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

SYNOPSIS

Submitted in partial fulfilment

of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

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This thesis is divided into four different chapters and each chapter is subdivided into four parts: (a) Introduction (b) Literature survey (c) Results and Discussion and (d) Experimental Section. Compounds isolated in the present studies are, in general, characterized by mp, IR, NMR, elemental analyses (representative compounds) and mass spectra (LC-MS and HR-MS). Wherever feasible, X-ray crystal structures are determined. Summaries as well as references are compiled at the end of each chapter.

(i) Synthesis of *γ*-aryl substituted vinylphosphonates and dialkyl (diarylmethyl) phosphonates:

The **first chapter** of thesis describes a $FeCl_3$ mediated regio- and stereoselective Friedel-Craft-type arylation of *α*-hydroxy phosphonates with unactivated arenes. However, the unstable allylphosphonate cations generated in the reactions get stabilized by extended conjugations. It provides a simple, efficient and economical approach to highly demanding stereoselective *γ*-aryl substituted vinylphosphonates and dialkyl (diarylmethyl)phosphonates with good regioselectivity. These reactions proceed under mild conditions, and can operate in the absence of any additional solvent.

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.

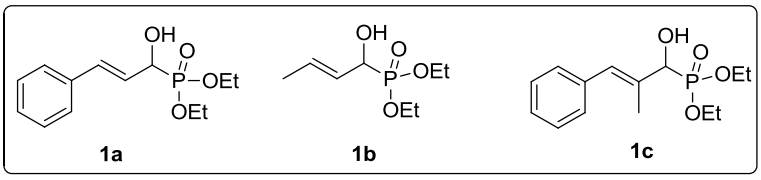
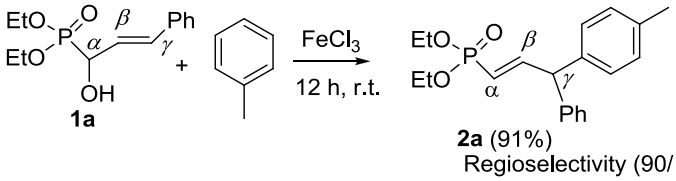


Fig 1 Hydroxyphosphonates used as starting materiels

For our initial studies, allylphosphonate **1a** (Fig 1) was chosen as it is a very stable crystalline and easily accessible inexpensive material. 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) in ~70% isolated yield at room temperature (rt). 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 to obtain compound **2a** (Scheme 1) in good yields. A control experiment (without using any metals) was failed to undergo this reaction. With the consideration of cost and accessibility, screening of several Lewis acids and Brønsted acids revealed that $FeCl_3$ is the best for this reaction under the present circumstances. we needed one equivalent of $FeCl_3$ for the completion of this reaction (Scheme 1) to facilitate the leaving of the hydroxyl group.



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

The reactions were very clean and almost quantitative conversions were observed by NMR (both ^{1}H and ^{31}P) even before purifications. 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 in the reactivities of allylic phosphonates. Interestingly, based on the literature report, the replacement of phosphonyl group with phenyl leads to a disproportionation reaction of the allylic alcohol. There was no arylation observed under the same reaction conditions. It demonstrates the different electronic, steric and conjugation effects of phosphonyl group compared to phenyl group and that make the phosphonate chemistry considerably rich.

Furthermore, we have confirmed the stereochemistry for the product **2a** by using an analogous solid compound **3** that was prepared by starting with (±)-(*E*)-$(OCH_2CMe_2CH_2O)P(O)CH(OH)CH=CHPh$ in a manner similar to the preparation of **2a**. The X-ray crystallographic studies for a crystal obtained from dichloromethane (DCM)/hexane solution of compound **3** showed the (*E*)-configuration (Fig 2).

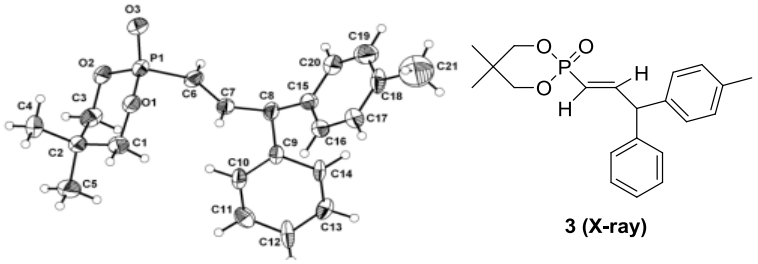


Fig 2 Molecular and ORTEP diagram (with 20% probability label) for compound **3**

Next, we studied the reactions with different unactivated arenes that gave the expected products **2a-n** in good yields and regioselectivities (Fig 3).

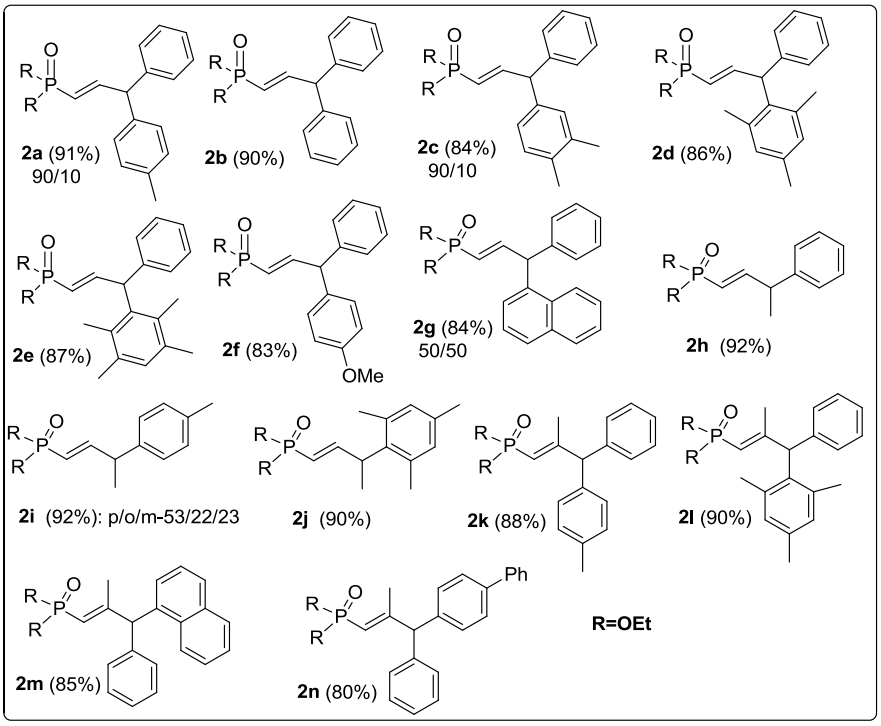


Fig 3 Synthesized γ- aryl substituted vinylphosphonates **2a-n**

The reactions with toluene and benzene underwent at rt, 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. Compounds **2h** and **2i** were also synthesized in high yields by using the inexpensive allylphosphonate **1b.** It is interesting to observe that the only one methyl group stabilizes the cation sufficiently.

