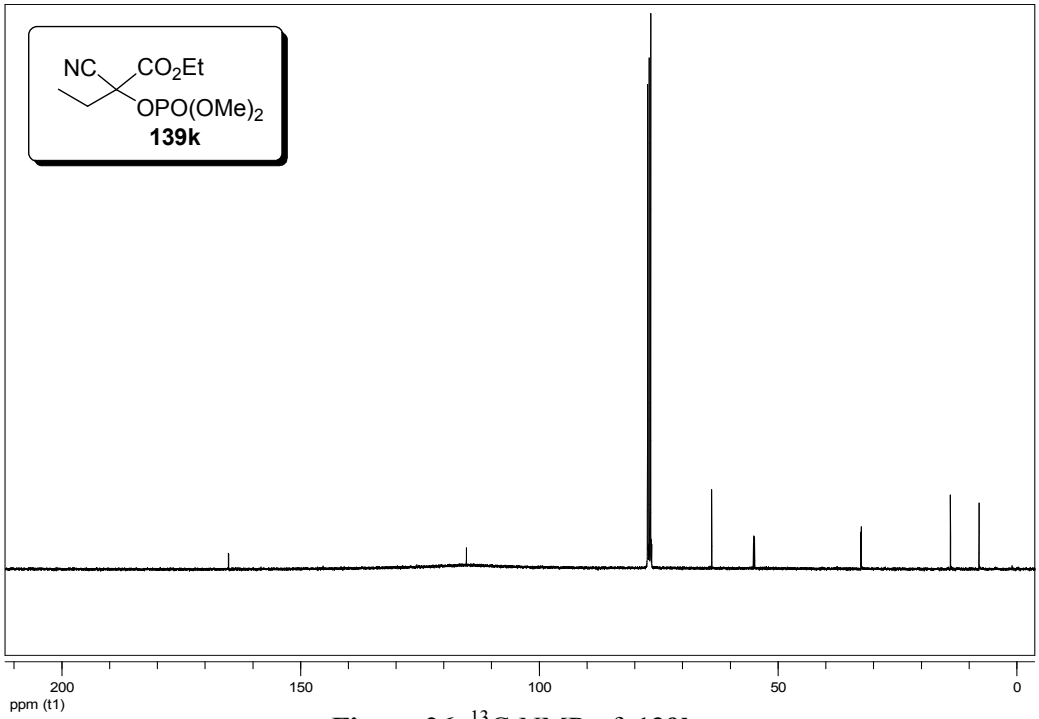

Figure 26. ^{13}C-NMR of **139k**

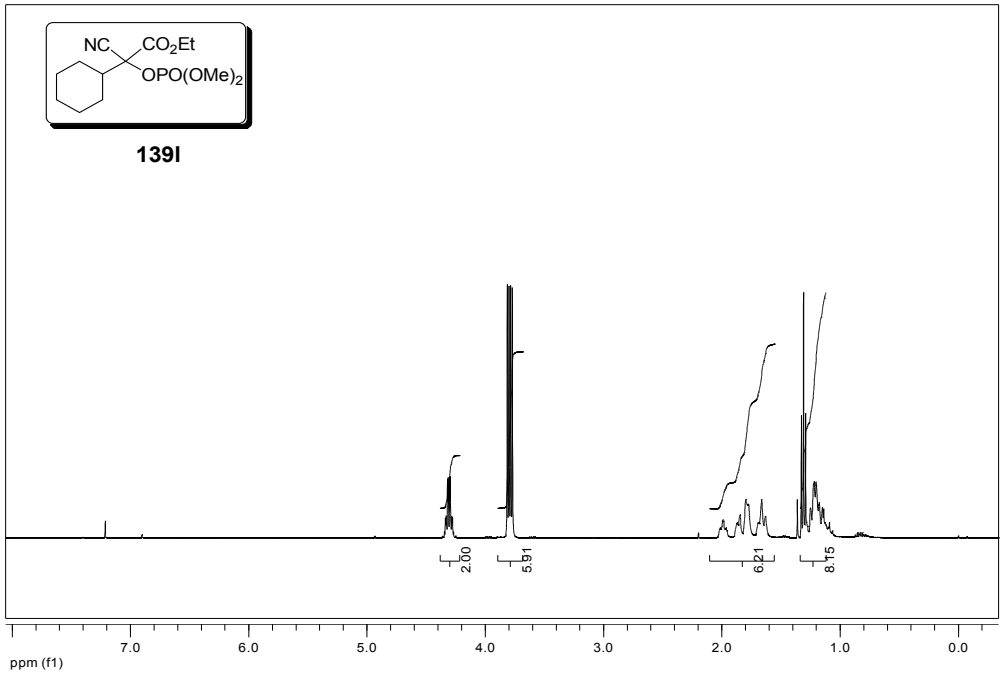

Figure 27. ^{1}H-NMR of **139l**

