SYNTHETIC STUDIES ON ORGANOPHOSPHONATES AND 9-CHLOROACRIDINES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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INDIA

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PART B

SYNTHETIC STUDIES ON 9-CHLOROACRIDINES

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of Prof. K. C. Kumara Swamy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Hyderabad

July 2010

Venu Srinivas

CERTIFICATE

This is to certify that the work described in this thesis entitled "*Synthetic Studies on Organophosphonates and 9-Chloroacridines*" has been carried out by Mr. Venu Srinivas, under my supervision and the same has not been submitted elsewhere for any degree.

Hyderabad

July 2010

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(Thesis supervisor)

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Venu Srinivas

LIST OF PUBLICATIONS

From the thesis work

1. Facile formation of phosphono-acridanes *via* chloroacridines
Venu Srinivas and K. C. Kumara Swamy*****.
ARKIVOC **2009**, *(xii),* 31.

2. Catalyst-free and Catalyzed Hydrophosphonylation/ Hydrophosphinylation of Phosphorylated Allenes/Alkynes and Allenyl/Alkynyl Phosphine Oxides: Use of a Robust, Recoverable Dinuclear Pd(I) Catalyst
Venu Srinivas, E. Balaraman, K. V. Sajna, and K. C. Kumara Swamy***.**
(*Submitted for publication*)

3. To stay as an allene or go further? Novel phosphonate-heterocycles *via* chlorophosphites and progargyl alcohols.
Venu Srinivas, K. V. Sajna, and K. C. Kumara Swamy *(to be communicated)*

4. $Zn(OTf)_2$/amine catalyzed addition-cyclization reactions involving propargyl alcohols and allenyl phosphine oxides leading to phosphino-furans.
Venu Srinivas and K. C. Kumara Swamy***** (*to be communicated)*

From the work not reported in the thesis

5. New-Anthracenyl-Substituted Phosphonates: Synthesis and Utility
K. C. Kumara Swamy*****, **Venu Srinivas**, K. V. P. Pavan Kumar and K. Praveen Kumar
Synthesis **2007**, 893.

6. Spiro- and Tricyclic Phosphoranes with Six- and Higher-Membered Rings
K. C. Kumara Swamy*****, M. Phani Pavan, **Venu Srinivas**
Top. Heterocycl. Chem. (2009), 20, pp: 99-145 (Book Chapter)

7. Hydrophosphonylation of activated alkenes and alkynes *via* fluoride ion activation in ionic liquid medium
E. Balaraman, **Venu Srinivas** and K. C. Kumara Swamy*****
Tetrahedron **2009**, *65*, 7603.

8. Efficient Water Mediated Pd-Catalyzed Double Arylation of Phosphonoalkynes and Diaryl-alkynes-Use of a Dinuclear Pd(I) Catalyst
K. V. Sajna, **Venu Srinivas** and K. C. Kumara Swamy***** *(Submitted for publication)*

Papers presented in symposia

1. New Anthracenyl Substituted phosphonates: Synthesis and Utility.
   K. C. Kumara Swamy*****, **Venu Srinivas**, K. V. P. Pavan Kumar and K. Praveen Kumar.
   9th National Symposium in Chemistry, University of Delhi, Delhi. INDIA, Jan' 31-Feb' 5, **2007**.
2. New Anthracenyl Substituted phosphonates: Synthesis and Utility.
   K. C. Kumara Swamy*****, **Venu Srinivas**, K. V. P. Pavan Kumar and K. Praveen Kumar.
   *Chemfest-**2007**,* School of Chemistry, University of Hyderabad, February-2007.

3. Double Phosphonylation of 9-Chloroacridines: A Novel Synthetic Route to Bisphosphonates (9,9-Bisphosphono-10-hydro-Acridane derivatives
Venu Srinivas and K. C. Kumara Swamy*
Presented in 5th Singapore-India Collaborative Cooperative Chemistry Symposium, School of Chemistry, University of Hyderabad, February 20-21, 2009. (**Oral presentation**).

4. Cu(II)-Catalyzed Michael Addition of 1,3-Diones to Alkylidene Malonates
   Venu Srinivas and K. C. Kumara Swamy*
   *Chemfest-**2009**,* School of Chemistry, University of Hyderabad, March 7-9, 2009. **(Oral Presentation)**.

Synopsis

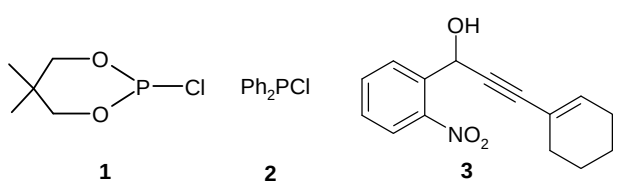
This thesis is divided into two parts: **Part-A** and **Part-B**. **Part-A** deals with (a) synthesis of novel phosphorus-containing dibenzo-azepines and *N*-hydroxy indolinone derivatives, (b) catalytic and non-catalytic hydrophosphonylation/hydrophosphinylation of allenes/alkynes, and (c) $Zn(OTf)_2$/amine-catalyzed addition-cyclization of allenyl phosphine oxides with propargyl alcohols leading to phosphorus-based furans. **Part-B** embodies the investigations on the synthesis of phosphorus-based acridine derivatives via 9-chloroacridines.

Each part is subdivided into three chapters: (a) Introduction (literature survey), (b) Results and Discussion and (c) Experimental Section. The compounds obtained in the present study are, in general, characterized by mp, IR and NMR (^{1}H, ^{13}C & ^{31}P) techniques followed by elemental analyses and mass spectra (LC-MS). Wherever feasible, X-ray structure determination is undertaken. Summary as well as references are compiled at the end of each part.

PART-A

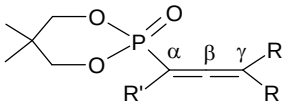
In Chapter 1, a review of literature on aspects relevant to this part is presented. In Chapter 2, the results obtained on these aspects are discussed while in Chapter 3, the experimental details are presented. Important results of this part are outlined here. The precursors used in the present study are shown in Charts 1 and 2. They are prepared by methodologies available (with modifications where necessary) in the literature.

Chart 1

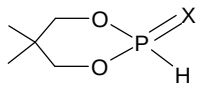


1 **2** **3**

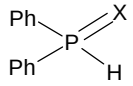
Chart 2



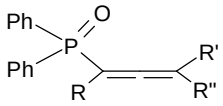
R' = R= H (**6**, δ(P): 7.4)
R' = H, R = Me (**7**, δ(P): 9.8)
R' = Ph, R = H (**8**, δ(P): 6.6)



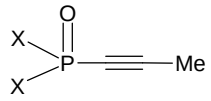
X = O (**15**, δ(P): 65.2)
S (**16**, δ(P): 22.8)



X = O (**17**, δ(P): 21.5)
S (**18**, δ(P): 22.8)



R = R' = R'' = H (**9**, δ(P): 24.6)
R = H, R' = R'' = Me (**10**, δ(P): 27.1)
R = Ph, R' = R'' = H (**11**, δ(P): 30.2)
R = *p*-anis, R' = R'' = H (**12**, δ(P): 29.3)
R = H, R' = Me, R'' = Ph (**13**, δ(P): 25.3)
R = Ph, R', R'' = -$(CH_2)_5$- (**14**, δ(P): 26.5)

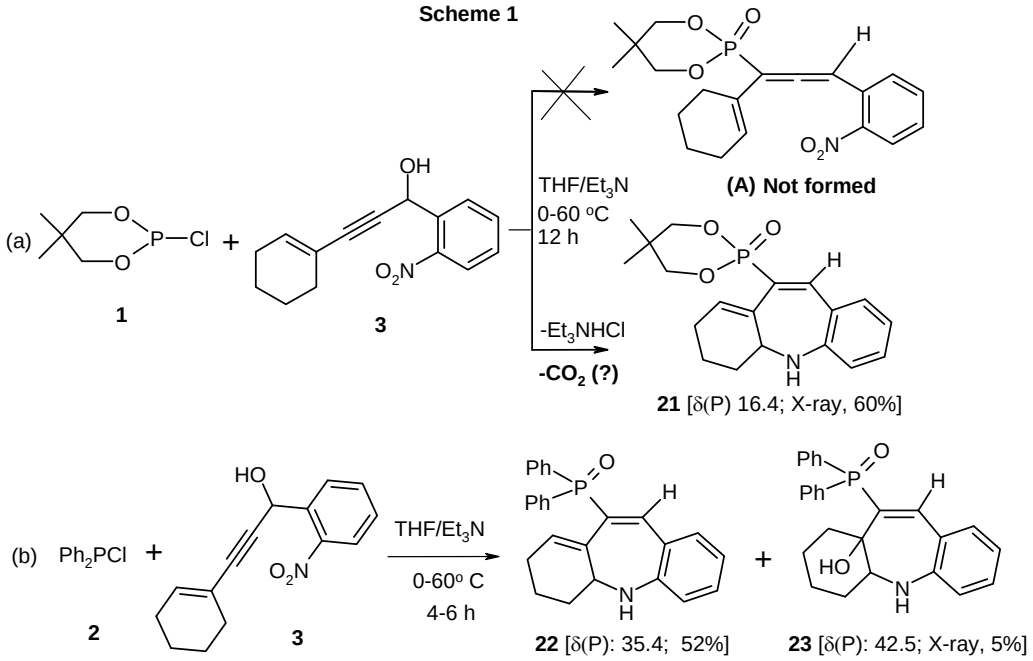


X = -$OCH_2CMe_2CH_2O$- (**19**, δ(P): -12.0)
X = Ph (**20**, δ(P): 7.4)

(i) Synthesis of phosphorus-containing heterocycles

As an extension of our work in allenylphosphonates preparation, we made an attempt to synthesize the allene (**A**) by treating ($OCH_2CMe_2CH_2O$)PCl (**1**) with the appropriate nitro substituted propargyl alcohol **3** (Scheme 1a). Rather surprisingly, we isolated the seven-membered heterocycle **21** (***dibenzo-azepine***) instead of allene (**A**) with ***loss of –CO_2*** from the expected product. A similar reaction of Ph_2PCl (**2**) with propargyl alcohol **3** (Scheme 1b) led to the heterocycles **22** and **23**; the latter compound is a H_2O addition product across the C=C bond of cyclohexenyl group. To our knowledge, reactions of this type are unprecedented.

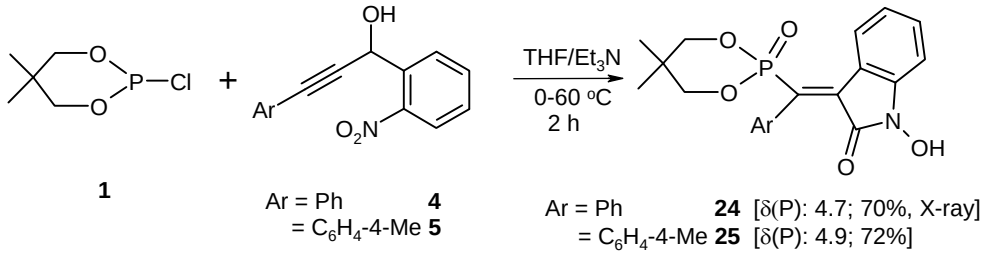
Scheme 1



In an attempt to prepare more examples of the above type of heterocycles, compound **1** was treated with propargyl alcohols **4-5**. Here, rather than allenylphosphonates (of type **A)** or the tricyclic compounds of type **21-23**, the unusual phosphono-*N*-hydroxy-indolinones **24-25** (Scheme 2) were obtained. The reaction of Ph_2PCl (**2**) with propargyl alcohol **4** also afforded a similar *N*-hydroxy-indolinone. A plausible pathway for the formation of these compounds is also presented in this section.

The structures of the compounds **21** (Fig.1, left)**, 23** (not shown here) and **24** (Fig.1, right) were confirmed by single crystal X-ray crystallography.

Scheme 2



1

Ar = Ph **4**
= C_6H_4-4-Me **5**

Ar = Ph **24** [δ(P): 4.7; 70%, X-ray]
= C_6H_4-4-Me **25** [δ(P): 4.9; 72%]

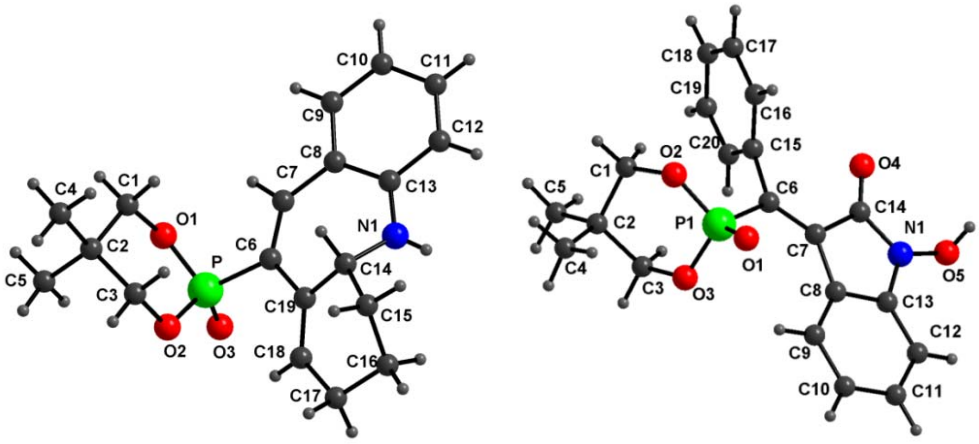


Fig. 1. Molecular structures of compounds **21** (left) and **24** (right).

(ii) Pd-catalyzed hydrophosphonylation/hydrophosphinylation of allenes and alkynes

A new dinuclear Pd(I)-complex **26** (Fig. 2) that can act as a robust catalyst was prepared from the reaction of $Pd(PPh_3)_4$ with $(OCH_2CMe_2CH_2O)P(S)H$ (**16**).

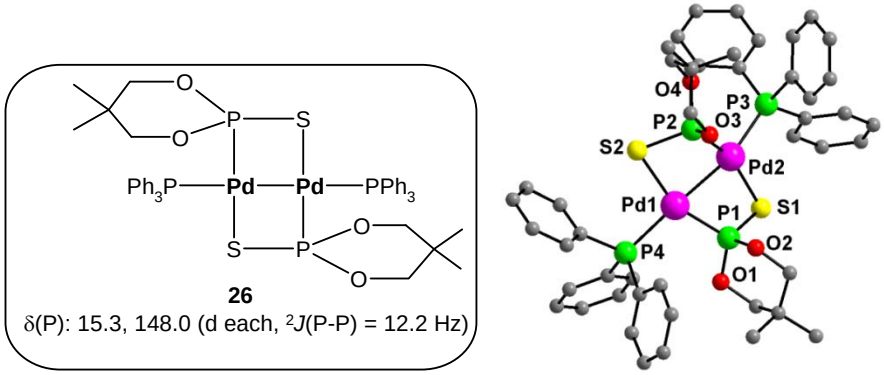
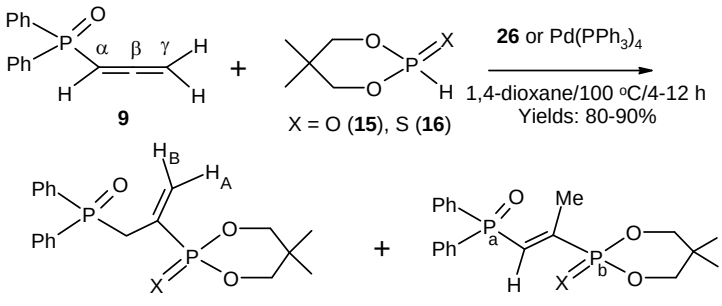


Fig. 2. Molecular structure of the dinuclear Pd(I) complex **26**

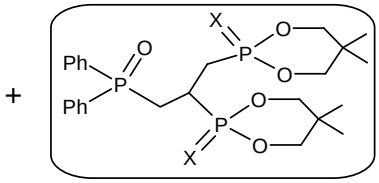
Hydrophosphonylation of allene $Ph_2P(O)C(H)=C=CH_2$ (**9**) with $(OCH_2CMe_2CH_2O)P(O)(H)$ (**15**) was performed by using the new Pd(I)-complex $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**26**) or $Pd(PPh_3)_4$ to yield the (β,α) and (β,γ)-P(O)-H addition products **27** and **28**, respectively (Scheme 3). The reactivity of dinuclear Pd(I) catalyst **26** is comparable with the catalyst $Pd(PPh_3)_4$. Other Pd-catalysts like $Pd(OAc)_2$, $Pd_2(dba)_3$ gave poor yields. In a manner similar to that described above, the reaction of allenyl phosphine oxide $Ph_2P(O)C(H)=C=CH_2$ (**9**) with cyclic thiophosphite $(OCH_2CMe_2CH_2O)P(S)H$ (**16**) in the presence of $Pd(PPh_3)_4$ or dinuclear Pd(I)-complex (**26**) afforded the products **29-30** along with bisthiophosphonylated compound **31** in good yields [combined yield >90%, ^{31}P NMR] (Scheme 3). The main point we observed was that the catalyst **26** could be recovered from this reaction whereas $Pd(PPh_3)_4$ could not be.

Scheme 3



X = O: **27** [δ(P): 11.7 and 29.8 (d, *J* = 22.0 Hz)] (*E*)-**28** [δ(P): 11.9 and 20.8 (d, *J* = 73.2 Hz)] (X-ray)

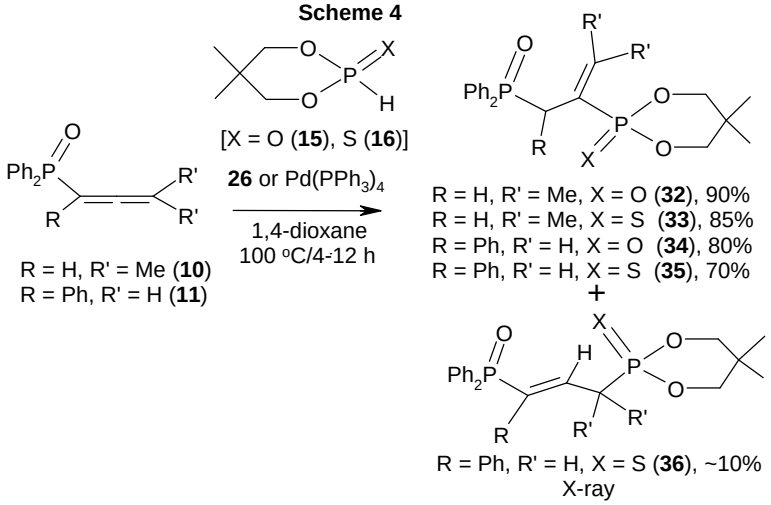
X = S: **29** [δ(P): 29.6 and 82.5 (d, *J* = 29.5 Hz)] (*E*)-**30** [δ(P): 20.9 and 84.8 (d, *J* = 75.0 Hz)]



X = S: **31** [δ(P): 30.0 (d, *J* = 36.8 Hz), 96.3 and 96.7 (m, ABX pattern)]

From the above results, it is also clear that the efficacy of dinuclear Pd-catalyst **26** is comparable to $Pd(PPh_3)_4$ in P(X)-H [X = O, S] addition reactions, but the former is more stable under aerobic conditions. Hence we investigated the hydrophosphonylation reactions of allenes $Ph_2P(O)C(H)=C=CMe_2$ (**10**) and $Ph_2P(O)C(Ph)=C=CH_2$ (**11**) with **15-16** by using the dinuclear Pd(I)-catalyst **26** (Scheme 4). In these cases, we obtained mainly (*β,α*)-P(O)-H addition products **32-35**. In the reaction of allene **11** with thiophosphite **16**, the (*β,α*)-P(O)-H addition product **35** formed along with a minor amounts (<10%) of (*γ,β,*)-P(O)-H addition product **36**. There was no significant difference in the products formed using either $Pd(PPh_3)_4$ or **26** in the reactions that we checked.

Scheme 4

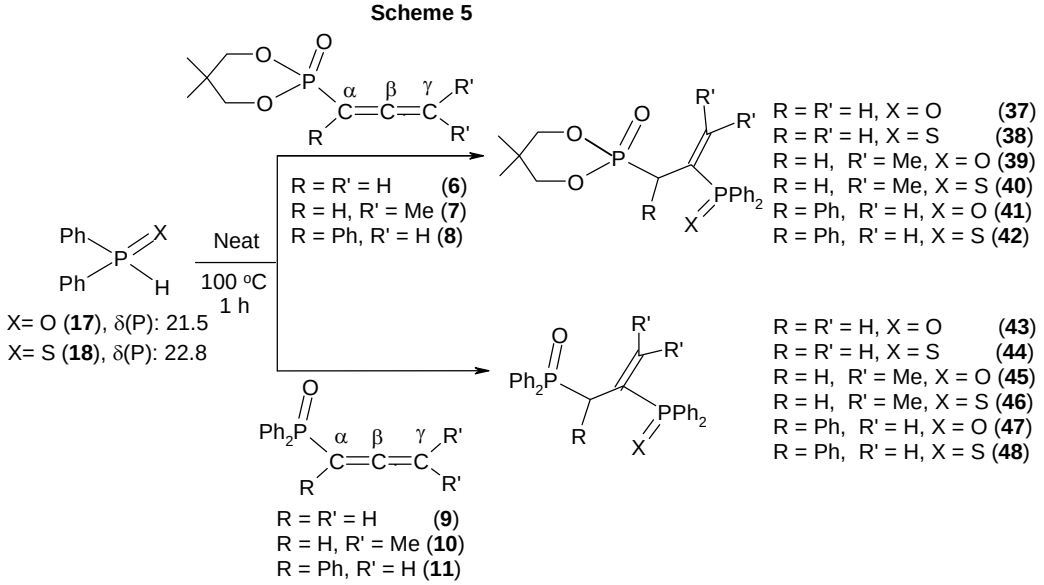


The *alkynes* $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**19**) and $Ph_2P(O)C{\equiv}CMe$ (**20**) are the isomers of the *allenes* $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**6**) and $Ph_2P(O)C(H)=C=CH_2$ (**9**), respectively. We extended the hydrophosphonylation/hydrophosphinylation to cover the reaction of alkynes **19** and **20** with $(OCH_2CMe_2CH_2O)P(X)H$ [X = O (**15**), S (**16**)] and $Ph_2P(X)H$ [X = O (**17**), S (**18**)]. In most of these hydrophosphonylation reactions of alkynes with phosphites, we isolated mainly (*β,α*)- addition products. Where appropriate, mechanistic pathways leading to these products are discussed.

(iii) Catalyst-free and solvent-free regioselective hydrophosphonylation/hydrophosphinylation of allenylphosphonates/allenyl phosphine oxides and alkyne $Ph_2P(O)C{\equiv}CMe$ (20)

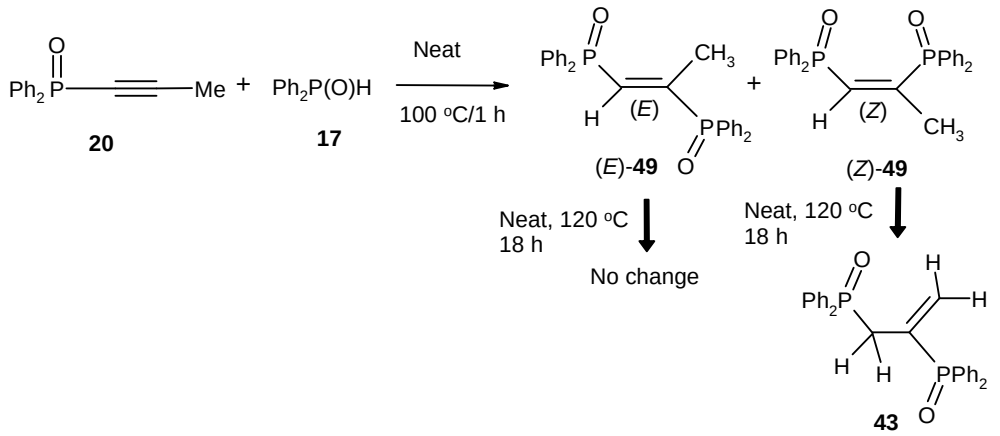
It shown in the present work that the reaction of $Ph_2P(X)H$ [X = O (**17**), S(**18**)] with allenes (**6-11**) *does not require a catalyst* and proceeds well under neat conditions at 100 °C to lead to (*β,α*)-P(X)-H [X = O, S] addition products (**37-48**) predominantly in a regioselective manner (Scheme 5).

Scheme 5



The reaction of $Ph_2P(O)C{\equiv}CMe$ (**20**) with $Ph_2P(O)H$ (**17**) under neat conditions (at 100 °C) afforded the (*E*)-**49** and (*Z*)-**49** isomers (Scheme 6). More interestingly, we also found that (*Z*)-**49**, upon continuous heating [120 °C (oil bath)/ 18 h] converts to **43**. To our knowledge, such an isomerization has not been recorded in the literature. However, compound (*E*)-**49** remains as such upon heating [^{31}P NMR evidence].

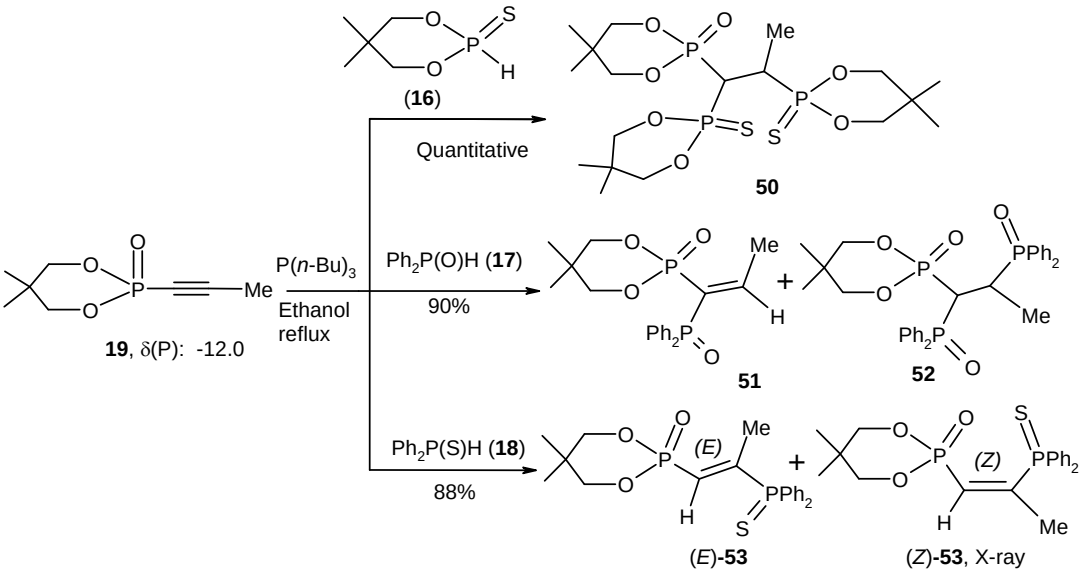
Scheme 6



(iv) P(n-Bu)$_3$ catalyzed hydrothiophosphonylation/hydrophosphinylation of activated alkynes (19-20): Synthesis of geminal bis- and tris-phosphorus compounds

In contrast to Pd-catalyzed reactions discussed above, the reaction of alkyne **19** with **16-17** under P(n-Bu)$_3$ catalyzed conditions preferentially led to geminal bis- and tris-phosphorus compounds **50-52**, while in the reaction with $Ph_2P(S)H$ (**18**) only the bis-phosphorus products (*E*)-**53** and (*Z*)-**53** were obtained (Scheme 7). The alkyne $Ph_2P(O)C{\equiv}CMe$ (**20**) behaved in a manner similar to $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**19**).

Scheme 7

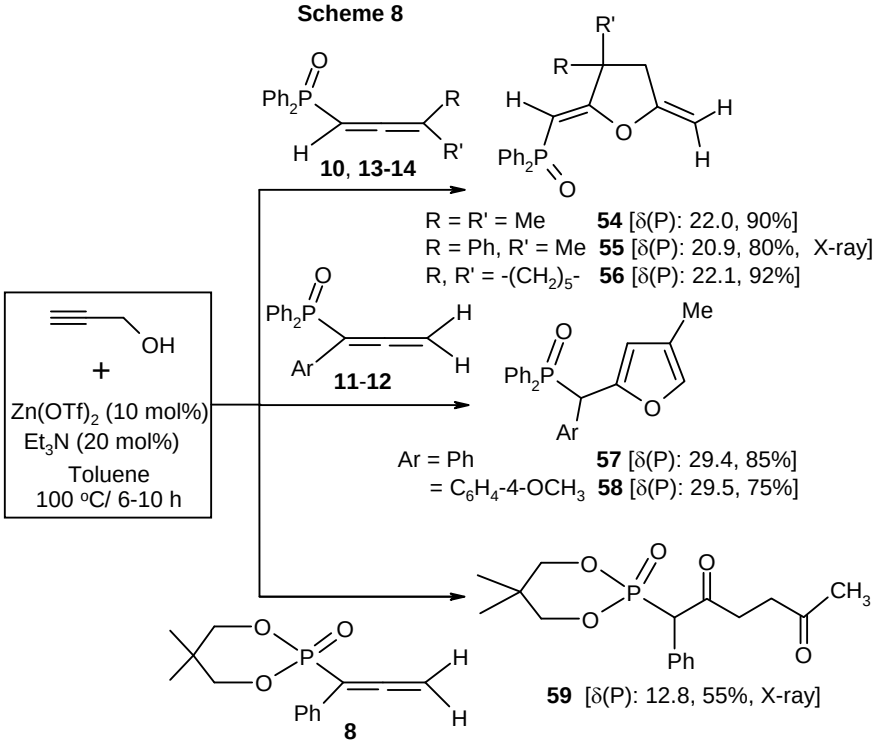


(v) $Zn(OTf)_2/Et_3N$ catalyzed addition-cyclization reactions of propargyl alcohols with allenyl phosphine oxides leading to phosphino-furans

After having access to a range of allenes as well as propargyl alcohols, we were interested in exploring reactions in which both the oxygen and the alkyne ends of the propargyl alcohols react with the allenes leading to cyclized products. Indeed, such a reaction of allene $Ph_2P(O)C(H)=C=CMe_2$ (**10**) with propargyl alcohol $HC{\equiv}CCH_2OH$ under $Zn(OTf)_2/Et_3N$ catalyzed conditions afforded the (β,γ)-addition-cyclization product **54** (Scheme 8) in 90% yield. In a similar manner compounds **55-56** were also prepared from the respective allenes **13-14**. We then explored the reactivity of allenyl phosphine oxides $Ph_2P(O)C(R)=C=CR'_2$ [R = Ph, R' = H (**11**), R = C_6H_4-*p*-OCH_3, R' = H (**12**)] with $HC{\equiv}CCH_2OH$; these reactions too gave (β,γ)-

addition-cyclization products **57-58** (Scheme 8), but the five membered ring was aromatized to lead to the furan ring. In contrast to these, the reaction of allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**8**) with $HC\equiv CCH_2OH$ surprisingly afforded a non-cyclized *β,ω*-diketophosphonate **59** (Scheme 8). It can be noted that this product is a result of addition of a molecule of water after the propargylic group adds to the allene. A product similar to **54** was obtained in the reaction of the allenyl phosphine oxide $Ph_2P(O)CH=C=CMe_2$ (**10**) with HC≡CC(Me)(H)(OH). A rationale for the formation of the furan derivatives so obtained is also presented.