Moreover, we also explored the scope of these $FeCl_3$-mediated arylation reactions with different hydroxy phosphonates (Fig 4) which afforded diethyl (diarylmethyl)phosphonates **5a-n** (Fig 5) in good yield with excellent regioselectivity under the mild conditions.

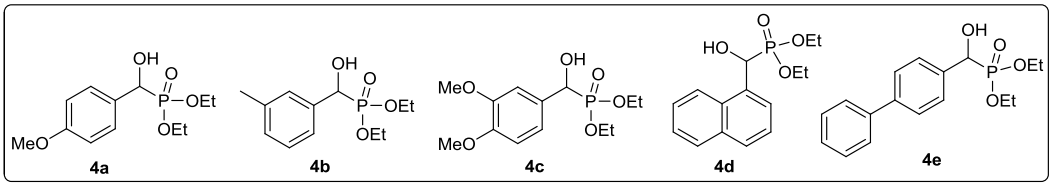


Fig 4 Hydroxyphosphonates used as starting materiels

As expected, the aryl groups for phosphonates should be attached with electron donating substituents which stabilize the carbocations and make a smooth progress for the reactions.

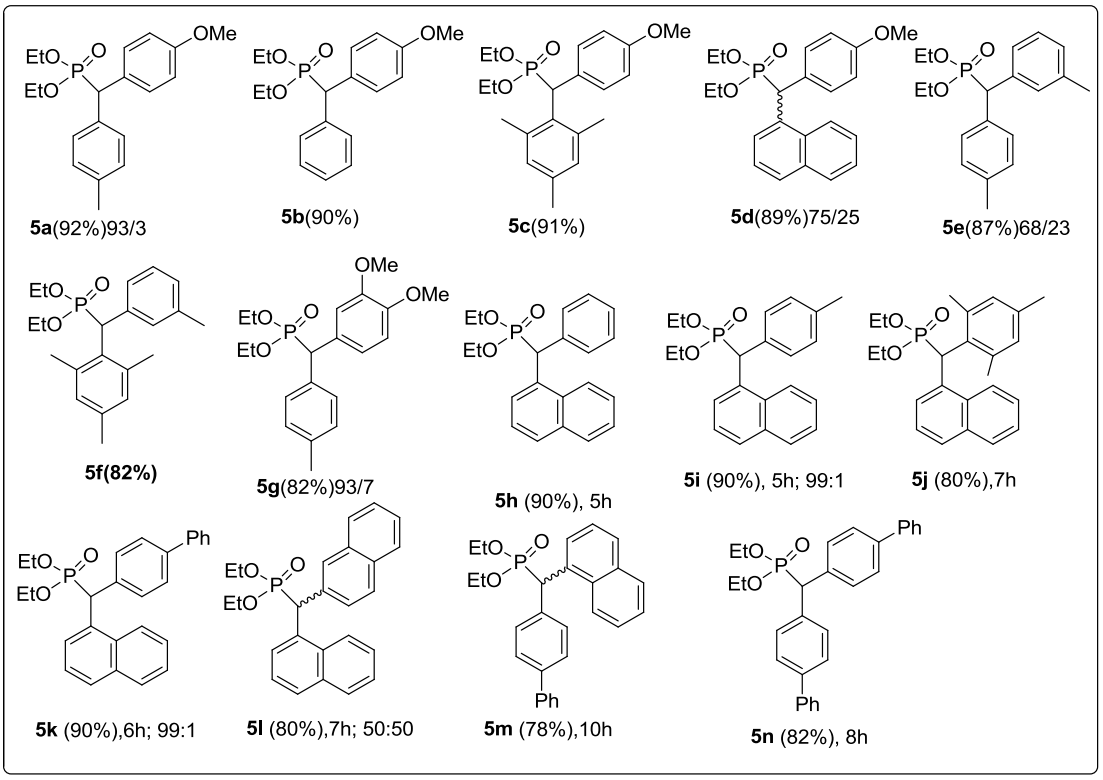
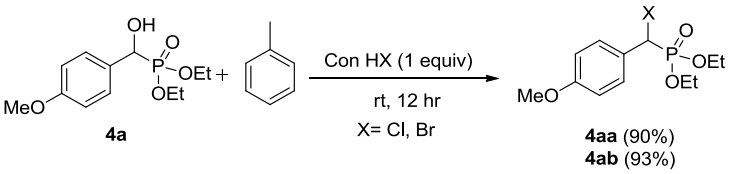


Fig 5 Synthesized diethyl (diarylmethyl)phosphonates

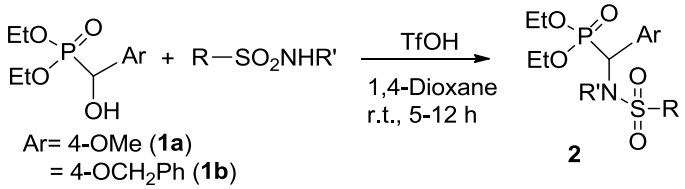
Surprisingly, as a replacement of $FeCl_3$, hydrochloric acid (HCl) produced diethyl (chloro(4-methoxyphenyl)methyl)phosphonate (**4aa**,) for the reaction of arenes with hydroxyphosphonates (**4a**). With this observation, we investigated the reaction of **4a** with hydrochloric acid (HCl) in the presence of dichloethane as solvent at room temp and the same product **4aa** was obtained almost quantitatively after 12 hr (Scheme 2).



Scheme 2 Synthesis of α-halophosphonates

(ii) Synthesis of α-Sulfonamidephosphonates:

The **second chapter** of thesis describes an operationally simple synthetic method for (±)-α-aryl/methylsulfonamidomethylphosphonates and new (±)-γ-aryl/methyl sulfonamidomethylvinylphosphonates through straightforward reactions of (±)-α-hydroxyphosphonates with sulfonamides in the presence of triflic acid (TfOH) under *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.



Initially, phosphonate (±)**-1a** and *p*-toluenesulfonamide ($TsNH_2$) were preferred as model substrates to optimize the suitable reaction conditions using different Lewis and Brønsted acids. Moreover, TfOH and its salts are extensively used for amination reactions of alcohols. 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**. 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.

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 Fig 6. 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 when comparatively more electron rich *N*-butylsulfonamide was used.