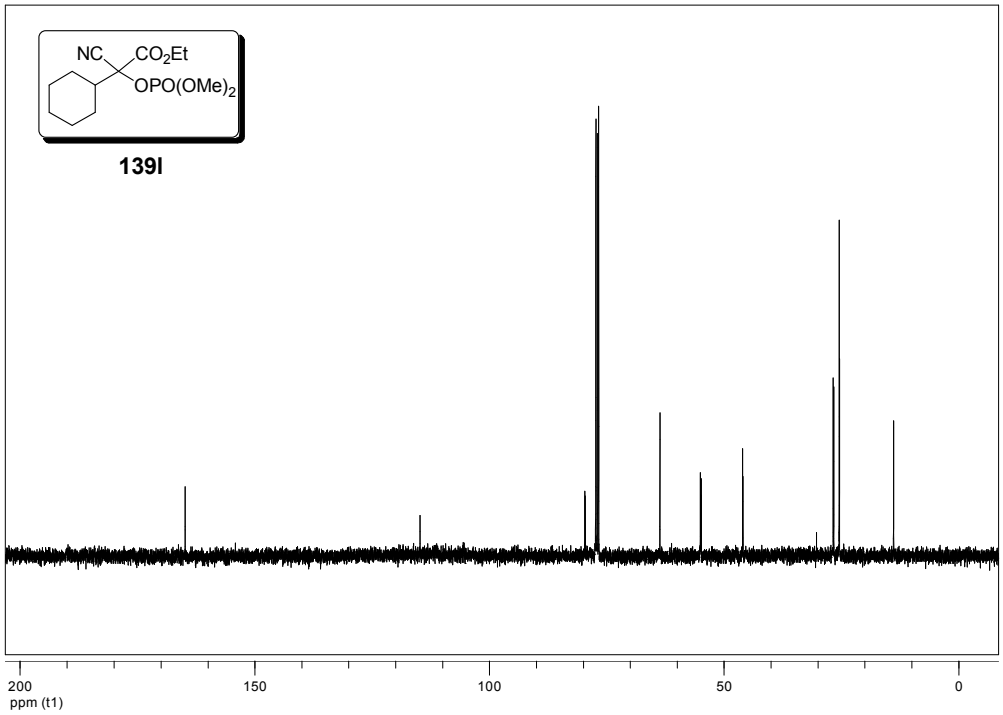

Figure 28. ^{13}C-NMR of **139l**

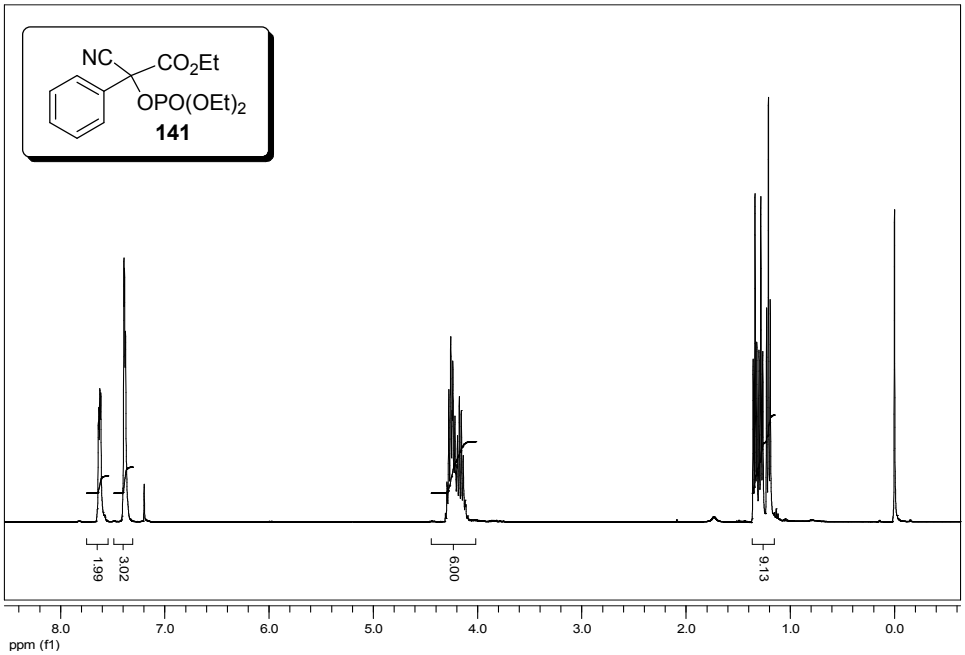

