DARZENS REACTION OF SUBSTITUTED ALFA-BROMO ACETOPHENONES WITH ACYL PHOSPHONATES

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DARZENS REACTION OF SUBSTITUTED ALFA-BROMO ACETOPHENONES WITH ACYL PHOSPHONATES

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ABSTRACT

DARZENS REACTION OF SUBSTITUTED ALFA-BROMO ACETOPHENONES WITH ACYL PHOSPHONATES

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Phosphorous containing small cycles are very important building blocks in organic and medicinal chemistry. Many of their derivatives, especially cyclopropyl- and 1,2-epoxypropylphosphonates, have attracted great attention due to the broad spectrum of their biological properties including antiviral, anticancer, antibiotic, antibacterial, pesticidal, insecticidal and enzyme inhibitory activities.

The Darzens condensation is one of the most potential methodologies for the preperation of α,β-epoxy carbonyl compounds with complete control of two stereogenic centers. The Darzens condensation reaction represents one of the classical C-C and C-O bond-forming processes.

In the first part of the thesis, reactions of a broad range of acyl phosphonates with substituted α-bromo acetophenones at room temperature in the presence of different bases were examined in order to illustrate the reaction and the substituent effect on the reaction. The reaction affords two diastereomeric epoxy phosphonates in good yields and high diastereoselectivities.

In the second part of the thesis, it is shown that a variety of radicals can be generated from the substituted aryl boronic acids with $Mn(OAc)_3$. In the presence of acetonitrile, these radicals were added to carbon of acetonitrile to afford the corresponding ketones after hydrolysis of the formed imine with moderate to good yields.

Keywords: Darzens condensation, acyl phosphonate, epoxyphosphonate, Manganese (III) acetate, aryl boronic acids

ÖZ

SUBSTİTÜE ALFA-BROMO ASETOFENONLARIN AÇİL FOSFONATLARLA DARZENS REAKSİYONLARI

Pirkin, Eser

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Kasım 2008, 77 sayfa

Fosfor içeren küçük halkalı yapılar organik kimyada ve ilaç kimyasında oldukça önemli yapıtaşlarıdır. Bu yapıların birçok türevi, özellikle siklopropil- ve 1,2-epoksipropilfosfonatlar, antiviral, antikanser, antibakteriyal, tarım ilacı, böcek öldürücü ve enzim inhibe etme özelliklerinden dolayı çok fazla dikkat çekmektedir.

Darzens kondenzasyon reaksiyonları klasik C-C ve C-O bağı oluşturma reaksiyonlarındandır. Bu yüzden, Darzens kondenzasyon reaksiyonları α,β-epoksi karbonil bileşiklerinin sentezlenmesinde en fazla kullanılan yöntemlerden biridir.

Tezin birinci kısmında, sentez ve substitüe etkisini göstermek amacıyla geniş bir aralıktaki açil fosfonatların oda sıcaklığında ve farklı bazlar varlığında substitüe α-bromo asetofenonlarla olan reaksiyonları incelenmiştir. Yüksek verimlerde ve yüksek diasteriyoseçicilikte iki diasteriyomerik epoksi fosfonat sentezlenmiştir.

Çalışmanın ikinci kısmında, $Mn(OAc)_3$ ile aril boronik asitlerden çeşitli radikallerin oluşturulabileceği gösterilmiştir. Asetonitril varlığında, bu radikaller asetonitrilin karbonuna eklenmiştir ve oluşan iminin hidrolizi sonucu yüksek verimlerde ilgili ketonlar sentezlenmiştir.

Anahtar kelimeler: Darzens kondenzasyonu, açil fosfonat, epoksifosfonat, Mangan (III) asetat, aril boronik asit

To My Family

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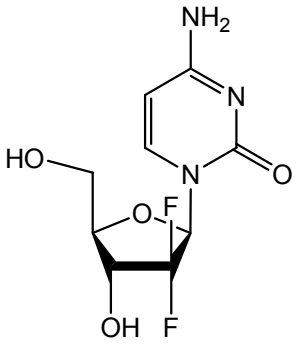
INTRODUCTION

1.1 Darzens condensation reactions with acyl phosphonates

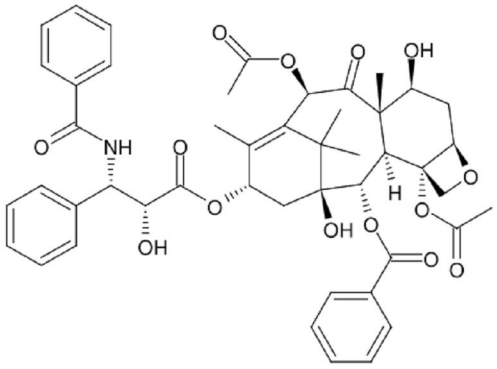
1.1.1 Darzens condensation reactions

Development of catalytic carbon-carbon and carbon-oxygen bond forming reaction is one of the most challenging aspects of the organic synthesis[1] and Darzens condensation reaction represents one of the classical C-C and C-O bond forming process[2]. Darzens condensation is one of the most potential methodologies for the preparation of α,β-epoxy carbonyl compounds[3] and it is widely used in the synthesis of numerous biologically active natural compounds, including Vitamin A, highly selective leukotriene receptor antagonists, the mosquito pheromone, the active component of the antibiotics Virginiamycin M and Roflamycoin, amastatin, N-substituted *L*-homophenylalanine, thiam- (R=OH) and fluorophenicol (R=F), gemcitabine **1**, the C-13 side chain of Taxol **2**, a calcium channel blocker of dilthiazem, etc[4].



Gemcitabine

1



Taxol

2

Figure 1. 1 Structures of some anticancer drugs

Condensation of α-halo carbonyl moieties with aldehydes and ketones known as Darzens reaction, is one of the most versatile tools in the synthetic organic chemistry for the preperation of α,β-epoxy carbonyl compounds and this reaction was discovered by the organic chemist Auguste George Darzens (1867-1954)[5]. although dramatic progres has been achieved in the past two decades, classical Darzens reaction is still performed in the presence of a strong base (RONa, ROK, $NaNH_2$) in organic solvents (THF, toluene, CH_2Cl_2, etc.) (Figure 1.2) under anhydrous conditions[6]. In addition, the reaction temperatures have been from many degrees below zero up to the boiling point of the solvent employed, depending on the nature of the reactans and catalyst[7].

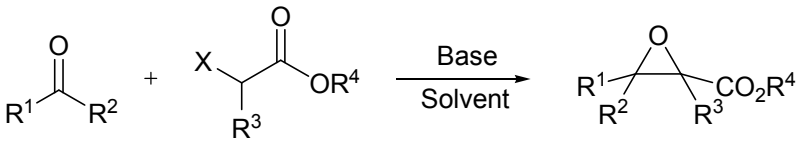


Figure 1. 2 General reaction scheme of Darzens condensation

It is generally agreed that aldol and related condensations proceed by the formation of the enolate ion as a first step. Darzens reaction is mechanistically includes the

aldol reaction of an α-halo carbonyl compound with an aldehyde or ketone to form C-C bond. After deprotonation, the α-halo ester adds to the carbonyl compound to give *syn* **3** and *anti* **4** diastereomers. In the subsequent step, by an intramolecular annulation of the intermediate halohydrin compound epoxy product is obtained. The stereochemistry of the Darzens reaction is determined by the steric requirements of the transition state of the aldol step and with most esters the intramolecular cyclization step favors the trans product **5b**. Typically, the *cis:trans* ratio of the epoxide formation lies between 1:1 and 1:2[8,9] (Figure 1.3).

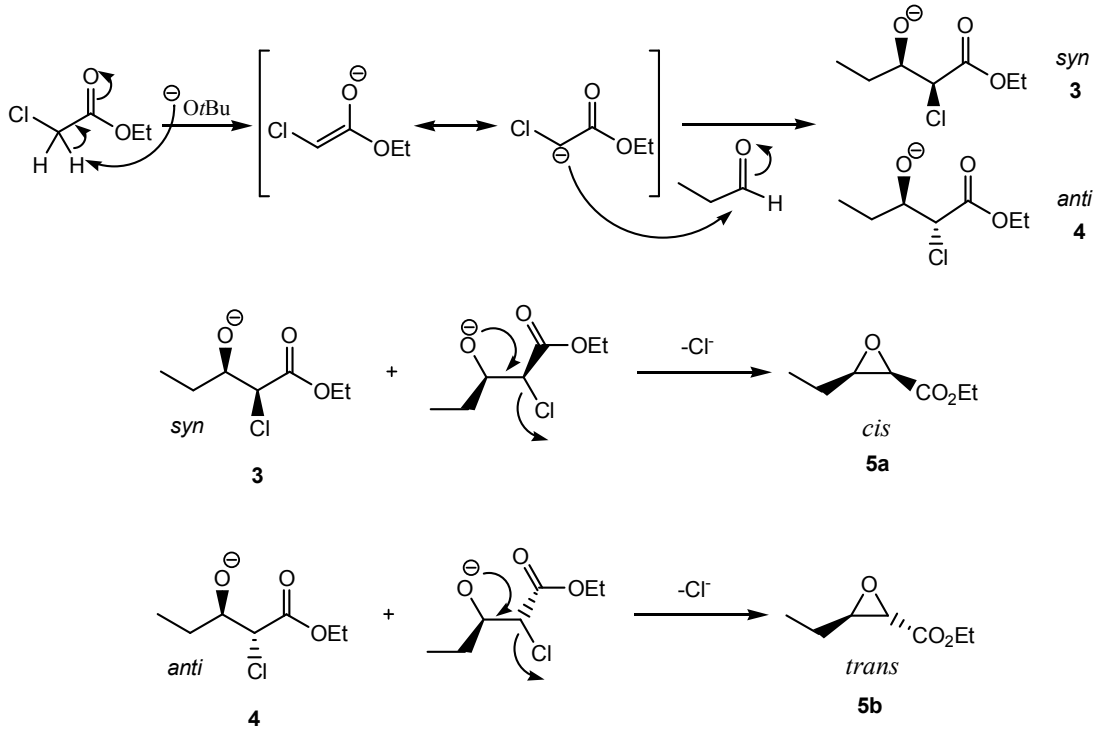


Figure 1. 3 Reaction mechanism of Darzens condensation

In addition, Darzens methodology was primarily used for the synthesis of aldehydes and ketones, as a homologation reaction without any consideration of stereocontrol in the epoxide formation. For this sequence, saponification of the α,β-epoxy ester **6** followed by decarboxylation gives the substituted carbonyl compound **7**[10] (Figure 1.4).

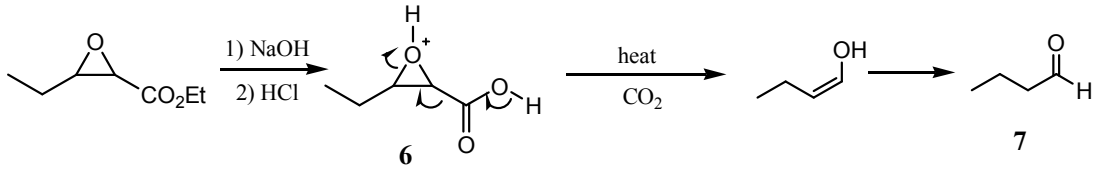


Figure 1. 4 Synthesis of aldehydes and ketones

During the darzens condensation reaction three types of product can be observed depending on the reaction medium. In the second step of the reaction when the halohydrin anion undergoes the intramolecular annulation, the epoxide product **8** is formed. On the other hand, if the halohydrin anion abstracts a proton from the medium, product **9** is formed. Finally, when the elimination of OH^- group occurs from the halohydrin anion, compound **10** is formed[11] (Figure 1.5).

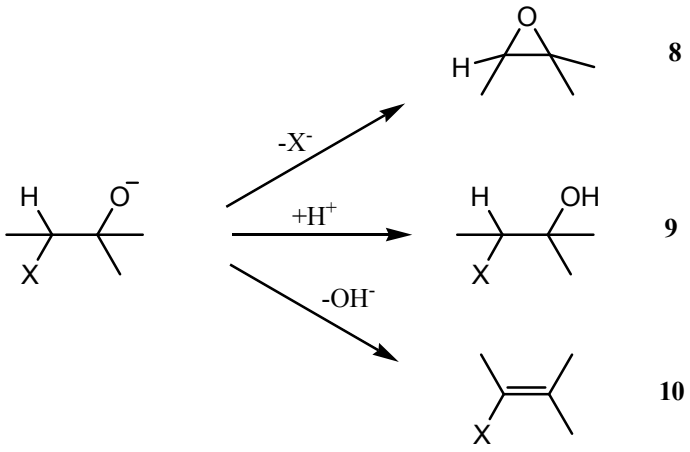


Figure 1. 5 Possible products of Darzens condensation

The control of diastereo- and enatio-selectivities in asymmetric Darzens reactions leading to α,β-epoxy carbonyl compounds is still a challenging goal. A significant problem to be solved is the establishment of an efficient catalytic cycle in which the inorganic salts or related compounds generated from both substrates and reagents are converted into effective reactive species. Past enantioselective Darzens reactions

promoted by metal reagents required stoichiometric amounts of chiral sources because of the metal reagents and harsh reaction conditions employed[12].

In order to overcome these problems Arai et. al. explored the use of N-(4-trifluoromethylbenzyl) cinchonidinium bromide as a PTC in Darzens reactions. They successfully sythesized the desired epoxy ketones **13** with the reaction of an aldehyde **11** and α-chloro ketone **12** by using 10% PTC with yields between 32-83% and ee's between 42-79%[13] as shown in Figure 1.6.

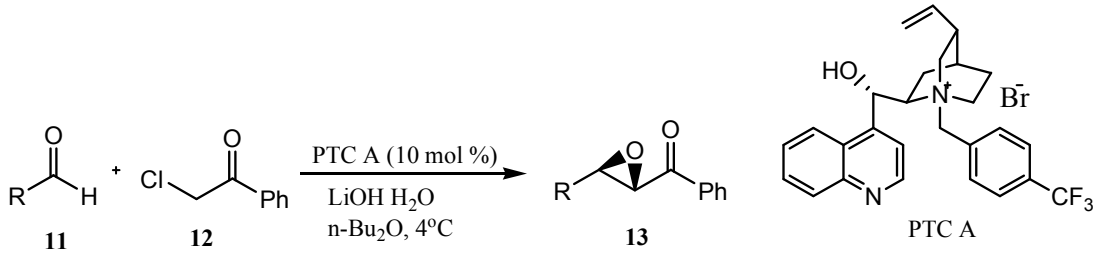


Figure 1. 6 Synthesis of epoxy ketones via PTC

Although PTC can even promote diastereoselective Darzens reactions via a catalytic cycle, development of cheaper, simpler, and more-efficient and recyclable catalysts is highly desirable[14]. One of the most important technical problems in industrial PTC applications with soluble phase-transfer catalysts, such as quaternary ammonium salts, is the need to separate the catalysts from the reaction mixture for subsequent reuse or disposal. Immobilization of the catalyst on a polymeric matrix can provide a simple solution to this problem[15]. Polymer-supported catalysts can be separated from the products easily and used repeatedly, and, thus, have been widely used in green chemistry[16].

In 2004 Wang repoerted the darzens condensation between aromatic aldehydes **14** and ethyl chloroacetate **15** for the synthesis of α,β-epoxy carbonyl compounds **16** as catalyzed by PsTEAC (polystyrene-triethylammonium chloride) **17** and PsCNC (polystyrene-cinchonidinium chloride) **18**[17] (Figure 1.7).

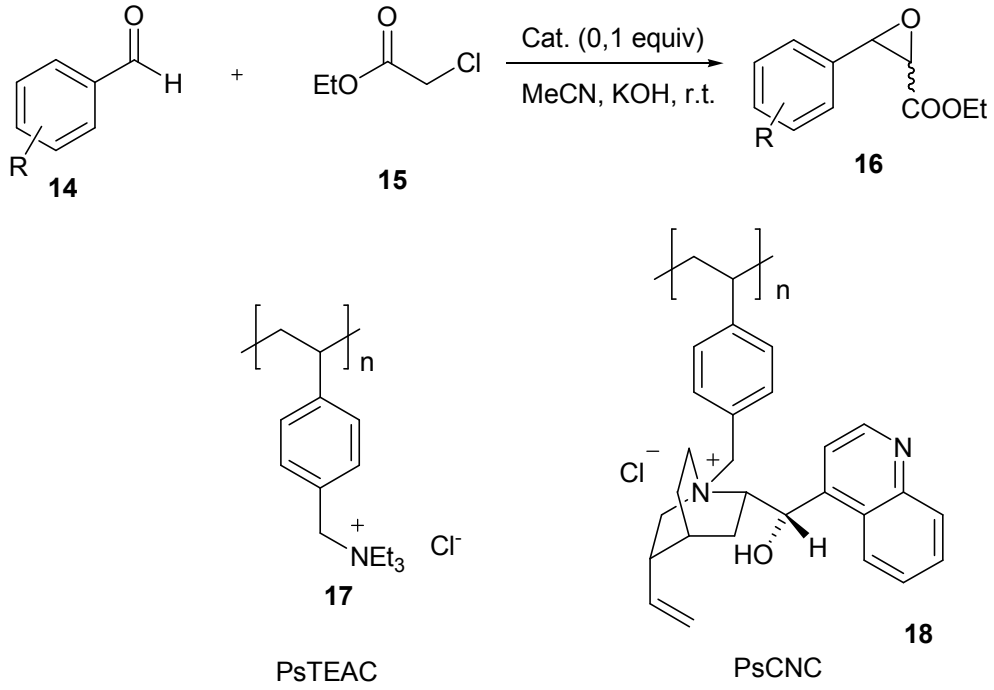
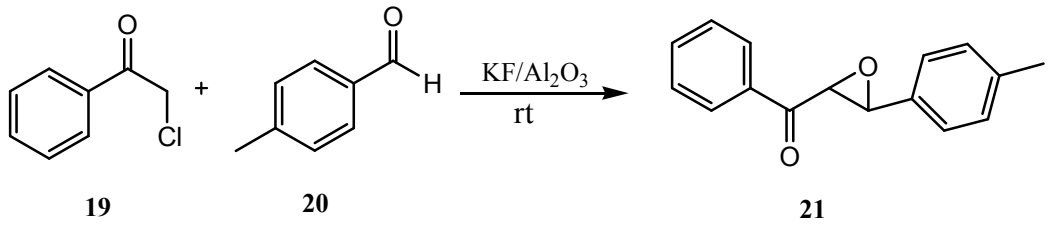


Figure 1. 7 Synthesis of α,β-epoxy carbonyl compounds via polymer-supported catalyst

Using safer and less hazardous reagents and media capable of including versatile organic transformations with fewer side products and solvent requirements has gained importance for the green and environmentally benign chemistry. For this purpose, potassium fluoride on alumina (KF/Al_2O_3) has emerged as a very powerful solid phase reagent for various organic reactions such as ring-closure reactions, epoxidation of alkenes, ether synthesis, amide and amine chemistry, Micheal addition, aldol condensation, rearrangement processes and cycloaddition reactions[18].

In 2007 Sharifi et al. revealed a study about Darzens condensation of α-chloroacetophenone **19** with various aromatic aldehydes **20** mediated by potassium fluoride on a alumina at room temperature and obtained trans-α,β-epoxy ketones **21** with good yields[19] (Figure 1.8).



19 **20** **21**

Figure 1. 8 Synthesis of trans-α,β-epoxy ketones by using KF/Al_2O_3

1.1.2 Acyl phosphonates in organic chemistry

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

1.1.2.1 Reactions with amine nucleophiles

Phosphorous-carbon (P-C) bonds are quite stable and can not be cleaved easily under the usual conditions[20]. Hence, the use of organophosphorus compounds as synthetic reagents is lacking. However, carboxylic acids **23** and phosphites **24** can be obtained due to the cleavege of C-P bond in acyl phosphonates **22** by moisture in air (Figure 1.9).

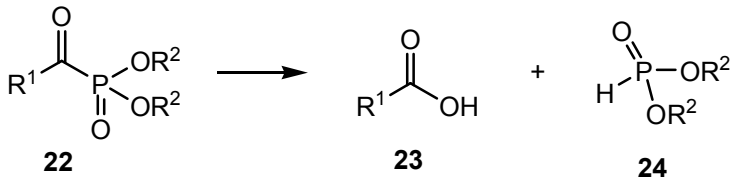


Figure 1. 9 Hydrolysis of acylphosphonates

In the light of this information, Sekine et al. reported acylation of amines by means of α-ketophosphonates[21]. In dry ether the reactions of alphatic and aromatic amines **25** with diethyl benzoylphosphonate were examined. The reactivity of amines for acylation changes with the basicity of amines. Higher reactivity means more basicity. However, it is observed that while aliphatic amines give the corresponding amides in good yields, aromatic (aniline) and 2-amino pyridine do not undergo this reaction. At the end of the reaction two major products and one minor product are isolated. Major products are the corresponding amide **26** and the ethyl phosphite **24**. α-(phosphory1oxy)benzylphosphonate **27** is isolated as a side product (Figure 1.10).

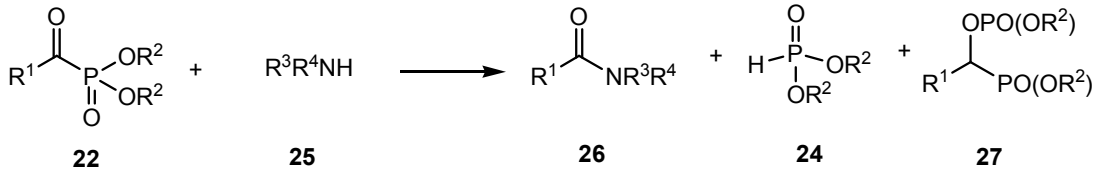


Figure 1. 10 Acylation of amines

On the other hand, when the reaction of mono sodium salts of acyl phosphonates **28** with amines were carried out, it was observed that imines **29** were formed. It is concluded that P-C bond in mono sodium salts of acyl phosphonates is stable to nucleophilic cleavage[22].

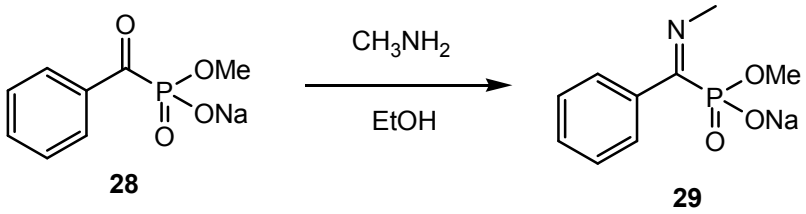


Figure 1. 11 Imine formation of mono sodium salt of benzoyl phosphonate

While amines react with acylphosphonates to give amides, the reactions of acyl phosphonates with hydroxyl amine and substituted hydrazines give oximes **30** and hydrazones **31**, respectively[23] (Figure 1.12).

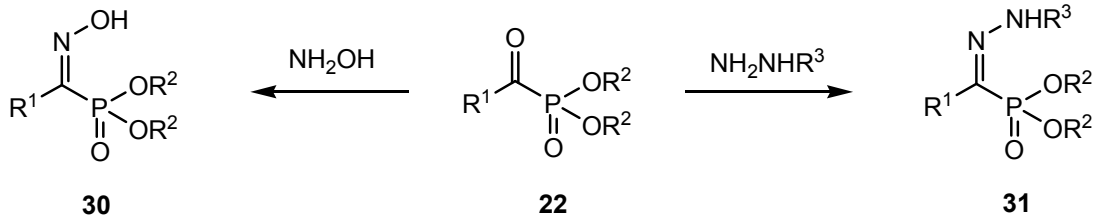


Figure 1. 12 Reaction of acyl phosphonates with hydrazines and hydroxyl amines

Hydrazones from acyl phosphonates can be in both the configurational isomers, ***Z*** and ***E***. However, the reaction between acyl phosphonates and phenylhydrazine results in the ***Z*** isomer **33** because it is stabilized by intramolecular H-bonding. Although ***E*** isomer is less sterically hindred, ***E*** isomer **35** lacks such stabilization. Therefore, ***E*** isomer is obtained by the isomerization of ***Z*** isomer in boiling acetic acid (Figure 1.13).

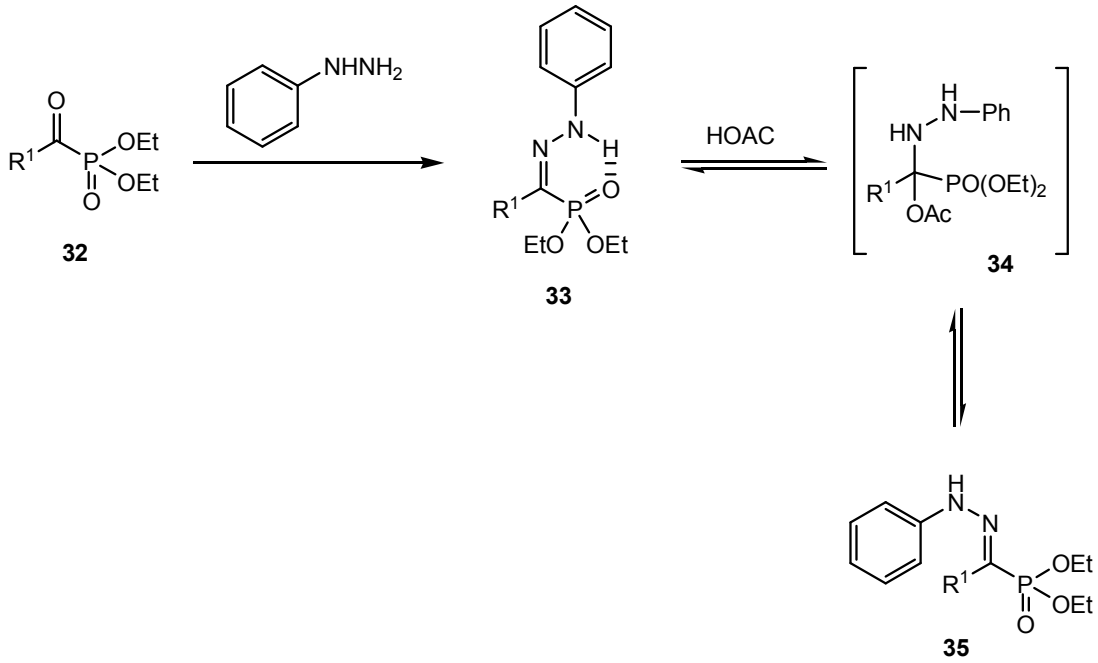


Figure 1. 13 Synthesis of hydrazines and isomerization of Z isomer

1.1.2.2 Decarbonylation of α-ketophosphonates

In 1989, Nakazawa et al. reported decarbonylation of α-ketophosphonates to give corresponding aryl- and alkyl-phosphonate[24]. The decarbonylation reaction is catalyzed by Pd-complexes in toluene in reflux conditions. The catalytic cycle is started by oxidative addition of α-ketophosphonates to PdL_2 at P-C bond to give intermediate **37**. Decarbonylation of **37** produces **38**. The reductive elimination of **38** yields aryl- or alkyl-phosphonates and PdL_2 reenters to catalytic cycle (Figure 1.14).

