Investigations on Acid / Base Mediated Synthesis of Organophosphonates / Phosphates and Their Applications

THESIS

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By

Gangaram Pallikonda
ID. No. 2011PHXF407H

Under the Supervision of
Prof. Manab Chakravarty

BITS Pilani

Pilani | Dubai | Goa | Hyderabad

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CERTIFICATE

This is to certify that the thesis entitled **"Investigations on Acid / Base Mediated Synthesis of Organophosphonates / Phosphates and Their Applications"** and submitted by **Gangaram Pallikonda** ID No **2011PHXF407H** for the award of Ph. D. of the institute embodies original work done by him under my supervision.

Signature of the Supervisor: _____

Name: **Prof. Manab Chakravarty**

Designation: **Associate Professor**
Department of Chemistry
BITS Pilani-Hyderabad Campus.

Date:

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Acknowledgement

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Date: *Gangaram Pallikonda*

ABSTRACT

The thesis entitled "**Investigations on Acid / Base Mediated Synthesis of Organophosphonates / Phosphates and Their Applications**" deals with the synthesis and applications of biologically and synthetically important organophosphorus compounds using straightforward synthetic methodologies. We have divided this thesis in four chapters along with a general introduction on organophosphorus chemistry.

General introduction describes the origin of organophosphorus chemistry and its importance in numerous research fields such as chemicals, materials, biological and pharmaceutical sciences. We have also discussed some highly relevant and renowned name reactions.

The **first chapter** of thesis describes a $FeCl_3$-mediated regio-and stereo selective Friedel-Crafts-type arylation of selected *α*-hydroxy phosphonates with unactivated arenes, in which the unstable allylphosphonate cations generated are stabilized by extended conjugation. This method provides a simple, efficient and economical approach to highly demanding stereo selective *γ*-aryl-substituted vinylphosphonates and dialkyl (diarylmethyl)phosphonates with good regioselectivity. These reactions proceed under mild conditions in the absence of any additional solvent. Synthesis of *α*-halophosphonates can be easily carried out at room temperature by the treatment of HX (HCl, HBr) with specific α-hydroxyphosphonates.

The **second chapter** of thesis briefly describes an operationally simple synthetic method to access (±)-*α*-aryl/methylsulfonamidomethylphosphonates and new (±)-*γ*-aryl/methyl sulfonamidomethylvinylphosphonates through straightforward reactions of (±)-*α*-hydroxyphosphonates with sulfonamides in the presence of triflic acid (TfOH) at room temperature in a vessel open to air. For *γ*-dimethylallylhydroxyphosphonate, the (*E*)-1,3-butadienylphosphonate was formed quantitatively using TfOH while $FeCl_3$ afforded the expected product in moderate yield unpredictably. The favourable sulfonoamidation of benzyl alcohol is also observed when TfOH was used for *α*-hydroxyphosphonates having a benzyloxy group.

The **third chapter** deals with the synthesis of a range of *α*-aryl substituted *γ*-ketophosphonates by Lewis acid mediated reactions of 1,3-diketones and easily accessible, inexpensive benzylic *α*-hydroxyphosphonates in an operationally simple method under solvent-free conditions without exclusion of air/moisture. A regioselective C-C bond cleavage for 1,3-diketones in a tandem fashion has also been demonstrated. Synthesis of a *γ*-ketophosphonates with phenol functionality at the *α*-position (structural analogue of raspberry ketone, a natural product) has also been presented. And also a straightforward and inexpensive synthetic protocol to access new *ω*-ketovinyl phosphonates is established from the Lewis or Brønsted acid mediated reactions of *α*-hydroxy allylic phosphonates with aromatic 1,3-diketones. Predominantly, $FeCl_3$ or $FeCl_3{\cdot}6H_2O$ has been preferred as easily available, inexpensive and efficient Lewis acid under solvent-free conditions. With experimental and theoretical support, we have demonstrated that some of the substituted open chain 1,3-diketones may exist predominantly in the keto form. Mild base mediated isomerization reactions for *ω*-ketovinyl phosphonates were carried out to generate corresponding allylic phosphonates. Utility of one of the allylic phosphonate in Horner–Wadsworth–Emmons (HWE) reactions facilitated access to variety of densely substituted 1,3-butadienes attached with 1,3-diketone functionality at the terminal carbon.

The **fourth chapter** of the thesis focuses on the variety of organophosphates that are synthesized from *n*-BuLi-triggered, (additional) solvent-free reactions of diethyl phosphite with both activated/unactivated ketones and aldehydes preferably at room temperature *via* phospha-Brook rearrangement. We could successfully synthesize the naphthylic/allylic phosphates using this approach further easily accessible electron-poor/rich primary and secondary benzylic phosphates are established as novel substrates for triflic acid catalyzed, (additional) solvent-free Friedel-Crafts (FC) arylation reactions to access structurally and electronically diverse polyarylated alkanes (triarylmethane and diarylmethane/ethane) with excellent yield and decent selectivity using *only 1.2 equiv* activated or deactivated arenes (including haloarenes) at *room temperature*. Using this strategy diversely substituted di- and tri-arylmethanes are generated within 2-30 min. significantly electron-deficient and unexplored polyarylated alkanes are efficiently obtained using unfavorable FC approach with the help of much electron-poorer benzylic phosphates that are abundantly produced *via favorable* phospha-Brook rearrangement.

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List of abbreviations and symbols

%	:	Percentage
λ	:	Wavelength
A°	:	Angstrom
Ac_2O	:	Acetic anhydride
α	:	Alfa
β	:	Beta
γ	:	Gama
ω	:	Omega
µg	:	Microgram
µM	:	Micromolar
^{13}C NMR	:	Carbon Nuclear Magnetic Resonance
^{1}H NMR	:	Proton Nuclear Magnetic Resonance
^{31}P NMR	:	Phosphorus Nuclear Magnetic Resonance
3D	:	Three Dimensional
Calcd	:	Calculated
EtoAc	:	Ethylacetate
$CDCl_3$	:	Chloroform deuterated
m	:	multiplet
t	:	Triplet
d	:	Doublet
DCM	:	Dichloromethane
DCE	:	Dichloroethane
DMF	:	*N*,*N*-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
DMSO-d_6	:	Dimethyl sulphoxide deuterated
DNA	:	Deoxyribonucleic acid
°C	:	Centigrade
Conc	:	Concentration
cm	:	Centimeter

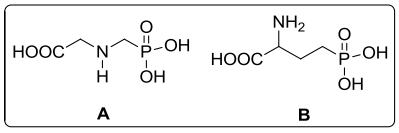
cm−1	:	Wave number
J	:	Coupling constant
EI	:	Electron ionization
ESI-MS	:	Electrospray ionization mass spectroscopy
LCMS	:	Liquid chromatography–Mass Spectrometry
m	:	Multiplet
M.p	:	Melting point
B.p	:	Boiling point
h	:	Hours
mg	:	Milligram
mL	:	Milliliter
mmol	:	Millimole
IR	:	Infrared
IUPAC	:	International Union of Pure and Applied Chemists
nM	:	Nanomolar
Lit.	:	Literature
MeOH	:	Methanol
MHz	:	Mega Hertz
min	:	Minute
ppm	:	Parts per million
mmol	:	Millimole
NMR	:	Nuclear Magnetic Resonance
rt	:	Room temperature
s	:	Singlet
TfOH	:	Trifluoromethanesulfonic acid
TMS	:	Tetramethylsilane
TMSCl	:	Trimethylsilyl chloride
TEA	:	Triethylamine
TFA	:	Trifluoroacetic acid
THF	:	Tetrahydrofuran
TLC	:	Thin-layer chromatography

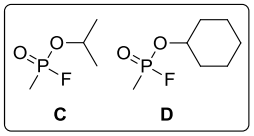
T_m	:	Melting temperature
δ	:	Chemical shift

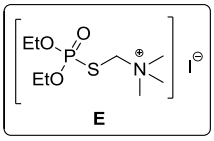
General Introduction I

I.I General introduction on organophosphorus chemistry

As an important member of main group chemistry, phosphorus can form bonds with various elements with coordination number ranging from 1 to 6 and more with preferable valences 3 or 5 because of energetically available empty *d*-orbitals.[1,2] Moreover, organophosphorus compounds are recognized in nature as a key building block in all known forms of life.[3,4] They also play a role as limiting nutrient in plant growth, explaining its huge economic and societal importance in the phosphate fertilizer industry.[5,6] This is also true for various phosphorus containing agrochemicals such as the herbicides [such as glyphosphate (**A**) and glufosinate (**B**), their associated genetically modified crops, the plant-growth regulator/ripening agent ethephon, etc.[7,8] They have also been used as nerve agents such as sarin (**C**) and cyclosarin (**D**),[9,10] that are used as chemical warfare and therapeutic agents, such as ecothiopate (E) used in the treatment of glaucoma.[11] The use of organophosphorus compounds as achiral or chiral ligands for transition metal catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial productions. Therefore, organophosphorus chemistry is of great importance to the researchers due to the recent advancement dealing with the generation of numerous phosphorus compounds that have real values and wide-spread applicability in the field of catalysis,[12] agricultural,[13] medicinal[14] and material sciences.[15] In addition, phosphorus-31 being nuclear magnetic resonance (**NMR**) active nuclei with 100% abundance, organophosphorus compounds offer a scope to characterize them and to investigate the reaction mechanism by ^{31}P-NMR spectroscopic studies.







Organophosphorus chemistry is one of the oldest subfields of organic chemistry with a rich tradition over its more than a century history by providing many powerful, synthetically useful renowned name reactions, such as Arbuzov, Michaelis-Becker, Perkow, Pudovik, Kabachnik-Fields, Wittig, and Horner-Wadsworth-Emmons etc. Not surprisingly, organophosphorus compounds play many key roles as flame retardants for fabrics and plastic plasticising and stabilising agents in the plastics industry,[16] selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors.[17] Hence, chemistry and applications of organophosphorus compounds are often considered to be a rich and vast field in the chemical and related sciences. As our research focus is limited to phosphonates and

phosphates, the following discussion is restricted only with these two subclasses of organophosphorus compounds.

I.II *Organophosphonates and phosphates*

Phosphonates are species of organic compounds containing R'-$PO(OR)_2$ groups (where R, R' =alkyl, aryl); the structure of phosphonate compounds includes a tetra coordinate phosphorus atom in the +5 oxidation state that is connected to two alkoxy groups with P-O single bond and a formally double bonded oxygen (known as a phosphoryl group). The fourth group and the R of the two alkoxy groups can be a variety of species, so changes can be made chemically. Phosphonates are often used as the precursors to prepare the corresponding phosphonic acids. On the other hand, organophosphates $(RO)_3P(O)$ contain a phosphorus-oxygen bond in place of a phosphorus-carbon bond in organophosphonates. The examples of phosphonates and phosphates are shown in **Fig 1.1.**

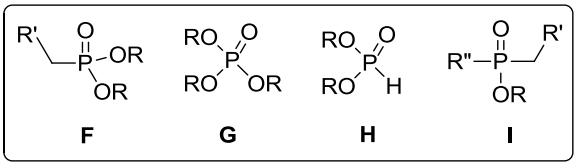


Fig I.I Examples of phosphorus containing compounds: phosphonate (**F**) phosphate (**G**); phosphite (**H**), and phosphonate (**I**). R, R' = aryl,alkyl. R" = C or H.

Phosphate is of central importance in cellular metabolism and is a vital nutrient required for sustaining life. It is a key component for cellular structures, energy storage, and is involved in mediating cellular signalling pathways. For instance, phosphate is found in the backbone of DNA and RNA, high energy compounds (ATP, phosphoenolpyruvate) and is involved in enzyme catalysis. Within biological systems phosphorus is typically bound to four oxygen atoms in its fully oxidized state as seen in **Fig I.I**, either as inorganic phosphate or as phosphate organic esters, amides and anhydrides.

In 1959, the first known naturally occurring organophosphonate, 2-aminoethylphosphonic acid (AEP, **Fig I.II**) was isolated from sheep rumen protozoa[18] where a carbon atom replaces one of the usually bonded oxygen atoms to form a C-P bond. Originally it was hypothesized that the C-P bond of 2-aminoalkylphosphonic acids was unstable.[19]

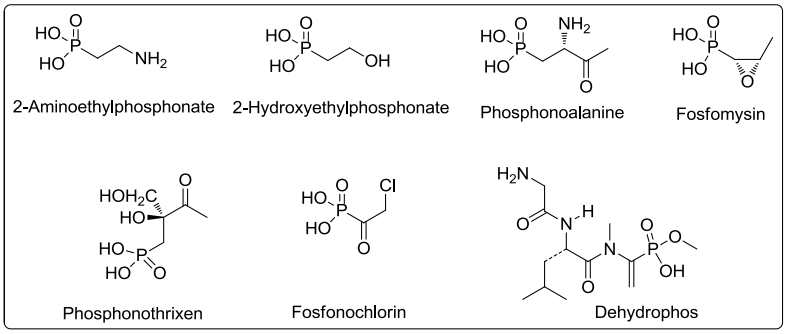


Fig I.II Naturally occurring bioactive organophosphonates and phosphates

In the late 40's aminocarboxylic acids were known to be distributed in all organisms and taurine (2-aminoethanesulfonic acid) was also found in many organisms.[21] However, aminoalkylphosphonic acids were not recognized in nature; Chavane and Hackspill suspected that their absence in nature was dependent on the instability of the CP bond.[21] Later, Chavane and Hackspill's investigations on the properties of synthetic aminophosphonic acids illustrated that the CP bond was sufficiently stable for isolation. Further investigation demonstrated that the CP bond is in fact highly resistant to chemical hydrolysis, thermal decomposition,[22] photolysis[23] and phospholipases.[24] After the discovery of AEP, organophosphonates have since been detected in many phyla ranging from lower plants to the animal kingdom, and have even been identified in human brain, liver, heart and skeletal muscle.[24] Organophosphonates are commonly found as phosphonolipids,[25] where the head group such as phosphocholine is replaced by an analogous organophosphonate, but have also been found as components of polysaccharides,[26] glycoproteins, glycolipids[27] and as small bioactive molecules. Bioactive organophosphonates have become greatly important in medicine and agriculture.[28] The majority of these molecules are produced by actinobacteria but many other microbes can also synthesize CP bond containing compounds.[29] Some important natural bioactive organophosphonates include antibiotics, such as fosfomycin, dehydrophos, and the plumbemycins; herbicides, such as phoshinothricin tripeptide (PTT) and phosphonothrixin; antimalarial compounds, such as fosmidomycin.

Although the biological role of organophosphonate incorporation into cellular structure is not understood, the bioactivity of organophosphonates has been fairly well studied. Organophosphonates and phosphinates can structurally mimic phosphate esters, carboxylic acids and tetrahedral intermediates formed during transformations of carbonyl groups, yet the CP bond makes them almost chemically inert. These properties allow for organophosphonates acting as potent enzyme inhibitors[30] by competing for enzyme active sites with structurally similar

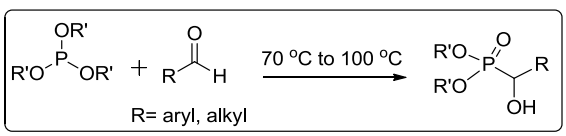
substrates, and then remain unchanged due to the unreactive nature of the CP bond.[31] The ubiquitous presence of phosphate esters, carboxylic acids and carbonyl chemistry in cellular metabolism and signalling pathways enables organophosphonates to serve as inhibitors for an array of processes including regulatory events.[32,33] The usefulness of their unique properties has not been overlooked with both manmade and natural organophosphonates, having found widespread use in the medicinal and agricultural industries.[34]

I.III *Synthetic organophosphonates*

Modern organophosphonate chemistry is an exciting and widely explored field of research. As mentioned earlier, the milestone discoveries of excellent chemists such as Arbuzov, Pudovik, Wittig, Horner, Wadsworth, Emmons, Kabachnik, Fields revealed the enormous potential of organophosphorus chemistry and its underlying principles, making it readily applicable in every organic chemistry laboratory all over the world. Nowadays, due to their reliability, accessibility, and generality, organophosphorus reagents play a pivotal role in contemporary organic chemistry and are readily employed by synthetic chemists. In addition to fascinating reactivity profiles offered by organophosphorus reagents, important aspects of their chemistry also relate to the natural occurrence of many organophosphorus compounds and their intriguing biological activity.[39] As such, organophosphorus compounds have become important synthetic targets in modern organic synthesis. Because phosphonates have proven to be incredibly useful,[40] there have been a substantial number of investigations regarding their syntheses. Several processes to synthesize mono-phosphonates through C-P bond formation have been established, some of the basic important (our research related) reactions are mentioned below.

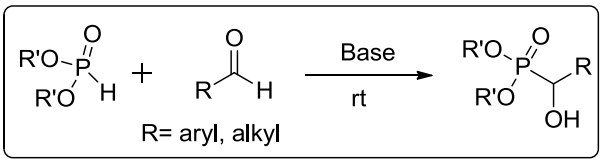
The Abramov[41] and Pudovik[42] reactions are the related conversions of trialkyl and dialkyl phosphites (respectively) to α-hydroxy phosphonates in the presence of carbonyl compounds. Both reactions proceed by similar mechanisms involving the attack of the nucleophilic phosphorus atom on the carbonyl carbon. They are named after Russian chemists Vasily Abramov (1904–1968) and Arkady Pudovik (1916–2006).

I.IV Abramov reaction: The Abramov reaction utilizes an aldehyde and a trialkylphosphite under heating condition to produce α-hydroxyphosphonate **(Scheme I.I)**.[41]



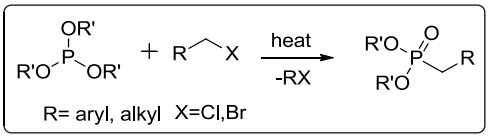
Scheme I.I General Abramov reaction

I.V Pudovik reaction: A similar transformation is the Pudovik reaction, where a dialkylphosphite under basic conditions adds to a carbonyl group to provide α-hydroxyphosphonate **(Scheme I.II)**..[42]



Scheme I.II General Pudovik reaction

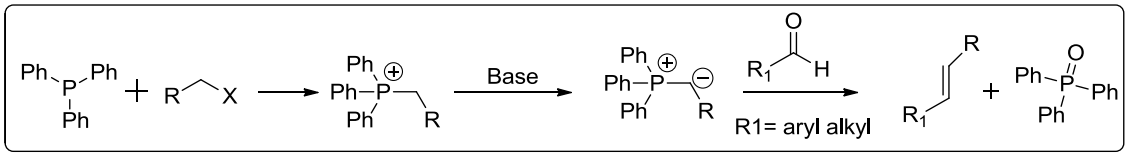
I.VI Michaelis-Arbuzov Reaction: The Michaelis-Arbuzov reaction is the most commonly used method for the synthesis of organophosphonates. This reaction was originally discovered in 1898 by August Michaelis and extensively studied by Aliksandr Arbuzov in the early 20th century. The reaction involves the treatment of alkyl halide with trivalent trialkyl phosphite, which undergoes rearrangement to form an organophosphonate after the nucleophilic substitution reaction **(Scheme I.III)**.[43,44]



Scheme I.III General Michaelis-Arbuzov reaction

I.VII Wittig reaction: The Wittig reaction **(Scheme I.IV)**.is a standard methodology for the synthesis of regioselective alkene due to its specificity of bond placement under relatively mild conditions. The classic method generates the requisite phosphorus ylide, using a base of appropriate basicity, which then reacts with an aldehyde or ketone to yield the corresponding alkene. Under the classical conditions, the Wittig reaction has certain limitations with base sensitive compounds, such as self-condensation of the carbonyl, disproportionation of the carbonyl via the Cannizzaro reaction, and epimerization of adjacent stereocenters. Modifications to the Wittig conditions to accommodate these limitations include use of LiCl with DBU and the lithium 1,1,1,3,3,3-hexafluoroisopropoxide.[45] The first Wittig olefination of non stabilized ylide was promoted by weak carbonate base (K_2CO_3) and achieved in the solid state under ball-milling conditions.[46] In solution-phase chemistry, potassium carbonate or sodium bicarbonate were used, but the reactions required elevated temperatures and were conducted only with stabilized or semistabilized ylides.[47] The Wittig reaction was successfully applied to the synthesis of

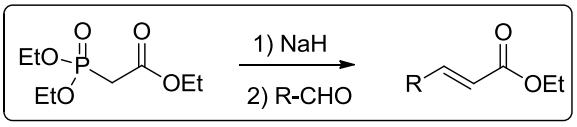
unsaturated amino acids without loss of stereochemical integrity, using K_3PO_4 as a strong base under phase-transfer conditions at elevated temperature (90 °C).[45,46]



Scheme I.IV General Wittig reaction

I.VIII Horner-Wadsworth-Emmons Reaction: In 1958, L. Horner published a novel Wittig reaction between phosphine-oxide stabilized carbanions and carbonyl compounds,[50,51] which was further modified by W.S. Wadsworth and W. D. Emmons by employing phosphonates.[52] Since then, the so called "Horner-Wadsworth-Emmons (HWE) olefination reaction" **(Scheme I.V)**.gained popularity and has become a widespread tool for *de novo* C=C bond formation.[53] The classical HWE reaction is predominantly an *E*-alkene formation tool. In spite of this, it has been demonstrated that the stereochemical outcome of the reaction depends both on the structure of the reactants as well as on the reaction medium. This includes the base and solvent but also the use of certain additives, such as metal salts, crown ethers, or even the deliberate exclusion of salts (resulting in the so-called "salt-free conditions").[54,55,56]

Since its inception and after more than 50 years, the HWE reaction has become one of the most powerful methods for C=C bond formation.[57] Modifications regarding novel phosphonate reagents and reaction conditions, as well as the development of intramolecular HWE reactions have widened the scope of the original method. Further developments have led to novel sequential reactions that are standard tools in modern synthetic organic chemistry. Additional features like robustness of the reaction, wide functional group tolerance, availability of a large variety of phosphonate reagents, ease of introduction of the phosphonate moiety in advanced synthetic precursors and predictable stereochemical outcome have established the HWE reaction as one of the most reliable tools in the field of natural product synthesis. The vast quantity of recent applications reflects its fundamental importance in this area in the preparation of building blocks of advanced synthetic precursors and very often as a key disconnection to assemble highly complex molecular frameworks.



Scheme I.V General Horner-Wadsworth-Emmons reaction

This general discussion reflects the importances of organophosphorus compounds, particularly, phosphonates and phosphates are appeared to be an exciting field with many opportunities for research and development. Consequently, this thesis deals with the investigations on synthesis and applications of vinylic & allylic phosphonates, sulphonamide phosphonates, γ-ketophosphonates and ω-ketovinylphosphonates including organophosphates and their applications in organic synthesis. We have discussed the research work on these areas separately in the respective chapters.

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Chapter 1

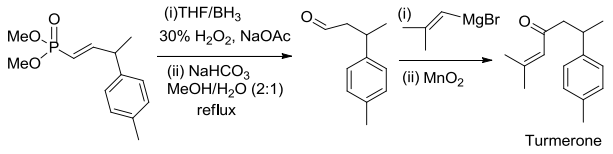
Synthesis of *γ*-aryl substituted vinylphosphonates and diaryl methylphosphonates

1.1 Introduction

In the enormous field of organophosphorus chemistry, organophosphonates have been recognized as an important class of compounds in the field of organic synthesis,[1,2] biological[3] and material sciences.[4] In particular, vinylphosphonates are well known sub-class of organo phosphonate compounds.[5] They are frequently used as intermediates in the synthesis of many important acyclic, carbocyclic and especially heterocyclic compounds.[6,7] They have also been extensively used in polymer sciences as additive[8] and flame-retardant[9] materials. In medicinal chemistry, vinylphosphonates often exhibit interesting biological properties.[10] These are valuable compounds due to their widespread applications in organic synthesis.[6] Among them, in particular, 2-(aryl)vinylphosphonates constitutes interesting group since they are commonly used as starting material for the synthesis of pharmaceutically relevant (as metabolites,[11] anticancer,[12] antiviral drugs,[13] immune suppressives,[14] insecticides,[15] antibacterial and antifungal[16]) molecules.

These building blocks are also involved in the preparation of flame retardant,[8,9] fuel and lubricant additives.[17] Some of them were evaluated for their own pharmaceutical activities.[18] Owing to these significances, several methodologies to access these compounds have been reported by several research groups.

Among vinylphosphonates, *γ*-arylsubstituted vinylphosphonates are also frequently employed for the synthesis of natural product turmerone (**Scheme 1.1**), an aromatic bisabolene sesquiterpene.[19]



Scheme1.1 Synthesis of turmerone from *γ*-arylsubstituted vinylphosphonates

Alkylphosphonates are another crucial intermediates which have been widely utilized as prominent precursors for the synthesis of various materials, as well as direct precursors of olefins through the Horner–Wadsworth–Emmons (HWE: modified version of the famous Wittig reaction) reaction.[20] On the other hand, dialkyl (diarylmethyl)phosphonates are essential precursors for introducing the diarylethene moiety by the HWE reactions into a range of molecules with various applications (**Fig 1.1**). In spite of their well-known uses, the scope of these phosphonates is very limited due to their accessibility with diverse substituents. Given the

interest in phosphonates, and their applications as reagents to prepare a host of useful molecules (**Fig 1.1**), there is a significant demand for their efficient synthesis in an inexpensive and convenient approach.

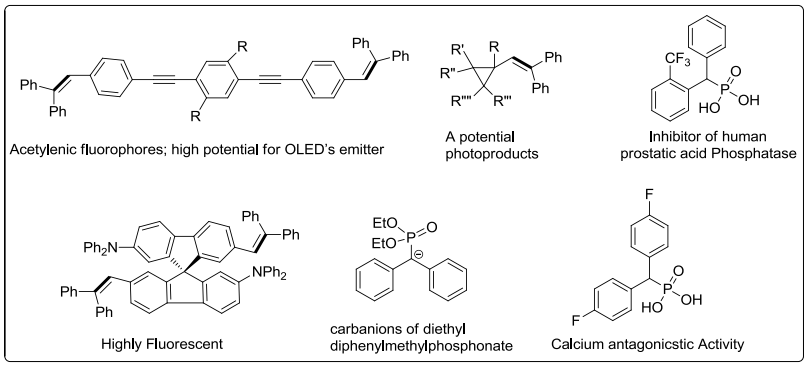


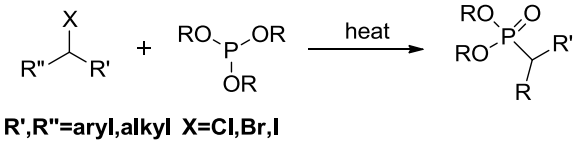
Fig 1.1 Examples of important reported molecules synthesized from γ-substituted vinylphosphonate and diethyl diphenylmethylphosphonate

1.2 Literature review

The synthesis and applications of vinyl- and arylphosphonates have attracted a considerable interest in recent years. This is based on the synthetic value of vinylphosphonates as well as the applications of phosphonates as biologically active materials.[3]

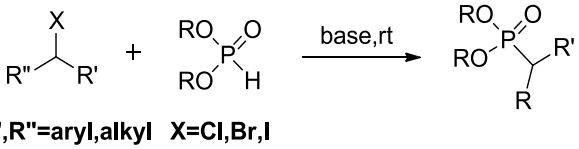
Because of such wide applications, there is continuous interest in efficient methods for the synthesis of substituted phosphonates. Methods of synthesis of these compounds can be divided into two major groups: synthesis of desired phosphonates from precursors that do not contain phosphorus *via* formation of new C-P bonds and modification of the carbon skeleton of the simpler phosphonates. The traditional methods to introduce phosphorus moiety into organic molecules include Michaelis-Arbuzov[21] and Michaelis-Becker[22] reactions.

1.2.1 *Michaelis-Arbuzov reaction*



Scheme1.2 Synthesis of alkylphosphonates

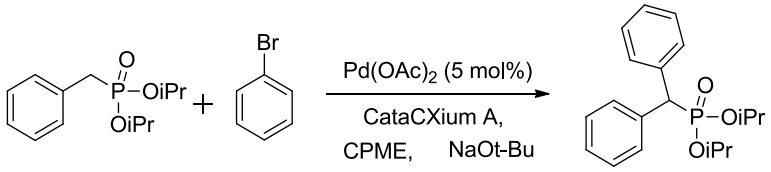
1.2.2 *Michaelis-Becker reaction*



Scheme1.3 Base mediated synthesis of alkylphosphonates

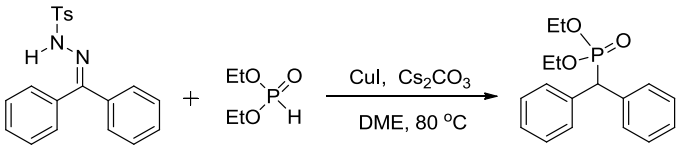
There are also many methods that can be used for modification or extension of the carbon skeleton of phosphonates. Perhaps the most common and versatile reactions of carbanions stabilized by phosphonate groups with a variety of electrophilic partners.[23] As aryl phosphonates and their derivatives are of great importance in chemistry, the synthesis of dialkylarylphosphonates has drawn much attention, and some efficient methods have been established. The general method to synthesize a phosphonate from the corresponding alcohol typically involves two steps: (i) conversion of the alcohol to a halide; (ii) the Michaelis-Arbuzov reaction of the halide with a trialkyl phosphite for several hours at high temperature.[21] (iii) This two-step procedure has drawbacks for very electron-rich benzylic-type alcohols such as 4-(diarylamino)benzyl alcohols and metallocenyl alcohols, which are potentially useful building blocks for electron-rich conjugated molecules. In particular, preparation of the halides can be complicated by oxidative or electrophilic side-reactions, and isolation of halides can be complicated by covalent/ionic equilibria.

Very recently, a new synthetic route was developed to access diarylmethylphosphonates by the group of Patric J .Walsh.[24] The transformation enables the introduction of aromatic groups on benzylic phosphonates via a deprotonative cross-coupling process (DCCP). The $Pd(OAc)_2$/ CataCXium A-based catalyst afforded a reaction between benzyl diisopropyl phosphonate derivatives and aryl bromides in good to excellent isolated yields (64−92%). Unfortunately, the replacement of -iPr to -OEt gave poor result under the similar reaction conditions **(Scheme1.4)**.



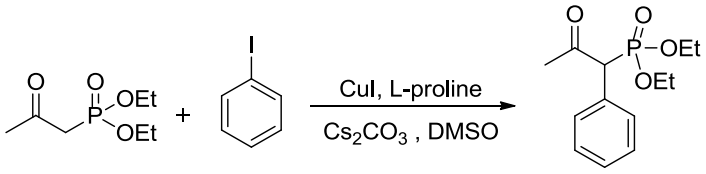
Scheme1.4 Palladium mediated synthesis of diarylmethylphosphonates

A new catalytic system was developed by Tang *et al.*[25] for the alkylation of H-phosphonates with *N*-tosylhydrazones. In the presence of copper(I) iodide and base, H-phosphonates reacted with *N*-tosylhydrazones to afford the corresponding coupled alkylphosphonates in good to excellent yields without any ligands. Alkylphosphonates can also be prepared in a one-pot process directly from carbonyl compounds without the isolation of tosylhydrazone intermediates **(Scheme1.5)**.



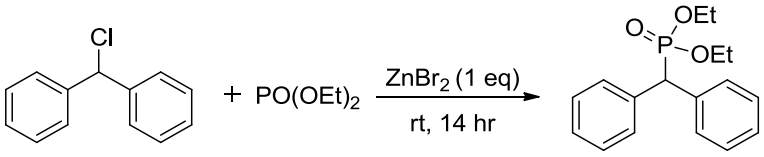
Scheme1.5 Copper mediated synthesis of Alkylphosphonates

Zhao *et al.*[26] and deacylative arylation of *β*-ketophosphonates with iodoarenes in presence of a copper (I) or a copper (II) salt as the catalyst. The corresponding *α*-aryl-substituted *β*-ketophosphonates and *α*-arylmethylphosphonates were obtained in good yields **(Scheme1.6)**.



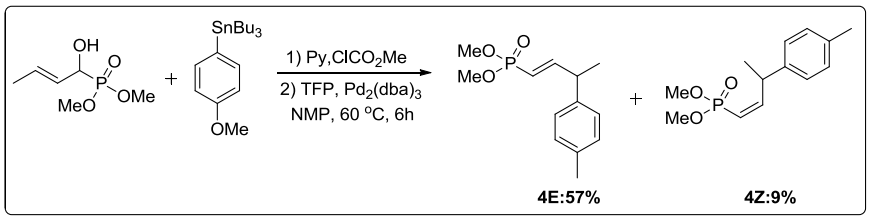
Scheme1.6 Copper catalyzed synthesis of *α*-arylmethylphosphonates

Mohanakrishnan *et al.*[27] developed arylmethyl and heteroarylmethyl phosphonate esters using a Lewis acid (stoichiometric ratios) mediated Michaelis-Arbuzov reaction at room temperature. Interaction of arylmethyl halides/alcohols with triethyl phosphite in the presence of Lewis acid at room temperature afforded phosphonate esters in good yields **(Scheme1.7).**



Scheme1.7 Lewis acid mediated synthesis of heteroarylmethyl phosphonate

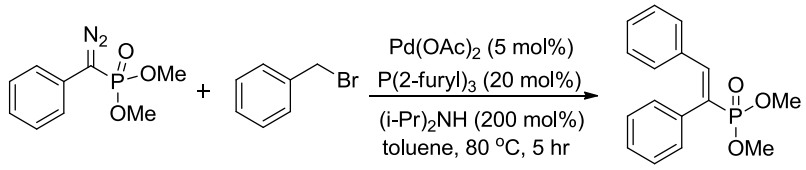
Spilling *et al.*[28] performed a reaction using non-racemic allylic hydroxyphosphonates with methyl chloroformate in pyridine yields the corresponding carbonates. The carbonates are excellent substrates for the palladium-catalyzed addition of nucleophiles. Addition of the nucleophile is highly regioselective, resulting in *γ*-substituted vinyl phosphonates. The reactions of the allylic carbonates with aryl stannanes and malonates were investigated **(Scheme1.8)**.



Scheme1.8 Palladium-catalyzed synthesis of *γ*-substituted vinyl phosphonates

An efficient method for the synthesis of organophosphonates through palladium catalyzed coupling of *α*-diazo phosphonates with benzyl or allyl halides developed by Wang *et*

al.[29] Trisubstituted alkenylphosphonates bearing versatile functional groups can be easily accessed in good yields and with excellent stereo selectivity through this method. Moreover, with similar strategy *α*- substituted vinylphosphonates can also be attained by the palladium catalyzed coupling reaction of *N*- tosylhydrazones and aryl bromides. Migratory insertion of palladium carbene is proposed as the key step in this reaction **(Scheme1.9)**.



Scheme1.9 Palladium catalyzed synthesis of *α*- substituted vinylphosphonates

So, prolonged time, harsh reaction conditions and production of copious waste make these current methods less attractive. Indeed, as far as we know, no other methods are established to synthesize various diethyl diarylmethylphosphonate that could help to extend the existing applications to a likely new prospect. Consequently, synthesis of *γ*-aryl substituted vinylphosphonates[30] and diethyl diarylmethylphosphonates[31] by simple, efficient and economical approach is highly desirable.

1.3 Results and Discussion

The above discussed reactions illustrate the kind of umpolung reactivity of allylic phosphonates[28] where the reactions proceed through the formation of allylic phosphonate cations, which is difficult to generate due to the electron-withdrawing effect of phosphoryl group.[19,28] However, because of the high cost of these metals as well as relatively more toxic nature of associated ligands, there is a need to look for inexpensive alternatives. In this respect, Fe(III) mediated organic transformations have shown potential benefits to organic synthesis.[32] The use of water soluble $FeCl_3$ as a mild and relatively non-toxic reagent for the activation of benzylic and allylic alcohols to generate the carbocationic intermediate and then addition to the nucleophile (Friedel-Craft type reaction) is very well established.[33] Hence, with this thought and the interest on synthesis of organophosphonates, we look into the $FeCl_3$ mediated new, simple and facile synthesis of *γ*-aryl substituted vinylphosphonates and diethyl diarylmethylphosphonates starting with easily accessible *α*-hydroxyphosphonates (**Fig 1.2**) under mild and solvent-free conditions. In this study, initially the following allylic *α*-hydroxyphosphonates (**Fig 1.2**, synthesized by following Pudovik reactions of phosphate and aldehydes) were preferred.

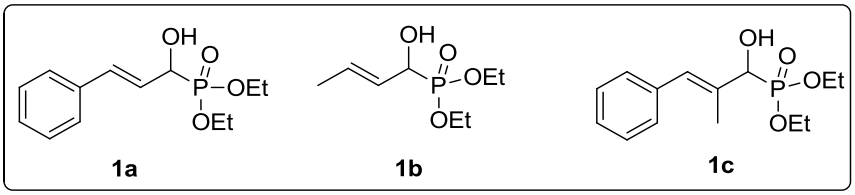
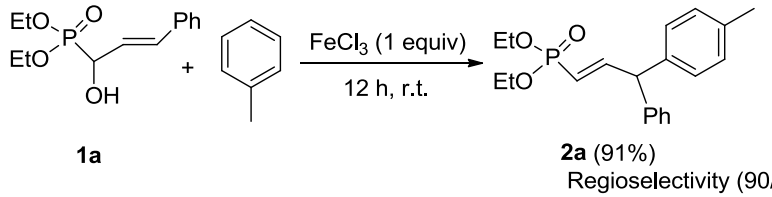


Fig 1.2 Hydroxyphosphonates used as starting materiels

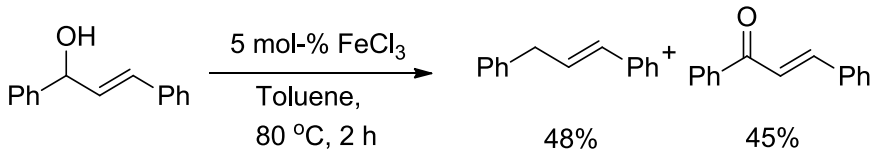
1.3.1 *Synthesis of (±)-(E)-γ-aryl substituted vinylphosphonate*

The intricacy to generate allylphosphonate cations could be circumvented by introducing a carbocation stabilizing group (like allyl, phenyl and methyl) at the adjacent position where the carbocation stabilizes through conjugation/inductive effect. In our initial studies, allylphosphonate **1a** was chosen as it is a very stable crystalline and easily accessible inexpensive material.[34] Moreover, similar kinds of allylic alcohols are widely used as precursors for the synthesis of synthetically and biologically important phosphonates.[35] The $FeCl_3$ mediated reaction of **1a** with anhydrous toluene in nitromethane led to the formation of regioisomeric (ortho/para ~9/1) mixture of **(±)**-(*E*)-*γ*-toluene substituted vinylphosphonate **2a** (**Scheme 1.10)** in ~70% isolated yield at room temperature (rt).



Scheme1.10 $FeCl_3$-mediated reaction of toluene with allylic hydroxyphosphonate **1a**

It is also very interesting to talk about the reported reactions mentioned in **Scheme 1.11** where allylic alcohol undergoes disproportionation reactions to afford corresponding alkene and *α,β*-unsaturated ketone.[36]

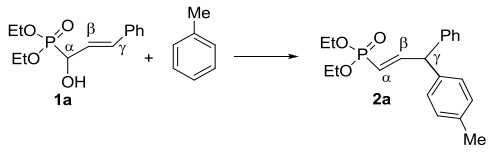


Scheme1.11 Reported $FeCl_3$ catalyzed disproportionation reaction of allylic alcohol

Under the same reaction conditions allylic alcohol **1a** afforded only **2a** with same regioselectivity mentioned in **Scheme1.10**. This demonstrates the different electronic, steric and conjugation effects of phosphonyl group compared to phenyl group and that make the phosphonate chemistry considerably rich.

With the idea of solvent-free approach, the reaction was performed only in anhydrous toluene under the same reaction conditions which afforded **2a** with identical selectivities. We have optimized the reaction conditions (**Table 1.1**) to obtain compound **2a (Scheme1.10)** in good yields. A control experiment (without using any metals) was failed to undergo this reaction.

Table 1.1 Optimization of the solvent-free reaction between toluene and phosphonate **1a.**



Entry	Catalyst (mol %)	T (°C)	Time(h)	Isolated yield of 2a, [%][b] (regioselectivity)[c]
1	$FeCl_3$ (5)	RT	12	<5
		80	6	<5
2	$FeCl_3$ (20)	RT	12	10
		80	6	15
3	$FeCl_3$ (40)	RT	12	20
		80	6	25
4	$FeCl_3$ (80)	RT	12	40
		80	6	60
5	$FeCl_3$ (100)	RT	12	91 (>90:10)
		80	6	91 (>90:10)
6	$FeCl_3.6H_20$ (100)	RT	12	Trace
		80	8	<5
7	$Fe(acac)_3$ (100)	RT	12	0
		80	8	0
8	$FeCl_2.H_2O$ (100)	RT	12	0
9	$ZnCl_2$ (100)	RT	12	Trace
10	$CuCl_2.2H_2O$ (100)	RT	12	0
11	$(CH_3COO)_2Cu.H_20$ (100)	RT	12	0
12	*p*-Toluenesulphonic acid (100)	RT	12	Trace
13	AcOH (100)	RT	12	5
14	$AlCl_3$ (100)	Reflux	8	0

[a] Reaction was performed with **1a** (1.85 mmol) in anhydrous toluene [20 mmol] [b] For all cases except entry 5 and 14, starting material was recovered. [c] regioselectivity ratio was obtained from ^{1}H and ^{31}P NMR.

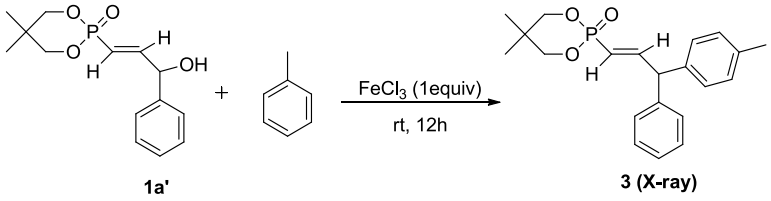
With the consideration of cost and accessibility, screening of several Lewis acids [such as $FeCl_3$, $FeCl_3.6H_2O$, $Fe(acac)_3$, $FeCl_2.H_2O$, $ZnCl_2$, $AlCl_3$, $CuCl_2.2H_2O$, $Cu(OAc)_2.2H_2O$] and Brønsted acids (such as AcOH and *p*-toluenesulphonic acid) were screened, and it was found that $FeCl_3$ is the best for this reaction.

Although Friedel-Craft type reactions of benzylic acetates/alcohols are reported using 10 mol% $FeCl_3$,[37] we needed one equivalent of $FeCl_3$ for the completion of this reaction (**Scheme 1.10**) to facilitate the leaving of the hydroxyl group.[38] Even though the reaction was more favourable (6h at rt) with the use of three equivalent of $FeCl_3$, one equivalent was only used to avoid the formation of more colour impurities and wastes. The reactions were very clean and almost quantitative conversions were observed by NMR (both ^{1}H and ^{31}P) even before purifications (reaction mixtures).

We surmise the fact that the carbocation is initially generated at the α-carbon and then get stabilized at the γ-carbon by conjugation effect. This reaction might be considered as a pseudo-umpolung given the reactivity's of allylic phosphonates. A close and continuous scrutiny of highly resolved ^{1}H and ^{13}C NMR spectra for regioisomeric mixture of **2a** showed the $^{3}J_{P\text{-}H}$ coupling constant (~ 20.0 Hz) for β-H and $^{3}J_{P\text{-}C}$ coupling constant (~21.0 Hz) for γ-C respectively. These data indicate the β-H is at the *cis* and γ-C is at the *trans* to phosphorus for both the regioisomers.[28] The formation of other stereoisomer (*Z*) for **2a** was not observed under the present reaction conditions whereas the Pd catalyzed arylation reactions of optically pure or racemic allylic hydroxy phosphonates with *p*-tolyl tributylstannane[19] and other nucleophiles[30] gave a mixture of *E/Z* isomers. Having the difference of 0.1 ppm in the ^{31}P NMR spectrum for the two regioisomers of **2a** and the comparative studies between the reported ^{31}P NMR data for the related compounds with **2a** suggest that the isomers of **2a** are not the *E/Z* isomers rather regioisomers (*ortho*/*para*).[19,28]

Furthermore, to confirm the stereochemistry for the product **2a**, we also prepared an analogous solid compound **3** by starting with (±)-(*E*)-$(OCH_2CMe_2CH_2O)P(O)CH(OH)CH{=}CHPh$ (**1a'**) in a manner similar to the preparation of **2a**. The X-ray crystallographic (see experimental 1.6 table crystal data) studies for a crystal obtained

from dichloromethane (DCM)/hexane solution of compound **3** showed the (*E*)-configuration (**Fig 1.3**).



Scheme 1.12 $FeCl_3$-mediated reaction of toluene with allylic hydroxyphosphonate **1a'**

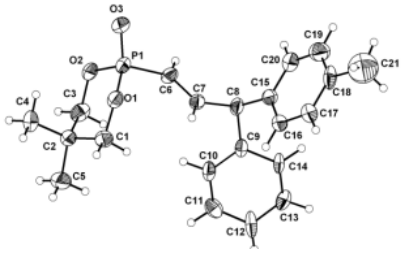
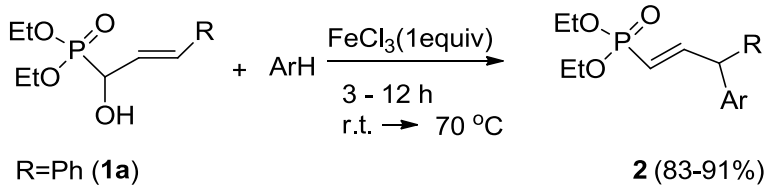


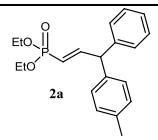
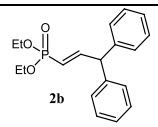
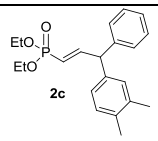
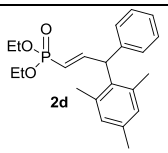
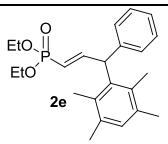
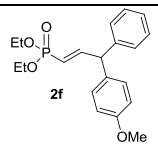
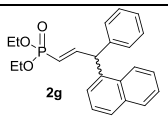
Fig 1.3 Molecular and ORTEP diagram for compound **3**

Next, we studied the reactions with different unactivated arenes that gave the expected products in good yields and regioselectivities (**Table 1.2**). The reactions with toluene and benzene proceeded at room temp., whereas the bulkier arenes like *o*-xylene, mesitylene and durene needed little more temperature (70 ^{o}C). Dry dichloroethane (DCE) was used as a solvent in the case of durene and naphthalene (solid in nature) to form a homogeneous mixture that might assist the formation of products.

Being interested in the use of naphthyl phosphonate systems as a functional materials,[39] our initial attempt to the reaction of naphthalene with the phosphonate **1a** gave both thermodynamically and kinetically controlled products γ-naphthyl substituted vinylphosphonates **2g** in 1:1 regioisomeric ratio (based on 1H NMR) under the present reaction conditions (70 ^{o}C/ 8 h in DCE) although it needs more detail scrutiny.

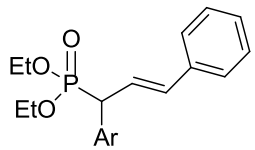
Table 1.2 Synthesis of γ- aryl substituted vinylphosphonates **2a-g** [a]



Entry	Phosphonate/Ar	Main product	Isolated Yield (%) Regioselectivity[b]
1	**1a**/Toluene	 **2a**	91% (~90/10)
2	**1a**/Benzene	 **2b**	90%
3	**1a** */o*-Xylene	 **2c**	84% (~90/10)
4	**1a**/Mesitylene	 **2d**	86%
5	**1a**/Durene[c]	 **2e**	87%
6	**1a**/Anisole[d]	 **2f**	83%
7	**1a**/Naphthalen[c]	 **2g**	84% (50/50)

[a] Reaction conditions: phosphonate (1 mol equiv), $FeCl_3$ (1 mol equiv) and arenes (2.0-20.0 mol equiv) at rt for entry 1, 2 and 6 and for the rest 70 ^oC was used. [b] Regioselectivity ratio (*ortho*/*para*) was obtained by using integrated intensity ratios of the peaks in $^1H/^{31}P$ NMR. [c] DCE was used as solvent. [d] ~7-8 % compound of type **2'** was observed along with this isolated compound.

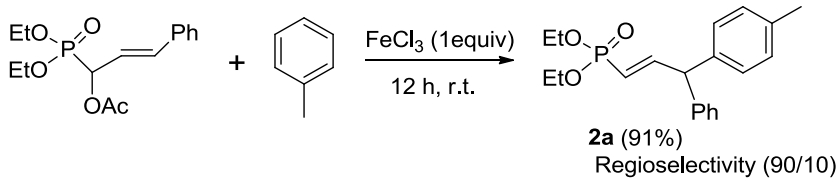
An activated arene, anisole gave the product **2f** as a regioisomeric mixture (~1:2) along with *α*-arylated compound of type **2'**(~7-8%,) at room temp.



2' δ(P)~ 25.0-25.2

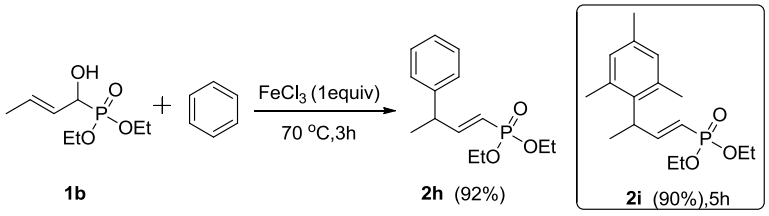
The formation of *α*-arylated compounds of type **2'** was presumably observed with ~5-8% yield. These compounds were not isolated in pure state and partially characterized by multinuclear NMR. For the reaction with toluene, xylene and anisole it showed multiplet at the range of δ = 6.51-6.60 in ^{1}H NMR and at δ = 48.9 (d, *J*=137.8 Hz) in ^{13}C NMR; The peaks at the range of δ = 25.0-25.2 as a singlet in ^{31}P NMR indicate the formation of compound of type **2'**. Further for more substituted compounds (mesitylene and durene) peaks arise at the range of ~ δ 4.55 as a dd,(*J*~32.0 and 6.0 Hz) in ^{1}H NMR and peaks at ~ δ 44.0 (d, *J*~120.0 Hz) in ^{13}C NMR. For ^{31}P NMR, singlet was observed at~ δ 27.0 which again supports our observations.

Also the acetate derivative of compound **1a** reacted smoothly with toluene in the presence of $FeCl_3$ under the present reaction conditions, affording **2a** in similar yield **(Scheme1.13)** and selectivity to that obtained when starting from **1a**.



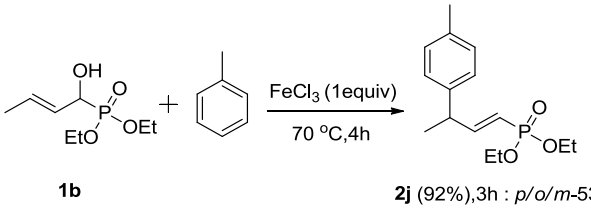
Scheme1.13 $FeCl_3$-mediated reaction of toluene with allylic acetoxyphosphonate

The other inexpensive allylphosphonate **1b** with a methyl group at *γ*-C also underwent the arylation reactions with arenes in the presence of $FeCl_3$ to afford compounds **2h** and **2i** in high yields **(Scheme1.14)**. It is interesting to observe that the only one methyl group stabilizes the cation sufficiently.



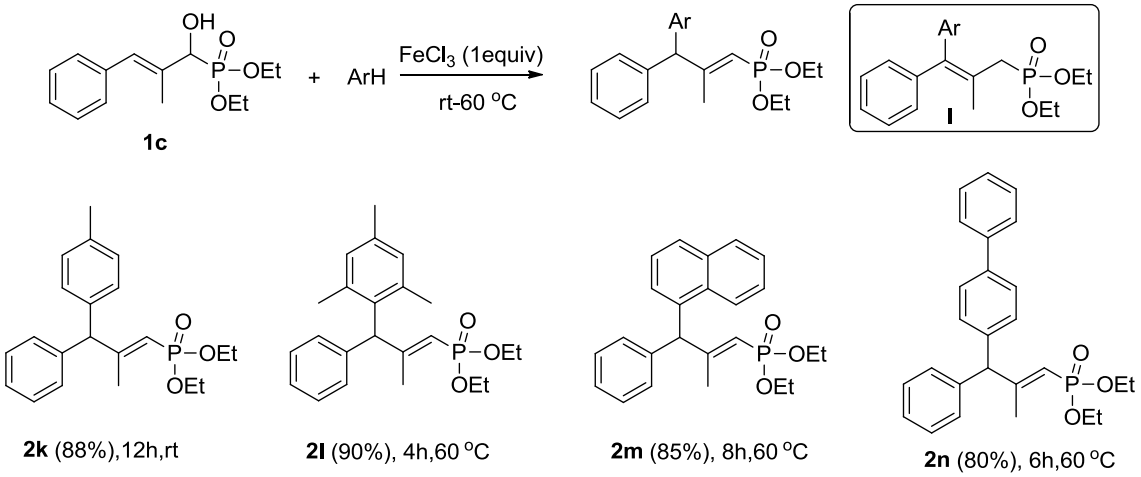
Scheme1.14 $FeCl_3$-mediated synthesis of *γ*- aryl substituted vinylphosphonates(**2h,2i**)

Next, the reaction of **1b** with toluene gave a mixture of three regioisomers (*p/o/m* 53:22:25 as indicated in the ^{31}P NMR spectrum of **2j.**



Scheme1.15 $FeCl_3$-mediated synthesis of *γ*- aryl substituted vinylphosphonates(**2j**)

Subsequently, in a similar manner we could prepare a variety of *γ*-aryl-*β*-methyl substituted vinylphosphonates in good yields by starting with hydroxyphosphonates (**1c**) as shown in **Scheme 1.16**. For the phosphonate **1c**, we also observed the formation of **I** (a higher substituted isomerized olefin) along with the expected product when the reaction was performed for long duration at high temperature. However, the formation of isomerized products needs more detail scrutiny.



Scheme1.16 $FeCl_3$-mediated synthesis of *γ*- aryl *β*-methyl substituted vinylphosphonates

The molecular structures for all these products were confirmed by multinuclear NMR spectroscopy. The *γ*- aryl substituted vinylphosphonates (**2a-n**) showed the characteristic doublet at ~ δ 4.88 (d, *J* ~ 6.3 Hz) due to =CH, and doublet of doublet of doublet at ~ δ 5.57 (ddd, *J* ~ 20.1, 17.1, 6.3 Hz) for P-C(α)*H* in ^{1}H NMR and a doublet at ~δ 119.0 (d, *J* ~ 185.0 Hz) for P-C(α)H appeared in ^{13}C NMR spectra**.** The representative ^{1}H and ^{13}C NMR spectra for compounds **2b** are shown in **Fig 1.4a-b.**

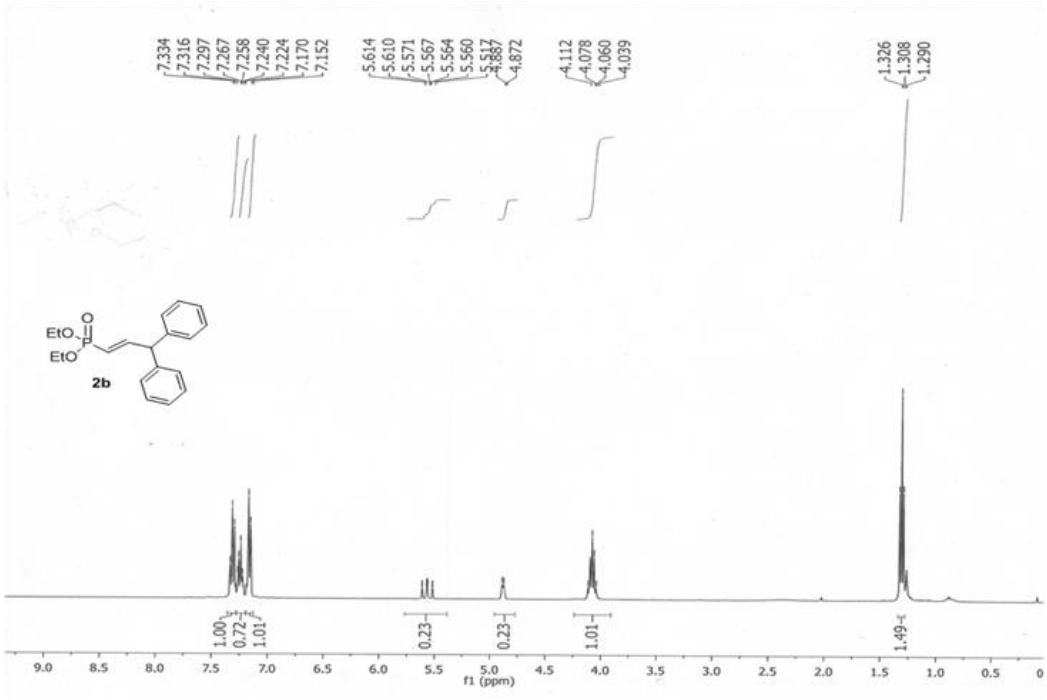


Fig 1.4a ^{1}H NMR spectrum of compound **2b**

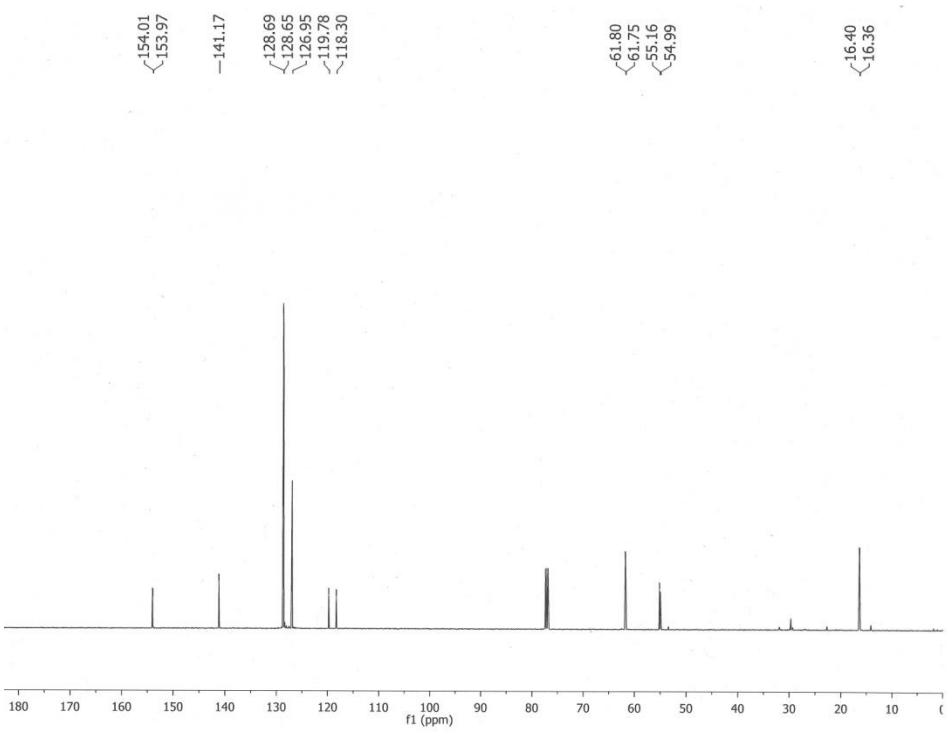


Fig 1.4b ^{13}C NMR spectrum of compound **2b**

1.3.2 *Synthesis of diethyl (diarylmethyl)phosphonates*

Further, we explored the scope of these $FeCl_3$-mediated arylation reactions with phosphonates **4a, 4a′, 4b-e(Fig 1.5)** which afforded diethyl (diarylmethyl)phosphonates **5a-n** in good yield with excellent regioselectivity under the mild conditions. It is observed as expected that the aryl groups for phosphonates should be attached with electron donating substituents which stabilize the carbocations and make a smooth progress for the reactions.

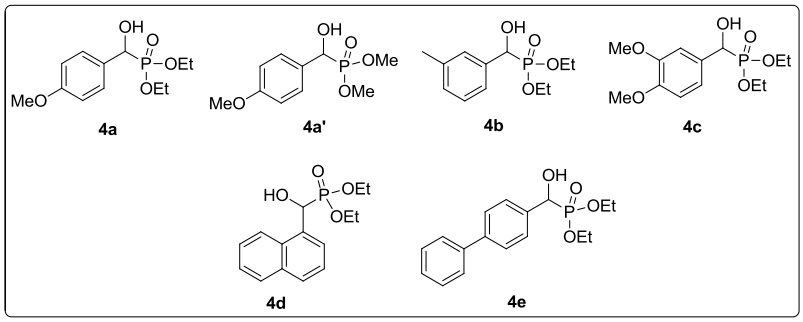
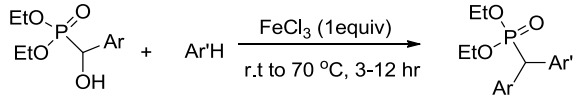


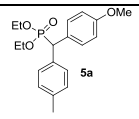
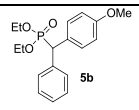
Fig 1.5 Hydroxyphosphonates used as starting materiels

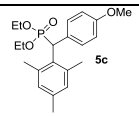
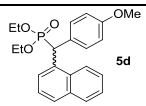
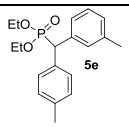
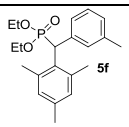
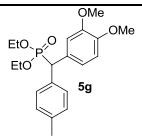
We began with the reactions of hydroxyphosphonates **4a** with different unactivated arenes and the expected products were obtained in good yields and regioselectives. Some arenes like toluene and benzene reacted at room temp whereas the other bulkier arene like mesitylene required higher temparature (70 ^oC) to complete the reaction. The solid arene, napthalene was treated in the presence of dichloroethane as solvent at 70 ^oC to get the expecte product(s) in maximum yield. The reaction of **4b** with toluene gave a mixture of three regioisomers (*probably ortho/para/meta*: 68/23/9) that are dictated in the ^{31}P NMR spectrum of **5e**. The another phosphonate **4c** afforded **5g** as a mixture of regioisomers as anticipated.

Table 1.3 Synthesis of diethyl (diarylmethyl)phosphonates **5a-g.**[a]



4a: Ar= 4-OMe-C_6H_4
4b: Ar= 3-Me-C_6H_4
4c: Ar= 3,4-OMe-C_6H_3

Entry	Ar/Ar‘	Main product	Isolated yield (%) Regioselectivity[b]	
1	**4a**/Toluene		92%	(~97/3)
2	**4a**/Benzene		90%	

3	**4a**/Mesitylene		91%	
4	**4a**/Napthalene[c]		89%	(~75/25)
5	**4b**/Toluene		87%	(~68/23/ 9)
6	**4b**/Mesitylene		82%	
7	**4c**/Toluene		82%	(~93/7)

[a] Reaction conditions: phosphonate (1 mol equiv), $FeCl_3$ (1 mol equiv) and arenes (3.0-20.0 mol equiv) for entry 1, 2, 5 and 7 at rt and for the rest 70 ^oC was required. [b] Regioselectivity ratio was obtained by using integrated intensity ratios of the peaks in $^1H/^{31}P$ NMR. [c] DCE was used as solvent.

All these compounds **5a-g** were very well characetrized by identifying the doublet at the range of δ 4.35-5.02 [*J* ~ 25.0-30.0 Hz, 1H, P- C(*α*)*H*] in ^1H NMR and the appearance of a doublet in the region of δ 44.0–50.0 [*J* ~ 135.0-144.0 Hz, P-*C*(*α*)H] in ^{13}C NMR. The representative ^1H and ^{13}C NMR spectra for compounds **5c** are shown in **Fig 1.6a-b.**

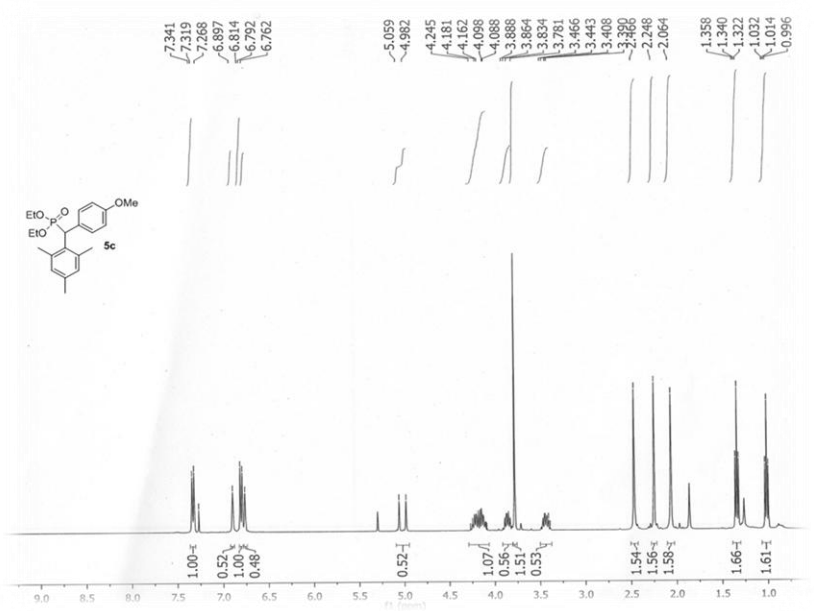


Fig 1.6a ^1H NMR spectrum of compound **5c**

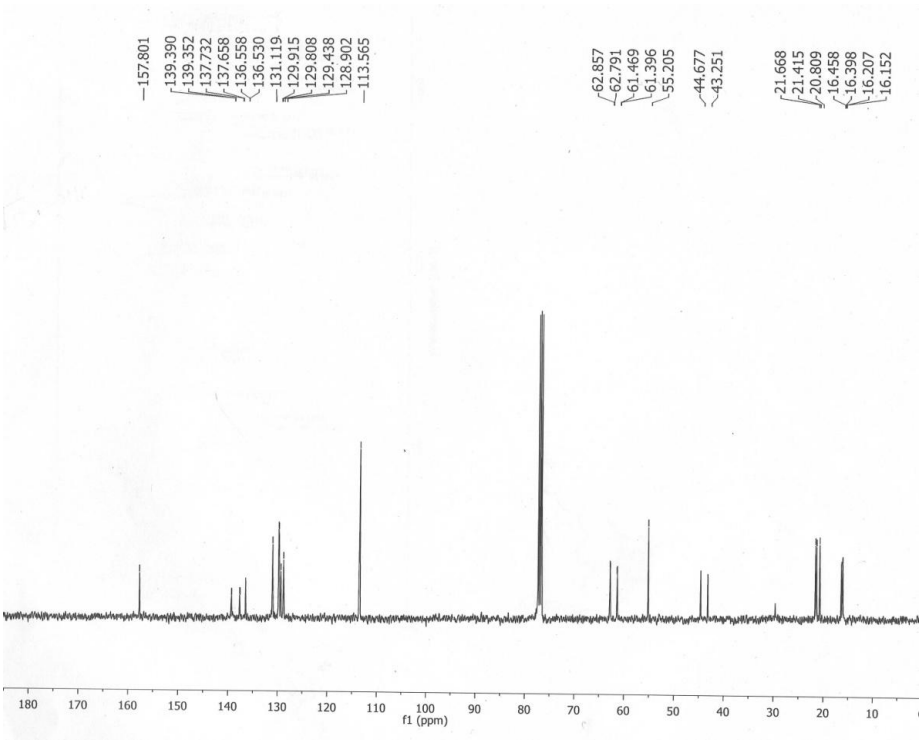
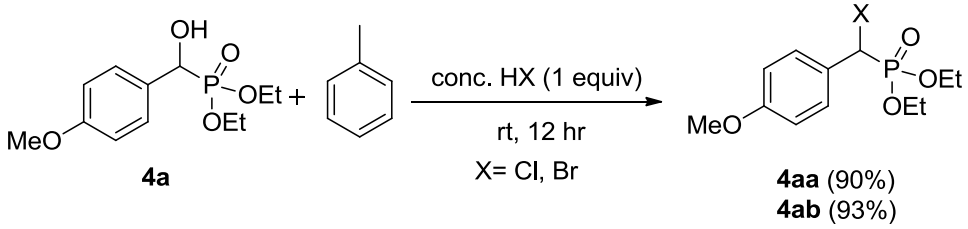


Fig 1.6b ^{13}C NMR spectrum of compound **5c**

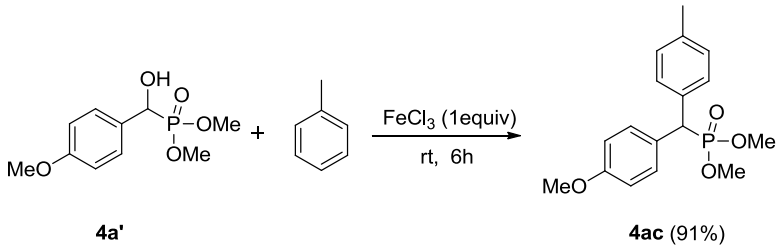
Surprisingly, as a replacement of $FeCl_3$, hydrochloric acid (HCl) produced diethyl (chloro(4-methoxyphenyl)methyl)phosphonate (**4aa**, **Scheme 1.17**) for the reaction of arenes with hydroxyphosphonates (**4a**). With this observation, we investigated the reaction of **4a** with hydrochloric acid (HCl) in the presence of dichloethane as solvent at room temp and the same product **4aa** was obtained almost quantitatively after 12 hr.