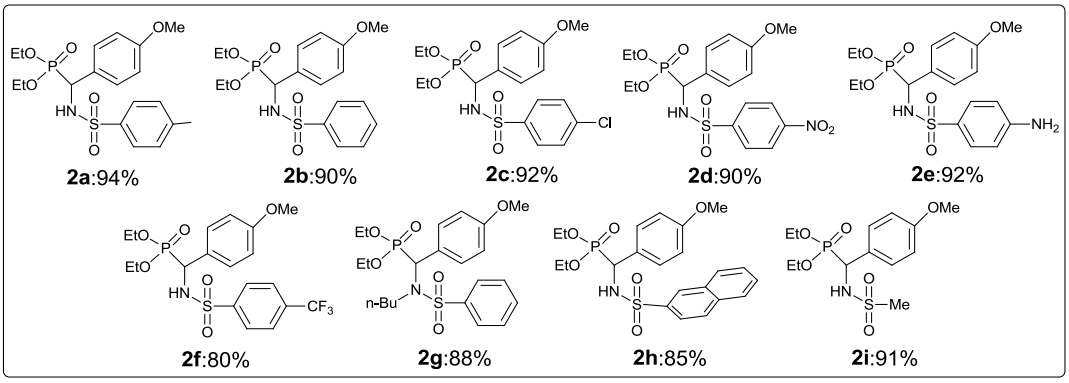
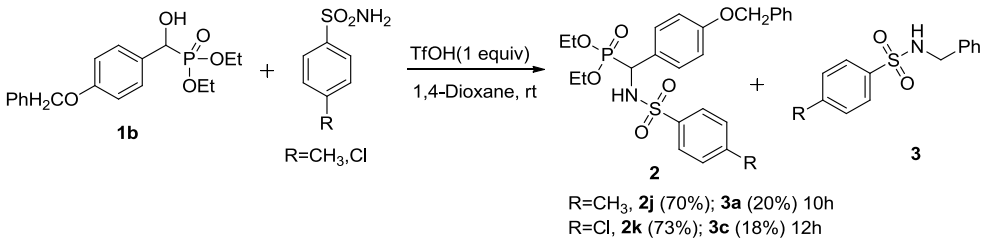


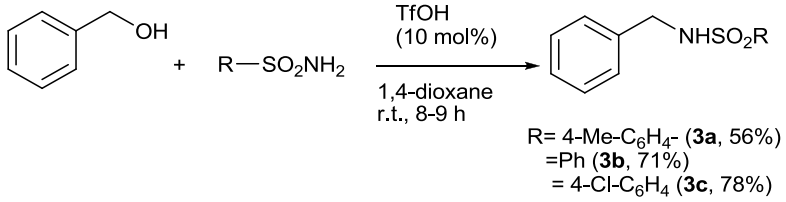
Fig 6 Synthesized α-sulfonamidephosphonates

Notably, the yield was relatively poor in case of phosphonate (±)-**1b**. Interestingly, along with the expected compound (**2j**), the synthetically useful sulfonamide (**3a**, Scheme 3) was isolated from the reaction mixture of (±)-**1b** and $TsNH_2$.



Scheme 3 Synthesized α-sulfonamidephosphonates (**2j-k**)

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. A separate treatment of benzyl alcohol with sulfonamides afforded compounds **3a-c** in a moderate to good yield in the presence of catalytic amount of TfOH (10 mol%) at room temperature using 1,4-dioxane as solvent (Scheme 4).



Scheme 4 TfOH catalyzed sulfonamidation of benzyl alcohol

Synthesis of (±)-γ-aryl/methyl sulfonamidovinylphosphonates

Further, we have extended our studies to synthesize new sulfonamide phosphonates(±)-(*E*)-**5a-g** regio- and stereoselectively (Fig 7) where the sulfonamide is attached to a γ-carbon of a vinylphosphonate by choosing the easily-accessible cheap phosphonates (±)-(*E*)-allylic hydroxyl phosphonates.

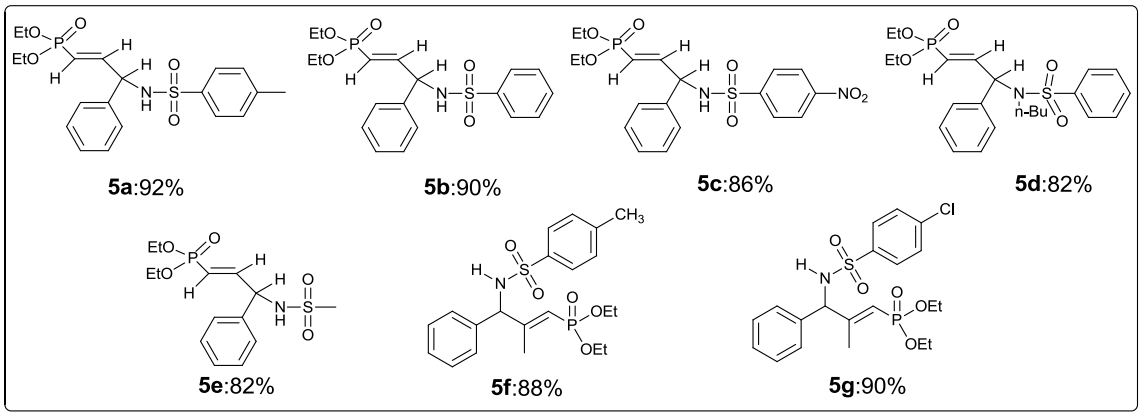
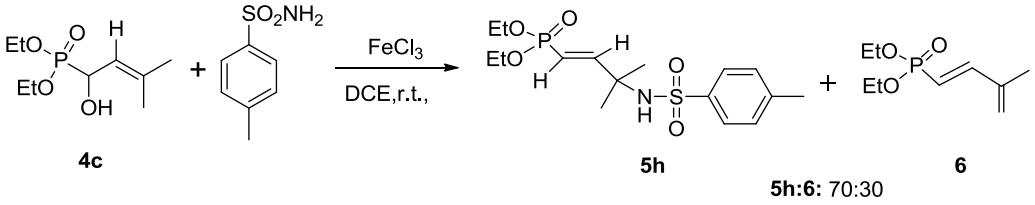


Fig 7 Synthesized (±)-γ-aryl/methyl sulfonamidovinylphosphonates

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. 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 (Scheme 5). 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. The formation of dienes could not be avoided even when the reaction was performed at -30 ^{o}C.



Scheme 5 Ferric chloride mediated synthesis of *γ*-Sulfonamide vinylphosphonates and 1,3-diene

(iii) Synthesis of *γ*-ketophosphonates:

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-ketophosphonate with phenol functionality at *α*- position (structural analogue of raspberry ketone, a natural product) has also been presented.

In this study, *α*-hydroxyphosphonates (**1a-e,** Fig **8)** and commercially available 1,3-diketones (**2a-d**, Fig **8**) were preferred with a consideration of accessibility, structural reactivity and diversity.

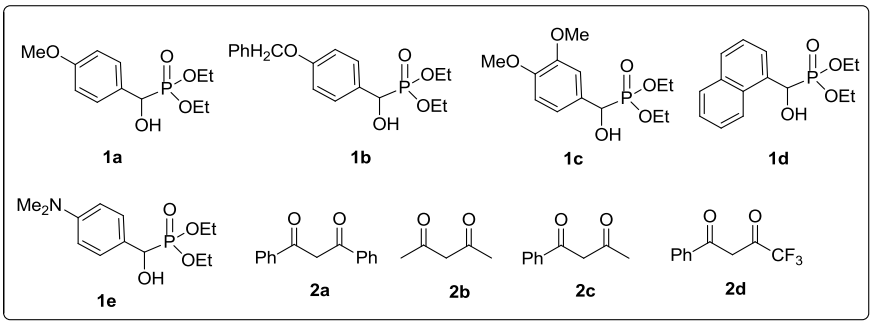
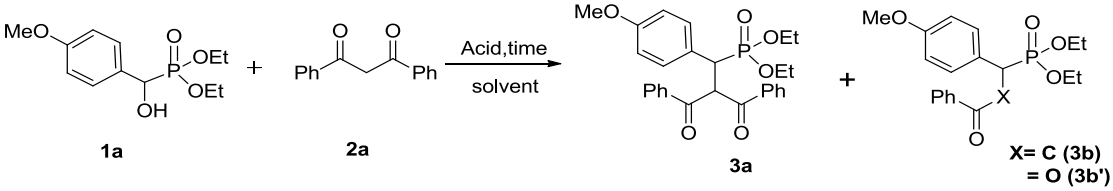


Fig 8 The hydroxyphosphonates and 1, 3-diketones used as precursors

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.