Scheme 8



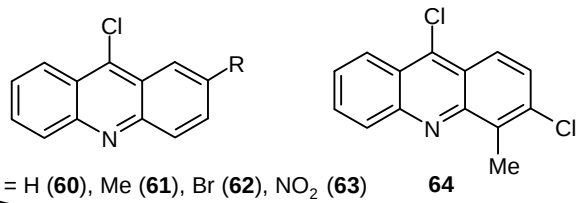
PART-B

The focus of Chapter 4 is to review the literature pertaining to the acridine derivatives. Chapter 5 describes the results obtained in the present study on these aspects. Chapter 6 is the experimental section for this part. Important results of this part are outlined below.

(i) Hydrophosphonylation of 9-chloroacridines with 15: Synthesis of phosphono-acridanes

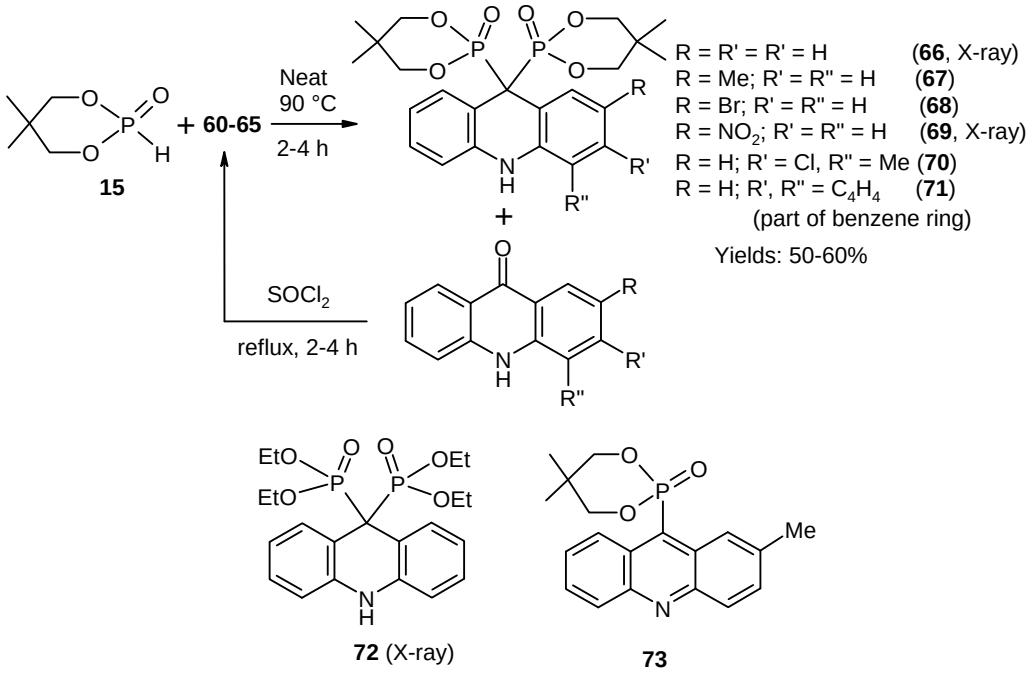
For this study, we have used the 9-chloroacridines **60-65** (Chart 3) which are prepared by literature methods, with modifications, as appropriate. When compounds **60-65** were treated with the cyclic phosphite ($OCH_2CMe_2CH_2O$)P(O)(H) (**15**) under neat conditions at 90 °C for 2-4 h, bisphosphonates **66-71** were formed (50-60%) along with the corresponding acridones (Scheme 9). We made an attempt to increase the yield of **66** by changing the reaction conditions; however, we always ended up in having acridone (30-40%) by-product, probably because of a competing –OH to -Cl exchange between 9-chloroacridine and phosphite. However, this problem is not very significant since the acridone formed was readily converted back to the 9-chloroacridine by simple treatment with thionyl chloride. An analogous reaction of 9-chloroacridine (**60)** with diethyl phosphite afforded the corresponding bisphosphonate **72**; this compound, is known in the literature. By using a lower stoichiometry of phosphite **15** in its reaction with 9-chloro-2-methylacridine (**61**), the monophosphonate **73** could also be isolated.

Chart 3



R = H (**60**), Me (**61**), Br (**62**), NO_2 (**63**) **64** **65**

Scheme 9

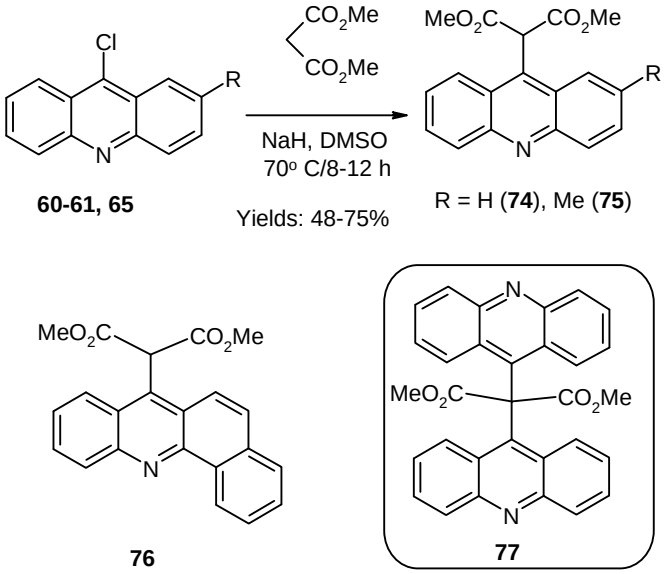


Cytotoxicity (IC_{50} in μM) for compound **67** with cell lines HepG2 and HeLa were found to be 150 and 79, respectively [courtesy; a colleague from School of Life Sciences, University of Hyderabad]. These data suggest that our compounds are fairly active; efforts are under way to obtain the corresponding bisphosphonic acids and check their activity.

(ii) Nucleophilic substitution reactions of 9-chloroacridines with dimethyl malonate: Synthesis of malono-acridines 74-76 and bis(acridinyl)malonate 77

We have prepared monosubstituted acridines **74-76** by reacting dimethyl malonate/NaH with 9-chloroacridines **60-61** and **65** (Scheme 10). These results show that a large number of 9-*C*-substituted acridines should be accessible *via* 9-chloroacridines and the plethora of available routes for C-C bond forming reactions. Perhaps more interesting is the fact that in addition to these mono-substituted products, we also obtained a small amount of the compound **77** that has malonate with two acridine residues (Scheme 10).

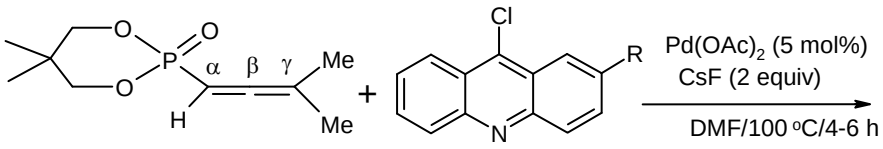
Scheme 10



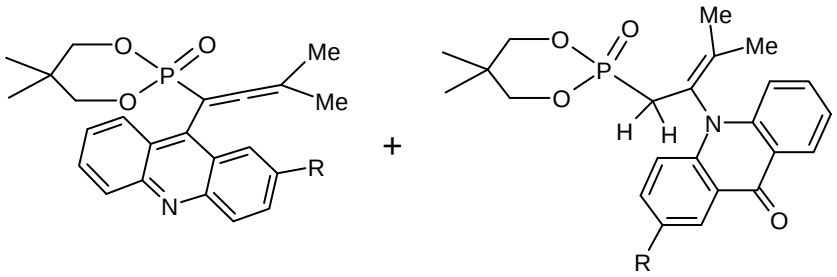
(iii) Pd-catalyzed Heck-coupling reactions of $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (7) with 9-chloroacridines 60-61

In connection with the synthesis of acridine-based organophosphonates, we planned to utilize 9-chloroacridines in Pd-catalyzed Heck-coupling reactions with allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)C(H)=C=Me_2$ (**7**). Thus we made an attempt to prepare vinyl acridines by coupling allenylphosphonate **7** with 9-chloroacridine (**60**). Interestingly, a rather unusual arylation at the α-position [instead of *β*-position] of allene occurred, leading to the *α*-acridinyl allene product **78** (Scheme 11). Another product **79** was also isolated along with **78**. Although ^{31}P NMR spectrum of the reaction mixture of 9-chloro-2-methylacridine (**61)** with allene **7** showed the peak corresponding to a product similar to **78**, it could not be isolated (Scheme 11). Here only the acridone-addition product (**80**) that is similar to compound **79** was isolated.

Scheme 11



7 [δ(P) 9.8]



R = H **78** [δ(P) 8.7, X-ray]; 20%

R = H **79** [δ(P) 19.5]; 55%
= Me **80** [δ(P) 19.5]; 58%

The formation of unexpected products **79-80** may be due to the addition of the acridone [formed *via* water (adventitious) addition to the 9-chloroacridine in the reaction mixture] to the allenes **7**. This assertion is confirmed by treating acridone directly with the allene (**7**) in the presence of CsF which led only to the product **79**. In a similar manner, compound **80** is also formed. It may be noted that derivatives **79-80** are examines. It may be noted that normal examines are hydrolytically unstable, for example, a diethyl amino group (-NEt_2) in place of acridone residue in **79** hydrolyzes readily to give *β*-ketophosphonate $(OCH_2CMe_2CH_2O)P(O)CH_2C(O)CHMe_2$. However our compounds **79-80** are fairly stable to moisture; we ascribe the stability of **79-80** to steric factors.

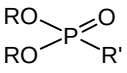
PART A

SYNTHETIC STUDIES ON ORGANOPHOSPHONATES

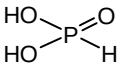
INTRODUCTION

1.1 General Introduction: Organophosphonates

The importance of organophosphorus compounds in synthetic, agrochemical, and medicinal chemistry has been well documented.[1-2] Among numerous organophosphorus compounds, organophosphonates (1.**1**) that are derivatives of phosphonic acid (1.**2**) and comprising a P-C bond are important in many living systems and have been found to display a range of bioactivities.[2-4] This chapter principally deals with the literature on the P-C bonded organophosphorus compounds (organophosphonates) that are relevant to the work presented in the thesis.



(1.**1**)

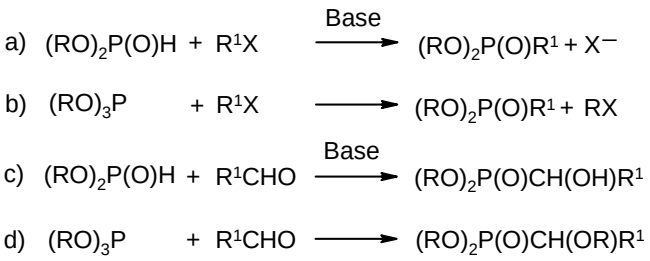


(1.**2**)

1.2 Synthesis of Organophosphonates

The preparation of organophosphonates generally involves one of the following: a) Michaelis-Becker reaction, b) Michaelis-Arbuzov reaction, c) Pudovik reaction or d) Abramov reaction (Scheme 1.1).[2c,5] Literature on addition of compounds with a =P(O)H moiety to carbon-carbon multiple bonds will be presented in a later section.

Scheme 1.1

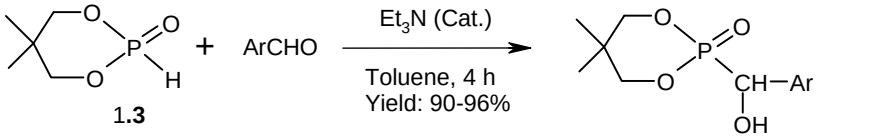


For method (a), sodium hydride works very nicely to generate the anion from the phosphite $(RO)_2P(O)H$ [in this thesis, we also use the names dialkyl/ diaryl phosphite or H-phosphonate for this type of compound]. The preferred solvents for method (a) are toluene, xylene or dioxane. The main problem here is the low solubility of the anion in the aprotic solvent. Method (b) remains the most common route for the creation of P-C bond in quinquivalent organophosphorus compounds; this is due not only to the relatively easy availability of the required starting materials, but also to the relative ease of performing the reaction. Generally, methyl or diethyl esters of phosphorus and alkyl iodides are used. A limitation to either method (a) or (b) is the use of the alkyl halide itself; once the phosphonate is formed, further introduction of functionalities at the α-carbon is more difficult, although possible. Methods (c)-(d) are discussed in the following section.

1.21 Hydrophosphonylation of carbonyl compounds (Pudovik or phospho-aldol reaction)

The Pudovik (phospho-aldol) reaction [method (c) in Scheme 1.1] is a well-known and increasingly exploited synthetic process for the construction of phosphorus-carbon bonds.[6] A wide range of α-hydroxyphosphonates can be prepared almost quantitatively by this route (Scheme 1.2).[7] These hydroxyphosphonates are valuable precursors for the synthesis of other α-functionalized phosphonates (Scheme 1.3)[1k,8] that could be utilized further in Horner-Wadsworth-Emmons (HWE) reactions.

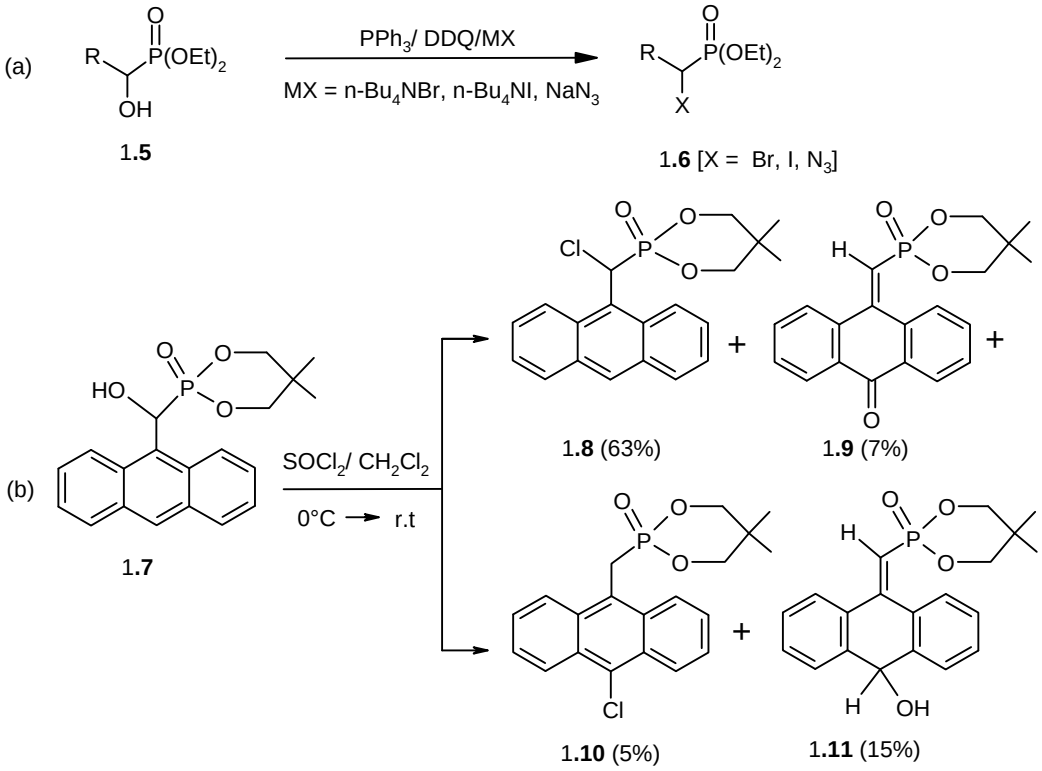
Scheme 1.2



1.3

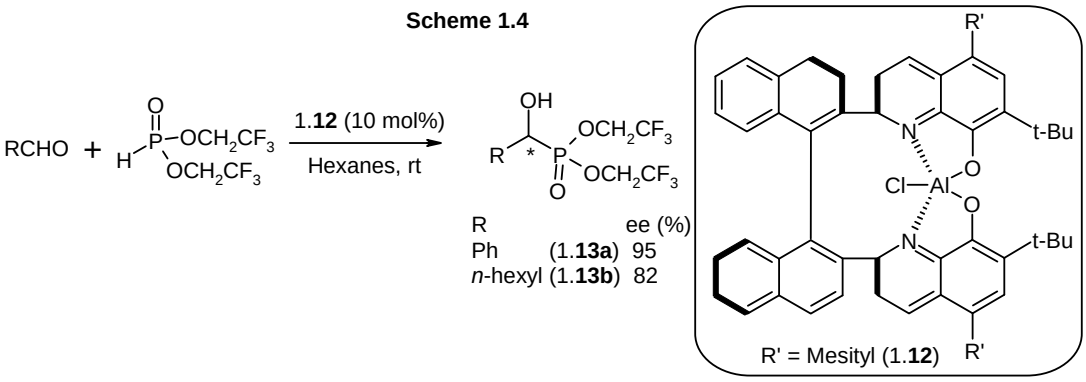
Ar = Ph [1.**4a**; δ(P): 13.3]
C_6H_4-4-Me [1.**4b**; δ(P): 13.6]
C_6H_4-4-OMe [1.**4c**; δ(P): 13.6]
C_6H_4-4-Cl [1.**4d**; δ(P): 12.9]
C_6H_4-4-Br [1.**4e**; δ(P): 12.9]
9-anthryl [1.**4f**; δ(P): 16.9]

Scheme 1.3

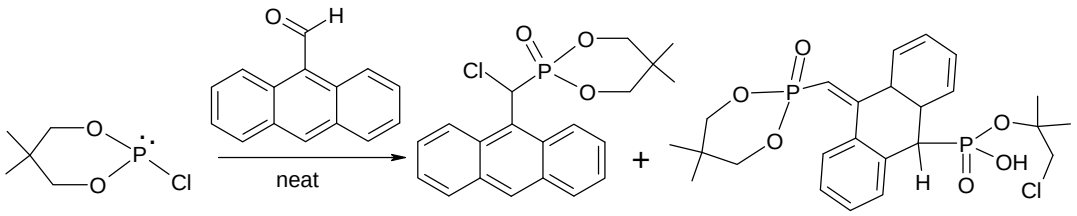


The catalytic asymmetric Pudovik (phospho-aldol) reaction[9-10] is also an extremely versatile process for the synthesis of α-hydroxyphosphonates. To date, several chiral organocatalysts (*e.g.* cinchona alkaloids, chiral phosphoric acids) as well as chiral modifications of SALEN or BINOL complexes of transition metals and aluminium have been utilized for this reaction.[11] The reported yields and *ee* are generally high. An example is given in Scheme 1.4. The Abramov reaction (method d) works under more drastic conditions and the yields are generally not that high. A modification of this reaction utilizes $P(OR)_2Cl$ in place of $P(OR)_3$ and the resulting products are α–chlorophosphonates; however, as shown in Scheme 1.5, use of anthraldehyde in such reactions leads to additional products also.[8c]

Scheme 1.4



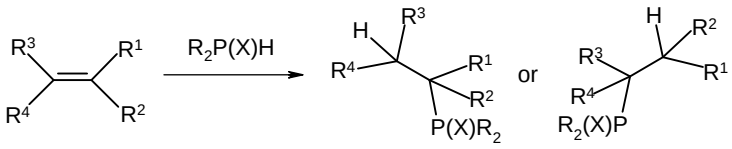
Scheme 1.5



1.22 Hydrophosphonylation of multiply bonded carbon-carbon systems

Compounds with a =P(O)H moiety can add on to multiply bonded (unsaturated) carbon-carbon systems leading to the formation of P-C bond in an atom-economic manner. When a compound with a P^V–H [In this thesis, P^V refers to systems in which phosphorus has five formal bonds including double bonds] group adds across unsaturated systems like C=C or C≡C affording phosphonates/ phosphine oxides having a P-C bond, the reaction can be termed as hydrophosphonylation/hydrophosphinylation (Scheme 1.6).

Scheme 1.6



Hydrophosphonylation/hydrophosphinylation of alkenes, alkynes or allenes is well documented.[1g,1j,12] Many of the C-C unsaturated systems undergo phosphonylation to lead to synthetically useful organophosphonates. There are three general approaches:

(a) Phospha-Michael reaction of activated alkenes, most commonly promoted by a base, Lewis acid or microwave,

(b) Addition to unactivated olefins promoted by radical initiators such as peroxide, AIBN and

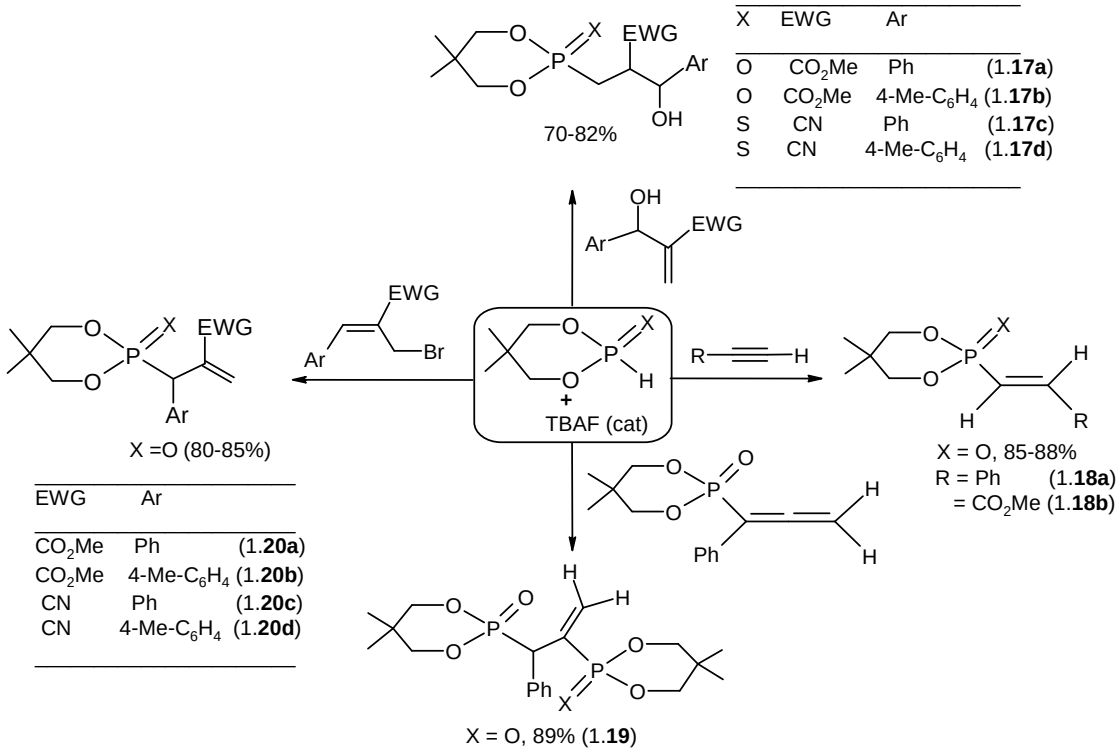
(c) Hydrophosphonylation of unactivated alkenes catalyzed by transition metals.

Generally base, Lewis acid and radical catalyzed P(O)-H addition to alkenes leads to anti-Markovnikov products. Major problems in many of these methods are the long reaction time and drastic conditions. Furthermore, many times, the regioselectivity of the addition is low.[13] In hydrophosphonylation of unactivated substrates catalyzed by transition metals, the selectivity depends on the metal complexes and works well mostly at higher temperature. Selected literature on these methods is discussed in the following sections.

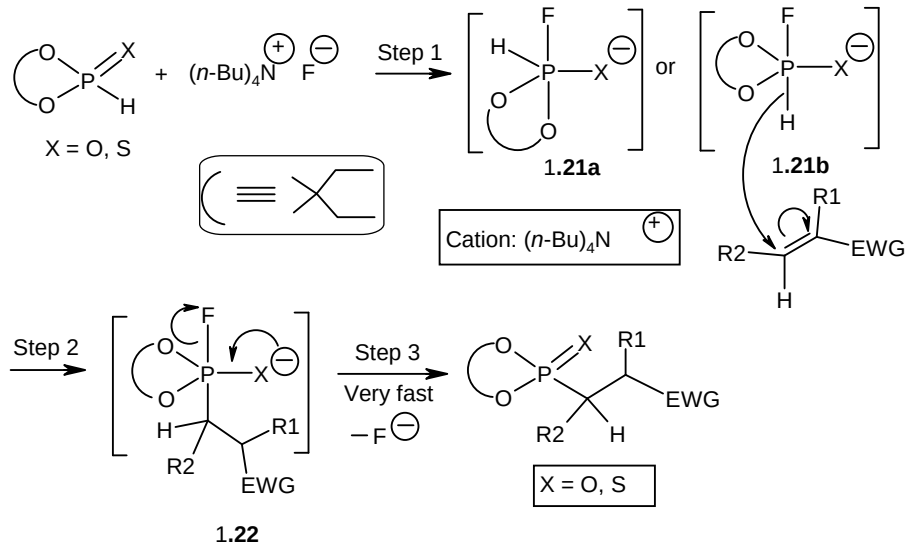
1.221 Base or Lewis-acid catalyzed hydrophosphonylation/hydrophosphinylation

Recently, from our laboratory, tetrabutylammonium fluoride (TBAF) catalyzed hydrophosphonylation/hydrothiophosphonylation of Baylis-Hillman adducts, substituted allyl bromides, allenylphosphonates and alkynes in ionic liquid medium leading to γ-hydroxyphosphonates and α-aryl allylphosphonates[14] was reported (Scheme 1.7). The yields were generally high. This reaction is activated *via* pentacoordinate phosphorus species of the type 1.**21a-b** (Scheme 1.8) as evidenced by ^{1}H, ^{19}F and ^{31}P NMR spectroscopic techniques.

Scheme 1.7

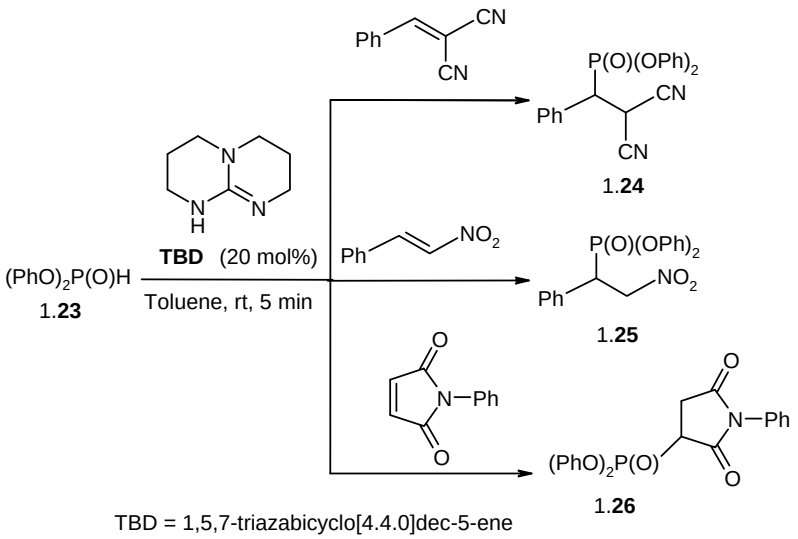


Scheme 1.8



Tan and co-workers reported the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) catalyzed mild and efficient protocol for the conjugate P(O)-H addition to various activated alkenes (Scheme 1.9).[15] The yields of the products 1.**24**-1.**26** were very good (85-90%).