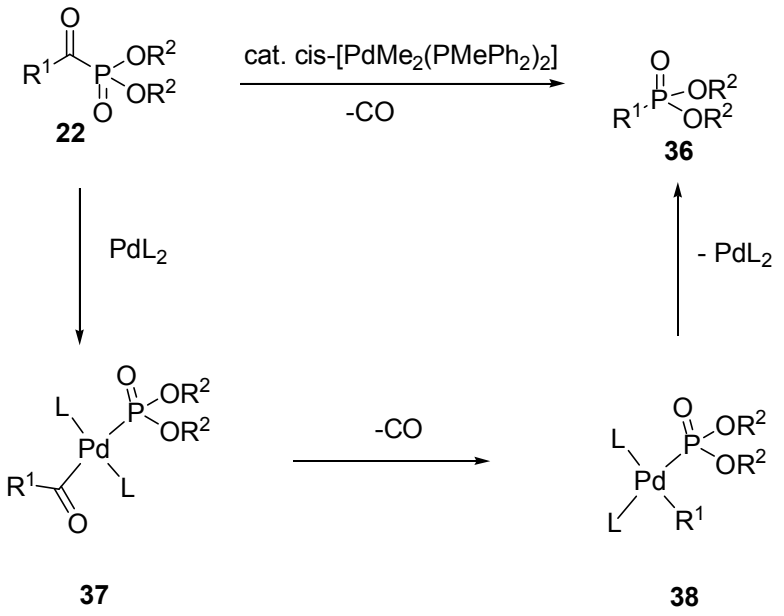


Figure 1. 14 Decarboxylation of acylphosphonates

In a crossover experiment performed by $(Ph)C(O)P(O)(OMe)_2$ **39a** and $(p\text{-}MeC_6H_4)C(O)P(O)(OEt)_2$ **39b** four products are isolated in almost equal amounts (Figure 1.15).

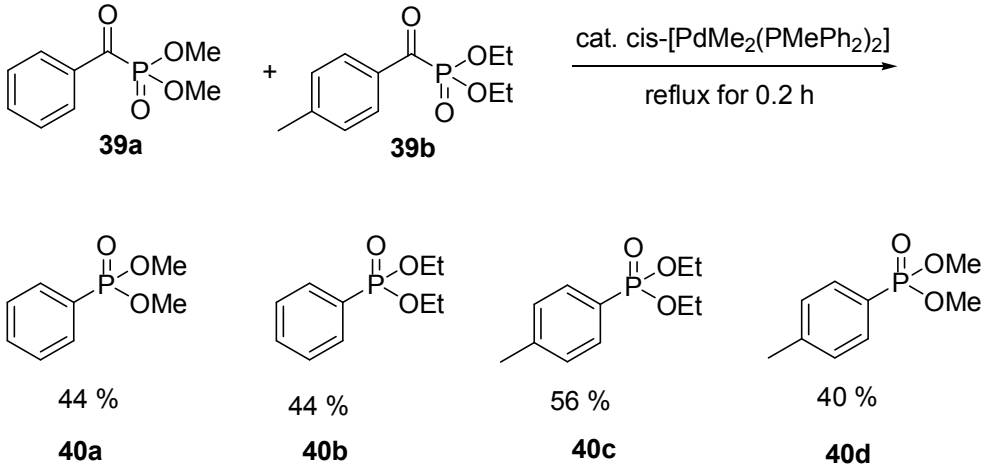


Figure 1. 15 Crossover decarbonylation of acyl phosphonates

Synthesis of $MeC(O)P(O)(OMe)_2$ **39f** from the crossover experiment performed with $MeC(O)P(O)(OEt)_2$ **39e** and $(Ph)C(O)P(O)(OMe)_2$ **39a** is the evidence of metathesis reaction before decarbonylation. Moreover, $PhC(O)P(O)(OEt)_2$ **39c** is not formed while its decarbonylation product **40b** is detected. This can be explained by the decarbonylation rate differences between aryl phosphonates and aliphatic phosphonates. Results show that decarbonylation rate of aryl phosphonates are greater than the decarbonylation rate of aliphatic phosphonates (Figure 1.16).

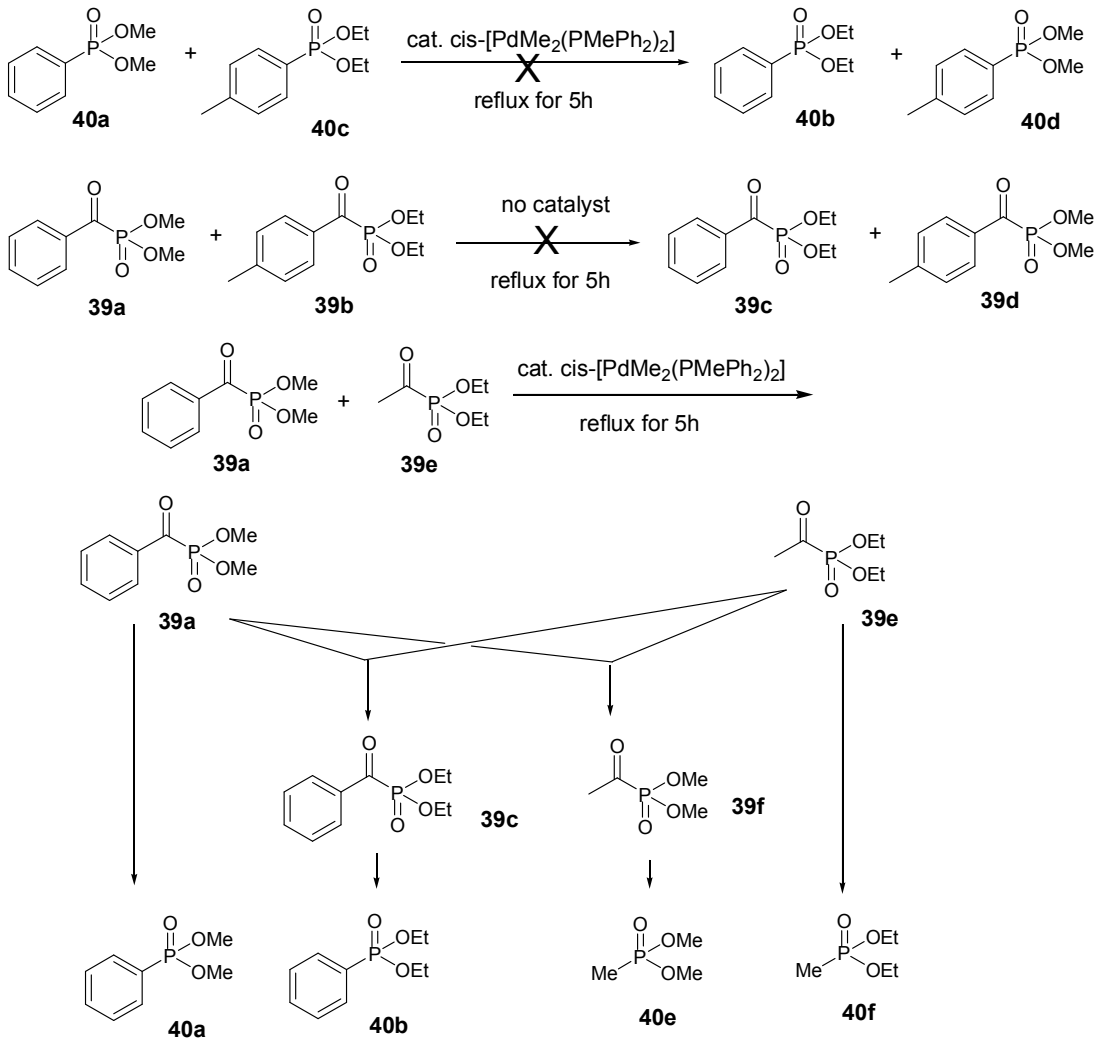


Figure 1. 16 Several crosover experiments on decarbonylation

1.1.2.3 Schmidt reaction of α-ketophosphonates

Schmidt reaction is the acid-catalysed reaction of hydrogen azide with electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes. After a rearrangement and extrusion of N_2, amines, nitriles, amides or imines are produced. In 1994, Sprecher et al. reported Scmidt reaction of dialkyl acyl phosphonates[26].

In the reaction of hydrogen azide with ketone, in order to form azidohdrine intermediate azide attacks to carbonyl group of ketone. Then, water is eliminated and reaarangement occurs. After the water addition and tautomerization an amide is obtained (Figure 1.17).

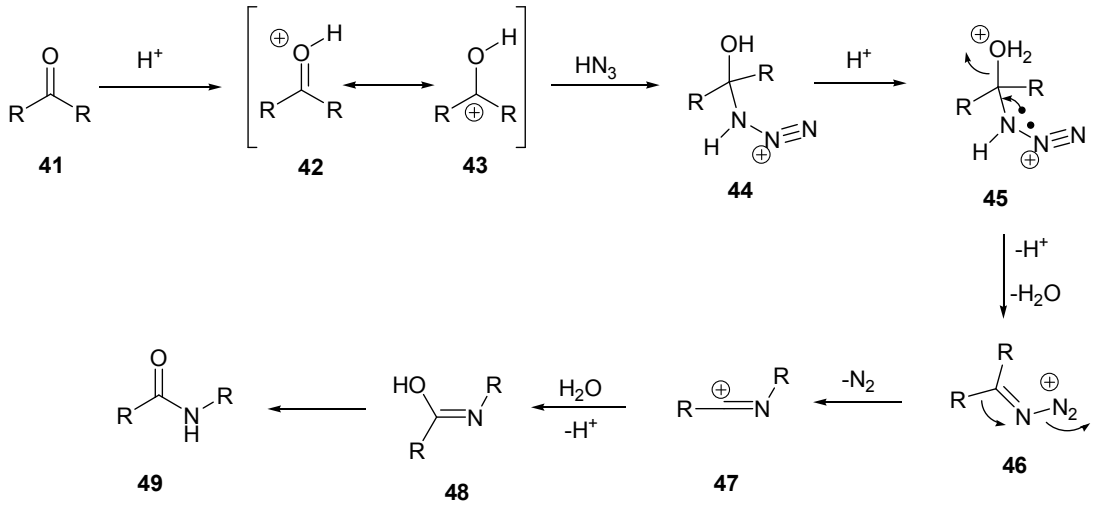


Figure 1. 17 Schmidt reaction of a ketone

When the reaction of hydrogen azide with α-ketophosphonates in conc. H_2SO_4 at 0 ^oC is investigated, depending on both R^1 and R^2 groups eight kind of products are synthesized. Nature of R^1 and R^2 groups also affects the yields of the products and in some cases they are not formed (Figure 1.18).

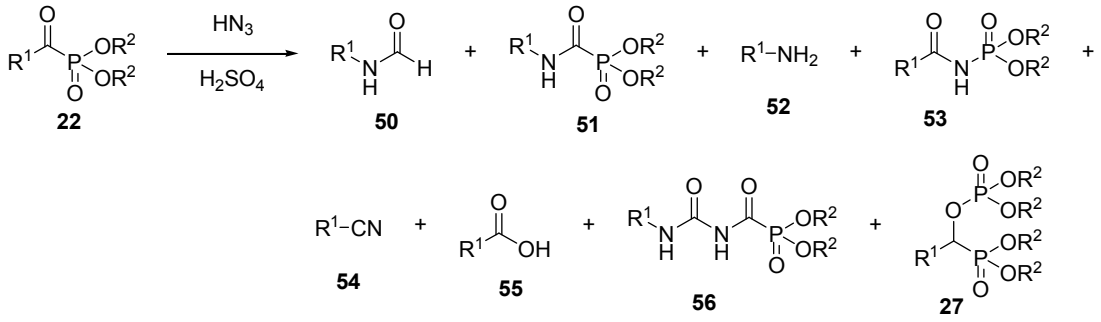


Figure 1. 18 Schmidt reaction of acyl phosphonates

1.1.2.4 Reactions of α-ketophosphonates with Grignard and organolithium reagents

Reactions of acyl phosphonates with Grignard and organolithium reagents carried out in THF at at -78 ^{o}C give corresponding α-hydroxy phosphonates and ketones[27] (Figure 1.19). however, between these two rections there is a difference about product distribution. While Grignard reagents give the corresponding α-hydroxy phosphonates, organolithium reagents produce corresponding ketones. This difference is explained by the intermediates formed during the reaction. In organolithium case, the **59b** is more unstable than **59a** and therefore, rapidly decomposes to ketone. After the formation of the ketone, it reacts rapidly with excess organolithium reagents to yield quarternery alcohols. This consideration is confirmed by treatment of α-hydroxy phosphonate with MeMgBr, MeLi and aq. NaOH-DME.

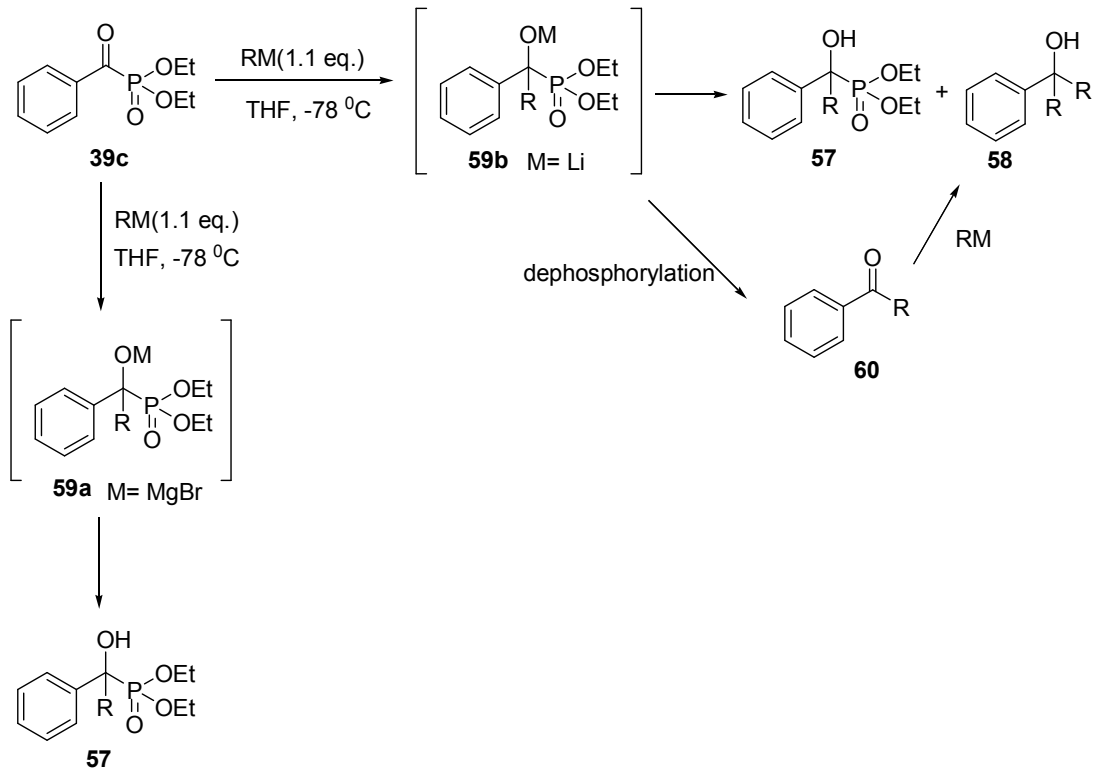


Figure 1. 19 Reactions of α-ketophosphonates with grignard and organolithium reagents

1.1.2.5 Reduction of α-ketophosphonates

The convienent method to synthesize α-hydroxy phosphonates is the reduction of α-ketophosphonates and the reduction can be performed by BH_3 or $NaBH_4$[28,29] (Figure 1.20). In order to synthesize α-hydroxy phosphonates enantioselectively, chiral boron catalysis are used[30]. Borane or catecholborane controlled by (S)-oxazaborolidines reduces diisopropyl α-ketophosphonate **65** to (S)-1-hydroxy benzylphosphonate **66** with 53-83% enantiomeric excess.

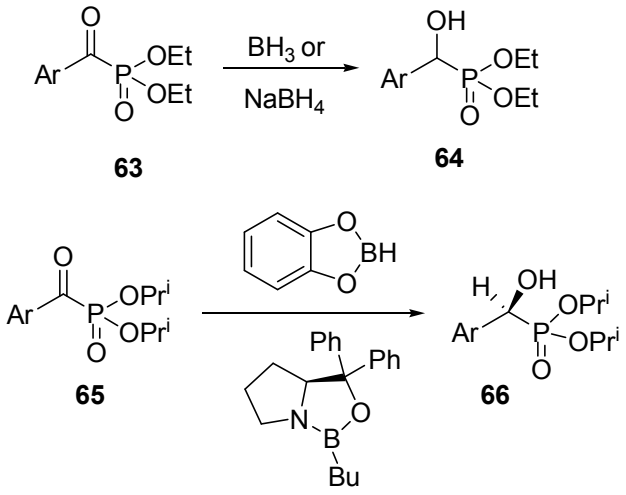


Figure 1. 20 Synthesis of α-hydroxy phosphonates via reduction

1.1.2.6 Addition of carbon nucleophiles to α-ketophosphonates

Phosphonate group in the α-ketophosphonates enhances the electrophilicty of carbonyl group due to its electron withdrawing properties. By this property quarternary α-hydroxy phosphonates can be synthesized by the addition of suitable carbon nuclephiles to carbonyl group. Hard nucleophiles such as organolithium compounds caose cleavage of P-C bond[27]. Wiemer et al. reported allylic addition to α-ketophosphonates by means of allylic bromide in the presence of indium metal[31]. The reaction is carried out in THF in the presence of acetic acid (Figure 1.21). In these conditions the products are synthesized in excellent yields. The scope of the reaction is quite wide because both aliphatic and aromatic phosphonates can be used and also the reaction proceeds with crowded allyl bromides with high level of yields.

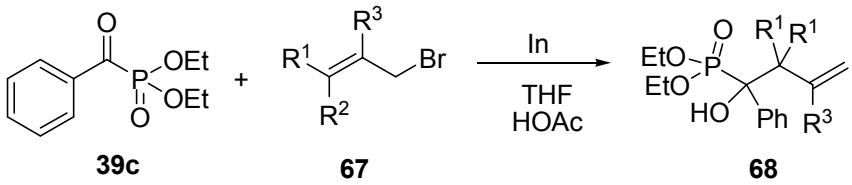


Figure 1. 21 Allylation of acyl phosphonates

L-proline and proline based organocatalysts have gained great importance since 2001[32]. Aldol condensation of α-ketophosphonates with acetone catalyzed by L-proline is the another method to synthesize the queternary α-hydroxy phosphonates[33]. In aldol reaction catalyzed by organocatalyst, while donors can be ketone or aldehydes, acceptors are mainly aldehydes. In their work, Samanta et al. take α-ketophosphonates as acceptor and acetone as donor. The reaction is carried out with both aliphatic and aromatic α-ketophosphonates and the results are moderate to high yields and high enetioselectivities in neat conditions. In this reaction when L-prolinamide is used as the catalyst, 2-Butanone and methoxyacetone are obtained as a precipitate and the reaction proceeds regioselectively.

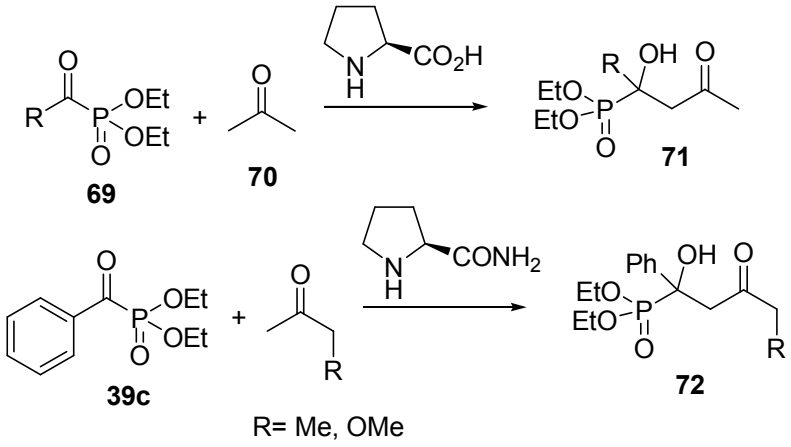


Figure 1. 22 Aldol reaction of acyl phosphonates

For the synthesis of α-hydroxyphosphonates, Demir et. al. was described a new method which is the the reaction of acyl phosphonates with trimethylsilyl cyanide[34]. This reaction gives the trimethylsilyloxycyanophosphonates as a product. As it is shown in Figure 1.23 further hydrolysis of the product with 1 N HCl results in the corresponding α-hydroxyphosphonates.

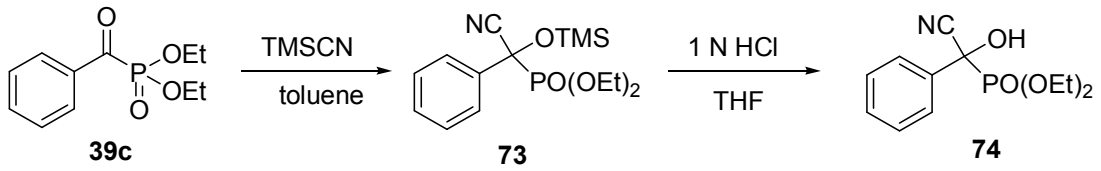


Figure 1. 23 TMSCN addition to acyl phosphonates

1.1.2.7 Umpolung reactions with phosphonates

Phosphorous has the ability of migration both from carbon to oxygen and from oxygen to carbon[35]. A well-known example of migrating ability of phosphorous is Perkow reaction[36]. Although its mechanism is not known exactly, it is generally accepted that a trivalent-phosphorus ends up as a pentavalent-phosphorus via a shift of phosphorus from carbon to oxygen. Perkow reaction competes with the classical Arbuzov reaction and mostly dominates the main reaction course (Figure 1.24).

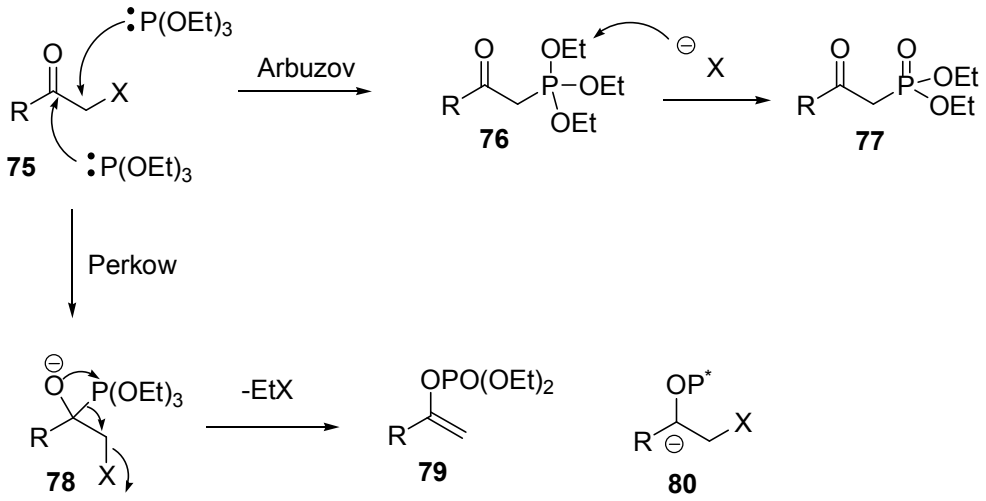


Figure 1. 24 Mechanisms of Perkow and Arbuzov reactions

The route of Perkow reaction inludes the rearrangement of phosphorous from carbon to oxygen yielding enol ether by elimination of X. Also, one can claim that mechanism of the Perkow reaction goes on an intermediate like **80**. Intermediate **80**

is actually an acyl anion equivalent eliminating X. It is obvious that replacing carbon bearing the leaving group with a carbanion stabilizing group like cyanide or phosphonate can provide a new generation of acyl anion precursors.

Base promoted migration of phosphorus from carbon to oxygen has been reported many times. **83** is synthesized by the deprotonation of α-hydroxyphosphonate **81** and rearrengement of the resulting intermediate **82**[37]. 85 is mainly obtained due to the protonation of **83** at the γ-position. However, as it seen in Figure 1.25 same reaction sequence results in the mixture of **84** and **85** in methoxide/methanol. This example shows the tendency of alkoxides of type **82** undergoing phosphonate-phosphate rearrangement.

