DEVELOPMENT OF ACYL ANION PRECURSORS AND THEIR APPLICATIONS

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DEVELOPMENT OF ACYL ANION PRECURSORS AND THEIR APPLICATIONS

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Approval of the Graduate School of Natural and Applied Science

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This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

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ABSTRACT

DEVELOPMENT OF NEW ACYL ANION PRECURSORS AND THEIR APPLICATIONS

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This thesis presents the development of new acyl anion precursors and their applications. The main concern of this thesis was to make use of acyl anion precursors in catalytic bond forming reactions. Toward this aim, previously known cyanide ion catalyzed cleavage of benzils was investigated in scope and efficiency in unsymmetrical benzoin condensation. Although benzils were proved to be useful entities as acyl anion precursors in benzoin condensation, they suffer some major drawbacks. Therefore acylphosphonates were proposed and investigated as a new generation of acyl anion precursor. They were found to be highly versatile and efficient in both catalytic unsymmetrical benzoin synthesis and other useful transformations.

Keywords: benzoin, catalytic, acyl anion, umpolung, benzil, acylphosphonate, organocatalysts

ÖZ

YENİ AÇİL ANYON EŞLENİKLERİNİN GELİŞTİRİLMESİ VE BUNLARIN UYGULAMALARI

Ömer Reis
Doktora, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan S. Demir
Mart 2005, 216 sayfa

Bu çalışma yeni açil anion öncüllerinin geliştirilmesi ve bunların uygulamalarını sunmaktadır. Bu çalışmanın ana amacı açil anion öncüllerinin katalitik bağ oluşturma reaksiyonlarında kullanılmasıdır. Bu amaç doğrultusunda daha önceden bilinen, benzil sınıfı molekullerin siyanür katalizörlüğünde kırılması reaksiyonu uygulanabilirlik açısından simetrik olmayan benzoin sentezinde kullanılmıştır. Benzil sınıfı moleküllerin bu amaç için verimli bir şekilde kullanılabilirliği görülmesine rağmen bu moleküllerin bazı açılardan dezavantajlı olduğu bulunmuştur. Dolayısı ile açilfosfonatlar yeni nesil açil anyon eşleniği olarak önerilmiş ve test edilmiştir. Açilfosfonatların katalitik simetrik olmayan benzoin sentezi ve diğer önemli bazı dönüşümlerde oldukça yararlı olduğu bulunmuştur.

Anahtar kelimeler: Benzoin, katalitik, açil anion, umpolung, açilfosfonat, organokatalitik

To my mother and father

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CHAPTER 1

INTRODUCTION

As a consequence of considerable efforts devoted to the development of new approaches for the construction of either complex synthetic targets or small synthetic building blocks, a plethora of methods are now available for a wide range of bond forming or functional group interconversion 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. Many of these methods naturally undergo a testing procedure for the synthesis of important small building blocks or complex targets. This development and testing cycle not only set standards of what is expected from a better method but also inspires synthetic chemist to recognize new transformations.

Since polar (or Lewis acid-base) reactions play a central role in the synthesis of organic molecules, organic chemists have endeavored to develop new, general ways in which such reactions can be employed in synthesis. In order to carry out transformations based on polar reactions, it is necessary to identify proper molecular fragments or ***synthons*** by

retrosynthetic analysis [1]. Synthon is an idealized fragment, probably an anion or cation, resulting from a disconnection during a retrosynthetic analysis. Once the synthons were identified, it is necessary to determine the synthetic equivalents that are real reagents carrying out the function of a synthon. To simplify the identification of synthons and required synthetic equivalents, an organizational format which correlates construction strategies to pair wise functional group relationships in a given target was proposed [2]. In this approach, the parity labels, (+) or (-), were used to denote the positional polar reactivity, or ***charge affinity pattern*** that is conferred upon to the carbon framework by the functional group in question. A nomenclature system based on charge affinity pattern was also proposed that identifies the parity of a given position relative to a functional group. In the next section, the definition and basis of this charge affinity pattern will be given together with its use in the identification of appropriate synthons. Since the main body of this work is related to carbonyl reactivity and α-hydroxy ketones, a special emphasize will be given to carbonyl as a functional group in a carbon skeleton and α-hydroxy ketones as a synthetic target where possible.

1.1 Charge Affinity Patterns: Generalizations on Conferred Site Reactivity

Lapworth was among the first to understand the effect of heteroatomic substituents not only on the reactivity of individual carbon centers but also how this effect propagated through the carbons atoms. This idea was developed by others into generalized set of rules to systematically identify the polar reaction sites in a given carbon skeleton.

In a given target, various bonds can be ionically disconnected that yield potentially suitable ionic precursors for the construction of the target molecule via polar coupling processes. The selection of suitable precursors will be possible from the use of charge affinity patterns, dictated by the functional groups in the target molecule. For example, possible polar disconnections for hydroxy ketone **1** are illustrated in Figure 1. Inspection of the parities on the target molecule suggests plausible

precursors (or synthons) from which the target molecule can be constructed. It is obvious that charge affinity patterns in **1** is conferred by functional groups =O and –OH.

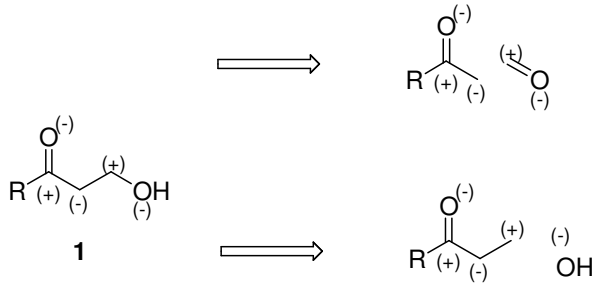


Figure 1. Charge affinity pattern of a hydroxy ketone

It is possible to provide a general scheme according to type of functional group. Functional groups (FG) interact inductively or mesomerically with the carbon atom to which they are connected. Since FG activation through induction and resonance are independent variables which contribute to overall FG reactivity pattern, four classes of functional groups can be defined. According to this, functional groups induce electrophilic, nucleophilic or amphibilic character at the point of attachment. To simplify the number of variables, three sets of hypothetical functions were defined as E, G or A for which the charge affinity patterns are shown in Figure 2.

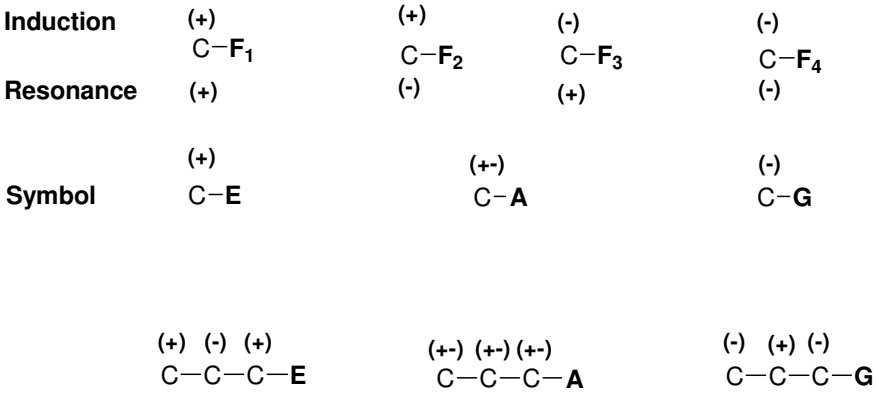


Figure 2. Definition of hypothetical E, A and G functions

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

Although these classifications seem to be unnecessarily complicating the obvious functional group dependent polar reactivity pattern of a carbon backbone, it is helpful for the inspection of several synthetic targets in order to identify the plausible bond disconnections. It is important to note that some difunctional relations in a target are not accessible through natural reactivity patterns. This classification scheme is also helpful for the quick analyzes of these ambiguous relations in a molecule.

Seebach developed a notation to classify the synthons for which the synthetic equivalents can be easily determined. According to this notation, nucleophilic sites are donated as "**d**" for donor and electrophilic sites are donated as "**a**" for acceptor. The position of the acceptor and donor sites is then numbered starting from the point of attachment of the heteroatom. For example, charge affinity pattern and Seebach notation of a ketone is shown below together with plausible bond disconnections dictated by the polar reactivity of each carbon and real reagents to carry out the identified polar transformation (Figure 3).

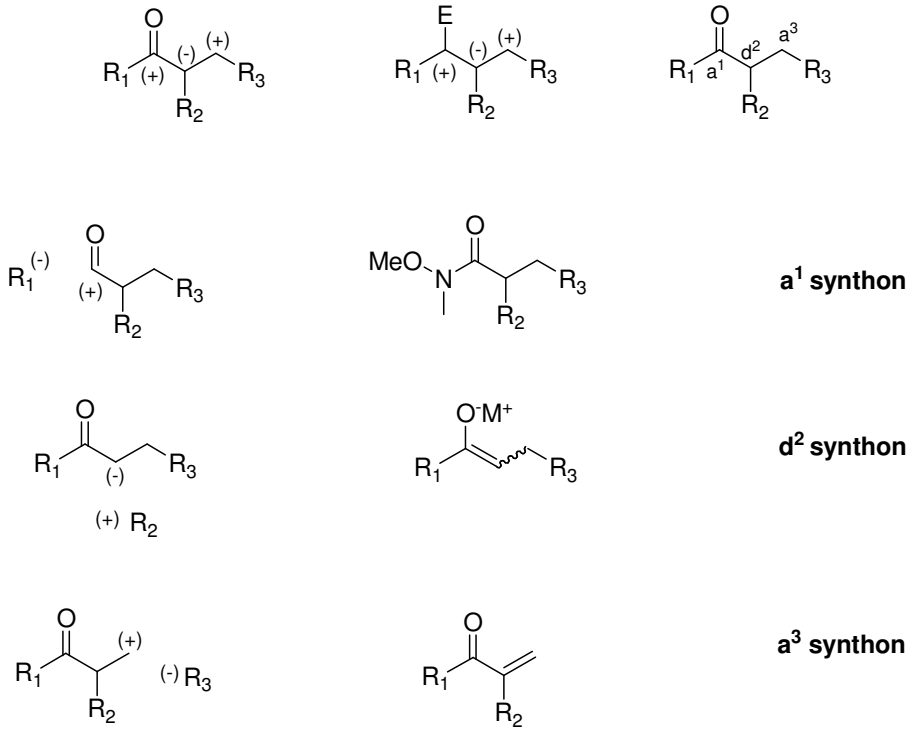


Figure 3. Seebach classification of synthons and corresponding real reagents

Disconnections shown in Figure 3 are plausible ones based on the natural charge affinity of a carbonyl compound (E function). An alternative approach would be inverting the inherent chemical reactivity that FGs confer upon the organic molecule. Such an operation would enable us to reverse the Lewis acid-base property of a given functionally activated carbon, adding new dimensions of flexibility to the design of complex molecules. The value of such an operation would be more obvious if the charge affinity pattern of an α-hydroxy ketone was examined. As depicted in Figure 4, several disconnections yield a variety of synthons for which synthetic equivalents were also given. Last two synthons are only available after proper synthetic operations on the carbonyl component. 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 the charge affinity pattern of one of the carbonyl moieties.

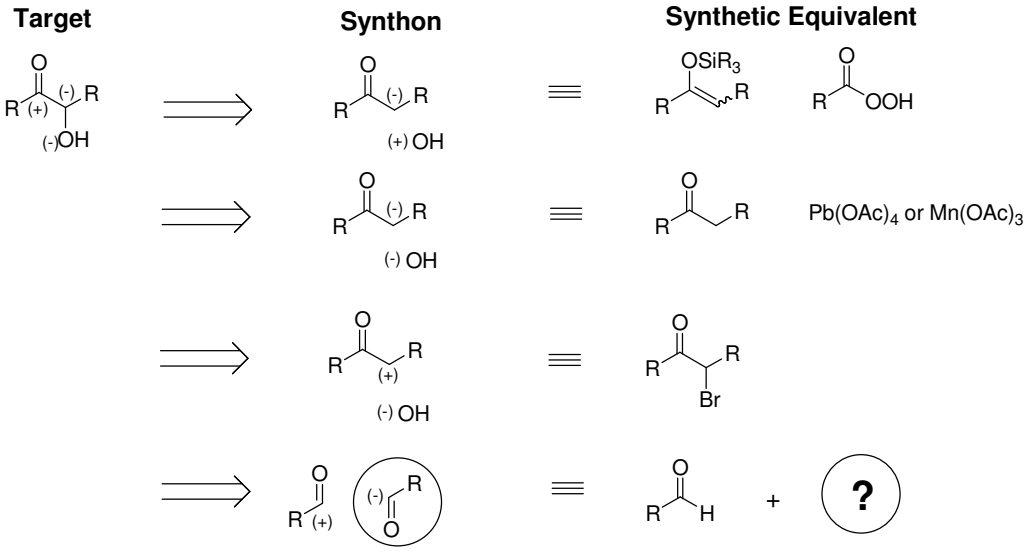


Figure 4. Retrosynthetic analysis of a α-hydroxy ketone

Transformations which invert Lewis acid-base properties of a given carbon atoms are generally referred to as "charge affinity inversion" or more commonly "umpolung". Synthetic operations that interconvert the normally electrophilic carbonyl function (E function, a^1, d^2 and a^3) with those classes of functions that are capable of stabilizing adjacent carbanions (G function, d^1, a^2 and d^3) would enable to establish a synthetic equivalency between electrophilic carbonyl (a^1) and unstable "carbonyl anion" (d^1 and d^3) (Figure 5).

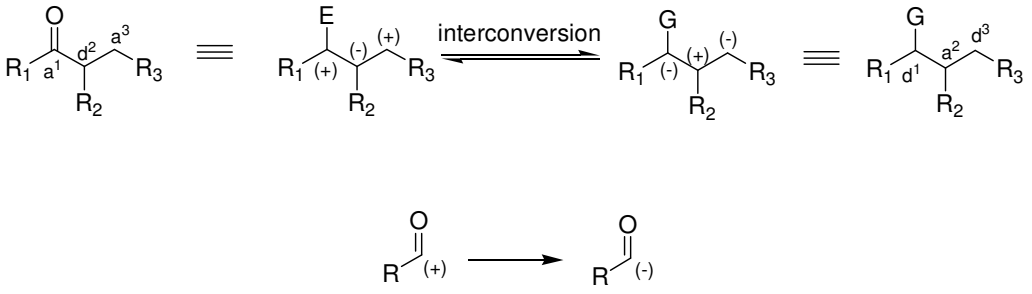


Figure 5. Functional group interconversion establishes equality between a^1 and d^1 reactivity

Entities nucleophilic at the carbonyl center (as in Figure 5) are generally named as masked “acyl anion” or “acyl anion equivalents”. These synthons provide interesting disconnections during retrosynthetic analysis, obviously not available from natural reactivity pattern of carbonyl functionality. So it is organic chemist’s task to find recourse in the conversion of carbonyls into a nucleophilic (d^1) center. However finding out an efficient conversion from E to G function is generally not a straightforward synthetic problem. This is why a considerable effort has been spent in this area of organic chemistry, so called “acyl anion chemistry”. The next part of this introductory chapter will largely be devoted to past and current developments of acyl anion chemistry. A special emphasize will be given to catalyzed reactions of acyl anion equivalents and benzoin synthesis that is the quintessential reaction of an acyl anion.

1.2 The Chemistry of Acyl Anion Equivalents and Precursors

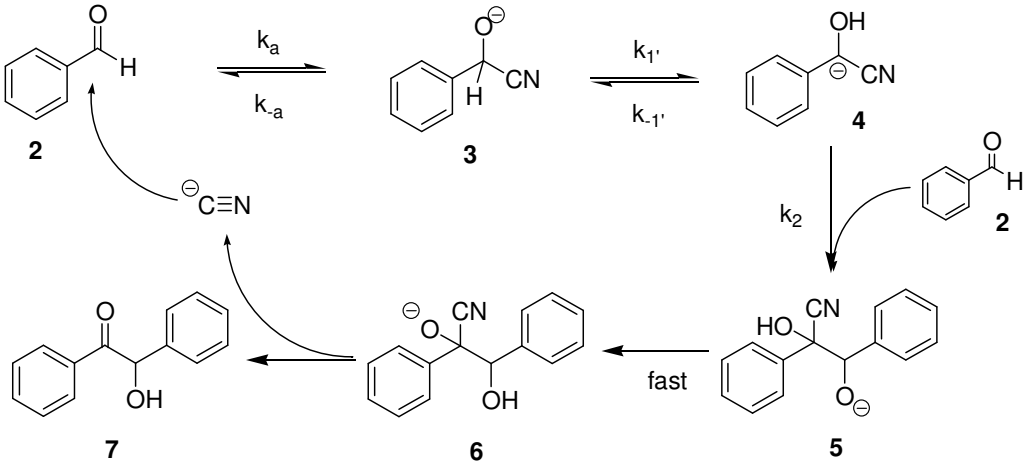
The area of acyl anion chemistry can be roughly divided into two parts. The first part is the conversion of an aldehyde carbonyl (=O, E function) into a functional group that is cabaple of stabilizing adjacent carbanions (G function). Strong base deprotonation of these acyl anion precursors (AAP) provides the corresponding acyl anion equivalents (AAE). Stoichiometric acyl anion chemistry has been proven extremely useful in a large number of contexts, but lack the step and atom economy. The second part is the catalytic generation of AAE from the appropriate AAP by operators like cyanide and thiamine [3]. The roots of this catalytic approach can be found in the historical benzoin condensation and Stetter reactions or in the nature’s several C-C bond forming processes [4]. Current effort has been devoted to the development of catalyzed reactions of AAE’s, in parallel with developments in other fields of organic chemistry.

Classical benzoin condensation reaction can be considered as the basis of acyl anion chemistry. So it is appropriate to look at the cyanide ion and thiamine catalyzed benzoin reaction to understand advantages and disadvantages of the reaction.

1.2.1 Benzoin Condensation: A Very Old Reaction with Considerable Impact in Organic Chemistry

1.2.1.1 Cyanide Ion Catalyzed Benzoin Condensation

Benzoin reaction was serendipitously discovered by Liebig and Wöhler more than a century ago [5]. Lapworth ingeniously established the mechanism of the reaction in 1903. Remarkably, Schowen reinvestigated the mechanism of this reaction and obtained essentially the same result with that of Lapworth [6] (Scheme 1). It was Lapworth's ability to elegantly identify the critical carbanion intermediate **4** of this reaction. According to excepted mechanism of benzoin reaction, cyanide ion plays a critical role from the initial to last step of the reaction. First of all, cyanide is a very good nucleophile with a linear cylindrical shape. Thus it provides nucleophilic activation in the first step that reversibly forms the corresponding cyanohydrin **3**. Second it has ability to stabilize the adjacent negative charge together with oxygen and the phenyl moiety. At last it behaves as a leaving group to re-enter the catalytic cycle. These properties make the cyanide a unique operator of this reaction.



Scheme 1

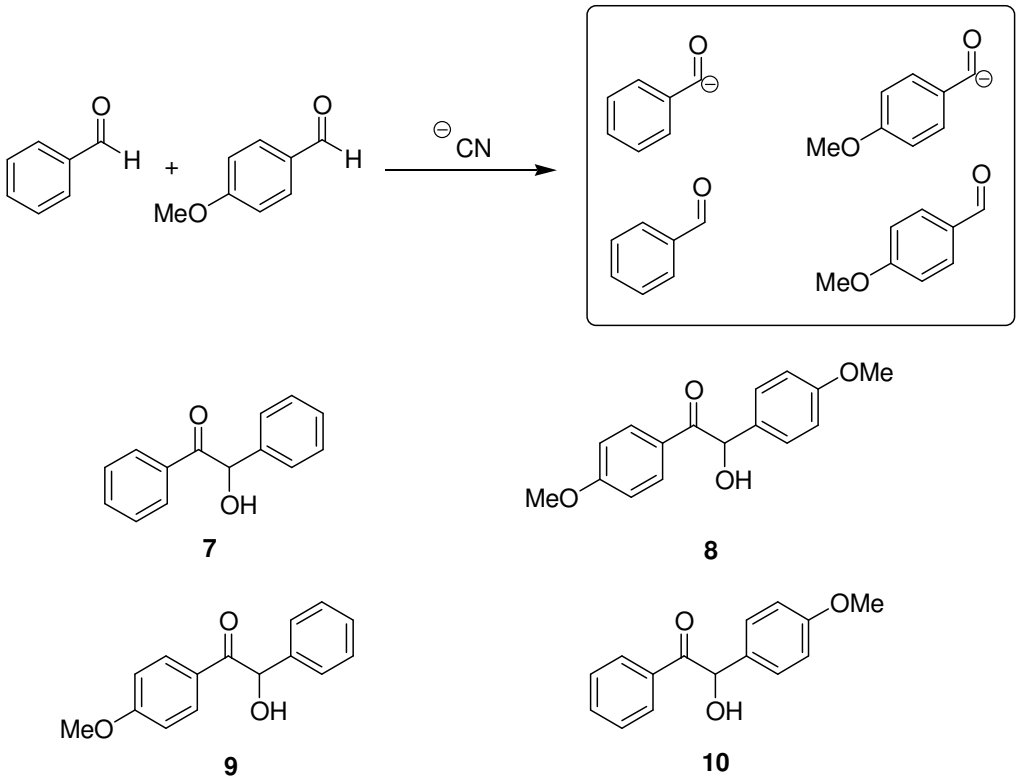
After reports by Schowen, we have information about kinetics of every single step of this reaction. It is important to note that kinetic data was obtained from reactions

carried out in absolute methanol and dependence of reaction rates on the composition of solvent can be quite complex as pointed out by Schowen. However the basic essence of the reaction can be assumed to be same although kinetics of steps may vary in different solvents. The first step is quick addition of cyanide ion to benzaldehyde **2**. A new carbon-carbon bond is formed in exchange of a weaker CO π bond and favorable solvation of alkoxide **3** compared to cyanide ion is a plus in terms of energy considerations. Critical acyl anion equivalent **4** 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 **7** as shown in Scheme 1.

Although benzoin condensation provides an easy access to synthetically important α-hydroxy ketones, the scope of this reaction proved to be quite narrow, since aromatic aldehydes with strong electron-donating or electron-withdrawing substituents do not react to give meaningful yields under classical reaction conditions. Since benzoin reaction is essentially assumed to take place via reversible steps, it generally suffers from incomplete conversions. To overcome this limitation, many variant of this reaction have been proposed that generally utilized different solvents or solvent combinations together with phase transfer catalysis depending on the solvent choice. These attempts did not provide a significant improvement in terms of yields [7].

Another 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 same rate constant is hypothetically assumed for 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 the 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 2 that shows an experiment designed for the synthesis of benzoin **10**. 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 **9**.



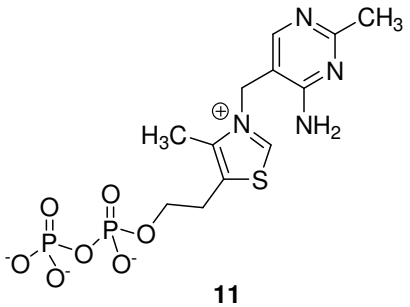
Scheme 2

Although benzoin condesantion is a highly useful reaction, it involves 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.

1.2.1.2 Thiamine Catalyzed Benzoin Condensation

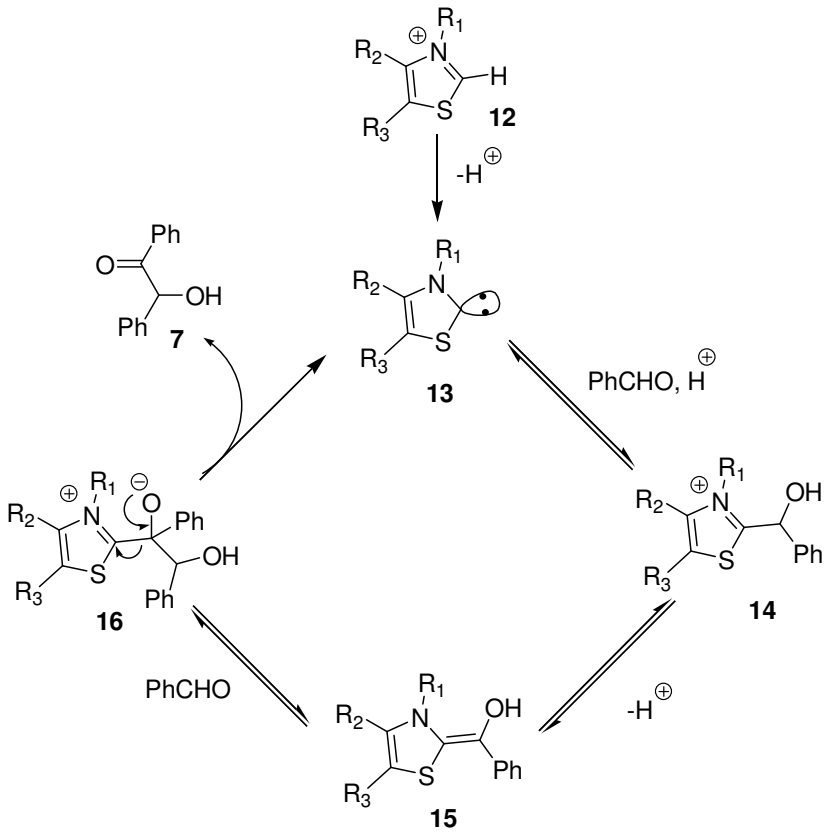
The coenzyme thiamine-pyrophosphate (TPP) **11**, a natural thiazolium salt, is involved in many enzymatic catalyses. TPP have three distinctive units, namely, a pyrophosphate part, a thiazolium core and a pyrimidine unit. TPP mainly engaged in a variety of carbon-carbon bond forming reactions and each unit has a special role in enzymatic catalyses [4, 8].



11

In 1943, Ukai showed that thiazolium salts can catalyze the benzoin condensation. Later it was shown by Mizuhara that catalytic activity of thiamine (lacking the pyrophosphate part) was due to its thiazolium unit [9]. Later, Breslow [10] proposed a mechanistic model based on Lapworth's cyanide ion catalyzed benzoin condensation mechanism (Scheme 3). Breslow identified thiazolium **12** unit as a nucleophilic carbene precursor on the basis of its acidity and showed that the hydrogen at the C-2 can be exchanged by deuterium in basic heavy water. Thus, thiazolium forms a thiazol-2-ylidene **13** under the influence of a base as catalytically active species. This nucleophilic carbene **13** behaves like the cyanide ion and couples with an aldehyde to form an enamine **15**. Enamine **15** is actually an acyl anion

equivalent (d^1 synthon) and reacts with another molecule of an aldehyde to provide benzoin **7** together with the release of active catalyst **13** via intermediate **16** [4,10].



Scheme 3

The mechanistic model proposed by Breslow [10] identifies the nucleophilic carbenes as benzoin condensation catalysts. These special intermediates have the ability to change the reactivity of a carbonyl center thus can be considered as an umpolung operators. After the identification of thiazolium ylides as nucleophilic catalysts, many attempts have been made for the synthesis of improved catalysis based on nucleophilic carbenes, parallel with the developments in the stable carbene chemistry. Today many catalyst systems are available based on thiazolium or triazolium salts and their asymmetric variants that made highly useful enantioselective transformations of d^1 synthons possible. It is more appropriate to present the reactions of this carbene catalysis under the class of catalyzed reactions of acyl anion equivalents in the proceeding chapters. However it is noteworthy that

carbene catalysts have similar limitations to that of cyanide in the synthesis of cross benzoin adducts and they are not useful as cross benzoin catalysis.

It is necessary to point out the role of TPP **11** in enzymatic transformations. There are enzymes providing benzoin products from aldehydes or from corresponding pyruvates. It is interesting that these enzymes operate in neutral pH. Thiazolium salts are active only in solution where pH is around 8.5 (above which thiazolium ring suffer decomposition) [9, 10]. It is believed that the pyrimidine moiety has a special role in the deprotonation of thiazolium at near neutral pH values. One of amine groups of pyrimidine is thought to be responsible of proton abstraction while its basicity is controlled by the protonation and deprotonation of the pyrimidine ring by the enzyme. Protonation of the pyrimidine by suitably positioned amino acids in enzyme backbone provides a positively charged ring of enhanced basicity that can remove the C-2 hydrogen of the thiazolium ring would be assisted by the amino group (in the form of imino) of the pyrimidine ring [11].

Thiamine is a very important coenzyme that acts via covalent interaction with the substrate. This covalent interaction offers a wealth of possibilities in synthetic transformations, especially in enantioselective transformations.

1.2.2 Stoichiometric Reactions: Synthesis of Acyl Anion Precursors and Generation of Acyl Anion Equivalents

The main achievements of acyl anion chemistry were due to the synthetic chemist's efforts to find recourse in the conversion of aldehydes in to nucleophilic carbanion centers (Figure 5). 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.

In search for the design of umpoled reactive centers, a variety of precursors have been developed by synthetic chemists some of which are shown in Figure 6 [12]. These precursors apparently rely on the carbanion stabilizing ability of certain functional groups. 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. **17**, **18** and **19**. Among these precursors developed so far, O-silyl-cyanohydrins **17**, α- amino nitriles **19** and (Corey-Seebach) dithianes **20** are most popular compared to vast of umpolung reagents developed so far.

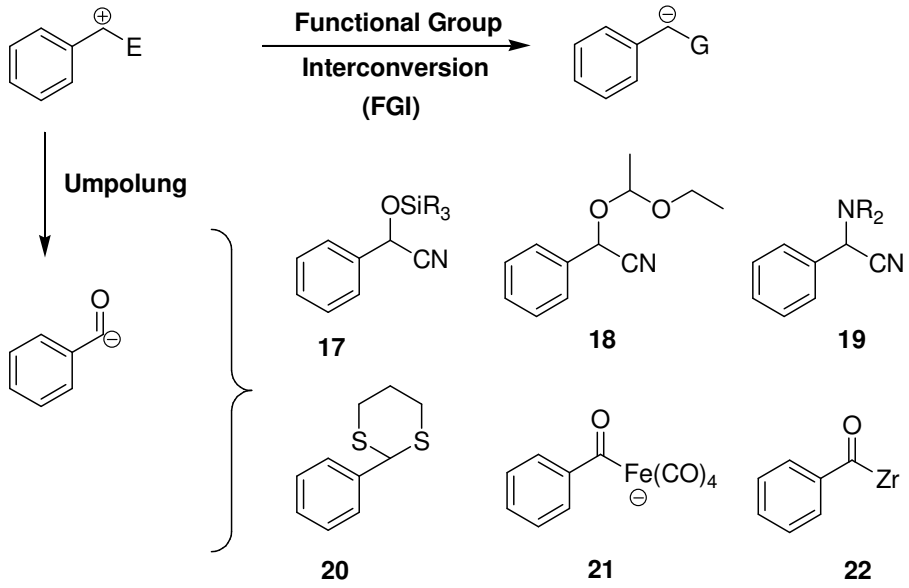
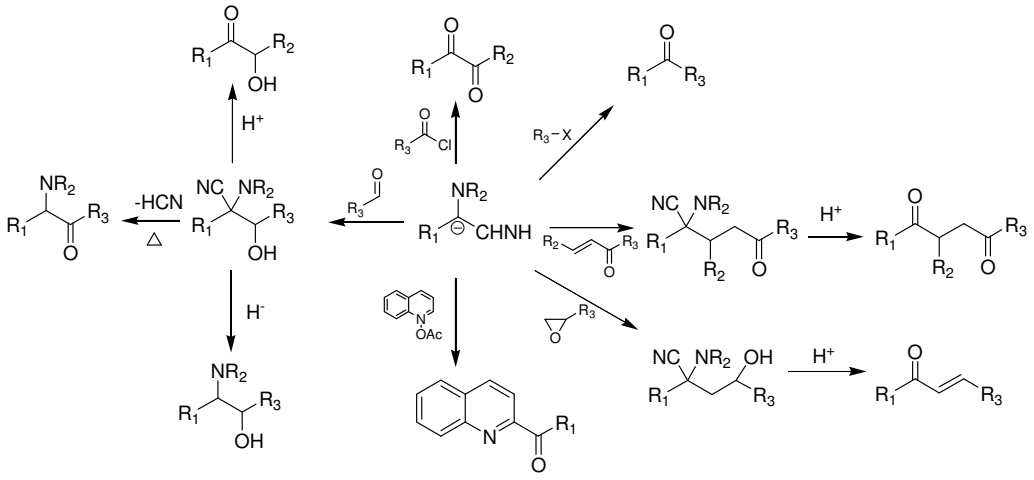


Figure 6. Some acyl anion precursors (AAP) by FGI of carbonyl group

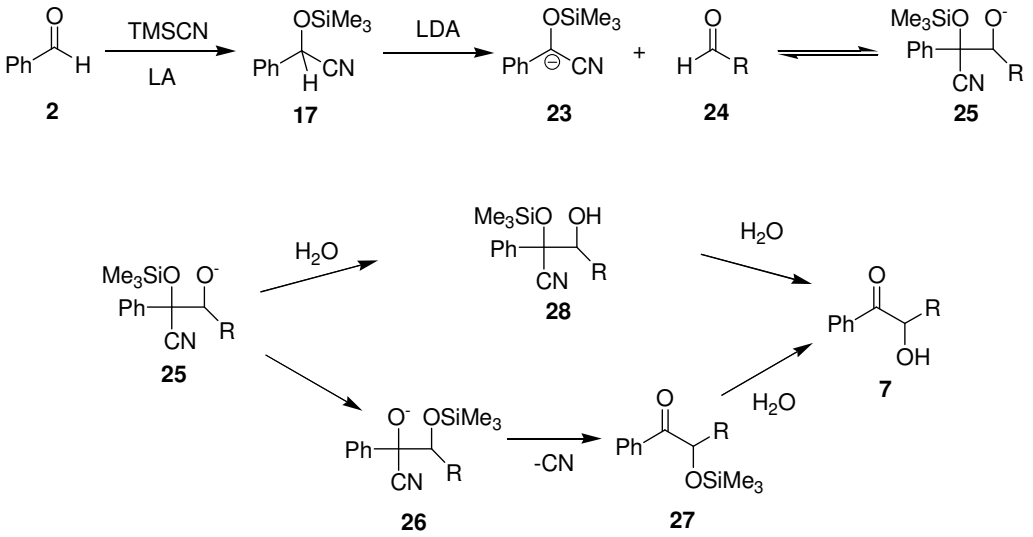
These reagents offer a great flexibility in the design of unusual strategies for the synthesis of small or complex targets. For example, the synthetic potential of carbanions generated from α-amino nitriles **19** is shown in Scheme 4 [12h]. Since α-amino nitriles are easily accessible from the reaction 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 4

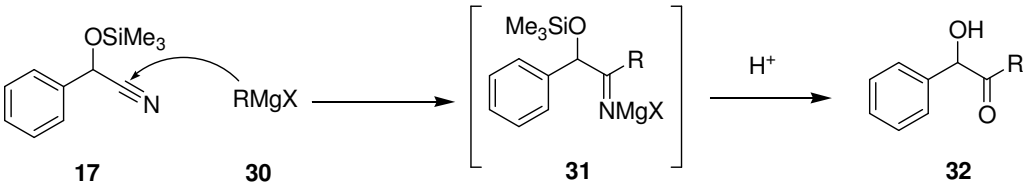
Transformations associated with α-amino nitriles [12h] are also possible (at least in theory) with other umpolung reagents. Indeed, there are lots of similar applications of dithianes [13] and O-Silyl-cyanohydrins [12a, b]. As far as the cross benzoin adducts is concerned, these two reagents are far more utilized.

O-trimethylsilyl cyanohydrins were developed by Hünig [12a, 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. A typical reaction scheme is depicted in Scheme 5. According to this scheme, cyanohydrin silyl ethers **17** are easily obtained from the corresponding aldehydes in the presence of Lewis acid catalysts. Strong base (LDA) deprotonation of **17** at low temperature generates the corresponding acyl anion equivalent **23**, quenching with electrophile **24** affords the corresponding adduct **25** in a potentially reversible step. Adduct undergoes a 1,4 oxygen to oxygen silyl shift to afford the product **27** in O-TMS protected form that can be hydrolyzed to benzoin **29**. Protonation of **25** would lead to **28** that will eventually provide the desired benzoin upon hydrolysis. This protected cyanohydrin strategy is widely used for the synthesis of cross benzoins.



Scheme 5

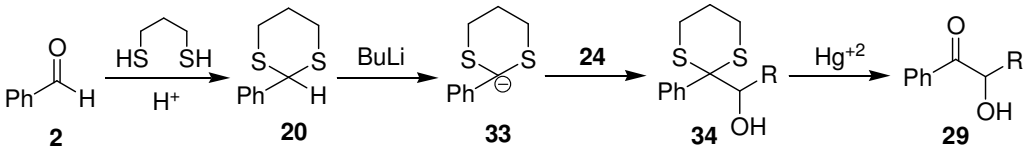
Silyl protected cyanohydrin methodology has also been used in a complementary fashion that allow the synthesis of both isomer of a given benzoin from the same starting material. According to this approach, Grignard reagents **30** can be added to nitrile moiety of **17** to obtain the benzoin **32**, isomeric to **29** [14] (Scheme 6).



Scheme 6

Corey-Seebach dithiane [12c] addition is another widely used method in cross benzoin synthesis. In this approach, aldehyde **2** is converted into the corresponding dithiane **20** that can be deprotonated by BuLi to afford a stabilized carbanion **33**. **33** can be quenched subsequently with **24** to provide the protected benzoin product **34** (Scheme 7). Hydrolysis of the product affords the desired benzoin **29**. Although this method is widely used and proved to be superior over others for certain benzoin derivatives [12d], 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 7

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 and esthetic aspects of the cyanide or thiamine catalyzed umpolung processes, it is not unexpected to see chemists trying to find out better means of accessing acyl anion equivalents.

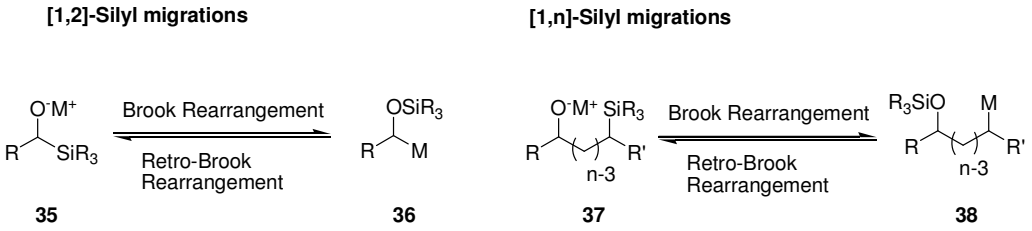
1.2.3 Catalytic Methods of Acyl Anion Generation

There is an increasing effort to devise catalytic methods of acyl anion generation from simple starting materials under convenient reaction conditions [3]. In this context many progresses have been made in this area that include the identification of better catalysts (mainly based on thiamine), new transformations and new acyl anion precursors (AAP). As the cross benzoin synthesis is considered, development of new AAP has a prime importance. Next sections present the current methodology, trends and developments in the catalyzed reactions of acyl anion equivalents. Although main body of d^1 synthons generated from acylsilanes make use of stoichiometric nucleophiles, these reagents nowadays are also at the heart of catalyzed reactions of acyl anion equivalents. Thus it is more appropriate to consider these reagents under the catalyzed reactions category.

1.2.3.1 Acyl Anion Precursors for Catalytic Acyl Anion Generation

1.2.3.1.1 Brook Rearrangement

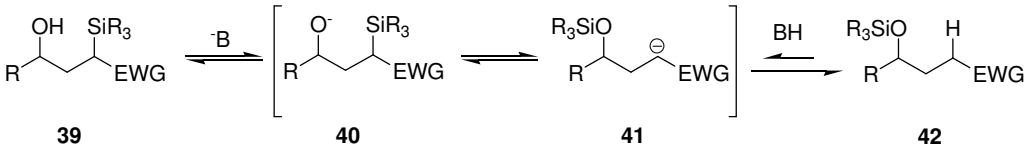
The intramolecular 1,2-anionic migration of a silyl group from a carbon atom to an oxygen atom (**35** to **36**) was originally recognized and studied by A. G. Brook in the late 1950s and early 1960s [15]. The migratory aptitude of silyl groups in this context has since been observed to be more general, comprising a family of [1,n]-carbon to oxygen silyl migrations (**37** to **38**)commonly referred to as Brook rearrangements [16] (Scheme 8).



Scheme 8

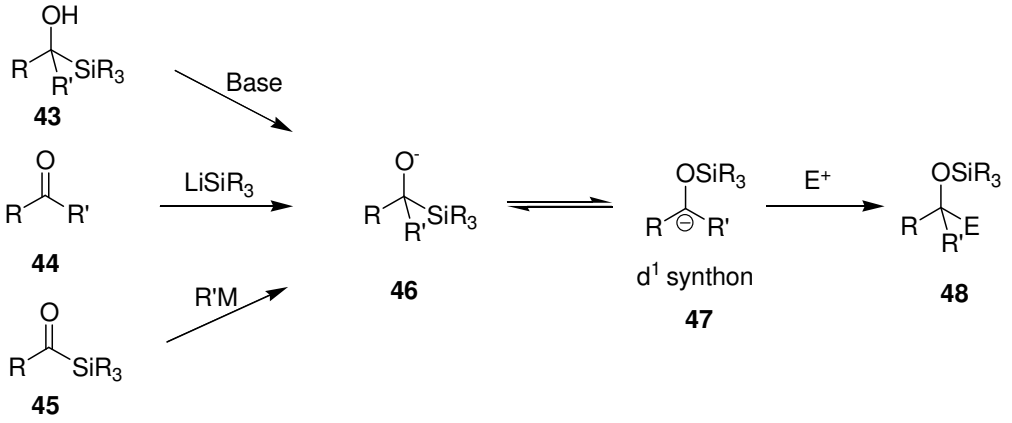
Brook rearrangement is an equilibrium process and understanding the factors governing this dynamic process has a paramount importance in terms of its synthetic applicability. When a Brook rearrangement is effected by trace base, relative stabilities of the silylcarbinol **39** and silanol **42** govern the position of the equilibrium. While the presence of an electron-withdrawing group enhances acidity, the strength of silicon-oxygen bond (120-130 kcal mol^{-1}) compared to carbon-silicon bond (70-85 kcal mol^{-1}) provides an extra driving force for complete conversion. However, under the influence of catalytic base, protonation of the **41** by the conjugate acid or starting silanol is rapid and irreversible that makes the method insufficient for carbon-carbon bond formation. Instead highly valuable tandem bond formations are viable in the presence of excess strong base since the relative stabilities of the alkoxide **40** and carbanion **41** determine the position of equilibrium. In order to establish new carbon-carbon bonds, one should be able to trap the

carbanion **41** by an electrophile. In this situation, the most important factors are the basicity of the carbanion and identity of the counterion. The presence of the EWG facilitates the sily migration while the counterion affects the alkoxide stability. Strongly binding or aggregating counter ions, like lithium, retards the sily migration and favors **40** while weaker binding ions, such as sodium, promote the sily migration from carbon to oxygen in favor of **41** (Scheme 9).



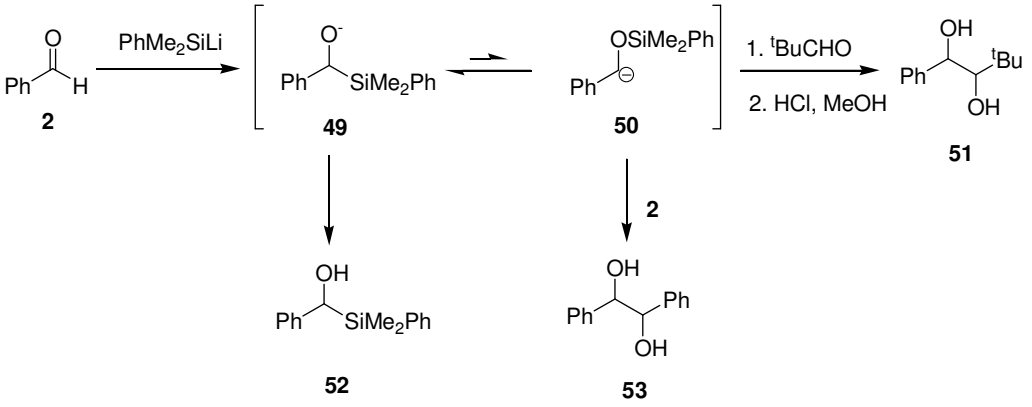
Scheme 9

1,2-Brook reaarangement intermediates **47** 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 **43** is treated with a base, when an aldehyde or ketone **44** is treated with a silyllithium reagent or when an acylsilane **45** is treated with a nucleophile (Scheme 10). 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 **23** of Hünig's method [12a, b] (Scheme 5).



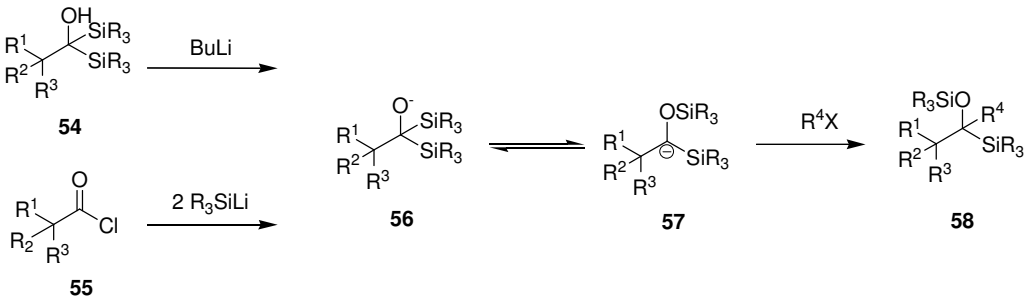
Scheme 10

When benzaldehyde is treated with dimethyl(phenyl)silyllithium, the products are the α-silylated benzyl alcohol **52** and pinacol **53** [17]. Pinacol is the product of **50** with benzaldehyde, but it is not possible to use this nucleophile with a range of electrophiles. Although homocoupling is easy, it is limited to aromatic substrates that can provide considerable carbananion stabilization. Only nonenolisable aldehydes can be used for cross pinacol synthesis (e.g. **51**) with low yields and several other side products (Scheme 11). Thus these substrates are not a general or reliable way of getting access to d^1 synthons.



Scheme 11

Fleming [17] developed 1,1-disilyl alcohols **56** in which a second silyl moiety helps stabilization of the carbanion **57** to be formed. In this way they were able to alkylate the carbanion with a wide range of alkyl halides to obtain **58**. They also improved the method to one-pot reaction of the acid chlorides successively **55** with the silyllithium reagent and alkyl halide (Scheme 12).



Scheme 12

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 [16].

1.2.3.1.1.1 Acylsilanes as Acyl Anion Precursors

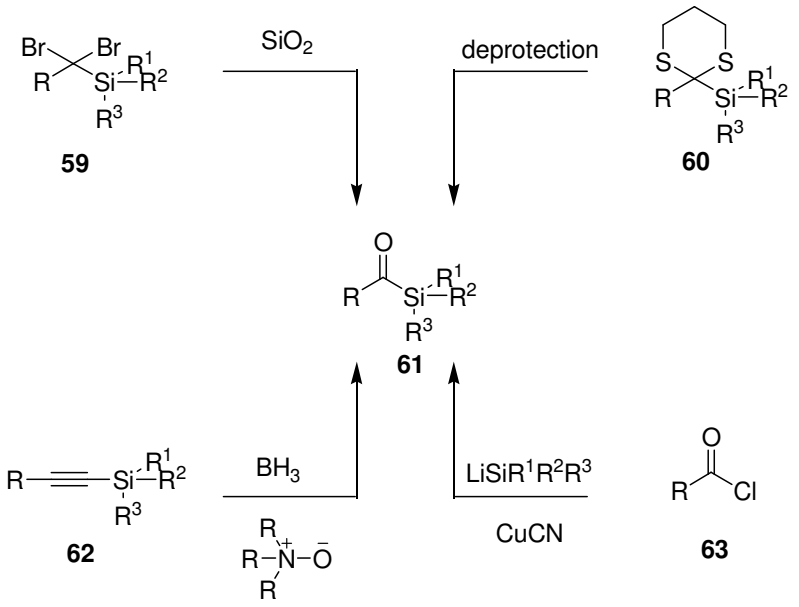
Acylsilanes are valuable compounds in organic synthesis primarily due to their ability to access the Brook rearrangement manifold upon the addition of a strong nucleophile. Acylsilanes have been employed in the synthesis of enolsilanes and alcohols and provide direct access to homoenolates upon addition of vinyl or alkynyl organometallic reagents. More recently, acylsilanes undergoing the Brook rearrangement have been the cornerstone for the development of tandem annulation

reactions, and the unique properties of the resulting anions have been exploited in the development of new catalytic acyl anion addition reactions [18].

1.2.3.1.1.2 Synthesis of Acylsilanes

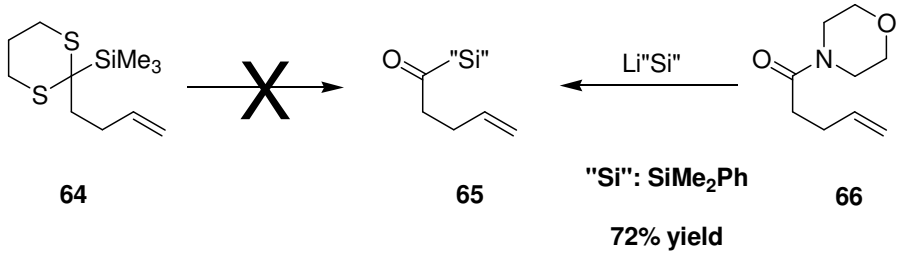
Alhthough acylsilanes **61** are useful entities, standart procedures for accessing these compounds have numerous limitations such as low overall efficiency and a reliance on stoichiometric quantities of a metal.

There are numerous methods to construct the carbonyl carbon-silicon bonds some of which is depicted in Scheme 13 [18, 19]. Unconventional approaches include the conversion of α,α-dibromobenzyl-silanes **59** to acylsilanes on silica gel, and the hydroboration of silylalkynes **62**. The trapping of deprotonated dithianes with chlorosilanes has been employed for years, but this strategy always requires the unmasking of the α-silyl dithiane **60**, which is not always compatible with the substrate. Although the addition of anionic silyl nucleophiles to acid chlorides **63** is typically the most direct method for the synthesis of acylsilanes, this method requries at least 2 equiv of the silyllithium reagent and suffers from stoichiometric copper(I) cyanide required for the reaction to proceed in high yield. Palladium catalyzed conversion of acyl chlorides to aryl acylsilanes has been reported, but this reaction is limited to the trimethylsilyl group and undergoes decarbonylation with eletron-deficient aromatic systems.



Scheme 13

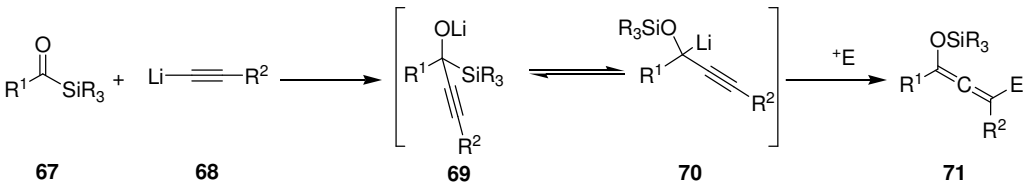
Many of these methods are potentially diffucult due to the unavailability of the starting materilas or their lack of atom economy. In fact, Scheidt [19] recently reported the inefficiency of the most widely used dithiane methodology in the synthesis of acylsilane **65** (Scheme 14). Instead they offered a new methodology based on the addition of silylnucleophiles to morpholine amides **66**. Morpholine amides are supposed to stabilize the intermediate adduct formed upon addition of the silyl nucleophile which provide the desired acylsilane **65** upon hydrolysis. Although morpholine amide strategy was proved to be useful for aliphatic substrates, it is not useful for aromatic acylsilanes. Thus there is not a completely reliable and practical methodology for the synthesis of these useful entities.



Scheme 14

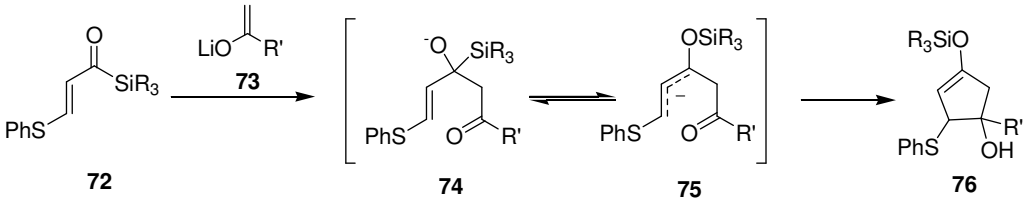
1.2.3.1.1.3 Acylsilanes in Synthesis

Acylsilanes have been utilized in a variety of tandem bond formation strategies and proved to be highly useful entities providing acyl anion intermediates [16]. 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 [20] had shown that addition of lithium acetylides **68** to acylsilanes **67** provide allenol silyl ethers. Reaction proceeds via addition of the alkynyl nucleophile to acylsilane followed by the Brook rearrangement forming a carbanion intermeadite **70** that reacts with an electrophile to provide the allenic product **71** (Scheme 15).



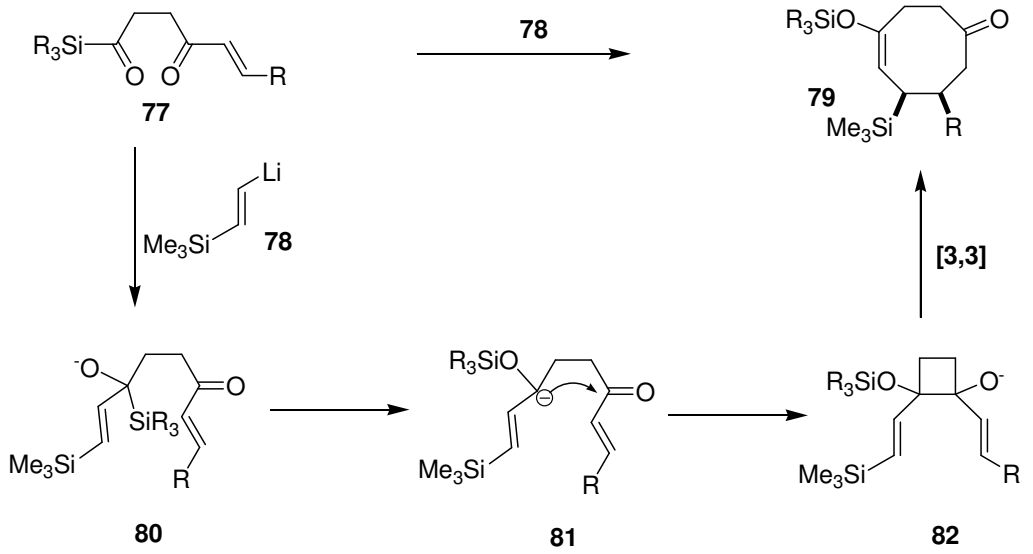
Scheme 15

Takeda and co-workers [21] 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 **72** with a lithium enolate **73** followed by rearrangement affords the delocalized carbanion **75** that traps the present electrophile 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 **76** in the form of nucleophilic silyenol ethers (Scheme 16).



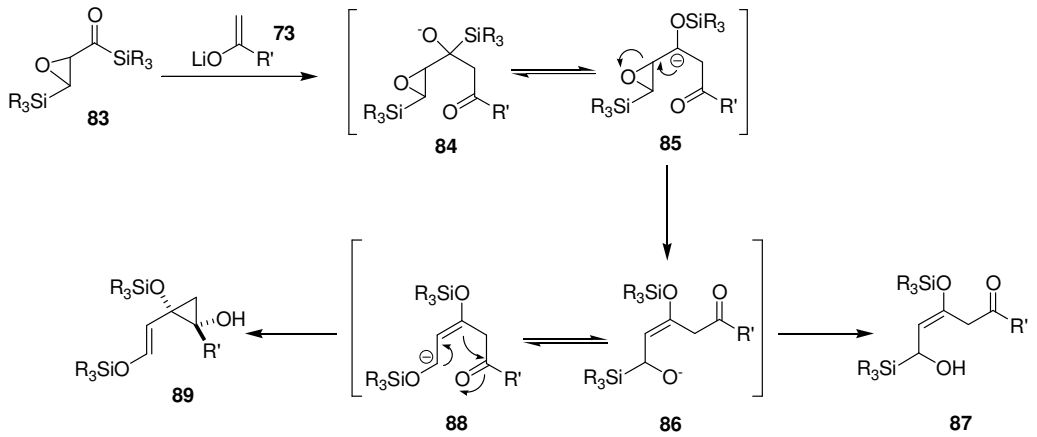
Scheme 16

The power of tandem bond formations utilizing acylsilanes have been nicely exemplified by Takeda in the synthesis of eight-membered carbocyles [22]. In this approach, nucleophile **78** promoted Brook rearrangement of **77** provides 1,2-divinyl butonolate **82** that undergoes an oxyanion-accelerated cope rearrangement to provide the highly functionalized eight-membered carbocyles of type **79** (Scheme 17).



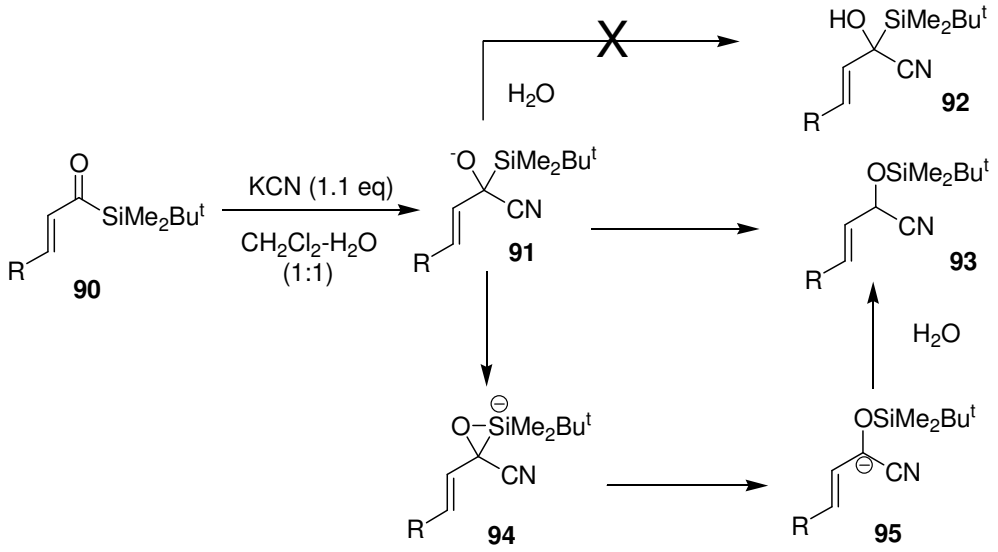
Scheme 17

It is also possible to induce double Brook rearrangement in a suitably designed substrate [23]. In fact Brook rearrangement of β-silyl-α,β-epoxyacylsilane **83** results in a internal epoxide ring opening that leads to **86** that is prone to a second Brook rearrangement. Takeda has shown that protonation of **86** provides the alcoholic product **87** whereas rearranged intermediate **88** affords the cyclopropanediol **89**.



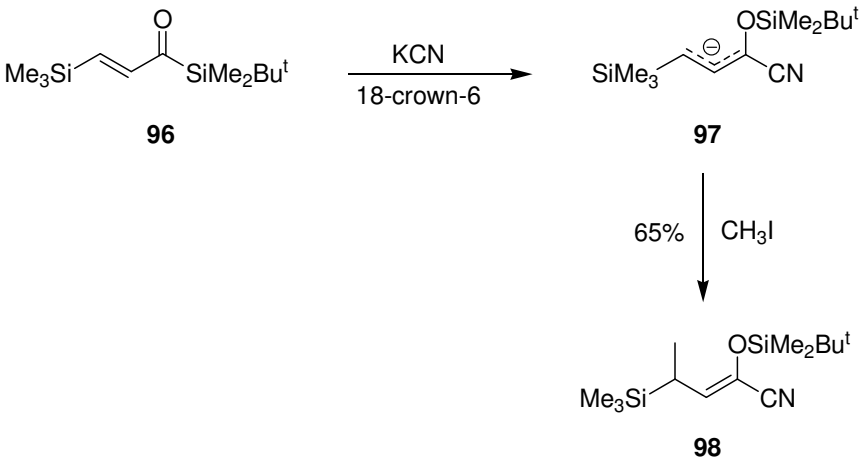
Scheme 18

Cyanide promoted Brook rearrangement of acylsilanes was first presented by Reich [24]. 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 [25] has shown that it possible to trap the carbanion **95** formed from acylsilane **90** and cyanide in aqueous media to provide the cyanohydrin product **93**. Interestingly, no product **92** arising from the O- protonation of **91** 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 **94** was also invoked. This reaction was also shown to be useful in alkylation of the carbanion **95** in nonaqeous organic media (Scheme 19).



Scheme 19

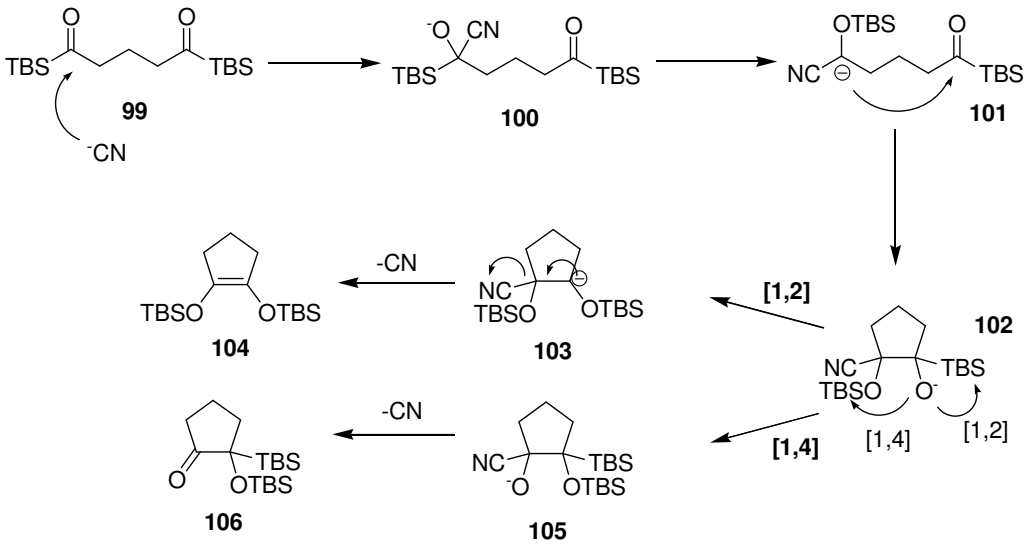
In a similar reaction shown above (Scheme 17-19), cyanide ion promoted Brook rearrangement of unsaturated acylsilanes **96** undergo reactions with electrophiles as homoenolate **97** providing product type **98** [21] (Scheme 20).



Scheme 20

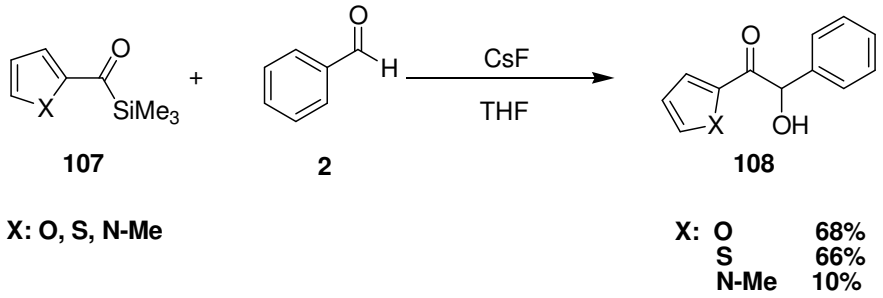
The reactions of bis(acylsilanes) were also reported [26]. Cyanide promoted rearrangement of **99** provides **101** that intramolecularly reacts with the other acylsilane moiety in close proximity to afford **102**. Intermediate **102** may undergo

[1,4]-O,O-silyl shift to provide **106** or a second 1,2-Brook rearrangement to furnish **104**. The release of cyanide from **103** or **105** in the last step of both reactions renders this process catalytic in nucleophile. This is quite interesting considering the possibility of designing reactions based on acyl anion equivalents that are catalytic in the promoting nucleophile (Scheme 21).



Scheme 21

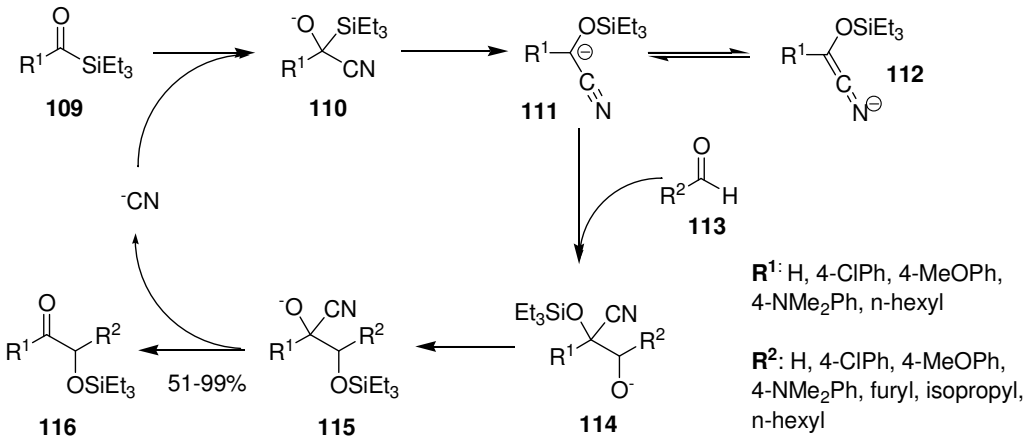
Synthesis of benzoins (or acyloins in general terms) requires the reaction of the carbanions of Brook rearrangement with carbonyl compounds as electrophiles. First example of this idea was reported by Degl'Innocenti [27a] in the fluoride catalyzed reaction of acylsilanes **107** with benzaldehyde to provide the expected benzoins **108** (Scheme 22). 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 [27b].



Scheme 22

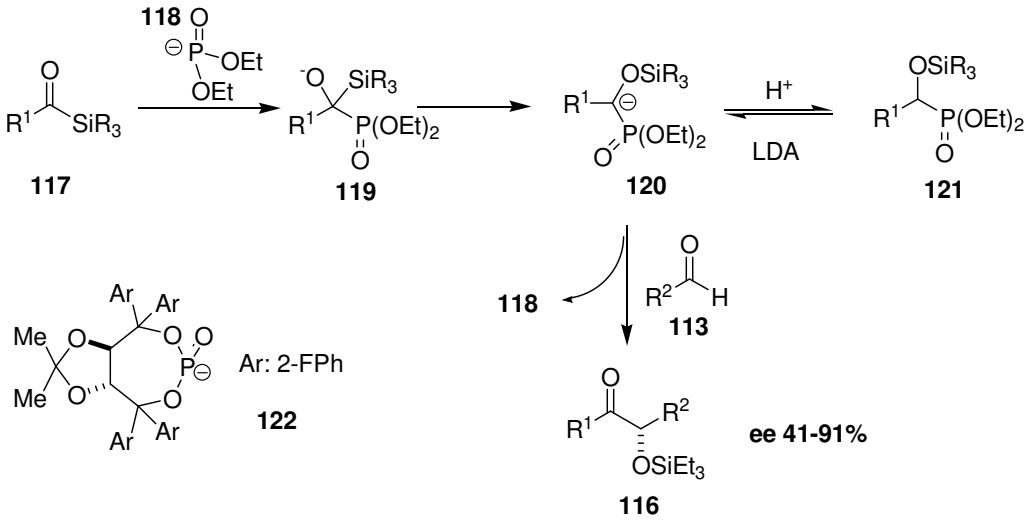
Recently cyanide ion catalyzed reaction of acylsilanes **109** with aldehydes **113** in the presence of catalytic KCN and 18-crown-6 in Et_2O providing O-silyl protected benzoin adducts was reported [28]. The proposed mechanism of the reaction (Scheme 23) is very similar to that of the classical benzoin condensation catalyzed by cyanide or thiamine. According to this mechanism, cyanide ion promoted Brook rearrangement of acylsilane **109** provides the acyl anion equivalent **111** 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 **111** is highly favored. Reaction with aldehyde and subsequent 1,4-silyl migration affords alkoxide **115**. Retrocyanation leads to product α-silyloxy ketone **116** 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. While aliphatic aldehydes as acceptors (aromatic-aliphatic combination) provide good yields (51-66%, 4 examples), aliphatic-aromatic variant was reported to give meaningful yield (51%, one example) only in the presence of excess acceptor aldehyde (5 equiv) and high PTC load. Reactants possessing enolizable protons on both reaction partners (aliphatic-aliphatic combination) were nonproductive. However, same investigators later have shown that counterion (M^+) in MCN catalysis is highly critical and lanthanum tricyanide $La(CN)_3$ were identified as the optimal catalysts after screening of various metal cyanides [28b]. $La(CN)_3$ was reported to be giving the expected

products in much shorter reaction times and even suitable for the reaction between an aliphatic acylsilane and an aliphatic aldehyde albeit in intermediate yield (48%, one example). Moreover use of excess aldehyde for the aliphatic-aliphatic combination was not necessary with $La(CN)_3$ catalyst .



Scheme 23

The use of acylsilanes in benzoin synthesis was also expanded to enantioselective variant of this reaction. Based on the Takeda's [29a] observation that metallophosphites **118** react stoichiometrically with acylsilanes to give carbanion **120** after Brook rearrangement and Zimmer's [29b] strong base deprotonation of acyl anion precursor **121**, diethylphosphite anion was shown to be catalyzing the expected benzoin condensation. Johnson [28d] has shown that the use of chiral metallophosphite **122** provides moderate to high enantioselectivity (81-91% ee, aryl-aryl combination; 41-73% ee, aryl-alkyl combination) in the synthesis of benzoin adducts **116** (Scheme 24). This is the first example of nonenzymatic cross benzoin condensation reaction reported so far.

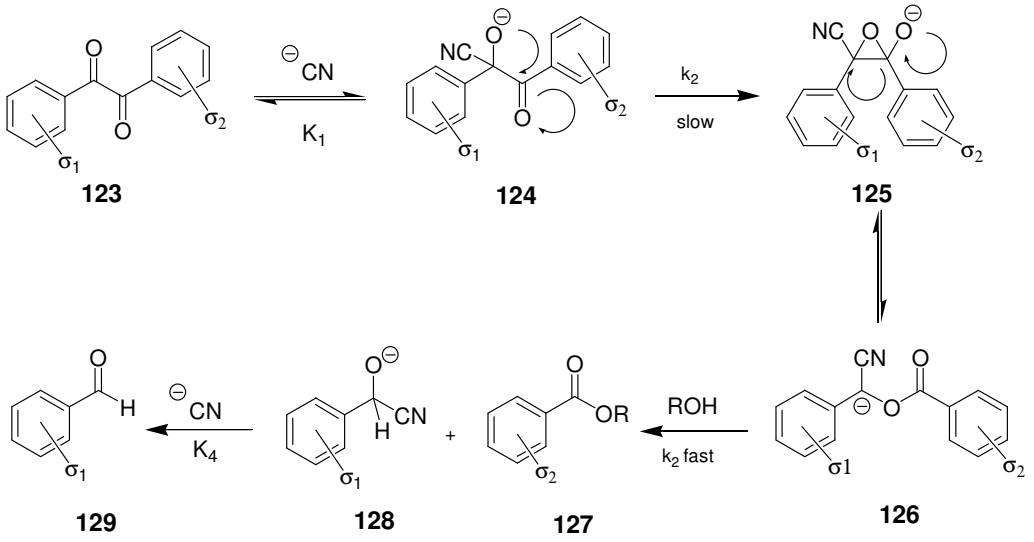


Scheme 24

Briefly acylsilanes are not only effective in nucleophile promoted reactions but also catalyzed reactions of carefully designed reactions. Cyanide promoted Brook rearrangement of acyl silanes is highly useful in benzoin (or acyloin) synthesis in which the release of the cyanide (or metallophosphite) renders the whole process catalytic in the nucleophile. Today, cyanide catalyzed sily benzoin reaction is the most prominent and practical cross-benzoin condensation reaction. It is the only well-established method utilizing catalyzed reactions of acyl anion equivalents. The seemingly major limitation of the reaction is the availability of the starting acylsilanes as mentioned above (section 1.2.3.1.2.1). The most widely employed methodology for the synthesis of them, namely dithiane method (not applicable to all types of acylsilanes), make use of deprotonated dithianes that are themselves acyl anion equivalents and react with aldehydes to provide the corresponding cross benzoin products (Scheme 7). Recently published alternative method for acylsilane synthesis also stem for the use of stoichiometric strong base in anhydrous solvents under strict temperature control.

1.2.3.1.2 Cyanide Ion Catalyzed Cleavage of Benzil

In 1923, Dakin and Harington [30a] showed that the cyanide ion catalyzes the cleavage of benzil **123** to benzaldehyde **129** and the corresponding ester of the benzoic acid **127** in alcoholic solvent. Later, the mechanism and kinetics of the reaction were investigated by Kwart and Baevsky [30b]. They showed that the cyanide ion was able to cleave a series of benzils depending on the substitution on the aromatic rings, and proposed a mechanism, correlating the kinetic data obtained (Scheme 25).

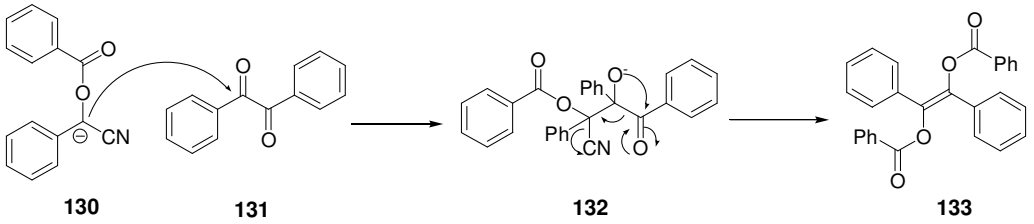


Scheme 25

It was shown that there is a linear free energy relationship with a large ρ= 3.45, where observed ρ represents an average value derived from the additive contributions of the ρ values for a rapidly established equilibrium (K_1) and a kinetic step (k_2). According to the mechanism, it was proposed that the carbonyl group linked to the more electron-deficient ring would be the preferred locus of cyanide attack to provide **124**. The nature of the substituent on the other ring will affect the product distribution as it may increase the ease of cleavage of the central carbon-

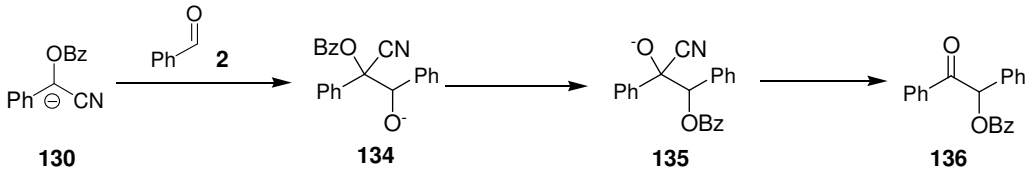
carbon bond in the transition state. Therefore, in each case, where σ_1 was more positive than σ_2, the expected aldehyde (σ_1) and ester (σ_2) were the sole products.

After Kwart and Baevsky proposed the intermediacy of **126** in the cyanide anion catalyzed cleavage of benzil, Trisler and Frye [31] showed that **130** derived from **131** reacts again with itself in aprotic solvent DMSO, where **130** is highly nucleophilic, to form *trans-α,α'*-stilbendiol dibenzoate **133** through 1**32** (scheme 26). This work showed that **130** is a potent nucleophile and can react with an electrophile in the medium.



Scheme 26

Later, Kuebrich and Schowen [32], in a study investigating the nature of α-hydroxycarbanions, used the benzil and cyanide in DMF to generate the intermediate **130** and examined its reaction with benzaldehyde providing benzoin derivative **136** via **135**. Although **130** could be generated efficiently under aprotic conditions, methods of utilizing it have not been developed and well understood; otherwise it would be quite useful for cross benzoin synthesis in both free and protected form.



Scheme 27

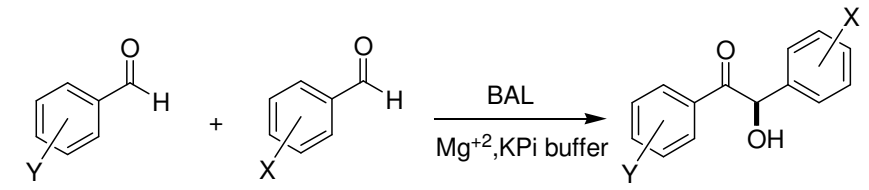
The formation of derivatives of **126** from the corresponding O-benzoyl cyanohydrin under highly basic conditions was reported [7a]. These intermediates have been shown to form corresponding benzoin benzoates in low to moderate yields. These low yields are possibly related to both poor reaction conditions for generating **126** and the stability of the products under the given conditions.

1.2.3.2 Organocatalyzed Reactions of Acyl Anion Equivalents

Reaction systems involving thiamine catalysts and catalytic nucleophilic acylation reactions in general have been thoroughly studied by numerous scientists. After Breslow's catalytic cycle invoking the intermediacy of carbenes, decisive progress in carbene chemistry made a great impact in this field [4].

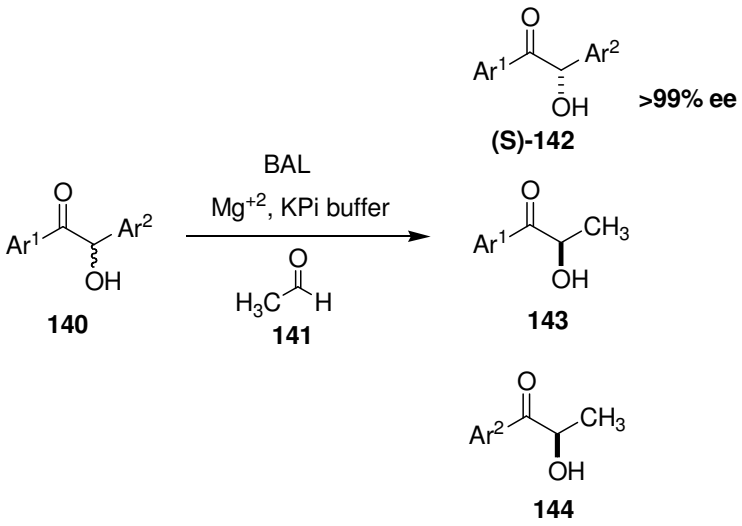
1.2.3.2.1 Carbon-Carbon Bond Formation by TPP Dependent Enzymes

Benzaldehyde lyase (BAL) or benzoyl formate decarboxylase (BFD) catalyses highly enantioselective carbon-carbon bond forming reactions between two aldehydes providing enantiopure benzoins or acyloins in aqueous media [33]. Recently BAL catalyzed benzoin condensation has been reported to provide cross benzoin products **139** from carefully selected pair of benzaldehydes [33e]. This variant requires a halogen in the ortho position of the acceptor aldehyde **138**, but a range of substitution pattern is possible for the donor aldehyde **137**. BAL is also capable of highly selective kinetic resolution through retro-benzoin condensation: the liberated aldehydes from the reversal of the fast reacting R enantiomer are trapped with acetaldehyde **141** leading to **143** and **144**. The unreacted S enantiomer **142** was recovered in an enantiopure form. In this way both enantiomers of a cross benzoin product is available by a tactical combination of forward and reverse reactions since formation of R enantiomer is favored in the forward reaction (Scheme 28).



Y= H, 3-CN, 4-Br, 4-CF_3,
3,4,5-(MeO), 3,5-$(MeO)_2$

X= 2-Cl, 2,6-F_2, 2,3,5-F_3



Scheme 28

Although this is the first enantioselective cross benzoin condensation reaction reported in literature, it actually seems not to be a true donor aldehyde-acceptor aldehyde concept; rather it is the preference of the enzyme to accept ortho substituted aldehydes as acceptors. So the applicability of the enzyme is limited to the use of only a few aldehydes and in many cases mutant enzymes were necessary to widen the substrate scope. Although there are some limitations, enzymes offer environmentally benign green chemistry approach with high level of enantioselectivities that is not possible with the current state of chemical transformations.

1.2.3.2.2 Nucleophilic Carbenes in Asymmetric Catalysis

The use of heteroazolium salts in their deprotonated carbene form as catalysts for umpolung reactions has always attracted researchers in construction of bifunctional targets. Benzoin condensation (1,2-bifunctionality) and Stetter reaction (1,4-bifunctionality) was always at the center of these umpolung strategies. Since the inspritaion of these studies was originated from the nature's carbon-carbon forming reactions utilizing thiazolium salts as cofactor, the prevalent chirality of the products possessed by the natural transformations was always one of the crucial aspects.

The first research on the asymmetric benzoin condensation was presented by Sheehan et al. employing the chiral thiazolium salt **145** as the catalyst precursor [4]. Yet the enantiomeric excess of the synthesized benzoin was as low as 2%. Afterwards several chiral thiazolium salts (**146**-**148**) were reported by several researchers but all of them suffer from low enantioselectivities and product yields (Figure 7).

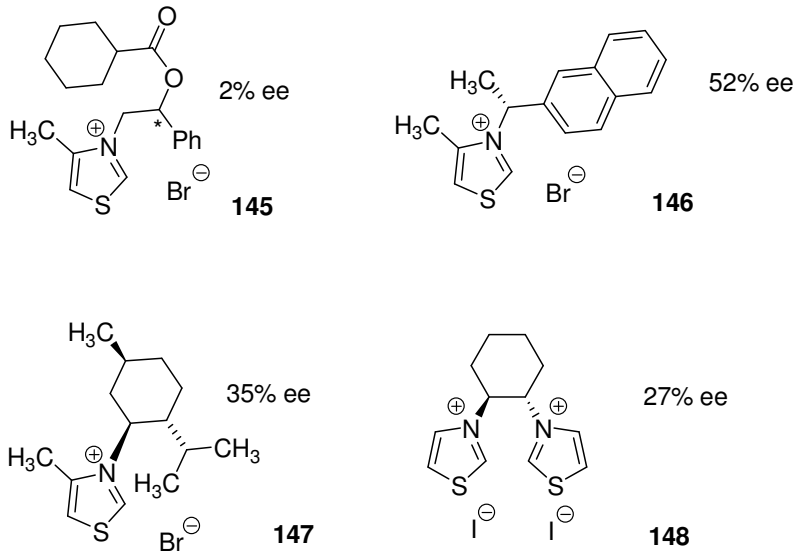
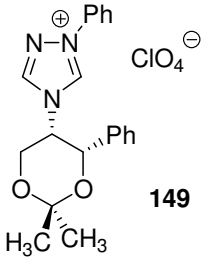
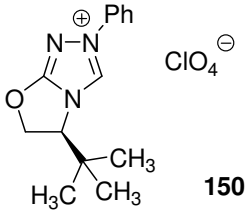


Figure 7. First generation of chiral Thiazolium salts for enantioselective benzoin condensation

The major breakthrough in this area came from Enders laboratories [34]. They reported triazolium salts to be superior to corresponding thiazolium salts in terms of air and moisture stability allowing high turnover numbers as organocatalysts. After examining a variety of chiral triazolium salts, they were able to obtain R benzoins up to 86% ee and a satisfactory yield of 66% with as low as 1.25% of catalyst of **149**. Later they have introduced the catalyst **150** as the best performing catalysts so far. They were able to obtain enantiomeric excesses up to 95% and chemical yields up to 83%. Today enantioselective benzoin condensation catalyzed by **150** represents the benchmark reaction in the area (Figure 8).