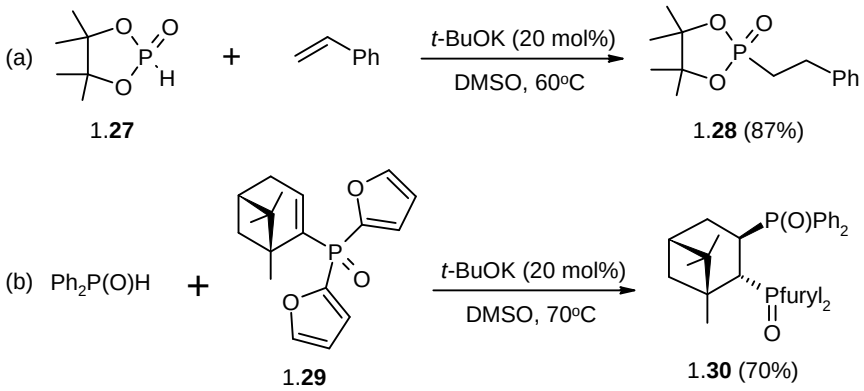
Scheme 1.9



TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene

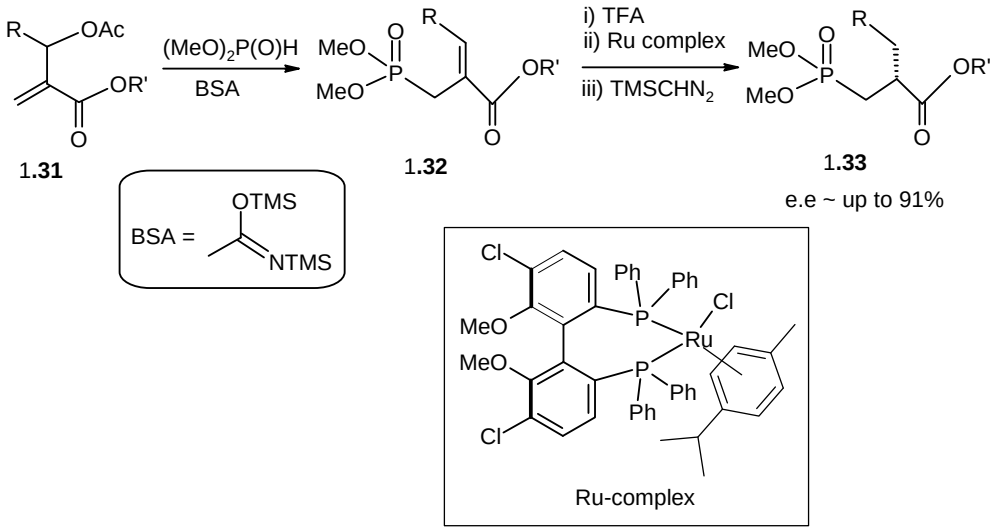
A novel synthesis of phosphonates 1.**28** and chiral phosphine oxide 1.**30** has been developed by using a ^{t}BuOK mediated hydrophosphonylation/hydrophosphinylation[16] of styrene and alkenyl phosphine oxide 1.**29** with dialkyl phosphite 1.**27** and $Ph_2P(O)H$, respectively (Scheme 1.10). The product 1.**30** was utilized further in the preparation of chiral phosphine ligand.

Scheme 1.10



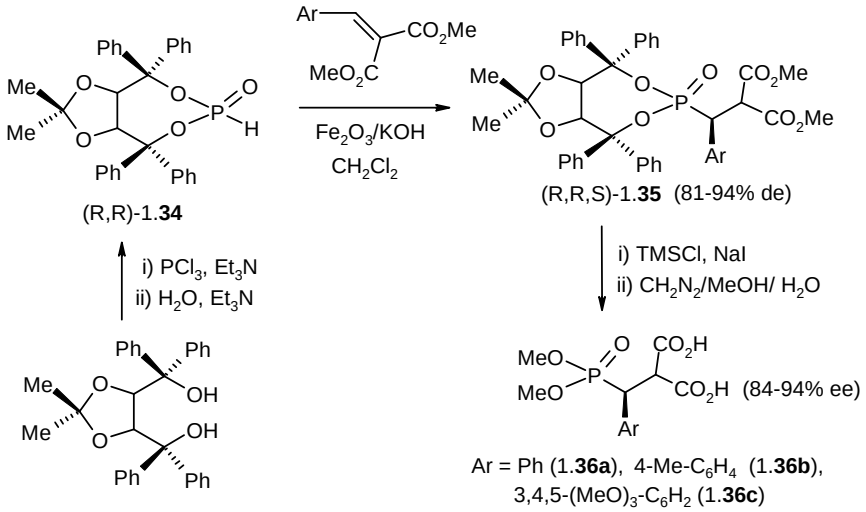
Allylic acetates (1.**31**) derived from Baylis-Hillman adducts[17a] undergo P(O)-H addition to give the *Z*-unsaturated esters (1.**32**) stereoselectively (Scheme 1.11).[17b] With the exception of benzyl phosphite, the yields for the addition-elimination reactions were good. Subsequent hydrogenation of 1.**32** using chiral Ru-complex led to the phosphonate 1.**33** with *ee* up to 91%.

Scheme 1.11



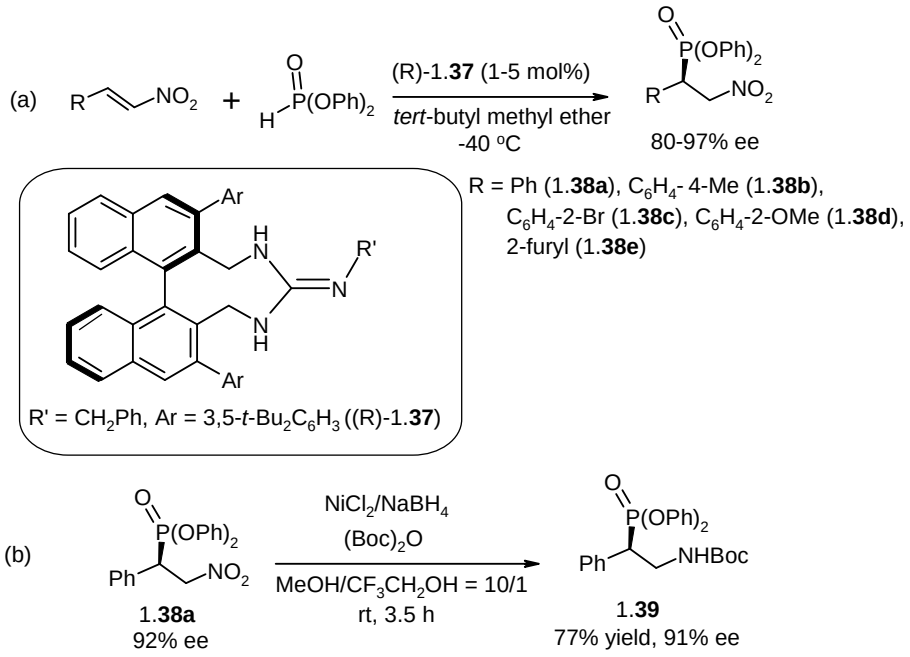
Enders and co-workers reported the conjugate addition of the enantiopure phosphite (*R*,*R*)-1**.34** to *α,β*-unsaturated malonates as a key step in the synthesis of optically active *β*-substituted *β*--phosphono malonates[18] 1.**35** (Scheme 1.12). For this purpose, the phosphorus nucleophile 1.**34** was synthesized from (-)-*trans*-α,α-(dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmetanol) (TADDOL) and phosphorus trichloride. The conjugate addition of (*R*,*R*)-1**.34** to the alkylidene malonates in the presence of Fe_2O_3/KOH as a solid base led to chiral *β*-phosphono malonates in good yields and high diastereomeric excess. Other solid bases like Al_2O_3/KOH, ZnO/KOH, Cu_2O/KOH, MnO_2/KOH, MgO/KOH could be employed in this reaction but Fe_2O_3/KOH was found to be the best combination. The cleavage of the chiral auxiliary under nonracemizing conditions in the final step led to the products (*S*)-1**.36a-d** in good yields.

Scheme 1.12



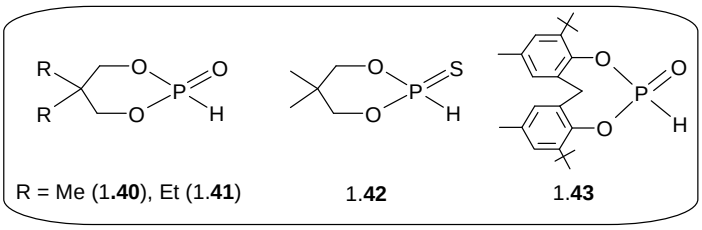
Terada and co-workers have utilized the axially chiral guanidine 1.**37** as a catalyst for phospha-Michael addition of diphenylphosphite to *β*–nitrostyrenes that leads to *β*–nitro-phosphonates 1.**38a-e** (Scheme 1.13a).[19] The reduction of product 1.**38a** in the presence of $(Boc)_2O$ [Boc = *t*-butyloxy carbonyl] afforded *N*-Boc-*α*-aminophosphonate 1.**39** without racemization (Scheme 1.13b).

Scheme 1.13

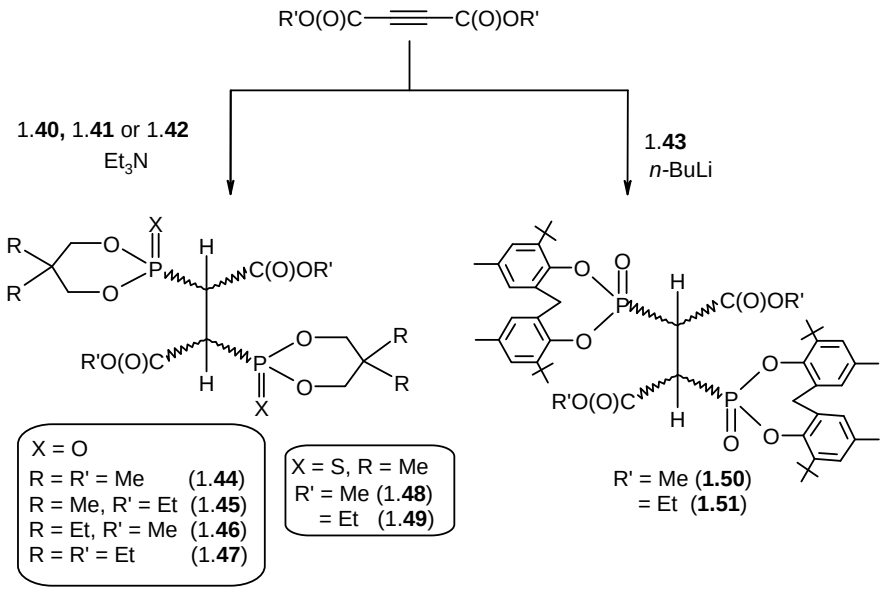


A novel route for bisphosphonates *via* activated alkynes and the phosphites 1.**40**-1.**43** has been developed in our laboratoty.[20] Thus, the bisphosphonates 1.**44**-

1.**51** were synthesized by reacting 1.**40**-1.**43** with disubstituted acetylenes at room temperature (Scheme 1.14). In the case of products 1.**44**-1.**49**, triethylamine was used as a base (catalyst) but for products 1.**50**-1.**51**, *n*-butyllithium was required to effect the reaction. The *dl*, *meso* and (*dl*+*meso*) forms of the bisphosphonates are isolated as crystalline solids. Conversion of *meso* to *dl* form (and *vice versa*) is demonstrated by means of ^{31}P NMR spectroscopy.

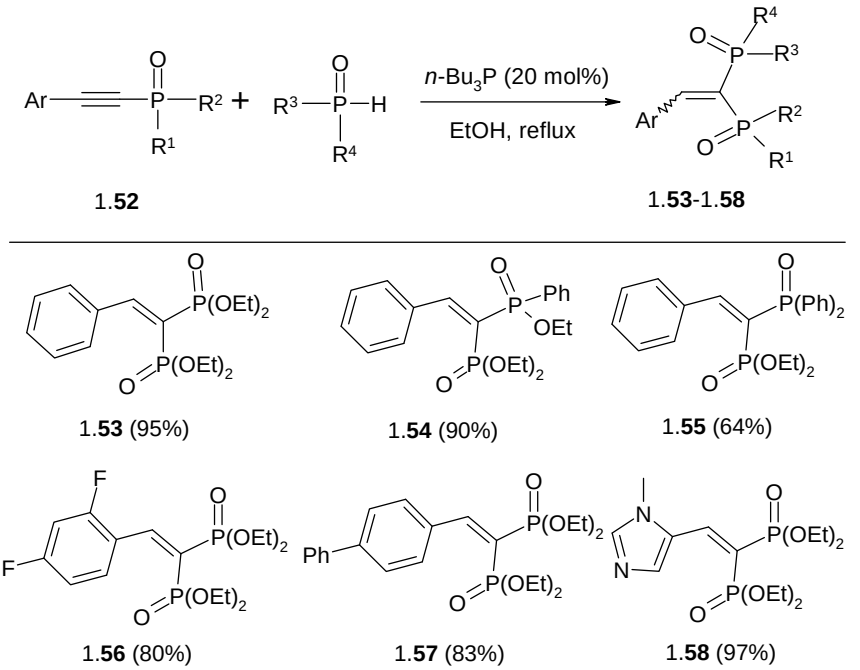


Scheme 1.14



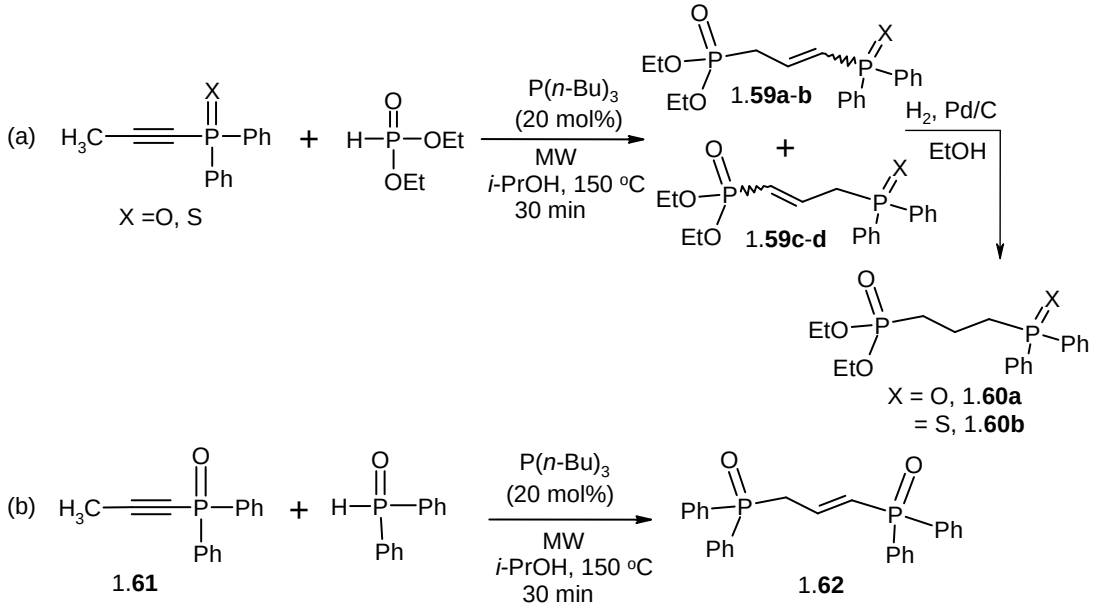
Taran and co-workers reported P(*n*-Bu)$_3$ catalyzed umpolung addition of phosphorus pronucleophiles (H-phosphonates, H-phosphine oxides) to alkynes bearing phosphine oxide moiety 1.**52**. The reaction leads to 2-aryl-1-vinyl-1,1-diphosphine dioxide derivatives 1.**53**-1.**58** (Scheme 1.15) in good yields affording a new route to compounds with P-C-P backbone.[21] Under these conditions, other phosphines (PPh_3, PPh_2Me) and solvents like toluene, DMF and DMSO gave very poor results.

Scheme 1.15



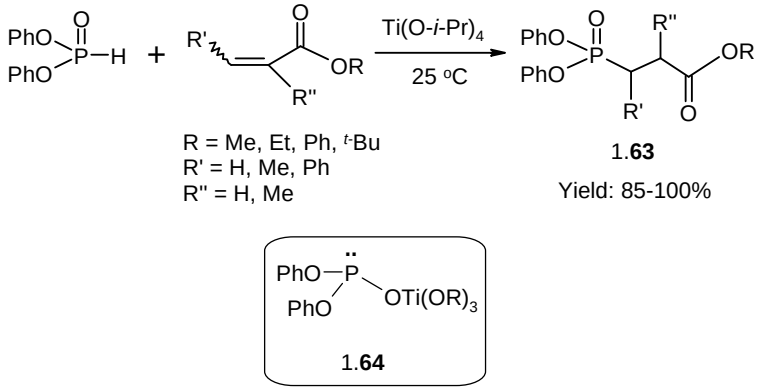
The same group explored the phosphine-catalyzed γ-addition (umpolung addition) of phosphorus pronucleophiles on alkynyl phosphonates under microwave (MW)-conditions[22] leading to unsymmetrical bisphosphonates 1.**59a-d** (Scheme 1.16a). Further reduction of these compounds led to products 1.**60a-b**. The reaction of phosphino alkyne 1.**61** with $Ph_2P(O)H$ also afforded the γ-phosphinylated product 1.**62** (Scheme 1.16b).

Scheme 1.16



An efficient, highly selective Ti(*i*-OPr)$_4$ catalyzed P(O)-H addition to activated alkenes was demonstrated by Yao and co-workers (Scheme 1.17).[23] The reactivity of the diaryl phosphites was found to be more than that of dialkyl phosphites. Under these conditions, other Lewis-acids like $AlCl_3$ and $TiCl_4$ were inactive. A species like metallo-phosphite 1.**64** is assumed to be involved in this reaction.

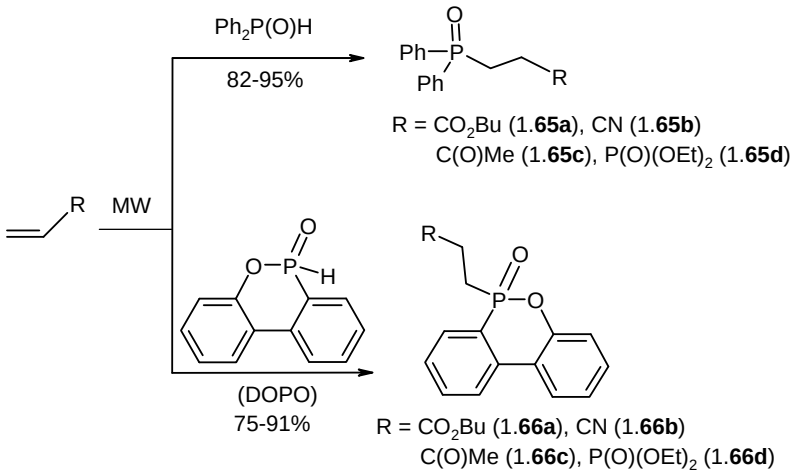
Scheme 1.17



1.222 Microwave (MW) mediated hydrophosphonylation/hydrophosphinylation

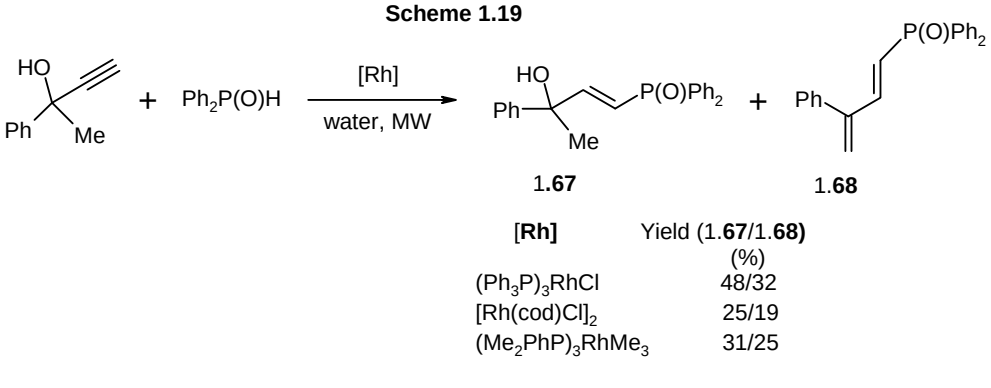
Microwave heating is fascinating field for chemical applications and has become a widely used method for performing organic reactions.[24-28] Treatment of a terminal alkene with $Ph_2P(O)H$ or 6*H*-dibenz[*c*,*e*][1,2]oxaphosphorin-6-oxide (DOPO) in the absence of solvent with microwave irradiation[29] as the heating source afforded high yields of the desired products (1.**65a-d** and 1.**66a-d**). The 1,1-addition product (cf. Scheme 1.17 above) was not observed. This method also tolerates the carbonyl group. A variety of alkenes were employed in this reaction, with the best results obtained when the alkene contained an activating group (Scheme 1.18).

Scheme 1.18

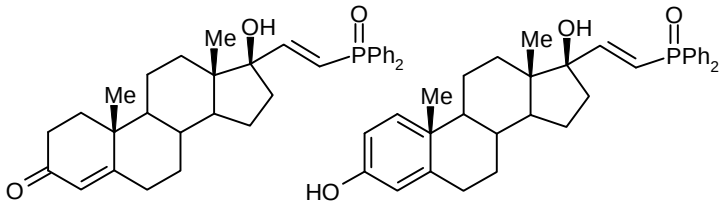


Stockland and co-workers reported microwave-assisted hydrophosphinylation of propargyl alcohols and ethynyl steroids in the presence of Rh-catalyst in water. Even though simple propargyl alcohols generated mixtures of products 1.**67**-1.**68** (Scheme 1.19), analogous reactions involving ethynyl steroids cleanly generated a single product under a variety of conditions. The phosphinylation of ethynyl steroids in aqueous medium were also remarkably tolerant to oxygen and could be carried out in air without any difficulty.[30] Some of the hydrophosphinylated products like 1.**69**-1.**70** (Fig. 1.1) of ethisterone and ethynyl estradiol were also obtained in good yields.

Scheme 1.19



[**Rh**]	Yield (1.**67**/1.**68**) (%)
$(Ph_3P)_3RhCl$	48/32
$[Rh(cod)Cl]_2$	25/19
$(Me_2PhP)_3RhMe_3$	31/25



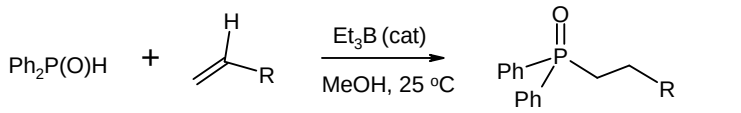
1.**69**(80%) 1.**70** (83%)

Fig. 1.1. Hydrophosphinylated products of ethynyl steroids.

1.223 Free-radical mediated hydrophosphonylation/hydrophosphinylation

Phosphonyl radicals can add across activated as well as unactivated unsaturated systems.[31] Here, photoactivation or chemical initiation is the most efficient method. Literature reports reveal that the addition of phosphonyl radicals to olefins (alkenes) occurs with a complete retention of configuration at phosphorus.[32] Piettre *et al* have shown that thiophosphites add more efficiently to alkenes than phosphites.[32b] This aspect has been attributed to the greater stability of the thiophosphonyl radical (compared to the phosphonyl radical). Taillades and co-workers reported Et_3B catalyzed hydrophosphinylation of functionalized alkenes leading to various diphenylalkyl phosphine oxides 1.**71a-e** in good yields (Scheme 1.20).[33] This reaction was initiated by phosphinyl radicals. Methanol as a solvent was found to be better than acetone or hexane.

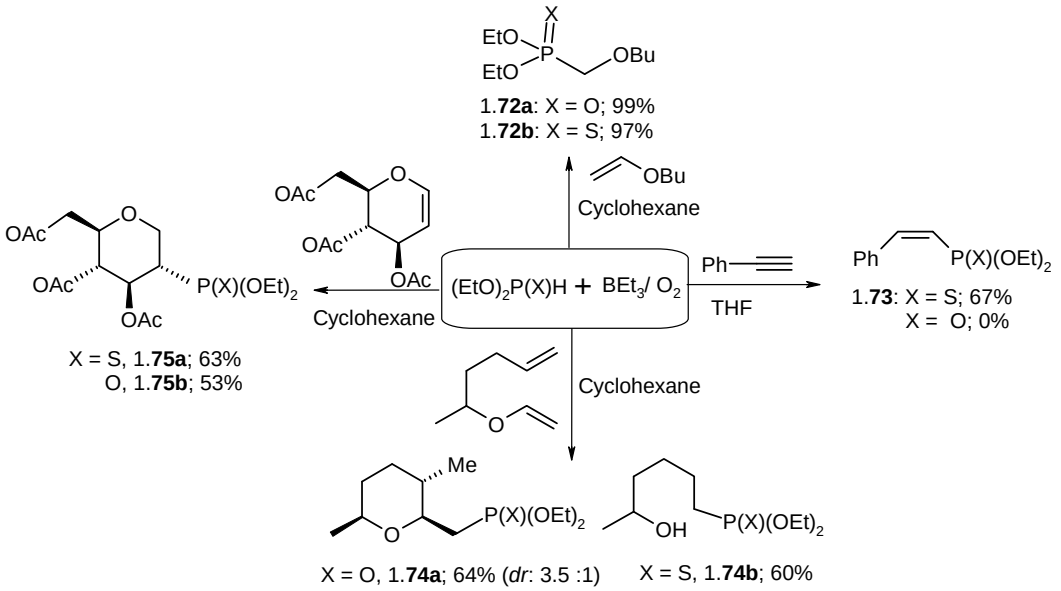
Scheme 1.20



R = $(CH_2)_5CH_3$ (1.**71a**)
CH_2COOH (1.**71b**)
$CHOH(CH_2)OH$ (1.**71c**)
CH_2CN (1.**71d**)
CH(OAc)CN (1.**71e**)

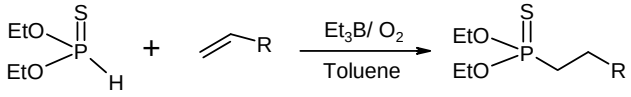
Parsons *et al* performed the addition of diethyl phosphite/ thiophosphite to enol ethers, phenyl acetylene in the presence of a radical initiator (BEt_3/O_2) leading to various products 1.**72-**1.**74**.[34] Stereoselective anti-addition of the thiophosphonyl radical to the double bond of tri-*O*-acetyl-D-glucal was observed to give 1.**75a** as a single diastereoisomer (Scheme 1.21). In this reaction, diethyl thiophosphite was found to be more reactive than diethyl phosphite.

Scheme 1.21



Piettre and co-workers have also utilized BEt_3/O_2 for addition of thiophosphites to alkyl substituted alkenes.[35a] Thiophosphonyl radicals were generated by aerobic decomposition of triethylborane and trapped by alkyl substituted olefins to produce thiophosphonates 1.**76a-c** in good yields (Scheme 1.22). In these reactions, it is possible to use *tert*-butyl peroxypivalate also in place of BEt_3/O_2.[35b]

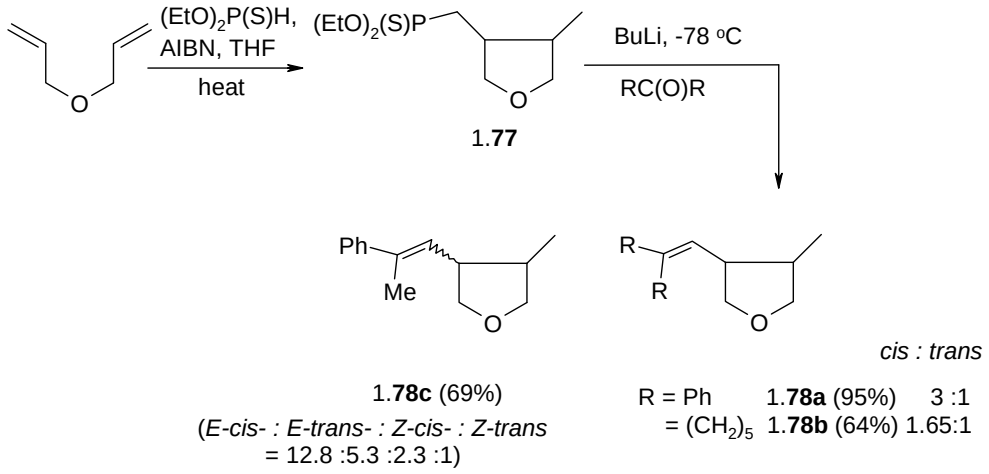
Scheme 1.22



R = $CH_3(CH_2)_5$- 1.**76a** (95%)
= $PhCH_2CH_2$- 1.**76b** (90%)
= $CH_3(CH_2)_3O$- 1.**76c** (79%)

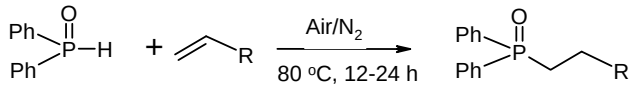
A protocol for the synthesis of substituted alkenes by the addition of diethylthiophosphite to alkenes in the presence of a radical initiator (AIBN) and subsequent HWE reaction with ketones has been developed by Parsons and coworkers (Scheme 1.23).[36] This method could be applied to stereoselective formation of sterically hindered tri- and tetra-substituted alkenes.

Scheme 1.23



Han and co-workers reported a protocol for the air-induced anti-Markovnikov addition of secondary phosphine oxides to activated and unactivated alkenes.[37] Air (oxygen) induces the addition of secondary phosphine oxides to alkenes to selectively produce the corresponding anti-Markovnikov adducts 1.**79a-g** in good to high yields. Mechanistic studies show that the addition probably proceeds via a radical chain mechanism (Scheme 1.24). However, this method is only applicable to H-phosphine oxides, but not for H-phosphonates.

Scheme 1.24

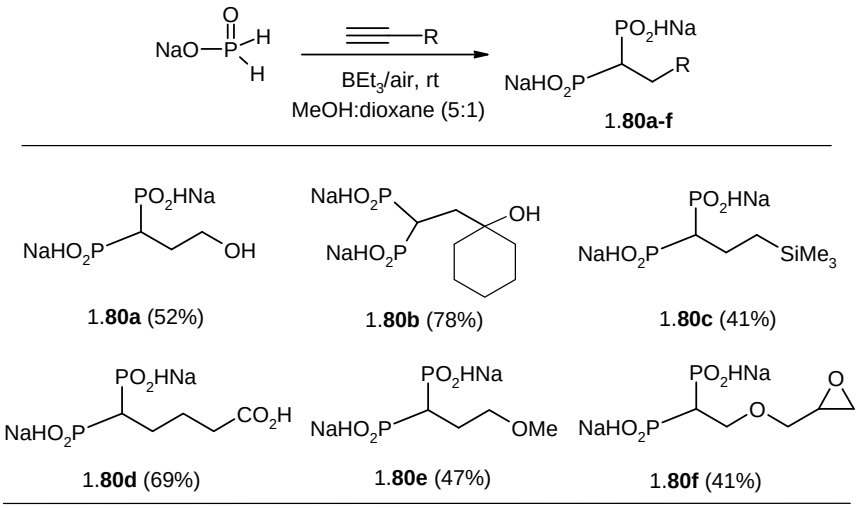


R = *n*-C_6H_{13} (1.**79a**)
= *n*-C_6H_{17} (1.**79b**)
= *cyclo*-C_6H_{11} (1.**79c**)
= $(CH_2)_4OH$ (1.**79d**)
= $(CH_2)_2CN$ (1.**79e**)
= $(CH_2)_2S(O)Ph$ (1.**79f**)
= $P(O)Ph_2$ (1.**79g**)

Montchamp and co-workers reported the bisphosphinylation of terminal alkynes with an excess of sodium hypophosphite to produce the 1-alkyl-1,1-bis-H-phosphine oxides in moderate yields.[38] The reaction is also initiated by Et_3B/air and proceeds under mild conditions (Scheme 1.25). Even though other solvents like THF, CH_3CN, and DMF were employed, methanol/dioxane (5:1) mixture was found to be the best medium for this reaction. The products 1.**80a-f** were precipitated

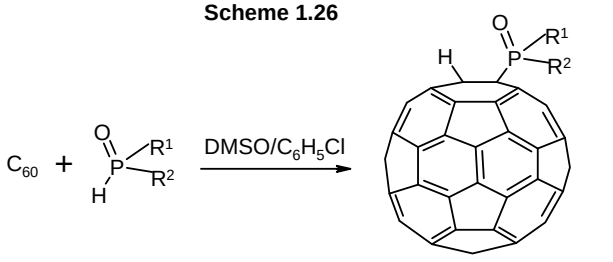
spontaneously from the reaction mixtures, thus providing a simple purification procedure.