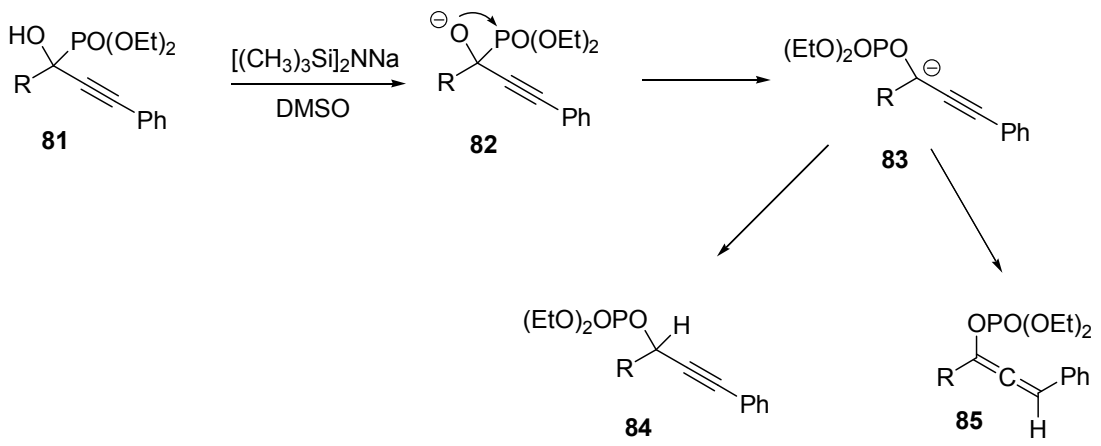


Figure 1. 25 Phosphonate to phosphate rearrangement

Another example of phosphonate-phosphate rearrangement is in the synthesis of α-hydroxyalkylidenediphosphonate esters **87**. McConnell and Coover reported that under basic conditions these compounds can be synthesized by the addition of dialkyl phosphites to acyl phosphonates **22**[38]. As it it seen in Figure 1.26 later it was shown that the product of this reaction was actually isomeric compound **27**[39]. It is formed from rearrangement of intermediate **86** to intermediate **87** before protonation to **87**. It was also shown that isolated **87** rearranges to **27** under basic conditions via the same intermediate **88**.

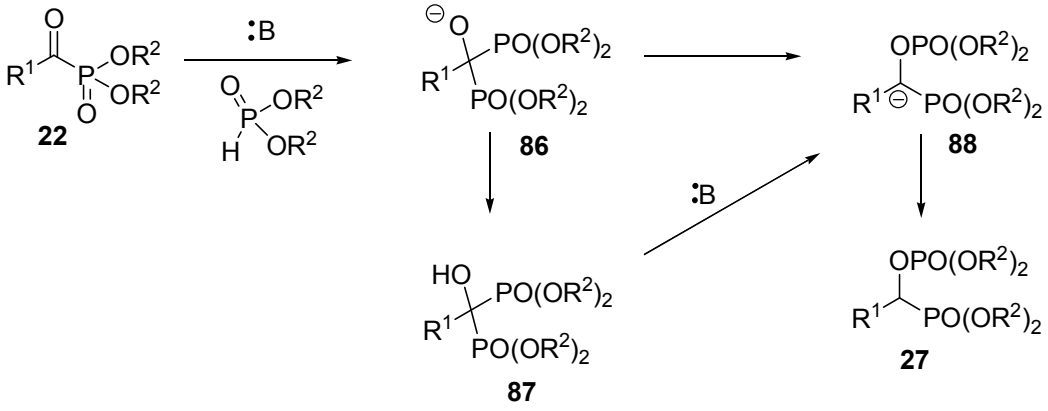


Figure 1. 26 Base promoted migration of phosphorous from carbon to oxygen

The use of derivatives of **91** as acyl anion precursors was reported by Kurihara et. al.[40].the reaction of aldehydes **89** with diethylphosphorocyanidate **90** and LiCN resulted in cyanophosphonates **91**. Deprotonation of **91** to **92** and subsequent reaction with various electrophiles including alkylhalides, acylhalides and aldehydes yielded alkylated **93**, acylated **94** and acyloins **95** type products, respectively. However, only starting materials were recovered when aliphatic derivatives of **91** were used. In addition, electron donating group substituted **96** were reported to be unstable, therefore, it was not useful for the generation of corresponding **92**.

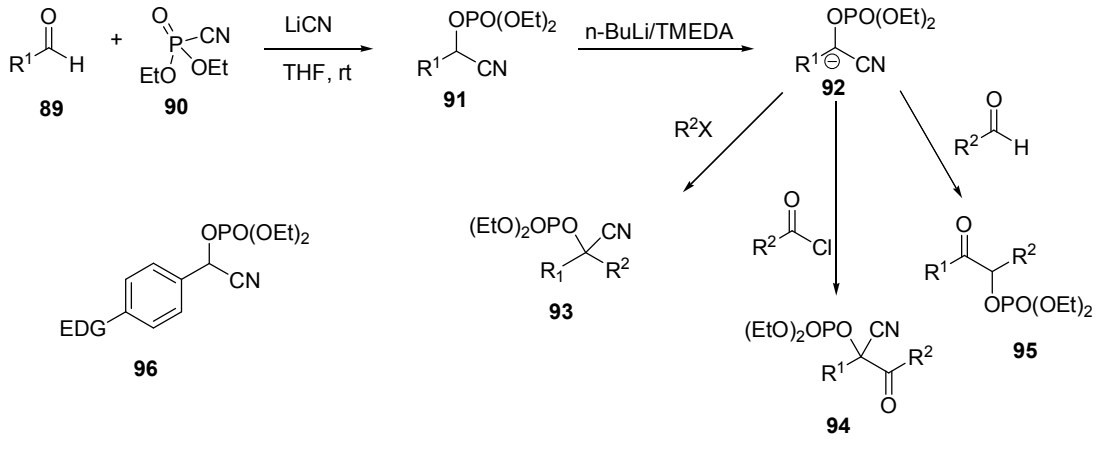


Figure 1. 27 Phosphate protected cyanohydrines as acyl anion precursors

1.1.2.8 Benzoylphosphonates as acyl anion equivalent

In hand of these informations, our group introduced acyl phosphonates as new generation of acyl anion precursor in benzoin reaction[41] (Figure 1.28). Cyanide promoted rearrangement from phosphonate to phosphate give the corrosponding acyl anion equivalent. These acyl anion equivalents react with variety of aldehydes to yield cross benzoin adducts. With this method, to synthesize a variety of aromatic-aromatic, aromatic-aliphatic, and aliphatic-aromatic acyloins is possible.

The mechanism is similar to classical benzoin reaction. The acyl anion equivalent is generated by the migration of phosphorous from carbon to oxygen after the addition of cyanide ion to carbonyl group. Reaction of this acyl anion equivalent with an aldehyde give the intermediate **99**. Retrocyanates following the 1-4 migration of phosphorous from O to O yields the benzoin adduct and close the catalytic cycle.

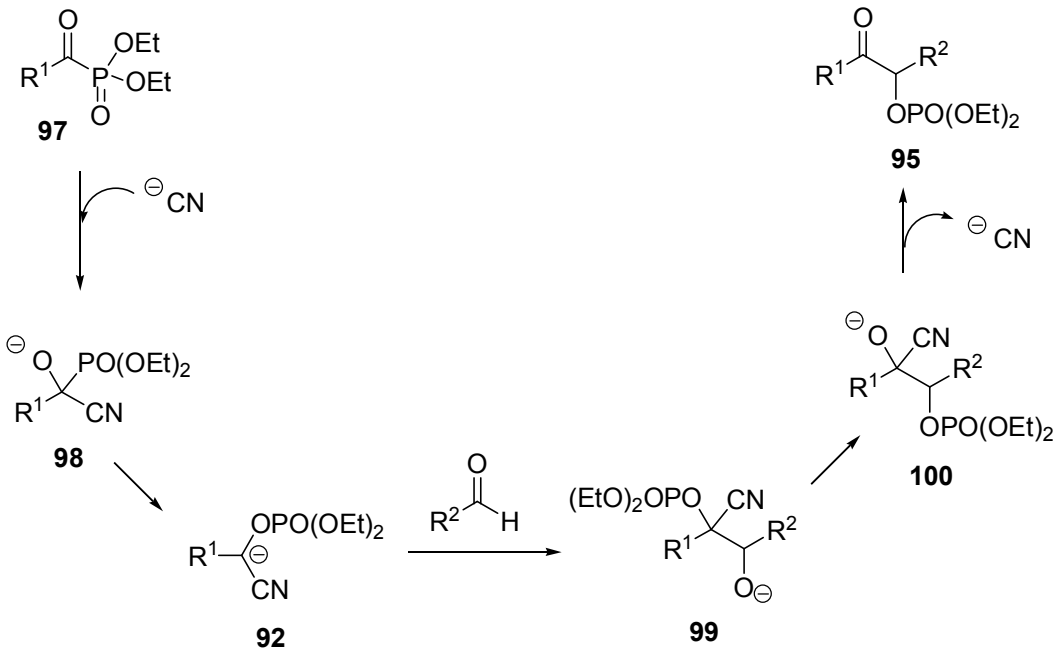


Figure 1. 28 Mechanism of benzoin reaction of acyl phosphonates

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

Compared to results reported by Kurihara et al., this method is superior. In Kurihara's work, aliphatic and electron rich aromatics failed to give corresponding benzoin products. However, cyanide catalyzed benzoin reactions of acyl phosphonates with aldehydes work with electron rich donors and both of aliphatic donors and acceptors.

Protonation of acyl anion equivalent generated from acyl phosphonates give valuable intermediates[42]. The main product is hydroxy protected cyanohydrines. From cyanohydrines, a variety of compounds can be synthesized (Figure 1.29).

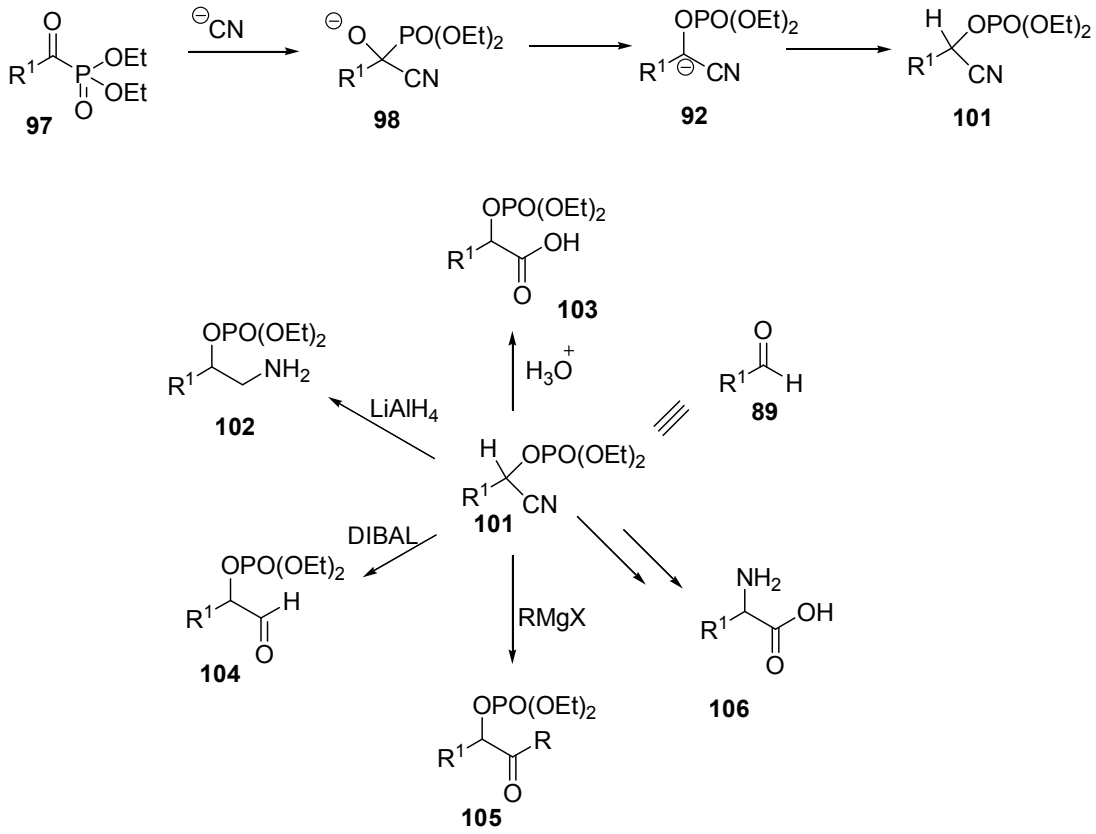


Figure 1. 29 Protonation of acyl anion equivalent and some transformations of the product

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

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

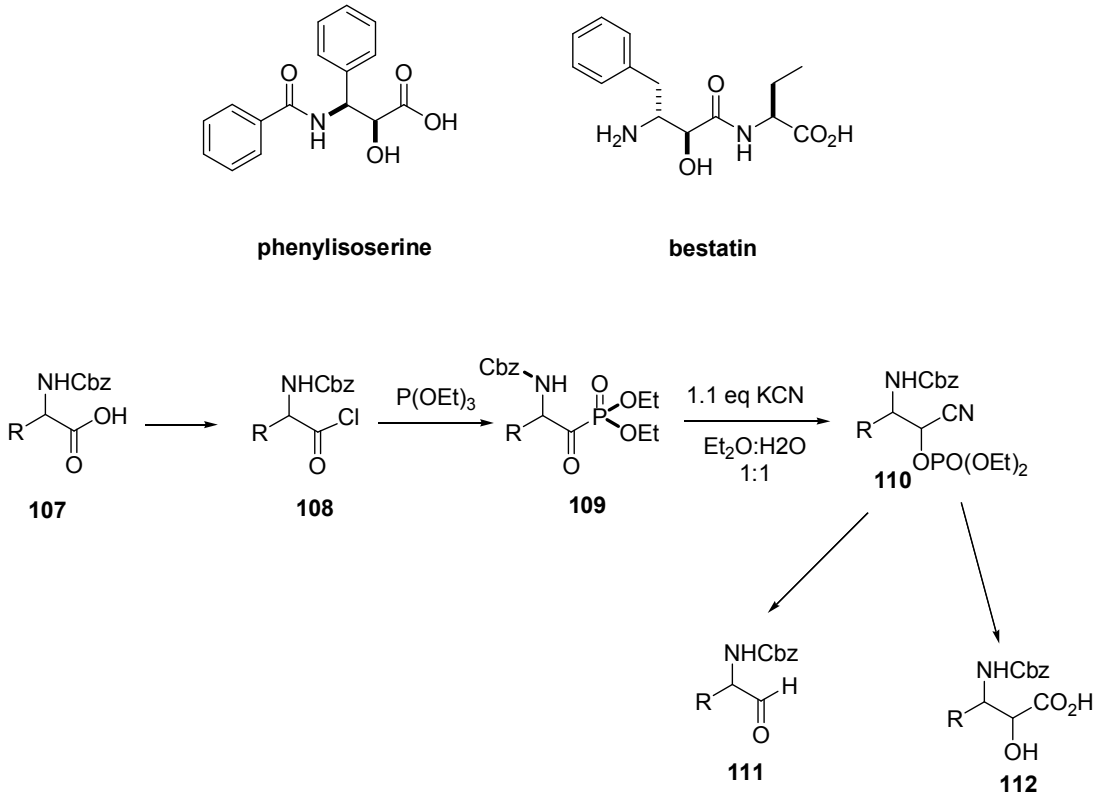


Figure 1. 30 Synthesis of some valuable compounds from α-amino acids using phosphonates

Reduction of carboxylic acids to aldehydes also can be performed by this method. The intermediate from protonation of acyl anion equivalents is equivalent to aldehyde under hydrolysis conditions. Under water free conditions corrosponding esters or amides with DIBAL are usually used to reduce carboxylic acids to aldehydes. However, by this method direct reduction of carboxylic acids to aldehydes under aqueous conditions can be achieved..

1.1.3 Synthesis of 1,2-epoxyphosphonates

1,2-Epoxypropylphosphonates are very important intermediates in organic synthesis. Many of their derivatives have attracted attention because of their antibacterial, antiviral, antibiotic, pesticidal, anti-cancer, and enzyme inhibitory properties. For example, (–)-(1*R*,2*S*)-(*Z*)-1,2-epoxypropylphosphonic acid, a derivative of *cis*-1,2-epoxypropylphosphonates, also called fosfomycin or phosphonomycin, is a low

molecular weight cell-wall active antibiotic found by Hendlin and coworkers in 1969[43]. As a consequence of this discovery, a lot of research has resulted in the extensive development of methodologies in order to prepare analogs of fosfomycin and to diversify the syntheses. Synthesis of dialkyl 1,2-epoxyalkylphosphonates may be classified into four main categories including (a) the Darzens reaction of dialkyl chloromethylphosphonates with carbonyl compounds, (b) the reaction of sodium dialkylphosphites with α-halo ketones, (c) the reaction of dialkyl halohydrinphosphonates with bases, (d) the oxidation of 1,2-unsaturated phosphonates with a peroxide and (e) the reaction of diazobenzylphosphonates with aldehydes and ketones[44].

1.1.3.1 Darzens reaction of dialkyl chloromethylphosphonates with carbonyl compounds

The Darzens synthesis of glycidic esters by the condensation of carbonyl compounds with α-halo esters[45] is an important and useful method, which has been extended in phosphorus chemistry. Unquestionably, the most general and perhaps most widely employed method for the synthesis of dialkyl 1,2-epoxyalkylphosphonates involves the reaction of dialkyl chloromethylphosphonates **113** with carbonyl compounds. By the treatment of dialkyl chloromethylphosphonate with an equimolecular amount of base and the further reaction of the intermediate compound **114** with the carbonyl compounds (aromatic aldehydes and ketones) gives the corresponding 1,2-epoxyalkylphosphonates **115** (Figure 1.31).

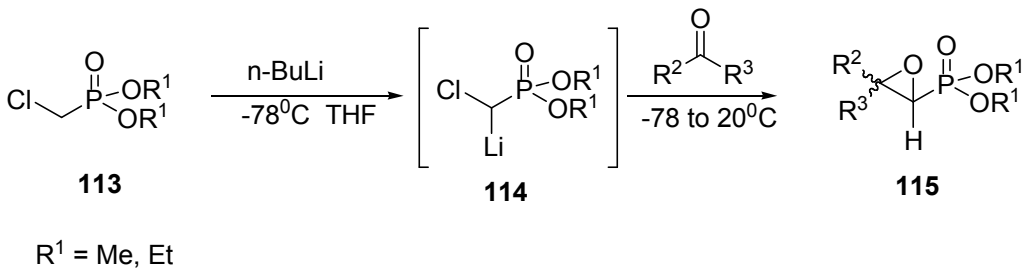


Figure 1. 31 Synthesis of 1,2-epoxyphosphonates via Darzens reaction

1.1.3.2 Reaction of sodium dialkylphosphites with α-halo ketones

It is well recognized that reaction of α-halo ketones **117** with the appropriate phosphorus nucleophiles can constitute an interesting but somewhat limited method of synthesis of dialkyl 1,2-epoxyalkylphosphonates **119**. Effectively, the conditions required for this procedure may not be compatible with the sensitive functionalities of α-halo ketones, and the reaction sometimes proceeds with a lack of regiospecificity to produce a mixture of phosphorus compounds. Thus, this reaction has been reported to give the epoxide alone[46,47], the vinyl phosphate alone[48,49], a mixture of the epoxide and vinyl phosphate[50], or a mixture of the epoxide and β-oxophosphonate[51,52].

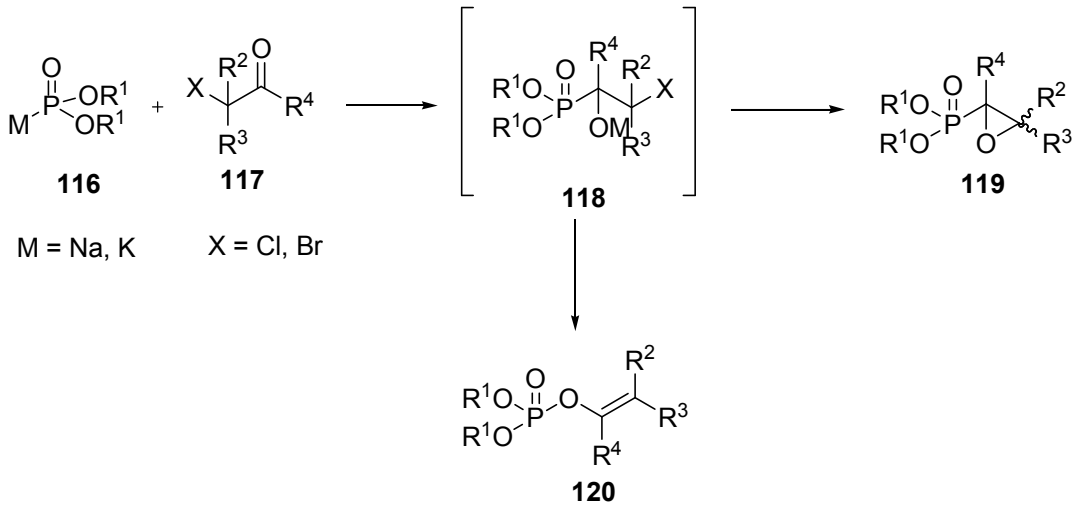


Figure 1. 32 Synthesis of 1,2-epoxyphosphonates via reaction of sodium dialkylphosphites with α-halo ketones

1.1.3.3 Reaction of dialkyl halohydrinphosphonates with bases

In addition to the two previous methodologies, there is a technique which employs the conversion of halohydrinphosphonates into epoxyphosphonates by formation of an alkoxide anion. This two-step procedure appears to be limited to the synthesis of dialkyl 1,2-epoxyethylphosphonates having hydrogens or only one non-hydrogen

substituent. Formation of halohydrinphosphonates can be accomplished by two procedures, which exploit either the condensation of a dialkylphosphite with an a-chlorocarbonyl compound or the halohydroxylation of a vinylphosphonate. After the formation of the corresponding dialkyl halohydrinhalophosphonate, it is converted to the epoxide by the furter treatment with base[53] (Figure 1.33).

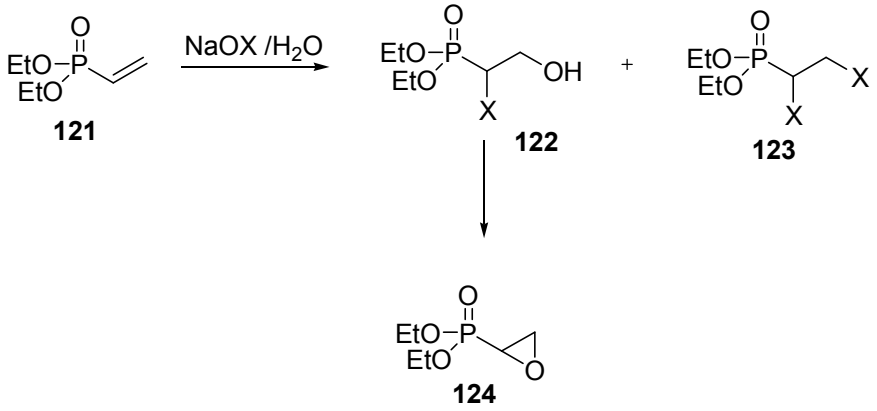


Figure 1. 33 Synthesis of 1,2-epoxyphosphonates via reaction of dialkyl halohydrinphosphonates with bases

1.1.3.4 Oxidation of 1,2-unsaturated phosphonates with a peroxide

The most attractive and potentially most general route for the synthesis of dialkyl 1,2-epoxyalkylphosphonates and their various α- and β-substituted analogs **119** appears to be the direct epoxidation of the corresponding dialkyl vinylphosphonates **125**. The synthesis of dialkyl vinylphosphonates with essentially any desired combination of α and β substituents can be achieved readily by a number of procedures.[54] The use of vinylphosphonates offers appreciable advantages. Not only are the two isomeric unsaturated phosphonates formed when R^2 or $R^3 \neq H$ readily separable prior to *cis* or *trans*-epoxidation of the appropriate isomer, but the use of these unsaturated intermediates permits an acid-catalyzed hydrolysis of the ester functions prior to epoxidation.

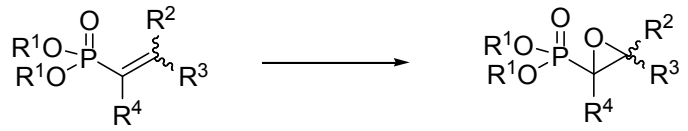


Figure 1. 34 Synthesis of 1,2-epoxyphosphonates via direct epoxidation

1.1.3.5 Reaction of diazobenzylphosphonates with aldehydes and ketones

Carbonyl ylides derived from the metal-catalyzed decomposition of diazo compounds have received much attention over the past number of years[55,56]. They can undergo some important reactions such as 1,3-dipolar cycloaddition reactions with a series of dipolarophiles, rearrangement reactions, and cyclizations to form three-membered ring compounds. Most of the reported carbonyl ylide reactions are 1,3-dipolar cycloadditions[57]. The cyclization of carbonyl ylides is an attractive and general method to give epoxides[58-62]. One of the methods to synthesize 1,2-epoxyalkylphosphonate is the reaction of carbonyl and diazo compounds in the presence of rhodium acetate.

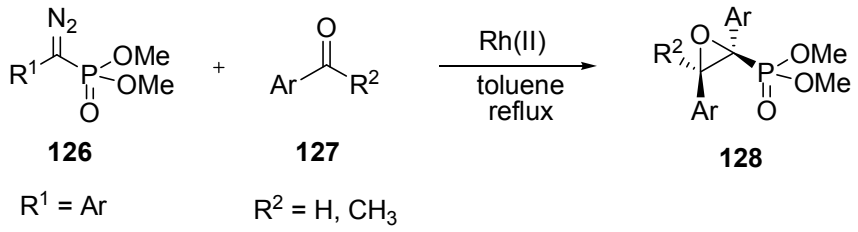


Figure 1. 35 Synthesis of 1,2-epoxyphosphonates via reaction of diazobenzylphosphonates with aldehydes and ketones

1.2 Manganese (III) acetate mediated acetylation of aryl boronic acids

1.2.1 Manganese (III) acetate in organic chemistry

Metal-promoted radical reactions have found widespread use in organic synthesis, in which one of the well-known examples of this application is the $Mn(OAc)_3$-mediated reaction[63]. Manganese (III) acetate dihydrate ($Mn(OAc)_3 2H_2O$)-mediated free-radical reactions have emerged as important synthetic methods for a new bond formation as well as bond breaking. The application of $Mn(OAc)_3$ promoted free-radical reactions in numerous regio-, chemo-, and stereoselective carbon–carbon, carbon–heteroatom bond formations have been developed in both inter- and intramolecular reactions[64].