Scheme1.17 Synthesis of α-halophosphonates

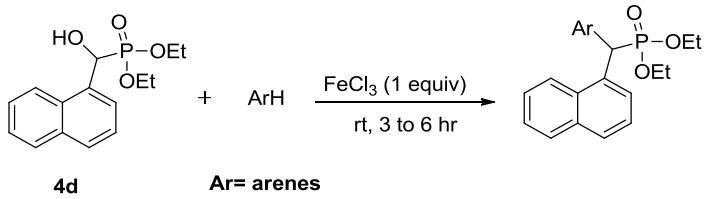
In an analogous manner, we could also generate the compound diethyl (bromo(4-methoxyphenyl)methyl)phosphonate **4ab** by using hydrobromicacid (HBr). It is pertinent to mention that these halogenated phosphonates are very important in organic synthesis [40] and are generally synthesized with the treatment of thionyl halides and phosphorus oxychloride.[41] We can firmly say that the α-halophosphonates can be easily prepared at room temperature by the treatment of HX with those phosphonates.

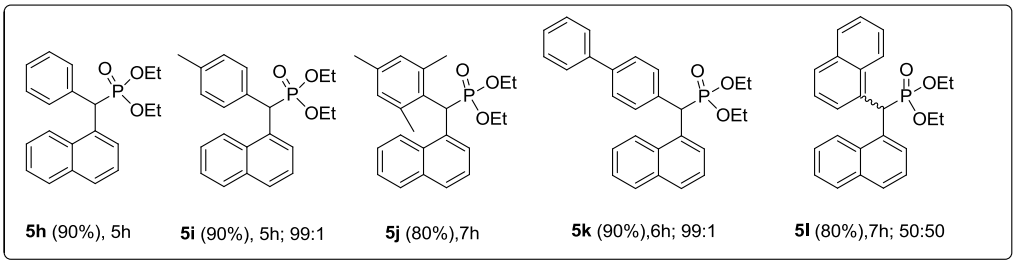
In few cases, it was observed that the replacement of -OEt to -OMe, the type of reactions got changed and led to form different products.[24] Therefore, the overall yields of expected products were very low. Hence, we attempted the arylation reaction with the phosphonate **4a'** using toluene under the above mentioned conditions and compound **4ac** was synthesized successfully in high yield **(Scheme1.18)**.



Scheme1.18 $FeCl_3$-mediated synthesis of diarylphosphonates(**4a'**)

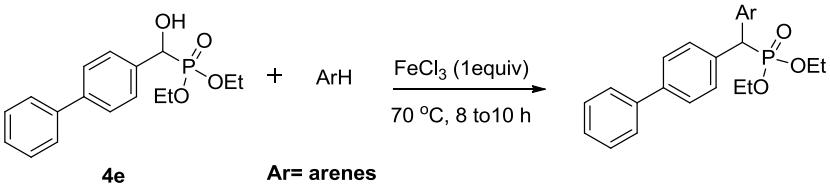
We also could synthesize (1-naphthyl)arylmethylphosphonates with excellent yield and regioselectivity preferably at room temperature by the reactions of unactivated/activated arenes with easily accessible *α*-hydroxyphosphonates (**4d**) in the presence of $FeCl_3$ (**Scheme 1.19**).

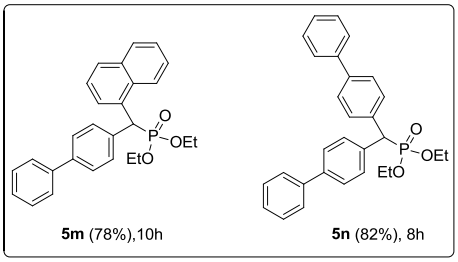




Scheme1.19 $FeCl_3$-mediated synthesis of (1-naphthyl)arylmethylphosphonates

Further, (1-biphenyl)arylmethylphosphonates were synthesized with excellent yield preferably at 70 ^oC by the reactions of unactivated arenes with easily accessible *α*-hydroxyphosphonates(**4e**). Dichloroethane was used as solvent in the case of solid arenes like napthalene and biphenyl **(Scheme1.20**).





Scheme1.20 $FeCl_3$-mediated synthesis of (1-biphenyl)arylmethylphosphonates

1.4 Conclusion

In this work, our initial efforts to develop a $FeCl_3$- mediated stereoselective method for synthesizing γ- aryl substituted vinylphosphonates and diethyl (diarylmethyl)phosphonates by starting with easily accessible α-hydroxy phosphonates and unactivated arenes is successful. We believe that this atom economic**,** (additionally) solvent free and cheap method will open a new entrance for the synthesis of several important phosphonates that could be used as precursors for synthesizing organic functional materials and also the analogues of natural products like turmerone. We could also synthesize the α-halophosphonates at room temperature by the treatment of hydrohaloacids with selected hydroxyphosphonates.

1.5 Experimental Section

All reactions were carried out under a nitrogen atmosphere using schlenk line or nitrogen filled balloons. Solvents were purified by distillation from appropriate drying agents under nitrogen atmosphere. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (100-200 mesh size) was used for the column chromatography. The reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). ^{1}H, ^{13}C, and ^{31}P NMR spectra (^{1}H, 400 or 500 MHz; ^{13}C, 101 or 125 MHz; ^{31}P, 162 or 212 MHz) were recorded using a 400 or 500 MHz spectrometer in $CDCl_3$ with shifts referenced to $SiMe_4$ (δ 0 ppm) or 85% H_3PO_4 (δ 0 ppm). IR spectra were recorded on an FT-IR spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out on a CHN analyzer. Electron impact (EI) and chemical ionization mass spectra were recorded at 70 eV. Some mass spectra were also recorded using LC-MS equipment.

1.5.1 ***General procedure for the synthesis of vinylphosphonates 2a-d***: To a stirred solution of **1a** (0.50 g, 1.85 mmol) in anhydrous toluene [0.51 g (~0.6 mL), 5.55 mmol], anhydrous $FeCl_3$ (0.30

g, 1.85 mmol equiv) was added and then the reaction mixture was stirred at rt for 12 h. After completion of the reaction as indicated by TLC, the reaction was quenched with saturated NH_4Cl Solution. The aqueous layer was extracted with ethyl acetate (3 x 20ml). After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using EtOAc/ pet ether (50/50) as the eluent to afford **2a** as a regioisomeric mixture (~90/10). All the other compounds **2b-i** were prepared analogously using similar molar quantities unless stated otherwise.

1.5.2 *Analytical data of 2a-n and 3*

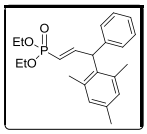
(±)-(*E*)-Diethyl 3-phenyl-3-*p*-tolylprop-1-enylphosphonate (2a): Yield: 0.58 g (91%). viscous liquid. IR (KBr): ν = 1627, 1448, 1247,1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.0 Hz, 6 H), 2.34 (s, 3 H), 4.06-4.13 (m, 4 H), 4.86 (d, *J* = 6.5 Hz, 1 H), 5.58 (ddd, *J* = 19.5, 17.9, 1.6 Hz, 1 H), 7.06-7.07 (m, 2 H), 7.13-7.20 (m, 4 H), 7.22-7.27 (m, 2 H), 7.31-7.34 (m, 2 H) ppm [Corresponding characterization peaks for 10% other regioisomer along with other peaks at δ = 5.45 (ddd, *J* = 19.7, 17.9, 1.8 Hz, 1 H) proves the (*E)*-stereoisomer for both regioisomers]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 6.1 Hz), 21.0, 54.7 (d, *J* = 21.4 Hz), 61.7 (d, *J* = 5.5 Hz), 118.8 (d, *J* = 185.5 Hz), 126.8, 128.5, 128.6, 128.7, 129.3, 136.5, 138.2, 141.4, 154.2 (d, *J* = 5.6 Hz). [Corresponding characterization peak for other 10% regioisomer along with other peaks appear at δ = 51.4 (d, *J* = 21.5 Hz), 119.1 (d, *J* = 185.5 Hz) which support again for the (*E)*-configuration for both regioisomers]. ^{31}P NMR (212 MHz, $CDCl_3$): δ =18.5 (s, ~90%) and 18.6 (s, ~10%) ppm. MS (70ev) m/z 345 $[M+1]^+$. anal. calcd. for $C_{20}H_{25}O_3P$: C 69.75, H 7.32; found: C 69.88, H 7.17.

(±)-(*E*)-Diethyl 3,3-diphenylprop-1-enylphosphonate (2b): Here stirring was continued only for 6 h at rt. Yield: 0.55 g (90%). brownish white solid. mp 48-50 ^oC. IR (KBr): ν= 1597, 1495, 1457, 1248, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 6 H), 4.04-4.11 (m, 4 H), 4.88 (d, *J* = 6.3 Hz, 1 H), 5.57 (ddd, *J* = 20.1, 17.1, 1.4 Hz, 1 H), 7.15-7.22 (m, 4 H), 7.24-7.27 (m, 3 H), 7.29-7.33 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 5.0 Hz), 55.1 (d, *J* = 21.2 Hz), 61.7 (d, *J* = 6.2 Hz), 119.0 (d, *J* = 185.0 Hz), 126.9, 128.6, 128.7, 141.2, 154.0 (d, *J* = 5.0 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.4 (s) ppm. anal. calcd. for $C_{19}H_{23}O_3P$: C 69.08, H 7.02; found: C 69.21; H 6.96.

(±)-(*E*)-Diethyl 3-(3,4-dimethylphenyl)-3-phenylprop-1-enylphosphonate (**2c):** The reaction was performed at 70^oC for 6 h and the product was isolated as a

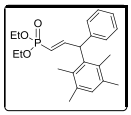
regioisomeric mixture. Yield: 0.56 g (84%). viscous liquid. IR (KBr) cm^{-1}: ν = 1627, 1497, 1448, 1248, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 6.8 Hz, 6 H), 2.23 and 2.22 (2s, 6 H), 4.05-4.12 (m, 4 H), 4.81 (d, *J* = 6.4 Hz, 1 H), 5.57 (ddd, *J* = 20.5, 17.1, 1.6 Hz, 1 H), 6.88-6.93 (m, 2 H), 7.06-7.17 (m, 3 H), 7.22-7.32 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.1 Hz), 19.2, 19.7, 54.6 (d, *J* = 21.2 Hz), 61.6 (d, *J* = 6.1 Hz), 118.8 (d, *J* = 187.8 Hz), 125.9, 126.7, 128.5, 128.5, 129.8, 135.0, 136.7, 138.5, 141.4, 126.8, 128.5, 128.6, 128.7, 129.3, 136.5, 138.2, 141.4, 154.2 (d, *J* = 5.0 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.6 ppm. anal. calcd. for $C_{21}H_{27}O_3P$: C 70.37, H 7.59; found: C 70.18, H 7.65.

(±)-(*E*)-Diethyl 3-mesityl-3-phenylprop-1-enylphosphonate (**2d):** This product was obtained

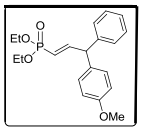


after heating at 70°C for 8 h. Yield: 0.59 g (86%, viscous liquid. IR (KBr): ν = 1623, 1447, 1248, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (m, 6 H), 2.10 (s, 6 H), 2.28 (s, 3 H), 4.06-4.12 (m, 4 H), 5.35 (br, 1 H), 5.53-5.72 (m, not well resolved, 1 H), 6.87 (s, 2 H), 7.11-7.22 (m, 5 H), 7.26-7.29 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.1 Hz), 20.8, 21.4, 48.8 (d, *J* = 21.2 Hz), 61.7 (d, *J* = 6.1 Hz), 118.4 (d, *J* = 187.9 Hz), 126.3, 127.4, 128.5, 130.1, 134.6, 136.5, 137.0, 141.1, 152.6 (d, *J* = 5.0 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.7 ppm. anal. calcd. for $C_{22}H_{29}O_3P$: C 70.95, H 7.85; found: C 70.69, H 7.78.

(±)-(*E*)-Diethyl 3-phenyl-3-(2,3,5,6-tetramethylphenyl)prop-1-enylphosphonate (**2e):** The reaction was performed starting with **1a** (0.50 g, 1.85 mmol) and durene (0.74 g, 5.55 mmol) at



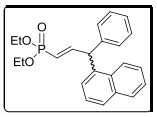
70 °C in anhydrous 1,2- dichloroethane (4 mL) as solvent for 8 h. Yield: 0.62 g, (87%). off-white solid. mp 82-84 °C. IR (KBr): ν = 1623, 1468, 1445, 1237,1021 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (m, 6 H), 2.01 (s, 6 H), 2.23 (s, 6 H), 4.06-4.12 (m, 4 H), 5.48 (br, 1 H), 5.57-5.66 (m, not well resolved, 1 H), 6.95 (s, 1 H), 7.11-7.21 (m, 5 H), 7.26-7.29 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 6.1 Hz), 17.3, 20.8, 48.8 (d, *J* = 22.2 Hz), 61.7 (d, *J* = 5.1 Hz), 118.3 (d, *J* = 188.9 Hz), 126.2, 127.2, 128.5, 130.9, 133.1, 134.6, 137.7, 141.6, 153.6 (d, *J* = 6.1 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.9 ppm. MS (70ev) m/z 387 $[M+1]^{+1}$. anal. calcd. for $C_{23}H_{31}O_3P$: C 71.48, H 8.01; found: C 71.25, H 8.16.



(±)-(*E*)-Diethyl 3-(4-methoxyphenyl)-3-phenylprop-1-enylphosphonate (2f): The reaction was performed at rt for 12 h using anisole (3 equiv); This product was isolated as regioisomeric mixture (~1:2). Yield: 0.55 g (83%,). a viscous liquid. IR

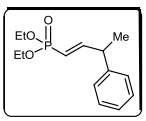
(KBr): ν = 1605, 1511, 1457, 1248, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, d, *J* = 7.2 Hz, 6 H), 3.76 and 3.7 (2s, for both isomer in ~1:2 ratio, 3 H), 4.06-4.09 (m, 4 H), 4.83 and 5.29 (two sets of broad peak, 1 H), 5.53 (m, 1 H), 6.84-7.02 (m, 2 H), 7.05-7.08 (m, 2 H), 7.16-7.38 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.2 Hz), 54.2 (d, *J* = 21.2 Hz), 55.2, 61.8 (d, *J* = 6.2 Hz), 114.1, 118.7 (d, *J* = 186.2 Hz), 126.9, 128.2, 128.6, 128.7, 129.6, 133.2, 141.5, 154.4 (d, *J* = 6.2 Hz), 158.5 ppm. The peaks at δ = 48.0 (d, *J* = 22.5 Hz), 55.4, 61.7 (d, *J* = 5.0 Hz), 110.8, 118.2 (d, *J* = 186.2 Hz), 126.6, 128.4, 128.8, 129.4, 140.9, 154.3 (d, *J* = 6.2 Hz), 156.8 ppm along with other merged peaks appear in the spectrum for the other regioisomers. ^{31}P NMR (162 MHz, $CDCl_3$): δ =18.6 (60%), 19.0 (32%), 25.1 (~8%) ppm. anal. calcd. for $C_{20}H_{25}O_4P$: C 66.66, H 6.99;. found: C 66.78, H 6.89.

(±)-(*E*)-Diethyl 3-(naphthalene-1/2-yl)-3-phenylprop-1-enylphosphonate (**2g)**: The reaction



was performed by starting with **1a** (0.50 g, 1.85 mmol) and naphthalene (0.47 g, 3.70 mmol) at 70 ^oC for 6 h using anhydrous 1,2- dichloroethane (4 mL) as solvent; The product was isolated as a mixture of two regioisomers in~ 1:1 ratio using 70% EtOAc in pet ether. Yield: 0.59 g (84%). as a reddish thick viscous liquid. IR (KBr): ν = 1627, 1599, 1449, 1245, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28-1.35 (m, 6 H), 4.03-4.14 (m, 4 H), 5.05 (d, *J* = 6.3 Hz, 1 H), 5.48 (ddd, *J* = 19.9, 17.2, 1.6 Hz, 1 H), 7.19-7.46 (m, 7 H), 7.48-7.64 (m, 3 H), 7.78-7.96 (m, 3 H) ppm. The peak at δ = 5.59-5.68 (m, not well resolved, peaks appeared due to the other isomer in 1:1 ratio). other peaks due to other isomer are merged. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 6.2 Hz), 50.9 (d, *J* = 21.2 Hz), 61.8 (d, *J* = 5.0 Hz), 119.6 (d, *J* = 185.0 Hz), 123.8, 125.4, 125.7, 126.3, 127.0, 127.1, 127.6, 128.0, 128.7, 128.9, 131.5, 134.1, 136.9, 140.6, 153.8 (d, *J* = 6.2 Hz) ppm. The peaks at δ = 16.4 (d, *J* = 6.25 Hz), 55.1 (d, *J* = 21.2 Hz), 61.8 (d, *J* = 5.0 Hz), 119.4 (d, *J* = 186.2 Hz), 125.9, 126.6, 127.0, 127.1, 127.8, 128.4, 128.8, 128.9, 132.4, 133.4, 138.7, 141.1, 153.8 (d, *J* = 5.0 Hz) ppm. some peaks due to other regioisomers are merged together. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.5 (s) and 18.3 (s) (1:1) ppm. anal. calcd. for $C_{23}H_{25}O_3P$: C 72.62, H 6.62; found: C 72.85, H 6.58.

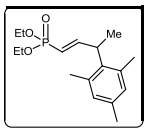
(±)-(*E*)-Diethyl 3-phenylbut-1-enylphosphonate (2h): This compound was synthesized in a



manner similar to compound **2a** by starting with **1b** (0.5 g, 2.40 mmol) and anhydrous benzene (0.42mL, 4.80 mmol) at 70 ^oC for 3h. Yield: 0.59 g, (92%). as a viscous liquid. IR (KBr): ν = 2978, 1627, 1246, 1054, 1028 cm^{-1}. ^1H NMR (400

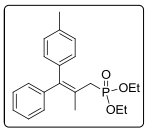
MHz, $CDCl_3$): δ = 1.23-1.29 (m, 6 H), 1.39 (d, *J* = 7.2 Hz, 3 H), 3.55-3.62 (m, 1 H), 4.01-4.07 (m, 4 H), 5.59 (ddd, *J* = 20.0, 17.2, 1.6 Hz, 1 H), 6.85-6.92 (m, 1 H), 6.96-7.30 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.1 Hz), 20.0, 43.6 (d, *J* = 21.2 Hz), 61.7 (d, *J* = 5.5 Hz), 115.6 (d, *J* = 187.8 Hz), 126.7, 127.3, 128.7, 142.9, 156.9 (d, *J* = 4.5 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.1 ppm. anal. calcd. for $C_{14}H_{21}O_3P$: C 62.67, H 7.89; found: C 62.76, H 7.79.

(±)-(*E*)-Diethyl 3-mesitylbut-1-enylphosphonate (2i): This compound was synthesized in a manner similar to compound **2h** at 70 ^{o}C for 5h. Yield: 0.67 g, (90%) as a viscous liquid; IR



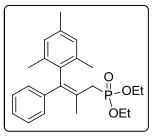
(KBr): ν = 2978, 1625, 1249, 1055, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J*= 7.1 Hz, 6H), 1.42 (d, *J* = 7.2 Hz, 3H), 2.21 (s, 3 H), 2.23 (s, 6H), 4.00-4.08 (m, 4H+ 1H merged), 5.58 (ddd, *J* = 20.0, 17.4, 2.6 Hz, 1H), 6.79 (s, 2H), 6.97-7.08 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 6.3 Hz), 16.9, 20.6, 21.0, 37.9 (d, *J* = 21.2 Hz), 61.5 (d, *J* = 5.4 Hz), 114.9 (d, *J* = 189.1 Hz), 129.9,135.9,136.2, 136.5, 157.5 (d, *J* = 4.7 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.6 ppm. anal. calcd. for $C_{17}H_{27}O_3P$: C 65.79, H 8.77; found: C 65.71, H 8.86.

(±)-(*E*)-Diethyl (2-methyl-3-phenyl-3-(p-tolyl)allyl)phosphonate(2k): The reaction was stirred for 12 h at room temp, Yield: 0.58 g (88%, viscous liquid. IR (KBr): ν = 1674, 1523, 1205, 1084



cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31-1.34 (t, *J* = 7.0 Hz 6H), 2.34 (s, 3H), 4.06-4.13 (m, 4H), 4.86-4.87 (d, *J* = 5.8 Hz 1H),5.53-5.63 (ddd, *J* = 20.4,17.2,1.4 Hz 1H), 7.06-7.16 (m, 2H), 7.17-7.18 (m, 5H), 7.23-7.25 (m, 2H), 7.26-7.34 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 20.1, 33.1 (d, *J* = 139.7 Hz), 61.2, 61.7, 115.81 (d, *J* = 187.3 Hz), 126.4, 128.1, 128.6,129.1, 129.2, 129.3, 129.4, 136.5, 164.1 (d, *J* = 126 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.5 ppm.

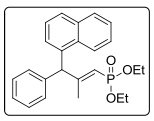
(±)-(*E*)-Diethyl (3-mesityl-2-methyl-3-phenylallyl)phosphonate(2l): This product was obtained after heating at 70^{o}C for 8 h. Yield: 0.65 g (90%, viscous liquid. IR (KBr): ν = 2936,



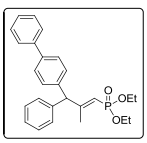
1504, 1275, 1008,974 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28-1.31 (m, 6 H), 1.74 (d, *J* = 22.9 Hz H) 2.15 (s, 3H), 2.2 (s, 3H),2.26 (s, 3H), 3.02 (d, *J* = 22.9 Hz H), 3.6 (d, J = 23.1 Hz H), 4.0-4.06 (m, 4 H), 6.86 (s, 2 H), 7.11-7.31 (m, 5 H), ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 6.3 Hz), 19.9,20.1, 20.8(d, *J* = 1.9 Hz), 32.4 (d, *J* = 137.6 Hz), 34.10 (d, *J* = 138.1 Hz), 61.5 (d, *J* = 6.8 Hz), 126.3, 127.8, 128.4,129.3 (d, *J* =

2.3 Hz), 135.6(d, *J* = 3.3 Hz),, 136.0, 138.5, 138.7,138.9, 140.0,140.3,140.4 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.0 ppm.

(±)-(*E*)-Diethyl (2-methyl-3-(naphthalen-1-yl)-3-phenylprop-1-en-1-yl)phosphonate (2m): This product was obtained after heating at 70^{o}C for 6 h. Yield: 0.62 g (85%, viscous liquid. IR (KBr): ν = 2952, 1452, 1206, 1082,928 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28-1.41 (t, *J* = 5.6 Hz 6H), 2.29-2.31 (m, 3H),3.94-4.07(m, 4H), 5.15 (d, *J* = 14.4 Hz 1H), 5.56 (s, 1H), 7.10 (d, *J* = 5.6 Hz 1H), 7.19 (d, *J* = 5.6 Hz 2H), 7.26-7.27 (m, 1H), 7.31-7.34 (m, 2H),7.38-7.49 (m, 3H), 7.76-7.78 (m, 1H),7.84-7.90 (m, 2H), ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.2,16.3 (d, *J* = 6.3 Hz), 21.4 (d, *J* = 7.06 Hz), 57.6 (d, *J* = 21.9 Hz), 61.2, 61.3 (d, *J* = 5.5 Hz), 116.7 (d, *J* = 187.2 Hz), 123.7, 125.3, 125.6,126.2, 126.9, 127.1, 127.9, 128.7, 128.9, 129.6, 131.9, 134.1, 136.9, 140.3, 163.5 (d, *J* = 7.8 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.5 ppm.



(±)-(*E*)-Diethyl (3-([1,1'-biphenyl]-4-yl)-2-methyl-3-phenylprop-1-en-1-yl)phosphonate (2n): This product was obtained after heating at 70^{o}C for 5 h. Yield: 0.62 g (80%, viscous liquid. IR (KBr): ν = 2974, 1406, 1286, 1038,956 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz 6H), 2.20-2.21 (m, 3H), 4.06-4.11 (m, 4H), 4.90 (s, 1H), 5.29 (d, *J* = 18 Hz 1H), 7.18-7.22 (m, 4H), 7.29-7.37 (m, 4H), 7.44-7.47 (m, 2H), 7.56-7.61 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.1 Hz), 21.0 (d, *J* = 7.2 Hz), 61.2, 61.4 (d, *J* = 5.8 Hz), 116.2 (d, *J* = 187.7 Hz), 126.9, 127.2, 127.3, 128.6, 128.74, 128.76, 129.3, 129.7, 139.77, 139.8, 140.62, 140.64, 163.6 (d, *J* = 7.4 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 18.6 ppm.



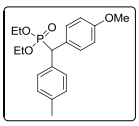
(±)-(*E*)-5,5-Dimethyl-2-(3-phenyl-3-*p*-tolyl-propenyl)-[1,3,2]dioxaphosphinane 2-oxide (3): The reaction was performed in a manner similar to the preparation of compound **2a** by starting with (±)-(*E*)-($OCH_2CMe_2CH_2O$)P(O)CH(OH)CH=CHPh (0.20 g, 0.71 mmol) and $FeCl_3$ (0.115 g, 0.71 mmol) in 2 mL toluene for 6 h at rt. The compound was isolated using chromatography with EtOAc/pet ether (40/60) as a regioisomeric mixture. Yield: 0.22 g (87%). brownish solid. mp: 113-115 ^{o}C. IR (KBr): ν= 1633, 1511, 1468, 1258, 1059 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 and 1.08 (2s, 6 H), 2.33 (s, 3 H), 3.77-3.83 (m, 2 H), 4.18-4.23 (m, 2 H), 4.87 (d, *J* = 8 Hz, 1 H), 5.61 (ddd, *J* = 21.4, 17.2, 1.7 Hz, 1 H), 7.04-7.06 (m, 1 H), 7.12-7.24 (m, 3 H), 7.27-7.34 (m, 6 H) ppm. The peaks at δ = 0.97, 1.00, 2.24, 6.52-6.53 (m) was observed due to the presence of other isomer (~4%). ^{13}C NMR (125

MHz, $CDCl_3$): δ = 21.0, 21.4, 21.7, 32.5 (d, *J* = 5.0 Hz), 54.8 (d, *J* = 21.2 Hz), 75.3 (d, *J* = 6.2 Hz), 116.7 (d, *J* = 186.2 Hz), 126.9, 128.5, 128.6, 128.7, 129.4, 136.7, 137.7, 141.2, 156.4 (d, *J* = 6.2 Hz). ^{31}P NMR (101 MHz, $CDCl_3$): δ = 14.2 (s) ppm. a small peak near δ 21.0 was observed in the spectrum which could be the isomer of type **2'**. anal. calcd.. for $C_{21}H_{25}O_3P$: C 70.77, H 7.07; found: C 70.62, H 7.16. We have crystallized this sample from DCM/ Hexane (2:8). X-ray structural analysis was done for this crystal to confirm the stereochemistry.

1.5.3 ***General procedure for the synthesis of Diethyl (diarylmethyl)phosphonates 5a-d:*** To a stirred solution of **4a** (0.20 g, 0.73 mmol) in anhydrous toluene [0.20 g, (0.23 mL), 2.19 mmol], anhydrous $FeCl_3$ (0.118 g, 0.73 mmol) was added and then the reaction mixture was stirred at rt for 12 h. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated NH_4Cl Solution. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using EtOAc/ pet ether (50/50) as the eluent to afford **5a** as a regioisomeric mixture (~97/3). All the other compounds **5b-d** were prepared analogously using similar molar quantities unless stated otherwise.

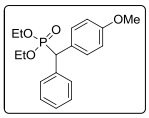
1.5.4 ***Analytical data of 5a-l & 4aa,4ab and 4a'***

(±)-Diethyl (4-methoxyphenyl)(*p*-tolyl)methylphosphonate (5a): Yield: 0.235 g (92%).



viscous liquid. IR (KBr): ν =2925, 1511, 1253, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.1 Hz, 6 H), 2.31 (s, 3 H), 3.77 (s, 3 H), 3.80-3.86 (m, 2 H), 3.93-4.03 (m, 2 H), 4.35 (d, *J* = 25.2 Hz, 1 H), 6.84 (d, *J* ~ 8.0 Hz, 2 H), 6.84 (d, *J* ~ 8.0 Hz, 2 H), 7.38-7.44 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 5.2 Hz), 21.0, 49.9 (d, *J* = 139.1 Hz), 55.2, 62.6 (d, *J* = 6.9 Hz), 113.9, 129.1, 129.2, 130.4, 130.5, 134.1, 136.6, 158.6. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.6 (s) ppm. A tiny peak at δ = 26.3 (~3%) was observed due to regioisomer in ^{31}P NMR; LC/MS m/z 349 $[M+1]^+$. anal. calcd. for $C_{19}H_{25}O_4P$: C 65.51, H 7.23; found: C 65.46, H 7.15.

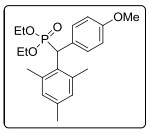
(±)-Diethyl (4-methoxyphenyl)(phenyl)methylphosphonate (5b): The reaction mixture was



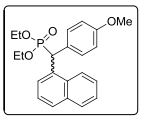
stirred at rt for 6 h. Yield: 0.22 g (90%); off-white solid; mp: 35-38 ^oC; IR (KBr): ν = 2927, 1511, 1254, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11-1.15 (m, 6 H), 3.78 (s, 3 H), 3.80-3.87 (m, 2 H), 3.96-4.02 (m, 2 H), 4.38 (d, *J* = 25.2 Hz, 1 H), 6.85 (d, *J* ~ 8.8 Hz, 2 H), 7.21-7.33 (m, 3 H), 7.45 (d, *J* ~ 8.4Hz, 2 H), 7.51 (d, *J* ~ 7.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3, 50.5 (d, *J* = 137.5 Hz), 55.2, 62.7, 113.9, 127.0,

128.5, 128.9 (d, *J* = 5.0 Hz), 129.3 (d, *J* = 8.7 Hz), 130.5 (d, *J* = 7.5 Hz), 137.2 (d, *J* = 3.7 Hz), 158.7 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.4 (s) ppm. anal. calcd. for $C_{18}H_{23}O_4P$: C 64.66, H 6.93. found: C 64.76, H 6.85.

(±)-Diethyl mesityl(4-methoxyphenyl)methylphosphonate (5c): The reaction mixture was stirred at 70^{o}C for 8 h. Yield: 0.25 g (91%). off-white solid. mp: 94-96 ^{o}C. IR (KBr): ν = 2917, 1509, 1256, 1015 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 2.06, 2.25, 2.47 (3s, each for 3 H), 3.39-3.78 (m, 1 H), 3.78 (s, 3 H), 3.83-3.88 (m, 1 H), 4.09-4.24 (m, 2 H), 5.02 (d, *J* = 30.8 Hz, 1 H), 6.76 (s, 1 H), 6.80 (d, *J* ~ 8.8 Hz, 2 H), 6.89 (s, 1 H), 7.33 (d, *J* ~ 8.8 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 5.6 Hz), 16.4 (d, *J* = 6.1 Hz), 20.8, 21.4, 21.7, 43.9 (d, *J* = 144.0 Hz), 55.2, 61.4 (d, *J* = 7.4 Hz), 62.8 (d, *J* = 6.7 Hz), 113.6, 128.9, 129.4, 129.8, 129.9, 131.1, 136.5 (d, *J* = 2.8 Hz), 137.7 (d, *J* = 7.4 Hz), 139.3 (d, *J* = 3.8 Hz), 157.8 ppm. a peak at δ =29.7 is also observed in the spectrum. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.5 (s) ppm. anal. calcd. for $C_{21}H_{29}O_4P$: C 67.01, H 7.77; found: C 67.12, H 7.63.

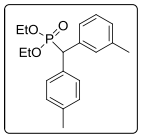


(±)-Diethyl (4-methoxyphenyl)(naphthalen-1-yl)methylphosphonate (5d): This reaction was performed by starting with **4a** (0.20 g, 0.73 mmol) and naphthalene (0.187g, 1.46 mmol) in anhydrous 1,2-dichloroethane (4 mL) at 70 ^{0}C for 6 h. The product was isolated using column chromatography as regioisomeric mixture in ~1:3 ratio using 70 % EtOAc in pet ether. Yield: 0.25 g (89%). red thick viscous liquid. IR (KBr): ν= 2980, 1607, 1510, 1252, 1027 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04-1.15 (m, 6 H), 3.74 (s, 3 H), 3.81-4.06 (m, 4 H, peaks due to other isomer are merged), 5.28 (d, *J* = 25.0 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.44-7.55 (m, 4 H; peaks due to other isomer are merged), 7.78- 7.86 (m, 3 H), 8.09 (d, *J* = 6.7 Hz, 1 H), 8.28 (d, *J* = 6.7 Hz, 1 H), The peaks at δ = 1.16-1.21 (m, 6 H), 3.78 (s, 3 H), 4.59 (d, *J* = 25.0 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.65 (d, *J* = 6.7 Hz, 1 H), 8.04 (br, 1 H) ppm along with other merged peaks appear in the spectrum for the other regioisomer in 1:3 ratio. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.2 Hz), , 45.0 (d, *J* = 143.7 Hz), 55.2, 62.6 (d, *J* = 6.2 Hz), 113.9 (d, *J* ~ 2.5 Hz), 123.1, 125.5, 126.4, 127.4 (d, *J* = 6.2 Hz), 127.9, 128.0, 128.2, 128.6 (d, *J* = 5.0 Hz), 129.0, 130.7 (d, *J* = 6.2 Hz), 131.7 (d, *J* = 12.5 Hz), 134.2, 158.7 (d, *J* = 2.5 Hz) ppm. Other Peaks at δ = 16.4 (d, *J* = 6.2 Hz), 50.4 (d, *J* = 142.5 Hz), 55.2, 62.7 (d, *J* = 6.2 Hz), 113.0 (d, *J* ~ 1.3 Hz), 125.4, 125.9, 126.1, 127.6 (d, *J* ~ 6.2 Hz), 128.0, 128.1, 128.8 (d, *J* = 5.0 Hz), 130.6 (d, *J* = 6.2 Hz), 132.4 (d, *J* = 2.5 Hz), 132.9 (d, *J*



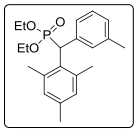
= 2.5 Hz), 133.4 (d, *J* = 1.2 Hz), 134.8 (d, *J* = 5.0 Hz), 158.7 (d, *J* = 1.2 Hz) ppm was appeared for other isomer. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.1 (s) and 25.3 (s) ppm appeared for other isomer in 1:3 ratio. anal. calcd. for $C_{22}H_{25}O_4P$: C 68.74, H 6.56;. found: C 68.85, H 6.49.

(±)-Diethyl *m*-tolyl(*p*-tolyl)methylphosphonate (5e): This compound was prepared in a manner similar to compound **5a** by starting with **4b** (0.100 g, 0.387 mmol) and anhydrous $FeCl_3$ (0.062 g, 0.387 mmol) in anhydrous toluene (0.5 mL, ~12 mmol) to afford **5e** as a regioisomeric mixture (~68/23/9). Yield: 0.112 g (87%). as a viscous liquid. IR (KBr): ν= 2924, 1605, 1248, 1022 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08-1.16 (m, 6 H), 2.31 and 2.32 (2s, 6 H), 3.78-3.88 (m, 2 H), 3.93-4.03 (m, 2 H), 4.35 (d, *J* = 25.2 Hz, 1 H), 7.03-7.21 (m, 4 H), 7.29-7.42 (m, 4 H) ppm. The peak at δ = 2.34 (s), 4.64 (d, *J* = 25.6 Hz) and 7.93 (d, *J* = 8 Hz) ppm along with other merged peaks appear in the spectrum for the other regioisomers. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (many lines), 20.1, 21.0, 21.5, 50.8 (d, *J* = 136.2 Hz), 62.7 (many lines), 126.4 (d, *J* = 7.5 Hz), 127.8 (d, *J* = 2.5 Hz, along with other merged peaks), 128.4, 129.2, 130.1 (d, *J* = 7.5 Hz), 130.6 (d, *J* = 8.7 Hz), 133.9 (d, *J* = 3.7 Hz), 136.7 (d, *J* = 2.5 Hz), 136.9 (d, *J* = 5.0 Hz), 138.1 (d, *J* = 1.2 Hz) ppm. Other Peaks at δ = 46.6 (d, *J* = 137.5 Hz), 51.0 (d, *J* = 137.5 Hz), 126.2 (d, *J* = 1.5 Hz), 126.5 (d, *J* = 6.2 Hz), 126.9 (d, *J* = 7.5 Hz), 127.1 (d, *J* = 2.5 Hz), 128.3 (d, *J* = 1.2 Hz), 129.3, 129.5 (d, *J* = 5.0 Hz), 130.2 (d, *J* = 7.5 Hz), 130.4 (d, *J* = 7.5 Hz), 135.3 (d, *J* = 5.0 Hz), 136.2 (d, *J* = 6.2 Hz), 136.3, 136.4, 136.8 (d, *J* = 5.0 Hz), 137.9 (d, *J* = 1.2 Hz) ppm were appeared for other isomers. ^{31}P NMR (212 MHz, $CDCl_3$): δ = 25.4 (s);The peak at δ = 25.3 (9%) and 26.1 (~23%) appears in the spectrum for the other regioisomers. anal. calcd. for $C_{19}H_{25}O_3P$: C 68.66, H 7.58; found: C 68.45, H 7.71.

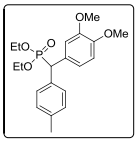
(±)-Diethyl mesityl(*m*-tolyl)methylphosphonate (5f): The reaction mixture was stirred at 80^{o}C



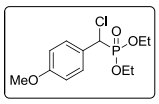
for 8 h by using **4b** (0.80 g, 3.10 mmol) and anhydrous $FeCl_3$ (0.50 g, 3.10 mmol), in anhydrous mesitylene (2 mL). The product was isolated in pure form from column chromatography using EtOAc / pet ether (70/30). Yield: 0.92 g (82%). white crystalline solid. mp: 86-90 ^{o}C. IR (KBr): 1606, 1448, 1246, 1021 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 6.8 Hz, 3H), 1.34 (t, *J* = 6.8 Hz, 3H), 2.07, 2.26, 2.29 (3s, each for 3H), 2.48 (s, 3H), 3.41-3.45 (m, 1H), 3.84-3.86 (m, 1H), 4.09-4.26 (m, 2H), 5.03 (d, *J* = 30.8 Hz, 1H), 6.77 (s, 1H), 6.91 (s, 1H), 7.01 (d, *J* ~ 7.6 Hz, 1H), 7.4-7.19 (m, 2H), 7.25 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 5.0 Hz), 16.4 (d, *J* = 6.2 Hz), 20.8, 21.4, 21.5, 21.7, 44.7 (d, *J* = 141.2 Hz), 61.4 (d, *J* = 7.5 Hz), 62.8 (d, *J* = 6.3 Hz), 125.9 (d, *J* = 11.2 Hz), 126.9, 128.0,

128.9, 129.4 (d, *J* = 11.2 Hz), 131.0 (d, *J* = 6.2 Hz), 131.1 (d, *J* = 2.5 Hz), 136.5 (d, *J* = 3.7 Hz), 137.4, 137.7, 137.8 (d, *J* = 6.2 Hz), 139.4 (d, *J* = 3.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.3 (s) ppm. anal. calcd. for $C_{21}H_{29}O_3P$: C 69.98, H 8.11; found: C 70.12; H 8.02.

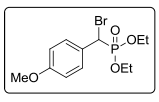
(±)-Diethyl (3,4-dimethoxyphenyl)(*p*-tolyl)methylphosphonate (5g): This compound was prepared in a manner similar to the preparation of **5a** by using **4c** (0.1 g, 0.329 mmol), and anhydrous $FeCl_3$ (0.053 g, 0.329 mmol) in anhydrous toluene (1 mL) at rt for 12 h. The crude product was purified by column chromatography using EtOAc / pet ether (80/20) as the eluent to afford **5g** as a regioisomeric mixture (~93/7). Yield: 0.102 g (82%). viscous liquid. IR (KBr): ν= 1599, 1510, 1256, 1015 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 6H), 2.30 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.91-4.02 (m, 4H), 4.33 (d, *J* = 25.2 Hz, 1H), 6.80 (d, *J* ~ 9.2 Hz, 1H), 7.04 (d, *J* ~ 8.8 Hz, 1H), 7.11 (s, 1H), 7.12 (d, *J* ~ 8.0 Hz, 2H), 7.40 (d, *J* ~ 7.6 Hz, 2H) ppm. Peaks at δ = 2.34 (s), 4.62 (d, *J* = 26.4 Hz) ppm were observed for other regioisomer (~7%). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3, 21.0, 50.2 (d, *J* = 139.1 Hz), 55.8 (2s), 62.6 (d, *J* = 6.9 Hz), 111.1, 112.6 (d, *J* = 7.8 Hz), 121.6, (d, *J* = 8.7 Hz), 129.1, 129.2, 129.3, 133.9, 136.7, 148.0, 148.7 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.5 (s) and 26.2 ppm were observed in ~93:7 ratio. LC/MS: m/z 379 $[M + 1]^+$. anal. calcd. for $C_{20}H_{27}O_5P$: C 63.48, H 7.19; found: C 63.36, H 7.28.



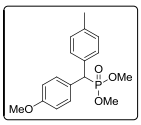
(±)-Diethyl (chloro(4-methoxyphenyl)methyl)phosphonate(4aa): Yield: 0.48 g (90%). viscous liquid. IR (KBr): ν =2874, 1469, 1224, 986cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 5.6 Hz, 3H), 3.62 (s, 3H), 3.7-3.75 (m, 1H), 3.824-3.852 (m, 1H), 4.03-4.07 (m, 2H), 4.76 (d, *J* ~ 13.5 Hz, 1H), 6.73 (d, *J* ~ 8.5 Hz, 2H), 7.32 (d, *J* ~ 9.0 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.1, 16.3 (d, *J* = 6.1 Hz), 52.6-53.9 (d, *J* = 42.5 Hz), 55.1, 63.6-63.8(d, J= 6.1 Hz), 113.9 (d, J=1.6 Hz), 126.1(d, J=3.3 Hz), 130.2 (d, J=6.4 Hz),, 160.1(d, J= 2.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 17.27 (s) ppm.



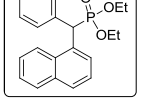
(±)-Diethyl (bromo(4-methoxyphenyl)methyl)phosphonate(4ab): Yield: 0.57 g (93%). viscous liquid. IR (KBr): ν =2975, 1584, 1241, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 6.8 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 3.79 (s, 3H), 3.82-3.89 (m, 1H), 4.01-4.07 (m, 1H), 4.19-4.24 (m, 2H), 4.86 (d, *J* = 12.7 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.49 (dd, *J* ~ 8.7 Hz,1.7 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.3, 16.4 (d, *J* = 6.1 Hz), 41.5 (d, *J* = 160 Hz), 55.3, 63.9, 64.1(d, J= 6.1 Hz), 114.1(d, J=1.1 Hz), 126.5(d, J=3.1 Hz), 130.8 (d, J=7.1 Hz),, 160.1(d, J= 2.2 Hz).



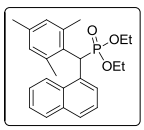
(±)-Dimethyl ((4-methoxyphenyl)(p-tolyl)methyl)phosphonate(4a'): The reaction was stirred for 12 h at room temp, Yield: 0.59 g (91%). viscous liquid. IR (KBr): ν =2934, 1628, 1457,1260, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.3 (s, 3 H), 3.59 (d, *J* = 10.8 Hz, 3 H),3.8 (s, 3 H), 4.41 (d, *J* = 25.3 Hz, 1 H), 6.87 (d, *J* ~ 8.5 Hz, 2 H), 7.15 (d, *J* ~ 7.9 Hz, 2 H), 7.40-7.46 (m, 4 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.9 49.5 (d, *J* = 138.7 Hz), 53.3 (d, *J* = 7.1 Hz), 55.2, 114.0, 128.8(d, J=5.3 Hz), 129.2, 129.3, 130.4, 130.7, 133.8(d, J=4.8 Hz), 136.8(d, J=1.8 Hz), 158.7(d, J=1.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.9 (s) ppm. A tiny peak at δ = 28.5 (~3%) was observed due to regioisomer in ^{31}P NMR;



(±)-Diethyl (naphthalen-1-yl(phenyl)methyl)phosphonate (5h). Colourless liquid (0.54 g, 90%); IR (KBr): ν = 3080, 2981, 1596, 1247, 1025, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 8.0 Hz, 3H), 1.18 (t, *J* = 8.0 Hz, 3H), 3.81-4.05 (m, 4H), 5.34 (d, *J* = 24.0 Hz, 1H), 7.20-7.33 (m, 3H), 7.44-7.62 (m, 5H), 7.80 and 7.87 (d, *J* = 8.0 Hz each, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.30-8.34 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.2 and 16.3 (d, *J* = 6.1 Hz each), 45.9 (d, *J* = 140.4 Hz), 62.7 and 62.8 (d, *J*= 6.1 Hz each), 123.1, 125.4, 125.5, 126.4, 127.1 (d, *J*= 2.0 Hz), 127.6 (d, *J*= 6.1Hz), 128.0, 128.5 (d, *J*= 7.1Hz), 129.0, 129.7 (d, *J*= 7.1 Hz), 131.7 (d, *J*= 12.1 Hz), 132.6 (d, *J*= 3.0 Hz), 134.2, 136.6 ppm (d, *J*= 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.7 ppm; LC/MS: m/z 355 $[M+H]^+$.



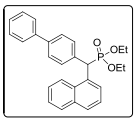
(±)-Diethyl (naphthalen-1-yl(*p*-tolyl)methyl)phosphonate (5i). This compound was isolated as a mixture of regioisomers (*o*/*p* 1:99). Colourless liquid (0.562 g. 90%); IR (KBr): ν = 2979, 1509, 1395, 1244, 1051, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* ~ 7.0 Hz, 3H), 1.20 (t, *J*= 8.0 Hz, 3H), 2.30 (s, 3H), 3.80-4.07 (m, 4H), 5.30 (d, *J* = 28.0 Hz, 1H), 7.12 (d, *J*= 8.0 Hz, 2H), 7.44-7.57 (m, 5H), 7.79 and 7.87 (d, *J*~8.0 Hz each, 2H), 8.11 (d, *J*= 8.0 Hz, 1H), 8.28 ppm (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.2 and 16.3 (d, *J* = 6.1 Hz each), 21.0, 45.5 (d, *J* = 140.4 Hz), 62.7 (d, *J*= 7.1 Hz), 123.1, 125.4 (d, *J*= 1.0 Hz), 125.5, 126.5, 127.5 (d, *J*= 6.1 Hz), 127.9, 129.0, 129.23, 129.5 (d, *J*= 8.1 Hz), 131.7 (d, *J*= 12.1 Hz), 132.8 (d, *J*= 3.0 Hz), 133.5 (d, *J*= 7.1 Hz), 134.3, 136.7 ppm (d, *J*= 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.9 ppm; LC/MS: m/z 369 $[M+H]^+$**.**



(±)-Diethyl (mesityl(naphthalen-1-yl)methyl)phosphonate (5j). White solid (0.572 g, 85%); m.p. 122 -124 ^{o}C; IR (KBr): ν = 3058, 2981, 1600, 1472, 1237, 1027, 962 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, *J*= 8.0 Hz, 3H), 1.33 (t, *J*= 8.0 Hz, 3H), 2.03 (s, 3H), 2.24 (s, 3H), 2.82 (s, 3H), 3.52-3.60 (m, 1H), 3.95-4.00 (m, 1H), 4.17-4.29

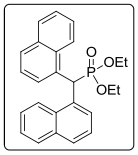
(m, 2H), 5.48 (d, *J*= 28.0 Hz, 1H), 6.66 (s, 1H), 7.02 (s, 1H), 7.28-7.40 (m, 2H), 7.52-7.60 (m, 2H), 7.80-7.82 (m, 2H), 8.58 ppm (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 and 16.4 (d, *J*= 6.0 Hz each), 20.8, 21.9, 22.2, 44.0 (d, *J*= 141.4 Hz), 61.8 (d, *J*= 7.1 Hz), 63.1 (d, *J*= 7.1 Hz), 123.7, 124.9, 125.2, 125.9, 127.8, 128.9, 129.4 (d, *J*= 6.7 Hz), 129.8, 130.2 (d, *J*= 6.7 Hz), 131.7, 132.5 (d, *J*= 15.5 Hz), 133.19, 134.0 (d, *J*= 2.22 Hz), 136.5 ppm (d, *J*= 5.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.0 ppm; LC/MS: m/z 397 $[M+H]^+$.

(±)-Diethyl [1,1'-biphenyl]-4-yl(naphthalene-1-yl)methyl)phosphonate (5k). This compound was synthesized as a regioisomeric mixture (99:1) in a fashion analogous to **3j**. Colourless solid



(0.585 g, 80%); m.p. 118-120 ^{o}C; IR (KBr): ν = 3042, 2986, 1590, 1232, 1025, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J*= 7.1 Hz, 3H), 3.85-4.19 (m, 4H), 5.46 (d, *J*= 26.5 Hz, 1H), 7.32-7.64 (m, 10H), 7.74 (d, *J* =8.0 Hz, 2H), 7.86 and 7.89 (d, *J*= 8.0 Hz each, 2H), 8.20 (d, *J*= 8.0 Hz, 1H), 8.42 ppm (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 and 16.5 (d, *J*= 6.1 Hz each), 45.6 (d, *J*= 140.4 Hz), 62.8 (d, *J*= 7.1 Hz), 62.9 (d, *J*= 8.1 Hz), 123.2, 125.6 (d, *J*= 13.1 Hz), 126.5, 127.0, 127.3 (d, *J*= 2.02 Hz), 127.3, 127.6 (d, *J*= 6.1 Hz), 128.2 (d, *J*= 1.0 Hz), 128.8, 129.2, 130.2 (d, *J*= 7.1 Hz), 131.7, 131.9, 132.7 (d, *J*= 2.02 Hz), 134.3, 135.8 (d, *J*= 6.1 Hz), 139.9 (d, *J*= 3.03 Hz), 140.6 ppm (d, *J*= 1.01 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.8 ppm; LC/MS: m/z 431 $[M+H]^+$.

(±)-Diethyl di(naphthalyl)methyl)phosphonate (5l). This compound was synthesized in a



manner analogous to **3j**. This compound was isolated as a mixture of regioisomers (~1:1). Colourless solid (0.549 g, 80%); IR (KBr): ν = 3058, 2982, 1590,1394, 1242, 1041, 961, 781 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03-1.21 (m, 12H), 3.71-3.81 (m, 2H), 3.87-4.12 (m, 6H), 5.59 (d, *J*= 28.0 Hz, 1H), 6.24 (d, *J*= 28.0 Hz, 1H), 7.43-7.54 (m, 10H), 7.60 7.64 (m, 1H), 7.75-7.88 (m. 10H), 8.18-8.26 (m, 4H), 8.31 (d, *J*= 8.0 Hz, 2H), 8.46 ppm (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.2 and 16.3 (d, *J*~ 6.0 Hz each), 16.4 and 16.5 (d, *J*~ 6.0 Hz each), 41.0 (d, *J* = 142.4 Hz), 46.1 (d, *J*= 137.4 Hz), 62.7 and 62.8 (d, *J*~ 6.0 Hz each), 62.8 and 62.9 (d, *J*~ 6.0 Hz each), 123.2, 123.3, 125.5 (d, *J*= 2.3 Hz), 125.59, 125.63, 125.9 (d, *J*= 0.6 Hz), 126.1 (d, *J*= 0.6 Hz), 126.5, 126.6, 127.6 (d, *J*= 1.2 Hz), 127.8 (d, *J*= 6.8 Hz), 127.9 (d, *J*= 6.4 Hz), 128.05, 128.07, 128.18 (d, *J*= 1.5 Hz), 128.2 (d, *J*= 1.3 Hz), 128.5 (d, *J*= 6.5 Hz), 128.7 (d, *J*= 8.1 Hz), 129.1, 129.2, 131.8 (d, *J*= 9.8 Hz), 131.9 (d, *J*= 11.5 Hz), 132.5 (d, *J*= 1.9 Hz), 132.7 (d, *J*= 3.2 Hz), 133.1 (d, *J*= 4.3 Hz), 133.4 (d,

J= 1.9 Hz), 134.1, 134.27, 134.29, 134.4 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.7 and 26.2 ppm (1:1); LC/MS: m/z 405 $[M+H]^+$.

1.6 Crystal data for compound (3)

Complex	**Compound (3)**
Chemical formula	$C_{21}H_{25}O_3P$
Formula weight	355.37
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	5.9093(10)
b (Å)	12.387(3)
c (Å)	26.617(6)
α (°)	90
β (°)	93.686(17)
γ (°)	90
V (Å^3)	1944.3(7)
Z	4
ρ (g cm^{-3})	1.214
μ (mm^{-1})	0.157
Reflections collected	7058
Reflections unique	3299
Reflections [$I \geq 2\sigma(I)$]	974
Parameters	226
*R*1, *wR*2 [$I \geq 2\sigma(I)$]	0.0861, 0.1731
*R*1, *wR*2 [all data]	0.2777, 0.2578
GOF on F^2	0.954
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.522 / −0.207

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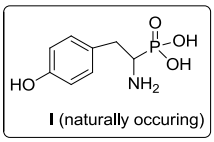
Chapter 2

Synthesis of sulfonamidephosphonates

2.1 Introduction

Naturally occurring amino acids play key role in the chemistry of life and also are identified as structural units in peptides, proteins, and enzymes. For a long time, the so-called "phosphorus analogues" of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, -$P(O)(OH)_2$, or phosphinic acid group, -P(O)(OH)R (in which R may be H, alkyl, or aryl) including phosphonates [e.g. C-$P(O)(OR)_2$, in which R may be alkyl, or aryl], have attracted particular interest in the preparation of isosteric or bioisosteric analogues of numerous natural products.



I (naturally occuring)

The α-aminophosphonic acid (for an example **I**, a naturally occurring amino phosphonic acid) as isostere of α-amino acid occupies an important place and reveals diverse biological[1] and biochemical[2] properties. These are recognized as antibacterial agents,[3] enzyme inhibitors,[4] haptens for catalytic antibodies,[5] and anti HIV agents.[6] In general, phosphonic acids with heteroatom's in the α-positions have attracted much attention recently for their involvement as inhibitor of renin,[7] HIV protease[8] and also in the field of agricultural sciences.[9] Many natural and synthetic α-aminophosphonic acids, α-amino phosphonates, and phosphonopeptides are also known to exhibit potential applications as anti-HIV,[6] antibacterial,[3] antibiotic,[10] anticancer,[11] antitumor,[12] and antiviral agents.[13] Furthermore, in agro chemistry a number of α-aminophosphonic acids and their derivatives are used as fungicidal[14] and herbicidal agents.[15] The biological activities of α-aminophosphonic acids or derivative depend on the absolute configuration of the stereogenic centre α to the phosphorus atom.[16,17] Therefore, the potential of aminophosphonates as synthetic intermediates and bio-active agents has prompted considerable research in recent years.

On the other hand, sulfonamide is an important class of pharmaceutical compounds that exhibit a wide spectrum of biological activities. The sulfa drugs have a veritable history of application for the treatment of bacterial infection. Over 30 drugs containing this functionality are in clinical use including antibacterial,[18] anticancer,[19] anti-inflammatory,[20] antiviral agent,[21] hypoglycaemic,[22] and HIV protease inhibitors.[23] Some of these drugs have also proved to be useful as herbicides[24] and plaguicides.[25] Arylsulfonyl substituent's have been used as protecting groups for oxygen and nitrogen functionalities.[26] Sulfonamide derivatives of azo dyes have been reported to improve light stability and fiber fixation.[27] Sulfonylation is a significant reaction in the synthesis of naturally occurring bioactive molecules and also for the protection of amines.

In particular, *N*-alkylsulfonamides display a large range of biological activities.[28] Recent examples include secreted frizzled related protein-1 (sFRP-1) inhibitors (**A**),[29] potent thromboxane receptor antagonists (**B**),[30] inhibitors of mycobacterium tuberculosis (**C**), [31] potential antitrypanosomal agents (**D**) (**Fig 2.1**).[32]

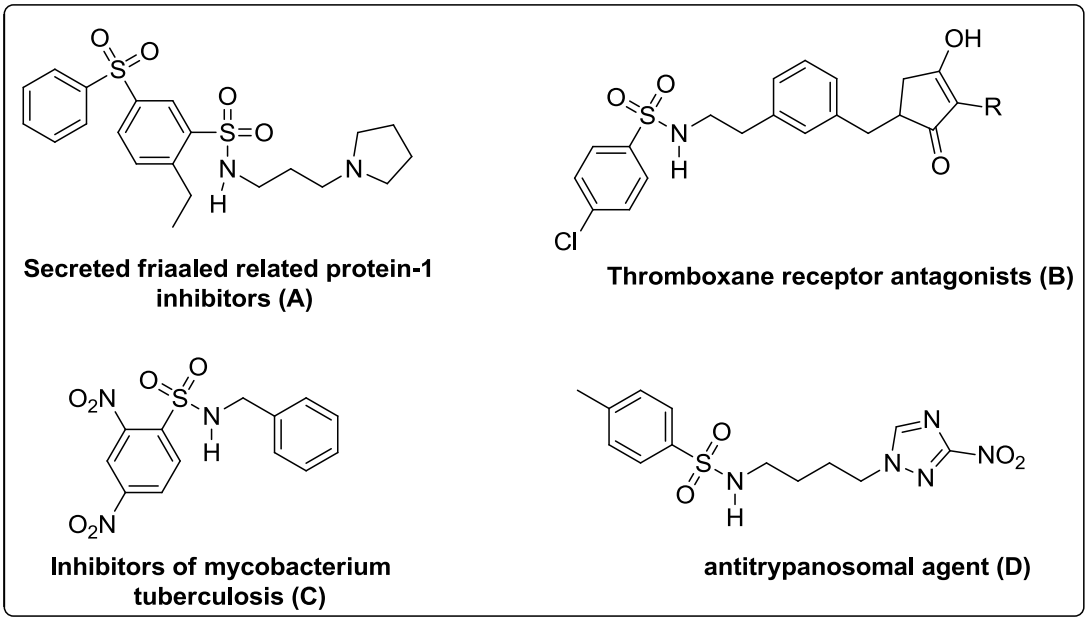


Fig 2.1 Biologically active *N*-alkylsulfonamides

With this platform on phosphonic acids/phosphonates and sulphonamides, we focus on the sulfonamide phosphonates that form a class of distinct organophosphorus compounds where medicinally renowned sulfonamide bears the phosphonate unit.[33] These compounds are utilized as potential candidates for fluorescent β-lactamase (**E**),[34] and matrix metalloproteinase (MMPs) inhibitors (**F**) as an analogue of known MMP inhibitors like carboxylate and hydroxamate.[35] In addition, these compounds are also well recognized as a flame retardant materials[36] along with its binding properties with selected lanthanides and actinides. Moreover, sulfonamide phosphonate is *N*-protected α- or γ-aminophosphonate, one of the most-desired structural motifs in bioorganic and medicinal chemistry due to its unique biological properties.[37,38] The related desulfonations are also well explored in the literature. [39] Thus, synthesis of protected[40] or deprotected[41] aminophosphonates has been pursued by several research groups. In this thesis, we will discuss the synthetic studies on various new sulphonamide phosphonates and also few well-known sulphonamides.

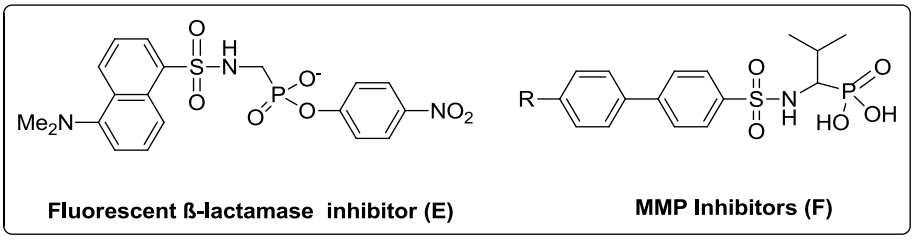
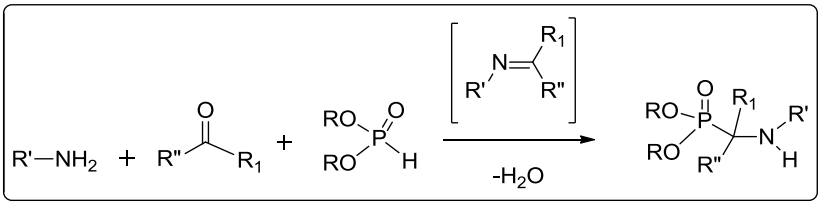


Fig 2.2 Known bioactive sulfonamidephosphonates

2.2 Literature Review

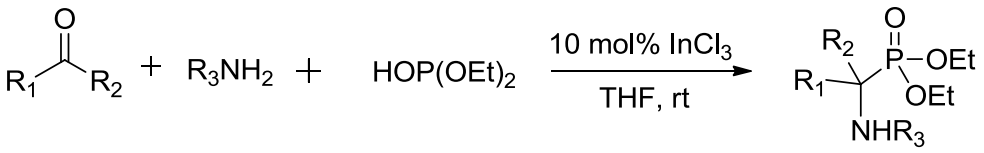
Due to numerous important applications of organophosphorus compounds, a detailed survey of literature has been made. Considerable interest has been focused on the synthesis of *α*-substituted phosphonic acid being structural analogous of naturally occurring *α*- amino acid in biological systems. Among the *α*-functionalised phosphonic acid, *α*- amino phosphonic acid derivatives are gaining interest in medicinal chemistry.[1,2] Therefore it is not surprising that research on their synthesis has received special attention. A variety of synthetic approaches were reported. However, Kabachnik–Fields reaction **(Scheme2.1)** is one of the well-known method where the formation of imines takes place from the reactions of aldehydes and amines and then subsequent nucleophilic addition of phosphites with imines produces desired *α*-amino phosphonates in the presence of Lewis acid[42] or a base.[43] A variety of catalysts that include $In(OTf)_3$,[44] $InCl_3$,[45] $Al(H_2PO_4)_3$,[46] $LiClO_4$,[47] $Mg(ClO_4)_2$,[48] $ZrOCl_2 \cdot 8H_2O$,[49] $SnCl_2$,[50] $BiCl_3$,[51] TiO_2,[52] ZnO,[53] NBS,[54] PPh_3[55] have been reported to promote this transformation.



Scheme 2.1 Kabachnik–Fields reaction

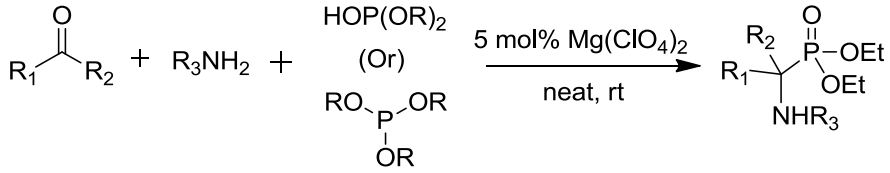
2.2.1 *Synthesis of α-amino phosphonates*

Jana *et al.*[45] developed an efficient and general method for the synthesis of *α*-amino phosphonates through one pot reaction of aldehydes or ketones and diethyl phosphite with amines in the presence of indium(III) chloride as a catalyst (**Scheme 2.2)**.



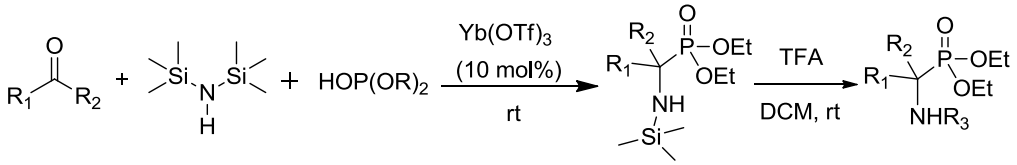
Scheme 2.2 Indium (III) chloride catalyzed synthesis of *α*-amino phosphonates

A one pot, three-component reaction of an amine, an aldehyde or a ketone, and a di-/trialkyl phosphite was performed by Chakraborti *et al.*[48] under solvent-free conditions to afford the corresponding α-aminophosphonates in high yields and short reaction times using magnesium perchlorate as a catalyst **(Scheme 2.3)**.



Scheme 2.3 Magnesium perchlorate catalyzed synthesis of α-amino phosphonates

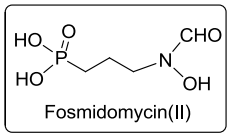
Jang *et al.*[56] synthesized *N*-silylated α-aminophosphonates and α-aminophosphonates from the reaction of aldehydes/ketones, hexamethyldisilazane, and diethylphosphite in the presence of ytterbium (III) triflate as a catalyst at rt under mild condition **(Scheme 2.4).**



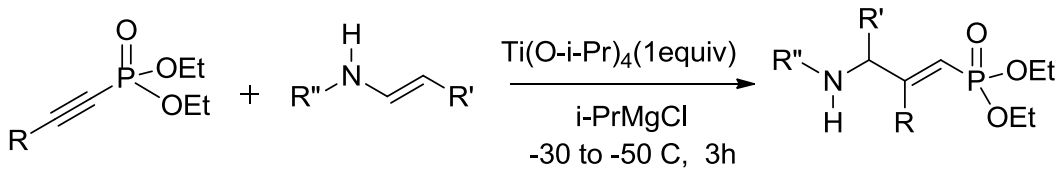
Scheme 2.4 Ytterbium (III) triflate catalyzed synthesis of α-amino phosphonates

2.2.2 *Synthesis of γ-amino phosphonates*

Although α- and β-aminophosphonates are well described in the literature, their γ-aminophosphonate homologues did not receive sufficient attention despite their structural resemblance to γ-amino butyric acid (GABA) and glutamates, which is responsible for their important therapeutic potential as GABA and glutamate receptor agonists and antagonists. Besides, one of the most promising γ-aminophosphonate derivatives, fosmidomycin (**II**), which is isolated from streptomyces lavendulae showed strong antimalarial activity.