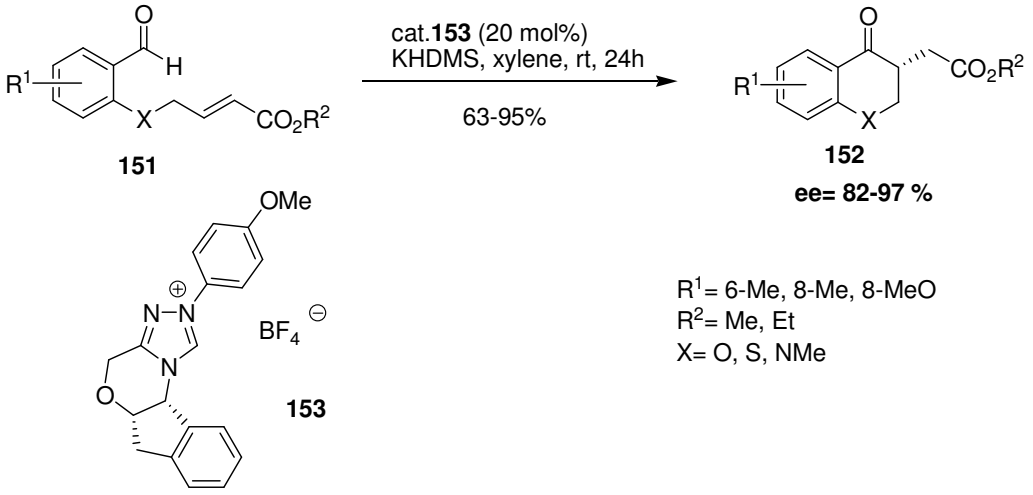
149



150

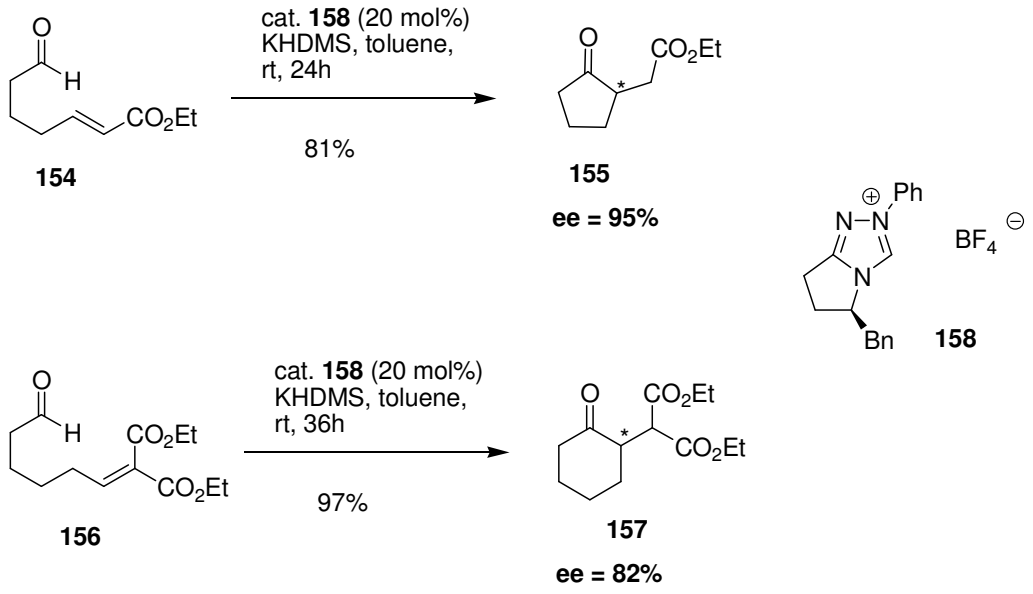
Figure 8. Chiral Thiazolium salts synthesized by Enders et al.

Enantioselective catalysis of intramolecular Stetter reaction was originally achieved by Enders and recent efforts by Rovis and co-workers established the benchmark for enantiocontrol in this family of the reactions [35a]. Triazolium carbene catalysis **153** derived from aminoindanol provided the annulated products **152** with excellent enantioselectivity and chemical yield (Scheme 29).



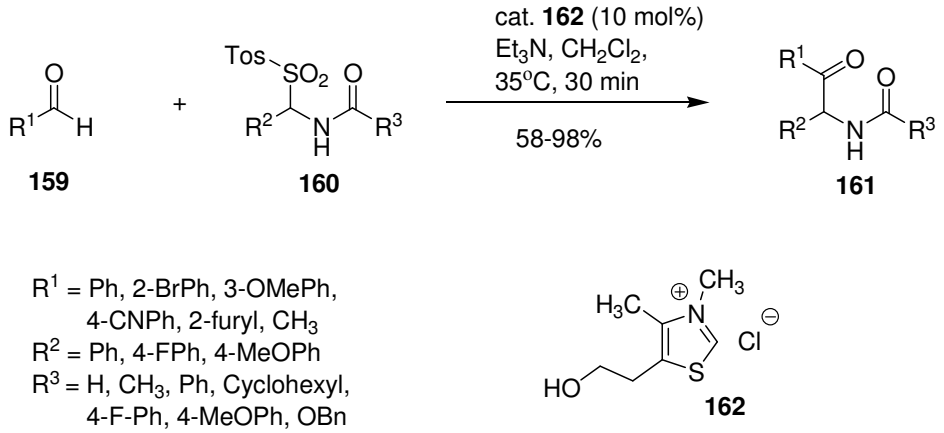
Scheme 29

Rovis et al. expanded the enantioselective Stetter reaction to aliphatic substrates such as **154** and **156** that led to cyclopentanone **155** and cyclohexanone **157**, respectively, with good yields and good enantioselectivities [35b]. The olefin part of **156** is doubly activated to enhance the reactivity as Michael acceptor because the greater conformational freedom of the aliphatic linker in compound **156** critically diminished the reactivity of the aliphatic substrate compared to substrate **154** (Scheme 30).



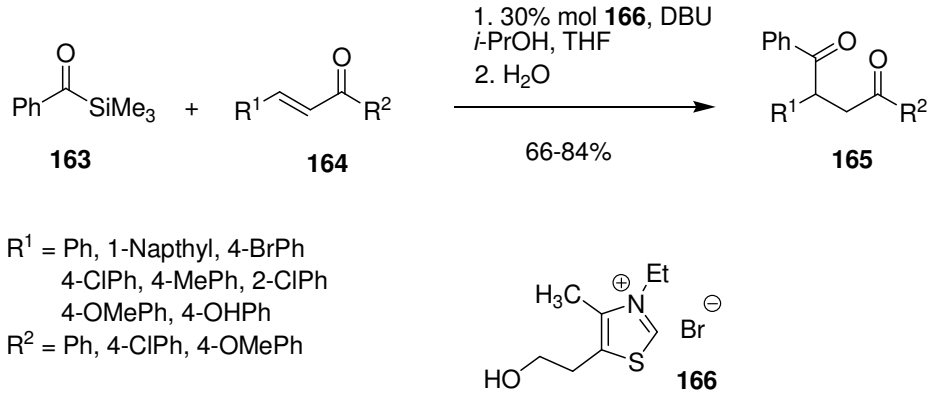
Scheme 30

Reider et al. reported the synthesis of α-amido ketones **161** in a cross-coupling reaction of aldehydes **159** and acylimines, catalyzed by the thiazolium salts **162** [36]. The acylimine, formed in situ from an arylsulfonamide **160**, function as the Michael acceptor. Although not enantioselective, this remarkable reaction demonstrates the versality of the nucleophilic carbenes in the synthesis of valuable targets (Scheme 31).



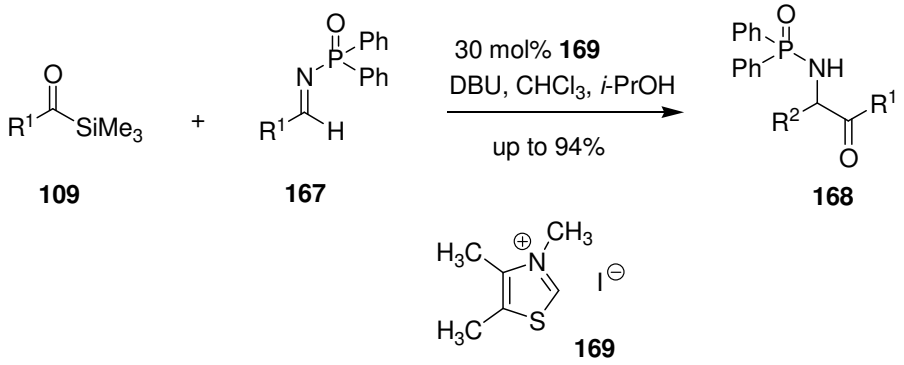
Scheme 31

Although Stetter reaction is highly powerful in constructing 1,4-dicarbonyl compounds, it is significantly limited by the high reactivity of the aldehyde, which results in large amounts of self-condensation, or benzoin products. This fact hampers the reaction's utility in intermolecular addition of the aldehydes to Michael acceptor. Recently a Sila-Stetter reaction has been reported in which acylsilanes **163** generates acyl anion equivalents that selectively react with the Michael acceptors **164** in an intermolecular fashion to provide 1,4-dicarbonyl products **165** [37] (Scheme 32).



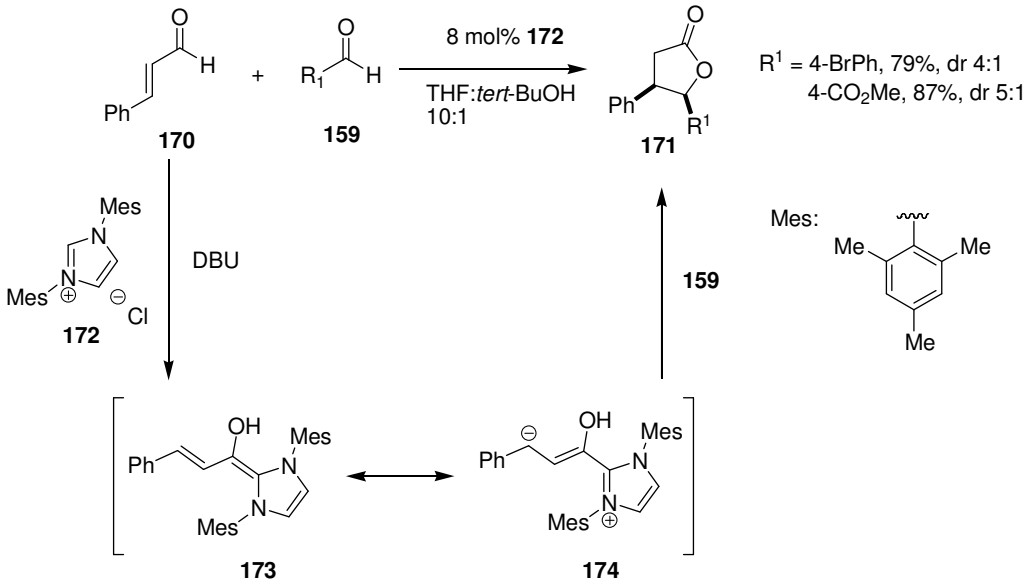
Scheme 32

A similar strategy for the addition of acylsilanes **109** to imines **167** has also been reported that led to an efficient synthesis of valuable α-amino ketones **168** [38] (Scheme 33).



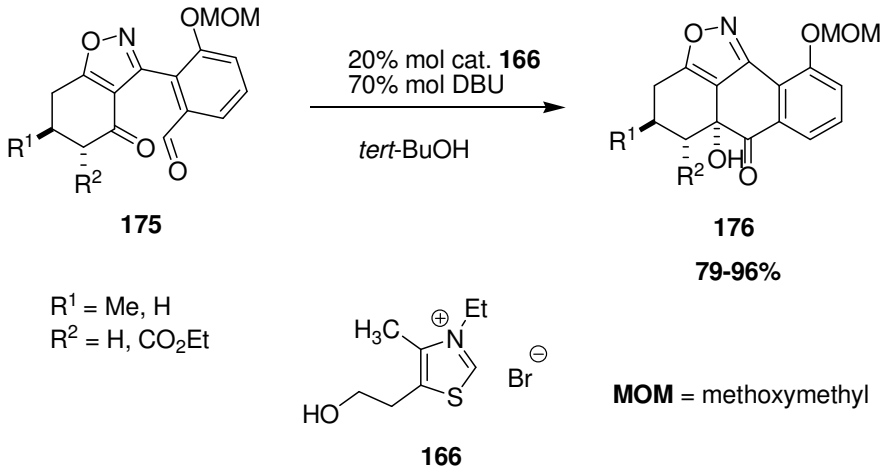
Scheme 33

Recently *N*-Heterocyclic carbene catalyzed generation of homoenolates has been independently reported by Bode [39a] and Glorius [39b]. While classical thiazolium salts and bisalkyl imidazolium salts were identified as unproductive, bisaryl imidazolium salt **172** led to the product **171** by the addition of homoenolate **174** to aldehyde **159** (Scheme 34). In addition to the synthetic utility of the resulting products, these studies disclose a versatile mechanistic platform for the development of novel carbon-carbon bond forming processes through the intermediacy of catalytically generated homoenolates and activated carbenes.



Scheme 34

Considering the difficulties with the cross benzoin condensation that requires the regioselective selective coupling of two different aldehydes, it is not suprising that there is no catalytic method for the intermolecular coupling of an aldehyde with a ketone. However Suzuki et al. [40] recently reported that it is possible to induce intramolecular dimerization of an aldehyde with a ketone in a suitably designed substrate like **175** in the presence of a thiazolium carbene catalyst **166** to provide α-hydroxy ketone **176** (Scheme 35). This is the first catalyzed chemical aldehyde-ketone coupling process reported.



Scheme 35

1.3 Aim of the Work

In last few years, many reports were published concerning the new developments in the area of acyl anion chemistry. This suggests a reemerging interest in developing new catalyzed methods involving d^1 nucleophiles. Efforts to produce more active catalysts, new acyl anion precursors and new transformations involving umpoled (d^1 or d^3) nucleophiles will undoubtedly be an active area of research.

In relation to our previous studies concerning the enantioselective synthesis of benzoin derivatives we had a strong interest to synthesis of unsymmetrical benzoin derivatives. Thus we aimed to develop new acyl anion precursors which are easily available or accessible from simple starting materials. We intended to develop generally applicable acyl anion precursors and use them in cross benzoin synthesis as a test platform.

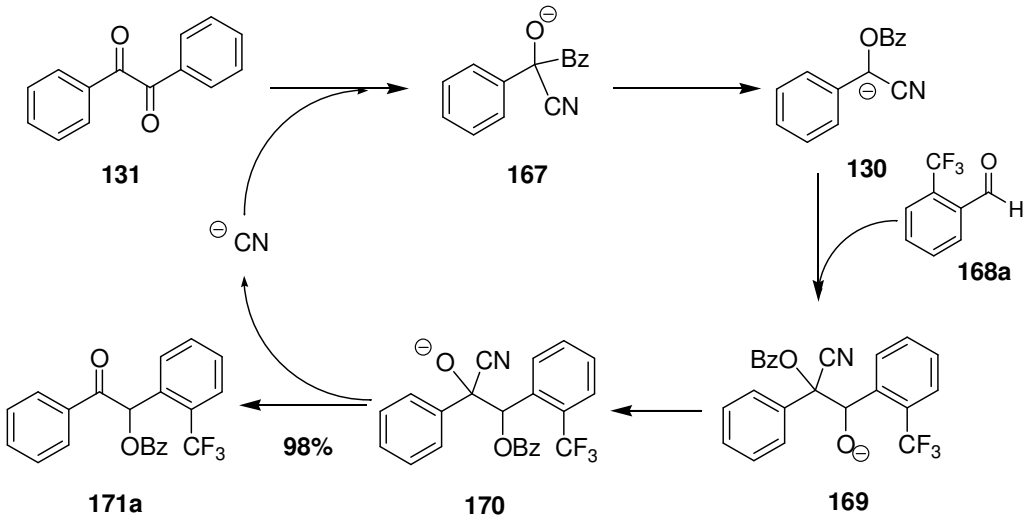
CHAPTER 2

RESULTS AND DISCUSSION

The main objective of this study was to develop new methods for the catalytic unsymmetrical benzoin synthesis. It is obvious that this question could be tackled by finding out suitable acyl anion precursors. We approached the question with two different strategies. First of them was the use of already established cleavage of benzils by cyanide ion catalysis to generate acyl anion equivalents [41]. We investigated the scope and limitations of this potentially useful approach. Second one was the development of new acyl anion precursors that was free of limitations attributable to the systems reported so far. In this context we proposed acyl phosphonates as new and practical acyl anion precursors.

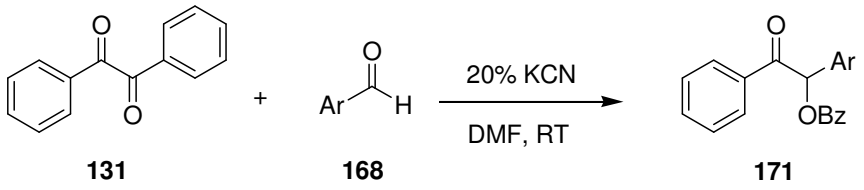
2.1 Synthesis of Unsymmetrical Benzoins *via* the Cyanide Ion Catalyzed Cleavage of Benzils

For initial studies we selected a competent benzaldehyde derivative **168a** as electrophile and examined its reaction with **131** in DMF in the presence of catalytic KCN. Gratifyingly the reaction proceeded smoothly and provided the expected product **171a** in agreement with the mechanism proposed by Kuebrich et al. [32] as shown in Scheme 36.



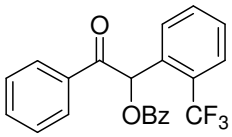
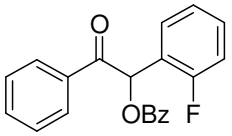
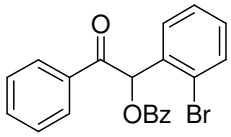
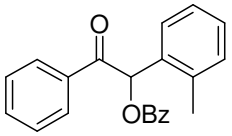
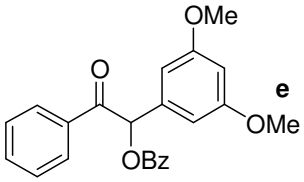
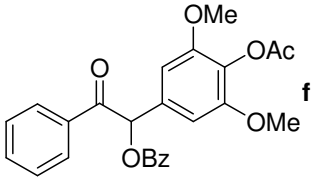
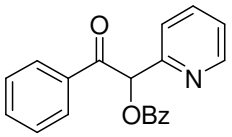
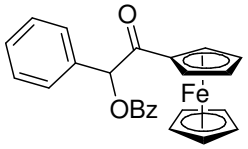
Scheme 36

After observing the high efficiency of the reaction, various acceptor aldehydes with diverse electronic properties were investigated (Scheme 37) under similar set of conditions in order to understand the scope of the reaction and the effect of the electronic nature of the substituents. Results are summarized in Table 1.



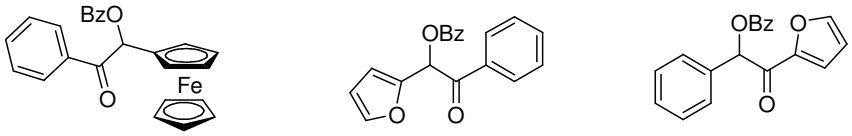
Scheme 37

Table 1. Yields and structures of unsymmetrical benzoin derivatives

entry	Aldehyde **168**	Product **171**	Yield(%)
1	**a** 2-CF_3Ph	 **a**	98
2	**b** 2-FPh	 **b**	99
3	**c** 2-BrPh	 **c**	95
4	**d** 2-MePh	 **d**	93
5	**e** 3,5-$(OMe)_2$Ph	 **e**	83
6	**f** 3,5-$(OMe)_2$-4-OAcPh	 **f**	85
7	**g** 2-pyridyl	 **g**	78
8	**h** ferrocenyl	 **h**	89

As can be seen in Table 1, reaction gave excellent results for electronically diverse range of aromatic aldehydes. Substituents at the ortho- position do not possess any steric problems (Table1, entries 1-4) and electron-withdrawing substituents gave slightly better yields. Various substitutions at the other positions are also tolerated (entries 5-7).

Particular attention to the structural integrity was required, because it was demonstrated by Corrie [42] that carbonyl derivatives of unsymmetrical benzoins may scramble to form isomeric compounds. Taking into account the fact that some unsymmetrical benzoins may also isomerize to the thermodynamically more stable isomer under typical basic hydrolysis conditions, the correct structural assignment of the initial structures gains prime importance. Reported ^{1}H-NMR shift values for a series of mono substituted benzoins show that two *ortho*– protons of benzoyl moiety consistently resonate at around δ 7.9. For the compounds listed in Table 1, we observed two doublets at around δ 7.9 and δ 8.1 that respectively originate from the benzoyl moiety of the benzoin and ester part. However, ferrocenecarboxaldehyde afforded the isomeric products **171h** instead of the expected compounds **171i** (Table 1, entry 8 and Figure 9). This observation was based on the lack of two *ortho*-protons of benzoyl moiety in benzoin portion of the molecule supported by 2D NMR analysis. The difference in reactivity can be attributed to the electron-rich nature of the ferrocenyl group. Although aldehyde **168e** has two electron-donating groups, methoxy substituent on the *meta*- position has a σ-value with a positive sign and yields the expected product. For a better understanding, 3,4,5-trimethoxybenzaldehyde was reacted in a similar manner and two isomeric products were isolated in an 1:2 ratio (in favor of isomeric product) just after the completion of the reaction. Changing the *p*-methoxy group with an acetoxy group resulted in the formation of the desired isomer **171f**. As mentioned previously, Kuebrich et al. reported the same reaction with electron-rich furfural. Although they reported the formation of **172** according to the mechanism in Scheme 36, their NMR data strongly resembles that of **173** lacking the two *ortho*- benzoyl protons. This supports the idea that electron-rich aldehydes have a propensity to yield isomeric products.



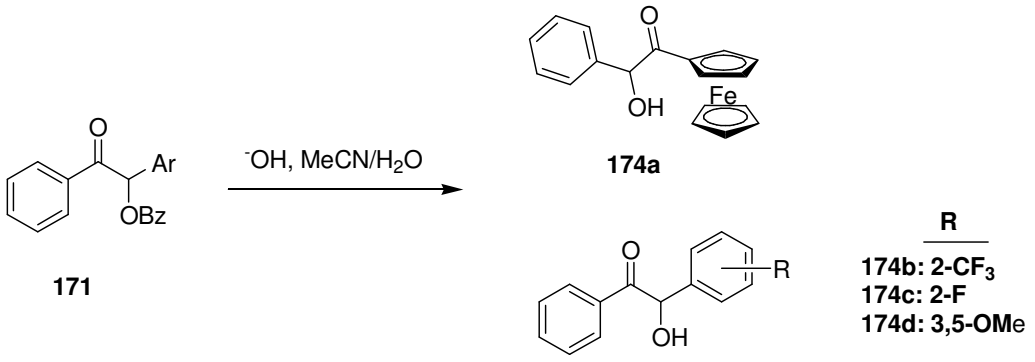
171i **172** **173**

Figure 9. Isomeric products formed under standart reaction conditions

Some derivatives of benzoins are very useful photolabile protecting group of carboxylic acids and phosphates [43]. Upon irradiation at ~350 nm they release the acid moiety. The best photosensitive benzoin developed so far can be obtained from **171e** after hydrolysis, and a recent report showed that **171e** itself releases the benzoate moiety almost quantitatively. Thus, the present method may allow the rapid synthesis of derivatives of **171**, which can then be tested for photolability, such as **171f**. In fact we found by competitive experiments that **171f** is a better photolabile protecting group in terms of benzoate release rate that allowed us to develop new photolabile protecting groups based on **171f** backbone. Recently reported synthesis of unprotected form of **171e** in 56% yield [43d] (overall 35% yield starting from benzaldehyde) by a dithiane method compared to 71% of this method (for hydrolysis, see below) is very promising in terms of yield and operational simplicity.

Products **171a-h** are in protected form and their hydrolysis can afford the corresponding unsymmetrical benzoins or benzils upon oxidation. Hydrolysis of the products to the corresponding benzoins **174** was carried out in a basic medium (Scheme 38). While isomerization was not a problem with electron-withdrawing substituents, the 2-methyl derivative **171d** afforded an isomeric mixture, and 2-Br derivative **171c** exhibited a small amount of isomerization. Hydrolysis of already isomeric **171h** furnished **174a**. Oxidation was a problem during hydrolysis if the oxygen was not removed from the medium before the reaction. Isomerization possibly occurs via an endiol and the yellow color developed during the hydrolysis was attributed to this intermediate. This intermediate is expected to be easily oxidized during hydrolysis if air is not excluded from the medium. In the hydrolysis of **171e** to the corresponding benzoin **174d**, 4:1 mixture of isomers was obtained under standard conditions. When the same reaction was carried out at lower pH

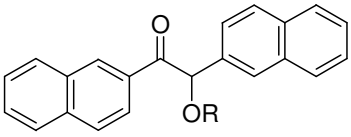
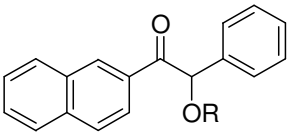
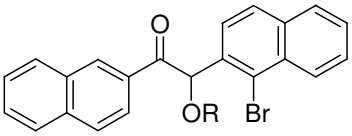
values, a 10:1 mixture of separable isomers was obtained with prolonged reaction times (6-8 h).

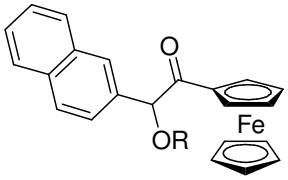


Scheme 38

We have also shown that 2-naphthil **175** can be used effectively instead of **131** to obtain the corresponding benzoins **176a-d** in good yields (Table 2). Reaction with ferrocenecarboxaldehyde furnished the isomeric product **176d** in agreement with the results obtained from the corresponding reaction of **131**.

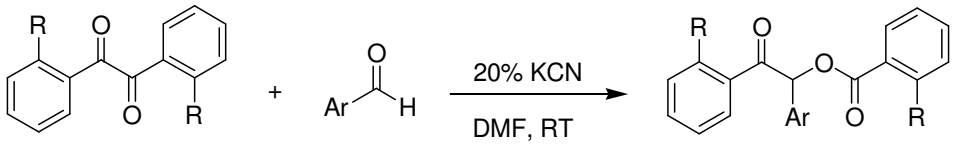
Table 2. Yields and structures of unsymmetrical benzoin derivatives derived from 2-naphthil

entry	Aldehyde **168**	Product[a] **176**		Yield(%)
1	**i** 2-naphthyl		**a**	77
2	**j** Ph		**b**	79
3	**k** 1-Br-2-naphthyl		**c**	73

4	**h** ferrocenyl		**d**	74

[a] R: 2-naphthoyl

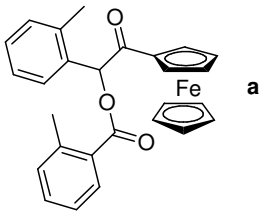
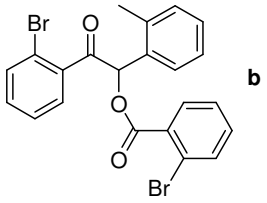
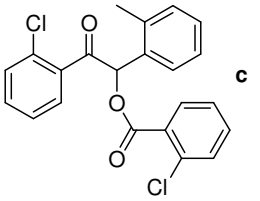
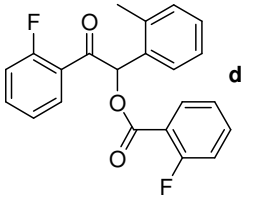
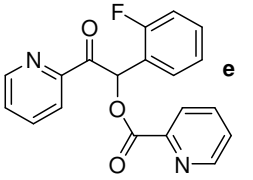
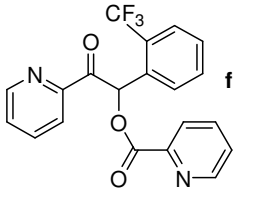
In order to obtain further insights into the scope of the reaction, a series of electronically diverse *ortho*–substituted symmetric α-diketones **177** were reacted with selected aldehydes as depicted in Scheme 39. *Ortho*–position was selected in order to asses the effect of the steric hindrance adjacent to the reacting center. The results are summarized in Table 3. Amongst these α-diketones, *o*-methoxy **177a** was unreactive under the reaction conditions. Increasing the temperature did not affect the transformation. This stability of the **177a** can be attributed to the strong electron-donating nature of –OMe, which disfavors cyanide addition. Although this type of group eases the shift of the carbonyl group, Kwart and Baevsky described the failure of an electron-donating group to significantly accelerate the cleavage if the resonance stabilization of the positive charge on the migrating carbonyl was the only important feature. Other *o*-substituted α-diketones were effectively converted into the corresponding benzoins as shown in Table 3.



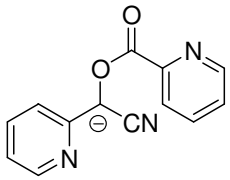
177 **168** **178**

Scheme 39

Table 3. Yields of disubstituted benzoin derivatives

entry	Benzil **177** **R**	Aldehyde **168**	Product **178**	% Yield
1	**a** 2-OMePh	**d**	No Reaction	-
2	**b** 2-MePh	**h**	 **a**	73
3	**c** 2-BrPh	**d**	 **b**	69
4	**d** 2-ClPh	**d**	 **c**	82
5	**e** 2-FPh	**d**	 **d**	72
6	**f** 2-pyridil	**b**	 **e**	65
7	**f** 2-pyridil	**a**	 **f**	77

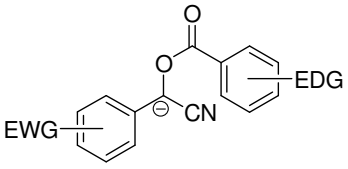
An interesting feature of the reaction was observed with 2,2'-bipyridil **177f**. When the reaction was carried out in the presence of 2-methylbenzaldehyde at 35°C, the reaction was very slow and only small amounts of product were observed after 5 days. Increasing the temperature resulted in the formation of side products. When 2-fluorobenzaldehyde was used instead of 2-methylbenzaldehyde (Table 3, entry 6), the yield was 65% after 72 h, even though the reaction was not complete. Increasing the temperature also increased the amounts of side products. Changing 2-fluorobenzaldehyde with the more electronegative 2-trifluoromethylbenzaldehyde **168a** furnished the product **178f** in 77% yield in 24 h. This behavior of the reaction can be attributed to the rate of formation of intermediate **179** from 2,2'-bipyridil and the rate of its reaction with the aldehyde. Although the cyanide attack should have been favored by the presence of pyridyl moiety, it disfavors the cleavage of the central C-C bond formation and retards the transfer of this group onto oxygen, which results in the slow formation of **179**. The increase in the reaction rate upon the use of an aldehyde substituted with a more electronegative group can be explained on the basis of the increased stability of the intermediate **179** which can rearrange back to the starting material and only reacts with an appreciable rate when the aldehyde is very reactive.



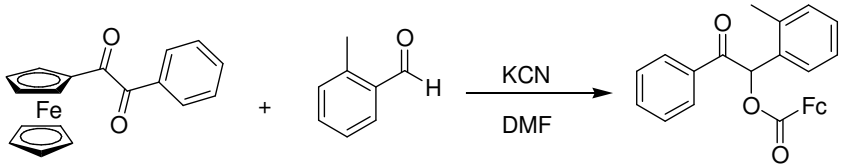
179

According to the mechanism of cyanide ion cleavage of benzil proposed by Kwart and Baevsky (Scheme 25), the phenyl ring having a substituent with a more positive σ-value ends up as aldehyde, while the other phenyl ring ends up in the ester or acid part through the decomposition of intermediate **180** that can be trapped with an aldehyde, thus forming disubstituted unsymmetrical benzoins. In fact, when compound **181** was treated with KCN in the presence of aldehyde **168d**, we isolated the product **182** where electron rich ferrocene ring occupied the ester part (Scheme

40). The hydrolysis of **182** furnished only ferrocene carboxylic acid and corresponding 2-methylbenzil in accordance with the proposed structure. Similarly, reaction of **183** with **168h** and subsequent hydrolysis of the crude product afforded **184** in 69% yield in accordance with these predictions.

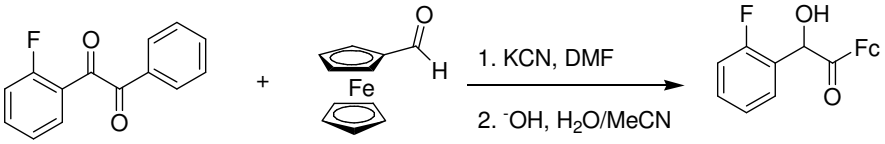


180



181 **168d** **182**

Fc= ferrocenyl



183 **168h** **184**

Scheme 40

We have shown that the cyanide ion-catalyzed cleavage of aromatic α-diketones can be used for the generation of various "masked" acyl intermediates of type **126**. These intermediates may be reacted with various aromatic aldehydes to form the corresponding esters of unsymmetrical benzoins in high yields. A variety of different benzoin derivatives can be synthesized in this way. This method does not require the handling of air sensitive reagents and protecting groups. It gave either better or at least comparable results for the synthesis of certain unsymmetrical benzoins such as the photolabile protecting group **171e**. Thus, this method generally offers the simplest approach for certain benzoins.

However there are several limitations and drawbacks associated with the presented method in its current state. First of all it was not possible to substitute EDGs on both rings. Benzils having EDGs were poor substrates whereas EDG in the acceptor aldehyde led to isomeric products. Thus access to all substitution patterns and cross benzoin isomers are limited. Actually substitution on benzils works against each other; while EWG on one ring favors the addition of the cyanide in the first step EWG on the other ring retards the reaction during rearrangement. The use of suitable substituted unsymmetrical benzils might be a partial solution to this as exemplified above (Scheme 40) however this require the synthesis of unsymmetrical benzoin from which the desired benzils are available. Another concern is the atom economy: a mole of benzoyl moiety is lost for every mole of benzoin synthesized.

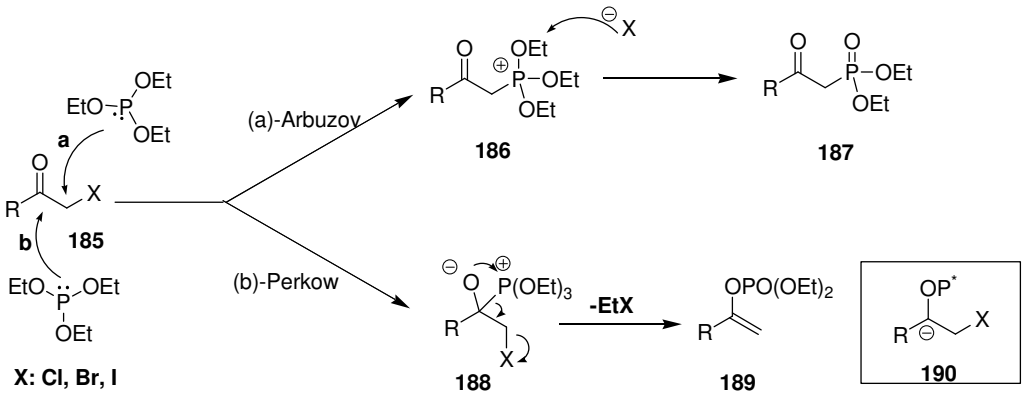
In conclusion cyanide ion catalyzed cleavage of benzils is the method of choice for certain benzoin derivatives. It constitutes the easiest possible approach to the mentioned derivatives. However it does not provide a general solution to the long standing cross benzoin problem. Thus there is still a demand for a generally applicable, flexible and highly practical method. The most probable solution lies in figuring out new acyl anion precursors. Next section will present our studies toward the development of new acyl anion precursors and its application in to the synthesis of cross benzoins.

2.2 Acylphosphonates as a New Generation of Acyl Anion Equivalents

Phosphorus, like silicon, has the ability to migrate both from carbon to oxygen and oxygen to carbon under appropriate conditions [44]. However this ability of phosphorus has not grown in to a well disciplined area as one could expect. We envisioned that typical nucleophilic catalysis of benzoin and Stetter reactions might promote acylphosphonates to generate an appropriate concentration of the corresponding acyl anion equivalents that are nucleophilic enough to participate in reactions with electrophiles. Determination of the suitable precursor and justification of the identified strategy was possible from inspection of the well known reactions of

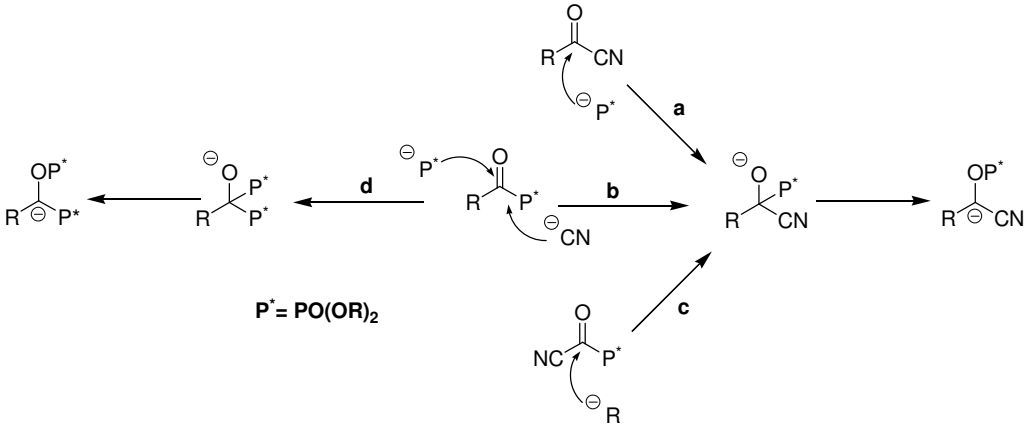
organophosphorus chemistry and from reports concerning the rearrangement of the phosphorus scattered to literature.

Probably the most intriguing example of migrating ability of phosphorus is the famous Perkow reaction [45]. 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 41.



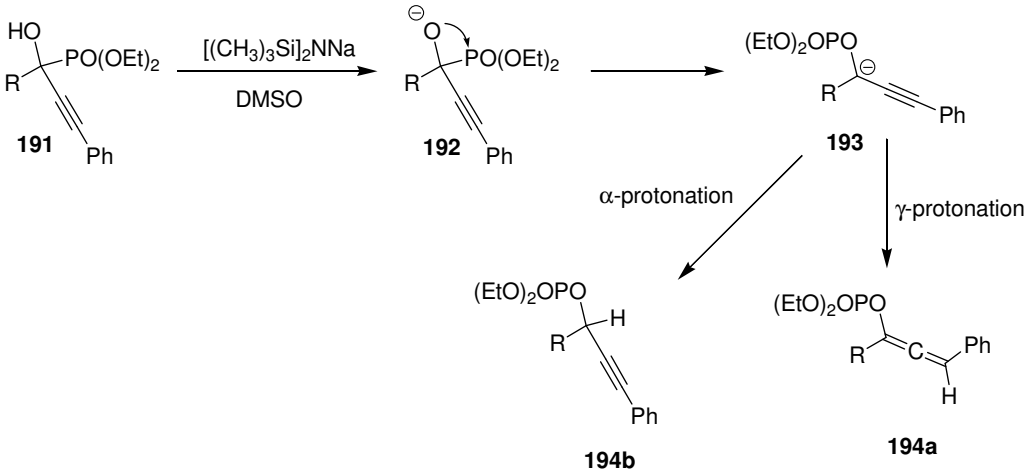
Scheme 41

The mechanism of Perkow route (Scheme 41, route b) involves the rearrangement of phosphorus from carbon to oxygen as in **188** resulting in enol ether **189**. Intermediates like **190** 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. Based on this idea, we proposed various idealized strategies to generate such intermediates from suitable precursors. These would include the addition of the phosphorus moiety (route **a** and **d**), addition of cyanide (route **b**) or addition of the carbon nucleophiles (route **c**) as depicted in Scheme 42.



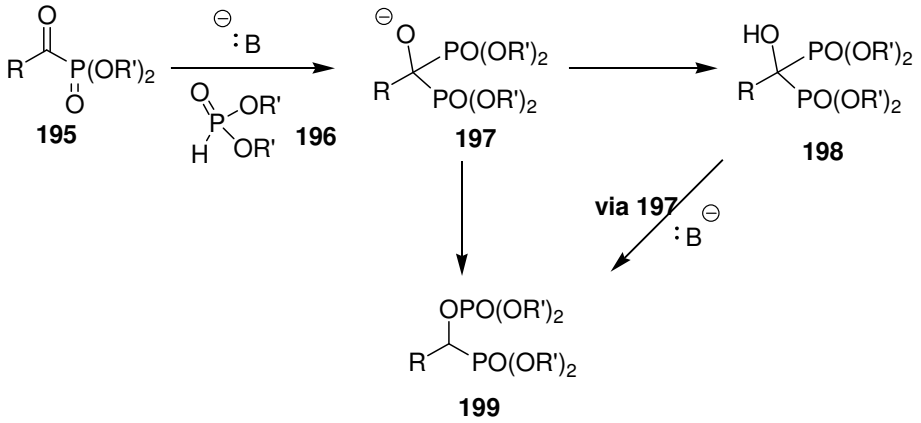
Scheme 42

The success of the method would certainly be dependent on the success of each individual steps. Information concerning the chemistry of each step can be collected from the literature precedents. From this end, there are many interesting reactions and observations involving the 1,2-rearrangement of phosphorus. For example base induced migration of phosphorus from carbon to oxygen has been reported many times. This rearrangement has close analogy to the corresponding 1,2-Brook rearrangement (Scheme 8 and 9). Deprotonation of α-hydroxyphosphonate **191** induces such a rearrangement resulting in a d^1 synthon **193** [46]. Protonation of **193** mainly occurs at the γ- position giving **194a** (homoenolate reactivity**,** Scheme 43). Same reaction sequence provides a mixture of **194a** and **194b** in methoxide/methanol. This is a nice example showing the propensity of alkoxides of type **192** undergoing Brook type phosphonate-phosphorus rearrangement. Although the mechanistic details of this type of rearrangements have not been investigated in much detail compared to Brook rearrangement, factors governing this process should be very similar to that of Brook rearrangement [44].



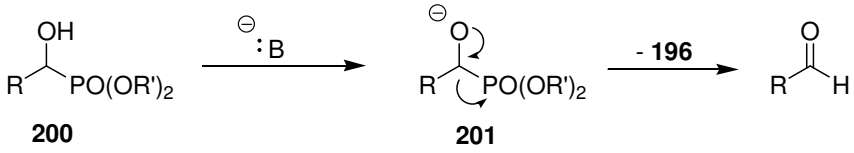
Scheme 43

Probably the most dominating examples of phosphonate-phosphate rearrangement were in the synthesis of controversial α-hydroxyalkylidenediphosphonate esters **198**. Synthesis of these compounds by the base catalyzed addition of dialkyl phosphites **196** to acylphosphonates **195** were reported by McConnell and Coover [47]. Later it was shown that the product of this reaction was actually isomeric compound **199** having two different phosphorus atoms [48]. It is formed from rearrangement of intermediate **197** before protonation to **198**. It was also shown that isolated **198** rearranges to **199** under basic conditions (Scheme 44). Later proper conditions that provide either **198** or **199** were also reported [49].



Scheme 44

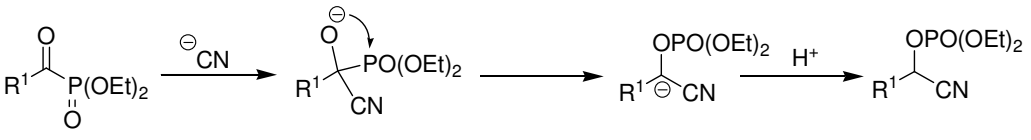
It is very important to recognize the effect of structural variations on the reactions outcome. For example it was shown that simple α-hydroxyphosphonates **200** did not undergo rearrangement instead **201** eliminates the phosphonate moiety to afford the corresponding aldehyde quantitavely [50] (Scheme 45). This structural variance shows the impact of substituents on the reaction course. As the 1,2-Brook rearrangement demands for anion stabilization and favors the carbanion over the alkoxide only in the presence of strong stabilizing groups, corresponding phosphonates can be expected to behave in a similar way. It seems that **201** is lacking the necessary driving force for rearrangement and eliminates the phosphonate unit.



200 **201**

Scheme 45

There is only one example reporting the cyanide ion promoted rearrangement of acylphosphonate **202** in the presence of alkali cyanide solution [51]. Similar to other rearrangements, the presence of cyanide provides considerable stabilization to carbanion **204** that provides **205** upon protonation (Scheme 46). Although no yield and side products were given, this is a very helpful report showing the potential of cyanide ion promoted rearrangement of acylphosphonates.

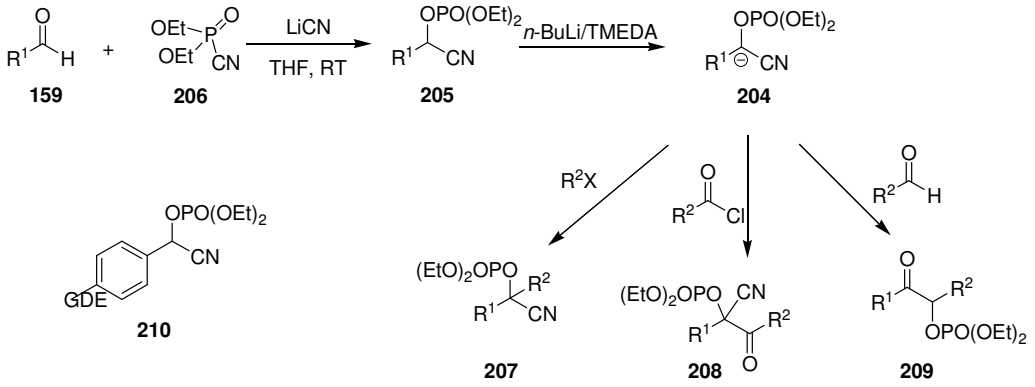


202 **203** **204** **205**

R^1= CH_3

Scheme 46

Interestingly there is no report, as far as we are aware, concerning the utilization of phosphonate-phosphate rearrangement in catalytic or stoichiometric carbon-carbon bond forming reactions. Examples depicted above show the glimpses of how a carefully designed reaction would provide very useful transformations. At this point it is important to note that Kurihara et al. [52a] reported the use of derivatives of **205** (Scheme 47) as acyl anion precursors. The cyanophosphates **205** used in their study were prepared by reaction of aldehydes **159** with diethylphosphorocyanidate **206** and LiCN. Deprotonation of **205** to **204** and subsequent reaction with various electrophiles including alkylhalides, acylhalides and aldehydes provided alkylated **207**, acylated **208** and benzoin (or acyloins) **209** type products respectively. Although this is a new type of acyl anion precursor, it has no apparent advantage over the corresponding O-silylcyanohydrins **17** or dithianes **20**. Besides aliphatic derivatives of **205** were failed to give any product and only starting materials were recovered. Moreover EDG substituted **210** were reported to be unstable thus it was not useful for the generation of corresponding **204** (Scheme 47). Schrader reported diastereoselective synthesis of **207** by use of asymmetrically modified derivatives of **205**.



159 206 205 204 210 207 208 209

Scheme 47

Under the light of these reports and guided by our initial proposal (Scheme 42), we primarily concentrated on the cyanide or phosphite anion promoted rearrangement of acylphosphonates (route **b** and **d**, Scheme 42) in the presence of aldehydes as potent electrophiles to devise a catalytic cross benzoin reaction. We also hoped to develop acylphosphonates into a new generation of acyl anion precursors.

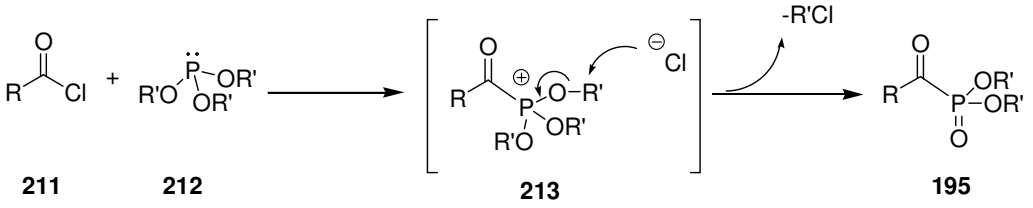
2.2.1 Acylphosphonates: Synthesis and Properties

Acylphosphonates (α-ketophosphonates) are very useful compounds. They were used as precursors to biologically active α-aminophosphonic acids and α-hydroxyphosphonic acids for years. The reactivity of acylphosphonates is particularly interesting. Inspection of the literature reveals a reactivity pattern that can be defined as hybrid of wide range of carbonyl compounds of varying oxidation states. Their reactivity is enhanced by the electron-withdrawing phosphonate moiety making them as excellent electrophiles and they are generally compared to ketones in this respect [53]. Some of their properties sometimes directly compared with trihaloketones [54]. Their reactions with Grignard reagents provide the corresponding ketones upon hydrolysis that can classify them as reminiscent of secondary amides [53]. On the other side they are very good acylating reagents and can easily be hydrolysed under the proper reaction conditions or reacts with secondary amines to afford secondary amides that put them into the same row with activated carboxylic acids [55]. Although these properties make acylphosphonates an interesting platform for a variety of transformations, they can be thought as an underutilized class of reagents.

The presence of phosphonate moiety provides a perfect binding site for protons and especially for metals. This Lewis acid activation site has already been utilized in enantioselective Michael addition, Diels-Alder and Mukaiyama-Aldol reactions [56]. Hovewer there is still much space for further applications in this area. This potential extra coordination ability could be very interesting in acyl anion chemistry which has not any precedent yet.

Acylphosphonates are easily available compounds. The most direct access to these compounds is the well-known Arbuzov reaction between acylchlorides **211** and trialkylphosphites **212** [53, 57]. Reaction proceeds via formation of unstable intermediate **213** that eventually leads to acylphosphonate **195** (Scheme 48). It is generally carried out by mixing neat reactants at or below room temperature. In cases

one of the reactants is solid, it can be carried out in organic solutions. Gaseous alkyl chloride is the only side product.



Scheme 48

Several aromatic and aliphatic acylphosphonates **202a**-**h** (Figure 10) were synthesized and routinely used in our studies. These compounds were synthesized via classical Arbuzov route according to literature procedures (Scheme 48). Although all derivatives were purified by vacuum distillation, we found that Arbuzov reaction generally provides crude products pure enough for most purposes. We sometimes used the crude products with similar efficiency to purified products. This easy access to acylphosphonates demonstrates an apparent advantage over the acylsilanes. In fact many derivatives of acylphosphonates are easily accessible for which acylsilanes possess serious problems [57b] (e.g., Scheme 14). Product of type **202h** was an apparent exception for which classical Arbuzov route only provided low yields with considerable amount of side products. This is probably due to the activated olefin functionality that is susceptible to Michael type addition of triethylphosphite. When this type of problem exists, an alternative high yield route to these compounds is possible via oxidation of the corresponding α-hydroxyphosphonates [58]. α-hydroxyphosphonates are easily synthesized by addition of phosphorus nucleophiles to corresponding aldehydes.

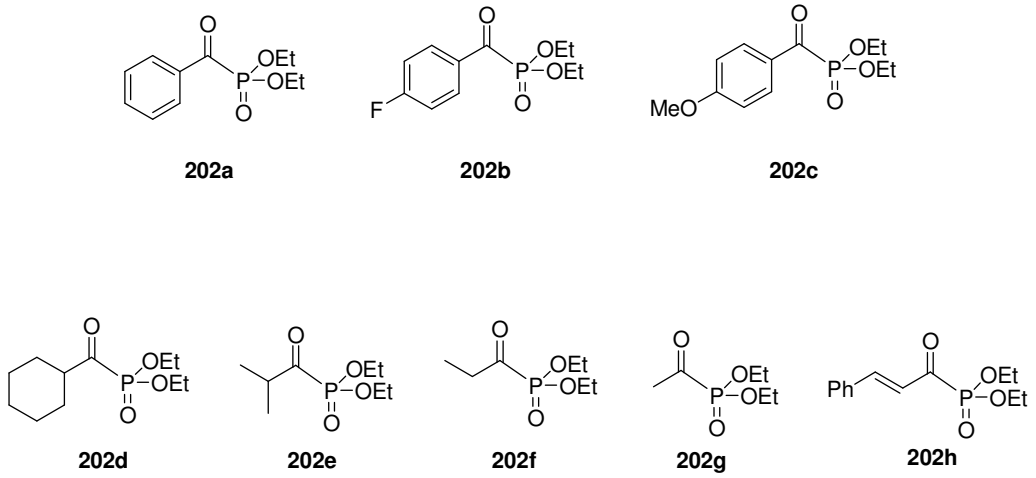
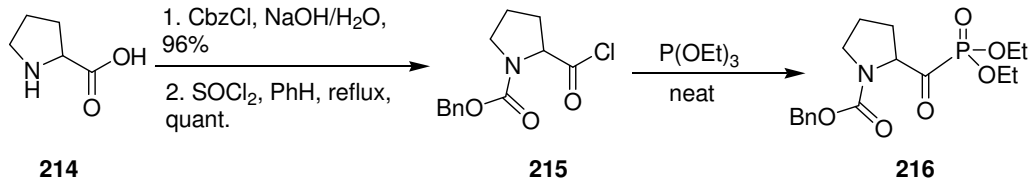


Figure 10. Acylphosphonates synthesized and used in this study

During our investigations we also synthesized acylphosphonates derived from amino acids. We obtained the diethylproloylphosphonate **216** in a three step procedure. Proline **214** was protected as relatively acid resistant benzyloxycarbamate [59] and converted to acylchloride **215** in 95% overall yield. Reaction of neat **215** with triethylphosphite afforded the desired acylphosphonate **216** in 90% yield (Scheme 49). Compounds **215** and **216** exhibit complex spectra resulting from restricted rotation around the CO-N bond of the protecting group. In **215** α-proton gave two separate multiplets in approximately 1:1 ratio. Similar situation was also observed for **216** and heating a DMSO solution of **216** resulted in peak broadening and collapsing as expected. At 90°C, only a multiplet was observable for the α-proton (Figure 11).



Scheme 49

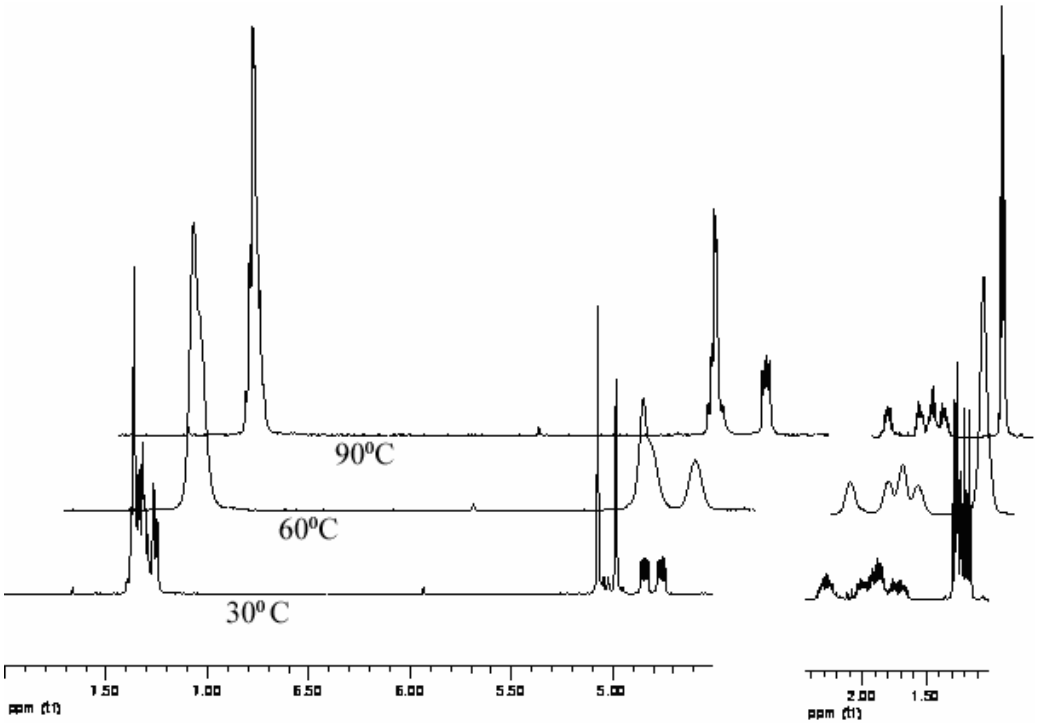


Figure 11. Variable temperature ^{1}H NMR spectrum of **216** in d_6-DMSO

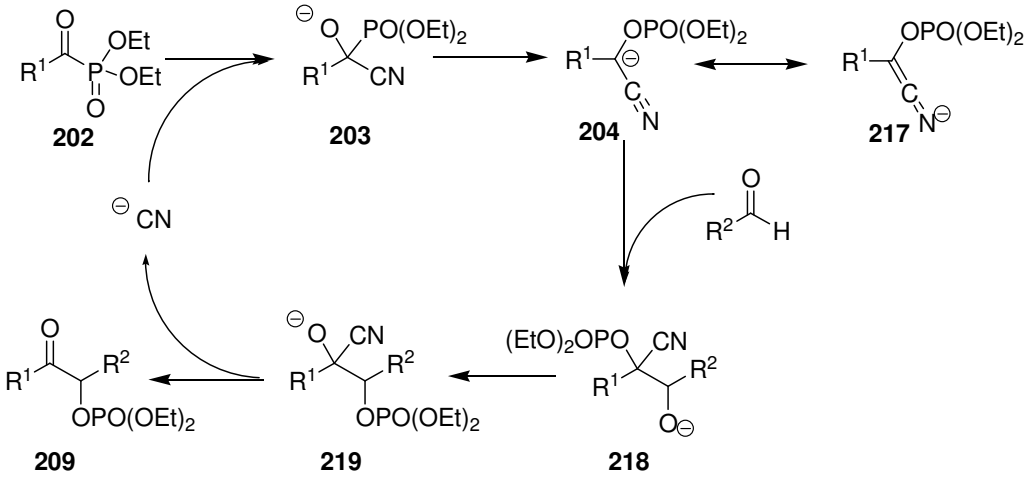
Acylphosphonates are easily accessible in multigram quantities and very high yields from simple starting materials [53, 57]. Their synthesis does not require any special condition or apparatus. Although they are reported to be sensitive to moisture, we found that they can be stored under argon filled flasks for months without any decomposition or hydrolysis. Moreover, they can be handled on benchtop without a special precaution and even their TLC sample solutions are hydrolysed slowly. Besides they can be used as they obtained without altering the efficiency of the reaction carried out. Their synthesis from carboxylic acids is highly intriguing since nature provides vast amount of compounds in this oxidation states. This also establishes a connection between acid oxidation state and acyl anion equivalents which generally obtained from aldehydes. At last phosphonate moiety in acylphosphonates provides a useful platform for fine tuning of their reactivity.

2.2.2 Reactions of Acylphosphonates

2.2.2.1 Synthesis of Unsymmetrical Benzoins

2.2.2.1.1 Synthesis of Unsymmetrical Aryl-Aryl Benzoins

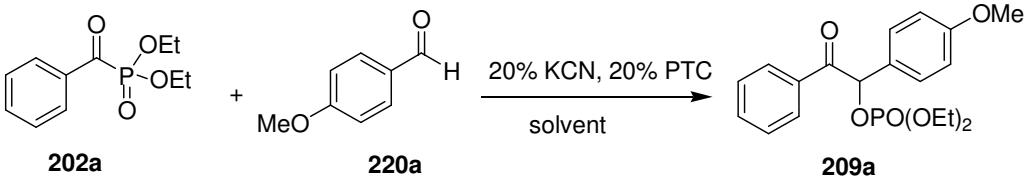
As explained above, we proposed the idea of using acylphosphonates in catalytic cross benzoin reaction which has considerable support by earlier works in literature. Proposed catalytic cycle is based on the classical route of the benzoin condensation that has common key steps for variety of congeners of this reaction like acylsilanes and benzils. Cyanide ion promoted rearrangement of **202** would provide the critical acyl anion equivalent **204**. Reaction of **204** with aldehyde afford the intermediate adduct **218** that undergoes a 1,4-O,O-phosphate migration leading to **219**. **219** retrocyanates as usual to give the desired benzoin **209** and close the catalytic cycle (Scheme 50).



Scheme 50

In our initial investigations, we chose the benzoylphosphonate **202a** and 4-methoxybenzaldehyde **220a** as model substrates to test the feasibility of the method for the synthesis of thermodynamically less stable benzoin isomer **209a**. Thus a 0,5 M solution of **202a** and 1.1 equiv of **220a** was treated with 20% KCN and 20% PTC (Bu_4NBr or 18-crown-6) in solvents of varying polarity (hexane, toluene, THF, DCM, MeCN) at room temperature (Scheme 51). TLC monitoring of the reactions

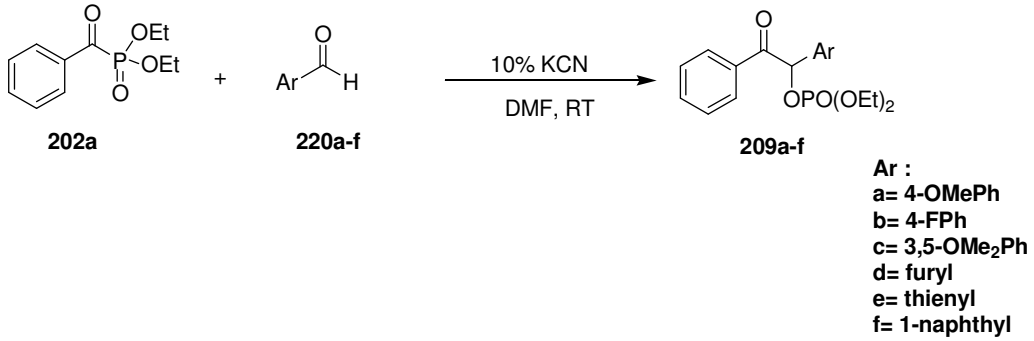
showed that reaction proceed smoothly in DMF to provide a product in less than 10 min. Moreover we found that PTC additive was not necessary for the reaction to occur smoothly. Analysis of the crude product indeed showed that the reaction afforded the benzoin **209a** with traces of side product(s) but no product arising from homobenzoin condensation was observed. Typical signals in identification of the product was the presence of benzylic proton resonating at 6.58 ppm as doublet with J_{PH}= 7.8 Hz. The presence of signal at 7.96 ppm resulting from two ortho- protons of the unsubstituted benzoyl moiety proved the structure to be **209a** not the thermodynamically more stable isomeric one.



202a **220a** **209a**

Scheme 51

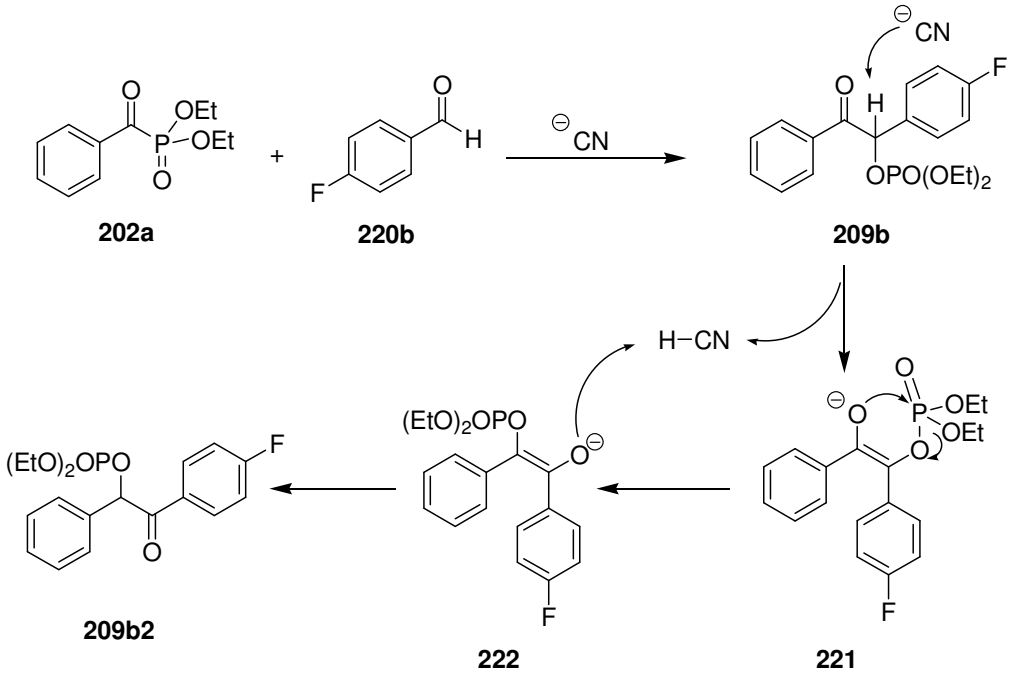
Reactions in other solvents either proceeded very slowly or not occurred at all. We found that heating the reaction mixtures slowly afforded the expected product. Interestingly a smooth reaction was observed even in highly nonpolar hexane or in toluene (20% Bu_4NBr as additive, reflux temperature) providing the expected product. As a result of these screening, it is obvious that the best solvent for this transformation is DMF in which KCN is highly soluble thus not requiring any additive. Moreover reaction is complete in a very short time that adds practicality to reaction. Thus we investigated the reaction of various aromatic aldehydes of differing electronic nature with benzoylphosphonate **202a** as depicted in Scheme 52.



Scheme 52

When reaction is carried out with assumingly more reactive 4-F-benzaldehyde **220b**, we observed interestingly longer reaction times (3-4 h) smoothly affording **209b**. Increasing the catalyst load not only accelerated the reaction but also resulted in formation of isomeric product **209b2**. Careful TLC and ^{1}H-NMR monitoring revealed that the isomeric product formed via the expected benzoin **209b**. In order to understand the nature of this observation we carried out some crossover and control experiments. We found that when isomer contaminated crude **209b** was subjected to 50% KCN in DMF, product ratios changed in favor of the isomer in 24 h. This was interesting since the isomeric product **209b2** was supposed to be the thermodynamically less stable product. Besides this isomerization was not observed in case of benzoin **209a** that was principally the less stable isomer. We assumed that **209b** isomerizes via endiols **221** and **222** catalyzed by the basic cyanide anion. We observed that isomerization was always accompanied by the formation of a colored (yellow) reaction mixture supporting the formation of species like **221** and **222** (Scheme 53). Dependence of isomerization rate on cyanide ion concentration is understandable in this context. The efficiency of this process might be related to benzylic C-H acidity that should be enhanced by the electron-withdrawing fluoride substituent. This can explain the lack of isomerization in **209a** incorporating an electron rich phenyl ring adjacent to benzylic C-H. Stability of the carbonyl moiety should also be a factor in this isomerization process. Thus carbonyl function highly stabilized by an adjacent electron rich phenyl ring may retard the isomerization even if the deprotonation of the benzylic C-H were possible. We have a strong proof for the isomerization pathway depicted in Scheme 53 and we can either prevent or keep

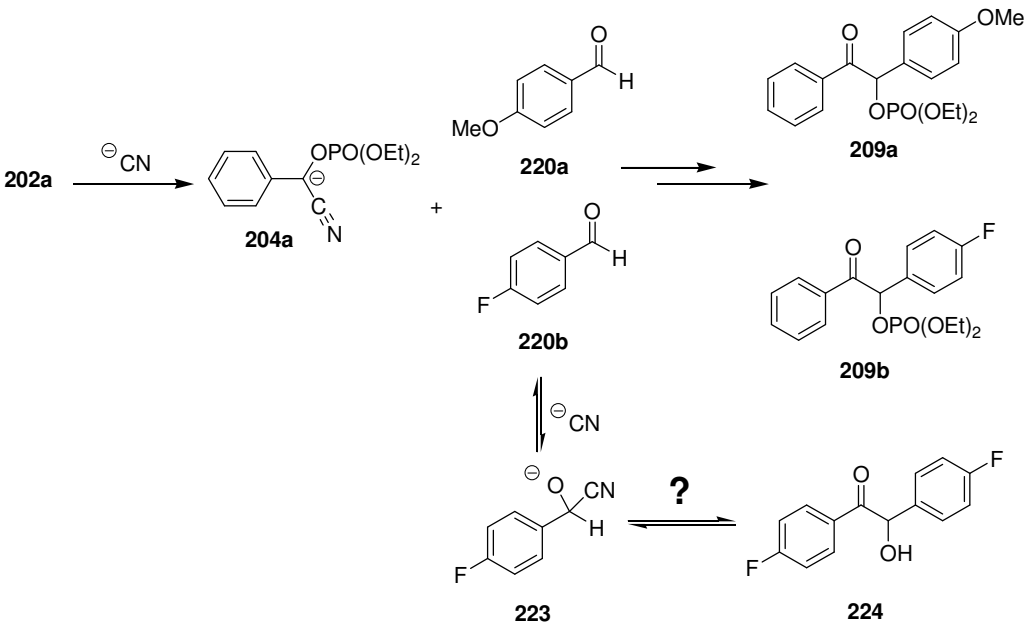
it at minimum by adjusting the amount of catalyst and carefully monitoring the reaction. We also showed that lowering the reaction temperature suppressed the isomerization process (see below, Scheme 55).



Scheme 53

In a crossover experiment, **220a** (1 mmol) was treated with 10% KCN in the presence of 1 equiv (1mmol) of each **220a** and **220b** and only product **209b** resulting from the reaction of **202a** with **220b** was observed in crude NMR mixture. This showed us that **202a** indeed reacts preferentially with the more reactive aldehyde **220b** and this addition step is one of critical steps of this reaction. Slower reaction of more reactive aldehyde seems to be controversial. Since we only observed products arising from the reaction of **202a** with aldehydes not with itself, it is obvious that aldehydes are the more reactive counterpart of this reaction. This fact also necessitates a more favorable interaction of aldehydes with the cyanide but this interaction should be reversible or unproductive because we never observed homobenzoin condensation product **224**. So a possible scenario is that cyanide strongly interacts with the **220b** to reversibly form **223** or **224**. This interaction deteriously lowers the available cyanide concentration for the formation of **204a** and stalls the reaction. Route to benzoins **209** should be irreversible providing clean

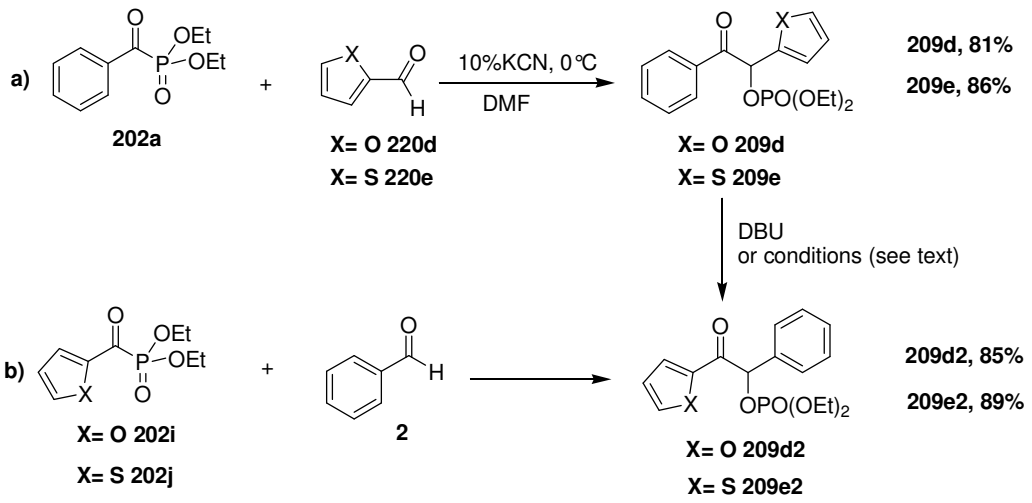
products (Scheme 54). These observations also point to out an important fact that the C-C bond forming step between **204a** and aldehydes **220a** or **220b** is possibly one of the rate determining step.



Scheme 54

Under the guidance of several information gathered from above experiments, we carried out reactions depicted in Scheme 52. We used 10% KCN in 0.5 M DMF solutions of benzoylphosphonate and aromatic aldehydes (1.05 equiv). Reaction was tolerant to wide range of substitution on the aldehyde; products were obtained in very good to excellent yields. We encountered the isomerization process in reactions with heterocyclic aldehydes **202d**-**e** where prolonged reaction times or high catalyst load (20% or higher) resulted in complete conversion to isomeric **209d2** and **209e2** (Scheme 55). Formation of isomeric products followed the formation of **209d** and **209e** as previously observed for 4-F-benzaldehdye. We used this process beneficially for the synthesis of either isomers of heterocyclic benzoins from the same precursors without need to synthesize the required donor heterocyclicphosphonates **202i** or **202j** (Scheme 55, route **b**). When reaction was carried out at 0°C, we obtained the product **209d** or **209e** without contamination with the isomeric products. In a control experiment, treatment of isolated **209e** with catalytic amount of DBU (estimated

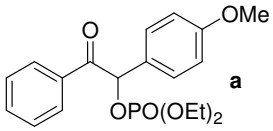
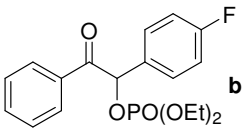
pKa=12) in DMF (0.5 M solution) afforded the isomeric benzoin **209e2**. This seem to be supporting our initial proposal of basic cyanide (pKa=9.4) catalyzed isomerization process depicted in Scheme 53.

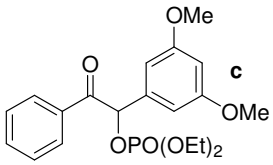
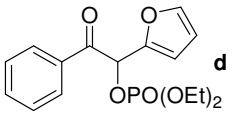
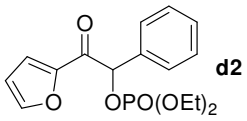
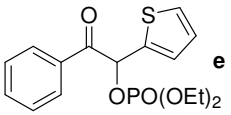
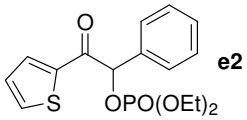
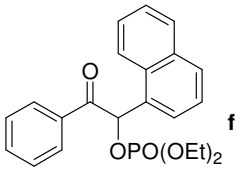


Scheme 55.

The results of reactions of benzoylphosphonate **202a** with various aldehydes are summarized in Table 4. Benzoin **209d** is unstable and slowly decomposes during chromatography or storage (refrigerated) under inert atmosphere so it was impossible to obtain highly pure product.

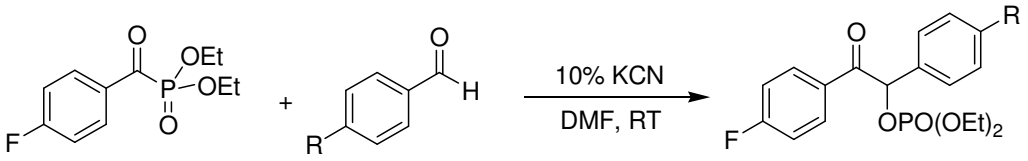
Table 4. Yields for aryl-aryl benzoins

entry	Aldehyde **220**	Product **209**	Yield(%)
1	**a** 4-OMePh	 **a**	93
2	**b** 4-FPh	 **b**	83

3	**c** 3,5-$(MeO)_2$Ph		88
4	**d** furyl		81
5	**d** furyl		85
6	**e** thienyl		86
7	**e** thienyl		89
8	**f** 1-naphthyl		87

The value of a cross benzoin method strongly depends on its applicability to the synthesis of both isomers of a benzoin product. So we turned our attention to the reactions of substituted aroylphosphonates. In this context we selected 4-F-benzoylphosphonate **202b** and 4-MeO-benzoylphosphonate **202c** as model substrates. In this way we would be also able to access all isomers of a given benzoin.

Reaction of **202b** with aldehydes **2** and **220a** smoothly provided the expected benzoins **209b2** and **209g** respectively (Scheme 56). Little isomeric product **209b** was observed with **2** (R=H) as the acceptor aldehyde.

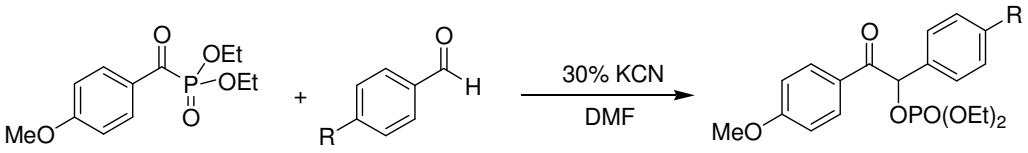


202b **2 R= H** **220a R= OMe** **209b2 R= H** **209g R= OMe**

Scheme 56

Reactions with 4-MeO-benzoylphosphonate **202c** turned out to be a little problematic. In initial experiments with **202c** and benzaldehyde **2**, reaction proceeded very slowly. At this point we screened several reaction conditions in reaction of **202c** and 4-MeO-benzaldehyde **220a** (Scheme 57). The selection of **220a** was due to not only its efficiency in its reactions with acylphosphonates carried out so far but also the homobenzoin type product would simplify the identification for initial investigations. We changed the temperature, used additives or increased the catalyst load. These screening studies provided us a wealth of information. For example we found that reaction gave only trace of the product **209h** at room temperature (10% KCN). While heating the reaction mixture at 50°C accelerated transformation, addition of Lewis acid $Sc(OTf)_3$ at room temperature also gave the expected product albeit in slower rates compared to heating. Morover increasing the catalyst load (30%) afforded **209h** smoothly without a deleterious effect on the product formation. Thus we selected the simplest route and used 30% of KCN in our studies utilizing **202c**. These screening experiments showed us that cyanide addition step is very critical at least in the case of **202c**. Although we did not carry out any crossover experiments, it is possible that the very first step of this reaction (cyanide addition) is the rate determining step or it has a similar rate constant to that of aldehyde addition step. Rate acceleration with $Sc(OTf)_3$ strongly suggests the activation of **202c** with Lewis acid coordination. Activation of α,β-unsaturated acylphosphonates with $Sc(OTf)_3$ in Michael addition and Diels-Alder reaction have been reported previously [56a]. In these studies simultaneous coordination of C=O and P=O to Sc(III) has been proposed. This coordination ability and rate acceleration of benzoin condensation with $Sc(OTf)_3$ give clues of a Lewis acid catalyzed enantioselective variant of this reaction.

Once the optimum reaction conditions for reactions with **202c** in hand, we investigated its reactions with aldehydes **2** and **220b** in order to gets access to all possible combinations of cross benzoin products incorporating 4-H, 4-F, 4-MeO substituents on both rings (except symmetrical ones) (Scheme 57).



202c

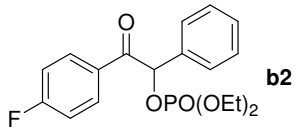
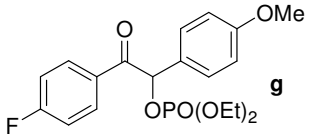
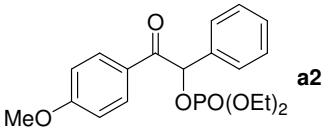
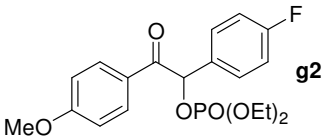
2 R= H
220a R= OMe
220b R= F

209a2 R= H
209h R= OMe
209g2 R= F

Scheme 57

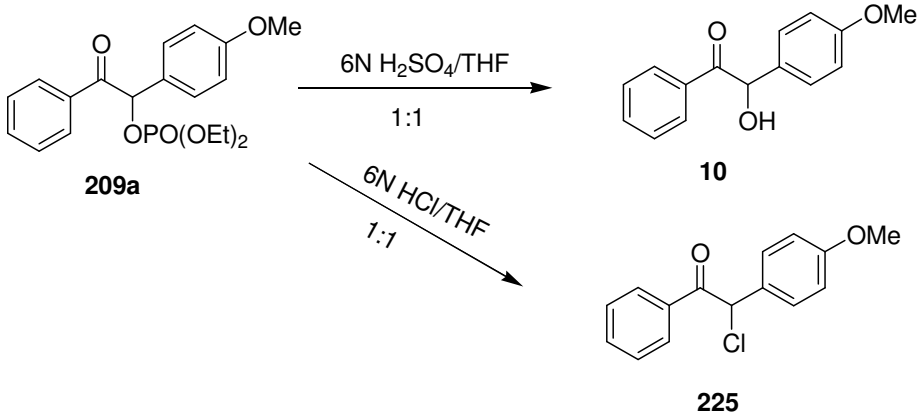
The results with **202b** and **202c** are summarized in Table 5. These results show that it is possible to synthesize all isomers of a given benzoin regioselectively in very good yields.

Table 5. Yields of benzoins from substituted acylphosphonates

entry	Aroylphosphonate **202**	Aldehyde	Product **209**	Yield(%)
1[a]	**b**	**2**	 **b2**	87
2[a]	**b**	**220a** 4-OMePh	 **g**	93
3[b]	**c**	**2**	 **a2**	92
4[b]	**c**	**220b**	 **g2**	95

[a] 10% KCN, 15-30 min [b] 30% KCN, 4-6 h

Reactions with **202a** and **202b** proceeds considerably fast with 10% KCN giving very good yields. Some products are prone to isomerization in high catalyst load or with prolonged reaction times. However this is not a problem with careful reaction monitoring, using lower catalyst load or lowering reaction temperature. Besides this isomerization process is beneficial in case of heterocyclic aldehydes; access to both isomers of a given heterocylic benzoin is possible from common starting materials. Reactions with **202c** requires higher catalyst loading and reacts slowly compared to **202a** and **202b**. We showed the potential of acylphosphonates in regioselective cross benzoin condensation with carefully selected sets of various benzoin products. This method offers great practicality in terms of easy availability of the starting materials from carboxylic acids. In fact we showed that it is possible to synthesize benzoin **209a** with a similar yield (89%) starting from benzoic acid without purification of the any intermediate and using crude **202a**. Products are in protected form and they can be hydrolyzed to free benzoins under acidic or basic conditions. For example we screened some simple aqueous acidic hydrolysis conditions for benzoin **209a**. **209a** was hydrolyzed slowly in 1N HCl/THF mixture to provide the benzoin **10**. In concentrated HCl solutions it quantitavely and quickly afforded α-chloro carbonyl product **225**. However 6N H_2SO_4/THF mixture furnished **10** quantitavely in a very fast reaction (Scheme 58). We did not try any basic hydrolysis conditions considering the benzoin's tendency to isomerize under alkaline conditions. Efforts to find out mild hydrolysis conditions are under investigation.