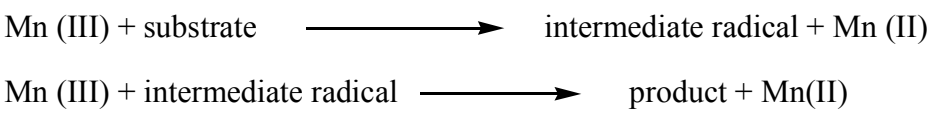
An extensive amount of work has been conducted using manganese (III) acetate as an oxidizing agent. Oxidations with manganese (III) acetate can be classified into two groups[63]:

1. Direct inner- and outer-sphere one-electron oxidation of the substrate after the formation of an inner- or outer-sphere substrate-Mn(III) complex.

The subsequent oxidation of an intermediate radical is often product determining. Numerous examples can be found in the oxidations of alcohols, amino- and thio-compounds, carboxylic acids and certain aromatics.

2. Indirect oxidation of the substrate after the formation of an intermediate adduct free radical from interaction of manganese (III) acetate and enolizable compound and subsequent addition or substitution of this radical to the substrate.

Manganese (III) acetate as a one electron oxidant has many similarities with respect to a given substrate class with other one electron oxidants such as Co(III), Ce(III) and some two electron oxidants such as Tl(III) and Pb(III). It is often observed that owing to its lower reactivity, higher selectivities can be obtained with manganese (III) acetate compared to other oxidizing agents[65]. Many of these reactions proceed accoding to the following path.



1.2.2 Manganese (III) acetate mediated coupling reactions with aryl boronic acids

C-C bond-forming reactions leading to biaryls are very important because this approach is the key step in the synthesis of many natural and unnatural biaryls. There are various biaryl coupling methods. One of the most common method for the synthesis of the simple unsymmetrical biaryls is the generation of aryl radicals in the presence of aromatic solvents. Although the product range of this approach is somewhat limited, it provides an easy access to a variety of unsymmetrical biaryls[66].

In 2002 Demir et. al. described the efficient generation of aryl radicals from aryl boronic acids by manganese (III) acetate. In this study they showed that in aromatic solvents, in situ generated aryl radicals afford the corresponding biaryls in very good yields. This method works selectively, and yields are better than those from similar, previously described methods. Aryl boronic acids carrying sensitive functional groups also work efficiently[67] (Figure 1.36).

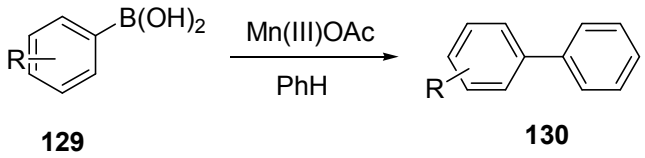


Figure 1. 36 Synthesis of biaryls by aryl boronic acids

1.2.3 Addition of radicals to acetonitrile

In contrast to the vast literature on carbocationic additions to nitriles, there are few reported examples of carbon-centered radicals adding to nitriles.[68] There are, however, several examples of intramolecular carbon radical cyclizations into the nitrile bond. For example, Ogibin et al. found that cyclopentanone was formed

ultimately as the major product upon generating the 4-cyanobutyl radical in aqueous media (i.e., the radical adds to the carbon of the nitrile)[69] (Figure 1.37).

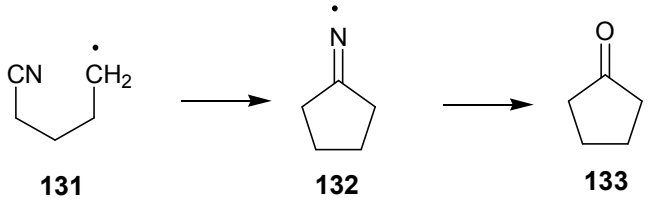


Figure 1. 37 Reaction of 4-cyanobuthyl radical

Shelton and Uzelmeier have observed some of the few reported additions of carbon-centered radicals to a nitrile. Both cyclohexyl radicals **134** (Figure 1.38) and phenyl radicals **137** (Figure 1.39) were added to benzonitrile [70].

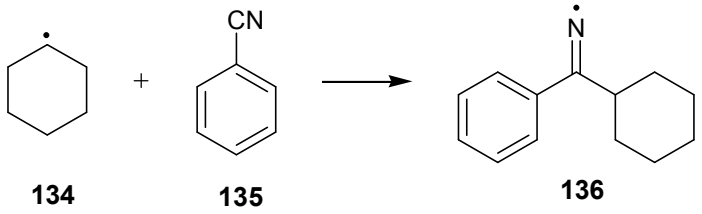


Figure 1. 38 Reaction of cyclohexyl radicals and benzonitrile

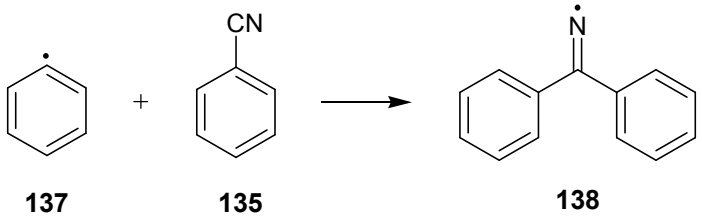


Figure 1. 39 Reaction of phenyl radicals and benzonitrile

Adamantyl radicals were found to undergo three types of reactions with acetonitrile[71]: (a) hydrogen-atom abstraction, (b) addition to the nitrogen of the cyano group, and (c) addition to the carbon of the cyano group (Figure 1.40).

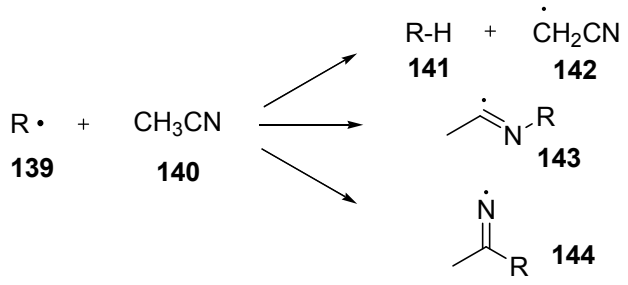


Figure 1. 40 Types of reaction of adamantyl radicals with acetonitrile

Addition to the nitrogen of the cyano group would lead to the amide (as in the reactions of carbocations with acetonitrile) but this product was present in very small amounts and this pathway is therefore of little significance. Radical addition to the carbon of the cyano group leads to an iminyl radical which ultimately yields a ketone[72] (Figure 1.41).

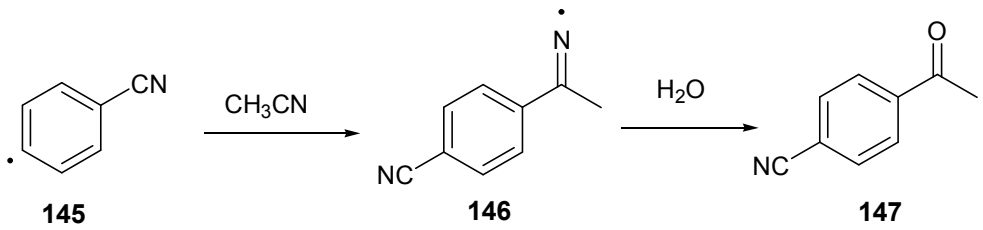


Figure 1. 41 Formation of iminyl radical and corresponding ketone

1.3 Aim of the work

Phosphorous containing small cycles are very important building blocks in organic and medicinal chemistry, mainly as a result of high degree of ring strain and rigidity of the system as well as due to the ability of phosphorus moiety to specific coordination with metal dependent enzymes. Many of their derivatives, especially cyclopropyl- and 1,2-epoxypropylphosphonates, have attracted great attention due to the broad spectrum of their biological properties including antiviral, anticancer, antibiotic, antibacterial, pesticidal, insecticidal and enzyme inhibitory activities. The aim of the first part of the thesis is shown retrosynthetically in Figure 1.42.

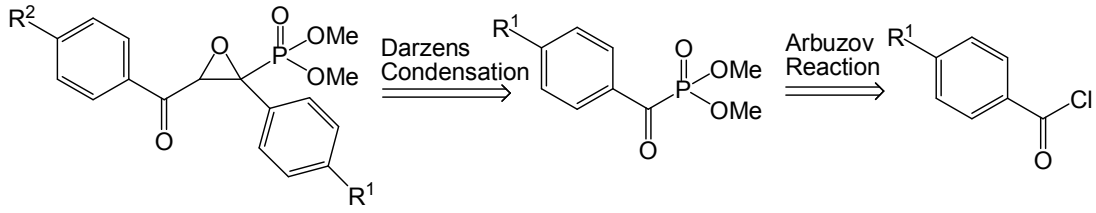


Figure 1. 42 Retrosynthetic pathway of 1,2-epoxyphosphonates

Our first approach to α,β-epoxyphosphonates was to synthesize acyl phosphonates starting from trimethyl phosphite and benzoyl chloride derivatives. Then, the corresponding α,β-epoxyphosphonates were aimed to synthesize by the further Darzens condensation reaction of substituted α-bromo acetophenones and acyl phosphonates in order to illustrate the substituent effect on the reaction.

In the second part of the thesis our aim was to generate aryl radical from aryl boronic acids via manganese (III) acteate and then acetylation of these aryl radicals by the reaction with acetonitrile.

Metal-promoted radical reactions have found widespread use in organic synthesis, in which one of the well-known examples of this application is the $Mn(OAc)_3$-mediated reaction. Manganese(III) acetate dihydrate ($Mn(OAc)_3.2H_2O$)-mediated free-radical reactions have emerged as important synthetic methods for a new bond formation as

well as bond breaking. The application of $Mn(OAc)_3$ promoted free-radical reactions in numerous regio-, chemo-, and stereoselective carbon–carbon, carbon–heteroatom bond formations have been developed in both inter- and intramolecular reactions. The aim of the second part of the thesis is shown retrosynthesically in Figure 1.43.

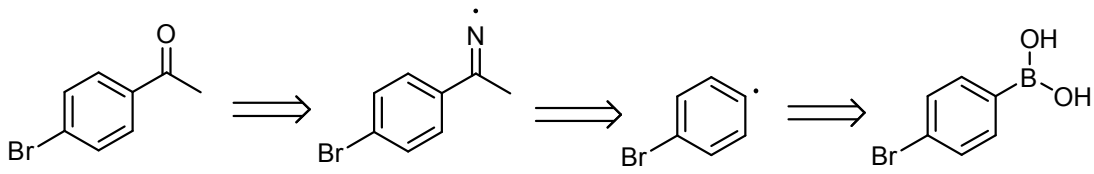


Figure 1. 43 Retrosynthetic pathway of acetylated aryl boronic acids

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Darzens condensation reactions with acyl phosphonates

2.1.1 Synthesis of acyl phosphonates

Acyl phosphonates are easily accessible compounds. The most convenient way to get these compounds is the well-known Arbuzov reaction between acyl chlorides and trialkylphosphites[73]. Reaction proceeds via formation of unstable intermediate **150** that eventually leads to acyl phosphonate. Reaction is very exothermic therefore it is generally carried out at 0 ^{o}C in neat conditions. Once one of the reactants is solid, it is carried out at room temperature or in organic solvents. In this reaction alkyl chloride is the only side product (Figure 2.1).

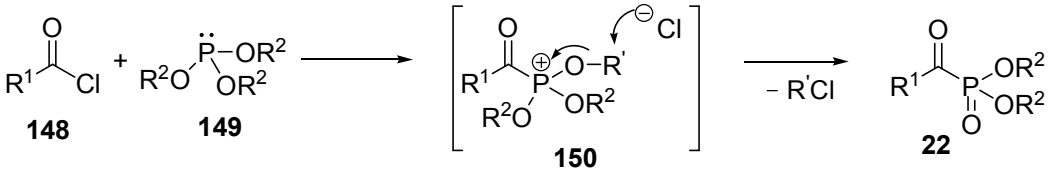


Figure 2. 1 Synthesis of acyl phosphonates

Therefore, acyl phosphonates used in that study were synthesized via classical Arbuzov route according to literature procedures. Purification was done by vacuum

distillation and yields were between %80 and %90. The acyl phosphonates synthesized for this work are outlined in Figure 2.2.

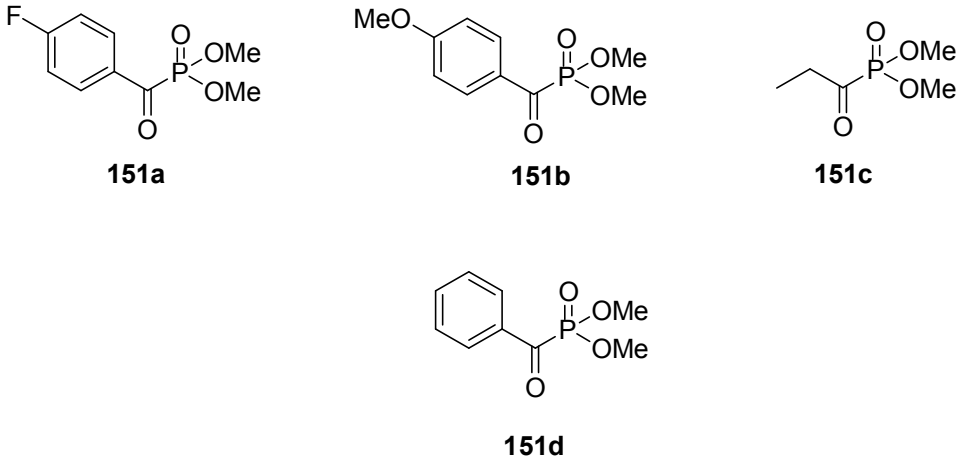


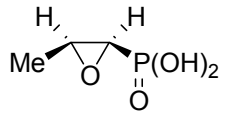
Figure 2. 2 Acyl phosphonates synthesized in this study

Acyl phosphonates can be synthesized in multigram quantities and very high yields from simple starting materials[73]. The reactions were carried out under inert atmosphere. Their synthesis does not require any other special conditions or apparatus. Since they are sensitive to moisture, they should be stored under argon filled flasks to prevent decomposition or hydrolysis. Moreover, they can be handled on benchtop without a special precaution and even their TLC sample solutions are hydrolysed slowly.

2.1.2 Darzens reaction of acyl phosphonates with α-bromo ketones

Epoxides rank among the most versatile synthetic intermediates, constituting convenient building blocks for the synthesis of many products of biological interest. Among them, 1,2-epoxyphosphonates have attracted considerable interest since the first discovery of the antibiotic fosfomycin **152**[74]. (1R, 2S)-(-)-(1, 2)-Epoxypropyl phosphonic acid is a clinically important drug with a wide spectrum antibiotic activity. A vast number of fosfomycin derivatives have been synthesized over the

years with biological activities, many of which have included the synthesis of epoxyphosphonates as intermediates[75] (Figure 2.3).



fosfomycin

152

Figure 2. 3 Structure of fosfomycin

A straightforward method for the preparation of epoxyphosphonates is the direct epoxidation of the corresponding alkenyl phosphorous compound[76], whereas several other methods are also available[77-79]. These methods include the reaction of α-halo ketones and α-tosyl ketones with metal dialkyl phosphites[75-77], the cyclization of halohydrins in the presence of a base[75,78], the Darzens type reaction of chloromethyl phosphonates with carbonyl compounds[75, 79] and a rather recently published work including a rhodium acetate mediated reaction of diazobenzylphosphonates with carbonyl compounds[80]. Although there are many methods for the preparation of these important intermediates, many of these methods lack stereoselectivity, efficiency, and ease of preparation of the starting materials, so that there is still a need for alternative synthetic approaches. Figure 2.4 shows the available methods fot the synthesis of α,β-epoxyphosphonates.

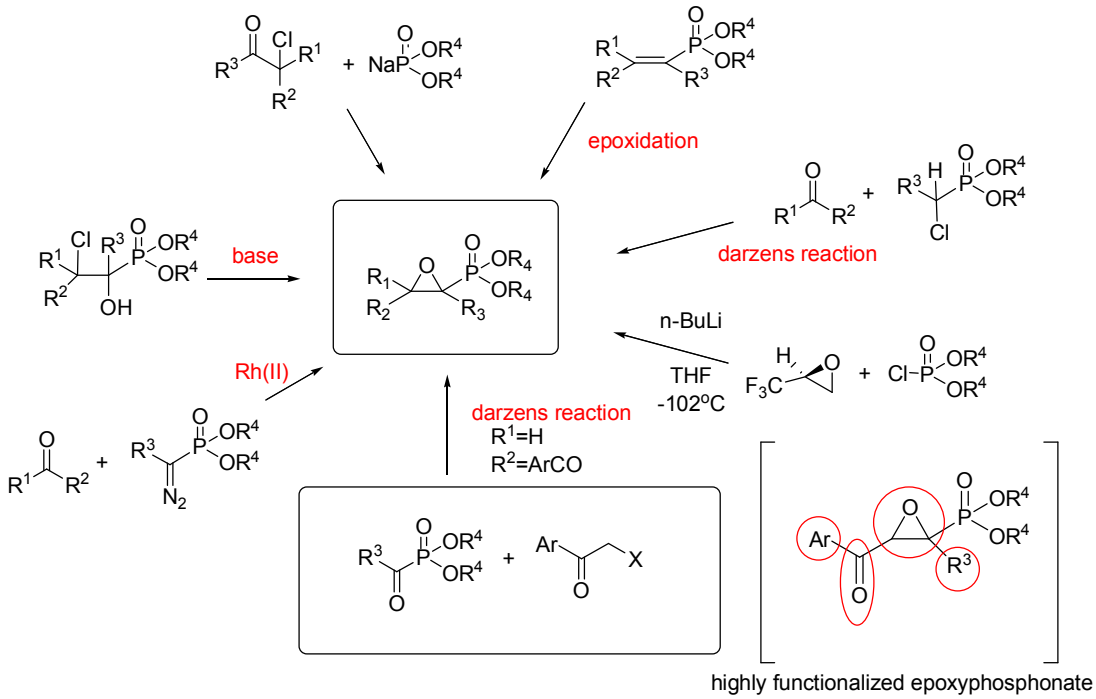


Figure 2. 4 Methods for the synthesis of α,β-epoxyphosphonates

The Darzens reaction is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds and, therefore, has been recognized as one of the most significant C–C, C-O bond forming processes in synthetic organic chemistry[81]. It employs the base induced condensation of α-halo carbonyl compounds with aldehydes for the construction of highly functionalized oxiranes.

In light of this reaction, and based on our previous studies carried out with acyl phosphonates[34,41,42,82], we report a novel approach for the diastereoselective synthesis of highly functionalized epoxyphosphonates by applying a Darzens type reaction of α-halo ketones with acyl phosphonates.

To the best of our knowledge, a Darzens type reaction including the use of acyl phosphonates has not been reported so far. Moreover, there are a vast number of methods for the synthesis of epoxyphosphonates,[74-80] in which there is no example to afford this type of highly functionalized epoxyphosphonates that could be useful intermediates to give several reactions.

In a previous work carried out by Demir et. al. reaction of aromatic acyl phosphonates containing electron withdrawing and electron donating substituents with α-bromo acetophenones under various conditions were examined. The reaction of benzoylphosphonate with α-bromoacetophenone was initially carried at room temperature in the presence of K_2CO_3 and the formation of the products was monitored by TLC. At the end of the reaction, two diastereomeric epoxyphosphonates (*trans/cis*) were isolated as a major product as shown in Figure 2.5.

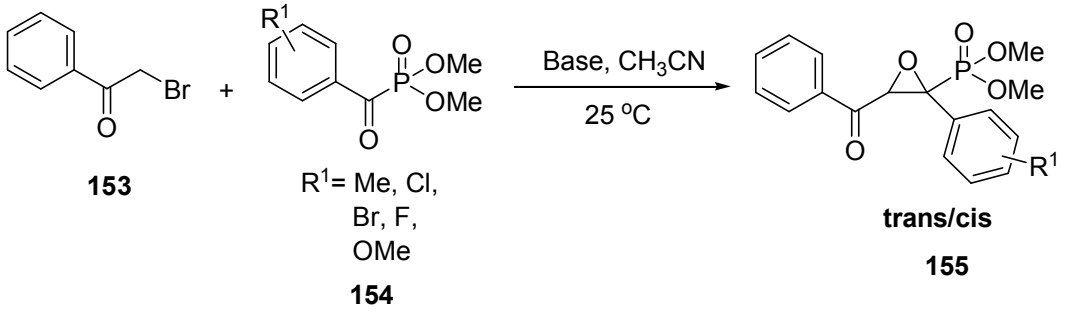


Figure 2. 5 General Darzens reaction of acyl phosphonates with α-bromoacetophenone

The reaction was carried out by using different bases such as KOH, ^{t}BuOK, Cs_2CO_3 in CH_3CN and THF. In addition, organic bases like DMAP, DABCO, DBU and triethylamine were also screened. Moreover, temperature effect was studied for that reaction and according to the all screening reaction results, reaction with Cs_2CO_3 in CH_3CN at room temperature was determined as the optimum reaction conditions. Finally, at this optimum conditions a range of acyl phosphonates were treated with α-bromo acetophenone[83].

In the present study, we examined the reaction of aromatic acyl phosphonates containing electron withdrawing and electron donating substituent with substituted α-bromo acetophenone in order to illustrate the generality of this reaction and determine the substituent effect.

At first, the reaction of 4-fluorobenzoyl phosphonate **151a** with α-bromo 4'-bromo acetophenone was carried out at room temperature in the presence of Cs_2CO_3 in CH_3CN. First of all Cs_2CO_3 was dried by heating under vacuum and CH_3CN was also distilled in order to remove water moiety. Then, 4-fluorobenzoyl phosphonate **151a**, α-bromo 4'-bromo acetophenone **157a** and Cs_2CO_3 were placed into a schlenk tube. Finally, freshly distilled CH_3CN was added to the reaction medium under argon atmosphere and allowed to stir at room temperature. The formation of the products was monitored by TLC. At the end of the reaction (7h) two diastereomeric epoxy phosphonates were isolated as white crystalline compounds. In addition, three more products **158**, **159** and **160** were also isolated with as minor products as shown in Figure 2.6

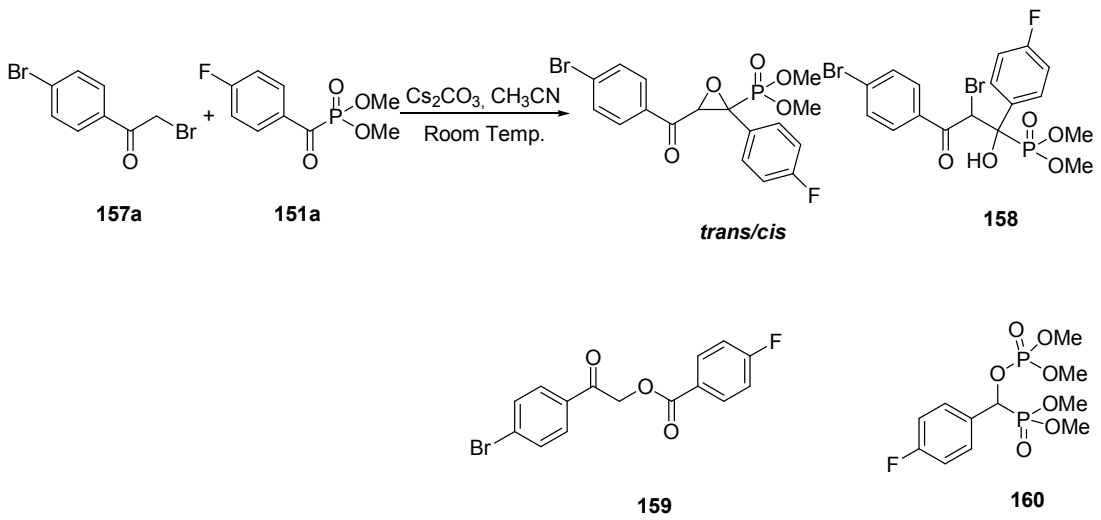


Figure 2. 6 Darzens reaction of 4-fluoro-benzoylphosphonate with α-bromo 4'-bromo acetophenone

Formation of the epoxides followed the following path as shown in Figure 2.7. Firstly, α proton of the α-bromo 4'-bromo acetophenone was abstracted by Cs_2CO_3 and further reaction of this compound with acyl phosphonate formed the intermediate **162**. Finally, elimation of Br formed the corresponding epoxy phosphonate.

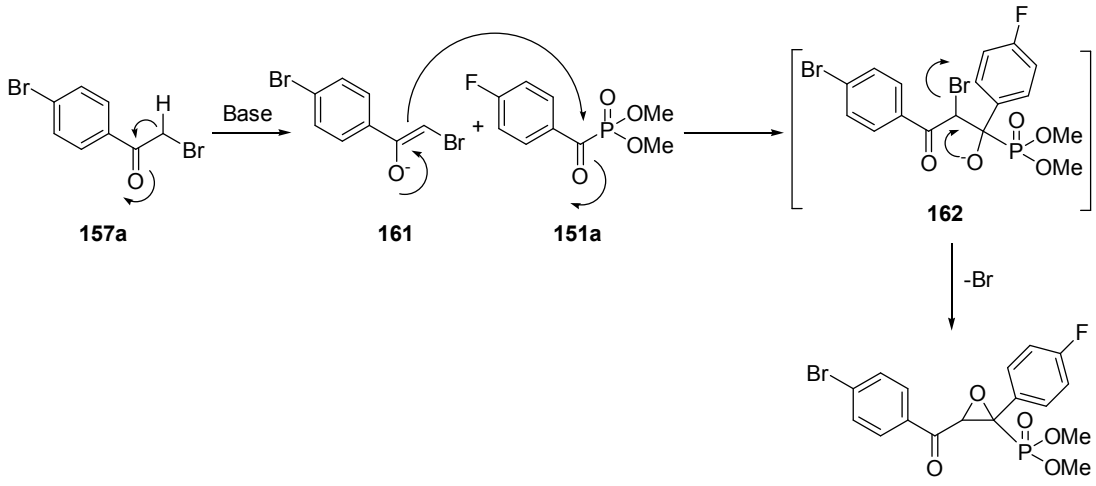


Figure 2. 7 Reaction mechanism of epoxide

However, in these reactions dry conditions were crutial. If dry conditions were not satisfied, proton abstraction of the intermediate **162** lead to the formation of halohydrin **158** and the yields were between 5% and 7% **(**Figure 2.8).