Scheme 1.25



A very interesting contribution to this field was made by Nakamura and co-workers.[39] Various phosphine oxides and phosphonates undergo addition to [60]fullerene in DMSO/C_6H_5Cl to produce hydrophosphonylated/phosphinylated fullerene derivatives 1.**81a-d** in moderate to high yields (Scheme 1.26). They propose the involvement of a diradical containing both the fullerene residue and the phosphorus moiety in this reaction.

Scheme 1.26

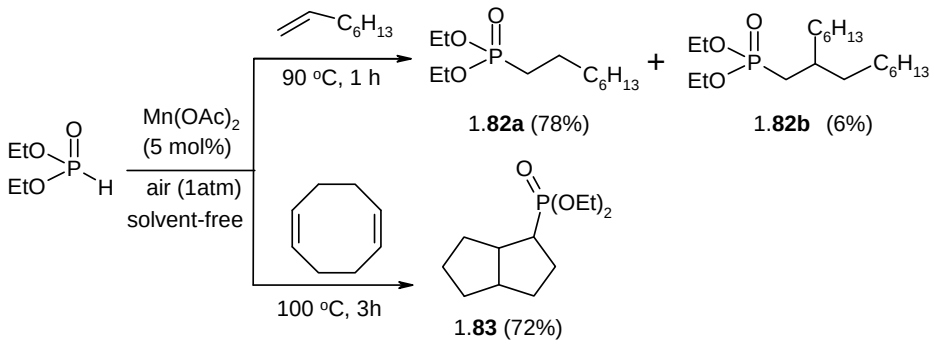


$R_1 = R_2$ =Ph (1.**81a**)
$R_1 = R_2$ =4-F-C_6H_4 (1.**81b**)
R_1 = Me, R_2 =Ph (1.**81c**)
R_1 = OEt, R_2 =Ph (1.**81d**)

Ishii *et al* found that $Mn(OAc)_2$ efficiently catalyzes the addition of dialkyl phosphites, $HP(O)(OR)_2$ to a variety of alkenes in air through a radical process.[40] Thus the reaction of 1-octene with diethyl phosphite in the presence of $Mn(OAc)_2$ in air at 90 °C led to diethyl octylphosphonate 1.**82a** and diethyl (2-

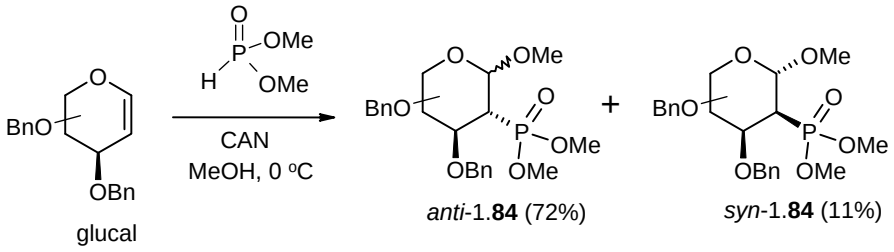
hexyl)decylphosphonate 1.**82b** (Scheme 1.27). In the absence of air, $Mn(OAc)_2$ did not catalyze the reaction. Under similar conditions, interestingly, the use of 1,5-cyclooctadiene produced the novel *cis*-fused product 1.**83** in 72% yield (Scheme 1.27).

Scheme 1.27



Linker and his co-workers investigated ceric ammonium nitrate (CAN) mediated addition of dimethyl phosphite to *O*-benzyl-protected glycols (Scheme 1.28).[41] This reaction occurs smoothly in methanol at 0 °C to afford carbohydrate-2-deoxy-2-phosphonates *anti*-1.**84** (72%) and *syn*-1.**84** (11%) in high yields in a single step, although complete conversion required 10 mole equivalents of the phosphite. The reaction is thought to proceed *via* phosphonyl radicals generated from dimethyl phosphite and CAN.

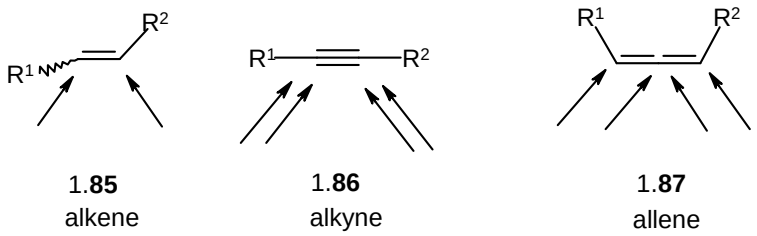
Scheme 1.28



1.224 Transition-metal catalyzed hydrophosphonylation

The most popular organic substrates for transition-metal catalyzed reactions are alkenes 1.**85** and alkynes 1.**86** (Fig 1.**2**).[42] Allenes 1.**87** have received much less attention. While in 1.**85** we face the question of regioselectivity (Markovnikov *vs* anti-Markovnikov orientation leading to constitutional isomers) and

stereoselectivity, in 1.**86**, mono or disubstitution is also possible. In allenes (1.**87**), there are three possible positions for the initial attack that could lead to additional products.



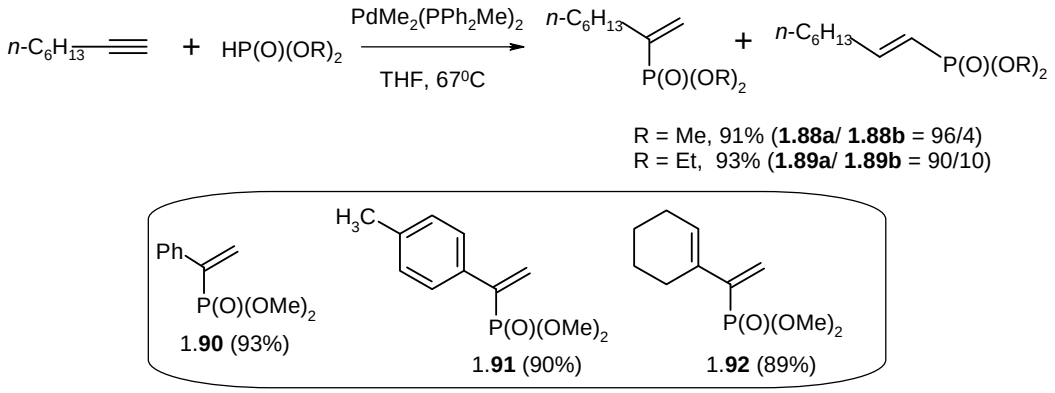
1.**85** alkene 1.**86** alkyne 1.**87** allene

Fig. 1.2. Possible modes of reactions of alkene, alkyne and allene in transition metal catalyzed reactions. Alkynes and allenes can undergo *double phosphonylation*.

(i) Addition of hydrogen phosphonates HP(O)(OR)$_2$

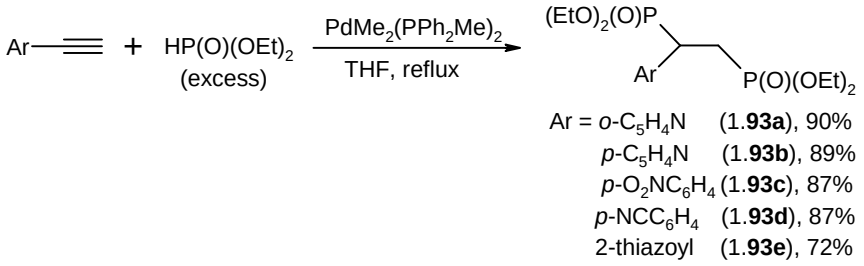
The transition-metal catalyzed hydrophosphonylation of alkynes was discovered by Tanaka's research group in 1996.[43] Pd-catalyzed hydrophosphorylation was readily applied to alkynes for the synthesis of alkenylphosphonates, which are not readily accessible by conventional methods (Scheme 1.29). The addition reaction of 1-octyne with dimethyl phosphite in the presence of a palladium complex in THF proceeds smoothly to afford dimethyl 1-octen-2-ylphosphonate 1.**90a** regio- and stereo-selectively in high yields (Scheme 1.29). It was found that the Pd^0 or readily reducible Pd^{II} species that have less basic ligands display high reactivity in the addition reaction. Thus, *cis*-$PdMe_2(PPh_3)_2$, $Pd(CH_2{=}CH_2)(PPh_3)_2$, $Pd(PPh_3)_4$ and the combination of $Pd(OAc)_2/PPh_3$ efficiently catalyze the reaction, while Pd^{II} complexes such as $PdCl_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(PhCN)_2$, $Pd(OAc)_2$ are totally inactive. Under similar conditions, other alkenyl phosphonates 1.**90**-1.**92** are prepared in high yields with high regioselectivity.

Scheme 1.29



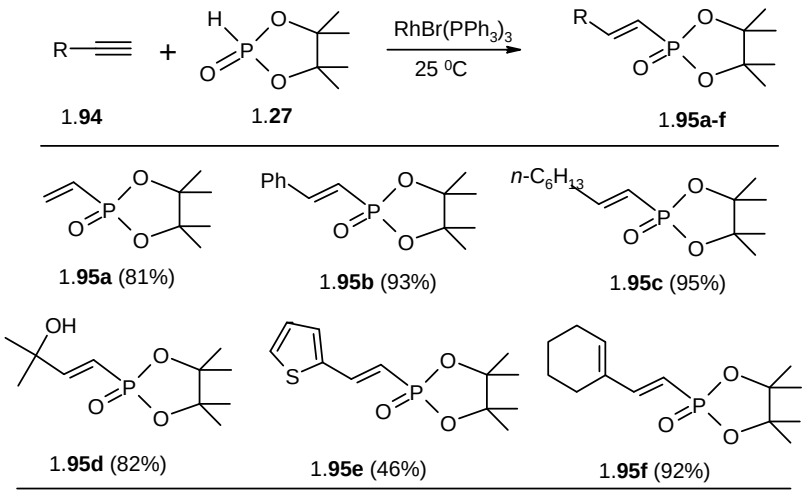
Double phosphonylation was also possible, when an excess of phosphite (3 equivalents) was employed in the reaction to form 1,2-bisphosphonates 1.**93a-e** as shown in Scheme 1.30.[44] The first addition affords the branched isomer with a trace of the linear by-product, as expected. Only the former is reactive to undergo the second addition forming the bisphosphonate.

Scheme 1.30



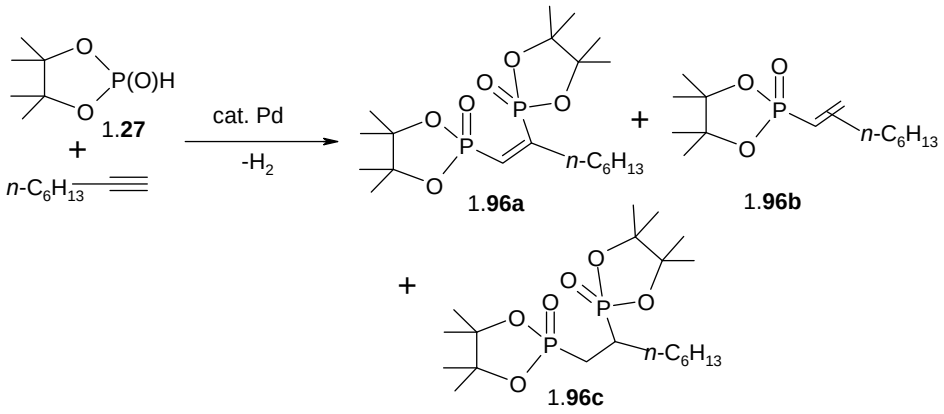
Taking advantage of the exceptionally high reactivity of the five-membered cyclic phosphite (1.**27**), the same group reported a Rh-catalyzed regio- and stereo-selective P(O)-H addition of various alkynes (1.**94)** to yield (*E*)-alkenyl phosphonates 1.**95a-f** under mild conditions (Scheme 1.31).[45] The regioselectivity was completely reversed compared to Pd-catalyzed reactions which is shown in Scheme 1.29. Other Rh-complexes like $RhX(PPh_3)_3$ (X =Cl, I) were also effective, but required high temperature (100 ^oC). Functional groups such as chloro, cyano, hydroxy, thienyl, and silyl are tolerated under these conditions. The en-yne type substrate, 1-ethynyl-1-cyclohexene selectively reacted at the triple bond to give the linear adduct 1.**95f**; this showing the inertness of the internal olefinic bond.

Scheme 1.31



Recently, Han and co-workers introduced a method for dehydrogenative *cis* double hydrophosphonylation of alkynes by using five-membered phosphite (1.**27**).[46] As shown in Table 1.1, this double phosphonylation reaction can be catalyzed by divalent Pd^{II} complexes, especially the chloro Pd^{II} complexes, but is poorly catalyzed by Pd^{0} complexes which predominantly produce the hydrophosphorylation adduct 1.**96b** rather than the double phosphonylation product 1.**96a**. Thus, $Pd(PPh_3)_4$ afforded 1.**96b** in 48% yield, and produced only trace amount of 1.**96a**. As expected, Pd^{II} complexes that are easily reducible to Pd(0) species are not good catalysts for this double phosphonylation either. On the other hand, other divalent phosphine-free chloropalladium complexes such as $PdCl_2(PhCN)_2$, and (η^3-allylPdCl)$_2$ could catalyze the dehydrogenative double phosphonylation as efficiently as $PdCl_2$, giving 1.**96a** in good yields. Additives like styrene, acrylonitrile and methyl acrylate increase the yield of the product 1.**96a**.

Table 1.1: Dehydrogenative double phosphonylation of 1-Octyne



catalyst	olefin (equiv)	yield(%)		
		1.**96a**	1.**96b**	1.**96c**
$PdCl_2$	none	49	28	13
$PdCl_2(PhCN)_2$	none	53	30	7
$Pd(PPh_3)_4$	none	10	48	1
$(\eta^3\text{-allylPdCl})_2$	none	51	30	7
$(\eta^3\text{-allylPdCl})_2$	CH_2=CHPh (3)	69	10	2
$(\eta^3\text{-allylPdCl})_2$	CH_2=CHCN (3)	72	14	1
$(\eta^3\text{-allylPdCl})_2$	CH_2=$CHCO_2$Me (1)	77	13	2

Very recently, Tanaka's group revealed a method for the addition-carbo cyclization of *α,ω*-diynes (1.**97**) with H-P(O)R_2 type of compounds under Pd^{II}/phosphine-catalyzed conditions.[47] Use of PPh_3 resulted low yielding non-selective formation of the products (1.**98a-f**), where chelating ligands like dppe (diphenylphosphinoethane) or dppbn (diphenylphosphinobenzene) afforded product 1.**98b** (Scheme 1.32) selectively in good yields. Shorter- or longer-chained *α,ω*-diynes did not cyclize smoothly or gave low yields. Some of the compounds synthesized in this study are shown in Chart 1.1.

Scheme 1.32

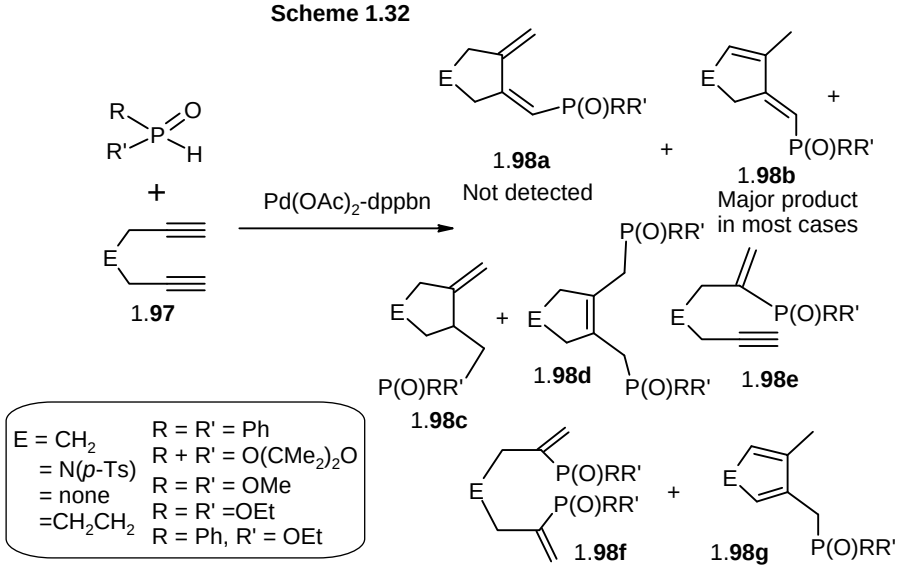
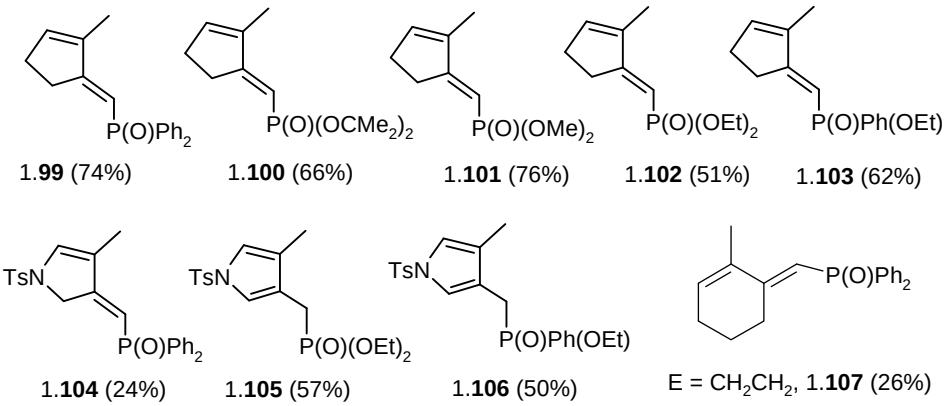
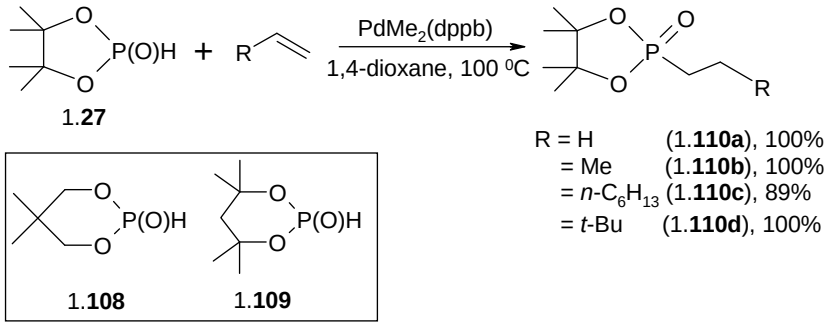


Chart 1.1



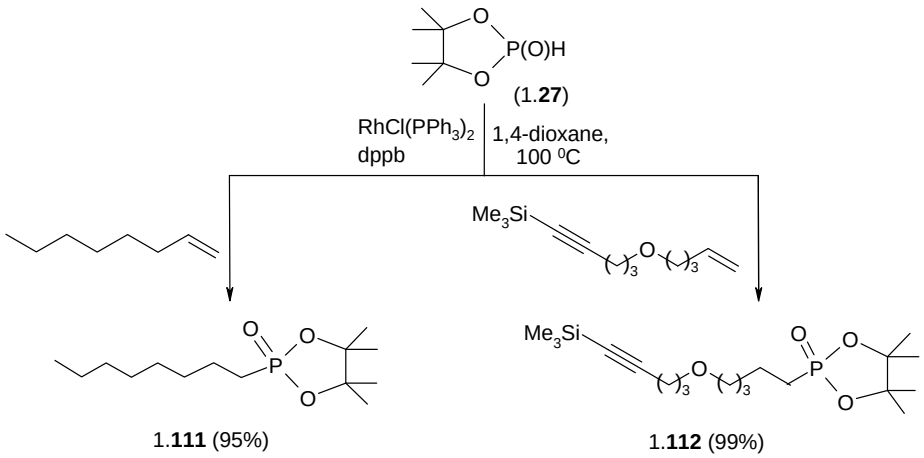
The same group reported Pd-catalyzed regioselective hydrophosphonylation of less reactive alkenes by using the five-membered hydrogen phosphonate 1.**27** leading to linear products 1.**110a-d** (Scheme 1.33).[48] Other phosphites [e.g. dimethyl phosphite, diphenyl phosphite and 1.**108**-1.**109**] were totally inactive under these conditions.

Scheme 1.33



Pagenkopf *et al* disclosed an efficient Rh-catalyzed (Wilkinson catalyst) hydrophosphonylation of long chain alkenes leading to product 1.**111** in the presence of diphenylphosphinobutane (dppb) as an additive (Scheme 1.34).[49] The dppb additive acts as a reductant to re-activate catalytically inactive oxidized rhodium species, which can be formed during the catalysis. They observed that the various substrates that have terminal two alkene linkages, or alkene and alkyne linkages undergo hydrophosphonylation, but the chemoselectivity was rather low leading to a mixture of products. But alkene moiety was selectively phosphonylated, when terminal alkyne moiety contained the bulky Me_3Si group (1.**112**).

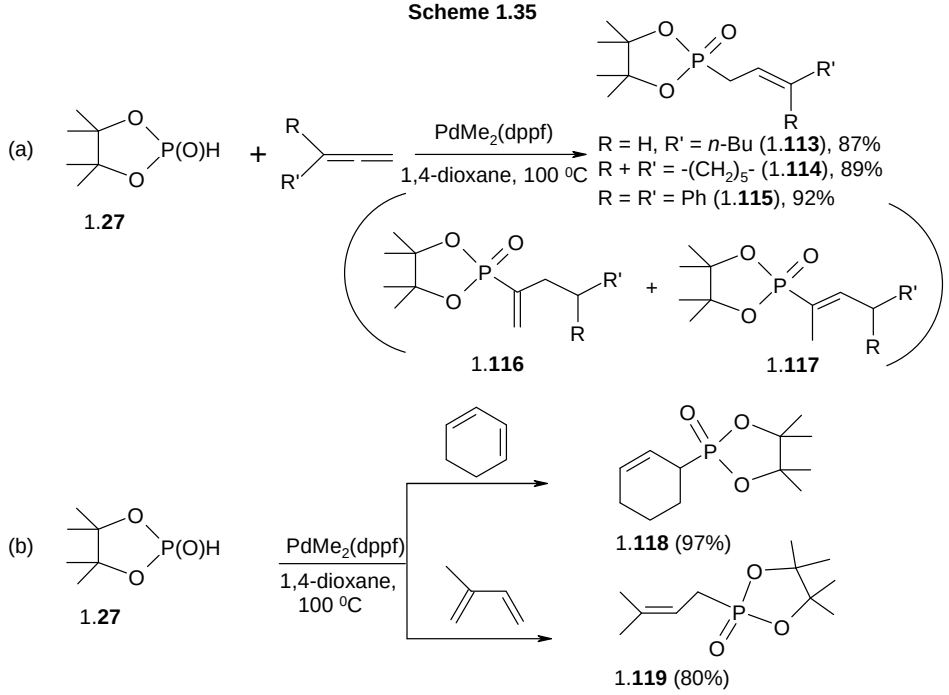
Scheme 1.34



The scope of the P(O)-H addition reaction further extended to 1,2-dienes (allenes) and 1,3-dienes by using $PdMe_2$(dppf) active catalyst to afford allylphosphonates. However, there are only a few reports on the reactions using allenes. In one of these, it is reported that monosubstituted allenes having either an aliphatic or an aromatic substituent reacted efficiently to give the corresponding

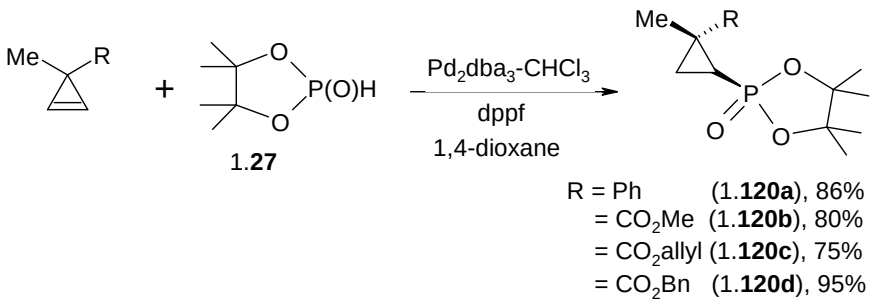
products 1.**113**-1.**115** with the phosphonyl group bound to the terminal carbon regioselectively (Scheme 1.35a).[50] Other isomers 1.**116**-1.**117** (regioisomers of 1.**113)** were formed in very minor quantities. Here an interesting point is that 1,3-dienes gave 1,4-addition products 1.**118**-1.**119 (**Scheme 1.35b),[51]whereas allenes gave 1,2-addition products. Dimethyl and diethyl hydrogen phosphonates were totally unreactive under these conditions.

Scheme 1.35



A novel transition-metal-catalyzed addition of P(O)-H entities (1.**27**) across the cyclopropene double bond has been developed by Rubin's group.[52] This transformation allows for mild and efficient preparation of phosphorus-containing cyclopropanes in good yields (1.**120a-d**) and high degree of diastereoselectivity (Scheme 1.36).

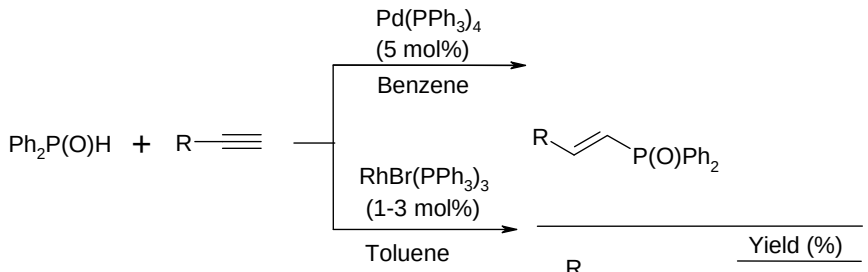
Scheme 1.36



(ii) Addition of secondary phosphine oxides $HP(O)R_2$

Addition of secondary phosphine oxides to unsaturated organic systems (hydrophosphinylation) proceeds in the presence of Pd, Ni, Cu complexes. Tanaka and co-workers found that the use of transition-metal complexes allowed regio and stereoselective control in the addition of secondary phosphine oxides to alkynes. They reported the regio- and stereo-selective synthesis of (*E*)-alkenyl phosphine oxides 1.**121a-d** in high yields by using $[Pd(PPh_3)_4]$[53] or $[RhBr(PPh_3)_3]$[54] (Scheme 1.37). These conditions are mild and compatible with different functionalities like halides, nitriles, protected amines, esters and unprotected alcohols. Addition to internal alkynes also proceeds in excellent yields, but higher temperature and longer duration of heating are necessary.

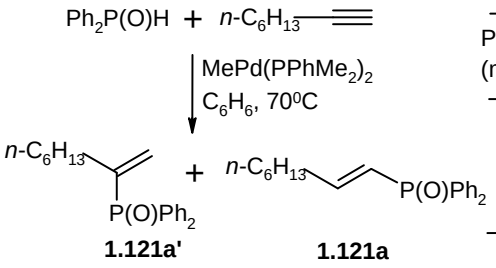
Scheme 1.37



R		Yield (%) Pd	Rh
n-C_6H_{13}	(1.**121a**),	81	91
Ph	(1.**121b**),	79	89
$NC(CH_2)_3$	(1.**121c**),	73	92
$HO(CH_2)_2$	(1.**121d**),	86	94

Tanaka's group also found that reversal of regioselectivity can be attained by adding minor amounts of diphenyphosphinic acid or other acidic compounds in Pd-catalyzed hydrophosphinylation reactions.[55] Branched product 1.**121a′** was predominantly formed under these conditions (Scheme 1.38). The regioselectivity for 1.**121a′** was further improved with an increased amount of $Ph_2P(O)OH$ (5 mol%) to achieve nearly quantitative formation of the adducts 1.**121a′** and 1.**121a** in a ratio of 95:5. Besides the phosphinic acid, dibutyl phosphate and phosphoric acid also gave 1.**121a′** as the major product, but hexamethyl phosphoramide (HMPA), acetic acid or benzoic acid are not effective for this transformation.