Figure 29. ^{1}H-NMR of **141**

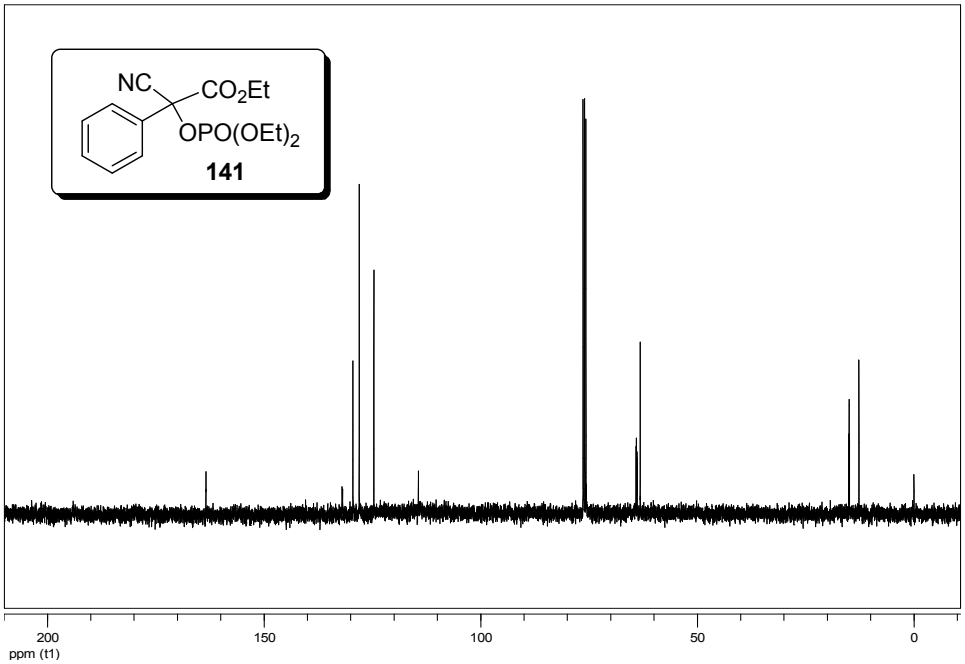

Figure 30. ^{13}C-NMR of **141**

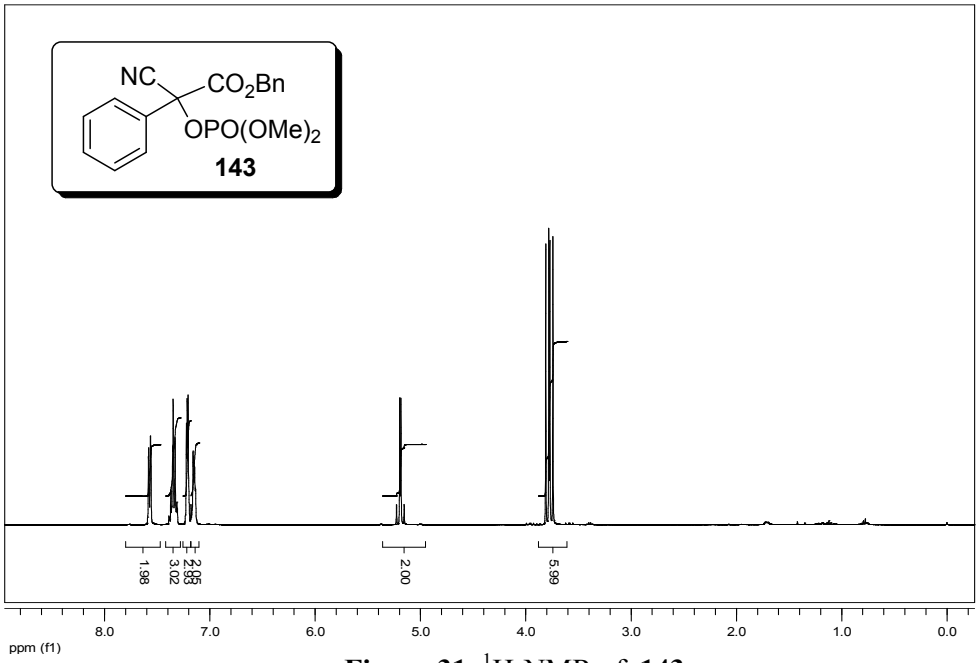