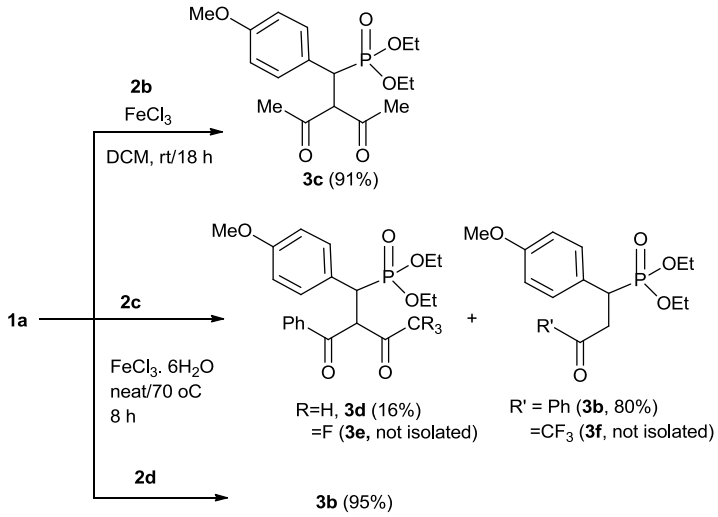


Scheme 6 Reactions of 1a with 2a under different reaction conditions

It was found that the acids, solvent and temperature affect the product ratio (**3a**:**3b**) significantly. Brønsted acids such as triflic acid (TfOH) and *p*-toluenesulfonic acid (p-TSA) were also quite effective for this reaction but are not much explored herein.

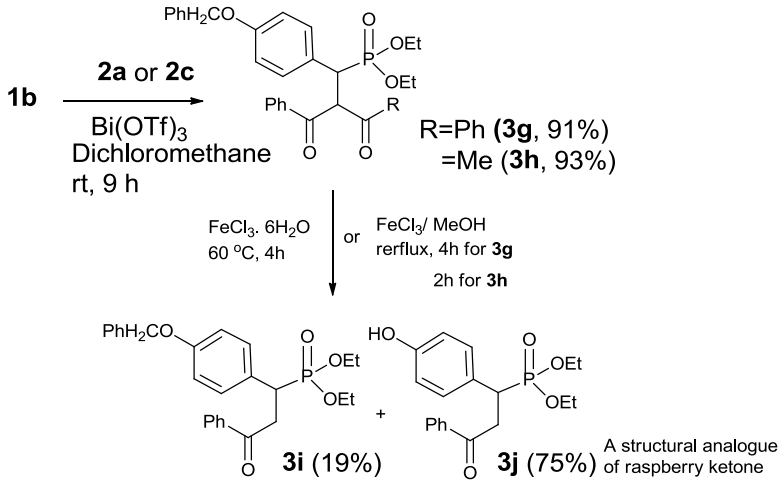
The results shown $FeCl_3$ and $FeCl_3.6H_2O$ incited us to perform the reaction using anhydrous $FeCl_3$ with two drops of water (0.08 ml) and that showed the consumption of both starting materials within 1 h at 90 ^{o}C to form compound **3a**. After 8h, **3a**/**3b** was isolated as a mixture in 1/3 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. 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**. The only phosphonylated 1,3-diketone (γ-ketophosphonate **3c**, Scheme 7) was obtained from the reaction of **2b** with **1a** at room temperature (28 ^oC) in dichloromethane (DCM) in the presence of anhydrous $FeCl_3$. No C-C bond cleaved product was obtained from **3c** even after repeated efforts under different reaction conditions. 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 (Scheme 6). Although phosphonylated diketone **3d** was isolated in 16% yield from the reaction with **2c** but compound of type **3e** (Scheme 6, expected from **2d**) could not be isolated. 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 $FeCl_3$. 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 7 Reaction of diketones **2b-d** with the *α*-hydroxyphosphonate **1a**

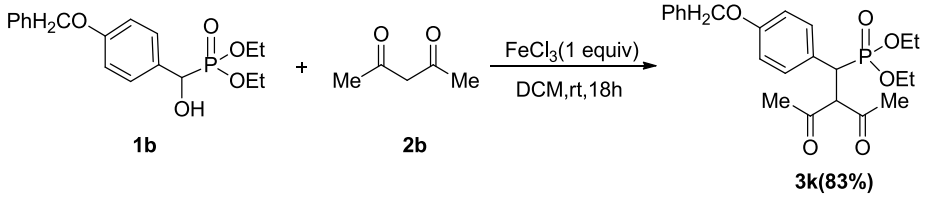
The phosphonate **1b** generated a mixture of products (of type **3g, 3i** and **3j**; Scheme 7) from reactions with **2a** or **2c** under the same reaction conditions ($FeCl_3.6H_2O$, 8h, 70 ^oC). Attempt to use anhydrous $FeCl_3$ under neat conditions at 70 ^oC or in nitromethane at 28 ^oC also led to the same result. Gratifyingly, the use of $Bi(OTf)_3$ as a Lewis acid produced the 1,3-diketones **3g-h** in >90% yield (Scheme 8). 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 8 $Bi(OTf)_3$ mediated reaction of **1b** with 1,3-diketones **2a** or **2c**

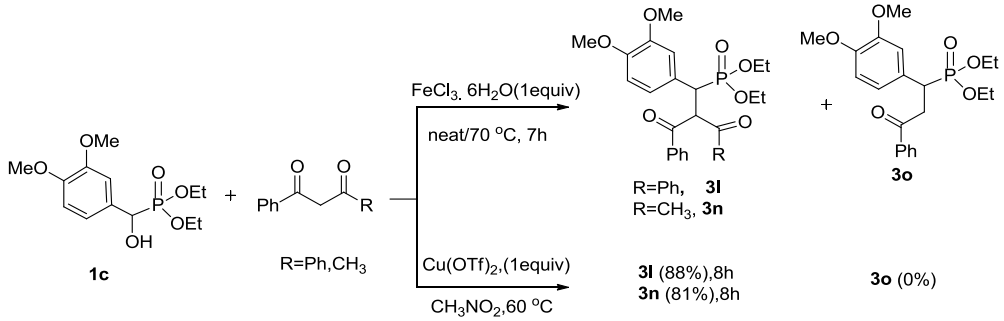
Compound **3h** was found to be more reactive compared to **3g** in terms of the C-C bond cleavage reaction. In this approach, *phenol functionality at α-carbon of γ-ketophosphonate* has been easily introduced by starting with **1b**. This ketone (**3j**) is a structural analogue of *raspberry ketone*, a low-abundant natural product that contains a phenolic group.