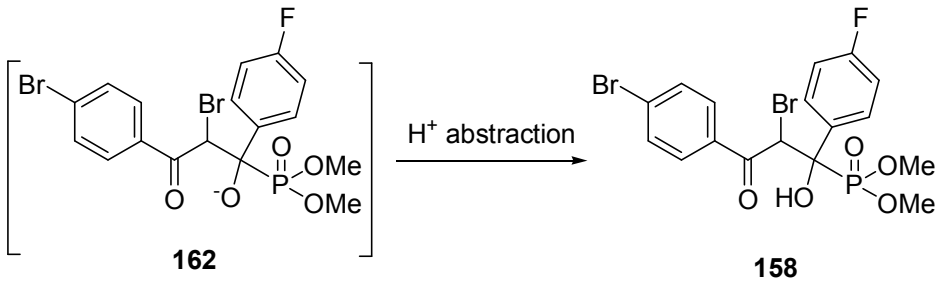


Figure 2. 8 Reaction mechanism of compound **158**

In addition to these products, one more side product **159** was isolated. Side product **159** was formed due to the hydrous reaction medium. If dry conditions were not satisfied, formation of α-hydroxy acetophenone occurred and further reaction of α-hydroxy acetophenone with acyl phosphonate gave the side product **159** with yields between 10-15% (Figure 2.9).

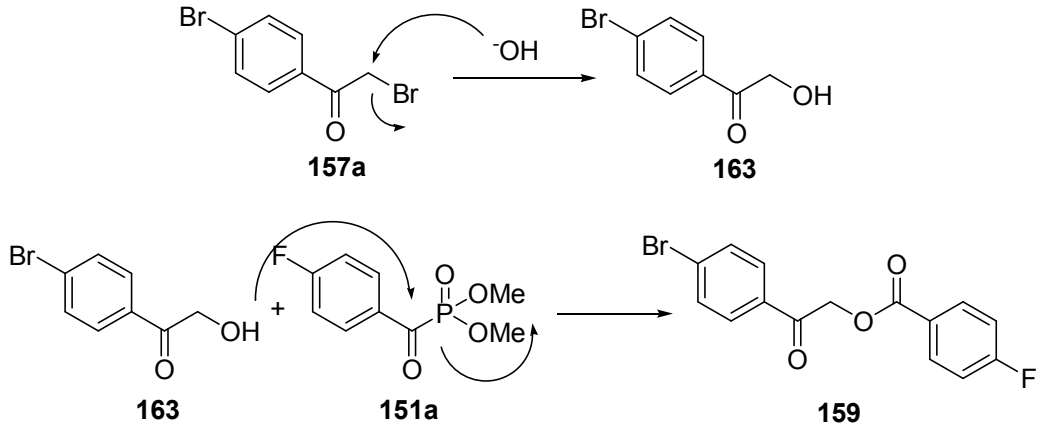


Figure 2. 9 Reaction mechanism of side product **159**

Moreover, **160** was also isolated as a third side product. This product was formed due to the dephosphorylation of acyl phosphonates. After the dephosphorylation occurred further reaction of compound **164** with acyl phosphonate yielded the intermediate **165** and as a result of the rearrangement of the intermedate **165**, compound **166** was formed. After proton abstraction the third side product **160** was obtained and the yields were changed from 13% to 18% (Figure 2.10).

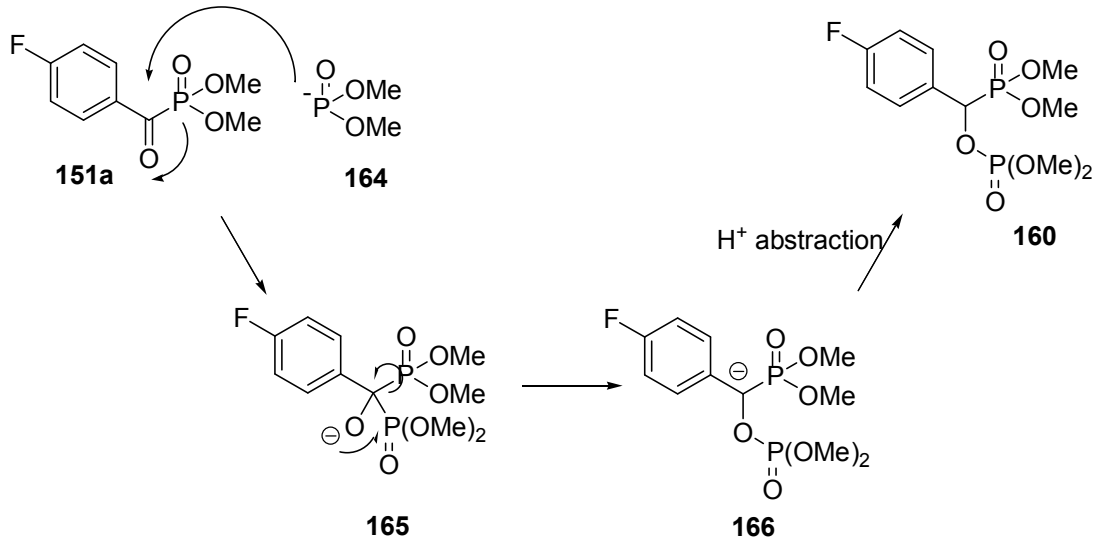


Figure 2. 10 Reaction mechanism of side product **160**

All of the products, nearby the side products are purified by chromatographic techniques. Both of the diasteromeric epoxides are easily separated by column chromatography and are characterized by spectroscopic methods. As it is seen from the ^{1}H-NMR in Figure 2.11 both isomers have the characteristic multiplet peaks between 6.80-7.90 ppm belong to aromatic rings. Moreover both isomer have two doublets between 3.50-3.80 ppm belong to –OMe groups. However, the basic difference between the diastereomers arises from the chemical shift of the single bridge proton which changes significantly according to structure of the epoxide. In the ^{1}H NMR spectra of *cis* isomer, the single bridge proton appeared as small doublet peak around 4.65 ppm, whereas the bridge proton for the *trans* isomer appeared around 3.80 ppm. The splitting of the single bridge protons to a doublet for both isomers is explained by the long range phosphorous coupling, moreover, the significant difference between the chemical shifts of the these protons is consistent with previously reported data of similar type of epoxides. This shift is caused by the interaction between the phosphonate group and the bridge proton. Phosphonate is an electron rich group and the bridge proton is affected more by the electron density of phosphonate group in trans epoxide. This results in a shift to high field in the trans isomer's ^{1}H NMR spectra. In addition to NMR techniques, the mass spectra for both diastereomers strongly proofed the fact that these two isolated compounds are the diastereomers of each.

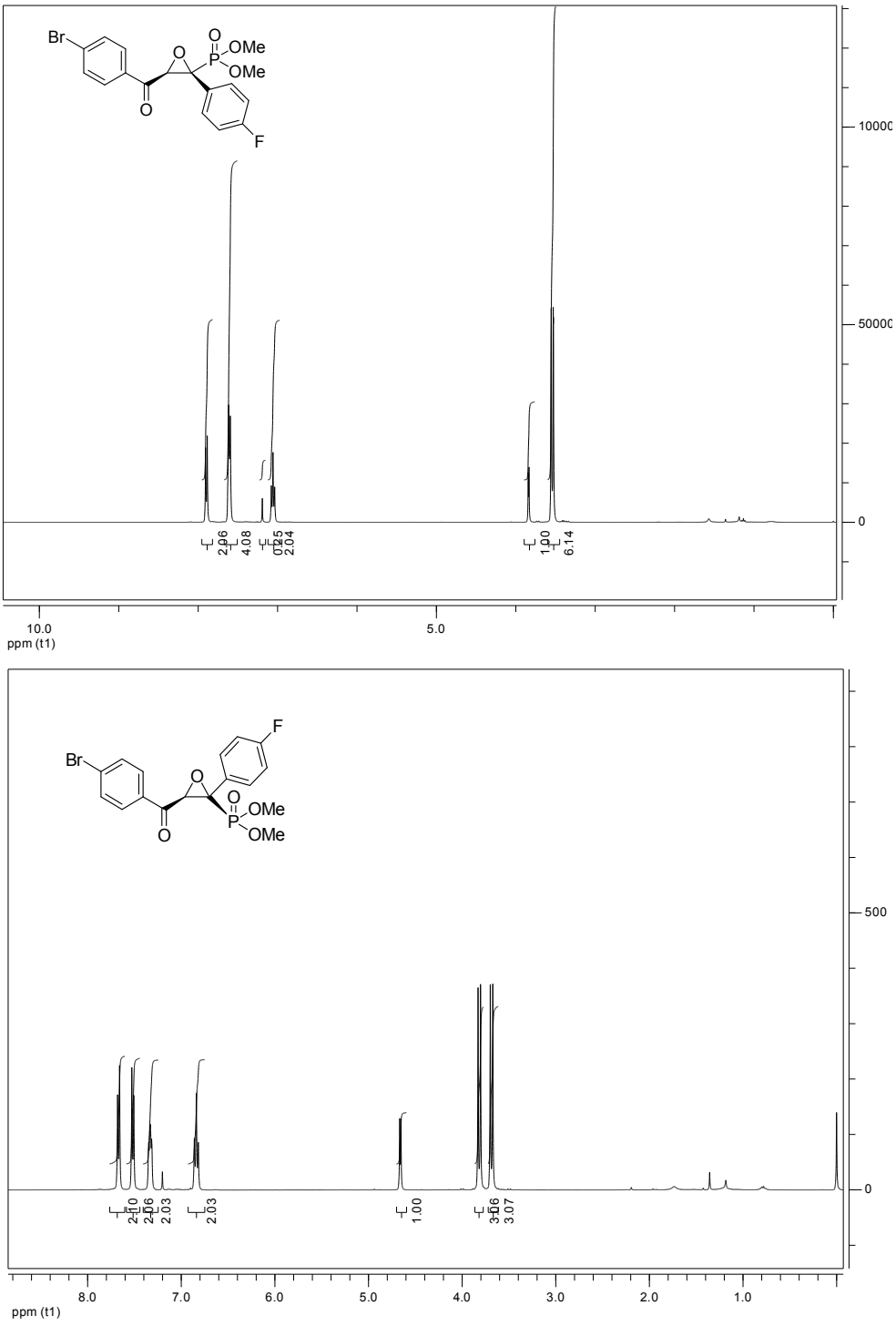
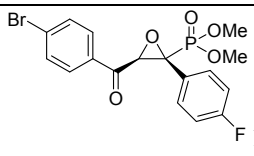
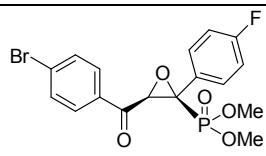
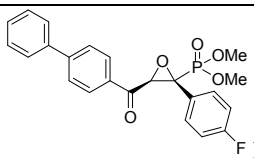
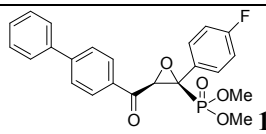
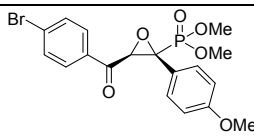
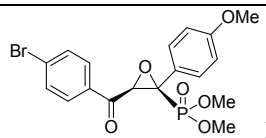
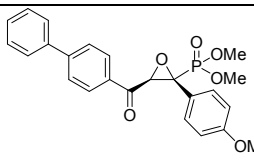
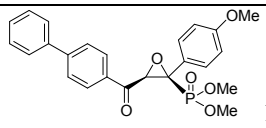


Figure 2. 11 NMR spectrums of *trans* and *cis* isomers of epoxy phosphonates

In further reactions, in order to illustrate the generality of this reaction and the substituent effect on the reaction, a range of acyl phosphonates **151a,b** were synthesized. These acyl phosphonates then reacted with both α-bromo 4'-bromo acetophenone **157a** and α-bromo 4'-phenyl acetophenone **157b** under optimized reaction conditions (Cs_2CO_3, CH_3CN, rt) which were determined in the previous study by performing secreening reactions. It was concluded that using electron donating and electron withdrawing groups furnished a comparable yield and results are shown in Table 1.

Table 1 Reaction of acyl phosphonates with α-halo ketones in the presence of Cs_2CO_3 in acetonitrile

Phosphonate	*Trans* Product	*Cis* Product	yields	trans/cis
151a	 **167a**	 **167b**	%51	3/2
151a	 **168a**	 **168b**	%52	3/2
151b	 **169a**	 **169b**	%46	3/2
151b	 **170a**	 **170b**	%42	3/2

[a]Isolated overall yields

In the light of the previous study carried out by Demir et. al.[83] the reaction of substituted acyl phosphonates with substituted α-bromo acetophenone in the presence of DBU in CH_3CN at room temperature was carried out for maximum conversion (monitoring by TLC). Before performing the experiment, Cs_2CO_3 was dried by heating under vacuum and CH_3CN was also distilled in order to remove

water moiety. Then, 4-fluorobenzoyl phosphonate **151a** and α-bromo 4'-bromo acetophenone **157a** were placed into a schlenk tube. After freshly distilled CH_3CN was added to the reaction medium under argon atmosphere, DBU was added dropwise and allowed to stir at room temperature. After the work up, the desired products were obtained in 43-49% yields. The isomeric ratio of the products was determined by NMR as 8/1-9/1 *trans*/*cis*. Both isomers were easily separated by flash column chromatography.

Moreover, when DBU used as a base, another side product **173** was observed due to the reaction between DBU and acyl phosphonate.[83] For the formation of **173**, first DBU reacted with acyl phosphonates in order to form intermediate **172** and the further hydrolysis of **172** afforded the corresponding seven membered ring amide **173** as shown in Figure 2.12. Similar reactions of DBU with alkyl halides have been reported in the literature[84].

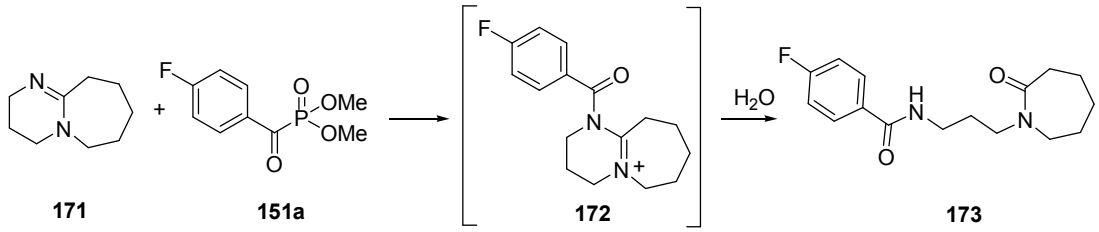


Figure 2. 12 Reaction of DBU with acyl phosphonate

Reaction used by DBU also performed with **151a,b** and **157a,b**. Results were outlined in Table 2. As it is seen from the results in Table 2, changing the base changed the stereoselectivity of this reaction. In general, the experiments performed in the presence of Cs_2CO_3 gave a product distribution of approximately 3/2 (*trans*/*cis*), whereas the use of DBU significantly increased the selectivity up to 9/1 (*trans*/*cis*).

Table 2 Comparison of Cs_2CO_3 with DBU

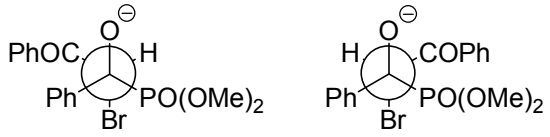
Entry	Ketone	Phosphonate	Epoxyphosphonate	Cs_2CO_3			DBU		
				time (h)	yield[a] (%)	*trans* /*cis*	time (h)	yield[a] (%)	*trans*/ *cis*
1	**157a**	**151a**	**167a,b**	7	51	3/2	6	48	9/1
2	**157b**	**151a**	**168a,b**	8	52	3/2	8	49	9/1
3	**157a**	**151b**	**169a,b**	7	46	3/2	6	43	9/1
4	**157b**	**151b**	**170a,b**	8	42	3/2	8	45	8/1

[a]Isolated overall yields

Close inspection of the reaction with DBU afforded interesting results.[83] With the careful monitoring of the reaction by TLC, the distribution for both diastereomers in the presence of DBU is easily controlled. Initially the *trans* isomer is formed in relative excess to *cis* isomer (9/1). However, at a prolonged reaction time, the *trans* isomer isomerizes to afford the *cis* isomer. To support this observation, both of the isolated diastereomeric epoxides are treated under the same reaction conditions with DBU in CH_3CN. As a result of this experiment, the *trans* epoxide isomerizes to afford the *cis* epoxide, whereas the reverse is not the case. The effect of temperature on this isomerization was also studied. The complete conversion of *trans* isomer to *cis* isomer was observed at room temperature in approximately 3 hours. Lowering the temperature to 0^oC increased the time to 6 hours for complete conversion. However, at -30^oC the conversion dramatically decreased, and even at 10 hours the conversion was not more than 30%. The results show that by using DBU, both isomers can be obtained in an almost pure form.[83]

By the Darzens condensation, the formation of the epoxide is the favored course of the reaction. The carbanion of α-halo ketones can attack the carbonyl carbon of phosphonate to form the intermediate halohydrins **174a** and **174b**. The positioning of the halide *trans* to the oxygen, which is involved in the nucleophilic attack, forms the epoxide.

According to Ballester[85], the Darzens intermediate (Figure 2.13) is commonly formed in the rate determining step, in which the exclusive formation of the *trans* product may be attributed to the steric inhibition in the formation of *cis* isomer.



174a **174b**

Figure 2. 13 Newman projection of Darzens intermediate

Clearly, a *cis* halohydrin anion **174b** is not the intermediate in the formation of the *cis* product in the Darzens reaction[86], but rather the only possible way in which *cis* can be obtained in the Darzens reaction is through the formation of the *trans* product followed by base catalyzed isomerization (Figure 2.14). The existence of a very large effect (in both the rates and equilibrium of the ring-forming reactions) opposing the formation of *cis* substituents on small rings constitutes a further basis for assigning greater thermodynamic stability to a *trans* versus a *cis* oxide. In the presence of the base, it is possible that after a significant yield of *cis* is obtained, separating a *cis* product where it precipitates from a solution as the least soluble component of the system, the result of the solubility tests of the isomers showed nearly no differences.[83] It is rather possible that the carbanion-enolate intermediate of the epoxide is responsible for the formation of the *cis*-isomer, where the formation of *trans* isomer from *cis* is not possible. This conclusion is only tentative, however, and is currently undergoing further investigation in our laboratory.

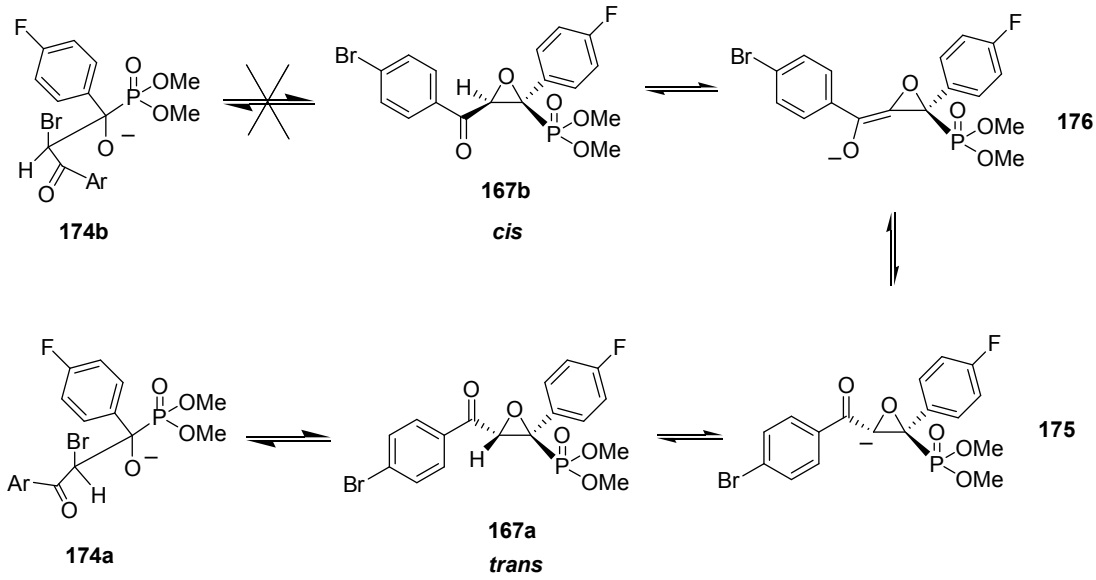


Figure 2. 14 Formation of *cis*-isomer from a *trans*-isomer[83]

In this study reaction of alkyl phosphonates was also studied. Substituted benzoyl phosphonates proceed efficiently to give epoxides; however, the treatment of alkyl phoshponates **151c** under the same reaction conditions never yields the corresponding epoxides. This result revealed that alkyl phosphonates are comperably much more reactive than benzoyl phosphonates when treated with bases and hydrolyze more easily. A great amount of work is done to optimize the conditions but unfortunately in all cases the product isolated is nothing else than the compound **177** and **178**.[83]

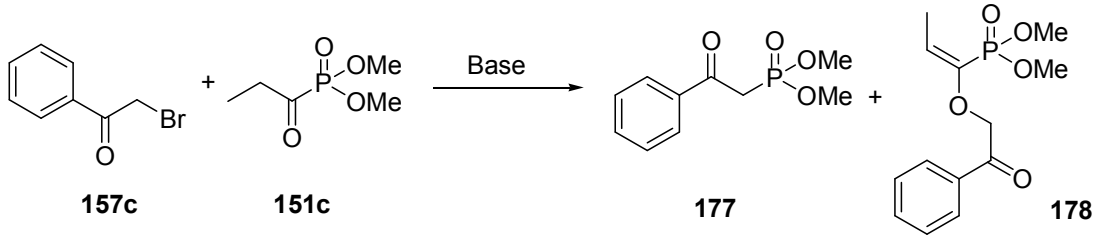


Figure 2. 15 Darzens reaction of aliphatic phosphonates with α-bromo acetophenone

Reaction mechanisms of the products **177** and **178** which were obtained by reaction of ethyl phosphonate and α-bromo acetophenone are outlined in Figure 2.16. For the formation of **177**, first the hydrolysis of alky phosphonate occured and then the resulting compound reacted with the α-bromo acetophenone. Moreover, **178** was obtained by the abstraction of α proton of ethyl phosphonate and the further reaction of the resulting intermediate with the α-bromo acetophenone.

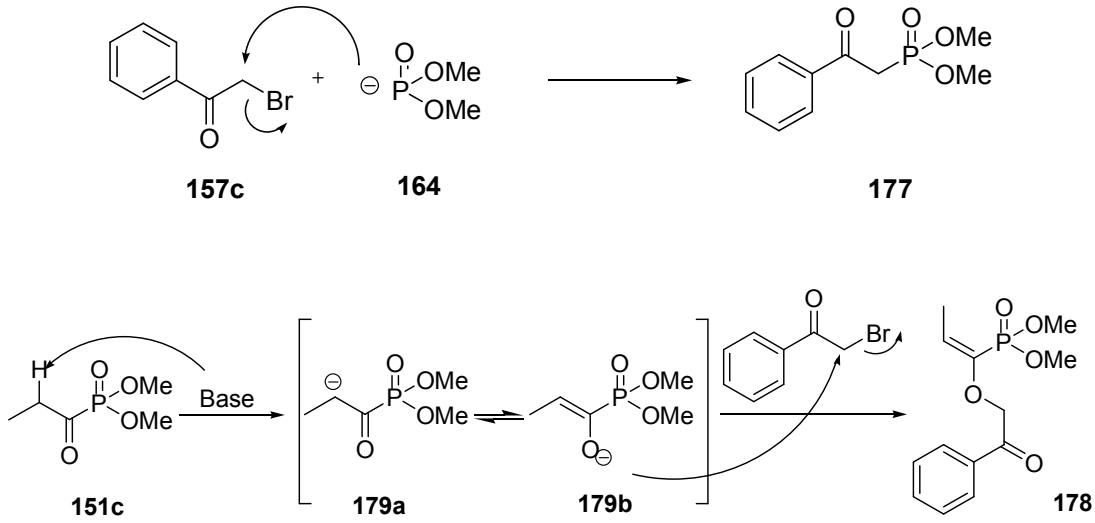


Figure 2. 16 Reaction mechanisms of **177** and **178**[83]

Darzens reaction carried out in the presence of water is known to afford epoxides efficiently[85]. On the basis of this application, benzoyl phosphonate **151d** was treated with α-bromo acetophenone **157c** in water, surprisingly the only isolated product is the Perkow product **180** (Figure 2.17). In addition, reaction mechanism of **180** resulted in the reaction of benzoyl phosphonate with α-bromo acetophenone in the presence of water was shown in Figure 2.18.[83]

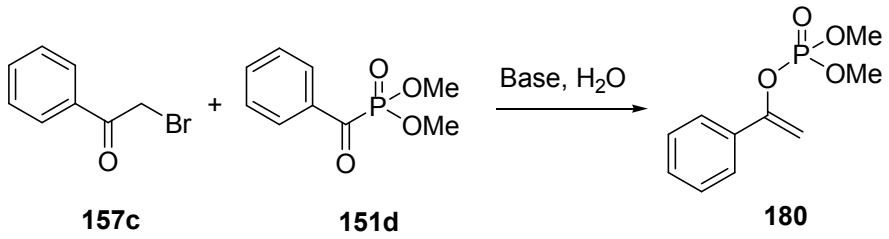


Figure 2. 17 Reaction of benzoyl phosphonate with α-bromo acetophenone in the presence of water

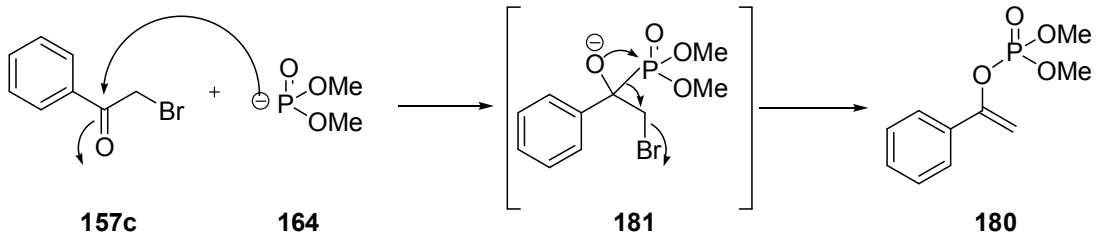


Figure 2. 18 Reaction mechanism of **180**

In summary, we described a practical synthesis of epoxyphosphonates applying Darzens type reaction to acyl phosphonates with substituted α-bromo acetophenone in the presence of different bases. The diastereoselectivity of this reaction is easily controlled by changing the nature of the base. Accordingly, changing the base from Cs_2CO_3 to DBU changed the diatereomeric ratio (*trans/cis*) from 3/2 to 9/1.