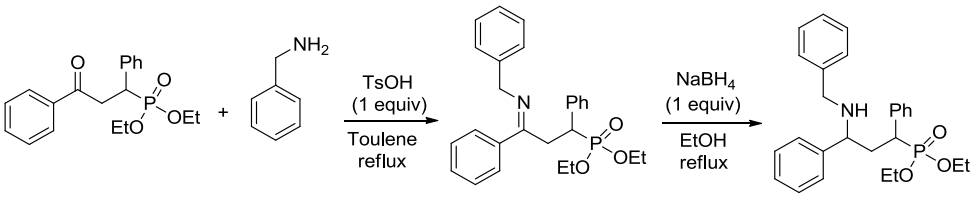


Srebnik *et al.*[57] described a new synthetic route for the preparation of 3-amino-1-alkenylphosphonates by the addition of excess imines to the alkynylphosphonate in the presence of Ti(II) complexes at very low temperature with high yields (**Scheme 2.5)**.



Scheme 2.5 Ti (II) complexes mediated synthesis of γ-amino phosphonates

An efficient methodology for the synthesis of *γ*-aminophosphonates was reported by Wahbi *et al*.[58] *via* reductive amination of *γ*-phosphonylketones, which use inexpensive and environmentally friendly sodium borohydride as reducing agent, in ethanol as solvent **(Scheme 2.6)**.

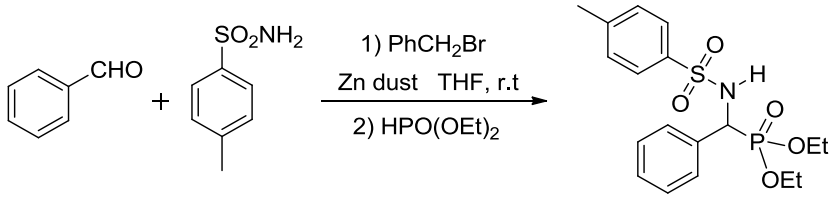


Scheme2.6 Synthesis of *γ*-amino phosphonates by reductive amination of *γ*-phosphonylketones

2.2.3 *Synthesis of α-sulfonamide phosphonates*

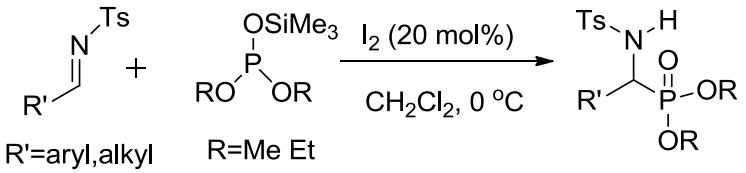
The direct addition of imines with phosphites, preferably in the presence of metal salt, is the most common approach for synthesizing *α*-aminophosphonates but synthesizing *N*-sulfonylimines require a special treatment due to the weak nucleophilicity of sulphonamides. Therefore, the attempts for the synthesis of specific *α*-sulfonamide phosphonates are sporadically mentioned in the literature, but *γ*-sulfonamide vinylphosphonates described herein are completely new. Most of these synthetic methods need the freshly prepared imines (because of their instability) and the metal salts (to activate the imines). Some related reports are discussed hrein.

Wang *et al.*[59] synthesised *N*-sulfonylimines by the condensation of aldehydes with sulfonyl amides in the presence of benzyl bromide and zinc dust at rt under Barbier-type conditions. The potential of this reaction system can be evaluated by its adaptability to a wide variety of aldehydes and the mild reaction conditions, followed by nucleophile addition of diethylphosphite to the sulfonylimines to get a sulfonamide phosphonate in good yields **(Scheme 2.7)**.



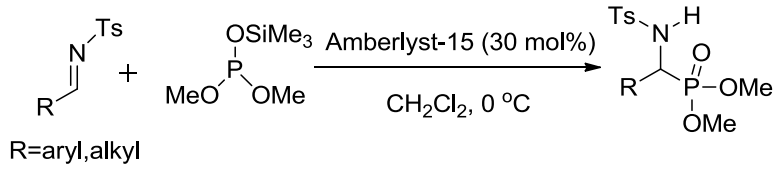
Scheme 2.7 Benzyl bromide and zinc dust mediated synthesis of *α*-Sulfonamidephosphonates

Das *et al.*[60] developed a facile method for the synthesis sulfonamide phosphonates from *N*-tosylaldemines and dialkyltrimethylsilylphosphites with iodine as a catalyst at 0 ^{o}C in excellent yields within 1.5 to 2.5 h **(Scheme 2.8)**.



Scheme 2.8 Iodine catalyzed synthesis of α-Sulfonamidephosphonates

Another route for the synthesis of sulfonamide phosphonates was reported by Rao *et al.* [61] from *N*-tosylaldimines and dimethyl/trimethylsilylphosphite in the presence of Amberl yst-15 as a heterogeneous catalyst. Operational simplicity, mild reaction conditions, reusability of the catalyst, and excellent yields are the notable advantages of this method **(Scheme 2.9).**



Scheme 2.9 Amberlyst-15 catalyzed synthesis of α-Sulfonamidephosphonates.

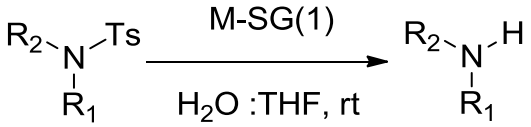
Most of the above synthetic methods need the freshly prepared imines (because of their instability) and the metal salts (to activate the imines). Recently reported I_2[60] and amberlyst-15[61] catalyzed method explored the synthesis of sulfonamide phosphonates by reacting only *N*-tosylaldimines (*freshly prepared*) with expensive and *moisture sensitive* dialkyl trimethylsilylphosphites at 0°C under *inert atmosphere* (**Scheme 2.8 & 2.9**). It is again noteworthy that the syntheses of *N*-sulfonylimines prefer the induction of $TiCl_4$, $Si(OEt)_4$, BF_3 etc. or multistep transformation along with the special apparatuses.[59]

2.2.4 *Desulfonation of secondary amines*

As sulphonamide phosphonates or sulphonamides can serve as an origin of amines, we would like to highlight some significant literature reports based on the desulfonation of secondary amines. Existing methods for sulfonamide cleavage fall into broad categories as follows: (a) strong acid treatment,[62] sometimes accelerated with microwaves,[63] (b) cleavage by strong bases or nucleophiles,[64] (c) photo reduction with various reagents,[65] (d) electrochemical reduction,[66] and (f) metal-based reductive cleavages,[67] acidic deprotections of tosylated amines use severe conditions such as H_2SO_4, 48% HBr, AcOH-$HClO_4$.[68]

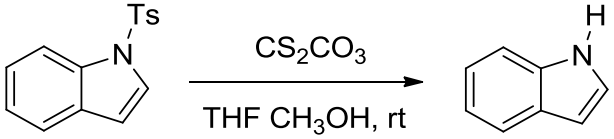
Jackson *et al.*[69] developed a novel method for the desulfonation of secondary amines. Absorbed alkali metals into nanostructured silica (M-SG) were found to be useful solid-state reagents for the desulfonation of a range of *N*,*N*-disubstituted sulfonamides. M-SG materials (Na or Na-K alloys absorbed in silica gel) can act as efficient reagents for removing sulfonyl

protecting groups from primary and secondary amines. These M-SG reagents offer simple alternatives to the other alkali-metal based reagents such as Na-NH_3 or Na-arenides, often used for sulfonamide deprotections **(Scheme 2.10).**



Scheme 2.10 M-SG mediated desulfonation of secondary amines

Blocklock *et al.*[70] performed a very mild and efficient convenient method for detosylation of a wide range of indoles, azaindoles, and imidazoles using cesium carbonate in THF–MeOH as solvents system at room temperature with good yields **(Scheme 2.11).**

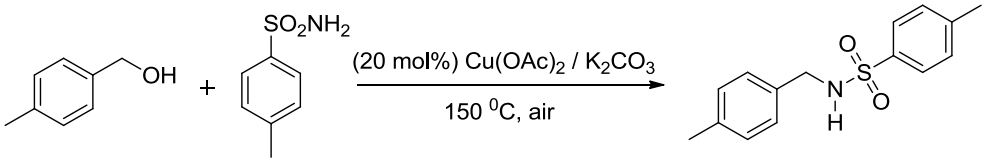


Scheme 2.11 Base mediated detosylation

2.2.5 *Alkylation of sulfonamides with alcohols*

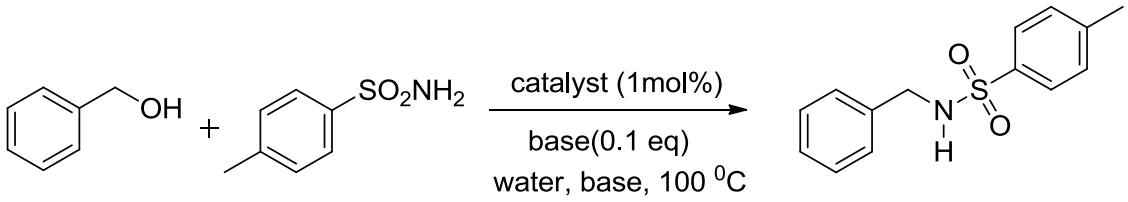
Alkyl amines are important functional groups in organic chemistry and the development of synthetic routes for these compounds is a challenging area of organic synthesis. In this context, *N*-alkylation reactions of sulfonamides have attracted significant attention due to the wide-spread applications of sulfonamide moiety as discussed before. In addition, sulfonamides have also been used as protecting groups, which can be readily removed. Thus, *N*-alkylated sulfonamides can be easily converted to yield primary or secondary alkyl amines. The traditional method for the synthesis of *N*-alkylsulfonamides involves the reaction of sulfonyl halides with *N*-alkylated amines. However, sulfonyl halides are highly toxic reagents, and are not suitable for long-term storage.

An efficient *N*-alkylation of sulfonamides with alcohols was reported by Deng *et al.*[71] in the presence of easily available copper catalysts *via* hydrogen borrowing methodology. The reaction of sulfonamides and alcohols produced the corresponding secondary amines in excellent yield by applying a copper acetate/potassium carbonate system **(Scheme 2.12).**



Scheme 2.12 Copper mediated *N*-alkylation of sulfonamides with alcohols

Feng Lia *et al.*[72] developed water-soluble iridium catalyst for the efficient *N*-alkylation of the poor nucleophilic sulfonamides with benzylic alcohols using water as a solvent **(Scheme 2.13).** Catalyst: {Cp*Ir-[6,6'-$(OH)_2$bpy] H_2O)} $[OTf]_2$ (Cp*=η^5-pentamethylcyclopentadienyl,bpy=2,2'-bipyridine)



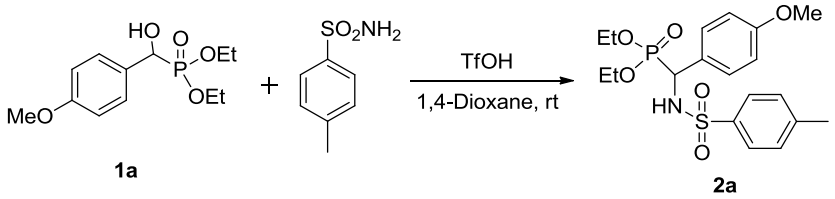
Scheme 2.13 Iridium catalyzed *N*-alkylation of sulfonamides with alcohols

2.3 Results and Discussion

Any simple synthetic method that avoids the common practice of using relatively unsafe and unstable imines, metals and also to perform in open air only at room temperature with water as a by-product would be attractive for medicinal/organic chemists. A synthetic method performed at room temperature is always beneficial as far as energy consumption is concerned. Hence, with our previous result in the umpolung reactivity of allyllic phosphonates, we have originated an operationally simple, new and efficient TfOH-mediated route to synthesize *α*-aryl/methylsulfonamidomethylphosphonates and more distinctively *γ*-*aryl/methylsulfonamidomethylvinylphosphonates* in moderate to high yield using cheap and easily accessible *α*-hydroxyphosphonates under mild conditions.

2.3.1 *Synthesis of (±)-α-aryl/methylsulfonamidomethylphosphonates*

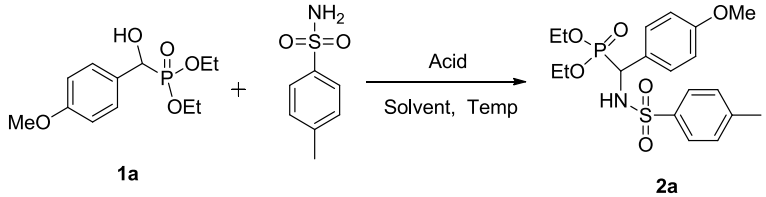
Initially, we preferred phosphonate (±)**-1a** and *p*-toluenesulfonamide ($TsNH_2$) as model substrates to optimize the suitable reaction conditions using different Lewis and Brønsted acids. The reported method of using $FeCl_3$ for this type of transformation could not offer a satisfactory result even under reflux in nitromethane.[73] With a possibility of hydrolyzing the alkoxy bonds of phosphonates, we tried the same reaction with TfOH, known to show comparative effect as $FeCl_3$ in allylic amination reactions starting from allylic/benzylic alcohols.[74] Both $FeCl_3$ and TfOH worked very well as a catalyst for the reaction of benzylic/allylic alcohols with $TsNH_2$ whereas sulfonamide phosphonate (±)-**2a** was isolated effectively from the reaction of hydroxyphosphonate (±)-**1a** with $TsNH_2$ only in the presence of TfOH **(Scheme 2.14)**.



Scheme 2.14 TfOH-mediated synthesis of α-Sulfonamidephosphonates (**2a**)

This different effect was observed probably due to the presence of phosphoryl group for (±)-**1a**. Moreover, TfOH and its salts are extensively used for amination reactions of alcohols.[75] Considering the generation of TfOH in the reaction medium using triflate salt, efforts of treating $Yb(OTf)_3$ and $Cu(OTf)_2$ in place of TfOH were in vain. Screening with different stoichiometry (mol%) of TfOH showed that this reaction was mostly favoured with 60-100 mol% and it might be due to the presence of strong co-ordinating group like phosphonate for (±)-**1a**. The only known direct approach from hydroxyphosphonates to only aminophosphonates with moderate yield was reported in the presence of acidic alumina using a kitchen-type microwave oven.[76] Using the same approach, we could isolate the product (±)-**2a** with only 25% yield whereas the γ–sulfonamide phosphonate was not formed even after 30 min by starting with phosphonate (±)-(*E*)-**4a (Table 2.1)**. Inspired by the report of Chan and co-workers on I_2 catalyzed allylic alkylation of sulfonamides,[77] our attempt to use I_2 for the synthesis of sulfonamide phosphonate failed under present reaction conditions. There was no difference in the outcome even when the reaction was performed using LR grade 1,4-dioxane without exclusion of air/moisture at room temperature. Thus, TfOH/1,4-dioxane at room temperature appears to be the most suitable condition for synthesis of sulfonamide phosphonates even in a vessel open to air.

Table 2.1 Screening of reaction conditions using commonly used Brønsted/Lewis acids.[a]



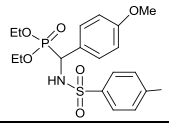
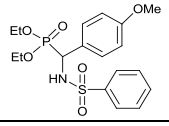
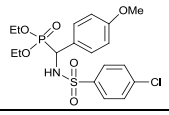
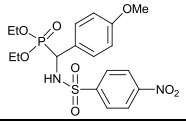
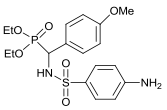
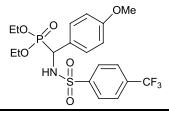
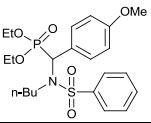
Entry	Bronsted/Lewis Acid (1 equiv)	Solvent/Time (h)/Temp	Isolated yield 2a [b]
1	TfOH	1,4-Dioxane/ 5/rt	94

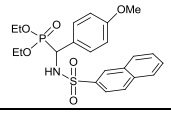
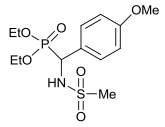
2	TfOH	Acetonitrile/10/rt	25
3	TfOH	Dimthylformamide/12/rt	0
4	AcOH	1,4-Dioxane/ 12/rt	0
5	TFA	1,4-Dioxane/ 12/rt	0
6	TsOH	1,4-Dioxane/ 12/rt	0
7	$FeCl_3$	1,4-Dioxane/ 12/rt	0
8	$FeCl_3$	DCE/60 ^oC	30
9	$FeCl_3$	Nitromethane/10/rt	0
10	$FeCl_3$	Nitromethane/10/reflux	0[c]
11	$Yb(OTf)_3$	1,4-Dioxane/12/rt	0
12	$Cu(OTf)_2$	1,4-Dioxane/12/rt	0
13	$ZnCl_2$	1,4-Dioxane/10/rt	0
14	$CuCl_2. 2H_2O$	1,4-Dioxane/10/rt	0
15	$FeCl_3. 6H_2O$	1,4-Dioxane/12/rt	0
16	$Fe(acac)_3$	1,4-Dioxane/12/rt	0
17	Acidic Al_2O_3	Neat/3 min [d]	25
18	I_2	I_2/10/reflux	0
19	$I_2/CaSO_4$	Dichloromethane/24/rt	30

[a] Reaction conditions: **1a** (1.824 mmol) and $TsNH_2$ (1.824 mmol) in dry 1,4-dioxane (4 ml) under nitrogen. [b] Except entry 1, 10 and 17 starting material was only observed. [c] no spot due to **2a** was found although starting material phosphonate was consumed. [d] under kitchen type microwave oven as reported.

As the variations of substituents for sulfonamides reflect the activity of sulfonamide phosphonates, we have explored this reaction using different types of sulfonamides. The examples are shown in **Table 2.2**. The yield and duration of the reaction did not differ much when the substituent (electron donating/accepting) is changed in aryl groups for arylsulfonamides. The methanesulfonamide also worked very well to yield (±)**-2i** effectively. The yield was also good (**Table 2.2**, entry 7) when comparatively more electron rich *N*-butylsulfonamide was used.

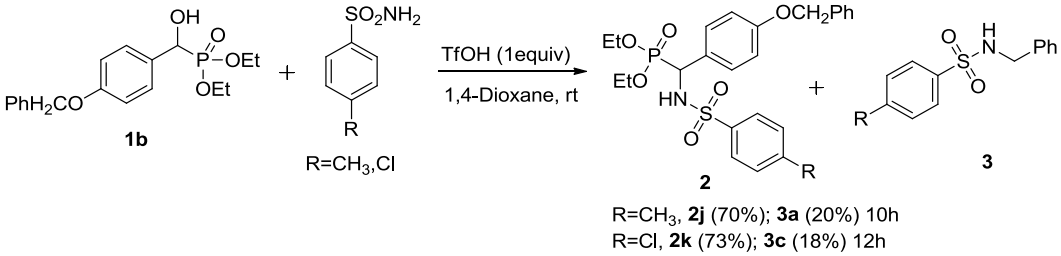
Table 2.2 TfOH mediated reactions of sulfonamides with α-hydroxyphosphonates (±)**-1a-c**[a]

Entry	Phosphonates (**1**)/Sulfonamides (R)[b]	Product	(±)**2**/Yield(%)[c]
1	**1a**/4-Me-C_6H_4-		**2a**/ 94
2	**1a**/ C_6H_5-		**2b**/ 90
3	**1a**/4-Cl-C_6H_4-		**2c**/ 92
4	**1a**/4-NO_2-C_6H_4-		**2d**/ 90
5	**1a**/4-NH_2-C_6H_4-		**2e**/ 92
6	**1a**/4-CF_3-C_6H_4-		**2f**/ 80
7	**1a**/ R=Ph;R'=*n*-C_4H_9-		**2g**/ 88

8	**1a**/2-naphthyl-		**2h**/ 85
9	**1a**/ Me-		**2i**/ 91

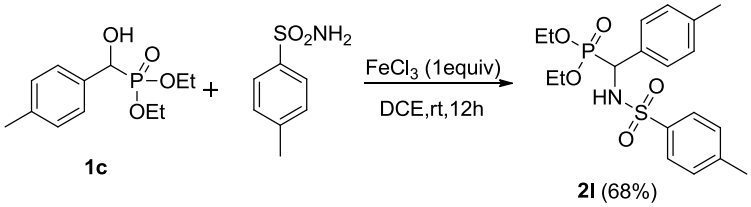
[a] Phosphonates (1 mmol), sulfonamide (1 mmol) and TfOH (1 mmol) in 1,4-dioxane (3 ml) under open air at room temperature. [b] Except entry 7, all R'=H. [c] Isolated yield. [d] $FeCl_3$/ Dichloroethane (DCE) was used under nitrogen atmosphere at room temperature.

Notably, the yield was relatively poor when the phosphonate (±)-**1b** was used. Interestingly, along with the expected compound (**2j**), we could also isolate the synthetically useful sulfonamide (**3a**, **Scheme 2.15**) from the reaction mixture of (±)-**1b** and $TsNH_2$. The compound **3a** was formed perhaps from the reaction of $TsNH_2$ with benzyl alcohol, generated by the partial acidic hydrolysis of phosphonate (±)-**1b** in the reaction mixture. This observation was further explored and showed a new route to access sulphonamides (discussed in section **2.3.2**).



Scheme 2.15 TfOH-mediated synthesis of *α*-Sulfonamidephosphonates (**2j-k**)

Surprisingly, unlike (±)-**1a** and **1b,** the phosphonate (±)-**1c** reacted with $TsNH_2$ in the presence of $FeCl_3$/dichloroethane (DCE) in place of TfOH at room temperature (**Scheme 2.16)**. As expected, the presence of electron donating group at the aryl part for phosphonates is needed for this method.



Scheme 2.16 Ferric chloride mediated synthesis of *α*-Sulfonamidephosphonates (**2l**)

The sulfonamide phosphonates, synthesized herein, are characterized using multinuclear NMR ($^{1}H/^{13}C/^{31}P$) spectroscopy.

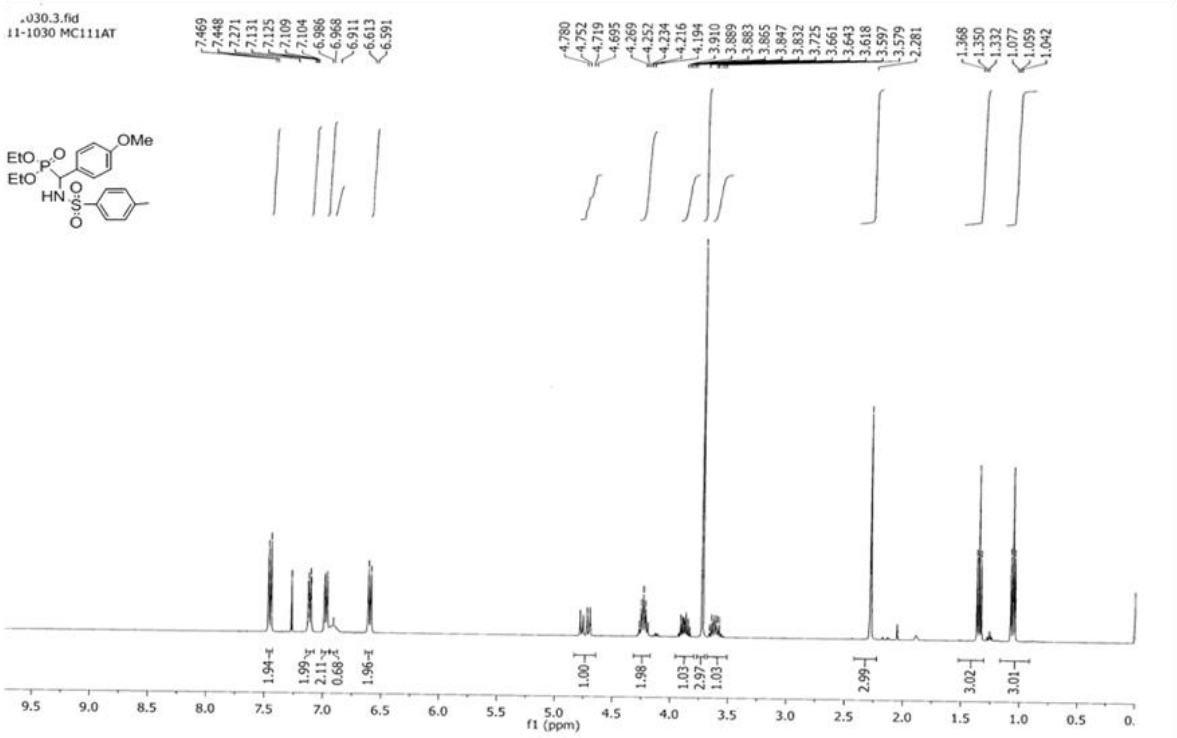


Fig 2.3a ^{1}H NMR spectrum of compound **2a**

The sulfonamide phosphonates (**2a-l**) showed the characteristic doublet of doublet at ~ δ 4.80 (dd, *J* ~ 9.6 and 24.0 Hz) for P-C(α)*H* in ^{1}H NMR and a doublet at ~δ 54.9 (d, *J* ~ 159.0 Hz) for P-C(α)H appeared in ^{13}C NMR spectra**.** Sulfonamides showed a band around 1335 cm^{-1} in the IR spectra duo to S=O stretching and phosphonates showed a band around 1230 and 1020 cm^{-1} in the IR spectra due to the stretching of P=O and P-OR esters. The ^{31}P NMR spectra of *α*-sulfonamidephosphonates showed a peak in the region of ~ δ19.4. The representative ^{1}H and ^{13}C NMR spectra for compounds **2a** are shown in **Fig 2.3a-b**.

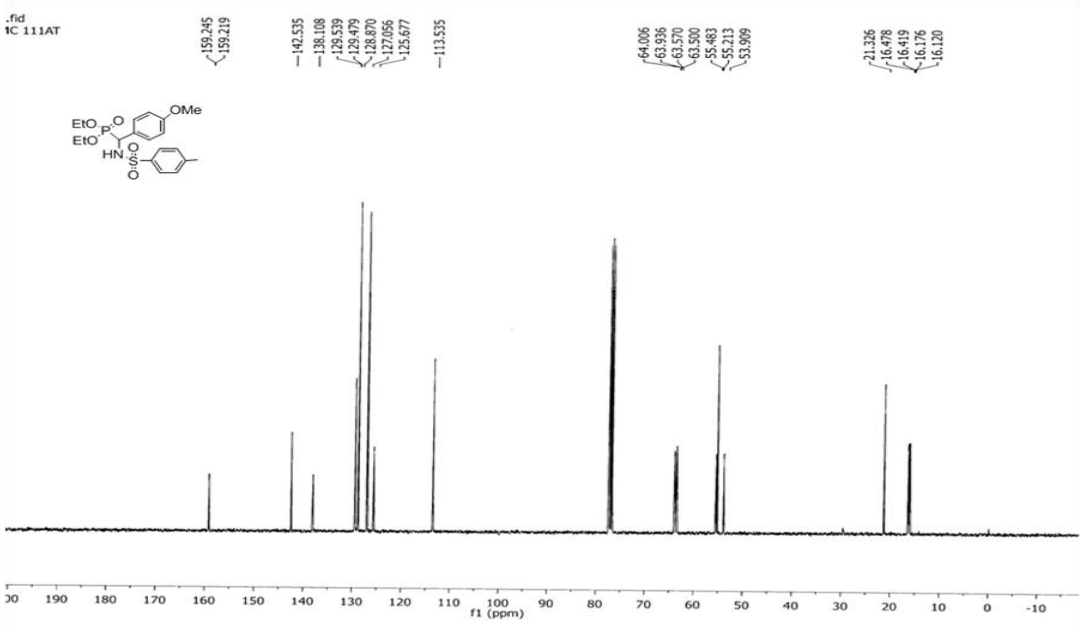
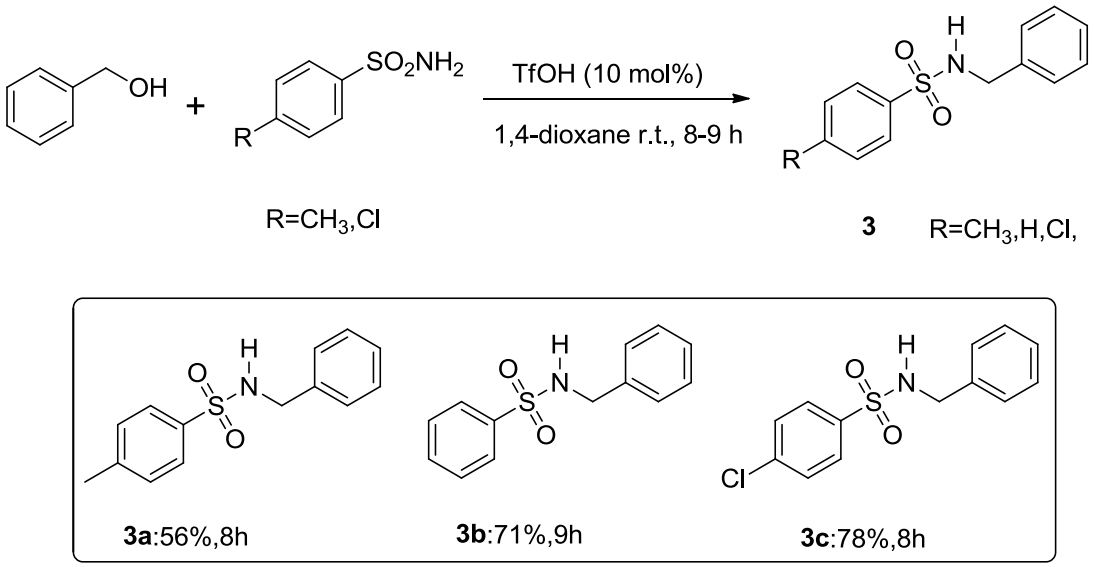


Fig 2.3b ^{13}C NMR spectrum of compound **2a**

2.3.2 *Synthesis of selected sulphonamides (a new approach)*

The known sulfonamide **3a** was synthesized recently using transition metal (Ru, Mn etc.) catalyzed reactions.[78] It is also noteworthy that the primary benzylic alcohols did not react with $TsNH_2$ using $FeCl_3$ even on prolonged heating.[73] Inspired by these related reports and just to verify our result, we treated benzyl alcohol with only three different sulfonamides separately in the presence of catalytic amount of TfOH (10 mol%) at room temperature using 1,4-dioxane as solvent and that afforded compounds **3a-c** in a moderate to good yield (**Scheme 2.17**). Even though the similar approach was reported with allylic alcohols, primary benzylic alcohol was not used in the literature using this method.[74] Thus we believe that this facile metal-free process should be added to the existing methods for the synthesis of sulfonamides of type **3**.



Scheme 2.17 TfOH-mediated *N*-alkylation of sulfonamides with alcohols

The sulfonamides, synthesized herein, are characterized using multinuclear ^{1}H NMR spectroscopy. The illustrative ^{1}H NMR spectra for compound **3a** is presented in Fig **2.4**. The sulfonamides **3a-c** showed the characteristic doublet at δ 4.11 (d, J ~ 6.2) and broad triplet at δ 4.87 (t, J ~ 6.1) for CH_2 and -NH in ^{1}H NMR and also sulfonamide show a band around ~ 1335 cm^{-1} in the IR spectra due to the S=O stretching. Analytical data for all synthesized compounds are consistent with the previous reports.[57, 78]

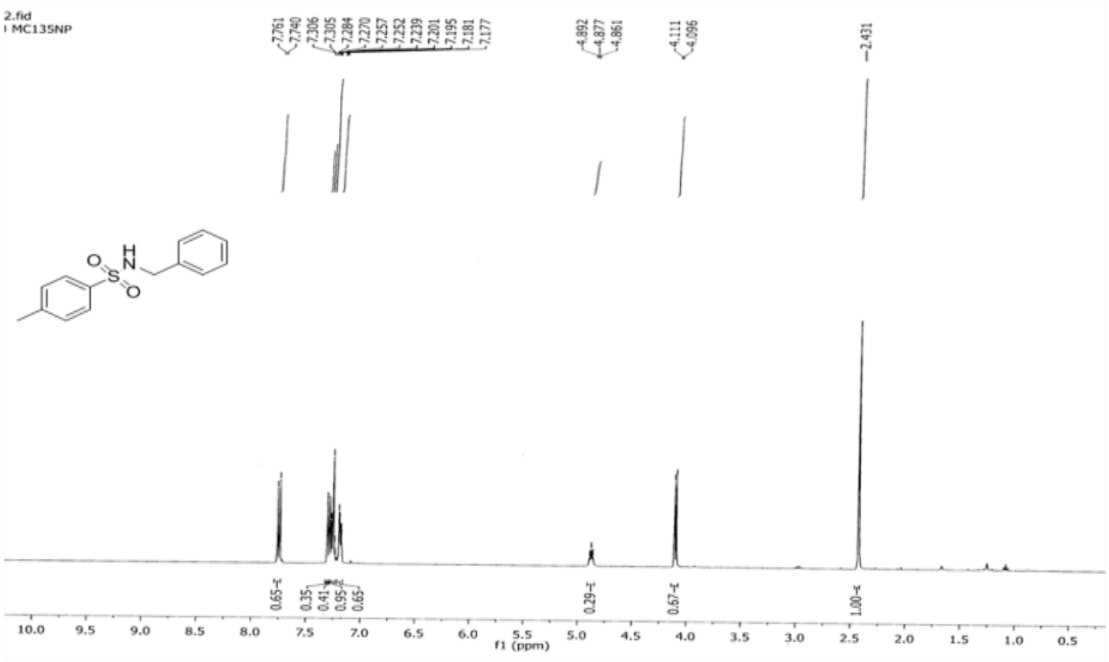


Fig 2.4 ^{1}H NMR spectrum of compound **3a**

2.3.3 *Synthesis of (±)-γ-aryl/methylsulfonamidovinylphosphonates*

Next, we have employed the above strategy to synthesize new sulfonamide phosphonates regio- and stereoselectively where the sulfonamide is attached to a γ-carbon of a vinylphosphonate by choosing the easily-accessible cheap phosphonates (±)-(*E*)-**4a-c (Fig 2.5)**.

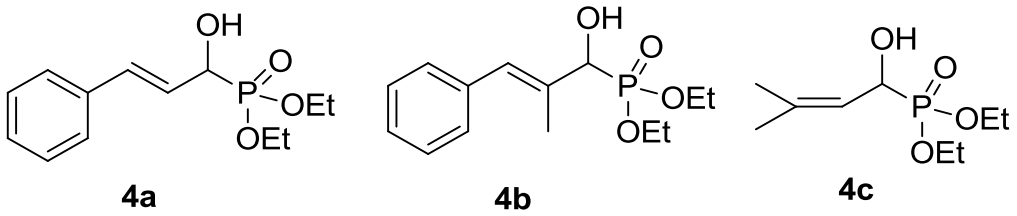
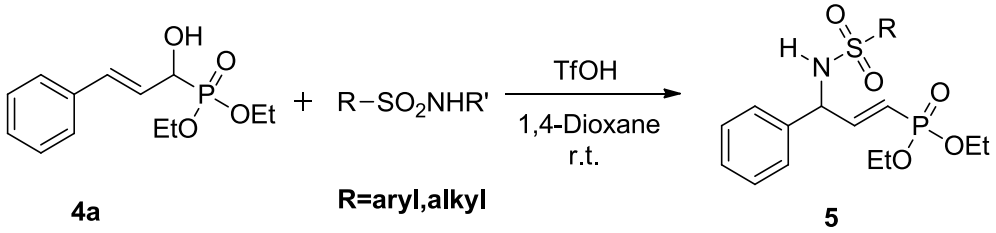


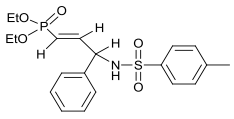
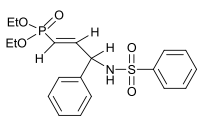
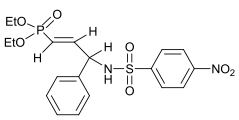
Fig 2.5 hydroxyphosphonates used as starting materials

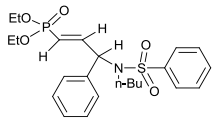
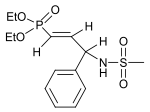
The newly synthesized sulfonamide phosphonates are shown in Table **2.3**. The reaction of (±)-(*E*)-**4a** with $TsNH_2$ was not clean in the presence of $FeCl_3$/DCE or nitromethane whereas TfOH/1,4-dioxane gave almost quantitative yield of (±)-(*E*)-**5a (Scheme 2.18)**.



Scheme 2.18 TfOH-mediated synthesis of γ-Sulfonamide vinylphosphonates (**5**)

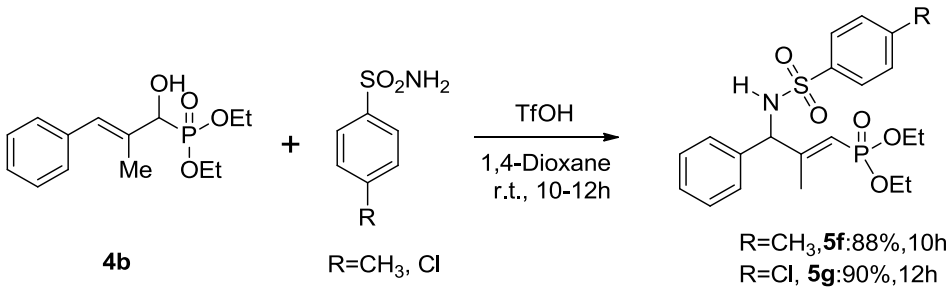
Table 2.3 TfOH mediated reactions of sulfonamides with α-hydroxyphosphonates(±)-**4a**[a]

Entry	Phosphonates (**4**)/ Sulfonamides (R)[b]	Product	(*E*)-**5**/Yield(%)[c]
1	**4a**/4-Me-C_6H_4-		**5a**/ 92
2	**4a**/ C_6H_5-		**5b**/90
3	**4a**/4-NO_2-C_6H_4-		**5c**/86

4	**4a/** R=Ph; R'= *n*-C_4H_9-Me-		**5d**/82
5	**4a**/Me-		**5e**/82

[a] Reaction conditions: Phosphonate (1 mmol), sulfonamide (1 mmol) and TfOH (1 mmol) in 1,4-dioxane (3 ml) in an open vessel. [b] Except entry 4, all R′=H. [c] Isolated yield. [d] TfOH gave the diene and hence $FeCl_3$/DCE was used under nitrogen atmosphere.

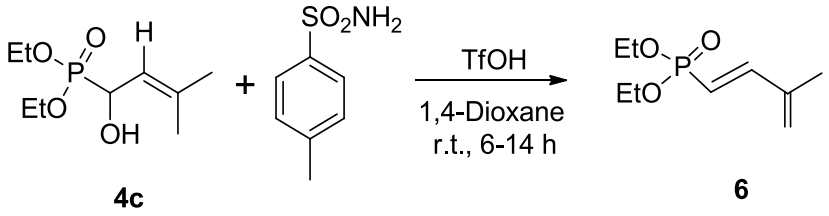
Indeed, compounds (±)-(*E*)-**5a-c** were isolated and purified by only crystallization from ethylacetate. The other phosphonate (±)-(*E*)-**4b** with an extra methyl group at *β*-C also afforded expected products (±)-(*E*)-**5f-g** in high yields **(Scheme 2.19)**.



Scheme 2.19 TfOH-mediated synthesis of *γ*-sulfonamide vinylphosphonates (**5f, 5g**)

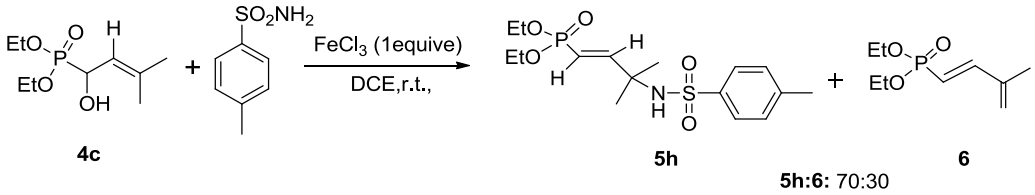
There was no evidence accounted for the formation of *γ*-aminophosphonate from the reported reaction of (±)-(*E*)-**4a** with amines in the literature.[76] The TfOH-mediated method did not produce any other possible isomeric products *neither* with a (*Z*)-configuration *nor* the sulfonamides attached at the *α*-carbon. It is important to note that the *γ*-aminovinylphosphonates were synthesized with mainly *E*–configuration [*Z*-isomers: (0-33%)] by Lu *et al*. using the umpolung reactivity of allylic phosphonates supported *by* expensive $Pd(PPh_3)_4$ starting from α-acetoxyallylic phosphonates and only amines under purified nitrogen.[79]

Using TfOH, attempted reactions of each sulfonamides (mentioned here) with phosphonate (*E*)-**4c** led to the formation of (*E*)-1,3-dienylphosphonate **6** quantitatively instead of forming sulfonamide phosphonates **(Scheme 2.20)**.



Scheme 2.20 TfOH-mediated synthesis of (*E*)-1,3-dienylphosphonate (**6**)

Unpredictably, the expected product (*E*)-**5h** was obtained with moderate yield along with diene **6** by the employment of $FeCl_3$/DCE at room temperature. The ^{31}P NMR for the reaction mixture showed that the ratio of product (*E*)-**5h** and diene (*E*)-**6** formed is 70/30 respectively **(Scheme 2.21)**.



Scheme 2.21 Ferric chloride mediated synthesis of *γ*-Sulfonamide vinylphosphonates and 1,3-diene

The sulfonamide vinylphosphonates, synthesized herein, are characterized using multinuclear ^1H & ^{13}C NMR spectroscopy. To show the patterns, the ^1H & ^{13}C NMR spectra for compounds **5c, 5h & 6** are given in Fig **2.7, 2.8 &2.9** respectively. The stereochemistry for compounds (*E*)-(±)-**5a-h** including **6** are depicted by analysing the coupling constant ($^3J_{P\text{-}C}$ ~22.0-24.0 Hz) between the phosphorus and γ-carbon in ^{13}C NMR by comparing the values that are reported in the literature.[83] Sulfonamide showed a band around ~ 1340 cm^{-1} in the IR spectra duo to the S=O stretching. The analytical data for the earlier reported compounds are consistent with the literature. Moreover, the single crystal X-ray crystallographic studies for (±)-**5a** confirmed the (*E*)-configuration as well as the position (*γ-C*) of sulfonamide unequivocally.

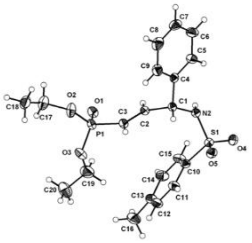


Fig 2.6 ORTEP diagram (with 20 %) probability label for compound (*E*)- (±)-**5a**

In the ^{1}H NMR spectrum (Fig **2.7a**), compound **5c** showed a characteristic doublet of doublet due to PC*H* at δ 6.78 (^{2}J(PH)= 21.9 Hz, 17.1 Hz, 5.5 Hz) and a characteristic doublet due to PC*α* at δ 118.4 (^{1}J(PC)= 188.0 Hz) was found in ^{13}C NMR spectrum (**Fig 2.7b**).

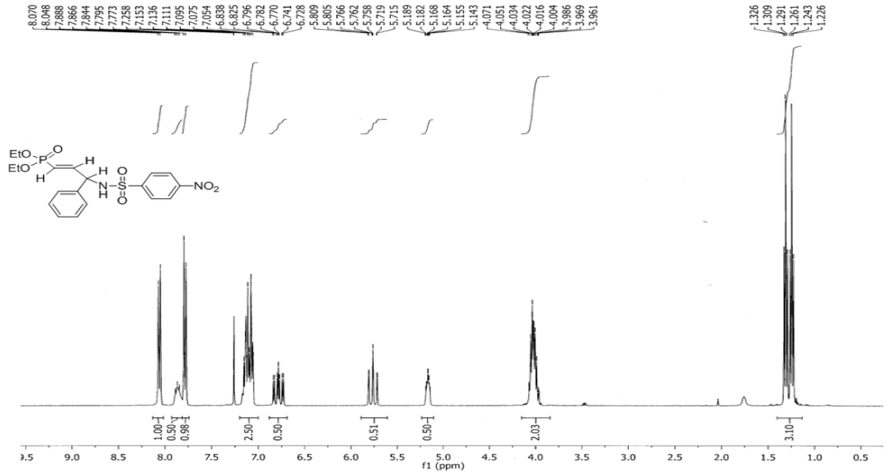


Fig 2.7a ^{1}H NMR spectrum of compound **5c**

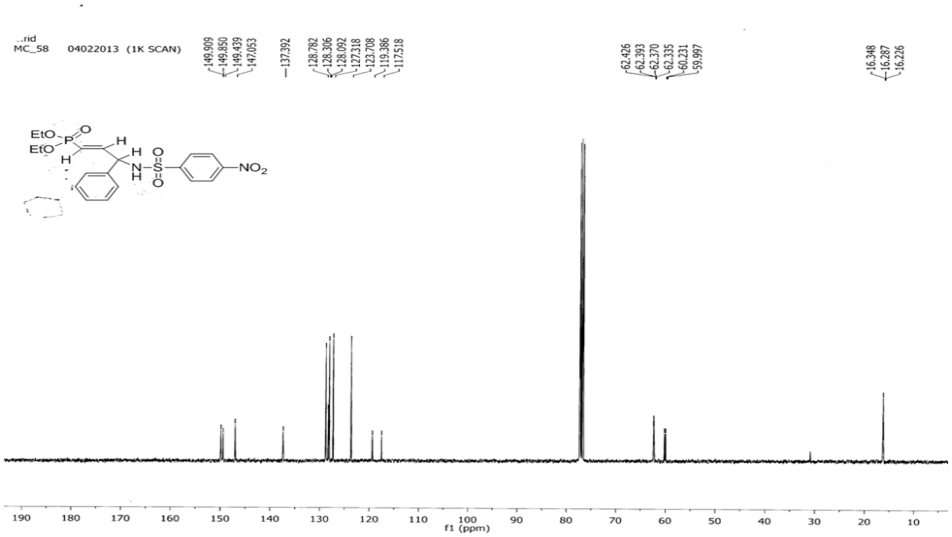


Fig 2.7b ^{13}C NMR spectrum of compound **5c**

The appearances of a distinctive doublet of doublet at δ 6.69 (^{2}J(PH)= 22.4 Hz, 17.6 Hz) and δ 114.9 [^{1}J(PC)= 187.0 Hz] in ^{1}H (Fig **2.8a**) and ^{13}C NMR (**Fig 2.8b**) spectrum respectively have proved the presence of -PCH(*α)* for compound **5h.**

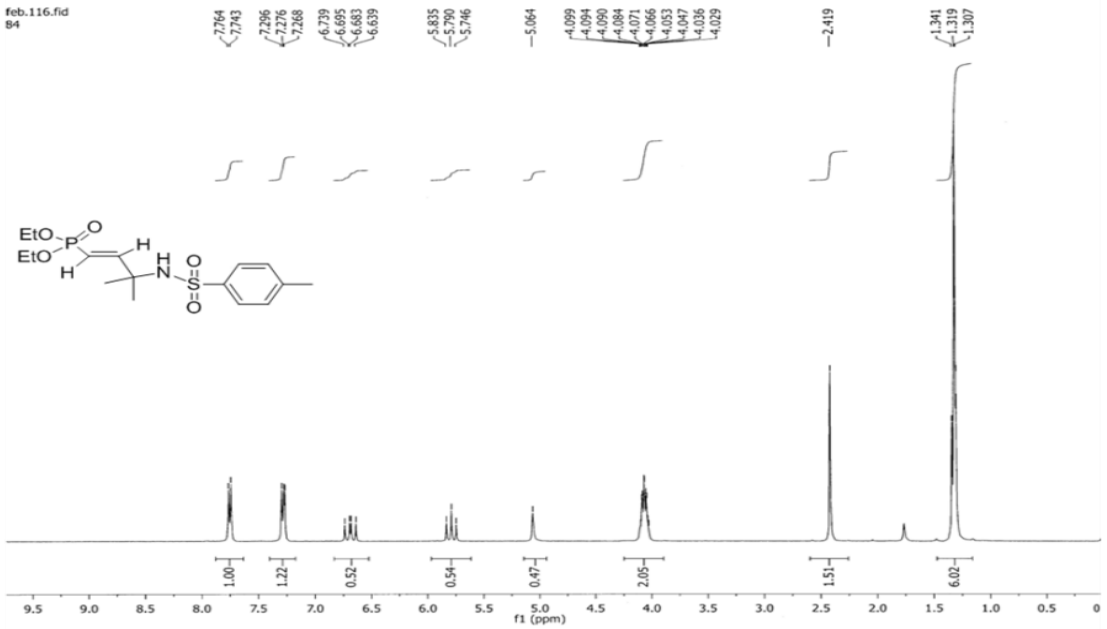


Fig 2.8a ^{1}H NMR spectrum of compound **5h**

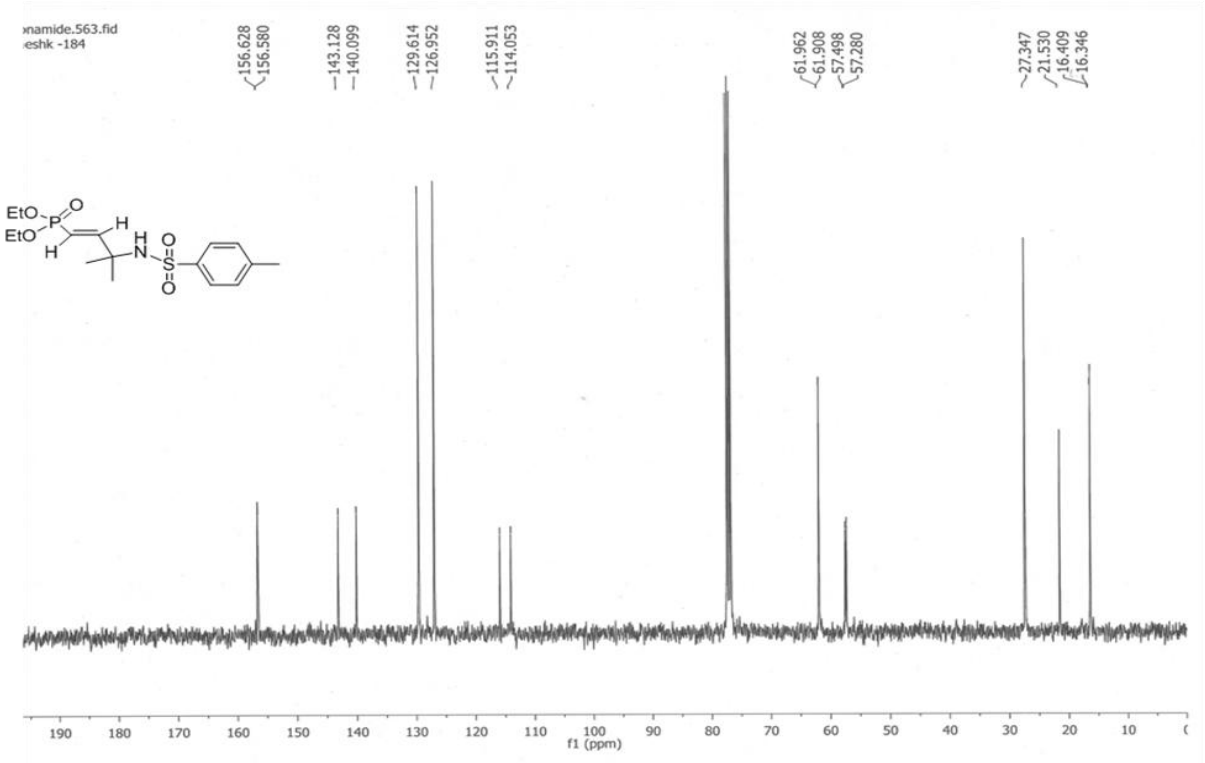
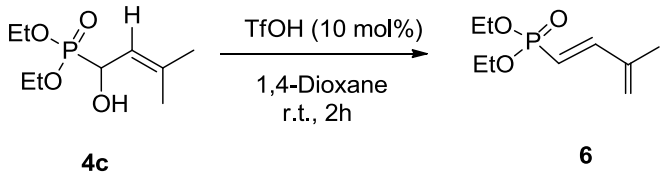


Fig 2.8b ^{13}C NMR spectrum of compound **5h**

2.3.4 *Synthesis of 1,3-Diene*

The formation of 1,3-dienes could not be avoided from the reaction described above in Scheme 2.21 even when the reaction was performed at -30 ^{o}C. It is worth noting that a similar type of

observation to form elimination product from 2-phenylpropan-2-ol was reported in the literature.[80] Moreover, the synthesis of 1,3-butadienylphosphonates is well demonstrated by Srebnik *et al. via* zirconation of 1-alkynylphosphonates.[81] This diene compound (**6**) was fruitfully uutilized as a precursor for the synthesis of phosphorus based polymers that are used in the biomedical field.[82] Hence, we treated compound **4c** separately with TfOH in dioxane at room temperature and the diene **6** was obtained almost in quantitative yield (**Scheme 2.22**).



4c **6**

Scheme 2.22 TfOH-mediated synthesis of (*E*)-1,3-dienylphosphonate (**6**)

In the ^{1}H NMR spectrum (**Fig 2.9a**) of compound **6** showed a characteristic doublet of doublet due to PC*H* at δ 7.09 (^{2}J(PH)= 21.8 Hz, 18 Hz), and multiplet at δ 5.23-5.25 was observed due to the presence of =CH_2. A typical doublet due to PC(*α)* at δ 114.6 (^{1}J(PC)= 187.0 Hz) was found in ^{13}C NMR spectrum (**Fig 2.9b**).

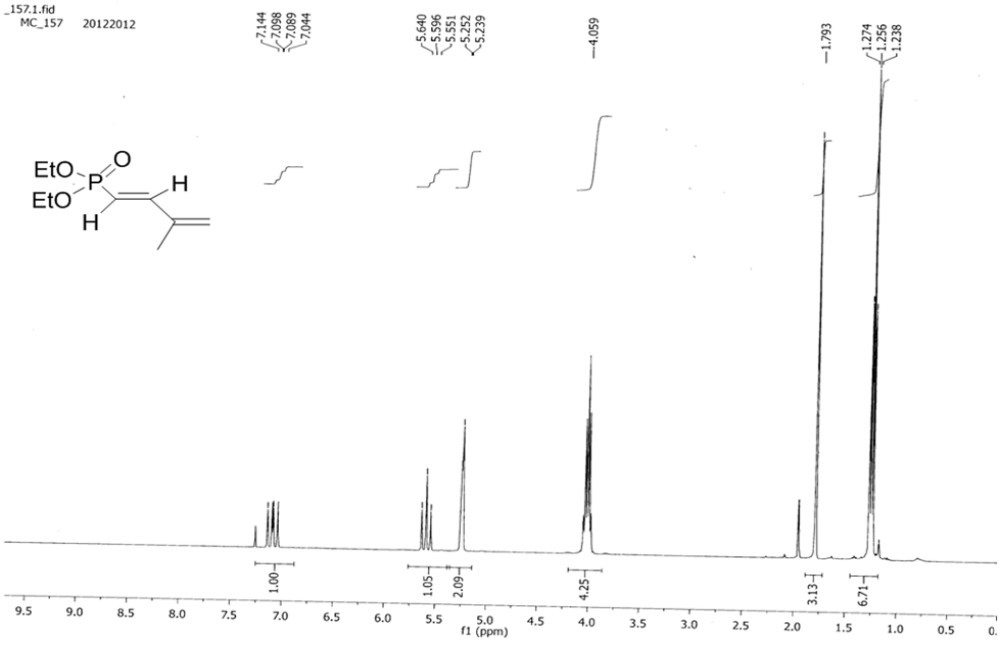


Fig 2.9a ^{1}H NMR spectrum of compound **6**

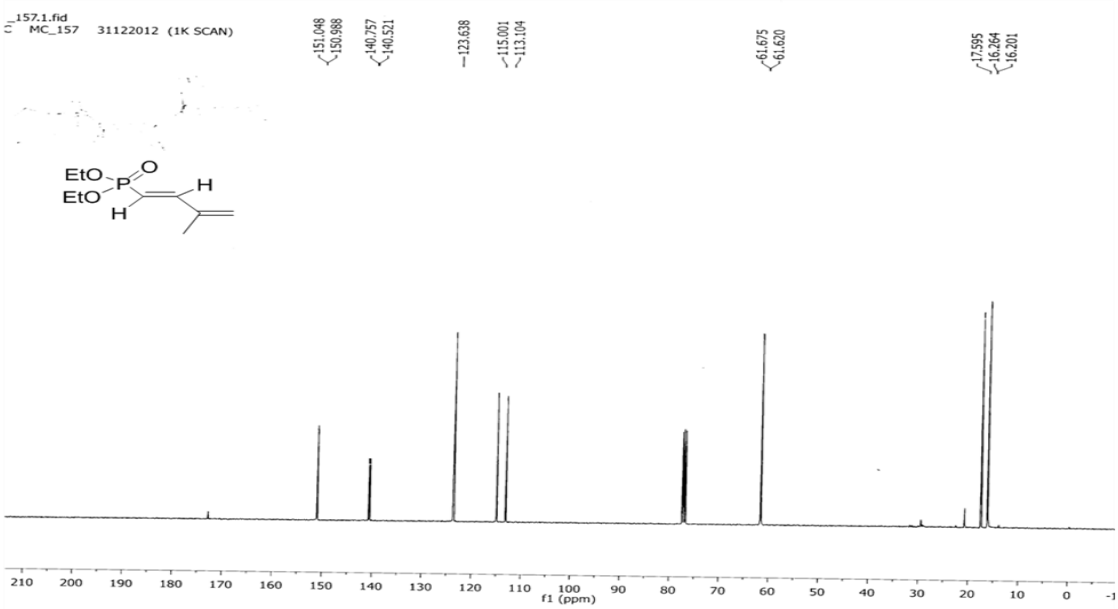
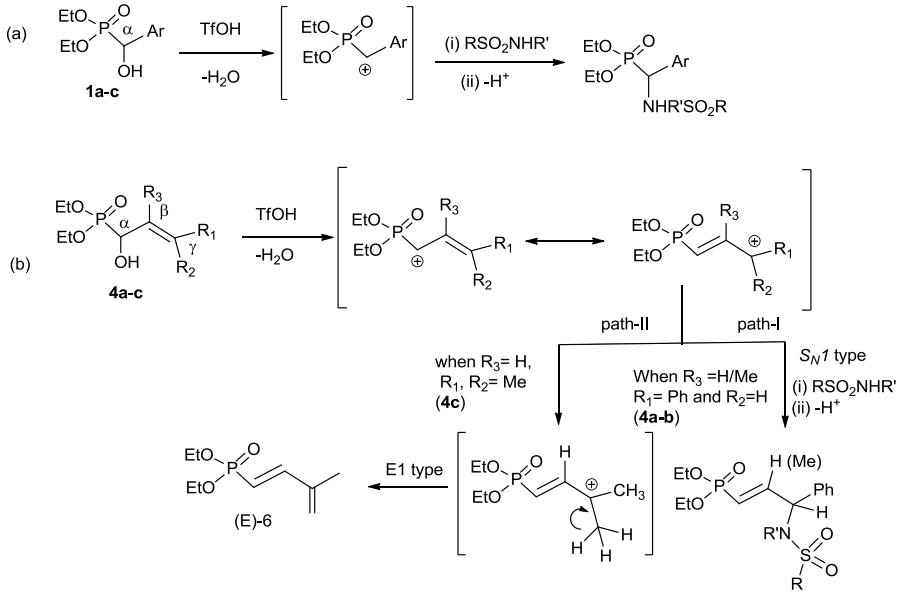


Fig 2.9b ^{13}C NMR spectrum of compound **6**

2.4 Mechanism

Thus, based on the observed experimental results and previous studies,[80] we believe that the reaction proceeds *via* carbocation intermediate that will be stabilized by inductive/conjugation effect of adjacent substituents **(Scheme 2.23)**. Unlike other Lewis acids, TfOH promotes the formation of carbocation from α-hydroxyphosphonate, which is relatively hard to achieve, without any other side reactions like coordination with phosphoryl group, alkene and sulfonamide.



Scheme 2.23 A plausible mechanism for the formation of sulfonamide phosphonates and diene

In case of simple *α*-hydroxy (aryl)phosphonates (**1a-c)**, the intermediate carbocation is stabilized by electron donating substituent present in the aryl group (+I effect), followed by nucleophilic attack of sulphonamide to yield desired (±)-*α*-aryl/methylsulfonamidomethylphosphonate. In case of α-hydroxy allylicphosphonates (**4a-b**; where R_1 = Ph and R_2 =H), it is expected that the generated carbocation at *α*-carbon (to phosphonate moiety) is stabilized by adjacent double bond *via* resonance effect and thus, generated more stable carbocation at *γ*-carbon (which is further stabilized by +R effect of aryl groups), followed by nucleophilic attack of sulphonamide (S_N1 type mechanism), selectively lead to (±)-*γ*-aryl/methyl sulfonamidomethylvinylphosphonates in very good yields . In case of compound **4c** (where R_1 = R_2 = Me), the carbocation (at *γ*-carbon) undergoes elimination (*E1* type) rather than nucleophilic substitution reaction, and yielded diene (*E*)-**6** as the sole product under this condition. Thus, we conclude that the reaction proceeds *via* carbocation intermediate and selectively leads to expected products in very good yields.

2.5 Application of sulfonamide phosphonates

The utility of some of these sulphonamide phosphonates **2c-d, 2h, 2k-l** are studied by our collaborators.[84] They have found that these compounds are good corrosion inhibitors for mild steel in 1M HCl and their inhibition efficiencies get enhanced with the concentration. Detailed studies showed that the compound **2h** (naphthalene sulphonamide) is very effective corrosion inhibitor compared to others. The decreasing order of corrosion inhibition efficiencies for the above compounds was appeared to be **2h**>**2d**>**2c**>**2k**>**2l.**

2.6 Conclustion

The direct addition of imines with phosphites, preferably in the presence of metal salt, is the most common approach for synthesizing *α*-aminophosphonates but synthesizing *N*-sulfonylimines require a special treatment due to the weak nucleophilicity of sulphonamides. Therefore, the attempts for synthesis of specific *α*-sulfonamide phosphonates are sporadically mentioned in the literature but new γ-sulfonamide vinylphosphonates are described here. We envisage that these new *γ-aryl/methylsulfonamidomethylvinylphosphonates*, described herein, will enhance the potential in the field of materials as well as biological sciences due to the presence of sulfonamide at the *γ*-position for a useful vinylphosphonate.

2.7 Experimental section

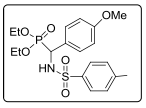
2.7.1 *General Information*

Solvents and chemicals were used as received without any further purification. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (100-200 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). ^{1}H, ^{13}C, and ^{31}P NMR spectra (^{1}H, 400 or 500 MHz; ^{13}C, 101 or 125 MHz; ^{31}P, 162 or 212 MHz) were recorded using a 400 or 500 MHz spectrometer in $CDCl_3$/DMSO-d_6 with shifts referenced to $SiMe_4$ (δ (ppm): 0) or 85% H_3PO_4 (δ (ppm): 0). IR spectra were recorded on an FT-IR spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out on a CHN analyzer. Mass spectra were recorded using LC-MS equipment.

2.7.2 ***General procedure for the synthesis of sulfonamide phosphonate*** **(±)-2a:** To a stirred solution of (±)-**1a** (0.5 g, 1.824 mmol) and *p*-toulenesulfonamide (0.31 g, 1.824 mmol) in 1,4-dioxane (4 mL) under open to air, TfOH (0.16mL, 1.824 mmol) was added. The reaction mixture was stirred for 5 h at room temperature. After completion of the reaction as indicated by TLC, the mixture was quenched with ice cold water, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over Na_2SO_4. After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using (65% ethylacetate/ petroleum ether) as the eluent to afford compound (±)-**2a** as a white solid. All the other compounds (±)-**2b**-**k** were prepared analogously unless stated otherwise.

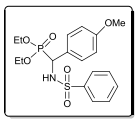
2.7.3 ***Analytical data for the synthesized compounds*** **2a-l**

(±)-Diethyl (4-methoxyphenyl)(4-methylphenylsulfonamido)methylphosphonate (2a) Yield 0.733 g (94%); white solid; mp 144-148 ^{o}C; IR (KBr, cm^{-1}) 3120, 2911, 1398, 1325,



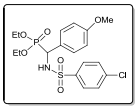
1229, 1159, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 and 1.35 (t, *J* = 7.1 Hz, 6H), 2.28 (s, 3H), 3.56-3.85 (m, 1H), 3.88 (s, 3H), 3.89-4.12 (m, 1H), 4.22-4.27 (m, 2H), 4.78 (dd, *J* = 9.6 and 24.0 Hz, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.95 (br, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 7.12 (dd, *J* = 8.7, 2.0, Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 and 16.4 (two sets of doublets, *J* = 5.8 Hz each), 21.3, 54.7 (d, *J* = 158.3 Hz), 55.2, 63.5 and 64.0 (two sets of doublets, *J* = 7.1 Hz each), 113.5, 125.7, 127.1, 128.9, 129.5 (d, *J* = 6.0 Hz), 138.1, 142.5, 159.2 (d, *J* = 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8; Anal. Calcd. for $C_{19}H_{26}NO_6PS$: C, 53.39; H, 6.13; N, 3.28; Found: C, 53.26; H, 6.19; N, 3.21.

(±)-Diethyl (4-methoxyphenyl)(phenylsulfonamido)methylphosphonate (2b): The reaction was stirred for 6 h at room temp.Yield 0.679 g (90%);white solid; mp 132-135^{o}C;IR (KBr, cm^{-1})



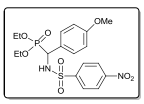
3117, 1611, 1516, 1460, 1394, 1325, 1232, 1157, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 and 1.36 (two sets of triplet, *J* = 7.1 Hz each, 6H), 3.58-3.81 (m, 1H), 3.85 (s, 3H), 3.87-3.91 (m, 1H), 4.23-4.28 (m, 2H), 4.56 (dd, *J* = 9.6 and 24.1 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 2H), 7.05-7.44 (m, 6H), 7.58 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.5 (two sets of doublets, *J* = 5.5 Hz each), 54.8 (d, *J* = 159.3 Hz), 55.2, 63.5 and 64.1 (two sets of doublets, *J* = 7.1 Hz each), 113.5, 125.5, 126.9, 128.2, 129.6, 131.7, 141.2, 159.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.7; Anal. Calcd. for $C_{18}H_{24}NO_6PS$: C, 52.29; H, 5.85; N, 3.39; Found: C, 52.15; H, 5.92; N, 3.31.