The phosphonylated 1,3-diketone (**3k**,) was synthesised from reaction of phosphonate (**1b)** with acetylacetone (**2b**) by using anhydrous $FeCl_3$ in dichloromethane (Scheme 9).



Scheme 9 Acid mediated synthetic route for γ-diketophosphonate(**3k**)

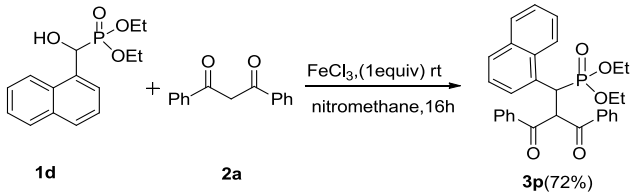
The ^{31}P NMR spectrum for the reaction mixture of Fe(III)-mediated reaction of phosphonate **1c** with 1,3-diketone **2c** showed the presence of two products that include phosphonylated 1,3-diketone **3n (**~82% with a diastereomeric ratio 1:4) and monoketone **3o** (18%). It was difficult to isolate these products in pure form. However, to our delight, use of $Cu(OTf)_2$ as a Lewis acid was successful to produce **3n** in high yiled. The monoketone **3o** could also be obtained by using **1c** and **2d** in the presence of $FeCl_3.6H_2O$. Again $Cu(OTf)_2$ worked well for synthesising phosphonylated diketone **3l** (Scheme 10).



Scheme 10 Acid mediated synthetic route for γ –di and monoketophosphonates

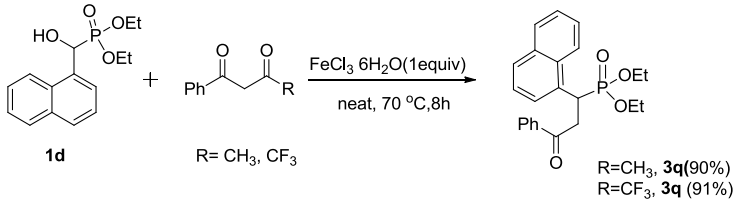
Naphthalene based α-hydroxyphosphonate **1d** gave a fruitful result with the reactions of 1,3-diketones (**2a-d)** to afford γ-ketophosphonates **3p** and **3q** in excellent yield using Fe(III) as Lewis acid. When the reaction between phosphonate **1d** and 1,3-diketone **2a** was

performed using $FeCl_3.6H_2O$ under neat conditions at 70 ^oC, 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. The diketone **3p** was isolated in 72% yield by using anhydrous $FeCl_3$ in nitromethane after 16 h.



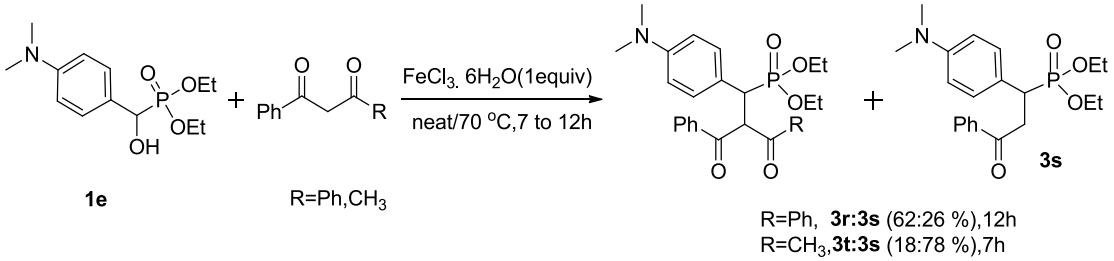
Scheme 11 Acid mediated synthetic route for γ –diketophosphonate(**3p**)

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



Scheme 12 Acid mediated synthetic route for γ –monoketophosphonate(**3q**)

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 ^oC 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** in 18% and 78% yields, respectively. Only phosphonylated monoketone **3s** was isolated when 1,3-diketone **2d** was used for the reaction.



Scheme 13 Acid mediated synthetic route for γ –di and monoketophosphonates(**3r,3t&3s**)

Synthesis of ω-ketovinyl phosphonates and its applications

This chapter also includes the 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 phosphonate with aromatic 1,3-diketones. Predominantly, $FeCl_3$ or $FeCl_3.6H_2O$ has been preferred as easily-available and efficient Lewis acid under solvent-free conditions.

Considering the availability, cost and reactivity, we have selected the allylic hydroxy phosphonates **11a-d** and aromatic 1,3-diketones **12a-d** (Fig 9) for the current studies.

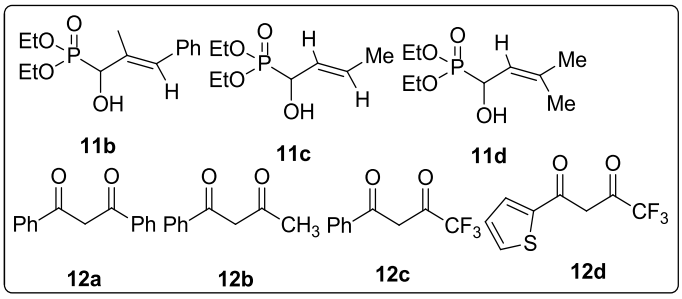
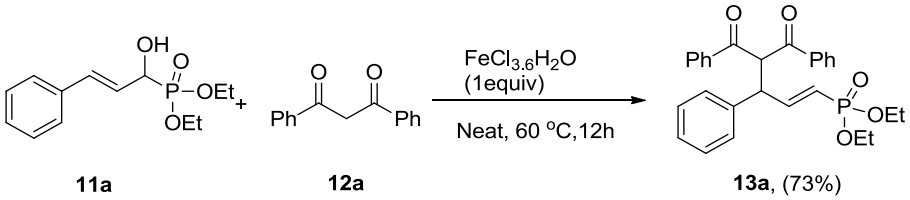


Fig 9 The hydroxyphosphonates and 1, 3-diketones used as precursors

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. 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 14). In fact, the reaction was more satisfactory under solvent-free conditions upon heating at 60-70 ^oC.



Scheme 14 Acid mediated synthetic route for ω –ketovinylphosphonate(**13a**)

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. 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. The newly synthesized ω-ketovinyl phosphonates **13b-i** are listed in Fig 10.