2.2 Manganese (III) acetate mediated acetylation of aryl boronic acids

Manganese (III) acetate is a one-electron oxidant, largely used as a radical generator. Since the pioneering work of Heiba et al. and Bush et al. in 1968, manganese (III) mediated oxidations have been extensively studied. Fristad et al. showed that the rate of radical generation with manganese (III) acetate with bridging acetates correlates with the enolizability and CH acidity of the substrates[87]. Thus, it is this reagent's ability to generate radicals in such systems that lead to highly efficient C-C bond forming reactions, especially for the construction of cyclic systems, a topic reviewed by Snider[88]. Recently Demir et al. showed that aryl boronic acids can be efficiently oxidized by manganese (III) acetate to produce aryl radicals that afford biaryls in benzene with very good yields.

In the light of this reaction, we examined the formation of manganese (III) acetate based aryl radicals from aryl boronic acids and addition of aryl radicals to acetonitrile[67].

At first, phenyl radical was generated from phenyl boronic acid by mangenese (III) acetate. In order to form phenyl radical phenyl boronic acid was heated under reflux. Then, this phenyl radical was reacted with acetonitrile to afford acetophenone. Formation of products is monitored by TLC and reaction path was outlined in Figure 2.19.

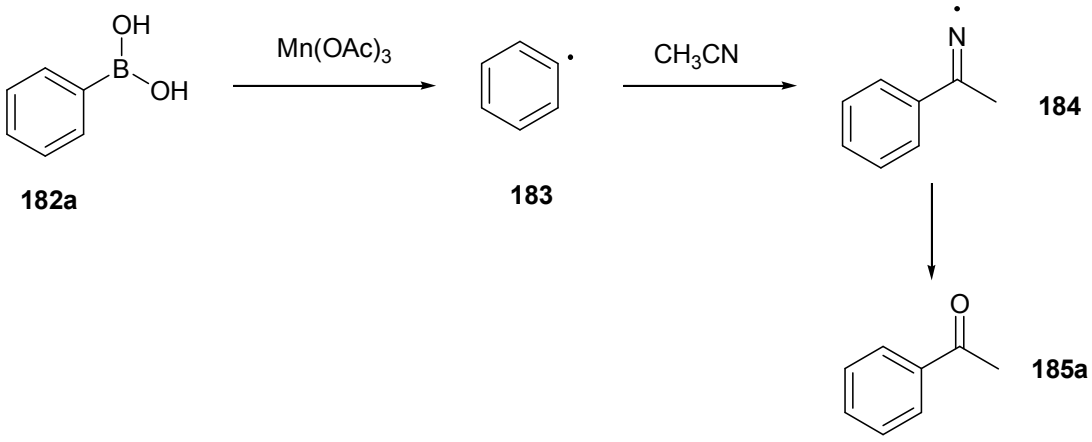


Figure 2. 19 General reaction for acetylation of aryl boronic acids

In order to establish the effect of the equivalence of manganese (III) acetate additional experiments were performed. Three screening reactions were carried out using 1, 2 and 3 equivalent of manganese (III) acetate and the results showed that using 2 equivalent of manganese (III) acetate gives the best results.

Moreover, the effect of manganese (III) acetate on the activation of the acetonitrile was examined. A mixture of manganese (III) acetate and acetonitrile were refluxed for several hours. The corresponding boronic acid was added to this solution in small portions, and the process was monitored by GC-MS and TLC. According to the GC-MS results, this resulted in an increase in the reaction yields. Therefore, it was concluded that this procces was crucial for the activation of the nitrile group as shown in Figure 2.20.

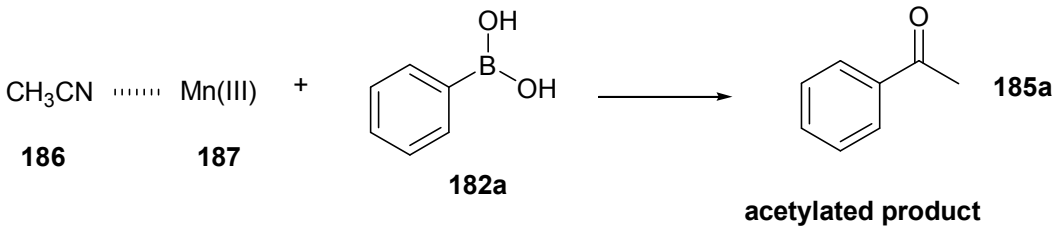


Figure 2. 20 Metal activation of acetonitrile

However, the yields of the acetylated product were lower than expected. The reason for low yields was the formation of self-coupled side products as shown in Figure 2.21. We performed some additional experiments such as changing the solvent amount to decrease the amount of self-coupled products. After many trials we observed that under high diluted reaction conditions the formation of these side products could be reduced.

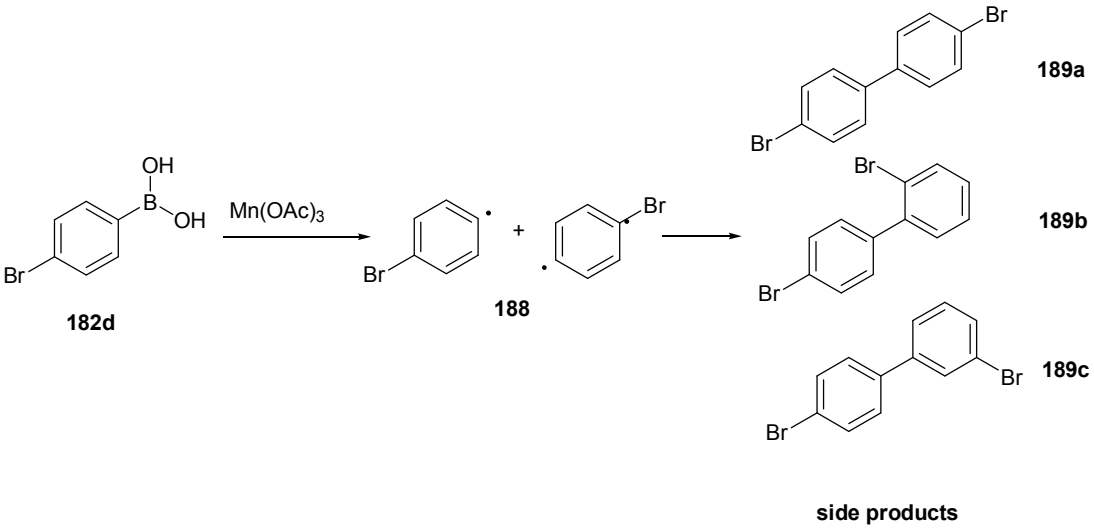
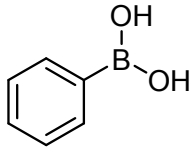
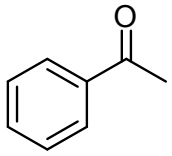
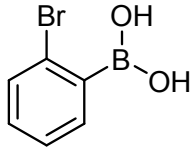
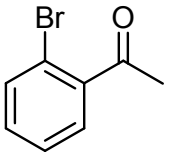
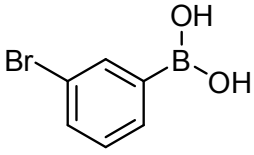
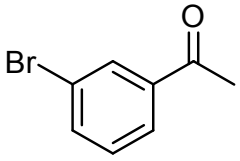
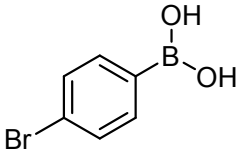
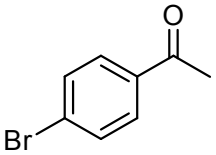


Figure 2. 21 General reaction for self-coupled side products

By using optimized conditions, variety of aryl boronic acids were used and the corresponding acetylation products were obtained with yields as shown in Table 3.

Table 3 Acetylated arylboronic acids

Entry	Aryl boronic acid	Product	Yield(%)/Time(h)
1	 **182a**	 **185a**	35/ 6
2	 **182b**	 **185b**	23/ 7
3	 **182c**	 **185c**	25/ 6
4	 **182d**	 **185d**	21/7

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 300 MHz or 400 MHz and 75 MHz or 100MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. All reactions were analyzed by TLC on silica gel 60 F_{254}. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

3.2 General Procedures

3.2.1 General Procedure for Preparation of Epoxyphosphonates

a. DBU (2 mmol) is added to a stirred solution of **151a,b** (1 mmol) and α-bromo ketone **157a,b** (2 mmol) in anhydrous acetonitrile at room temperature under an argon atmosphere. The reaction mixture is stirred for several hours (2-12 h). The reaction is monitored by TLC. Water is added, and the mixture is extracted with ethyl acetate, in which the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford **167a,b-170a,b** (ether- petroleum ether) (5–1).

b. Benzoylphosphonate **151a,b** (1 mmol) is added to a mixture of α-bromo ketone **157a,b** (1.2 mmol) and Cs_2CO_3 (1.5 mmol) in anhydrous acetonitrile at room temperature under an argon atmosphere. The reaction mixture is stirred for several hours (2-12 h). The reaction was monitored by TLC. Water is added, the mixture is extracted with ethyl acetate, and the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford **167a,b-170a,b** (ether- petroleum ether) (5–1).

3.2.1.1 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*) (167a)

Yield: 31%, white solid (mp=115 °C), IR (KBr): 3001, 2348, 1657, 1213, 1049 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (3H, s), 3.55 (3H, s), 3.84 (1H, d, *J*=4.0 Hz), 7.03-7.90 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.6 (d, J_{C-P}=7.4 Hz), 54.4 (d, J_{C-P}=6.3 Hz), 61.2 (d, J_{C-P}=203 Hz), 65.7, 115.9 (d, J_{C-P}=21.7 Hz), 128.7 (d, J_{C-P}= 9.4 Hz) , 129.4, 129.8 (d, J_{C-P}=15.1 Hz), 130.2, 132.2, 133.7, 163.1 (d, J_{C-F}=247 Hz), 189.9; ^{31}P NMR: 15.976. Anal. calcd. for $C_{17}H_{15}BrFO_5P$: C, 47.58; H, 3.52. Found: C, 47.46; H, 3.61.

3.2.1.2 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*) (167b)

Yield: 20%, white solid (mp=121 °C), IR (KBr): 2990, 2363, 1644, 1227, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (3H, d, *J*=11.0 Hz), 3.81 (3H, d, *J*=11.0 Hz), 4.66 (1H, d, *J*=6.0 Hz), 6.82-7.72 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.4 (d, J_{C-P}=4.9 Hz), 53.6 (J_{C-P}=7.0 Hz), 58.8 (d, J_{C-P}=200 Hz), 60.7, 114.4 (d, J_{C-P}=21.8 Hz), 124.3, 124.5, 128.5, 128.6, 131.2, 132.6, 160.7 (d, J_{C-F}=247 Hz), 188.5; ^{31}P NMR: 16.288. Anal. calcd. for $C_{17}H_{15}BrFO_5P$: C, 47.58; H, 3.52. Found: C, 47.51 ; H, 3.44.

3.2.1.3 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*) (168a)

Yield: 33%, white solid (mp=119 °C), IR (KBr): 3011, 2344, 1660, 1226, 1045 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (3H, d, *J*=2.4 Hz), 3.66 (3H, d, *J*=2,4 Hz), 4.01 (1H, d, *J*=4.2 Hz), 7.14-8.20 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.7 (d, J_{C-P}=7.1 Hz), 54.4 (J_{C-P}=6.4 Hz), 61.2 (d, J_{C-P}=203 Hz), 66.1, 115.8 (d, J_{C-P}=21.6 Hz), 127.3, 127.4, 128.5, 128.8 (d, J_{C-P}=2.7 Hz), 128.9 (d, J_{C-P}=2.7 Hz), 129.0, 129.3, 133.6, 139.7, 146.8, 163.1 (d, J_{C-F}=247 Hz), 190.2; ^{31}P NMR: 16.62. Anal. calcd. for $C_{23}H_{20}FO_5P$: C, 64.58; H, 4.73. Found: C, 64.62 ; H, 4.65.

3.2.1.4 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*) (168b)

Yield: 19%, white solid (mp=125-126 °C), IR (KBr): 2995, 2351, 1671, 1231, 1054 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, d, *J*=10.0 Hz), 3.83 (3H, d, *J*=11.0 Hz), 4.75 (1H, d, *J*=5.0 Hz), 6.82-7.90 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.4 (d, J_{C-P}=6.3 Hz), 53.5 (d, J_{C-P}=7.2 Hz), 58.8 (d, J_{C-P} =198 Hz), 60.8, 114.4 (d, J_{C-P}=21.8 Hz) 126.2, 126.4, 127.5, 127.8, 128.0, 128.6 (d, J_{C-P}=2.7 Hz), 128.7 (d, J_{C-P}=2.7 Hz), 132.7, 138.5, 145.8, 162.9 (d, J_{C-F}=247 Hz), 188.7; ^{31}P NMR: 16.288. Anal. calcd. for $C_{23}H_{20}FO_5P$: C, 64.58; H, 4.73. Found: C, 64.45; H, 4.80.

3.2.1.5 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*) (169a)

Yield: 30%, white solid (mp=121 °C), IR (KBr): 2987, 2359, 1675, 1241, 1047 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 3.54 (3H, s), 3.76 (3H, s), 3.86 (1H, d, *J*=4.0 Hz), 6.87-7.92 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 52.6 (d, J_{C-P}=7.5 Hz), 53.3 (J_{C-P}=6.2 Hz), 54.4, 60.5 (d, J_{C-P}=202 Hz), 64.7, 113.2, 124.9 (d, J_{C-P}=14.9 Hz), 127.3, 128.3, 129.2, 131.1, 132.8, 159.3 189.2; ^{31}P NMR: 17.028. Anal. calcd. for $C_{18}H_{18}BrO_6P$: C, 49.00; H, 4.11. Found: C,49.12 ; H, 4.16.

3.2.1.6 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*) (169b)

Yield: 16%, white solid (mp=128 °C), IR (KBr): 2990, 2365, 1673, 1248, 1044 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (3H, s), 3.67 (3H, d, *J*=11.0 Hz), 3.80 (3H, d, *J*=11.0 Hz), 4.64 (1H, d, *J*=5.0 Hz), 6.65-7.70 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.4 (d, J_{C-P}=5.5 Hz), 53.5 (d, J_{C-P}=2.8 Hz), 54.1, 59.1, 60.1 (d, J_{C-P}=200 Hz), 112.8, 120.3 (d, J_{C-P}=13.8 Hz), 127.9 (d, J_{C-P}=2.9 Hz), 128.4, 128.7, 131.2, 132.8, 159.0, 188.4; ^{31}P NMR: 16.741. Anal. calcd. for $C_{18}H_{18}BrO_6P$: C, 49.00; H, 4.11. Found: C, 49.08; H, 4.21.

3.2.1.7 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*) (170a)

Yield: 27%, white solid (mp=123 °C), IR (KBr): 3000, 2341, 1679, 1243, 1052 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.51 (3H, d, *J*=1.0 Hz), 3.56 (3H, d, *J*=1.0 Hz), 3.76 (3H, s), 3.92 (1H, d, *J*=4.0 Hz), 6.88-8.12 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$): 54.1 (d, J_{C-P}=7.2 Hz), 54.8 (d, J_{C-P}=6.5 Hz), 55.7, 61.9 (d, J_{C-P}= 204 Hz), 66.6, 114.9, 126.9 (d, J_{C-P}=14.8 Hz), 128.1, 128.2, 129.1 (d, J_{C-P}=3.1 Hz), 129.3, 129.8, 130.2, 134.4, 140.6, 147.6, 161.2, 191.7; ^{31}P NMR: 20.800. Anal. calcd. for $C_{24}H_{23}O_6P$: C, 65.75; H, 5.29. Found: C, 65.67; H, 5.21.

3.2.1.8 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*) (170b)

Yield: 15%, white solid (mp=128 °C), IR (KBr): 3012, 2361, 1682, 1255, 1061 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.68 (3H, d, *J*=11.0 Hz), 3.82 (3H, d, *J*=11.0 Hz), 4.74 (1H, d, *J*=6.0 Hz), 6.66-7.93 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8 (d, J_{C-P}=5.8 Hz), 55.9 (J_{C-P}=4.8 Hz), 56.5, 62.6 (d, J_{C-P}=200 Hz), 63.3, 115.2, 122.9 (d, J_{C-P}=14.8 Hz), 128.7 (d, J_{C-P}=15.1 Hz), 129.9, 130.2, 130.4 (d, J_{C-P}=14.8 Hz), 130.5, 133.6, 135.3, 140.9, 148.0, 161.4, 191.4; P NMR: 17.594. Anal. calcd. for $C_{24}H_{23}O_6P$: C, 65.75; H, 5.29. Found: C, 65.79; H, 5.33.

3.2.1.9 Dimethyl-1-(1-phenyletanonoxy)-prop-1-ene phosphonate (178)

Oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, dd, *J*= 2.6 Hz, *J*=6.8 Hz), 3.65 (3H, s), 3.67 (3H, s), 5.13 (2H, s), 6.07 (1H, m), 7.38-7.91 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1, 11.3, 52.7, 76.7, 127.8, 128.7, 128.9, 129.9, 133.6, 134.6, 143.2, 145.3, 194.2.^{31}P NMR: 14.08. Anal. calcd for. $C_{13}H_{17}O_5P$: C, 54.93; H, 6.03; Found: C, 54.89; H, 6.10.

3.2.2 General Procedure for Acetylation of Aryl Boronic Acids

Phenyl boronic acid (1 mmol) was added to manganese (III) acetate (2 mmol $Mn(OAc)_3$ $2H_2O$) in 15 mL of acetonitrile in small portions and the resulting mixture was refluxed for 6 hours. The formation of the products was monitored by TLC and GCMS. Water is added, and the mixture is extracted with ethyl acetate, in which the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel (hexane–ethyl acetate) (4:1).

3.2.2.1 Acetophenone (185a)

Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (3H, s), 7.37-7.86 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 28.9, 131.3, 131.5, 136.9, 198.6.

3.2.2.2 2-Bromo acetophenone (185b)

Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (3H, s), 7.31-7.54 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 28.6, 121.3, 127.7, 131.0, 131.6, 135.4, 140.4, 199.1

3.2.2.3 3-Bromo acetophenone (185c)

Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (3H, s), 7.26-8.03 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 29.3, 123.0, 127.8, 130.9, 132.3, 136.1, 139.0, 197.8.

3.2.2.4 4-Bromo acetophenone (185d)

Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 (3H, s), 7.54-7.75 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 29.5, 127.5, 131.0, 131.6, 135.8, 199.8.

CHAPTER 4

CONCLUSION

In the first part of the thesis, we describe a new synthesis of epoxyphosphonates applying a Darzens type reaction to acyl phosphonates with substituted α-bromo acetophenones in the presence of different bases and illusturate the effect of the substituents on the reaction. The diastereoselectivity of this reaction is easily controlled by changing the base. Accordingly, changing the base from Cs_2CO_3 to DBU changed the diatereomeric ratio (*trans/cis*) from 3/2 to 9/1.

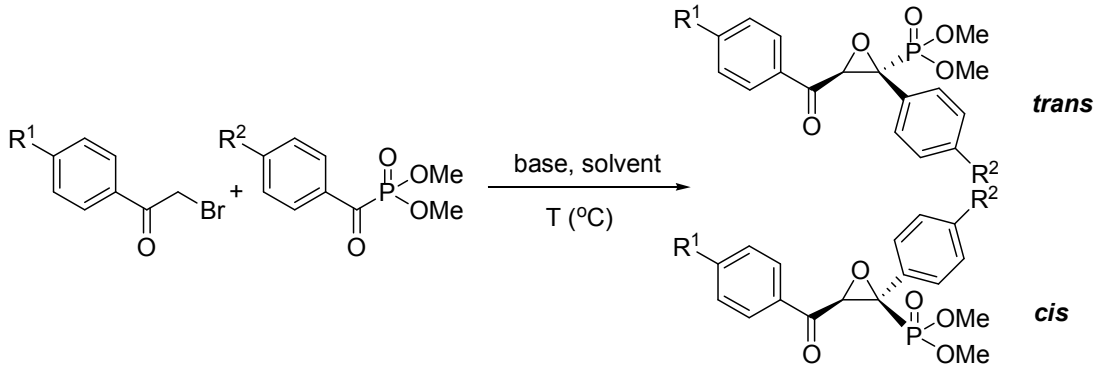


Figure 4. 1 Synthesis of 1,2-epoxyphosphonates

In the second part of the thesis, we showed that a variety of radicals can be generated from the corresponding arylboronic acids with $Mn(OAc)_3$. In the presence of acetonitrile, these radicals were added to carbon of acetonitrile to afford the corresponding ketones after hydrolysis of the imine with moderate to good yields.

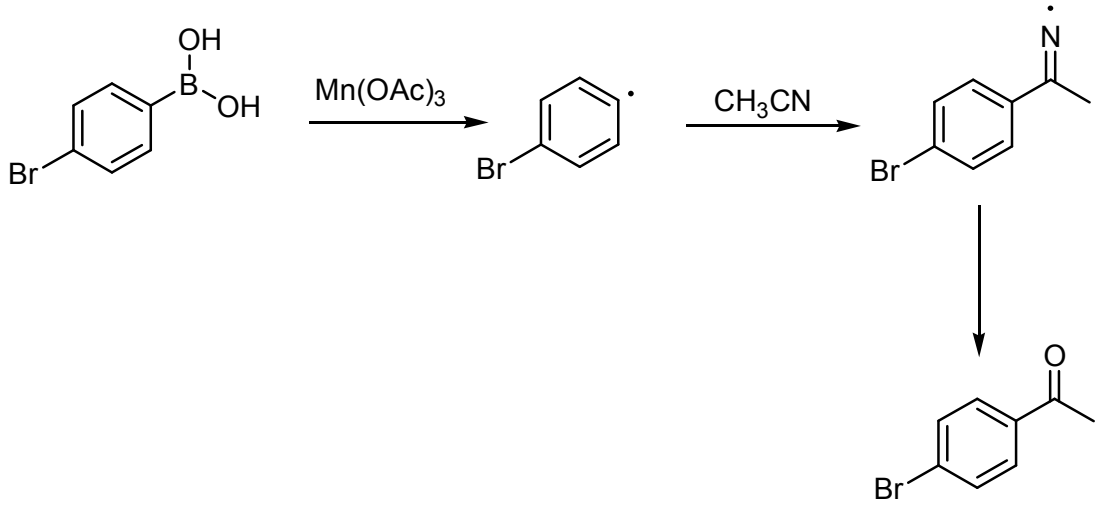


Figure 4. 2 Manganese (III) acetate mediated acetylation of aryl boronic acids

REFERENCES

[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, New York, 1994;

[2] Ed. O. Isler, Birkhauser, Basel-Stuttgart,*Carotenoids*, 1971, 344.

[3] V. K. Aggarwal, G. Hynd, W. Picoul, and J. L.Vasse, *J. Am. Chem. Soc.*, 2002, 124, 9964.

[4] J. R. Flisak, K. J. Gombatz, M. M. Holmes, A. A. Jarmas, I. Lantos, W. L. Mendelson, V. J. Novack, J. J. Remich, and L. Snyder, *J. Org. Chem.*, 1993, 58, 6247.

[5] J. G. Gleason, R. F. Hall, C. D. Perchonock, K. F. Erhard, J. S. Frazee, T. W. Ku, K. Kondrad, M. E. McCarthy, S. Mong, S. T. Crooke, G. Chi Rosso, M. A. Wasserman, T. J. Torphy, R. M. Muccitelli, D. W. Hay, S. S. Tucker, and L. Vickery Clark, *J. Med. Chem.*, 1987, 30, 959.

[6] L. Guo Qiang, X. Hai Jian, W. Bi Chi, G. Guong Zhong, and Z. Wei Shan, *Tetrahedron Lett.*, 1985, 26, 1233.

[7] R. D. Wood and B. Ganem, *Tetrahedron Lett.*, 1982, 23, 707.

[8] B. H. Lipshutz, H. Kotsuki, and W. Lew, *Tetrahedron Lett.*, 1986, 27, 4825.

[9] T. Hiranuma, K. Kitamura, T. Taniguchi, T. Kobayashi, R. Tamaki, M. Kanai, K. Akahori, K. Iwao, and T. Oka, *Naunyn Schmiedeberg's Arch. of Pharm.*, 1998, 357, 276.

[10] H. Urbach and R. Henning, *Tetrahedron Lett.*, 1984, 25, 1143.

[11] R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, 1952, 74, 5475.

[12] Eur. Pat. Appl. 14437; *Chem Abstr.*, 1981, 94, 139433c.