(±)-Diethyl (4-chlorophenylsulfonamido)(4-methoxyphenyl)methylphosphonate (2c): This



compound is synthesized in a manner analogous to compound **2b** by starting with **1a**(0.300 g, 1.094 mmol).Yield 0.450 g (92%); white solid; mp 163-165 ^{o}C; IR (KBr, cm^{-1}) 3092, 2930, 1614, 1516, 1470, 1394, 1333, 1237, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 and 1.40 (two sets of triplet, *J* ~ 7.2 Hz each, 6H), 3.57-3.81 (m, 1H), 3.84 (s, 3H), 3.87-3.91 (m, 1H), 4.27-4.34 (m, 2H), 4.77 (dd, *J* = 9.6 and 25.6 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 7.08-7.12 (m, 4H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.54-7.57 (br, m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.5 (two sets of doublets, *J* = 5.7 Hz each), 54.9 (d, *J* = 159.2 Hz), 55.3, 63.7 and 63.9 (two sets of doublets, *J* = 7.1 Hz each), 113.6, 125.2, 128.4, 128.5, 129.6 (d, *J* = 6.0 Hz), 138.1, 139.8 (d, *J* = 2.1 Hz), 159.4 (d, *J* = 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.5; LC/MS m/z 448 $[M+1]^{+}$; Anal. Calcd. for $C_{18}H_{23}ClNO_6PS$: C, 48.27; H, 5.18; N, 3.13; Found: C, 48.36; H, 5.08; N, 3.21.

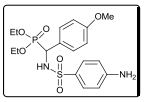
(±)-Diethyl (4-methoxyphenyl)(4-nitrophenylsulfonamido)methylphosphonate (2d): This compound also was synthesized analogously by starting with **1a** (0.300 g, 1.094 mmol) by stirring the reaction mixture for 8 h. Yield 0.450 g (90%); light yellow solid; mp 186-188 ^{o}C; IR (KBr, cm^{-1}) 3101, 1611, 1525, 1344, 1236, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 and



1.45 (two sets of triplet, *J* =7.1 Hz each, 6H), 3.58-3.65 (m, 1H), 3.67 (s, 3H), 3.88-3.92 (m, 1H), 4.34-4.41 (m, 2H), 4.83 (dd, *J* = 24.2 and 10.1 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 2H), 7.09-7.12 (m, 2H), 7.71 (d, *J* = 9.0 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 8.21 (br, dd, *J* = 10.0, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.5 (two sets of doublets, *J* = 5.5 Hz each), 55.1 (d, *J* = 160.8 Hz), 55.2, 63.8 and 64.3 (two sets of doublets, *J* = 7.3 Hz each),

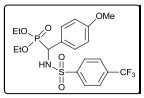
113.6, 123.2, 124.8, 128.3 129.7 (d, *J* = 5.9 Hz), 147.2 (d, *J* = 2.4 Hz), 149.2, 159.6 (d, *J* = 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.2; LC/MS m/z 459 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{23}N_2O_8PS$: C, 47.16; H, 5.06; N, 6.11; Found: C, 47.23; H, 5.12; N, 6.21.

(±)-Diethyl (4-aminophenylsulfonamido)(4-methoxyphenyl)methylphosphonate (2e): The reaction was performed in manner similar to 2d using similar molar quantities. No column



chromatography was used. The product was isolated by crystallization method from ethylacetate. Yield 0.430 g (92%); white solid; mp 197-199 ^{o}C; IR (KBr, cm^{-1}) 3089, 2992, 2875, 1614, 1514, 1461, 1328, 1230, 1164, 1023; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.01 and 1.21 (t, *J* = 7.1 Hz, 6H), 3.62-3.66 (m, 1H), 3.68 (s, 3H), 3.79-3.84 (m, 1H), 4.03-4.05 (m, 2H), 4.56 (dd, *J* = 10.3 and 24.1 Hz, 1H), 5.78 (br, 2H), 6.33 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 7.14-7.16 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 8.26 (dd, *J* = 10.3 and 1.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d6) δ 16.0 and 16.2 (two sets of doublets, *J* = 5.6 Hz each), 53.8 (d, *J* = 158.3 Hz), 54.9, 62.2 (d, *J* = 6.9 Hz), 62.7 (d, *J* = 6.9 Hz), 112.0, 113.1, 126.4, 126.6, 128.3, 129.4 (d, *J* = 5.9 Hz), 152.0, 158.4 (d, *J* = 2.6 Hz); ^{31}P NMR (162 MHz, DMSO-d6) δ 20.6; LC/MS m/z 429 $[M+1]^+$; Anal. Calcd. for$C_{18}H_{25}N_2O_6PS$: C,50.46; H, 5.88; N, 6.54; Found: C, 50.61; H, 5.82; N, 6.61.

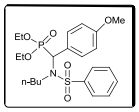
(±)-Diethyl(4-methoxyphenyl) (4 (trifluoromethyl) phenyl sulfonamido) methylphosphonate (2f): This reaction was performed using **1a** (0.200 g, 0.729



mmol) and reaction time was 8 h. Yield 0.280 g (80%); white solid; mp 154-156 ^{o}C; IR (KBr, cm^{-1}) 3087, 1615, 1516, 1462, 1321, 1235, 1172, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 and 1.43 (two sets of triplet, *J* =7.1 Hz each, 6H), 3.57-3.63 (m, 1H), 3.68 (s, 3H), 3.82-3.91 (m, 1H), 4.30-4.38 (m, 2H), 4.80 (dd, *J* = 10.1 and 24.2 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 10.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.96 (br, dd, *J* = 9.9, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.5 (two sets of doublets, *J* = 5.7 Hz each), 55.0, 54.9 (d, *J* = 160.4 Hz), 63.8 and 64.2 (two sets of doublets, *J* = 7.1 Hz each), 113.5, 124.8, 125.1, 125.2, 127.6, 129.7 (d, *J* = 6.0 Hz), 133.3 (q, *J* = 32.8 Hz), 144.8, 159.4 (d, *J* = 2.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.3; LC/MS m/z 482 $[M+1]^+$; Anal. Calcd. for $C_{19}H_{23}F_3NO_6PS$: C, 47.40; H, 4.82; N, 2.91; Found: C, 47.56; H, 4.76; N, 2.98.

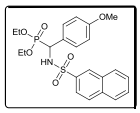
(±)-Diethyl (*N*-butylphenylsulfonamido)(4-methoxyphenyl)methylphosphonate (2g): This reaction was performed using 1a (0.500 g) and reaction time was 12 h. Yield 0.750 g (88%),

Colorless gummy liquid; IR (KBr, cm^{-1}) 2960, 1610, 1513, 1445, 1348, 1252, 1159, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79-0.82 (m, 3H), 1.06-1.09 (m, 3H), 1.15-1.18 (m,



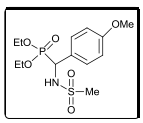
2H), 1.25-1.31 (m, 5H), 3.397-3.422 (m, 2H), 3.79 (s, 3H), 3.94-4.21 (m, 4H), 5.43 (d, *J* = 25.6 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.40-7.78 (m, 5H), 7.79 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.6, 16.2 and 16.4 (two sets of doublets, *J* = 5.7 Hz each), 20.2, 31.7, 46.6, 55.2, 56.8 (d, *J* = 162.6 Hz), 62.7 and 63.0 (two sets of doublets, *J* = 7.4 Hz each), 113.8, 125.3 (d, *J* = 6.3Hz, 2H), 127.6, 128.7, 131.5 (d, *J* = 8.6 Hz, 2H), 132.3, 140.7, 159.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.4; LC/MS m/z 492 $[M+Na]^+$; Anal. Calcd. for $C_{22}H_{32}NO_6PS$: C, 56.28; H, 6.87; N, 2.98; Found: C, 56.15; H, 6.93; N, 2.85.

(±)-Diethyl (4-methoxyphenyl)(naphthalene-2-sulfonamido)methylphosphonate (2h): This reaction was performed using **1a** (0.300 g) and reaction time was 8 h. Yield 0.430 g (85%); white



solid; mp 142-144 ^oC; IR (KBr, cm^{-1}) 1614, 1514, 1461, 1328, 1230, 1023; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 and 1.35 (two sets of triplet, *J* =7.2 Hz each, 6H), 3.43 (s,3H), 3.53-3.81 (m, 1H), 3.87-3.91 (m, 1H), 4.22-4.29 (m, 2H), 4.82 (dd, *J* = 9.7 and 23.8 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 2H), 7.05-7.08 (m, 2H), 7.14-7.18 (br, m, 1H), 7.47-7.75 (m, 6H), 8.01 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 and 16.4 (two sets of doublets, *J* = 5.8 Hz each), 54.9 (d, *J* = 158.2 Hz), 54.9, 63.7 and 63.9 (two sets of doublets, *J* = 7.1 Hz each), 113.4 (d, *J* = 2.1 Hz), 122.5, 125.1, 126.9, 127.5, 128.3, 128.4, 128.6, 129.0, 129.5 (d, *J* = 6.0 Hz), 131.8, 134.3, 137.8 (d, *J* = 1.9 Hz), 159.0 (d, *J* = 2.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.7; LC/MS m/z 464 $[M+1]^+$; Anal. Calcd. for $C_{22}H_{26}NO_6PS$: C, 57.01; H, 5.65; N, 3.02; Found: C, 57.12; H, 5.58; N, 3.07.

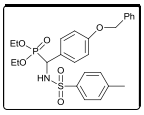
(±)-Diethyl (4-methoxyphenyl)(methylsulfonamido)methylphosphonate (2i): This reaction was performed using **1a** (0.400 g) and reaction time was 8 h. Yield 0.466 g (91%); white solid;



mp 146-148 ^oC; IR (KBr, cm^{-1}) 3118, 1614, 1585, 1518, 1464, 1322, 1255, 1039; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 and 1.39 (two sets of triplet, *J* ~ 7.1 Hz each, 6H), 2.59 (S, 3H), 3.64-3.90 (m, 1H), 3.91 (s, 3H), 3.92-3.96 (m, 1H), 4.23-4.31 (m, 2H), 4.82 (dd, *J* = 9.8 and 23.8 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.4 (two sets of doublets, *J* = 5.8 Hz each), 42.1, 54.5 (d, *J* = 163.9 Hz), 55.3, 63.7 and 64.0 (two sets of doublets, *J* = 7.1 Hz each), 114.3, 126.4, 129.6 (d, *J* = 5.9 Hz), 159.8 (d, *J* = 2.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.9; LC/MS m/z 352

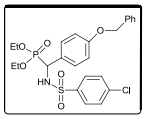
$[M+1]^+$; Anal. Calcd. for $C_{13}H_{22}NO_6PS$: C, 44.44; H, 6.31; N, 3.99; Found: C, 44.56; H, 6.38; N, 3.91.

(±)-Diethyl (4-(benzyloxy)phenyl)(4-methylphenylsulfonamido)methylphosphonate (2j): This compound was synthesized by starting with **1b** (0.300 g, 0.856 mmol) using the same procedure as **2g**. Along with the product compound **3a** was also isolated from column by using 10 % EtOAc in pet ether.



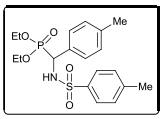
Yield 0.300 g (70%); white solid; mp 147-149 ^oC; IR (KBr, cm^{-1}) 3117, 2872, 1609, 1509, 1332, 1234, 1161, 1052; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 and 1.35 (two sets of triplet, *J* =7.2 Hz each, 6H), 2.28 (s, 3H), 3.55-3.65 (m, 1H), 3.84-3.90 (m, 1H), 4.18-4.26 (m, 2H), 4.74 (dd, *J* = 23.9 and 9.6 Hz, 1H), 4.97 (s, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.83-6.87 (m, br, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.12 (dd, *J* = 8.7 and 2.0 Hz, 2H), 7.33-7.39 (m, 5H), 7.46 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 and 16.5 (two sets of doublets, *J* = 5.8 Hz each), 21.4, 54.7 (d, *J* = 158.2 Hz), 63.5 and 64.0 (two sets of doublets, *J* = 7.1 Hz each), 69.9, 114.5, 126.0, 127.1, 127.4, 128.0, 128.6, 128.9, 129.5 (d, *J*= 8.5 Hz), 136.7, 138.1, 142.6, 158.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8; LC/MS m/z 504 $[M+1]^+$;Anal. Calcd. for $C_{25}H_{30}NO_6PS$: C, 59.63; H, 6.01; N, 2.78; Found: C, 59.48; H, 6.08; N, 2.71.

(±)-Diethyl (4-(benzyloxy)phenyl)(4-chlorophenylsulfonamido)methylphosphonate (2k): This compound was synthesized using similar procedure and molar quantities as **2j** for 12 h**.** Yield 0.320 g (73%); white solid; mp 138-142 ^oC; IR (KBr, cm^{-1}) 3122, 1609, 1513, 1455, 1335, 1243, 1165, 1024; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 and 1.39 (two sets of triplet, *J* =7.1 Hz each, 6H), 3.58-3.64 (m, 1H), 3.85-3.90 (m, 1H), 4.73-4.81 (m, 2H), 4.77 (dd, *J* = 24.0 and 9.7 Hz, 1H), 4.99 (s, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 4H), 7.34-7.42 (m, br, 6H), 7.48 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.5 (two sets of doublets, *J* = 5.7 Hz each), 54.8 (d, *J* = 157.9 Hz), 63.7 and 64.0 (two sets of doublets, *J* = 7.1 Hz each), 70.1, 114.6 (d, *J*= 1.9 Hz),, 125.4, 127.5, 128.1, 128.5, 128.6, 129.6 (d, *J*= 6.0 Hz), 136.6, 138.3, 139.6 (d, *J*= 1.9 Hz), 158.7 (d, *J*= 2.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.5; LC/MS m/z 524 $[M+1]^+$; Anal. Calcd. for $C_{24}H_{27}ClNO_6PS$: C, 55.01; H, 5.19; N, 2.67; Found: C, 55.16; H, 5.08; N, 2.58.



(±)-Diethyl (4-methyphenylsulfonamido)(*p*-tolyl)methylphosphonate (2l): Anhydrous $FeCl_3$ (0.188 g, 1.161 mmol) was added to a stirred solution of **1c** (0.3 g, 1.161 mmol) and *p*-toulenesolfonamide (0.19g, 1.161 mmol) in 1,2-dichloroethane (3.0 mL) and then the reaction

mixture was stirred at room temperature under N_2 for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (2 x 15mL). The combined organic layer was dried over Na_2SO_4. After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using (70% ethylacetate/ petroleum ether) as the eluent to afford the compound.

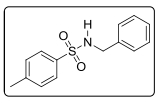


Yield 0.320 g (68 %); white solid; mp 152-154 ^oC; IR (KBr, cm^{-1}) 3142, 2889, 1598, 1459, 1341, 1241, 1162, 1050; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 and 1.35 (two sets of triplet, *J* =7.2 Hz each, 6H), 2.24 (s, 3H), 2.28 (s, 3H), 3.56-3.64 (m, 1H), 3.86-3.90 (m, 1H), 4.19-4.26 (m, 2H), 4.74 (dd, *J* = 24.0 and 9.7 Hz, 1H), 6.89-6.97 (m, 5H), 7.08 (dd, *J* = 8.1, 2.0 Hz, 2H),7.45 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 and 16.5 (two sets of doublets, *J* = 5.8 Hz each), 21.0, 21.3, 55.1 (d, *J* = 157.5 Hz), 63.5 and 64.0 (two sets of doublets, *J* = 7.0 Hz each), 127.0, 128.2 (d, *J* = 6.0 Hz), 128.6, 128.7 (d, *J* = 2.1 Hz), 130.6, 137.4 (d, *J* = 3.1 Hz), 138.1 (d, *J* = 1.8 Hz), 142.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.7; LC/MS m/z 412 $[M+1]^+$; Anal. Calcd. for $C_{19}H_{26}NO_5PS$: C, 55.46; H, 6.37; N, 3.40; Found: C, 55.38; H, 6.32; N, 3.51.

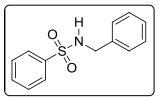
2.7.4 ***General procedure for the TfOH catalyzed sulfonamidation of benzyl alcohol***: To a stirred solution of benzylalcohol (0.500 g, 4.629 mmol), *p*-tolunesolfonamide (0.790 g, 4.629mmol) in 1,4-dioxane (5.0mL), TfOH (0.04mL, 0.4629 mmol) was added under N_2 at room temperature and the reaction mixture was stirred for 8 h. After completion of the reaction as indicated by TLC, the mixture was quenched with ice cold water, and the aqueous layer was extracted with ethyl acetate (2 x 100mL). The combined organic layer was dried over Na_2SO_4. After filtration and removal of solvent in vacuum, the crude product was purified by column chromatogram using (30% ethylacetate/ petroleum ether) as the eluent to afford compound. All the other compounds were prepared analogously using similar molar quantities unless stated otherwise. All these compounds are known in literature.

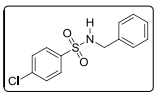
2.7.5 ***Analytical data for the synthesized compounds 3a-c***

***N*-benzyl-4-methylbenzenesulfonamide (3a)**: yield 0.68 g (56%).mp = 115-117 °C;Yield 0.045



g (20%); white solid;IR (KBr, cm^{-1}) 3272, 1598, 1496, 1319, 1167, 1089; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.11 (d, *J* =6.2 Hz, 2H), 4.87 (bt, *J* =6.1 Hz, 1H), 7.18-7.31 (m, 7H), 7.75 (d, *J* =8.3 Hz, 2H); LC/MS m/z 262 [M + 1.

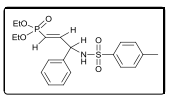
***N*-benzylbenzenesulfonamide (3b):** The reaction was stirred for 9 h at room temp. yield 0.810  g, (71%), as a white solid. IR (KBr, cm^{-1}): 3332, 2926, 1967, 1895, 1447, 1325,1221, 1157, 1065; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (d, *J* =6.0 Hz, 2H), 4.87 (bt, *J* ~ 6.0 Hz, 1H), 7.18-7.25 (m, 5 H), 7.49-7.60 (m, 3H), 7.87 (d, *J* =8.4 Hz, 2H); LC/MS m/z 246 $[M-1]^+$.

***N*-benzyl-4-chlorobenzenesulfonamide (3c):** The reaction was stirred for 8 h at room temp.  Yield 1.020 g (78%), as a white solid. IR (KBr, cm^{-1}): 3248, 2643, 1916, 1575, 1475, 1331, 1177, 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (d, *J* =6.4 Hz, 2H), 4.81 (bt, *J* ~ 6.0 Hz, 1H), 7.18-7.29 (m, 5 H), 7.47 (d, *J* =8.4 Hz, 2H), 7.78 (d, *J* =8.4 Hz, 2H); LC/MS m/z 280 $[M-1]^+$.

2.7.6 ***General procedure for the synthesis of (±)-γ-sulfonamidephosphonates 5a-g:***

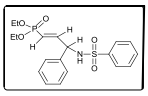
To a stirred solution of **4a** (0.200 g, 0.740 mmol), *p*-toulenesulfonamide(0.120 g, 0.740 mmol) and 1,4-dioxane (3.0 mL), in a round-bottom flask open to air at room temperature TfOH (0.06 mL, 0.740 mmol) was added. The reaction mixture was stirred for 6-7 h. After completion of the reaction as indicated by TLC, reaction mixture was quenched with ice cold water, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried over Na_2SO_4. After filtration and removal of solvent in vacuum, the crude product was washed with ethylacetate (2 x 5 mL). The resulting solid was recrystallized from ethylacetate to yield the compound **5a**. All the other compounds **5b-c** were prepared analogously using similar molar quantities unless stated otherwise. In case of **5d-g**, crude product was purified by column chromatography using (80% ethylacetate/ petroleum ether) as the eluent.

2.7.7 ***Analytical data for the synthesized compounds 5a-g***

(*E*)-Diethyl 3-(4-methylphenylsulfonamido)-3-phenylprop-1-enylphosphonate (5a): This compound was sparingly soluble in $CDCl_3$. Yield 0.288 g (92%); white solid; mp 155-160 ^oC; IR (KBr, cm^{-1}) 3118, 2911, 1477, 1398, 1325, 1229, 1159, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ  1.26-1.32 (m, 6H), 2.39 (s, 3H), 3.98-4.05 (m, 4H), 5.05 (br, 1H), 5.81-5.90 (m, 2H), 6.72-6.83 (m, 1H), 7.05-7.20 (m, 7H), 7.62 (d, *J*= 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.4 (d, *J* = 6.3 Hz each), 21.5, 59.6 (d, *J* = 23.3 Hz), 61.9 and 62.0 (d, *J* = 5.2 Hz), 118.5 (d, *J*= 187.6 Hz), 127.2 (d, *J* = 16.4 Hz), 128.2, 128.9, 129.5, 137.6, 137.8, 137.9, 143.3, 150.1 (d, *J*= 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.1; LC/MS m/z 424

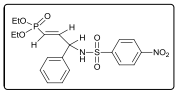
$[M+1]^+$; Anal. Calcd. for $C_{20}H_{26}NO_5PS$: C, 56.73; H, 6.19; N, 3.31; Found: C, 56.61; H, 6.07; N, 3.45; X-ray structural analysis was done for this sample to confirm the stereochemistry.

(*E*)-Diethyl 3-(phenylsulfonamido)-3-phenylprop-1-enylphosphonate (5b): This compound



was also moderately soluble in $CDCl_3$. Yield 0.274 g (90%); white solid; mp 178-184 ^oC; IR (KBr, cm^{-1}) 3108, 2903, 1476, 1395, 1325, 1234, 1162, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.31 (m, 6H), 3.99-4.05 (m, 4H), 5.07 (br, 1H), 6.71-6.82 (m, 1H), 7.03-7.04 (m, 2H), 7.15-7.18 (m, 3H), 7.35-7.38 (m, 2H), 7.46-7.49 (m, 1H), 7.71-7.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.4 (d, J = 6.3 Hz each), 59.6 (d, J = 23.1 Hz), 61.9 and 62.0 (d, J = 5.2 Hz), 118.6 (d, J= 187.1 Hz), 126.9, 127.2, 128.3, 128.9, 132.5 (two peaks are merged), 137.7, 140.6, 149.9 (d, J = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.1; LC/MS m/z 410 $[M+1]^+$; Anal. Calcd. for $C_{19}H_{24}NO_5PS$: C, 55.74; H, 5.91; N, 3.42; Found: C, 55.61; H, 5.98; N, 3.49.

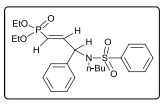
(*E*)-Diethyl 3-(4-nitrophenylsulfonamido)-3-phenylprop-1-enylphosphonate (5c): Reaction was performed for 10h at room temperature using **4a** (0.300 g). Yield 0.434 g (86%); light



yellow solid;

mp 162-164 ^oC; IR (KBr, cm^{-1}) 3113, 1525, 1468, 1350, 1221, 1166, 1039; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 and 1.31 (two sets of triplet, J =7.1 Hz each, 6H), 3.96-4.07 (m, 4H), 5.14-5.18 (m, br, 1H), 5.76 (ddd, J =18.8 Hz, 17.2 Hz, 1.6 Hz, 1H), 6.78 (ddd, J =21.9 Hz, 17.1 Hz, 5.5 Hz, 1H), 7.05-7.78 (m, 5H), 7.78 (d, J= 8.8 Hz, 2H), 7.83-7.89 (m, 1H), 8.06 (d, J= 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.3 (d, J = 6.2 Hz each), 60.1 (d, J = 23.5 Hz), 62.3 and 62.4 (d, J = 5.7 Hz), 118.4 (d, J= 188.0 Hz), 123.7, 127.3, 128.1, 128.3, 128.8, 137.4, 147.1, 149.4, 149.9 (d, J = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.6; LC/MS m/z 455 $[M+1]^+$; Anal. Calcd. for $C_{19}H_{23}N_2O_7PS$: C, 50.22; H, 5.10; N, 6.16; Found: C, 50.32; H, 5.06; N, 6.23.

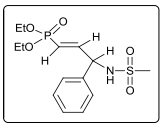
(*E*)-Diethyl 3-(*N*-butylphenylsulfonamido)-3-phenylprop-1-enylphosphonate (5d): Reaction was performed with **4a** (0.500 g) for 12h at room temperature. Yield 0.706 g (82%),



gummy collorless liquid; IR (KBr, cm^{-1}) 2985, 1634, 155, 1324, 1031, 974; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66-0.69 (m, 3H), 0.991-1.04 (m, 3H), 1.28-1.34 (m, 7H), 3.03-3.05 (m, 2H), 3.99-4.08 (m, 4H), 5.71-5.79 (m, 2H), 6.82-6.94 (m, 1H), 7.12-7.13 (m, 2H), 7.27-7.28 (m, 3H), 7.46-7.58 (m, 3H), 7.79-7.82 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.4, 16.3 and 16.4 (d, J = 6.3 Hz each), 19.9, 32.3, 45.6, 61.8 and 61.9 (d, J = 5.7 Hz each), 62.9

(d, *J* = 23.3 Hz), 121.1 (d, *J*= 186.7 Hz), 127.2, 128.4, 128.5, 128.7, 129.1, 132.5, 136.7, 140.7, 148.1 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.9. a small peak (~8%) was appeared at δ 18.7 might be due to the other isomers. LC/MS m/z 466 $[M+1]^+$; Anal. Calcd. for $C_{23}H_{32}NO_5PS$: C, 59.34; H, 6.93; N, 3.01. Found: C, 59.42; H, 6.85; N, 3.08.

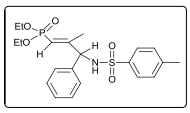
(*E*)-Diethyl 3-(methylsulfonamido)-3-phenylprop-1-enylphosphonate (5e): This reaction was performed using **4a** (0.200 g, 0.740 mmol), methanesolfonamide (0.14 g, 1.48 mmol) and TfOH



(0.065mL,0.740 mmol) in b1,4-dioxane (3.0 mL) under air at room temperature for 14 h. Yield 0.21 g (82%), white solid; mp 93-95 ^oC; IR (KBr, cm^{-1}) 3133, 1625, 1464, 1317, 1151, 1043; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.33 (m, 6H), 2.70 (s, 3H), 4.02-4.11 (m, 4H), 5.21-5.23 (br, 1H), 5.89-5.98 (m, 1H), 6.13 (d, *J* = 8.2 Hz, 1H), 6.88 (ddd, *J* = 21.8, 17.1, 5.3 Hz, 1H), 7.32-7.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.4 (d, *J* = 6.2 Hz each), 41.9, 59.7 (d, *J* = 23.2 Hz), 62.1 and 62.2 (d, *J* = 5.7 Hz each), 118.4 (d, *J* = 187.4 Hz), 127.4, 128.5, 129.2, 138.5, 150.4 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.9; LC/MS m/z 348 $[M+1]^+$; Anal. Calcd. for $C_{14}H_{22}NO_5PS$: C, 48.41; H, 6.38; N, 4.03. Found: C, 48.29; H, 6.31; N, 4.07.

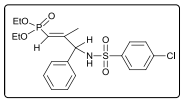
(*E*)-Diethyl 2-methyl-3-(4-methylphenylsulfonamido)-3-phenylprop-1-enylphosphonate (5f): This compound was synthesized by using **4b** (0.300 g, 1.055 mmol), *p*-toulenesolfonamide (0.18 g, 1.055 mmol) and 1,4-dioxane (3.0mL) in open air at room temperature for 10 h in the presence of TfOH (0.09mL,1.055 mmol). Yield 0.410 g (88 %);

White solid; mp 140-142 ^oC; IR (KBr, cm^{-1}) 3122, 1628, 1476, 1325, 1224, 1163, 1020; ^{1}H



NMR (500 MHz, $CDCl_3$) δ 1.29-1.33 (m, 6H), 1.90-1.91 (m, 3H), 2.41 (s, 3H), 3.98-4.07 (m, 4H), 4.80 (d, *J*= 7.0 Hz, 1H), 5.05 (d, *J*= 6.9 Hz, 1H), 5.88 (d, *J*= 17.5 Hz, 1H), 6.99 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.22-7.24 (m, 5H), 7.65 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.5 and 16.6 (d, *J* ~ 5.8 Hz each), 18.0 (d, *J* = 6.8 Hz), 21.7, 61.6 and 61.8 (d, *J* = 5.6 Hz), 64.7 (d, *J* = 23.0 Hz), 114.4 (d, *J*= 188.4 Hz), 127.3, 127.4, 128.7, 129.2, 129.8, 137.4, 137.8, 143.8, 158.4 (d, *J*= 8.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.4; LC/MS m/z 438 $[M+1]^+$; Anal. Calcd. for $C_{21}H_{28}NO_5PS$: C, 57.65; H, 6.45; N, 3.20; Found: C, 57.73; H, 6.41; N, 3.12.

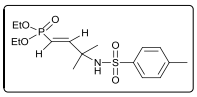
(*E*)-Diethyl 2-methyl-3-(4-chlorophenylsulfonamido)-3-phenylprop-1-enylphosphonate (5g): The reaction mixture was stirred for 12 h by staring with **4b** (0.500 g, 1.759 mmol).

Yield 0.73 g (90%); white solid; mp 120-125 ^{o}C; IR (KBr, cm^{-1}) 3102, 2897, 1643, 1478, 1327,  1218, 1163, 1026; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28-1.33 (m, 6H), 1.91 (s, 3H), 3.98-4.07 (m, 4H), 4.87 (d, *J*= 8.0 Hz, 1H), 5.79–5.83 (m, 2H), 7.01-7.02 (m, 2H), 7.19-7.24 (m, 3H), 7.35-7.36 (m, 2H), 7.64-7.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.5 and 16.6 (d, *J* ~ 5.8 Hz each), 18.2 (d, *J* = 6.8 Hz), 61.8 and 61.9 (d, *J* = 5.6 Hz), 64.7 (d, *J* = 22.9 Hz), 114.4 (d, *J*= 189.1 Hz), 127.5, 128.6, 128.7, 129.2, 129.4, 137.5, 139.1, 139.2, 158.3 (d, *J*= 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.2; LC/MS m/z 458 $[M+1]^+$; Anal. Calcd. for $C_{20}H_{25}NClO_5PS$: C, 52.46; H, 5.50; N, 3.06; Found: C, 52.36; H, 5.58; N, 3.12.

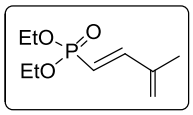
2.7.8 *$FeCl_3$ mediated reaction 4c with $TsNH_2$:*

Anhydrous $FeCl_3$ (0.218 g, 1.35 mmol) was added to a stirred solution of **4c** (0.300 g, 1.35 mmol) and $TsNH_2$ (0.230 g, 1.35 mmol) in 1,2-dichloroethane (4.0 mL) and the reaction mixture was stirred at room temperature under N_2 for 6 h. The crude product was purified by column chromatography using EtOAc/petroleum ether as the eluent to afford the diene **6** (using 20 % EtOAc in pet ether) followed by compound **5h** (70 % EtOAc in pet ether)**.**

2.7.9 *Analytical data for the synthesized compound 5h*

(*E*)-Diethyl 3-methyl-3-(N-butylphenylsulfonamido)-3-phenylprop-1-enylphosphonate (5h): Anhydrous $FeCl_3$ (0.218 g, 1.35 mmol) was added to a stirred solution of **4c** (0.300 g, 1.35 mmol) and *p*-toulenesolfonamide (0.230 g, 1.35 mmol) in 1,2-dichloroethane (4.0mL) and the  reaction mixture was stirred at room temperature under N_2 for 6 h. The crude product was purified by column chromatography using (70% ethylacetate/petroleum ether) as the eluent to afford **5h.** Yield 0.285 g (56%); white solid; mp 92-95 ^{o}C; IR (KBr, cm^{-1}):3114, 1631, 1322, 1222, 1144, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.34 (m, 12H), 2.42 (m, 3H), 4.03-4.09 (m, 4H), 5.06 (s, br, 1H), 5.79 (dd→t, *J* = 17.6 Hz each, 1H), 6.69 (dd, *J* = 22.4 and 17.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.4 (d, *J* = 6.3 Hz), 21.5, 27.3, 57.4 (d, *J* = 21.9 Hz), 61.9 (d, *J* = 5.4 Hz), 114.9 (d, *J*= 187.0 Hz), 126.9, 129.6, 140.1, 143.1, 156.6 (d, *J* = 4.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.2; LC/MS m/z 376 $[M+1]^+$; Anal. Calcd. for $C_{16}H_{26}NO_5PS$: C, 51.19; H, 6.98; N, 3.73. Found: C, 51.26; H, 6.91; N, 3.65.

2.7.10 *Analytical data of 1,3-diene*

 **(*E*)-Diethyl 3-methylbuta-1,3-dienylphosphonate (6):** In the presence of TfOH, the phosphonate 4c gives this diene 6 with a quantitative yield at room

temperature within 2 h under nitrogen atmosphere using 1,4-dioxane as a solvent.

Yield 0.055 g (20 %);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* =7.2 Hz each, 6H), 1.79 (s, 3H), 3.88-4.12 (m, 4H), 5.24-5.25 (br, 2H), 5.55-5.64 (m, 1H), 7.09 (dd, *J* ~18 and 21.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 (d, *J* = 6.3 Hz each), 17.6, 61.6 (d, *J* = 5.6 Hz), 114.6 (d, *J* = 191.6 Hz), 123.6, 140.6 (d, *J*= 23.8 Hz), 151.0 (d, *J*= 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.9; LC/MS m/z 205 $[M+1]^+$.

2.8 Crystal data for compound 5a

Complex	**Compound (5a)**
Chemical formula	C_{20} H_{26} N O_5 P S
Formula weight	423.45
Crystal system	Triclinic
Space group	*P-1*
a (Å)	10.8332(8)
b (Å)	10.9777(8)
c (Å)	10.9787(8)
α (°)	93.9990(10)
β (°)	107.3030(10)
γ (°)	116.9270(10)
V (Å^3)	1078.87(14)
Z	2
ρ (g cm^{-3})	1.303
μ (mm^{-1})	0.157
Reflections collected	10411
Reflections unique	3780
Reflections [$I \geq 2\sigma(I)$]	974
Parameters	448
*R*1, *wR*2 [$I \geq 2\sigma(I)$]	0.0472, 0.1290
*R*1, *wR*2 [all data]	0.0538, 0.1353
GOF on F^2	1.052
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.514 / -0.362

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Chapter 3

Synthesis of ketophosphonates

3.1 Introduction

In the family of organophosphonates, *γ*-ketophosphonates, a subclass of ketophosphonates, have received significant concern in synthetic and biological chemistry. These phosphonates are extensively explored to exhibit diverse biological activities. For some examples **(Fig 3.1)**, these are used as herbicides[1] (**1A**), fungicides[1] (**1B**) and also as antihypertensive agents (**1C**).[2] Compounds (**1D-E)** have been proposed as remedies for the treatment of osteoporosis,[3] and compounds (**1F-G)** are employed as inhibitors of matrix-metalloprotease (MMP-2) and kininogenase.[4] The *γ*-ketophosphonic acid (**1H)** is recognized as an inhibitor of 5-alanine levulinic acid dehydratase, an early enzyme on the tetrapyrrole biosynthetic pathway.[5] Another *γ*-keto phosphonate (**1I)** is also identified as a tight binding inhibitor of D-alanine and D-alanine ligase, an essential enzyme in bacterial wall synthesis.[6] Notably, the presence of a substituent at *α*-position plays a key role to make these *γ*-ketophosphonates (**Fig 3.1**) more biologically active.[7-8] Furthermore, these *γ*-ketophosphonates have also been considered as precursors for the synthesis of biologically relevant *γ*-hydroxyphosphonates [9] and also to synthesise *methylenomycin-B,* a natural product that belongs to a family of cyclopentanoid antibiotics.[10]

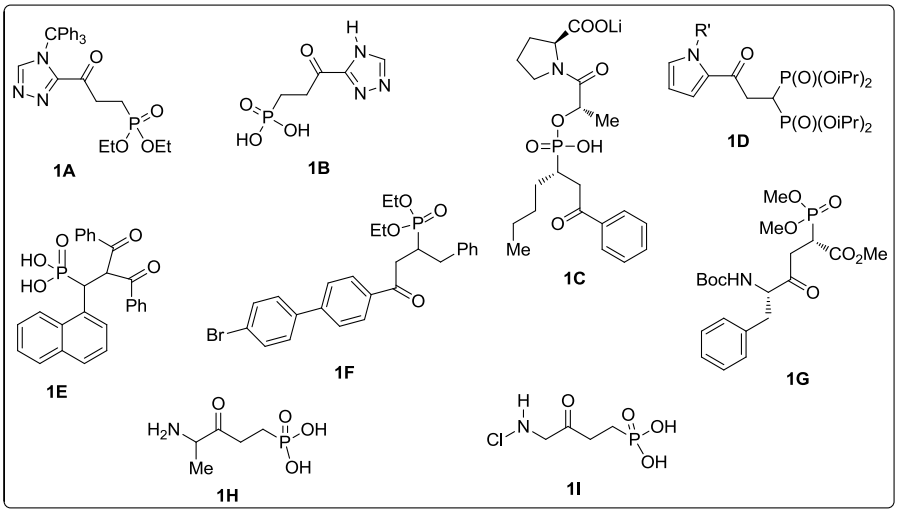


Fig 3.1 Few known examples of biologically significant γ-ketophosphonates **1A-1I**

Further, the *ω*-ketovinylphosphonates are another subclass of organophosphonates containing both keto and vinyl functionalities. The vinyl and ketophosphonates have shown their individual identities as useful classes of compounds in the field of organic synthesis[11, 12] and material sciences.[13, 14] The phosphonates bearing both vinyl and keto functionalities have also revealed their utility to synthesize natural products having cyclopentenone ring system like Jasmone.[15] An effective antitumor agent, sarkomycin was produced using several steps starting

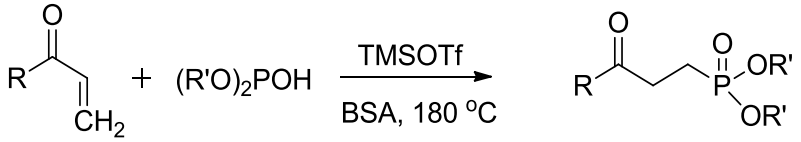
from similar type of phosphonates.[16] In literature, these are known to be used in Wacker oxidation to obtain diketophosphonate, a novel precursor to generate cyclopentenone *via* intramolecular HWE reaction.[17] Further, *ω*-ketovinyl phosphonates were utilized to synthesize the first phosphonate analogue of cyclophostin a natural acetylcholinesterase inhibitor.[18] Therefore, we intend to explore on the advancement of the synthetic methodologies for these phosphonates and their new analogues. Subsequently we also plan to apply these keto phosphonates in the organic synthesis to generate new 1,3-aromatic diketones linked with extended π-conjugated systems.

3.2 Literature review

3.2.1 *Synthesis of α- substituted and unsubstituted γ-ketophosphonates*

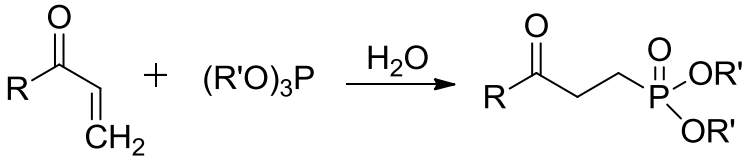
Some available methods for the synthesis of *α- substituted* and *unsubstituted γ*-ketophosphonates are discussed below. The conjugate addition of phosphites/phosphines with enones is the most common approach for the formation of γ-keto phosphonates.

Birum *et al.*[19] developed a method for the formation of *γ*-ketophosphonates involved the addition of silyl phosphites to *α,β*-unsaturated carbonyls (**Scheme 3.1**). The lack of specific reaction conditions and unreported product ratios led other research groups to study this reaction in greater detail. Further Evans *et al.*[20] studied this reaction, competition between 1,2- and 1,4-addition pathways were observed, yet the 1,4 addition pathway could be optimized when reactions were performed at 180 °C in a sealed tube **(Scheme 3.1)**.



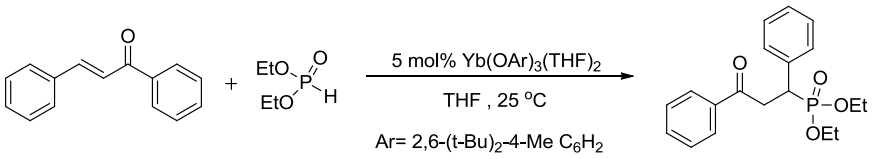
Scheme 3.1 Addition of silyl phosphites to α,*β*-unsaturated carbonyls to synthesis of *γ*-ketophosphonates

A route to synthesis of *γ*-ketophosphonates was reported by Gorenstein *et al.*[21] and further same method was developed by McClure and co-workers [22] through the conjugate addition of trialkylphosphite to *α,β*-unsubstituted ketones followed by hydrolysis of the intermediate oxaphospharane **(Scheme 3.2)**.



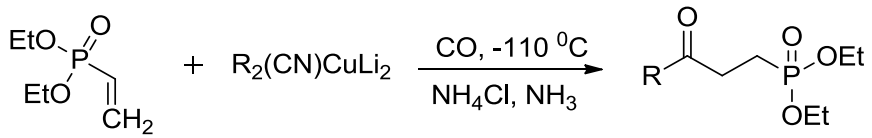
Scheme 3.2 Addition of trialkyl phosphites to *α,β*-unsaturated ketone to synthesis of *γ*-ketophosphonates

Qi Shen *et al.* [23] developed lanthanide aryl oxides as an efficient catalytic system for the phospha-Michael addition of diethylphosphite with chalcones under mild conditions to afford *γ*-ketophosphonates in good yields **(Scheme 3.3)**.



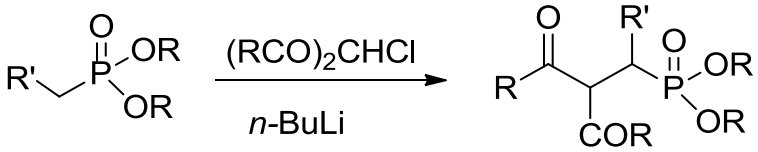
Scheme 3.3 Lanthanide aryl oxides catalyzed synthesis of *γ*-ketophosphonates

The formation of *γ*-ketophosphonates from acylcyanocuprate reagents was reported by Kabalka *et al.*[24] this reagent was prepared in situ *via* the carbonylation of dialkylcyanocuprates with carbon monoxide at -110 °C using a mixed solvent system of THF/diethylether and pentane, react with diethyl vinylphosphonate at -110 °C. Hydrolysis of the reaction mixture at 0 °C gives 3-ketoalkylphosphonates in good yields **(Scheme 3.4)**.



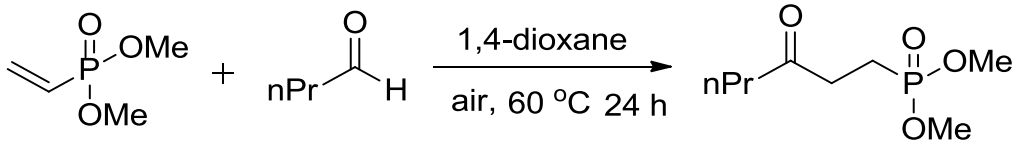
Scheme 3.4 Acylcyanocuprate catalyzed synthesis of *γ*-ketophosphonates

The *γ*-ketophosphonates was also synthesised by Lau *et al.*[25] *via* deprotonation of alkylphosphonate using very strong, air/moisture sensitive base *n*-BuLi followed by the treatment of halogenated compounds **(Scheme 3.5)**.



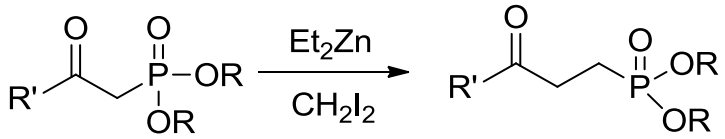
Scheme 3.5 *n*-BuLi meadiated synthesis of γ-ketophosphonates

Caddick *et al.*[26] synthesised *γ*-ketophosphonates under mild conditions *via* aerobic hydroacylation of vinyl phosphonates with both simple and notably functionalised aldehydes. Reported aerobic hydroacylation of vinylphosphonates was ineffective to afford *α*- substituted *γ*-ketophosphonates **(Scheme 3.6)**.



Scheme 3.6 Synthesis of *γ*-ketophosphonates from aerobic hydroacylation of vinylphosphonates

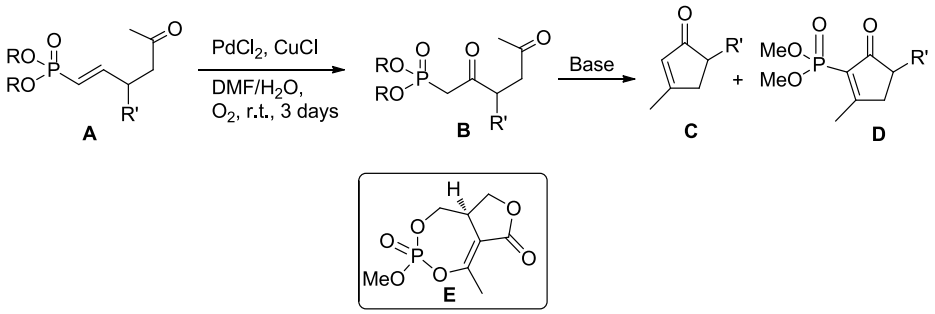
Zercher *et al.*[27] reported the conversion of *β*-keto phosphonates to *γ*-keto phosphonates using the reagent ethyl(iodomethyl)zinc. The presence of *α*-alkyl substituents, Lewis basic functionality, and modestly acidic *NH* protons are accommodated in substrates of this reaction **(Scheme 3.7**).



Scheme 3.7 Diethylzinc meadiated synthesis of *γ*-ketophosphonates

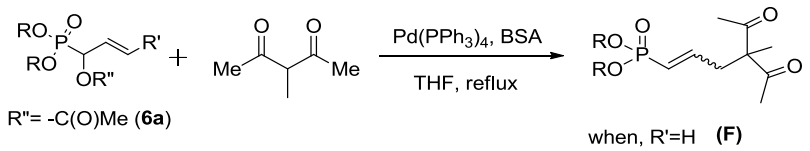
3.2.2 *Synthesis of ω-ketovinyl phosphonates*

The relevant research work on *ω*-ketovinyl phosphonate (**A**) by Spilling *et al.*[17] brings special attention where these compounds are used in Wacker oxidation to obtain diketophosphonate (**B**), a noble precursor to generate cyclopentenone (**C**) (*via* intramolecular HWE reaction) along with phosphonocyclopentenone (**D**) (**Scheme 3.8**).[17] The compound (**D**) was also obtained from diketophosphonate (**B**) at room temperature in the presence of silica gel.



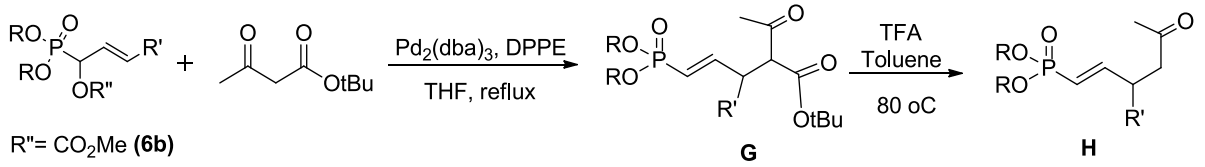
Scheme 3.8 Reported synthetic routes for *ω*-ketovinyl phosphonates

Further, *ω*-ketovinyl phosphonate was utilized by the same research group to synthesize the first phosphonate analogue of cyclophostin (**E)** (**Scheme 3.8**), a natural acetyl cholinesterase inhibitor.[18] Hence, an easy synthesis of *ω*-ketovinyl phosphonate followed by applications would be a topic of significant interest. The original approach for synthesizing *ω*-ketovinyl phosphonate (**F)** (**Scheme 3.9**) includes the $Pd(PPh_3)_4$-catalyzed reactions of *α*-acetoxy allylic phosphonate (**6a)** with 1,3-diketone *via* umpolung[27] in allylic phosphonates.



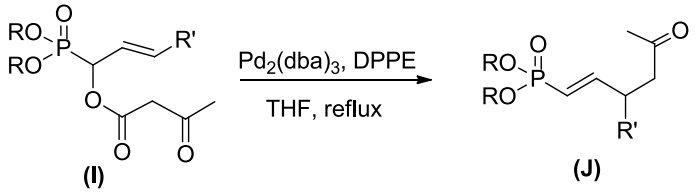
Scheme 3.9 Reported synthetic routes for *ω*-ketovinyl phosphonates

Later, compound (**G)** was prepared from the reaction of phosphono allylic carbonate (**6b)** with *t*-butylacetoacetate using Pd/DPPE as catalyst and then successive trifluoroacetic acid (TFA) mediated hydrolysis of (**G)** led to the formation of ω-ketovinyl phosphonate (**H)** (**Scheme 3.10)**.[27]



Scheme 3.10 Reported synthetic routes for ω-ketovinyl phosphonates

The Pd-catalyzed decarboxylative rearrangement of phosphono allylic acetoacetate **I (Scheme 3.11)** also led to the formation of ω-ketovinyl phosphonate(**J**).[17] Although these are undoubtedly useful processes, these synthetic strategies suffer with difficulties such as necessity of expensive palladium/ligand, synthesis of starting materials (**6a-b** or **I**) using environmentally hazardous pyridine, methylchloroformate or unstable diketene. The other potential pitfalls include less yield, decomposition of starting material on prolonged storage and competitive unavoidable formation of phosphonodiene along with the desired ketophosphonate.

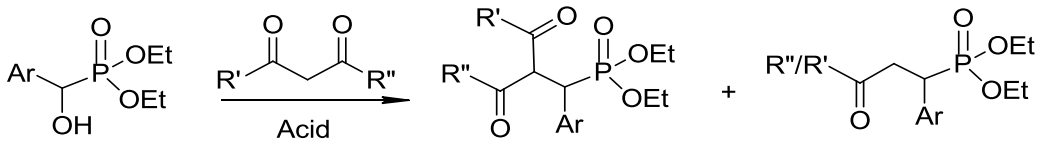


Scheme 3.11 Reported synthetic routes for ω-ketovinyl phosphonates

3.3 Results and discussion

3.3.1 *Synthesis of γ-ketophosphonates*

From our investigations, we could develop a handy and economical Lewis acid mediated route to access a range of α-aryl substituted γ-ketophosphonates from easily accessible α-hydroxyphosphonates and 1,3-diketones mostly under solvent free conditions as shown in **Scheme 3.12**.



Scheme 3.12 Acid mediated synthetic routes for γ-Di&mono ketophosphonates

Even though Lewis acid catalysed benzylation of 1,3-diketones is familiar,[28-29] the presence of phosphoryl group makes the chemistry more interesting[30, 31] to afford the biologically important *γ*-ketophosphonates efficiently in a convenient protocol. A subsequent regioselective C-C bond cleavage for the phosphoryl substituted 1,3-diketones is also discovering *via* tandem fashion on employing different reaction conditions *exclusive of any separate alcohol treatment.* The iron(III)/other metal mediated C-C bond cleavage to produce a ketone is known in the literature only *in the presence of alcohol*.[32]

In this study, *α*-hydroxyphosphonates (**1a-e, Fig 3.2**, synthesised by following Pudovik reaction of phosphite and aldehydes) [33] and commercially available 1,3-diketones (**2a-d**, **Fig 3.2**) were preferred with a consideration of accessibility, structural reactivity and diversity.

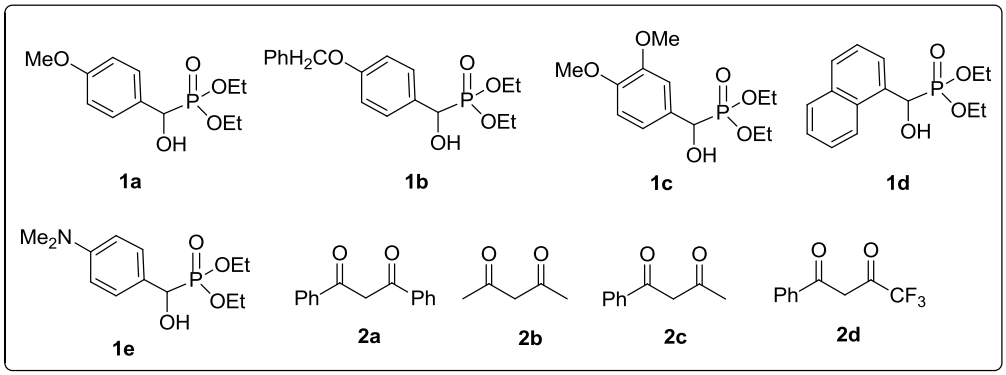
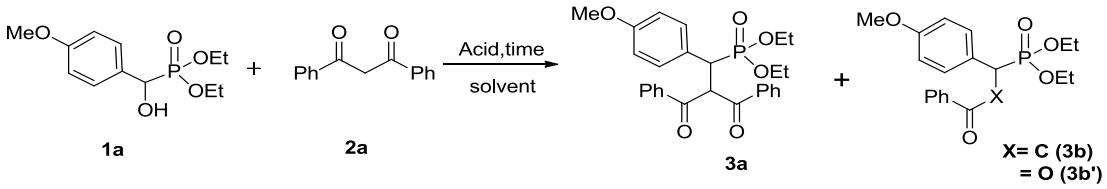


Fig 3.2 The hydroxyphosphonates and 1, 3-diketones used as precursors

The initial study was focused on the screening of different acids for the reactions of easily accessible inexpensive phosphonate (**1a)** and symmetrical 1,3-diketone (**2a)** to afford the *γ*-ketophosphonates **3a** and **3b** where **3b** is a C-C bond cleaved product. It was found that the acids, solvent and temperature affect the product ratio (**3a**:**3b**) significantly (**Table 3.1**). Brønsted acids such as triflic acid (TfOH) and *p*-toluenesulfonic acid (*p*-TSA) were also quite effective (entries **14-16, Table 3.1**) for this reaction but are not much explored herein.

Table 3.1 Reactions of 1a with 2a under different reaction conditions [a]



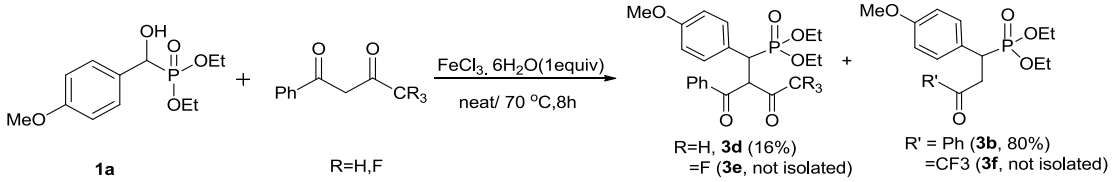
Entry	Acid	Solvent	Time(h)/Temp (^oC)	Isolated yield:3a/3b
1.	$FeCl_3$	neat	8/70	90/trace
2.	$FeCl_3$	nitromethane	10/70	90/trace
3	$FeCl_3$	nitromethane	6/28	90/0
4	$FeCl_3$	dichloroethane	8/28	85/0
5.	$FeCl_3$	water (0.08 ml)	1/90	80/0
6.	$FeCl_3$	water (0.08 ml)	8/90	25/75
7.	$FeCl_3.6H_2O$	neat	8/70	trace/90[b]
8.	$FeCl_3.6H_2O$	dichloroethane[c]	12/70	30/70
9	$FeCl_3.6H_2O$	dichloroethane[c]	15/28	40[d]
10	$FeCl_3.6H_2O$	1,4-dioxane	15/28	60/40
11.	$Cu(OTf)_2$	nitromethane	12/28	80/trace
12.	$CuCl_2$	nitromethane	12/28	80/trace
13.	$Cu(OAc)_2$	nitromethane	12/28	No reaction
14	TfOH	1,4-dioxane	12/28	70/0[e]
15	AcOH	neat	12/28 or 70	No reaction
16	p-TSA	nitromethane	12/60	80/0

[a] Reaction conditions: **1a** (1 equiv), **2a** (1 equiv) and acid (1 equiv) in a stoppered flask without exclusion of moisture/air using the LR grade solvent. [b] The ^{31}P NMR spectrum of reaction mixture showed the formation of **3b** in 98%. [c] nitromethane solvent also showed the same result. [d] remaining starting material (**1a**) was recovered. [e] The ^{31}P NMR spectrum for the reaction mixture showed another unassigned peak at δ22.1 (~30%).

The results shown in entries 1 and 7 (**Table 3.1)** incited us to perform the reaction using anhydrous $FeCl_3$ with two drops of water (0.08 ml) and that showed the consumption of both starting materials within 1 h at 90 ^oC to form compound **3a**, After 8h, **3a**/**3b** was isolated as a mixture in 1/3 ratio. The mixture of **3a** and **3b** was easily converted to only **3b** by treating with $FeCl_3.6H_2O$ at 60 ^oC for 5-6 h or by refluxing the mixture in the presence of $FeCl_3$ and methanol for 4 h. Although another C-C bond cleaved product, ester (**3b'**, **Table 3.1**) is expected from the reported Lewis acid mediated reactions of secondary alcohols and 1,3-diketones,[34] we could not find any product of type **3b'** during our investigations (verified by ^{31}P NMR spectrum of the

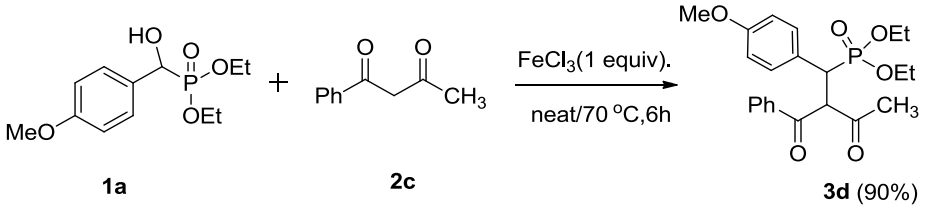
reaction mixture). Being inexpensive and efficient Lewis acid, $FeCl_3.6H_2O$ was selected to run other reactions of phosphonate **1a** with diketones **2b-d** under solvent-free conditions at 70 ^oC but the reaction was not clean in case of symmetrical 1,3- diketone **2b**.

For both unsymmetrical 1,3-diketones **2c** and **2d**, phosphonate **1a** generated **3b** as a major regioselective C-C bond cleaved product in 80% and 95% yield respectively when $FeCl_3.6H_2O$ was used under neat conditions at 70 ^oC. Although phosphonylated diketone **3d** was isolated in 16% yield from the reaction with **2c** but compound of type **3e** (expected from **2d**) could not be isolated **(Scheme 3.13)**.



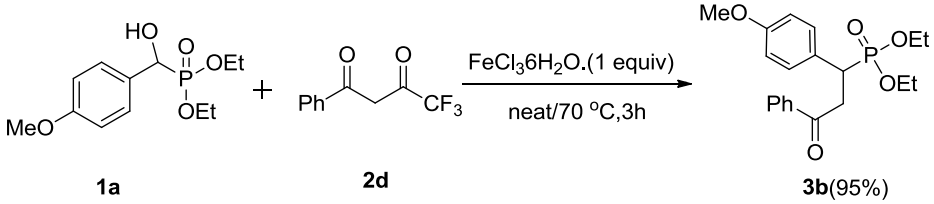
Scheme 3.13 Acid mediated synthetic route for γ –di and mono ketophosphonates(**3b&3d**)

This observation was even consistent for the reactions of other phosphonates **1b-e** with unsymmetrical 1,3-diketones like **2c-d**. The yield of **3d** was increased to ~90% by replacing $FeCl_3.6H_2O$ with anhydrous $FeCl_3$ **(Scheme 3.14)**.



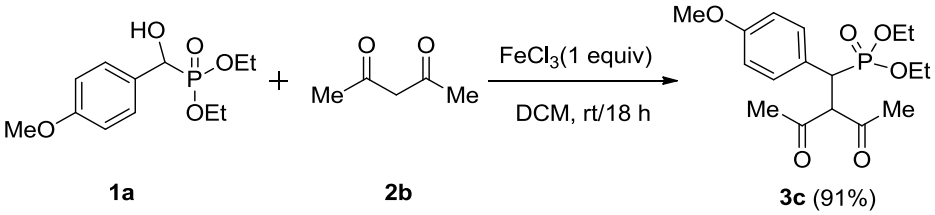
Scheme 3.14 Acid mediated synthetic route for γ –diketophosphonates(**3d**)

The presence of $-CF_3$ group made the system comparatively more reactive to form the C-C bond cleaved product **3b** in 95% yield **(Scheme 3.15)**.



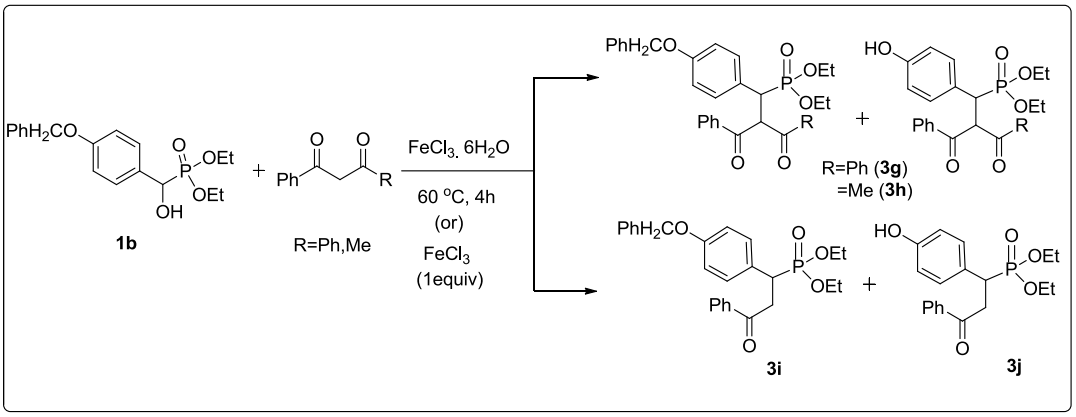
Scheme 3.15 Acid mediated synthetic route for γ –monoketophosphonates(**3b**)

The only phosphonylated 1,3-diketone (γ-diketophosphonate **3c**) was obtained from the reaction of **2b** with **1a** at room temperature (28 ^oC) in dichloromethane (DCM) in the presence of anhydrous $FeCl_3$ **(Scheme 3.16)**. No C-C bond cleaved product was obtained from **3c** even after repeated efforts under different reaction conditions.



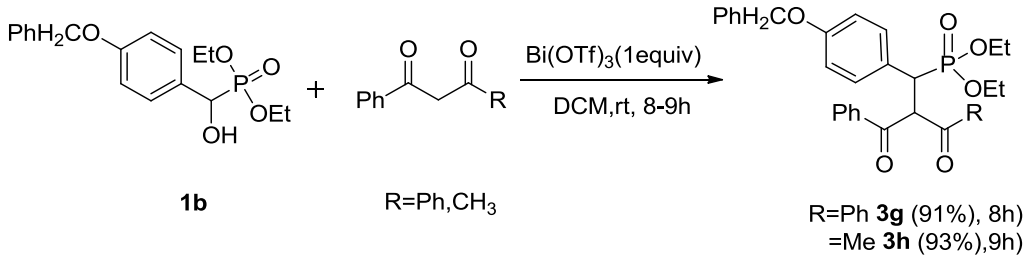
Scheme 3.16 Acid mediated synthetic route for γ–diketophosphonates(**3c**)

The phosphonate **1b** generated a mixture of products (of type **3g-h, 3i** and **3j**) from reactions with **2a** or **2c** under the same reaction conditions ($FeCl_3.6H_2O$, 8h, 70 ^oC) **(Scheme 3.17)**. Attempt to use anhydrous $FeCl_3$ under neat conditions at 70 ^oC or in nitromethane at 28 ^oC also led to the same result.



Scheme 3.17 Ferric chloride mediated reaction of **1b** with 1,3-diketones **2a** or **2c**

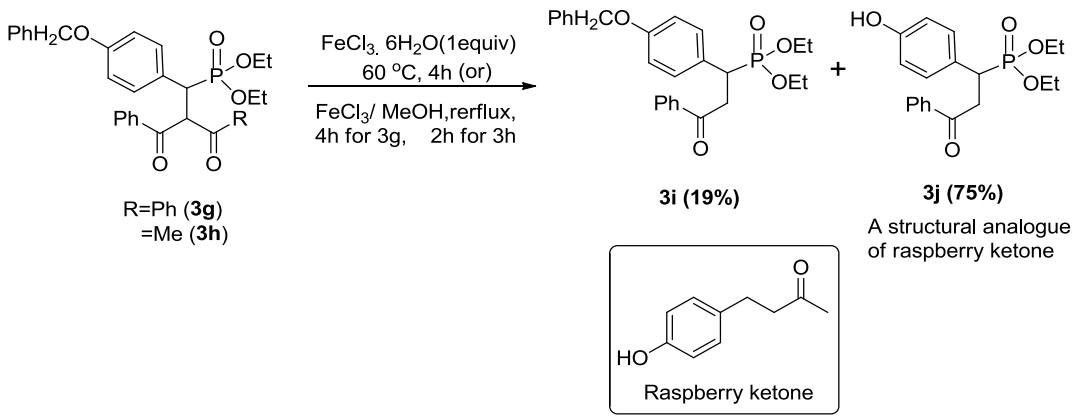
Gratifyingly, the use of $Bi(OTf)_3$ as a Lewis acid produced the 1,3-diketones **3g-h** in >90% yield (**Scheme 3.18**).



Scheme 3.18 $Bi(OTf)_3$ mediated reaction of **1b** with 1,3-diketones **2a** or **2c**

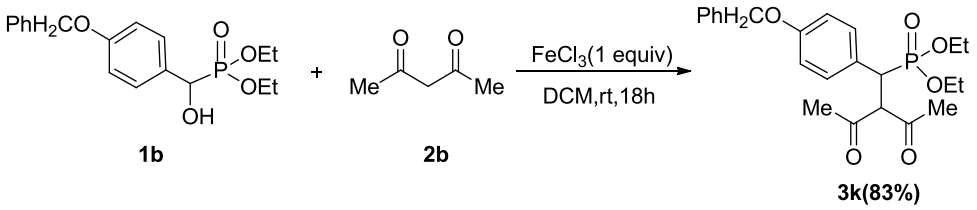
Moreover, Fe(III) mediated regioselective bond cleavage for both compounds **3g-h** afforded expected compound **3i** (19%) as a minor product along with **3j** (75%) as a major product due to the favourable acid mediated O-CH_2Ph bond breakage **(Scheme 3.19)**. Compound **3h** was found to be more reactive compared to **3g** in terms of the C-C bond cleavage reaction. In this approach, phenol functionality at α-carbon of γ-ketophosphonate has been easily introduced by starting

with **1b**. This ketone (**3j**) is a structural analogue of *raspberry ketone*, [11] a low-abundant natural product that contains a phenolic group.



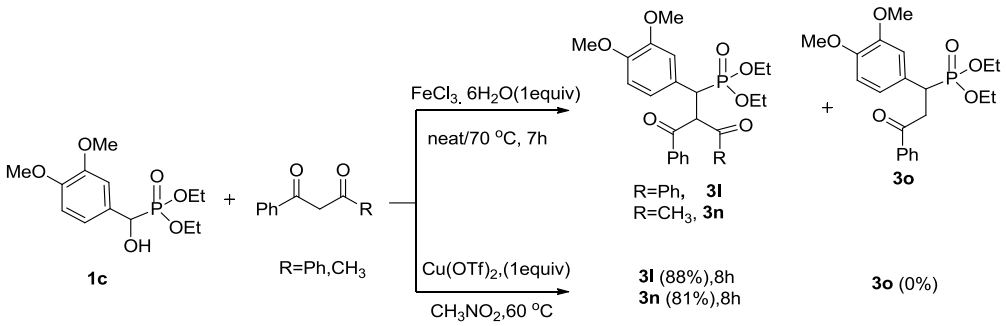
Scheme 3.19 Acid mediated synthetic route for γ –monoketophosphonate(**3i&3j**)

The phosphonylated 1,3-diketone (**3k**) was synthesised from reaction of phosphonate (**1b)** with acetylacetone (**2b**) by using anhydrous $FeCl_3$ in dichloromethane at rt. It is noted that the duration of reaction with phosphonates is comparatively higher for **2b** (18-30 h) than for other 1,3-diketones **(Scheme 3.20)**.