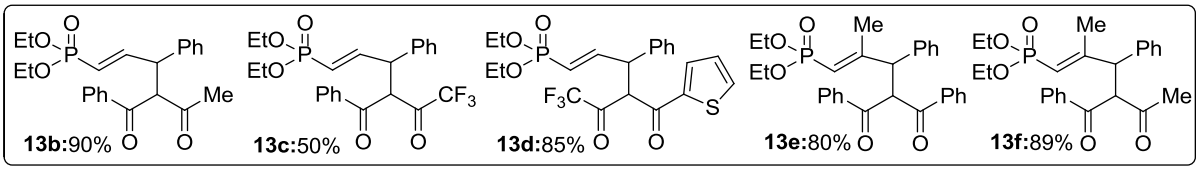
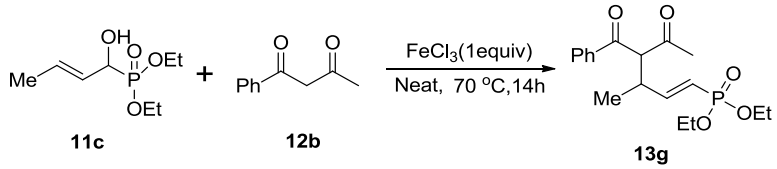


Fig 10 Synthesized ω-ketovinyl phosphonates

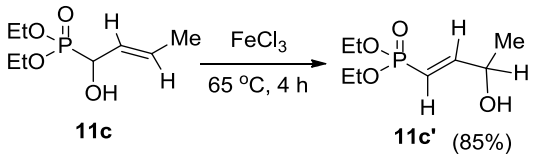
The compound **13b** was formed as 1:1 diastereomeric mixture from the reaction of **11a** and **12b**. We could isolate one of the diastereomers in pure isomeric form and the other diastereomer was separated only with ~80% pure isomeric form. Both *p*-TSA and $FeCl_3.6H_2O$ worked satisfactorily to generate compound **13b** in high yield. The 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 $FeCl_3.6H_2O$. The phosphonate **11b** furnished very promising result to obtain **13e** as single isomer and **13f** as mixture of diastereomers (1:1) from the reactions with **12a** and **12b,** respectively.

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.



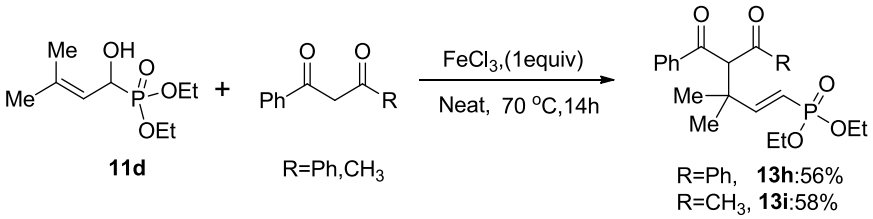
Scheme 15 Acid mediated synthetic route for ω –ketovinylphosphonate(**13g**)

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 16).



Scheme 16 Isomerization of α-hydroxy allylphosphonate to γ-hydroxy vinylphosphonate

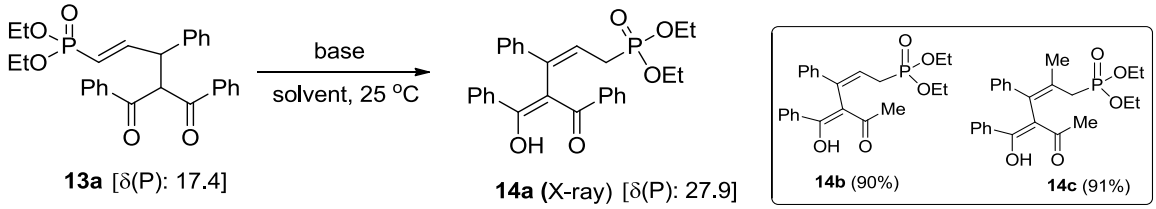
The reaction of **11d** with **12a-b** could afford the expected compounds **13h-i** respectively, in pure form with moderate yields (Scheme 17).



Scheme 17 Acid mediated synthetic route for ω –ketovinylphosphonate(**13h & 13i**)

Isomerization studies of ω-ketovinyl phosphonates

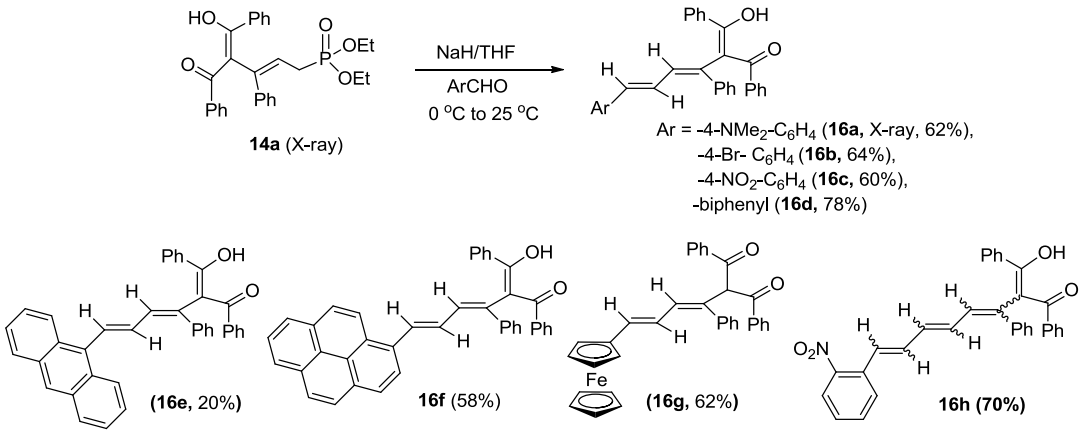
We have explored the isomerization reaction of ω-ketovinyl phosphonate **13a** to ω-ketoallyl phosphonate **14a** under different reaction conditions. Surprisingly, a much weaker base K_2CO_3 has been proved to be suitable to generate the desired products (**14a-c**) in the presence of tetrahydrofuran (THF) or DMSO as solvent (Scheme 18). 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.



Scheme 18 Isomerization of ω-ketovinylphosphonate to ω-ketoallylphosphonate

Route for 1,3-diketone functionalized conjugated 1,3-butadiene using 14a

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-h** (Scheme 19).



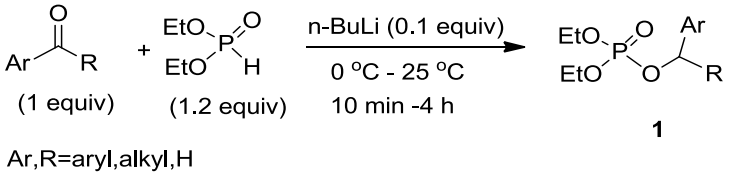
Scheme 19 Intermolecular HWE reactions of **14a** to obtain the functionalized 1,3-butadienes

The reactions were straightforward in the presence of inexpensive base NaH at room temperature for 10-14 h by using tetrahydrofuran as solvent.