[13] L. W. Hertel, J. S. Kroin, J. W. Misner, and J. M. Tustin, *J. Org. Chem.*, 1988, 53, 2406.

[14] H. Hamamoto, V. A. Mamedov, M. Kitamoto, N. Hayashi, and S. Tsuboi, *Tetrahedron: Asymmetry*, 2000, 11, 4485.

[15] T. Komiyama, V. A. Mamedov, H. Hamamoto, and S. Tsuboi, in *Proc. 80th Spring Annual Meeting of the Chemical Society of Japan (Chiba, September 20—23, 2001)*, Chiba, 2001, Abst. No. 3P4B 10.

[16] K. Mori and T. Ebata, *Tetrahedron*, 1986, 42, 3471.

[17] Wang, Z.; Xu, L.; Xia, C.; Wang, H, *Helvetica Chemicia Acta*, 2004, 87,1958

[18] Peschke, B.; Bundgaard, J. G.; Breinholt, J. Synthesis of amino alcohols on solid support via sulfonium-ion mediated Darzens reaction. *Tetrahedron Lett*. 2001, 42, 5127

[19] Sharifi, A.; Salimi, R.; Mirzai, M.; Abaee, M. S. *Synth. Comm*., 2007, 37, 1825

[20] (a) P. C. Crofts, Q. *Rev., Chem.* Soc. 1963, 12, 624; (b) L. D. Freedman and G. 0. Doak, *Chem. lieu,* 1957, 57, 479.

[21] Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* 1980, 45, 4162.

[22] Breuer, E.; Safadi, M.; Chorev, M.; Gibson, D. *J. Org. Chem.* 1990, 55, 6147.

[23] Kaushik, M. P.; Lal, B.; Raghuveeran, C. D.; Vaidyanathaswamy, R. *J. Org. Chem.* 1982, 47, 3503.

[24] Nakazawa, H.; Matsuoka, Y.; Yamaguchi, H.; Kurolwa, T.; Miyoshi, K.; Yoneda, H. *Organometallics* 1989, 8, 2272.

[25] Nakazawa, H.; Matsuoka, Y.; Nakagawa, I.; Miyoshi, K. *Organometallics* 1992, 11, 1385.

[26] Sprecher, M.; Kost, D. *J.* Am. Chem. Soc. 1994, 116, 1016.

[27] Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron* 1998, 54, 12233.

[28] Gajda, T. *Tetrahedron: Asymmetry* 1994, 5, 1965.

[29] Nesterov, V. V.; Kolodiazhnyi, O. I. *Zh. Obshch. Khim*. 2005, 75, 1225.

[30] Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry* 1996, 7, 89.

[31] Kim, D. Y.; Wiemer, D. F. *Tet. Lett.* 2003, 44, 2803.

[32] List, B. *Tetrahedron* 2002, 58, 5573.

[33] Sampak Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc* 2006, 128, 7442.

[34] Demir, A. S.; Reis, Ö.; Kayalar, M.; Eymur, S.; Reis, B. *Synlett* 2006, 19, 3329.

[35] (a) Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem*. 2000, 2239; (b) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem*. 2000, *65*, 6121.

[36] (a) Chopard, P. A.; Clark, V. M.; Hudson, R. F.; Kirby, A. J. *Tetrahedron* 1965, *21*, 1961. (b) Borowitz, I. J.; Anshel, M.; Firstenberg, S. *J. Org. Chem*. 1967, 32, 1723.

[37] Hammerschmidt, F.; Schneyder, E.; Zbiral, E. *Chem. Ber*. 1980, *113*, 3891.

[38] McConnell, R. L.; Coover Jr, H. W. *J. Am. Chem. Soc*. 1956, *78*, 4450.

[39] Fitch, S.; Moedritzer, K. *J. Am. Chem. Soc*. 1962, *84*, 1876.

[40] Kurihara, T.; Santo, K.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull*. 1987, *35*, 4777.

[41] Demir, A. S.; Reis, Ö.; İğdir, A. Ç.; Esiringü, İ.; Eymur, S. *J. Org. Chem.* 2005, 70,10584.

[42] Demir, A. S.; Reis, Ö.; Esiringü, İ.; Reis, B.; Barış, Ş. *Tetrahedron* 2007, 63,160.

[43] Newmann, M.S.; Magerlein, B. J. *Org. React.* 1949, 5, 413.

[44] Iorga, B.; Eymery, F.; Savignac, P. *Synthesis*, 1999, 2, 207

[45] Newmann, M.S.; Magerlein, B. J. *Org. React.* 1949, 5, 413.

[46] Sturtz, G. *Bull. Soc. Chim. Fr.* 1964, 2333.

[47] Arbuzov, B. A.; Movsesyan, M. E. *Dokl. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1959, 267; *Chem. Abstr.* 1959, 53, 19850f.

[48] Abramov,V. S.; Shalman, A. L.; Molodykh, Zh. V. *J. Gen. Chem.USSR (Engl. Transl.)* 1968, 38, 529.

[49] Russell, G. A.; Ros, F. *J. Am. Chem. Soc.* 1985, 107, 2506.

[50] Meisters, A.; Swan J. M. *Aust. J. Chem.* 1965, 18, 168.

[51] Arbuzov, B. A.; Vinogradova, V. S.; Polezhaeva, N. A. *Izv. Akad. Nauk. SSSR, Otdel. Khim. Nauk* 1959, 41; *Chem. Abstr.* 1959, 53, 15035e.

[52] Coutrot, P.; Savignac, P. *Synthesis* 1978, 34.

[53] Arbuzov, B. A.; Vinogradova, V. S.; Polezhaeva, N. A. *Dokl. Akad. Nauk SSSR* 1956, 111, 107; *Chem. Abstr.* 1957, 51, 8001g.

[54] Minami, T.; Motoyoshiya, J. *Synthesis* 1992, 333.

[55] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Chap. 7; John Wiley and Sons: New York, 1998, 397.

[56] Padwa, A.; Hornbuckle, S. *Chem. Rev.* 1991, *91*, 263.

[57] Padwa, A.; Weingarten, M. D. *Chem. Rev.* 1996, *96*, 223.

[58] Huisgen, R.; De March, P. *J. Am. Chem. Soc.* 1982, *104*, 4955.

[59] Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* 1997, *62*, 7210.

[60] Doyle, M. P.; Hu, W. H.; Timmons, D. J. *Org. Lett.* 2001, *3*, 933.

[61] Davies, H. M. L.; DeMeese, J. *Tetrahedron Lett.* 2001, *42*, 6803.

[62] Muthusamy, S.; Gunanathan, C.; Nethaji, M. *Synlett* 2004, 639.

[63] De Klein, W. J. *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H. I., Eds.; Plenum: New York, NY, 1986.

[64] Demir, A. S.; Emrullahoglu, M. Curr. Org. Synth. 2007, 4, 321

[65] Aylward, J. B. J. Chem. Soc. B 1969, 1663.

[66] Gomberg, M.; Bachmann, W. *J. Am. Chem. Soc.* 1924, *46*, 2339.

[67] Demir, A. S.; Reis, Ö.; Emrullahoğlu, M. *J. Org. Chem.* 2003, 68, 578-580

[68] Kirvan, J. N.; Roberts, B. P. *J. Chem Soc., Perkin Trans.* 2 1989, 593.

[69] Ogibin, Yu. N.; Troyanski, E. I.; Nikishin, G. I. *Iz*V. *Akad. Nauk. SSSR, Ser. Khim*. **1975**, 1461.

[70] Shelton, J. R.; Uzelmeier, C. W. *J. Am. Chem. Soc*. 1966, *88*, 5222.

[71] Engel, P. S.; Lee, W.-K.; Marschke, G. E.; Shine, H. J. *J. Org. Chem*. 1987, *52*, 2813.

[72] Roberts, B. P.; Winter, J. N. *J. Chem. Soc., Perkin Trans. 2* 1979, 1353.

[73] Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron*, 1998, *54*, 12233.

[74] Hendlin, D.; Stapley, E. O.; Jackson, M.; Wallick, H.; Miller, A. K.; Wolf, F. J.; Miller, T.; Chaiet, W. L.; Kahan, F. M.; Foltz, E. L.; Woodruff, H. B.; Mata, J. M.; Hernandez, S.; Mochales, S. *Science* 1969, 166, 122

[75] Iorga, B.; Eymery, F.; Savignac, P. *Synthesis* 1999, 207

[76] Glamkowski, E. J.; Gal, G.; Purick, R.; Davidson, A. J.; Sletzinger, M. *J. Org. Chem*. 1970, *35*, 3510-3512.

[77] Haake, P.; Springs, B. *J. Org. Chem*, 1976, *41*, 1165-1168

[78] Bandini, C.; Martinelli, F.; Spinta, G.; Panunzio, M. Tetrahedron: Asymmetry, 1995, 2127-2130.

[79] Sturtz. G. Bull. Soc. Chim. Fr., 1964, 2333. Ulman, A.; Sprecher, M. J. Org. Chem. 1979, *44*, 3703-3707.

[80] Li, Z.-C.; Zhang, Ji.; Hu, W.-H.; Chen, Z.-Y.; Yu, X.-Q. *Synlett*, 2005, *11*, 1711-1715.

[81] Newman, M.S.; Magerlein, B.J. Org. React. 1949, 5, 413. (b) Ballester, M. Chem. Rev. 1955, 55, 283.

[82] (a) Demir, A. S.; Eymur, S. *J. Org. Chem.* 2007, *72*, 8527-8530. (b) Demir, A. S.; Reis, B.; Reis, Ö.; Eymür, S.; Göllü, M.; Tural, S.; Sağlam, G. *J. Org. Chem.* 2007, *72*, 7439-7442.

[83] Emrullahoğlu, M. PhD. Thesis, 2008, Middle East Technical University.

[84] (a) T. R. Juneja, D. K. Garg, *Tetrahedron* 1982, *38*, 551. (b) R. W. Alder, R. B. Sessions, *Tetrahedron Lett*. 1982, *23*, 1121.

[85] Tanaka, K.; Shiraishi, R. *Green Chemistry*, 2001, *3*, 135–136.

[86] Berson, J.A. ***J.*** *Am. Chem. Soc.,* 1952**,** *74*, 5177.

[87] Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* 1985, *50*, 10.

[88] Snider, B. B. *Chem. Rev*. 1996, *96*, 339.

APPEN DIX A

NMR DATA

NMR spectra were recorded on a Bruker DPX 400.

Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards.

^1H and ^{13}C NMR spectra of products are given below.