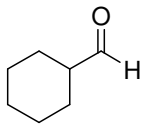


Scheme 58

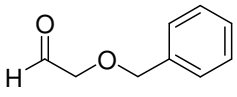
2.2.2.1.2 Synthesis of Unsymmetrical Aryl-Alkyl Benzoins

Incorporation of enolizable aldehydes in to benzoin (acyloin) structures is always problematic. This is obvious from the relatively small numbers of reactions utilizing aliphatic aldehydes in acyl anion chemistry. Although partial success is possible with thiamine catalysis, cross benzoin products having aliphatic unit in either part is along standing problem. In this context, we investigated the aryl-alkyl combination as a natural extension of this work.

We initially investigated the reactions of aroylphosphonates with our model aliphatic aldehydes cyclohexanecarboxaldehyde **220g** and densely functionalized benzyloxyacetaldehdye **220h**.

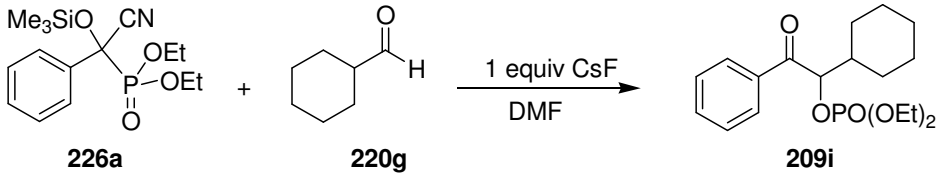


220g



220h

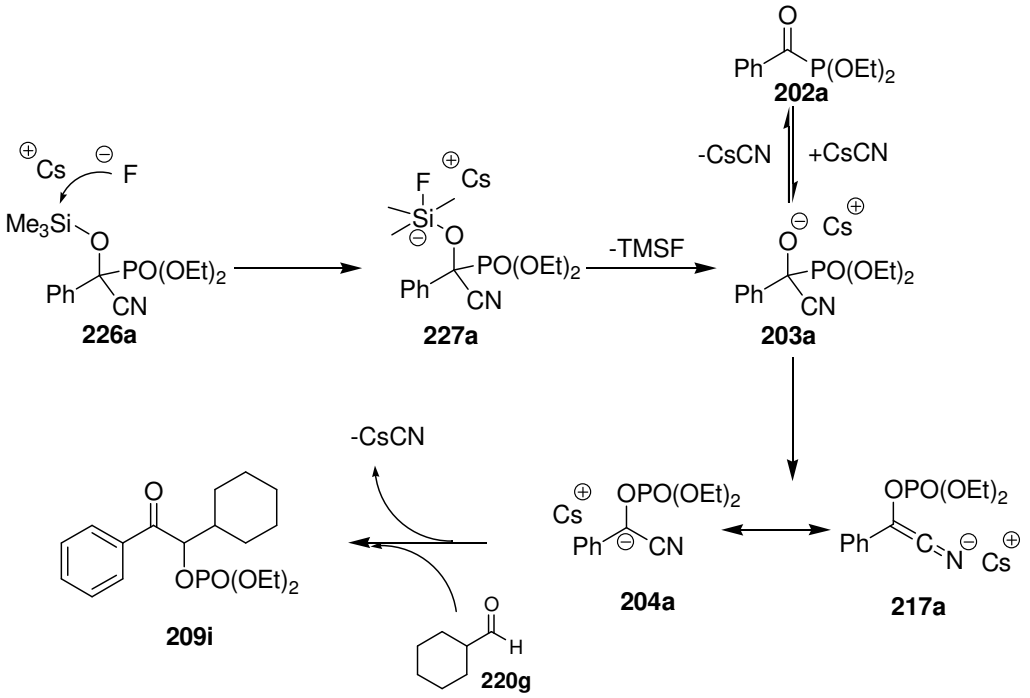
Gratifyingly all combinations of aroylphosphonates and aliphatic aldehydes afforded the desired products in screening reactions. However the amount of side products, especially with **202c**, compared to aryl-aryl combination prompted us to find out better reaction conditions. In our search for a better reaction conditions we found out some potential candidates. For example reaction of **202a** and **220g** in refluxing toluene (20%KCN, 20%Bu_4NBr) provided us a clean product whereas the product recovery was not satisfactory. Therefore we did not spend time on optimizing this reaction conditions and concentrated on other possible approaches. During our investigations toward understanding the nature and reactivity of aroylphosphonates and corresponding acyl anion equivalents, we observed that O-Silyl cyanohydrin **226a** decomposes with CsF in the presence of **220g** to afford the benzoin adduct **209i** in an instantaneous reaction (Scheme 59).



226a **220g** **209i**

Scheme 59

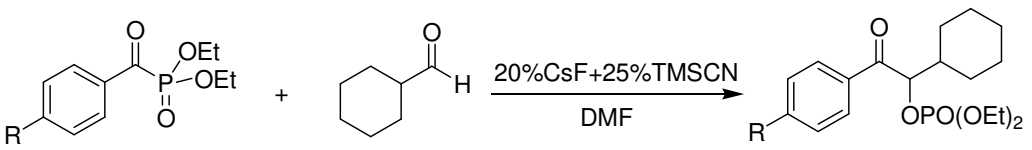
The fluoride anion promoted deprotection of silyl groups is well known in the literature. Fluoride anion is also used for the activation of silyl nucleophiles (e.g. phenylsilanes). This activation is supposed to occur via pentavalent negatively charged silicon. We can suppose that fluoride activates the silylether moiety in **226a** as **227a** that release the TMSF to provide cesium salt of cyanohydrin **203a**. Alkoxide **203a** rearranges in the usual manner generating the acyl anion **204a** and affords the product **209i** in the presecence of aldehyde **220g**. Another possibility is that **203a** reversibly retrocyanates to **202a**. Although it is hard to predict relative rates of two processes they eventually lead to product **209i**. Both routes provide a very high concentration of **203a** and leads to a very fast reaction (Scheme 60).



Scheme 60

This observation prompted us to investigate possibility of CsCN catalyzed reactions between **202a**-**c** and aldehydes **220g**-**h**. We tested catalytic activity of a mixture made by mixing CsF (20% respect to aroylphosphonates) and slight excess of TMSCN (25%) in DMF assuming that stronger Si-F bond would result in a solution containing CsCN. In fact, addition of DMF solutions of **202a** and **220g** onto the resulting mixture quickly (<5 min) afforded the expected product **209i** (Scheme 61). This reaction proceeded not only faster but also better in terms of crude product purity and isolated yields. As far as we know this is the first CsCN catalyzed reactions of acyl anion equivalents. At this stage we do not have an apparent explanation to better activity of CsCN but it is expected that charged intermediates having cesium as counter ion may show quiet different reactivity than that of potassium in terms of alkoxide stability. This is a well known phenomenon in reactions with alkali metals as counterions of alkoxides. For example lithium is known to be strongly binding to alkoxides and form aggregates. The looser binding of cesium to **203a** may favor the rearrangement making considerable impact on its reactivity. The effect of counterion in the analogous Brook rearrangement is well documented (page 29, Scheme 9). The greater solubility of cesium salts should also be accounted that obviously would provide higher concentrations of the catalyst available for the catalytic cycle. The independent synthesis and use of CsCN is under investigation.

The CsF+TMSCN system was also proved to be useful in reactions of **202b** and **202c** with **220g**. Products were obtained in very good yields. We gratifyingly obtained better results compared to KCN in reactions of **202c**.



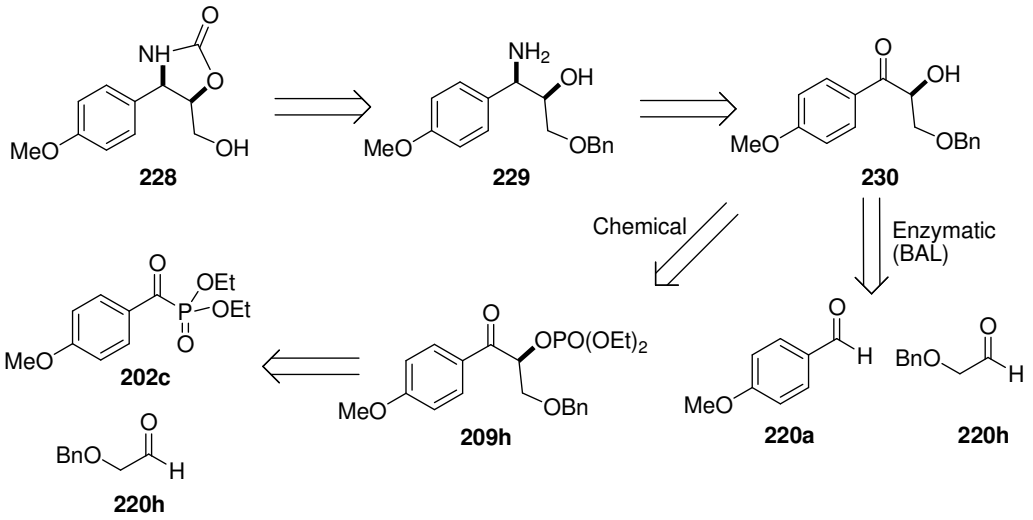
202a R= H
202b R= F
202c R= OMe

220g

209i R= H
209j R= F
209k R= OMe

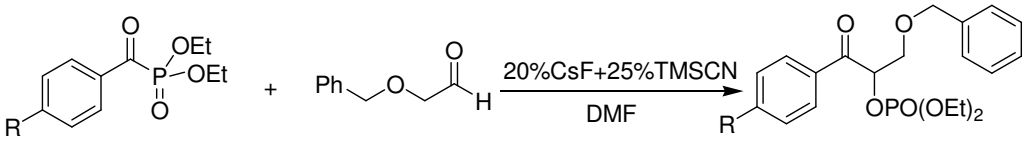
Scheme 61

We next turned our attention to seemingly more challenging electrophile benzyloxyacetaldehdye **220h**. Although it would not be the first choice in method development phase, its extra functionality opens a door to highly functionalized products. Morover we have interest in the enzymatic synthesis of cytokine modulator cytoxazone **228**. There is not a simple synthesis method for this biologically active compound. We proposed that acyl anion reactivity would provide an easy access to this compound according to retrosynthetic scheme 62. We proposed BAL catalyzed enzymatic route would provide a direct entry to intermediate **230** that is an advanced intermediate in the known synthesis of **228**. **230** would also be chemically available from **209n** that was theoretically accessible from **202c** and **220h** according to the method presented here. It should be mentioned that contrary to chemoenzymatic route, pure chemical approach begs for an enantioselective variant of this reaction. Efforts for both enantioselective variant of acylphosphonate methodology and chemoenzymatic synthesis of **228** are underway.



Scheme 62

Reactions of **202a-c** with **220h** was examined under the catalysis of CsF+TMSCN and reaction provided the expected benzoins **209l-n** in good yields (Scheme 63). Results concerning the reactions of aroylphosphonates with aliphatic aldehdyes are summarized in Table 6.



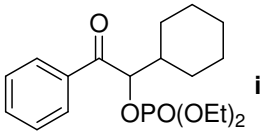
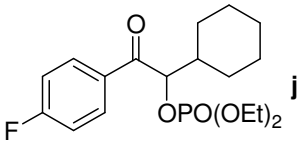
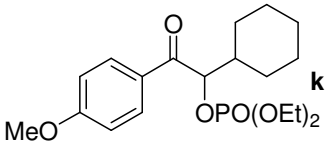
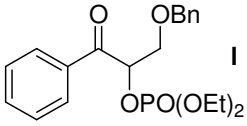
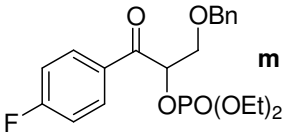
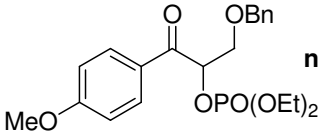
202a R= H
202b R= F
202c R= OMe

220h

209l R= H
209m R=F
220n R= OMe

Scheme 63

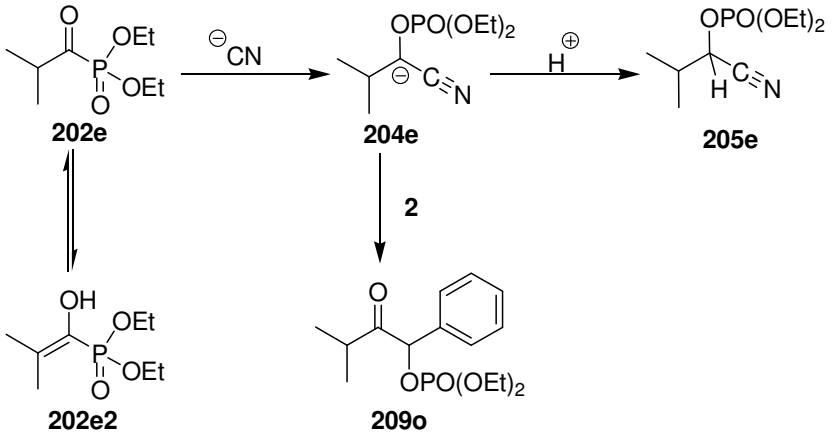
Table 6. Yields of aryl-alkyl benzoins

entry	Aroylphosphonate **202**	Aldehyde **220**	Product **209**	Yield(%)
1	**a**	**g**	 **i**	87
2	**b**	**g**	 **j**	81
3	**c**	**g**	 **k**	85
4	**a**	**h**	 **l**	81
5	**b**	**h**	 **m**	75
6	**c**	**h**	 **n**	77

In conclusion catalytic generation of acylphosphonates is applicable to the synthesis of a wide range of aromatic-aliphatic benzoin adducts. Moreover we find that CsCN is a very good catalyst for this transformation. This shows that the current method is open to variations in the counter cation that will hopefully lead to enantisolective cross benzoin condensation. We believe that coordination ability of acylphosphonates will provide highly ordered transition states in reactions with acylphosphonates and aldehydes.

2.2.2.1.3 Synthesis of Unsymmetrical Alkyl-Aryl Benzoins

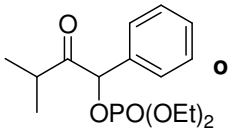
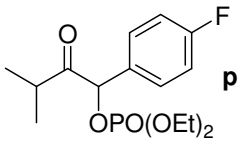
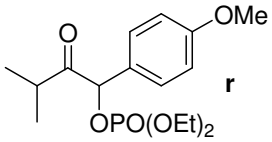
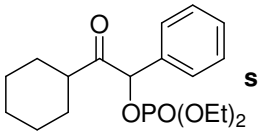
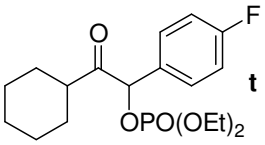
The use of alkyl donors in benzoin type (catalytic) acyl anion reactions is much more troublesome. In fact our early attempts using aliphatic phosphonate **202e** resulted in lower yields and some irreproducible results. Both KCN and CsF+TMSCN systems suffered from the same drawbacks. The most frequent problem was the presence of a side product observed under various reaction conditions. This side product was identified as **205e** resulted from protonation of the acyl anion equivalent. Its identity was proved by an independent synthesis (see below, section 2.2.2.2). These type of products were observed only in trace (or not at all) amounts in aryl-aryl benzoins and minor amounts in aryl-alkyl combinations. We attributed this difference to highly enolizable nature of aliphatic acylphosphonates where their tautomeric form **202e** protonates the critical carbanion **204e** (Scheme 64).



Scheme 64

Instead of concentrating ourselves figuring out the exact facts behind this problem, we tried to find out a better reaction conditions. Based on our findings in our preliminary investigations concerning aryl-aryl benzoin synthesis, we found that reactions of aliphatic acylphosphonates with aromatic aldehydes (2 equiv) proceeds reproducibly in toluene (at 100°C, 4-8 hours) in the presence of 30%KCN and 20% 18-crown-6. Yields were good (60-70%) but crude products were always contaminated with ~10% protonation products **205**. Unfortunately complete separation of these side products proved to be problematic and unsuccessful each time. Several aliphatic acylphosphonates and aromatic aldehydes were tested and results are summarized in Table 7.

Table 7. Yields of alkyl-aryl benzoins

entry	Acylphosphonate **202**	Aldehyde	Product **209**	Yield(%)[a]
1	**e**	**2**	 **o**	68
2	**e**	**220b**	 **p**	64
3	**e**	**220a**	 **r**	nd
4	**d**	**2**	 **s**	66
5	**d**	**220b**	 **t**	nd

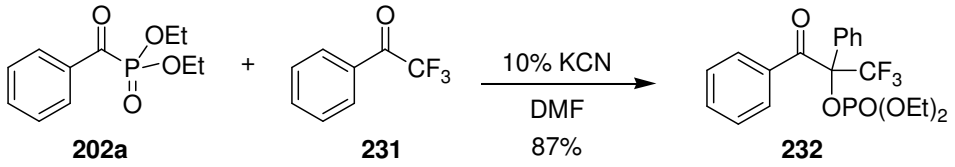
[a] nd: not determined

Our ongoing studies in alkyl-aryl cross benzoins are concentrated upon finding a better $M(CN)_n$. We hope increasing the yields to a level that of aryl-aryl and aryl-alkyl benzoins and suppress the protonation product.

The most challenging alkyl-alkyl combination has been unsuccessful to date providing only <20% estimated yields.

2.2.2.1.4 Reactions of Acylphosphonates with Ketones: A Surrogate for Aldehyde-Ketone coupling

Intermolecular catalyzed addition of aldehydes to ketones has not been reported so far and remains as a challenging reaction. Therefore we also investigated this reaction and started with highly reactive non-enolizable 2,2,2-Trifluoroacetophenone **231**. The reaction of **202a** and **231** in DMF (10% KCN) smoothly afforded the expected product **232** in 87% yield (Scheme 65).



202a **231** **232**

Scheme 65

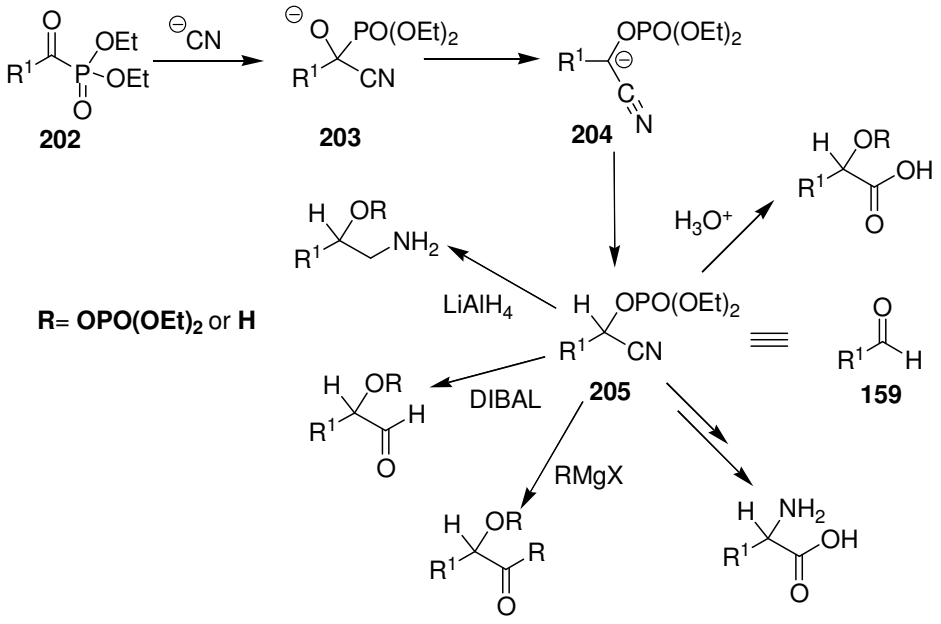
This is the first intermolecular benzoin type (catalytic) reaction between an acyl anion precursor and a ketone. However same reaction between acetophenone and **202a** afforded only trace amount of product in prolonged reaction times (4-5h). At this point it is noteworthy that starting material was recovered almost unchanged. This is an indication of reversible formation of acyl anion equivalent of type **204a** because it is obvious from reactions presented so far that **202a** completely is consumed in the presence of reactive aldehydes **220** or ketone **231**. Therefore recovery of **202a** is only possible if formation of **204a** was reversible. A control experiment showed that a complex mixture of products (together with recovered starting material) formed from reaction of **202a** with catalytic amount KCN (several days) in the absence or presence of acetophenone. We do not have a clear

explanation for this. The failure of reaction between **202a** and acetophenone should not arise from the enolizable nature of the ketone since no protonation product **205a** was observed. Thus this useful transformation deserves more attention.

2.2.2.2 Protonation of Acyl Anion Equivalents: A Nonhydride Access to Aldehyde Oxidation State from Carboxylic Acid Oxidation State

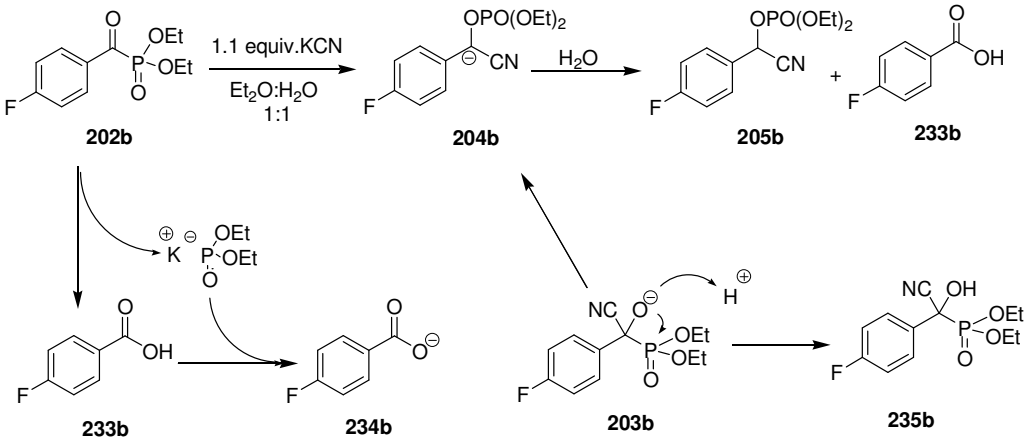
Protonation of acyl anion equivalents generated from acylphosphonates has potential consequences. From our point of view these consequences are twofold. First of all protonation of these intermediates not only provides a practical nonhydride reduction of carboxylic acids but also provides products that can be used as synthons to a variety of targets (Scheme 66). Secondly they gave us opportunity to identify the side products of their reactions with aldehydes to be proton abstraction from environment or from reactants. This was the case in reaction utilizing aliphatic acyl phosphonates.

As depicted in Scheme 66, protonation of **204** would lead to **205** that is equivalent to aldehyde under appropriate hydrolysis conditions. Normally synthesis of aldehydes from carboxylic acids is possible via DIBAL reduction of corresponding ester or $LiAlH_4$ reduction of special amides (e.g. Weinreb amides). When this strategy fails, carboxylic acids are generally reduced all the way to alcohol and re-oxidized to aldehydes by mild oxidants. Therefore this protonation strategy has the advantage of direct reduction of carboxylic acids to aldehydes under aqueous conditions. Same transformation is known for the corresponding acylsilanes [25] (Scheme 19). However it is not a feasible approach because the synthesis of acylsilanes is laborious and generally obtained from aldehydes from which cyanohydrins are already available.



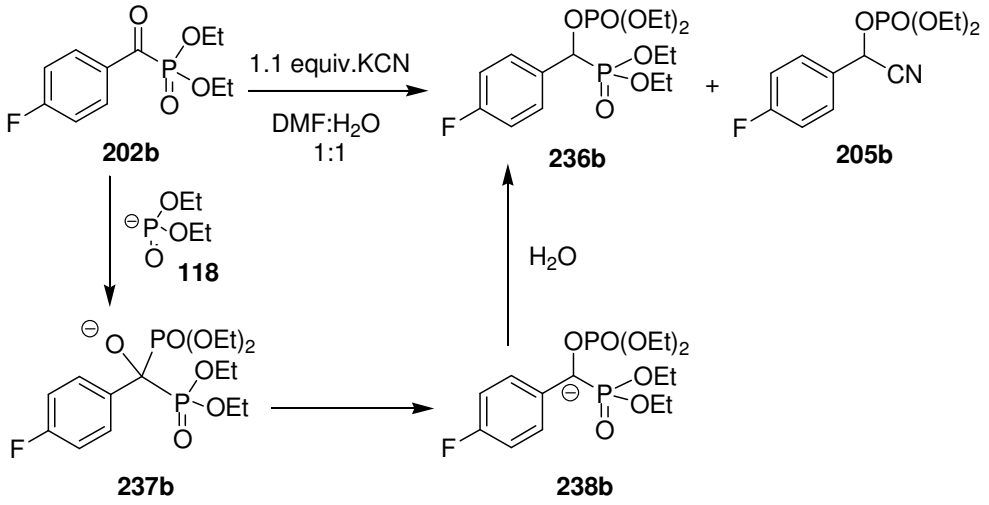
Scheme 66

We examined the protonation of the **204b** under two phase conditions. Briefly 1mL organic solution (1 M DMF, Toulene or ether) of **202b** was mixed with a 1 mL aqueous solution of 1.1 mmol KCN. All reactions were complete in minutes by TLC monitoring. Organic phases were diluted with ether and separated; subsequent examination with NMR showed that reactions in toluene and ether provided the expected the **205b** in pure form, however yields were just 51% and 66%, respectively. When reaction carried out in ether, quenched and extracted with 1N HCl, crude products showed the presence of both **205b** and 4-F-benzoic acid **233b**. The generation of **233b** probably results from the hydrolysis of **202b** but it was not obvious if **233b** is formed directly by the action of water or cyanide ion promotion has a role. In anyway, strong base potassium diethylphosphite is released and it deprotonates the **233b**. Thus direct separation of organic phase affords the pure **205b**. We did not observe any products **235b** (synthesized independently, look below) arising from the protonation of intermediate **203b** so this alkoxide must be undergoing a fast intramolecular attack on the phosphonate to form **204b** (Scheme 67).



Scheme 67

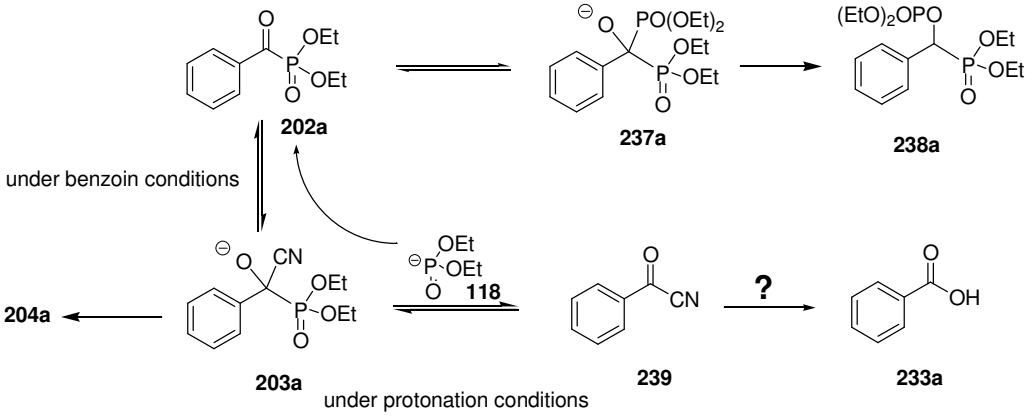
In DMF crude product recovery was higher but contaminated with a side product. Closer examination of the side product and comparison with literature values revealed the side product as **236b**. This product probably arises from the reaction of **118** with **202b**. Addition of **118** to **202b** promotes a phosphonate-phosphate rearrangement via **237b** forming **238b** that subsequently abstracts proton to provide **236b**. This shows that reactions in both solvents occur via similar intermediates but **118** behaves as a competent nucleophile even in aqueous DMF solution. This also indicates the potential of **118** as a potential catalyst of reactions between acylphosphonates and aldehydes in cross benzoin condensation. Although phosphonate-phosphate rearrangement promoted by **118** is well known [46-49], generated carbanions have not been used in catalytic or stoichiometric C-C bond forming reactions (Scheme 68).



Scheme 68

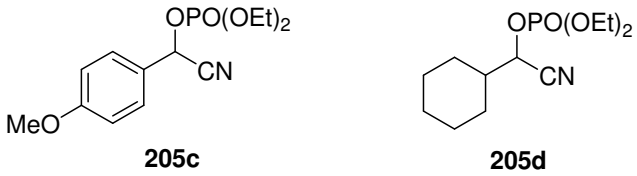
In order to shed light onto hydrolysis question, to a 1M DMF and ether solutions of **202a** was added 1mL of water (pH=7 and 10, without KCN). TLC monitoring of these mixtures for several hours showed that **202a** is stable in the absence of cyanide anion and only traces of corresponding acids was observable. When **202a** was stirred in MeOH (1M), only traces of methylbenzoate was observed. However same mixture in the presence of KCN instantaneously provided methyl benzoate. These are strong indications of a cyanide ion catalyzed hydrolysis pathway. It is possible that in aqueous media, intermediate **203a** expels **118** that is protonated immediately. It would be more of a speculation to talk about possibilities without more data in hand but we can underline a few known supporting facts. It is well known that DMSO and H_2O acidities of compounds differ markedly because DMSO is not able to provide anion (conjugate base) stabilization. This fact is further supported by the diminished acidity differences between compounds that are able to stabilize conjugate bases by resonance (or internal solvation). Therefore in nonaqeous polar aprotic DMF, **203a** can reversibly retrocyanide whereas expulsion of more basic **118** (basicity is comparable to methoxide) is much less probable (or slower). Therefore we did not observe any product arising from the attack of **238a** to aldehydes in reactions of **202a** with aldehydes giving cross benzoin products **209a-f**. However water can provide extra stabilization to **118** and expulsion of **118** might occur albeit to a lesser extent. Although **118** is not active as nucleophile in two phase system, it attacks to

remaining **202a** in homogeneous aqueous DMF solution. This can explain the different behavior of reactions in dry DMF and aqueous DMF. Of course this scenario requires the formation of benzoylcyanide that is a question under investigation (Scheme 69).



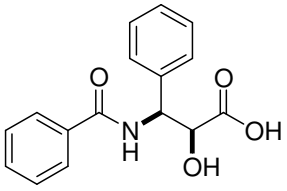
Scheme 69

We also showed that **202c-d** provide the expected products **205c** and **205d** in 59% and 65% yield respetively.

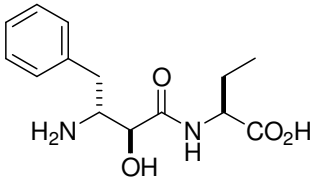


205c **205d**

α-amino aldehydes and α-hydroxy-β-amino acids are highly important compounds. The former is a valuable synthon for the synthesis of interesting targets. The latter can be found in the structure of many biologically active compounds. Anticancer drug Taxol's side chain N-Benzoyl-phenylisoserine **240** and bestatin **241** are just two of many important compounds in this class. α-hydroxy-β-amino acids are generally synthesized from α-amino aldehydes. This is done by cyanohydrin formation from α-amino aldehydes and their subsequent acidic hydrolysis. Acylphosphonates are easily available from carboxylic acids and protonation of their cyanide promoted rearrangement intermediates would lead to a common intermediate for the synthesis of α-amino aldehydes and α-hydroxy-β-amino acids.

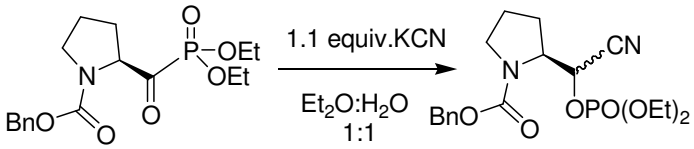


240



241

Therefore we carried out a preliminary experiment to test the feasibility of this approach. When proloylphosphonate **216** was subjected to KCN in aqueous ether, product **242** was obtained in minutes with complete consumption of **216**. Reaction afforded pure **242** in this case too but again in an intermediate yield of 65%. NMR spectrum of **242** was complex and critical peaks were broad at room temperature due to hindered rotation of the amide bond of the protecting group. Therefore NMR spectrum of the crude product was obtained at 90°C in DMSO that provided sharp signals. Based on the signals of α-CH, diaseteromeric ratio is estimated as 1:1.5 (Scheme 70).



216 **242**

65%, dr ~1:1.5

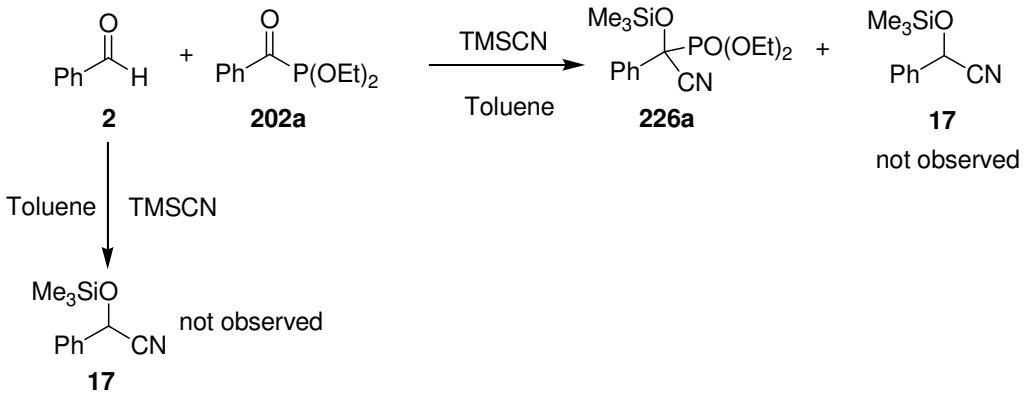
Scheme 70

This reaction is highly practical but unfortunately yields are lower than expected. Thus further examples with different acylphosphonates especially that of derived from phenylglycine (for paclitaxel side chain, **240**) and phenylalanine (for bestatin, **241**) requires optimization of reaction conditions. Our observations in this study and experience with cross benzoin synthesis points out the use of nonaqueous reaction conditions and nonnucleophilic protonation reagents (possibly organic acids or hindered alcohols) can be helpful. For example we observed better results in a mixture of ether:*t*-butanol mixture. Investigations in this direction are going on.

2.2.2.3 Uncatalyzed Addition of TMSCN to Acylphosphonates

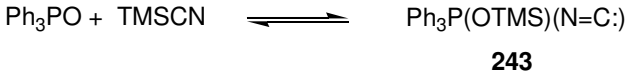
During our investigations regarding the nature of carbanionic intermediates generated via phosphonate-phosphate rearrangement, we needed to synthesize compound **226a**. The general route to O-TMS cyanohydrins is the addition of TMSCN to the aldehydes (or ketones) that only occurs in the presence of Lewis acid catalysis (e.g. ZnI_2) [60]. Considering the value of O-TMS cyanohydrins, it is not surprising that hundreds of catalysis were reported so far for this particular transformation and continue to be reported at the same pace [61]. However we found that TMSCN adds to **202a** quantitavely without the influence of a catalyst.

After a quick screening with **202a** and **202b**, we found that reaction indeed proceeds smoothly in various solvents. For example we observed similar purities in DMF, toluene, DCM and MeCN. Moreover neat **202b** reacted with TMSCN providing a quantitative conversion. Although reaction in DMF provided faster conversions, we chose the toluene as the reaction medium because of practical reasons. We initially attributed the enhanced reactivity of acylphophonates to the presence of phosphonate moiety that could interact with TMSCN through P=O and activates it to an intramolecular attack. Interestingly Belatskaya [62] reported the reaction of acylphosphonates with TMSCN to only occur with catalytic Bu_3SnCN at elevated temperatures (50°-60°C, 6-8 h). This report obviously stood against our observations. Therefore we carried out some control experiments before going into the details. In two separate experiments benzaldehyde **2** and a one to one mixture of benzaldehyde **2** and benzoylphosphonate **202a** was reacted with 1 equiv of TMSCN. Crude reaction mixtures were inspected for two possible products, namely **226a** and **17**. We undoubtedly saw that there were no traces of the product **17** in both reaction mixtures whereas **226** was the single product in the latter reaction (Scheme 71). Although we don't have any explanation for the Belatskaya's report, we surely saw that **202a** did react with TMSCN without need to a catalyst in 15-30 minutes (<5 min in DMF).



Scheme 71

Shibasaki and co-workers showed that enantioselectivies in chiral Lewis acid catalyzed addition of TMSCN to aldehydes sometimes enhanced by the addition of "promoters" such as Bu_3PO, $CH_3P\text{-}(O)Ph_2$ and Ph_3PO [63]. These phosphine oxide activation effect led to the incorporation of phosphine oxide moitites into the catalytic Lewis acid structures as a Lewis acid-Lewid base pair for what have been described as "two center" catalysis. Later Corey and Ryu [63] investigated the effect of phosphine oxide and proposed that a reaction between phosphine oxide and TMSCN as follows:



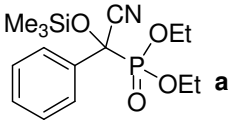
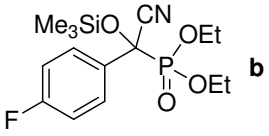
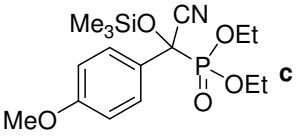
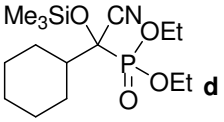
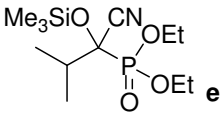
They have supported their proposal with several NMR and IR experiments and identified **243** as a more reactive cyanosilylating reagent than the isomeric cyanide. This seems to be in agreement with our initial proposal where phosphonate moiety activates the TMSCN through interaction via P=O bond as in **244** to afford **226a** (Scheme 72).

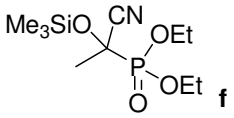
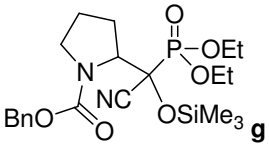
244 **226a**

Scheme 72

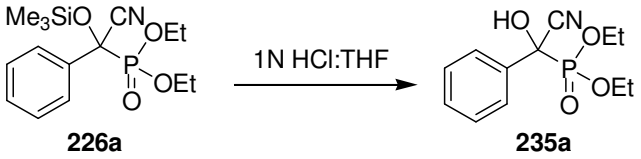
Several aromatic and aliphatic acylphophonates were reacted with TMSCN in toluene and results are summarizes in Table 8. Compound **226h** derived from proloylphosphonate **216** showed complex spectrum at room temperature as for the previous reactions utilizing **216**.

Table 8. Yields of uncatalyzed addition of TMSCN to acylphosphonates

entry	Aroylphosphonate	Product **226**	Yield(%)
1	**202a**	 **a**	98
2	**202b**	 **b**	98
3	**202c**	 **c**	97
4	**202d**	 **d**	97
5	**202e**	 **e**	94

6	**202g**	 **f**	87
7	**216**	 **g**	93

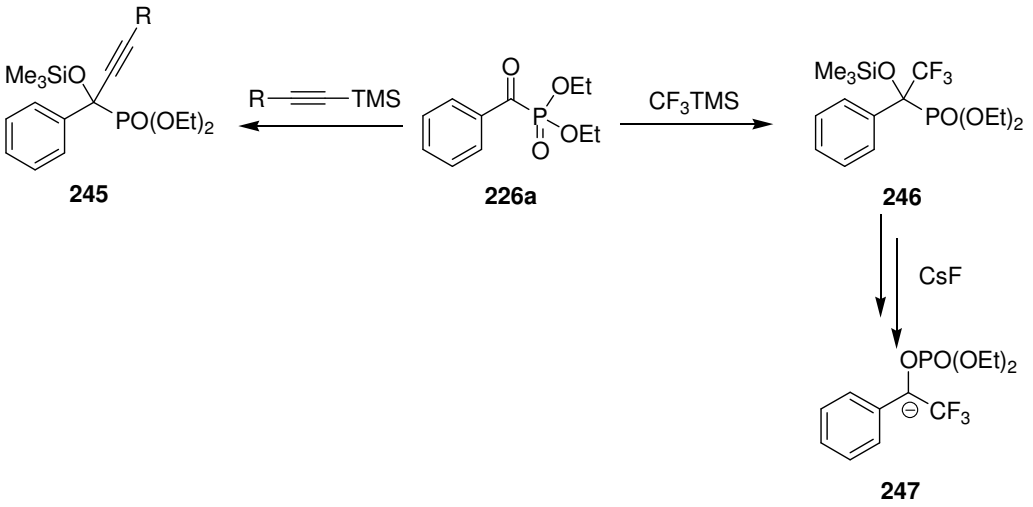
Products of type **226** can be quantatively hydrolyzed to corresponding alcohols by acidic hydrolysis. For example compound **226a** was readily hydrolyzed in a mixture of 1N HCl and THF affording **235a** (Scheme 73).



226a **235a**

Scheme 73

From synthetic point of view this reaction provides not only biologically active α-hydroxyphosphonates with quaternary carbon but also in highly functionalized form. Besides we previously showed that fluoride ion mediated hydrolysis of **226a** provides the acyl anion equivalent via phosphonate-phosphate rearrangement. Although nature of this decomposition is not exact, products of type **226** and **235** can be used for generation valuable acyl anion equivalents in the same way. As a general extension of this work we are currently investigating the reaction of trifluoromethylation agent CF_3TMS and acetylTMS with acylphosphonates. We are planning to gain a direct and uncatalyzed access to valuable α-hydroxyphosphonates **245** and **246**. Moreover we hope that CF_3- group can provide considerable carbanion stabilization to provide **247** that can give a wide range of fluorinated carbinols upon reaction with electrophiles (Scheme 74).



Scheme 74

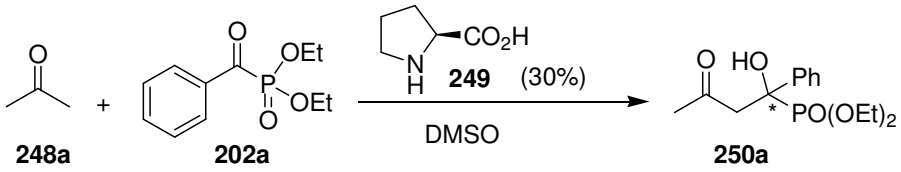
2.2.2.4 Proline Catalyzed Enamine Nucleophiles in Reactions with Acylphosphonates

During our studies we identified acylphosphonates as highly valuable and practical acyl anion precursors. By this approach we were able to carry out catalytic synthesis of various cross benzoin adducts. Moreover we showed that they are good precursors to some other valuable products including cyanohydrins and α-hydroxyphosphonates. Although α-hydroxyphosphonates were not utilized in C-C bond forming reaction neither by us nor by others, there is considerable evidence for their potential as acyl anion precursors both from our observations and literature reports. In this regard acylphosphonates and α-hydroxyphosphonates constitutes a full complementary to well known Brook rearrangement or it is even superior in terms of substrate functionalization flexibility, easy synthesis and presence of an extra coordination site provided by the phosphonate moiety. Therefore we sought that it would be great to find out practical and enantioselective synthesis of both acylphosphonates and α-hydroxyphosphonates. It is evident from recent reviews about α-hydroxy- and α-aminophosphonates that there are not highly practical synthesis methods for these compounds [64]. In this context we decided to investigate the reactivity of acylphosphonates with recently emerging proline catalyzed d^2 chemistry [65]. There are two possible uses of acylphosphonates in this

field: as electrophiles (a^1) and as donor molecules (d^2). We also synthesized a phosphonate analog of proline as a new iminium ion and enamine catalyst. Herein our preliminary results in this field can be found.

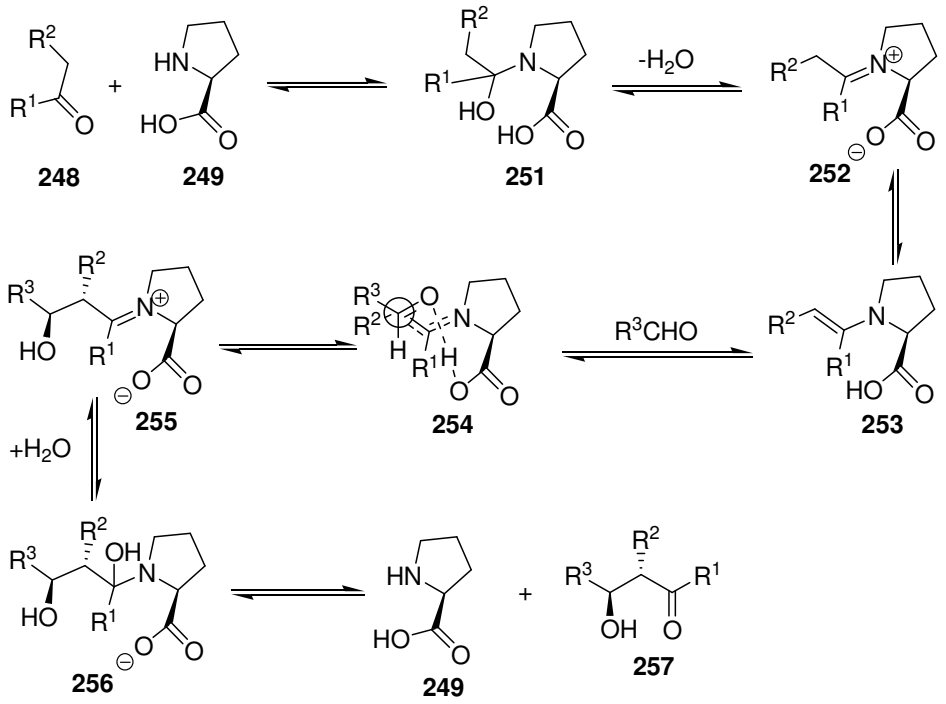
2.2.2.4.1 Acylphosphonates as electrophiles: Synthesis of quaternary α-hydroxyphosphonates

There is limited number of methods for the synthesis of α-hydroxyphosphonates, especially for products with quaternary carbon centers [64c]. So we initially investigated the reaction of acylphosphonates with ketones according to previously reported reaction between ketones and aldehydes [65]. When a mixture of 1 equiv benzoylphosphonate **202a** and 4 equiv acetone **248a** was mixed in DMSO in the presence of 30% proline **249**, product **250a** was obtained in 99% yield. This obviously constitutes an excellent entry to α-hydroxyphosphonates (Scheme 75).



Scheme 75

The mechanism of the reaction should be very similar to that of proline catalyzed aldol mechanism proposed by List and Houk shown in Scheme 76. Ketone **248** reacts with **249** to form aminocarbinol **251** that is dehydrated to iminium ion **252**. **252** tautomerizes to form enamine **253** that is an excellent nucleophile. **253** reacts with the aldehyde in a highly ordered transition state **254**. The aldehyde is both energetically activated and geometrically directed by hydrogen bonding provided by the carboxylic acid moiety of the proline. Therefore reacting face of the enamine is on the same side with the carboxylic acid and aldehyde is positioned to reduce to steric interactions. Therefore both diastereoselectivity and enantioselectivity is perfectly dictated by the proline. After bond forming process **255** is hydrated to **256** subsequently releasing the product **257** and catalyst **249** (Scheme 76).



Scheme 76. Mechanism of proline catalyzed aldol reaction

The mechanism of aldol type reaction between benzoyphosphonate **202a** and acetone **248a** is mot likely proceeds via similar intermediates. However there can be subtle differences in the structure of enantioselectivity determining step (**254**, Scheme 76) since **202a** not only has an additional site for hydrogen bonding but also a large phosphonate moiety instead of the aldehydic hydrogen. **254** is a nine membered cyclic transition state whereas binding through phosphonate P=O would make a 10 membered cyclic transition state. There are three possibilities at this point. **202a** can bind both from carbonyl oxygen and phosphonate oxygen, binds from phosphonate oxygen and only binds from carbonyl oxygen.

258 and **259** represents C=O binding. In this case there are two conformers (among the other possibilities) relative energies of which possibly will be determined by the relative size of phosphonate and aryl moieties. Of course there can be stereoelectronic effects resulting from quite different nature of C-P (high energy LUMO) bond compared to C-C C-H bonds. **260** and **261** is two of possible transition states that would result from P=O binding. Similar arguments to that of **258** and **259**

hold in this case too. **262** is the only possible transition state when both C=O and P=O engages in a hydrogen bonding. **262** is highly ordered, enantio- and diastereoselectivity would be certain from such a transition state (Figure 12).

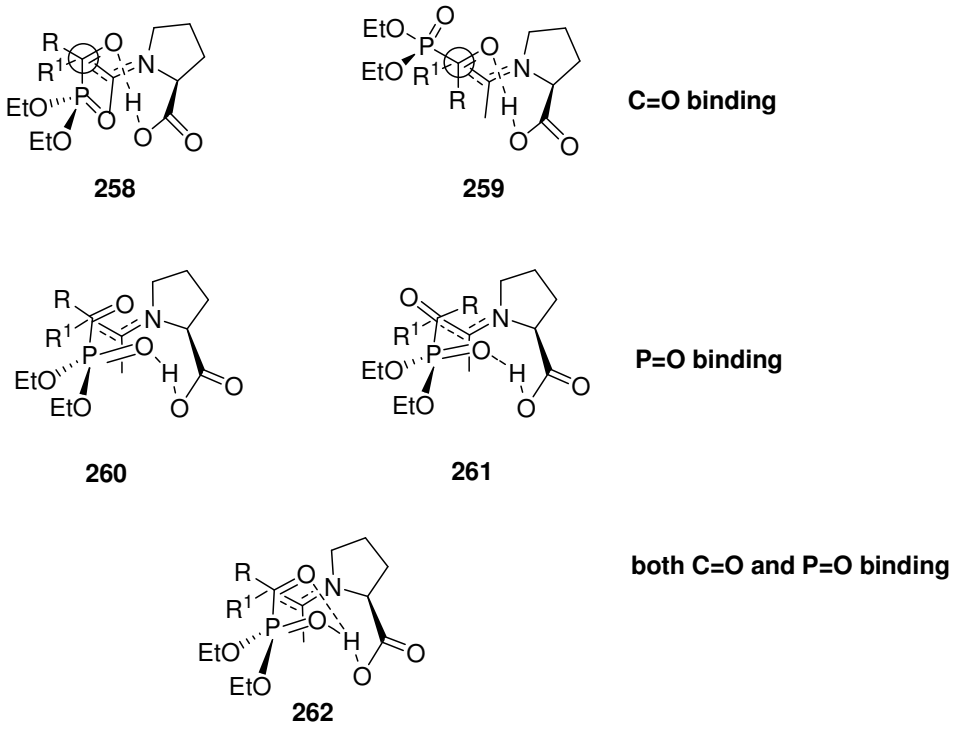
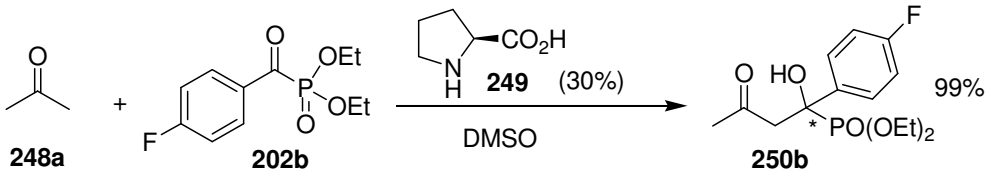


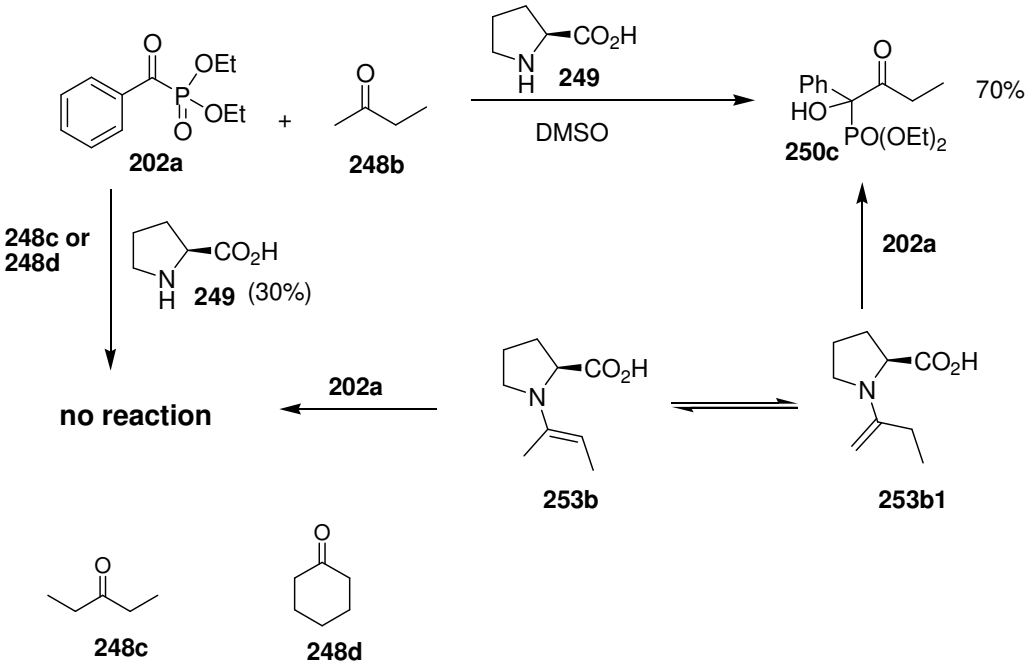
Figure 12. Some possible transition states in proline catalyzed reaction of enamine nucleophiles with acylphosphonates

Briefly the presence of the phosphonate moiety might have a considerable impact on the reaction's course. This happened to be true when we screened different substrates under same reaction conditions. While the use 4-F-benzoylphosphonate **202b** provided the expected product **250b** in 99% (Scheme 77), variation in the nucleophilic displayed a huge reactivity difference (see below).



Scheme 77

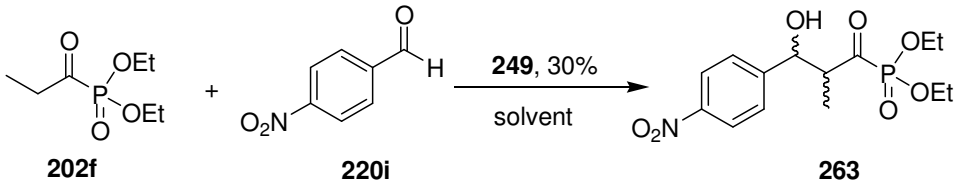
Nucleophiles methylethyl ketone **248b**, diethyl ketone **248c** and cyclohexanone **248d** were reacted with **202a** in the presence of 30% **249**. While **248c** and **248d** did not afford any product after prolonged reaction times, **248b** afforded a product after 72 hours (compared to 4-5 h for acetone) and in lower yields (~70%); product was identified as **250c** formed via **253b1**. This is quite interesting considering proline's preference to react via more substituted (E)-enamine **253b** in aldol reactions. **202a** strongly bias between two enamine structures and do not tolerate further substituent at the nucleophilic center. Thus ketones **248c** and **248d** do not react at all. The lower availability of **253b1** compared to **253b** and/or steric interaction of an extra methyl substituent on **248b** might be reasons behind the slower reaction rates. Efforts to understand this observation is going on. In anyway synthesis of kinetic product from a proline catalyzed reaction is very intriguing (Scheme 78).



Scheme 78

2.2.2.4.2 Functionalization of Acylphosphonates: Generation of Enamine Nucleophiles from Acylphosphonates

We showed that acylphosphonates are beneficial acyl anion precursors and highly functionalized enantiopure acylphosphonates would be of high value. Therefore we envisioned their proline catalyzed reactions with electrophiles as d^2 nucleophiles. Functionalized acylphosphonates that will be obtained in these reactions would be useful not only as acyl anion precursors. Proline catalyzed reactions are limited to aldehydes and ketones; acylphosphonates show behavior of both reactive ketones and activated carboxylic acids. Thus this approach indirectly would add carboxylic acid oxidation state to substrate range of proline catalyzed reactions. Proline catalyzed reactions utilize arylnitroso compounds for α-hydroxylation, azadicarboxylates for α-amination, aldehydes for aldol and activated olefins for Michael reaction [65]. Among these possibilities we selected aldol type reaction between **202f** and 4-nitrobenzaldehyde **220i** as model reaction (Scheme 79).

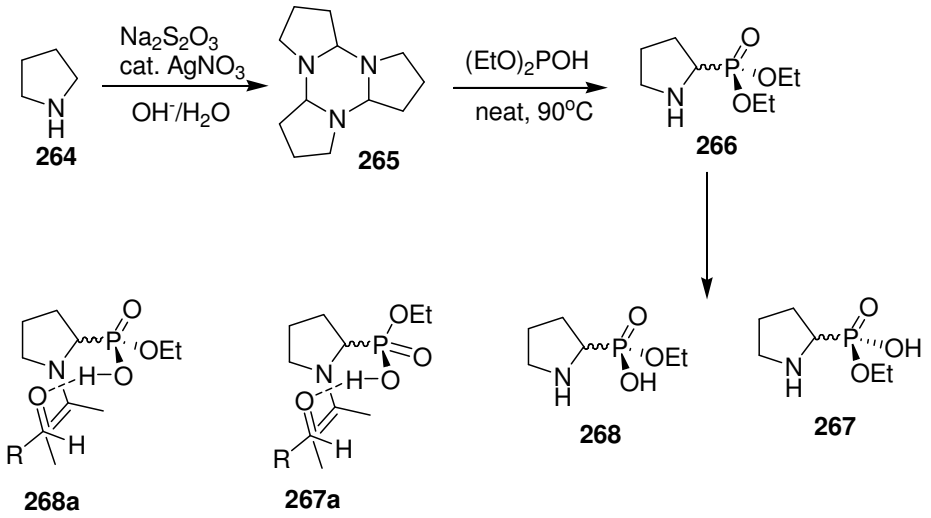


202f **220i** **263**

Scheme 79

Our initial attempts met with little success and we believe that this is due to the initial formation of the enamine. Although **202f** is expected to be highly enolizable, enamine formation from acylphosphonates is not known as far as we are aware. Reactions of acylphosphonates with secondary amines were reported to be affording secondary amides [55a]. However we recovered only unreacted **202f** and little unidentified products. Thus decomposition of **202f** by proline is out of concern. We did not carry out enough experiments yet to make further conclusions in this project. Our studies in this area will concentrate on the use of different reaction conditions and alternative enamine catalysts will be screened, especially those that provide positive results where proline fails [65].

We recently synthesized a new aminophosphonate analog of proline **266** and **267** (or **268**) as a potential iminium ion and enamine catalysis. They are easily available by a two step procedure from pyrrolidine **264**. **264** was oxidized to corresponding imine that readily trimerizes to **265**. Neat **265** was treated with diethylphosphite to afford **266**. It is easily mono hydrolyzed in basic aqueous solution to give **267** or **268**. Although exact structure of the hydrolysis product was not determined, crude NMR spectra showed the presence of a single product. We supposed that the hydrolysis step proceeds with complete diasteroselectivity to afford either **267** or **268** (Scheme 80). These catalysts resembles proline structure but have marked differences resulting from longer C-P and P-O bonds. Moreover **266** and **267** (or **268**) can be expected to have different nucleophilicity at the nitrogen and different acidity in monoacidic form. Derivatives of **267** and **268** should provide different geometries upon aldehyde binding (**267a** vs. **268a**). Both monoacidic forms are principally available by sequential selective hydrolysis and esterification steps. Thus fine tuning of both chemical and physical properties of new proline analog is possible.



Scheme 80

Although we do not have the exact structure of the catalyst yet, we used the mono acidic **267** (or **268**) in an aldol reaction between acetone and 4-nitrobenzaldehdye. Control experiments with proline catalysts were always made to compare transformation rates and product id. Preliminary experiments showed that **267** (**268**)

indeed provides the expected aldol product albeit with much slower rates. This result is highly promising and studies toward the full development of this type of compounds to new type enamine catalysts are going on. We also made an interesting observation that **267** (**268**) provides a product in reaction between **202f** and **220i** that is supposed to be **263** but have not proven yet (see Scheme 79).

CHAPTER 3

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to C*H*Cl_3 (^{1}H: δ = 7.26) and *C*DCl_3 (^{13}C: δ = 77.0) as an internal standard; coupling constnats are reported in Hz. Column chromatography was conducted on silica gel 60 (mesh size 40-63 um). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ = 254 nm). MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). Melting points were measured on a capillary tube apparatus and are uncorrected.

3.1 Synthesis of Unsymmetrical Benzoins *via* the Cyanide Ion Catalyzed Cleavage of Benzils

All aldehydes were purchased (Aldrich) and used as obtained. **168k** was prepared from 1-Bromo-2-methyl-naphthalene (see below). Benzils **175** and **177a**-**g** (**177f** commercially available from Aldrich) were synthesized by the oxidation of the corresponding benzoins, prepared by classical benzoin condensation and structure of benzils was confirmed by comparison of the analytical data with published values [41].

1-Bromo-2-naphthaldehyde (168k): To a solution of 1-bromo-2-methyl-naphthalene (3.58ml, 23 mmol) and NBS (12 g, 67 mmol) in CCl_4 (250 ml), benzoyl peroxide (0.75 g, 3 mmol) was added in multiple portions and the resulting solution was heated under reflux for 7 hours. The reaction mixture was filtered and evaporated under reduced pressure to obtain waxy brownish solid. Crystallization from hot ethanol gave 5.86 g yellowish crystals of 1-bromo-2-dibromomethyl

naphthalene **168k2** in 85% yield: mp 82.5-83.5°C; MS(EI), m/z 378-380 ($M^{+\cdot}$, 18), 299 (100), 219 (12), 149 (32), 139 (82), 109 (22), 86 (24), 69 (74); ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, s), 7.44-7.48 (1H, m), 7.51-7.54 (1H, m), 7.72 (1H, d, J=8), 7.78 (1H, d, J=8.6), 7.97 (1H, d, J=8.6), 8.2 (1H, 8.5); ^{13}C NMR ($CDCl_3$) δ 41.3, 119.9, 127.2, 128.2, 128.5, 128.8, 129.2, 131.6, 135.0, 138.4 ; Anal. Calcd. for $C_{11}H_7Br_3$: C, 34.87; H 1.86 found C, 34.95; H, 1.85.

To a solution of 1-bromo-2-dibromomethyl naphthalene **171k1** (1.89 g, 5 mmol) in 200 ml EtOH, a solution of $AgNO_3$ (1.7 g, 10 mmol) in 50 ml water was added and resulting solution was refluxed. After 75 min. green precipitate was filtered by suction from hot solution. White crystals appeared upon concentration under reduced pressure and crystals were washed with cold EtOH:H_2O (4:1) to obtain 1-Bromo-2-naphthaldehyde (**171k**) quantitatively. Analytical data were in agreement with published values [41].

3.1.1 General Procedure for the Synthesis of Protected Benzoins

To a solution of 5 mmol diketone and 5 mmol of aromatic aldehyde in 3 ml DMF was added 0.2 equiv of KCN (the course of reaction generally was not affected by the amount and source of DMF). The reaction was monitored by TLC. After completion of reaction, the mixture was directly subjected to chromatography through to a pad of silica to remove DMF and side products and eluted with 1:7 EtOAc:Hexane. Evaporation of the solvent with rotary evaporator followed by high vacuum furnished the desired product. For some reactions, the product was pure enough for most purposes. Otherwise, products were purified with a second column chromatography with 1:7 EtOAc:Hexane as eluent or crystallized from a mixture of EtOAc:Hexane.

1-(2-Trifluoromethylphenyl)-2-oxo-2-phenylethyl benzoate (171a): colorless viscous oil; ^{1}H NMR ($CDCl_3$) δ 7.32-7.38 (4H, m), 7.41-7.53 (6H, m), 7.72 (1H, d,

J=7.6), 7.86 (2H, d, J=8.2), 7.98 (2H, d, J=8.2); ^{13}C NMR ($CDCl_3$) δ 73.1 (1.5 Hz long range coupling is observable), 127.0 (q, J=5.5), 127.1 (q, J=273), 129.7 (q, J=30), 128.7, 129.10, 129.17, 129.8, 130.6, 131.2, 132.7, 132.8, 133.6, 133.9, 135.0, 165.4, 193.2; Anal. Calcd. for $C_{22}H_{15}F_3O_3$: C, 68.75; H 3.93 found C, 68.88; H, 4.07.

1-(2-Fluorophenyl)-2-oxo-2-phenylethyl benzoate (171b): white solid, mp 102-103°C; ^{1}H NMR ($CDCl_3$) δ 7.03-7.11 (2H, m), 7.25-7.31 (1H, m), 7.34-7.38 (5H, m), 7.44-7.54 (3H, m), 7.93 (2H, m), 8.03 (2H, m); ^{13}C NMR ($CDCl_3$) δ 70.7, 116.4 (d, J=22), 121.8 (d, J=13), 125.2 (d, J=2.7), 128.7, 128.9, 129.12, 129.7, 130.4, 130.5 (d, J=1.9), 131.7 (d, J=8.2), 133.6, 134.0, 134.7, 160.5 (d, J=250), 165.9, 192.8; Anal. Calcd. for $C_{21}H_{15}FO_3$: C, 75.44; H 4.52 found C, 75.45; H, 4.61.

1-(2-Bromophenyl)-2-oxo-2-phenylethyl benzoate (171c): white solid, mp 110-111°C; MS(EI), m/z 394-396 ($M^{+\cdot}$, <2), 289 (32), 183-185 (100), 155-157 (35), 105 (100), 77 (100); ^{1}H NMR ($CDCl_3$) δ 7.17 (1H, m), 7,25 (1H, m), 7,34-7,48 (8H, m), 7,92 (2H, d, J=7.3), 8.02 (2H, d, J=7.2); ^{13}C NMR ($CDCl_3$) δ 76.8, 125.1, 128.5, 128.7, 129.10, 129.17, 129.7, 130.4, 131.0, 131.3, 133.6, 133.90, 133.98, 134.2, 134.9, 165.7, 193.3; Anal. Calcd. for $C_{21}H_{15}BrO_3$: C, 63.81; H 3.83 found C, 63.84; H, 3.83.

1-(2-Methylphenyl)-2-oxo-2-phenylethyl benzoate (171d): white solid, mp 133-134 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (3H, s, Me), 7.19-7.23 (1H, m), 7.27-7.29 (2H, m), 7.38-7.47 (5H, m), 7.52- 7.59 (2H), 7.90 (2H, d, J=7.4), 8.13 (2H, d, J=7.3); ^{13}C NMR ($CDCl_3$) δ 19.9, 75.8, 127.1, 128.7, 129.0, 129.8, 129.9, 130.4, 131.6, 132.8, 133.5, 133.6, 135.5, 137.5, 166.1, 194.1; Anal. Calcd. for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49 found C, 79.82; H, 5.45.

1-(3,5-Dimethoxyphenyl)-2-oxo-2-phenylethyl benzoate (171e): white solid, mp 136-137 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (6H, s), 6.37 (1H, t, J=2), 6.63 (2H, d, J=2),

6.91 (1H, s), 7.31-7.39 (4H, m), 7.44-7.52 (2H, m), 7.93 (2H, d, J=7.4), 8.05 (2H, d, J=7.5); ^{13}C NMR ($CDCl_3$) δ 55.8, 78.3, 101.5, 107.1, 128.8, 129.1, 129.2, 129.8, 130.4, 133.8, 133.9, 135.1, 136.1, 161.6, 166.3, 193.9; Anal. Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H 5.36 found C, 73.27; H, 5.48.

1-(3,5-Dimethoxy-4-acetoxyphenyl)-2-oxo-2-phenylethyl benzoate (171f): white solid, mp 141.5-142°C; ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 3.75 (6H, s), 6.70 (2H, s), 6.91 (1H, s), 7.92 (2H, d, J=8.4), 8.04 (2H, 8.3); ^{13}C NMR ($CDCl_3$) δ 20.7, 56.5, 77.9, 105.7, 128.7, 129.0, 129.1, 129.7, 129.9, 130.4, 132.1, 133.6, 133.8, 135.2, 153.0, 166.0, 168.2, 193.5; Anal. Calcd. for $C_{25}H_{22}O_7$: C, 69.12; H, 5.10 found C, 69.28; H, 5.15.

1-(2-Pyridyl)-2-oxo-2-phenylethyl benzoate (171g): white solid, mp 125-126°C; ^{1}H NMR ($CDCl_3$) δ 7.16-7.2 (1H, m), 7.35-7.39 (4H, m), 7.44-7.55 (2H, m), 7.89 1H, d, J=7.8), 7.64-7.69 (1H, m), 8.05 (2H, d, J=8.4), 8.1 (2H, d, J=8.5), 8.52 (1H, d, J=4.2); Anal. Calcd. for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41 found C, 75.44; H, 5.08; N, 4.35.

1-Phenyl-2-oxo-2-ferrocenylethyl benzoate (171h): red solid, mp 146.5-147°C; MS(EI), m/z 423 ($M^{+\cdot}$, 100), 213 (100), 185 (46), 153 (26), 129 (34), 105 (60), 77 (36); ^{1}H NMR ($CDCl_3$) δ 4.1 (5H, s), 4.34 (1H, s), 4.41 (1H, s), 4.58 (1H, s), 4.82 (1H,m), 6.58 (1H, s), 7.19-7.37 (5H, m), 7.46-7.51 (3H, m), 8.06 (2H, d, J=7.4); ^{13}C NMR ($CDCl_3$) δ 70.0, 70.1, 72.5, 72.6, 76.4, 79.2, 128.6, 129.1, 129.3, 129.5, 130.1, 130.4, 133.4, 135.6, 165.9, 197.7; Anal. Calcd. for $C_{25}H_{20}FeO_3$: C, 70.77; H, 4.75 found C, 70.62; H, 4.78; HRMS Calcd: 424.0761, found: 424.0762.

2-(2-Naphthyl)-2-oxo-1-(2-naphthyl)ethyl 2-naphthoate (176a): white solid, mp 150-151°C; ^{1}H NMR ($CDCl_3$) δ 7.3-7.43 (6H, m), 7.61-7.79 (9H, m), 7.94-7.96 (1H, m), 7.56-8.05 (2H, m), 8.50 (1H, s), 8.60 (1H, s); ^{13}C NMR ($CDCl_3$) δ 78.5, 124.8,

125.9, 126.1, 126.8, 126.9, 127.0, 127.2, 128.11, 128.17, 128.5, 128.6, 128.7, 128.9, 129.2, 129.5, 129.9, 130.1, 131.17, 131.91, 132.1, 132.6, 132.8, 132.9, 133.8, 134.0, 136.0, 136.1, 166.3, 193.6; Anal. Calcd. for $C_{33}H_{22}O_3$: C, 84.96; H, 4.75 found C, 84.91; H, 4.88.

2-(2-Naphthyl)-2-oxo-1-phenylethyl 2-naphthoate (176b): white solid, mp 169-171°C (decompose); ^{1}H NMR ($CDCl_3$) δ 7.21 (1H, s), 7.28-7.38 (3H, m), 7.43-7.50 (4H, m), 7-57-7.59 (2H, m), 7.72- 7.80 (4H, m), 7.84-7.88 (2H, m), 7.94-7.97 (1H, m), 8.04-8.07 (1H, m), 8.49 (1H, s), 8.62 (1H, s); ^{13}C NMR ($CDCl_3$) δ 78.3, 124.7, 125.9, 126.9, 127.10, 127.18, 128.12, 128.14, 128.5, 128.6, 128.94, 128.98, 129.1, 129.5, 129.6, 129.8, 130.1, 131.0, 132.0, 132.6, 132.8, 132.9, 134.5, 136.0, 136.1, 166.3, 193.6; Anal. Calcd. for $C_{29}H_{20}O_3$: C, 83.63; H, 4.84 found C, 83.37; H, 4.74.

2-(2-Naphthyl)-2-oxo-1-(1-bromo-2-naphthyl)ethyl 2-naphthoate (176c): white solid, mp 153.5-154°C; ^{1}H NMR ($CDCl_3$) δ 7.39-7.55 (6H, m), 7.61 (1H, d, J=8.6), 7.70-7.98 (8H, m), 7.99-8.06 (3H(2H+CH), m), 8.33 (1H, d, J=8.5), 8.62 (1H, s), 8.64 (1H, s); ^{13}C NMR ($CDCl_3$) δ 78.4, 124.5, 125.8, 126.1, 126.4, 126.9, 127.0, 127.2, 128.10, 128.14, 128.19, 128.4, 128.61, 128.66, 128.7, 128.8, 129.0, 129.1, 129.2, 129.8, 130.2, 131.3, 132.1, 132.2, 132.7, 132.8, 132.9, 135.1, 136.1, 136.3, 166.3, 194.0; Anal. Calcd. for $C_{33}H_{21}BrO_3$: C, 72.67; H 3.88 found C, 72.41; H, 3.93.

2-(Ferrocenyl)-2-oxo-1-(1-bromo-2-naphthyl)ethyl 2-naphthoate (176d): red solid, mp decompose >190°C; ^{1}H NMR ($CDCl_3$) δ 4.13 (5H, s), 4.33 (1H, s), 4.41 (1H, s), 4.63 (1H, s), 4.88 (1H, s), 6.83 (1H, s), 7.35-7.51 (4H, m), 7.62-7.64 (1H, m), 7.77-7.88 (6H, m), 7.97 (1H, br s), 8.06-8.09 (1H, m), 8.63 (1H, s); ^{13}C NMR ($CDCl_3$) δ 70.0, 70.2, 70.65, 72.5, 72.6, 76.5, 79.5, 125.9, 126.3, 126.8, 126.9, 127.1, 127.3, 128.12, 128.18, 128.4, 128.5, 128.6, 129.1, 129.3, 129.8, 132.0, 132.92, 132.96, 133.6, 133.9, 136.1, 166.1, 197.7; Anal. Calcd. for $C_{33}H_{24}FeO_3$: C, 75.58; H, 4.61 found C, 75.30; H, 4.79. HRMS Calcd: 524.1074, found: 524.1066.

2-(2-Methylphenyl)-1-ferrocenyl-2-oxoethyl 2-methylbenzoate (178a): red solid, mp 101-102°C; MS(EI), m/z 452 ($M^{+\cdot}$, 50), 213 (100), 185 (28), 119 (48), 91 (46); ^{1}H NMR ($CDCl_3$) δ 2.61 (3H, s, Me), 2.68 (3H, s, Me), 4.30 (5H, s), 4.40 (2H, s), 4.50 (1H, s), 4.94 (1H, s), 7.01 (1H, s), 7.2-7.32 (5H, m), 7.36-7.43 (2H, m), 8.06 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.9, 22.1, 69.8, 69.9, 70.6, 72.3, 72.6, 76.5, 76.6, 126.0, 127.0, 129.6, 130.1, 131.4, 131.5, 131.8, 132.3, 134.1, 137.3, 140.8, 167.1, 198.1; Anal. Calcd. for $C_{27}H_{24}FeO_3$: C, 71.69; H, 5.35 found C, 71,51; H, 5,16. HRMS Calcd: 452.1075, found: 452.1076.

2-(2-Bromophenyl)-1-(2-methylphenyl)-2-oxoethyl 2-bromobenzoate (178b): white solid, mp 115-116°C; ^{1}H NMR ($CDCl_3$) δ 7.19-7.27 (3H, m), 7.3-7.5 (5H, m), 7.56-7.60 (2H, m), 7.68 (1H, d, J=7.5), 7.83 (1H, d, J=7.5), 8.04 (1H, d, J=6.3); ^{13}C NMR ($CDCl_3$) δ 21.0, 78.6, 122.7, 125.1, 126.0, 127.4, 128.2, 129.2, 130.7, 131.1, 131.5, 132.02, 132.1, 132.4, 133.1, 133.2, 133.8, 134.7, 135.7, 139.0, 165.1, 196.2; Anal. Calcd. for $C_{22}H_{16}Br_2O_3$: C, 54.13; H, 3.30 found C, 54.44; H, 3.68.

2-(2-Chlorophenyl)-1-(2-methylphenyl)-2-oxoethyl 2-chlorobenzoate (178c): white solid, mp 95°C; ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, s, Me), 7.04-7.39 (10H, m), 7.49-7.52 (1H, m), 7.73 (1H, d, J=1.9), 7.96 (1H, dd, J=7.6, 1.2); ^{13}C NMR ($CDCl_3$) δ 20.9, 76.2, 126.0, 126.8, 127.6, 129.0, 129.5, 130.4, 130.5, 130.9, 131.50, 131.52, 132.0, 132.1, 132.4, 133.1, 134.6, 134.8, 135.7, 139.0, 164.7, 196.1; Anal. Calcd. for $C_{22}H_{16}Cl_2O_3$: C, 66.18; H, 4.04 found C, 66.07; H, 4.25.

2-(2-Fluorophenyl)-1-(2-methylphenyl)-2-oxoethyl 2-fluorobenzoate (178d): white solid, mp 94°C; ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s, Me), 6.92-6.97 (1H, m), 7.04-7.27 (8H, m), 7.43-7.54 (2H, m), 7.72-7.74 (1H, m), 7.96-7.99 (1H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 72.8, 116.2 (d, J=22), 117.4 (d, J=22), 118.4 (d, J=9.5), 121.1 (d, J=14.1), 124.2 (d, J=3.6), 125.0 (J=3.6), 125.9, 128.7, 130.1, 130.2, 131.4 (d, J=8.3), 131.9, 132.0, 132.9, 135.1 (d, J=9), 135.6, 160.4 (d, J=248), 162.7 (d, J=260), 163.5

(d, J=3.7), 195.8; Anal. Calcd. for $C_{22}H_{16}F_2O_3$: C, 72.13; H, 4.40 found C, 71.99; H, 4.58.

2-(2-Pyridyl)-1-(2-fluorophenyl)-2-oxoethyl 2-pyridoate (178e): white solid, mp 121-122°C; ^{1}H NMR ($CDCl_3$) δ 6.94-7.04 (2H, m), 7.12-7.25 (1H, m), 7.31-7.45 (3H, m), 7.65-7.76 (2H, m), 7.85 (1H, s), 7.98 (1H, d, J=7.8), 8.09 (1H, d, J=7.7), 7.86 (1H, d, J=4.4), 8.70 (1H, s); ^{13}C NMR ($CDCl_3$) δ 74.8, 118.5 (d, J=21), 123.8 (d, J=14), 125.2, 126.8 (d, J=3.6), 128.0, 129.5, 130.0, 133.0 (d, J=2.7), 133.5 (d, J=8.3), 139.3, 139.4, 149.9, 151.4, 152.5, 153.6, 163.3 (d, J=250), 166.8, 195.6; Anal. Calcd. for $C_{19}H_{13}FN_2O_3$: C, 67.85; H, 3.90; N, 8.33 found C, 67.95; H, 4.01; N, 8.17.

2-(2-Pyridyl)-1-(2-trifluoromethylphenyl)-2-oxoethyl 2-pyridoate (178f): white solid, mp 113-114.5°C; ^{1}H NMR ($CDCl_3$) δ 7.3-7.34 (1H, m), 7.34-7.47 (4H, m), 7.69-7.75 (3H, m), 7.93 (1H, s), 8.0-8.06 (2H, m), 8.47 (1H, d, J=4), 8.68 (1H, d, J=3); ^{13}C NMR ($CDCl_3$) δ 73.3 (1.7 Hz long range coupling is observable), 123.0 (q, J=272), 121.8, 124.5, 125.9 (q, J=5.5), 126.0, 126.5, 128.1, 128.7 (q, J=30), 129.3, 131.11, 131.29, 135.8, 135.9, 146.4, 148.0, 149.0, 150.0, 163.0, 192.7; Anal. Calcd. for $C_{20}H_{13}F_3N_2O_3$: C, 62.18; H, 3.39; N, 7.25 found C, 61.71; H, 3.62; N, 7.15.

1-(2-Methylphenyl)-2-oxo-2-phenylethyl ferrocenecarboxylate (182): red solid (73%), MS(EI), m/z 438 ($M^{+\cdot}$, 5), 230 (82), 213 (100), 185 (23), 166 (28), 129 (37), 104 (32), 76 (44); ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 4.24 (5H, s), 4.33 (2H, s), 4.78 (1H, s), 4.82 (1H, s), 7.10-7.25 (4H, m), 7.28-7.5 (4H, m), 7.86 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.0, 70.8, 71.1, 71.20, 71.26, 72.0, 72.1, 75.4, 127.7, 129.73, 129.79, 130.4, 130.6, 132.39, 133.9, 134.2, 136.7, 138.3, 172.3, 195.8; Anal. Calcd. for $C_{26}H_{22}FeO_3$: C, 71.07; 5.01 found C, 71.36; H, 5.17.

3.1.2 General Procedure for the Hydrolysis of Protected Benzoins

Benzoins were obtained according to following procedure. Compound **174d** was isolated in 85% yield and data was in agreement with the published values [41] (^{1}H NMR can be seen in Figure 37).

2-Hydroxy-2-ferrocenyl-1-phenylethan-1-one (174a): 0.5 g (1.18 mmol) **171h** was dissolved in 50 ml MeCN and argon was bubbled through the solution for 15 min to remove the oxygen from medium. While refluxing the solution, 0.06 g NaOH in 20 ml of water was added dropwise in 15 min. Resulting solution was refluxed for an additional 30 min and concentrated under reduced pressure to get slurry, which was then extracted with EtOAc. Organic phase was dried over $MgSO_4$ and concentrated to obtain brownish-red solid **174a** with 87% yield. During reaction or work up some contamination of the product with **181** might occur. This oxidation product can easily be separated by flash column chromatography. Red solid (0.32 g), mp 107°C; MS(EI), m/z 318 ($M^{+\cdot}$, 100), 213 (92), 185 (55), 129 (52), 121 (16), 105 (16), 77 (24); ^{1}H NMR ($CDCl_3$) δ 4.09 (5H, s), 4.47 (1H, s), 4.54 (2H, s, 1H exchangeable with D_2O), 4.66 (1H, s), 4.86 (1H, s), 5.47 (1H, s), 7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 68.9, 69.2, 69.4, 71.6, 71.7, 76.2, 126.8, 127.2, 127.7, 139.8, 202.3; Anal. Calcd. For $C_{18}H_{16}FeO_2$: C, 67,52; H, 5.03 found C, 67.62; H, 5.02.