Scheme 1.38

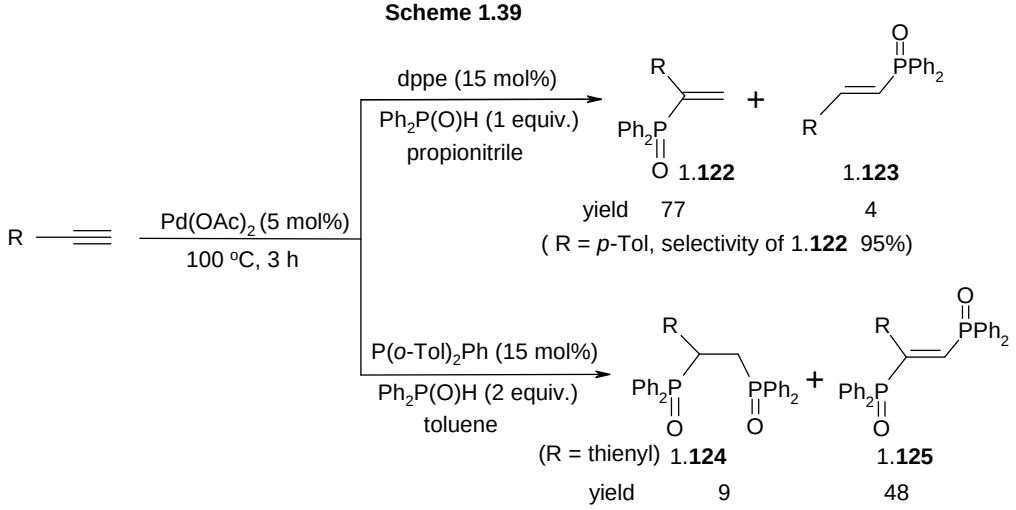


1.121a' **1.121a**

$Ph_2P(O)OH$ (mol %)	Yield of **1.121 (a'/a)** (%)
0	75 (12/88)
1	92 (79/21)
5	99 (95/5)
10	96 (96/4)

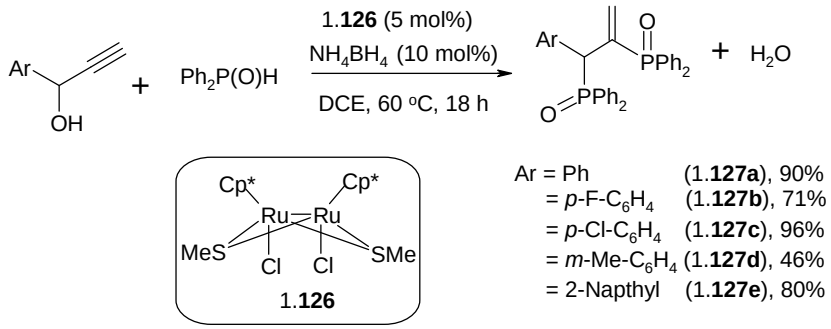
Hydrophosphinylation of a variety of terminal alkynes can also achieved by $Pd(OAc)_2$/phosphine complex under reflux conditions. Use of $Pd(OAc)_2$/dppe combination [dppe-diphenylphosphinoethane] afforded selective mono phosphinylation of alkyne leading to branched isomer 1.**122** as major product and linear isomer 1.**123** as minor ptoduct**.**[56] Use of $Pd(OAc)_2$/P(*o*-tol)$_2$Ph combination with an excess of diphenyl phosphine oxide afforded dehydrogenative *trans*-phosphinylated product 1.**125** in moderate yield (48%) along with bisphosphonylated product 1.**124** in a small quantity (9%) (Scheme 1.39).

Scheme 1.39



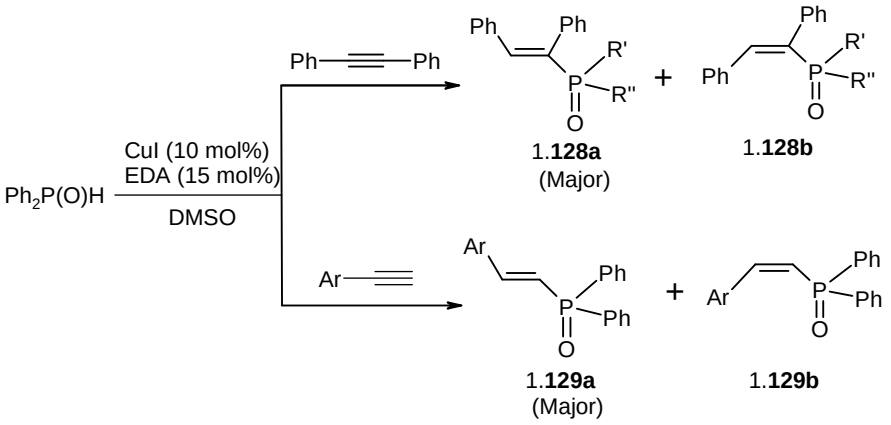
Nishibayashi and his co-workers discovered the ruthenium-catalyzed double phosphinylation of propargylic alcohols with diphenylphosphine oxide that gives the corresponding 2,3-bis-(diphenylphosphinyl)-1-propenes (1.**127a-e**) in high yields with complete selectivity.[57] The active ruthenium-catalyst (1.**126**, Cp* = η^5-C_5Me_5) is also shown in Scheme 1.40.

Scheme 1.40



Copper-catalyzed (CuI/ ethylenediamine) addition of diphenylphosphine oxide to an internal or a terminal alkyne provided the (*E*)-alkenylphosphine oxides 1.**128a** or 1.**129a**, regio- and stereo-selectively (Scheme 1.41). The best yield of the product was obtained when DMSO was used as the solvent.[58]

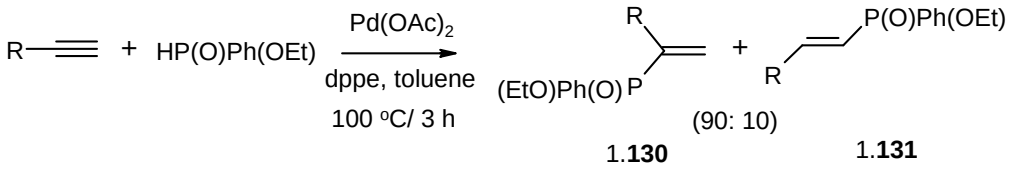
Scheme 1.41



(iii) Addition of hydrogen phosphine oxides HP(O)R(OR')

Hydrogen phosphine oxides HP(O)R(OR') add to alkynes in the presence of the $Pd(OAc)_2$/dppe catalytic system in toluene leading to branched isomers as the major products **1.130a-f** (Scheme 1.42).[59] The regioselectivity could be reversed by changing the solvent from toluene to ethanol or the ligand from dppe to tri-*tert*-butylphosphine leading to linear type product 1.**131** as the major product.

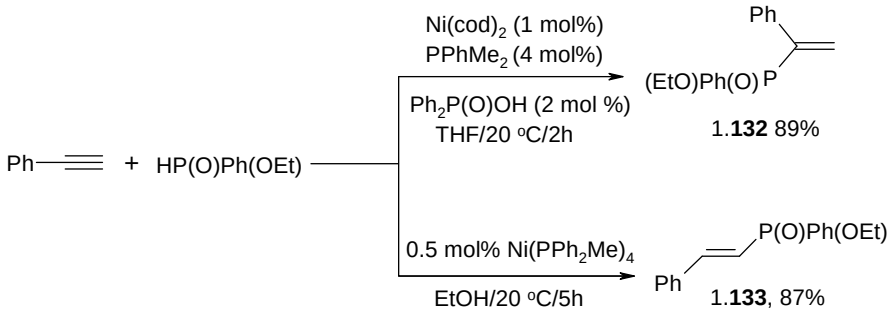
Scheme 1.42



R = -C_6H_5 (1.**130a**), 89%
= -C_6H_4-4-Me (1.**130b**), 87%
= -$(CH_2)_3CN$ (1.**130c**), 88%
= -$(CH_2)_2OH$ (1.**130d**), 72%
= -H (1.**130e**), 76%
= -1-cyclohexenyl (1.**130f**), 85%

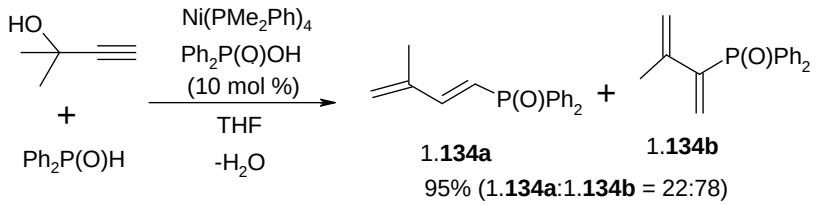
The Ni-catalyzed addition of HP(O)Ph(OEt) compounds to simple terminal alkyne like PhC≡CH in a protic solvent (EtOH) produced the *anti*-Markovnikov *trans*-alkenylphosphorus compound 1.**133** as the major product while a similar addition carried out in an aprotic solvent (THF) using $Ni^0/Ph_2P(O)OH$ as catalyst gave the Markovnikov vinylphosphorus adduct 1.**132** as shown in Scheme 1.43.[60]

Scheme 1.43



In the last example of this section, diphenyl phosphine oxide was reacted with propargyl alcohol at room temperature in the presence of a catalytic amount of $Ni(PMe_2Ph)_4$ and $Ph_2P(O)OH$ to produce high yields of phosphinoyl-1,3-dienes 1.**134a-b** through an efficient *in situ* dehydration process (Scheme 1.44).[61]

Scheme 1.44

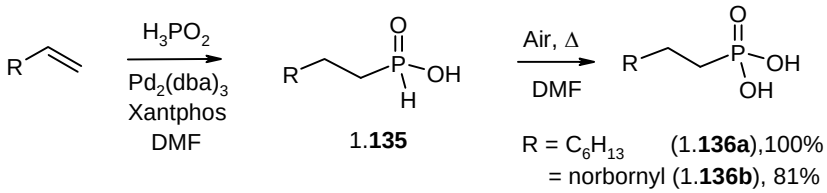


95% (1.**134a**:1.**134b** = 22:78)

(iv) Addition of hypophosphites $H_2P(O)(OR)$

Montchamp and co-workers developed a general and convenient Pd-catalyzed dehydrative allylation of H_3PO_2 with allylic alcohols to synthesize *H*-phosphonic acids 1.**135** (Scheme 1.45). The oxygen present in the system completely oxidizes *H*-phosphinic acid 1.**135** to phosphinic acids 1.**136a-b**.[62]

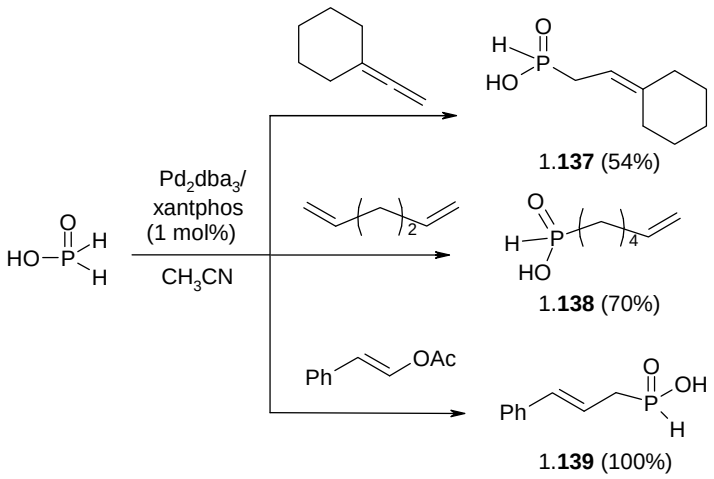
Scheme 1.45



Xantphos = 9,9'-dimethyl-4,5-bis(diphenylphosphino)xanthene

Activated allylic electrophiles, dienes and allenes can also effectively participate in metal-catalyzed P-C bond-forming reactions with hypophosphorous compounds [$MOP(O)H_2$, M = H, R_3NH] under mild conditions leading to compounds 1.**137**-1.**139** (Scheme 1.46).[63] However, as mentioned before, there are not many reports on the reactions using allenes.

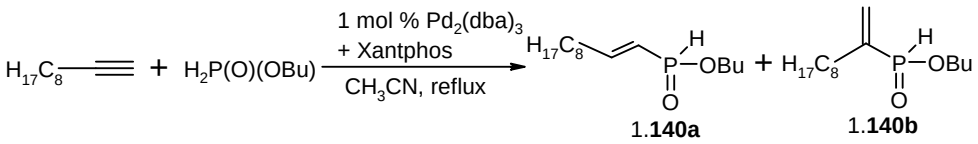
Schcme 1.46



The regioselectivity in the reactions using alkynes is very much dependent on the structure of the ligand. The H-P bond in hypophosphites appears to be much more reactive than that in the phosphine oxide products 1.**140a–b** (Scheme

1.47).[12e,64] Hence the reactions of alkynes do not form symmetrically dialkenyl-substituted phosphine oxides $R_2P(O)(OR')$ (R = alkenyl group) by further reaction.

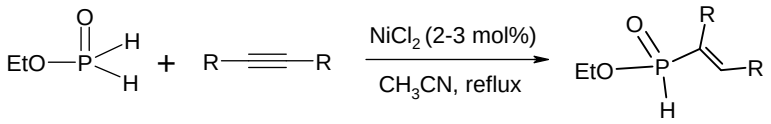
Scheme 1.47



$Pd_2(dba)_3$ + xantphos 78% (linear / branched = 5/1)
$PdCl_2(PPh_3)_2$ + 2 MeLi 70% (branched only)

A ligand-free, $NiCl_2$ catalyzed hydrophosphinylation of alkynes was demonstrated by the same research group of Montchamp.[65] The reaction generally proceeds in high yields, even with internal alkynes (Scheme 1.48), which were poor substrates in the previously reported[64] Pd-catalyzed hydrophosphinylation of alkyl phosphine oxides.

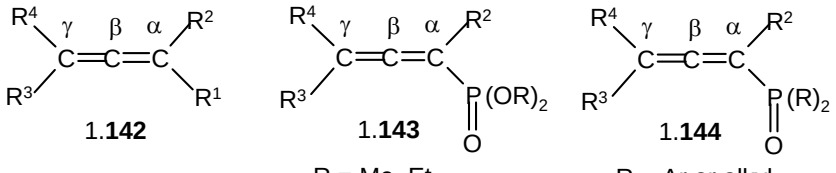
Scheme 1.48



R = ^{i}Pr (1.**141a**), 75%
Bu (1.**141b**), 76%
Ph (1.**141c**), 85%

1.23 Allenylphosphonates/allenyl phosphine oxides-Synthesis and reactivity

1,2-dienes (allenes) with different functionalities (1.**142-**1.**144**) are ubiquitous in organic chemistry for the synthesis of highly complex and strained target molecules of biological and industrial importance.[66-68] The central carbon in such compounds is sp-hybridized (it has only two bonding partners), and the double bond array is linear as a result. Since the π-bonds of allenes are orthogonal, the planes defined by the end carbon substituents are also orthogonal. If one of the substituents of allenes is the $-P(O)(OR)_2$ or $P(O)(R)_2$ moiety, the resulting compounds are allenylphosphonates (1.**143**) or allenyl phosphine oxides (1.**144**).



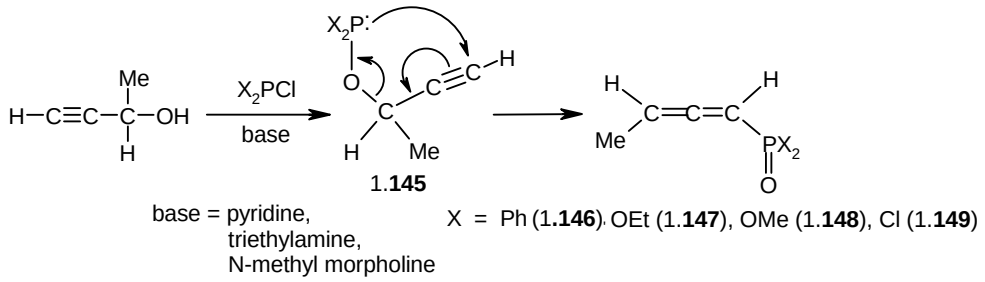
1.**142** 1.**143** 1.**144**

R = Me, Et R = Ar or alkyl

1.231 Synthesis of allenylphosphonates/allenyl phosphine oxides

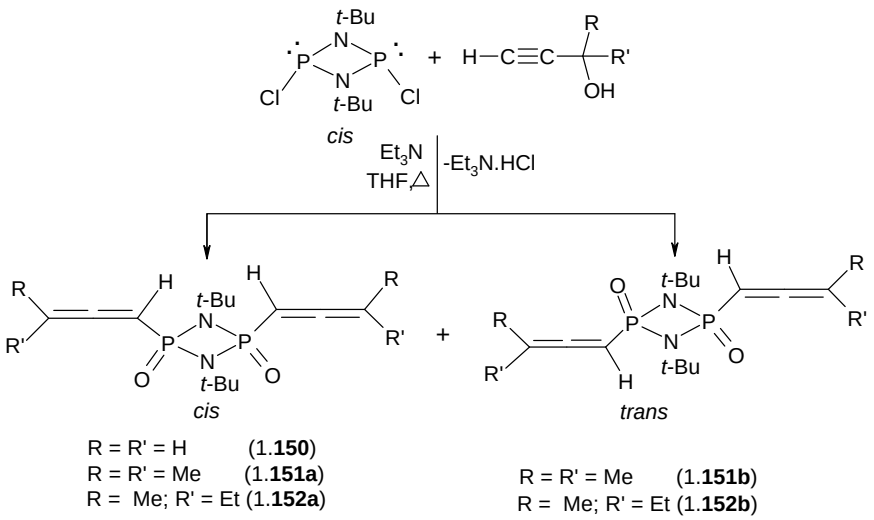
Several methods are available in the literature for the synthesis of allenylphosphonates.[69] The simplest is the treatment of propargyl alcohols (e.g. Me(H)C(OH)C≡CH) with the trivalent phosphorus chlorides X_2PCl in the presence of a base in a suitable solvent (e.g. ether, THF, toluene). This leads to an intermediate 1.**145** [^{31}P NMR: δ ~120-125] which undergoes a pseudo-Claisen type rearrangement, usually at temperatures less than 25 ºC, to afford the allenylphosphonates/allenyl phosphine oxides 1.**146**–1.**149** (Scheme 1.49). The conditions used in this method are mild and the yields are moderate to high.

Scheme 1.49



More recently, the bis-(allenyl)phosphoramidates *cis*-[$(H_2C{=}C{=}CH)(O)P(\mu$-N-*t*-Bu)$]_2$ (1.**150**), *cis*- and *trans*-[$(Me_2C{=}C{=}CH)(O)P(\mu$-N-*t*-Bu)$]_2$ (1.**151a-b**) and *cis*- and *trans*-[(Me)(Et)C=C=CH)(O)P(μ-N-*t*-Bu)$]_2$ (1.**152a-b**) based on a cyclodiphosph(V)azane skeleton have been synthesized in our laboratory by treating *cis*-[ClP(μ-N-*t*-Bu)$]_2$ with the respective propargylic alcohol in the presence of triethylamine (Scheme 1.50).[70]

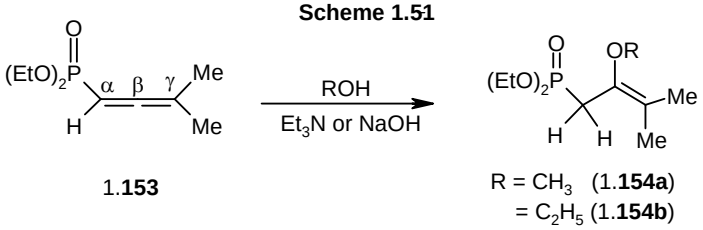
Scheme 1.50



1.232 Nucleophilic addition reactions of allenylphosphonates/allenyl phosphine oxides

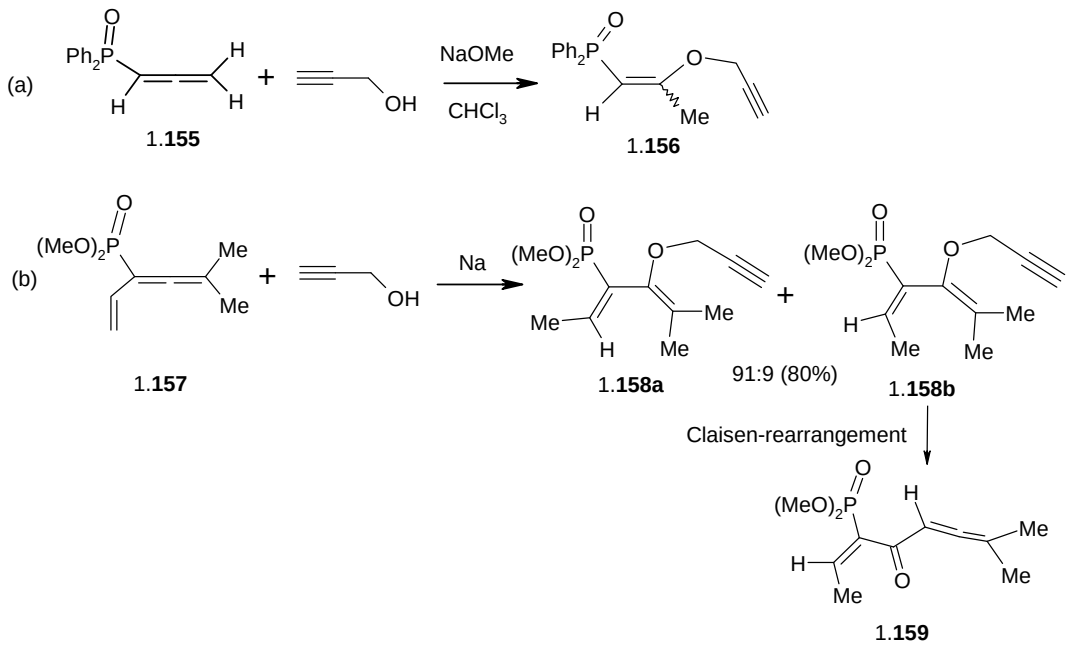
Simple allenes do not have strong tendency and selectivity towards the nucleophilic addition reactions. However allenes containing electron withdrawing groups (-CO_2R, -$P(O)R_2$, -SO_2R) can undergo nuleophilic addition reactions selectively without any difficulty due to the electrophilic nature of the central carbon atom.[71] Thus, allenylphosphonate 1.**153** reacts with alcohols in the presence of NaOH or triethylamine to produce allylphosphonates 1.**154a-b** (Scheme 1.51).[72]

Scheme 1.51



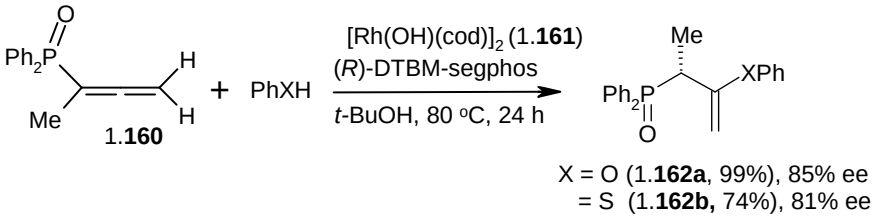
Reaction of propargyl alcohol with the allenyl phosphine oxide 1.**155** in the presence of NaOMe leads to the *β*-addition (vinyl phosphine oxide) product **1.156** (Scheme 1.52a)**.**[73] In contrast, addition of propragyl alcohol to *α*-vinyl allenylphosphonate 1.**157** leads to 1,4-addition products 1.**158a-b**. Claisen-rearrangement of 1**.158b** affords *β*-ketophosphonate product (1.**159**) containing an allene moiety (Scheme 1.52b).[74]

Scheme 1.52



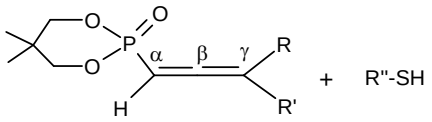
Recently Hayashi and co-workers reported asymmetric addition of phenol or thiophenol to allenyl phosphine oxide 1.**160** to give chiral vinyl ether 1.**162a** or vinyl thioether 1.**162b** with 81-85% *ee* in the presence of a hydroxorhodium complex (1.**161**) co-ordinated with a chiral bisphosphine ligand [(R)-DTDM-segphos] (Scheme 1.53).[75]

Scheme 1.53



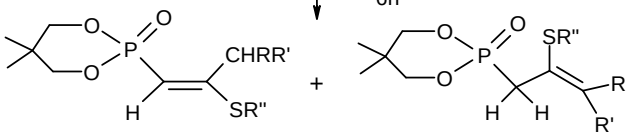
Reaction of ethanethiol, 2-mercaptoethanol and ethane-1,2-dithiol with the phosphorylated allenes have been investigated before; one or two molecules of the thiol adds to the allene in these cases.[76] Very recently, the addition of thiophenols to various allenylphosphonates (1.**163a-c**) under neat conditions (Scheme 1.59) has been reported from our laboratory.[67b] The yields are quite good; both the vinyl- and allyl-phosphonates 1.**164-**1.**168** are formed in this reaction.

Scheme 1.54



R, R'= H (1.**163a**)
R= Me, R'= H (1.**163b**)
R, R'= Me (1.**163c**)

Neat, 110 °C
6h

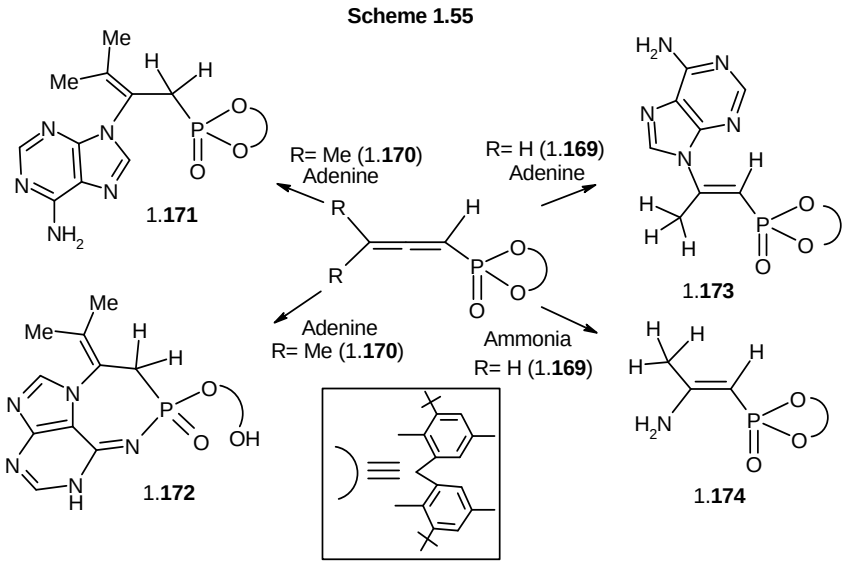


R, R' = H, R'' = 4-Cl-C_6H_4 (1.**164a**)
R = Me, R' = H, R'' = 4-Cl-C_6H_4 (1.**165a**)
R, R'= H, R''= C_6H_{11} (1.**166**)

R, R' = H, R'' = 4-Cl-C_6H_4 (1.**164b**)
R = Me, R' = H, R'' = 4-Cl-C_6H_4 (1.**165b**)
R, R'= Me, R''= 4-Cl-C_6H_4 (1.**167**)
R, R'= Me, R''= CH_2CH_2OH (1.**168**)

Nucleophilic addition of secondary amines to allenylphosphonate produces enamines which upon subsequent acid hydrolysis lead to *β*-ketophosphonates.[69a] Recently from our laboratory, the reaction of allenylphosphonates 1.**169**-1.**170** with nucleobases as well as gaseous ammonia leading to a variety of allylic and vinylic phosphonates has been reported.[77] The reaction of allenes 1.**169**-1.**170** with nucleobase (adenine) furnished both (*E*)-vinyl and allyl phosphonates 1.**171-1.173**, whereas in the reaction of allene 1.**169** with ammonia the (*Z*)-vinylphosphonate 1.**174** is preferentially formed (Scheme 1.55). The latter result was ascribed to hydrogen bonding effects. It is interesting to note that both the N(9) [1.**171**] and N(7) addition products [1.**172**] are isolated and in the formation of 1.**172**, a novel cyclization has occurred after the cleavage of the dioxaphosphocin ring.