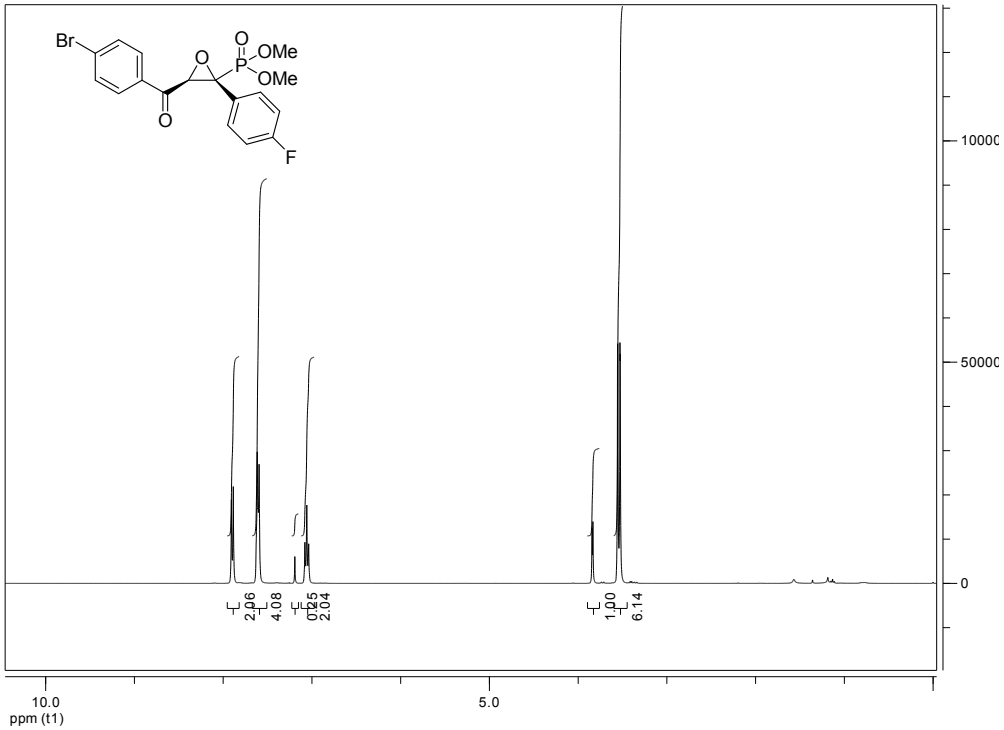


Figure A. 1 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*) **167a**

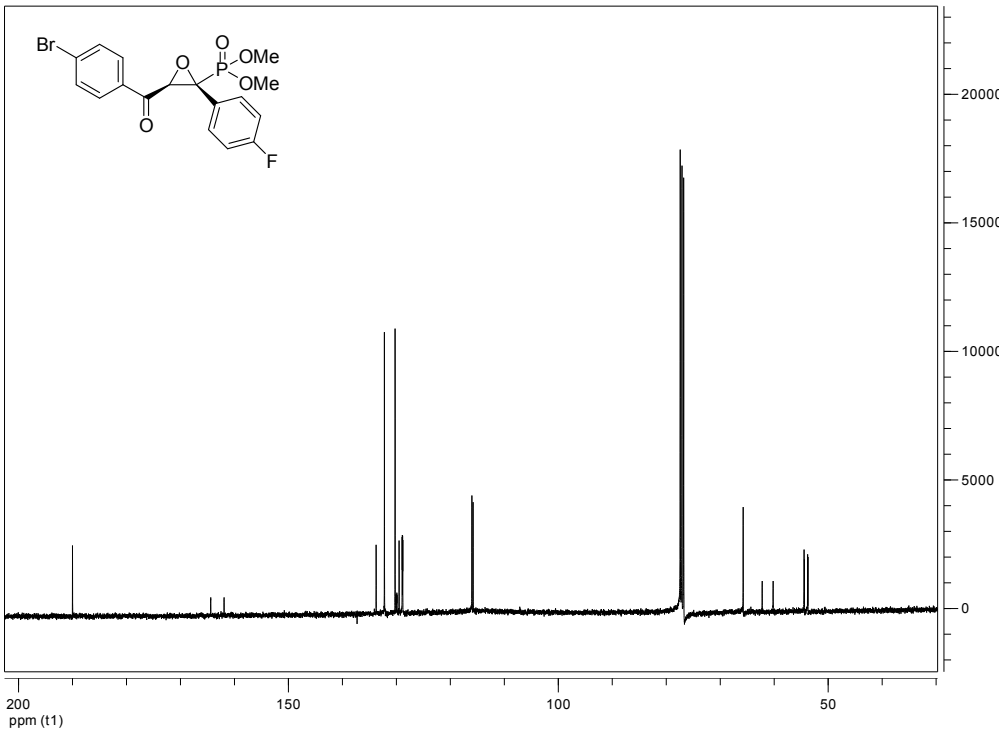


Figure A. 2 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*) **167a**

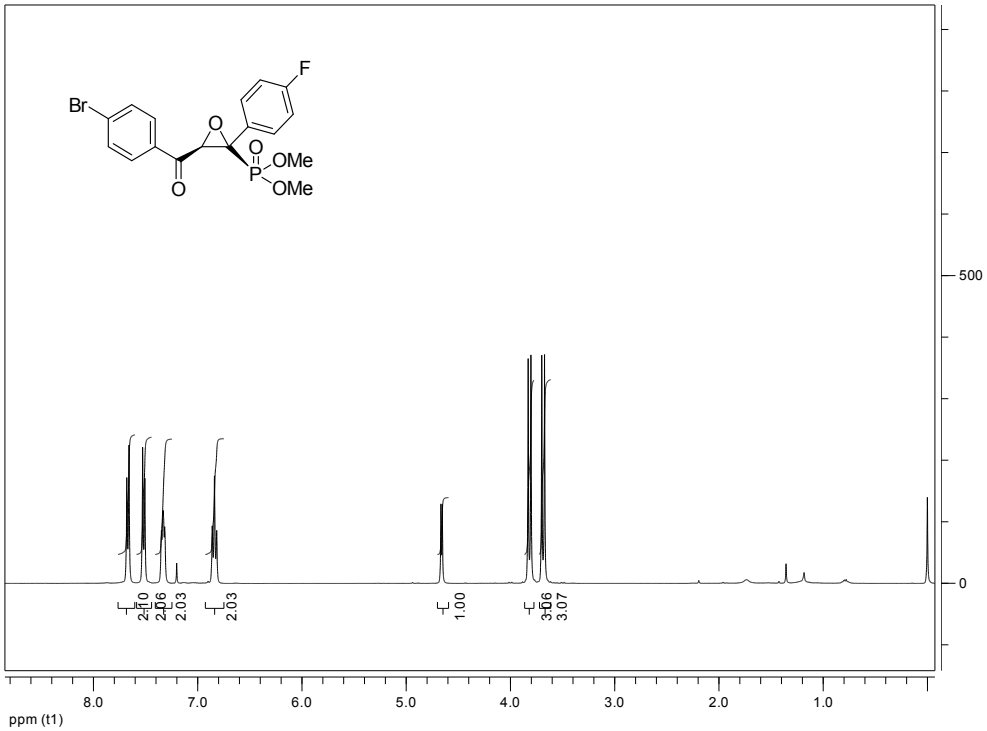


Figure A. 3 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*) **167b**

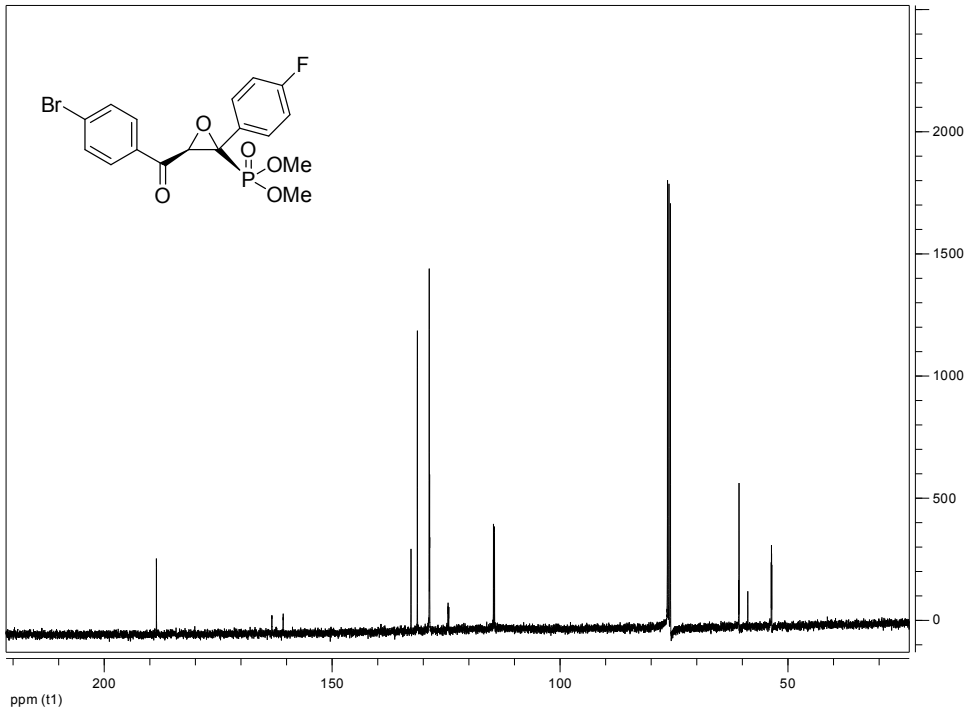


Figure A. 4 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*) **167b**

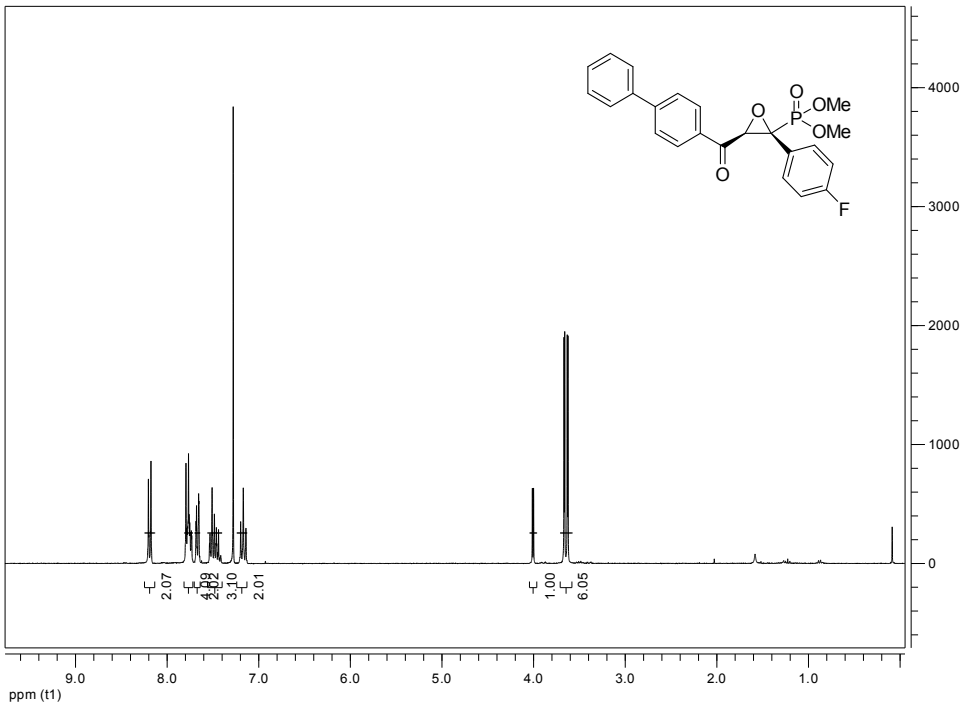


Figure A. 5 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*) **168a**

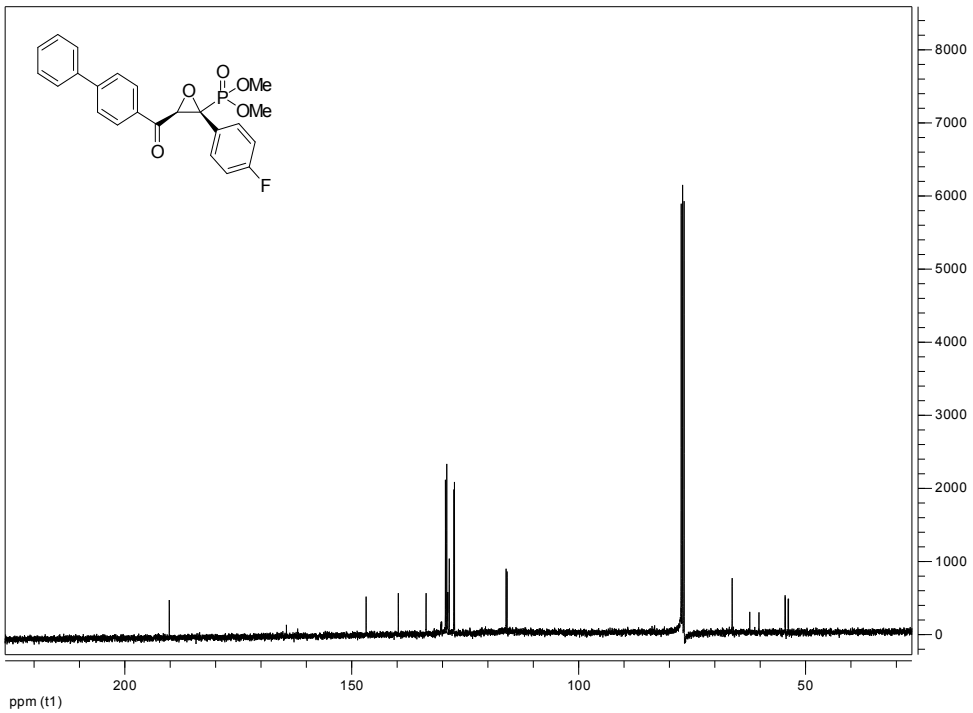


Figure A. 6 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*) **168a**

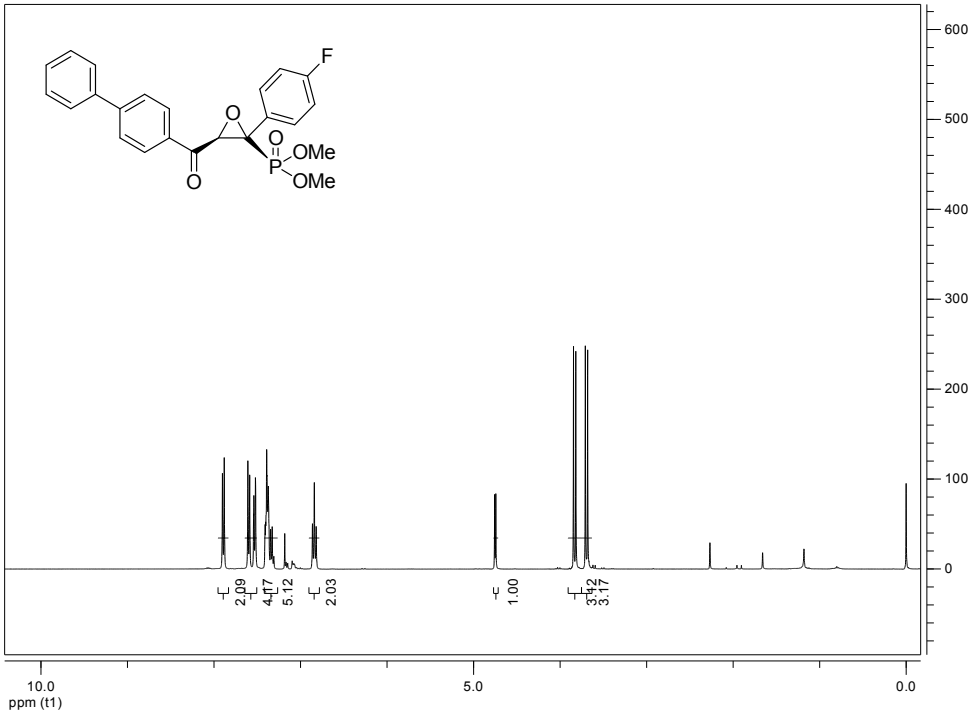


Figure A. 7 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*) **168b**

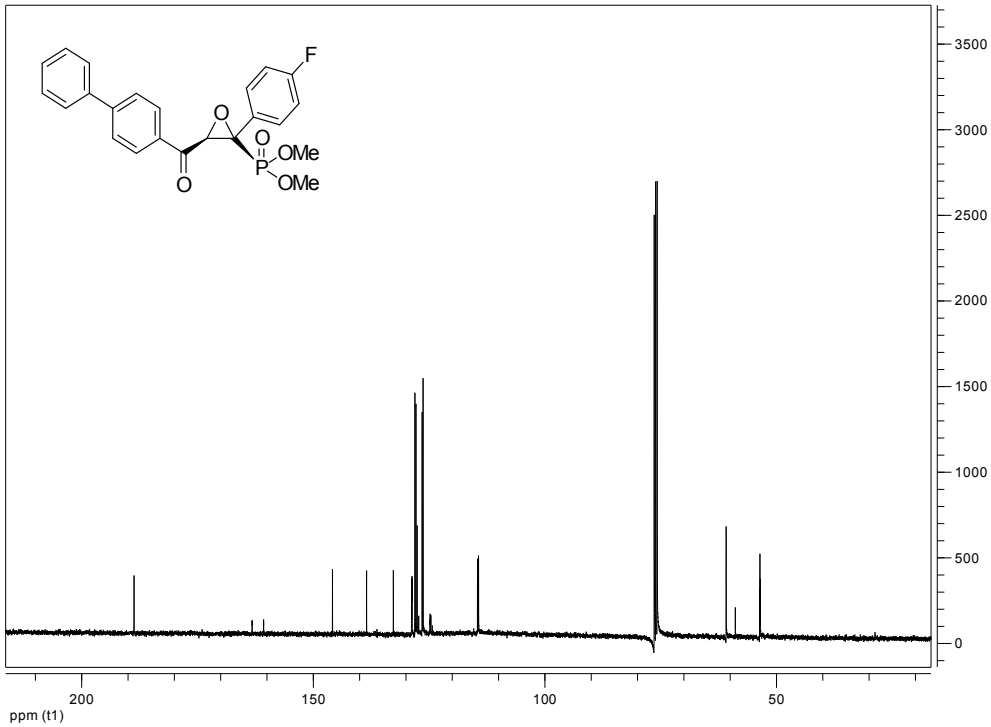


Figure A. 8 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*) **168b**

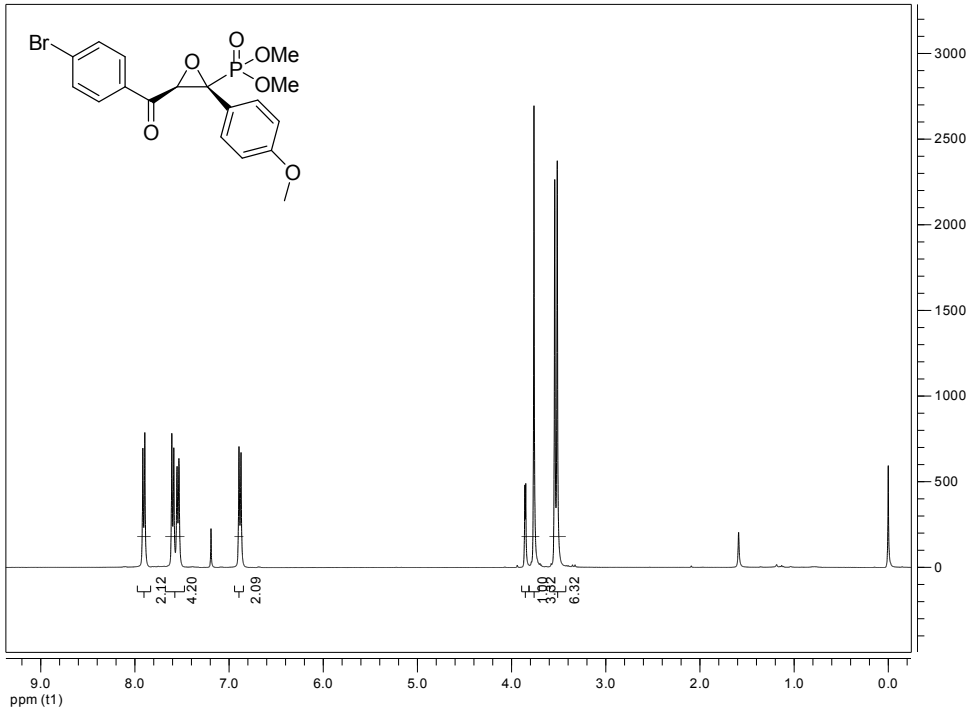


Figure A. 9 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*) **169a**

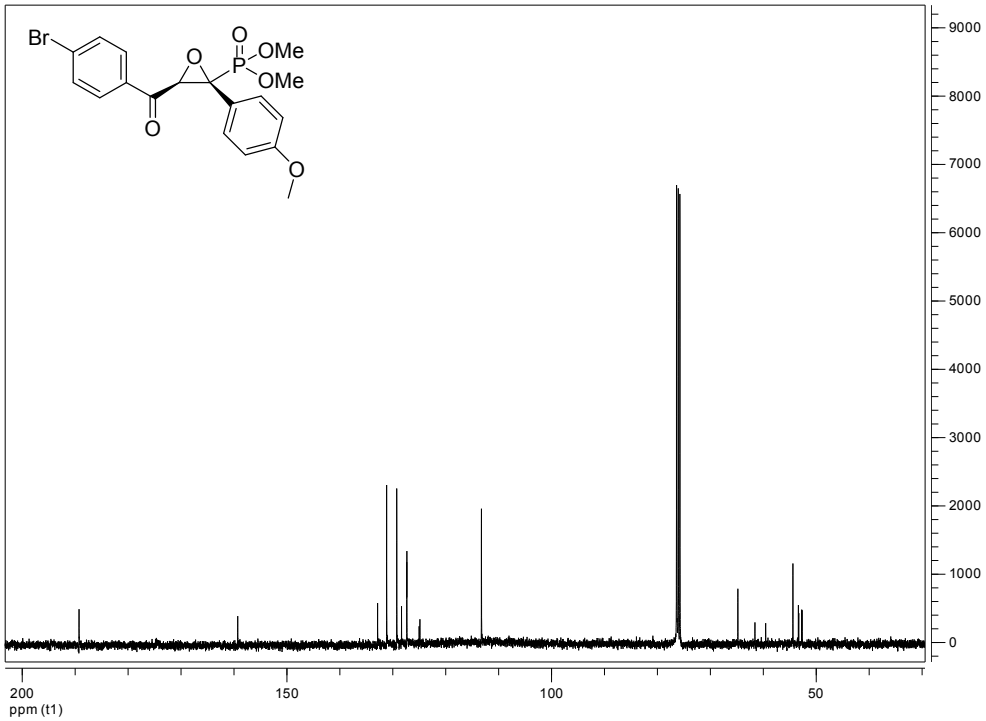


Figure A. 10 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*) **169a**

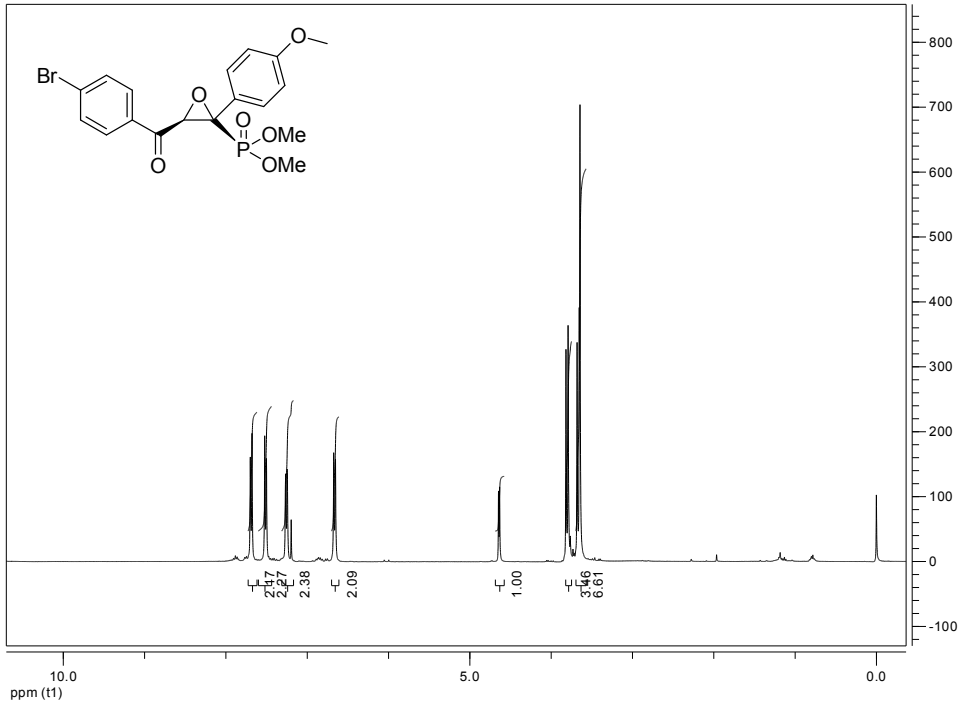


Figure A. 11 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*) **169b**

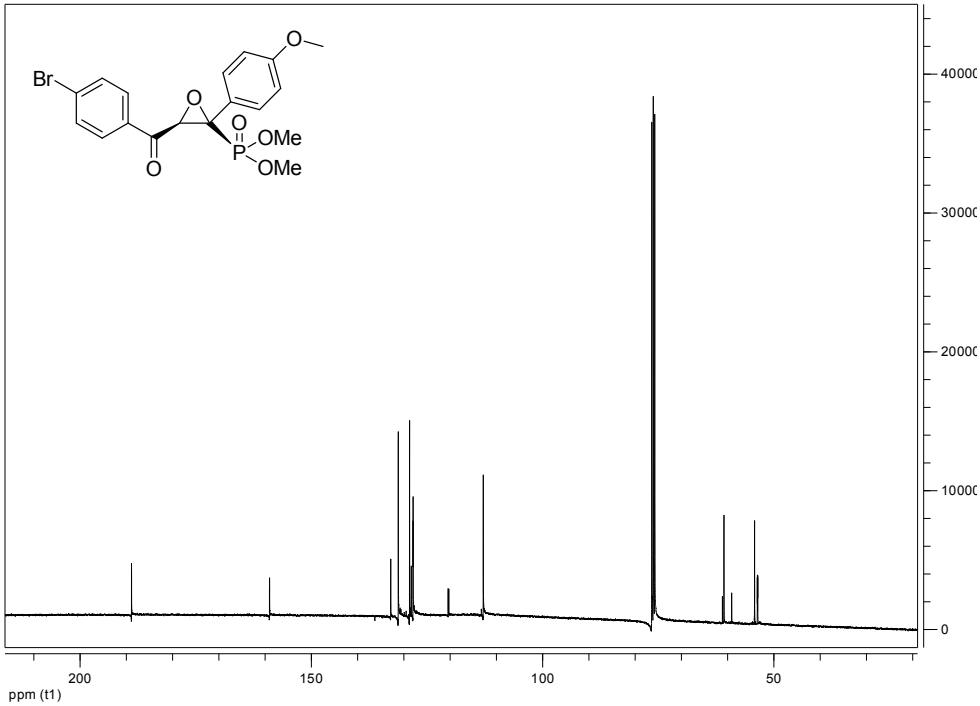


Figure A. 12 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*) **169b**

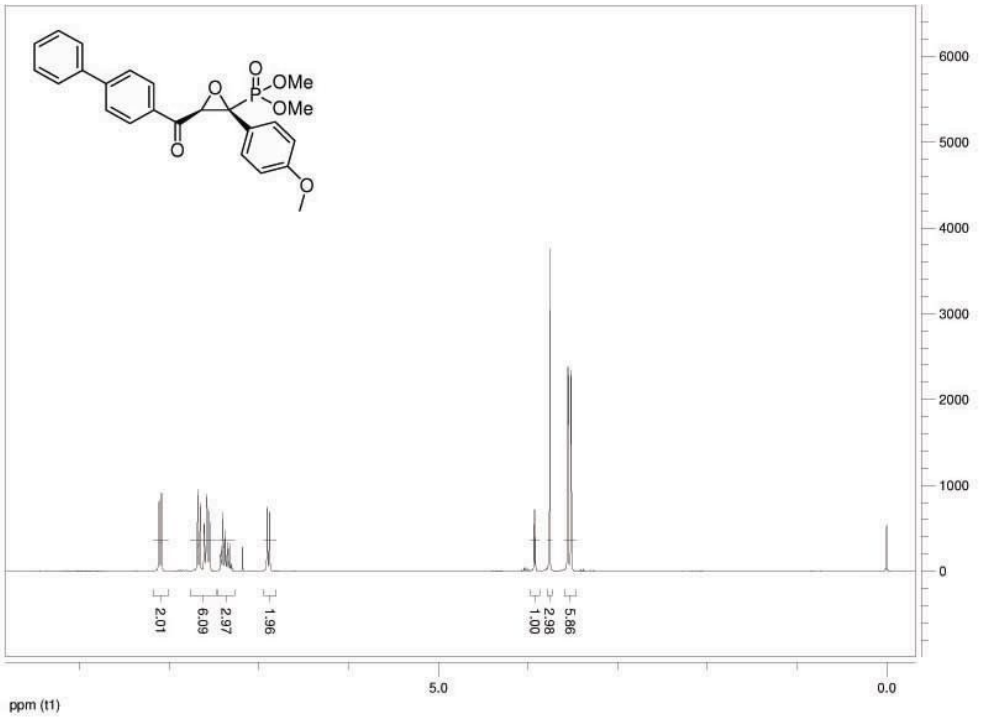


Figure A. 13 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*) **170a**

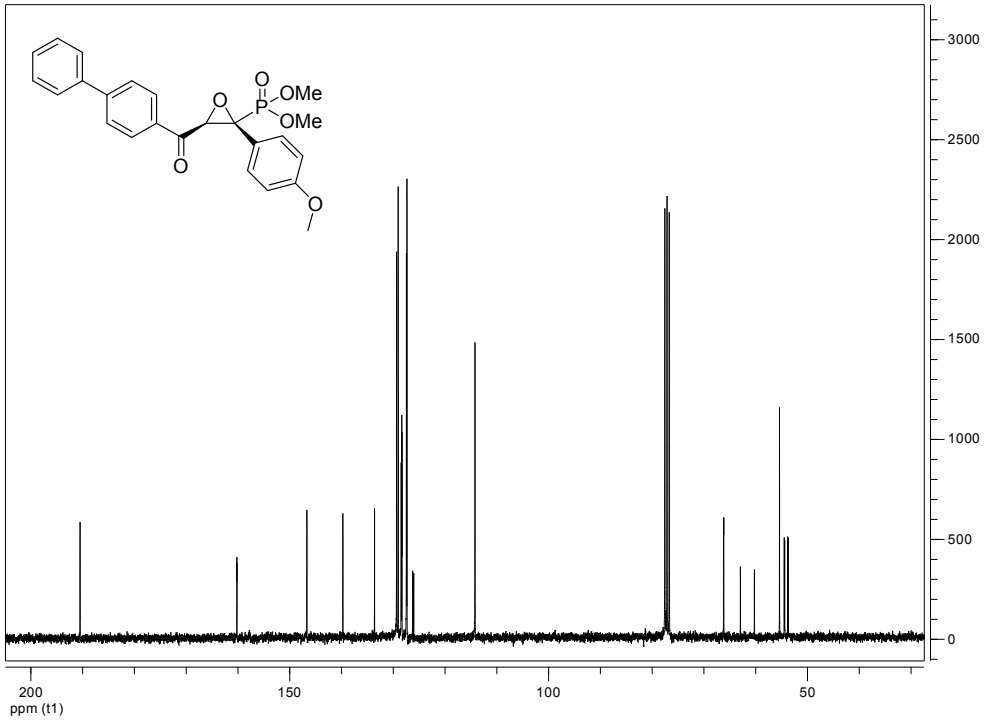


Figure A. 14 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*) **170a**

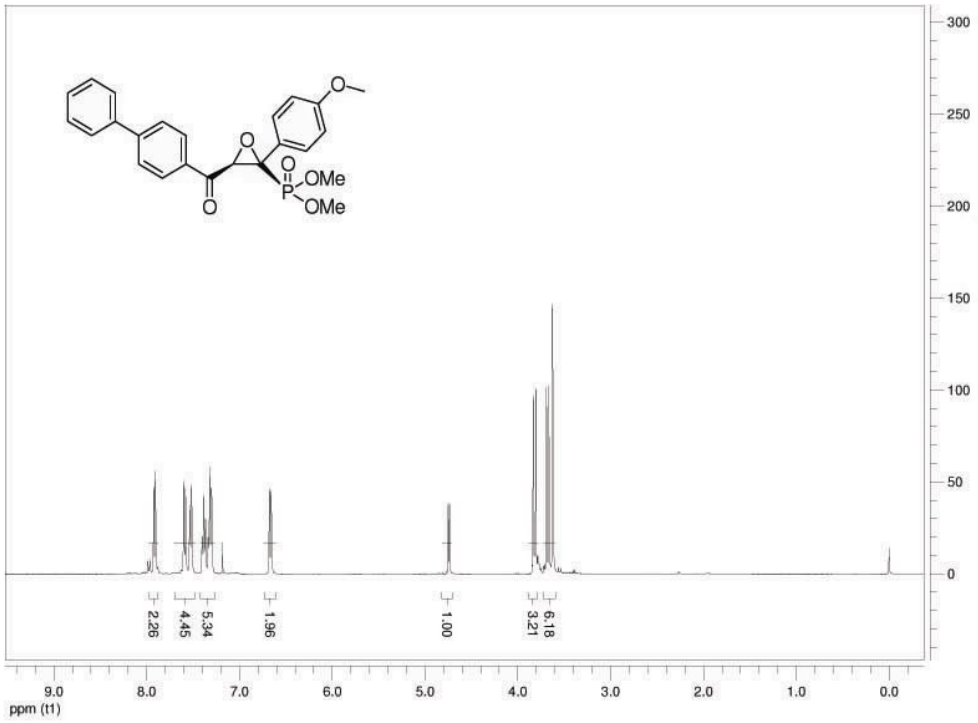


Figure A. 15 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*) **170b**

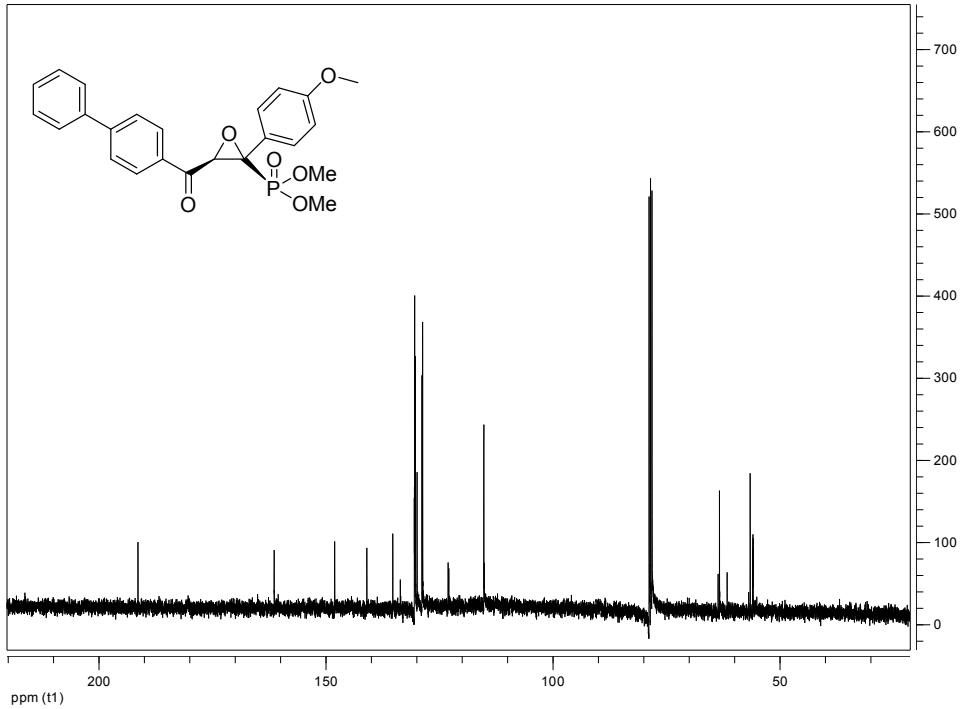


Figure A. 16 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*) **170b**

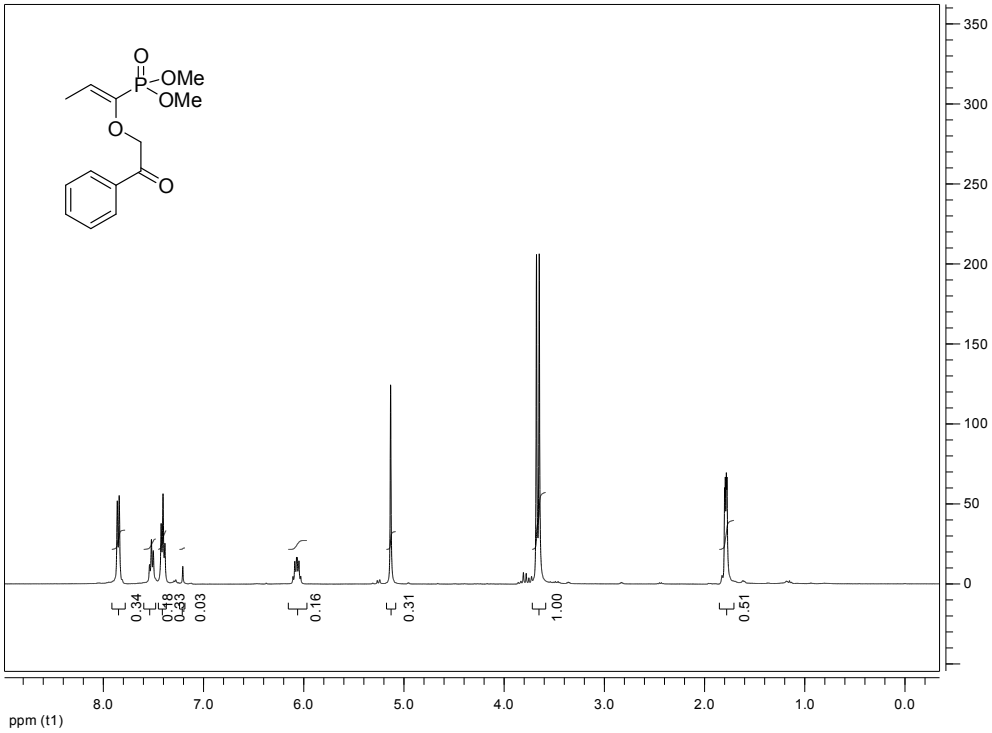


Figure A. 17 Dimethyl-1-(1-phenyletanonoxy)-prop-1-ene phosphonate **178**

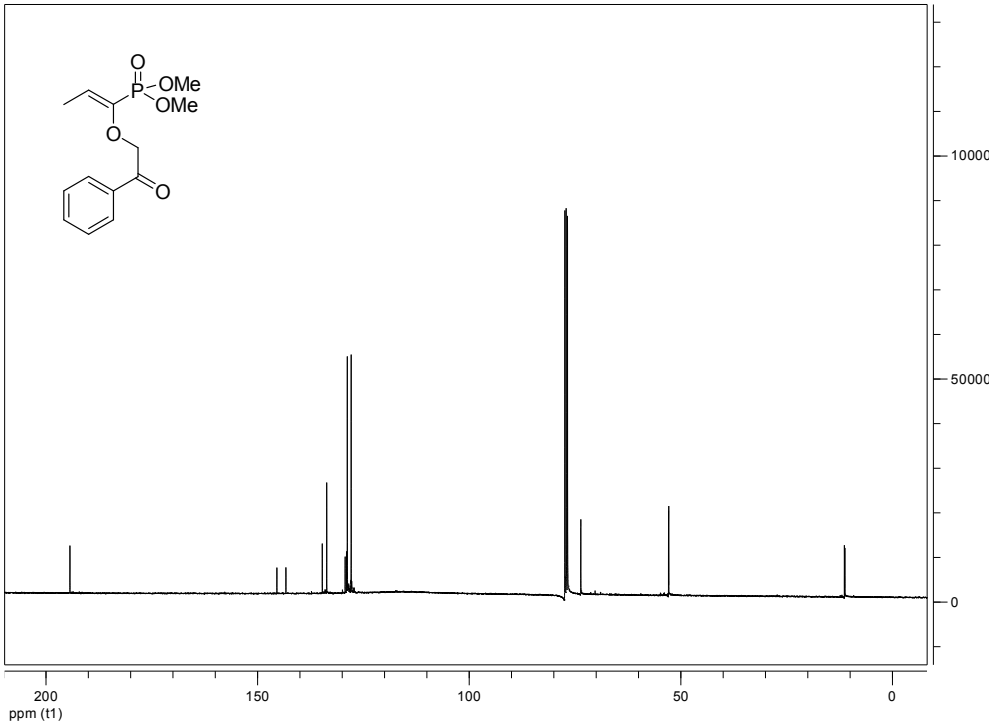


Figure A. 18 Dimethyl-1-(1-phenyletanonoxy)-prop-1-ene phosphonate **178**