2-(2Trifluoromethylphenyl)-2-hydroxy-1-phenylethan-1-one (174b). Hydrolysis was carried out as for **171h** except that the reaction was carried out at RT. Reaction was monitored by TLC and after all of the starting material has been consumed, mixture was worked up as above; 94% yield, white solid, mp 82°C; ^{1}H NMR ($CDCl_3$) δ 4.23 (1H, br s), 6.12 (1H, s), 6.98 (1H, d, d=6.4), 7.12-7.35 (4H, m), 7.4-7.43 (1H, m), 7.68 (1H, m), 7.76 (2H, d, J=7.4); ^{13}C NMR ($CDCl_3$) δ 72.1, 124.6 (q, J=272), 127.0 (q, J=5.5), 129.02, 129.08 (q, J=30), 129.1, 129.4, 129.5, 133.0, 133.5, 134.3, 137.9, 198; Anal. Calcd. for $C_{15}H_{11}F_3O_2$: C, 64.29; H 3.96 found C, 64.45; H, 4.13.

2-(2-Fluorophenyl)-2-hydroxy-1-phenylethan-1-one (174c). 95% yield, white solid, mp 87°C; ^{1}H NMR ($CDCl_3$) δ 4.44 (br s, 1H), 6.13 (s, 1H), 6.90-7.00 (2H, m), 7.08-7.19 (2H, m), 7.29-7.33 (2H, m), 7.41-7.45 (1H, m), 7.84 (2H, m); ^{13}C NMR ($CDCl_3$) δ 69.6, 116.4 (d, J=22), 125.1 (d, J=3.4), 127.0 (d, J=14.1), 129.0, 129.1, 129.5 (d, J=3.6), 130.7 (d, J=8.5), 133.5, 134.3. 160.4 (d, J=246), 198.4; Anal. Calcd. for $C_{14}H_{11}FO_2$: C, 73.03; H 4.82 found C, 73.09; H, 4.91.

2-(2-Fluorophenyl)-2-hydroxy-1-ferrocenylethan-1-one (184). 69% yield from **183** (two steps), mp 126.5-127.5°C; ^{1}H NMR ($CDCl_3$) 4.01 (5H, s), 4.4 (1H, s), 4.48 (2H, m, 1H from OH), 4.63 (1H, s), 4.82 (1H, s), 5.73 (1H, d, d=5.9), 7.02-7.08 (2H, m), 7.17-7.24 (2H, m), 7.29 (1H, m); ^{13}C NMR ($CDCl_3$) δ 70.1, 70.5, 73.1, 73.2, 73.3, 74.5, 116.2 (d, J=22), 125.0 (d, J=3.3), 128.1, 129.4 (d, J=3.7), 130.5 (d, J=8.3), 160.5 (d, J=245), 202.6; Anal. Calcd. for $C_{18}H_{15}FFeO_2$: C, 63.89; H 4.47 found C, 63.64; H, 4.24; HRMS Calcd: 338.0405, found: 338.0396.

3.1.3 General Procedure for the Oxidation of Benzoins

174a was oxidized according to a known procedure [41] with 81% yield to obtain **181**. All analytical results were in agreement with published data [41].

1-(2-Fluorophenyl)-2-phenylethane-1,2-dione (183). (87% yield); yellowish-white solid; MS(EI), m/z 228 ($M^{+\cdot}$, 4), 123 (44), 105 (100), 95 (24), 77 (59); ^{1}H NMR ($CDCl_3$) δ 7.02-7.07 (1H, m), 7.25-7.29 (1H, m), 7.42-7.46 (2H, m), 7.53-7.59 (2H, m), 7.89 (2H, m), 7.95-7.99 (1H, m); ^{13}C NMR ($CDCl_3$) δ 116.9 (d, J=21.6), 122.9 (d, J=10.8), 125.2 (d, J=3.4), 129.2, 130.2, 131.2, 132.5, 134.7, 136.83 (d, J=8.7), 163.2 (d, J=257), 191.7, 192.7; Anal. Calcd. for $C_{14}H_9FO_2$: C, 73.68; H, 3.97 found C, 73.71; H, 4.19.

3.2 Experimental Details for Reactions of Acylphosphonates

Acylphosphosphonates **202a-h** and **216** were synthesized according to literature procedures [53, 57]. Briefly 1 equiv of neat triethylphosphite was added drop wise onto the neat acylchloride in a water bath under a positive inert atmosphere. After completion of the addition, resulting mixture was stirred at room temperature for 60min. Representative spectra for **202a-c** and **202h** can be seen in Figure 63-70 (appendix A). **215** was obtained from thionyl chloride and protected proline [59] by refluxing in benzene for 15 min. Crude product (99%) was used as obtained. KCN was dried at 100°C under vacuum. DMF was distilled under reduced pressure and stored under nitrogen.

3.2.1 Synthesis of Unsymmetrical Benzoins

3.2.1.1 Synthesis of Unsymmetrical Aryl-Aryl Benzoins

3.2.1.1.1 General Procedure for the Synthesis of Unsymmetrical Aryl-Aryl Benzoins

To a solution of 1 mmol acylphosphonate in 2 mL dry DMF was added 1.05 mmol aldehyde and 10% KCN. Reaction was monitored by TLC. After completion of the reaction, mixture was diluted by 10 mL of ether and water. Organic phase was separated and aqueous phase extracted with 10 mL ether three times. Combined organic phase extracted with brine, separated and dried over $MgSO_4$. Organic phase was concentrated under reduced pressure. Crude product was purified by flash column chromatography on silica gel with eluents ether or mixture of ether: petroleum ether.

Diethyl 1-(4-methoxyphenyl)-2-oxo-2-phenylethyl phosphate (209a): white solid, mp:58-60°C; ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, dt, J=0.8, 7.1 Hz), 1.25 (3H, dt, J=0.8, 7.1 Hz), 3.77 (3H, s), 3.85-4.0 (2H, m), 4.1-4.25 (2H, m), 6.6 (1H, d, J=7.9 Hz), 6.87 (2H, m), 7.3-7.4 (4H, m), 7.45-7.5 (1H, m), 7.9 (2H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$)

δ 16.2 (d, J=7.1 Hz), 16.4 (d, J=6.9 Hz), 55.6, 64.2 (d, J=6.0 Hz), 64.6 (d, J=6.0), 80.0 (d, J=4.83 Hz), 114.9, 127.3 (d, J=5.1), 129.0, 129.3, 130.1, 133.8, 134.8, 160.8, 193.9 (d, J=4.9 Hz); ^{31}P NMR ($CDCl_3$) δ -1.19.

Diethyl 1-(4-fluorophenyl)-2-oxo-2-phenylethyl phosphate (209b): colorless liquid; ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, dt, J=0.8, 7.1 Hz), 1.25 (3H, dt, J=0.8, 7.1 Hz), 3.80-3.90 (2H, m), 4.0-4.20 (2H, m), 6.54 (1H, d, J=8.0 Hz), 6.95-7.0 (2H, m), 7.32-7.47 (5H, m), 7-85 (2H,m); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, J=6.7 Hz), 16.0 (d, J=6.9 Hz), 64 (d, J=6.2 Hz), 64.3 (d, J=6.0 Hz), 75.1 (d, J=4.7 Hz), 116.1 (d, J=22.0 Hz), 128.7, 128.9, 139.0 (d, J=8.6 Hz), 163.2 (d, J=249 Hz), 193.5 (d, J=5.0 Hz); ^{31}P NMR ($CDCl_3$) δ -2.33.

Diethyl 1-(3,5-dimethoxyphenyl)-2-oxo-2-phenylethyl phosphate (209c): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, dt, J=0.9, 7.0 Hz), 1.35 (3H, dt, J=0.9, 7.0 Hz), 3.75 (3H, s), 3.9-4.0 (2H, m), 4.14-4.20 (2H, m), 6.4 (1H, t, J=2.2 Hz), 6.50 (1H, d, J=7.1 Hz), 6.62(2H, d, J=2.2 Hz), 7.39 (2H, m), 7.51 (2H, m), 7.92 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J=6.8 Hz), 16.3 (d, J=6.9 Hz), 55.8, 64.4 (d, J=6 Hz), 64.6 (d, J=6.0 Hz), 80.5 (d, J=4.7 Hz), 101.5, 106.3, 129.0, 129.3, 133.9, 134.7, 137.2 (d, J=5.6 Hz), 161.6, 193.9 (d, J=4.4 Hz); ^{31}P NMR ($CDCl_3$) δ -1.21.

Diethyl 1-(furan-2-yl)-2-oxo-2-phenylethyl phosphate (209d): yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, dt, J=0.8, 6.8 Hz), 1.27 (3H, dt, J=0.8, 7.2 Hz), 3.89-3.99 (2H, m), 4.10-4.18 (2H, m), 6.30 (1H, m), 6.44 (1H, m), 6.65 (1H, d, J=8.0 Hz), 7.33-7.40 (3H, m), 7.45-7.52 (1H, m), 7.85-7.92 (2H, m).

Diethyl 2-(furan-2-yl)-2-oxo-1-phenylethyl phosphate (209d2): yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, t, J=7.1 Hz), 1.25 (3H, t, J=7.1 Hz), 3.82-3.91(2H, m), 4.02-4.17 (2H, m), 6.35 (1H, d, J=8.2 Hz), 6.43 (1H, dd, J=1.7, 3.6 Hz), 7.22 (1H, d, J=3.6 Hz), 7.25-7.32 (3H, m), 7.40-7.50 (3H, m); ^{13}C NMR ($CDCl_3$) δ 14.8 (d, J=7.4 Hz), 15.0 (d, J=7.1 Hz), 62.7 (d, J=6.1 Hz), 63.0 (d, J= 5.9 Hz), 78.5 (d, J=4.5 Hz), 111.4, 118.1, 127.0, 127.7, 128.2, 133.7 (d, J=4.9 Hz), 145.7, 149.3, 181.0 (d, J=4.6 Hz); ^{31}P NMR ($CDCl_3$) δ -2.45.

Diethyl 2-oxo-2-phenyl-1-(thiophen-2-yl)ethyl phosphate (209e): yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, dt, J=1, 7 Hz), 1.31 (3H, dt, J=1, 7.9 Hz), 3,9-4,05 (2H, m), 4.1-4.25 (2H, m), 6.9 (1H, dj, J=7.9 Hz), 6.96 (1H, dd, J=3.6, 5.1 Hz), 7.17 (1H, dd, J=1.1, 3.6 Hz), 7.36 (1H, dd, J=1.1, 5.1 Hz), 7.4-7.44 (2H, m), 7.51-7.57 (1H, m), 7.95-7.9 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.73 (d, J=7.3 Hz), 15.85 (d, J=6,8 Hz), 63.9 (d, J=6.3 Hz), 64.3 (d, J=5.9 Hz), 74.7 (d, J=4.2 Hz), 127.2, 128.2, 128.6, 128.7, 128.9, 133.6, 134.0, 136.6 (d, J=6.2 Hz), 192.2 (d, J=4.8 Hz); ^{31}P NMR ($CDCl_3$) δ -2.61.

Diethyl 2-oxo-1-phenyl-2-(thiophen-2-yl)ethyl phosphate (209e2): white solid, mp: 67.3-68.3°C; ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, dt, J=1.1, 7.1 Hz), 1.29 (3H, dt, J=1.0, 7.0 Hz), 3.87-3.98 (2H,m), 4.10-4.21 (2H,m), 6.35 (1H, d, J=8.2 Hz), 7.055 (1H, dd, J=3.9, 4.9 Hz), 7.3-7.38 (3H,m), 7.51-7.54 (2H,m), 7.62 (1H, dd, J=1.0, 4.9 Hz), 7.79 (1H, dd, J=1.0, 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.7 (d, J=7.0 Hz), 15.92 (d, J=7.3 Hz), 64.0 (d, J=6.1 Hz), 64.28 (d, J=5.9 Hz), 80.8 (d, J=5.0 Hz), 127.8, 128.2, 129.0, 129.3, 133.7, 134.6, 135.1 (d, J=5.0 Hz), 140.3, 186.6 (d, J=4.9 Hz); ^{31}P NMR ($CDCl_3$) δ -2.52.

Diethyl 1-(naphthalen-1-yl)-2-oxo-2-phenylethyl phosphate (209f): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 3.70-3.84 (2H, m), 4.20-4.34 (2H, m), 7.25-7.30 (2H, m), 7.31 (1H, d, J=8.6 Hz), 7.35-7.41 (2H, m), 7.49-7.53 (2H, m), 7.60-7.64 (1H, m), 7.71-7.79 (3H, m), 8.45 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 15.6 (d, J=6.9 Hz), 16.0 (d, J=7.3 Hz), 63.9 (d, J=6.2 Hz), 64.4 (d, J=6.1 Hz), 78.2 (d, J=5.5 Hz), 123.5, 125.3, 126.3, 127.3, 128.2, 128.5, 128.6, 129.0, 130.5, 130.93, 130.98, 131.0, 133.4, 134.2, 134.6, 194.2 (d, J=4.4 Hz); ^{31}P NMR ($CDCl_3$) δ -2.33.

Diethyl 2-(4-fluorophenyl)-2-oxo-1-phenylethyl phosphate (209b2): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, t, J=7.1 Hz), 1.27 (3H, t, J=7.1 Hz), 3.76-3.90 (2H, m), 4.03-4.17 (2H, m), 6.45 (1H, d, J=8.1 Hz), 6.93-7.00 (2H, m), 7.25-7.30 (3H, m), 7.35-7.41 (2H, m), 7.80-7.90 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, J=7.3 Hz), 16.1 (d, J=6.6 Hz), 63.8 (d, J=6.1 Hz), 64.2 (d, J=5.9 Hz), 80.1 (d, J=4.8 Hz), 115.8 (d,

J=21.6 Hz), 128.0, 129.1, 129.3, 130.8 (d, J=3.1 Hz), 131.8 (d, J=9.6 Hz), 135.0 (d, J=5.0 Hz), 165.8 (d, J=256 Hz), 191.8 (d, J=4.7 Hz); ^{31}P NMR ($CDCl_3$) δ -2.30.

Diethyl 2-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-oxoethyl phosphate (209g): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, J=7.0 Hz), 1.33 (3H, t, J=6.7 Hz), 3.76 (3H, s), 3.88-3.96 (2H, m), 4.14-4.26 (2H, m), 6.58 (1H, d, J=7.8 Hz), 6.89 (2H, d, J=(8.7 Hz), 7.05 (2H, m), 7.41 (2H, d, J=8.7 Hz), 7.94-7.98 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J=6.9 Hz), 16.3 (d, J=6.9 Hz), 55.6, 64.2 (d, J=6.3 Hz), 65.0 (d, J=6.0 Hz), 80.0 (d, J=4.8 Hz), 114.9, 116.1 (d, J=22.0 Hz), 127.1, 130.0, 131.1 (d, J=2.9 Hz), 132 (d, J=9.2 Hz), 160.8, 166.1 (d, J=255 Hz), 192.4 (d, J=4.7 Hz); ^{31}P NMR ($CDCl_3$) δ -1.19.

Diethyl 2-(4-methoxyphenyl)-2-oxo-1-phenylethyl phosphate (209a2): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, t, J=7.1 Hz), 1.31 (3H, t, J=7.1 Hz), 3.82 (3H, s), 3.86-3.95 (2H, m), 4.13-4.22 (2H, m), 6.6 (1H, d, J=8.1 Hz), 6.86 (2H, d, J=8.9 Hz), 7.27-7.37 (3H, m), 7.45-7.55 (2H, m), 7.93 (2H, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.7 (d, J=7.0 Hz), 15.9 (d, J=7.0 Hz), 55.4, 63.8 (d, J=6.1 Hz), 64.2 (d, J=5.9 Hz), 79.8 (d, J=4.8 Hz), 113.8, 127.1, 163.7, 191.9 (d, J=4.8 Hz).

Diethyl 1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-oxoethyl phosphate (209g2): ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz), 3.84 (3H, s), 3.89-3.98 (2H, m), 4.14-4.24 (2H, m), 6.60 (1H, d, J=8.1 Hz), 6.9 (2H, d, J=8.8 Hz), 7.06 (2H, m), 7.45-7.55 (2H, m), 7.93 (2H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, J=7.1 Hz), 16.0 (d, J=7.0 Hz), 55.4, 63.9 (d, J=6.2 Hz), 63.3 (d, J=6 Hz), 78.8 (d, J=4.9 Hz), 114, 116 (d, J=22.1 Hz), 130 (d, J=8.2 Hz), 131.3, 163.1 (d, J=251 Hz), 163.9, 191.7 (d, J=4.9 Hz); ^{31}P NMR ($CDCl_3$) δ -2.30.

Hydrolysis of the 209a: Hydrolysis of **209a** in a 1:1 mixture of THF:6N H_2SO_4 provided the known compund **10** [28b]. Hydrolysis reaction in a 1:1 mixture of THF:6N HCl quantatively provided the α-chloroketon 2-chloro-2-(4-methoxyphenyl)-1-phenylethanone **225**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 6.32 (1H, s), 6.89 (2H, m), 7.39-7.44 (4H, m), 7.5-7.56 (1H, m), 7.94 (2H, m).

3.2.1.2 Synthesis of Unsymmetrical Aryl-Alkyl Benzoins

3.2.1.2.1 General Procedure for the Synthesis of Unsymmetrical Aryl-Alkyl Benzoins

Reactions with KCN were carried out as for aryl-aryl benzoins. Reactions with TMSCN+CsF were done as follows: 20% (0.2 mmol) CsF were placed in 1 mL dry DMF. Upon this solution, 25% (0.25 mmol) TMSCN were added via syringe under nitrogen. Resulting mixture was stirred at room temperature for 30 min during which solution may colorize to yellow. After 30 min a solution of 1 mmol aroylphosphonate and 1.05 mmol acceptor aldehyde in 1 mL dry DMF were added to the above solution. Reaction's color instantly changes to brownish red. After 5 min. Reaction was quenched with 1 mL of water and immediately worked-up as usual. Products were purified by column chromatography with ether and petroleum ether mixtures.

1-Cyclohexyl-2-oxo-2-phenylethyl diethyl phosphate (209i): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.07-1.34 (11H ($2CH_3$ + 5H), m), 1.55-1.75 (5H, m), 1.91 (1H, m), 4.04-4.17 (4H, m), 5.38-5.41 (1H, m), 7.45-7.49 (2H, m), 7.56-7.60 (1H, m), 7.95 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, J=7.3 Hz), 15.9 (d, J=7.1 Hz), 25.5, 25.7, 25.8, 27.0, 29.1, 41.0 (d, J=7.0 Hz), 63.8 (2C, m), 82.1 (d, J=6.2 Hz), 128.4, 128.6, 133.3, 135.3, 196.5; ^{31}P NMR ($CDCl_3$) δ -0.76.

1-Cyclohexyl-2-(4-fluorophenyl)-2-oxoethyl diethyl phosphate (209j): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.05-1.25 (11H ($2CH_3$ + 5H), m), 1.50-1.70 (5H, m), 1.84 (1H, m), 3.98-4.10 (4H, m), 5.24-5.27 (1H, m), 7.06-7.10 (2H, m), 7.90-8.0 (2H, m).

1-Cyclohexyl-2-(4-methoxyphenyl)-2-oxoethyl diethyl phosphate (209k): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.14-1.32 (11H ($2CH_3$ + 5H), m), 1.61-1.92 (6H, m), 3.87 (3H, s), 4.04-4.16 (4H, m), 5.31-5.35 (1H, m), 6.94 (2H, d, J=8.9 Hz), 8.0 (2H, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.9 (2C, m), 25.6, 25.9, 27.4, 29.2, 41.2, 41.3, 55.4, 63.9 (2C, m), 82.0 (d, J=6.0 Hz), 114.0, 128.3, 131.0, 163.8, 195.0.

3-(Benzyloxy)-1-oxo-1-phenylpropan-2-yl diethyl phosphate (209l): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.1-1.23 (6H, m), 3.8-3.83 (2H, m), 3.96-4.09 (4H, m), 4.43-4.52 (2H, m), 5.74-5.79 (1H, m), 7.14-7.23 (5H, m), 7.36-7.41 (2H, m), 7.49-7.53 (1H, m), 7.86-7.89 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, J=2.76 Hz), 16.0 (d, J=2.79 Hz), 64.12 (d, J=6.0 Hz), 64.2 (d, J=6.0 Hz), 70.4 (d, J=6.1 Hz), 73.4, 77.9 (d, J=5.4 Hz), 127.6, 127.8, 128.3, 128.8, (d, J=3.0 Hz), 133.6, 134.9, 137.3, 194.8 (d, J=3.0 Hz).

3-(Benzyloxy)-1-(4-fluorophenyl)-1-oxopropan-2-yl diethyl phosphate (209m): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.15-1.25 (6H, m), 3.80-3.82 (2H, m), 3.95-4.08 (4H, m), 4.43-4.51 (2H, m), 5.64-5.68 (1H, m), 7.03-7.07 (2H, m), 7.14-7.25 (5H, m), 7.92-7.95 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, J=3.1 Hz), 15.9 (d, J=3.0 Hz), 64.1 (d, J=5.5 Hz), 64.2 (d, J=4.50 Hz), 70.2 (d, J=6.0 Hz), 73.4, 77.8 (d, J=5.3 Hz), 115.8 (d, J=21.9 Hz), 127.6, 127.8, 128.3, 131.3 (d, J=2.8 Hz), 131.6 (d, J=9.6 Hz), 137.2, 166.0 (d, J=256.3), 193.5 (d, J=3.3 Hz); ^{31}P NMR ($CDCl_3$) δ -2.24.

3-(Benzyloxy)-1-(4-methoxyphenyl)-1-oxopropan-2-yl diethyl phosphate (209n): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.15-1.25 (6H, m), 3.75-3.81 (5H (OMe + 2H), m), 3.97-4.09 (4H, m), 4.45-4.52 (2H, m), 5.68-5.75 (1H, m), 6.85 (2H, d, J=8.9 Hz), 7.15-7.24 (5H, m), 7.87 (2H, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.9, 16.1, 55.5, 70.5, 70.6, 73.3, 77.5 (d, J=5.9 Hz), 113.9, 127.6, 127.7, 128.3, 131.2, 137.4, 164.0, 192.9 (d, J=2.7 Hz); ^{31}P NMR ($CDCl_3$) δ -2.24.

3.2.1.3 Synthesis of Unsymmetrical Alkyl-Aryl Benzoins

3.2.1.3.1 General Procedure for Synthesis of Unsymmetrical Alkyl-Aryl Benzoins

30% (0.3 mmol) KCN and 20% (0.2 mmol) 18-crown-6 were placed in a round bottom flask and 5 ml dried toluene was added via syringe. 1 mmol aliphatic acylphosphonate and 2 mmol aromatic aldehyde was added onto the reaction mixture under inert atmosphere. Reaction mixture was heated to 100°C and reaction monitored by TLC or NMR (4-8 h). After completion (TLC or NMR monitoring),

reaction mixture was diluted with 15 mL ether and worked up as aryl-aryl reactions. Column chromatography provided partially pufiried (~90%) unsymmetrical benzoins.

Diethyl 3-methyl-2-oxo-1-phenylbutyl phosphate (209o): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, d, J=6.8 Hz), 1.07 (3H, d, J=6.8 Hz), 1.16 (3H, dt, J=1.0, 6.9 Hz), 1.34 (3H, dt, J=1.0, 7.0 Hz), 2.77 (1H, m), 3.84-3.94 (2H, m), 4.09-4.23 (2H, m), 5.77 (1H, d, J=8.2 Hz), 7.31-7.40 (5H, m).

Diethyl 1-(4-fluorophenyl)-3-methyl-2-oxobutyl phosphate (209p): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, d, J=6.8 Hz), 1.05 (3H, d, J=6.8 Hz), 1.17 (3H, t, J=7.2 Hz), 1.34 (3H, t, J=7.2 Hz), 2.80 (1H, m), 3.87-3.96 (2H, m), 4.10-4.23 (2H, m), 5.80 (1H, d, J=8.2 Hz), 7.04-7.10 (2H, m), 7.37-7.43 (2H, m).

2-Cyclohexyl-2-oxo-1-phenylethyl diethyl phosphate (209s): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, dt, J=0.9, 7.2 Hz), 1.34 (3H, dt, J=0.9, 6.9 Hz), 1.10-1.45 (5H, m), 1.60-1.83 (5H, m), 2.50 (1H, m), 3.84-3.94 (2H, m), 4.11-4.21 (2H, m), 5.75 (1H, d, J=8.1 Hz), 7.30-7.40 (5H, m).

3.2.1.4 Reactions of Acylphosphonates with Ketones

Reaction between **202a** and **231** were carried out exactly as in aryl-aryl benzoins.

Diethyl 3,3,3-trifluoro-1-oxo-1,2-diphenylpropan-2-yl phosphate (232): white crystal, mp: 94.9-95.3°C; ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, dt, J=1.0, 7.1 Hz), 1.20 (3H, dt, J=1.0, 7.1 Hz), 3.61-3.78 (2H, m), 3.93-4.09 (2H, m), 7.15-7.21 (2H, m), 7.32-7.37 (4H, m), 7.45-7.55 (2H, m), 7.60-7.63 (2H,m); ^{13}C NMR ($CDCl_3$) δ 15.7 (d, J=3.7 Hz), 15.8 (d, J=3.8 Hz), 64.2 (d, J=6.1 Hz), 64.7 (d, J=6.1 Hz), 86.3 (d, J=28 Hz), 125.0 (q, J=287 Hz), 126.4, 128.0, 128.9, 130.0, 130.3, 132.1 (d, J=10.4 Hz), 133.0, 134.0, 189.6; ^{31}P NMR ($CDCl_3$) δ -6.38.

3.2.2 Protonation of Acyl Anion Equivalents

3.2.2.1 General Procedure for Protonation Acyl Anion Equivalents

To a solution of 1M ether solution of acylphosphonate was added 1.1 M aqueous KCN solution at once. After completion of the reaction (<5 min), mixture diluted with 5 mL ether and 5 mL water. Organic phase separated and washes with brine solution. Organic phase was filtered and dried with $MgSO_4$ and evaporated under reduced pressure. Reactions carried out in this way provided pure protonation products **205** without need for further purification.

Cyano(4-fluorophenyl)methyl diethyl phosphate (205b): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, dt, J=1.0, 7.1 Hz), 1.38 (3H, dt, J=1.0, 7.1 Hz), 3.94-4.01 (2H, m), 4.15-4.25 (2H, m), 6.04 (1H, d, J=8.9 Hz), 7.11-7.17 (2H, m), 7.53-7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, J=6.5 Hz), 15.9 (d, J=6.6 Hz), 64.6 (d, J=6.1 Hz), 64.9 (d, J=6.1 Hz), 65.7 (d, J=4.4 Hz), 116.0 (d, J=6.2 Hz), 116.4 (d, J=22.2 Hz), 128.6 (m), 129.7 (d, J=8.8 Hz), 163.8 (d, J=251.6 Hz); ^{31}P NMR ($CDCl_3$) δ -2.17.

Cyano(4-methoxyphenyl)methyl diethyl phosphate (205c): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J=7.3 Hz), 1.38 (3H, t, J=7.2 Hz), 3.84 (3H, s), 3.94-4.04 (2H, m), 4.09-4.27 (2H, m), 6.00 (1H, d, J=8.6 Hz), 6.95 (2H, d, J=8.7 Hz), 7.49 (2H, d, J=8.7 Hz).

Cyano(cyclohexyl)methyl diethyl phosphate (205d): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 1.06-1.25 (5H, m), 1.29-1.36 (6H, m), 1.60-1.90 (6H, m), 4.06-4.25 (4H, m), 4.72 (1H, dd, J=5.8, 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 16.0 (2C, m), 25.20, 25.24, 25.7, 27.4, 27.7, 41.5 (d, J=5.7 Hz), 64.7 (2C, m), 69.4 (d, J=6.1 Hz), 116.1 (d, J=2.8 Hz); ^{31}P NMR ($CDCl_3$) δ -2.41.

242: Protonation product provided a complex NMR resulting from restricted rotation of the protection group. NMR data in DMSO at different temperatures can be found in Figure 159-160 (Appendix A). ^{1}H NMR ($CDCl_3$) δ 1.10-1.40 (6H, m), 1.65-2.65

(4H, m), 3.33-3.55 (2H, m), 3.91-4.22 (4H, m), 4.96-5.15 (2H, m), 5.28 (0.4 H, m), 5.50-5.56 (0.6 H, m), 7.20-7.35 (5H, m); ^{31}P NMR (DMSO) δ -2.17, -2.05, -1.65.

3.2.3 Uncatalyzed Addition of TMSCN to Acylphosphonates

3.2.3.1 General Procedure for TMSCN Addition

1 mmol acylphosphonate was dissolved in 1 mL toluene and 1.2 mmol (1.2 equiv) of TMSCN was slowly added via syringe. After completion of the reaction (15-30 min), reaction mixture concentrated under vacuum and (if needed) purified by column chromatography (ether eluent) to obatin **226**. Reaction can be carried out on 5 mmol scale without loss of efficiency. Reaction is considerably exothermic and care should be taken at large scale experiments.

Diethyl cyano(trimethylsilyloxy)(phenyl)methylphosphonate (226a): white solid; ^{1}H NMR ($CDCl_3$) δ 0.19 (9H, s), 1.22 (3H, dt, J=0.6, 7.1 Hz), 1.35 (3H, t, J=7.1, 0.5 Hz), 3.90-4.00 (1H, m), 4.02-4.13 (1H, m), 4.17-4.28 (2H, m), 7.37-7.45 (3H, m), 7.66-7.71 (2H, m); ^{13}C NMR ($CDCl_3$) δ 0.98, 16.2 (d, J=5.2 Hz), 16.4 (d, J=5.9 Hz), 64.8 (d, J=7.4 Hz), 65.4 (d, J=7.2 Hz), 73.1 (d, J=176.5 Hz), 117.9, 126.9 (d, J=4.5 Hz), 128.4 (d, J=2.2 Hz), 129.5 (d, J=3.3 Hz), 134.5 (d, J=3.6 Hz); ^{31}P NMR ($CDCl_3$) δ 11.3.

Diethyl cyano(silyloxy)(4-fluorophenyl)methylphosphonate (226b): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 0.19 (9H, s), 1.23 (3H, t, J=7.1 Hz), 1.35 (3H, t, J=7.39 Hz), 3.95-4.03 (1H, m), 4.05-4.14 (1H, m), 4.17-4.28 (2H, m), 7.08-7.13 (2H, m), 7.64-7.68 (2H, m); ^{13}C NMR ($CDCl_3$) δ 0.96, 16.2 (d, J=5.3 Hz), 16.4 (d, J=5.3 Hz), 64.8 (d, J=7.4 Hz), 65.5 (d, J=7.4 Hz), 72.4 (d, J=178 Hz), 115.4 (dd, J=1.7, 21.1 Hz), 117.7, 128.8 (dd, J=4.0, 8.5 Hz), 130.5 (m), 163.3 (dd, J=2.8, 250 Hz); ^{31}P NMR ($CDCl_3$) δ 11.1.

Diethyl cyano(silyloxy)(4-methoxyphenyl)methylphosphonate (226c): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 0.18 (9H, s), 1.21 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz),

3.83 (3H, s), 3.86-3.97 (1H, m), 3.90-4.11 (1H, m), 4.17-4.31 (2H, m), 6.91 (2H, m), 7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 1.0, 16.2 (d, J=5.2 Hz), 16.4 (d, J=5.6 Hz), 55.3, 64.7 (d, J=7.4 Hz), 65.3 (d, J=7.2 Hz), 72.7 (d, J=179 Hz), 113.7 (d, J=1.9 Hz), 118.0, 126.2 (d, J=3.7 Hz), 128.3 (d, J=4.7 Hz), 160.5 (d, J=2.3 Hz) ; ^{31}P NMR ($CDCl_3$) δ 11.4.

Diethyl cyano(silyloxy)(cyclohexyl)methylphosphonate (226d): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 0.3 (9H, s), 1.16-1.30 (5H, m), 1.40 (6H, m), 1.68-1.71 (1H, m), 1.84-2.07 (5H, m), 4.15-4.33 (4H, m); ^{13}C NMR ($CDCl_3$) δ 1.3, 16.4 (2C, m), 25.8, 26.0, 27.1 (d, J=5.8 Hz), 27.7 (d, J=3.7 Hz), 30.8, 45.2, 65.3 (d, J=7.4 Hz), 64.5 (d, J=7.5 Hz), 74.4 (d, J=175.5 Hz), 117.4 (d, J=2.4 Hz); ^{31}P NMR ($CDCl_3$) δ 14.0.

Diethyl cyano(silyloxy)(isopropyl)methylphosphonate (226e): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 0.29 (9H, s), 1.10 (3H, d, J=6.7 Hz), 1.15 (3H, d, J=6.8 Hz), 1.35-1.41 (6H, m), 2.14-2.29 (1H, m), 4.19-4.30 (4H, m); ^{13}C NMR ($CDCl_3$) δ 1.4, 16.5 (2C, m), 17.6 (d, J=6.3 Hz), 18.0 (d, J=3.7 Hz), 36.1, 64.2 (d, J=7.2 Hz), 64.3 (d, J=7.5 Hz), 74.6 (d, J=176 Hz), 117.0 (d, J=3.4 Hz); ^{31}P NMR ($CDCl_3$) δ 14.20.

Diethyl cyano(silyloxy)(methyl)methylphosphonate (226f): colorless liq.; ^{1}H NMR ($CDCl_3$) δ 0.27 (9H, s), 1.31-1.40 (6H, m), 1.74 (3H, d, J=14.9 Hz), 4.18-4.29 (4H, m); ^{13}C NMR ($CDCl_3$) δ 1.30, 16.4 (2C, m), 24.8, 64.3 (d, J=7.2 Hz), 64.8 (d, J=7.3 Hz), 66.6 (d, J=182.5), 118.4; ^{31}P NMR ($CDCl_3$) δ 13.71.

226g: This product presents a complex spectrum due to restricted rotation of the protecting group. A room temperature NMR ($CDCl_3$) can be seen in Figure 152 (appendix A).

3.2.3.2 General Procedure for Hydrolysis of 226

1 mmol **226a** was dissolved in 1 mL THF and 1 mL 1N HCl was slowly added onto the mixture. After completion of the reaction (TLC, ~15 min.), Reaction was diluted

with ether and washed with brine to obtain pure hydrolysis product **235a** quantatively.

Diethyl cyano(hydroxy)(phenyl)methylphosphonate (235a): white solid; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, J=7.1 Hz), 1.28 (3H, t, J=7.1 Hz), 3.96-4.20 (4H, m), 4.90 (1H, broad s), 7.32-7.42 (3H, m), 7.61-7.64 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.2 (2C, m), 65.6 (d, J=7.8 Hz), 65.8 (d, J=7.3 Hz), 71.0 (d, J=166.6 Hz), 117.8 (d, J=3.1 Hz), 126.3 (d, J=3.8 Hz), 128.4 (d, J=2.3 Hz), 129.4 (d, J=3.1 Hz), 133.6 (d, J=4.7 Hz); ^{31}P NMR ($CDCl_3$) δ 12.04.

3.2.4 Proline Catalyzed Enamine Nucleophiles in Reactions with Acylphosphonates

3.2.4.1 Acylphosphonates as Electrophiles

3.2.4.1.1 General Procedure for Reactions Between Ketones and Acylphosphonates

4 mmol ketone **248** and 30% (L)-Proline **249** was dissolved in 1 mL DMSO and stirred for 15 min prior to addition of 1 mmol acylphosphonate **202**. Reaction was monitores by TLC and after completion (4-5h for **248a** and 72h for **248b**) mixture was diluted with EtOAc. Organic phase washed with brine, separated, filtered and dried over $MgSO_4$. Products can be purified further if desired by eluting with ether from silica gel to obtain **250**.

Diethyl 1-hydroxy-3-oxo-1-phenylbutylphosphonate (250a): white solid; ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, t, J=7.1 Hz), 1.31 (3H, t, J=7.1 Hz), 2.14 (3H, s), 3.33-3.36 (2H, m), 3.66-3.70 (1H, m), 3.83-3.90 (1H, m), 4.11-4.18 (2H, m), 5.04 (1H exchangable, d, J=18.3 Hz), 7.26-7.30 (1H, m), 7.34-7.38 (2H, m), 7.60-7.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J=5.8 Hz), 16.4 (d, J=5.9 Hz), 32.1 (d, J=2.4 Hz), 47.7 (d, J=3.1 Hz), 63.5 (d, J=7.6 Hz), 63.8 (d, J=7.3 Hz), 75.4 (d, J=167 Hz), 125.9 (d, J=4.7 Hz),

127.7 (d, J=2.8 hz), 128.2 (d, J=2.3 Hz), 139.5, 209.7 (d, J=12.2 Hz); ^{31}P NMR ($CDCl_3$) δ 19.80.

Diethyl 1-(4-fluorophenyl)-1-hydroxy-3-oxobutylphosphonate (250b): white solid; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, t, J=7.1 Hz), 1.31 (3H, t, J=7.1 Hz), 2.14 (3H, s), 3.25-3.35 (2H, m), 3.69-3.75 (1H, m), 3.86-3.92 (1H, m), 4.09-4.19 (2H, m), 5.09 (1H exchangable, d, J=17.8 Hz), 7.02-7.07 (2H, m), 7.56-7.61 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J=5.1 Hz), 16.4 (d, J=5.20 Hz), 35.1 (d, J=2.1 Hz), 47.6 (d, J=3.2 Hz), 63.5 (d, J=7.6 Hz), 63.8 (d, J=7.4 Hz), 75.0 (d, J=167.9 Hz), 115.1 (dd, J=2.3, 20.9 Hz), 127.8 (m), 135.4 (d, J=2.5 Hz), 162.3 (dd, J=3.4, 248 Hz), 209.6 (d, J=12.3 Hz); ^{31}P NMR ($CDCl_3$) δ 19.53.

(250c): ^{1}H NMR of the crude product can be seen in Figure 167 (Appendix A). The regioselectivity was determined based on the lack of singlet -CH_3 at ~2 ppm and presence of triplet -CH_3 at ~1 ppm.

CHAPTER 4

CONCLUSION

This study can be divided in two parts. First one is the unsymmetrical benzoin synthesis by cyanide ion catalyzed cleavage of benzils. Second part is the development of acylphosphonates as new acyl anion precursors and their reactions.

Benzils were found to be useful in cross benzoin synthesis but there were some major drawbacks. These drawbacks limited the scope of the reaction to certain benzoin derivatives. Therefore we concluded that cyanide ion catalyzed cleavage of benzils provide very good results but does not provide a general solution as an acyl anion precursor.

Acylphosphonates were found to be providing a highly practical and flexible access to all isomers of cross benzoins except for alkyl-alkyl combination. However it is obvious that these precursors are quiet new and open to improvements. Therefore it is highly probable that synthesis of alkyl-alkyl cross benzoins will be possible after further investigations. The first intermolecular aldehyde-ketone coupling was accomplished but it was limited to higly reactive 2,2,2-Trifluoroacetophenone **231**. We also showed that protonation of acyl anion equivalents generated from acylphosphonates is possible albeit in low yields. We have also shown that TMSCN adds to acylphosphonates without need to a catalsyst and provide the corresponding cyanohydrins **226** in excellent yields. These products can be decomposed in the presence of CsF to generate the corresponding acylanion equivalents. We also investigated the reactions of acylphophonates as electrophiles against proline catalyzed enamine nucleophiles. This approach provided us quarternar α-hydroxyphosphonates in excellent yields.

In conclusion acylphosphonates were developed as a new generation of acyl anion precursors. These reagents are superior to acylsilanes in terms of easy availability. In fact one can synthesize any benzoin derivative in a few hours starting from acylchlorides without using any special apparatus or taking any special precautions. Presence of phosphonate moiety provides a useful platform for functionalization and thus opportunity for fine tuning of their reactivity. We believe that acylphosphonates will be a highly useful and original addition to the known methods of bond forming reactions via acyl anion equivalents.

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APPENDIX A

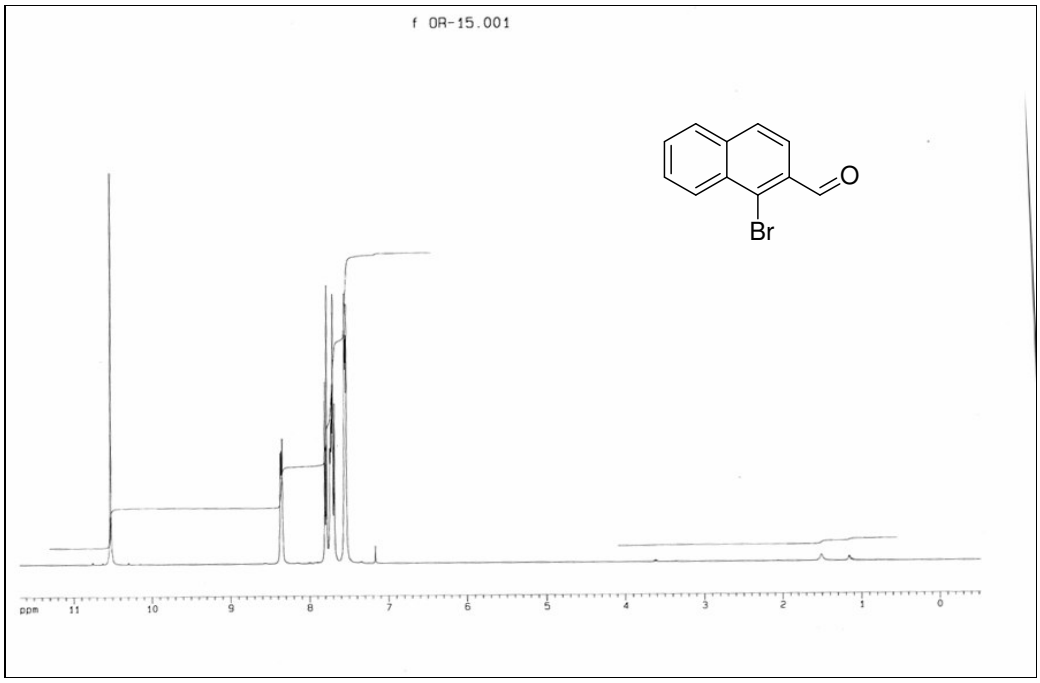

Figure 13. ^{1}H NMR spectrum of **168k**

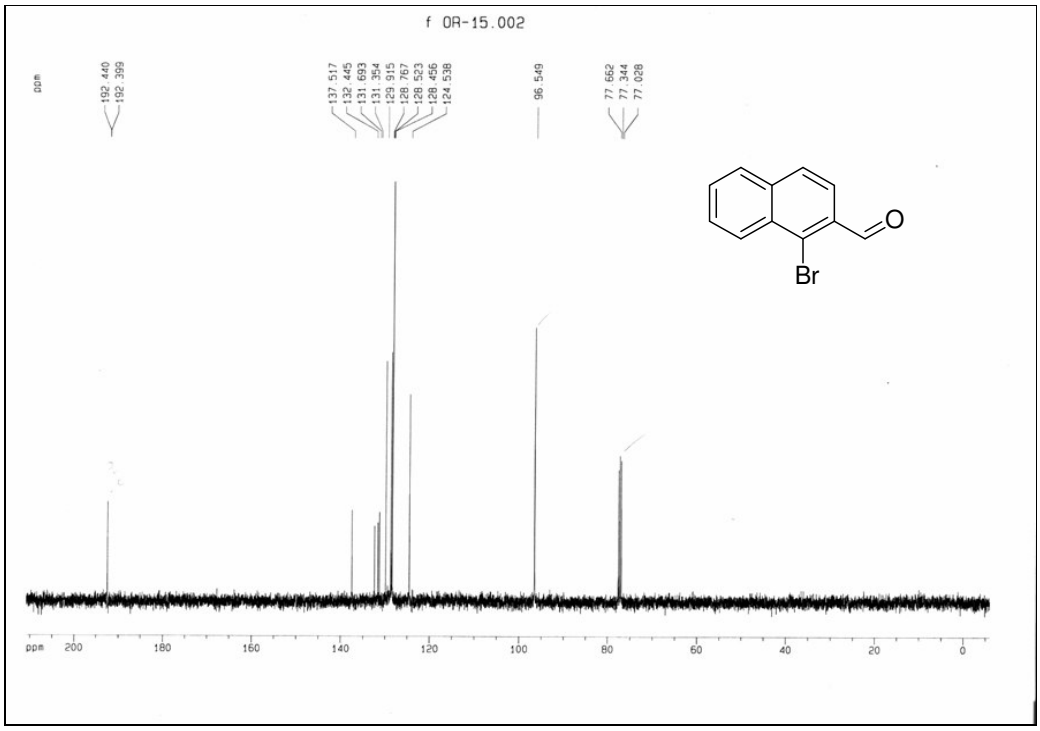

Figure 14. ^{13}C NMR spectrum of **168k**

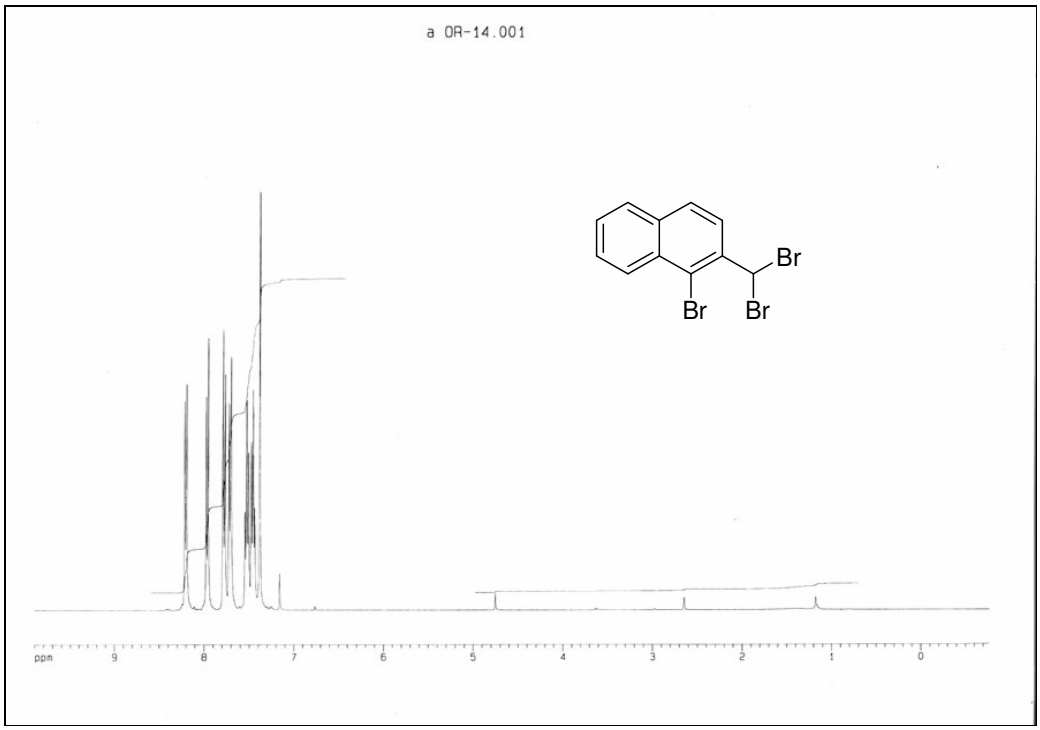

Figure 15. ^{1}H NMR spectrum of **168k2**

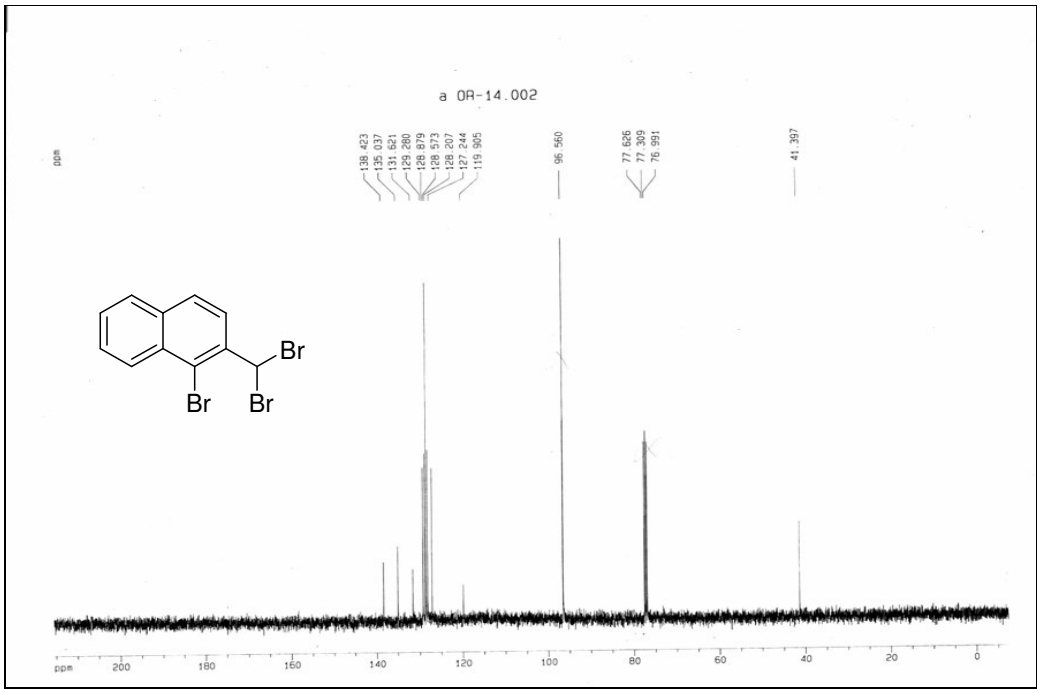

Figure 16. ^{13}C NMR spectrum of **168k2**

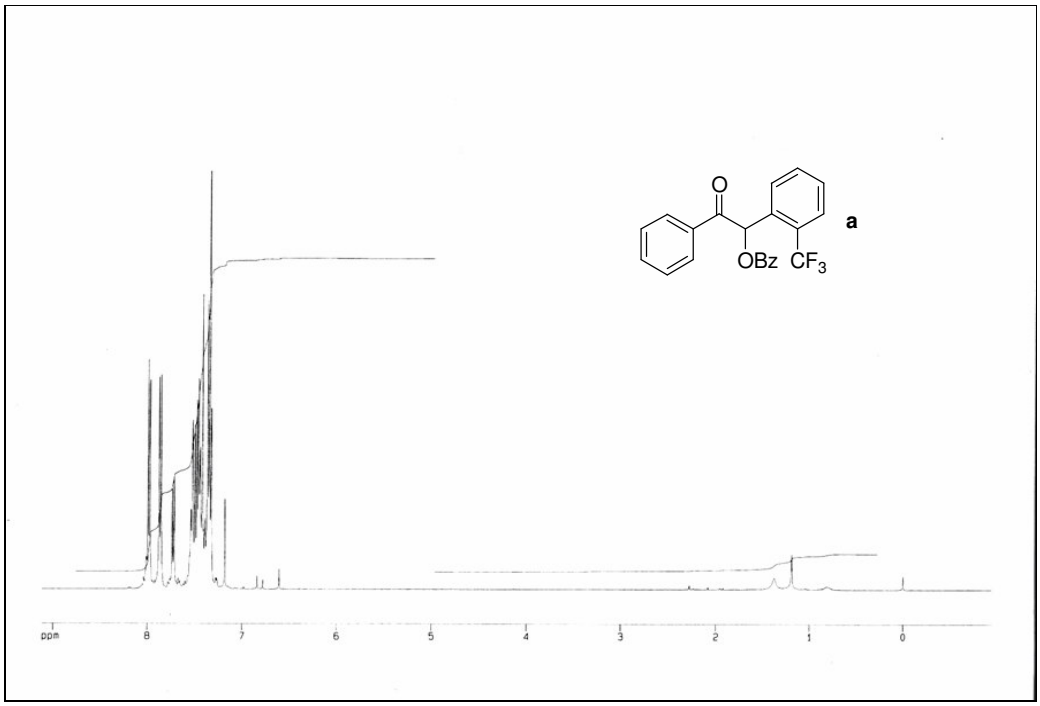

Figure 17. ^{1}H NMR spectrum of **171a**

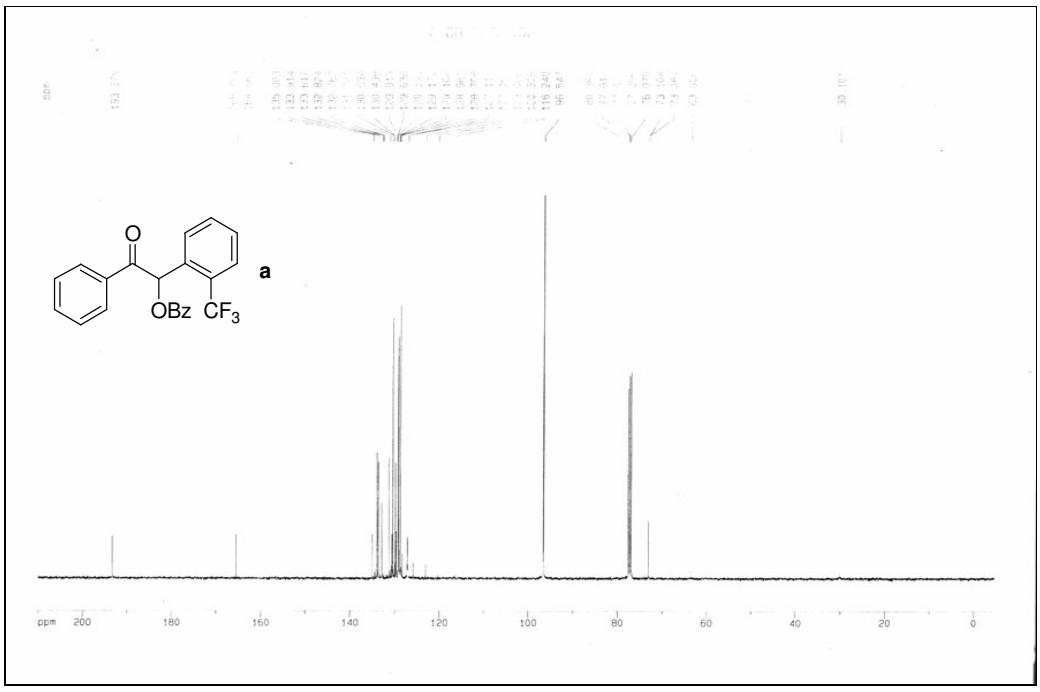

Figure 18. ^{13}C NMR spectrum of **171a**

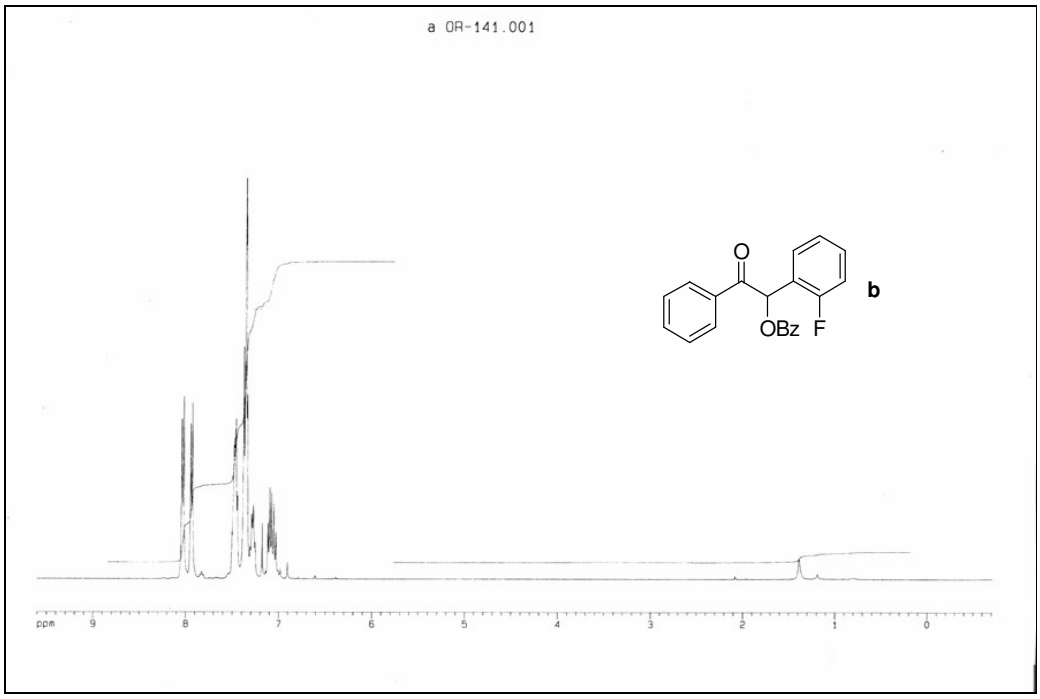

Figure 19. ^{1}H NMR spectrum of (**171b**)