Scheme 1.55

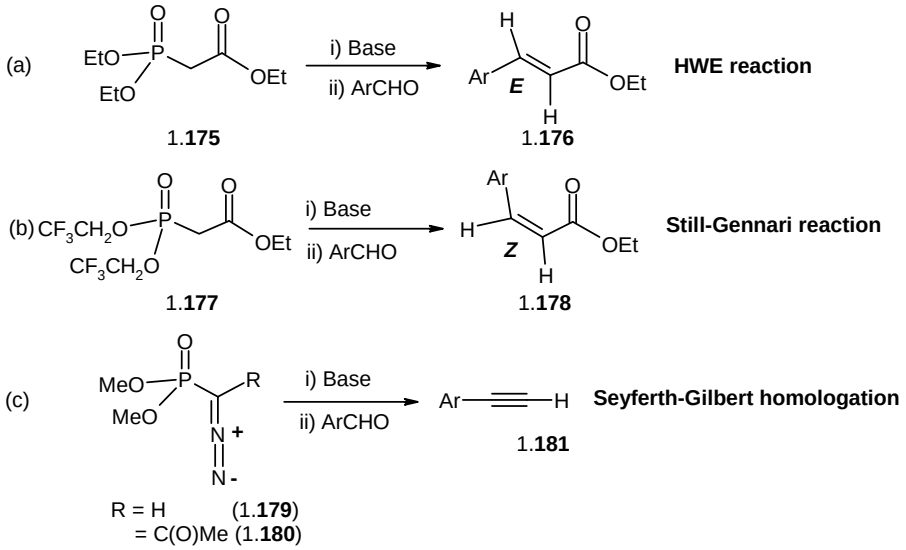


1.3 Importance of Organophosphonates

1.31 Utility in organic synthesis

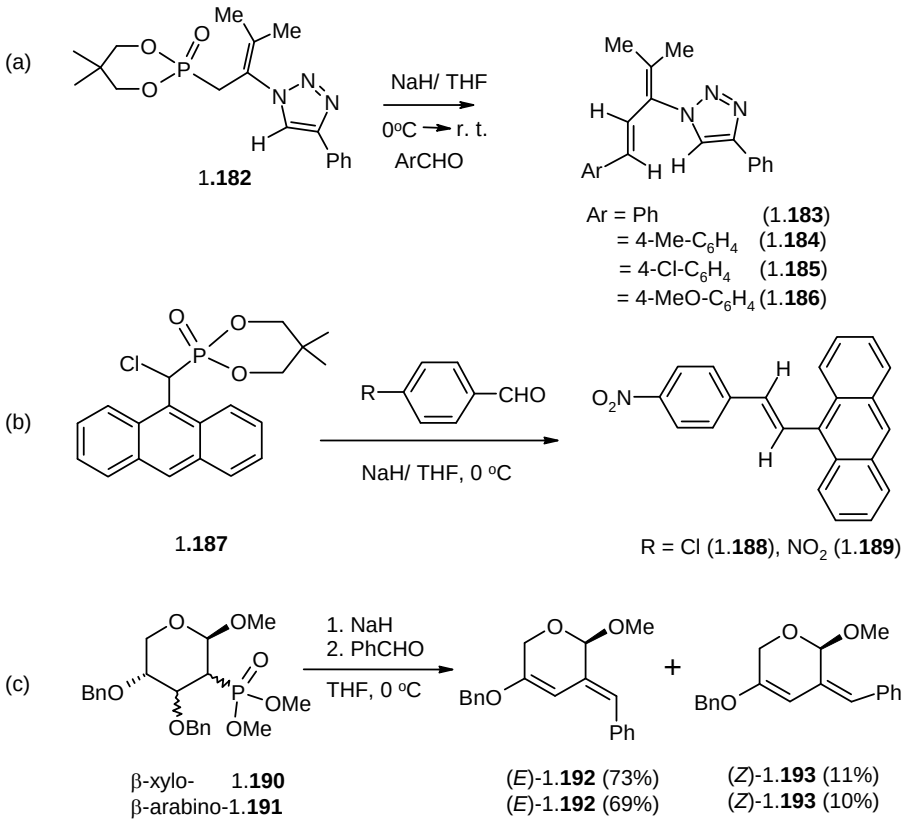
Organophosphonates containing proton on carbon α- to phosphorus are utilized in the C-C bond forming reactions with aldehydes to afford alkenes or alkynes. The Horner-Wadsworth-Emmons (HWE) reaction favors the formation of *E*-alkenes. In general, the more equilibration amongst intermediates, the higher the selectivity for *E*-alkene (1.**176**) formation (Scheme 1.56a).[78] Still and Gennari have developed the conditions by using phosphonates with electron-withdrawing groups (trifluoroethyl) (1.**177**) to give *Z*-alkenes (1.**178**) with excellent stereoselectivity (Scheme 1.56b).[79] Seyferth-Gilbert developed a method for the synthesis of aryl-substituted acetylenes (1.**181**) by treating aromatic aldehyde with dimethyl (diazomethyl)phosphonate (1.**179**) in the presence of KO^{t}Bu as base (Scheme 1.56c).[80] Bestmann modified the reaction by using dimethyl (1-diazo-2-oxopropyl)phosphonate (1.**180**) with potassium carbonate as a base (Scheme 1.56c).[81] The use of the potassium carbonate makes this procedure much more compatible with a wide variety of functional groups.

Scheme 1.56



The literature on the use of phosphonates in HWE reaction is vast[82a] and only a few recent examples are given here (Scheme 1.57). First two examples are from our laboratory. One involves the synthesis of triazoles (1.**183**-1.**186**) and the other involves conjugated systems bearing anthracene residue (1.**188**-1.**189**) (Scheme 1.57a-b).[8c,82b] The next example relates to the work of Linker and co-workers who prepared substituted carbohydrates (1.**192**-1.**193**) by using carbohydrate-2-deoxy-2-phosphonates (1.**190**-1.**191**) (Scheme 1.57c).[41]

Scheme 1.57



1.32 Biological activity

The potential of phosphonates as phosphate mimics is well-known.[83] Unlike a phosphate group, the phosphonate linkage is not readily hydrolyzed in a biological environment, and this unique property has made these compounds attractive as phosphate analogues in numerous applications.[84] The naturally occurring phosphonate, 2-(aminoethyl)phosphonic acid, was first isolated in 1959 from sheep rumen.[85] Since then a large number of compounds were synthesized, isolated and tested for their biological activity. Among these, aminophosphonic acids, bisphosphonates, epoxyalkylphosphonates, hydroxyalkylphosphonates, poly(alkylene)-H-phosphonates and nucleoside H-phosphonates constitute a few of the important biologically active phosphorus compounds. Some of the clinically accepted drugs (1.**194**–1.**196**) and a herbicide 1.**197** are shown in Fig. 1.3. The α-aminophosphonate anion 1.**198** is the phosphorus analogue of alanine 1.**199**. Salts of 1.**198** exhibit diverse biological activities that include antibacterial, antiviral, antifungal, pesticidal and glycine antagonism.[2b,2i-m]

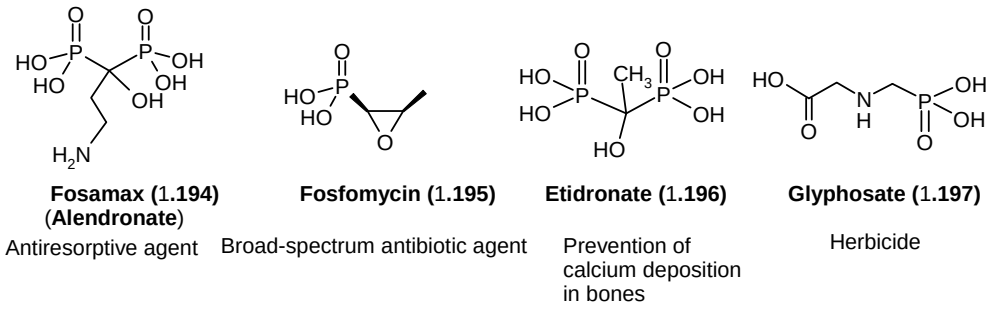
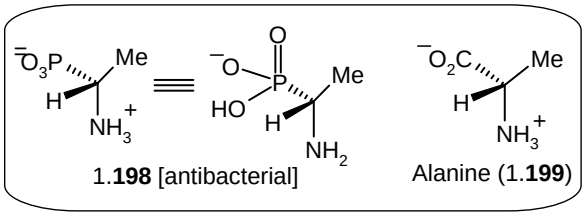


Fig. 1.3. Some useful phosphonate drugs and a phosphonate herbicide



Bisphosphonates are used for osteoporosis and several other bone diseases.[86a] The most potent bisphosphonate drugs currently used to treat bone metabolism disorders such as osteoporosis contain an amino or other N-containing group (N-BPs) and have been shown to hinder bone resorption by inhibiting farnesyl

diphosphate synthase (FPPS), thereby blocking the synthesis of isoprenoid lipids required for the prenylation of small GTPases in osteoclasts.[86] There are also several phosphonate and phosphine oxide based enzyme inhibitors that show very potent activity.[87] Compounds 1.**200**–1.**204** are representative examples (Fig 1.4). Thus it appears that this is a fertile area for pharmaceutical research.

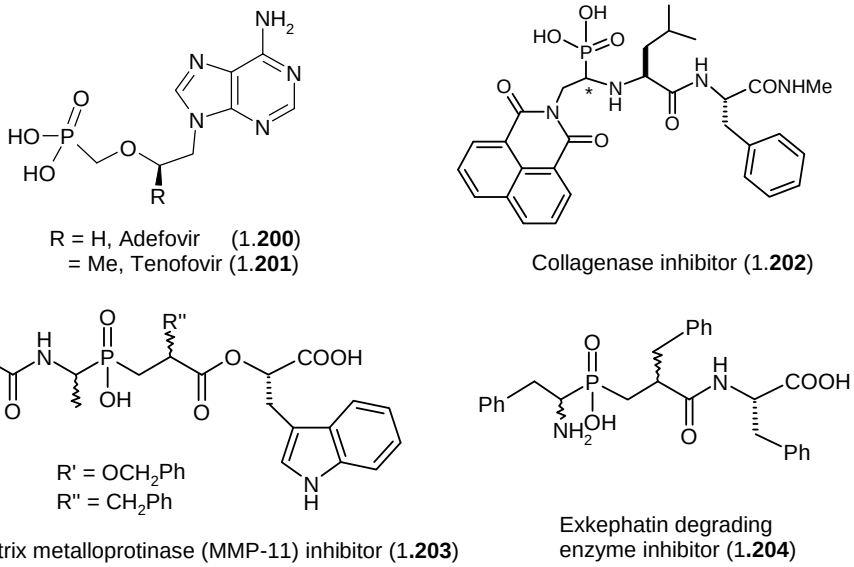


Fig. 1.4. Some useful phosphonate and phosphine oxide based enzyme inhibitors.

OBJECTIVES OF THE PRESENT WORK - PART A

The main objective of this part of the present work is to develop organophosphonate chemistry. Specifically, it is intended to explore the following:

(i) Synthesis of new functionalized allenylphosphonates using a variety of propargyl alcohols and a suitable P^{III}-Cl precursor.

(ii) (a) Pd-catalyzed [in this thesis, the term 'Pd-catalysis' is used to mean catalysis by Pd^{II}, Pd^{I} or Pd^{0} complexes] hydro(thio)phosphonylation/hydro(thio)phosphinylation of allenylphosphonates/allenyl phosphine oxides and an alkynylphosphonate/alkynyl phosphine oxide.

(b) Solvent-free, catalyst-free hydro(thio)phosphinylation of allenylphosphonates/allenyl phosphine oxides

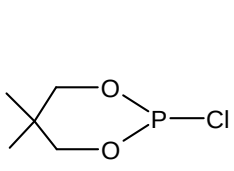
(c) P(*n*-Bu)$_3$-catalyzed hydrothiophosphonylation/ hydro(thio)phosphinylation of allenes and alkynes, and

(iii) $Zn(OTf)_2$/amine catalyzed cyclization involving propargyl alcohols and allenes leading to five-membered heterocycles (furans).

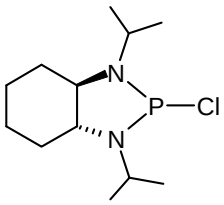
RESULTS AND DISCUSSION

2.1 General comments on the synthesis and characterization of phosphorus precursors and allenes

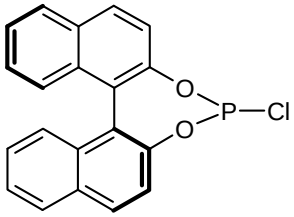
The P^{III}-Cl precursors **1-3** have been prepared by established methods available in the litereature,[88-91] with only minor modifications where necessary. The P-Cl functionality present in these compounds is utilized in subsequent reactions as detailed below.



1 [δ(P): 145.8]



(±)-**2** [δ(P): 178.8]

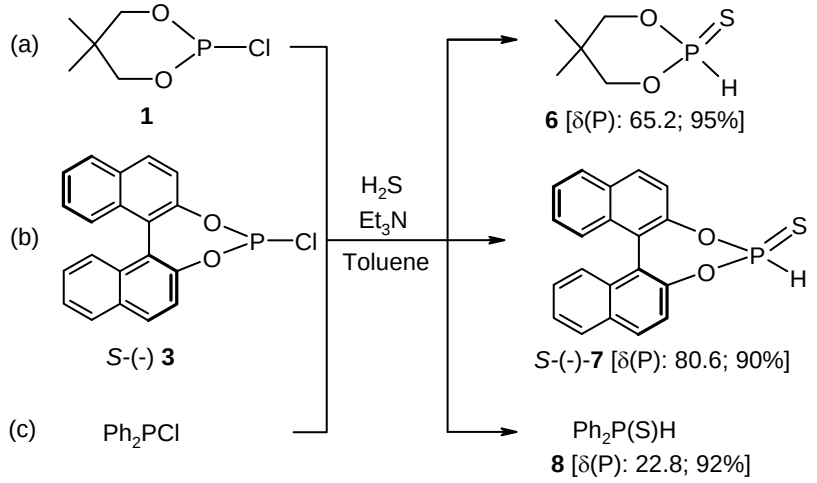


(***S***)-**3** [δ(P): 177.8]

Compound **1** readily hydrolyzes in water to give the cyclic phosphite $(OCH_2CMe_2CH_2O)P(O)H$ [**4**; δ(P) 2.3].[88] The phosphine oxide $Ph_2P(O)H$ [**5**; δ (P) 21.5][92] was prepared by treating Ph_2PCl with water in the presence of K_2CO_3. Compounds **4-5** were distilled in vacuum prior to use. Compound **4** is comparable in cost to the commercially available diethyl phosphite [$(EtO)_2P(O)H$], since the precursor diol is very inexpensive.

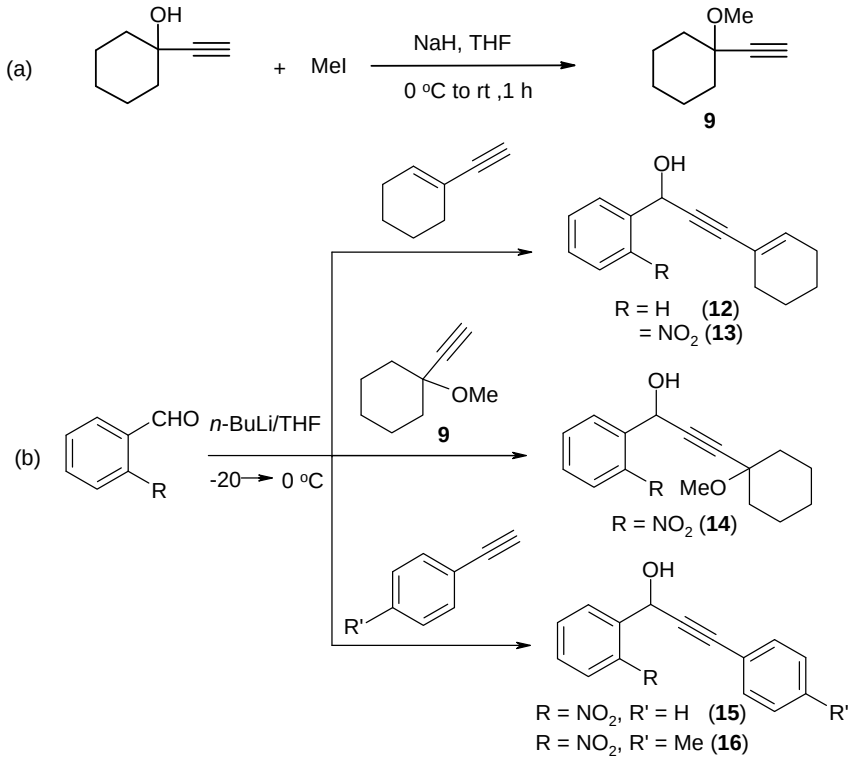
To assess the reactivity of cyclic phosphite **4** vis a vis other phosphonylating agents in Pd-catalyzed phosphonylation reactions, the sulphur analogue $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) was prepared from the reaction of $(OCH_2CMe_2CH_2O)PCl$ (**1**) with hydrogen sulphide in the presence of triethylamine (Scheme 1a).[14] In an analogous manner, compounds *S*-(-)-$(C_{20}H_{12}O_2)P(S)H$ (**7**) and $Ph_2P(S)H$ (**8**) were also prepared by using the respective chlorophosphite precursors (Scheme 1b-c).[14]

Scheme 1



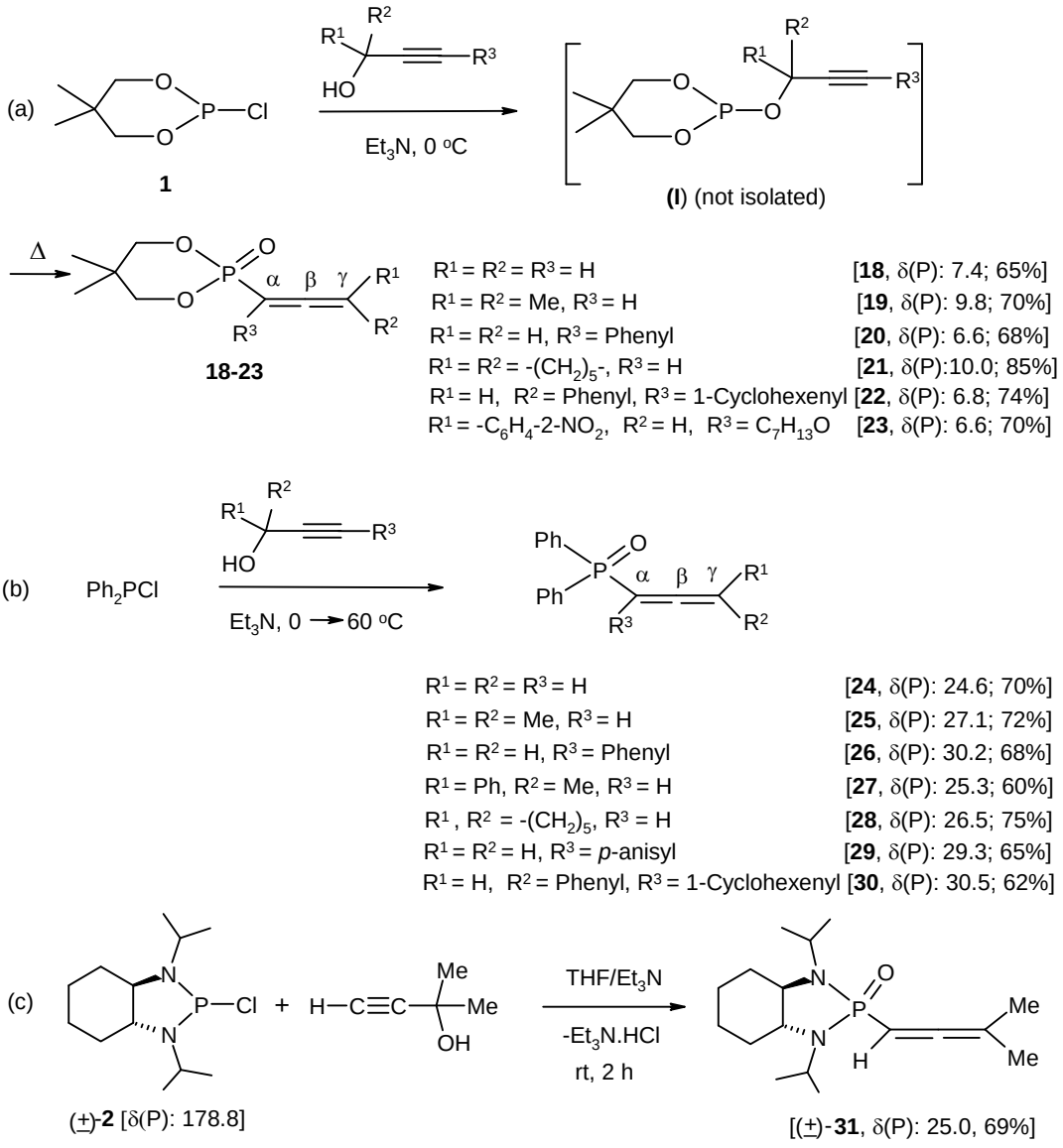
For the synthesis of allenylphosphonates, it was necessary to have a library of propargyl alcohols. The propargylic ether **9**,[93] required precursor for the propargyl alcohol **14**, was prepared by treating the corresponding propargyl alcohol with methyl iodide in the presence of sodium hydride (Scheme 2a). Propargyl alcohols PhC≡CCH$_2$(OH) (**10**) and *p*-MeO-C$_6$H$_4$-C≡CCH$_2$(OH) (**11)** are prepared by using literature procedures.[94-95] The substituted propargyl alcohol **12** and nitro-group containing propargyl alcohols **13-16** were also prepared by modifying a literature method (Scheme 2b).[96-97] The function of *n*-BuLi is to form the lithium acetylide using the terminal (acetylinic) proton. This acetylide adds across the carbonyl carbon to form an -OLi salt which upon treatment with aqueous NH_4Cl affords the corresponding propargyl alcohol. It is possible to use a Grignard reagent also, but the yields would be lower. Ester allene [EtO$_2$C-C(H)=C=CH$_2$] **(17)** was prepared by a procedure reported previously from our laboratory.[98] This route involves the reaction of the ylide Ph$_3$P=CHCO$_2$Et with acetyl chloride [MeC(O)Cl] in the presence of the base triethylamine in dichloromethane as the solvent. The byproduct Ph$_3$P(O) precipitates out upon addition of hexane while triethylamine takes up a molecule of HCl in the reaction. This allene **(17)** needs to be stored at -5 ^{o}C under nitrogen to prevent polymerization.

Scheme 2



Allenylphosphonates **18-23** [*via* intermediate (**I**)] and allenyl phosphine oxides **24-30** were prepared by the method previously reported from our laboratory (Scheme 3a-b) by utilizing propargyl alcohols.[69] Allenylphosphoramidate **31** was obtained by the reaction of **2** with propargyl alcohol HC≡CCMe$_2$(OH) as depicted in Scheme 3(c). Among these, **21-23** and **29-31** are new. Allenes **18-31** are fairly stable in air in the solid state and in solution under inert atmosphere. In the IR spectra, they show a characteristic strong band at 1920-1975 cm^{-1} due to ν_{asym}(C=C=C).[69] In the ^{1}H NMR spectrum of compound **18**, a multiplet observed in the region of δ 5.02-5.30 is ascribed to the proton attached to the *α*-carbon (to phosphorus). This feature is due to the coupling ^4J(H-H) in addition to ^2J(P-H). The *α*-carbon appears as a doublet at δ 80.5 with a ^1J(P-C) value of 216.7 Hz in the ^{13}C NMR spectrum. The *β*- and *γ*- carbon nuclei appear around δ 213.2 and 88.9, respectively. However, the observed coupling constants [*J*(P-H) or *J*(P-C)] of allenyl phosphine oxides **24-30** are low compared to allenylphosphonates **18-23**. In compound **31**, the signals corresponding four –*C*H$_3$ groups on the isopropyl moiety connected to nitrogen show four distinct doublets, showing that these groups are in different environments.

Scheme 3



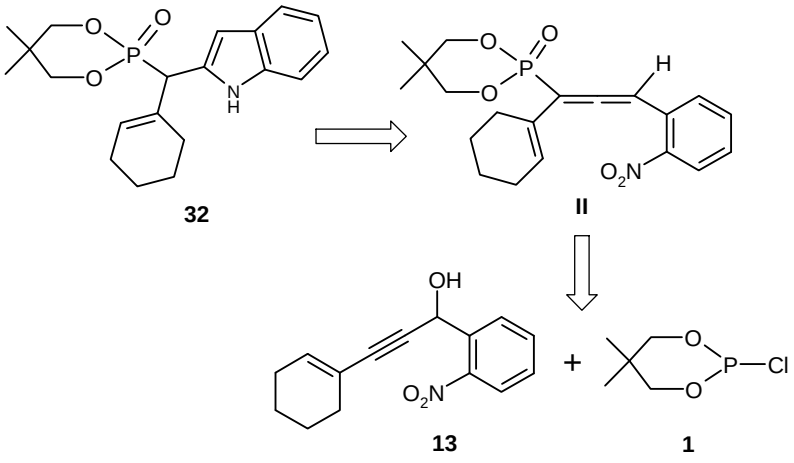
2.2 Synthesis of phosphorus-containing heterocycles *via* propargyl alcohols

2.21 Formation of dibenzo-azepines

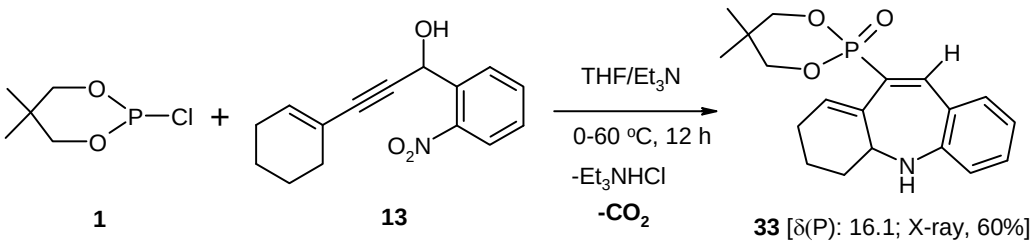
As an extension of our work in allenylphosphonate preparation, we made an attempt to synthesize the allene (**II**) by treating ($OCH_2CMe_2CH_2O$)PCl (**1**) with the appropriate nitro substituted propargyl alcohol **13** (Scheme 4). Another reason for our interest in this compound was the possibility of using this allene (**II**) to prepare phosphono-indole derivative of type (**32**) by reductive cyclization.[99] However, rather surprisingly, the ^{31}P NMR spectrum of the reaction mixture showed two peaks at δ 11.2 (minor, 20%) and 16.1 (major, 80%) instead of the expected one in the allene region [δ ~6.5-8.0; cf. Scheme 3(a), compounds **22-23**]. There was no reaction in the

absence of Et_3N. We have been able to isolate the species with δ(P) 16.1. IR spectrum of this compound did not exhibit any band in the region 1900-2000 cm^{-1} expected for the allene. The ^{13}C NMR spectrum did not show any signal at δ 213-214 (central carbon of allene moiety); also, a signal centered at δ 51.3 indicating an aliphatic carbon away from normal C-C bonded region is seen [Fig. 1]. Hence this species was subjected to single crystal X-ray crystallographic investigation. This study revealed that the compound in question was the phosphorus containing tricyclic aromatic derivative **33** (Scheme 5, Fig. 2). It is interesting to note that this compound is a reductive cyclized product, and contains ***one carbon less than what is expected***. The newly formed **seven-membered ring** comprises the atoms C6, C7, C8, C13, N1, C14 and C19. The presence of the NH group is revealed by its hydrogen-bonding interactions with the phosphoryl oxygen as shown on the right side of Fig. 2. The C(6)-C(7) distance of 1.344(5) Å shows that there is a double bond between these two atoms as shown in the structural drawing in Scheme 5. Clearly, the oxygen atoms of the -NO_2 group in the precursor propargyl alcohol **13** as well as an additional carbon atom are missing in the structure. Thus, in addition to $Et_3N.HCl$, a carbon and two oxygen atoms are eliminated (possibly as CO_2).

Scheme 4



Scheme 5



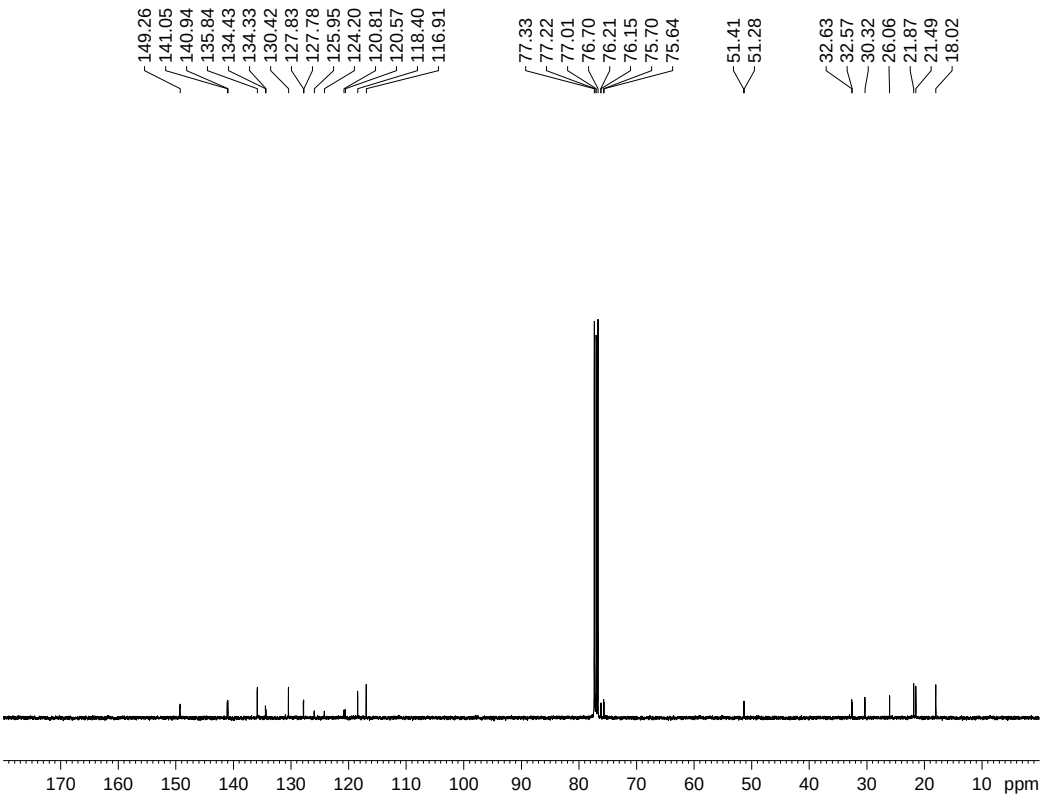


Fig. 1. ^{13}C NMR spectrum of compound **33**

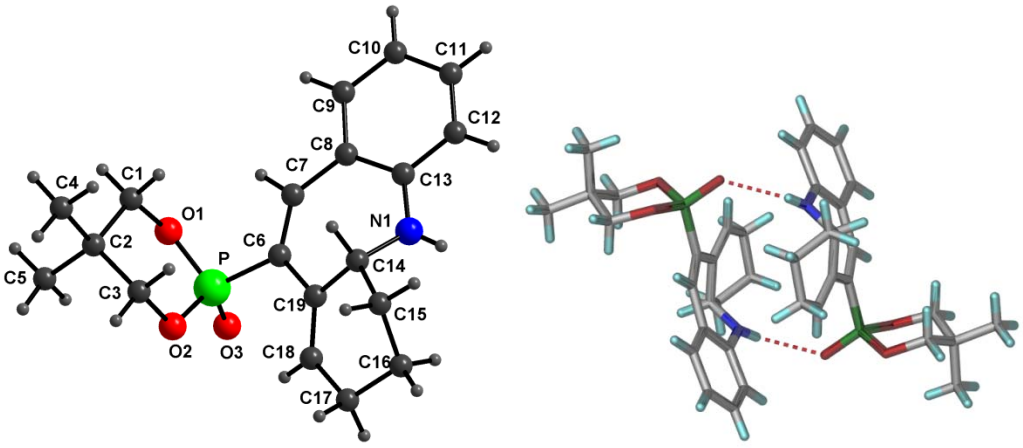
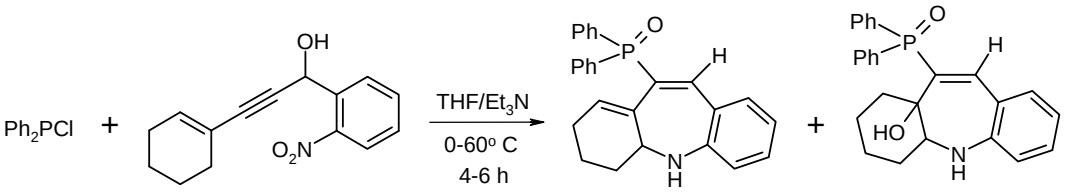


Fig. 2. Molecular structure of compound **33**.$CHCl_3$ (left). The solvent molecule is omitted for clarity. Selected bond lengths [Å] with esd's in parentheses: P-C(6) 1.795(3), N(1)-C(14) 1.430(5), C(6)-C(7) 1.344(5), C(7)-C(8) 1.457(5). Dimeric structural unit of compound **33**.$CHCl_3$ due to the hydrogen bonding (right). Hydrogen bond parameters: N(1)-H(1D)…O(3) 0.77(2), 2.32(4), 2.997(4) Å, 147.89(6)°; symmetry code: 1-x, -y+2, -z.