(iv) Synthesis of organophosphates and its applications

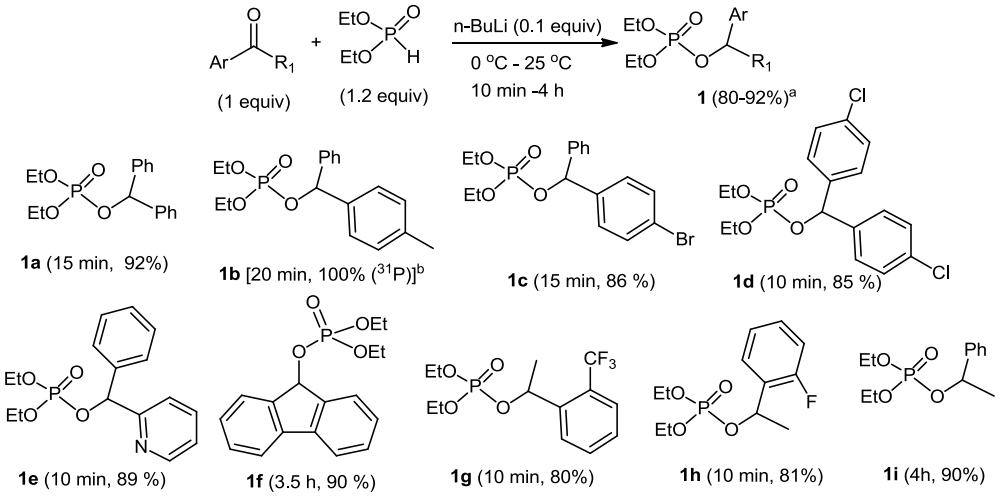
The **fourth chapter** of the thesis focuses on the synthesis of organophosphates from *n*-BuLi-triggered, (additional) solvent–free reactions of diethyl phosphite with both activated/unactivated ketones and aldehydes preferably at room temperature *via* phospha-Brook rearrangement. We could successfully synthesize the naphthylic/allylic phosphates using this approach.

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 (Scheme 20).



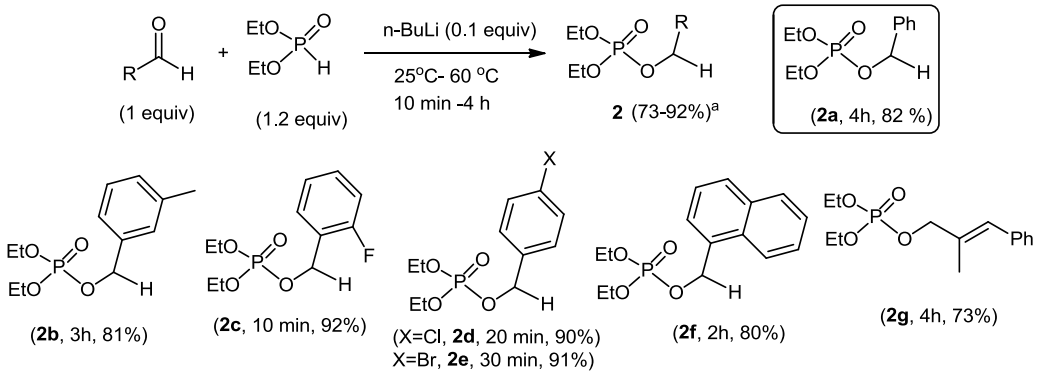
Scheme 20 *n*-BuLi catalyzed synthesis of organophosphates

As ketones were proved earlier to be less reactive in phosphate formation, we initiated our studies with easily available, cheap benzophenone and diethyl phosphite to optimize the reaction conditions by varying different bases. 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 21.



Scheme 21 Synthesis of phosphates from the reactions of ketones and diethyl phosphite [a]yields refer to chromatographically purified products. [b]yield is calculated based on $^{31}P/^{1}H$ NMR of the reaction mixture.

Aldehydes also generated the corresponding phosphates **2a-g** (Scheme 22) efficiently as expected. 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 °C.



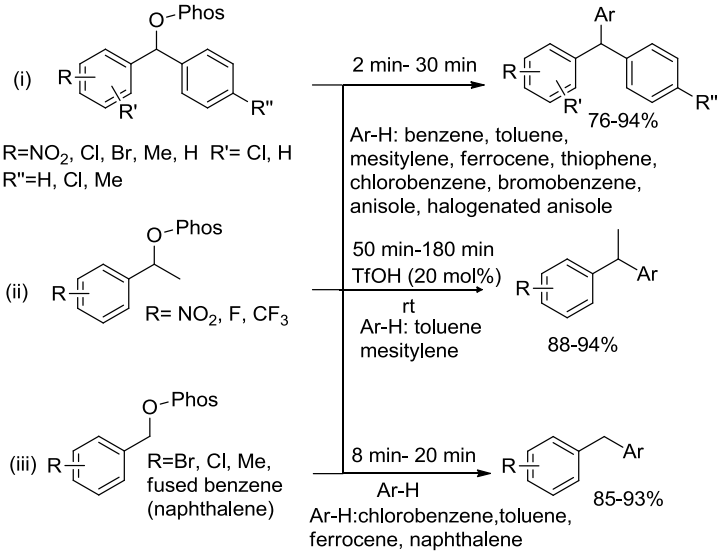
Scheme 22 Synthesis of phosphates from the reactions of aldehydes and diethyl phosphite [a]yields refer to chromatographically purified products.

Application of these phosphates to access polyarylated alkanes

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.

We synthesized 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 (Scheme 23-i) predominantly, along with diarylethanes (Scheme 23-ii) and diarylmethanes (Scheme 23-iii) at rt within short duration using *only 1.2 equiv* of both activated or unactivated arenes.



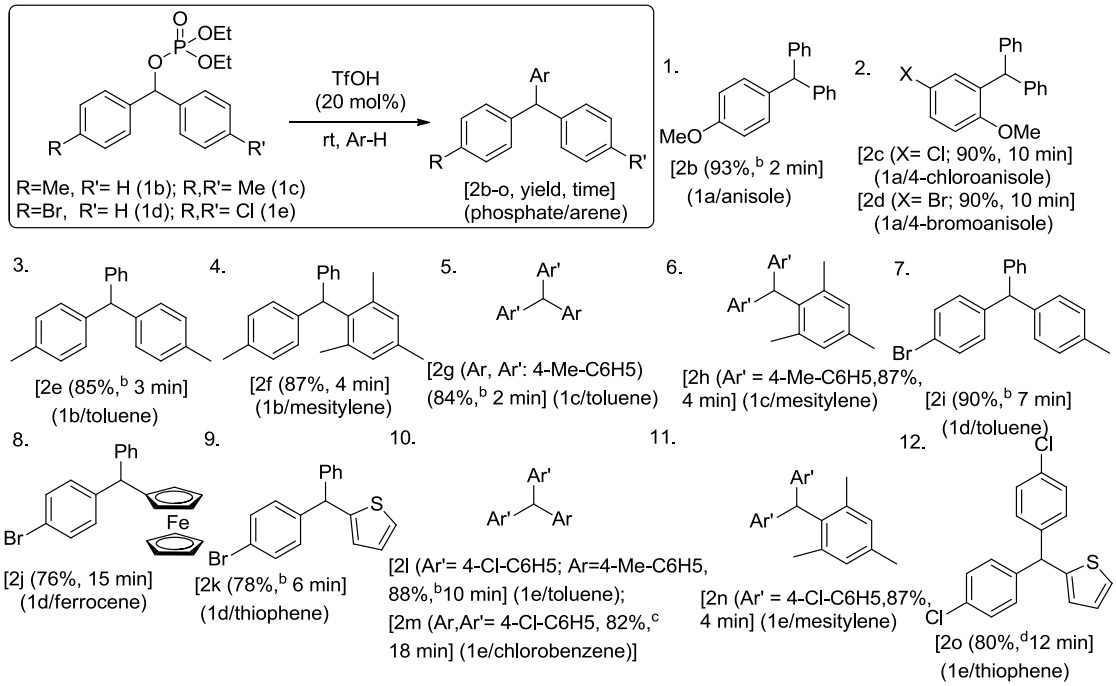
Scheme 23 Phosphates in FC arylation reactions using TfOH (20 mol%) at rt to afford polyarylated alkanes. Phos: $P(O)(OEt)_2$