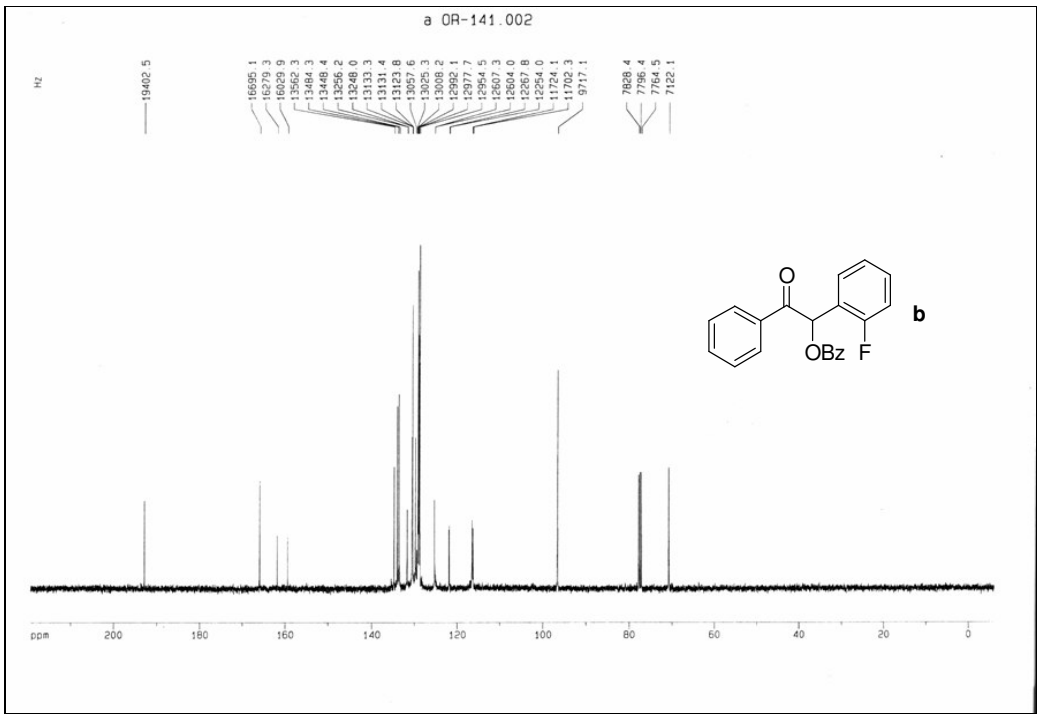

Figure 20. ^{13}C NMR spectrum of **171b**

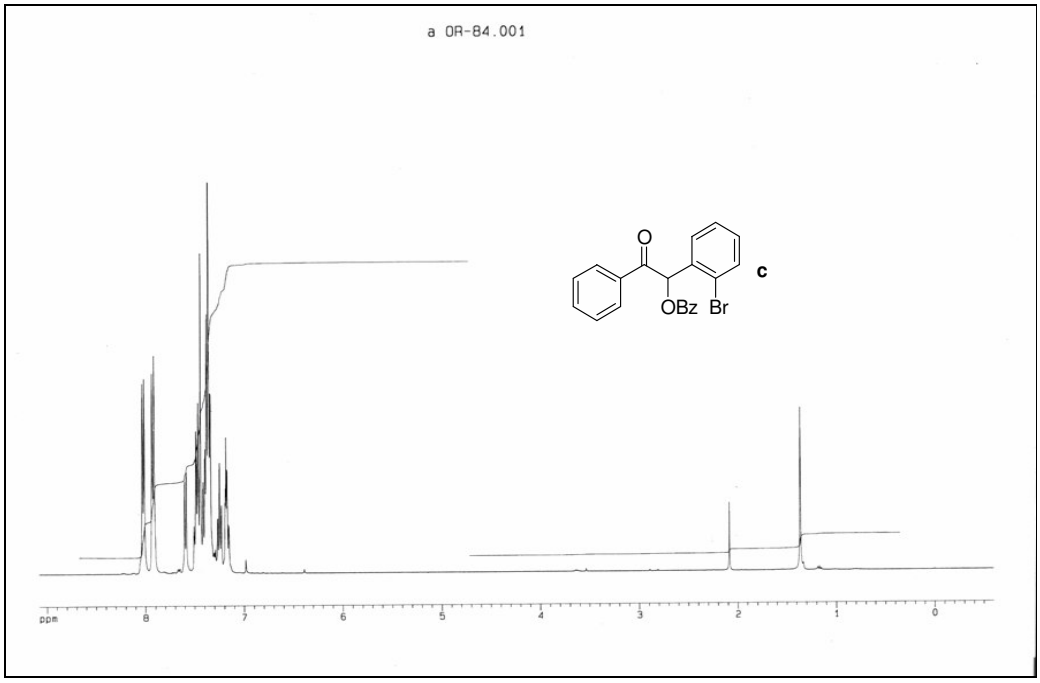

Figure 21. ^{1}H NMR spectrum of 171c

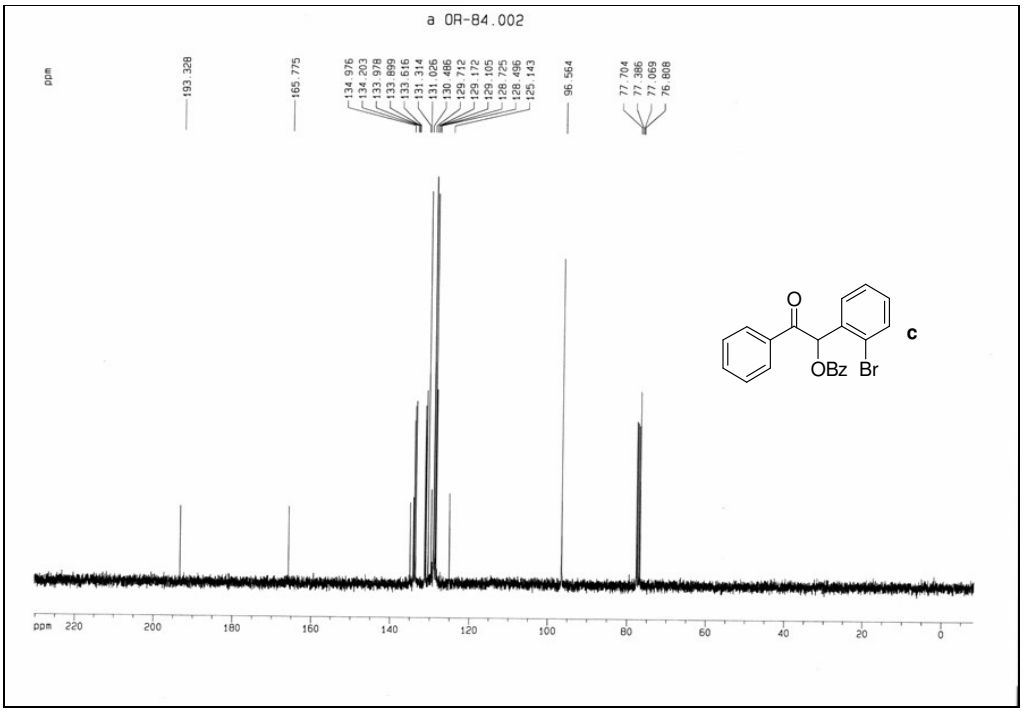

Figure 22. ^{13}C NMR spectrum of **171c**

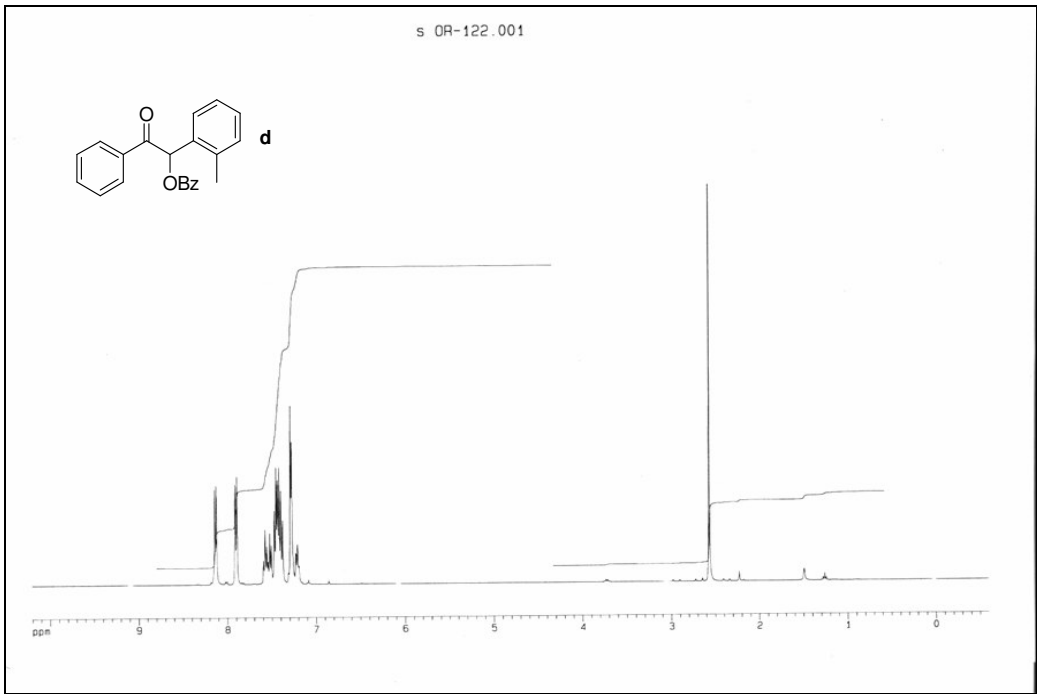

Figure 23. ^{1}H NMR spectrum of 171d

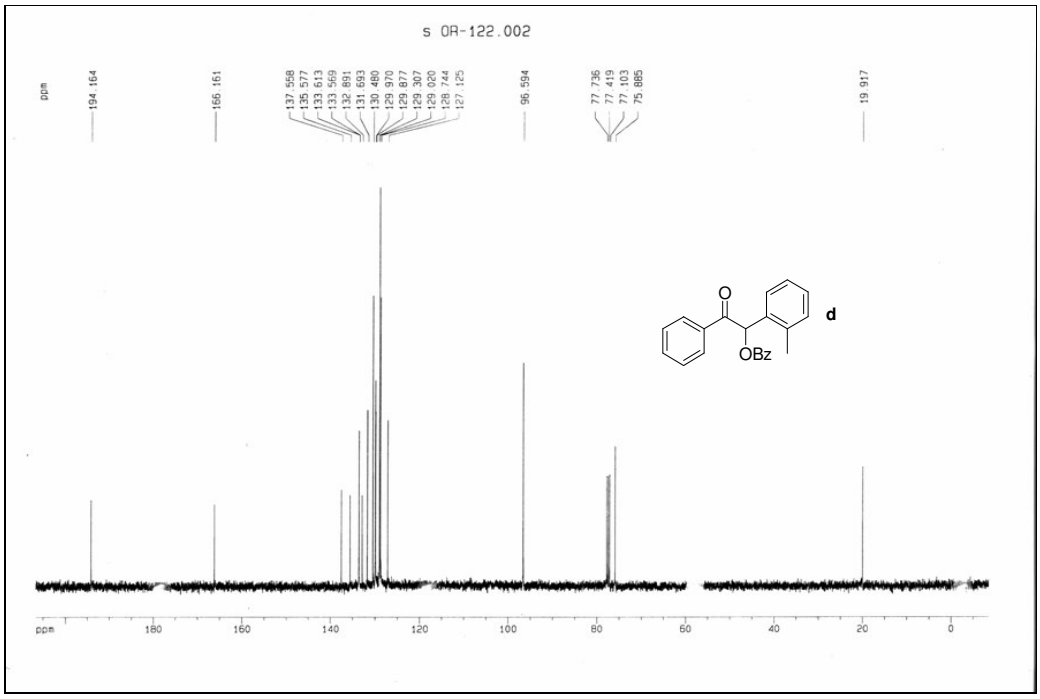

Figure 24. ^{13}C NMR spectrum of **171d**

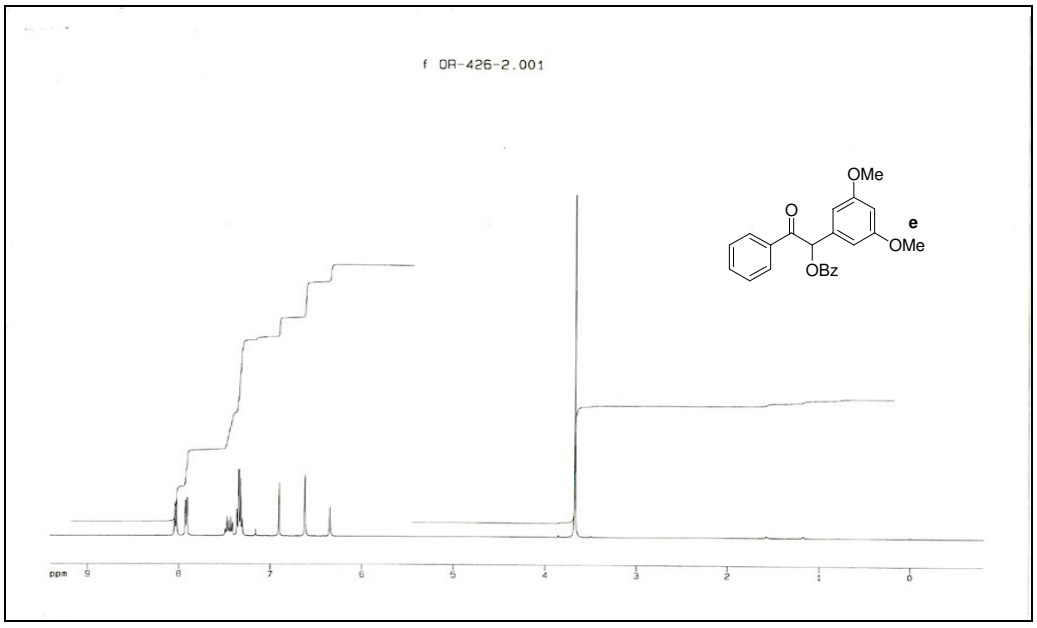

Figure 25. ^{1}H NMR spectrum of 171e

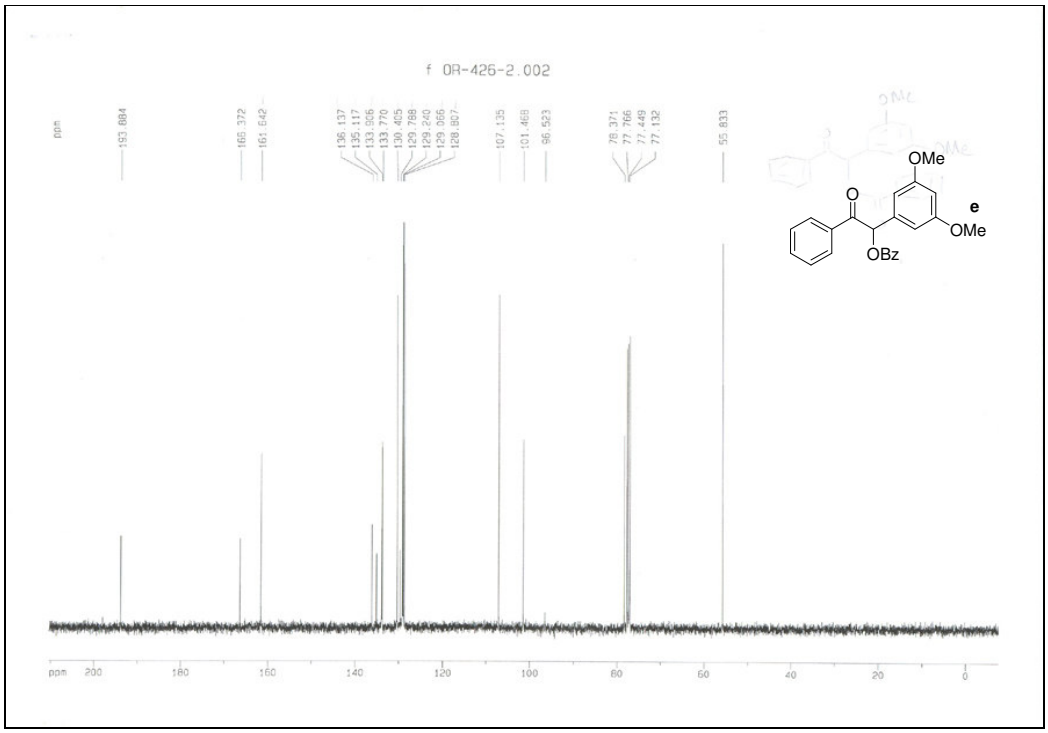

Figure 26. ^{13}C NMR spectrum of 171e

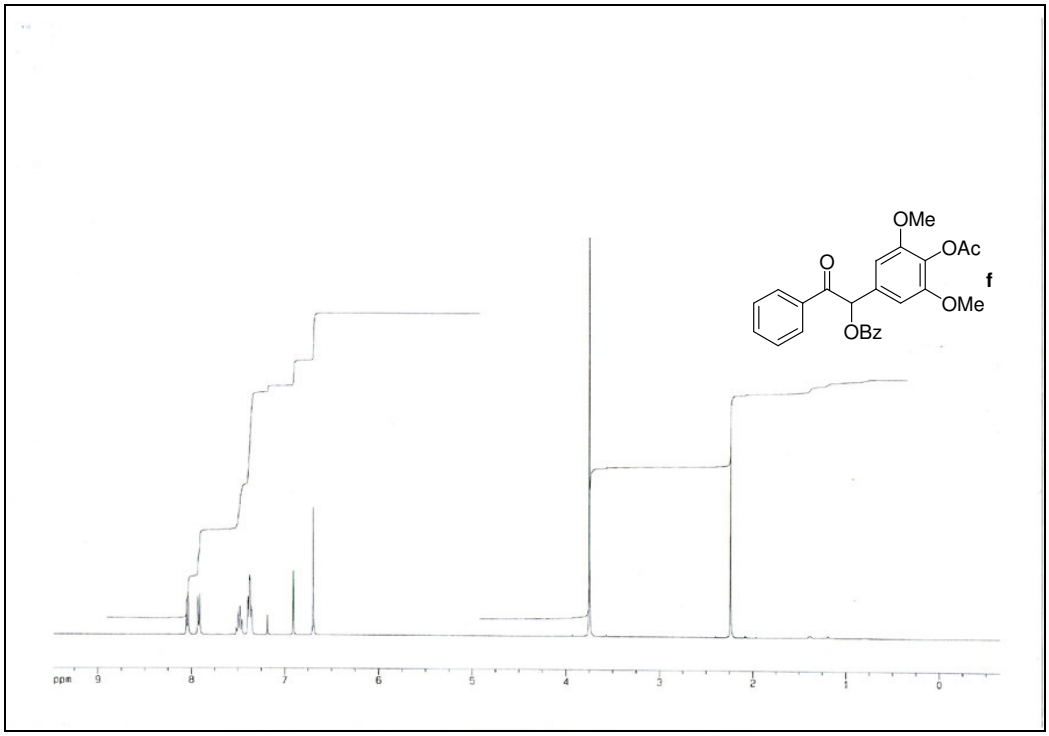

Figure 27. ^{1}H NMR spectrum of 171f

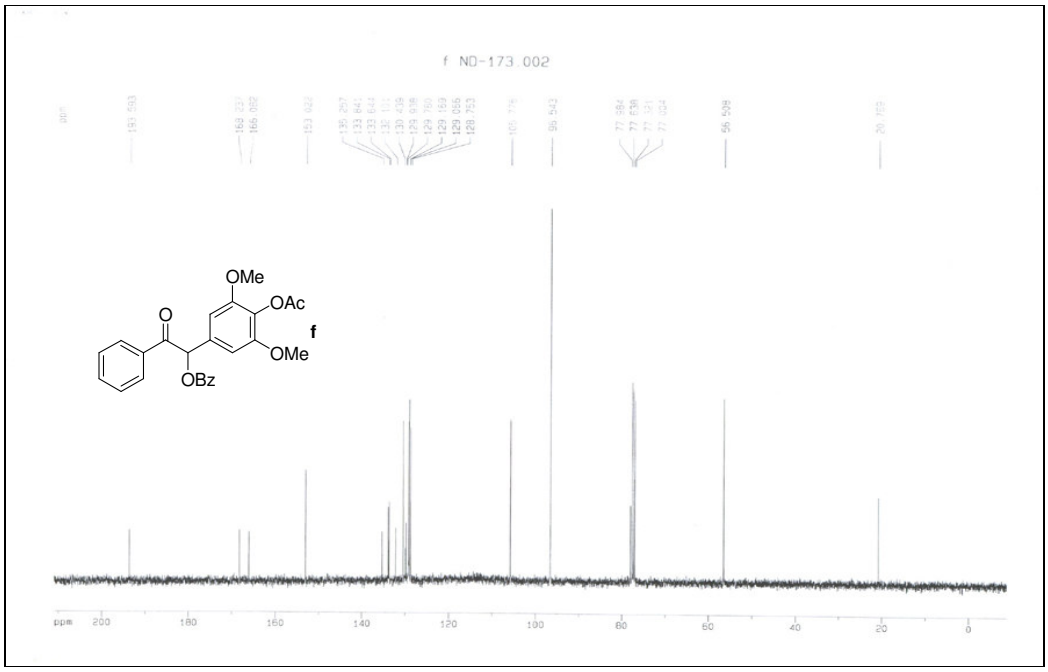

Figure 28. ^{13}C NMR spectrum of **171f**

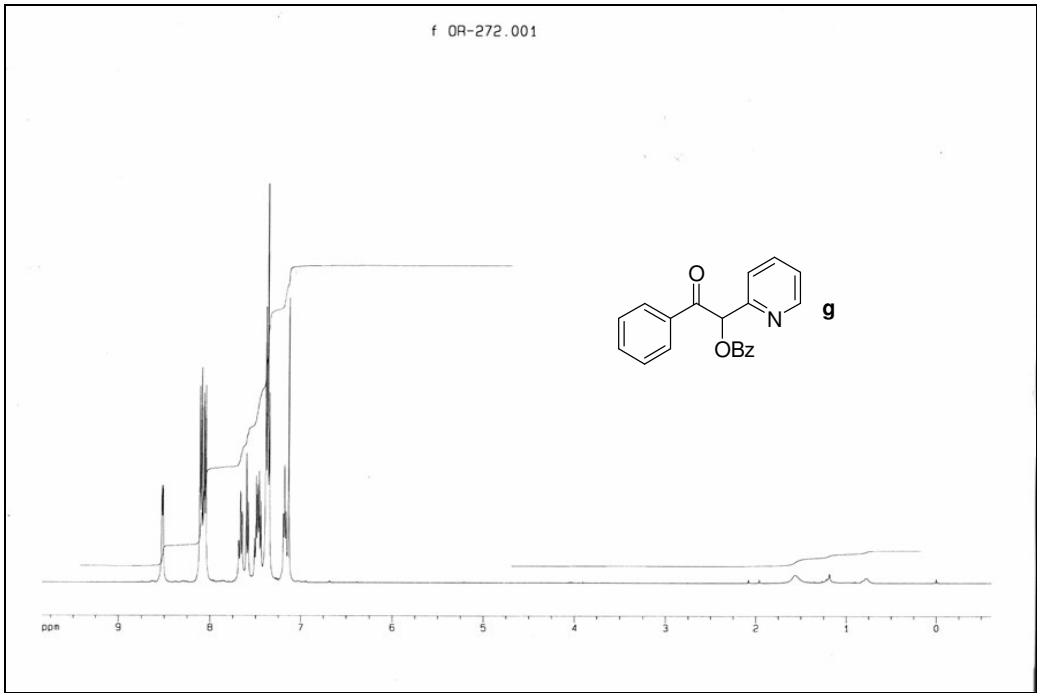

Figure 29. ^{1}H NMR spectrum of **171g**

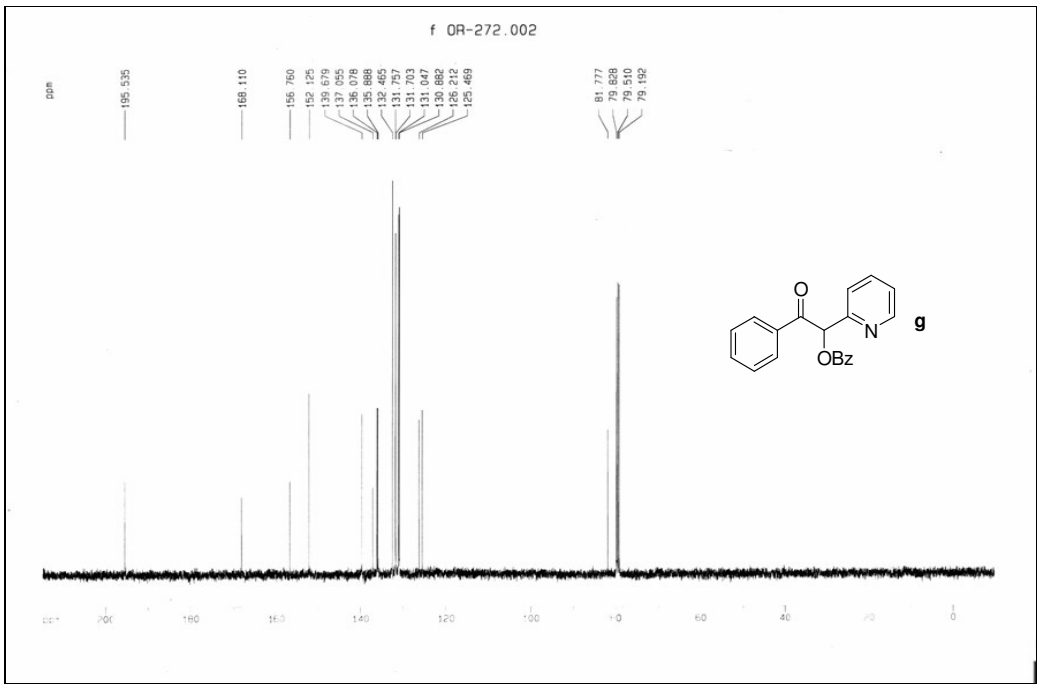

Figure 30. ^{13}C NMR spectrum of **171g**

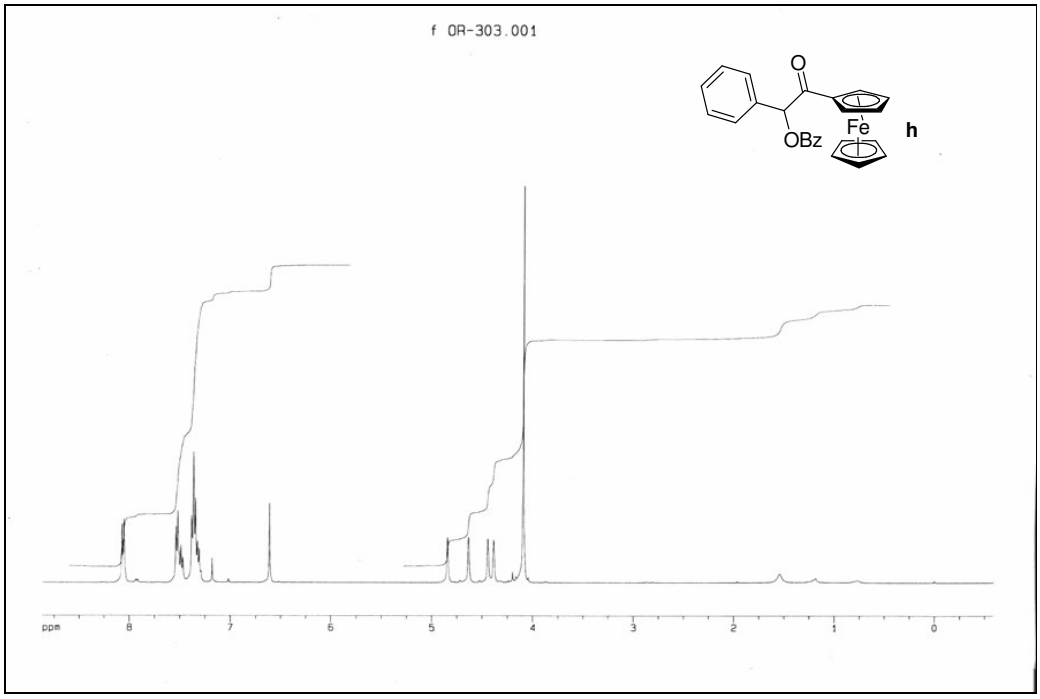

Figure 31. ^{1}H NMR spectrum of **171h**

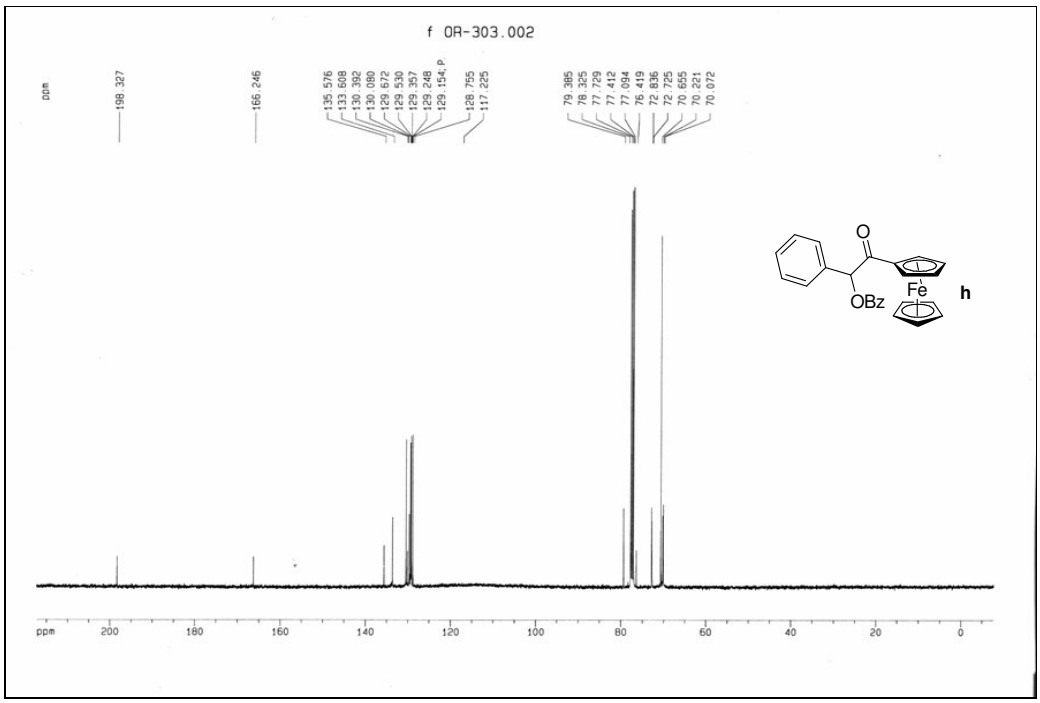

Figure 32. ^{13}C NMR spectrum of 171h

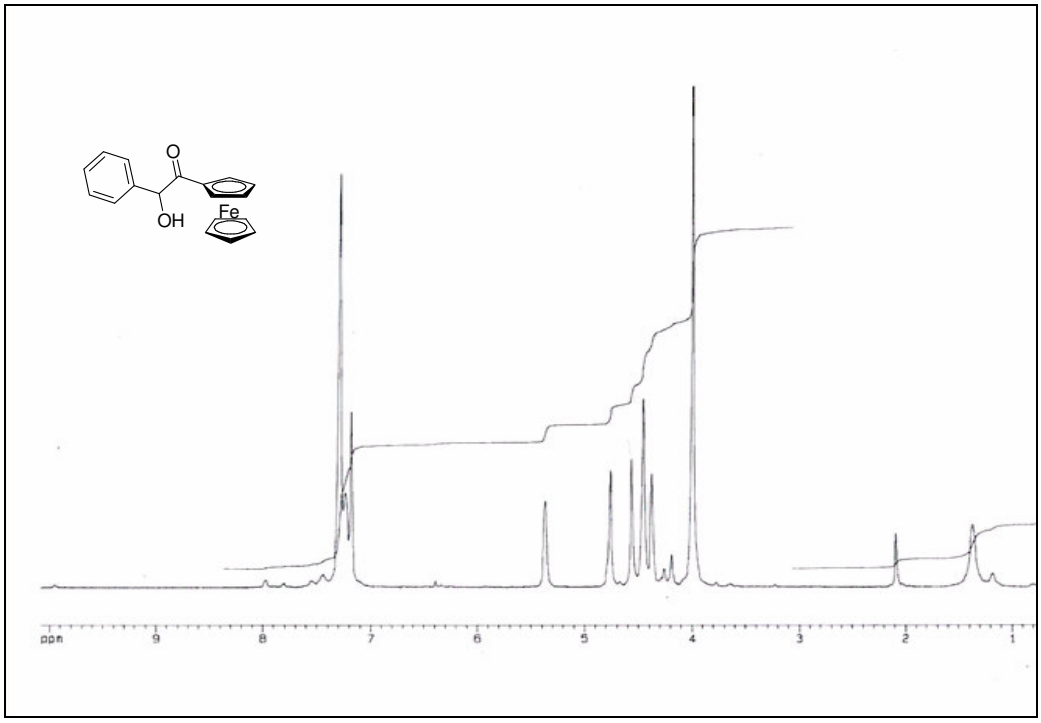

Figure 33. ^{1}H NMR spectrum of **174a**

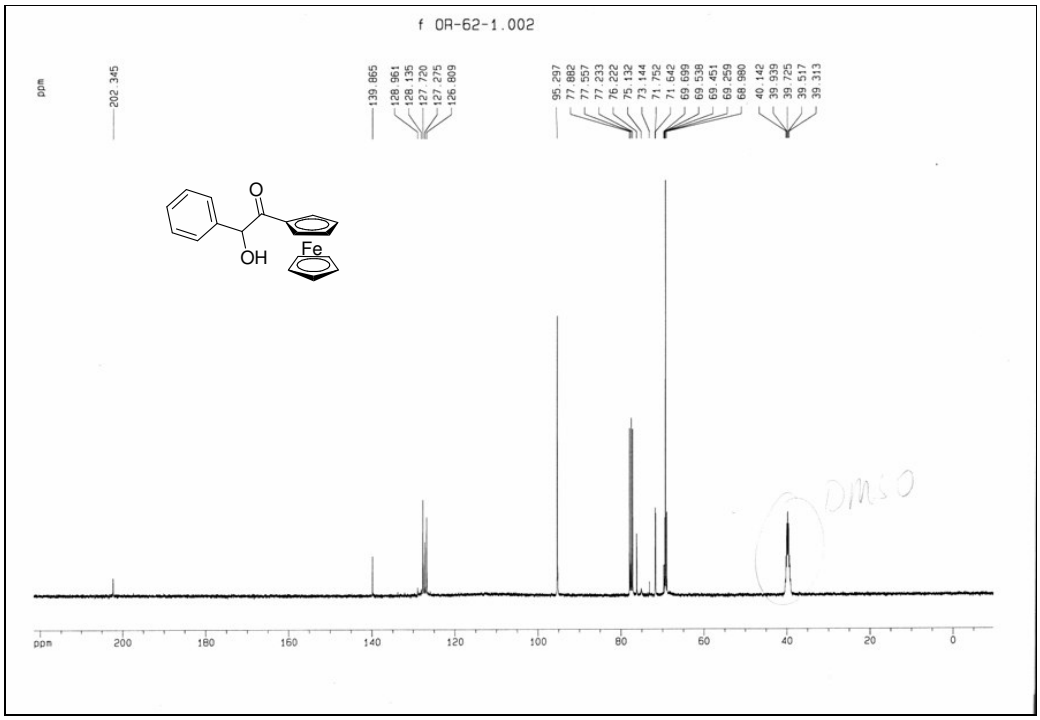

Figure 34. ^{13}C NMR spectrum of **174a**

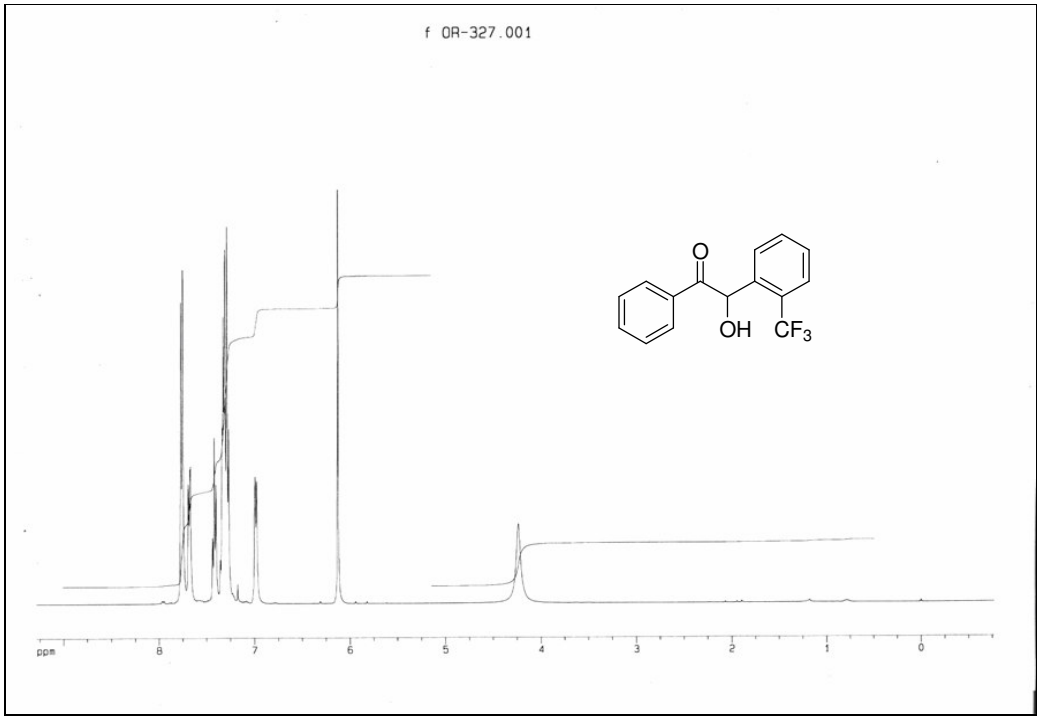

Figure 35. ^{1}H NMR spectrum of **174b**

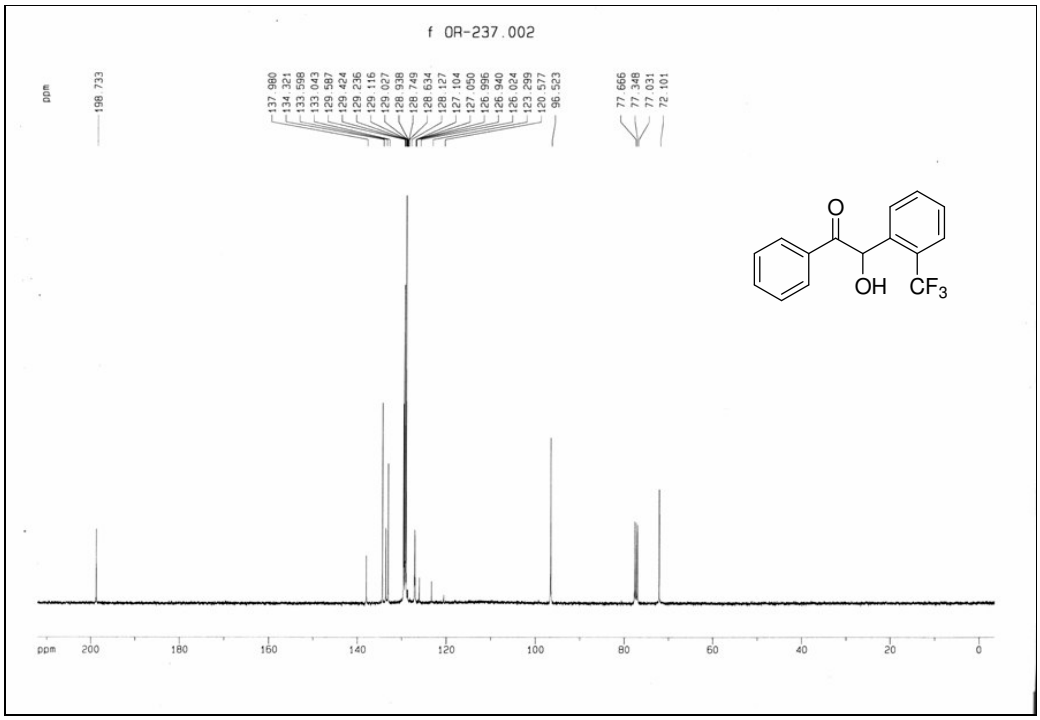

Figure 36. ^{13}C NMR spectrum of **174b**

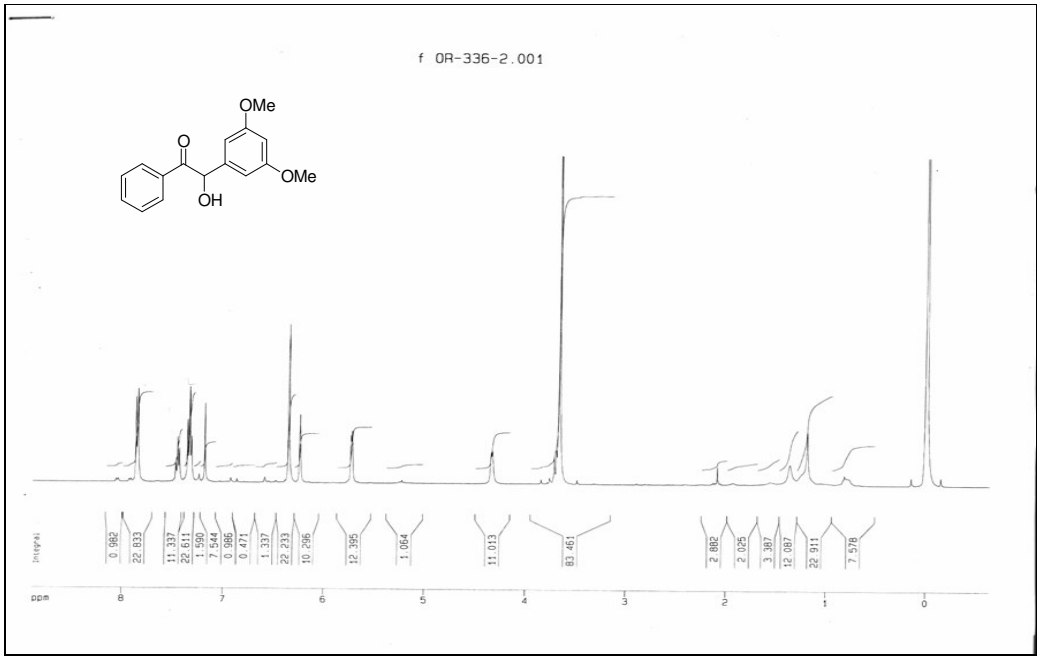

Figure 37. ^{1}H NMR spectrum of **174d**

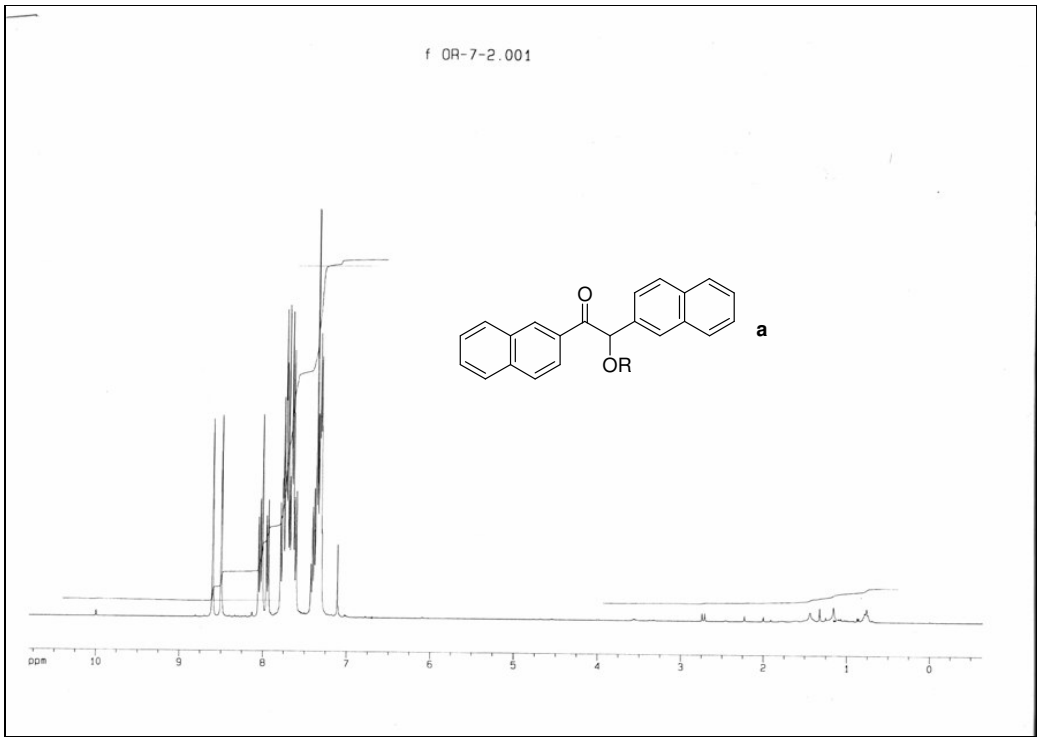

Figure 38. ^{1}**H NMR spectrum of 176a**

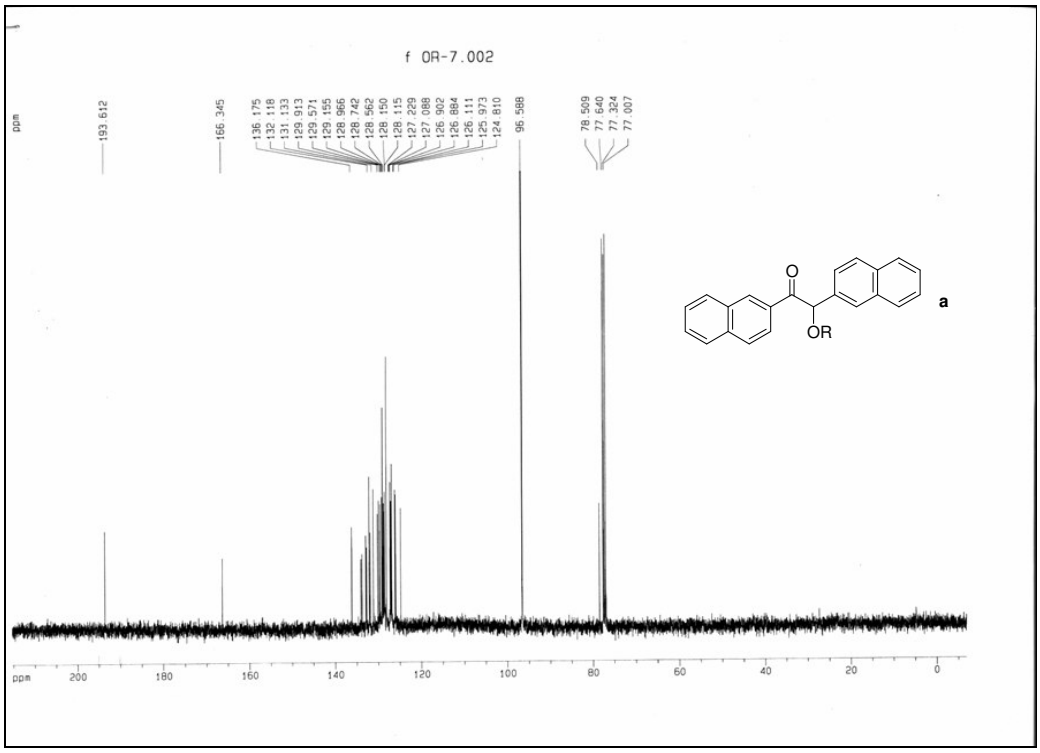

Figure 39. ^{13}C NMR spectrum of **176a**

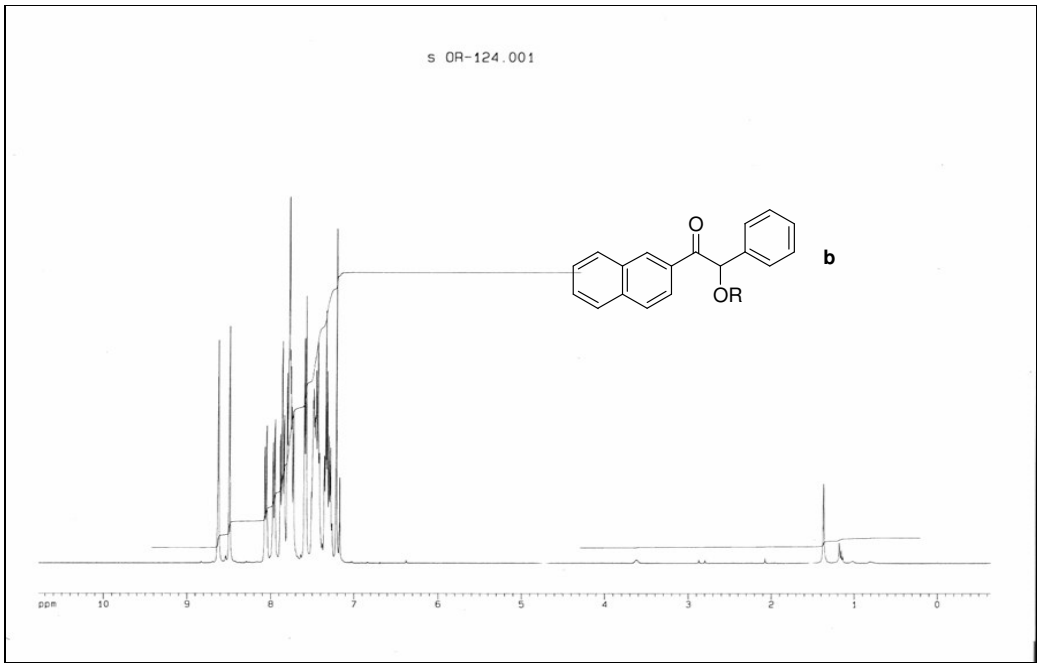

Figure 40. ^{1}H NMR spectrum of **176b**

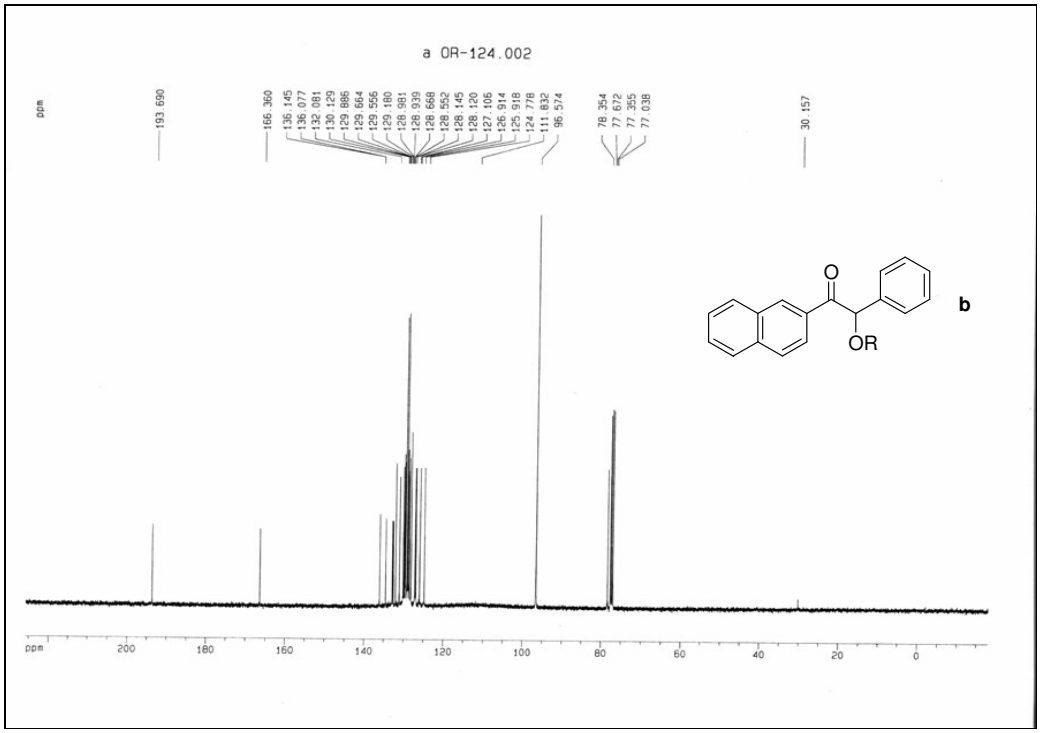

Figure 41. ^{13}C NMR spectrum of **176b**

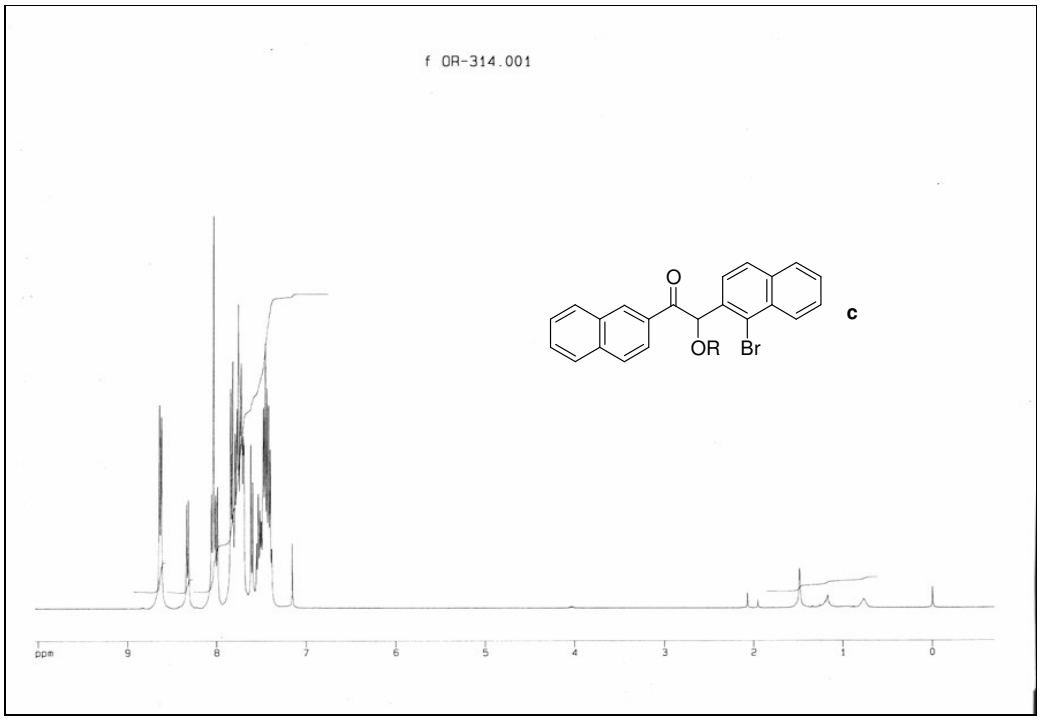

Figure 42. ^{1}H NMR spectrum of **176c**

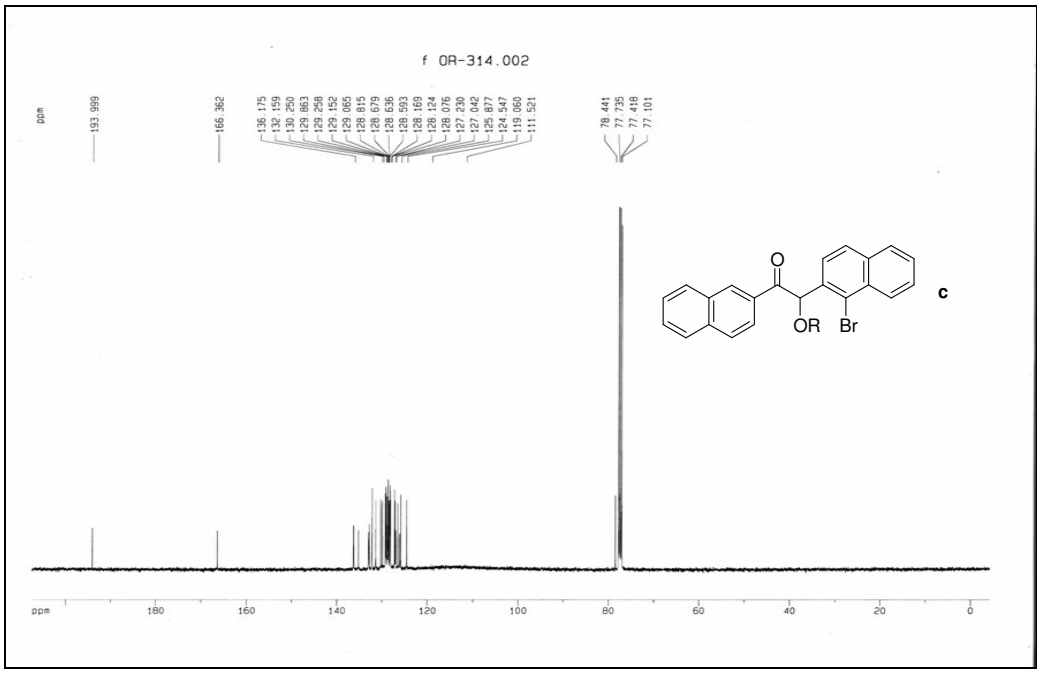

Figure 43. ^{13}C NMR spectrum of **176c**

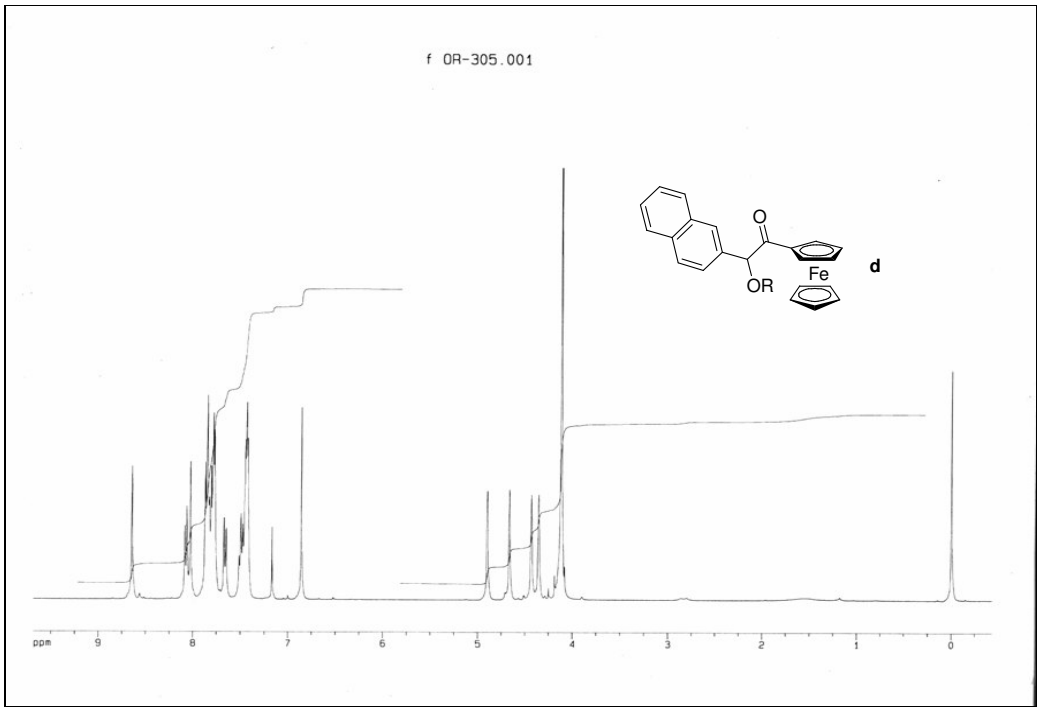

Figure 44. ^{1}H NMR spectrum of **176d**

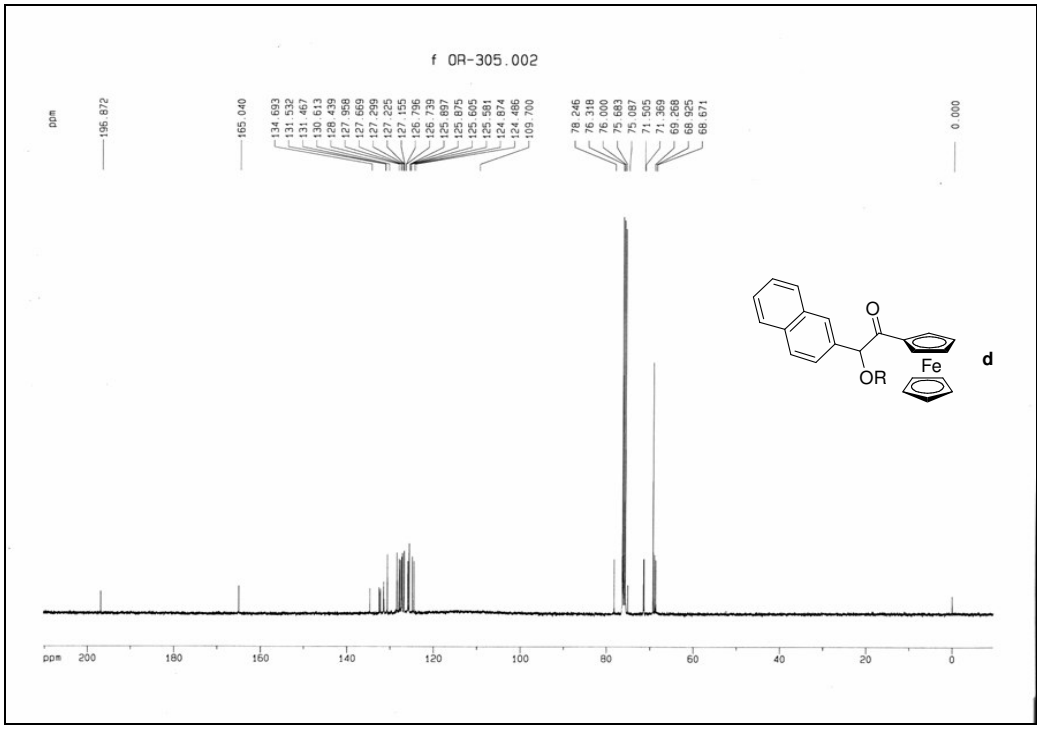

Figure 45. ^{13}C NMR spectrum of **176d**

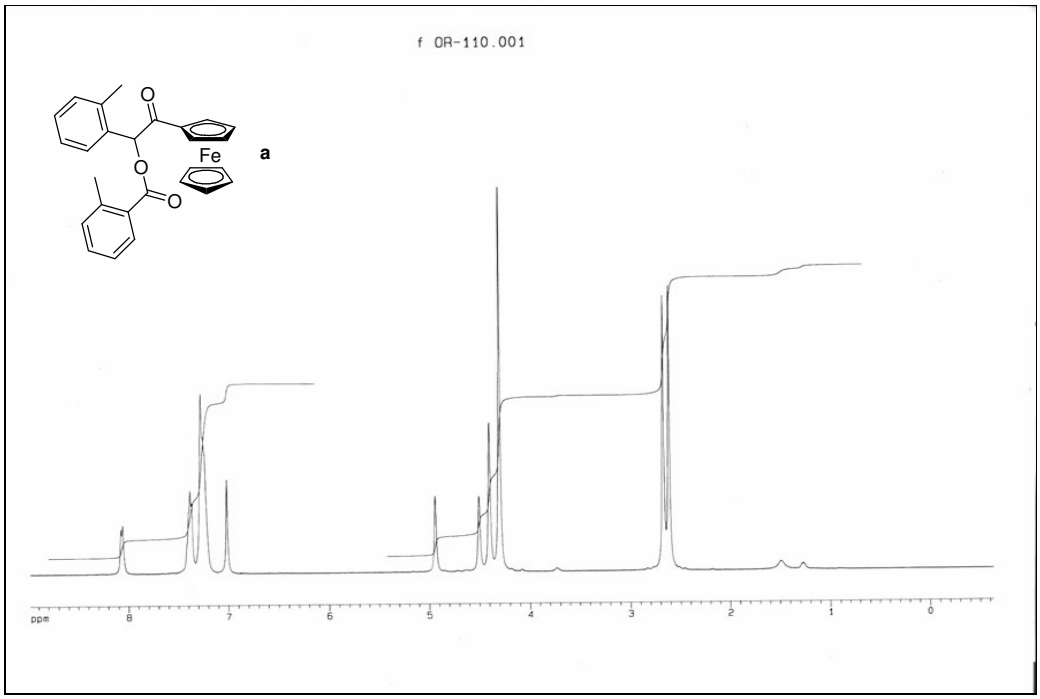

Figure 46. ^{1}H NMR spectrum of **178a**

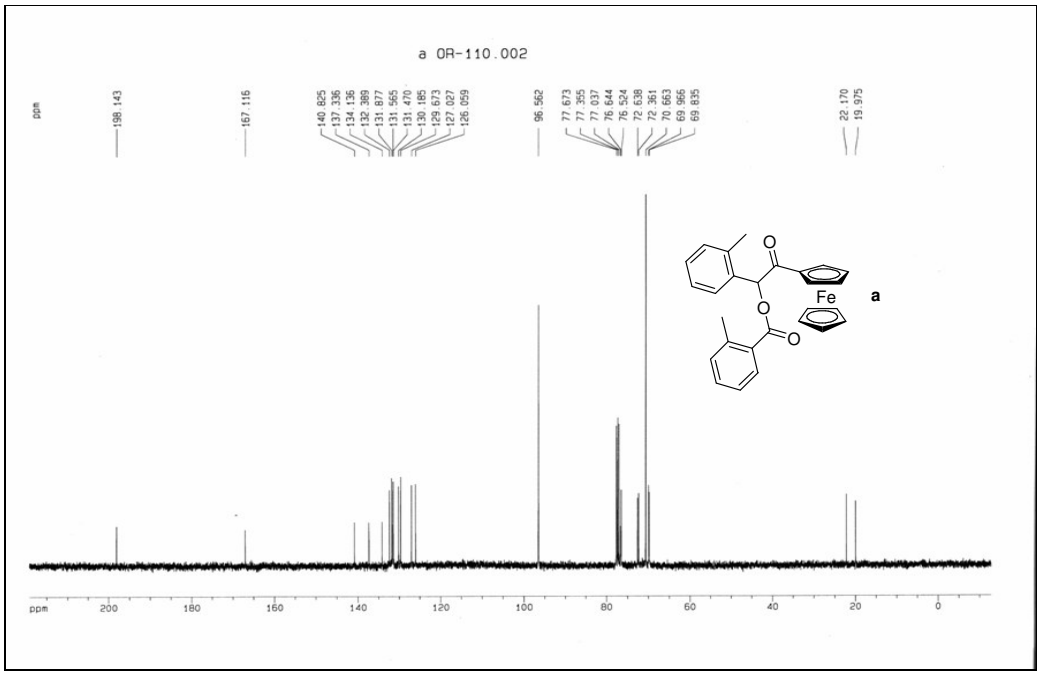

Figure 47. ^{13}C NMR spectrum of **178a**

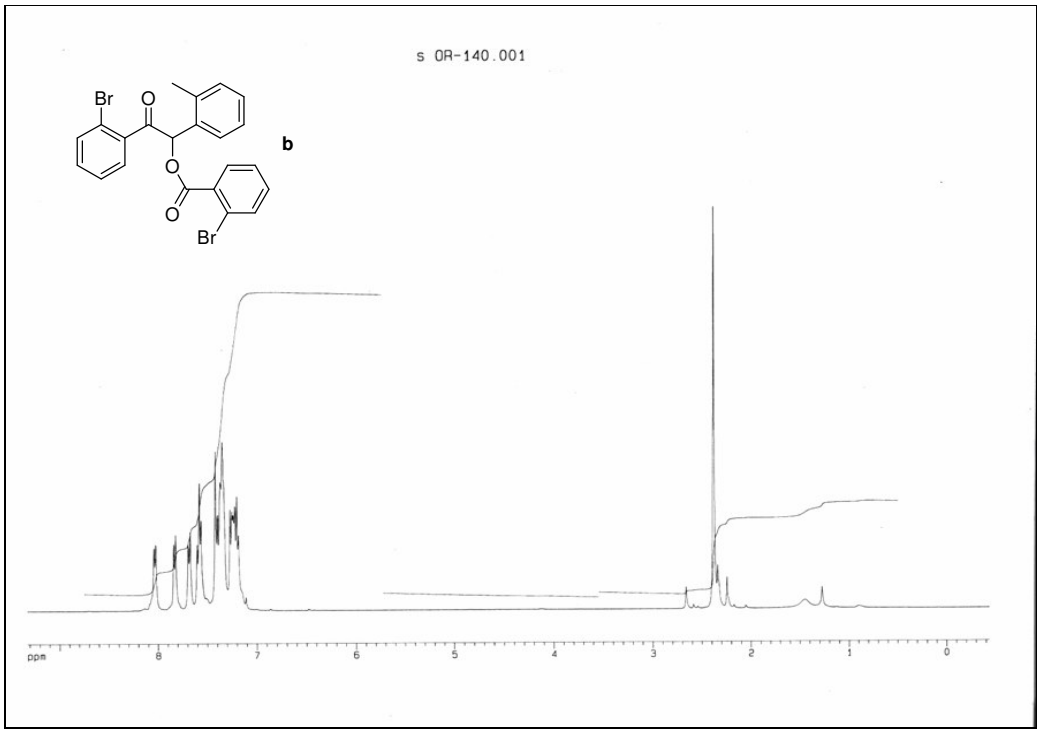

Figure 48. ^{1}H NMR spectrum of **178b**

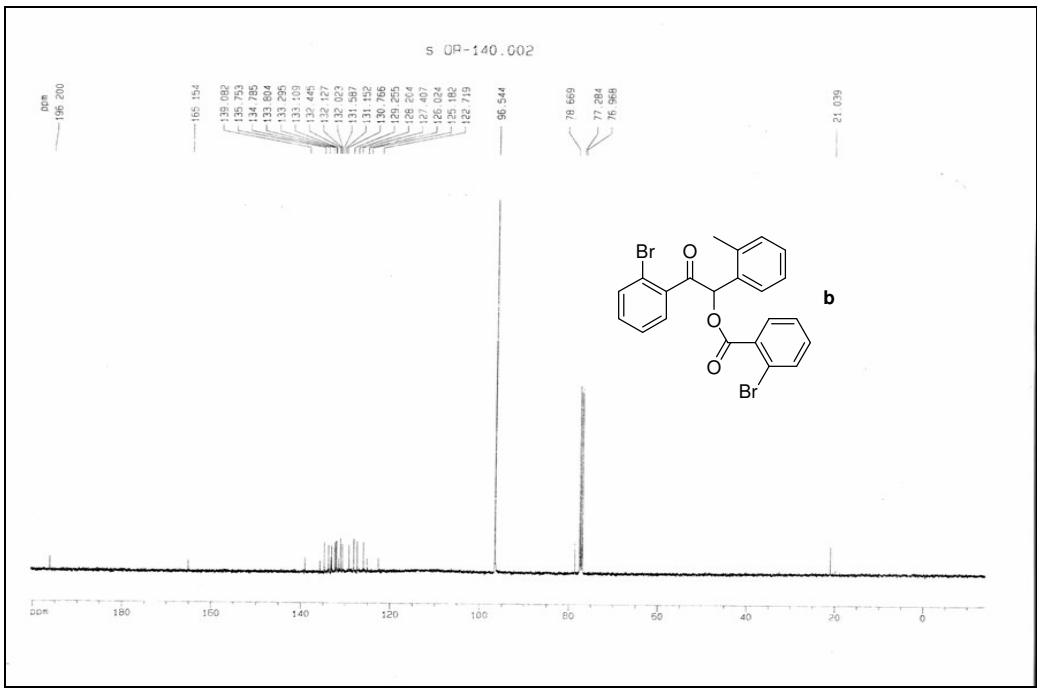

Figure 49. ^{13}C NMR spectrum of **178b**

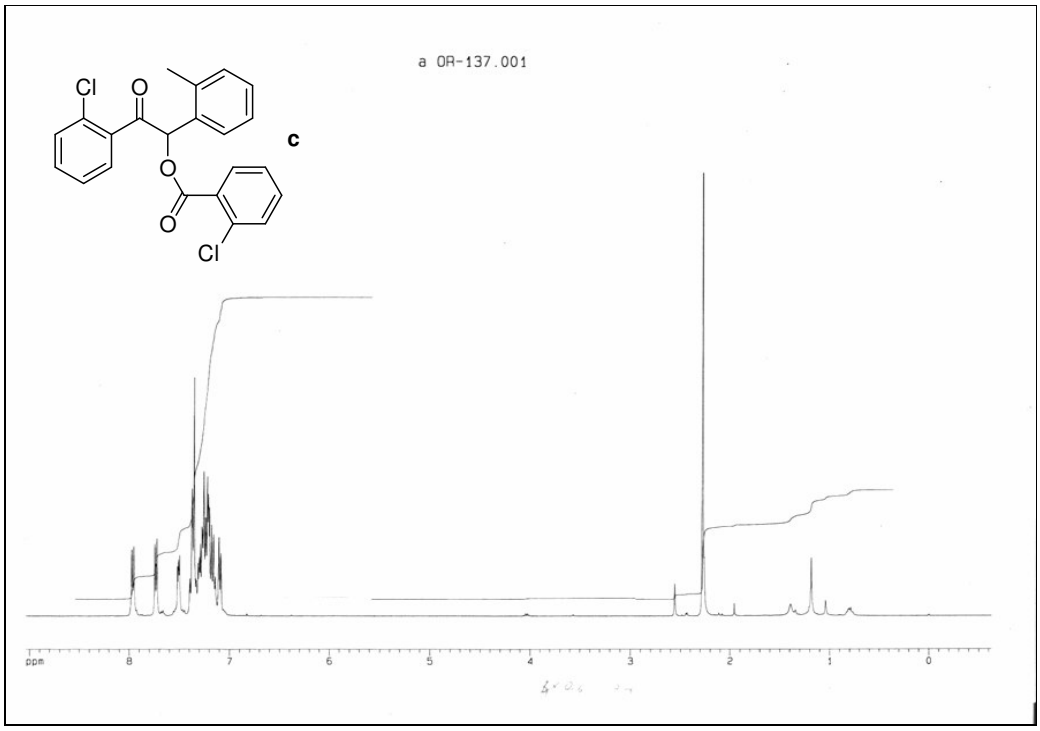

Figure 50. ^{1}H NMR spectrum of **178c**

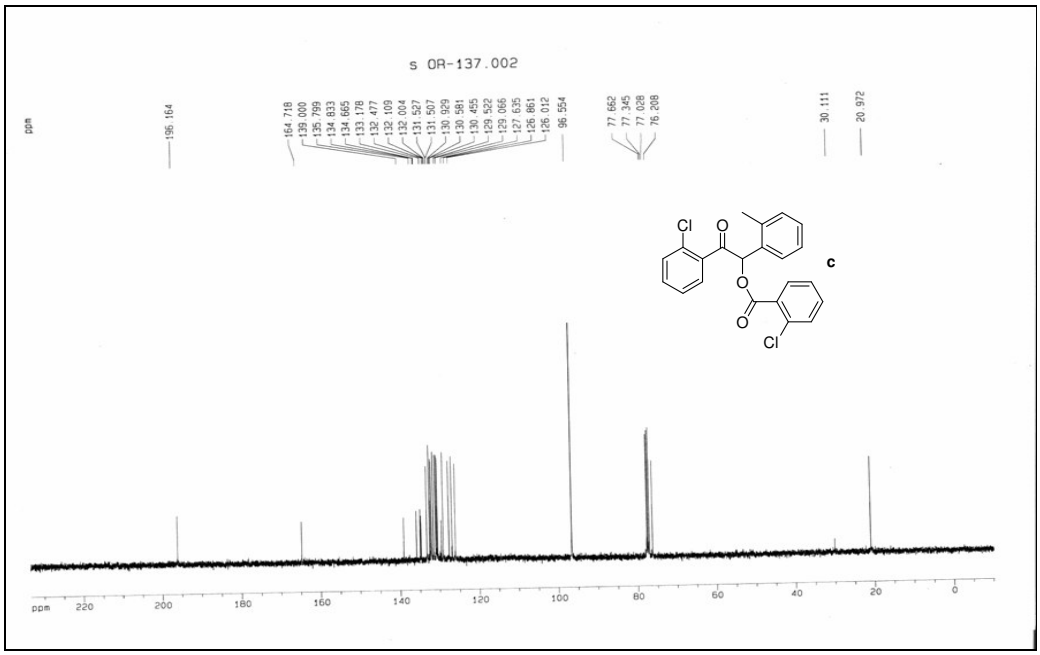

Figure 51. ^{13}C NMR spectrum of **178c**

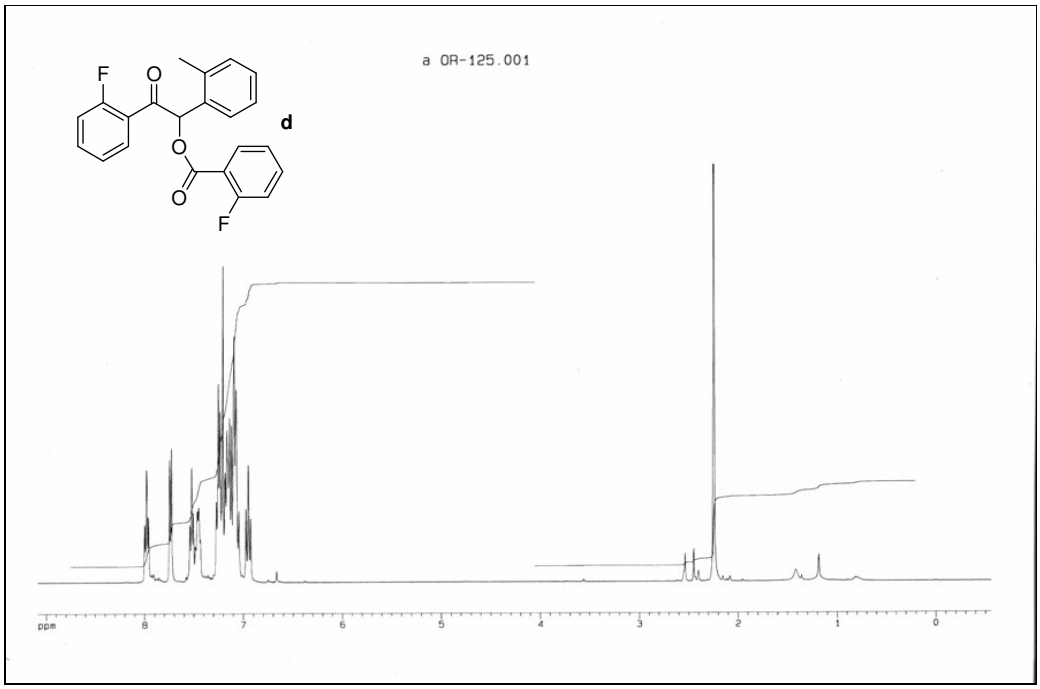

Figure 52. ^{1}H NMR spectrum of **178d**

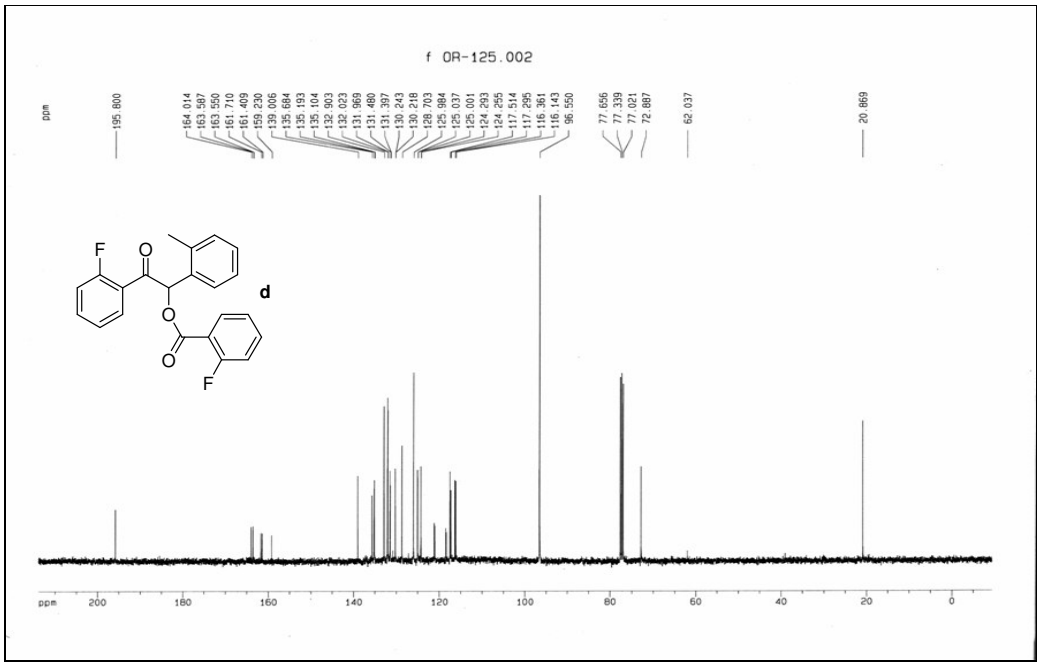

Figure 53. ^{13}C NMR spectrum of **178d**

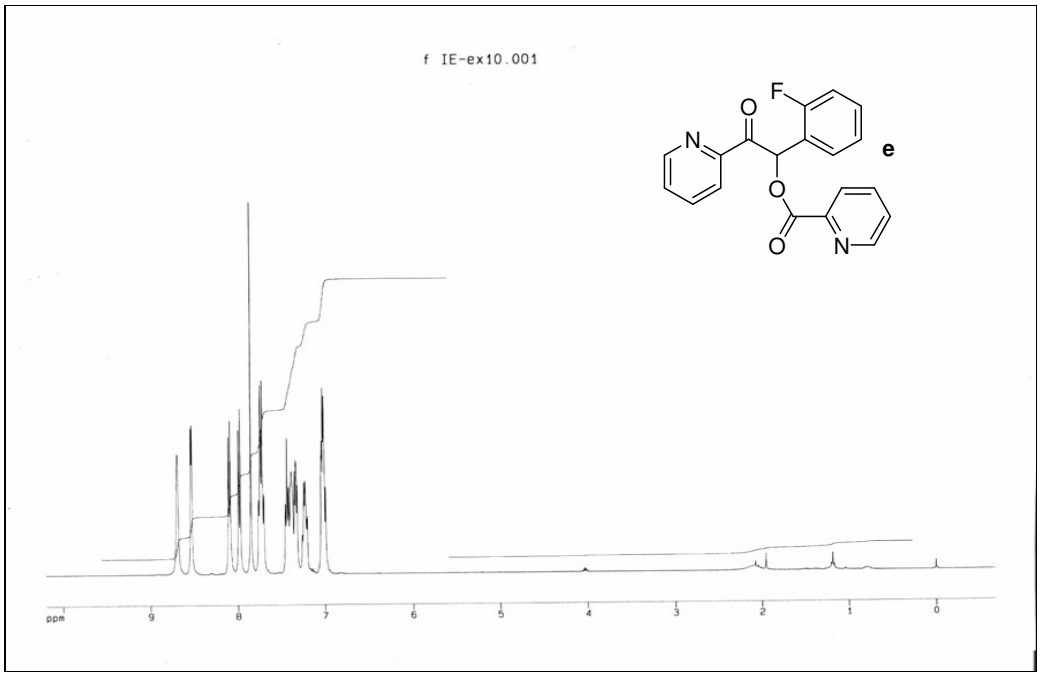

Figure 54. ^{1}H NMR spectrum of **178e**

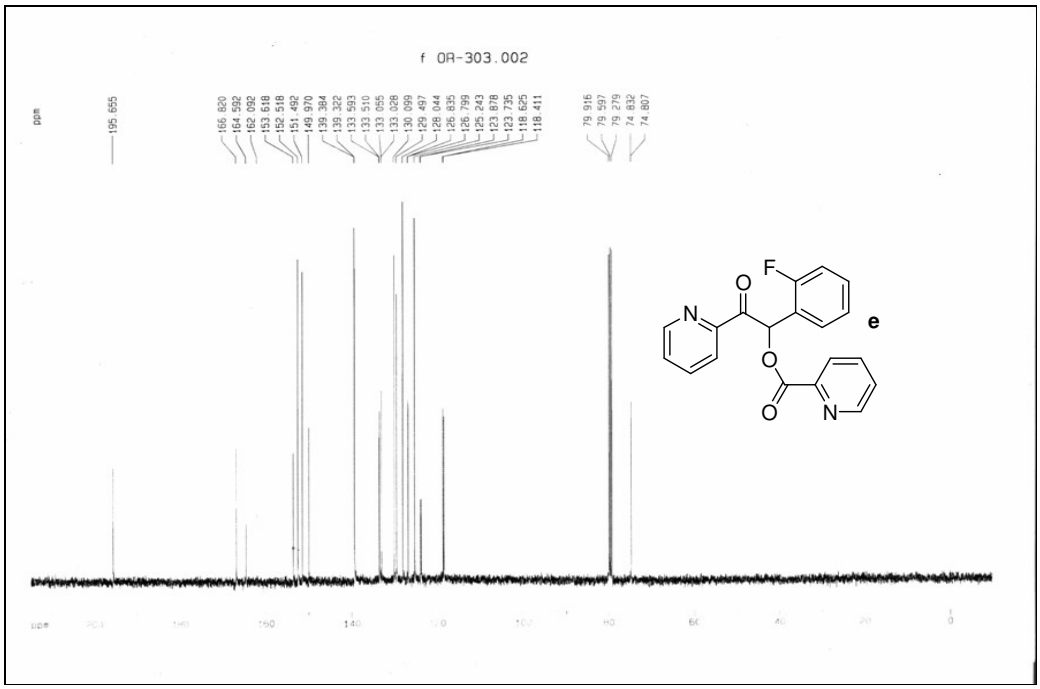

Figure 55. ^{13}C NMR spectrum of **178e**

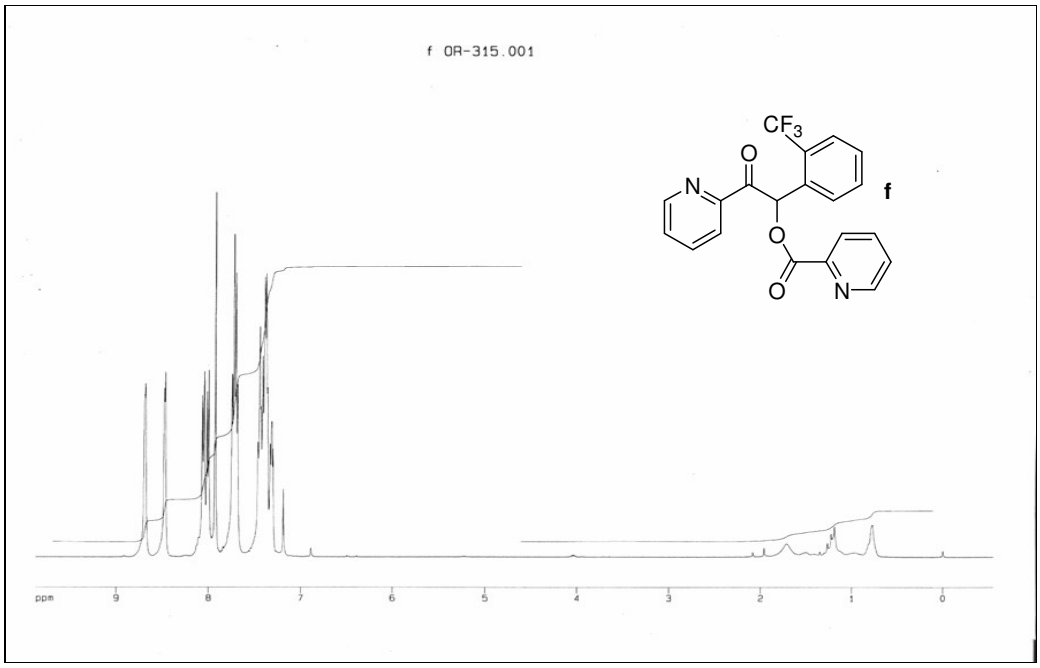

Figure 56. ^{1}H NMR spectrum of **178f**

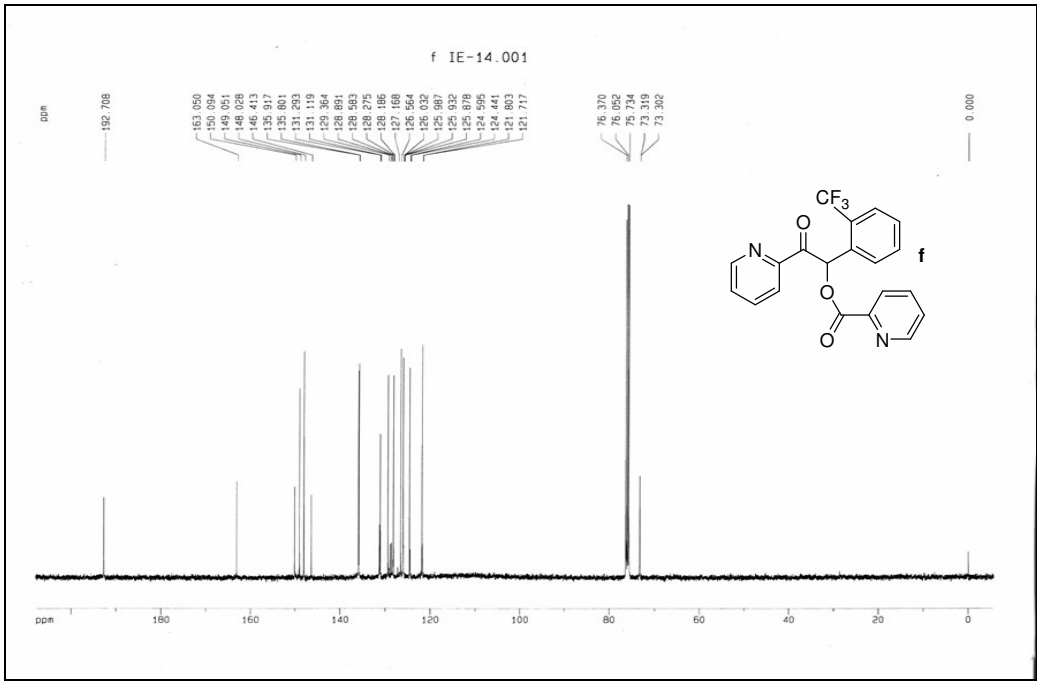

Figure 57. ^{13}C NMR spectrum of **178f**

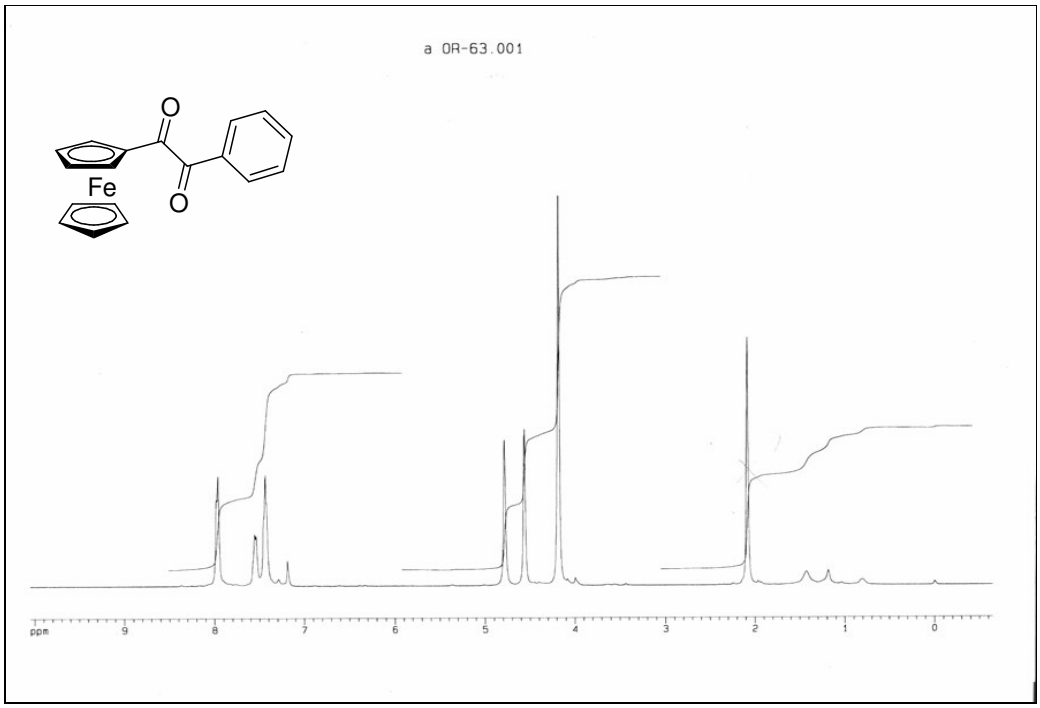

Figure 58. ^{1}H NMR spectrum of **181**

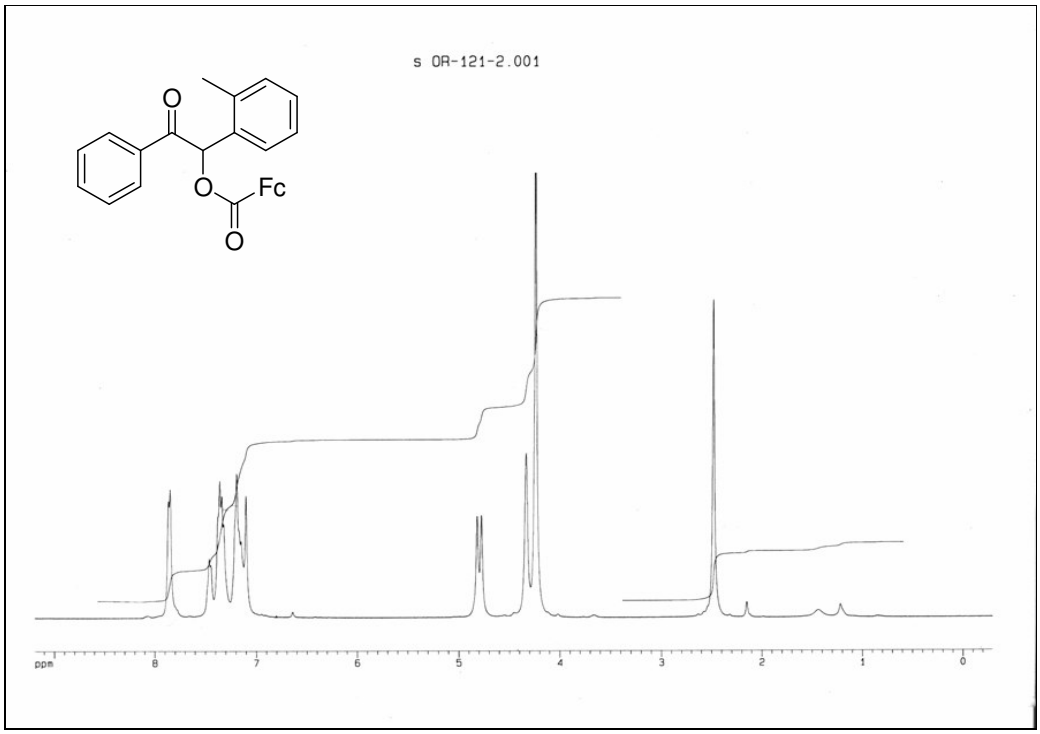

Figure 59. ^{1}H NMR spectrum of **182**

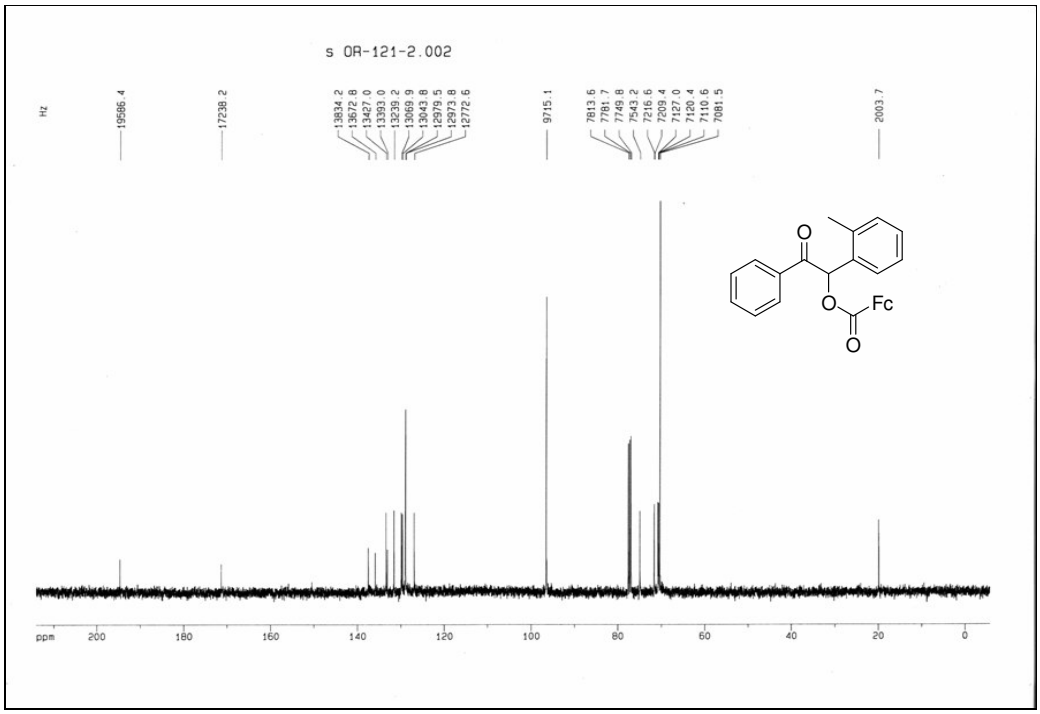

Figure 60. ^{13}C NMR spectrum of **182**

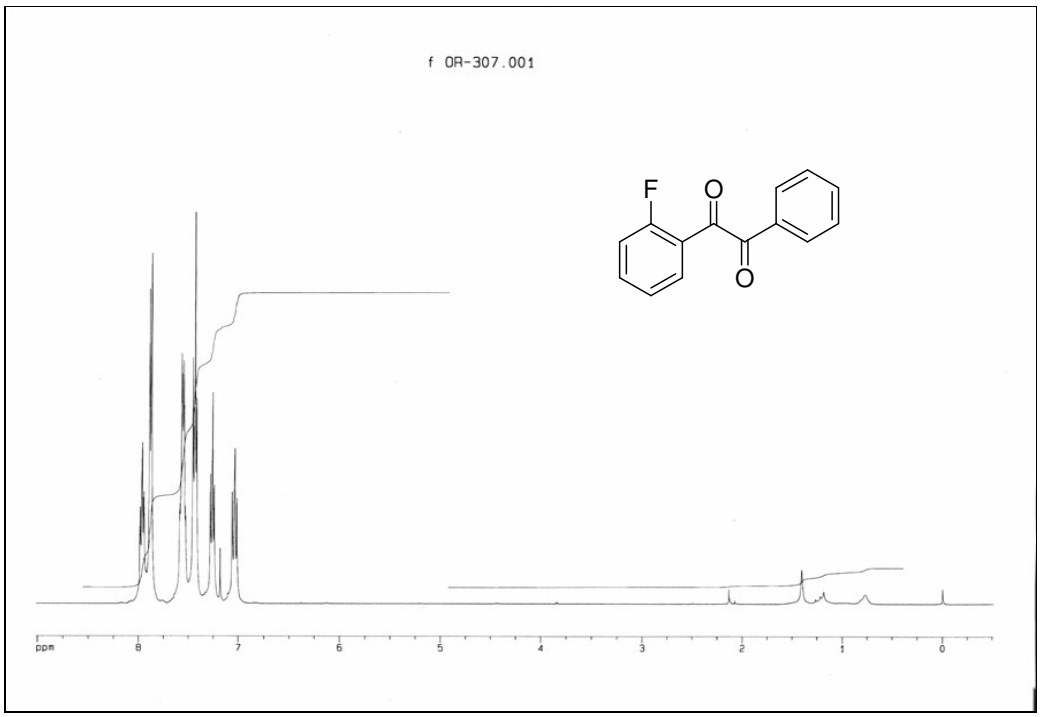

Figure 61. ^{1}H NMR spectrum of **183**