To confirm the generality of the formation of the compound **33**, we made an attempt to synthesize a similar compound **34** by treating Ph_2PCl with the propargyl alcohol **13** (Scheme 6). Interestingly, in addition to compound **34** another product **35** was also isolated as a minor product (~5%). This compound is a H_2O addition product across the C=C bond of cyclohexenyl group. Product **35** was structurally characterized by X-ray crystallography (Fig. 3). Here, the newly formed **seven-membered ring** comprises the atoms C13, C14, C15, C20, N1, C21 and C26. The C(25)-C(26) distance of 1.522(3) Å clearly shows a single bond between these two atoms. The presence of additional –OH group is readily discerned by the observation of H-bonding with the P=O acceptor (Fig. 4).

Scheme 6



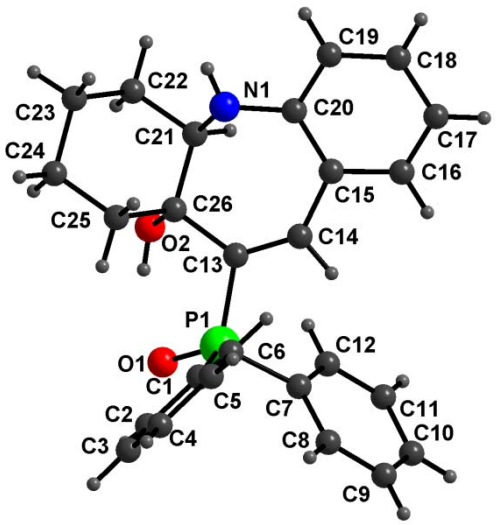


Fig. 3. Molecular structure of compound **35**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(13) 1.799(2), O(2)-C(26) 1.439(2), N(1)-C(21) 1.462(3), C(13)-C(14) 1.345(3), C(25)-C(26) 1.522(3).

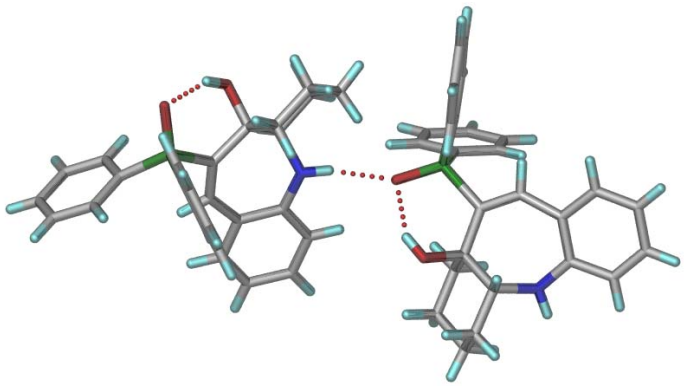


Fig.4. A diagram showing intra- and inter-molecular hydrogen bonding interaction in compound **35**. Parameters for intramolecular hydrogen bonding: O(2)-H(2B)…O(1) 0.84(4), 1.94(2), 2.705(2) Å, 150.8(4)°. Parameters for intermolecular hydrogen bonding: N(1)-H(1A)…O1 0.85(3), 2.09(6), 2.925(2) Å, 166.8(8)°; symmetry code: -x+1, y-1/2, -z+1/2.

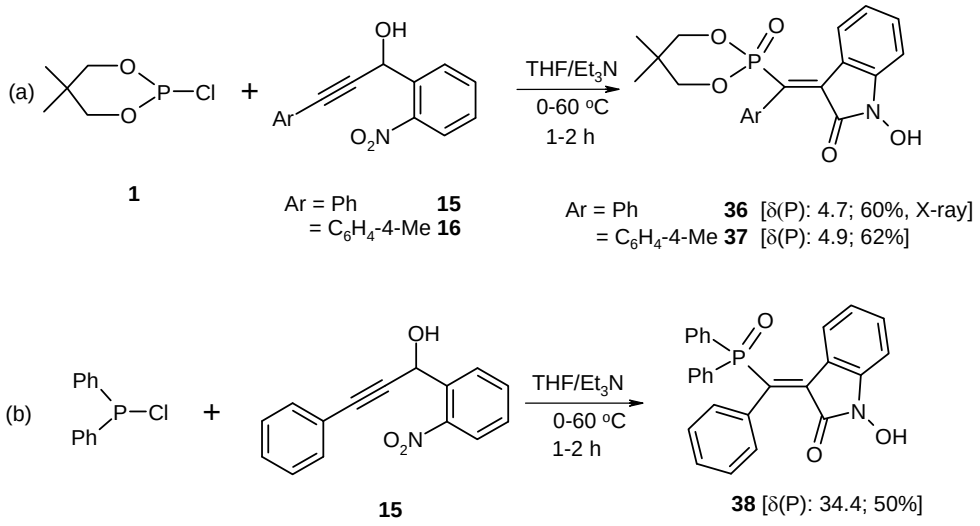
Compounds **33-35** were characterized by spectroscopic and analytical data. Some points about compound **33** are already mentioned above. They all show a band at 3250-3400 cm^{-1} in the IR spectra due to the NH stretch. Compound **35** shows an additional band at 3300 cm^{-1} due to the OH stretch. In the ^{1}H NMR spectrum of compound **33**, a broad signal at δ 2.10 is obseved due to the N-*H* proton. The proton *cis* to phosphorus is seen as a doublet at δ 7.14 [^{3}J(P-H) ~ 26.4 Hz]. It may be noted here that *cis*-^{3}J(P-H) values are more than double that of *cis*-^{3}J(H-H) values.[100] A broad signal for PCCC*H*(cyclohexenyl)) proton at δ 6.57 is also observed. Compared to compound **34** that has two olefinic protons, compound **35** shows only one olefinic proton, as expected. The ^{13}C NMR spectrum of **33** exhibits a characteristic doublet [^{1}J(P-C) = 175.0 Hz] for the P-*C* carbon at δ 125.1 (*cf* Fig. 1). But in the case of **34-35** the doublet is observed in the downfield region [δ 133-134]; also, the ^{1}J(P-C) values [103.7 Hz for **34** and 96.1 Hz for **35**] are lower than that observed for compound **33**.

2.22 Formation of N-hydroxy-indolinones

We then made an attempt to extend this work to include some more examples by using propargyl alcohols **15-16**. But rather than allenylphosphonate or the tricyclic compounds of type **33-35**, these reactions furnished the phosphono-*N*-hydroxy-indolinones **36-37** (Scheme 7a) that are rather uncommon heterocycles.

The reaction of Ph_2PCl with propargyl alcohol **15** also afforded *N*-hydroxy-indolinone **38** (Scheme 7b). The structure of compound **36** was confirmed by X-ray crystallography (Fig. 5). Here, the newly formed **five-membered heterocycle** comprises the atoms C7, C8, C13, N1 and C14. The presence of the N-OH was confirmed by the hydrogen bonding interaction between N-OH and phosphoryl oxygen moiety (Fig. 6). In this case, fairly strong hydrogen bonds [O(5)...O(6) 2.635(4) Å and O(10)...O(1') 2.596(4) Å] were observed, but these hydrogen bond distances are significantly longer than those reported previously from our laboratory.[101]

Scheme 7



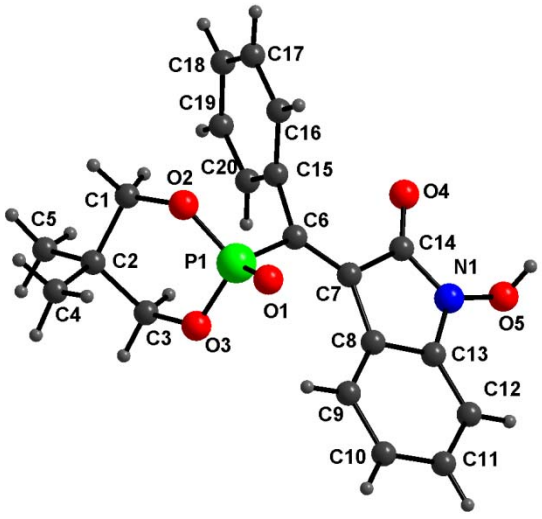


Fig. 5. Molecular structure of compound **36**.CH_2Cl_2. Solvent molecule is not shown for clarity. Only one molecule in the asymmetric unit is shown. Selected bond lengths [Å] with esd's in parentheses: P(1)-O(1) 1.460(3), P(1)-C(6) 1.812(3), O(4)-

C(14) 1.218(4), O(5)-N(1) 1.380(4), N(1)-C(13) 1.387(4), N(1)-C14 1.362(5), C(6)-C(7) 1.348(5), C(7)-C(8) 1.477(5), C(7)-C(14) 1.522(5).

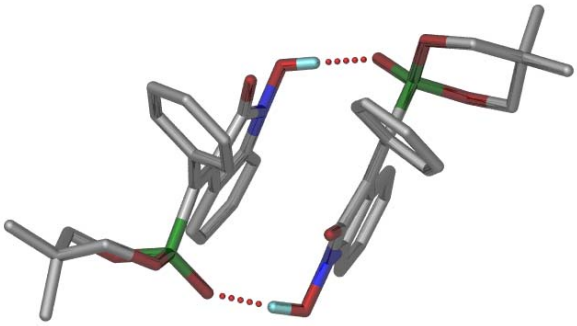


Fig. 6. A diagram showing hydrogen bonding interactions in compound **36**.CH_2Cl_2. Two molecules present in the asymmetric unit form an H-bonded unsymmetrical dimer. Hydrogen bonding parameters: O(5)-H(5D)...O(6) 0.84 (2), 1.80 (6), 2.635(4) Å, 174.9 (4)°; O(10)-H(10B)...O(1) 0.84 (3), 1.77 (6), 2.596(4) Å, 168.3 (8)°.

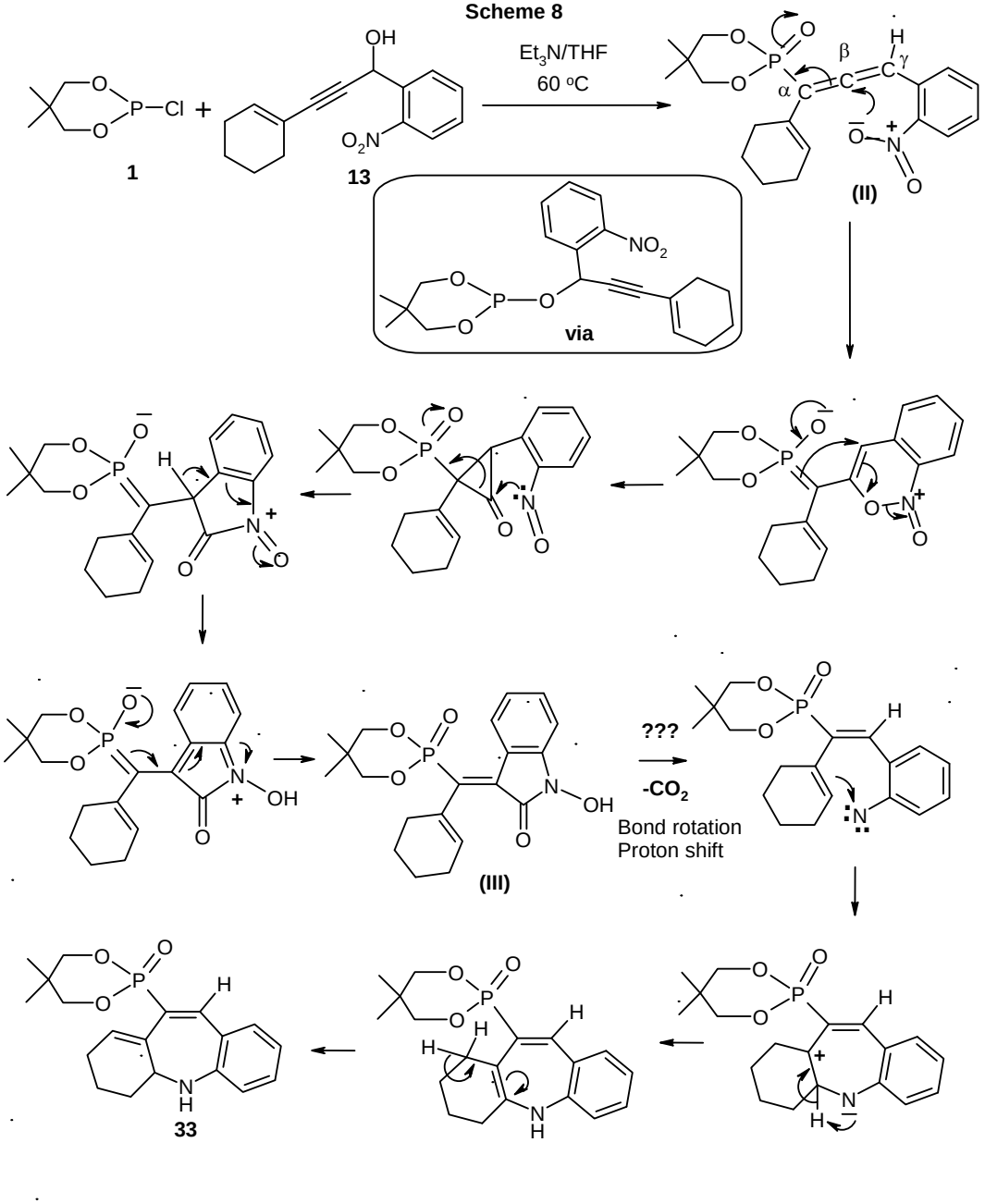
Compounds **36-38** show characteristic bands in the region of 3100-3300 cm^{-1} and 1700-1720 cm^{-1} due to υ(NH) and υ(C=O) stretches, respectively. In the ^1H NMR, compounds **36-37** show a peak at δ 9.75 due to N-O*H* proton, while compound **38** exhibits a more downfield peak at δ 11.1 due to the same type of proton. In the ^{13}C NMR, compounds **36-38**, displayed doublets in the region of δ 161.7-161.8 due to the *C*=O carbon [^3J(P-C) = 26.0 Hz for **36**, ^3J(P-C) = 25.8 Hz for **37** and ^3J(P-C) = 18.4 Hz for **38**]. This feature also gives evidence for the presence of C=O moiety. For compounds **36-37**, the olefinic carbon connected to phosphorus gave a doublet in the region of δ 137.1-137.5 [^1J(P-C) ~ 168.0 Hz], whereas in compound **38** the doublet was observed at δ 136.5, but with a lower ^1J(P-C) value of 64.0 Hz. Analytical data are also consistent with the structures as depicted.

2.23 Mechanistic pathway for the formation of the heterocycles 33-35

At the moment, it is not very clear to us, as to how exactly these heterocycles are formed, but we presume that initially the allenylphosphonates (e.g. **II**) are formed (Scheme 8). Any explanation should include the fact that the one of the C-C bonds involving *β*-carbon of the allene (**II**) should be cleaved. This process necessarily involves several steps and a tentative pathway is shown in Scheme 8.[102] In our earlier work, we have realized that nucleophiles attack the *β*-carbon,[67b-d,77]

and this forms the basis for the directions of attack shown in structure **II**. Isolation of *N*-hydroxy-indolinones **36-38** (cf. similar structure **III** also) in the reaction of ($OCH_2CMe_2CH_2O$)PCl (**1**) or Ph_2PCl with the propargyl alcohols **15-16** indicates that an aryl group at the α-position (in place of the cyclohexenyl group as in **II**) intervenes in the formation of the dibenzo-azepine (7-membered cyclic system) ring system. Assuming that species **III** is an intermediate in the formation of compound **33**, we then have to rationalize how a molecule of CO_2 is eliminated from the system. This region becomes more speculative and hence we left this part in the scheme shown. However, we suspect that there is the involvement of a nitrene intermediate at a later stage and this is shown in the scheme. Compound **34** is similar to compound **33**, but the hydroxy-substituted derivative **35** indicates that one or more of the intermediate/s is/are susceptible to attack by moisture [note: It is obvious that without the use of crystallography, these studies would not have been possible]. We also do not know whether the amine hydrochloride present in the system has a role to play or not. Currently, a more detailed investigation is being undertaken in the laboratory to understand the intricacies of this reaction.

Scheme 8

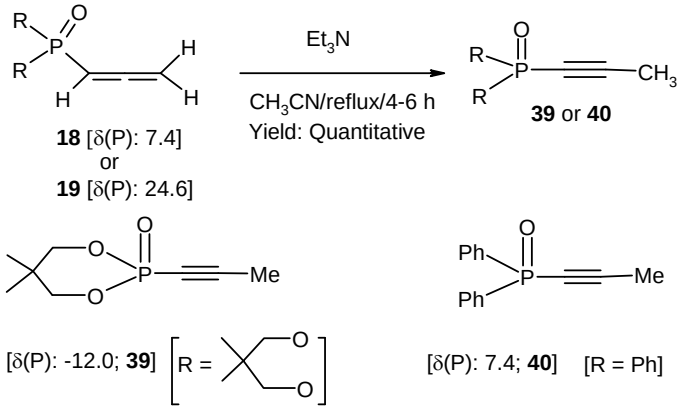


2.3 Catalytic and non-catalytic hydro(thio)phosphonylation/hydro(thio)phosphinylation of allenes and alkynes

2.31 Synthesis of alkynes 39-40 and dinuclear Pd^{I} complexes 41-42

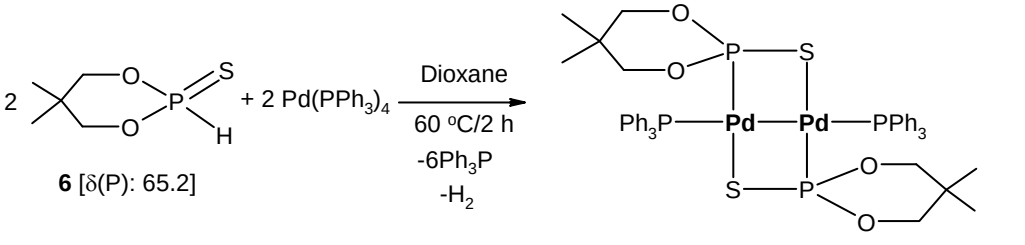
Alkynylphosphonate **39**[67a] and alkynyl phosphine oxide **40**[103] were prepared by isomerization of respective allenes $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**) and $Ph_2P(O)C(H)=C=CH_2$ **(24**) in the presence of base (Scheme 9). Such reactions are well-documented in the literature.[67]

Scheme 9



We intended to carry out the hydrophosphonylation of allenylphosphonates synthesized as above (section 2.1) in the presence of Pd-complexes as catalysts. In this process, we obtained the dinuclear Pd^{I} complex $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**41**) in one of the reactions and found that it itself is an effective catalyst. Hence it was thought appropriate to synthesize this compound in a straightforward manner. Thus it was prepared by treating the thiophosphite $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) with $Pd(PPh_3)_4$ in 1,4-dioxane in excellent yield (Scheme 10). Complex **41** shows only a doublet of doublet with a low J(P-P) of 12.2 Hz in the ^{31}P NMR; these data are close to that available in the literature for a similar compound.[104] The X-ray structure [Fig. 7] clearly establishes the presence of dinuclear motif with a Pd-Pd distance of 2.607(1) Å.[105] It can be noted that in the formation of this compound, a molecule of hydrogen, originally belonging to the thiophosphite, has to be eliminated. The phosphorus, which is formally pentavalent in the precursor **6**, coordinates to the metal as a normal P^{III} compound in the final complex **41**.

Scheme 10



41

[δ(P): 15.3, 148.0 (d each, ^2J(P-P) = 12.2 Hz)]

Yield 95%

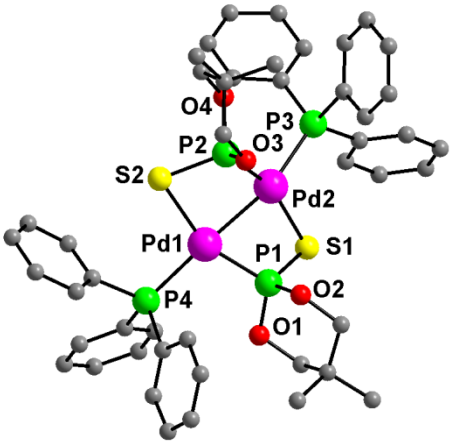
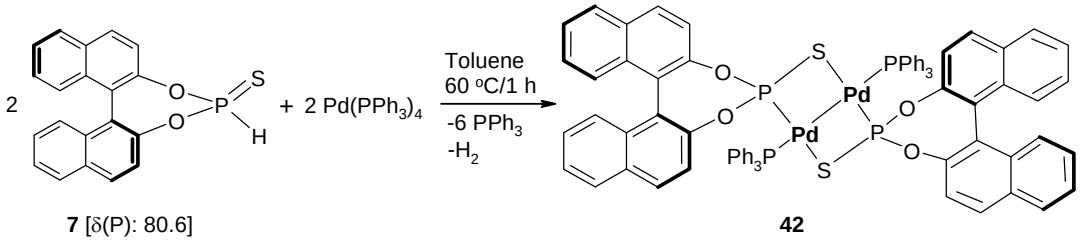


Fig. 7. Molecular structure of **41**.2$C_4H_8O_2$. Solvent molecules and hydrogen atoms are not shown for clarity. Selected bond lengths [Å] with esd's in parentheses: Pd(1)-Pd(2) 2.607(1), Pd(1)-P(1) 2.211(1), Pd(1)-P(4) 2.323(1), Pd(1)-S(2) 2.398(1), Pd(2)-P(2) 2.206(1), Pd(2)-P(3) 2.317(1), Pd(2)-S(1) 2.385(1), P(1)-S(1) 2.017(2), P(2)-S(2) 2.016(2).

Following the above clue, the BINOL based chiral *S*,*S*-(-)-dinuclear Pd^{I}-complex $[(C_{20}H_{12}O_2)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**42**) was also synthesized in a manner similar to that for compound **41**, by using *S*-(-)-$(C_{20}H_{12}O_2)P(S)H$ (**7**) (Scheme 11). This compound shows two doublets of doublets at δ 17.2 and 191.9 [*J*(P-P) = 30.4 and 6.8 Hz] in the ^{31}P NMR [Fig. 8]. This feature is most likely due to the slight nonequivalence of each type of phosphorus. Although the purpose of preparing this compound was to use it in asymmetric catalysis, we have not explored its utility in this work.

Scheme 11



7 [δ(P): 80.6]

42

[δ(P): 17.2, 191.8 (dd each, *J*(P-P) ~ 30.4 Hz, *J*(P-P) ~ 6.8 Hz)]

Yield: 90 %

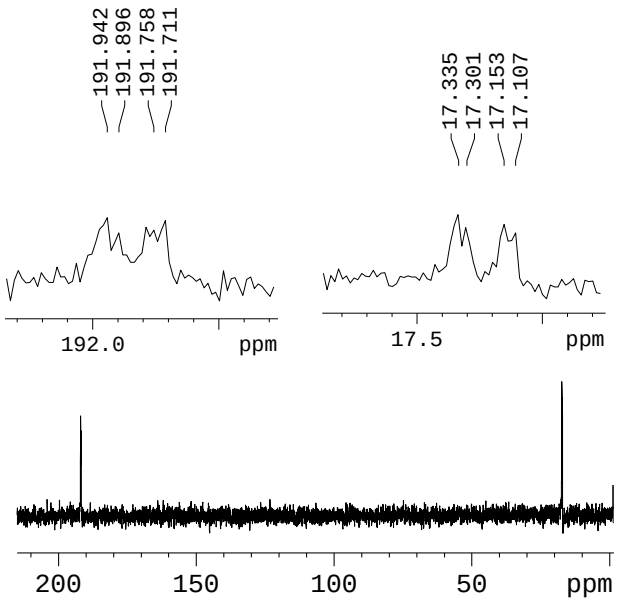


Fig. 8. The ^{31}P NMR spectrum of compound **42**

2.32 Pd-catalyzed hydrophosphonylation/hydrothiophosphonylation of allenylphosphonates/allenyl phosphine oxides

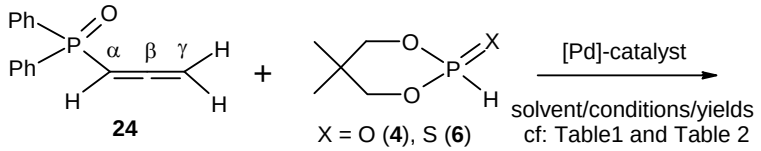
The Pd-catalyzed nucleophilic addition/cyclization reactions with allenes to construct C-C or C-heteroatom bond have become an important area in synthetic organic chemistry.[66c-f] A wide variety of phosphorus-based heterocycles were also synthesized in our laboratory by using Pd-catalyzed reactions.[67a,67f] However, to date studies on the Pd-catalyzed P(O)-H addition reactions of allenes are very limited in the literature.[50,63] Hence we explored these reactions by using the air stable and novel dinuclear Pd^{I}-catalyst **41** and compared the catalytic activity with the traditional Pd-catalysts like $Pd(OAc)_2$ and $Pd(PPh_3)_4$. We have also compared the reactivity of phosphites and thiophosphites as well.

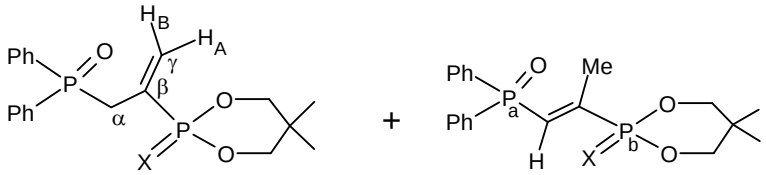
We first treated allenyl phosphine oxide $Ph_2P(O)C(H)=C=CH_2$ (**24**) with phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**4**) and the thiophosphite $(OCH_2CMe_2CH_2O)P(S)(H)$ (**6**) under different conditions (Scheme 12). These results are summarized in Table 1. The reaction of **4** with allenyl phosphine oxide **24** in the presence of $Pd(PPh_3)_4$ catalyst afforded the (β,α) and (β,γ)-P(O)-H addition products **43** and **44**, respectively. The use of dinuclear Pd^{I}-complex (**41**) also afforded the same products (**43-44**) in good yields (Table 1, entry 5). There was no reaction in the absence of Pd-catalyst (entry 1). Other Pd-catalysts like $Pd(OAc)_2$, $Pd_2(dba)_3$ gave poor yields (Table 1, entry 2-3). The effect of solvents on this

reaction is shown in Table 2. There was no reaction at room temperature in 1,4-dioxane as solvent (Table 2, entry 1). Thus the Pd-catalyzed phosphonylation works well at higher temperatures only. Reaction was completed in 12 h when 1,4-dioxane was used as solvent at 100 ^{o}C (Table 2, entry 2). Other solvents like dichloroethane (DCE), acetonitrile (CH_3CN), tetrahydrofuran (THF) did not improve the yield of the products (Table 2, entries 3-5)**.** Toluene also gave the better results but more time was required for the completion of the reaction (Table 2, entry 6). From these data, we conclude that 1,4-dioxane at 100 ^{o}C is optimum for this reaction.

In a manner similar to that described above, the reaction of allenyl phosphine oxide $Ph_2P(O)C(H)=C=CH_2$ (**24**) with cyclic thiophosphite $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) in the presence of $Pd(PPh_3)_4$ or dinuclear Pd^{I}-complex $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**41**) (5 mol%) afforded the products **45-46** along with bisthiophosphonylated compound **47** in good overall yield [Table 1, entries 9-10, combined >90%, ^{31}P NMR] (Scheme 12). The main point we observed was that the catalyst **41** could be recovered from this type of reaction whereas $Pd(PPh_3)_4$ could not be. Formation of **41** in $Pd(PPh_3)_4$ catalyzed reaction of allene **24** with thiophosphite **6** was proven by means of recording the ^{31}P NMR spectrum of the reaction mixture. From these observations, we conclude that the $Pd(PPh_3)_4$ catalyzed reaction to afford the products **45-47** is taking place *via* the formation of dinuclear Pd^{I}-complex **41**. When the reaction was conducted in the absence of any catalyst, after 36 h, some amount (50%) of product **45** was obtained (Table 1, entry 6). Since no reaction occurred under similar conditions using **4**, we conclude that cyclic thiophosphite **6** is more reactive than cyclic phosphite **4**. Other Pd-catalysts like $Pd(OAc)_2$ and $Pd_2(dba)_3$ did not give better yields of the products **45-47** (Table 1, entries 7-8).