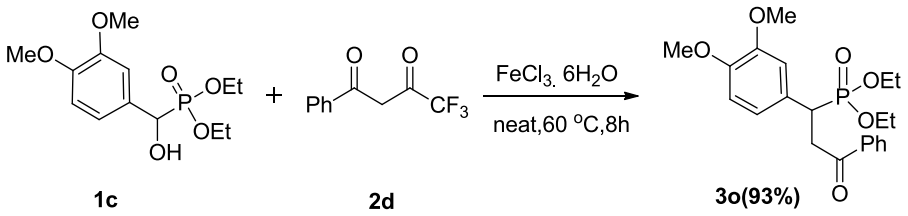
Scheme 3.20 Acid mediated synthetic route for γ-diketophosphonate(**3k**)

While dealing with the phosphonate **1c,** Fe(III)-mediated reaction of phosphonate **1c** with 1,3-diketone **2a** and **2c** generated a mixture of products (di-keto and mono keto). The ^{31}P NMR of the reaction mixture for the reaction with **1c** and **2c** showed the presence of products of type **3n** (~82% with a diastereomeric ratio 1:4) and regioselective C-C bond cleaved product monoketone **3o** in 18%.



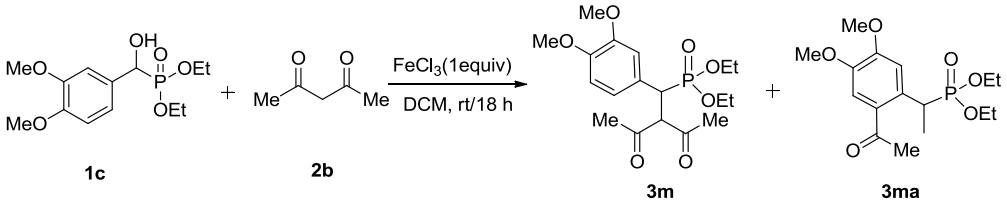
Scheme 3.21 Acid mediated synthetic route for γ –di and monoketophosphonates

It was very difficult to isolate the product **3l**, **3n** and **3o** in pure form from these reaction mixtures therefore inspiring with the result obtained from table 1 (entry 11), $Cu(OTf)_2$ gave a promising outcome to obtain **3l** and **3n** in pure form with high yield (**Scheme 3.21**). Surprisingly, using $Cu(OTf)_2$ reaction was not clean in case of diketones **2b** and **2d**. The diketone **2d** produced only the **3o** in the presence of $FeCl_3.6H_2O$ under neat condition for 8h at 60°C **(Scheme 3.22)**.



Scheme 3.22 Acid mediated synthetic route for γ –monoketophosphonate(**3o**)

The acetylacetone (**2b**) reacted with phosphonate **(1c)** in the presence of $FeCl_3$ at rt using DCM as solvent to afford the mixture of products **3m** & **3ma** in 1:1 ratio after 18 h **(Scheme 3.23)**. Fortunately, we could isolate the compound **3ma** in pure form by crystallization (DCM/Hexane 1:1). The formation of **3ma** is quite unexpected from this reaction.



Scheme 3.23 Acid mediated synthetic routes for γ –diketophosphonates

In the ^{1}H NMR spectrum (Fig **3.3**) of compound **3ma,** a specific doublet of doublet at δ 2.44 (^2J(PH)= 2.0 Hz, 5.5 Hz) [due to PCH*CH*$_3$] and singlet at δ 2.53 (for O=C-C*H*$_3$.) were observed and that helped us to predict the primary structure of **3ma.**

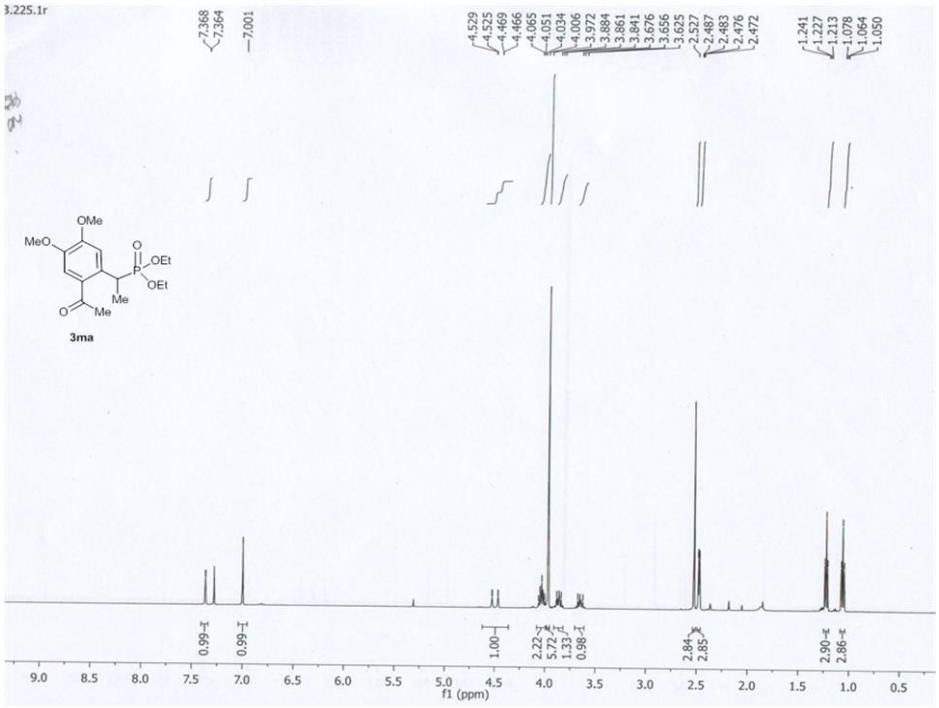
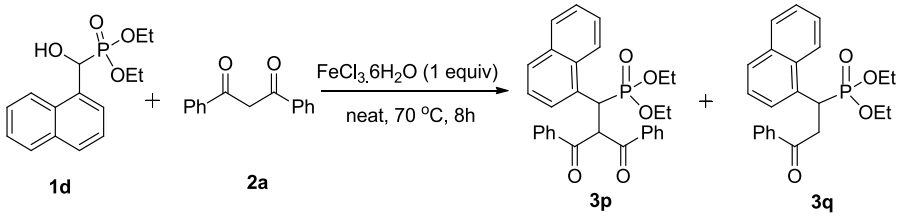


Fig 3.3 ^{1}H NMR spectrum of **3ma**

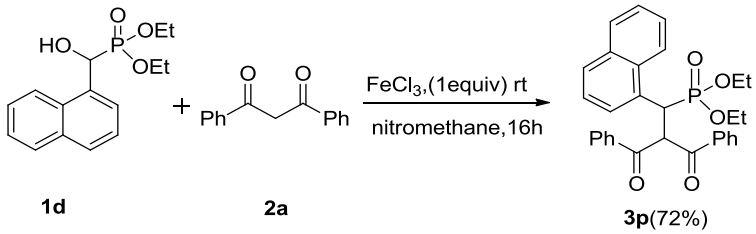
The similar product formation was observed from the reaction mixture from Fe(III) mediated reaction of **1c** with dissymmetric diketone **2c.** As the product is not relevant to *γ*-ketophosphonates, no other examples are included herein. The related studies on this type of unexpected product formation are not explored here and are under further investigations. The only phosphonylated 1,3-diketone (*γ*-ketophosphonate, **3m**) was obtained from the reaction of **2b** with **1c** at room temperature (28 ^{o}C) in dichloromethane (DCM) in the presence of anhydrous $FeCl_3$. In this case also C-C bond cleaved product was not obtained from **3m** even after repeated efforts under different reaction conditions.

With the concern of synthesising useful reported compound of type **1E** (naphthylic phosphonate, **Fig 3.1**), our effort to use naphthalene based *α*-hydroxyphosphonate **1d,** gave a fruitful result with the reactions of 1,3-diketones (**2a-d)** to afford *γ*-ketophosphonates **3p** (phosphonylated 1,3-diketone) and **3q** (phosphonylated monoketone) in excellent yield using Fe(III) as Lewis acid (**Scheme 3.24).** When the reaction between phosphonate **1d** and 1,3-diketone **2a** was performed using $FeCl_3.6H_2O$ under neat conditions at 70 ^{o}C, the reaction mixture showed the presence of diketone **3p** (5%) and regioselective C-C bond cleaved product monoketone **3q** (92%) in the ^{31}P NMR spectrum. It was very difficult to isolate the diketone **3p** through this method.



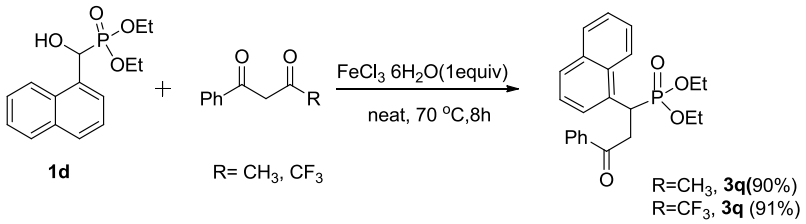
Scheme 3.24 Acid mediated synthetic route for γ –di and monoketophosphonate

The diketone **3p** was isolated in 72% yield by using anhydrous $FeCl_3$ in nitromethane after 16 h (**Scheme 3.25)**. The same reaction was also run using $Bi(OTf)_3$ but partial (~40%) conversion from **1d** to **3p** was observed, even after heating for 8 h(remaining 60% starting was consumed).



Scheme 3.25 Acid mediated synthetic route for γ –diketophosphonate(**3p**)

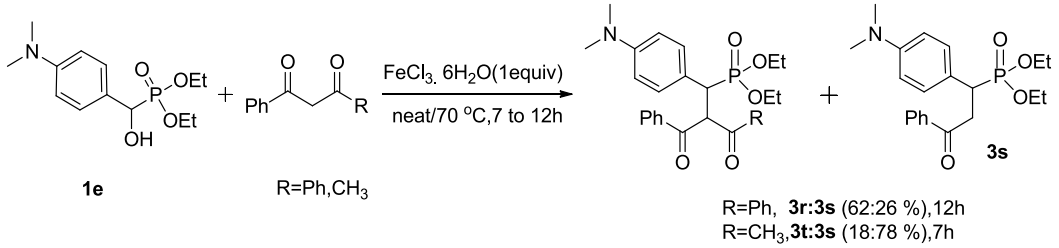
Both the unsymmetrical diketones **2c-d** generated compound **3q** in excellent yield, **(Scheme 3.26)** but corresponding phosphonylated 1,3-diketones were not isolated.



Scheme 3.26 Acid mediated synthetic route for γ –monoketophosphonate(**3q**)

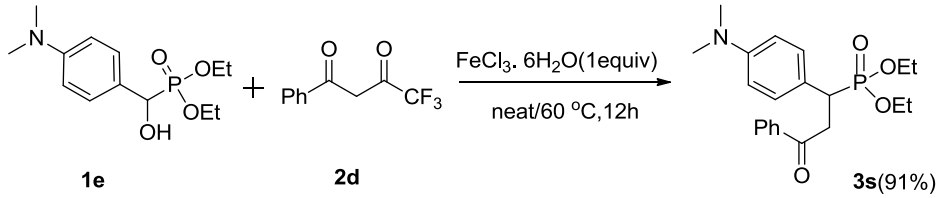
Using this protocol, one can avoid using toxic halogenated and air/moisture sensitive compounds or pathways[25] to synthesise α-naphthyl substituted γ-ketophosphonates (**3p-q)** efficiently. The acetylacetone (**2b**) was not reactive towards phosphonate **1d** to obtain the desired product under the present reaction conditions.

The α-dimethylamino substituted γ-ketophosphonates [phosphonylated 1,3-diketones **3r** and **3t-u** and monoketone **3s** were obtained by starting from phosphonate **1e** and diketones **2a-d** using Fe(III)-mediated reactions. All these reactions were carried out under neat conditions at 70 ^{o}C except in case of synthesising **3u** as mentioned before. The reaction of **1e** with **2a** generated **3r** in 63% and **3s** in 27% yield where **2c** gave almost the same result like **2a** to afford compounds **3t** and **3s** (**Scheme 3.27**) in 18% and 78% yields, respectively.



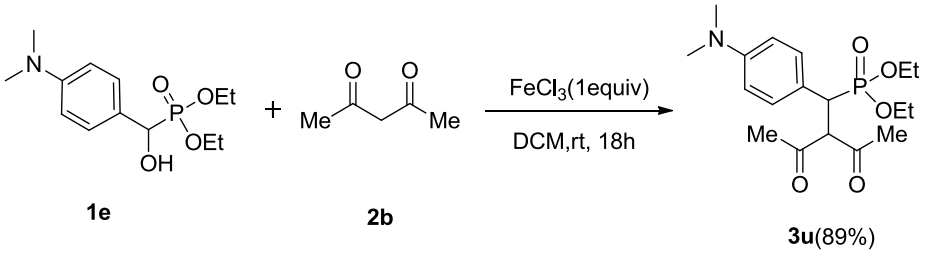
Scheme 3.27 Acid mediated synthetic route for γ –di and monoketophosphonates(**3r,3t&3s**)

Only phosphonylated monoketone **3s** was isolated when 1,3-diketone **2d** was used for the reaction **(Scheme 3.28)**.



Scheme 3.28 Acid mediated synthetic route for γ –monoketophosphonate(**3s**)

The acetylacetone **2b** reacted with phosphonate **1e** in the presence of $FeCl_3$ at rt using DCM as solvent to afford the product **3u** after 18h **(Scheme 3.29)**.



Scheme 3.29 Acid mediated synthetic route for γ –diketophosphonate(**3u**)

3.3.2 *Spectroscopic characterization*

The γ-ketophosphonates, synthesized herein, are characterized using multinuclear NMR (^{1}H / ^{13}C/ ^{31}P) spectroscopy. The phosphonates bearing 1,3-diketones (**3a, 3c-d, 3g-h, 3k-n, 3p, 3r, 3t-u**) showed the characteristic doublet of doublet at ~ δ 4.50 (dd, J ~ 22 and 12.0 Hz) for P-C(α)*H* in ^{1}H NMR and a doublet at ~ δ 44.2 (d, J ~ 139.1 Hz) for P-*C*(α)H including peaks at δ ~193.6 [for Ph*C*(O)] and δ ~ 201.5 [CH_3*C*(O)] in ^{13}C NMR spectroscopy. In ^{31}P NMR, a singlet peak was observed at ~δ 28.8 for these compounds. These phosphonates showed bands around ~ 1230 and ~ 1020 cm^{-1} due to the (P=O)/P-OR esters and the peak around ~ 1723 cm^{-1} corresponded to the carbonyl stretching in the IR spectra. The representative ^{1}H and ^{13}C NMR spectra for compound **3g** are shown in **Fig 3.4a-b.**

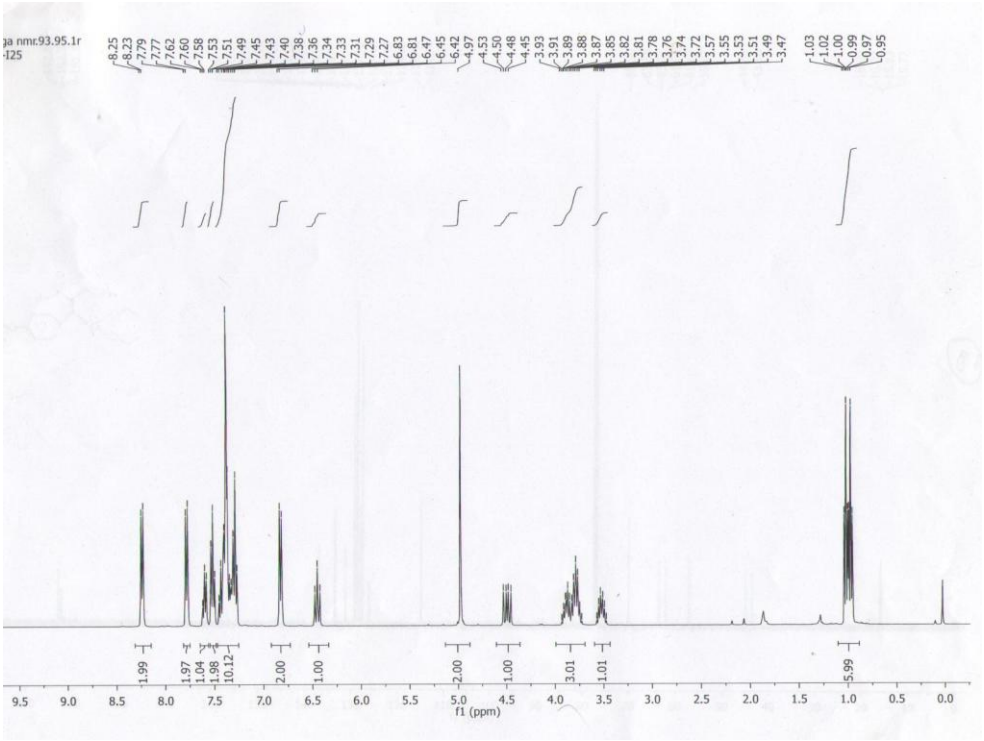


Fig 3.4a ^{1}H NMR spectrum of compound **3g**

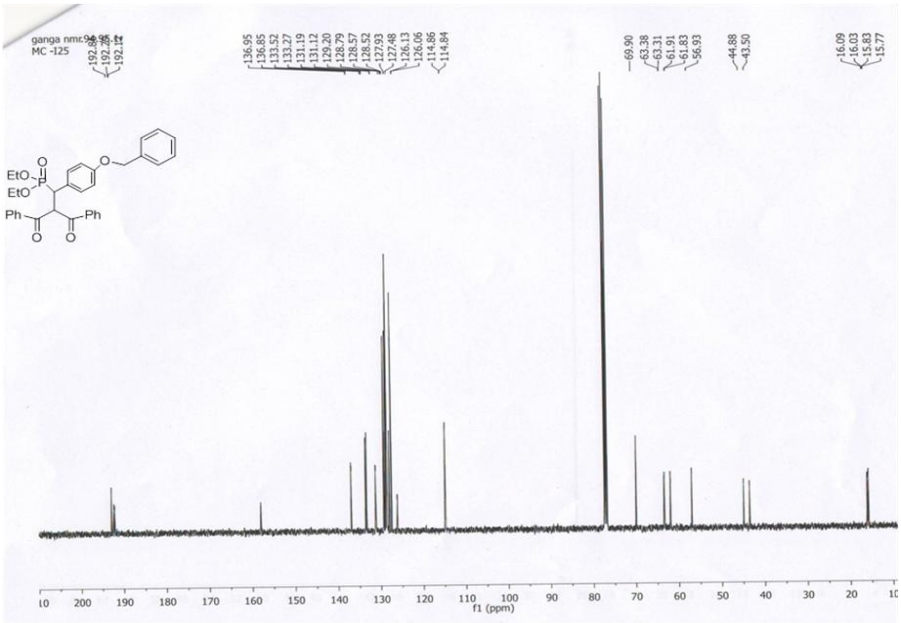


Fig 3.4b ^{13}C NMR spectrum of compound **3g**

The *γ*-monoketophosphonates, synthesized herein, are characterized using multinuclear NMR (^{1}H/^{13}C/^{31}P) spectroscopy. The phosphonates bearing monoketone functionality (**3b,3i,3j,3o,3q,3s**) showed the multiple at ~δ 3.50 for P-C(α)*H* in ^{1}H NMR and a signal at ~δ

28.8 appeared in ^{31}P NMR spectroscopy. The characteristic ^{1}H and ^{13}C NMR spectra for compounds **3j & 3b** are shown in Fig **3.5a-b**& **3.6a-b** respectively.

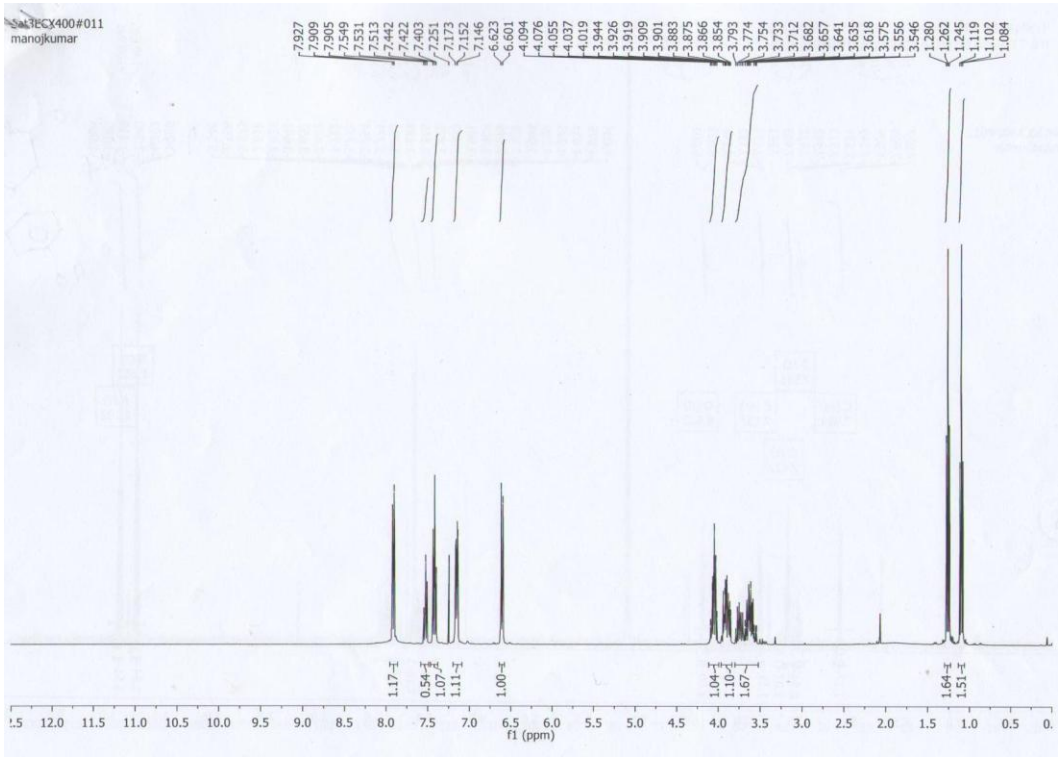


Fig 3.5a ^{1}H NMR spectrum of compound **3j**

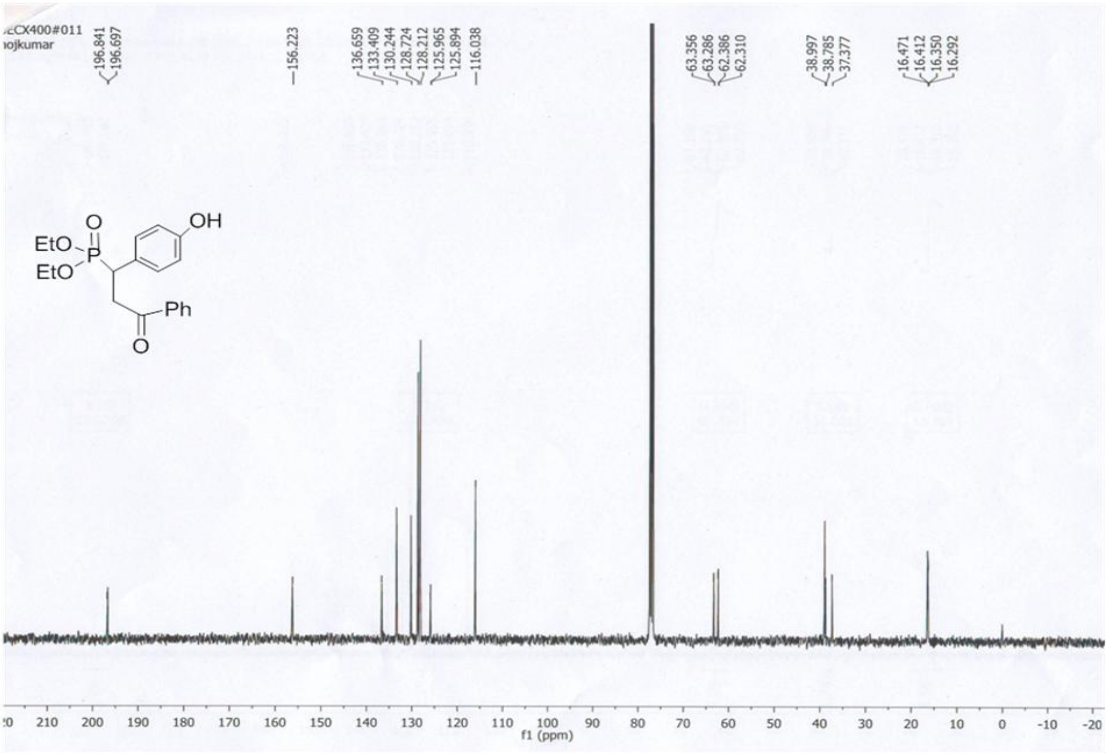


Fig 3.5b ^{13}C NMR spectrum of compound **3j**

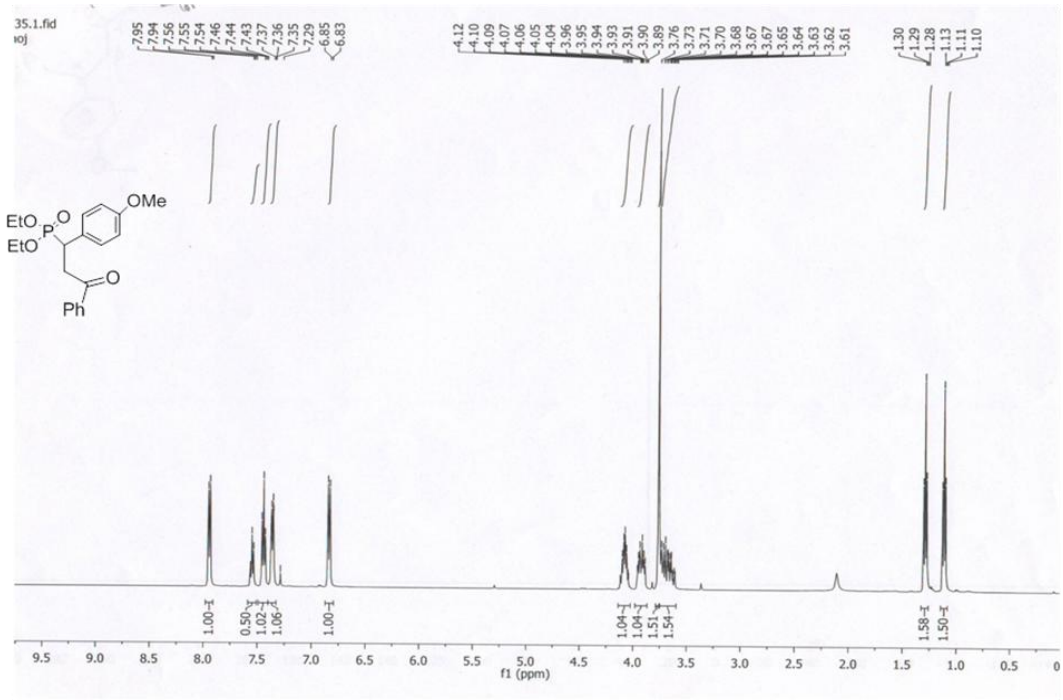


Fig3.6a ^{1}H NMR spectrum of compound **3b**

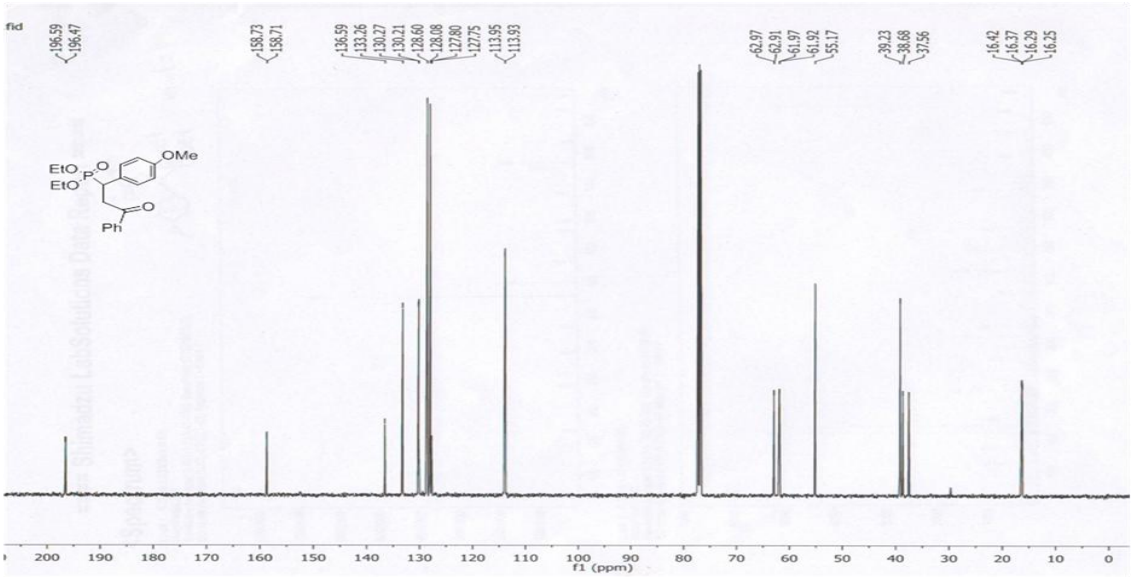
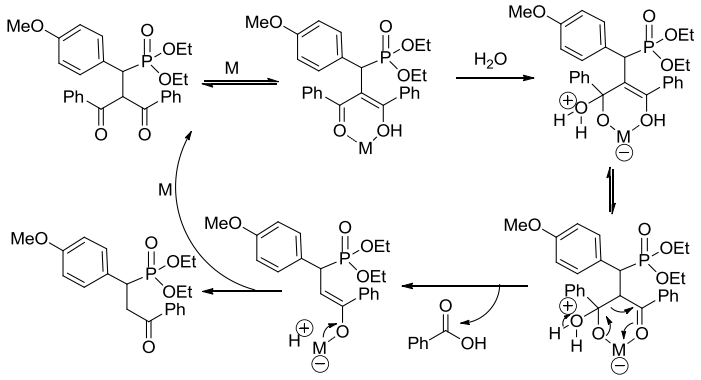


Fig 3.6b ^{13}C NMR spectrum of compound **3b**

3.3.3 *Plausible Mechanism*

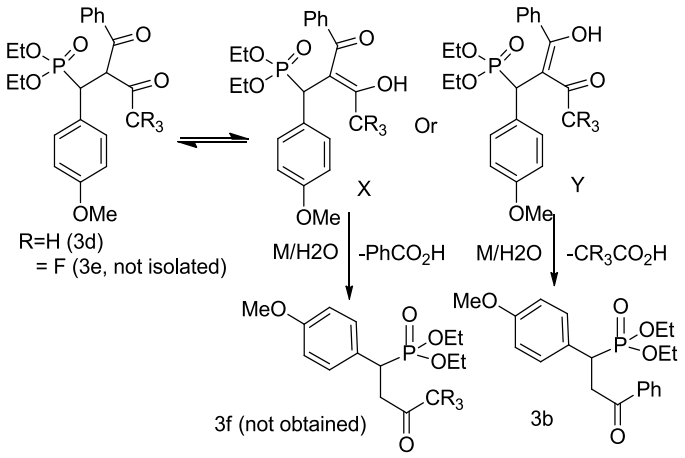
From the literature survey[35-37] and the results obtained herein, the reaction mechanism could be explained by a direct alkylation of 1,3-diketones with a suitable carbocation obtained by the Lewis acid mediated activation of hydroxyl group (a poor leaving group) from *α*-

hydroxyphosphonates. Generation of cations are subjective to the substituents (electron-donating/ extended conjugation) present in the benzene ring. Furthermore, nucleophilic reaction might depend on the keto/enol ratio including the steric factor of the 1,3-diketones. Notably, 1,3-diketones are also known to act as bidentate ligands to decrease the Lewis acidity of the metals.[36] Along with that, the subsequent regioselective C-C bond cleavage is also a reason to stabilise the best reaction conditions for different combinations of α-hydroxyphosphonates and 1,3-diketones to afford the desired γ-ketophosphonates. Moreover, with all these experimental results, we believe the C-C bond cleavage occurs with the help of water molecules present in the reaction mixture. Based on the literature,[8] proposed metal mediated C-C bond cleavage mechanism (**Scheme 3.30**) predicts the formation of benzoic acid that was successfully isolated in sublimed form from the wall of the reaction flask. With this result, helpful evidence is established for the proposed mechanism which has not been demonstrated so far due to the formation of volatile ester as a side product because alcohol was used in place of water.[37]



Scheme 3.30 Proposed pathway for the C-C bond cleavage.

With the experimental observations obtained from the reactions of unsymmetrical 1,3-diketones and considering the stability of the possible tautomeric forms (**X** and **Y**, **Scheme 3.31)** we surmise that the more conjugated enol form **Y** is the most favourable one to obtain the product **3b** under the present reaction condition.



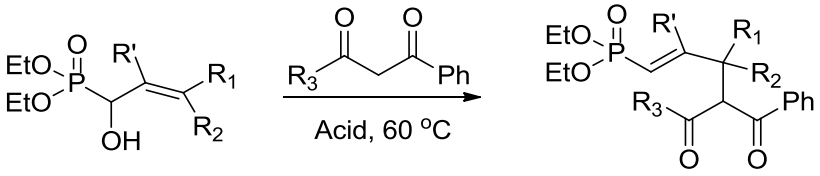
Scheme 3.31 The reaction of **1a** with unsymmetrical 1,3-diketones

3.3.4 *Theoretical support:*

A theoretical calculation considering **3d** showed a small difference in energy between the form **X** and **Y**. Considering **3d,** using B3LYP/6-31G**, the difference in energy for optimised structures of **X** (-1033773.793 kcal/mol) and **Y** (-1033773.712 kcal/mol) is only 0.081 kcal/mol. The product of type **3f** was not formed under these reaction conditions. In the literature, enol form of type **X** was considered to be the most stable one based on the experimental observations.[32]

3.4 Synthesis of *ω*-ketovinyl phosphonates

Next, we have developed a simple, efficient and inexpensive acid mediated approach to generate new *ω*-ketovinyl phosphonates starting directly from *α*-hydroxy allylic phosphonates and aromatic 1,3-diketones **(Scheme 3.32**). Especially, aromatic 1,3-diketones are widely studied and used as UVA sunscreens.[38]

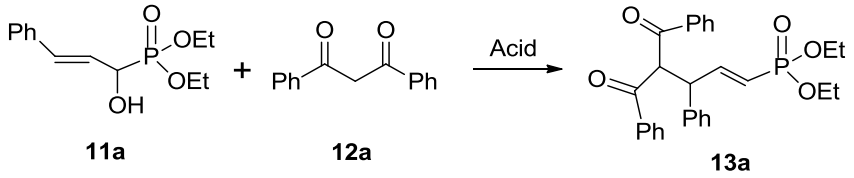


Scheme 3.32 Acid mediated synthetic route for *ω* –ketovinylphosphonate

Further, base catalyzed isomerization of simple vinyl phosphonate to allylic phosphonate is reported earlier with a significance to generate the precursor for the synthesis of valuable *trans*-retinoic acid.[39] Moreover, this isomerization also helps to generate allylic phosphonium and phosphoryl ylides[40] that undergo both conventional as well as vinylogus Wittig/HWE reactions to afford a range of multi-substituted 1,3-butadienes.[41] Notably, the regio- and stereoselective synthesis of multisubstituted conjugated 1,3-butadienes with proximal functionalities is really

hard although these dienes are valuable building blocks for several products and advanced materials.[42] Therefore, herein, we further demonstrate both acid and base mediated isomerization studies of new ω-ketovinylphosphonates to its allylic isomers with the support from theoretical calculations and utilized one of these allylic phosphonates in HWE reactions to access new conjugated 1,3-butadienes attached with 1,3-diketone functionality at the terminal carbon.

In this work, the reported issues related to the synthesis of essential starting materials for ω-ketovinyl phosphonates were avoided by the direct use of α-hydroxy allylic phosphonates as precursors. Initially, the phosphonate **11a** and 1,3-diketone **12a** were used to obtain the new type of ω-ketovinyl phosphonate **13a** in high yield by varying different acids (both Lewis or Brønsted) under several reaction conditions (**Table 3.2**).



11a **12a** **13a**

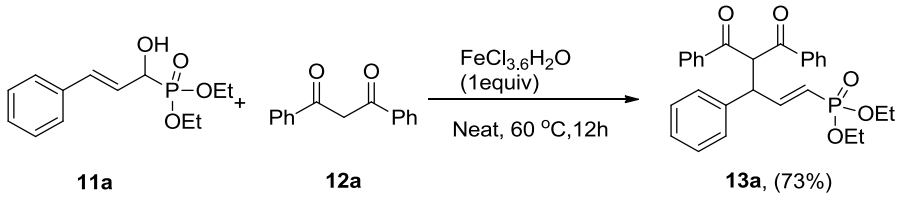
Table 3.2 Screening of reaction conditions to synthesize **13a**[a]

Entry	Acid	Solvent	Time (h)	Isolated yield of 13a (%)
1	$FeCl_3.\ 6H_2O$	Neat	12	73[b]
2	$FeCl_3.\ 6H_2O$	1,2-dichloroethane	10	60
3	$FeCl_3.\ 6H_2O$	nitromethane	12	60
4	$FeCl_3$	Neat	14	0
5	$FeCl_3$	nitromethane	12	0
6	$Cu(OTf)_2$	1,2-dichloroethane	12	10[c]
7	$Cu(OAc)_2$	1,2-dichloroethane	12	0[c]
8	$CuCl_2.\ 2H_2O$	1,2-dichloroethane	14	20
9	$Fe(acac)_3$	Dichloromethane	14	0[c]
10	$Bi(OTf)_3$	1,2-dichloroethane	8	80
11	$ZnCl_2$	1,2-dichloroethane	36	50[c]
12	AcOH	Dichloromethane	12	0
13	CF_3CO_2H	1,2-dichloroethane	12	0[c]
14	CH_3SO_3H	1,4-dioxane	12	0

15	p-TSA	1,2-dichloroethane	14	80
16	TfOH	1,2-dichloroethane	14	85

[a] Reactions were performed with **11a** (1mmol) and **12a** (1.2 mmol) using acid (1 mmol) at 60-65 ^{o}C; only for entries 7 &9 the reaction was heated under reflux. [b] The ^{31}P NMR for the reaction mixture showed another peak at δ 28.5 (~20%) but could not be isolated in pure form. The NMR (^{31}P, ^{1}H &^{13}C) spectra partly support presumably the formation of *α*-substituted product. [c] Starting material was recovered.

Encouraged with our previous results, Fe(III) was selected as a Lewis acid for this reaction. Experimentally, no product could be isolated when anhydrous $FeCl_3$ was used whereas $FeCl_3.6H_2O$ afforded much better result to yield **13a** efficiently **(Scheme 3.33)**.



11a **12a** **13a**, (73%)

Scheme 3.33 Acid mediated synthetic route for *ω* –ketovinylphosphonate(**13a**)

In fact, the reaction was more satisfactory under solvent-free conditions upon heating at 60-70 ^{o}C. Compared to other Lewis acids such as the Cu(II) and Zn(II) used herein, $Bi(OTf)_3$ worked well for this reaction (entry **10**, Table **3.2**). Among the selected Brønsted acids, *p*-toluenesulfonic acid (*p*-TSA) and triflic acid (TfOH) were effective to afford **13a** in higher yields (entries **15** and **16**, **Table 3.2**). However, as noted before, Fe(III) was employed for all other reactions of *α*-hydroxy allylic phosphonates with aromatic 1,3-diketones and utilized successfully to obtain a range of *ω*-ketovinyl phosphonates in high yields. In literature, starting from In(III)[43], Fe(III)[44] or Brønsted acids[45] were also reported for the fruitful reactions of allylic alcohols and acetylacetone to obtain the *C*-alkylated product. Moreover, this product was isolated as regioisomeric mixture in case of unsymmetrically substituted allylic alcohols. In those reports, except aromatic 1,3-diketones, all other active methylene compounds including *β*-ketoester and diester were used. Reaction of cinnamyl alcohol with dibenzoylmethane (aromatic 1,3-diketone) was reported only with 52% isolated yield in the presence of expensive $La(OTf)_3$.[46] Gratifyingly, we could generate a range of valuable regio- and stereoselective *ω*-ketovinyl phosphonates in good yields by acid mediated direct reactions of aromatic 1,3-diketones with *α*-hydroxy allylic phosphonates. Considering the availability, cost and reactivity, we have selected the allylic hydroxy phosphonates **11b-d** and aromatic 1,3-diketones **12a-d** (**Fig 3.7**) for the current studies. The newly synthesized *ω*-ketovinyl phosphonates **13b-i** are listed in below.

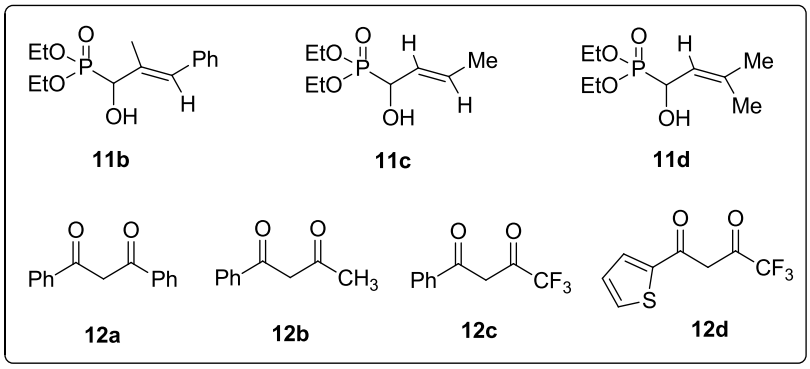
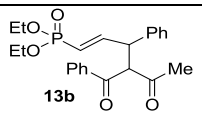
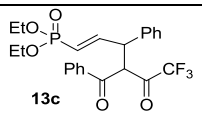
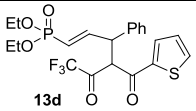
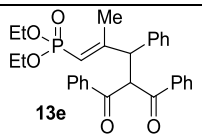
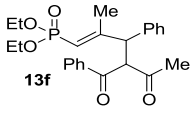


Fig 3.7 The hydroxyphosphonates and 1,3-diketones used as precursors

The compound **13b** was formed as 1:1 diastereomeric mixture from the reaction of **11a** and **12b**. We could isolate one of the diastereomers in pure isomeric form and the other diastereomer was separated only with ~80% pure isomeric form. Both *p*-TSA and $FeCl_3.6H_2O$ worked satisfactorily to generate compound **13b** in high yield. With the interest on fluorinated organophosphonates, *ω*-ketovinyl phosphonate **13c** was synthesized in pure form with moderate yield. Furthermore, the reaction of another thiophene containing fluorinated aromatic 1,3-diketone **12d** and phosphonate **11a** generated desired compound **13d** with good diastereoselectivity (dr 1:0.2) in excellent yield only in the presence of $FeCl_3.6H_2O$ (**Table 3.3**). The phosphonate **11b** furnished very promising result to obtain **13e** (**Table 3.3**) as single isomer and **13f** (**Table 3.3**) as mixture of diastereomers (**1:1**) from the reactions with **12a** and **12b,** respectively.

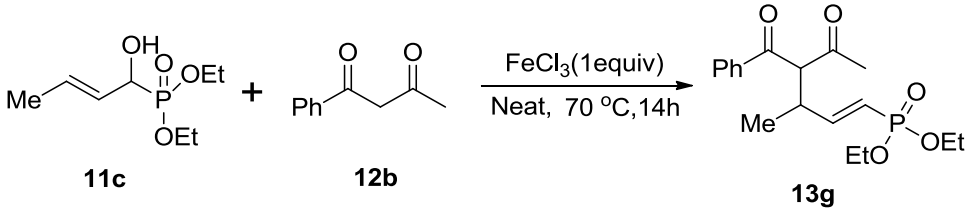
Table 3.3 List of synthesized *ω*-ketovinyl phosphonates synthesized from phosphonates **11a, 11b** and aromatic 1,3-diketones **12b-d** including the preferred reaction conditions.[a]

Entry	**11/12**	Main product	reaction conditions: [b] acid / solvent/ temp (^oC) /time (h)	Isolated yield (%)
1	**11a/12b**	 **13b**	$FeCl_3$. $6H_2O$/ Neat/ 60/ 10	90[c]
2	**11a**/**12c**	 **13c**	$FeCl_3$. $6H_2O$/ Neat/ 60/ 10	50[d]
3	**11a**/**12d**	 **13d**	$FeCl_3$. $6H_2O$/ Neat/ 60/ 10	85[e]

3	**11b**/**12a**	 **13e**	$FeCl_3$. $6H_2O$/ Neat/ 60/ 10	80
4	**11b**/**12b**	 **13f**	$FeCl_3$. $6H_2O$/ Neat/ 60/ 10	89[c]

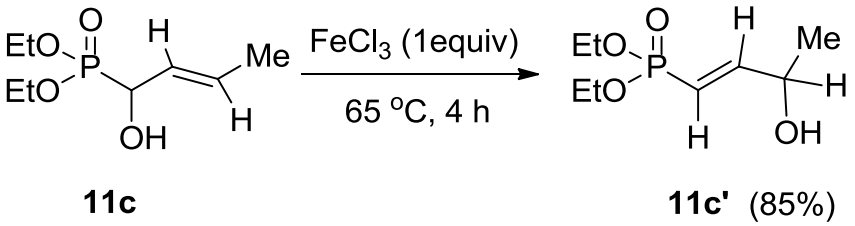
[a] Reaction stoichiometry: **11** (1 mmol) and **12** (1.2 mmol) using acid (1 mmol). [b] In entries 1, 4 & 5 reactions worked well with *p*-TSA/ dichloroethtane/ 25^{o}C/ 10h. [c] Almost quantitative formation (^{1}H & ^{31}P NMR) was observed as a mixture of diastereomers (1:1). [d] The ^{31}P NMR of the reaction mixture showed the formation of diastereomeric mixture (1:0.4) in 70% yield.

Additionally, the other phosphonates **11c-d** were also examined under the same reaction conditions (solvent-free at 70 ^{o}C) where $FeCl_3$ worked better to produce **13g-i** in very low to moderate yield. Although starting material **11c** was totally consumed by the reaction with **12b**, the expected compound **13g** could not be isolated in pure form **(Scheme 3.34)**.



Scheme 3.34 Acid mediated synthetic route for ω –ketovinylphosphonate(**13g**)

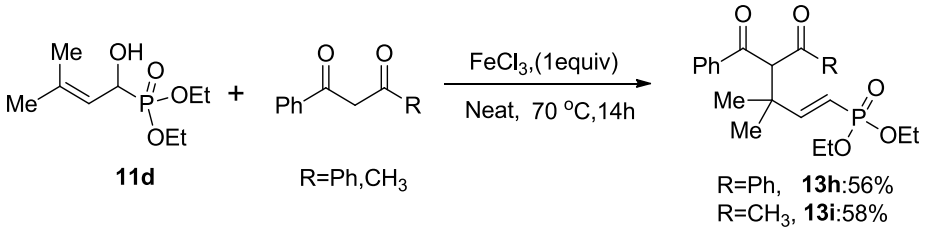
The reflected low yield in the case of α-hydroxy phosphonate **11c** incited us to investigate the reaction carefully and that showed the formation of γ-hydroxy vinylphosphonate (**11c′**) as a major product (~75%) in the presence of $FeCl_3$. A separate treatment of **11c** with anhydrous $FeCl_3$ under solvent-free condition at 65 ^{o}C produced the isomerized product **11c′** as a sole product (85% isolated yield; **Scheme 3.35**). It is worth noting that this γ-hydroxy vinylphosphonate **11c′** was reported in the literature as a valuable substrate[48] and prepared by rearrangement of diethyl (2,3-epoxy-1-butyl)phosphonate or palladium catalyzed acetoxylation of diethyl (1-butenyl)phosphonate followed by saponification.[49] We believe that this new $FeCl_3$ mediated solvent-free strategy for synthesizing phosphonate **11c′** is very much straightforward, relatively greener and inexpensive in comparison to the existing methodologies, reported so far.



11c **11c'** (85%)

Scheme 3.35 Isomerization of α-hydroxy allylphosphonate to γ-hydroxy vinylphosphonate

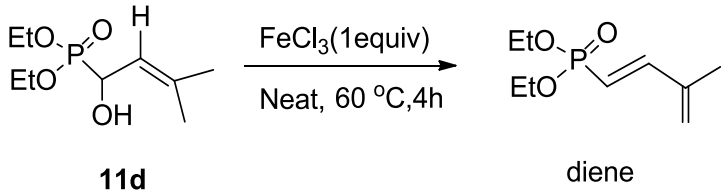
The reaction of **11d** with **12a-b** could afford the expected compounds **13h-i** respectively, in pure form with moderate yields **(Scheme 3.36)**. Unfortunately, the attempt of using other acids under different reaction conditions could not improve the yield of phosphonates **13g-i**.



11d R=Ph,CH_3

Scheme 3.36 Acid mediated synthetic route for *ω*-ketovinylphosphonate(**13h&13i**)

The moderate yield for **13h-i** could be explained with the fact that the phosphonate **11d** has tendency to form 1,3-butadienylphosphonate in the presence of acid (**Scheme 3.37)** as mentioned in the previous chapter.



11d diene

Scheme 3.37 Acid mediated synthetic route for 1,3-butadienylphosphonate.

3.4.1 *Spectroscopic characterization*

The *trans*-sterochemistry for the products **13a-i** was determined by the $^{3}J_{P\text{-}C}$ coupling (~22.0 Hz) for *γ*-C in ^{13}C NMR spectra. The stereochemistry was reconfirmed by the $^{3}J_{P\text{-}C}$ [*β*-C (CH_3)] *cis*-coupling (~7.1 Hz) along with predetermined $^{3}J_{P\text{-}C}$ (*γ*-C) *trans*-coupling (~22.0 Hz) in ^{13}C NMR spectra for compounds **13e-f**. These coupling constant values are consistent with the reported data for the relevant compounds.[50] Even though all these hydroxy allylic phosphonates are unsymmetrically substituted allylic alcohols, no other regioisomeric products are isolated unlike the earlier reports on similar alcohols.[43]

Furthermore, we have also performed the density functional theory (DFT) calculations for compound **13a**. Interestingly, it has been found that compound **13a** preferably exists in keto form as obtained from geometry optimized ground state energy (keto form is ~ 6.0 kcal/mol lower than enol form). This is mainly because of the strained spatial arrangement of the phenyl groups in the enol form of **13a**. This observation is also in part with the experimental NMR spectrum of **13a.** Although several factors including electronic and steric influences involved in this process, the formation of *ω*-ketovinyl phosphonates *through* exclusive nucleophilic attack of aromatic 1,3-diketone (*via* keto-enol form) on *γ*-C support the generation of most stabilized carbocation. The initially formed carbocation at *α*-C is very much unstabilized by the significant electron withdrawing effect of phosphoryl group.

ω-ketovinylphosphonates (**13a-i**) showed the characteristic doublet of doublet of doublet at δ 6.93 (ddd, *J* = 21.5 and 17.0 and 7.9 Hz, 1H) for P-C(α)*H,* and doublet 1H at δ 5.92 due to HC=C in ^{1}H NMR and a doublet at ~ δ 119.2 (d, *J* = 184.7 Hz) for P-*C*(α)H and also peaks at δ193.1, δ193.4 due to diketo functional groups in ^{13}C NMR spectroscopy. The representative ^{1}H and ^{13}C NMR spectra for compounds **13a** are shown in **Fig 3.8a-b**.

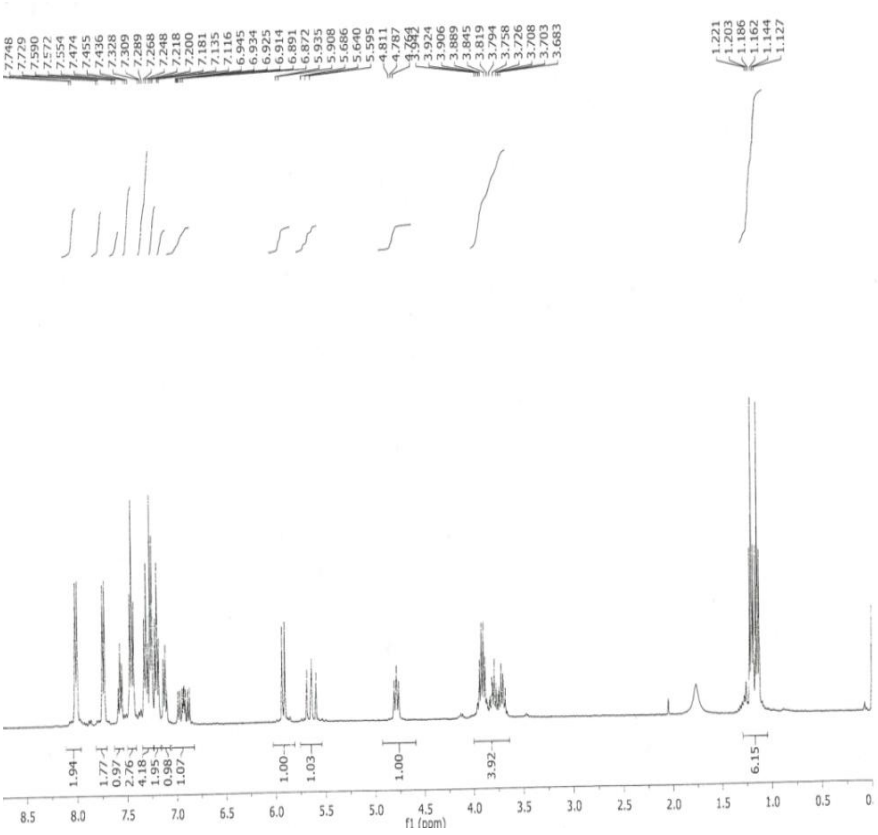


Fig 3.8a ^{1}H NMR spectrum of compound **13a**

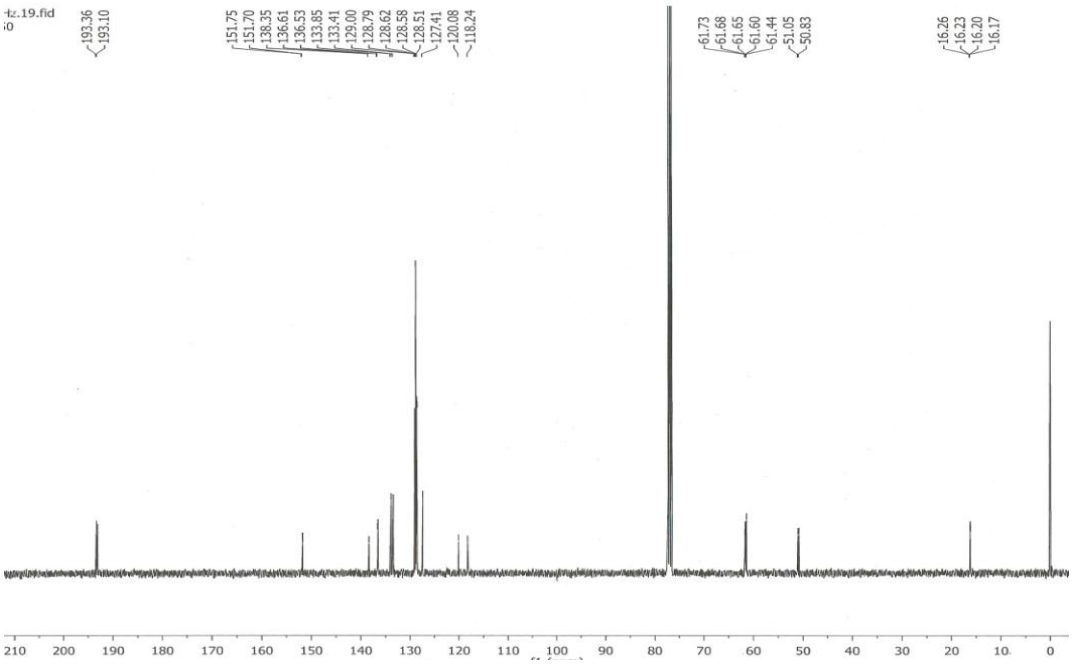
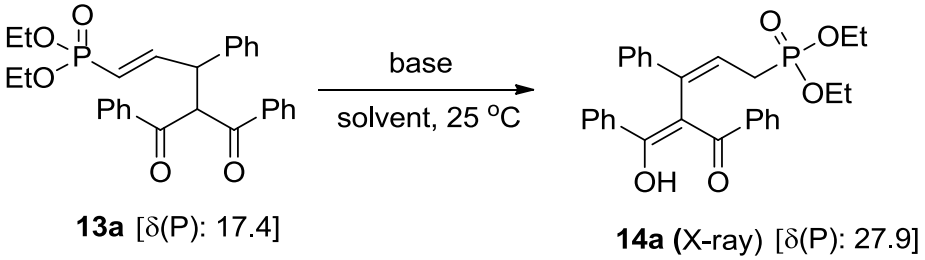


Fig 3.8b ^{13}C NMR spectrum of compound **13a**

3.4.2 *Isomerization studies of ω-ketovinyl phosphonates*

The isomerization of simple vinyl phosphonate was successfully described by using very strong base like potassium *tert*-butoxide in dimethylsulfoxide (DMSO) at 25 ^{o}C whereas the relatively weaker base potassium carbonate could not generate the isomerized product even in the presence of 18-crown-6.[39] Therefore, we have explored the isomerization reaction of *ω*-ketovinyl phosphonate **13a** to *ω*-ketoallyl phosphonate **14a (Scheme 3.38)** under different reaction conditions (**Table 3.4**). Surprisingly, a much weaker base K_2CO_3 has been proved to be suitable to generate the desired products (**14a-c**) in the presence of tetrahydrofuran (THF) or DMSO as solvent. Being relatively inexpensive and having much lower boiling point (66 ^{o}C) for THF compare to DMSO (189 ^{o}C), THF was chosen for these reactions and that facilitate smooth work-up followed by evaporation. The compound **14c** was formed almost quantitatively in the presence of K_2CO_3 using DMSO as solvent.



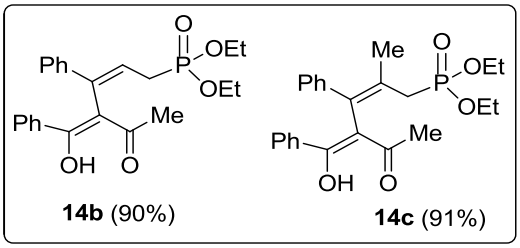
13a [δ(P): 17.4]

14a (X-ray) [δ(P): 27.9]

Scheme 3.38 Isomerization of *ω*-ketovinylphosphonate to *ω*-ketoallylphosphonate

Table 3.4 Screening of different reaction conditions for the isomerization study

Entry	Base(1equiv)	Solvent/time (h)	Yield for **14a**
1	K^{t}Buo	DMSO/10	90
2	K^{t}Buo	THF/10	0
3	K_2CO_3	DMSO/9	70
4	K_2CO_3	THF/7	92



Further, the transition metals (Ru or Ir) are known to be used for isomerization studies for allylic arenes.[17] In this context, our attempt on Fe(III)-mediated isomerization showed only 50% conversion from **13a** to **14a**. Both the diasteromeric mixtures (1:1, two peaks at ^{31}P NMR) for **13b** (δ 17.2 and 17.4) and **13f** (δ 17.0 and 17.1) were directly used for the isomerization reactions and that led to the formation of enantiomeric mixtures (1:1, single peak in ^{31}P NMR) of **14b** (δ 27.4) and **14c** (δ 27.3) respectively. The stereochemical outcome was confirmed by determining the X-ray crystal structure of compound **14a** (**Fig 3.9**).

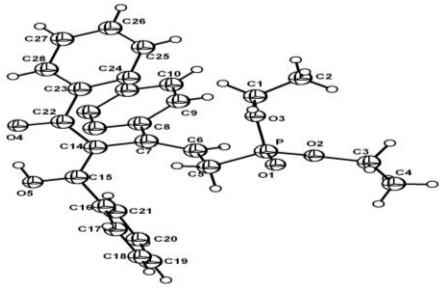
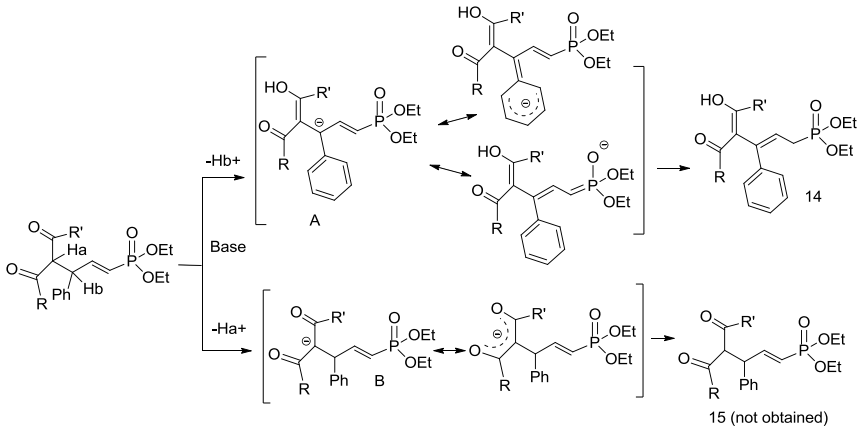


Fig 3.9 The ORTEP diagram for compound **14a** (with 20% probability label); The O5-(H)…O4 1.717 Å that indicates a very strong intramolecular H-bonding

The diastereotopic protons are very much prominent with two distinct sets of protons (properly resolved for **14b** with *J* = 20.4, 15.6, 9.7 Hz] as expected from -PC*HaHb* protons for both **14b** and **14c**. The peak for carbonyl carbon in ^{13}C NMR spectrum for diketo compound **13a** appeared at δ ~193.0 whereas the compound **14a** showed the shift at δ ~190.0 and that could be

due to the formation of enol. The single crystal X-ray structure for **14a** also reveals the presence in enol form. Both the unsymmetrical diketones **13b** and **13f** showed two peaks at δ ~193.6 [for Ph*C*(O)] and δ ~ 201.5 [CH_3*C*(O)] whereas the corresponding shifts at δ ~182.0 [for Ph*C*(O)] and δ ~ 199.3 [CH_3*C*(O)] were found for both the isomerized compounds **14b** and **14c**. These data again support the existence of these compounds **14a-c** in enol form for both solid and solution state ($CDCl_3$) and that lead to achieve more stable structure *via* extended π-conjugations as well as effective intramolecular hydrogen bonding. This is further verified from DFT calculations where geometry optimized structure of enol form for **14a** is lower by ~4.8 kcal/mol compare to keto form.

The presence of two replaceable acidic protons with these *ω*-ketovinyl phosphonates makes them important substrate for isomerization studies. Therefore, for *ω*-ketovinyl phosphonates **13a-f,** two acidic protons (H_a and H_b) need to be considered and that lead to form the carbanions **A** and **B** by the treatment of base **(Scheme 3.39)**.



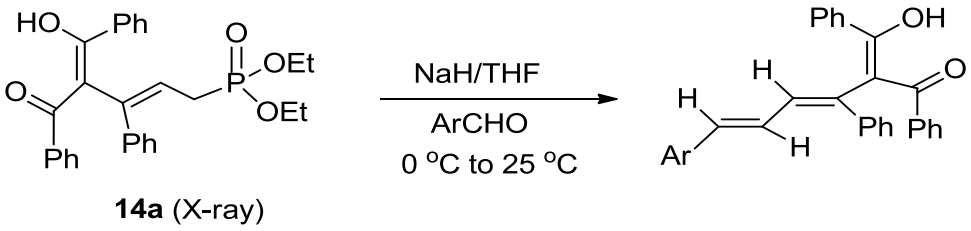
Scheme 3.39 The possible base mediated isomerization of *ω*-ketovinyl phosphonates

An extensive theoretical calculation using DFT has been performed to examine the relative energies for the possible intermediates of type **A** and **B** (where R, R′ =Ph) and the corresponding products **14a** and **15a** (where R, R'=Ph) with respect to **13a.** From the geometry optimized ground state energy of intermediate **A**, we found that **A** can exist in both keto and enol form and preferably rearranges to enol (stabilized by ~ 4.8 kcal/mol relative to the keto form) to facilitate better delocalization of the negative charge. Finally, the intermediate **A** forms **14a** that preferably exist in enol form as noted before. The compound **14a** is energetically stabilized by ~ 9.5 kcal/mol with respect to compound **13a**. On the other hand, the possible intermediate **B** can exist only in keto form. The energy of the intermediate **B** (keto form) is very much comparable with

that of **A** (in stable enol form). However, the difference in geometry optimized energy between **15a** and **13a** is very small (~1.5 kcal/mol) and that is why the formation of compound **15a** is not favored from the intermediate **B.** The details of the geometry optimized structures and corresponding energies are tabulated in SI. It is worth noting that similar DFT calculations on isomerization of double bonds with variety of functional groups were performed by the group of W. L. Jorgensen.

3.4.3 *Route for 1,3-diketone functionalized conjugated 1,3-butadiene*

We intended to employ these synthesized phosphonates for intermolecular HWE reactions, and in that directions, the suitable precursors, isomerized allylic phosphonates **14a-c** (with -PCH_2) could be preferred to synthesize 1,3-butadienes of type **16a-g** attached with aromatic 1,3-diketone functionality at the terminal carbon as shown in **Scheme 3.40**.



14a (X-ray)

Scheme3.40 Intermolecular HWE reactions of **14a** to obtain the functionalized 1,3-butadienes

The easily synthesized and well-characterized solid phosphonate **14a** was chosen here for the HWE reactions to afford the important functionalized 1,3-butadienes **16a-g (Fig 3.10)**. The reactions were straightforward in the presence of inexpensive base NaH at room temperature for 10-14 h by using tetrahydrofuran as solvent.[51] With the interest on wide range of applications for extended π-conjugated systems,[52] we could successfully synthesize the biphenyl (**16d**), anthracene (**16e**) and pyrene (**16f**) substituted 1,3-butadienes in low to moderate yields. The compound **16e** was isolated in pure form only with 20% yield from the mixture of other diastereomers. The ferrocenyl substituted 1,3-butadiene **16g** was also generated in 62% yield. The compounds **16a, 16c-g** were isolated in a single stereoisomeric form whereas compound **16b** was isolated as a mixture of diastereomers. The conjugated 1,3,5-triene **16h**, was synthesized as a mixture of diastereomers by starting with *trans*- 2-nitrocinnamaldehyde.