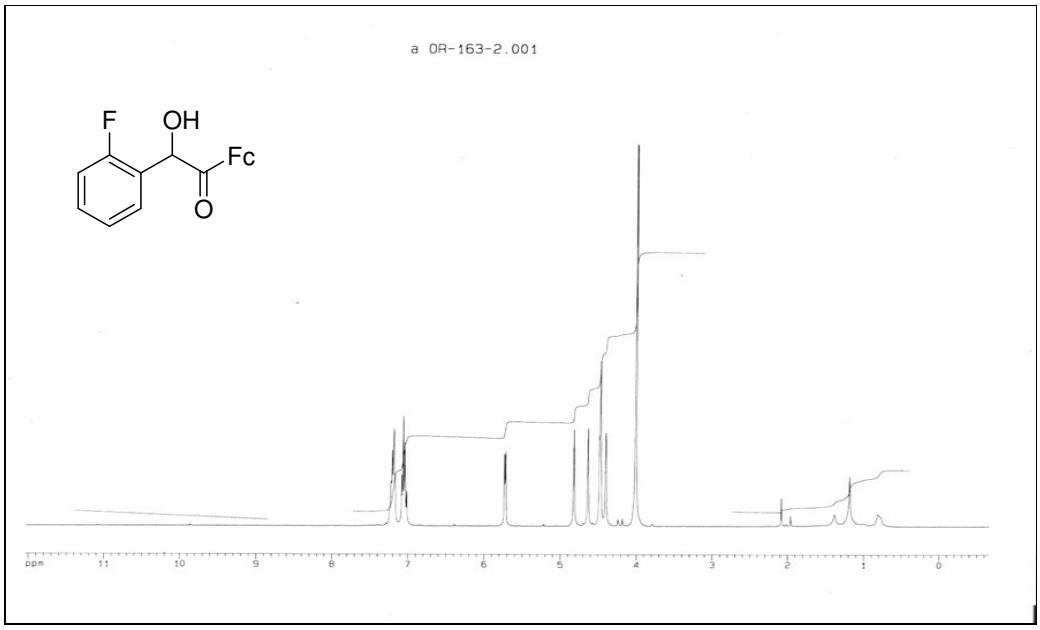

Figure 62. ^{1}H NMR spectrum of **184**

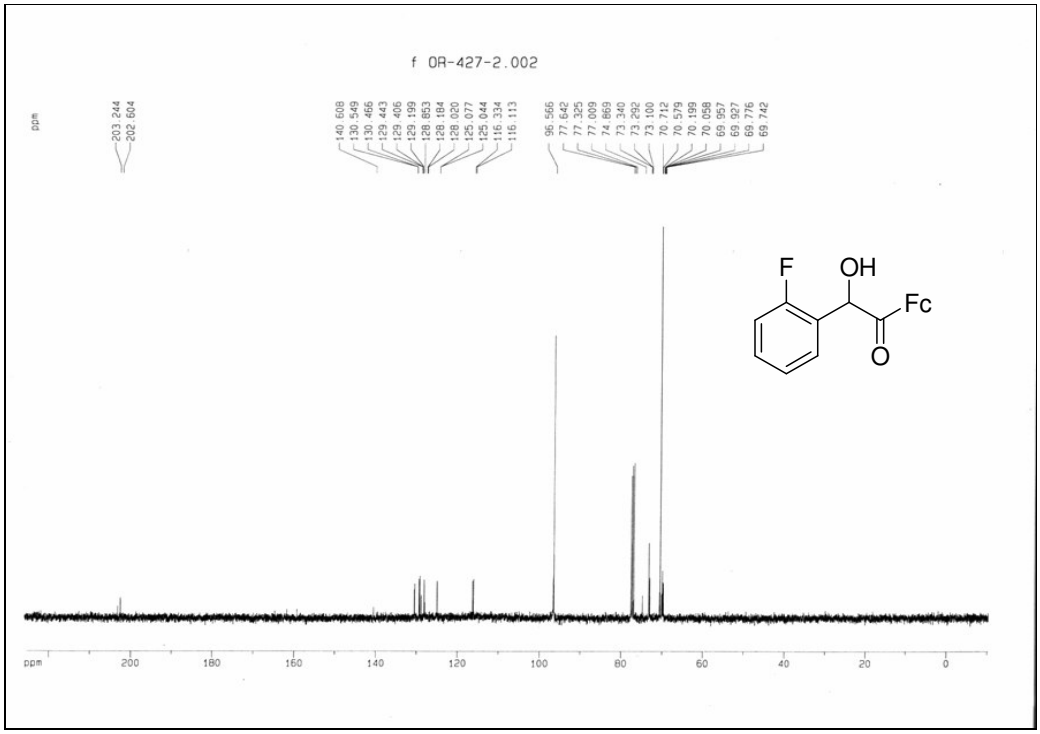

Figure 63. ^{13}C NMR spectrum of **184**

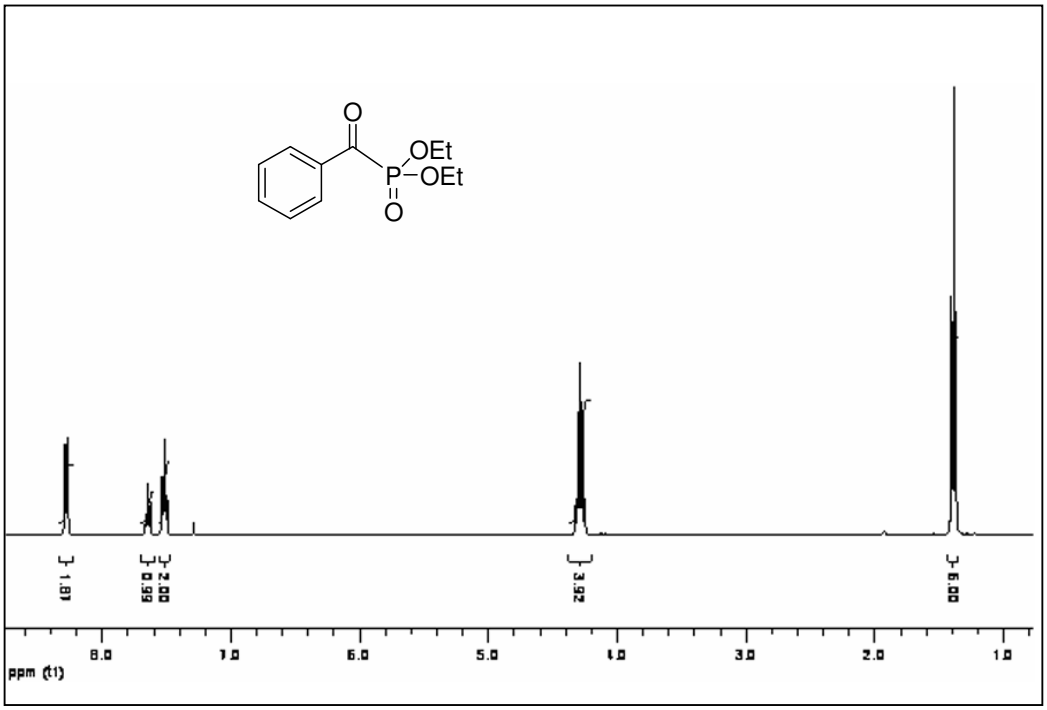

Figure 64. ^{1}H NMR spectrum of **202a**

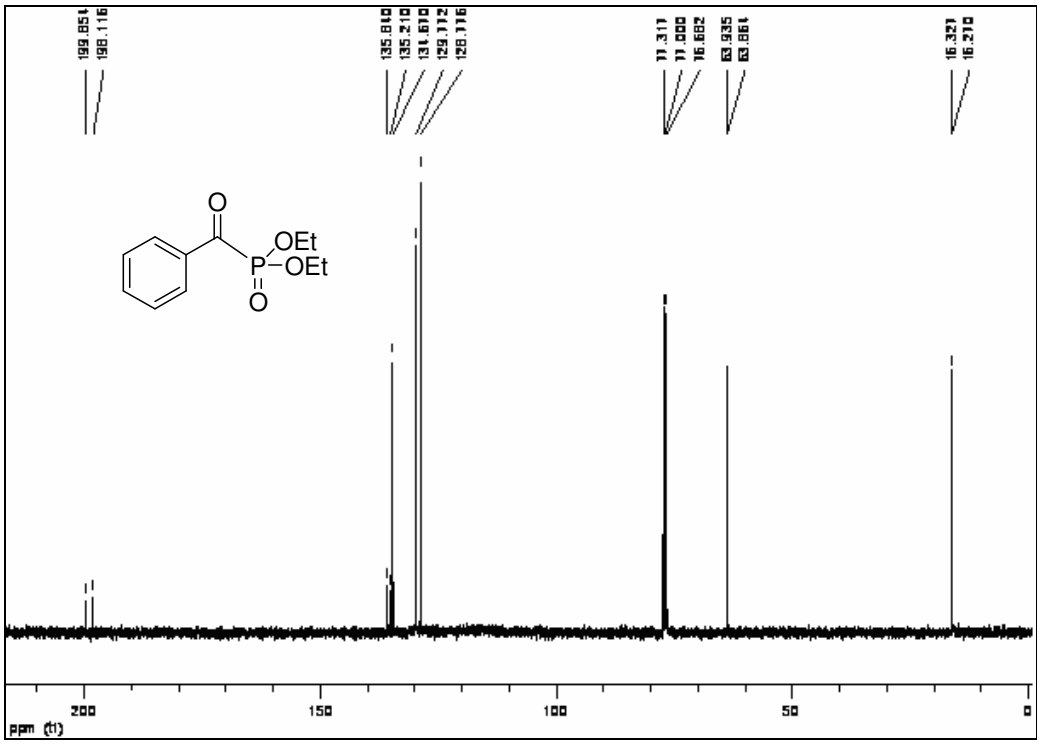

Figure 65. ^{13}C NMR spectrum of **202a**

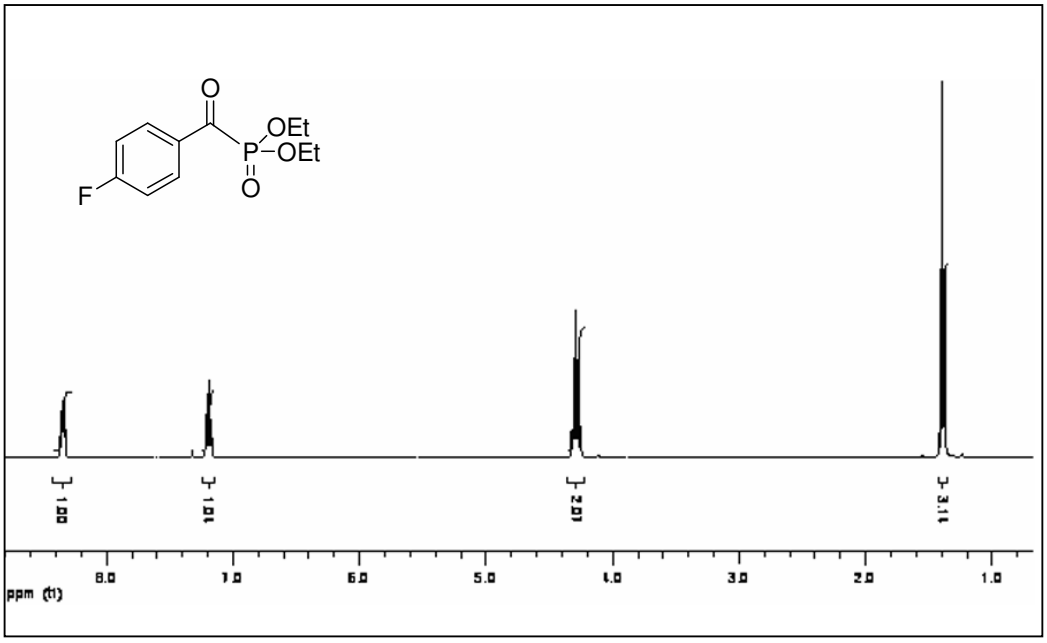

Figure 66. ^{1}H NMR spectrum of **202b**

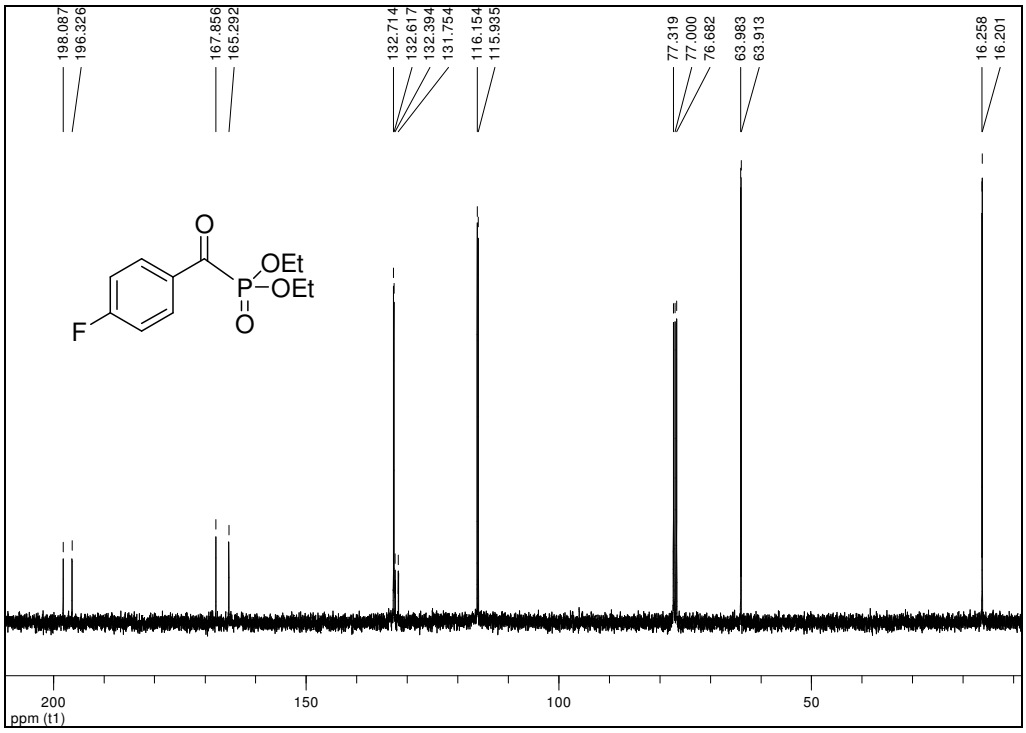

Figure 67. ^{13}C NMR spectrum of **202b**

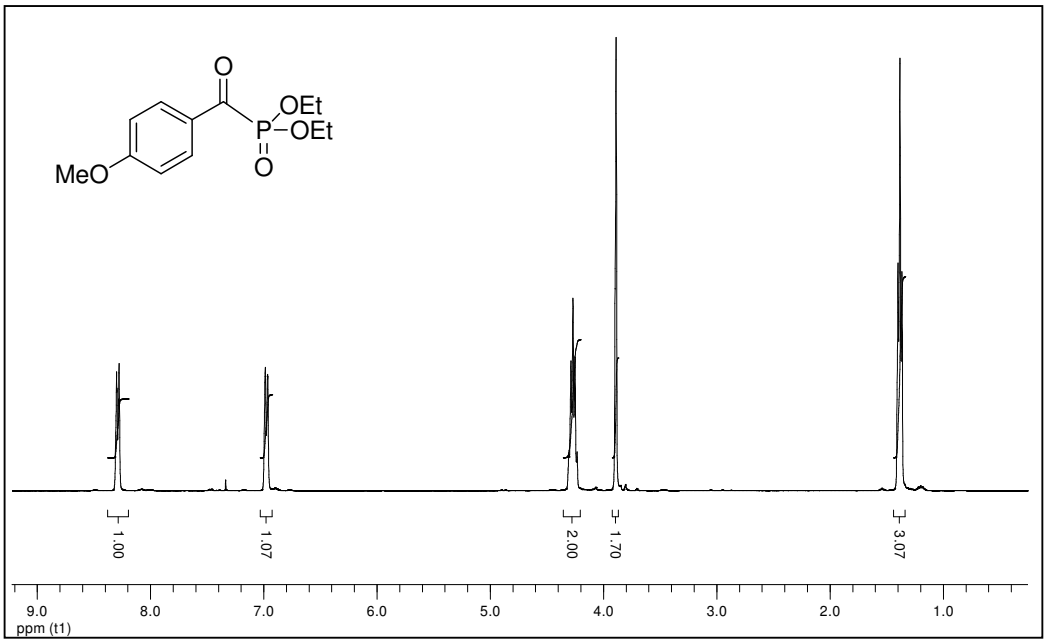

Figure 68. ^{1}H NMR spectrum of **202c**

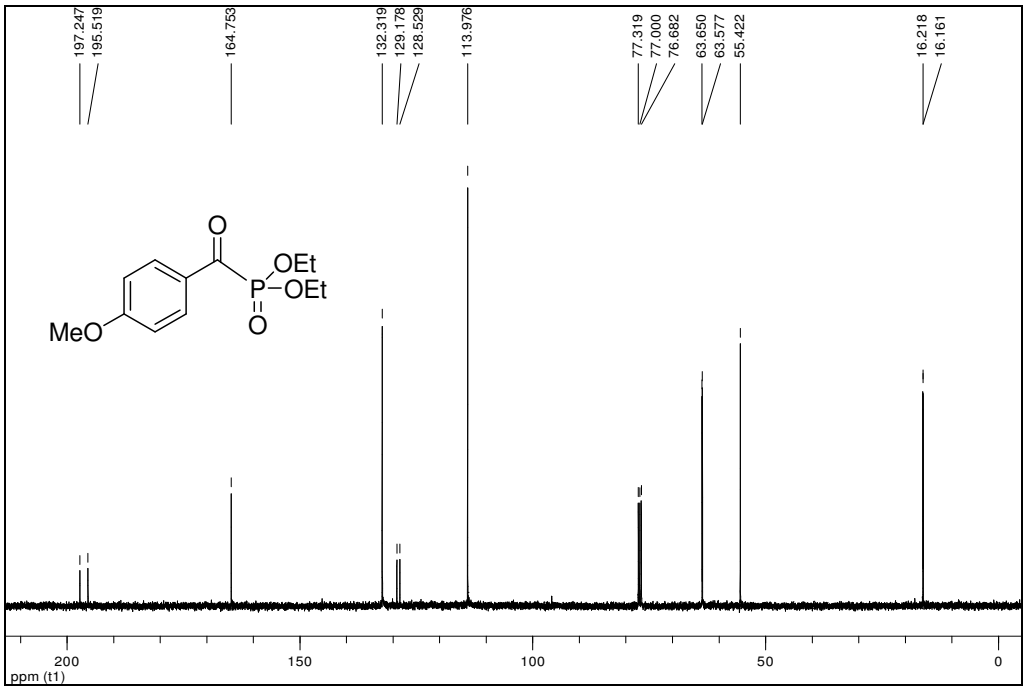

Figure 69. ^{13}C NMR spectrum of **202c**

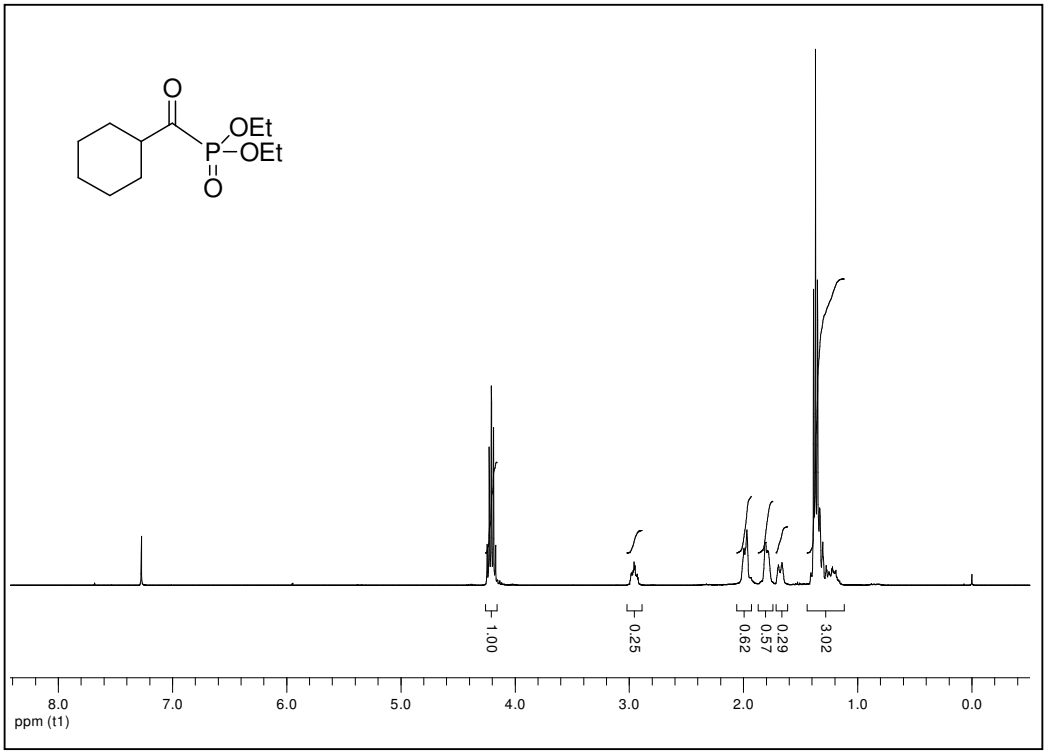

Figure 70. ^{1}H NMR spectrum of **202h**

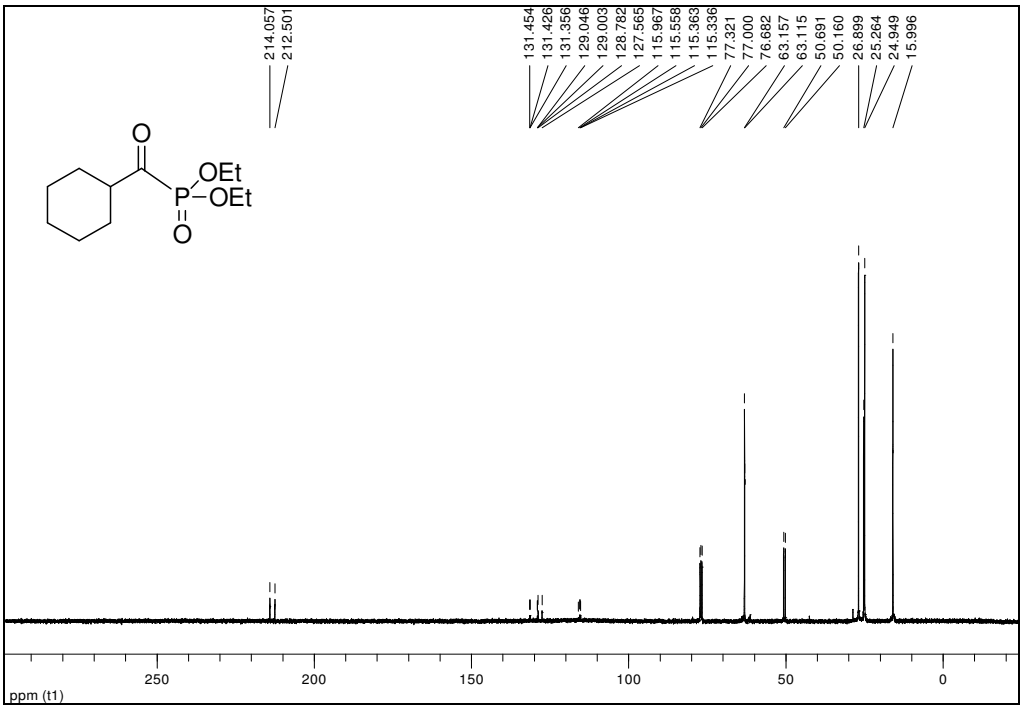

Figure 71. ^{13}C NMR spectrum of **202h**

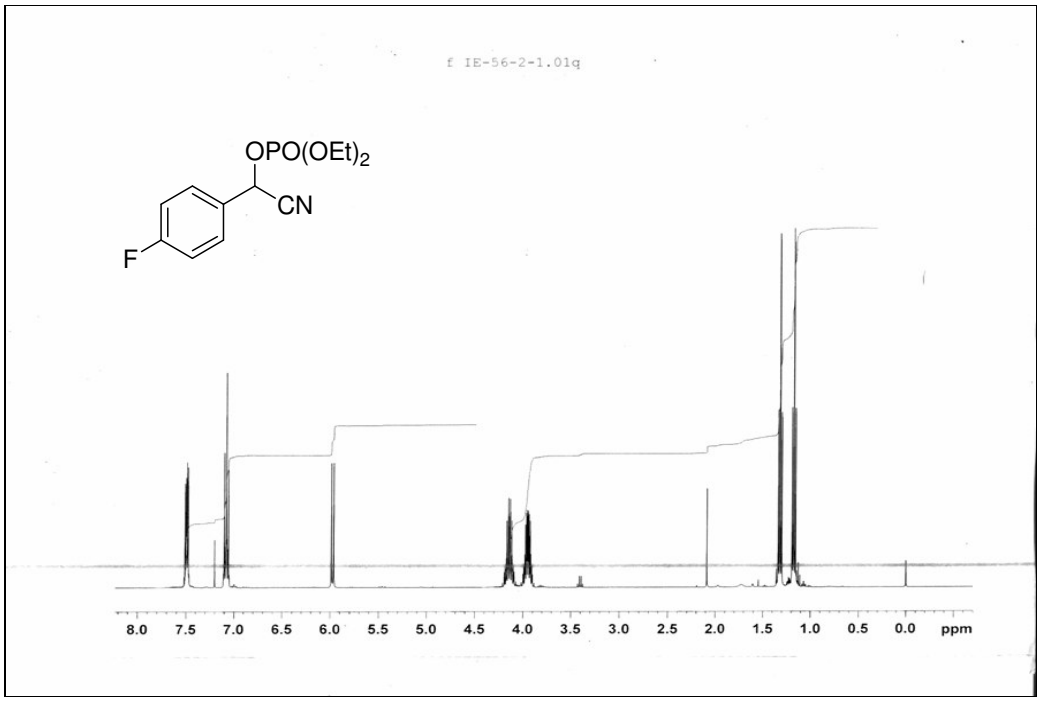

Figure 72. ^{1}H NMR spectrum of **205b**

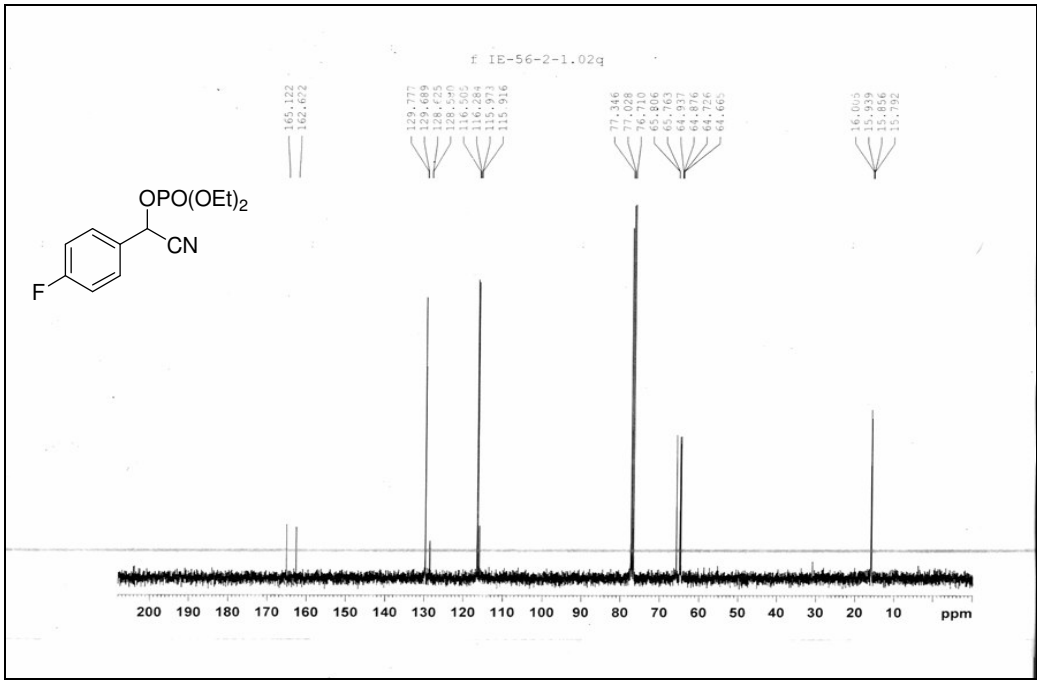

Figure 73. ^{13}C NMR spectrum of **205b**

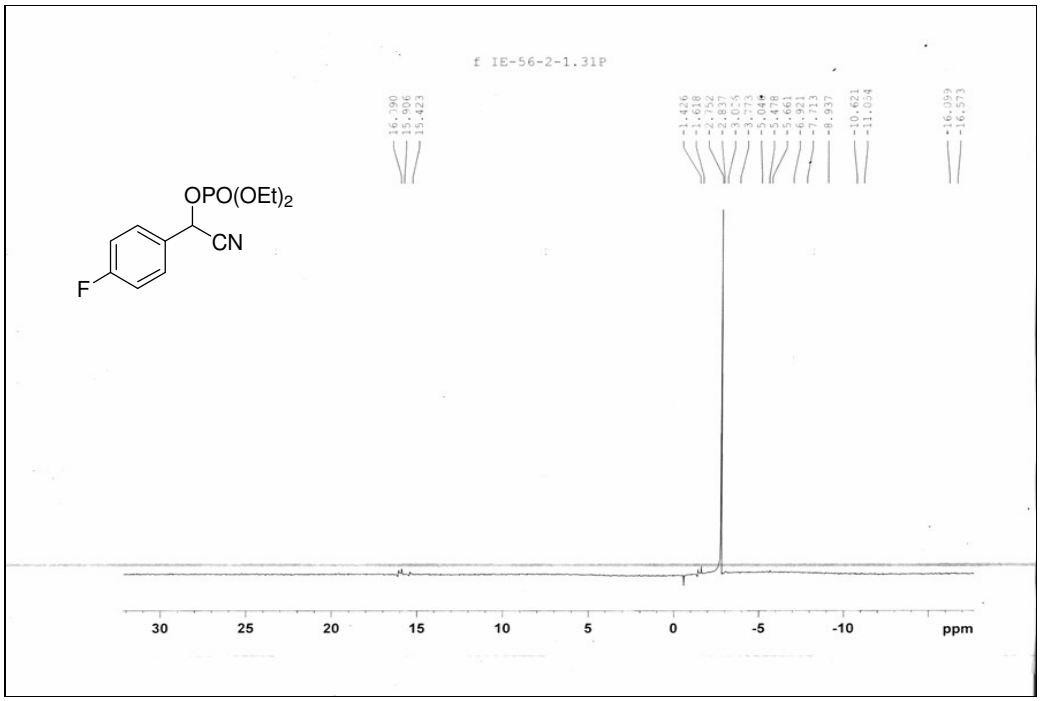

Figure 74. ^{31}P NMR spectrum of **205b**

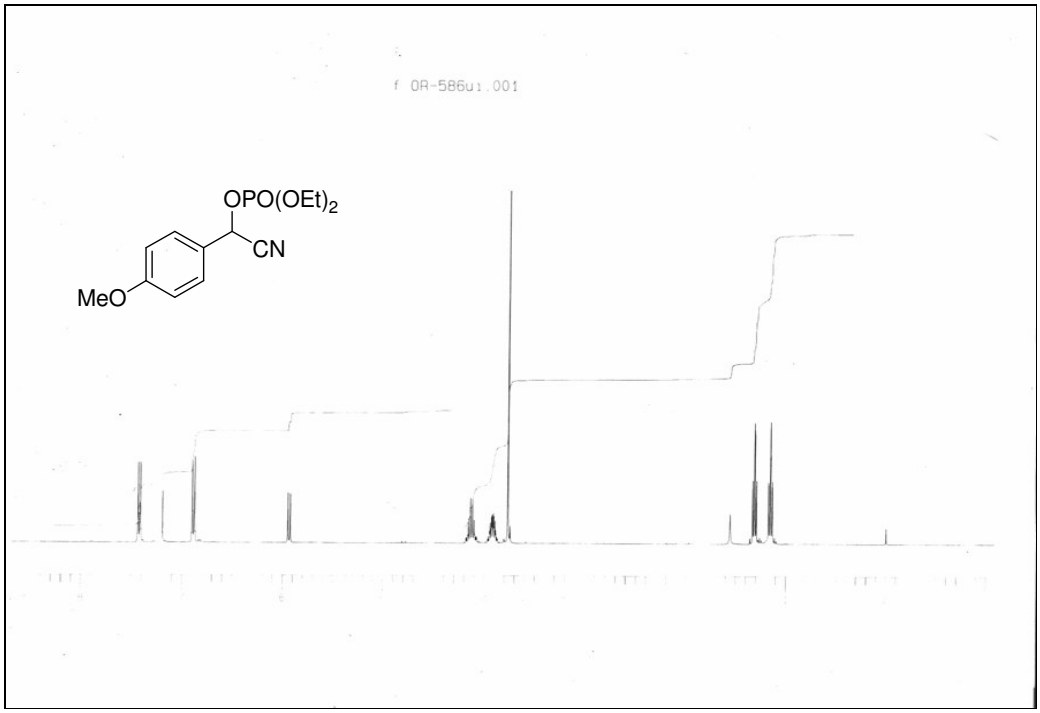

Figure 75. ^{1}H NMR spectrum of **205c**

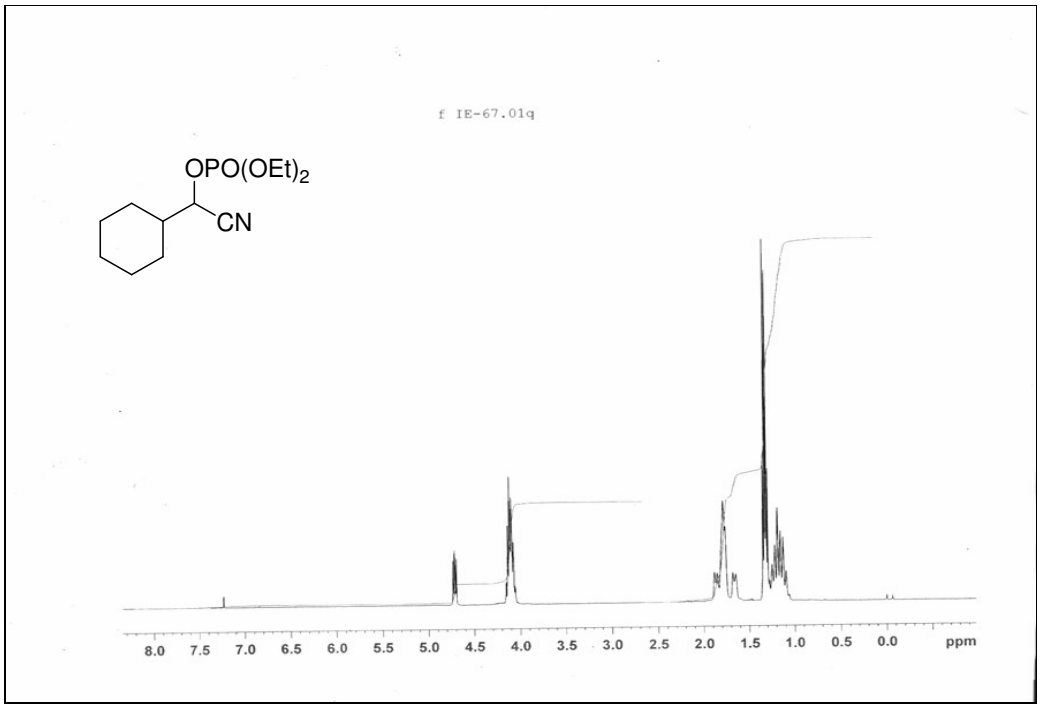

Figure 76. ^{1}H NMR spectrum of **205d**

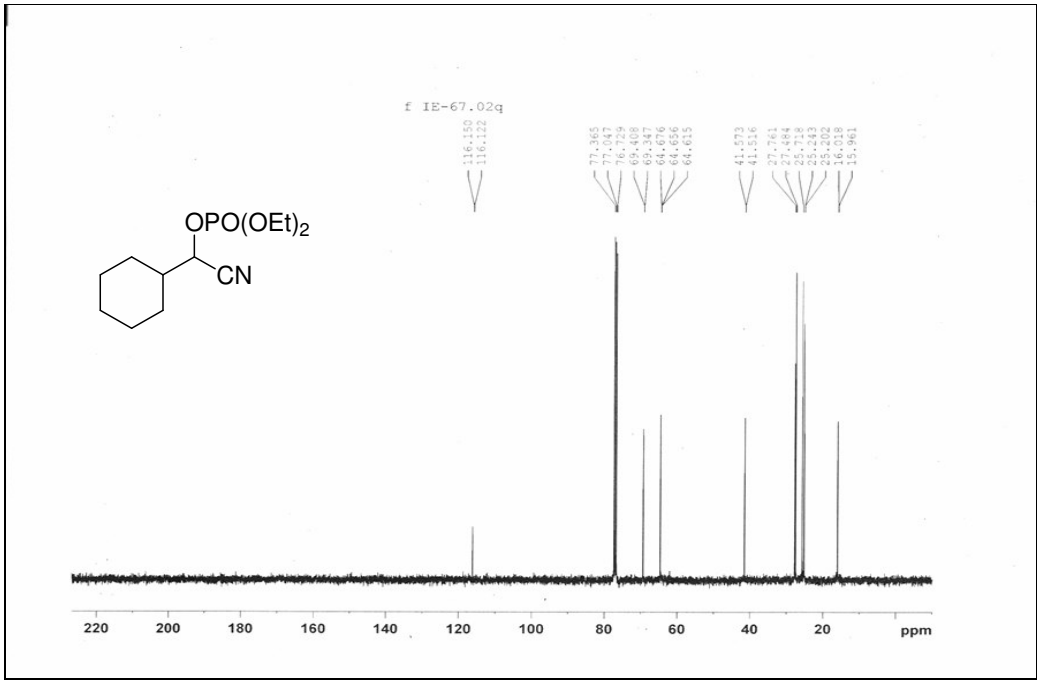

Figure 77. ^{13}C NMR spectrum of **205d**

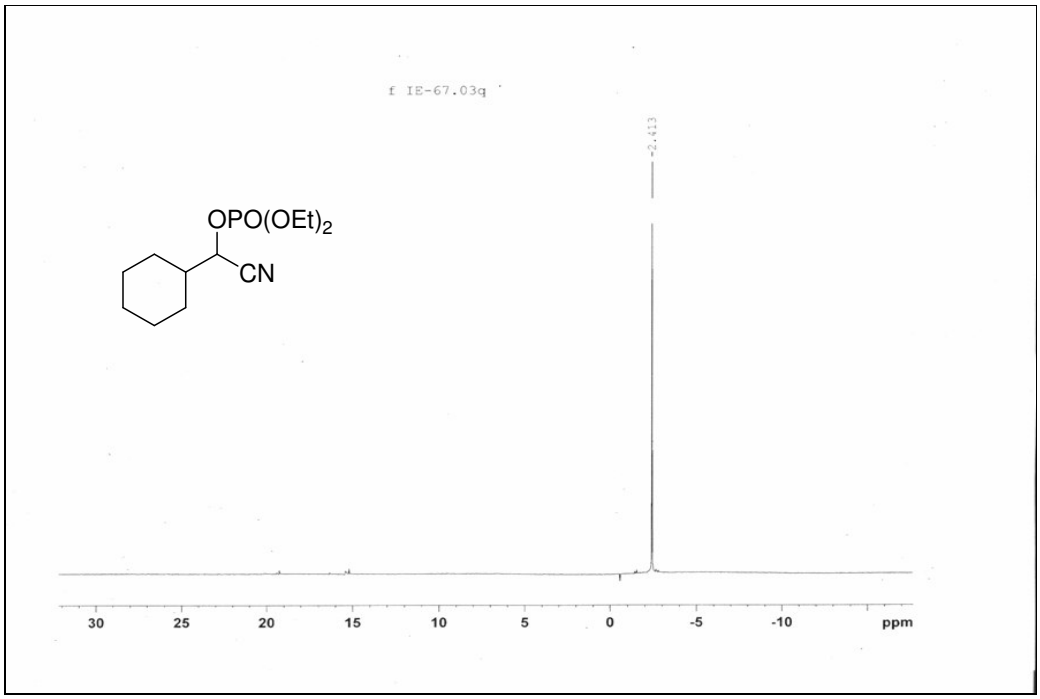

Figure 78. ^{31}P NMR spectrum of **205d**

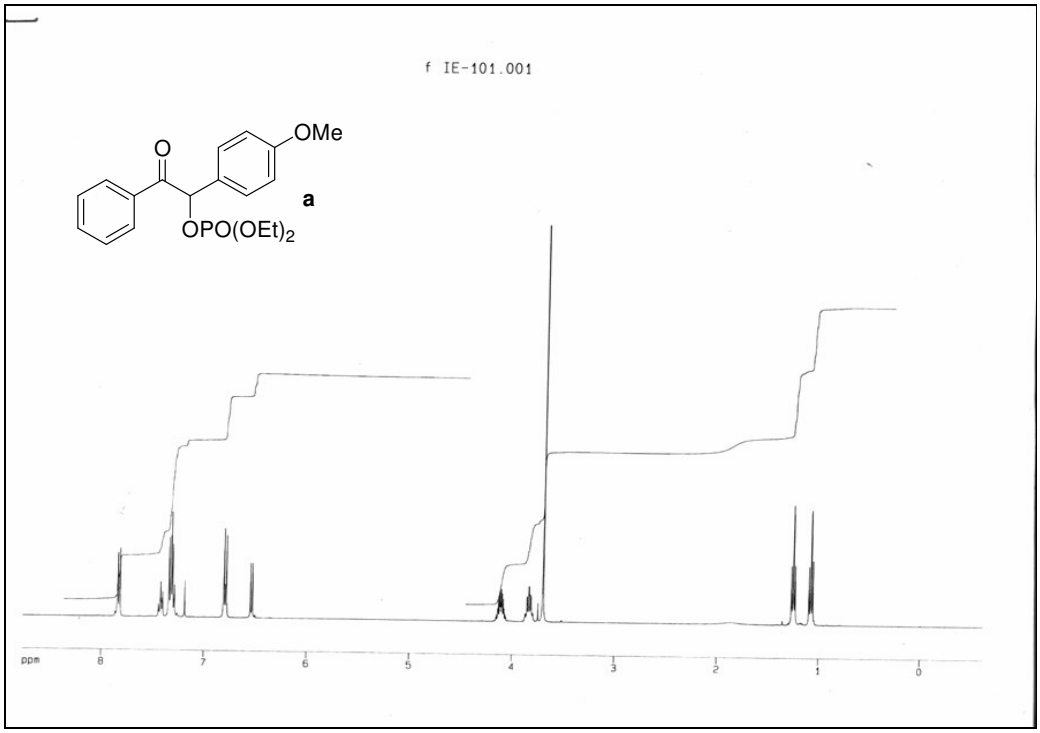

Figure 79. ^{1}H NMR spectrum of **209a**

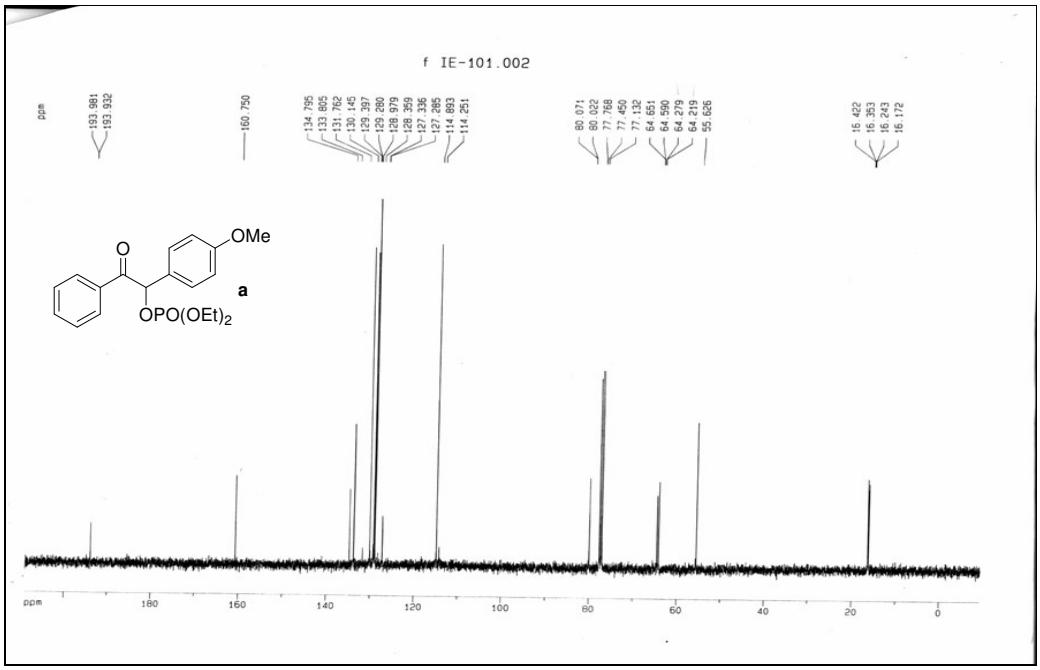

Figure 80. ^{13}C NMR spectrum of **209a**

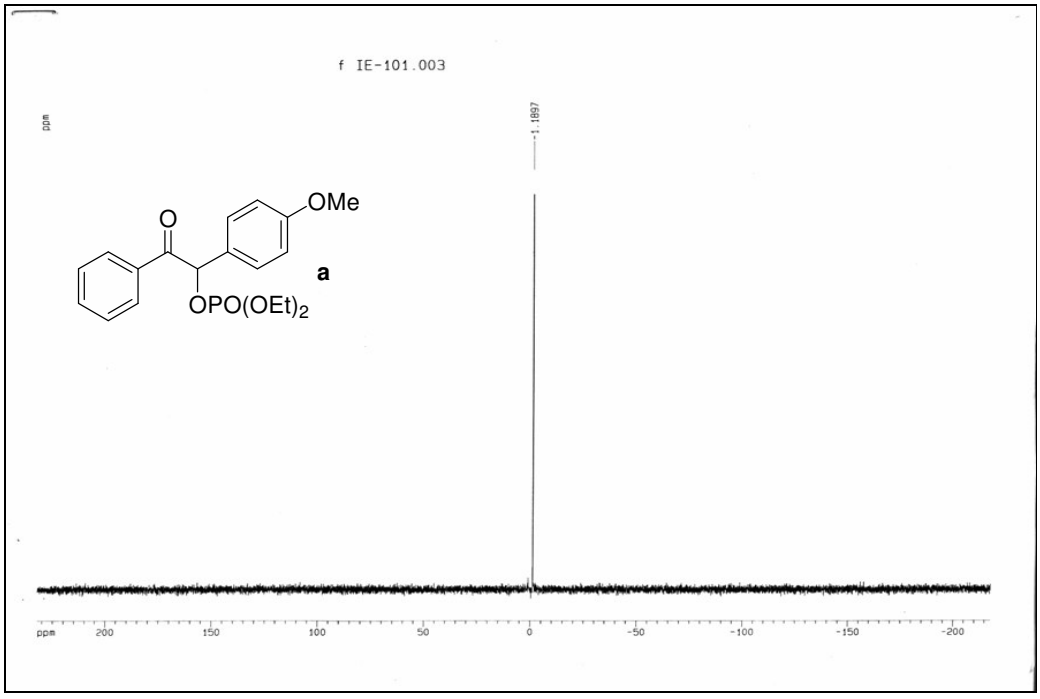

Figure 81. ^{31}P NMR spectrum of **209a**

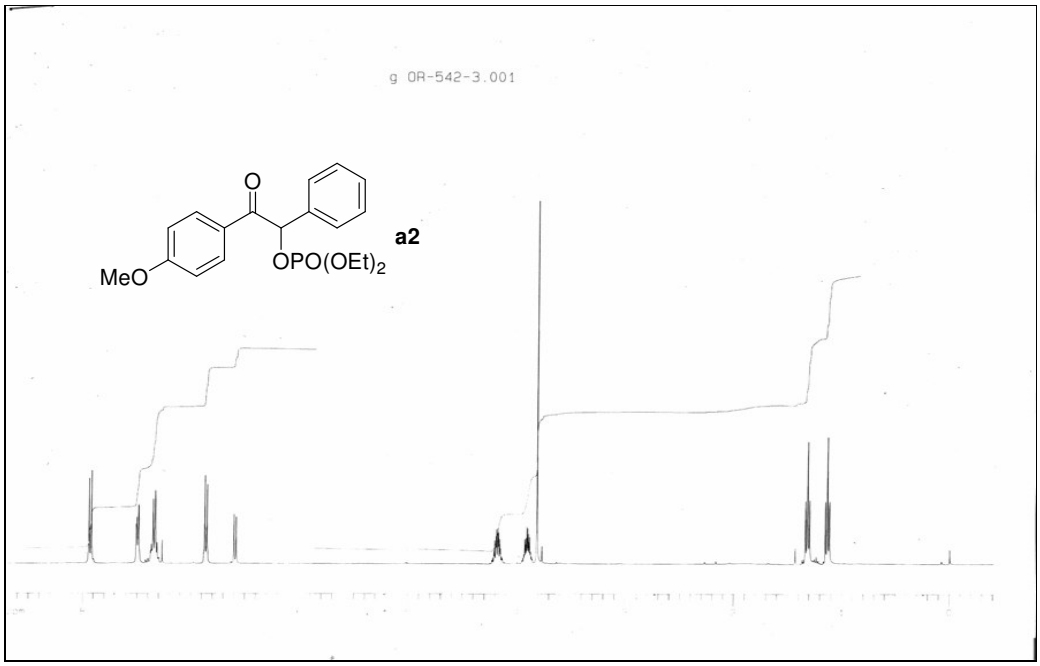

Figure 82. ^{1}H NMR spectrum of **209a2**

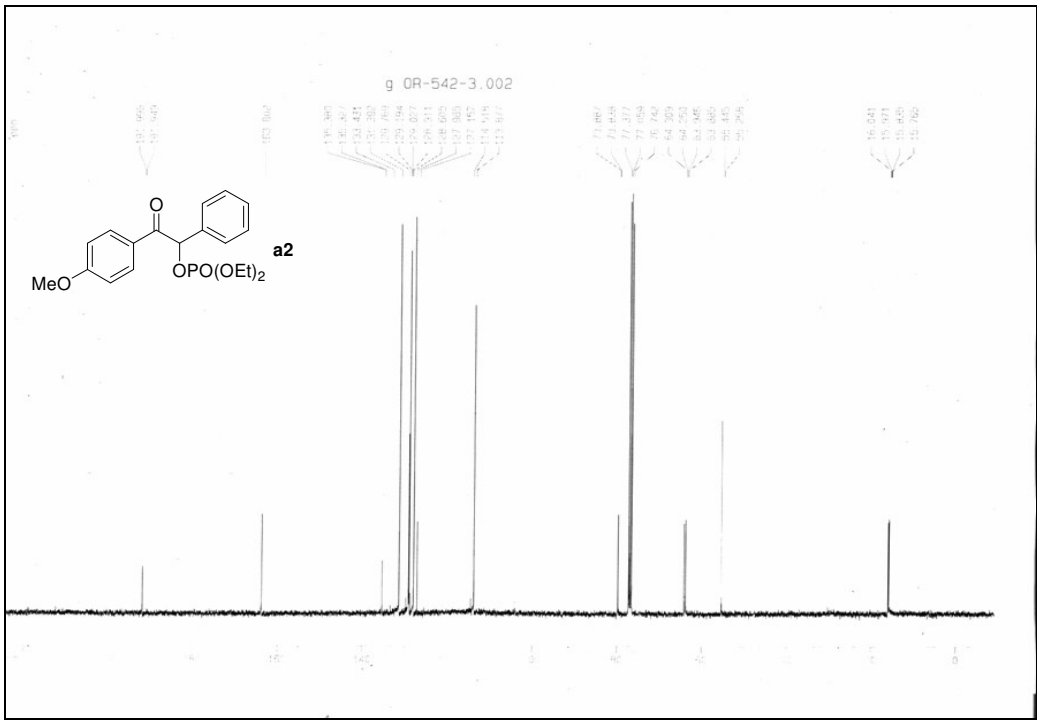

Figure 83. ^{13}C NMR spectrum of **205a2**

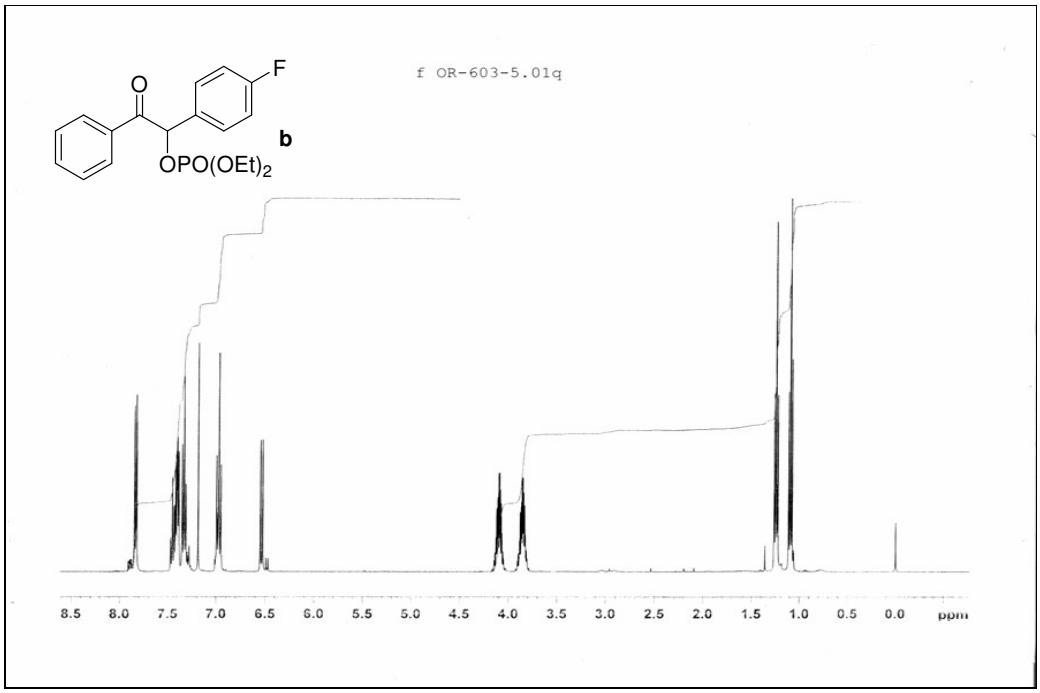

Figure 84. ^{1}H NMR spectrum of **209b**

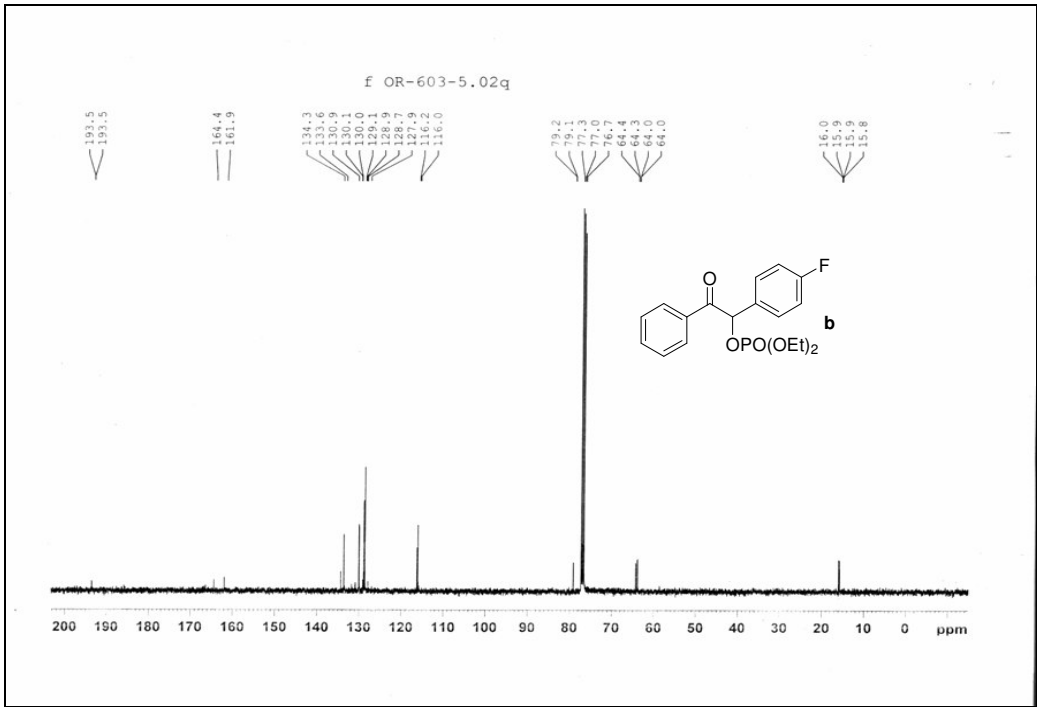

Figure 85. ^{13}C NMR spectrum of **209b**

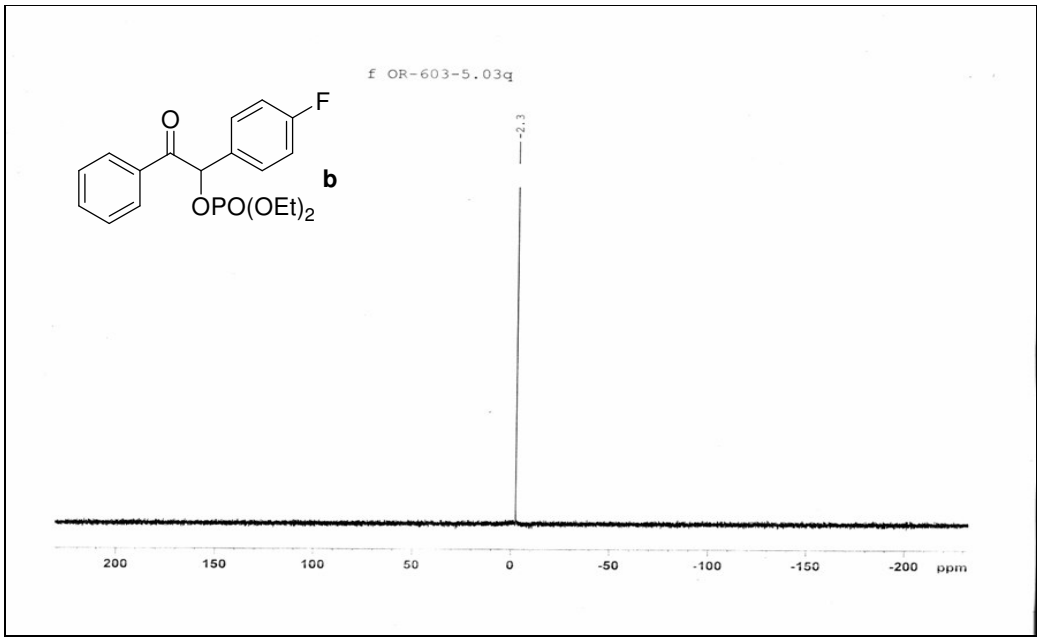

Figure 86. ^{31}P NMR spectrum of **209b**

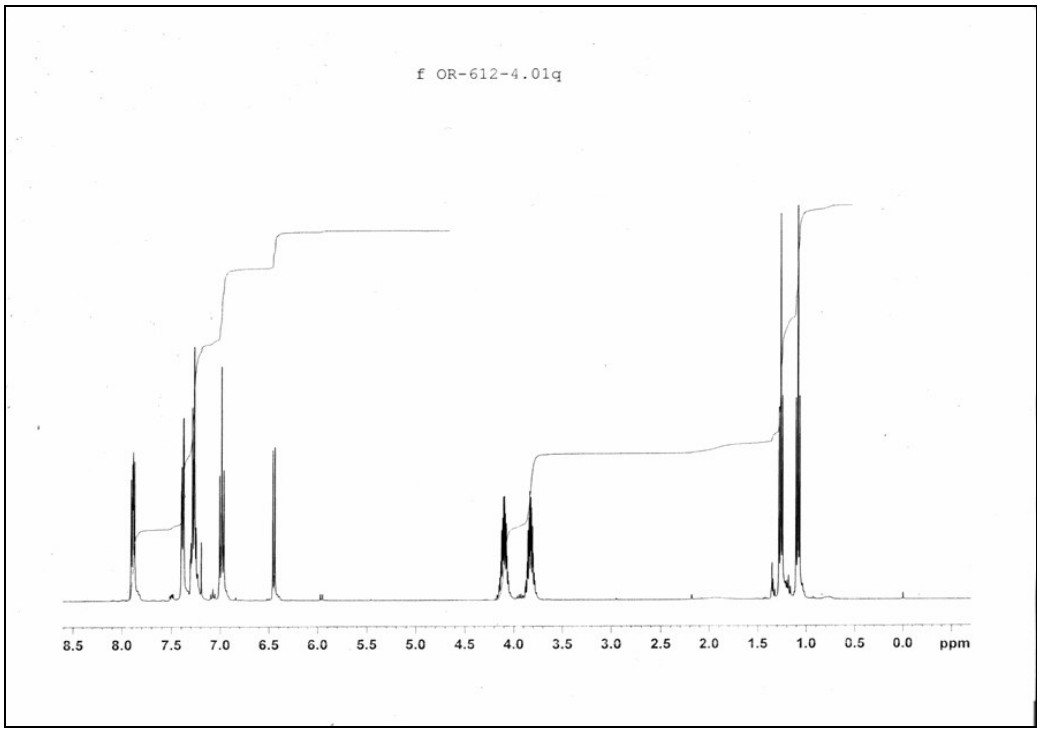

Figure 87. ^{1}H NMR spectrum of **209b2**

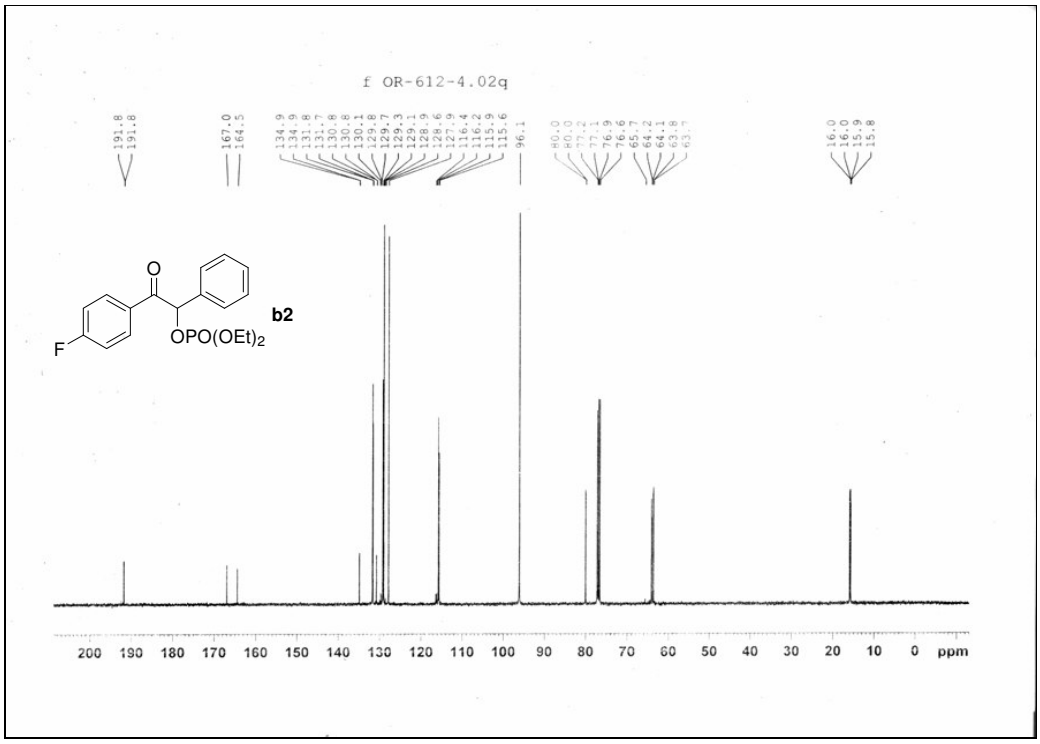

Figure 88. ^{13}C NMR spectrum of **209b2**

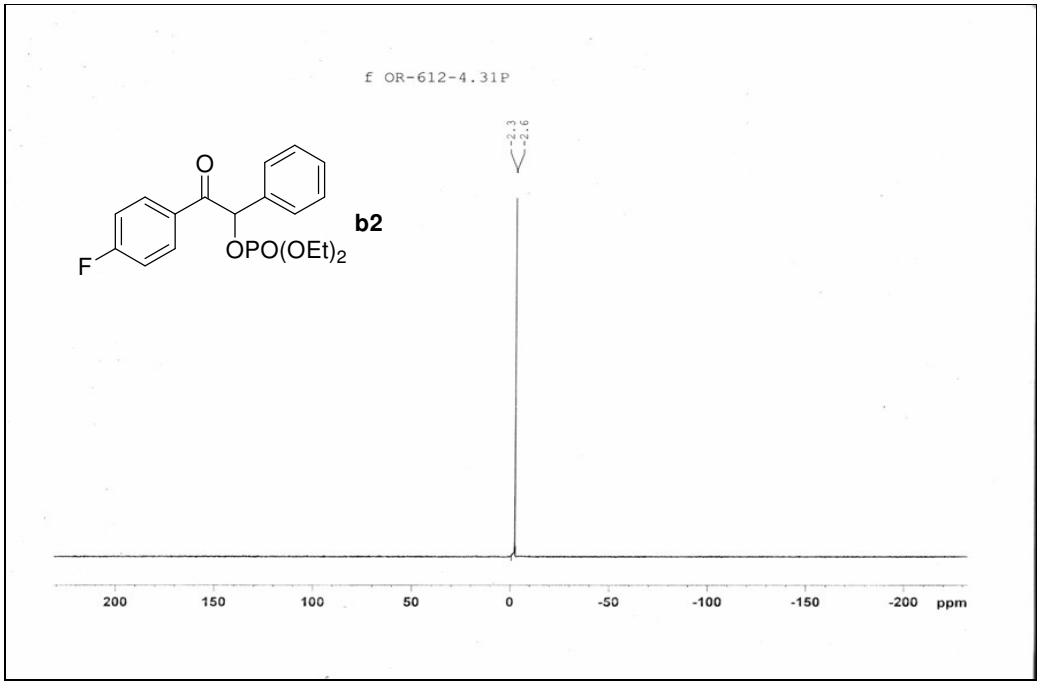

Figure 89. ^{31}P NMR spectrum of **209b2**

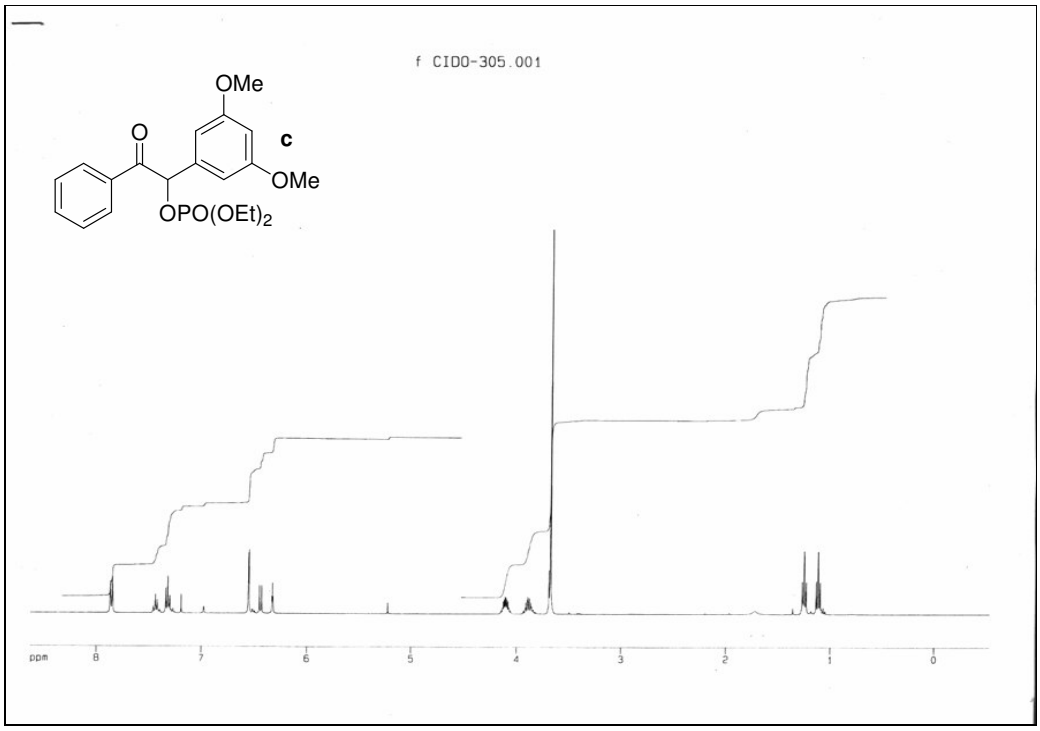

Figure 90. ^{1}H NMR spectrum of **209c**

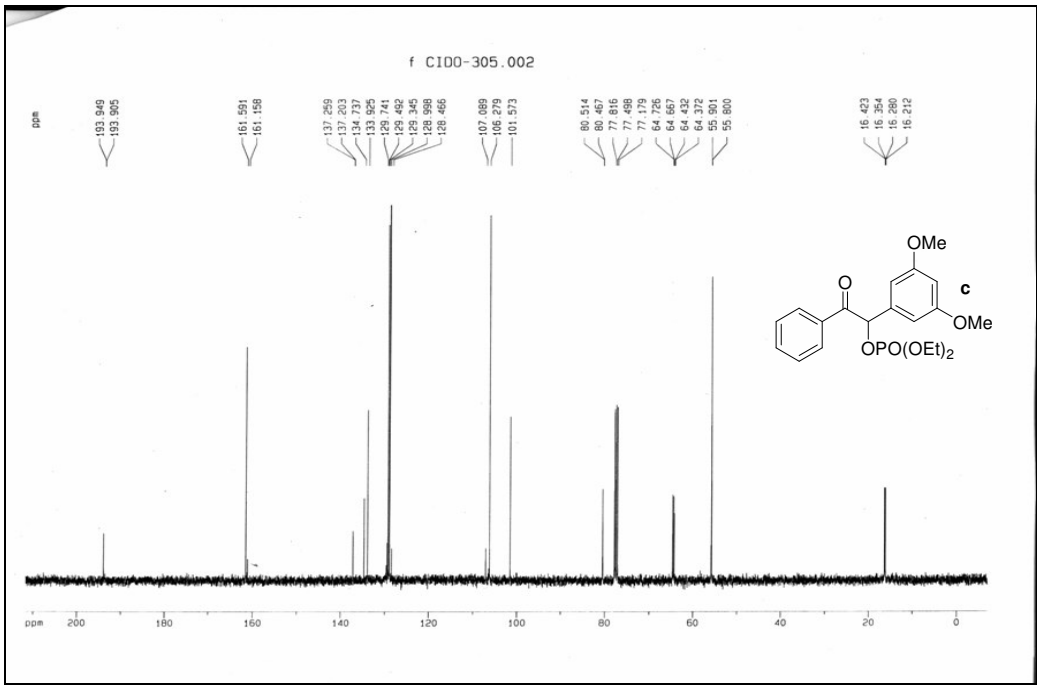

Figure 91. ^{13}C NMR spectrum of **209c**

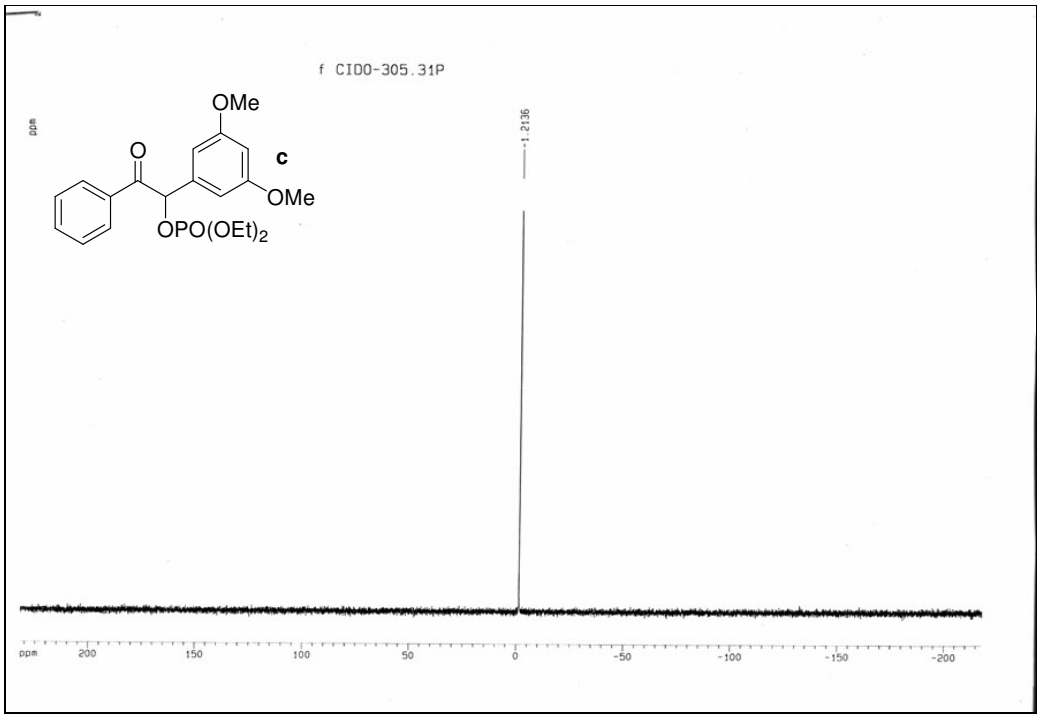

Figure 92. ^{31}P NMR spectrum of **209c**

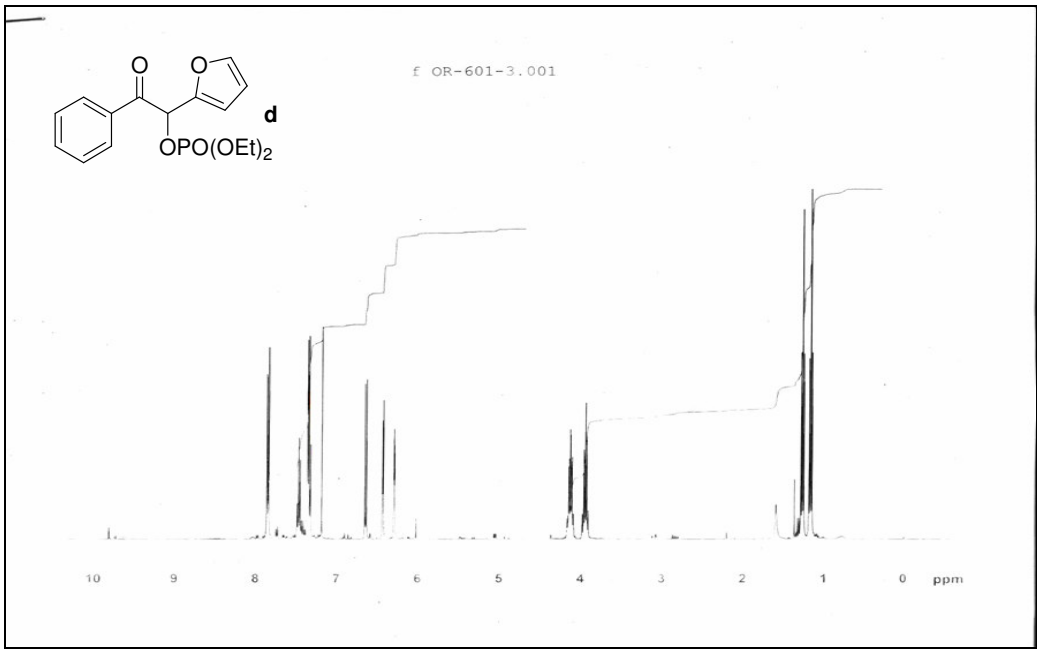

Figure 93. ^{1}H NMR spectrum of **209d**

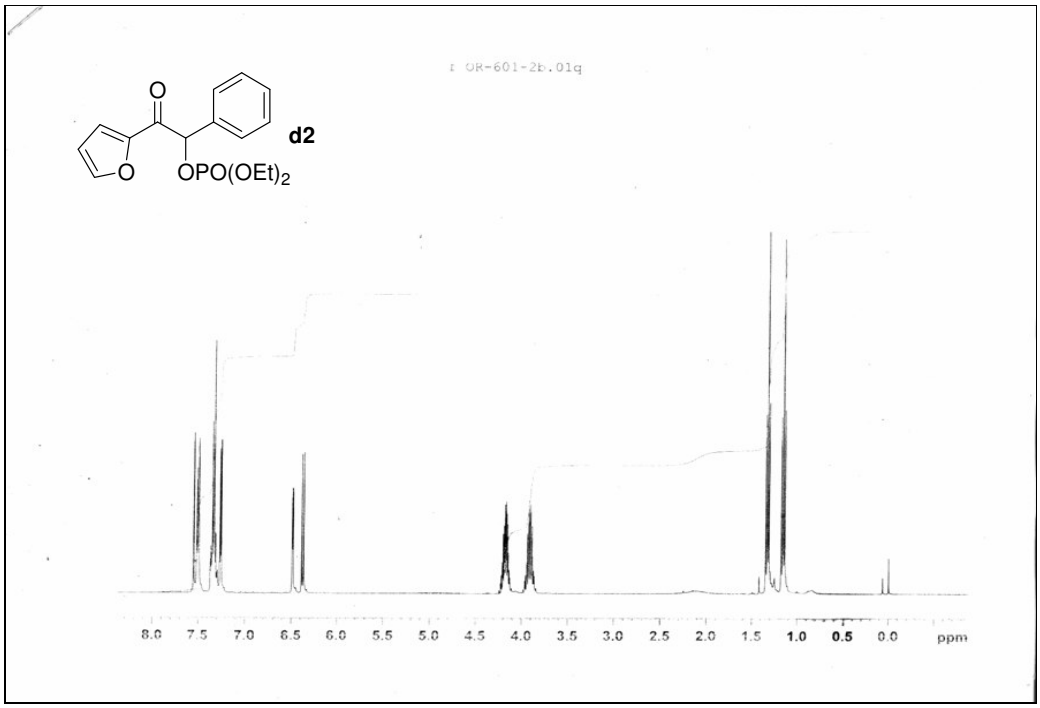

Figure 94. ^{1}H NMR spectrum of **209d2**

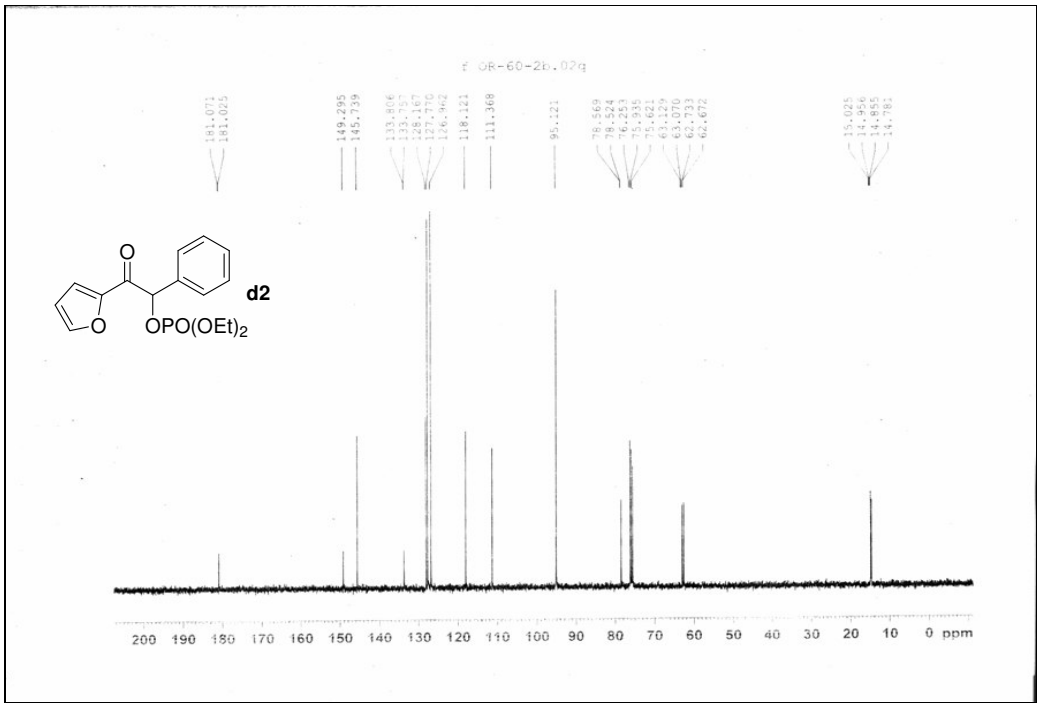

Figure 95. ^{13}C NMR spectrum of **209d2**

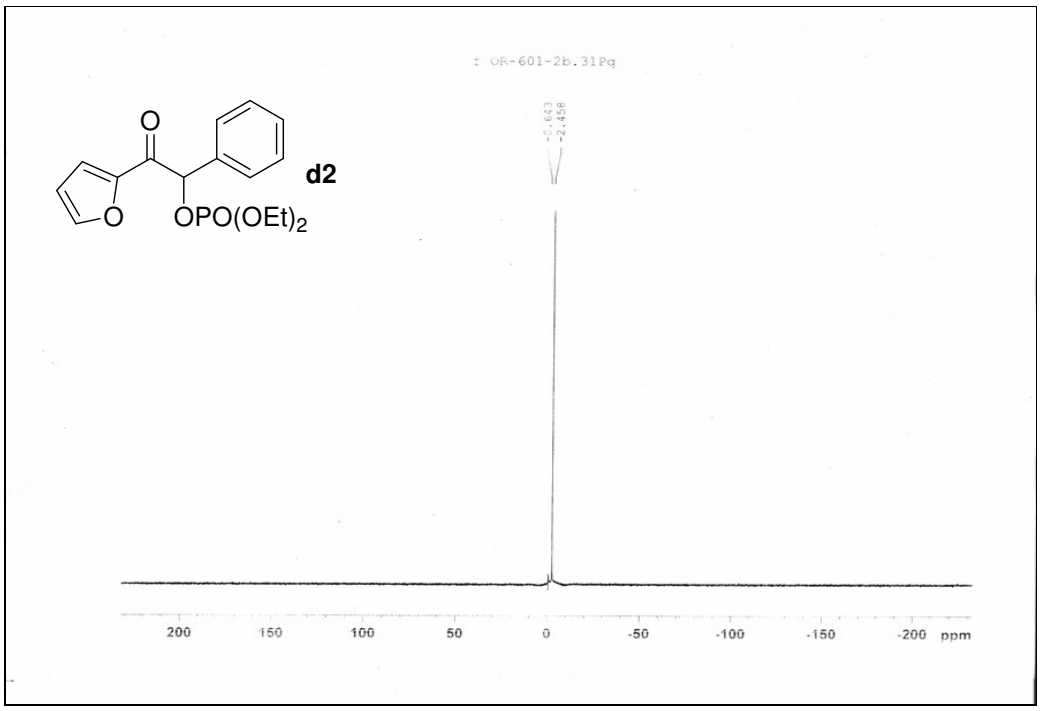

Figure 96. ^{31}P NMR spectrum of **209d2**

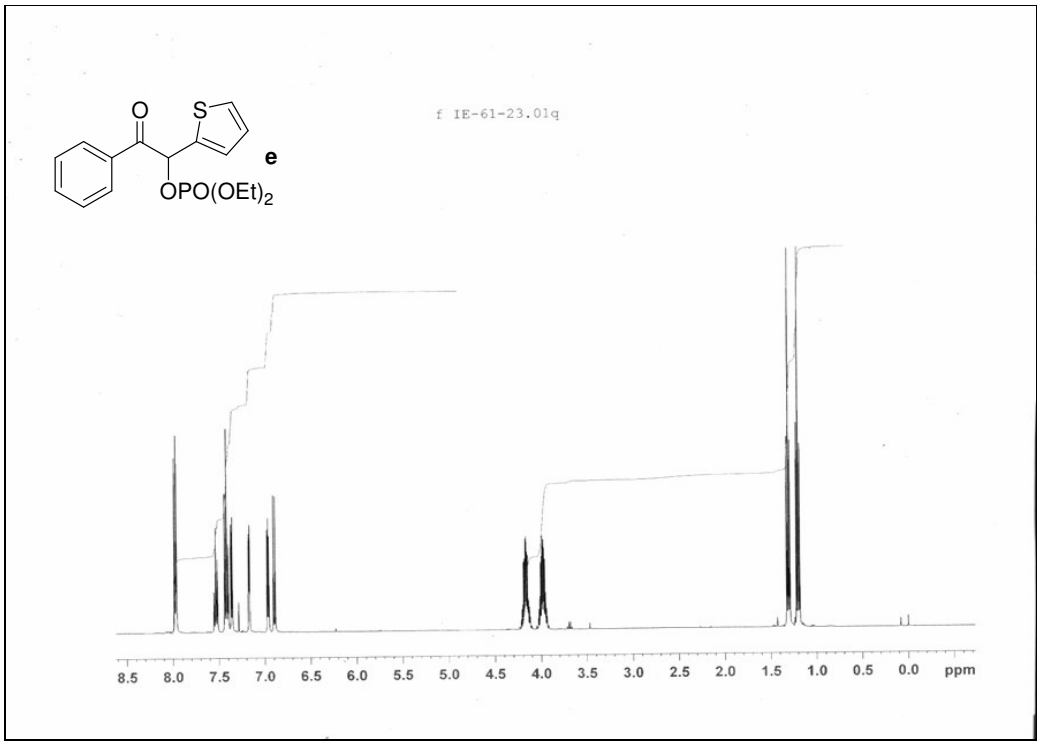

Figure 97. ^{1}H NMR spectrum of **209e**

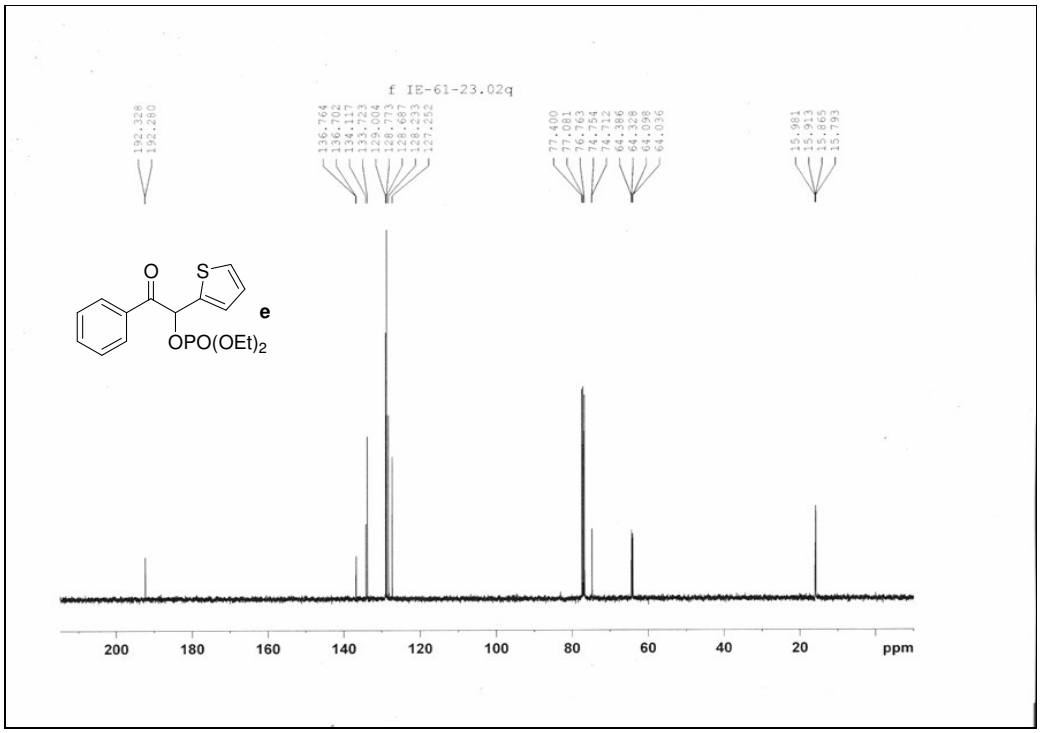

Figure 98. ^{13}C NMR spectrum of **209e**

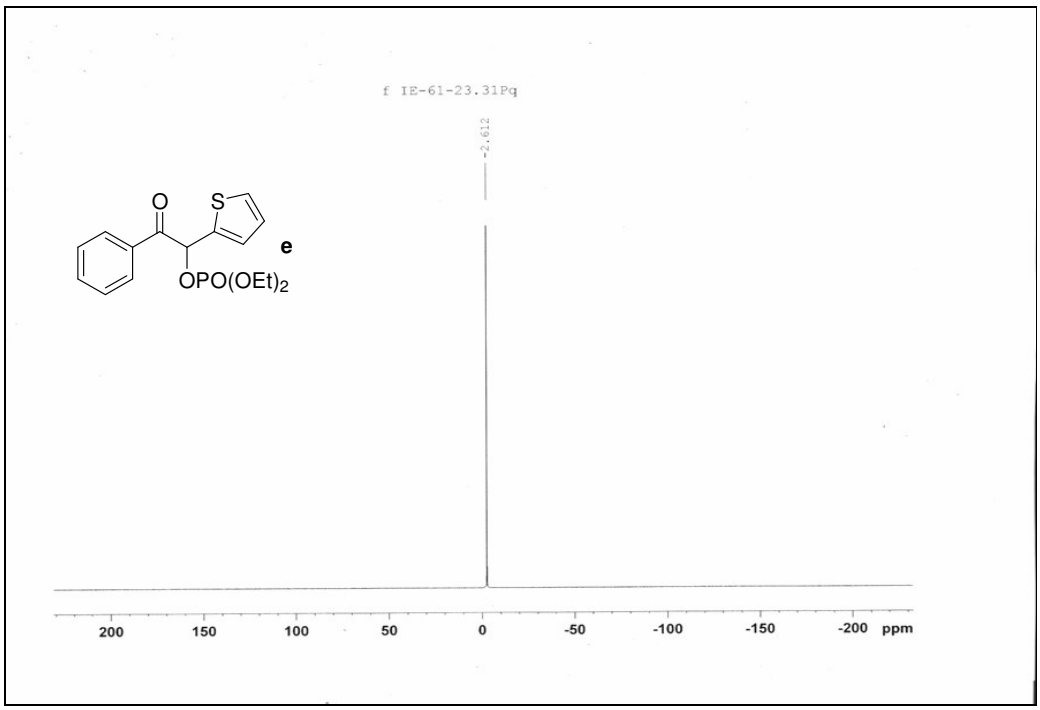

Figure 99. ^{31}P NMR spectrum of **209e**

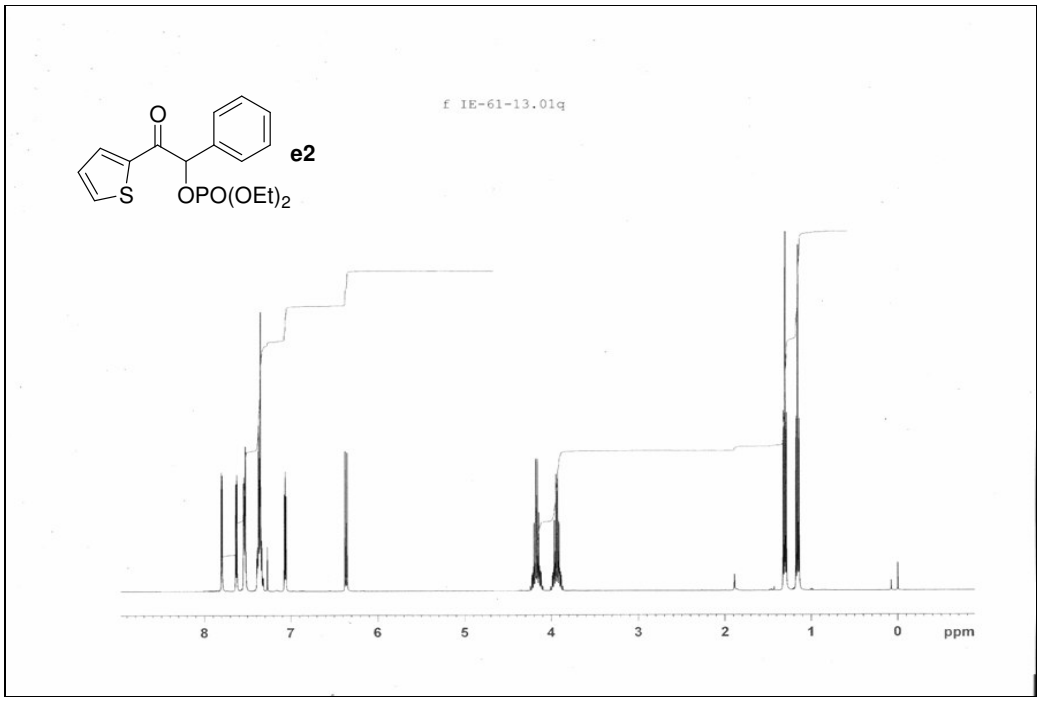

Figure 100. ^{1}H NMR spectrum of **209e2**

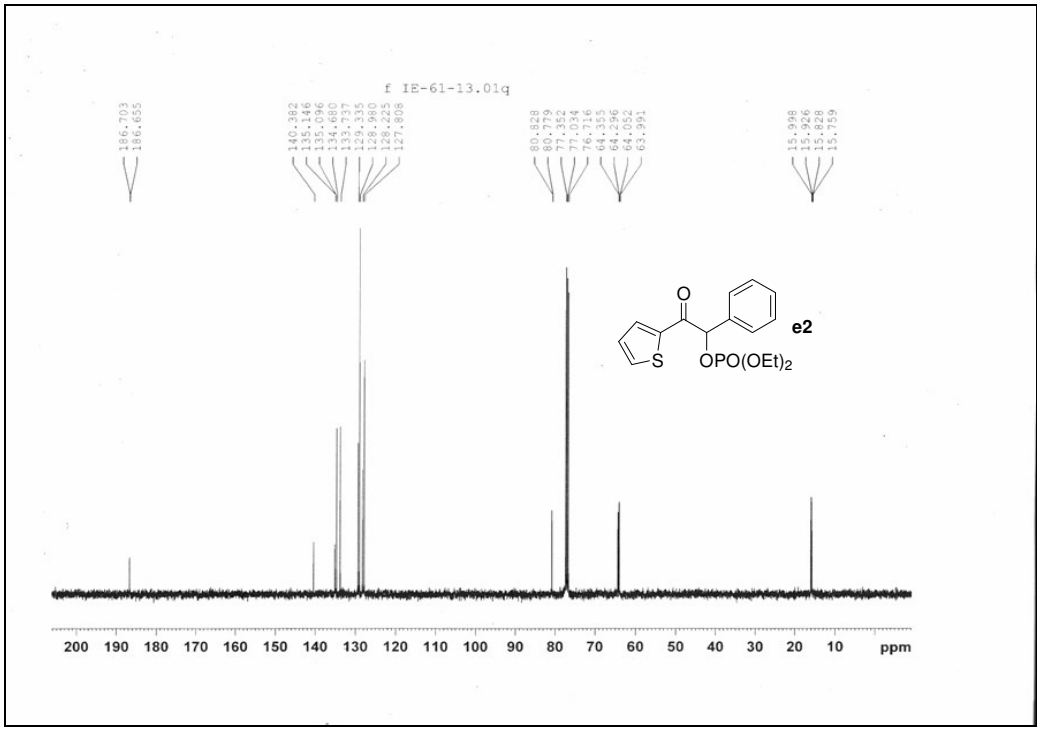

Figure 101. ^{13}C NMR spectrum of **209e2**

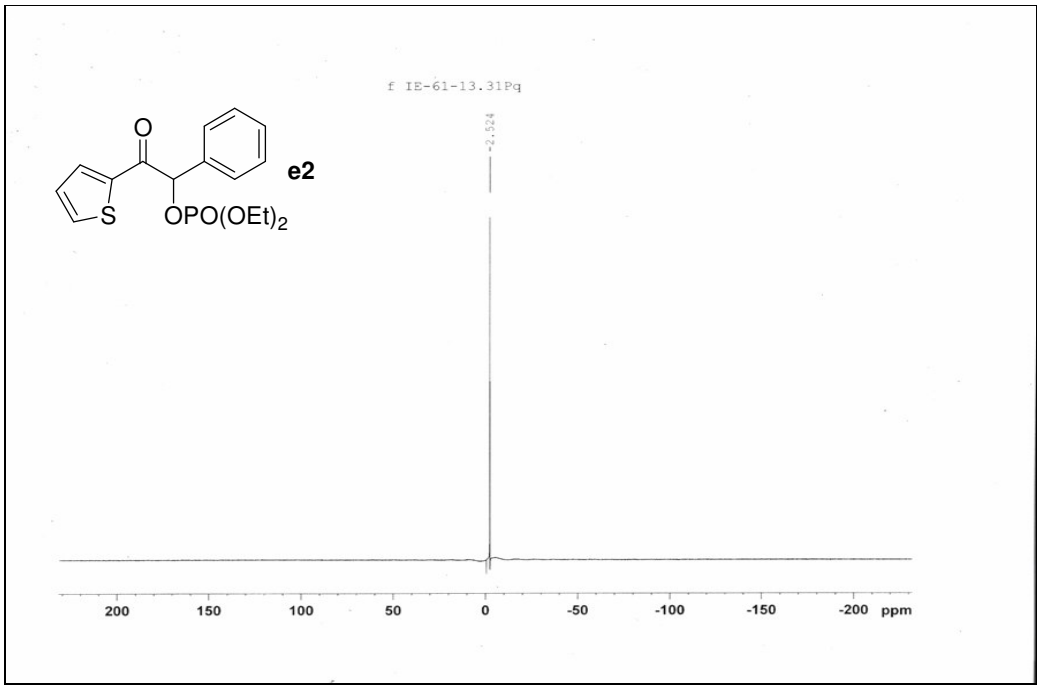

Figure 102. ^{31}P NMR spectrum of **209e2**