Figure 31. ^{1}H-NMR of **143**

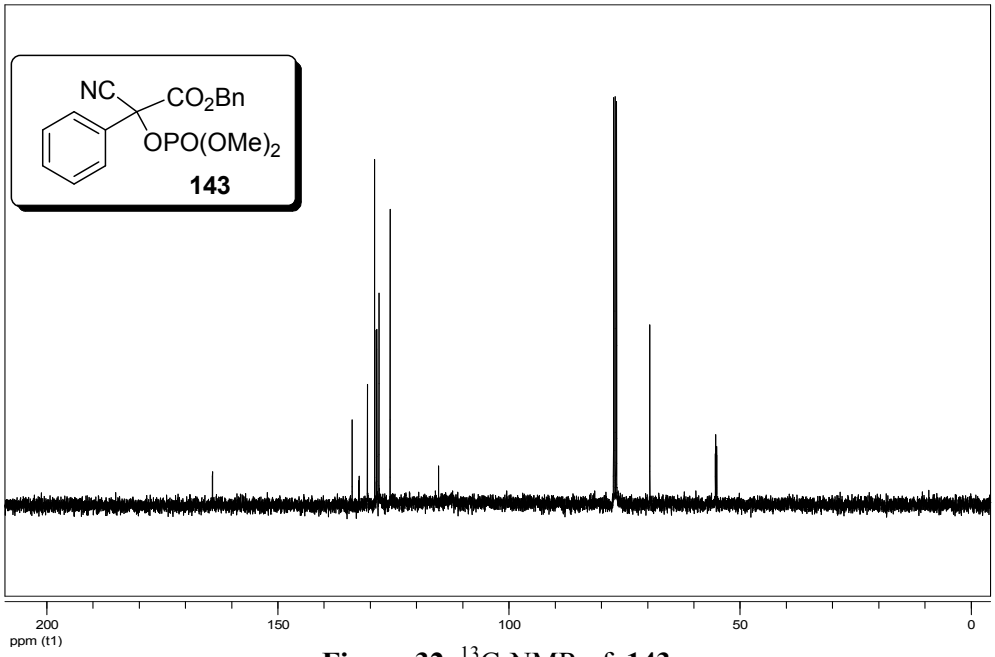

Figure 32. ^{13}C-NMR of **143**