More importantly, this route can also afford electron-poor polyarylated methanes efficiently, which is not an expected outcome from traditional FC arylation reactions. Thus, one of the major drawbacks on synthesis of elctron-deficient polyarylated alkanes *via* FC route has been circumvented using these phosphates as a source of electrophiles *at rt.* Further, we are able to make the process much cleaner, economical and less cumbersome by using catalytic amount of Trilic acid (TfOH) instead of commonly used metal chlorides as an activator.

Being primarily interested on demanding 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 **2a** under key reaction parameters such as variety of acid catalysts in different quantities and reaction times. As the formation of desired compound was satisfactory at rt, we could avoid the need of excess volatile arenes. Although there were many choices for the selection of Lewis or protic acids, the catalytic amount of TfOH (20 mol%,) 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 for this reaction

Phosphate **1a** reacted admirably with both activated anisole as well as non-activated halogenated anisoles to synthesize functionalized triarylmethanes **2b-d** in excellent yields and regioselectivity within 2-10 min. 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 tend to form diarylalcohols or ethers during the purification through column chromatography (SiO_2).

Table 2: List of triarylmehanes synthesized using phosphates

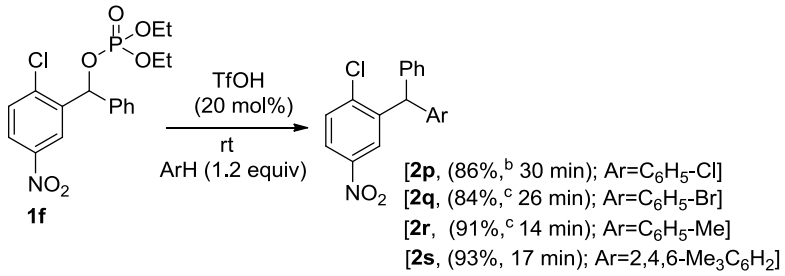


[a]reaction conditions: **1** (1 equiv), ArH (1.2 equiv); only for **2j**, dichloroethane [DCE] (3 mL) was used. regioisomeric ratio determined by ^{1}H NMR [b] ~85:15; [c]75:25; [d]90:10.

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

Further, we have extended the scope of this route by using stable phosphates **1d-e** (bearing weakly deactivated haloarenes) where arylation of **1d** afforded the synthetically unexplored triarylmethanes **2i-k** satisfactorily and electronically diverse triarylmethanes **2l-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 **2j-k** and **2o**, respectively. It is pertinent to note that being weakly inactive groups, syntheses of such electronically deactivated triarylmethanes **2i-o** are considerably challenging using traditional FC route.

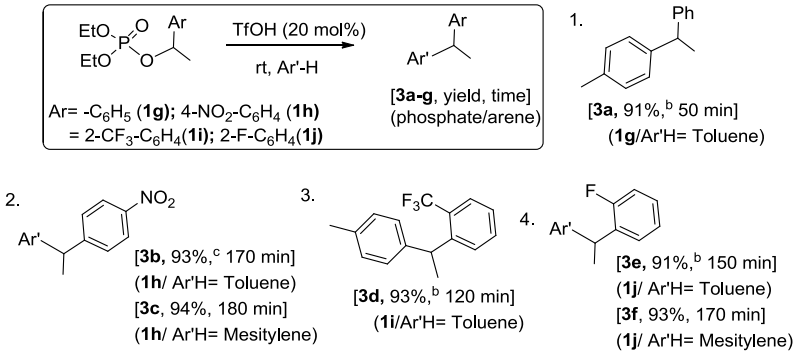
With this success, we next concentrated on the synthesis of much electron-poorer unsymmetrical triarylmethanes under these reaction conditions. In that context, the arylation reactions of inexpensive elctron-poor phosphate **1f** with chloro- and bromobenzene (unsuited for FC arylation) afforded desired functionalized triarylmethanes **2p-q** within 30 min (scheme 24). In a similar fashion, the other related products **2r-s** (Scheme 24) were successfully accomplished in excellent quantity as expected. These highly functionalized unsymmetrical triarylmethanes **2p-s** are completely new and challeging to acheive within this short reaction time at rt. 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 24 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

As synthesis of diarylethane from Pd-catalyzed cross coupling reaction of **1g** with $PhB(OH)_2$ was unsucessful, 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.

Table 3: List of diarylethanes synthesized using phosphates[a]



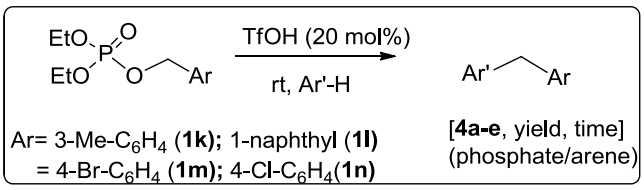
[a]reaction conditions: 1 (1 equiv), Ar'H (1.2 equiv); regioisomeric ratio (determined by ^{1}H NMR) [b] ~80:20; [c] 67:33

To our delight, the expected diarylethanes **3a-f** [Table 3] were generated appreciably at rt although the reaction time in this case was somewhat longer (50-180 min). 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]. 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.

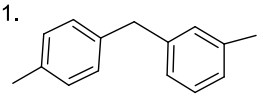
Although the synthesis of diarylmethanes are very well established, we planned to examine the approachability of diarylmethanes using few limited primary benzylic phosphates **1k-n** under these reaction conditions. The diarylmethanes bearing weakly activated (**4a-c**) and deactivated (**4d-e**) benzene rings were conveniently synthesized at rt within 8-15 min (Table 4) 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 and inspired by these outcomes, useful *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.

Table 4: List of diarylmethanes synthesized using phosphates[a]

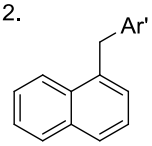


1.



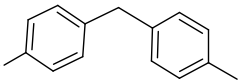
[**4a,** 88%,[b] 8 min]
(**1k**/Ar'H=Toluene)

2.



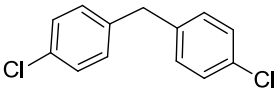
[**4b,** 85%,[c] 19 min]
(**1l**/ Ar'H= Naphthalene)
[**4c**, 80%, 15 min]
(**1l**/ Ar'H= Ferrocene)

3.



[**4d,** 93%,[b] 12 min]
(**1m**/Ar'H=Toluene)

4.



[**4e,** 93%,[b] 18 min]
(**1n**/Ar'H= Chlorobenzene)

[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.