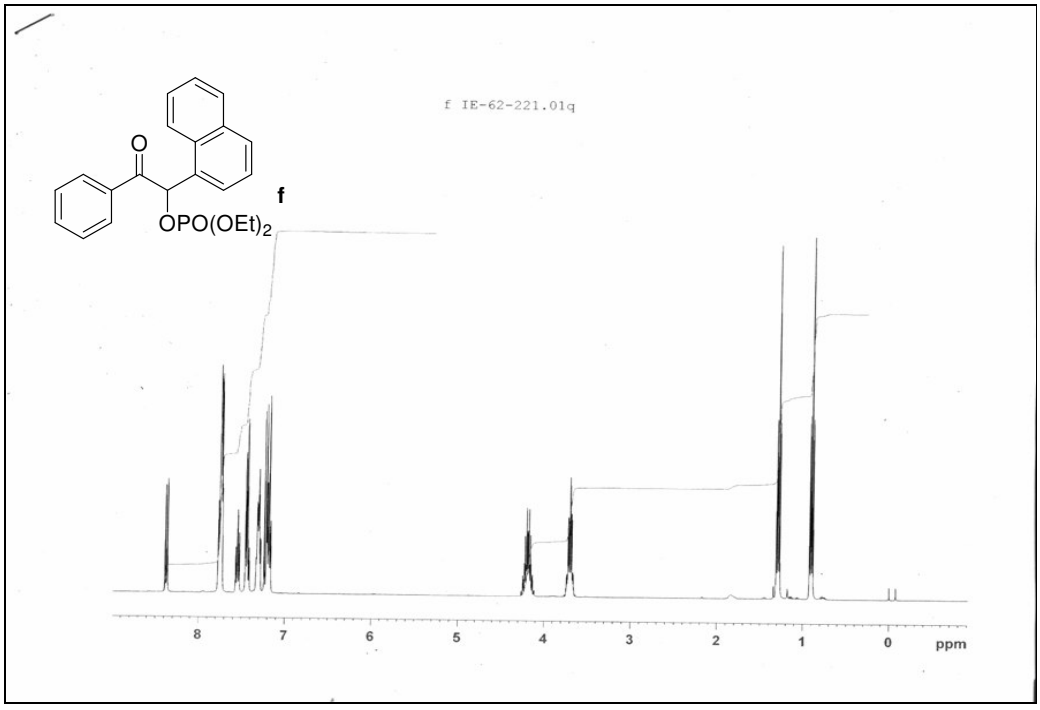

Figure 103. ^{1}H NMR spectrum of **209f**

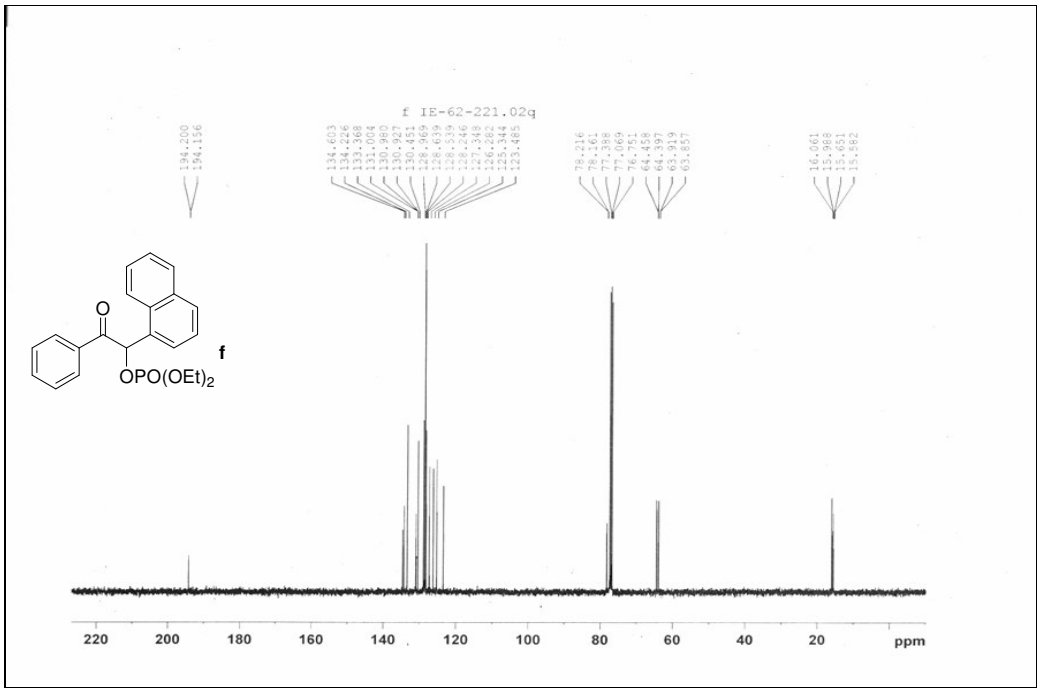

Figure 104. ^{13}C NMR spectrum of **209f**

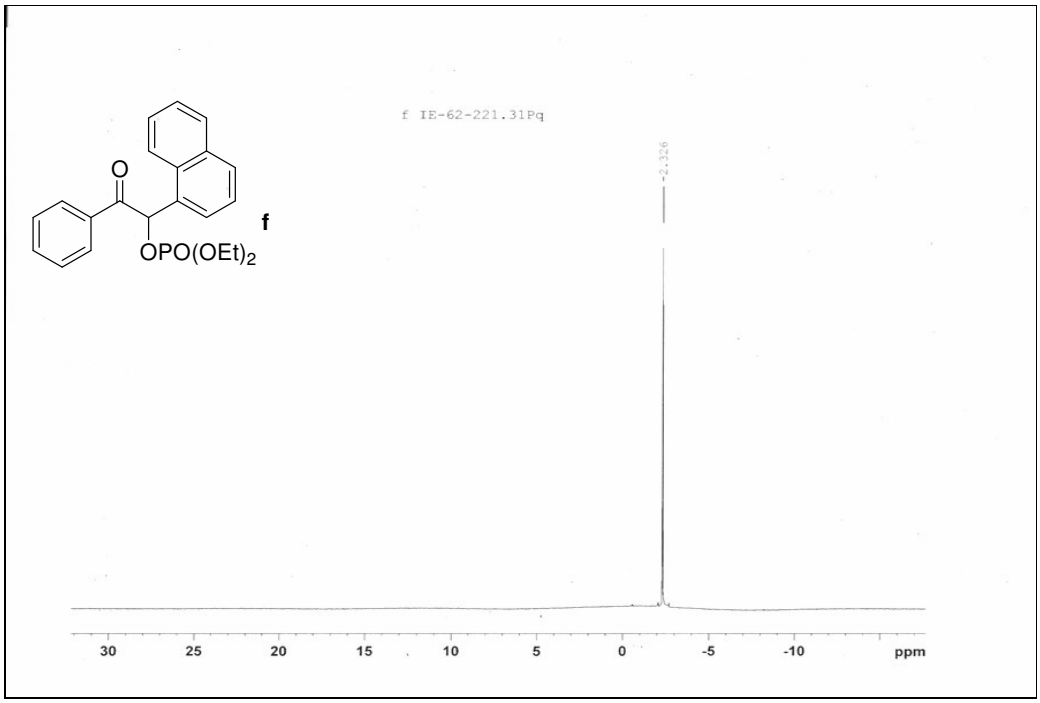

Figure 105. ^{31}P NMR spectrum of **209f**

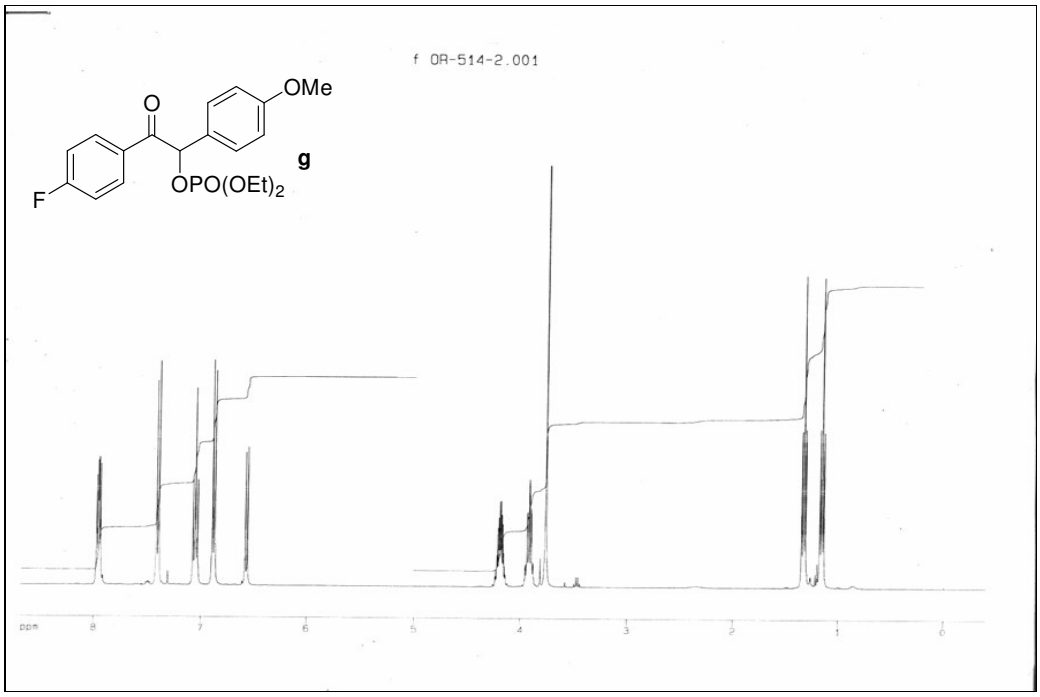

Figure 106. ^{1}H NMR spectrum of **209g**

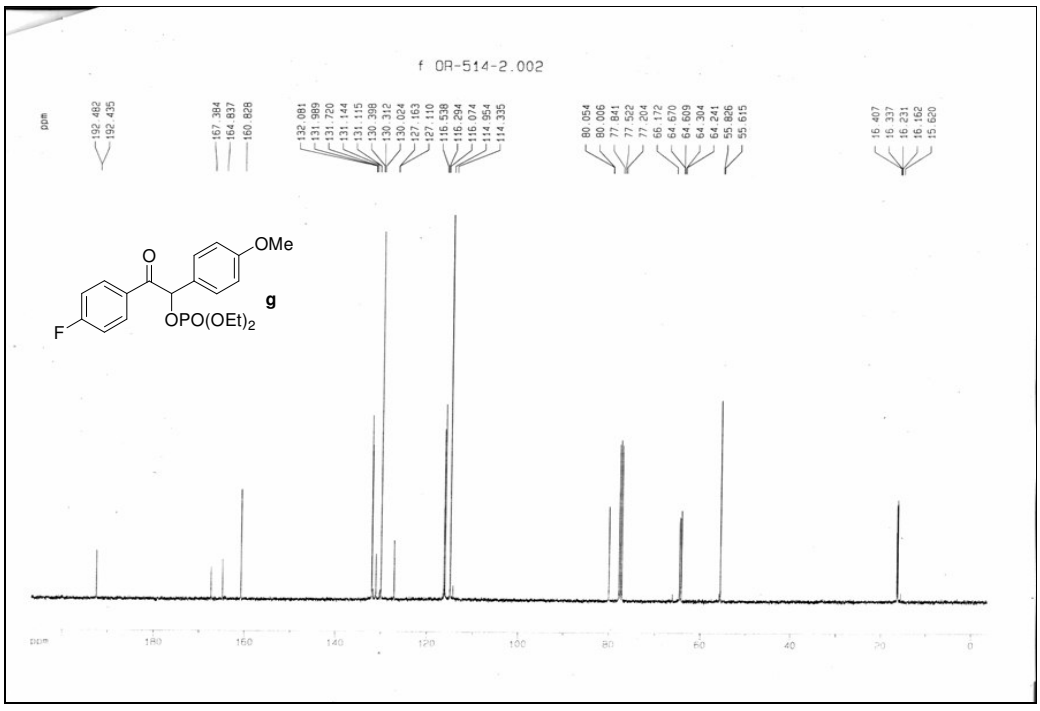

Figure 107. ^{13}C NMR spectrum of **209g**

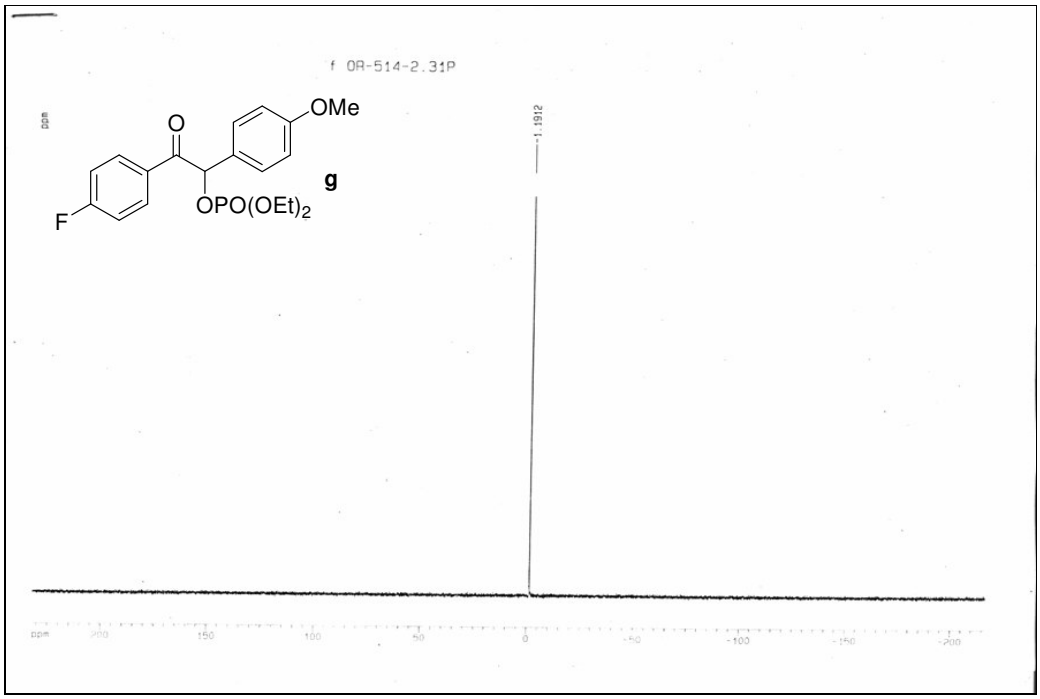

Figure 108. ^{31}P NMR spectrum of **209g**

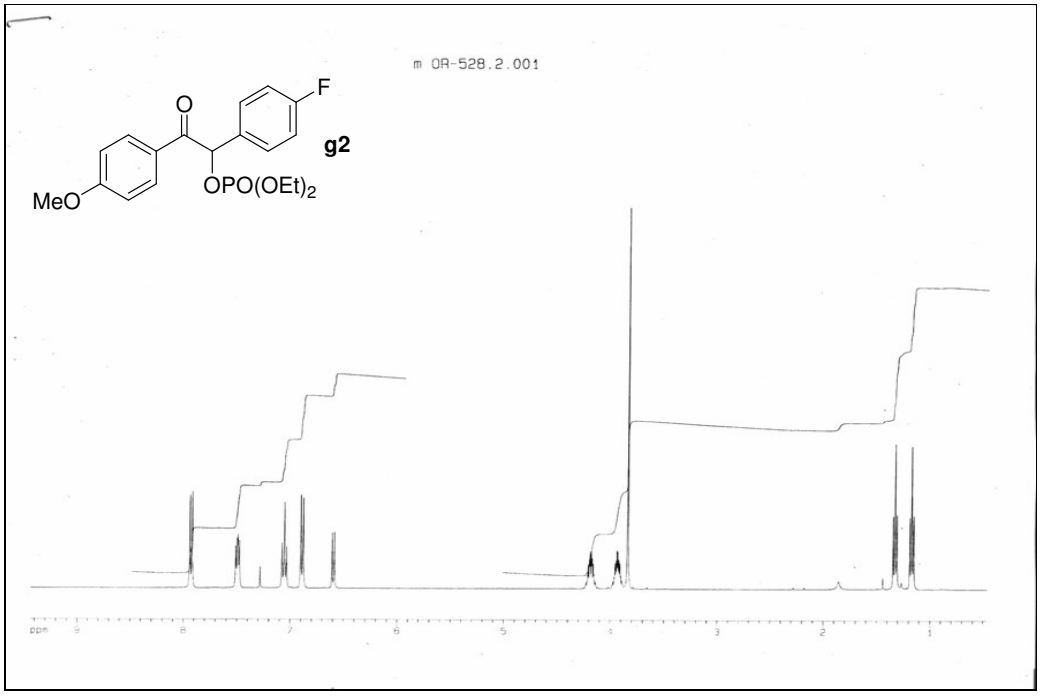

Figure 109. ^{1}H NMR spectrum of **209g2**

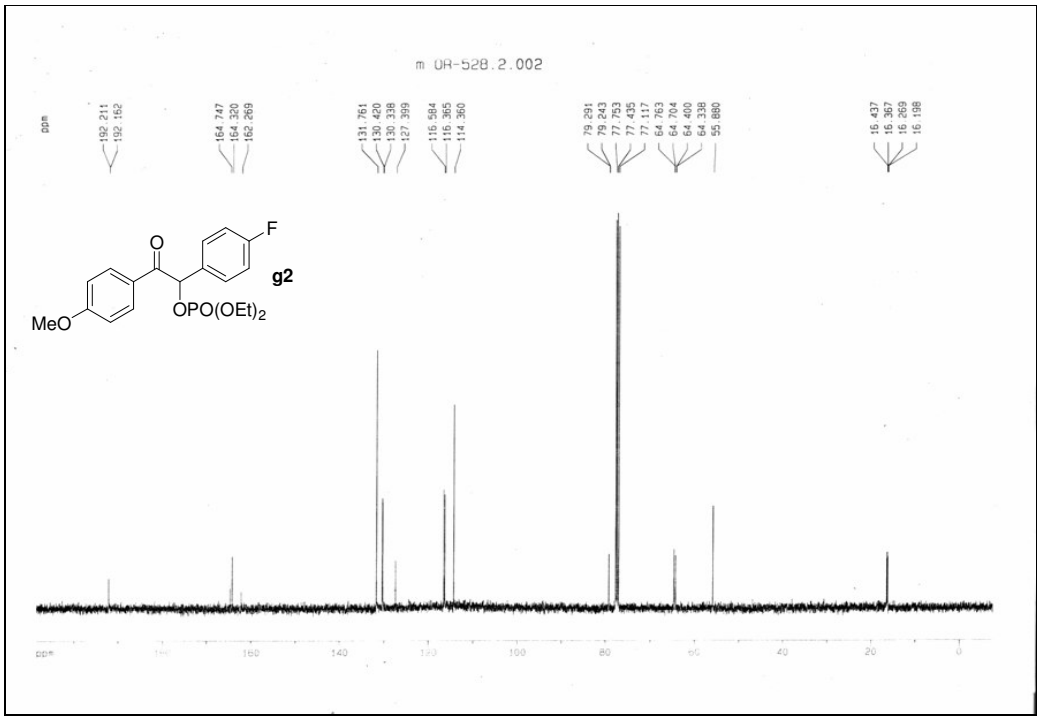

Figure 110. ^{13}C NMR spectrum of **209g2**

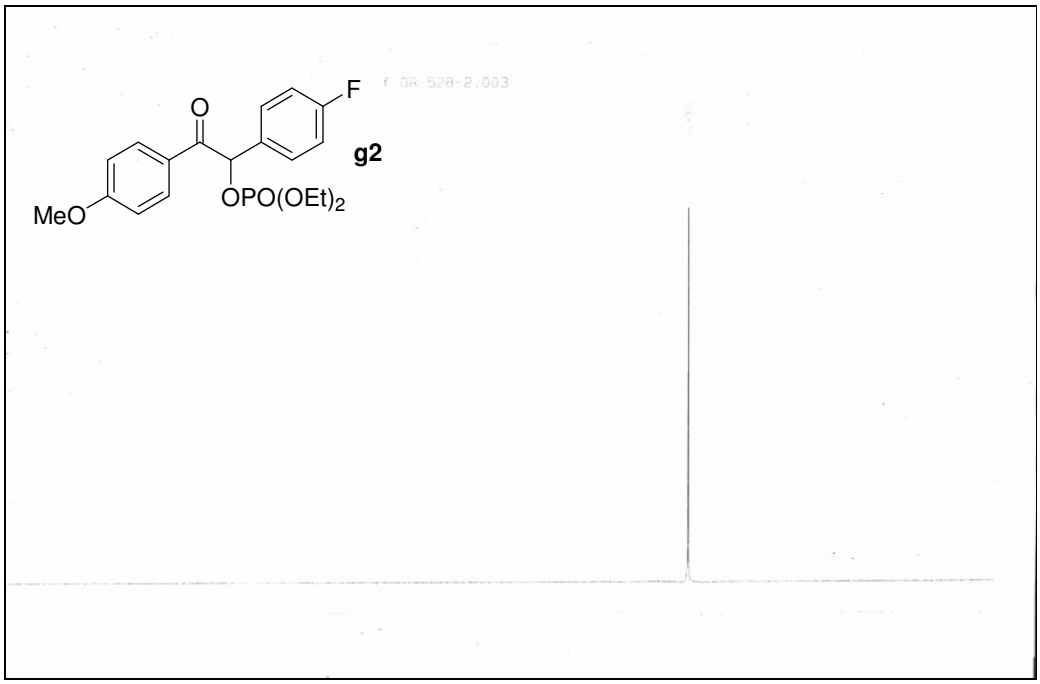

Figure 111. ^{31}P NMR spectrum of **209g2**

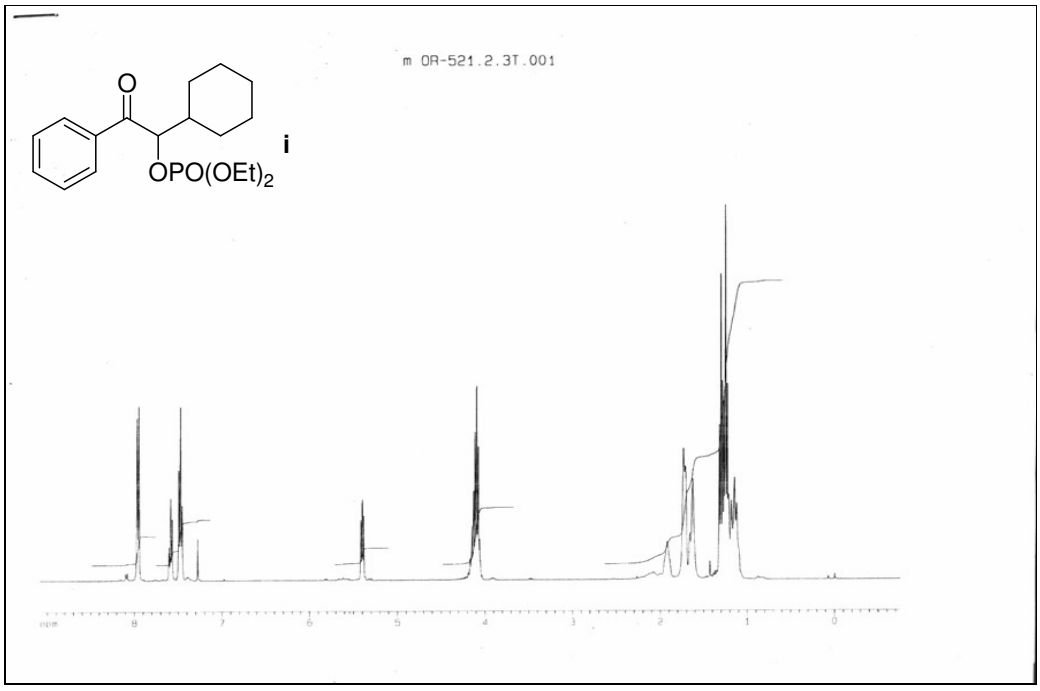

Figure 112. ^{1}H NMR spectrum of **209i**

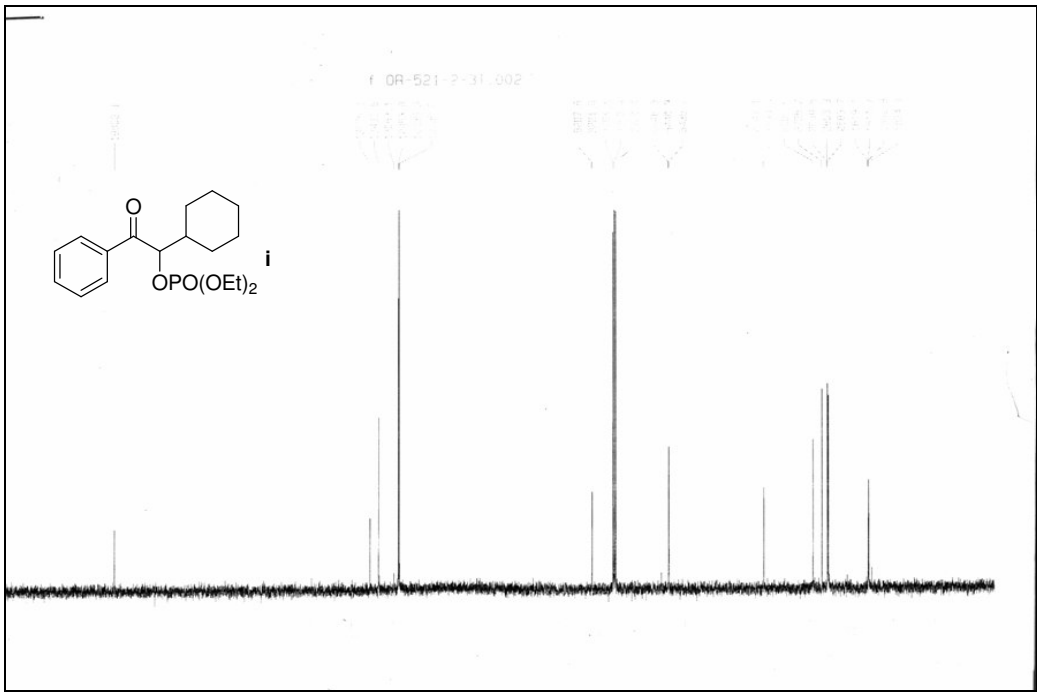

Figure 113. ^{13}C NMR spectrum of **209i**

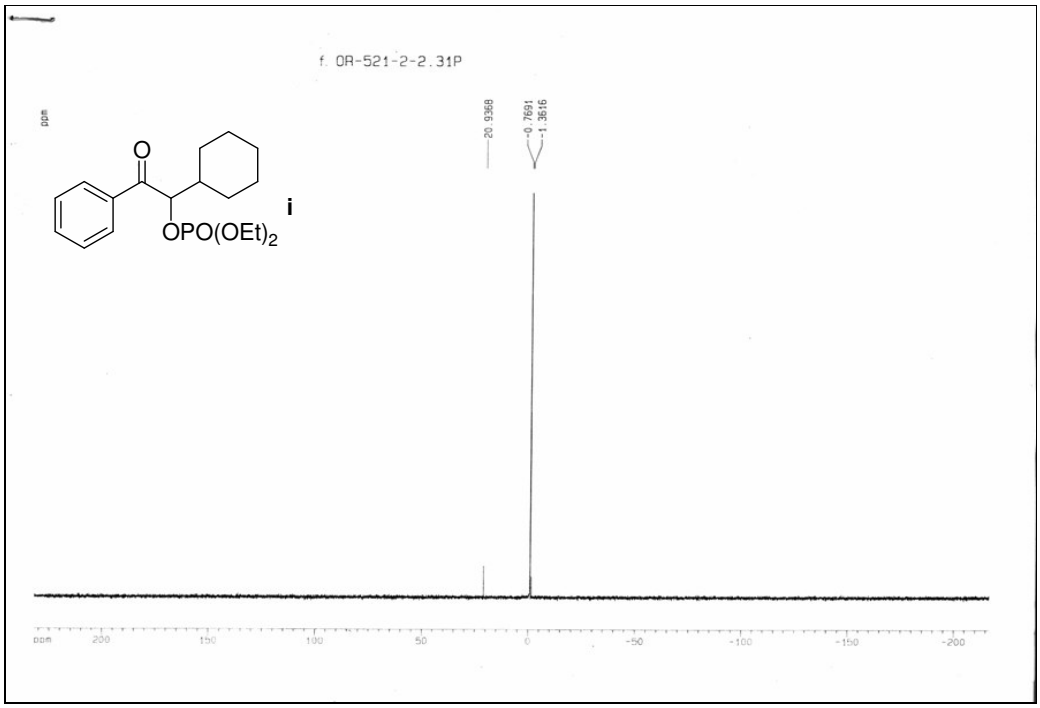

Figure 114. ^{31}P NMR spectrum of **209i**

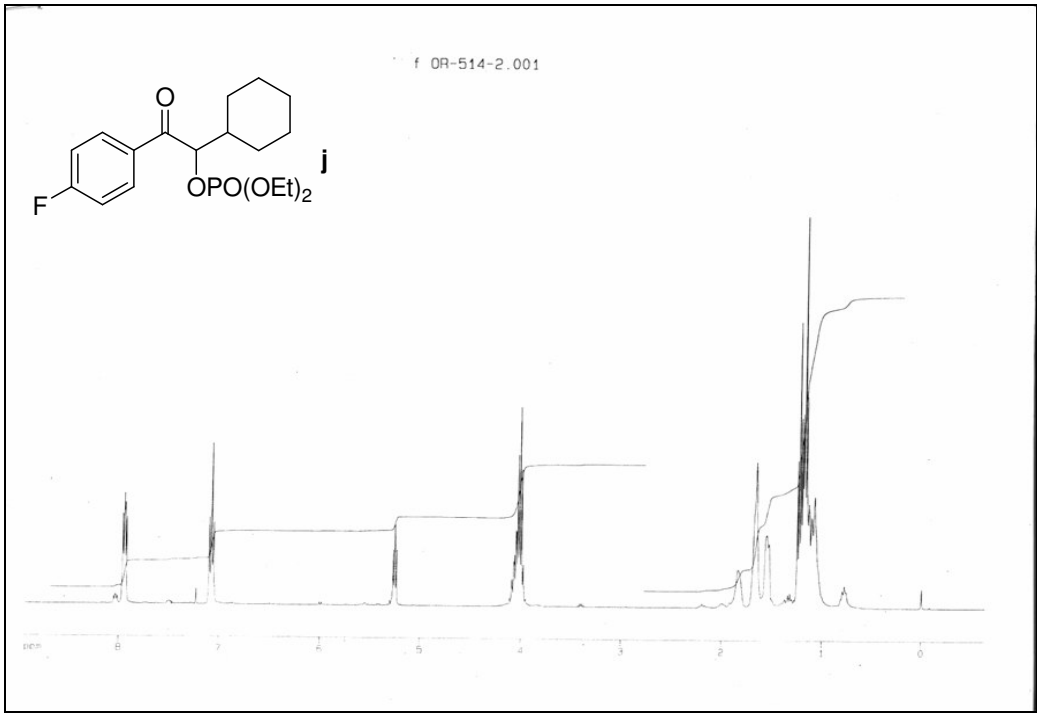

Figure 115. ^{1}H NMR spectrum of **209j**

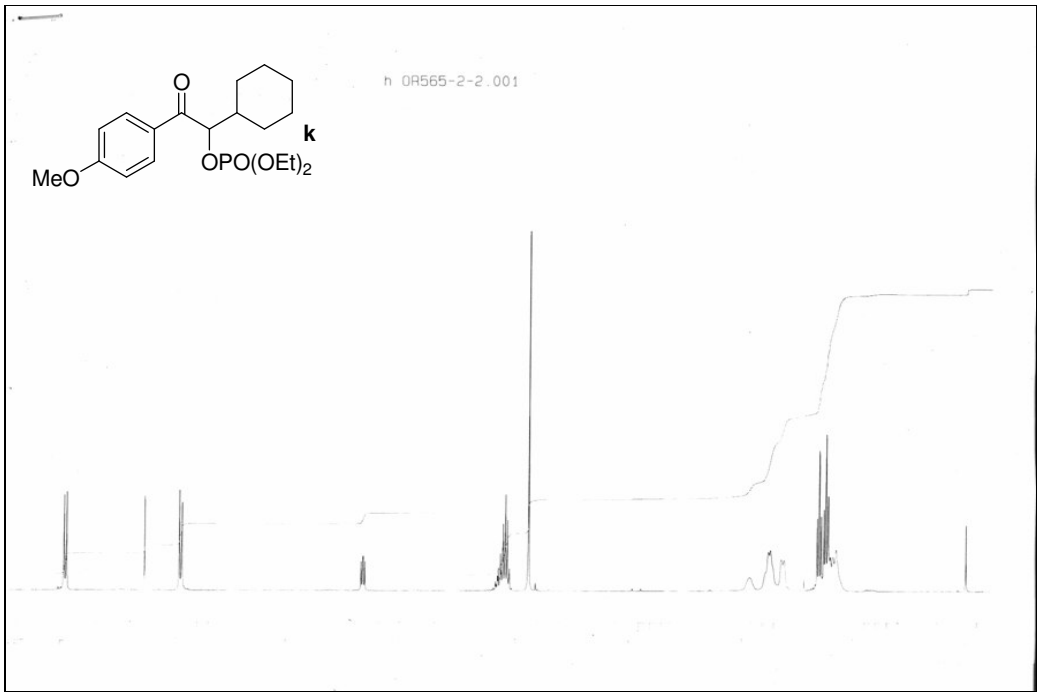

Figure 116. ^{1}H NMR spectrum of **209k**

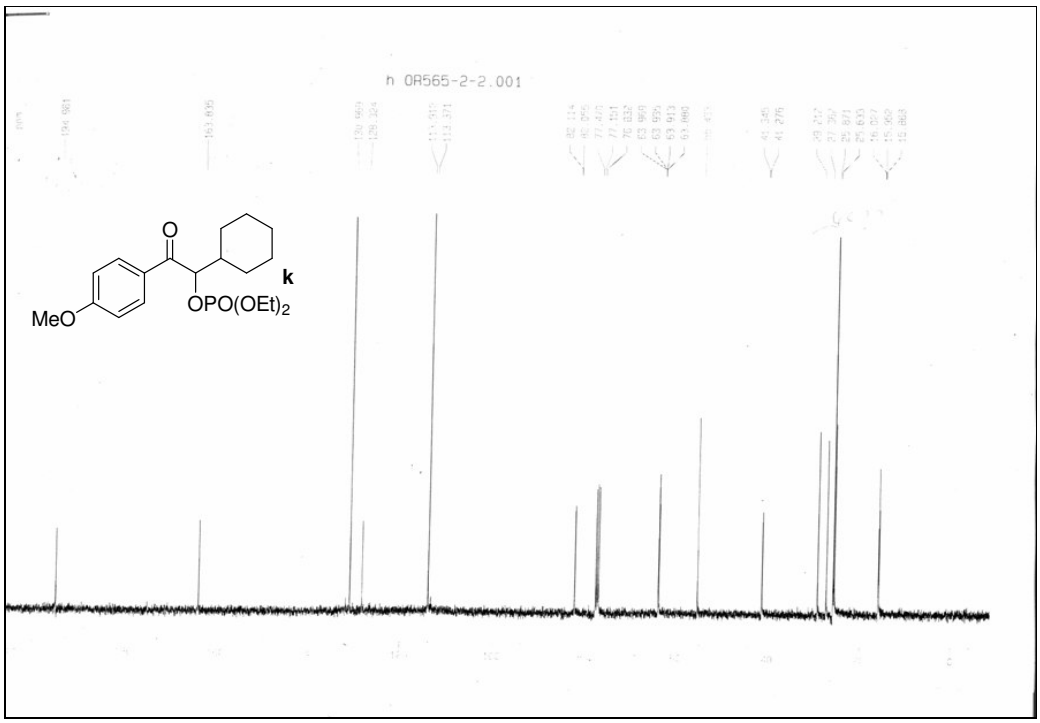

Figure 117. ^{13}C NMR spectrum of **209k**

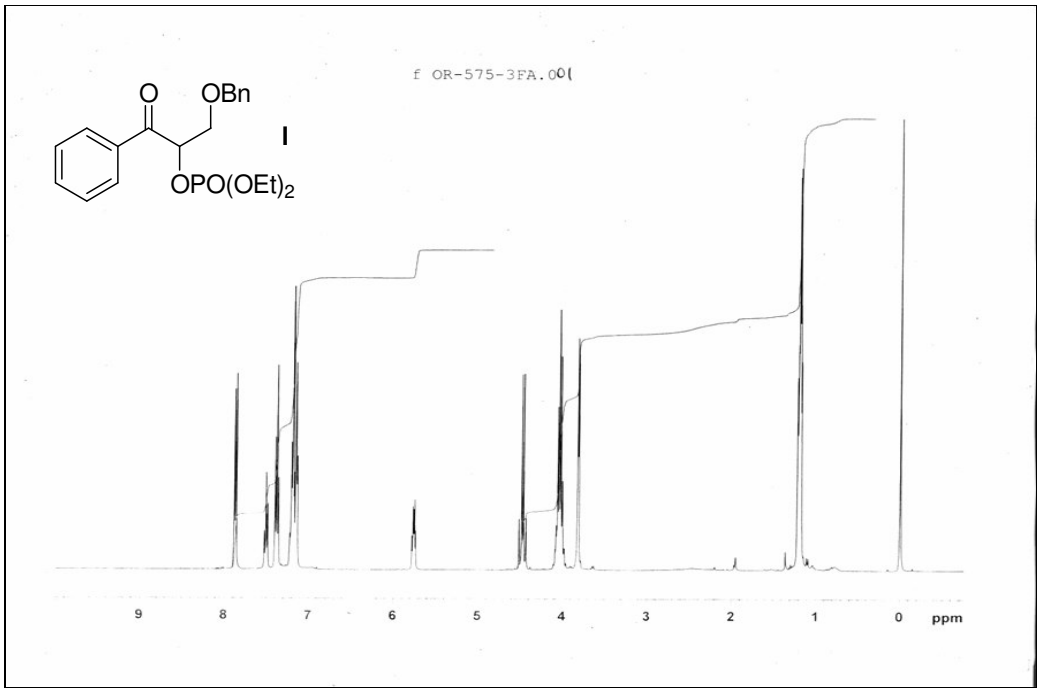

Figure 118. ^{1}H NMR spectrum of **209l**

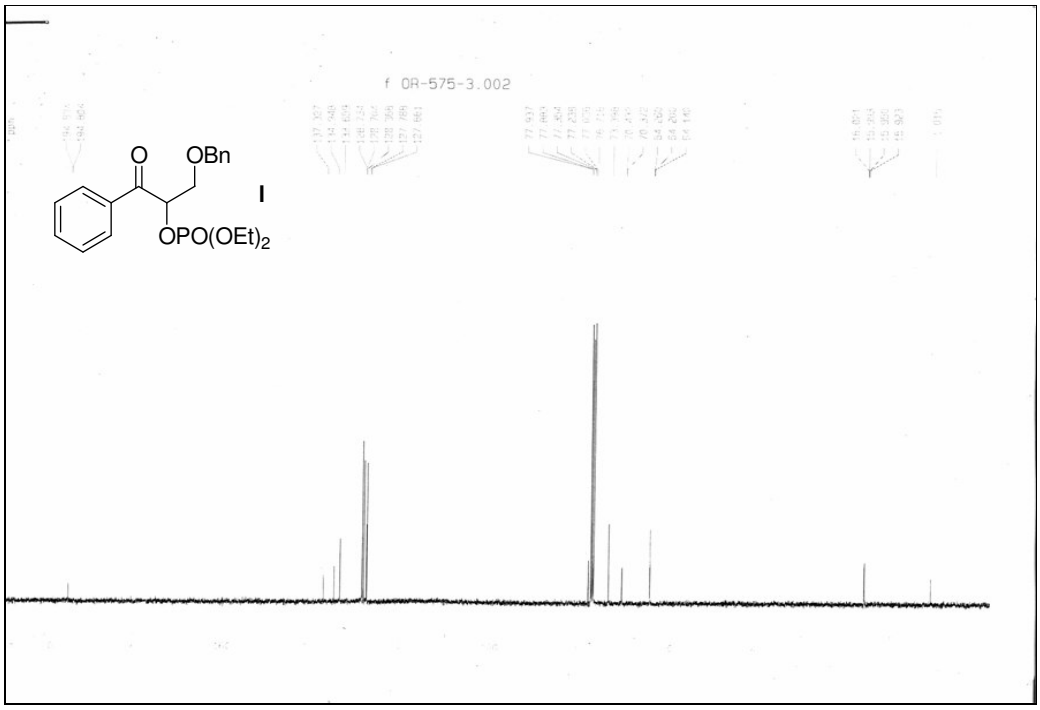

Figure 119. ^{13}C NMR spectrum of **209l**

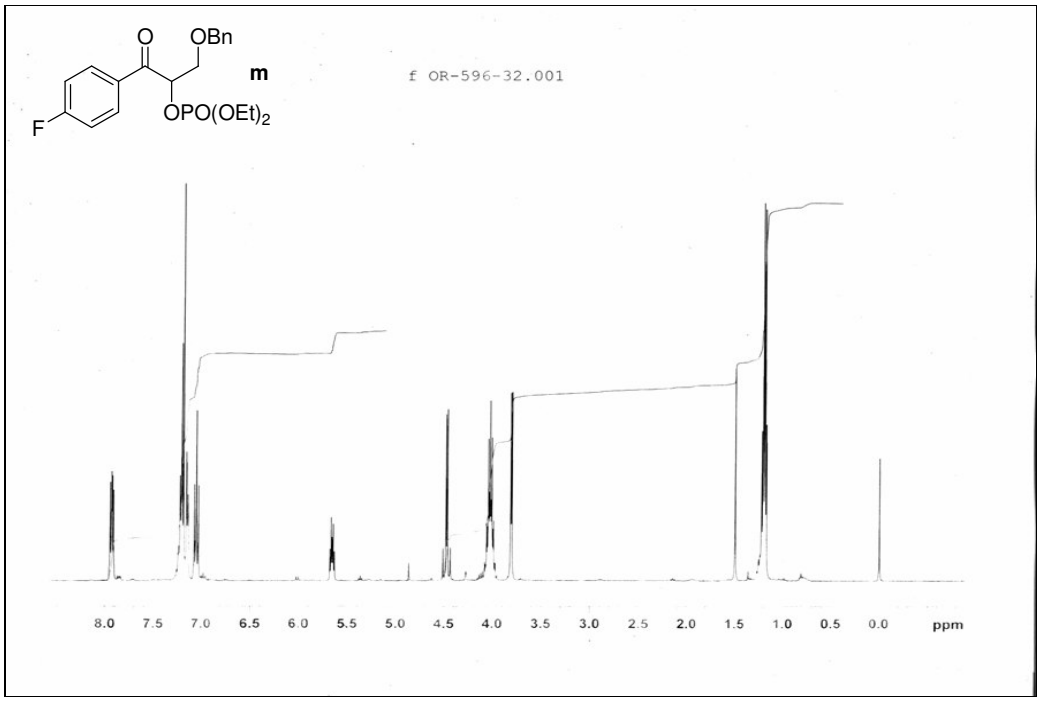

Figure 120. ^{1}H NMR spectrum of **209m**

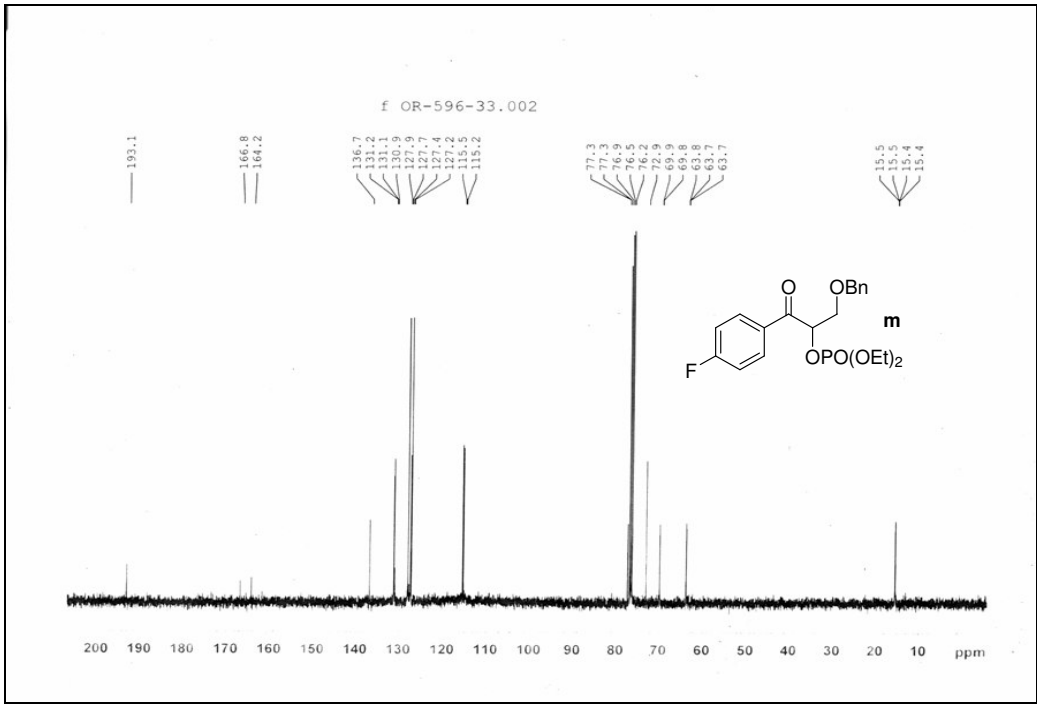

Figure 121. ^{13}C NMR spectrum of **209m**

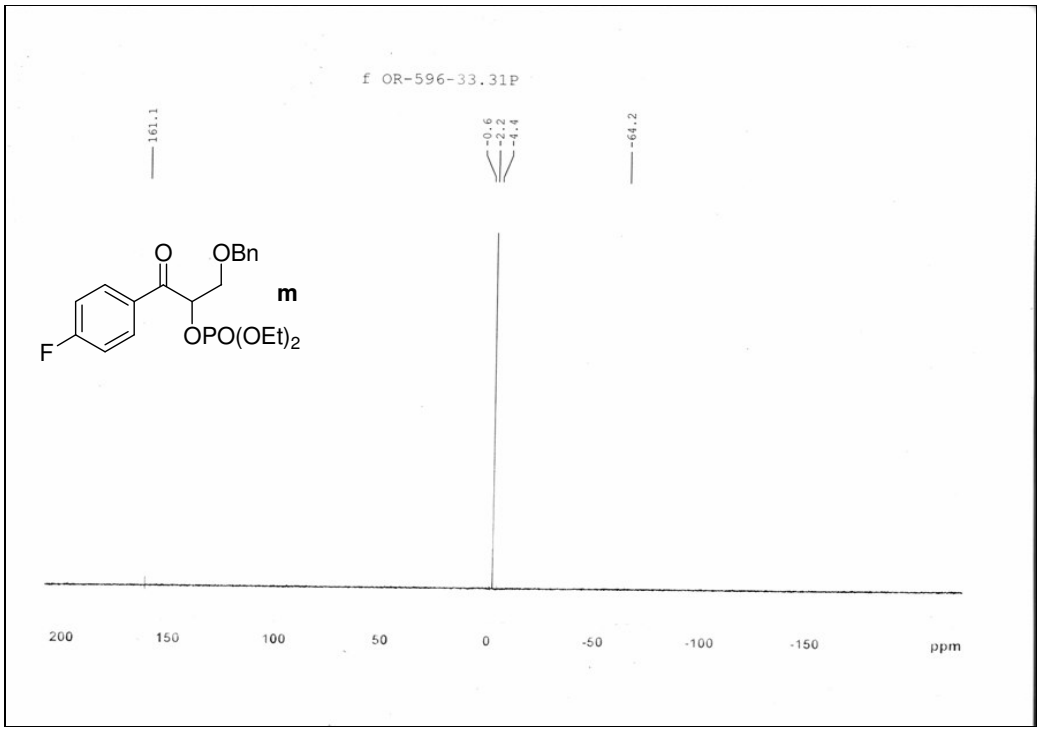

Figure 122. ^{31}P NMR spectrum of **209m**

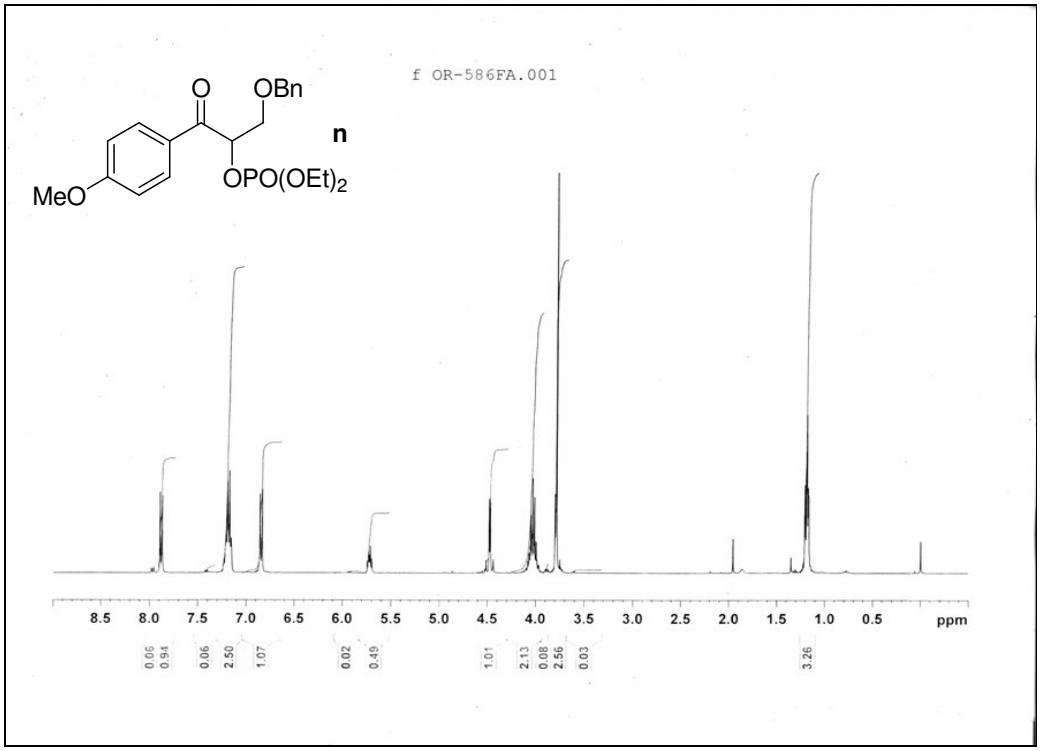

Figure 123. ^{1}H NMR spectrum of **209n**

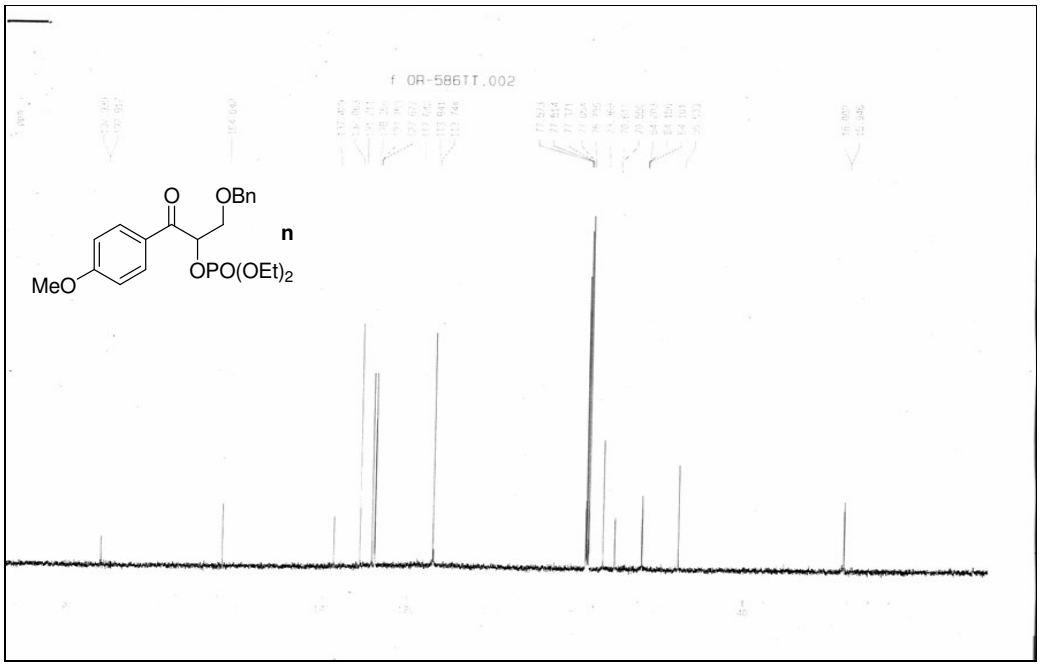

Figure 124. ^{13}C NMR spectrum of **209n**

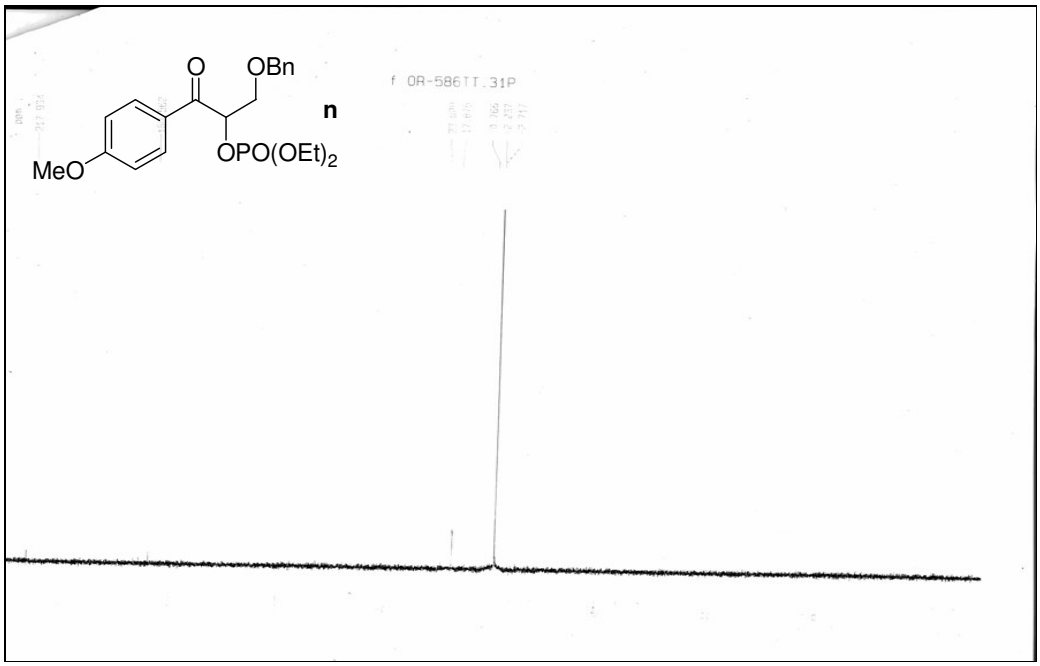

Figure 125. ^{31}P NMR spectrum of **209n**

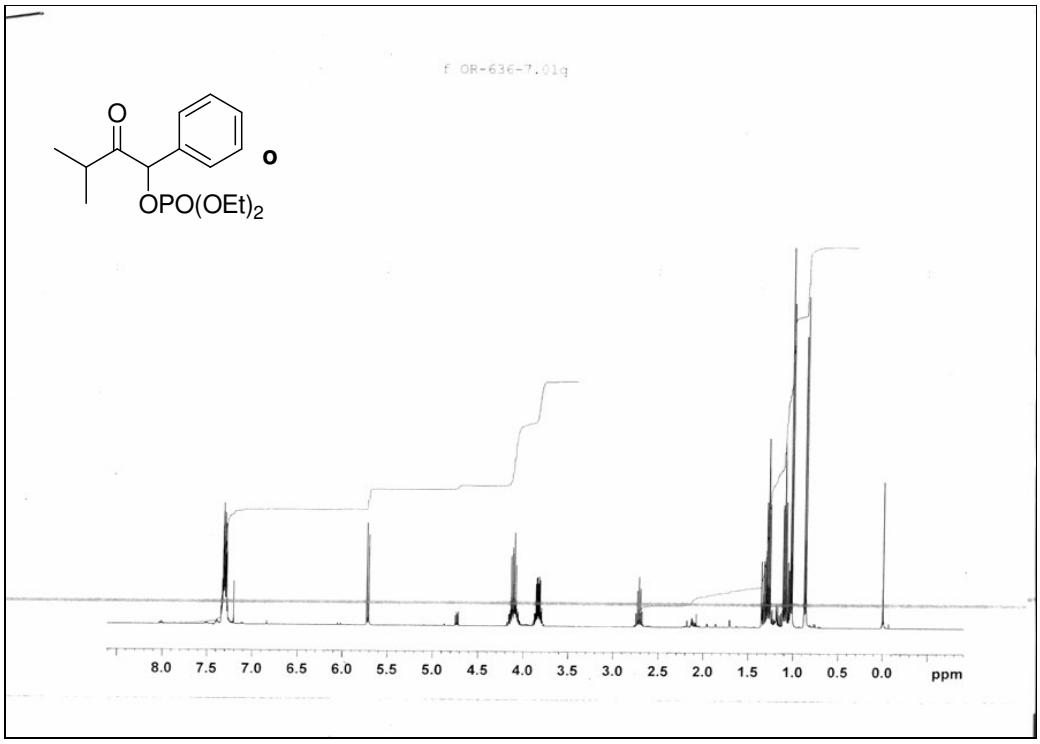

Figure 126. ^{1}H NMR spectrum of **209o**

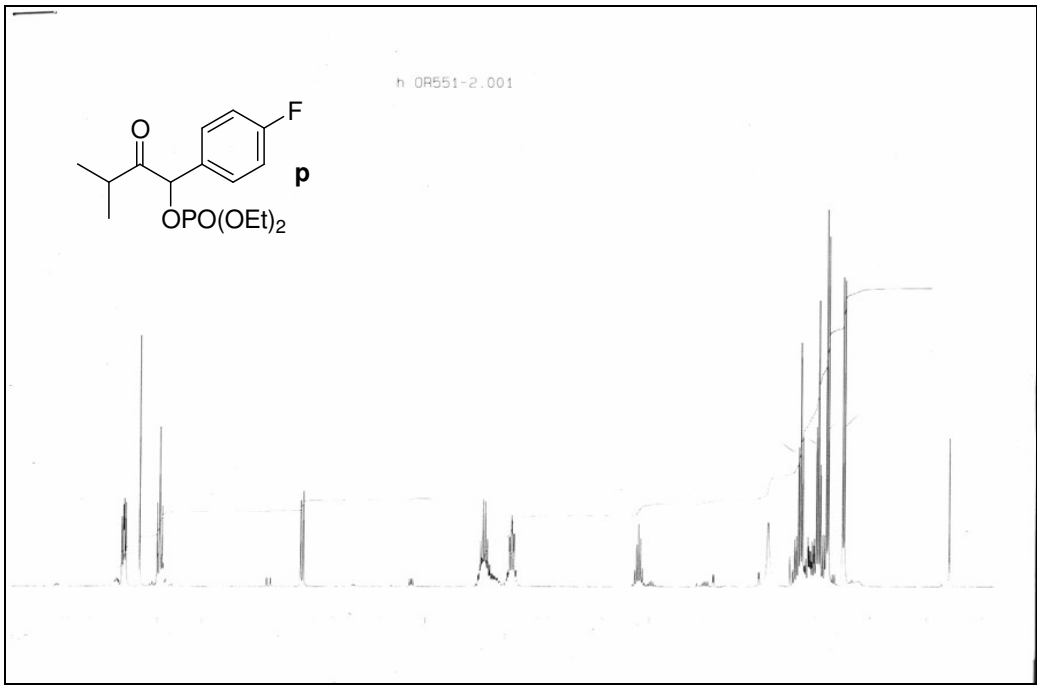

Figure 127. ^{1}H NMR spectrum of **209p**

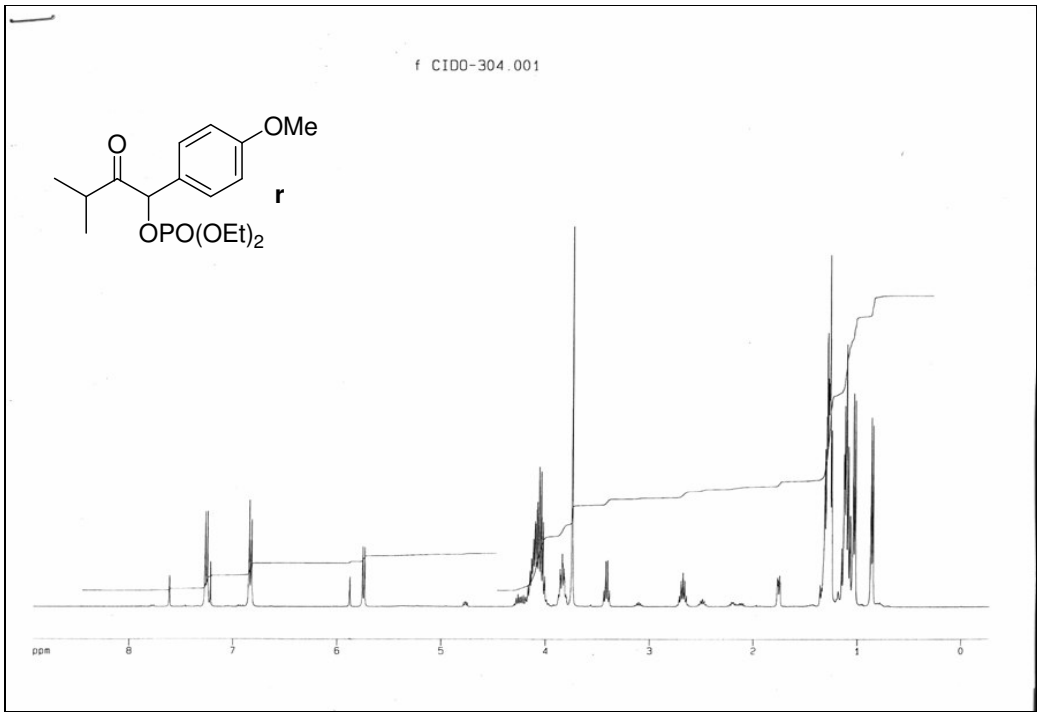

Figure 128. ^{1}H NMR spectrum of crude **209r**

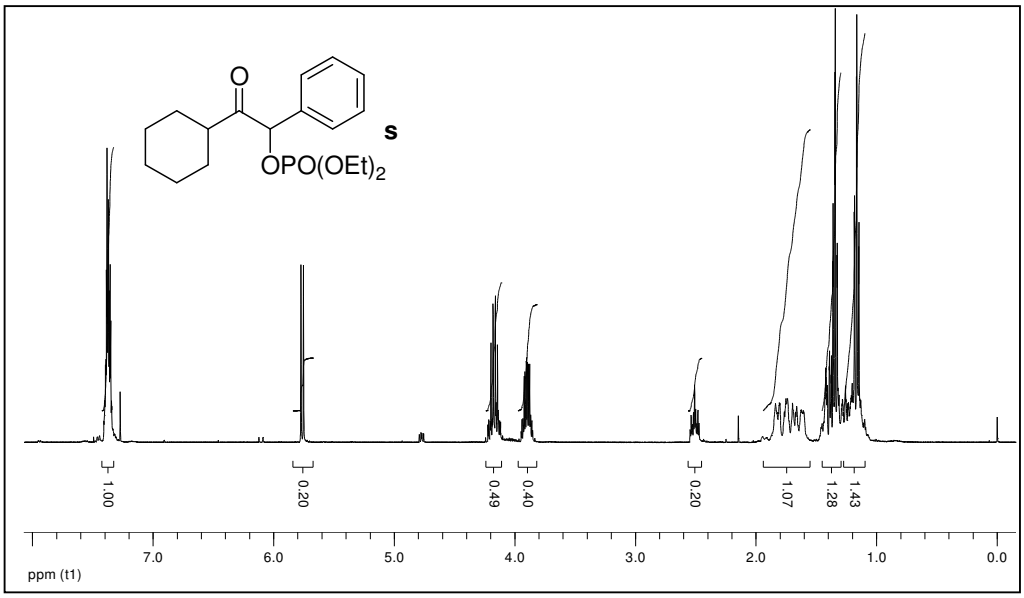

Figure 129. ^{1}H NMR spectrum of **209s**

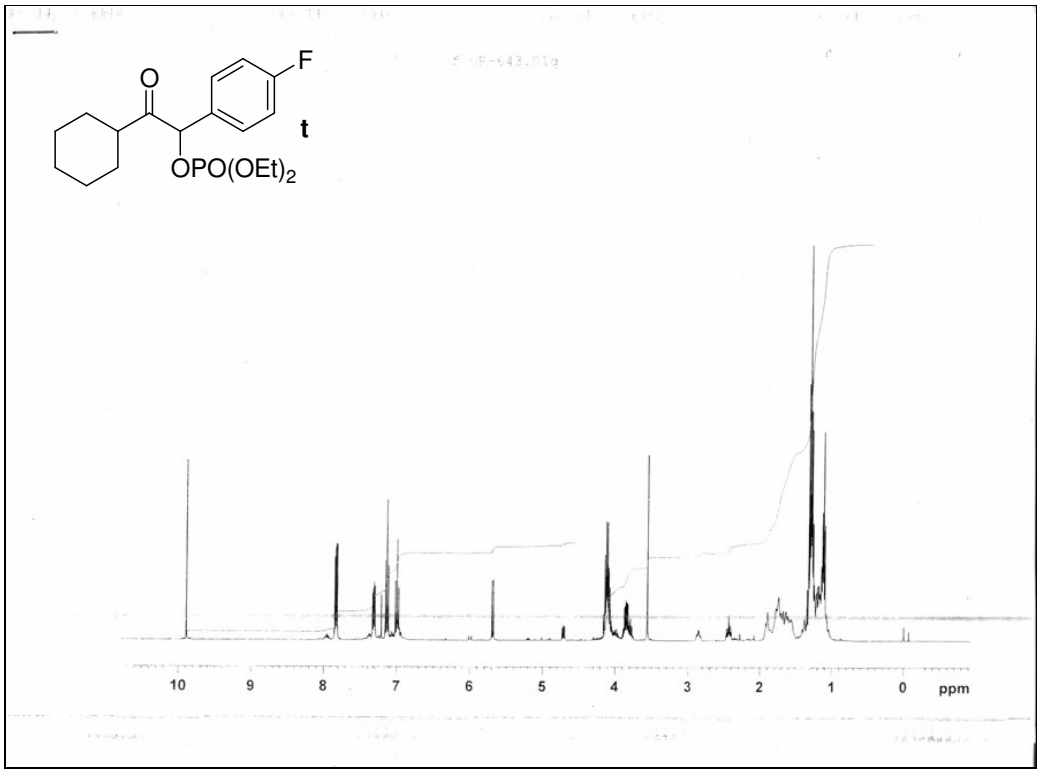

Figure 130. ^{1}H NMR spectrum of crude **209t**

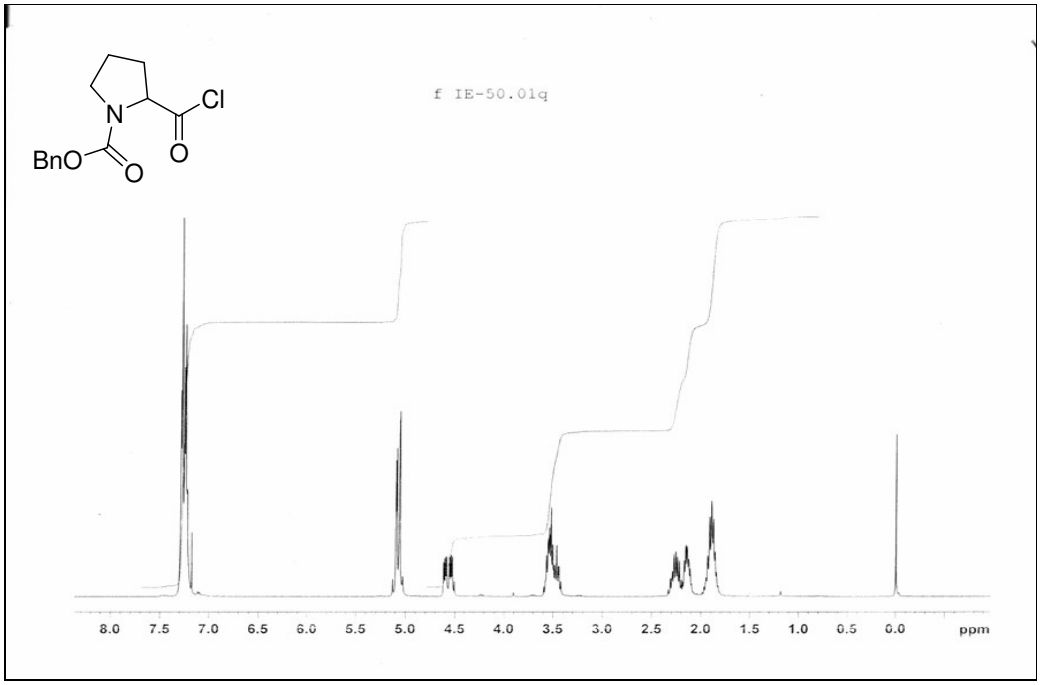

Figure 131. ^{1}H NMR spectrum of **215**

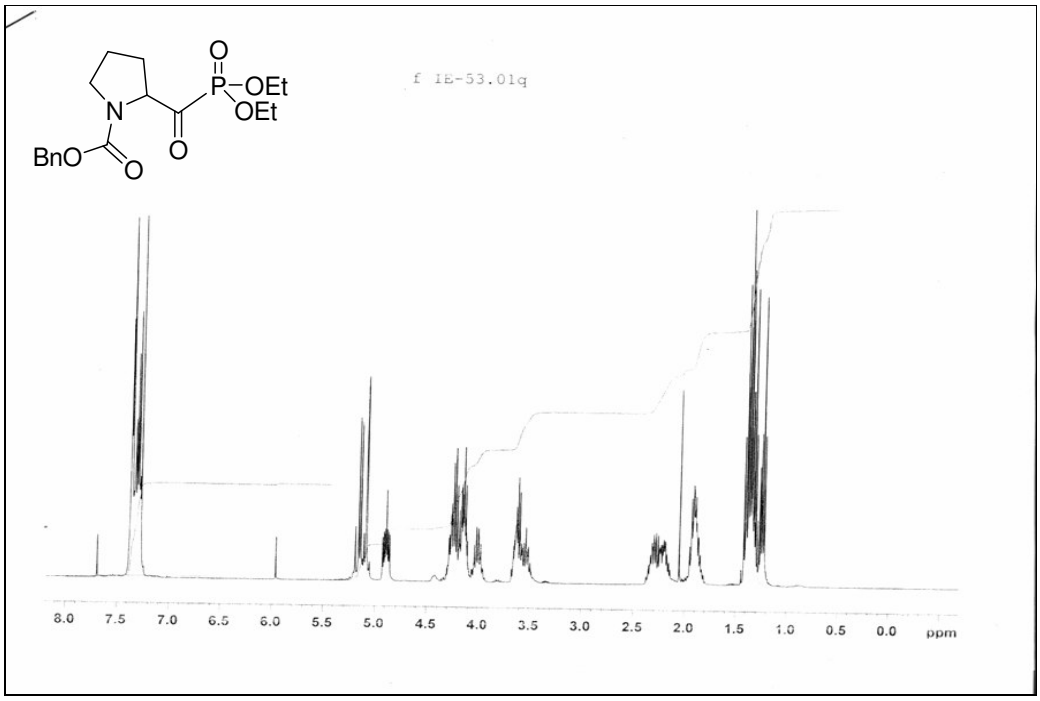

Figure 132. ^{1}H NMR (CDl_3, RT) spectrum of **216**

Figure 133. ^{1}H NMR spectrum of **225**

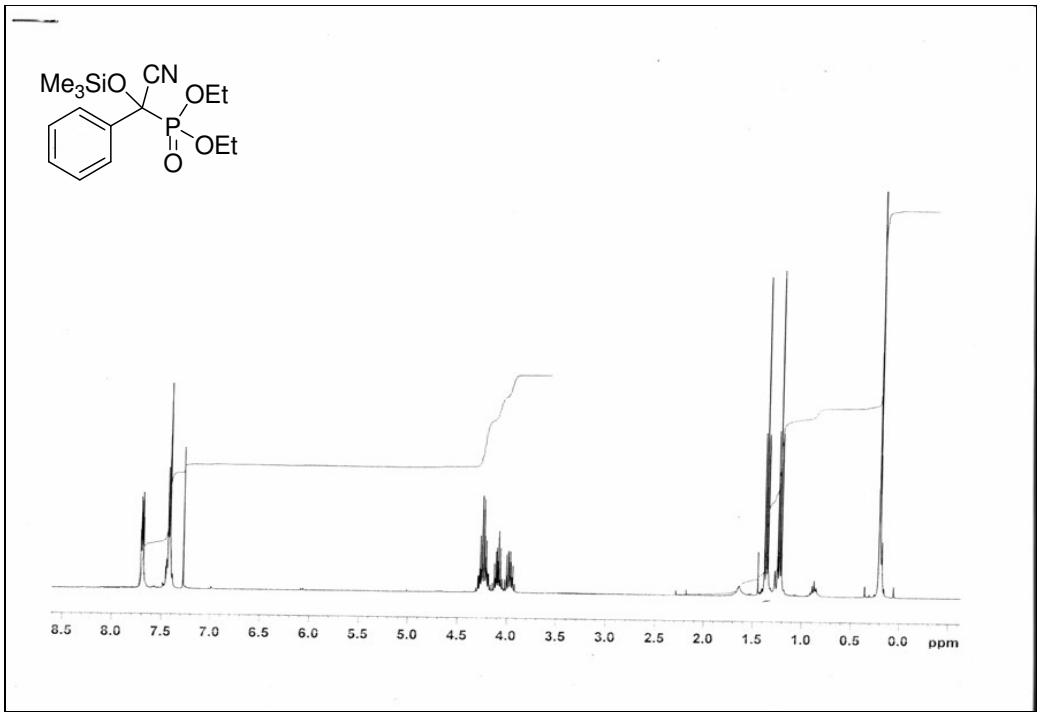

Figure 134. ^{1}H NMR spectrum of **226a**

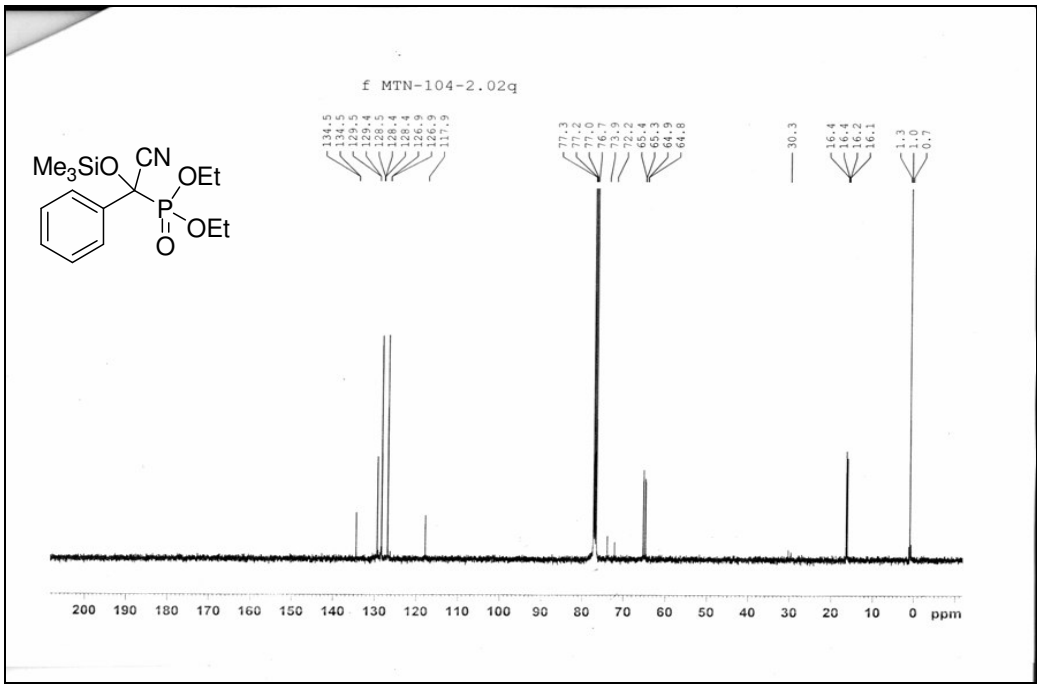

Figure 135. ^{13}C NMR spectrum of **226a**

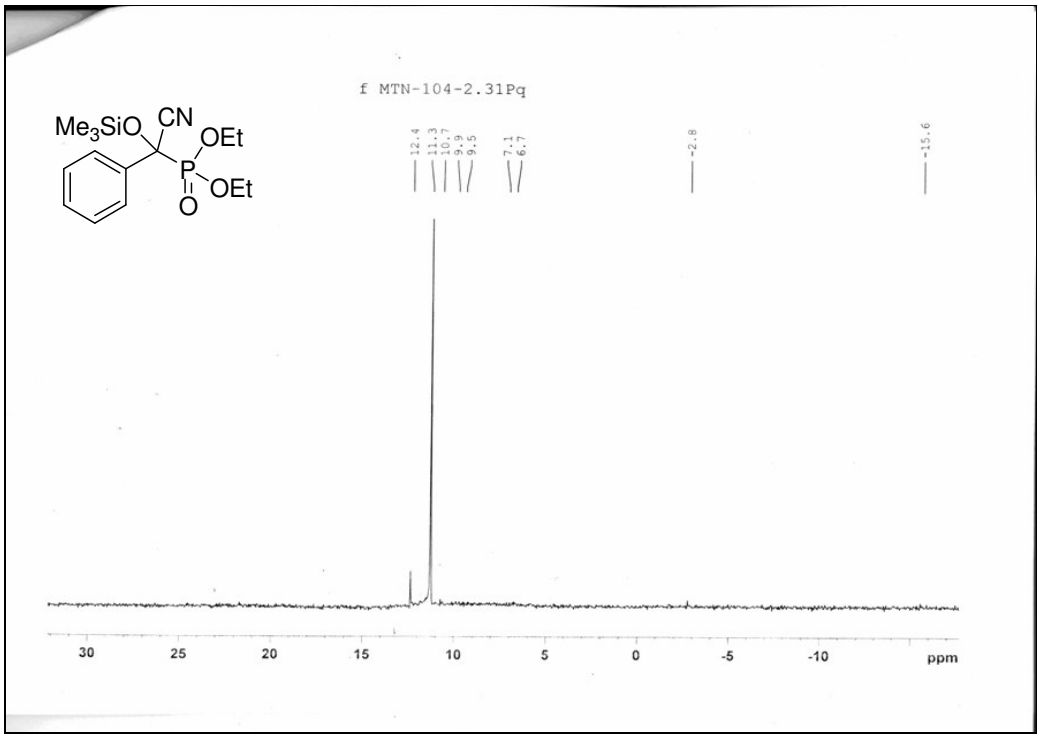

Figure 136. ^{31}P NMR spectrum of **226a**

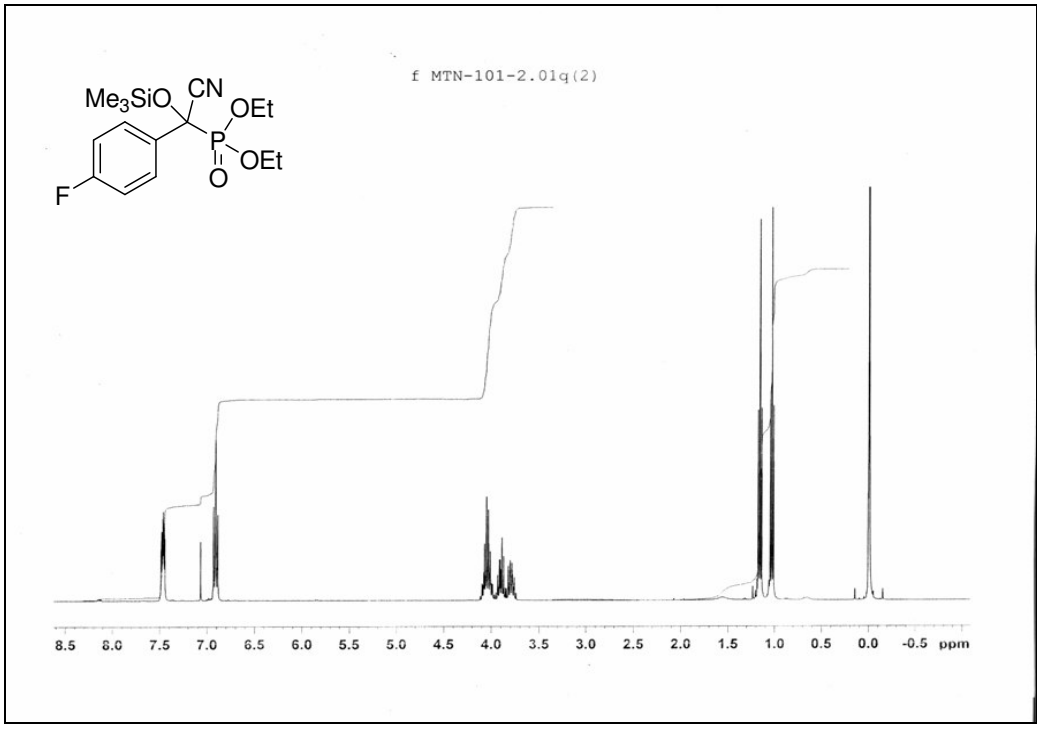

Figure 137. ^{1}H NMR spectrum of **226b**

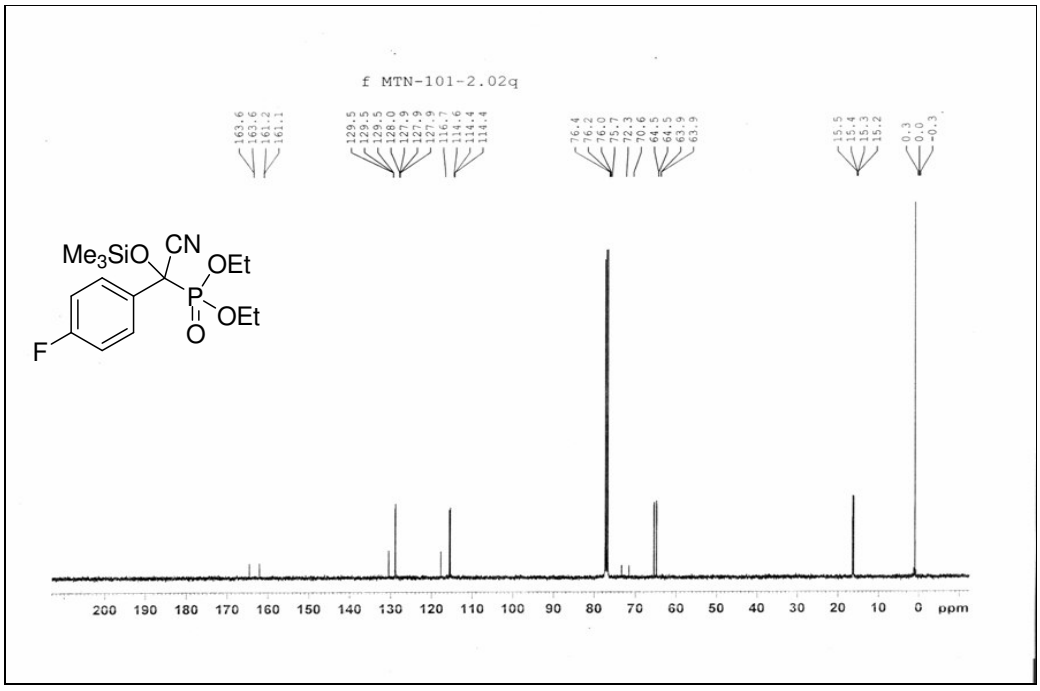

Figure 138. ^{13}C NMR spectrum of **226b**

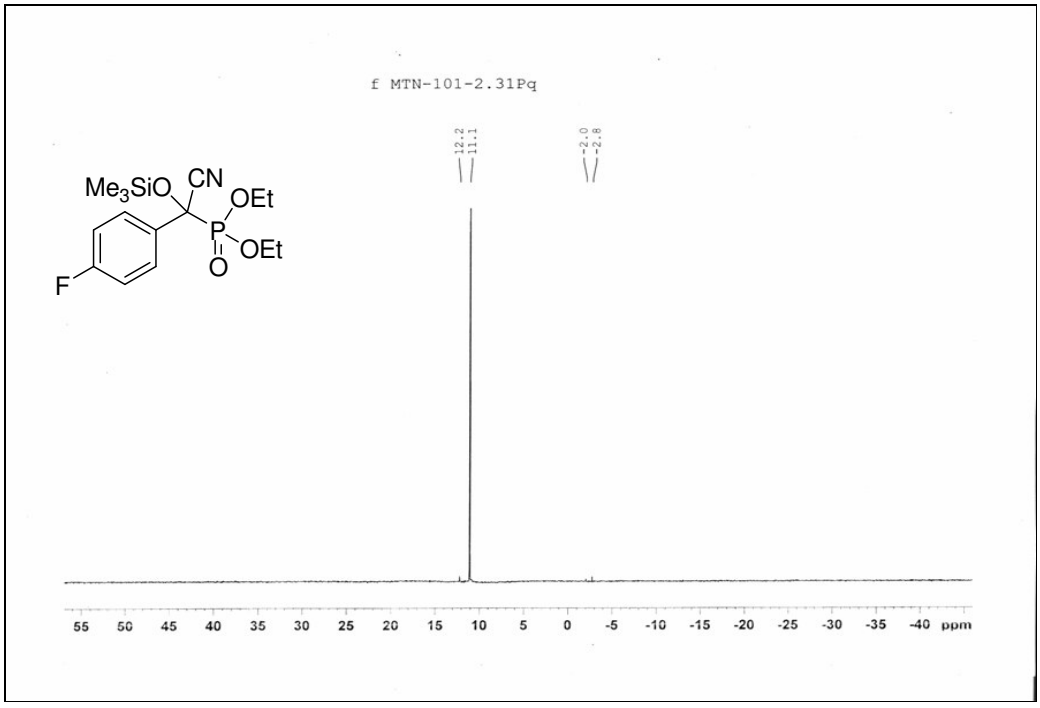

Figure 139. ^{31}P NMR spectrum of **226b**

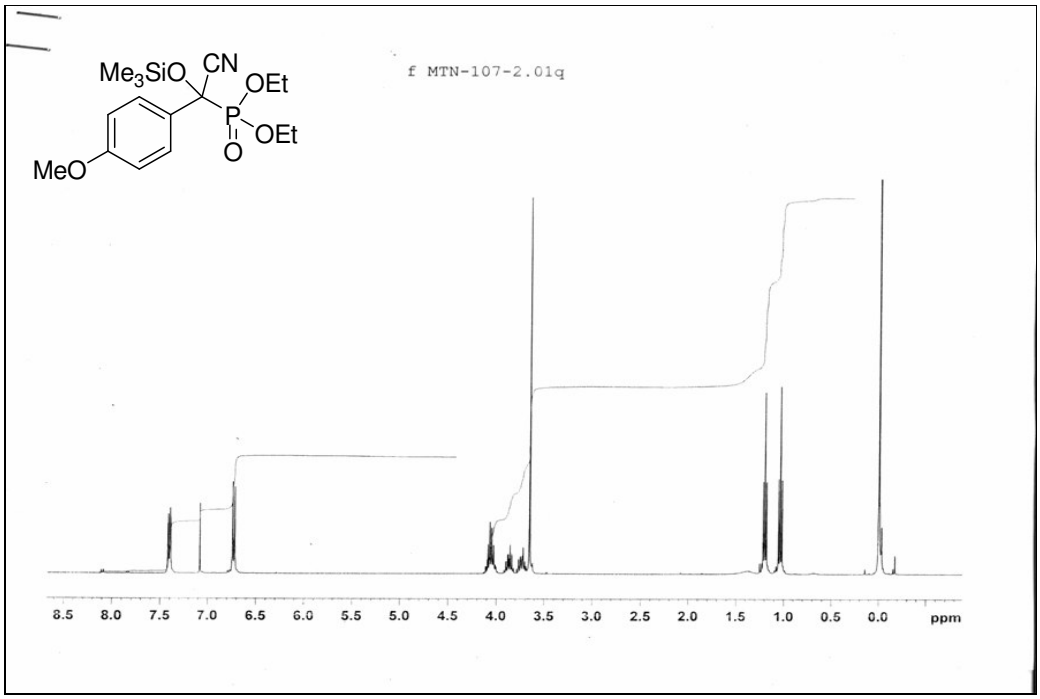

Figure 140. [1]H NMR spectrum of **226c**

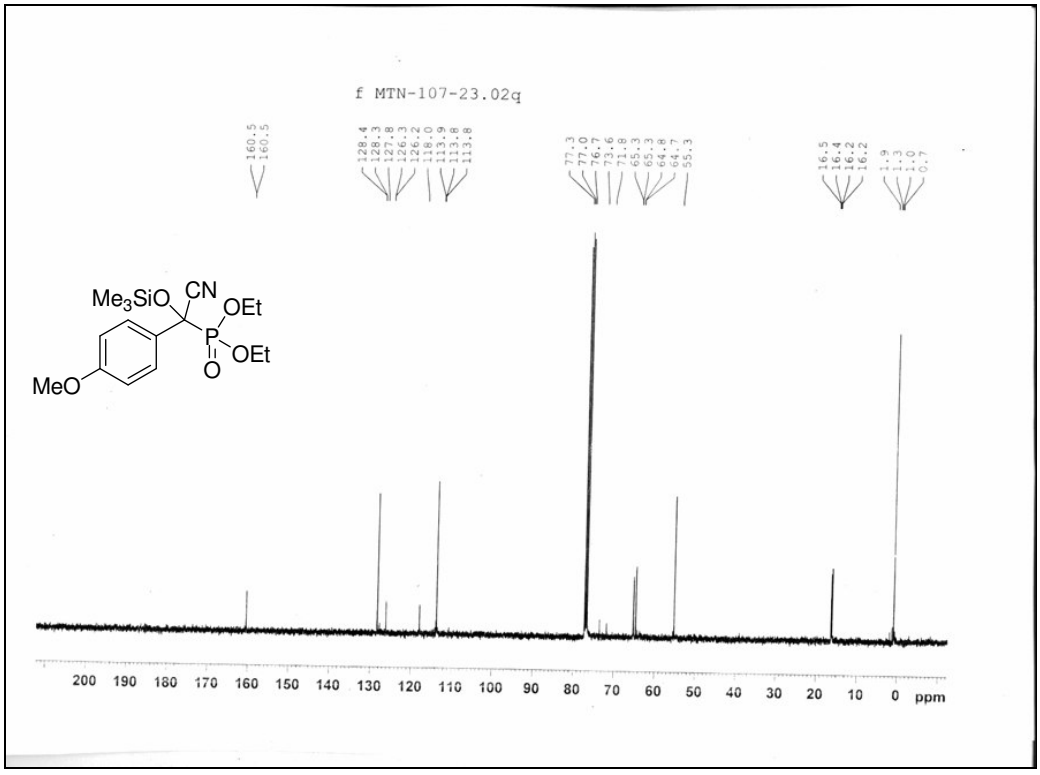

Figure 141. [13]C NMR spectrum of **226c**

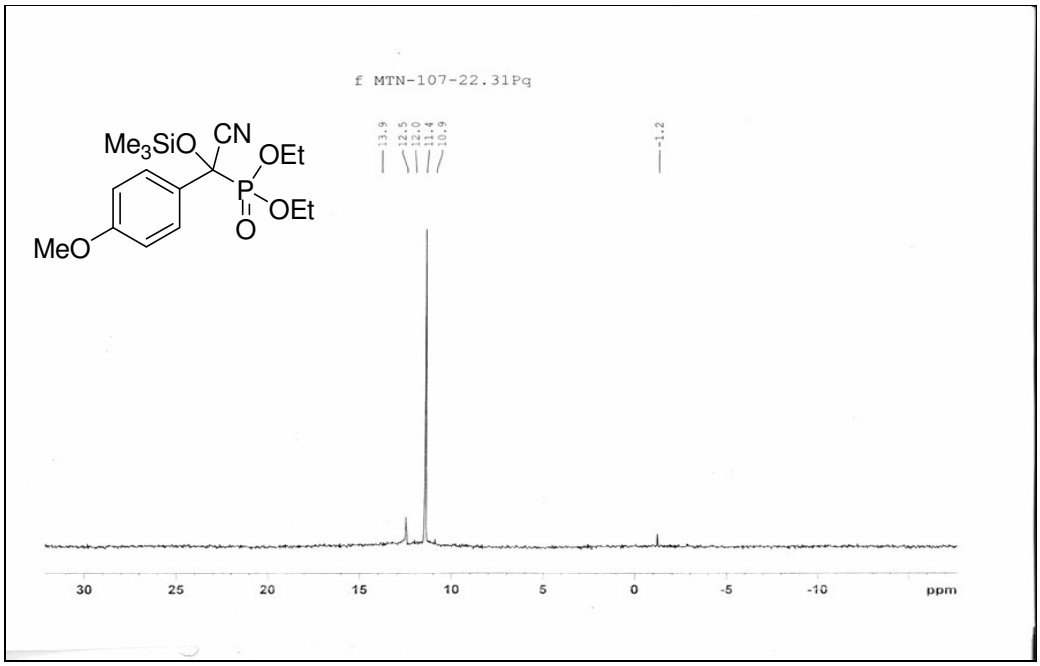

Figure 142. ^{31}P NMR spectrum of **226c**

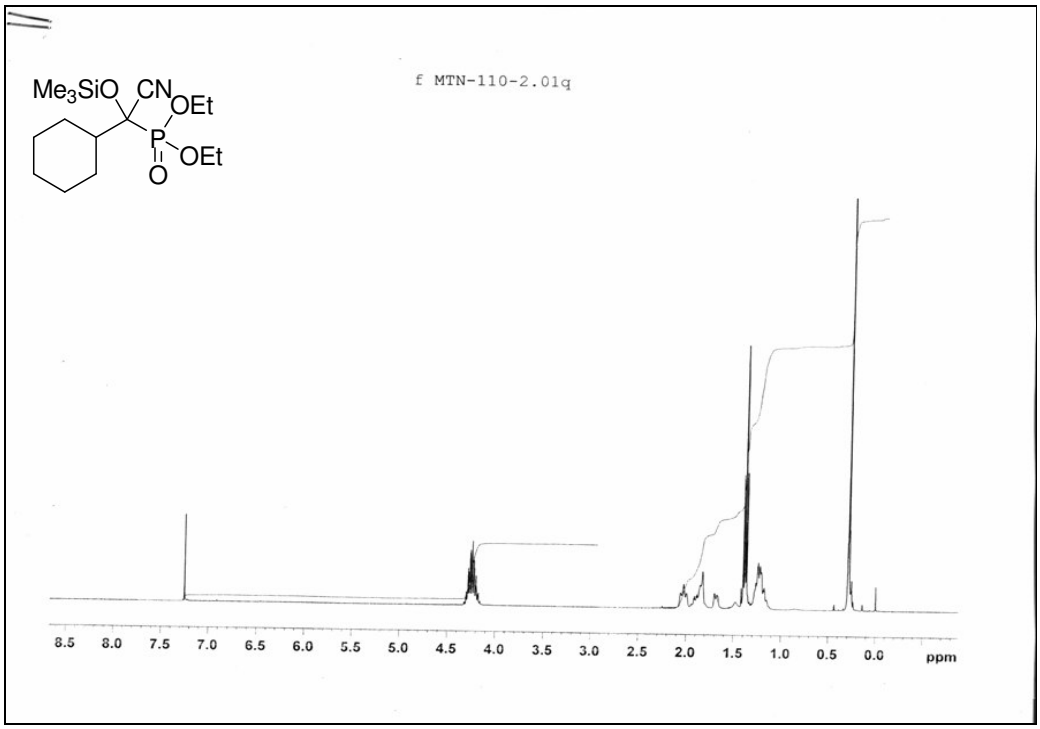

Figure 143. ^{1}H NMR spectrum of **226d**