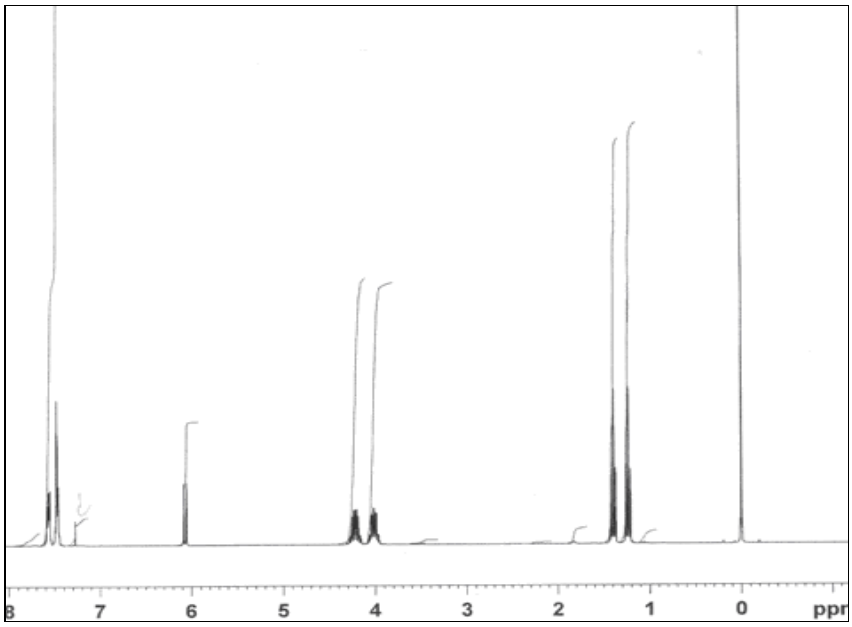

Figure 33. ^{1}H-NMR of **162**

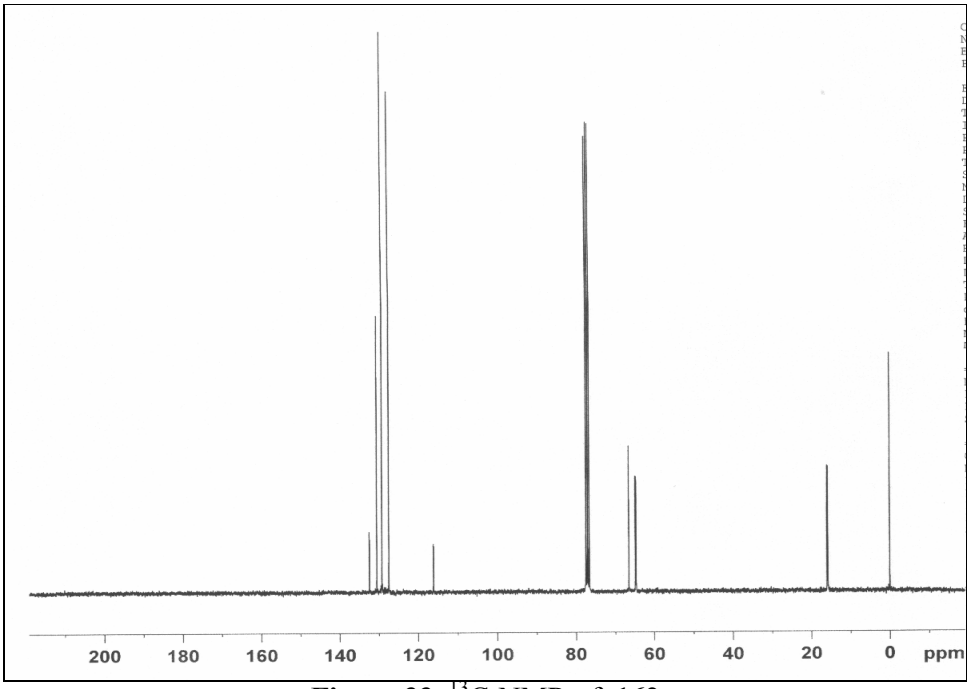

Figure 33. ^{13}C-NMR of **162**