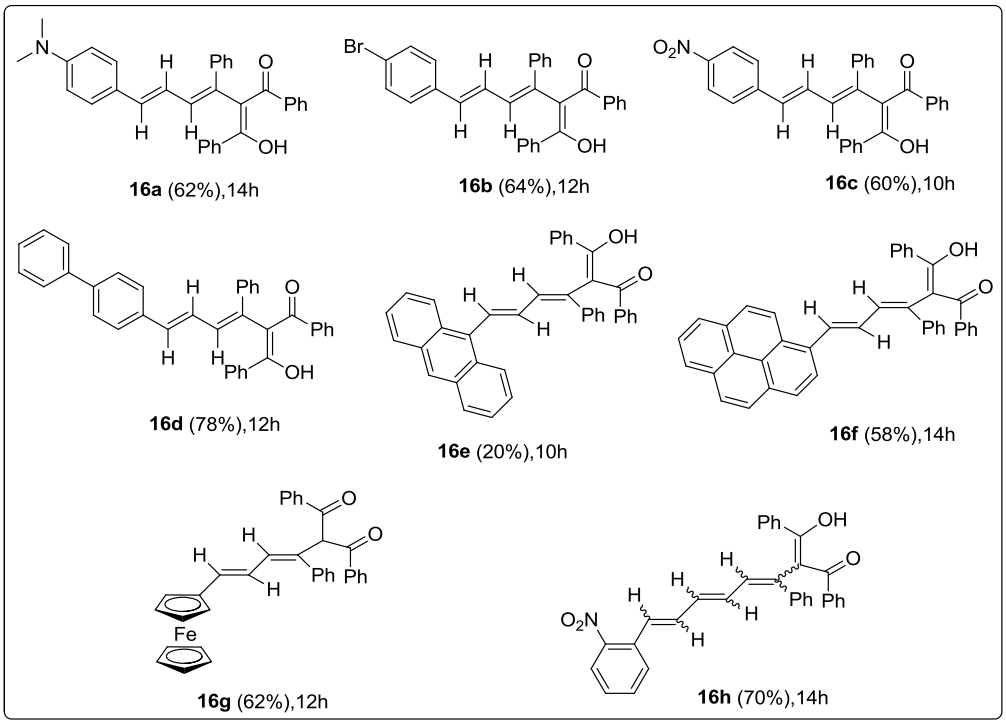


Fig 3.10 List of synthesized 1,3-butadienes**16a-h** from intermolecular HWE reactions of **14a** with aldehydes

The stereochemistry of these 1,3-butadienes is confirmed by proving the single crystal x-ray structure for **16a** (**Fig 3.11**). The presence of diketone was confirmed by the peak at ~δ 180-200 in ^{13}C NMR spectra and proved the existence of enol form using ^{13}C NMR spectra as mentioned before. Surprisingly, the compound **16g** was found in the form of diketone only. It is noteworthy that the chemistry of aromatic 1,3-diketones has significant interest to the chemists.[53]

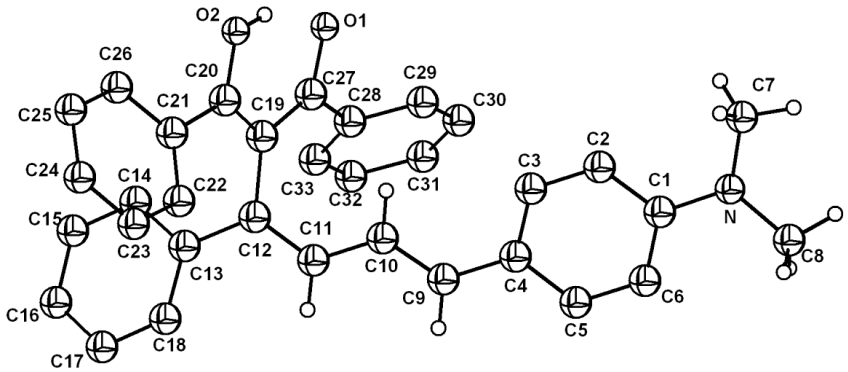


Fig 3.11 An ORTEP drawing of **16a** (with 20% probability label); The O2-(H)…O1 1.644 Å that indicates a very strong intramolecular H-bonding. Some hydrogen atoms are removed to get the clarity.

The synthesized 1,3-butadienes (16a-h) showed the characteristic doublet at δ 6.45 (d, *J* = 15.0 Hz, 1H) for C=CH, And also peak at δ190.3 [for Ph*C*(O)] in ^{1}H&^{13}C NMR spectrum. The representative ^{1}H and ^{13}C NMR spectra for compounds **16a** are shown in **Fig 3.12a-b**.

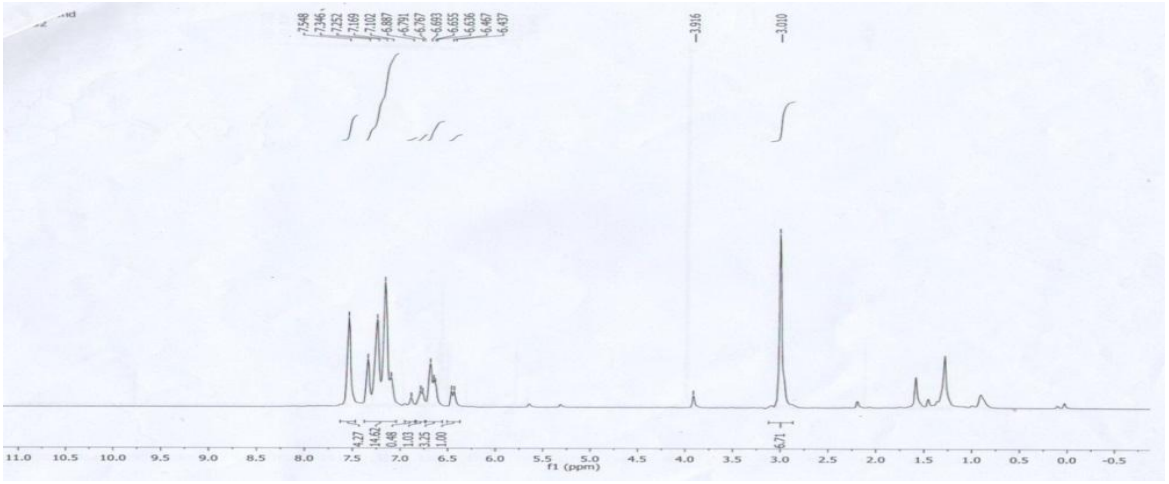


Fig 3.12a ^{1}H NMR spectrum of **16a**

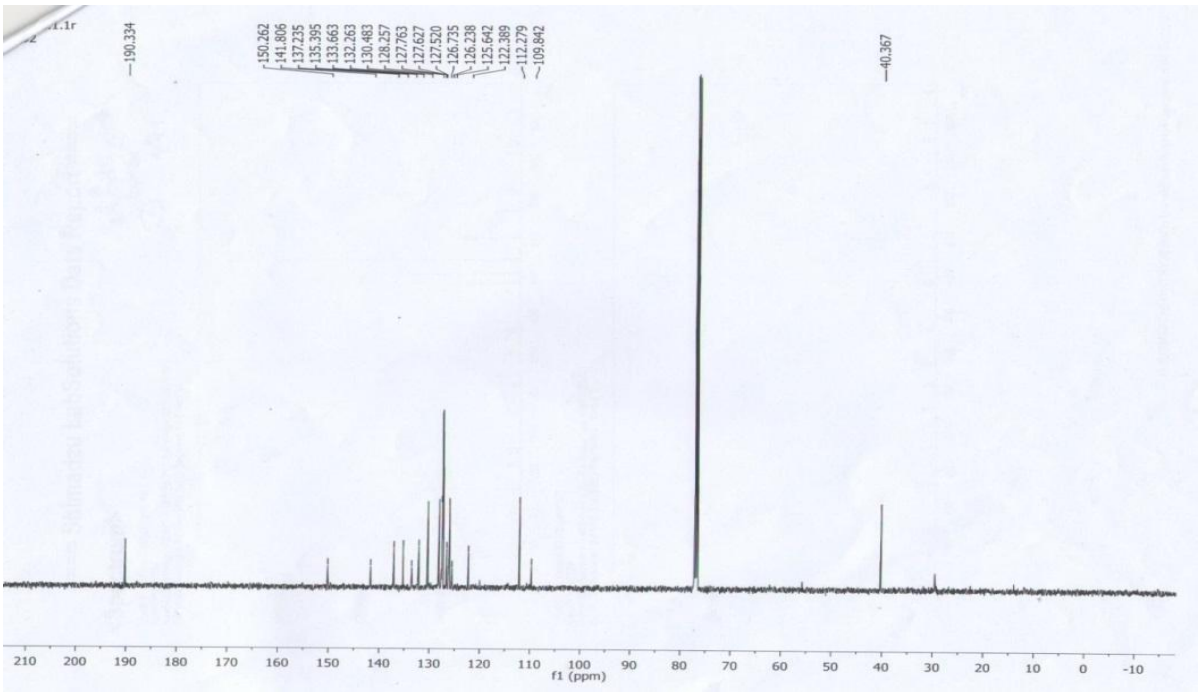


Fig 3.12b ^{13}C NMR spectrum of **16a**

3.5 Conclusions

The γ- keto phosphonates describes a new convenient and inexpensive method to synthesize a variety of biologically important γ-ketophosphonates in good yields. The reaction conditions are optimised for different combinations of α-hydroxyphosphonates and 1,3-diketones to generate the desired compounds effectively. Fe(III) is the Lewis acid of choice to generate most of the phosphonylated di/monoketones. Only for generating phosphonylated diketones **3g-h**, $Bi(OTf)_3$ was used and $Cu(OTf)_2$ was chosen to synthesize posphonylated diketones **3l** & **3n**. The Lewis acid $FeCl_3.6H_2O$ is successfully used for the C-C bond cleavage reactions to synthesise phosphonylated monoketones. Finally, we are able to accomplish the synthesis of the structural

analogue of raspberry ketone. Also developed an acid mediated inexpensive synthesis of *ω*-ketovinyl phosphonates directly from the reactions of allylic hydroxyphosphonates with aromatic 1,3-diketones. Synthesis of the γ-hydroxy vinylphosphonate from *α*-hydroxy allylicphosphonate in the presence of $FeCl_3$ is also demonstrated. The predominant existence for *ω*-ketovinyl phosphonate as diketones is observed experimentaly and also supported by DFT calculations. Based on the theoretical calculations, some of these *ω*-ketovinyl phosphonates were isomerized to the corresponding allylic phosphonates using simple K_2CO_3 as base. The isomerization was partly successful in the presence of Lewis acid Fe(III). One of these allylic phosphonates is presented to undergo smooth HWE reactions to provide conjugated 1,3-butadienes with aromatic 1,3-diketone functionality. We believe that this strategy would be useful to avail a wide range of 1,3-diketone functionalized conjugated 1,3-butadienes.

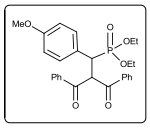
3.6 Experimental Section

Solvents were purified by distillation from appropriate drying agents under nitrogen atmosphere. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (100-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). ^{1}H, ^{13}C, and ^{31}P NMR spectra (^{1}H, 400 or 500 MHz; ^{13}C, 101 or 125 MHz; ^{31}P, 162 or 212 MHz) were recorded using a 400 or 500 MHz spectrometer in $CDCl_3$ with shifts referenced to $SiMe_4$ (δ 0) or 85% H_3PO_4 (δ 0). IR spectra were recorded on an FT-IR spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and were uncorrected. Elemental analyses were carried out on a CHN analyzer. Mass spectra were recorded using LC-MS equipment. Compounds diethyl hydroxyl(aryl)methylphosphonates **1a-e** were prepared by following methods reported in the literatures.[9] Reactions were run without exclusion of air/moisture in a stoppered reaction flask.

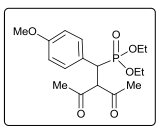
Silica gel (100-200 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). ^{1}H, ^{13}C, and ^{31}P NMR spectra (^{1}H, 400 or 500 MHz; ^{13}C, 101 or 125 MHz; ^{31}P, 162 or 212 MHz) were recorded using a 400 or 500 MHz spectrometer in $CDCl_3$ with shifts referenced to $SiMe_4$ (δ 0) or 85% H_3PO_4 (δ 0). IR spectra were recorded on an FT-IR spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out on a CHN analyzer. Mass spectra were recorded using LCMS and HRMS equipment.

3.6.1 *General procedure and analytical data 3a-h*

(±)-Diethyl2-benzoyl-1-(4-methoxyphenyl)-3-oxo-3 phenylpropylphosphonate (3a): To a stirred solution of **1a** (0.50 g, 1.82 mmol), dibenzoylmethane (**2a**, 0.400 g, 1.82 mmol), anhydous $FeCl_3$ (0.29 g, 1.82 mmol) was added and then the reaction mixture was heated at 70^oC for 8 h. After completion of the reaction as indicated by TLC, the reaction was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 x 20 ml). After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using EtOAc/ pet ether (70/30) as the eluent to afford **3a.** Yield 0.788 g (90%); off-white solid; mp 172-174 ^oC; IR (KBr, cm^{-1}) 2983, 1700, 1602, 1508, 1257, 1024, 966; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93-0.97 (m, 6H), 3.45-3.69 (m, 1H), 3.72 (s, 3H), 3.74-3.87 (m, 3H), 4.45 (dd, *J* = 19.7 and 11.3 Hz, 1H), 6.42 (dd, *J* = 11.1 and 10.0 Hz, 1H), 6.69-6.72 (m, 2H), 7.24-7.34 (m, 2H), 7.41-7.59 (m, 6H), 7.75 (d, *J* = 8.6 Hz, 2H), 8.20 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 and 16.1 (d, *J* ~ 6.0 Hz each), 44.2 (d, *J* = 139.1 Hz), 55.2, 56.9, 61.9 and 63.5 (d, *J* = 7.3 Hz each), 113.9, 125.8 (d, *J* = 7.0 Hz), 128.6 (d, *J* = 4.5 Hz),, 128.9, 129.3, 131.2 (d, *J* = 6.4 Hz), 133.4, 133.6, 136.9, 137.0, 158.8, 192.2 (d, *J* = 16.5 Hz), 192.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.0 (s); LC/MS m/z 481 $[M+H]^+$; Anal. Calcd. for $C_{27}H_{29}O_6P$ C 67.49, H 6.08; found C 67.58, H 6.14.



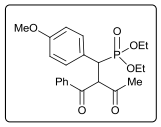
(±)-Diethyl 1-(4-methoxyphenyl)-3-oxo-3-phenylpropylphosphonate (3b): This compound was synthesised in a manner similar to the synthesis of **3a** with similar molar quantities using $FeCl_3$. $6H_2O$. Yield 0.618 g (90%); viscous liquid; IR (KBr, cm^{-1}) 2983, 1686, 1605, 1510, 1450, 1246, 1034, 959; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 and 1.29 (two sets of triplet, *J* ~ 7.1 Hz each, 6H), 3.61-3.73 (m, 3H), 3.76 (s, 3H), 3.89-3.91 (m, 2H), 3.94-4.12 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 7.35-7.37 (m, 2H), 7.43-7.56 (m, 3H), 7.94 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.4 (two sets of doublets, *J* = 5.0 Hz each), 38.1 (d, *J* = 138 .0Hz), 39.2, 55.2, 61.9 and 62.9 (two sets of doublets, *J* = 7.5 Hz each), 113.9 (d, *J* = 2.5 Hz), 127.8 (d, *J* = 6.2 Hz), 128.1, 128.6, 130.2 (d, *J* = 7.5 Hz), 133.3, 136.6, 158.7 (d, *J* = 2.5 Hz), 196.5 (d, *J* = 15.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.9. LC/MS m/z 377 $[M + H]^+$.



(±)-Diethyl 2-acetyl-1-(4-methoxyphenyl)-3-oxobutylphosphonate (3c): To a stirred solution of **1a** (0.50 g, 1.82 mmol) and acetylacetone (**2b**, 0.18 g, 1.82 mmol), in anhydrous dichloromethane (4 mL) as solvent, anhydrous $FeCl_3$ (0.29 g,

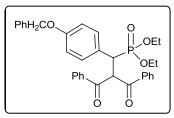
1.82 mmol) was added and then the reaction mixture was stirred at 28 ^{o}C for 18 h**.** The compound **3c** was isolated using column chromatography (EtOAc/Hexane) with partial (~14%) enol form. Yield 0.590g, (91%); off-white solid; mp 192-194 ^{o}C; IR (KBr, cm^{-1}) 2356, 1690, 1515, 1361, 1265, 1176, 1026, 937; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 and 1.23 (two sets of triplet, *J* ~ 7.2 Hz each, 6H), 1.81 (s, 3H), 2.33 (s, 3H), 3.64-3.74 (m, 1H), 3.76 (s, 3H), 3.82 – 4.04 (m, 4H), 4.59 (dd→t, *J* = 11.4 and 11.6 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.17-7.19 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.3 (d, *J* ~ 6.0 Hz each), 28.2, 30.6, 43.1 (d, *J* = 138.9 Hz), 55.3, 62.5 and 63.2 (d, *J* = 7.0 Hz each), 69.5, 114.3, 124.9 130.8, 159.2, 201.5, 201.7 (d, *J* = 17.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.6 (s); LC/MS m/z 357 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{25}O_6P$ C 57.30, H 7.07; found C 57.42, H 6.87.

(±)-Diethyl 2-benzoyl-1-(4-methoxyphenyl)-3-oxobutylphosphonate (3d): Reaction was performed in a manner similar to the synthesis of **3b** using benzoylacetone (**2c**) with a similar quantity as **2a**. The product **3d** (0.534 g, yield 16%) was isolated followed by **3b (**0.550g, yield



80%). Under the same reaction conditions ($FeCl_3.6H_2O$, neat, 70 ^{o}C, 80 h), the reaction of **1a** with **2d** gave exclusively compound **3b** in 95% yield. The yield of **3d** was increased to 90% by performing the reaction using anhydrous $FeCl_3$. off-white solid; mp 96-98 ^{o}C; IR (KBr, cm^{-1}) 2980, 1726, 1680, 1511, 1253, 1028, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 and 1.02 (two sets of triplet, *J* ~ 7.0 Hz each, 6H), 1.83 (s, 3H), 3.56-3.88 (m, 7H, the singlet at δ 3.73 was also merged), 4.31 (dd, *J* = 21.6, 11.8 Hz, 1H), 5.49 (dd→t, *J* = 9.6 and 11.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.32-7.34 (m, 2H), 7.48-7.62 (m, 3H), 8.15 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 and 16.1 (d, *J* ~ 5.6 Hz each), 27.5, 43.5 (d, *J* = 137.5 Hz), 55.3, 62.3 and 63.2 (d, *J* = 7.0 Hz each), 63.6, 114.3, 124.9, 128.9, 129.2, 131.2, 133.9, 136.6, 159.2, 193.4, 201.7 (d, *J* = 17.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.8 (s); LC/MS m/z 419 $[M+H]^+$; Anal. Calcd. for $C_{22}H_{27}O_6P$ C 63.15, H 6.50; found C 62.89, H 6.72.

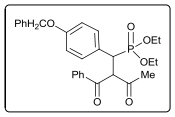
(±)-Diethyl 2-benzoyl-1-(4-(benzyloxy)phenyl)-3-oxo-3-phenylpropylphosphonate (3g): To a stirred solution of **1b** (0.50 g, 1.42 mmol) and dibenzoylmethane (**2a**, 0.31 g, 1.42 mmol), in



anhydrous dichloromethane (4 mL) as solvent, $Bi(OTf)_3$ (0.46 g, 0.70 mmol) was added and then the reaction mixture was stirred at rt for 9 h**.** The compound was isolated using column chromatography. Yield 0.720 g, (91%); off-white solid; mp 170-172 ^{o}C; IR (KBr, cm^{-1}) 2987, 1695, 1602, 1510, 1445, 1253, 1026, 954; ^{1}H NMR (400

MHz, $CDCl_3$) δ 0.95-1.03 (m, 6H), 3.47-3.57 (m, 1H), 3.72-3.93 (m, 3H), 4.49 (dd, J = 22 Hz, 12 Hz, 1H), 4.97 (s, 2H), 6.42-6.47 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 7.2-7.49 (m, 10H), 7.50-7.62 (m, 3H), 7.78 (d, *J* = 8.0 Hz, 2H) 8.24 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.8 and 16.0 (two sets of doublets, *J* = 6.1 Hz each), 44.2 (d, *J* = 139.4 Hz), 56.9, 61.9 and 63.3 (two sets of doublets, *J* = 7.1 Hz each), 69.9, 114.8, 114.9, 126.1 (d, *J* = 7.0 Hz), 127.5, 127.9, 128.5, 128.6, 128.8, 129.2,131.2, 133.3, 133.5, 136.8, 136.9, 158.0, 192.2 (d, *J* = 17.2 Hz), 192.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.3; LC/MS m/z 557 $[M + H]^+$; Anal. Calcd for $C_{33}H_{33}O_6P$ C, 71.21; H, 5.98; Found C, 71.28 H, 5.83.

(±)-Diethyl 2-benzoyl-1-(4-(benzyloxy)phenyl)-3-oxobutylphosphonate (3h): By starting with **2c**, this compound was synthesised using similar procedure and molar quantities as **3g.** Yield 0.650 g, (93%); viscous liquid; IR (KBr, cm^{-1}) 1723, 1680, 1602, 1508, 1450, 1253, 1035, 969;

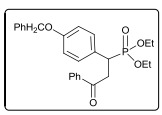


^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 and 1.04 (two sets of triplet, *J* = ~7.5 Hz each, 6H), 1.86 (s, 3H), 3.59-3.89 (m, 4H), 4.37 (dd, *J* = 24 Hz, 12 Hz, 1H), 5.06 (s, 2H), 4.53 (dd→t, *J* = 12.0 Hz each, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.34-7.65 (m, 10H), 8.18 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 and 16.0 (two sets of doublets, *J* = 6.1 Hz each), 27.4, 43.5 (d, *J* = 138.4 Hz), 62.1 and 63.1 (two sets of doublets, *J* = 7.1 Hz each), 63.5, 70.1, 115.2 (d, *J* = 3.0 Hz), 125.3 (d, *J* = 8.0 Hz), 127.6, 128.0, 128.6, 128.8, 129.1, 131.2 (d, *J* = 6.0 Hz), 133.8, 136.6, 136.8, 158.4 (d, *J* = 3.0 Hz), 193.3, 201.5 (d, *J* = 18.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.2. LC/MS m/z 495 $[M + H]^+$; Anal. Calcd for $C_{28}H_{31}O_6P$ C, 68.01; H, 6.32. Found C, 68.15; H, 6.26.

3.6.2 *Regioselective C-C bond cleavage for 3g and 3h*

Synthesis of 3i and 3j: A solution of **3h** (0.40 g, 0.81 mmol) in methanol was heated under reflux using $FeCl_3$ (0.13 g, 0.81 mmol) for 2 h. The compound **3i** was isolated using column chromatography followed by **3j**. In case of **3g,** the reaction mixture had to stir for 4h. The same result was also obtained by using $FeCl_3.6H_2O$ at 60 ^oC for 6h.

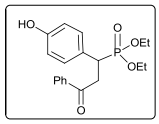
(±)-Diethyl (1-(4-(benzyloxy)phenyl)-3-oxo-3-phenylpropyl)phosphonate (3i): Yield 0.071g, (19%); viscous liquid; IR (KBr, cm^{-1}) 2925, 1687, 1604, 1508, 1445, 1225, 1025,



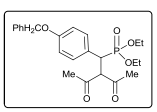
969; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 and 1.28 (two sets of triplet, *J* =6.8 Hz each, 6H), 3.58-3.74 (m, 3H), 3.87-3.97 (m, 2H), 4.01-4.11 (m, 2H), 5.00 (s, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.29-7.56 (m, 10H), 7.92 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.5 (two sets of doublets, *J* = 6.1 Hz each), 38.2 (d, *J* = 142.0

Hz), 39.3, 62.1 and 63.1 (two sets of doublets, J = 7.1 Hz each), 70.1, 114.9, 127.6, 128.0, 128.2, 128.6, 128.7, 130.3, 130.4, 133.4, 136.7, 137.0, 158.1 (d, J = 2.7 Hz), 196.6 (d, J = 15.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5; LC/MS m/z 453 $[M + H]^+$.

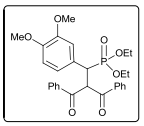
(±)-Diethyl 1-(4-hydroxyphenyl)-3-oxo-3-phenylpropylphosphonate (3j): Yield 0.220 g, (75%); off-white solid; mp 114-116 ^{o}C; IR (KBr, cm^{-1}) 3207, 1686, 1604, 1512, 1450, 1229, 1027, 975; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 and 1.27 (t, J = 7.0 Hz each , 6H), 3.55-3.79 (m, 3H), 3.85-3.94 (m, 2H), 4.02-4.09 (m, 2H), 6.61 (d, J = 8.5 Hz, 2H), 7.15-7.17 (m, 2H), 7.40-7.54 (m, 3H), 7.90- 7.93 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.4 (two sets of doublets, J = 5.8 Hz each), 38.1 (d, J = 141.5 Hz), 38.9, 62.3 and 63.3 (two sets of doublets, J = 7.3 Hz each), 116.0, 125.9 (d, J = 7.2 Hz), 128.2, 128.7, 130.2, 133.4, 136.6, 156.2, 196.8 (d, J = 14.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.7. LC/MS m/z 363 $[M + H]^+$; Anal. Calcd for $C_{19}H_{23}O_5P$ C, 62.98; H, 6.40. Found C, 63.17; H, 6.51.



(±)-Diethyl 2-acetyl-1-(4-(benzyloxy)phenyl)-3-oxobutylphosphonate (3k): This compound is synthesised in a manner analogous to compound **3c** by starting with **1b** (0.50 g) using similar molar quantitites. Yield 0.510 g, (83%); off-white solid; mp 118-120 ^{o}C; IR (KBr, cm^{-1}) 2984, 1696, 1607, 1512, 1360, 1244, 1029, 965; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 and 1.24 (two sets of triplet, J = 7.2 Hz each, 6H), 1.83 (s, 3H), 2.34 (s, 3H), 3.63-3.71 (m, 1H), 3.81-4.05 (m, 4H), 4.60 (dd→t, J~ 11.6 Hz each, 1H), 5.01 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.18- 7.21 (m, 2H), 7.30-7.41 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.3 (two sets of doublets, J = 5.5 Hz each), 28.2, 30.5, 43.1 (d, J = 138.1 Hz), 62.5 and 63.2 (two sets of doublets, J = 7.1 Hz each), 69.5, 70.1, 115.3, 125.4 (d, J = 7.8 Hz), 127.6, 128.1, 128.7, 130.8 (d, J = 5.7 Hz), 136.8, 158.4, 201.5, 201.7 (d, J = 17.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.6. LC/MS m/z 433 $[M + H]^+$; Anal. Calcd for $C_{23}H_{29}O_6P$ C, 63.88; H, 6.76. Found C, 63.94; H, 6.49.



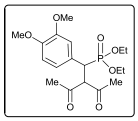
(±)-Diethyl 2-benzoyl-1-(3,4-dimethoxyphenyl)-3-oxo-3-phenylpropylphosphonate (3l): To a stirred solution of **1c** (0.50 g, 1.64 mmol), dibenzoylmethane (0.36 g, 1.64 mmol) in anhydrous nitromethane (4 mL) as solvent, copper(II)trifluoromethanesulfonate (0.59 g, 1.63 mmol) was added and then the reaction mixture was stirred at 60^{o}C for 8 h**.** The compound **3l** was isolated using column chromatography. Yield 0.740 g, (88%); off-white solid; mp 147-149 ^{o}C; IR (KBr, cm^{-1}) 2983, 1693, 1589, 1515, 1452, 1258, 1153, 1034, 962; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-1.00 (m, 6H) 3.46-3.54 (m, 1H), 3.73 (s, 3H),3.76-3.91



(m, 6H), 4.45 (dd, *J* = 19.8 and 11.1 Hz, 1H), 6.44 (dd→t, *J* = 11.1 and 10.0 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.92-6.98 (m, 2H), 7.25-7.29 (m, 2H), 7.39-7.58 (m, 4H), 7.77 (d, *J* = 7.5 Hz, 2H), 8.19 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 and 16.2 (d, *J* ~ 5.9 Hz each), 44.6 (d, *J* = 138.7 Hz), 55.7, 55.8, 56.7, 57.4, 61.9 and 63.5 (d, *J* = 7.2 Hz each), 110.9 (d, *J* = 1.6 Hz), 113.3 (d, *J* = 6.0 Hz), 122.6 (d, *J* = 7.0 Hz), 126.0 (d, *J* = 6.6 Hz), 128.6, 128.7, 128.9, 129.2, 133.4, 133.6, 136.9, 127.1, 148.2, 148.6, 192.3 (d, *J* = 16.1 Hz), 192.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.0 (s); LC/MS m/z 511 $[M + H]^+$; Anal. Calcd. for $C_{28}H_{31}O_7P$ C, 65.87; H, 6.12. Found C, 65.94; H, 6.03.

Reaction of acetylacetone (2b) with 1c: This reaction was performed in a manner analogous to synthesis of compound **3c** by starting with **1c** (0.50 g, 1.42mmol) using similar molar quantitites at 28 ^{o}C for 24 h**.** The compound **3m** was isolated along with **3ma** in 1:1 ratio. The amount isolated from column 0.55 g (mixture of **3m** & **3ma**), The compound **3ma** (0.25 g, 44 %) was crystalised from this mixture from dichloromethane/hexane mixture (1:2).

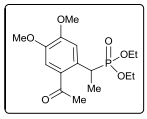
Spectroscopic data for the mixture of **3m** & **3ma**:



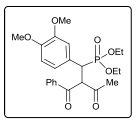
IR (KBr, cm^{-1}) 2989, 1697, 1658, 1350, 1242, 1030, 964; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 and 1.18 (two sets of triplet, *J* = 7.2 Hz each, 6H), 1.81 (s, 3H), 2.28 and 2.32 (s, 3H), 3.58-3.65 (m, 1H), 3.70-3.82 (m, 2H), 3.79 & 3.81 (s, each 3H), 3.86-4.03 (m, 1H), 4.49-4.55 (m, 1H), 4.61 (dd→t, *J*~ 11.4 &11.6 Hz each, 1H), 6.75-6.81 (m, 3H); Peaks for **3ma** appeared at δ 1.09 and 1.23 (two sets of triplet, *J* = 7.2 Hz each, 6H), 2.44 (dd, *J*~ 1.9 & 5.4 Hz, 3H), 2.48 (s, 3H), 3.58-3.68 (m, 1H), 3.84-3.88 (m, 1H), 3.93 (s, 6H), 4.01-4.06 (m, 2H), 4.42-4.49 (qd, *J* = 2 &29.5 Hz, not well resolved, 1H), 6.96 (s,1H), 7.32 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.3 (d, *J* ~ 5.7 Hz each), 28.2, 30.6, 43.5 (d, *J* = 138.7 Hz), 55.8, 56.1, 62.5 and 63.3 (d, *J* = 7.2 Hz each), 69.5, 111.2 (d, *J* = 2.3 Hz), 112.7 (d, *J* = 5.1 Hz), 122.0 (d, *J* = 6.4 Hz), 125.4 (d, *J* = 7.9 Hz), 148.6 (d, *J* = 2.3 Hz), 149.0 (d, *J* = 2.5 Hz), 150.6 (d, *J* = 9.6 Hz); Peaks for **3ma** appeared at δ 13.2, 16.3 (d, *J* ~ 6.1 Hz), 31.0, 49.7 (d, *J* = 131.2 Hz), 56.0, 56.3, 62.9 and 63.1 (d, *J* = 7.2 Hz each), 104.1, 108.5, 132.5 (d, *J* = 6.2 Hz), 135.0 (d, *J* = 8.2 Hz), 137.9 (d, *J* = 4.4 Hz), 149.7, 150.1 (d, *J* = 2.1 Hz),196.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.6 (s) & 23.9 (s) (1:1); LC/MS m/z 387 [M + H] for **3m** and 369 $[M + Na +2H]^+$ for **3ma**.

Data for the 3ma obtained after crystallization

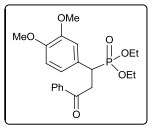
White crystalline solid; mp 126-128 ^{o}C; IR (KBr, cm^{-1}) 2989, 1656, 1555, 1338, 1243, 1031, 965; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 and 1.23 (two sets of triplet, *J* = 7.2 Hz each, 6H), 2.44 (dd, *J*~ 2.0 & 5.5 Hz, 3H), 2.53 (s, 3H), 3.62-3.68 (m, 1H), 3.84-3.88 (m, 1H), 3.97 (s, 6H), 4.01-4.06 (m, 2H), 4.46-4.53 (qd, *J* = 2.0 & 29.5 Hz, not well resolved, 1H), 7.00 (s,1H), 7.37 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 16.2 (d, *J* ~ 6.2 Hz), 30.9, 49.7 (d, *J* = 130.0 Hz), 56.1, 56.2, 62.9 and 63.1 (d, *J* = 7.2 Hz each), 104.1, 108.5, 132.5 (d, *J* = 6.2 Hz), 135.0 (d, *J* = 8.2 Hz), 137.9 (d, *J* = 4.4 Hz), 149.7, 150.0, 196.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s) [96%]; ~4% of **3m** also was observed in ^{31}P NMR]. LC/MS m/z 369 $[M + Na + 2H]^+$; Anal. Calcd. for $C_{16}H_{25}O_6P$ C 55.81, H 7.32; found C 56.19, H 6.35.



(±)-Diethyl (2-benzoyl-1-(3,4-dimethoxyphenyl)-3-oxobutyl)phosphonate (3n): Similar procedure and molar quantities as **3l** are used. The reaction mixture of **1c** and **2c** was stirred at 60 ^{o}C for 6h. Yield 0.600 g, (81%); viscous liquid; IR (KBr, cm^{-1}) 2986, 1722, 1679,1589, 1513, 1254, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 and 1.01 (two sets of triplet, *J* = 7.0 Hz each, 6H), 1.83 (s, 3H), 3.56-3.82 (m, 4H), 3.85 (s, 3H), 3.90 (s, 3H), 4.31 (dd, *J* = 21.7 and 11.7 Hz, 1H), 5.51 (dd→t, *J* = 11.9 and 12.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.92-6.96 (m, 2H), 7.48-7.62 (m, 3H), 8.14-8.16 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1 and 16.2 (d, *J* ~ 6.0 Hz each), 27.5, 43.8 (d, *J* = 138.3 Hz), 55.8, 55.9, 62.2 and 63.2 (d, *J* = 7.6 Hz each), 63.6, 11.2, 113.2, 122.5 (d, *J* = 7.1 Hz), 125.4 (d, *J* = 7.9 Hz), 128.9, 129.2, 133.9, 136.6, 148.7 (d, *J* = 3.3 Hz), 149.0 (d, *J* = 2.2 Hz), 193.3, 201.7 (d, *J* = 17.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.8 (s); LC/MS m/z 449 $[M + H]^+$; Anal. Calcd for $C_{23}H_{29}O_7P$ C, 61.60; H, 6.52. Found C, 61.38; H, 6.26.

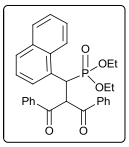


(±)-Diethyl (1-(3,4-dimethoxyphenyl)-3-oxo-3-phenylpropyl)phosphonate (3o): This compound was synthesised using similar procedure and molar quantities as **3b** for 8 h from the reaction of **1c** with **2d.** Yield 0.620 g, (93%); viscous liquid; IR (KBr, cm^{-1}) 2983, 1685, 1593, 1514, 1253, 1152, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 and 1.27 (two sets of triplet, *J* ~ 6.8 Hz each, 6H), 3.57-3.73 (m, 3H), 3.75 (s, 3H), 3.82 (s, 3H), 3.88-3.94 (m, 2H), 4.05-4.09 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.95-6.98 (m, 2H), 7.41-7.45 (m, 2H), 7.52-7.56 (m, 1H), 7.93 (d, *J* = 9.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 and 16.4 (two sets of doublets, *J* = 6.1 Hz each), 38.5 (d, *J* = 141.4 Hz), 39.3, 55.8, 55.9, 61.9



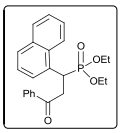
and 62.9 (two sets of doublets, *J* = 7.1 Hz each), 111.1 (d, *J* = 3.0 Hz), 112.6 (d, *J* = 6.1 Hz), 121.4 (d, *J* = 7.1 Hz), 128.1, 128.2 (d, *J* = 7.1 Hz), 128.6, 133.3, 136.6, 148.2 (d, *J* = 3.0 Hz), 148.7 (d, *J* = 3.0 Hz), 196.5 (d, *J* = 15.1 Hz);; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.8. LC/MS m/z 407 $[M + H]^+$; Anal. Calcd for $C_{21}H_{27}O_6P$ C, 62.06; H, 6.70. Found C, 61.86; H, 6.48.

(±)-Diethyl 2-benzoyl-1-(naphthalene-1-yl)-3-oxo-3-phenylpropylphosphonate (3p): To a stirred solution of **1d** (0.50 g, 1.7 mmol) and dibenzoylmethane (**2a**, 0.38 g, 1.7 mmol), in anhydrous nitromethane (4 mL) as solvent, anhydrous $FeCl_3$ (0.27 g, 1.7 mmol equiv) was added and then the reaction mixture was stirred at 28 ^oC for 16 h**.** Yield 0.610 g, (72%); off-white solid;



mp 186-188; IR (KBr, cm^{-1}) 2982, 1706, 1589, 1445, 1257, 1241, 1016, 969; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 and 0.97 (two sets of triplet, *J* = 7.1 Hz each, each 3H), 3.01-3.08 (m, 1H), 3.49-3.58 (m, 1H), 3.69-3.89 (m, 2H), 5.46 (dd, *J* = 20.5 and 11.0 Hz, 1H), 6.69 (dd→t, *J* = 11.1 and 10.0 Hz, 1H), 7.17-7.26 (m, 3H), 7.31-7.35 (m, 1H), 7.44-7.54 (m, 3H), 7.58-7.77 (m, 7H), 8.29-8.31 (m, 2H), 8.46 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.7 and 15.9 (d, *J* ~ 6.0 Hz each), 38.7 (d, *J* = 138.6 Hz), 57.4, 62.0 and 63.5 (d, *J* = 7.2 Hz each), 124.1, 124.7 (d, *J* = 3.3 Hz), 125.9, 126.6 (d, *J* = 4.7 Hz), 128.2 (d, *J* = 3.2 Hz), 128.5, 128.6 (d, *J* = 5.7 Hz), 128.9, 129.4, 130.7 (d, *J* = 6.6 Hz), 132.6, 132.65, 133.2, 133.7, 133.9, 136.8, 137.0, 191.9 (d, *J* = 16.0 Hz), 193.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.1 (s); LC/MS m/z 501 $[M +H]^+$; Anal. Calcd for $C_{30}H_{29}O_5P$ C, 71.99; H, 5.84. Found C, 72.13; H, 5.76.

(±)-Diethyl 1-(naphthalene-1-yl)-3-oxo-3-phenylpropylphosphonate (3q): This compound was synthesised using similar procedure and molar quantities as **3b** for 8 h using the diketone **2a.**

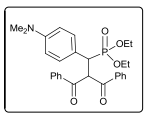


Yield 0.610g, (91%); viscous liquid; IR (KBr, cm^{-1}) 1684, 1236, 1026, 959; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 and 1.25 (two sets of triplet, *J* ~ 8 Hz each, each 3H), 3.35-3.44 (m, 1H), 3.68-3.76 (m, 1H), 3.90-3.93 (m, 2H), 4.05-4.10 (m, 2H), 4.91-4.95 (m, br, 1H), 7.39- 7.42 (m, 3H), 7.43-7.50 (m, 2H), 7.53-7.58 (m, 1H), 7.60-7.74 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 8.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 and 16.4 (two sets of doublets, *J* = 5.5 Hz each), 32.7 (d, *J* = 135.5 Hz), 40.2, 62.2 and 63.1 (two sets of doublets, *J* = 7.2 Hz each), 123.7, 125.2, 125.3, 125.8, 126.5, 127.9, 128.2, 128.7, 128.8, 132.3 (d, *J* = 6.1 Hz), 132.7 (d, *J* = 6.1 Hz), 133.4, 133.9, 136.6, 196.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5; LC/MS m/z 397 $[M + H]^+$; Anal. Calcd for $C_{23}H_{25}O_4P$ C, 69.69; H, 6.36. Found C, 69.74; H, 6.27.

The other diketones **2c** and **2d** also produced **3q** in 80% yield under the same reaction conditions after 12 h.

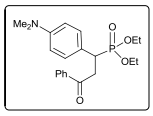
The reaction of phosphonate 1e with diketones 2a, 2c and 2d: The reaction was performed in a manner analogous to the reaction for synthesizing **3b** using similar molar quantities**.** The compound **3r** (yield 0.540 g, 63%; off-white solid. mp 170-172 ^{o}C) was isolated followed by **3s** (yield 0.180, 27%; viscous liquid) using column chromatography. In case of **2c**, reaction mixture was stirred at 80 ^{o}C for 7 h to produce **3t [**Yield: 0.130g, (18%), light brown solid] and **3s** [Yield: 0.530 g, (78%); viscous liquid]. For **2d**, the reaction mixture was stirred at 70 ^{o}C for 12 h to afford **3s** with isolated yield 0.610 g (91%).

(±)-Diethyl 2-benzoyl-1-(4-(dimethylamino)phenyl)-3-oxo-3-phenylpropylphosphonate (3r): IR (KBr, cm^{-1}) 1696, 1605, 1522, 1253, 1050, 965; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96-0.98 (m,



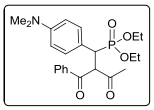
6H), 2.84 (s, 6H), 3.47-3.53 (m, 1H), 3.79-3.88 (m, 3H), 4.42 (dd, *J* = 19.7 and 11.3 Hz, 1H), 6.45 (dd→t, *J* = 12 and 8.0 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 2H), 7.25-7.38 (m, 4H), 7.56-7.59 (m, 4H), 7.79 (d, *J* = 7.9 Hz, 2H), 8.23 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 and 16.2 (d, *J* = 6.1 Hz), 40.4, 44.1 (d, *J* = 139.4 Hz), 56.8, 61.7 and 63.4 (d, *J* = 7.2 Hz), 112.5, 120.9 (d, *J* = 7.2 Hz), 128.5, 128.6, 128.7, 129.2, 130.6 (d, J = 6.1 Hz), 133.1, 133.4, 137.0, 149.7, 192.3 (d, *J* = 16.7 Hz), 193.1; ^{31}P NMR (212 MHz, $CDCl_3$) δ 26.8 (s); LC/MS m/z 494 $[M + H]^+$; Anal. Calcd for $C_{28}H_{32}NO_5P$ C, 68.14; H, 6.54; N, 2.84; Found C, 68.31; H, 6.32; N, 2.75.

(±)-Diethyl 1-(4-(dimethylamino)phenyl)-3-oxo-3-phenylpropylphosphonate (3s): IR (KBr, cm^{-1}) 2934, 1733, 1690, 1523, 1257, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, *J*~7.0 Hz, 3H),

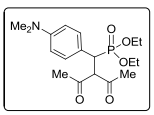


1.28 (t, *J* ~7.0 Hz, 3H), 2.89 (s, 6 H), 3.60-3.76 (m, 3H), 3.90-3.95 (m, 2H), 4.04-4.09 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 7.29-7.30 (m, 2H), 7.42-7.45 (m, 2H), 7.52-7.55 (m, 1H), 7.95 (d, *J* = 7.5 Hz, 2H); Some unassigned peaks at δ 2.98 (s) and 6.87-6.95 (m) also appeared in the spectrum; ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3 and 16.4 (d, *J* = 5.6 Hz), 37.9 (d, *J* = 140.6 Hz), 39.3, 40.5, 61.9 and 63.0 (d, *J* = 7.4 Hz each), 110.9, 112.6, 114.7, 120.0, 121.4, 123.2 (d, *J* = 6.8 Hz), 128.1, 128.6, 129.8 (d, *J* = 6.6 Hz), 133.1, 136.8, 145.9, 146.8, 149.8 (d, *J* = 1.4 Hz), 196.8 (d, *J* = 15.0 Hz); Other peaks at δ 55.9 and in the region of 110.0-150.0 corresponds to unassigned peaks in ^{1}H NMR; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.0 (s); LC/MS m/z 390 $[M + H]^+$.

(±)-Diethyl 2-benzoyl-1-(4-(dimethylamino)phenyl)-3-oxobutylphosphonate (3t): yield: 0.130g, (18%); light brown solid; mp 172-174 ^{o}C; IR (KBr, cm^{-1}) 1696, 1605, 1522, 1448, 1253, 1050, 965; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 and 1.05 (t, *J* = 7.1 Hz each, 6H), 1.87 (s, 3H), 2.95 (s, 6H), 3.60-3.63 (m, 1H), 3.65-3.82 (m, 3H), 4.29 (dd, *J* = 21.5 and 11.8 Hz, 1H), 5.51 (dd→t, *J* = 11.9 and 11.8 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 2H), 7.26- 7.28 (m, 2H), 7.51-7.54 (m, 2H), 7.60-7.64 (m, 1H), 8.17 (d, *J* = 9.5 Hz, 2H); Some unassigned peaks at δ 2.98 (s) and 6.87-6.95 (m) also appeared in the spectrum. ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 and 16.1 (d, *J* = 6.6 Hz), 27.1, 40.4, 43.3 (d, *J* = 138.1 Hz), 62.1 and 62.9 (d, *J* = 7.1 Hz), 63.6, 110.7, 112.6, 114.6, 120.1, 121.5, 128.7, 19.1, 130.7, 133.6, 136.8, 145.7, 146.6, 150.0, 193.6, 202.0 (d, *J* = 17.1 Hz), The peaks at δ 55.9 and extra peaks at the region of 110.0-150.0 correspond to the unassigned peas in ^{1}H NMR; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.6 (s); LC/MS m/z 432 $[M + H]^+$.



(±)-Diethyl 2-acetyl-1-(4-(dimethylamino)phenyl)-3-oxobutyl)phosphonate (3u): A method similar to the synthesis of **3k** was used using similar molar quantities**.** Yield 0.570 g, (89%); off-white solid; mp 198-200 ^{o}C; IR (KBr, cm^{-1}) 1698, 1609, 1517, 1357, 1236, 1160, 1050,; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 and 1.24 (two sets of triplet, *J* = 7.2 Hz each, 6H), 1.82 (s, 3H), 2.33 (s, 3H), 2.89 (s, 6H), 3.63-3.72 (m, 1H), 3.81-3.99 (m, 4H), 4.60 (dd→t, *J*~ 11.6 Hz each, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2 and 16.3 (two sets of doublets, *J* = 5.5 Hz each), 28.1, 30.7, 40.5, 42.9 (d, *J* = 139.3 Hz), 62.4 and 63.2 (two sets of doublets, *J* = 7.1 Hz each), 69.6, 112.7, 120.1 (d, *J* = 7.8 Hz), 130.4 (d, *J* = 5.7 Hz), 149.9, 201.8, 202.1 (d, *J* = 18.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.0. LC/MS m/z 370 $[M + H]^+$; Anal. Calcd for $C_{18}H_{28}NO_5P$ C, 58.53; H, 7.64; N, 3.79. Found C, 58.31; H, 7.43; N, 3.88.

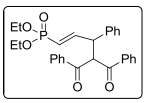


3.6.3 *Procedure for the synthesis of ω-ketovinylphosphonates 13a and 13b-i*

To a mixture of 11a (0.500 g, 1.85 mmol), dibenzoylmethane (12a, 0.498 g, 2.22 mmol), $FeCl_3.6H_2O$ (0.500 g, 1.85 mmol) was added and then the reaction mixture was stirred at 65 ^{o}C for 8-12 h. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 x 30 ml). After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using ethylacetate/ pet ether (90/10) as the eluent to afford 13a in 73% yield (0.648 g). However, the yield was improved to 85% when TfOH acid was used. All the other

compounds 13b-i were prepared analogously using similar molar quantities of phosphonates and aromatic 1,3-diketones.

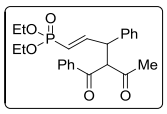
3.6.4 ***Analytical data 13a-i and 11c'***

(*E*)-Diethyl (4-benzoyl-5-oxo-3,5-diphenylpent-1-en-1-yl)phosphonate (13a): White solid; mp: 186-188 ^{o}C; IR (KBr): ῡ = 2986, 1603, 1547, 1253, 1034, 955 cm^{-1}; ^{1}H NMR (400 MHz, 

$CDCl_3$): δ= 1.14 and 1.20 (d, *J* ~ 7.0 Hz, 3H each set), 3.68-3.94 (m, 4H), 4.76-4.81 (m, 1H), 5.59-5.69 (m, 1H), 5.92 (d, *J* = 10.7 Hz, 1H), 6.93 (ddd, *J* =21.5, 17.0, 7.9 Hz, 1H), 7.09-7.13 (m, 1H), 7.18-7.22 (m, 2H), 7.25-7.32 (m, 4H), 7.44-7.47 (m, 3H), 7.55-7.59 (m, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 8.01 ppm (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.1 and 16.2 (two sets of doublets, *J* = 6.4 Hz each), 50.9 (d, *J* = 22.0 Hz), 61.4, 61.7 (d, *J* = 5.1 Hz), 61.8 (d, *J* = 5.1 Hz), 119.2 (d, *J* = 184.7 Hz), 120.1, 120.5 (d, *J* = 184.8 Hz), 127.4, 128.5, 128.6, 128.62, 128.8, 128.9, 133.4, 133.8, 136.5, 136.6, 138.3, 151.7 (d, *J* = 5.3 Hz), 193.1, 193.4 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ= 17.4 ppm; LCMS m/z: 477 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + Na], calcd for $C_{28}H_{29}O_5PNa$ 499.1651, found 499.1626.

(*E*)-Diethyl (4-benzoyl-5-oxo-3,5-diphenylhex-1-en-1-yl)phosphonate (13b): The crude reaction mixture solution in EtOAc was run through a small celite pad and then the solvent was evaporated to get the white solid that showed the presence of compound 13b as 1:1 diastereomeric mixture (see the SI for details). Yield: 0.69 g (90%); Further, the column chromatography was performed to separate the diastereomers where one of the diastereoisomers was isolated first by EtOAc /Hexane (80/20) as a mixture of diastereomers (~86:14) followed by other diastermer in pure form.

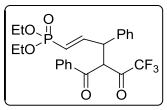
Data for one diasteromer in pure form. Yield: 0.315 g (41%; White solid); mp: 158-160 ^{o}C; IR (KBr): ῡ = 2985, 1712, 1673, 1447, 1367, 1245, 1174, 1037, 965 cm^{-1};



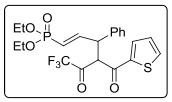
^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.25-1.32 (m, 6H), 2.21 (s, 3H), 3.97-4.06 (m, 4H), 4.54-4.58 (m, 1H), 5.15 (d, *J*= 11.2 Hz, 1H), 5.69-5.78 (m, 1H), 6.90 (ddd, *J*= 21.5, 17.1, 7.9 Hz, 1H), 7.11-7.27 (m, 5H), 7.37-7.40 (m, 2H), 7.50-7.54 (m, 1H), 7.79-7.82 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.3 and 16.4 (d, *J* = 6.2 Hz each), 28.6, 49.9 (d, *J* = 21.9 Hz), 61.8 and 61.9 (d, *J* = 5.4 Hz each), 67.8, 119.2 (d, *J* = 185.8 Hz), 127.4, 128.2, 128.6, 128.8, 128.85, 133.8, 136.6, 138.0 (d, *J* = 2.0 Hz), 151.3 (d, *J* = 5.2 Hz), 193.6, 201.6 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ 17.2 (s) ppm; LCMS m/z: 415 [M^+ + 1]; HRMS (ESI) m/z: [M + Na]$^+$, calcd for $C_{23}H_{27}O_5PNa$ 437.1494, found 437.1471.

Spectroscopic data for mixture of diasteremers for 13b (86:14): Yield: 0.375 g (49%; White solid); IR (KBr): ῡ = 2987, 1723, 1673, 1447, 1361, 1241, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 1.13-1.20 (m, 6H), 1.94 (s, 3H), 3.75-3.93 (m, 4H), 4.59-4.69 (m, 1H), 5.18 (d, *J*=12.0 Hz, 1H), 5.55-5.64 (m, 1H), 6.70 (ddd, *J*= 21.5, 17.1, 7.9 Hz, 1H), 7.28-7.36 (m, 5H), 7.52-7.55 (m, 2H), 7.60-7.64 (m, 1H), 8.07-8.09 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.1 and 16.2 (d, *J* = 6.2 Hz each), 28.2, 50.0 (d, *J* = 21.9 Hz), 61.6 and 61.7 (d, *J* = 5.4 Hz each), 67.4, 118.7 (d, *J* = 185.8 Hz), 127.9, 128.5, 128.9, 129.0, 129.2, 134.2, 136.8, 138.0, 151.5 (d, *J* = 5.5 Hz), 193.5, 201.4 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ= 17.4 (s) ppm. The peaks for other diastereoisomer (~14%) were visible in all the NMR spectra.

(*E*)-Diethyl (4-benzoyl-6,6,6-trifluoro-5-oxo-3-phenylhex-1-en-1-yl)phosphonate (13c): Yield: 0.434 g (50%, White solid); mp: 141-143 ^oC; IR (KBr): ῡ = 1764, 1675, 1450, 1204, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 1.06 and 1.16 (d, *J* = 6.4 Hz, 3H each set), 3.49-3.86 (m, 4H), 4.54-4.59 (m, 1H), 5.56-5.67 (m, 2H), 6.70 (ddd, *J* = 20.8, 17.2, 8.5 Hz, 1H), 7.27-7.35 (m, 5H), 7.56-7.58 (m, 2H), 7.66-7.68 (m, 1H), 8.04 ppm (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3): δ= 16.1 and 16.2 (two sets of doublets, *J* = 6.0 Hz each), 51.0 (d, *J* = 23.2 Hz), 58.7, 61.7 (d, *J* = 6.0 Hz), 61.8 (d, *J* = 6.0 Hz), 114.5 (not well resolved, appeared as doublet, *J* = 292.9 Hz), 120.5 (d, *J*= 184.8 Hz), 127.9, 128.06, 128.1, 128.7, 128.8, 129.0, 129.2, 129.3, 133.3, 134.7, 136.1, 137.3, 149.5 (d, *J*= 4.8 Hz), 183.4 (m, not well resolved), 190.6 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ= 16.2 ppm; LCMS m/z: 469 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + H], calcd for $C_{23}H_{25}O_5F_3P$ 469.1391, found 469.1378.

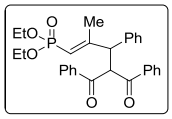


(*E*)-Diethyl (6,6,6-trifluoro-5-oxo-3-phenyl-4-(thiophene-2-carbonyl)hex-1-en-1-yl) phosphonate (13d): Yield: 0.747 g (85%, White solid); mp: 142-144 ^oC; IR (KBr): ῡ = 2991, 1765, 1640, 1512, 1407, 1220, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 1.15-1.21 (m, 6H), 3.64-3.92 (m, 4H), 4.57-4.61 (m, 1H), 5.40 (d, *J* = 10.8 Hz, 1H), 5.64-5.73 (m, 1H), 6.71-6.83 (m, 1H), 7.30-7.36 (m, 6H), 7.85-7.86 (m, 1H), 7.94-7.95 ppm (m, 1H); ^{13}C NMR (126 MHz, CDCl3): δ= 16.2 (d, *J* = 6.4 Hz), 50.8 (d, *J* = 22.6 Hz), 60.6, 61.6 (d, *J* = 5.3 Hz), 61.7 (d, *J* = 5.5 Hz), 115.0 (not properly resolved, appear as doublet with *J*= 292.0), 120.6 (d, *J* = 184.3 Hz), 128.0, 128.2, 129.0, 129.3, 134.1, 137.1, 143.4, 149.3 (d, *J* = 5.5Hz), 182.3, 183.1 ppm (not properly resolved, appear as a doublet *J* = 36.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ= 16.3 ppm. Peak at δ= 16.5 ppm was observed (6%) for other isomer; LCMS m/z: 493

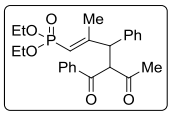


[M^+ + Na]. HRMS (ESI) m/z: [M^+ + H], calcd for $C_{21}H_{23}O_5F_3PS$ 475.0956, found 475.0932. Other diasteromer [~6% (^{1}H and ^{31}P NMR)] is also present with this sample.

(*E*)-Diethyl (4-benzoyl-2-methyl-5-oxo-3,5-diphenylpent-1-en-1-yl)phosphonate (13e): Yield: 0.691 g (80%, White solid); mp: 126-128 ^oC; IR (KBr): ῡ = 2992, 1693, 1597, 1492, 1448, 1273, 1223, 1046, 1025, 963 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.16 (t, *J* = 6.8 Hz, 3H), 1.21 (t, *J*= 6.8 Hz, 3H), 2.07 (s, 3H), 3.78-3.94 (m, 4H), 4.66 (d, *J*= 11.6 Hz, 1H), 5.53 (d, *J*= 15.1 Hz, 1H), 6.05 (d, *J*= 11.6 Hz, 1H), 7.03-7.07 (m, 1H), 7.09-7.52 (m, 10H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.94 ppm (d, *J*= 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.2 and 16.3 (d, *J* = 6.1 Hz), 20.7 (d, *J* = 7.1 Hz), 56.2 (d, *J* = 21.2 Hz), 60.7, 61.3 and 61.4 (d, *J* = 5.1 Hz), 111.8 (d, *J* = 187.9 Hz), 127.6, 128.5, 128.6, 128.63, 128.8, 128.9, 133.6 (d, *J* = 34.3 Hz), 136.4, 136.6, 137.4, 162.3, 192.9, 194.2 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ= 17.5 (s) ppm; LCMS m/z: 491 [M^+ + 1]; HRMS (ESI) m/z: [M + H]$^+$, calcd for $C_{29}H_{32}O_5P$ 491.1987, found 491.1970.



(*E*)-Diethyl (4-benzoyl-2-methyl-5-oxo-3,5-phenylhex-1-en-1-yl)phosphonate (13f): ^{31}P/^{1}H NMR for the reaction mixture showed the product formed in (0.672 g, 89% yield) with 1:1 diastereomeric ratio. We could isolate one of the diastereomers in pure form. Yiled: 0.287 (38%, viscous liquid); IR (KBr): ῡ = 1722, 1682, 1450, 1240, 1026, 965 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.31 (t, *J* = 5.8 Hz, 6H), 2.07 (s, 3H), 2.21 (s, 3H), 4.05-4.08 (m, 4H), 4.48 (d, *J* = 11.8 Hz, 1H), 5.33 (d, *J* = 12.1 Hz, 1H), 5.74 (d, *J* = 15.5 Hz, 1H), 6.87 (br, 1H), 7.16-7.17 (m, 4H), 7.35-7.55 (m, 3H), 7.83-7.85 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.3 and 16.4 (d, *J* = 6.4 Hz), 19.4 (d, *J* = 7.0 Hz), 27.8, 55.3 (d, *J* = 21.3 Hz), 61.4 and 61.6 (two doublets →triplet, *J* = 7.4 Hz), 110.8, 113.4 (d, *J* = 187.5 Hz), 114.6, 120.1, 121.4, 127.5, 128.2, 128.6, 128.68, 128.7, 133.8, 136.7, 137.6, 161.2 (d, *J* = 6.1 Hz), 193.7, 201.9 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 16.9 (s) ppm; LCMS m/z: 429 [M^+ + 1]; HRMS (ESI) m/z: [M^++ H], calcd for $C_{24}H_{30}O_5P$ 429.1830, found 429.1815.

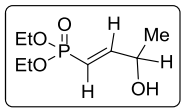


Formation of (*E*)-diethyl (3-hydroxybut-1en-1-yl)phosphonate (11c′) and (*E*)-diethyl (4-benzoyl-3-methyl-5-oxohex-1-en-1-yl)phosphonate:

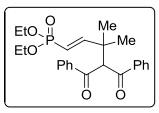
The reaction was performed in a manner similar to the synthesis of 13a using similar molar quantities. Instead of $FeCl_3.6H_2O$, anhydrous $FeCl_3$ was used in this case. Compound 11c′ was isolated in 70% yield whereas compound 13g was isolated in trace amount as diastereomeric

mixtures. The isolated yield of 11c′ was 85% when compound 11c was separately treated with anhydrous $FeCl_3$ at 65 ^oC under solvent–free condition for 4 h.

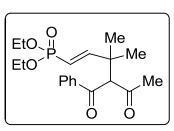
Yield: 0.350 g (70%, viscous liquid); IR (KBr): ῡ = 3468, 2982, 1633, 1445, 1389, 1246, 1022, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 1.26 (t, *J* = 7.2 Hz, 6H), 1.55 (d, *J* = 6.8 Hz, 3H), 3.98-4.06 (m, 4H), 4.48-4.54 (m, 1H), 5.79-5.88 (m, 1H), 6.69 ppm (ddd, *J*= 22.0, 16.0, 6.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (d, *J* = 6.2 Hz), 23.9, 55.8 (d, *J* = 25.0 Hz), 61.9, 62.0 (d, *J* = 5.2 Hz), 117.8 (d, *J* = 188.3 Hz), 151.1 ppm (d, *J* = 6.1 Hz); ^{31}P NMR (126 MHz, $CDCl_3$): δ 17.1 (s) ppm.



Partial supportive spectroscopic data for 13g as mixture of diastereomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13-1.19 (m, 6H), 1.31-1.33 (m, 6H), 1.35-1.37 (m, along with C=C-C(CH_3)], 2.10 and 2.12 (2s, 6H), 3.92-4.01 (m, 2H), 4.02-4.14 (m, 8H), 4.53 and 4.49 (d, *J* = 10 Hz, 2H), 5.63-5.88 (m, 4H), 6.57 (ddd, *J*= 21.8, 17.1, 7.8 Hz, 1H), 6.71 (m, merged with other peaks, 1H), 7.54-7.47 (m, 4H), 7.56-7.65 (m, 2H), 7.96-7.98 (m, 2H), 8.01-8.03 ppm (m, 2H); ^{13}C (CDCl3 ,101 MHz): Ther peaks at δ= 118.2 (d, *J* = 185.9 Hz), 116.8 (d, *J* = 189.4 Hz), 194.62 & 194.65, 202.2 & 202.4 (two sets of peaks for two diastereomers) proves the presence of the compound 13g; ^{31}P: δ= 17.8 and 17.7 (1:1); Another peak at δ 17.5 also appeared. LCMS 353 [M^++1].



(*E*)-Diethyl (4-benzoyl-3,3-dimethyl-5-oxo-5-phenylpent-1-en-1-yl)phosphonate (13h): Instead of $FeCl_3.6H_2O$, anhydrous $FeCl_3$ was used. Yield: 0.54 g (56%, White solid); mp: 116-118 ^oC; IR (KBr,): ῡ = 2983, 1721, 1690, 1234, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 1.29 (t, *J*= 6.8 Hz, 6H), 1.33 (s, 6H), 3.93-4.04 (m, 4H), 5.56-5.65 (m, 2H, merged with the singlet at 5.61), 7.14 (dd, *J*= 22.9, 17.4 Hz, 1H), 7.44-7.47 (m, 4H), 7.55-7.58 (m, 2H), 7.95-7.96 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.3 (d, *J* = 6.6 Hz), 25.8, 41.6 (d, *J* = 20.5 Hz), 61.7 (d, *J* = 5.6 Hz), 61.9, 114.2 (d, *J* = 187.7 Hz), 128.5, 128.9, 133.4, 137.5, 159.1 (d, *J* = 5.1 Hz), 193.7 ppm; ^{31}P NMR (126 MHz, $CDCl_3$): δ = 19.3 (s) ppm; LCMS m/z: 429 [M^+ + 1]; anal. calcd. for $C_{24}H_{29}O_5P$: C 67.28, H 6.82; found: C 67.15, H 6.89; HRMS (ESI) m/z: [M^+ + H] calcd for $C_{24}H_{30}O_5P$ 429.1831, found 429.1834.



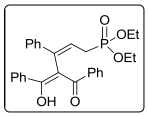
(*E*)-Diethyl (4-benzoyl-3,3-dimethyl-5-oxohex-1-en-1-yl)phosphonate (13i): Instead of $FeCl_3.6H_2O$, anhydrous $FeCl_3$ was used for this synthesis. Yield: 0.48 g (58%, viscous liquid); IR (KBr) : ῡ = 2952, 1690, 1454, 1239, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 1.26 (s, 6H), 1.29-1.34 (m, 6H), 2.13 (s, 3H), 3.99- 4.12 (m,

4H), 4.66 (s, 1H), 5.57-5.66 (m, 1H), 7.08 (dd, *J*= 22.0, 18.3 Hz, 1H), 7.29-7.52 (m, 2H), 7.59-7.61 (m, 1H), 7.94-7.96 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.3 (d, *J* = 4.0 Hz), 25.2, 25.3, 41.3 (d, *J* = 20.1 Hz), 61.8 (two doublets, *J* = 5.2 Hz each), 68.7, 114.4 (d, *J* = 188.1 Hz), 128.5, 129.0, 133.8, 137.8, 158.6 (d, *J* = 4.4 Hz), 195.7, 201.8 ppm; ^{31}P NMR (126 MHz, $CDCl_3$): δ= 19.1 (s) ppm; LCMS m/z: 367 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + H] calcd for $C_{19}H_{28}O_5P$ 367.1674; found 367.1656.

3.6.5 ***Procedure for the isomerization of ω-ketovinyl phosphonates 13a-b and 13f*****:** To a stirred solution of *ω*-ketovinyl phosphonates (13a-b, 1.05 mmol) in THF (5 mL), K_2CO_3 (0.144 g, 1.05 mmol) was added. The reaction mixture was stirred vigorously at room temperature for 7 h in a closed glass vessel. After completion of the reaction (monitored by TLC), the mixture was quenched with water and extracted with EtOAc (3x30 mL). The combined organic layer was washed with saturated brine and dried over anhydrous Na_2SO_4.After filtration and removal of solvent in vacuo, the crude product was purified by silica gel column chromatography (EtOAc/Hexane 80/20) to afford the desired compound. The isomerization reaction of compound 13f was carried out in DMSO for 4h at room temperature to afford the compound 14c.

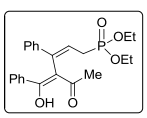
3.6.6 ***Analytical data14a-c***

Diethyl ((2Z,4Z)-4-benzoyl-5-hydroxy-3,5-diphenylpenta-2,4-dien-1-yl)phosphonate (14a):



Yield: 0.46 g (92%; White solid); mp: 152-154 ^{o}C; IR (KBr) : ῡ = 2986, 1544, 1542, 1254, 1157, 1027, 952 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J*= 7.1 Hz, 6H), 2.28 (dd, *J* = 21.7, 7.4 Hz, 2H), 4.05-4.12 (m, 4H), 5.89 (dt, *J*= 9.0, 7.4 Hz, 1H), 7.11-7.21 (m, 7H), 7.29-7.33 (m, 4H), 7.57-7.59 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ= 16.5 (d, *J* = 5.8 Hz), 28.6 (d, *J* = 140.5 Hz), 61.9 (d, *J* = 6.6 Hz), 108.6, 121.7 (d, *J* = 9.0 Hz), 126.7, 127.4, 127.7, 127.8, 128.3, 130.8, 136.8, 139.8 (d, *J* = 15.6 Hz), 141.3 (d, *J* = 2.6 Hz), 189.9 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ= 27.9 (s) ppm; LCMS m/z: 477 [M^+ + 1]; HRMS (ESI)m/z: [M^+ + H] calcd for $C_{28}H_{30}O_5P$ 477.1831; found 477.1808; X-ray structure is done for this sample.

Diethyl ((2Z,4Z)-4-(hydroxy(phenyl)methylene)-5-oxo-3-phenylhex-2-en-1-yl) phosphonate (14b): Yield: 0.45 g (90%, viscous liquid); IR (KBr) : ῡ = 3486, 2984, 1596, 1544, 1247, 1157, 1031, 948 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.29-1.33 (m, 6H), 2.01 (s, 3H), 2.07-2.19 (m, 1H), 2.64 (ddd, *J*= 20.4, 15.6, 9.7 Hz, 1H), 4.03-4.11 (m, 4H), 6.15 (ddd, *J*= 9.6, 8.4, 5.5 Hz, 1H), 7.23-7.29 (m, 2H), 7.32-7.40 (m, 4H), 7.51-7.53 (m, 2H), 7.60-



7.62 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 16.5 (d, *J* = 5.8 Hz), 25.6, 28.3 (d, *J* = 140.5 Hz), 61.8 and 61.9 (two doublets appeared as triplet, *J* = 6.1 Hz), 108.8 (d, *J* = 2.4 Hz), 121.4, 121.5, 126.3, 127.9, 128.0, 128.9, 131,l 135.4, 139.3 (d, *J* = 15.1 Hz), 140.6 (d, *J* = 3.0 Hz), 182.2, 199.0 ppm (d, *J* = 1.7 Hz); ^{31}P NMR (125 MHz, $CDCl_3$): δ = 27.4(s) ppm; LCMS m/z: 415 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + H] calcd for $C_{23}H_{28}O_5P$ 415.1674, found 415.1661.