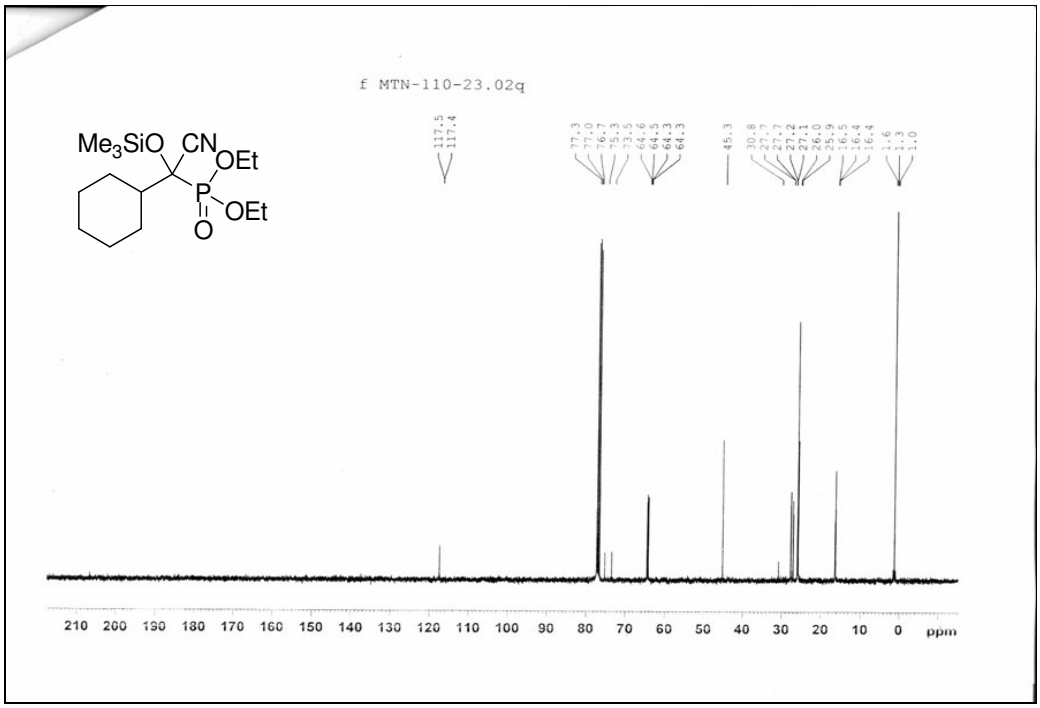

Figure 144. ^{13}C NMR spectrum of **226d**

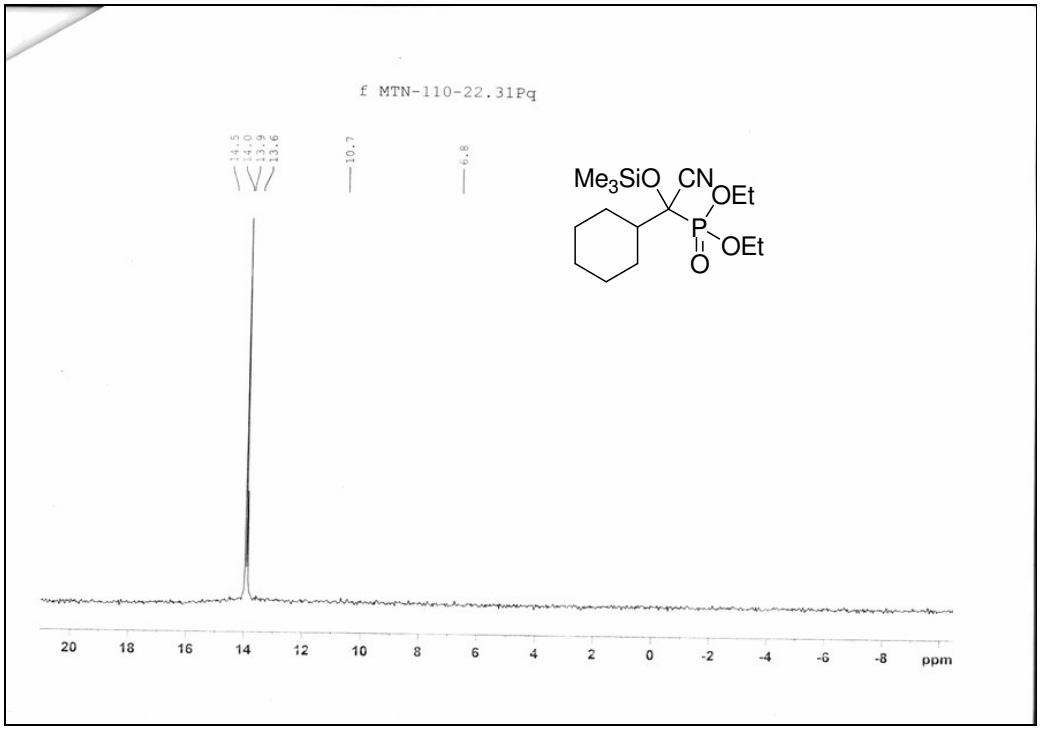

Figure 145. ^{31}P NMR spectrum of **226d**

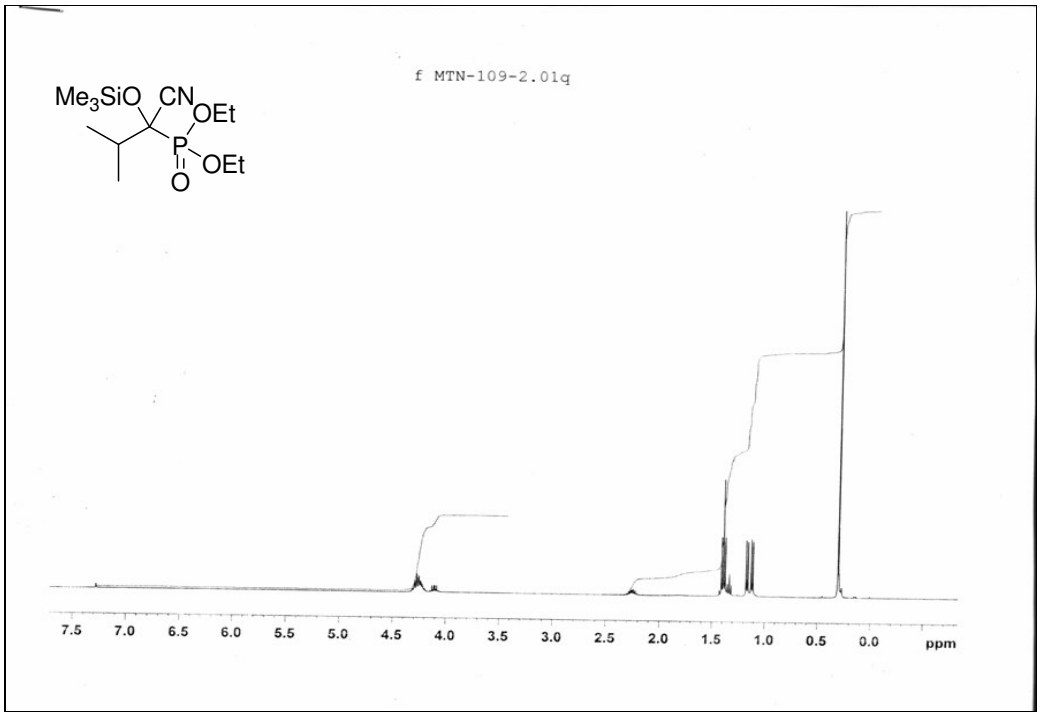

Figure 146. ^{1}H NMR spectrum of **226e**

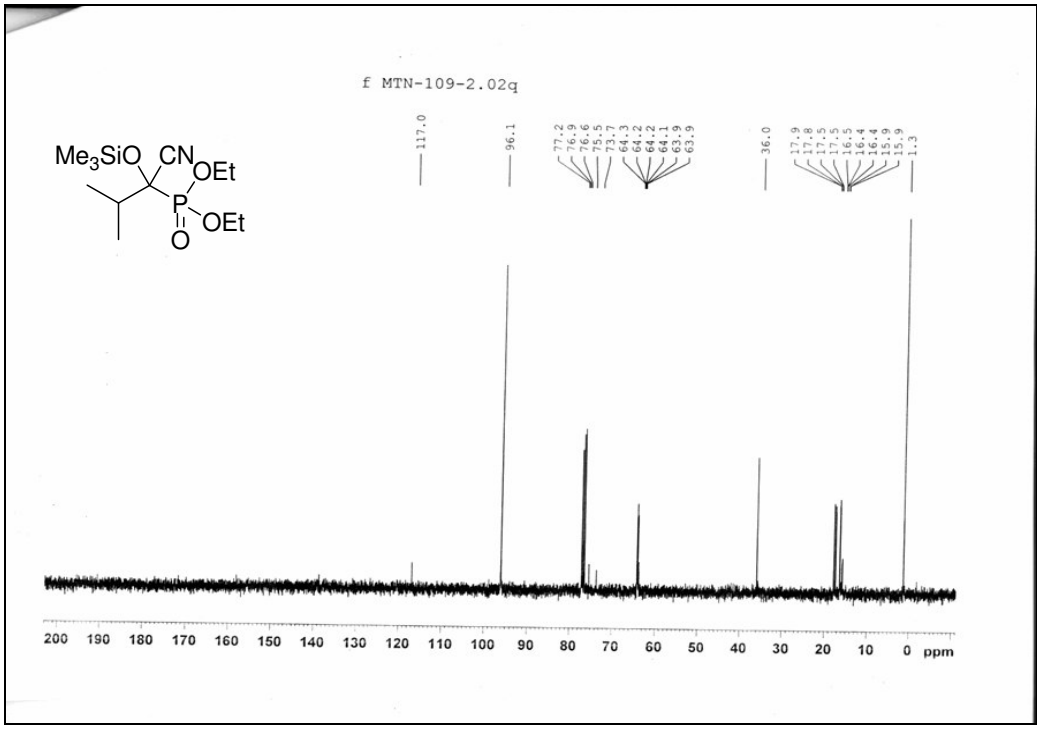

Figure 147. ^{13}C NMR spectrum of **226e**

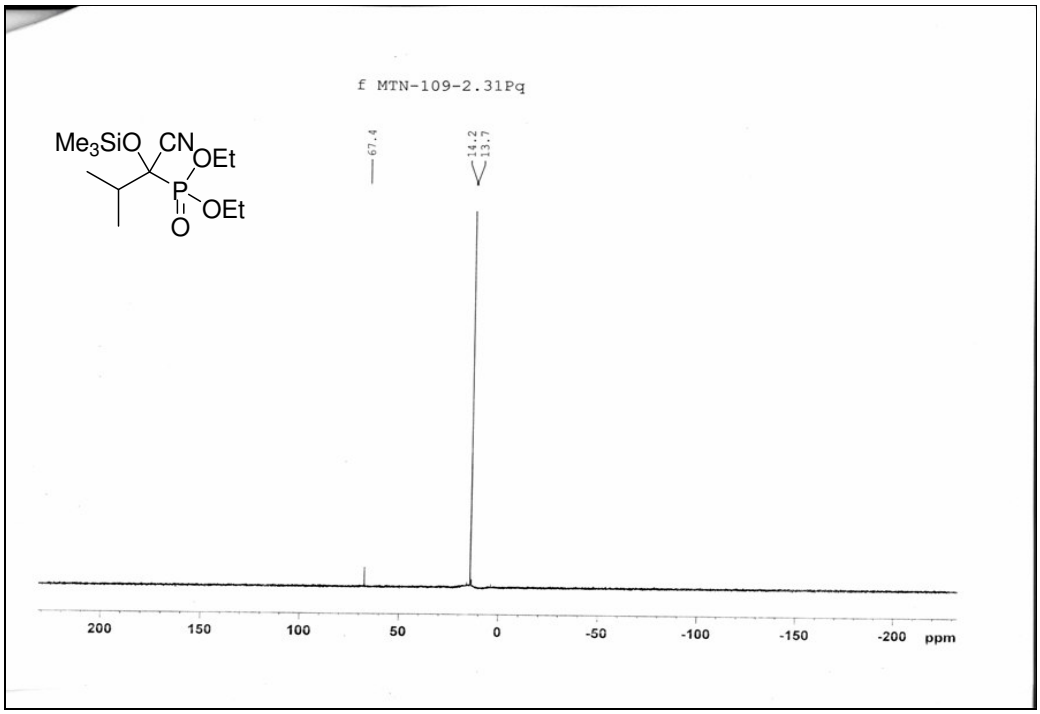

Figure 148. ^{31}P NMR spectrum of **226e**

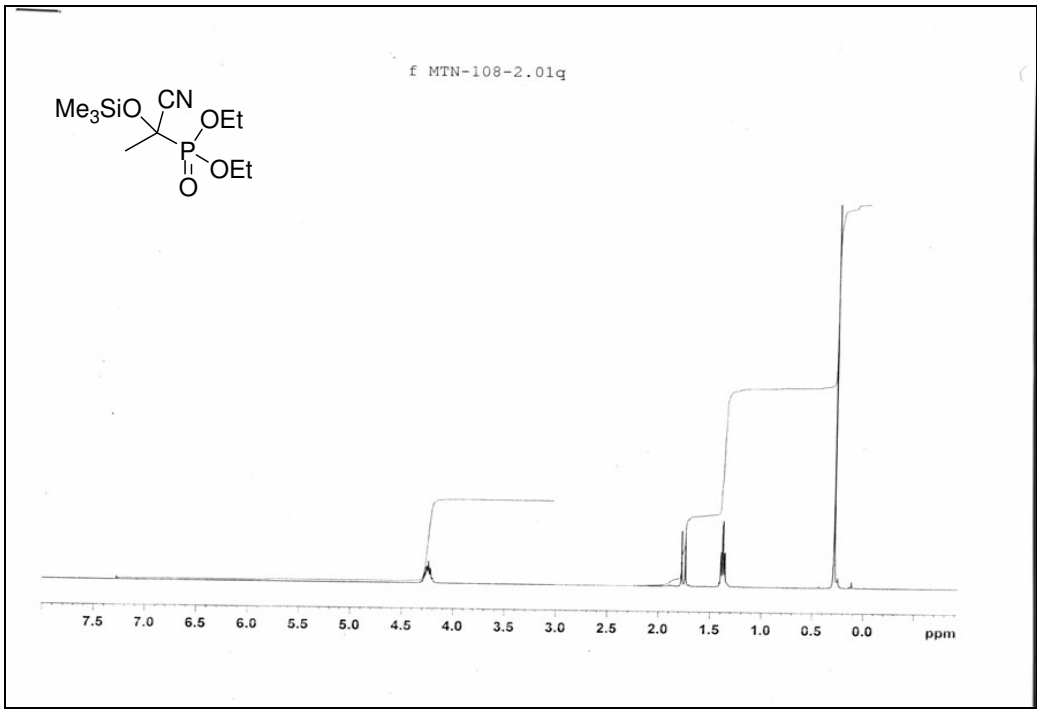

Figure 149. ^{1}H NMR spectrum of **226f**

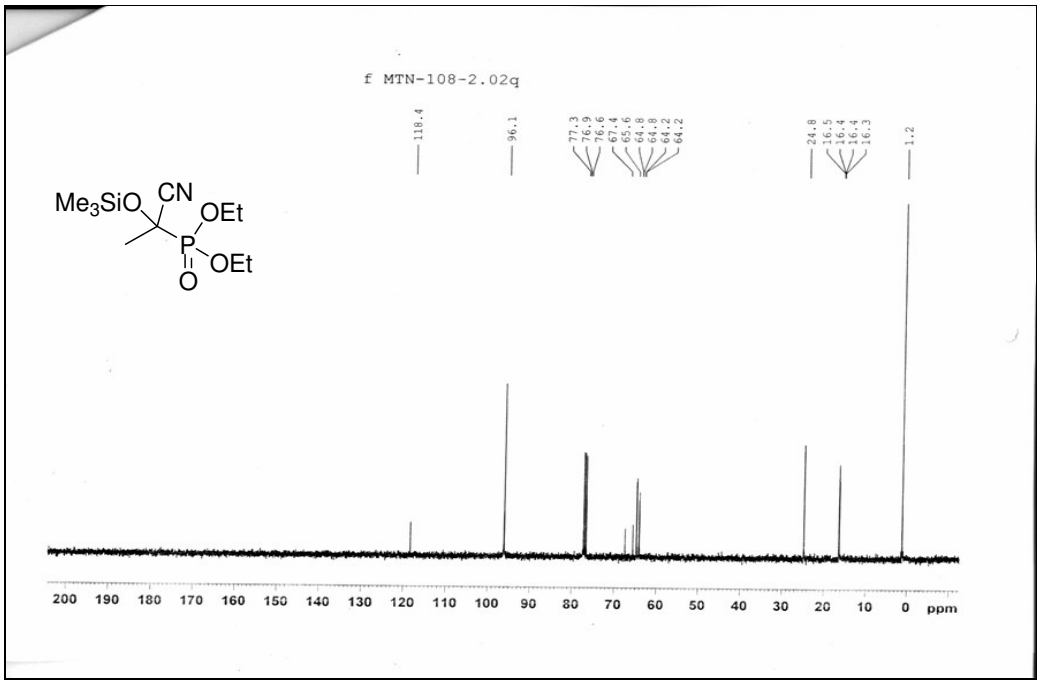

Figure 150. ^{13}C NMR spectrum of **226f**

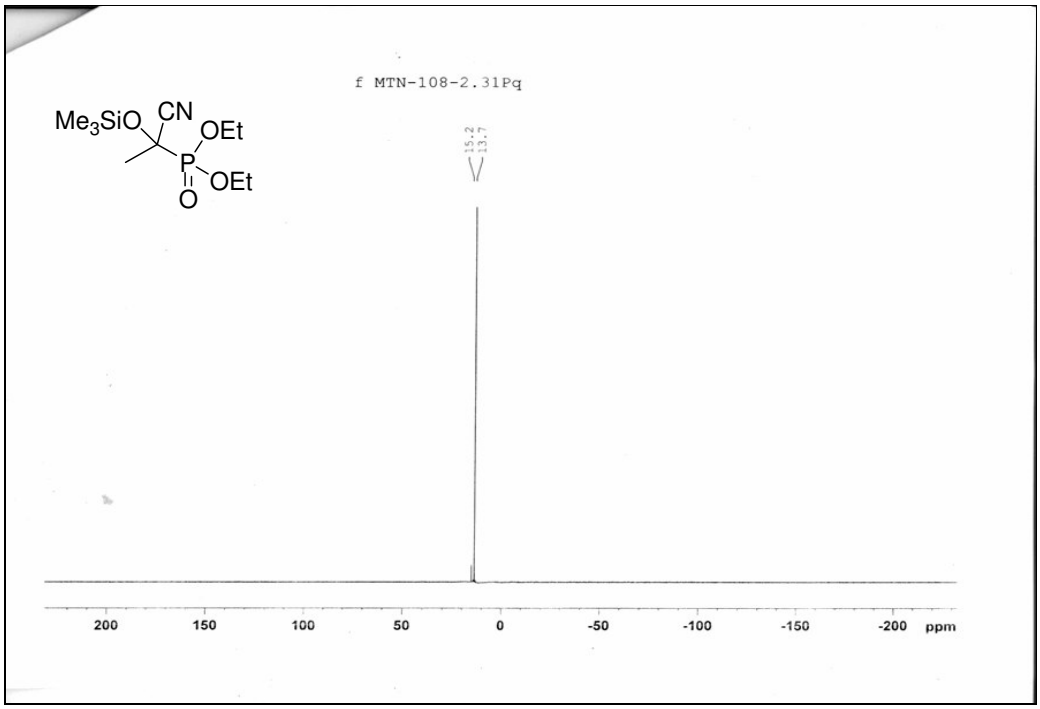

Figure 151. ^{31}P NMR spectrum of **226f**

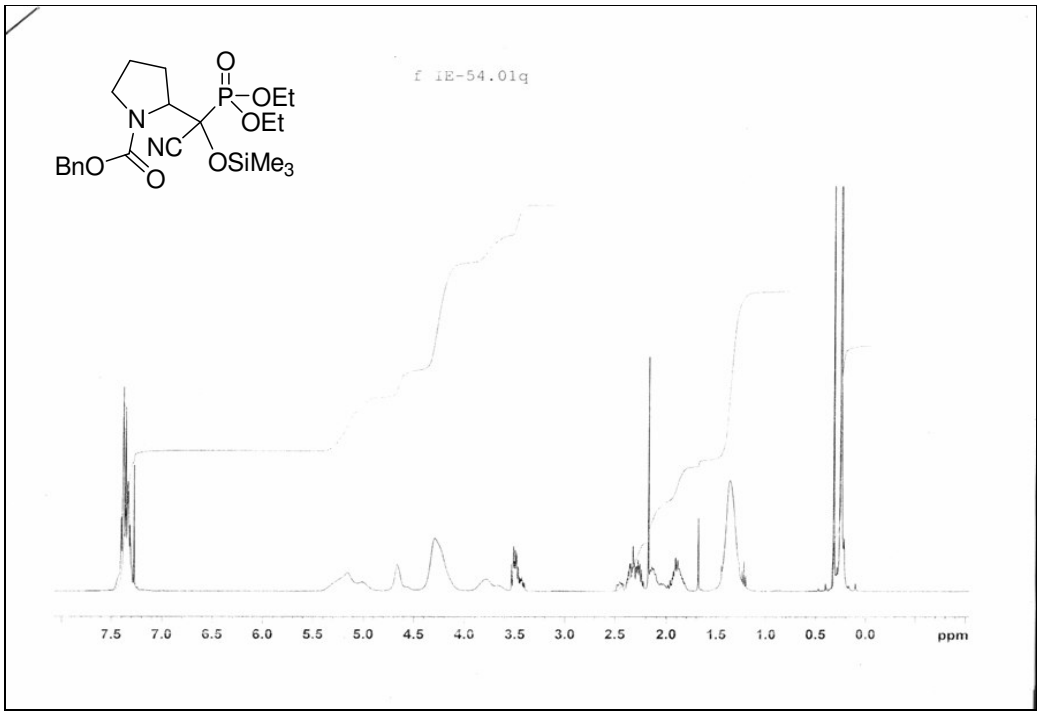

Figure 152. ^{1}H NMR ($CDCl_3$, RT) spectrum of **226g**

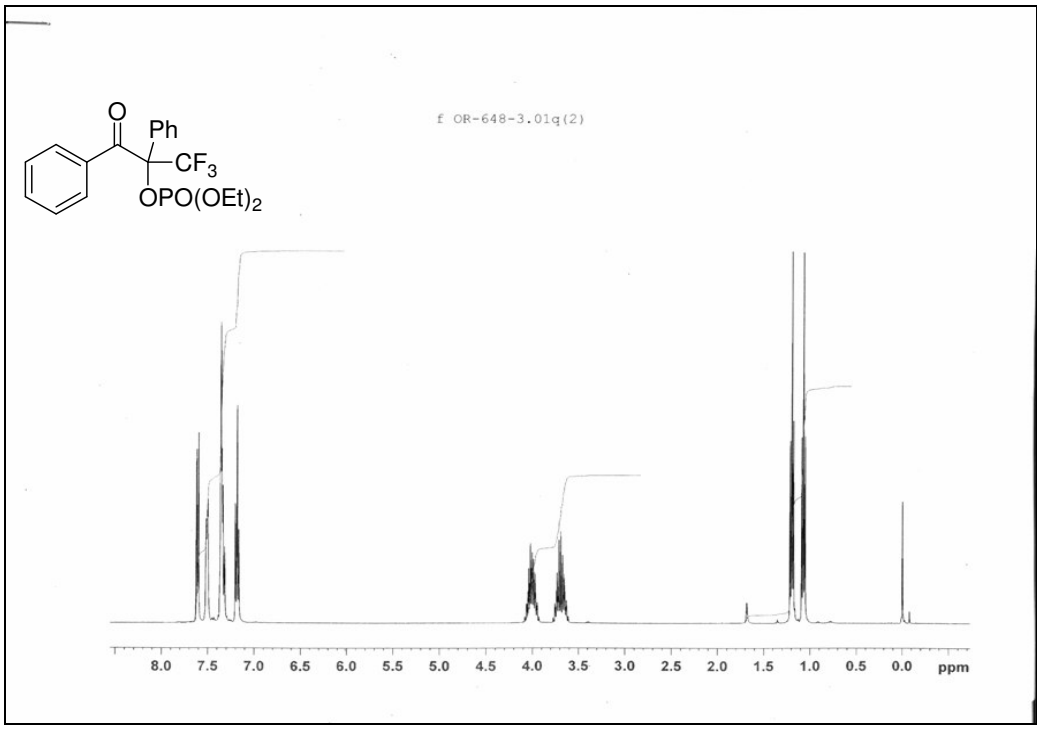

Figure 153. ^{1}H NMR spectrum of **232**

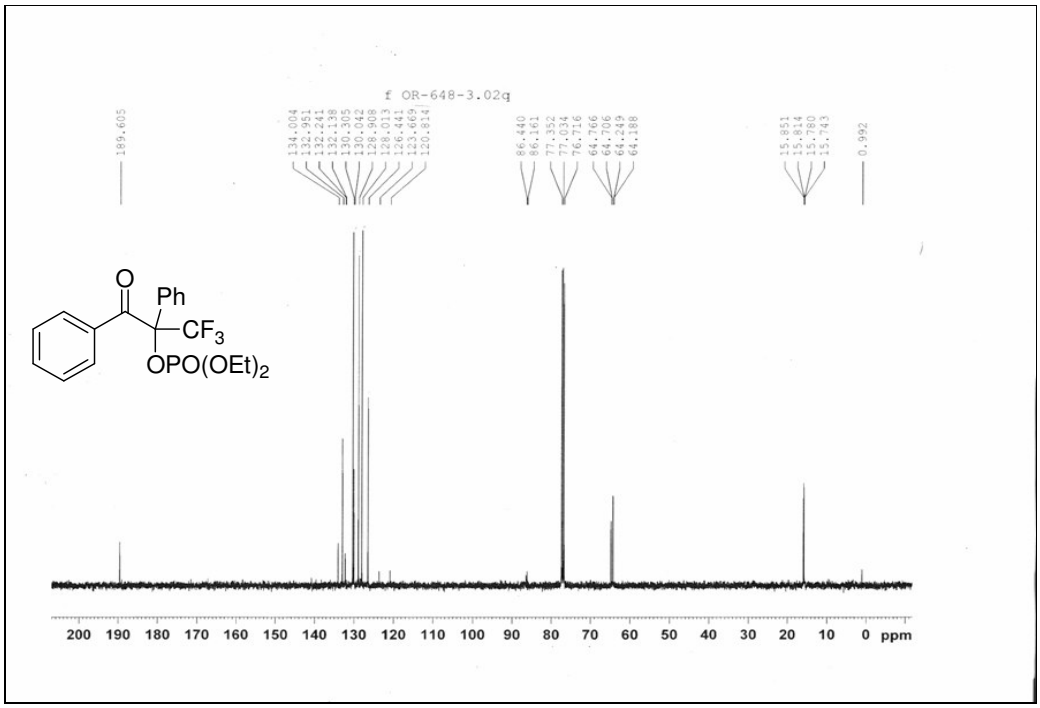

Figure 154. ^{13}C NMR spectrum of **232**

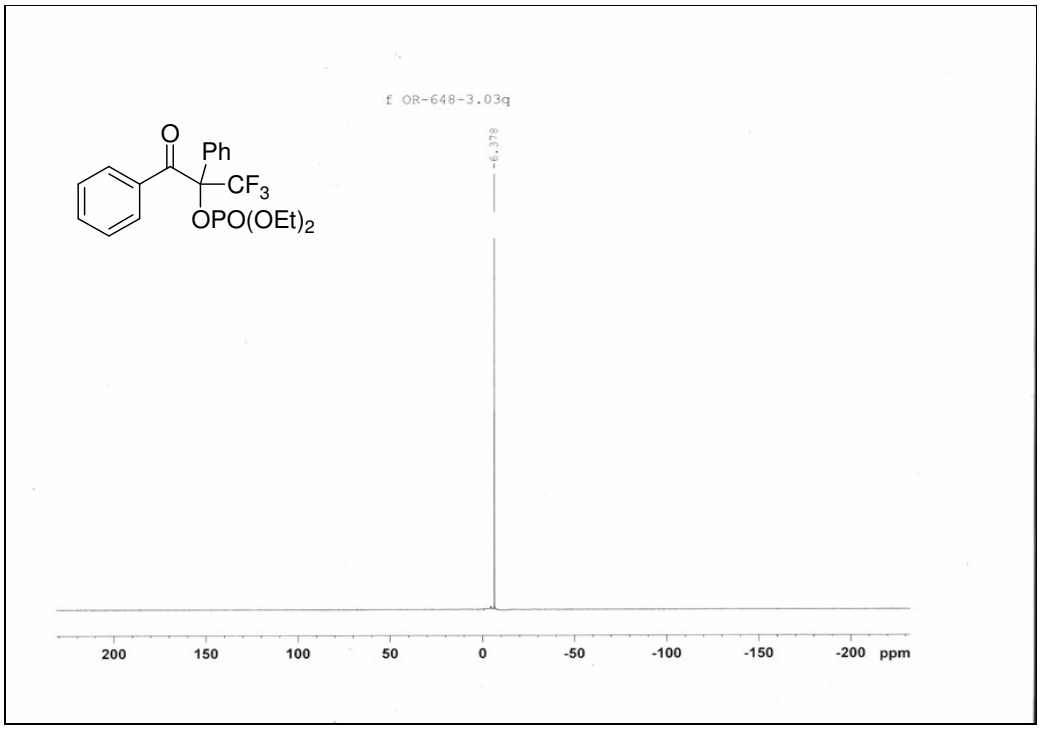

Figure 155. ^{31}P NMR spectrum of **232**

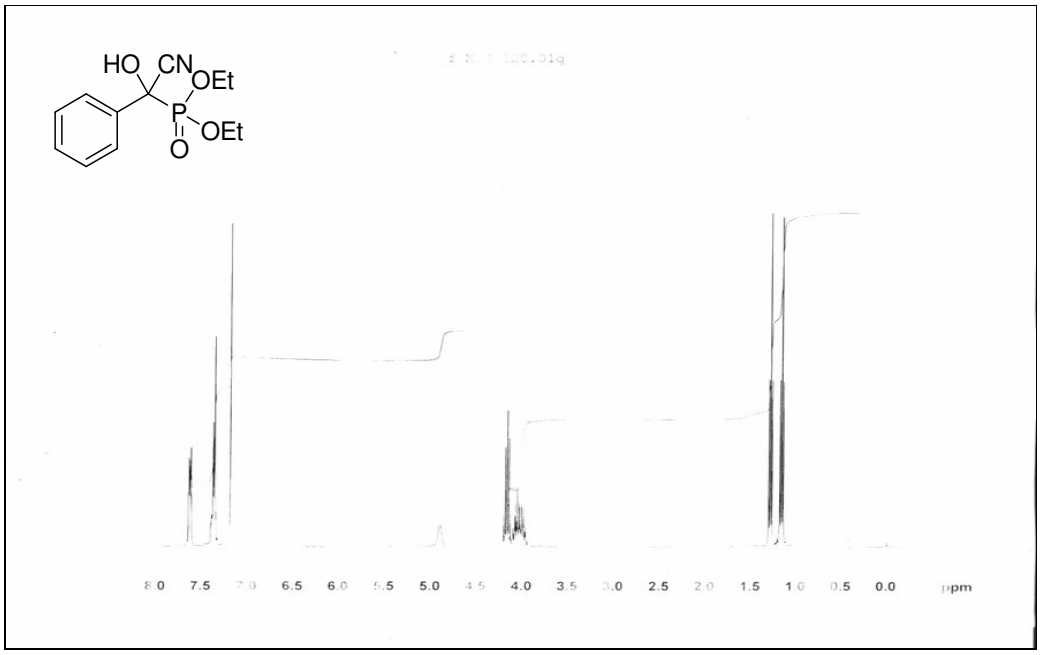

Figure 156. ^{1}H NMR spectrum of **235a**

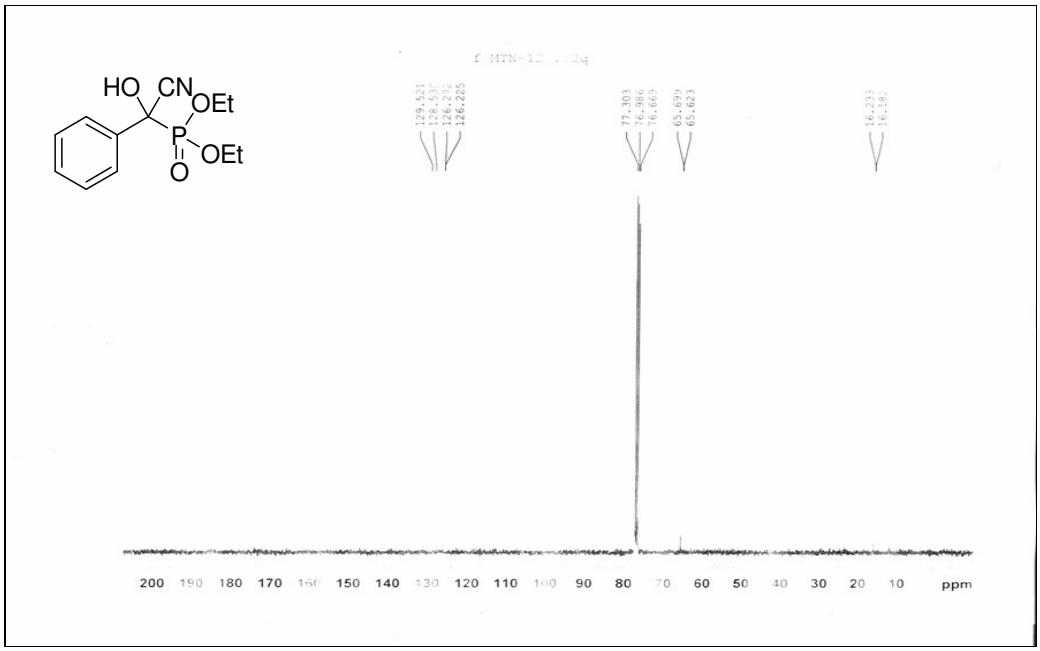

Figure 157. ^{13}C NMR spectrum of **235a**

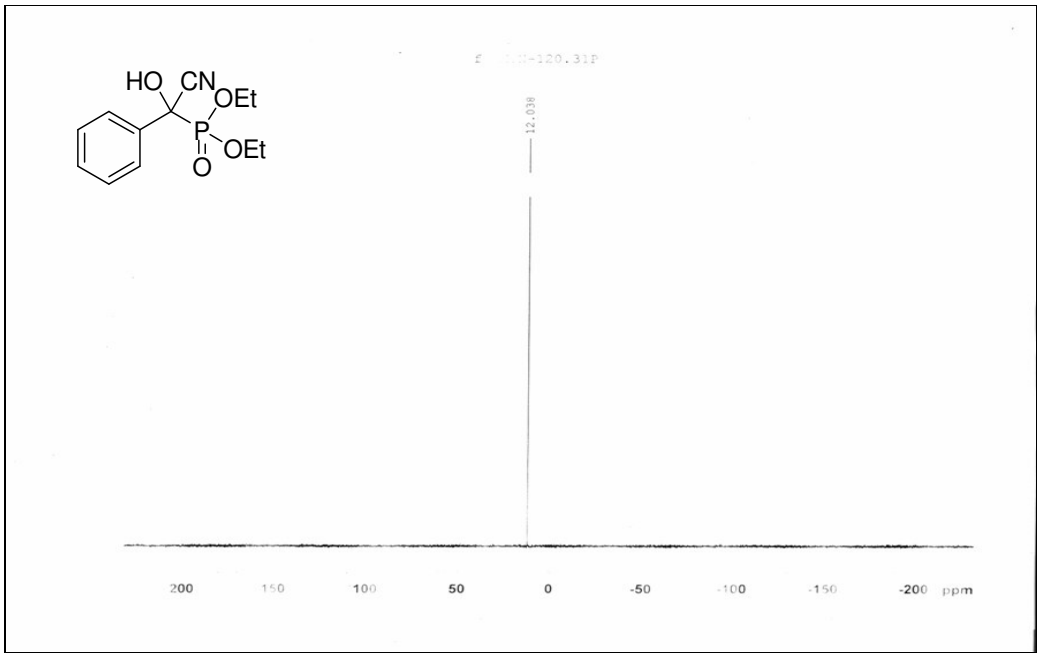

Figure 158. ^{31}P NMR spectrum of **235a**

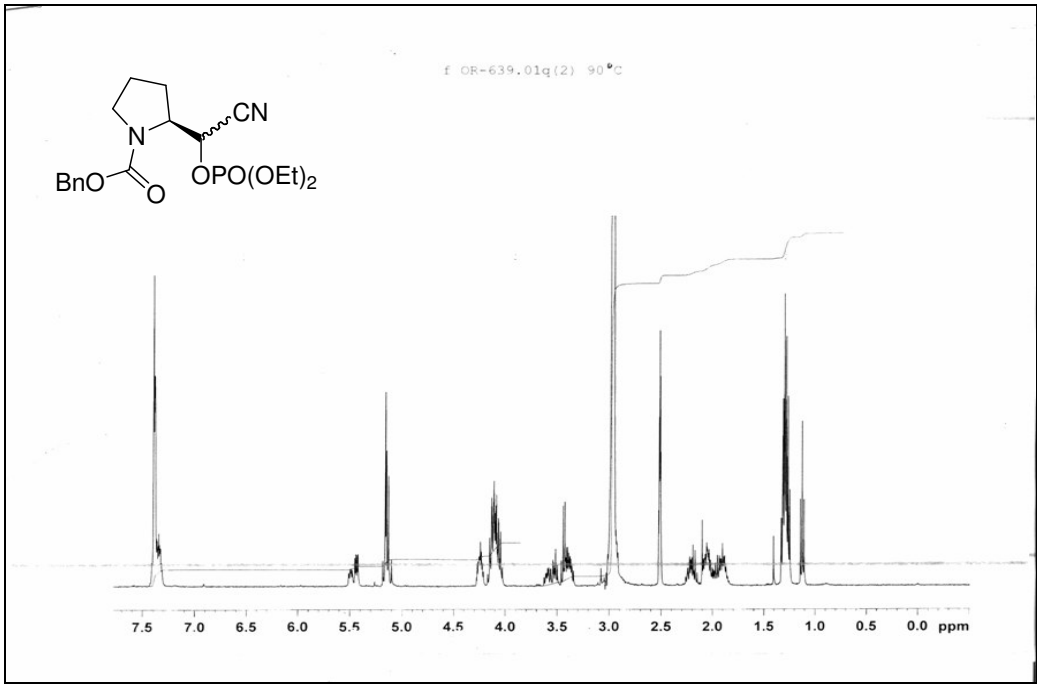

Figure 159. ^{1}H NMR (DMSO, 90°C) spectrum of **242**

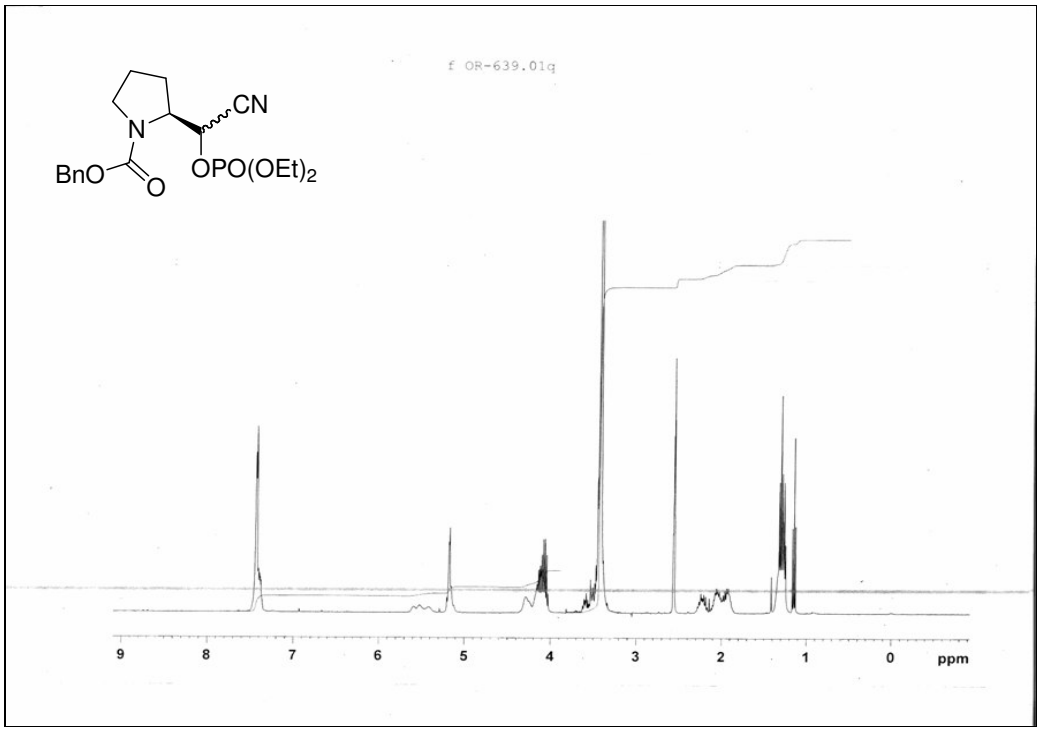

Figure 160. ^{1}H NMR (DMSO, RT) spectrum of **242**

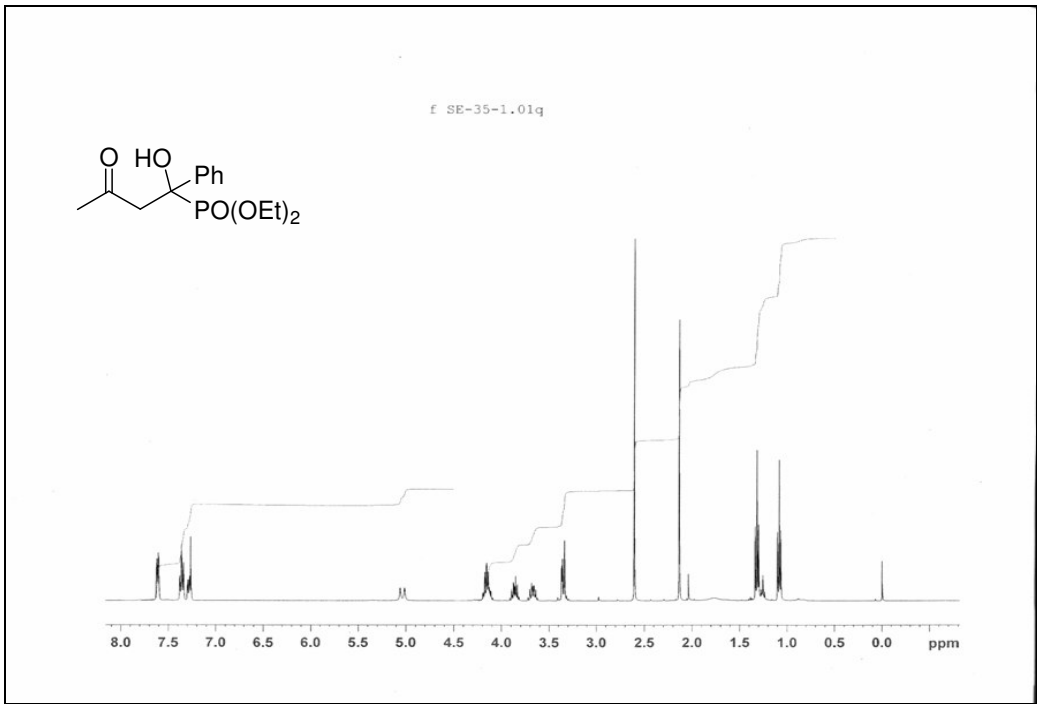

Figure 161. ^{1}H NMR spectrum of **250a**

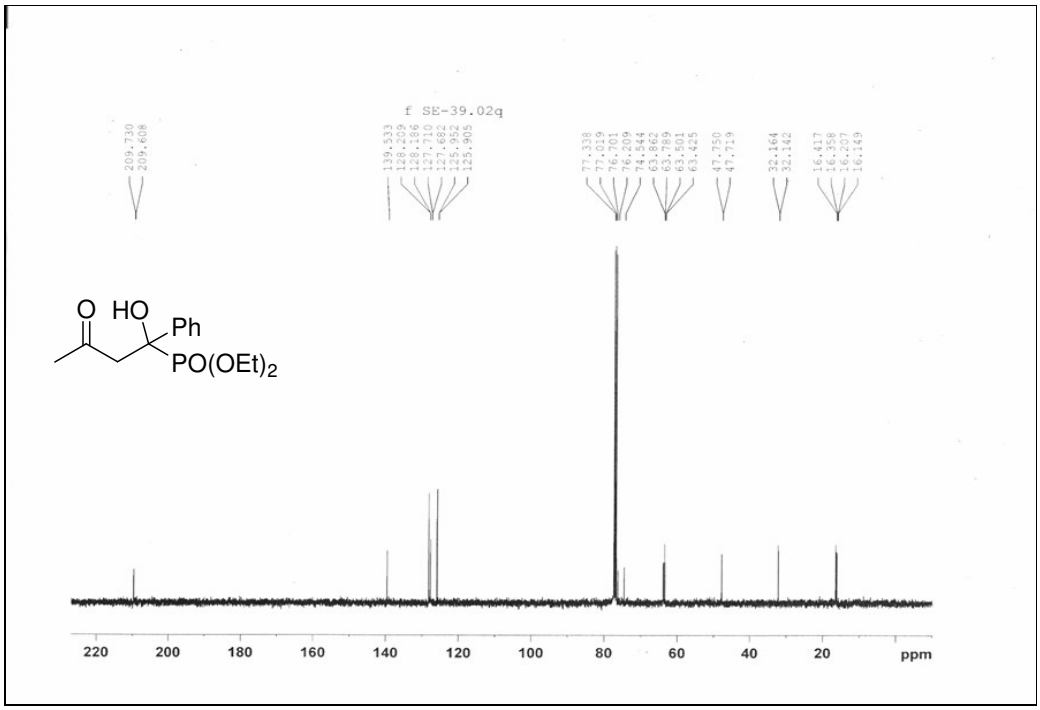

Figure 162. ^{13}C NMR spectrum of **250a**

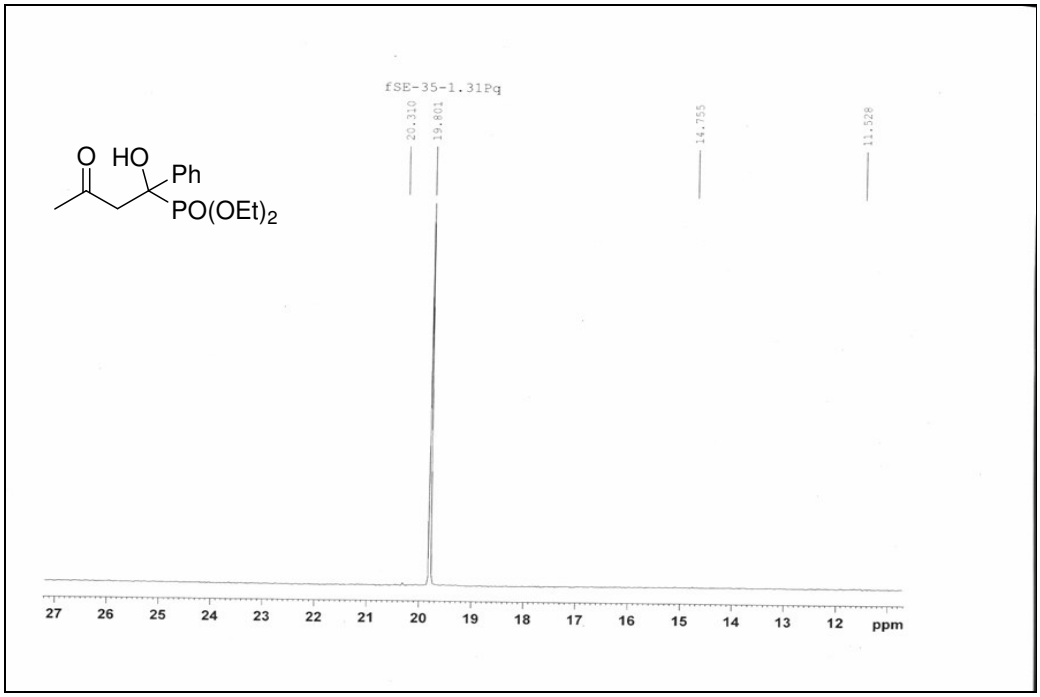

Figure 163. ^{31}P NMR spectrum of **250a**

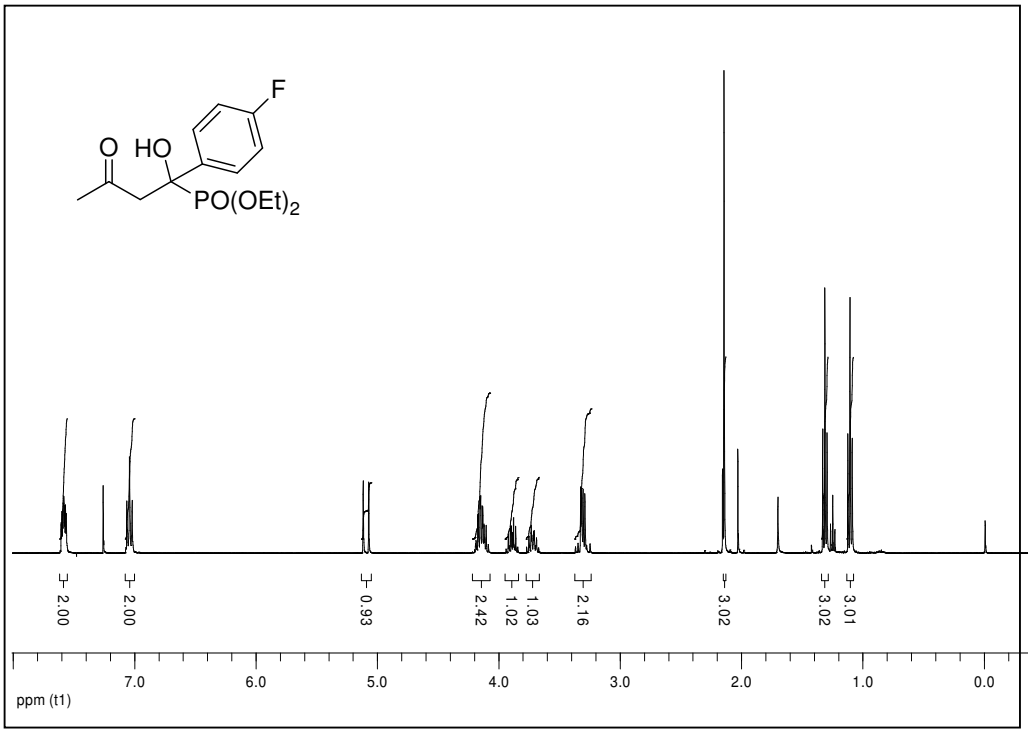

Figure 164. ^{1}H NMR spectrum of **250b**

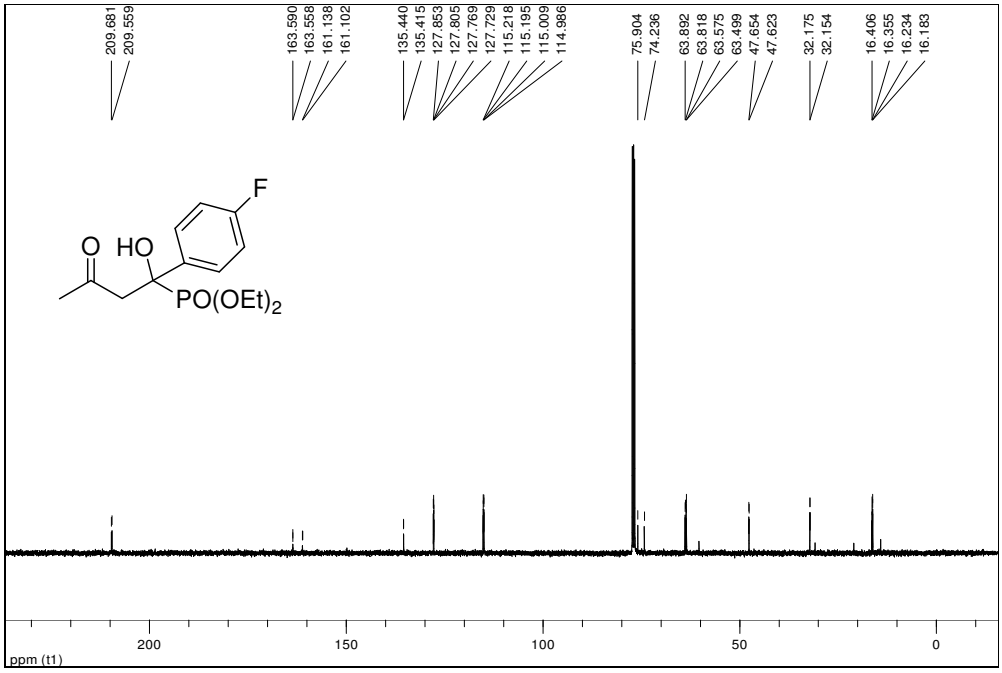

Figure 165. ^{13}C NMR spectrum of **250b**

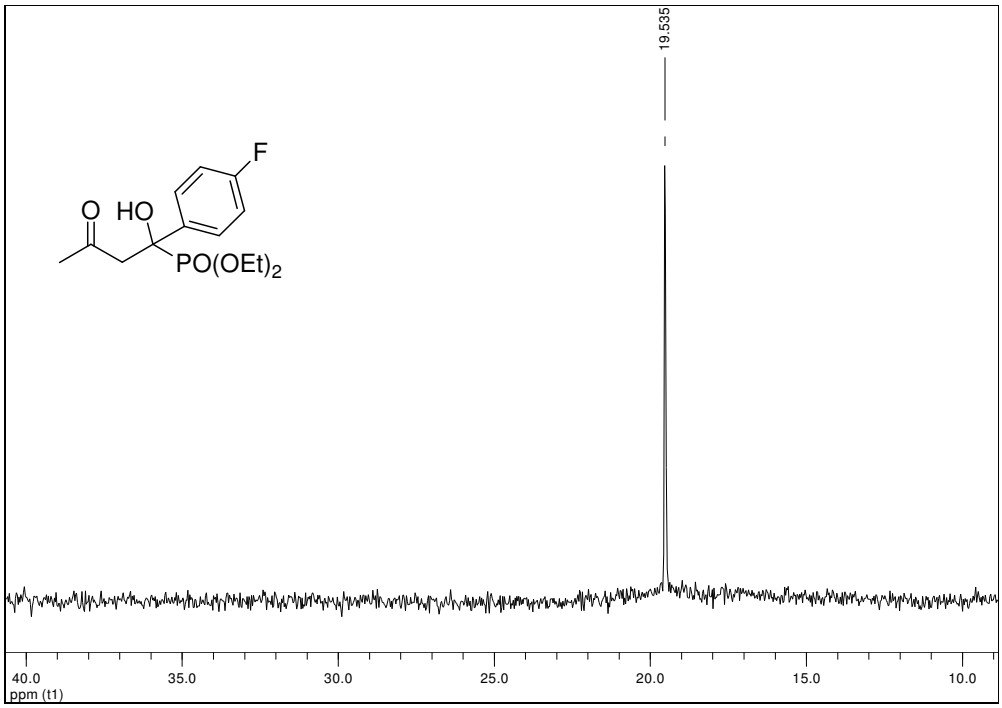

Figure 166. ^{31}P NMR spectrum of **250b**

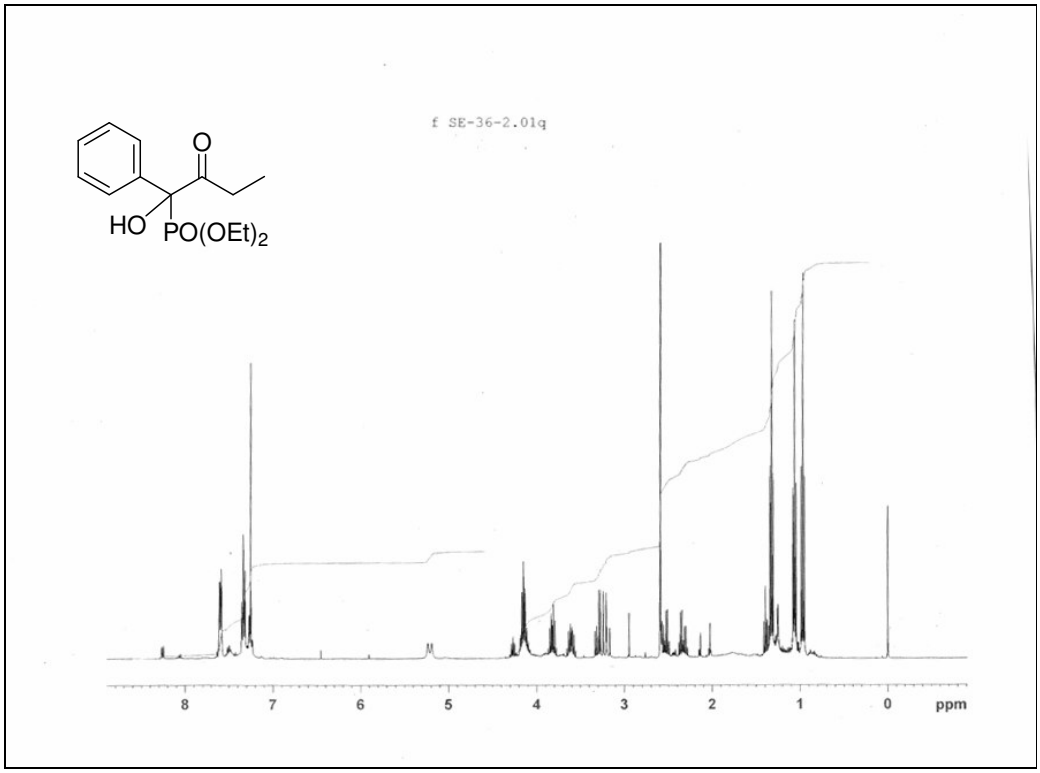

Figure 167. Crude ^{1}H NMR spectrum of **250c**

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BS	METU Chemistry	1998

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PUBLICATIONS

1. "A convenient and selective synthesis of unsymmetrical benzoins via the cyanide ion catalyzed cleavage of benzils," Demir, A. S.; Reis, O. *Tetrahedron*, **2004**, *60*, 3803.

2. "Reinvestigation of the synthetic and mechanistic aspects of Mn(III) acetate mediated oxidation of enones," Demir, A. S.; Reis, O.; Igdir, A. C. *Tetrahedron*, **2004**, *60*, 3427.

3. "Role of Copper Species in the Oxidative Dimerization of Arylboronic Acids: Synthesis of Symmetrical Biaryls" Demir, A. S.; Reis, O.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 10130.

4. "Generation of Aryl Radicals from Arylboronic Acids by Manganese(III) Acetate: Synthesis of Biaryls and Heterobiaryls" Demir, A. S.; Reis, O.; Emrullahoglu, E. *J. Org. Chem*. **2003**, *68*, 578.

5. "Manganese(III) acetate-mediated oxidative coupling of phenylhydrazines with furan and thiophene: a novel method for hetero biaryl coupling" Demir, A. S.; Reis, O.; Emrullahoglu, E. *Tetrahedron*, **2002**, *58*, 8055.

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7. "Butenolide annelation using a manganese(III) oxidation. A synthesis of chromolaenin (Laevigatin)**"** Demir, A. S.; Gercek, Z.; Duygu, N.; Igdir, A. C.; Reis, O. *Can. J. Chem*. **1999**, *77*, 1336.

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