Diethyl ((2Z,4Z)-4-(hydroxy(phenyl)methylene)-2-methyl-5-oxo-3-phenylhex-2-en-1-yl)phosphonate (14c): Yield: 0.455 g (91%, viscous liquid); IR (KBr) : ῡ = 2980, 1716, 1648, 1561, 1490, 1244, 1026, 959 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.29-1.33 (m, 6H), 1.96-2.04 (m, 7H, PC*H*$_a$H$_b$ +2 C*H*$_3$), 2.85 (dd, *J* = 22.8, 14.7 Hz, 1H), 4.06-4.09 (m, 4H), 7.22-7.23 (m, 1H), 7.29-7.39 (m, 7H), 7.72-7.73 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 16.4 (d, *J* = 5.8 Hz), 21.6, 25.9, 34.9 (d, *J* = 137.8 Hz), 61.7 and 61.8 (two doublets, *J* = 9.2, 6.8 Hz), 113.4 (d, *J* = 3.0 Hz), 127.0, 127.9, 128.0, 128.1, 130.0, 130.2, 130.8, 134.2 (d, *J* = 14.3 Hz), 135.9, 140.8 (d, *J* = 3.4 Hz), 181.5, 199.6 ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.3(s) ppm; LCMS m/z 429 [M^+ + 1]; HRMS (ESI): calcd for $C_{24}H_{30}O_5P$ [M^+ + H], 429.1831, found 429.1798.

3.6.7 Typical Procedure for the synthesis of conjugated 1,3-butadiene with 1,3-diketone functionality at the terminal carbon.

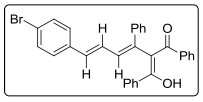
(2*Z*,3*E*,5*E*)-6-(4-(dimethylamino)phenyl)-2-(hydroxy(phenyl)methylene)-1,3-diphenylhexa-3,5-diene-1-one (16a): The phosphonate 14a (0.5 g, 1.05 mmol) was dissolved in THF (5mL) and slowly added to a suspension of NaH (0.05g, 2.10 mmol) in dry THF (10 mL) at 0 ^{o}C for 5min. The mixture was stirred at this temperature for 0.5h. Then, *N*,*N*-dimethyl benzaldehyde aldehyde (0.157g, 1.05 mmol) was added and the mixture stirred at rt for 14 h. The reaction mixture was quenched by addition of H_2O (5 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (EtOAc:Hexane=3:97) to give compound as white solid. All the other compounds 16b-h were prepared analogously using similar molar quantities of ketophosphonates, aldehydes and NaH.

3.6.8 ***Analytical data16a-h***

Compound 16a: Yield: 0.307 g (62%, White solid); mp: 174-176 ^{o}C IR (KBr) : ῡ = 2802, 1663.3, 1595, 1513 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 3.01 (s, 6H), 6.45 (d, *J*= 15.0 Hz, 1H), 6.64-6.89 (m, 4H), 7.10-7.35 (m, 14H), 7.55 ppm (br, 4H);

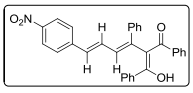
^{13}C NMR (126 MHz, $CDCl_3$): δ= 40.3, 109.8, 112.3, 122.4, 125.6, 126.2, 126.7, 127.5, 127.6, 127.8, 128.3, 130.5, 132.3, 133.7, 135.4, 137.2, 141.8, 150.3, 190.3 ppm; LCMS m/z: 472 [M^+ + 1]; HRMS (ESI) m/z: calcd for $C_{33}H_{30}NO_2$ [M^+ + H], 472.2276, found 472.2251. X-ray structure is done for this sample.

(2*Z*,3*E*,5*E*)-6-(4-bromophenyl)-2-(hydroxy(phenyl)methylene)-1,3-diphenylhexa-3,5-diene-1-one (16b): Separated as a mixture of diastereomers; Yield: 0.342 g (64%, Yellowish solid); mp: 168-172 ^{o}C; IR (KBr): ῡ = 3057, 1592, 1528, 1485, 1299 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.36-6.41 (m, 2H), 6.47-6.52 (m, 1H), 6.59- 6.61 (m, 1H), 6.65-6.67 (m, 2H),



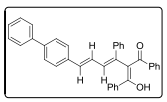
6.72-6.75 (m, 1H), 6.91-6.97 (m, 1H), 7.15- 7.22 (m, 17H), 7.24-7.27 (m, 2H), 7.31-7.37 (m, 6H), 7.44-7.46 (m, 2H), 7.50-7.53 ppm (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 109.56, 109.64, 121.2, 121.5, 126.6, 126.86, 126.95, 127.48, 127.52, 127.56, 127.6, 127.7, 127.9, 128.38, 128.43, 130.5, 130.6, 130.7, 130.9, 131.2, 131.24, 131.8, 133.3, 136.12, 136.14, 137.0, 137.2, 137.4, 139.6, 141.2, 141.5, 190.3, 190.4 ppm; LCMS m/z: 507 [M^+ + 1]; HRMS (ESI) m/z: [M]$^+$ and [M^++2], calcd for $C_{31}H_{23}BrO_2$ 506.0881 and 508.0881, found 506.0800 and 508.0781 (1:1) respectively.

(2*Z*,3*E*,5*E*)-2-(hydroxy(phenyl)methylene)-6-(4-nitrophenyl)-1,3-diphenylhexa-3,5-diene-1-one (16c): Yield: 0.300 g (60%, Reddish brown solid); mp: 152-154 ^{o}C; IR (KBr) : ῡ = 3064,



1591, 1512, 1399, 1335 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.48 (d, *J* = 15.5 Hz, 1H), 6.63 (d, *J* = 11.1 Hz, 1H), 7.10 (dd, *J* = 15.5, 11.1 Hz, 1H), 7.13-7.22 (m, 7H), 7.22-7.29 (m, 2H), 7.37-7.44 (m, 4H), 7.49-7.51 (m, 4H), 8.19 ppm (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 109.4, 124.1, 126.7, 126.8, 127.5, 127.8, 128.5, 130.2, 130.6, 130.8, 131.7, 136.9, 140.2, 141.2, 143.6, 146.7, 190.3 ppm; LCMS m/z: 474 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + H] calcd for $C_{31}H_{24}O_4N$ 474.1705; found 474.1672.

(2*Z*,3*E*,5*E*)-6-([1,1'-biphenyl]-4-yl)-2-(hydroxy(phenyl)methylene)-1,3-diphenylhexa-3,5-diene-1-one (16d): Yield: 0.415 g (78%, yellow solid); mp: 182-184 ^{o}C; IR (KBr) : ῡ = 3028,



1602, 1538, 1486, 1382, 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.54 (d, *J*= 15.4 Hz, 1H), 6.68 (d, *J*= 11.4 Hz, 1H), 7.08 (dd, *J*= 15.4, 11.1 Hz, 1H), 7.14-7.21 (m, 7H), 7.25-7.27 (m, 2H), 7.36-7.43 (m, 5H), 7.46-7.49 (m, 2H), 7.54-7.61 (m, 6H), 7.63-7.65 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 109.7, 126.4, 126.5, 126.8, 126.9, 127.3, 127.33, 127.4, 127.47, 127.5, 127.7, 128.4, 128.8, 130.6, 131.4, 134.3, 136.3, 136.7, 137.1, 140.6, 141.5, 190.3 ppm; LCMS m/z 505 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + H] calcd for

$C_{37}H_{29}O_2$ 505.2167, found 505.2156. anal. calcd. for $C_{37}H_{28}O_2$: C 88.07, H 5.59; found: C 88.16, H 5.52.

(2*Z*,3*E*,5*E*)-6-(anthracen-9-yl)-2-(hydroxy(phenyl)methylene)-1,3-diphenylhexa-3,5-diene-1-one (16e): Yield: 0.112 g (20%, White solid); mp: 176-178 ^{o}C; IR (KBr) : ῡ = 2917, 1724, 1672, 1588, 1466, 1291 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.91 (dd, *J* = 15.6, 11.0 Hz, 1H), 7.05 (d, *J* = 11.6 Hz, 1H), 7.21-7.29 (m, 7H), 7.35-7.35 (m, 2H), 7.42-7.52 (m, 6H), 7.56-7.58 (m, 3H), 7.84 (dd, *J* = 5.8, 3.3 HZ, 1H), 7.94 (d, *J*= 9.5 Hz, 2H), 8.02 (d, *J*= 8.2 Hz, 2H), 8.36 (dd, *J*= 5.8, 3.3 Hz, 1H), 8.40 ppm (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 110.2, 125.1, 125.6, 125.8, 126.7, 127.2, 127.6, 127.7, 127.8, 128.5, 128.7, 129.3, 130.7, 131.4, 131.7, 134.1, 134.9, 136.9, 137.1, 141.4, 145.4, 189.9 ppm; HRMS (ESI) m/z: [M^+ + H] calcd for $C_{39}H_{29}O_2$ 529.2167, found 529.2139.

(2*Z*,3*E*,5*E*)-2-(hydroxy(phenyl)methylene)-1,3-diphenyl-6-(pyren-1-yl)hexa-3,5-diene-1-one (16f): Yield: 0.338 g (58%, yellow solid); mp: 207-209 ^{o}C; IR (KBr): ῡ = 3046, 1597, 1518, 1398, 1299 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.14-4.19 (m, 1H), 6.89-6.92 (m, 1H), 7.18-7.27 (m, 10H), 7.46-7.48 (m, 2H), 7.57-7.63 (m, 5H), 8.02-8.19 (m, 7H), 8.29-8.32 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 109.7, 122.7, 123.4, 124.9, 125.0, 125.1, 125.2, 125.4, 126.1, 126.6, 127.42, 127.43, 127.5, 127.6, 127.8, 128.1, 128.4, 129.0, 130.7, 130.9, 131.0, 131.4, 131.45, 131.5, 131.8, 137.09, 137.1, 141.6, 190.4 ppm; LCMS m/z: 553 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + H] calcd for $C_{41}H_{29}O_2$ 553.2167, found 553.2143.

(2*Z*,3*E*,5*E*)-2-(hydroxy(phenyl)methylene)-1,3-diphenyl-6-(ferrocene-1-yl)hexa-3,5-diene-1-one (16g): Yield: 0.350 g (62%, brick red solid); mp: 182-184 ^{o}C; IR (KBr) : ῡ = 3468, 2982, 1633, 1445, 1389, 1246, 1022, 962 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 4.2 (s, 5H), 4.33-4.34 (m, 2H), 4.46-4.47 (m, 2H), 6.60 (d, *J* = 16.0 Hz, 1H), 7.11 (d, *J* = 15.9 Hz, 1H), 7.23-7.32 (m, 12H), 7.34-7.43 (m, 1H), 7.69-7.77 (m, 2H), 7.86-7.88 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 67.0, 69.3, 69.4, 82.8, 112.0, 126.4, 127.2, 128.3, 128.4, 128.5, 128.53, 129.4, 129.8, 131.9, 133.3, 48.9, 150.9, 193.5 ppm; HRMS (ESI) m/z: [M - H]$^+$ calcd for $C_{35}H_{27}FeO_2$ 535.1361, found 535.1329.

(5*E*,7*E*)-2-(hydroxy(phenyl)methylene)-8-(2-nitrophenyl)-1,3-diphenylocta-3,5,7-trien-1one (16h): This compound was isolated as mixture of diastereomers. Yield: 0.368 g (70%, yellowish solid); mp: 116-118 ^{o}C; IR (KBr) : ῡ = 2919, 1586, 1523, 1482, 1383, 1340, 1288 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30-6.47 (m, 3H), 6.58-

6.69 (m, 3H), 6.75-6.86 (m, 2H), 7.00-7.04 (m, 2H), 7.09-7.19 (m, 9H), 7.27-7.32 (m, 8H), 7.36-7.39 (m, 4H), 7.48-7.58 (m, 12H), 7.69-7.71 (m, br, 2H), 7.92 (d, *J* = 8.1 Hz, 2H), 8.06 ppm (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 109.3, 109.4, 124.80, 124.83, 125.8, 126.4, 126.59, 126.64, 126.9, 127.0, 127.49, 127.5, 127.68, 127.71, 127.75, 127.8, 128.0, 128.3, 128.4, 129.9, 130.6, 130.7, 130.8, 132.1, 132.4, 132.5, 132.7, 132.74, 132.8, 133.2, 133.9, 134.1, 134.7, 136.9, 137.0, 138.1, 138.2, 141.1, 141.2, 147.8, 147.9, 147.92, 190.18, 190.2 ppm; LCMS m/z: 500 [M^+ + 1]; HRMS (ESI) m/z: [M^+ + Na] calcd for $C_{33}H_{25}NO_4Na$ 522.1682, found 522.1677.

3.7 Crystal data for compound (5a)

Complex	**Compound (14a)**	**Compound (16a)**
Chemical formula	$C_{34}H_{31}NO_2$	$C_{28}H_{29}O_5P$
Formula weight	485.60	476.48
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a (Å)	9.6670(9)	9.0764(6)
b (Å)	10.5514(10)	10.8628(8)
c (Å)	14.5221(14)	13.8858(10)
α (°)	93.650(2)	106.9800(10)
β (°)	99.050(2)	101.0750(10)
γ (°)	114.4040(10)	98.1960(10)
V (Å^3)	1318(2)	1255.89(15)
Z	2	2
ρ (g cm^{-3})	1.223	1.260
μ (mm^{-1})	0.075	0.145
Reflections collected	13642	13165
Reflections unique	5150	4933
Reflections [$I \geq 2\sigma(I)$]	3531	3999
Parameters	327	311
*R*1, *wR*2 [$I \geq 2\sigma(I)$]	0.0612, 0.1996	0.0557, 0.1635

*R*1, *wR*2 [all data]	0.0847, 0.2347	0.0655, 0.1731
GOF on F^2	0.872	1.065
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.304/ −0.178	0.473/ −0.338

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Chapter 4

Synthesis of Organophosphates and its applications

4.1 Introduction

Being one of the valuable organophosphorus compounds, the chemistry of organophosphates has been extensively studied due to its significant roles in many major physiological processes such as energy transfer, photosynthesis etc.[1,2] A molecule composed of a phosphorus atom bonded to four oxygen atoms, is an integral component of many important bio molecules, such as the genetic workhorses DNA and RNA and the energy transporter adenosinetriphosphate.[3] In environments with a limited supply of inorganic phosphate, an important source is thought to be a compound called 2-aminoethylphosphonic acid, which is found in the cell membranes of many plants and animals.[4] Conversion of 2-aminoethylphosphonic acid to inorganic phosphate involves breaking its carbon-phosphorus bond and replacing it with an oxygen-phosphorus bond, but the mechanism of this transformation is not well characterized.[5] Nature has selected phosphate diesters to hold the genetic code together.[6] This linkage needs to be very stable to keep the sequence of bases intact, but is also the site at which DNA is hydrolysed in the course of its repair and destruction by nucleases. To be able to understand the efficiency of the enzymes and ribosome's which catalyse hydrolysis, it is important to quantify the background reactivity.[4] Phosphate esters are also an integral part of a variety of naturally occurring molecules, such as proteins, carbohydrates, steroids, and coenzymes, these are also used as pro-drugs.[7]

Phosphonates are useful because they are approximately isosteric with phosphates but the phosphorus-carbon bond found in phosphonates is more stable to hydrolysis than the phosphorus-oxygen bond found in phosphates.[8] The synthesis of phosphate esters is an important objective in organic synthesis, since they have found use in the preparation of biological active molecules, and also versatile intermediate in synthesis of amides and esters.

Further the desired bioactivity, in principle, may be rationalized with a particular conformational structure of a small molecule and towards this perspective, the design of new chemical entities and synthetic routes for their assembly have typically focused on the accessibility of diverse compounds with the correct conformations. Also for quickly generating these pharmaceutically relevant molecules, small building blocks which can be readily obtained with very short synthetic endeavour are desired. In this regard, many small organic molecules containing diaryl and triaryl methyl cores have come up which has caused a high demand of various synthetic approaches towards diarylmethanols, diarylmethanes, triarylmethanes various trisubstituted methanes and the molecules derived thereof. The chemistry of polycyclic aromatic

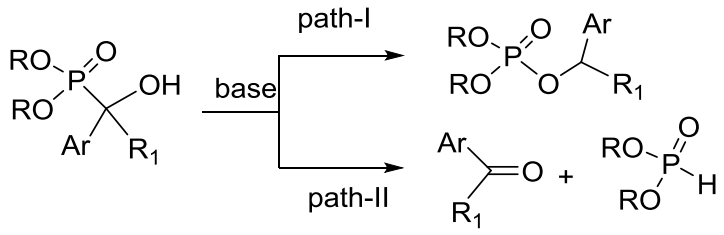
hydrocarbons (PAHs) has become a field of increasing interest during the past decades due to their unique properties in material sciences.[9] For example, they are widely used in organic electronics, such as light-emitting diodes, field-effect transistors, and solar cells. The synthesis of triarylmethanes and related structures has attracted much attention in the area of medicinal chemistry and materials sciences.[10] Indeed, the triarylmethane motif is ubiquitous in dyes,[11] fluorescent probes,[12] natural products,[13] and biologically active compounds.[14] In this thesis, we will subsequently discuss a new synthetic approach to generate a range of phosphates and their applications as an electrophilic substrate to access electronically and structurally diverse polyarylated methanes.

4.2 Literature methods for the synthesis and related applications of phosphates

The related reports on the synthesis of phosphates are discussed below.

4.2.1 *Phospha-Brook rearrangement*

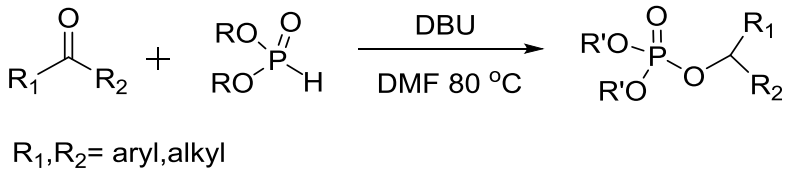
The organophosphates were also obtained as a minor/major product from the base mediated synthesis of α-hydroxyphosphonates[15,16] starting from aldehydes or few selective ketones *via* phosphorylation rearrangement (phospha-Brook) (path I, **Scheme 4.1**). It is also relevant to mention that α-hydroxyphosphonates can also undergo base catalyzed retro-hydrophosphonylation reactions as shown in path-II (**Scheme 4.1**).[17] These transformations depend upon the substrates, bases and the reaction conditions employed for a particular reaction. This phospha-Brook rearrangement is subjected to vary with the type of aldehydes or ketones and also the bases.



Scheme 4.1 Transformations of α-hydroxyphosphonates in the presence of base

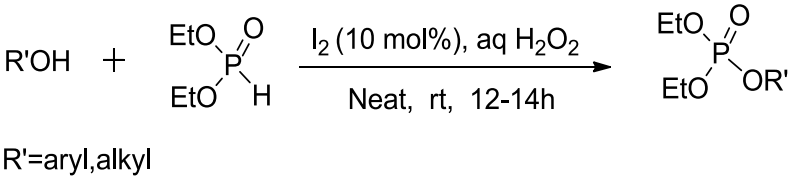
Santos *et al.* [18] developed a solvent- dependent method by adding dialkylphosphites to aromatic aldehydes (Pudovik reaction) in the presence of a base. The traditional Pudovik adduct was obtained using nonpolar solvents, whereas the use of DBU in a polar solvent allowed the formation of a phosphate ester *via* phospha-Brook rearrangement of the intermediate hydroxyphosphonates. Only electron-poor aldehydes and ketones gave the best yields, aromatic

aldehydes substituted by an electron-donating gave the phosphate in a low yield due to the formation of hydroxyphosphonates predominant **(Scheme 4.2).**



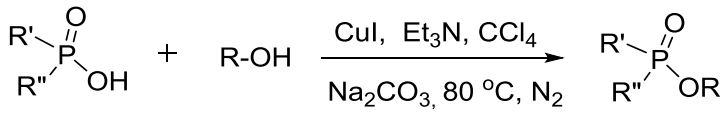
Scheme 4.2 DBU mediated synthesis of phosphates

Phosphorylation of alcohols was reported by Ramaiahprabhu *et al.*[19] using molecular iodine as a catalyst and H_2O_2 as the sole oxidant under mild reaction conditions. This method provided an easy route for synthesizing a variety of phosphates with good yields **(Scheme 4.3).**



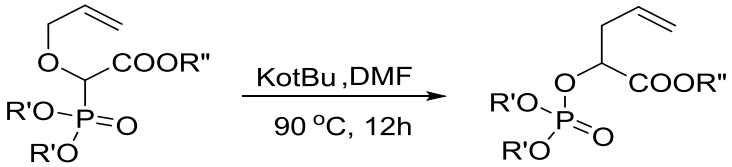
Scheme 4.3 I_2 catalyzed synthesis of phosphates

Yin *et al.*[20] performed copper-catalyzed aerobic oxidative esterification of -P(O)OH compounds using alcohols as efficient esterification reagents, giving the expected products with good to moderate yields (**Scheme 4.4).**



Scheme 4.4 Copper-catalyzed synthesis of phosphates

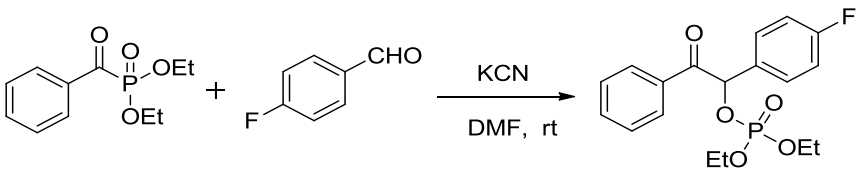
Recently, Terada *et al.*[21] developed a Brønsted base catalyzed rearrangement reaction of 2-allyloxy-2-phosphonoacetate derivatives. This reaction proceeded *via* a [2,3]-Wittig rearrangement followed by a phospha-Brook rearrangement (**Scheme 4.5).**



Scheme 4.5 A Brønsted base catalyzed synthesis of phosphates

Eymur *et al.*[22] found acylphosphonates are potent acyl anion precursors that generate acyl anion equivalents under the promotion of cyanide anion via phosphonate-phosphate rearrangement. These anions readily reacted with aldehydes to provide cross benzoin products.

In this way it is possible to synthesize a variety of aromatic-aromatic, aromatic-aliphatic, and aliphatic-aromatic benzoins (phosphates) (**Scheme 4.6).**

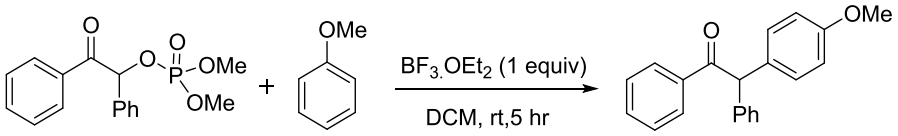


Scheme 4.6 KCN mediated synthesis of phosphates

Owing to their synthetic and biological values, the chemistry of phosphates has stimulated an increasing interest and the development of new methodologies for their preparation is still meaningful.

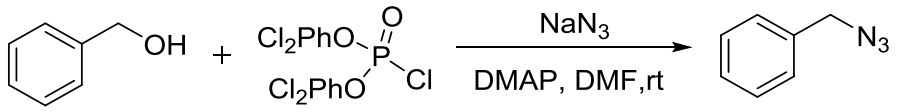
4.2.2 *Related applications of phosphates in organic synthesis*

Johnson *et al.*[23] discovered a Lewis acid ($BF_3.OEt_2$) promoted route to *α*,*α*-diaryl ketones that proceeds in one step from an easily prepared *α*-ketophosphate and invokes an umpolung strategy to induce arene alkylation at the *α*-carbon. The reaction proceeds at room temperature with sufficiently electron-rich *α*-ketophosphates, whereas electron-poor or neutral *α*-ketophosphates reacted upon heating. The cationic intermediate could be successfully trapped with both heteroatom and nonaromatic nucleophiles **(Scheme 4.7)**.



Scheme 4.7 $BF_3.OEt_2$ mediated synthesis of diarylketones

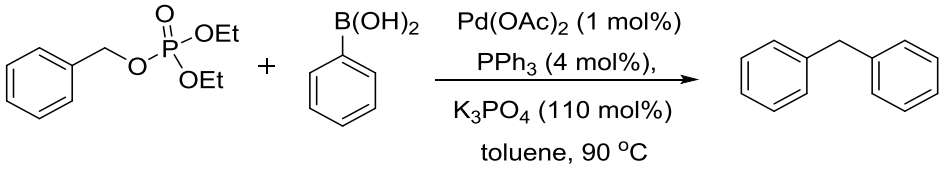
A one-pot procedure was developed by Longqin Hu *et al.*[24] to prepare alkyl azides from alkanols using bis(2,4-dichlorophenyl) phosphate activation. 4-(Dimethylamino)pyridine was used as a base, and phosphorylpyridinium azide is believed to be the activating agent under this condition **(Scheme 4.8).**



Scheme 4.8 phosphorylpyridinium azide mediated synthesis of alkyl azides

The Suzuki-Miyaura cross-coupling reaction of benzylic phosphates and arylboronic acids was investigated by McLaughlin *et al.*[25] This facile reaction was efficiently catalyzed by the simple combination of palladium acetate and triphenylphosphine. The generality of this

cross-coupling was demonstrated using a variety of substrates and afforded high yields of the expected diarylmethanes **(Scheme 4.9)**.



Scheme 4.9 Palladium acetate and triphenylphosphine mediated synthesis of diarylmethanes

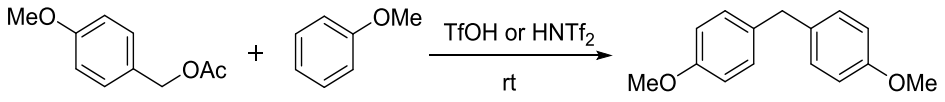
We have explored the utility of phosphates as substrates for Friedel-Crafts reactions to access polyarylated alkanes. Therefore, few selected synthetic strategies for the synthesis of polyarylated alkanes are deliberated herein.

4.2.3 *Literature methods for the synthesis of polyarylated alkanes*

Historically renowned simple and powerful Friedel-Crafts (FC) arylation reaction[26] is one of the major traditional synthetic protocols for polyarylated alkanes. The potential pitfalls of this route are the low reactivity, selectivity, limitation for only electron rich substrates and the need for harsh reaction conditions including hazardous solvents/reagents. The beneficial alternative source for functionalized polyarylated alkanes includes metal catalyzed cross-coupling reactions.[27] Even, the modified FC reactions were performed using Pd as catalyst to obtain triarylmethanes from aldehydes.[28] Although these all are certainly remarkable processes, however, the major concerns are the necessity of expensive transition metals and their toxicities,[29] solvents, long duration, elevated temperature (60-140 ^{o}C) and special care for moisture/air sensitive organometallic reagents.

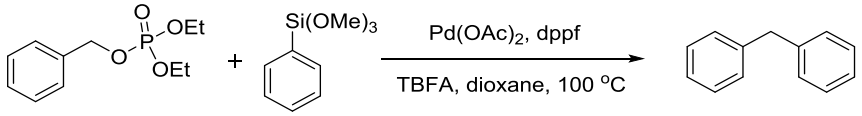
4.2.4 *Synthesis of diarylmethanes*

Ghosez *et al.*[30] found triflic acid and triflimide are efficiently catalyze the formation of a wide diversity of diarylmethanes from the benzylic acetates and electron-rich arenes or heteroarenes, for electron poor substrates of arenes, this method was not efficient. The reaction worked best with acetates capable of generating a stabilized benzylic cationic species. In most cases, the reactions were conveniently run in the absence of solvent under mild conditions (**Scheme 4.10).**



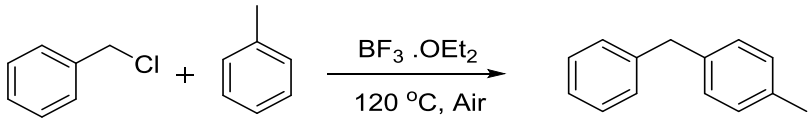
Scheme 4.10 Triflic acid and triflimide catalyzed the formation of diarylmethanes

Zhao *et al.*[31] developed an efficient approach that is related to the benzylation of arenes. The described reactions provide straightforward access to diarylmethanes through Pd-catalyzed coupling of benzylic phosphates with arylsilanes in good to excellent yields. The reaction tolerates a wide range of functionalities such as halide, alkoxyl, and nitro groups (**Scheme 4.11).**



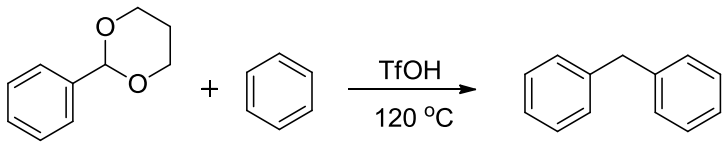
Scheme 4.11 Pd-catalyzed the formation of diarylmethanes

A synergistic metal-free system of $BF_3.H_2O$/ BF_3.HX-promoted benzylation of (hetero)arenes with benzylhalides was developed by Xiong *et al.*[32] and using this method various diarylmethanes were furnished with yields of up to 98% and regioselectivities above 99% (**Scheme 4.12).**



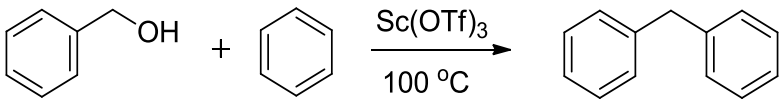
Scheme 4.12 $BF_3.H_2O$/ BF_3.HX mediated synthesis of diarylmethanes

Hiyama *et al.*[33] synthesized diarylmethanes starting from 2-aryl-1,3-dioxane with arenes in the presence of a catalytic amount of trifluoromethanesulfonic acid gave the corresponding diarylmethanes in good to excellent yields. The acid-catalyzed Friedel-Crafts benzylation of arenes could altenatively be carried out using arenecarbaldehyde and 1,3-propanediol (**Scheme 4.13).**



Scheme 4.13 Triflic acid catalyzed the formation of diarylmethanes

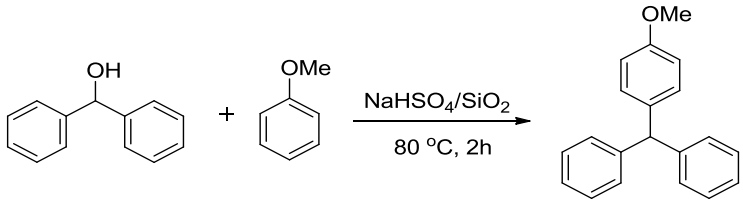
Fukuzawa *et al.*[34] performed $Sc(OTf)_3$-catalyzed Friedel-Crafts alkylation reaction with an alcohol, an aromatic compounds, or an arenecarbaldehyde or an arenecarbaldehyde acetal as the alkylating agent affords a diarylmethane derivative highly selectively. The salient feature of this reaction is that only a catalytic amount of $Sc(OTf)_3$ can affect the reaction (**Scheme 4.14).**



Scheme 4.14 $Sc(OTf)_3$ catalyzed synthesis of diarylmethanes

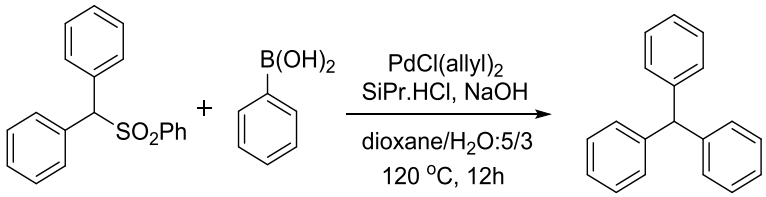
4.2.5 *Synthesis of triarylmethanes*

Kodomari *et al.*[35] developed simple and efficient protocol for alkylation of aromatics from alcohols in the presence of $NaHSO_4/SiO_2$. Various triarylmethanes were obtained in good yields in short reaction time. $NaHSO_4/SiO_2$ was regenerated by simple treatment and could be recycled eight times with equal efficiency (**Scheme 4.15).**



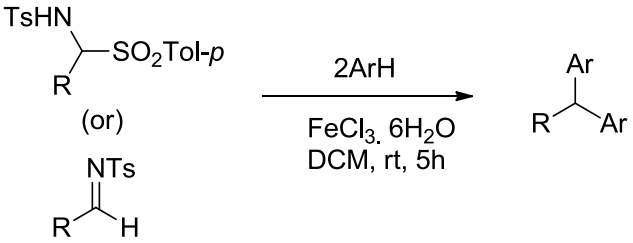
Scheme 4.15 $NaHSO_4/SiO_2$ mediated synthesis of triarylmethanes

Crudden *et al.*[36] synthesized a variety of triarylmethanes starting from methyl phenyl sulfone as an inexpensive and readily available template by Pd-catalyzed C-H arylation followed by arylative desulfonylation. This method provides a new synthetic approach to multisubstituted triarylmethanes using readily available haloarenes and aryl boronic acids (**Scheme 4.16).**



Scheme 4.16 Pd-catalyzed C-H arylation followed by arylative desulfonylation

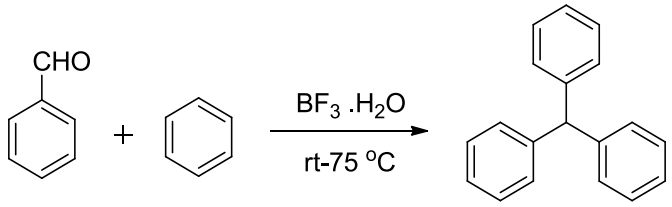
Kim *et al.*[37] performed a $FeCl_3.6H_2O$-catalyzed Friedel-Crafts arylation reactions of *N*-sulfonyl aldimines or sulfonamidesulfones with electron-rich arenes and heteroarenes, which lead to the formation of triarylmethanes and bis-heteroarylarylmethanes. The advantage of this method includes mild reaction conditions, low catalytic loading, high yield, and single step synthesis to synthesis of triarylmethanes (**Scheme 4.17).**



Scheme 4.17 $FeCl_3.6H_2O$ catalyzed the formation of triarylmethanes

Olah *et al.*[38] found BF_3-monohydrate is an efficient and strong Bronsted acid catalyst for the hydroxyalkylation of aromatics with aldehydes. These reactions show that BF_3-H_2O can be used

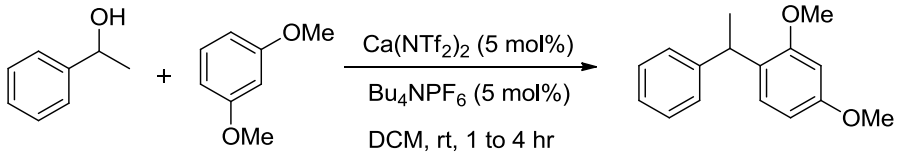
as a very effective protosolvating medium as well as a catalyst without the use of any additional solvent during the reaction (**Scheme 4.18).**



Scheme 4.18 BF_3-monohydrate mediated synthesis of triarylmethanes

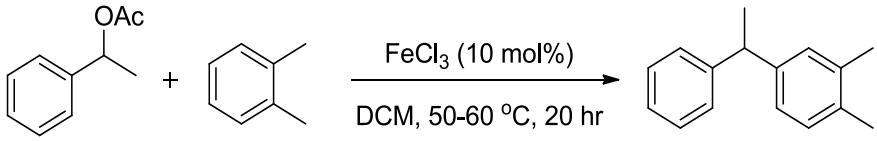
4.2.6 *Synthesis of diarylethanes*

Meel *et al.*[39] developed a calcium-based catalyst system for the alkylation of electron-rich arenes using secondary and tertiary benzylic, allylic, and propargylic alcohols at room temperature with good yields (**Scheme 4.19).**



Scheme 4.19 Calcium catalyzed synthesis of triarylethanes

Beller *et al.*[40] developed a general method for the arylation of benzyl carboxylates and benzyl alcohols. Using iron catalysts ($FeCl_3$) an easy and practical synthesis of many kinds of diarylethanes and arylheteroarylethanes is possible. Typically reactions proceed under mild conditions (50–80 °C, without strong acid or base) and it is not necessary to exclude air or moisture (**Scheme 4.20).**



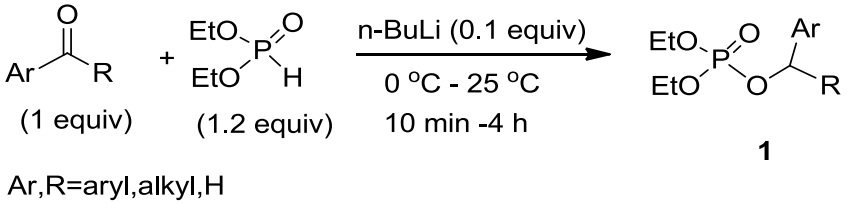
Scheme 4.20 Iron catalyzed synthesis of triarylethanes

4.3 Results and discussion

4.3.1 Synthesis of phosphates

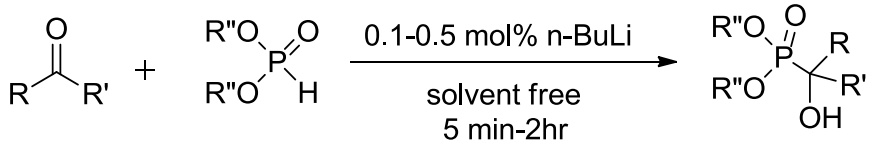
All the aforementioned routes suffer from several drawbacks like the requirement of stoichiometric amount of bases, higher temperature, longer time and the presence of unsafe solvents etc. It has been observed that the aldehydes or ketones only with electron withdrawing substrates prone to undergo the phospha-Brook rearrangement.[41,42] The attempt to get phosphates from the reactions of H-phosphonates with acetophenone was not satisfactory as mentioned in

most of those reports. Therefore, we have explored an interesting *n*-BuLi- triggered approach for the synthesis of organophosphates from the direct reactions of diethyl phosphite with activated/unactivated ketones or aldehydes preferably at r.t. (25 ^{o}C) under additional solvent-free conditions **(Scheme 4.21).**



Scheme 4.21 *n*-BuLi catalyzed synthesis of organophosphates

In very recent studies, catalytic amount of organolanthanides [43] and *n*-BuLi [44] (0.1 mol%) were employed to synthesize *α*-hydroxyphosphonates from the reactions of unactivated ketones with dialkyl phosphite under mild and solvent-free conditions **(Scheme 4.22).** By increasing the mol% (5-10) of *n*-BuLi the yield of *α*-hydroxyphosphonates got reduced due to aforementioned retro-hydrophosphorylation reactions.[44] The same observation was reported in the presence of hexane, used as additional solvent.

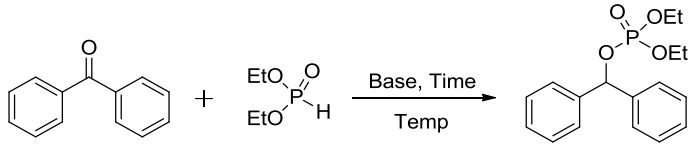


Scheme 4.22 *n*-BuLi catalyzed synthesis of *α*-hydroxyphosphonates

Surprisingly, in those reports, the formation of phosphates was not stated under any circumstances. We could isolate phosphates effectively when diethyl phosphite was treated with ketones or aldehydes in the presence of 10 mol% *n*-BuLi (1.6 M in hexane) at r.t. *n*-BuLi was not explored as a triggering agent to synthesize phosphate before in the literature. It is pertinent to note that the unexpected phosphate formation is one of the major pitfalls for the base catalyzed synthesis of *α*-hydroxyphosphonates starting from phosphites and ketones/ aldehydes and therefore the Lewis acid catalyzed hydrophosphorylation of ketones is described in the literature.[45]

As ketones were proved earlier to be less reactive in phosphate formation, [46, 47] we initiated our studies with easily available, cheap benzophenone and diethylphosphite to optimize the reaction conditions by varying different bases (**Table 4.1**).

Table 4.1 Screening of reaction conditions to optimize the yield for phosphate **1a**.[a]



1a

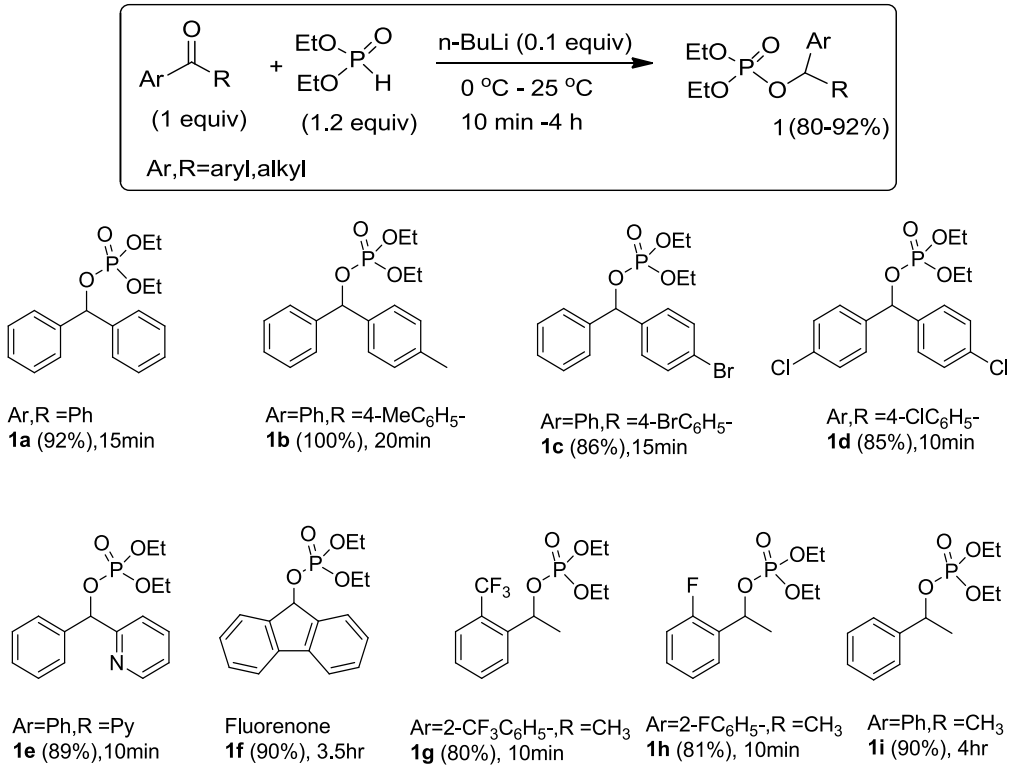
Entry	Base (mol %)	Time (h)	Temp (^{o}C)	Yield of **1a**[b]
1	NEt_3 (100)	8 -14	25- 65	n.r[c]
2	DIPEA (100)	8 -14	25-65	n.r
3	K_2CO_3 (100)	14	25	n.r
4	K_2CO_3 (100)	6	65	40
5	^{t}BuOK (100)	8	65	30
6	NaH (100)	12	25	90
7	NaH (10)	8-14	25-65	5
8	Cs_2CO_3 (100)	12	25	92
9	Cs_2CO_3 (10)	14	25	30
10	NMP (100)	8-14	25-60	n.r.
11	piperazine	8-14	25-60	n.r.
12	*n*-BuLi [d](0.1-5)	10	0-25	n.r.
13	*n*-BuLi (10)	0.4	0-25	92

[a] Reaction conditions: benzophenone (1 mmol), diethyl phosphite (1.2 mmol) under additional solvent free conditions (except for entry 4 where THF was used as solvent) in the presence of N_2 balloon. [b] Isolated yield [c] n.r.:No reaction [d] The used *n*-BuLi strength: 1.6M in hexane.

Among different organic and inorganic bases, *n*-BuLi (10 mol%) was much more effective to afford the phosphate **1a.** Surprisingly no reaction could be observed even with 0.1-5 mol% of *n*-BuLi. Although the bases NaH and Cs_2CO_3 were equally effective for this reaction but stoichiometric amount of bases were necessary to access **1a** in higher yield.

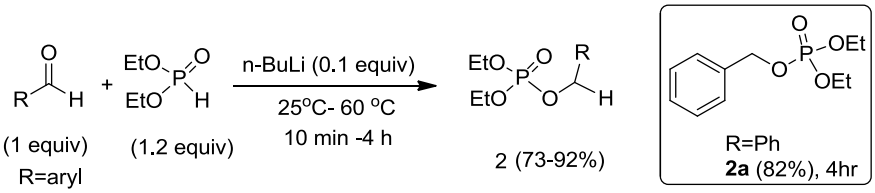
A range of organophosphates (**1a-i**), synthesized herein, are demonstrated in **Scheme 4.23.** To our delight, both benzophenone and acetophenone reacted with diethyl phosphite smoothly to furnish the phosphates **1a** and **1i** respectively in excellent yields under the present conditions whereas the earlier reported attempt to synthesize these phosphates was not satisfactory.[46,47,48] Unexpectedly, the presence of methyl group(s) in one of the benzene rings for benzophenone also led to the smooth formation of compounds **1b** (100%, verified by $^{31}P/^{1}H$

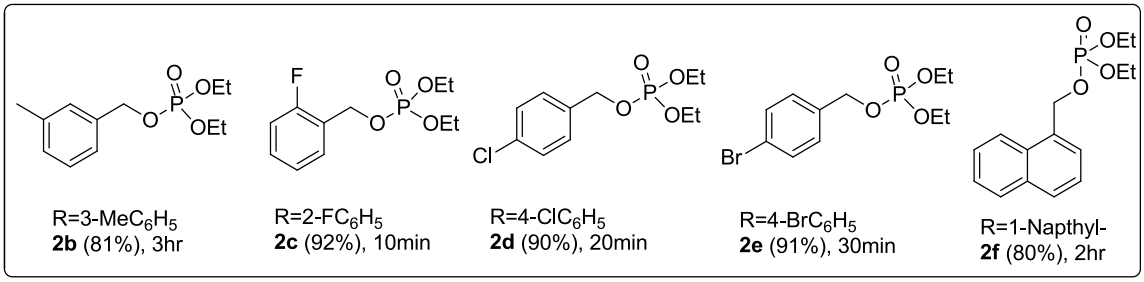
NMR). Unfortunately **1b** could not be purified using column chromatography (SiO_2) as it got decomposed in the column and afforded the compound phenyl(*p*-tolyl)methanol. Fluorene based phosphate **1f** [48] was also successfully produced at room temperature in a manner similar to other phosphates. Most of these phosphates were formed within 10-20 min excluding **1f** and **1i** (3-4 h). The presence of electron withdrawing groups in case of **1g-h** (analogues of **1i)** makes the reactions faster as expected. We could not isolate the corresponding α-hydroxyphosphonates under the present reaction conditions in the case of ketones.



Scheme 4.23 Synthesis of phosphates from the reactions of ketones and diethyl phosphite. Yields refer to chromatographically purified products.

Aldehydes also generated the corresponding phosphates **2a-f** (**Scheme 4.24**) efficiently as expected.



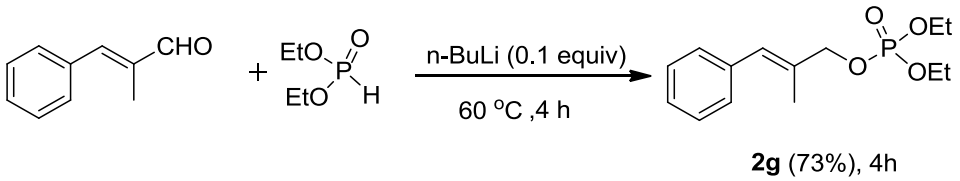


Scheme 4.24 Synthesis of phosphates from the reactions of aldehydes and diethyl phosphite. Yields refer to chromatographically purified products

Surprisingly, our attempt to perform these reactions at r.t. was not promising to obtain the phosphates. In the case of compounds 4-chlorobenzaldehyde, 2-fluorobenzaldehyde and 1-naphthaldehyde, the phosphate formation was observed at r.t. only after 8-10 h. The reaction times were reduced by heating the reaction mixture at 60 ^{o}C.

The reactions of aldehydes with diethyl phosphite generated corresponding *α*-hydroxyphosphonates initially at r.t. and subsequently formed phosphates upon heating. In comparison to the earlier report on DBU-catalayzed phosphate synthesis,[47] important phosphates **2d** and **2f** were synthesized here in excellent yields using *n*-BuLi as a triggering agent. Replacement of *n*-BuLi with NaH failed to afford the product **1i** as reported earlier.[49]

Furthermore, we could generate very useful allylic phosphate **2g** successfully from the reaction of (*E*)-*α*-methylcinnamaldehyde with diethyl phosphite in the absence of any additional solvent **(Scheme 4.25).** The room temperature reaction produced compound **2g** along with the corresponding *α*-hydroxyphosphonate as a mixture (1:1), from which compound **2g** was isolated in moderate yield (40%). The yield of **2g** was improved to 73% when the reaction was performed at 60 ^{o}C. Notably this compound **2g** has been used in asymmetric allylic silylation[50] and formation of enantioselective intermediates that have applications to natural product synthesis.[51] It is interesting to note that the alkyl lithium mediated reverse phosphate- *α*-hydroxyphosphonate rearrangement is reported in the literature, [52] however, we could not observe such a fact from our studies.



2g (73%), 4h

Scheme 4.25 Synthesis of allylic phosphates

4.3.2 *Spectroscopic characterization*

The phosphates, synthesized herein, are characterized using multinuclear NMR ($^{1}H/^{13}C/^{31}P$) spectroscopy. The phosphates (**1a-f** and **2a-g**) showed the characteristic doublet due to POC*H* at δ 6.40 (d, *J*= 8.4 Hz, 1H) and at δ 4.90 (d, *J*= 8.2 Hz, 2H) for *sec* and *primary* benzylic hydrogen in ^{1}H NMR spectra respectively and these values do not correspond to compound *α*-hydroxyphosphonates. The formation of phosphate was reconfirmed by ^{31}P NMR that showed the peak at δ~-1.3 where *α*-hydroxyphosphonates usually appear at δ~17.5 in ^{31}P NMR spectroscopy. Phosphates showed a band around 1268 and 1008 cm^{-1} in the IR spectra due to the stretching of P=O and P-OR esters. The characteristic ^{1}H and ^{13}C NMR spectra for compound **2a** are shown in **Fig 4.1a-b**.

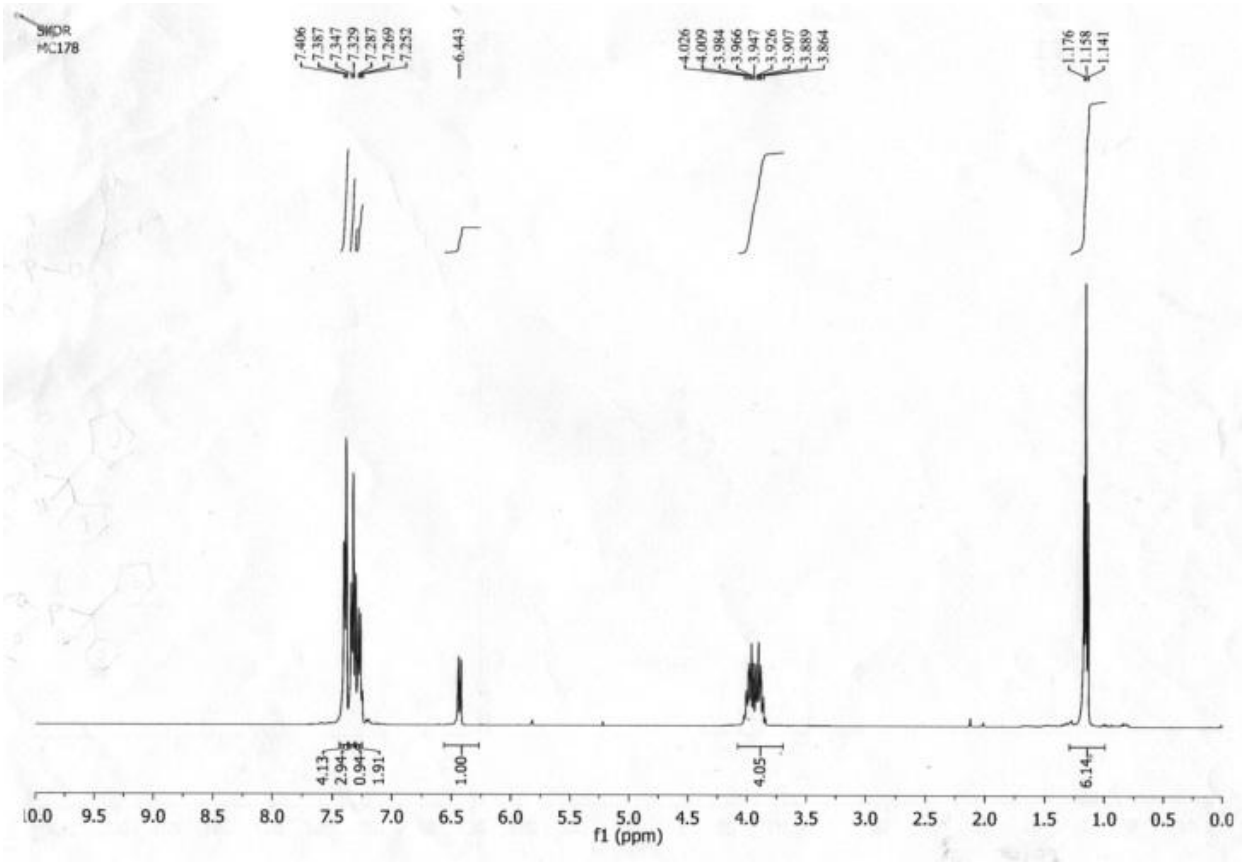


Fig 4.1a ^{1}H NMR of compound **1a**

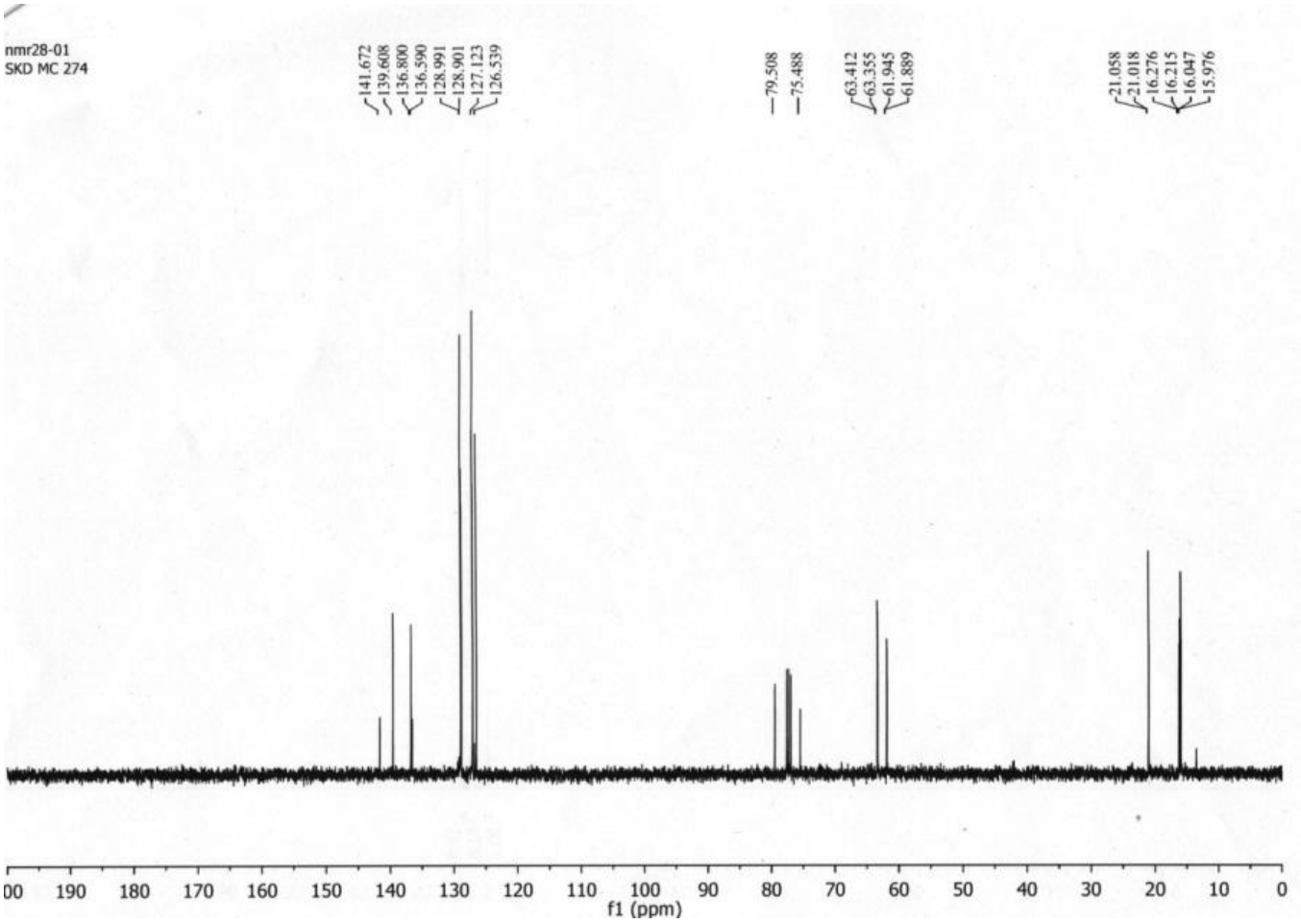
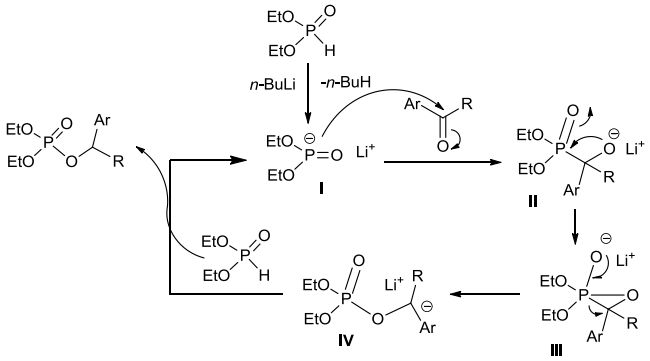


Fig 4.1b ^{13}C NMR of compound **1a**

4.3.3 *Plausible Mechanism*

Based on the earlier reports[41,42] and our experimental observations, the mechanistic scheme for synthesis of phosphates is presented in **Scheme 4.26**. In case of aldehydes, the intermediate **II** was isolated and the corresponding product *α*-hydroxyphosphonates were obtained upon work-up whereas the intermediate **II** could not be isolated for ketones as mentioned earlier. To understand this difference in reactivity, density functional theory (DFT) studies were performed and that revealed the carbanion **IV** is formed *via* three-membered transition state **III**. It was found that the activation energy to form **III** is much higher (~10 Kcal/mol, see SI for details) in case of benzaldehyde compared to benzophenone. Therefore, the transformation from **II** to **IV** is much slower for benzaldehyde. Presumably, for that reason, we could isolate the corresponding *α*-hydroxyphosphonates for aldehydes but not for ketones at r. t. Thus, we can also explain the favourable phosphate formation for ketones in comparison to aldehydes.



Scheme 4.26 Plausible Mechanistic pathway for the formation of phosphates

From this **Scheme 4.26** it is clear that *n*-BuLi triggers the reaction. This could explain the fact that the transformation does not work at lower loadings of this reagent because the concentration of the carbanion would be too low to maintain a workable concentration of the phosphite anion, and the catalytic cycle would fade out. The stability of the intermediate **IV** in the presence of electron donating substituent(s) could be explained by the fact of tight ion-pair formation (not much polar bond) with smaller alkali metal Li. The extra stability of this intermediate could also arise due to the coordination of Li ion with the phosphoryl (P=O) oxygen and that led to the formation of stable five membered chelatering.[53]

4.3.4 Application of these phosphates to access polyarylated alkanes

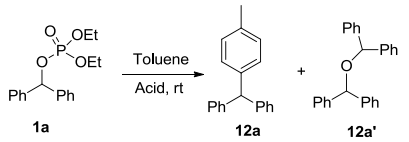
We have explored the Friedel-Craft (FC) type arylation reactions for these di or monoarylated phosphates (above discussed) to achieve polyarylated methanes. We present here both secondary and primary benzylic phosphates as an easily accessible, effective and new substrate for FC arylation reactions to access electronically and structurally diverse triarylmethanes predominantly, along with diarylethanes and diarylmethanes at rt within short duration using only 1.2 equiv of both activated or unactivated arenes.

4.3.5 Synthesis of tri-arylmethanes

As we mentioned above *via n*-BuLi triggered phospha-Brook rearrangement has made both electron-poor/rich primary and secondary benzylic phosphates easily reachable. Being primarily interested on triaryl methanes as an important scaffold, we kept our focus on FC type arylation reactions of the most inexpensive diphenylphosphate **1a** (secondary benzylic phosphate) with toluene (*only* 1.2 equiv) at rt to afford the desired product **12a** under key reaction parameters such as variety of acid catalysts in different quantities and reaction times (**Table 4.2**). As the formation of desired compound was satisfactory at rt, we could avoid the need of excess volatile

arenes. In some cases, the formation of ether **12a′** was also observed as expected.[54] Although there were many choices for the selection of Lewis or protic acids, the catalytic amount of TfOH (20 mol%, entry 9, **table 4.2**) was selected for all the reactions to afford desired products efficiently *within few minutes at rt.* The control experiment showed that the acid is necessary (entry 18, Table **4.2**) for this reaction.

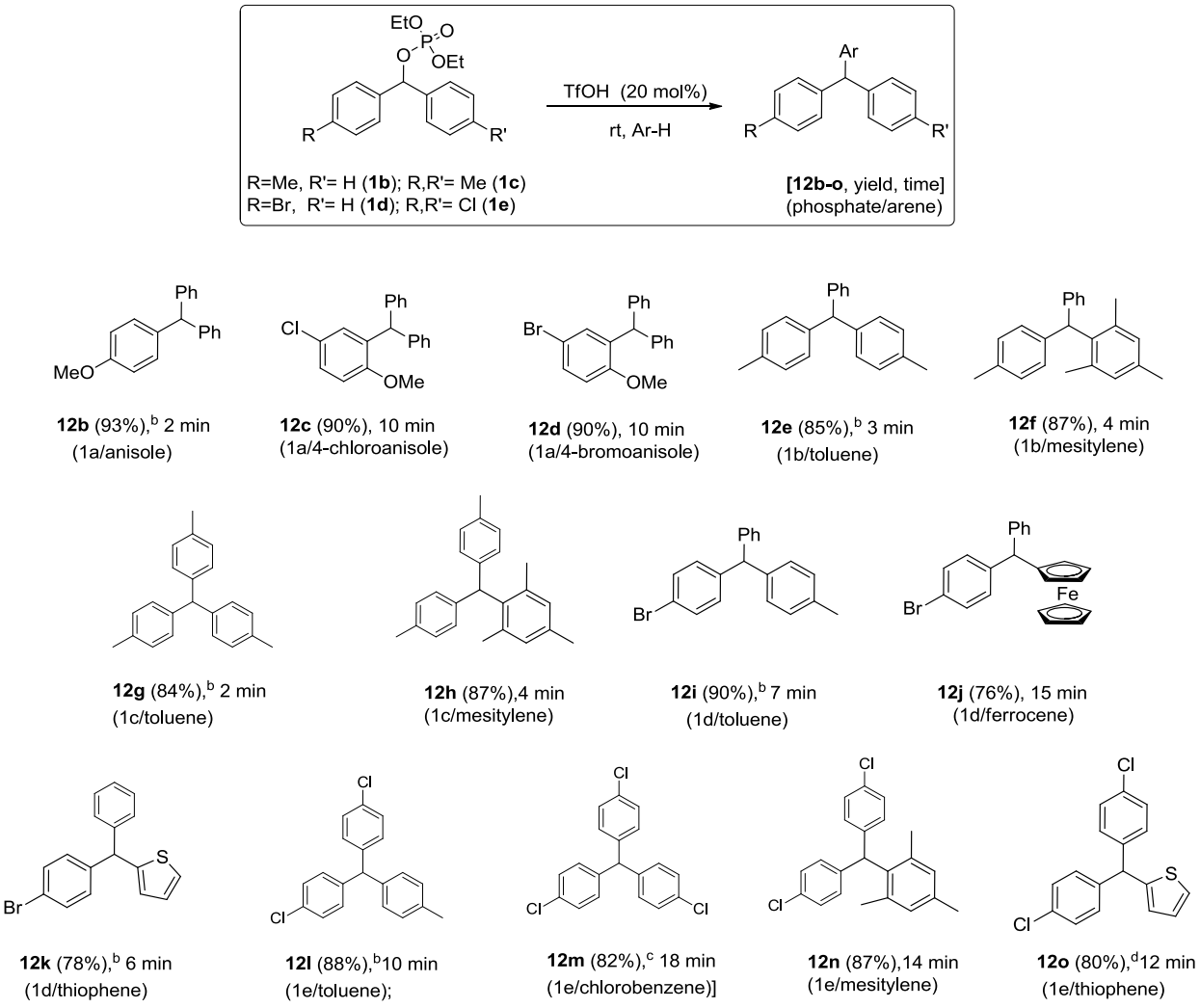
Table 4.2 Screening of reaction conditions to synthesize **12a**[a]



entry	Acid (mol%)	Time	Yield of 1**2a**[b] (%)	Yield of 1**2a'** (%)
1	$BF_3.Et_2O$ (0.1)	14 h	No reaction[c]	-
2	$BF_3.Et_2O$ (10)	14 h	10	90
3	$BF_3.Et_2O$ (20)	14 h	50	50
4	$BF_3.Et_2O$ (100)	14 h	100	0
5	TfOH (0.1)	12 h	6 [b]	0
6	TfOH (1)	12 h	20[b]	30
7	TfOH (5)	12 h	30	70
8	TfOH (10)	4 h	60	40
9	TfOH (20)	5 min	100	0
10	TfOH (50-100)	2 min	100	0
11	$FeCl_3$ (10)	8 h	10	90
12	$FeCl_3$ (20)	6 h	30	70
13	$FeCl_3$ (100)	1.5 h	100	0
14	$ZnCl_2$ (20)[d]	12	trace	90
15	$Cu(OTf)_2$	10	20	80
16	DNBA	6h	0	100
17	p-TSA	8h	0	100
18	No acid	12h	0	0

[a] reactions were performed with **1a** (1 equiv) and toluene (1.2 equiv) using acid (required amount) at rt; [b] NMR Yield with regioisomeric mixture 85:15. [c] starting material was unreacted. [d] heating at 60 ^oC was needed.

Phosphate **1a** reacted admirably with both activated anisole as well as non-activated halogenated anisoles to synthesize functionalized triarylmethanes **12b-d** in excellent yields and regioselectivity within 2-10 min **(Scheme 4.27).** In fact halogenated compounds **12c-d** could be utilized for further derivatization through well-known metal catalyzed C-C or C-N coupling reactions. The other electronically different phosphates **1b-e** are used herein to access a wide range of triarylmethanes. We have experienced the instability of mainly electron-rich secondary benzylic phosphates **1b-c** that tends to form diarylalcohols or ethers during the purification through column chromatography (SiO_2).

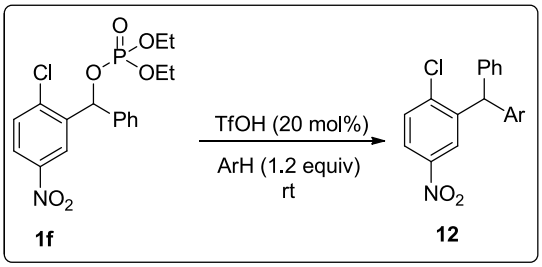


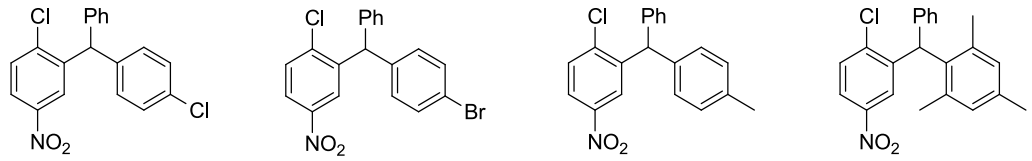
Scheme 4.27 List of triarylmehanes synthesized using phosphates[a]. [a] reaction conditions: **1** (1 equiv), ArH (1.2 equiv); only for **2j**, dichloroethane [DCE] (3 mL) was used. regioisomeric ratio determined by ^{1}H NMR [b] ~85:15; [c] 75:25; [d] 90:10

However, without further purification both these phosphates are succesfully used in the arylation reactions to generate **12f-h (Scheme 4.27)** appreciably within 2-4 min. Notably, both unsymmetrical and symmetrical crowded triarylmethanes **12f** and **12h** are completely new and synthesized comfortably using this approach at rt.

Further, we have extended **(Scheme 4.27)** the scope of this route by using stable phosphates [easily synthesized by favorable phospha-Brook rearrangement] **1d-e** (bearing weakly deactivated haloarenes) where arylation of **1d** afforded the synthetically unexplored triarylmethanes **12i-k** satisfactorily and electronically diverse triarylmethanes **12l-o** were generated conveniently within 6-20 min. from arylation reaction of **1e.** Of note, arenes such as ferrocene and thiophene are positively used for these reactions to access the corresponding unsymmetrical triarylmethanes **12j-k** and **12o**, respectively. It is pertinent to note that being weakly inactive groups, syntheses of such electronically deactivated triarylmethanes **12i-o** are considerably challenging using traditional FC route. These compounds were chracterized by ^{1}H and ^{13}C NMR spectra that showed the peak at ~ δ 5.70 and 56.1 respectively for Ar_3CH and the value is consistent with the literature report (see experimental section).

With this success, we next concentrated on the synthesis of much electron-poorer unsymmetrical triarylmethanes under these reaction conditions. In that context, the arylation reactions of inexpensive elctron-poor phosphate **1f** with chloro- and bromobenzene (unsuited for FC arylation) afforded desired functionalized triarylmethanes **12p-q** within 30 min. In a similar fashion, the other related products **12r-s** (**Scheme 4.28**) were successfully accomplished in excellent quantity as expected. Notably, phosphates with electron-poor systems are easily synthesized by aforementioned method.[57] These highly functionalized unsymmetrical triarylmethanes **12p-s** are completely new and challeging to acheive within this short reaction time at rt.[60] Thus, these reactions offer a time-saving path to achieve a large number of unsymetrical and electron-poorer triarylmethanes in a simple, economic and convenient manner.





Scheme 4.28 Reactions of phosphate **1f** with arenes including halogenated arenes. regioisomeric ratio (determined by ^{1}H NMR) [b] *p/o:* 74:26; [c] *p/m/o*: 81:7:12.

All these new compounds are characterized by IR and NMR spectroscopy. In IR, two peaks at ~1550, 1360 cm^{-1} were observed and that confirms the presence of –NO_2 group. In ^{1}H and ^{13}C NMR spectra, peaks at ~ δ 5.85 and 53.5 were appeared respectively for Ar_3CH. The representative ^{1}H and ^{13}C NMR spectra for compounds 1**2s** are shown in **Fig 4.2 a-b**.

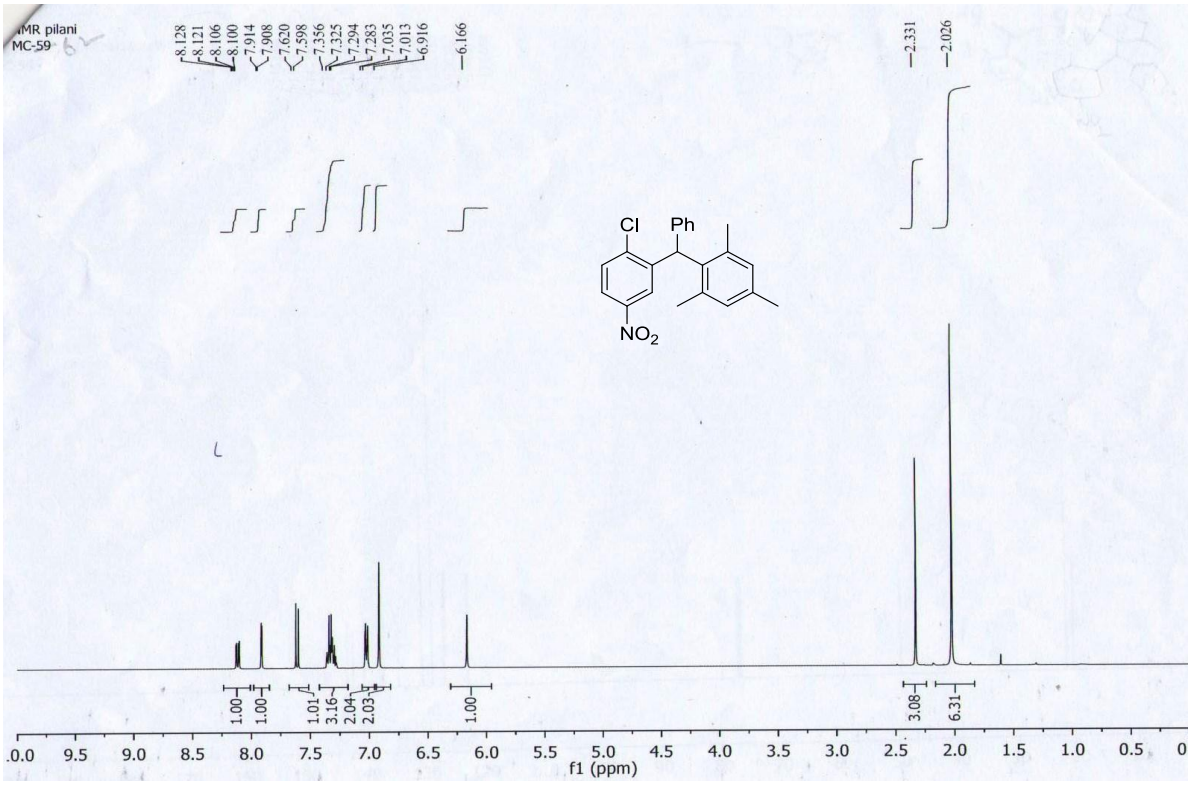


Fig 4.2a ^{1}H NMR spectrum of compound **2s**

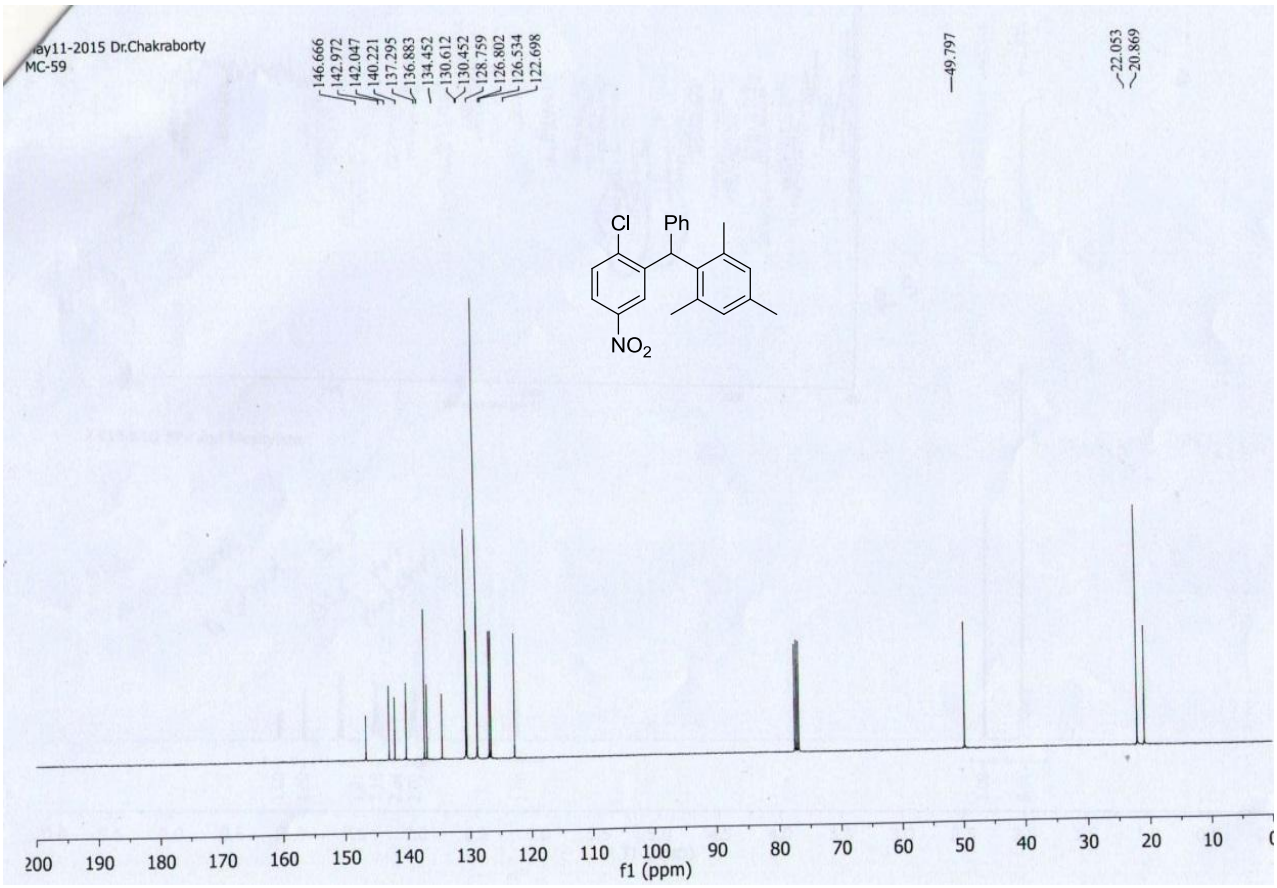
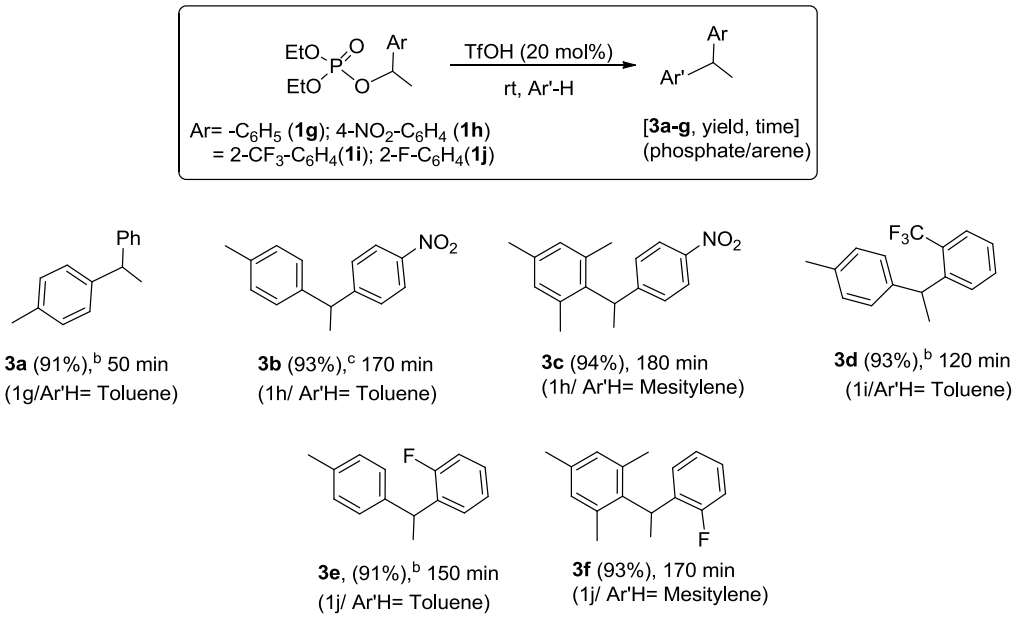


Fig 4.2b ^{13}C NMR spectrum of compound **2s**

4.3.6 *Synthesis of diarylethanes*

As synthesis of diarylethane from Pd-catalyzed cross coupling reaction of **1g** with $PhB(OH)_2$ was unsucessful,[57] we took an effort for the same by starting with electronically diverse secondary benzylic phosphates **1g-j** that were also easily obtained from variously substituted acetophenones.[55] To our delight, the expected diarylethanes **3a-f** were generated appreciably at rt although the reaction time in this case was somewhat longer (50-180 min) **(Scheme 4.29)**. It reflects that these phosphates are comparatively less reactive towards the arenes under the similar reaction conditions [TfOH(20 mol%)/rt, 1.2 equiv arenes].



Scheme 4.29 List of diarylethanes synthesized using phosphates[a]. [a] reaction conditions: 1 (1 equiv), Ar'H (1.2 equiv); regioisomeric ratio (determined by ^{1}H NMR) [] ~80:20; [c] 67:33

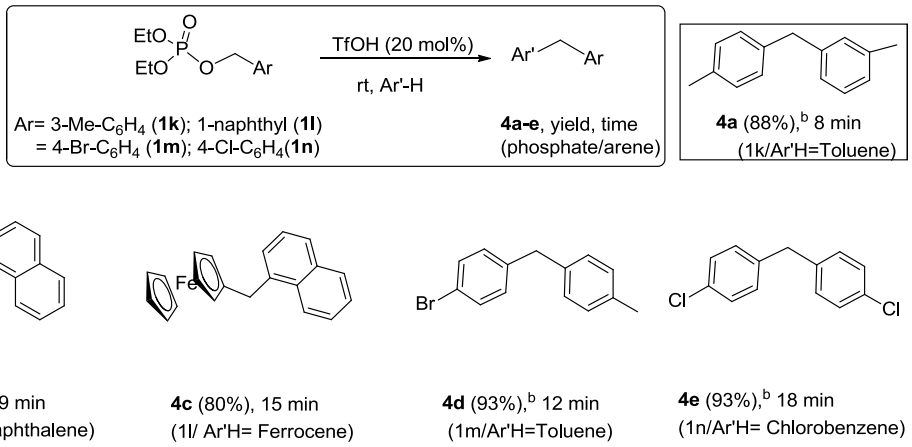
Although only toluene or mesitylene were choosen as arenes, the used electrophile phosphates **1h-j** are significantly electron-poor systems due to the presence of strongly deactivating group like –NO_2,-F and -CF_3. The required timimgs for the synthesis of **1h-j** indicate that the reactivity of these phosphates are very much comparable to each other. The electron-poor structually diverse diarylethanes **3c-f** are unknown in the literature and most likely difficult to access through FC route by using other electrophilic species. Therefore, these phosphates have openned a new door to access such electron-poor diarylethanes successfully.

These compounds were chracterized by ^{1}H NMR spectra that showed the characteristic doublet at ~ δ 1.69 (d, *J* ~ 7.2 Hz) and quartet at ~ δ 4.20 (*J* ~ 7.0 Hz) and signals at ~ δ 21.1, 37.4 were observed in ^{13}C NMR spectra for Ar_2*CH* and -*CH*$_3$. These spectral data is consistent with the literature report (see experimental section).

4.3.7 *Synthesis of diarylmethanes*

Although the synthesis of diarylmethanes are very well established,[58] we planned to examine the approachability of diarylmethanes using few limited primary benzylic phosphates **1k-n** under these reaction conditions. The diarylmethanes bearing weakly activated (**4a-c**) and deactivated (**4d-e**) benzene rings were conveniently synthesized at rt within 8-15 min **(Scheme 4.30)** and hence these phosphates are essentially efficient substrates for the synthesis of variety of diarylmethanes. The 1-naphthylphosphate **1l** was recently used for the Pd-catalyzed cross

coupling reactions to produce the polycylic diarylmethanes[59] and inspired by these outcomes, useful[60] *polycyclic* di(1-naphthylmethane) **4b** was synthesized in pure isomeric form. In addition, we could also conveniently synthesize diarylmethane **4c** where ferrocene was connected with 1-naphthalene.

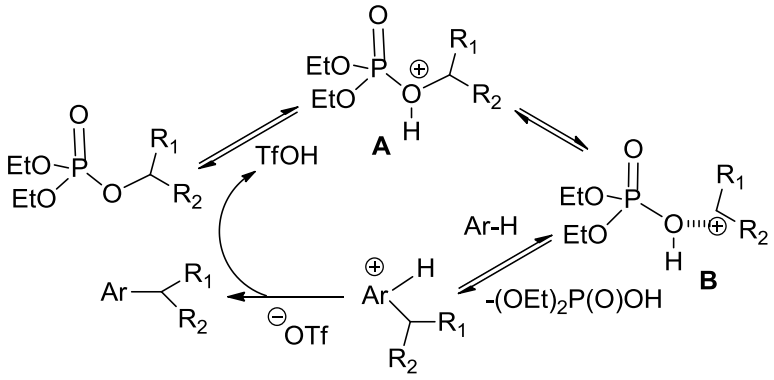


Scheme 4.30 List of diarylmethanes synthesized using phosphates[a]. [a] reaction conditions: 1 (1 equiv), Ar'H (1.2 equiv), only for **4b-c,** DCE (3 mL) wad used. [b] regioisomeric ratio (determined by ^{1}H NMR): 60:40; [c] reaction mixture showed the quantitative conversion with regioisomeric ratio~ 90:10.

These compounds were chracterized by ^{1}H and ^{13}C NMR spectra that showed the peak at ~ δ 4.18 and 41.7 respectively for Ar_2*CH* and the value is consistent with the literature report (see experimental section).

4.3.8 *Plaussible reaction mechanism*

On the basis of experimental results and reported literature, we propose the reaction mechanism as shown in scheme **4.31**. The formation of products with strongly electron withdrawing substituents can presumably be justified due to the formation of relatively stable species of type **A** followed by **B**. There is no considerable solvent effect to stabilize the intermediate **B**, however strong ion-dipole interaction between cation and phosphate (leaving group) may lead to gain the optimum stability of **B** to facilitate FC type arylation reactions of electron–poor electrophiles as well as unactivated arenes within short time.



Scheme 4.31 Plaussible reaction mechanism for FC reactions of benzylic phosphates

Furthermore, we anticipated to study the reaction of phosphate **1a** with toluene using ^{31}P NMR spectroscopy that showed the peak at δ_P -1.67 for **1a** in $CDCl_3$ [**Fig 4.3-(a)].** The broad signals at δ_P –1.81 along with -1.67 (~1:1) [**Fig 4.3-(b)]** were appreared soon after the *slow addition* of toluene and TfOH. This could be likely due to the existence of both **1a** and the intermediate of type **A** in equillibium (Scheme **4.31**). After 4 min, other new broad signals appeared at δ_P -1.57 along with -1.83 (~1: 0.3) [**Fig 4.3-(c)]** and that perhaps could be attributed to the fomation of stabilized species of type **B**. Finally after 6 min., the peak at δ_P -0.36 [**Fig 4.3-(d)]** resulted due to the formation of diethylphosphate. When the same experiment was repeated by shaking the reaction mixture well in NMR tube soon after the addition of TfOH and toluene, the peak at δ_P -1.67 (for **1a**) was completely converted to δ_P -0.36 and no other signals were detected. The close values within the range of δ_P -1.83 to δ_P -1.57 imply that the structure of **1a** has resemblance with structures of **A** and **B**.

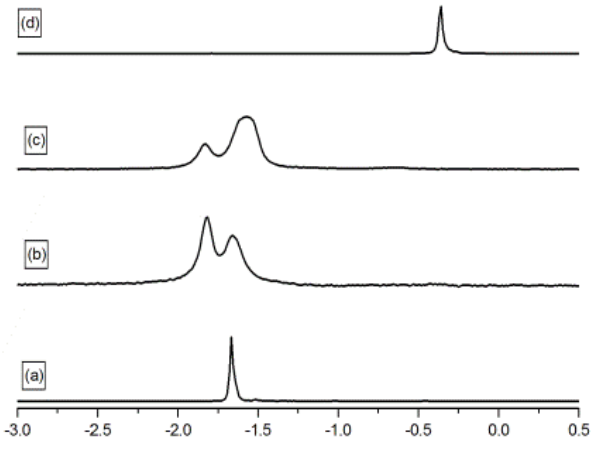


Fig 4.3 ^{31}P NMR spectra ($CDCl_3$) of (a) phosphate (**1a**); After addition of toluene and TfOH (b) immediately, c) after 4 min. and d) after 6 min

4.4 Conclusion

Both ketones and aldehydes are conveniently used to generate phosphates from the *n*-BuLi- triggered reactions with diethyl phosphites under solvent-free and mild conditions. In this approach, the ketones with electron donating substituents can also be applied successfully and also TfOH catalyzed (20 mol%), solvent (additional) free arylation reactions of electron-poor and rich seconday/primary benzylic phosphates are developed at room temperature to access structurally and electronically diverse polyarylated alkanes. Both activated and unactivated arenes (1.2 equiv) including halobenzenes are suitable for this approach. Moreover, the reaction was complete within 2-30 min to access a wide variety of di- and triarylmethanes and thus this method offers a time-saving approach towards these alkanes. The synthesis of electron-poor polyarylated alkanes has become much easier through this strategy due to the ample accessibility of the electron-poor phosphates *via* favorable phospha-Brook rearrangement. Phosphate as a leaving group play a crucial role for this success and an attempt to establish the fact using ^{31}P NMR is also demonstrated.

4.5 Experimental section

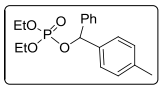
4.5.1 ***General procedure for the synthesis of phosphates:*** *n*-BuLi (0.17 mL of a 1.6 M solution in hexanes, 0.274 mmol, 0.1 equiv) was added drop wise to diethyl phosphite (0.45 mL, 3.29 mmol) at room temperature (rt) under N_2 balloon at 0 ^oC. The resulting solution was stirred at rt for 2 min. Then, benzophenone (500 mg, 2.74 mmol) was added and the resulting solution was stirred at rt for 15 min. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 x 25 ml). After filtration and removal of solvent in vacuum, the crude product was purified by column chromatography using ethylacetate/ pet ether (20/80) as the eluent to afford **1a**. Unless otherwise stated, all the other compounds **1b-i** were prepared analogously using similar molar quantities of carbonyl compounds, diethyl phosphite and *n*-BuLi. In case of aldehydes, reactions were performed in a manner similar to the phosphates **1a-i** at 60 ^oC. All the spectroscopic data is included in the supporting information.

4.5.2 ***Spectroscopic data for phosphates 1a-i and 2a-g***

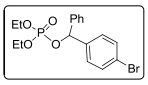
Benzhydryl diethylphosphate (1a) Colourless liquid; yield 92% (0.806 g); IR (KBr, cm^{-1}) 2921, 1452, 1265, 1000, 963; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J* ~ 7.0 Hz, 6H), 3.86-4.02 (m, 4H), 6.44 (d, *J* = 8.4 Hz, 1H), 7.25-7.28 (m, 3H), 7.32-7.34

(m, 3H), 7.38-7.41 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.9 (*J* = 7.0 Hz), 63.6 (d, *J* = 5.7 Hz), 80.9 (d, *J* = 5.3 Hz), 126.9, 128.0, 128.4, 140.5 (d, *J* = 5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.59.

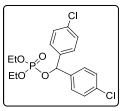
Diethyl (phenyl(p-tolyl)methyl)phosphate (1b) Colourless liquid; yield: quantitative [based on ^{31}P and ^{1}H NMR]; IR (KBr, cm^{-1}) 2983, 1450, 1268, 1004, 807,737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, *J* ~ 6.8 Hz, 6H), 2.33 (s, 3H), 3.90-3.99 (m, 4H), 6.41 (d, *J* = 8.4 Hz, 1H), 7.15-7.16 (m, 2H), 7.17-7.4 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 (d, *J* = 7.1 Hz), 21.1, 63.6 (d, *J* = 5.6 Hz), 80.9 (d, *J* = 5.2 Hz), 126.8, 126.9, 127.9, 128.4, 129.1, 137.6 (d, *J* = 5.1 Hz), 137.8, 140.7 (d, *J* = 5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.54. We could not purify this sample using column chromatography (see manuscript). Therefore the excess (0.2 equiv) diethyl phosphite is also present along with this sample.



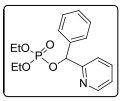
(4-Bromophenyl)(phenyl)methyl diethylphosphate (1c) Colourless liquid; yield 86% (0.66 g); IR (KBr, cm^{-1}) 2984, 1486, 1268, 1028, 895; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 and 0.95 (t, *J* ~ 7.0 Hz, 3H each set), 3.65-3.86 (m, 4H), 6.20 (d, *J* = 6.2 Hz, 1H), 7.01-7.08 (m,5H), 7.14-7.16 (m,2H),7.19-7.22 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.7 and 15.8 (two sets of doublets, *J* = 6.6 Hz each), 63.5 (d, *J* = 5.7 Hz), 79.9 (d, *J* = 5.0 Hz), 121.8, 126.6, 128.1, 128.4, 128.5, 131.4, 139.6 (d, *J* = 5.3 Hz), 139.9 (d, *J* = 4.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.72; Anal. Calcd for $C_{17}H_{20}O_4BrP$: C, 51.15; H, 5.05. Found: C, 50.56; H, 4.80.



Bis(4-chlorophenyl)methyl diethylphosphate (1d) Colourless liquid; yield 85% (0.66 g); IR (KBr, cm^{-1}) 2925, 1590, 1486, 1402, 1268, 1084, 1030, 808; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* ~ 7.0 Hz, 6H), 3.87-3.98 (m, 4H), 6.32 (d, *J* = 8.4 Hz, 1H), 7.24-7.28 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9(d, *J* = 7.0 Hz), 63.8 (d, *J* = 5.7 Hz), 79.3 (d, *J* = 5.0 Hz), 128.2, 128.7, 134.1, 138.6 (d, *J* = 5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.66.



Diethyl (phenyl(pyridin-2-yl)methyl)phosphate (1e) Colourless liquid; yield 89% (0.78 g); IR (KBr, cm^{-1}) 2986, 1582, 1445, 1269, 1025, 895,754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 and 1.11 (t, *J* ~ 7.0 Hz each, 3H each set), 3.79-3.98 (m, 4H), 6.37 (d, *J* = 8.8 Hz, 1H), 7.08-7.10 (m, 1H), 7.21-7.26 (m,3H), 7.37-7.39 (m,2H), 7.50-7.52 (m,1H), 7.60-7.62 (m,1H), 8.44-8.45 (m,1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.8 and 15.9 (two sets of doublets, *J* ~ 7.0 Hz each), 63.7 and 63.8 (d, *J* ~ 6.0 Hz), 81.4 (d, *J* = 5.2 Hz), 120.3, 122.8, 127.0, 128.3,



128.5, 136.9, 139.3, 149.1, 159.4 (d, *J* = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.97. LC/MS: m/z 322 [M^+ + H]. This sample contains some diethyl phosphite (~15%).

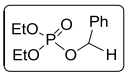
Diethyl 9H-fluoren-9-ylphosphate (1f) White solid; yield 90% (0.79 g); mp 54-58 ^oC; IR (KBr, cm^{-1}) 2984, 1616, 1448, 1271, 1022, 881, 809,749; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33-1.36 (m, 6H), 4.15-4.21 (m, 4H), 6.24 (d, *J* = 9.0 Hz, 1H), 7.28-7.31 (m, 2H),7.35-7.38 (m, 2H), 7.60 (d, *J*= 7.5 Hz, 2H), 7.74 (d, *J*= 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.1(d, *J* = 6.9 Hz), 64.1 (d, *J* = 6.1 Hz), 78.2 (d, *J* = 5.7 Hz), 120.0, 125.9, 127.9, 129.7, 140.5, 141.9 (d, *J* = 4.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -0.07. LC/MS: m/z 319 [M^+ + H].

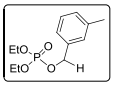
Diethyl (1-(2-(trifluoromethyl)phenyl)ethyl)phosphate (1g) Colourless liquid; yield 80% (0.69 g); IR (KBr, cm^{-1}) 2987, 1600, 1452,1384, 1276,1123, 1015, 929; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* ~ 6.5 Hz, 6H), 1.30 (d, *J* ~ 6.5 Hz, 3H), 3.63-3.79 (m, 4H), 5.53-5.55 (m, 1H), 7.08-7.11 (m, 1H), 7.28-7.32 (m, 2H), 7.48-7.49 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.5 (d, *J* = 6.9 Hz), 24.9 (d, *J* = 5.0 Hz), 63.3 (d, *J* = 5.6 Hz), 71.7 (d, *J* = 4.2 Hz), 123.9 (q, *J* = 274.1 Hz), 124.9 (q, *J* = 5.8 Hz), 125.8 (q, *J* = 30.5 Hz), 127.2, 127.7, 132.2, 141.0 (d, *J* = 4.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.68. LC/MS: m/z 327 [M^+ + H]; Anal. Calcd for $C_{13}H_{18}O_4F_3P$: C, 47.86; H, 5.56. Found: C, 47.75; H, 5.91.

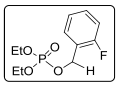
Diethyl (1-(2-fluorophenyl)ethyl)phosphate (1h) Colourless liquid; yield 81% (0.81 g); IR (KBr, cm^{-1}) 2985, 1587,1487, 1270, 1029, 979,813; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13-1.22 (m, 6H), 1.56 (d, *J* ~ 6.4 Hz, 3H), 3.90 - 4.05 (m, 4H), 5.67-5.72 (m, 1H0), 6.93-6.97(m, 1H), 7.06-7.09 (m, 1H), 7.19-7.21 (m, 1H), 7.39-7.43 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.8 (d, *J* = 6.9 Hz), 23.2 (d, *J* = 4.7 Hz), 63.6 (d, *J* = 5.8 Hz), 70.5 (d, *J* = 5.1 Hz), 115.3 (d, *J* = 21.6 Hz), 124.2 (d, *J* = 3.5 Hz), 127.1 (d, *J* = 3.7 Hz), 129.0 (dd, *J* = 13.2 and 5.1 Hz), 129.5 (d, *J* = 8.2 Hz), 159.2 (d, *J* = 247.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.05. LC/MS: m/z 553 [$2M^+$ + H]; Anal. Calcd for $C_{12}H_{18}O_4FP$: C, 52.17; H, 6.57. Found: C, 51.75; H, 6.60.

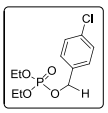
Diethyl (1-phenylethyl)phosphate (1i). The reaction mixture was stirred for 4h. Colourless liquid; yield 90% (0.96 g); IR (KBr, cm^{-1}) 2930, 1450, 1204, 1175, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 and 1.29 (t, *J* ~ 7.0 Hz, 3H each set), 1.63 (d, *J* = 6.5 Hz, 3H),3.92-4.05 (m, 4H), 5.44-5.50 (m, 1H), 7.21-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 and 16.0 (two sets of doublets, *J* = 6.8 Hz each), 24.1 (d, *J* = 5.1 Hz), 63.4 and 63.5 (d, *J* =

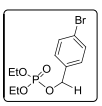
5.7 Hz each), 76.6 (d, *J* = 5.5 Hz), 125.8, 128.1, 128.4, 141.7 (d, *J* = 4.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.83.

Benzyl diethylphosphate (2a). Colourless liquid; yield 82% (0.94 g); IR (KBr, cm^{-1}) 2985,  1643, 1454, 1385, 1266, 1022,859, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.18 (m, 6H), 3.91-3.98 (m, 4H), 4.93 (d, *J* = 8.2 Hz, 2H), 7.18-7.27 (m, 5H);^{31}P NMR (162 MHz, $CDCl_3$) δ -1.04. LC/MS: m/z 245 [M^+ + H].

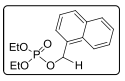
Diethyl 3-methylbenzylphosphate (2b) Colourless liquid; yield 81% (0.87 g); IR (KBr, cm^{-1}) 2911, 1604, 1482,1379, 1272,1162, 1018, 852; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* ~ 7.2 Hz,  6H), 2.26 (s, 3H), 3.95-4.03 (m, 4H), 4.93 (d, *J* = 8.0 Hz, 2H),7.03-7.17 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.9(d, *J* = 6.7 Hz), 21.1, 63.6 (d, *J* = 5.9 Hz), 68.9 (d, *J* = 5.5 Hz), 124.8, 128.3, 128.4, 129.0, 135.9 (d, *J* = 6.7 Hz), 138.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.01; LC/MS: m/z 259 [M^+ + H].

Diethyl 2-fluorobenzylphosphate (2c). Colourless liquid; yield 92% (0.97 g); IR (KBr, cm^{-1}) 2982, 1621, 1589, 1490, 1266, 1000, 969, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 -1.21 (m,  6H), 3.96-4.01 (m, 4H), 5.02 (d, *J* = 8.0 Hz, 2H), 6.93-6.97 (m,2H), 7.05-7.06 (m, 1H), 7.34-7.37 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.9 (d, *J* = 6.6 Hz), 62.7 (t, *J* = 4.9 Hz), 63.7 (d, *J* = 5.9 Hz), 115.2 (d, *J* = 21.1 Hz), 123.2 (dd, *J* = 14.4 and 7.2 Hz), 124.1 2 (d, *J* = 3.7 Hz), 130.2 (d, *J* = 3.6 Hz), 130.3 (d, *J* = 8.2 Hz), 160.5 (d, *J* = 248.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.19. LC/MS: m/z 263 [M^+ + H]; Anal. Calcd for $C_{11}H_{16}O_4FP$: C, 50.39; H, 6.15. Found: C, 50.26; H, 6.25.

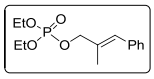
4-Chlorobenzyl diethylphosphate (2d). Colourless liquid; yield 90% (0.89 g); IR (KBr, cm^{-1})  2905, 1598, 1488, 1267, 1012, 955,804;^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* ~ 6.8 Hz, 6H), 3.97-4.04 (m, 4H), 4.95 (d, *J* = 8.0 Hz, 2H), 7.19-7.29 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.9 (d, *J* = 6.6 Hz), 63.8 (d, *J* = 5.8 Hz), 68.0 (d, *J* = 5.4 Hz), 128.6, 129.1, 134.2, 134.6 (d, *J* = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.04.

4-Bromobenzyl diethylphosphate (2e) Colourless liquid; yield 91% (0.79 g); IR (KBr, cm^{-1}) 2908, 1592, 1483, 1269, 1027, 809; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* ~ 6.8 Hz, 6H), 3.91-  3.98 (m, 4H), 4.89 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.9 (d, *J* = 6.6 Hz), 63.8 (d, *J* = 5.6 Hz), 68.0 (d, *J* = 5.2 Hz), 122.3, 129.4, 131.6, 135.1 (d, *J* = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.08. LC/MS: [m/z 323 [M + H]$^+$ and 325 [(M+2) + H]$^+$ (~1:1)].

Diethyl (naphthalen-2-ylmethyl)phosphate (2f) Colorless liquid; yield 80% (0.75 g); IR (KBr, cm^{-1}) 2910, 1509, 1472, 1274, 1037,841, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* ~ 7.0 Hz, 6H), 3.99-4.07 (m, 4H), 5.52 (d, *J* = 8.0 Hz, 2H), 7.39 -7.56 (m, 4H), 7.81-7.85 (m, 2H), 8.09-8.11 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.0 (d, *J* = 6.7 Hz), 63.8 (d, *J* = 5.9 Hz), 67.4 (d, *J* = 5.4 Hz), 123.5, 125.2, 126.6, 127.1, 128.6, 129.5, 131.6 (d, *J* = 6.8 Hz), 133.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ -0.96. LC/MS: m/z 295 [M^+ + H]



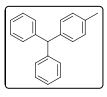
(*E*)-Diethyl (2-methyl-3-phenylallyl)phosphate (2g) Colourless liquid; yield 73% (0.71 g); IR (KBr, cm^{-1}) 2906, 1662, 1485, 1268, 1038, 974, 823, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* ~ 7.0 Hz, 6H), 1.78 (s, 3H), 3.95-4.03 (m, 4H), 4.44 (d, *J* = 7.2 Hz, 2H), 6.43 (s, 1H), 7.04-7.20 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.9, 16.0 (d, *J* = 6.6 Hz), 63.6 (d, *J* = 5.8 Hz), 72.9 (d, *J* = 5.6 Hz), 126.7, 128.1, 128.2, 128.7, 132.8 (d, *J* = 6.8 Hz), 136.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ -0.924. LC/MS: m/z 285 [M^+ + H].



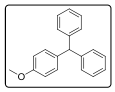
4.5.3 ***General procedure for synthesis of polyarylated methanes from phosphates*:** Trifluoromethanesulfonic acid (0.027 ml, 0.312 mmol) was added dropwise to a solution of phosphate **1a** (0.500 g, 1.561 mmol), toulene (0.198 ml, 1.874 mmol) at room temperature. The mixture was stirred at room temperature until the phosphate disappeared (by tlc). The reaction was quenched with water and the required compounds were extracted with EtOAc (25x3 ml). The combined organic layer was washed with brine, was dried with Na_2SO_4, and then was evaporated under reduced pressure. The residue was purified with a flash column chromatography (EtOAc/hexane ~1:99) to give triarylmethane **2a**. Unless otherwise stated, all other triaryl/diaryl methanes and diarylethanes are synthesized using similar molar quantities of the respective phosphates in a manner similar to the synthesis of **2a**. In case of solid arenes such as naphthalene and ferrocene, dichloroethane (DCE, 3 mL) was used and then dichloromethane was used for the extraction followed by the purification through column chromatography.

4.5.4 ***Spectroscopic data for triarylmethanes:***

(*p*-Tolylmethylene)dibenzene (12a).The reaction mixture was stirred for 5 min. viscous liquid; yield 94% (0.38 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 5.71 (s, 1H), 7.26-7.30 (m, 2H), 7.32- 7.35 (m, 6H), 7.39-7.43 (m,2H), 7.44-7.46 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2, 56.5, 126.3, 128.4, 129.1, 129.4, 129.5, 129.7, 135.9, 141.0, 144.2; The other regioisomer (*ortho*) was also present in ~15% along with this sample.

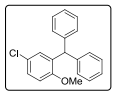


(4-Methoxyphenyl)methylene)dibenzene (12b). The reaction mixture was stirred for 2 min.



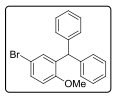
viscous liquid; yield 93% (0.39 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 5.56 (s, 1H), 6.87-6.89 (m, 2H),7.07-7.09 (m, 2H), 7.16- 7.18 (m, 4H), 7.26-7.28 (m, 2H), 7.32-7.35 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.2, 56.1, 113.7, 126.3, 128.3, 129.4, 130.4, 136.2, 144.3, 158.1; The other regioisomer (*ortho*) was also present in ~15% along with this sample.

(4-Chloro-2-methoxyphenyl)methylene)dibenzene (12c). The reaction mixture was stirred for



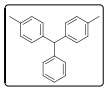
10 min. white solid; mp 118-120 ^{o}C; (lit 120 ^{o}C)[3]; yield 90% (0.43 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 5.94 (s, 1H), 6.84 (d, *J*= 8.7 Hz, 1H), 6.89 (d, *J*= 2.1 Hz, 1H), 7.13-7.15 (m, 4H), 7.21- 7.23 (m, 1H), 7.27-7.28 (m, 2H), 7.31-7.35 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 49.6, 55.9, 111.9, 125.4, 126.4, 127.4, 128.4, 129.4, 130.2, 134.7, 143.1, 155.8.

(4-Bromo-2-methoxyphenyl)methylene)dibenzene (12d). The reaction mixture was stirred for 10 min. white solid; mp 128-130 ^{o}C (lit 133 ^{o}C)[4b]; yield 90% (0.49 g); ^{1}H NMR (400 MHz,



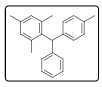
$CDCl_3$) δ 3.73 (s, 3H), 5.94 (s, 1H), 6.79 (d, *J*= 8.8 Hz, 1H, 6.80 (d, *J*= 2.1 Hz, 1H), 7.02-7.03 (m, 1H), 7.13-7.15 (m, 4H), 7.25- 7.31 (m, 2H), 7.34-7.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 49.6, 55.8, 112.5, 126.4, 128.3, 129.4, 130.4, 133.0, 135.1, 143.1, 156.3.

4,4'-(Phenylmethylene)bis(methylbenzene) (12e). The reaction mixture was stirred for 3



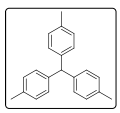
min. viscous liquid; yield 85% (0.34 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 6H), 5.58 (s, 1H), 7.06-7.12(m, 4H), 7.29-7.38 (m, 7H), 7.35-7.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 56.1, 126.2, 128.3, 129.1, 129.3, 129.4, 135.7, 141.1, 144.3; The other regioisomer (*ortho*) was also present in ~15% along with this sample.

1,3,5-Trimethyl-2-(phenyl(p-tolyl)methyl)benzene (12f). The reaction mixture was stirred for



4 min. viscous liquid; yield 87% (0.39g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 6H), 2.47 (s, 3H), 2.51 (s, 3H), 6.16 (s, 1H), 7.04 (s, 2H), 7.19-7.20 (m, 2H), 7.26-7.36 (m, 4H), 7.37-7.41 (m, 1H), 7.43-7.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0, 21.2, 22.2, 50.8, 125.9, 128.3, 129.1, 129.4, 130.3, 135.5, 136.1, 137.4, 137.7, 139.4; LC/MS m/z 300 $[M]^{+}$.

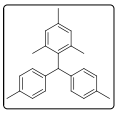
Tri-*p*-tolylmethane (12g) The reaction mixture was stirred for 2 min. viscous liquid; yield



84% (0.34 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 9H), 5.62 (s, 1H), 7.18 (d, *J* = 8.0 Hz), 7.25 (d, *J* = 8.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2, 55.9, 129.1, 129.4,

135.8, 141.5; The other regioisomer (*ortho*) was also present in ~15% along with this sample.

4,4'-(Mesitylmethylene)bis(methylbenzene) (12h). The reaction mixture was stirred for 4 min. white solid; mp 88-90 ^{o}C. yield 87% (0.39 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16, (s, 6H), 2.43

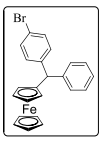


(s, 3H), 2.47 (s, 6H), 6.09 (s, 1H), 6.99 (s, 2H), 7.13-7.15 (m, 4H), 7.20-7.22(m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.9, 21.1, 22.1, 50.4, 128.9, 129.3, 130.2, 135.4, 135.9, 137.5, 137.7, 139.8; Anal. Calcd. for $C_{24}H_{26}$: C, 91.67; H, 8.33, Found: C, 91.29; H, 8.58.

1-Bromo-4-(phenyl(p-tolyl)methyl)benzene (12i). The reaction mixture was stirred for 7 min.

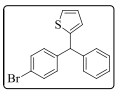
viscous liquid; yield 90% (0.38 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s,3H), 5.54 (s, 1H), 7.05-7.07 (m, 4H), 7.16-7.18 (m, 4H), 7.29-7.31 (m, 1H), 7.34-7.38 (m, 2H), 7.46 (d, *J*= 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 55.9, 120.3, 126.5, 128.4, 129.2, 129.3, 129.4, 131.2, 131.4, 136.1, 140.4, 143.3, 143.6; LC/MS m/z 336 $[M]^+$, 338 $[M+2]^+$; The other regioisomer (*ortho*) was also present in ~15% along with this sample.

(4-Bromophenyl(phenyl)methyl)ferrocene (12j). The reaction mixture was stirred for 15 min. Gummy solid; yield 76% (0.41 g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (d, *J*= 9.2 Hz, 2H), 4.02



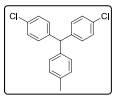
(s, 5H), 4.23 (br, 2H), 5.23 (s, 1H), 7.06-7.08 (m, 2H), 7.16-7.17 (m, 2H), 7.21-7.24 (m 1H), 7.3-7.31 (m, 2H), 7.40-7.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.4,67.9, 68.1, 68.9, 69.1, 119.9 126.4, 128.2, 128.7, 130.5, 131.2, 144.1, 144.4.

2-((4-Bromophenyl)(phenyl)methyl)thiophene (12k). The reaction mixture was stirred for 6 min. viscous liquid; yield 78% (0.32 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 1H), 6.72-



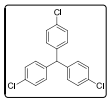
6.73(m, 1H), 6.97-6.99 (m, 1H), 7.12-7.14 (m, 1H), 7.23-7.25(m, 2H), 7.23-7.31(m, 3H),7.33 (m, 1H), 7.36-7.37 (m, 2H),7.46-7.48 (m, 2H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.6, 120.7, 124.8, 126.5, 126.7, 126.9, 128.6, 128.8, 130.6, 131.5,142.9,143.2,147.2. LC/MS m/z 328 $[M]^+$, Anal. Calcd. for $C_{17}H_{13}BrS$: C, 62.01; H, 3.98; S, 9.74. Found: C, 62.51; H, 4.13; S, 9.32. The other regioisomer was also present in ~15% along with this sample.

4,4'-(*p*-Tolylmethylene)bis(chlorobenzene) (12l). The reaction mixture was stirred for 10 min. viscous liquid; yield 88% (0.37 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.50 (s, 1H), 7.00-

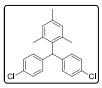


7.02 (m, 2H), 7.06-7.08 (m, 4H), 7.15-7.17 (m, 2H), 7.29-7.31 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 55.2, 126.8, 128.6, 129.3, 130.9, 132.4, 136.4, 139.9, 142.2; LC/MS: m/z 325 $[M^+-1]$;.The other regioisomer (*ortho*) was also present in ~15% along with this sample.

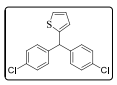
Tris(4-chlorophenyl)methane (12m). Gummy liquid; The reaction mixture was stirred for 18 min. yield 82% (0.36 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 1H), 7.04-7.06 (m, 7H), 7.31-7.33 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.2, 54.9, 128.7, 130.7, 132.7, 141.4. The other isomer was also present (~25%) with this sample.



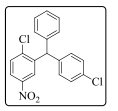
4,4'-(Mesitylmethylene)bis(chlorobenzene) (12n). The reaction mixture was stirred for 4 min. Gummy solid; yield 87% (0.39g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 6H), 2.33 (s, 3H), 5.94 (s, 1H), 6.91 (s, 2H), 7.05 (d, *J*= 8.4 Hz, 4H), 7.28-7.29 (d, *J*= 8.4 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.8, 21.9, 49.9, 128.4, 130.4, 130.6, 131.9, 136.1, 136.6, 137.4, 140.6.



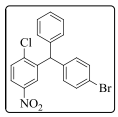
2-(Bis(4-chlorophenyl)methyl)thiophene (12o). The reaction mixture was stirred for 12 min. viscous liquid; yield 80% (0.32 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.7 (s, 1H), 6.74-6.75(m, 1H), 7.00 (m, 1H), 7.01-7.02(m, 4H), 7.18-7.19 (m, 1H), 7.33-7.36 (m, 4H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 50.9, 125.1, 126.7, 126.8, 128.7, 130.2, 132.9, 141.9, 146.7; LC/MS m/z 318 $[M]^+$, 320 $[M+2]^+$, 322 $[M+4]^+$; Anal. Calcd. for $C_{17}H_{12}Cl_2S$: C, 63.96; H, 3.79; S, 10.04. Found: C, 64.36; H, 4.10; S, 10.03.The other regioisomer was also present in ~10% along with this sample.



1-Chloro-2-((4-chlorophenyl)(phenyl)methyl)-4-nitrobenzene (12p): The reaction mixture was stirred for 30 min. light yellow solid, m.p.108-110 ^{0}C, yield 86% (0.38g); IR (KBr, cm^{-1}) 1519, 1342; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.98 (s, 1H), 7.03-7.10 (m, 4H), 7.33-7.48 (m, 5H), 7.61 (d, *J*= 8.8 Hz, 1H), 7.85 (d, *J*= 2.8 Hz, 1H), 8.10 (dd, *J*= 8.0 Hz, 2.8 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 52.9, 123.0, 125.7, 127.5, 128.9, 129.6, 130.1, 130.6, 130.7, 134.6, 140.5, 141.4, 141.8, 146.6, 146.7; peaks at δ 50.9, 125.3, 127.1, 128.8, 128.9, 129.3, 129.5, 130.7, 130.8, 133.1, 139.1, 139.2, 139.5, 142.7, 143.3 were observed for other isomers. Anal. Calcd. for $C_{19}H_{13}Cl_2NO_2$: C, 63.71; H, 3.66; N, 3.91. Found: C, 63.83; H, 4.00; N, 2.57. The other regioisomer was also present in ~26% along with this sample.

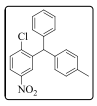


2-((4-Bromophenyl)(phenyl)methyl)-1-chloro-4-nitrobenzene(12q) The reaction mixture was stirred for 26 min. light yellow gummy solid, yield 84% (0.42g); IR (KBr, cm^{-1}) 1523, 1345, 1046; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.94 (s, 1H), 6.96 (d, *J*= 8.4Hz, 2H), 7.06 (d, *J*= 8.0Hz, 2H), 7.31-7.38 (m, 3H), 7.47 (d, *J*= 8.0Hz, 1H), 7.60 (d, *J*= 8.8Hz, 2H), 7.82 (d, *J*=2.8 Hz, 1H), 8.11 (dd, *J*= 8.0 Hz, 2.8 Hz, 1H); ^{13}C-NMR (101MHz, $CDCl_3$) δ 52.9, 121.2, 122.9, 125.6, 127.4, 128.9, 129.2, 130.8, 131.0, 131.9, 140.0, 140.3, 141.4, 143.2,

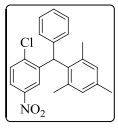


146.6; the other minor peaks are at δ 123.3, 125.3, 127.6, 128.6, 128.9, 129.6, 133.6, 139.3, 140.7; All the regioisomers were observed with the ratio (*p/o/m* 81:12:7) with this sample.

1-Chloro-4-nitro-2-(phenyl(p-tolyl)methyl)benzene (12r) The reaction mixture was stirred for 14 min. white solid, mp 90-92 ^{o}C, yield 91% (0.38g); IR (KBr, cm^{-1}) 1516, 1343, 1046; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.85 (s, 1H), 6.87 (d, *J*=8.1Hz, 2H), 6.97 (d, *J*= 12Hz,2H), 7.04 (d, *J*=8.1 Hz, 2H), 7.19-7.25 (m, 3H), 7.45 (d, *J*=5.0Hz, 1H), 7.76 (d, *J*= 2.8 Hz, 1H), 7.94-7.96 (m, 1H); ^{13}C-NMR (101MHz, $CDCl_3$) δ 21.1, 53.5, 122.7, 125.7, 126.2, 129.3, 129.5, 129.6, 130.6, 130.9, 137.9, 139.5, 141.4, 141.5, 144.1, 146.6; the other isomers are at δ 19.7, 50.6, 122.8, 125.8, 127.1, 127.3, 127.5, 128.7, 128.8, 128.9, 129.2, 136.6, 136.9, 141.2, 143.7. All the regioisomers were observed with the ratio (*p/o/m* 82:14:4) with this sample.

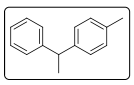


2-((2-Chloro-5-nitrophenyl)(phenyl)methyl)-1,3,5-trimethylbenzene (12s). The reaction mixture was stirred for 17 min. light yellow solid, mp 126-128 ^{o}C, yield 93% (0.42g); IR (KBr, cm^{-1}) 1596, 1512, 1343; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 6H), 2.33 (s, 3H), 6.17 (s, 1H), 6.92 (s, 2H), 7.02 (d, *J*= 8.8 Hz, 2H), 7.28-7.36 (m, 3H), 7.61 (d, *J*= 8.8 Hz, 1H), 7.91 (d, *J*= 2.4Hz, 1H), 8.12 (dd, *J*= 8.0 Hz, 2.8 Hz, 1H); ^{13}C-NMR (101MHz, $CDCl_3$) δ 20.9, 22.0, 49.8, 122.7, 126.5, 126.8, 128.7, 130.4, 130.6, 134.4, 136.9, 137.3, 140.2, 142.1, 142.9, 146.7.

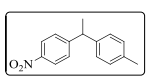


4.5.5 *Spectroscopic data for diarylethanes*

1-Methyl-4-(1-phenylethyl)benzene (3a) The reaction mixture was stirred for 50 min. viscous liquid; yield 91% (0.34 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (d, *J* = 7.2 Hz, 3H), 2.38 (s, 3H), 4.20 (q, *J* ~ 7.0 Hz, 1H), 7.16-7.19 (m, 5H), 7.29-7.30 (m, 2H), 7.33 - 7.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0, 21.9, 44.4, 125.9, 127.5, 127.6, 128.4, 129.1, 135.5, 143.5, 146.7; The other regioisomer (*ortho*) was also present in ~20% along with this sample.

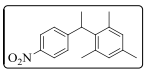


1-Methyl-4-(1-(4-nitrophenyl)ethyl)benzene(3b) The reaction mixture was stirred for 170 min. viscous liquid; yield 93% (0.37 g); Isolated as a mixture of regioisomer 67:33 (*p/o*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (d, *J* = 7.2 Hz, 3H), 1.66 (d, *J* = 7.2 Hz, 1.5H), 2.23 (s, 1.5 H), 2.35 (s, 3H), and 4.24 (q, *J* ~ 7.2 Hz, 1H), 4.44 (q, *J*= 7.2 Hz, 0.5H), 7.10-7.27 (m, 5H), 7.27-7.28 (m, 1H), 7.32 -7.34 (m, 1H), 7.38-7.40 (m, 2H), 8.14-8.17 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.7, 21.0, 21.6, 21.8, 41.1, 44.4, 123.7, 126.4, 126.6, 126.8, 127.4,



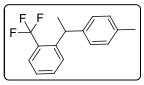
128.4, 128.5, 129.4, 130.7, 136.0, 136.3, 141.6, 142.2, 146.3, 154.1, 154.4. The other regioisomer (*ortho*) was also present in ~33% along with this sample.

1,3,5-Trimethyl-2-(1-(4-nitrophenyl)ethyl)benzene (3c): The reaction mixture was stirred for



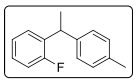
180 min. yellow solid; mp 172-174 ^{o}C; yield 94% (0.41 g); IR (KBr, cm^{-1}) 1523, 1448, 1344; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (d, *J* = 7.2 Hz, 3H), 2.15 (s, br, 6H), 2.32 (s, 3H), 4.72 (q, *J* ~ 7.2 Hz, 1H), 6.9 (s, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.9, 20.8, 21.1, 38.3, 123.4, 127.7, 130.3, 136.2, 136.3, 138.7, 145.9, 153.8.

1-(1-(*p*-Tolyl)ethyl)-2-(trifluoromethyl)benzene (3d). The reaction mixture was stirred for 120



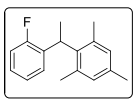
min. viscous liquid; yield 93% (0.37 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (d, *J* ~ 7.1 Hz, 3H), 2.40 (s, 3H), 4.71 (q, *J* ~ 7.0 Hz, 1H), 7.18-7.21 (m, 2H), 7.25-7.27 (m, 2H), 7.32-7.35 (m, 2H), 7.47-7.50 (m, 1H), 7.72 (d, *J* =8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0, 22.2, 39.1 (d, *J* =1.8 Hz), 125.6 (q, *J* = 5.9 Hz), 125.9, 126.5 (*J*= 35.0 Hz), 127.6, 127.1 (q, *J* = 259.1 Hz), 129.1, 129.8, 132.1, 135.8, 142.1, 146.5 (d, *J* = 1.3 Hz). Anal. Calcd. for $C_{16}H_{15}F_3$: C, 72.71; H, 5.72. Found: C, 72.15; H, 6.17; The other regioisomer (*ortho*) was also present in ~20% along with this sample.

1-Fluoro-2-(1-(*p*-tolyl)ethyl)benzene (3e). The reaction mixture was stirred for 150 min. viscous liquid; yield 91% (0.35 g);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (d, *J* = 7.2 Hz, 3H), 2.68



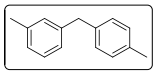
(s, 3H), 4.87 (q, *J* ~ 7.0 Hz, 1H), 7.34-7.40 (m, 2H), 7.42-7.50 (m, 3H), 7.54-7.69 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 21.3, 37.6 (d, *J*= 2.6 Hz), 115.7 (d, *J* = 22.5 Hz), 124.4 (d, *J* = 3.6 Hz), 126.4, 127.9 (d, *J* = 8.2 Hz), 128.8 (d, *J* = 4.5 Hz), 130.8, 133.9 (d, *J* = 14.4 Hz), 135.9, 142.4, 160.9 (d, *J* = 245.4 Hz). The other regioisomer (*ortho*) was also present in ~20% along with this sample.

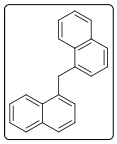
2-(1-(2-Fluorophenyl)ethyl)-1,3,5-trimethylbenzene (3f). The reaction mixture was stirred for

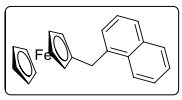


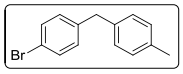
170 min. white solid; yield 93% (0.40 g); mp 98-100 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (d, *J* = 7.4 Hz, 3H), 2.53 (s, 6H), 2.58 (s, 3H), 5.08 (q, *J* = 7.3 Hz, 1H), 7.14 (s, 2H), 7.21-7.26 (m, 1H), 7.39-7.49 (m, 2H), 7.72-7.74 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.3, 21.0, 21.3, 21.35, 34.3 (d, *J* = 1.5 Hz), 115.5 (d, *J* = 1.5 Hz), 123.7 (d, *J* = 3.5 Hz), 127.7 (d, *J* = 8.2 Hz), 129.2 (d, *J* = 4.8 Hz), 130.5, 132.4 (d, *J* = 13.7 Hz), 135.6, 136.3 138.9, 61.8 (d, *J* = 245.2 Hz). Anal. Calcd. for $C_{17}H_{19}F$: C, 84.26; H, 7.90, Found: C, 84.38; H, 8.04.

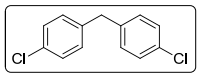
4.5.6 *Spectroscopic data for diarylmethanes*

1-Methyl-3-(4-methylbenzyl)benzene (4a) The reaction mixture was stirred for 8 min. viscous liquid; yield 88% (0.33 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 and 2.59 (s, 6H), 4.18 (s, 2H),  7.20-7.24 (m, 4H), 7.27-7.29 (m, 2H), 7.37-7.46 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.3, 21.7, 41.7, 126.2, 126.7, 126.9, 128.6, 129.9, 136.8, 138.5, 139.3, 140.5, 141.6; The other regioisomer (*ortho*) was also present in ~40% along with this sample.

Di(naphthalen-1-yl)methane (4b) The reaction mixture was stirred for 19 min. yield 85% (0.38  g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.9 (s, 2H), 7.13 (d, *J*= 7.1 Hz, 2H), 7.37-7.40 (m, 2H), 7.51-7.54 (m, 4H), 7.81 (d, *J*= 8.2 Hz, 2H), 7.94-7.96 (m, 2H), 8.07- 8.09 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.7, 123.9, 125.6, 125.7, 126.1, 127.1, 127.14, 128.8, 132.2, 133.8, 136.2.

(Naphthalen-1-ylmethyl)ferrocene (4c) The reaction mixture was stirred for 15 min. Orange  solid; mp: 98-100 ^{o}C; yield 80% (0.44 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (m, 2H), 4.17 (m, 2H), 4.19 (s, 5H),4.21(s, 2H), 7.29-7.3(m, 1H), 7.4-7.43(m,1H), 7.51-7.55(m, 2H), 7.74-7.76(m, 1H), 7.87-7.89(m, 1H), 8.12-8.14(m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 33.2, 67.1, 67.4, 68.8, 69.1, 123.9, 125.5, 125.54, 125.8, 126.1, 126.8, 128.7, 131.9, 133.7, 137.8. This compound was isolated with 90% purity.

1-Bromo-4-(4-methylbenzyl)benzene (4d) The reaction mixture was stirred for 12 min. viscous  liquid; yield 93% (0.37 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 4.01 (s, 2H), 7.16-7.19 (m, 4H), 7.25-7.31 (m, 2H), 7.50-7.53 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2, 41.0, 120.0, 126.8, 128.9, 130.0, 131.6, 136.7, 138.4, 140.6; The other regioisomer (*ortho*) was also present in ~40% along with this sample.

Bis(4-chlorophenyl)methane (4e). The reaction mixture was stirred for 18 min.viscous liquid; yield 93% (0.39 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 2H), 7.11-7.24 (m, 4H), 7.31-7.34 (m,  4H); other peaks at δ 4.10 (s), 7.16-7.21 (m), 7.38-7.43 (m) were observed for other isomer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 40.6, 128.7, 132.1, 139.1); peaks at δ 38.6, 126.9, 127.9, 129.7, 130.2, 130.9, 134.3, 138.1 were observed for other isomer. The other regioisomer (*ortho*) was also present in ~40% along with this sample

4.6 References

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Future Perspective

Future perspectives

The present thesis described the development of new convenient, inexpensive synthetic routes to access a wide range of biologically as well as synthetically important organophosphonates and phosphates.

The further scope of the first chapter will be to afford synthetically important novel anthracenyl phosphonates, *γ*-heteroaryl-substituted vinylphosphonates, di-heteroaryl phosphonates, and followed by Horner-Wadsworth-Emmons reactions towards the synthesis of tri or tetra-substituted dienes and 1,3-butadienes that are highly useful materials for polymer chemistry and molecular materials. In fact, these phosphonates are also capable to afford several new ketones *via* oxy-Wittig reactions.

A variety of sulphonamides can be explored for generating a wide range of sulphonamide phosphonates. The sulfonamide phosphonates and sulfonamide vinylphosphonates are already established as important molecules in various fields. Therefore, the related new molecules, synthesized herein, should be potential substrates for studying antibacterial, antifungal and corrosion inhibition properties.

The keto phosphonates will be good precursors in synthesizing phosphono-based heterocycles by using the keto functionality. One newly observed reaction as described will be explored to generate new type molecules by C-C bond cleavage reactions. Analogues of raspberry ketones can be synthesized using this strategy. The synthesized 1,3-diketones attached with extended π-conjugation will also serve as a completely new ligands for the chelation chemistry.

n-BuLi triggered route to generate organophosphates will also offer electronically and structurally diverse organophosphates by starting with wide variety of ketones and aldehydes. However, the reaction mechanism should be established in more details. These organophsphates are proved to be good substrates to generate polyarylated alkanes and these can be further utilized to generate molecules, having importance in material sciences.

Appendices

List of publications

1. **G. Pallikonda** and M. Chakravarty, $FeCl_3$-Mediated Arylation of α-Hydroxyphosphonates with Unactivated Arenes: Pseudo-umpolung in Allylic Phosphonates, ***Eur. J. Org. Chem.*** 2013, 944.
2. **G. Pallikonda** and M. Chakravarty, Triflic Acid Mediated Functionalization of α-Hydroxyphosphonates: Route for Sulfonamide Phosphonates, ***RSC Adv.*** 2013, **3**, 20503.
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4. **G. Pallikonda,** R. Santosh, S. Ghosal, M. Chakravarty, *n*-BuLi-Triggered Phospha-Brook Rearrangement: Efficient Synthesis of Organophosphates from Ketones and Aldehydes, ***Tetrahedron Lett.*** 2015, 56(24), 3796.
5. **G. Pallikonda,** S. Maloth, K. K. Satish, M. B. Z. Khalid, A. R. Kumar, S. Ghosal, M. Chakravarty. New ω-ketovinyl phosphonates: inexpensive synthesis, isomerization studies and route for functionalized 1,3-butadienes, ***Tetrahedron.*** 2015, 34, 5538.
6. C. B. Verma, A. Singh, **G. Pallikonda,** M. Chakravarty, M. A. Quraishi, I. Bahadur, E. E. Ebenso. Aryl sulfonamidomethylphosphonates as new class of green corrosion inhibitors for mild steel in 1 M HCl: Electrochemical, surface and quantum chemical investigation. ***J Mol. Liq***. 2015, 209, 306.
7. **G. Pallikonda** and Manab Chakravarty. Benzylic Phosphates as unexplored substrate for Friedel-Crafts Arylation: Time-Saving Approach to Diverse Polyarylated Alkanes **(**manuscript under review in ***The Journal of Organic Chemistry* (*JOC*)).**
8. M. B. Z. Khalid, **G. Pallikonda** R. N. P. Tulichala and Manab Chakravarty. oxy-Wittig Reactions of Newly Developed 1-Naphthyl(aryl)methylphosphonates: Synthesis of Naphthylarylketones (manuscript under review in ***Tetrahedron*)**.

List of papers presented in conferences

1. Recent Advances and Current Trends in chemical and Biological Sciences, held on 2-5th Mar, 2013, Udaipur, India
2. International Conference on Chemical Biology: Disease Mechanisms and Therapeutics (ICCB-2014) held 6-8th Feb, 2014 at CSIR-IICT, Hyderabad, India.
3. National Symposium on Human Diseases, held on 15-16th Mar, 2014, at BITS Pilani, Hyderabad Campus, Hyderabad, India.
4. 13th Eurasia Conference on Chemical Sciences held on 14-18th Dec, 2014 at Indian Institute of Science, Bangalore, India

BIOGRAPHY OF Gangaram Pallikonda

Mr. Gangaram Pallikonda completed his Bachelor of Science in Chemistry and Master of Science in Chemistry from Osmania University, Hyderabad, Telangana. He has about 3 years of experience in synthetic organic chemistry at Sapala Organics Pvt.Ltd, and Jubilant Chemsys, a contract research organizations in the field of drug discovery from 2008-2011. In 2011, he joined the department of chemistry, BITS Pilani-Hyderabad campus for his doctoral research under the supervision of Prof. Manab Chakravarty. During his doctoral study he received assistantship from a DST sponsored project and fellowship from BITS Pilani. He has published six scientific publications in well-renowned international journals and presented papers at various national and international conferences.

BIOGRAPHY OF THE SUPERVISOR

Prof. Manab Chakravarty was born in Hooghly, West Bengal. He completed his M. Sc. from Visva-Bharati University, Shantiniketan with the specialization in inorganic chemistry. By securing CSIR junior/senior research fellowship, he joined for his Ph.D. degree on organophosphonate chemistry from School of Chemistry, University of Hyderabad under the supervision of Prof. K. C. Kumara Swamy. After completing Ph. D. in 2007, he joined at Chembiotek Pvt. Ltd as a research associate for few months and then moved to department of chemistry, University of New Mexico, Albuquerque, New Mexico, USA for his postdoctoral studies with Prof. Robert T. Paine on synthesis of phosphorus based molecules that act as ligands for radioactive elements. Prof. Manab Chakravarty joined BITS Pilani, Hyderabad campus in 2010 as an assistant professor and promoted as associate professor in 2015. He has 13 years of research experience and 5 years of teaching experience. Currently, he is working with two Ph. D students in DST projects. He has completed one research project as PI sponsored by DST. Currently, he has two major projects from DST and UGC.