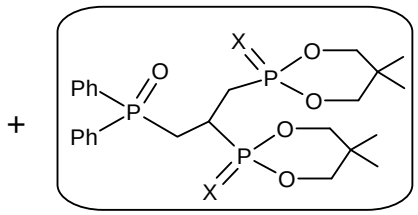
Scheme 12





X = O: **43** [δ(P): 11.7 and 29.8 (d, *J* = 26.0 Hz)] (*E*)-**44** [δ(P): 11.9 and 20.8 (d, *J* = 73.2 Hz)] (X-ray)

X = S: **45** [δ(P): 29.6 and 82.5 (d, *J* = 29.5 Hz)] (*E*)-**46** [δ(P): 20.9 and 84.8 (d, *J* = 75.0 Hz)]



X = S: **47** [δ(P): 30.0 (d, *J* = 36.8 Hz), 96.3 and 96.7 (m, ABX pattern)]

Table 1. Reaction conditions leading to the formation of **43-44** and **45-46** (cf. Scheme 12)[a]

Entry	[Pd]	X	Time (h)	Yield (%)[b]	Ratio[c] **43:44** or **45:46**
1	None	O	36	n.r.	-
2	$Pd(OAc)_2$	O	36	36	100:0
3	$Pd_2(dba)_3$	O	36	40	60:40
4	$Pd(PPh_3)_4$	O	10	80	60:40
5	**41**	O	12	80	75:25
6	None	S	36	50	100:0
7	$Pd(OAc)_2$	S	36	70	85:15
8	$Pd_2(dba)_3$	S	36	60	90:10
9	$Pd(PPh_3)_4$	S	4	90	75:25[c]
10	**41**	S	4	90	75:25[c]

[a]Based on ^{31}P NMR analysis.

[b]All reactions were conducted at 100 °C (oil bath temperature).

[c]The ratio **47:**(**45+46**) was 3:5 using the stoichiometry 1:1.1 (**24**:**6**); rest was starting material because of the bisthiophosphonylated product **47**. Yield of **47** could be maximized by adding more of the thiophosphite **6**.

Table 2: Effect of the solvent on Pd-catalyzed hydrophosphonylation of allene **24** with cyclic phosphite **4** (Scheme 12)[a]

Entry	Solvent	Temperature (^oC)	Reaction time (h)	Yield (**43+44**)[b]
1	1,4-dioxane	25	16	n.r
2	1,4-dioxane	100	12	80
3	dichloroethane	80	16	65
4	CH_3CN	80	20	50
5	THF	60	14	60
6	Toluene	110	15	74

[a]Dinuclear Pd^I-complex **41** was used as catalyst.

[b]Yields are based on ^{31}P NMR.

The final products **43-47** were characterized by spectroscopic and analytical data. In the ^1H NMR spectrum of **43**, a doublet of doublet to triplet (dd→t) at δ 3.32 [$^{2,3}J$(P-H) = 12.1 Hz] clearly indicates the presence of PCH_2CP moiety. A doublet each for PC=CH_AH$_B$ (*cis*) [δ 6.10, ^3J(P-H) = 23.2 Hz] and PC=CH$_A$$H_B$ (*trans*) [δ 6.38, ^3J(P-H) = 48.5 Hz] gave evidence for the presence of C=CH_2 group. The observed *trans*-^3J(P-H) coupling constant is higher than that of *cis*-^3J(P-H) coupling constant, as expected. In the ^{13}C NMR spectrum, the P(O)CH$_2$ carbon appears as a doublet of doublet at δ 30.7 [^1J(P-C) = 67.1 Hz, ^2J(P-C) = 11.6 Hz] due to coupling to both the phosphorus atoms. The signal due to PC=CH$_2$ is not clear because it is buried in the peaks due to aromatic carbon atoms. The =CH$_2$ carbon is observed at δ 134.5 as a dd→t with $^{2,3}J$(P-C) = 7.0 Hz. In the ^{31}P NMR spectrum, compound **43** shows a doublet each in the phosphonate and phosphine oxide region at δ 11.7 and 29.8 [^3J(P-P) = 26.0 Hz], respectively.

In the ^1H NMR spectrum of **44**, a clear-cut ddd→td observed at δ 2.32 [^3J(P$_b$-H) = 15.8 Hz, ^4J(P$_a$-H) ~ ^4J(H-H) = 2.0 Hz] (cf Scheme 12 for the labels P$_a$ and P$_b$] can be ascribed to the C=CCH_3 protons. The P$_a$CH=C-P$_b$ proton shows up as a dd at δ 7.09 [^2J(P$_a$-H) = 29.2 Hz, ^3J(P$_b$-H) = 24.4 Hz]. The smaller ^3J(P$_b$-H) value

observed indicates that the P_aCH=C-P_b proton is *cis* to phosphorus and consequently, the two phosphorus atoms are *trans* to each other. The ^{13}C NMR spectrum shows a dd→t at δ 16.0 [$^{2,3}J$(P-C) ~ 8.0 Hz], confirming the presence of a methyl group. A dd each for P_a-*C*H [δ 135.7, $^{1}J(P_a\text{-C})$ = 90.0 Hz, $^{2}J(P_b\text{-C})$ = 6.0 Hz] and P_b-*C*= [δ 147.2, $^{1}J(P_b\text{-C})$ = 164.0 Hz, $^{2}J(P_a\text{-C})$ = 4.1 Hz] is also consistent with the structure as shown. In the ^{31}P NMR spectrum, this compound shows two doublets at δ 11.9 and 20.8 with ^{3}J(P-P) = 73.2 Hz. This coupling constant is much higher than that for **43** because the two phosphorus moieties in **44** are connected *via* a C=C double bond and are *trans* to each other while in **43** they are connected through saturated carbon atoms. The structure of the compound **44** was also confirmed by X-ray crystallography (Fig. 9).

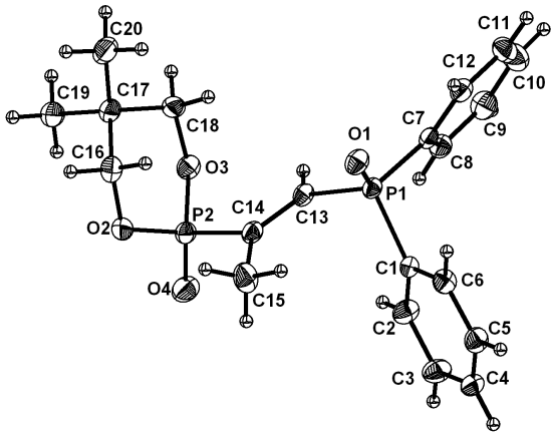


Fig. 9. An ORTEP diagram for compound **44**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(1) 1.806(2), P(1)-C(7) 1.802(2), P(1)-C(13) 1.809(2), P(2)-C(14) 1.808(2), C(13)-C(14) 1.335(3), C(14)-C(15) 1.500(3).

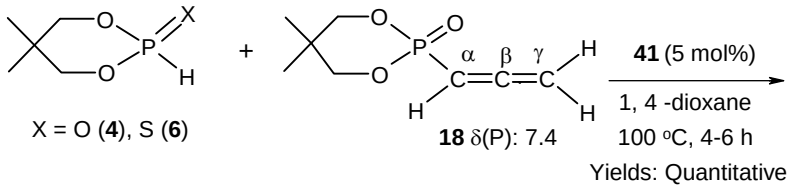
The NMR spectra of **45** and **46** are similar to those of **43** and **44**, respectively, except that the thiophosphonyl phosphorus appears much downfield in the ^{31}P NMR [δ 82.5 or 84.8 respectively] spectra.

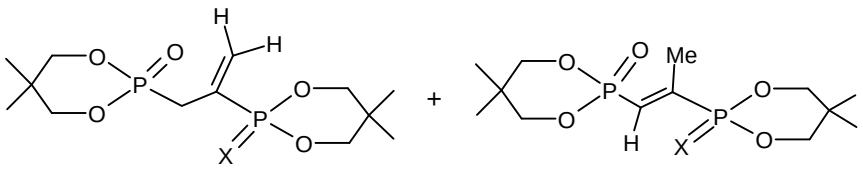
For the trisphosphorus compound **47**, multiplets at δ 2.66-2.92 and δ 3.48-3.51 corresponding to P-CH_2 and P-C*H* protons, respectively, are seen in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, two doublets at δ 32.5 [^{3}J(P-C) = 6.0 Hz] and 33.1 [^{3}J(P-C) = 6.1 Hz] due to two *C*$(CH_3)_2$ moieties gives evidence for the presence of two 1,3,2-dioxaphosphorinane rings. Thus, in both ^{1}H and ^{13}C NMR spectra, peaks corresponding to olefinic moiety were not observed. The ^{31}P NMR

spectrum shows an ABX pattern with peaks centered at δ 30.0 [d, ^3J(P-P) = 36.8 Hz, *P*(O)], 96.3 and 96.7 [m, AB part of the ABX spectrum where X = P(O)]. Thus the presence of three phosphorus atoms, two thiophosphonyl and one diphenyl phosphinyl, is confirmed and is consistent with the structure as written. Analytical data are also consistent with these spectra.

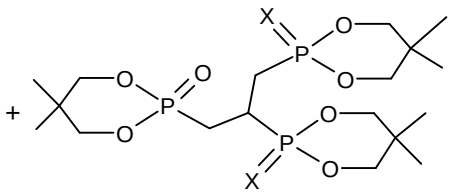
An analogous hydrophosphonylation reaction of allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**) with phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**4**) was earlier conducted by my colleague in our laboratory by using $Pd(PPh_3)_4$ as catalyst.[106] The same reaction was repeated with my catalyst **41** (Scheme 13). This reaction is very clean [~95% by ^{31}P NMR] and the resulting products **48-49** (Scheme 13) are structurally similar to **43-44**. The reaction using allene **18** and thiophosphite $(OCH_2CMe_2CH_2O)P(S)(H)$ (**6**) also gave (by ^{31}P NMR) similar products **50-51** along with the trisphosphorus compound **52**, as expected. There was no reaction in the absence of the Pd-catalyst. Products **48-50** and **52** have been previously characterized, with two of these [**48** and **52**] having single crystal X-ray structural confirmation. These data also provide credence to the assigned structures for **43-47**. The spectroscopic data of **51** are similar to that of **46** and hence are not discussed here.

Scheme 13





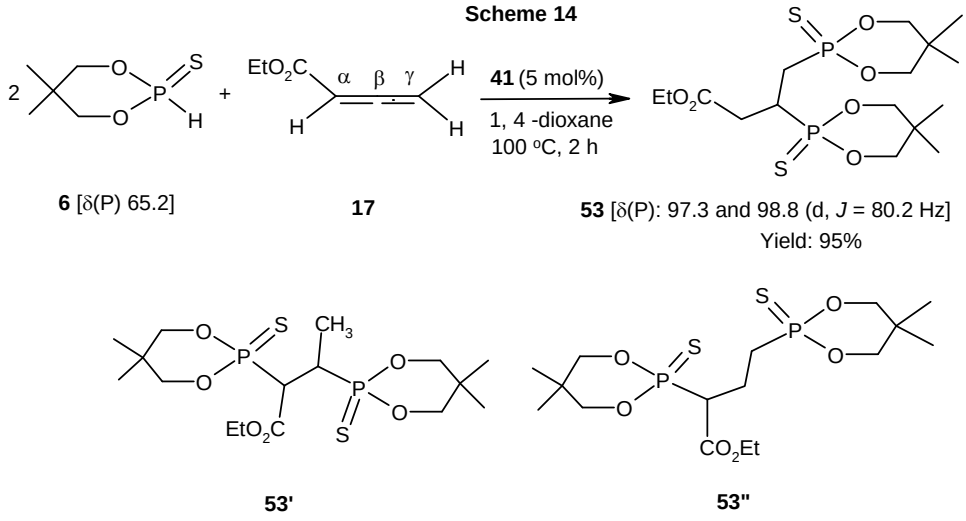
X = O: **48** [δ(P): 11.6 and19.4 (d, *J* = 27.5 Hz)] (*E*)-**49** [δ(P): 6.2 and 10.3 (d, *J* = 99.2 Hz)]
X = S: **50** [δ(P): 16.2 and 82.0 (d, *J* = 48.0 Hz)] *(E)*-**51** [δ(P): 7.6 and 83.0 (d, *J* = 102.9 Hz)]



X = S: **52** [δ(P): 22.1 (d, *J* = 22.4 Hz), 96.1 and 96.8 (m, ABX pattern)]

In continuation of the above studies, we were curious to know whether an ester allene like $(EtO_2C)CH=C=CH_2$ (**17**) also would undergo double thiophosphonylation or not. Indeed, this reaction with thiophosphite **6** afforded the bisthiophosphonate **53** (Scheme 14) which is structurally similar to compounds **47** and **52**.

Scheme 14



6 [δ(P) 65.2] **17** **53** [δ(P): 97.3 and 98.8 (d, *J* = 80.2 Hz] Yield: 95%

53' **53"**

Compound **53** shows four singlets δ 0.95, 1.06, 1.12 and 1.21 in the ^{1}H NMR spectrum, indicating the presence of four methyl groups attached to 1,3,2-dioxaphosphorinane ring. An additional peak due to the α-methyl (CH_3) group in expected in structure **53'** was not observed; hence the compound isolated does not have the structure **53'**. Four multiplets at δ 2.42-2.48, 2.64-2.68, 2.91-3.01 and 3.38-3.53 are observed ($CH + CH_2 + CH_2$) and may be assigned for the compounds **53** or **53"**. But the large coupling constant value [*J*(P-P) = 80.2 Hz] in the ^{31}P NMR spectrum at δ 97.3 and 98.8 provides the information that these two phosphorus atoms are connected through three single bonds but not through four single bonds. Hence the structure **53"** is ruled out and the one depicted in Scheme 14 is correct for the isolated compound.

From the above observations, it is clear that the efficacy of dinuclear Pd-catalyst **41** is comparable to $Pd(PPh_3)_4$ in P(X)-H [X = O, S] addition reactions. But the former compound is more stable under aerobic conditions. Hence we also investigated the hydrophosphonylation reactions with allenes $Ph_2P(O)C(H)=C=CMe_2$ (**25**) and $Ph_2P(O)C(Ph)=C=CH_2$ (**26**) by using the dinuclear Pd^I-catalyst **41** (Scheme 15). In these cases, we obtained only (*β,α*)-P-H addition

products **54-57** predominantly. These are structurally similar to **43** and are isolated in good yields (see Table 3). In the reaction of allene **26** with thiophosphite **6** (*β,α*)-P(S)-H addition product **57** formed along with a minor amount (<10%) of (*γ,β,*)-P(S)-H addition product **58**. It is important to note that compound **57** did not undergo the second thiophosphonylation reaction. There was no significant difference in the products formed using either $Pd(PPh_3)_4$ or **41** in the reactions that we checked.

Scheme 15

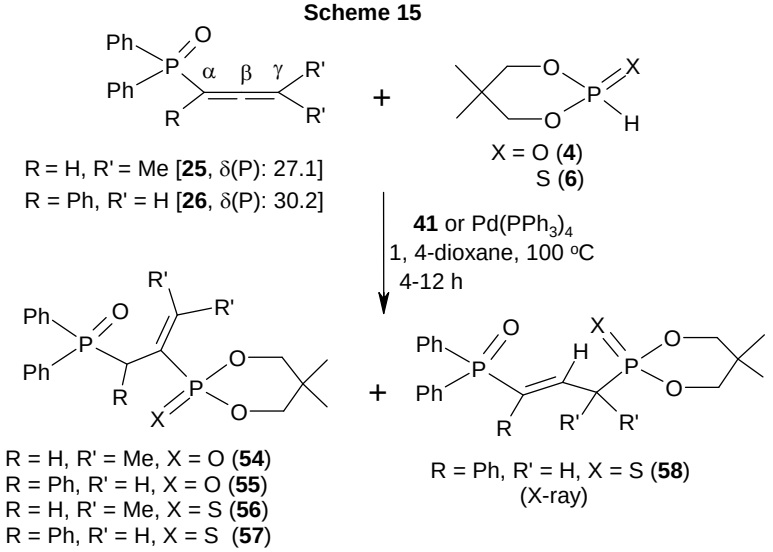


Table 3: Details on the yields and ^{31}P NMR of the products **54-58** (Scheme 15).

Entry	Allene	Phosphite	Product(s)	Yield (%)[a]	^{31}P NMR
1	**25**	**4**	**54**	95	16.4, 28.6 (^3J = 6.6 Hz)
2	**26**	**4**	**55**	80	11.6, 32.8 (^3J = 37.6 Hz)
3	**25**	**6**	**56**	85	27.4, 83.4 (^3J = 7.3 Hz)
4	**26**	**6**	**57**	80[b]	32.2, 82.1 (^3J = 39.1 Hz)
			58 (X-ray)		27.8, 91.8 (^4J = 8.0 Hz)

[a]Yields were determined by ^{31}P NMR (accuracy ±5%)

[b]Combined yield of **57** and **58**.

Characterization of compounds **54-58** was done by spectroscopic and analytical data. In the ^1H NMR spectrum for compound **54**, a dd→t for PCH_2 at δ 3.46 [$^{2,3}J$(P-H) ~ 15.0 Hz] was seen. Two distinct signals for two CH_3 groups at δ 1.62 and 2.09 indicated that these moieties (CH_3) are connected to unsaturated

carbon and they are chemically not equivalent. In the ^{13}C NMR spectrum, the P(O)*C*H_2 carbon was observed as a doublet of doublet (dd) at δ 32.8 [^1J(P-C) = 70.0 Hz, ^2J(P-C) = 13.1 Hz] as expected. Doublet of doublets for P-*C*=C [δ 113.7, ^1J(P-C) = 187.2 Hz, ^2J(P-C) = 9.8 Hz] and for =*C*Me$_2$ [δ 158.2, $^{2,3}J$(P-C) = 9.5 Hz] are also consistent with the assigned structure. Compound **56** has similar spectral features.

In the ^1H NMR spectrum of compound **55**, a doublet of doublet for P(O)C*H*Ph appears at δ 4.55 [^2J(P-H) = 13.8 Hz and ^3J(P-H) = 8.6 Hz]. A doublet of doublet for PC=CH_A (*cis*) at δ 6.10 [^3J(P-H) = 22.8 Hz and ^2J(H-H) = 1.2 Hz] and a multiplet (partly buried) for PC=CH_B (*trans*) centered at δ 7.17 indicate the presence of the C=CH_2 group. Characteristic peaks for P(O)*C*HPh [δ 46.6, dd, ^1J(P-C) = 63.4 Hz, ^2J(P-C) = 11.5 Hz] and P(O)*C*=CH_2 [δ 134.8, dd, ^1J(P-C) = 170.0 Hz, ^2J(P-C) ~ 5.0 Hz] in the ^{13}C NMR spectrum are observed. The ^{31}P NMR spectrum shows a doublet each at δ 11.6 and 32.8 [^3J(P-P) = 37.6 Hz]. Compound **57** also exhibited similar spectra.

Compound **58** has a structure different from the rest of the compounds hitherto discussed. In the ^1H NMR spectrum, a signal due to P(S)-CH_2 protons appears as a dd at δ 3.05 [^2J(P-H) = 20.0 Hz and ^3J(H-H) = 6.8 Hz]. A multiplet centered at δ 6.70 is observed for the vinylic P(O)CPh=C*H* proton. The ^{31}P NMR spectrum shows two doublets at δ 27.8 and 91.8 with ^4J(P-P) ~ 8.0 Hz. The coupling constant in compound **58** is much lower than that observed for **57** due to the long range [***four*** intervening bonds] between the two phosphorus atoms. X-ray structure of **58** [Fig. 10] clearly establishes that the thiophosphonylation has occurred at the γ-position. The C(13)-C(20) distance of 1.326(2)Å is in the C=C range, as expected (Fig. 10).

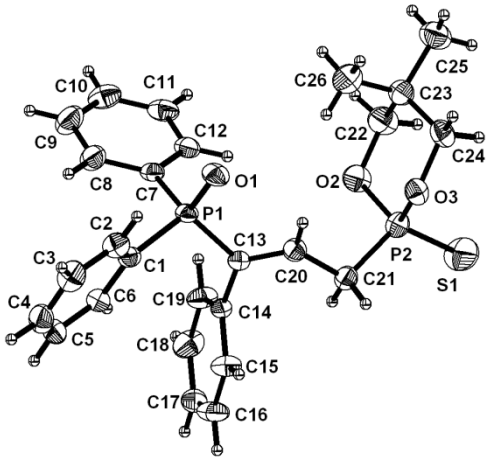
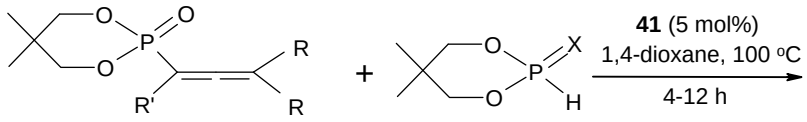


Fig. 10. An ORTEP diagram for compound **58**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(1) 1.808(2), P(1)-C(7) 1.804(2), P(1)-C(13) 1.811(2), P(2)-C(21) 1.788(2), P(2)-S(1) 1.9110(8), C(13)-C(20) 1.326(2), C(20)-C(21) 1.497(3).

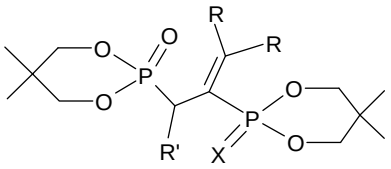
The reaction of cyclic phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**4**) and cyclic thiophosphite $(OCH_2CMe_2CH_2O)P(S)(H)$ (**6**) with allenylphosphonates $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (**19**) and $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**20**) to afford **59-62** was done earlier in our laboratory by using $Pd(PPh_3)_4$ (5.0 mol%) as the catalyst.[106] The use of dinuclear Pd^I-catalyst **41** (5.0 mol%) in these reactions in the present study also afforded the same [(*β,α*)-addition] products **59-62** but in better yields (Scheme 16). These products are similar to the compounds **54-57** shown earlier in Scheme 15. The reaction of thiophosphite **6** with sterically encumbered *γ*-substituted cyclohexyl allenylphosphonate **21** also afforded the (*β,α)*-P(S)-H addition product **63** exclusively in good yield (Scheme 16). Compound **63** is characterized by using IR and NMR spectroscopic methods.

Scheme 16

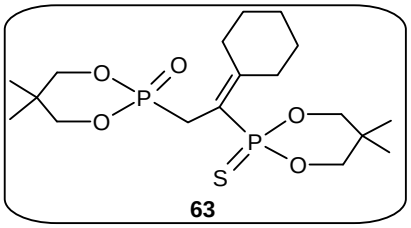


R' = H, R = Me **19** [δ(P): 9.8]
R' = Ph, R = H **20** [δ(P): 6.6]
R' = H, R,R = -$(CH_2)_5$- **21** [δ(P): 10.0]

X = O (**4**), S (**6**)



R' = H, R = Me, X = O (**59**) [δ(P):14.3, 22.2 (*J* = 10.1 Hz)];90%
R' = Ph, R = H, X = O (**60**) [δ(P):12.2, 16.6 (J = 47.0 Hz)];90%
R' = H, R = Me, X = S (**61**) [δ(P): 22.2, 82.4 (*J* = 9.7 Hz)]; 85%
R' = Ph, R = H, X = S (**62**) [δ(P):16.2, 81.9 (*J* = 49.0 Hz)];89%
R' = H, R,R = -$(CH_2)_5$-, X = S (**63**) [δ(P): 22.8, 83.0 (*J* = 9.8 Hz)]; 90%

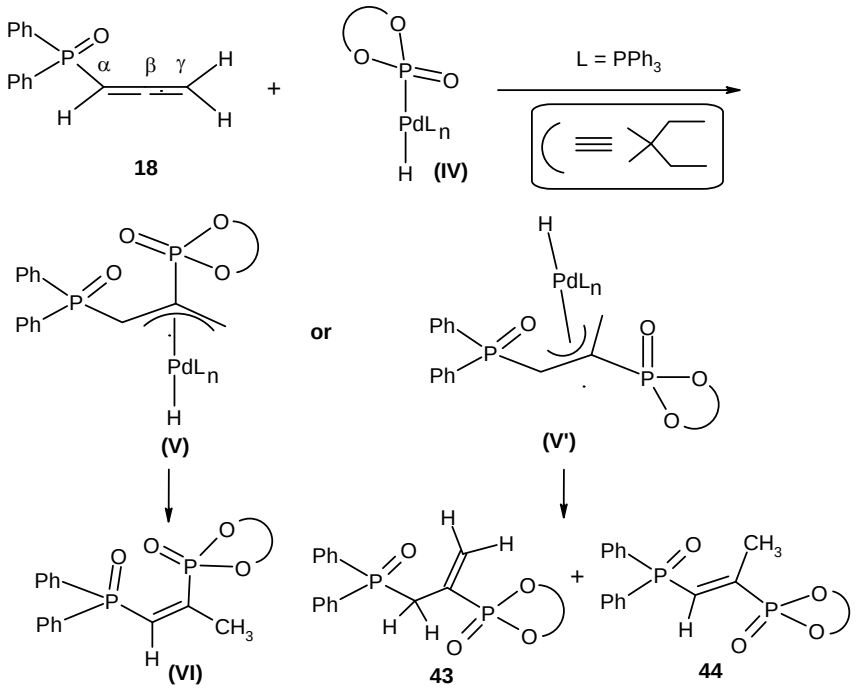


63

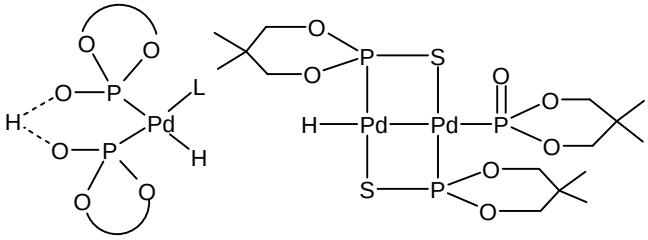
Mechanistic pathway leading to compounds 43-63

Mechanistic pathway for the formation of the compounds **43-44** is shown in Scheme 17. Initially The P-H bond needs to get inserted into the Pd-complex; a feasible species at this stage is (**IV**). The species **V** and **V'** are analogous to those proposed in the literature.[50] As can be seen readily, the *Z*-alkene (**VI**) should have been formed, but we could not identify it in this reaction mixture. It may be noted that in lieu of **V**, it is also possible to have an intermediate of type **VII**,[53] but this would require two mole equivalents of phosphite per palladium. What is perhaps more intriguing is the nature of intermediate while using our dinuclear catalyst **41**; a possible structure is (**VIII**). However, at the moment it is only a speculation. Since we observe that the catalyst **41** can be recovered after the reaction, it is possible that the PPh_3 ligand may still be present on the two palladium centers at the intermediate stages. In any case, the catalytic activity of **41** poses interesting challenges in our understanding of these Pd-catalyzed reactions. In a similar way, formation of compounds **45-63** is also rationalized by this route.

Scheme 17



(*Note*: An additional ligand 'L' on Pd in **IV**-**V** is also possible.)

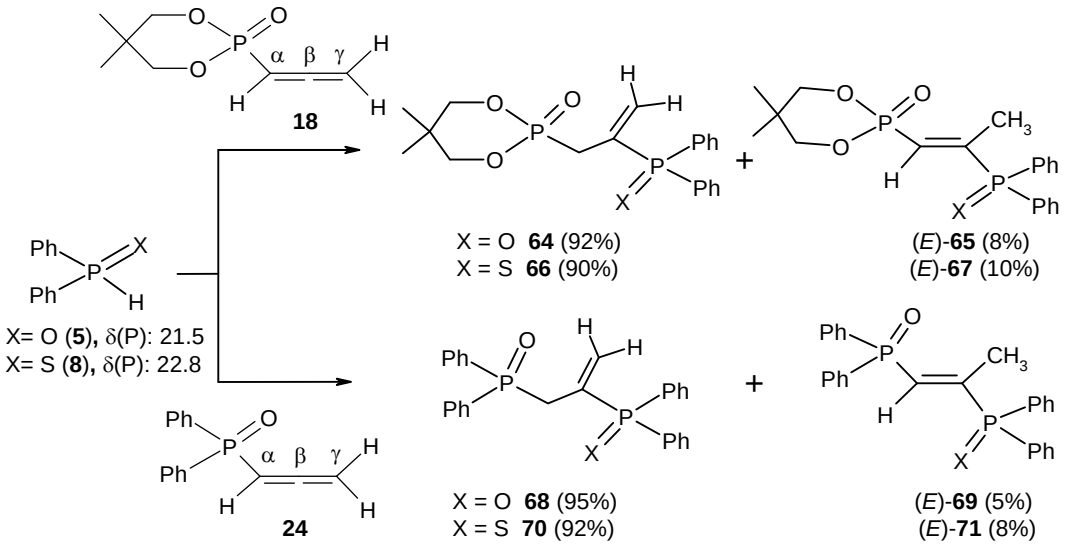


2.33 Solvent-free and catalyst-free regioselective hydro(thio)phosphinylation of allenylphosphonates/allenyl phosphine oxides

Realizing that not all the compounds with a ≡P(X)H [X= O, S] moiety will behave in the same manner, we wanted to compare the reactivity of $(OCH_2CMe_2CH_2O)P(X)H$ [X= O (**4**) or S (**6**)] with $Ph_2P(X)H$ [X= O (**5**) or S (**8**)] in the Pd-catalyzed hydrophosphonylation/hydrophosphinylation of allenes **18-20** and **24-26**. Later, we realized that some of these reactions do not require any Pd-catalyst and can be conducted smoothly under solvent-free, catalyst-free conditions. The results are summarized in Schemes 18-19. The P-H addition reaction of $Ph_2P(X)H$ [X = O (**5**), S (**8**)] with less substituted phosphorus allenes **18** or **24** proceeds well

under neat conditions at 100 °C to lead to allylphosphonates/allenyl phosphine oxides (**64**, **66**, **68** and **70**) in a regioselective manner (Scheme 18). Vinyl phosphonates/phosphine oxides [(*E*)-**65**, (*E*)-**67**, (*E*)-**69** and (*E*)-(**71**) were also formed but in minor quantities [~5-10%, by ^{31}P NMR]. Details on the yields and ^{31}P NMR spectra for compounds **64-71** are shown in Table 4.

Scheme 18



Conditions: Neat/ 100 °C/1h or
$Pd(PPh_3)_4$ or $[(OCH_2CMe_2CH_2O)P(O)\text{-}S\text{-}Pd(PPh_3)]_2$ (**41**) (5 mol%)/ dioxane/ 100 °C/ 1h

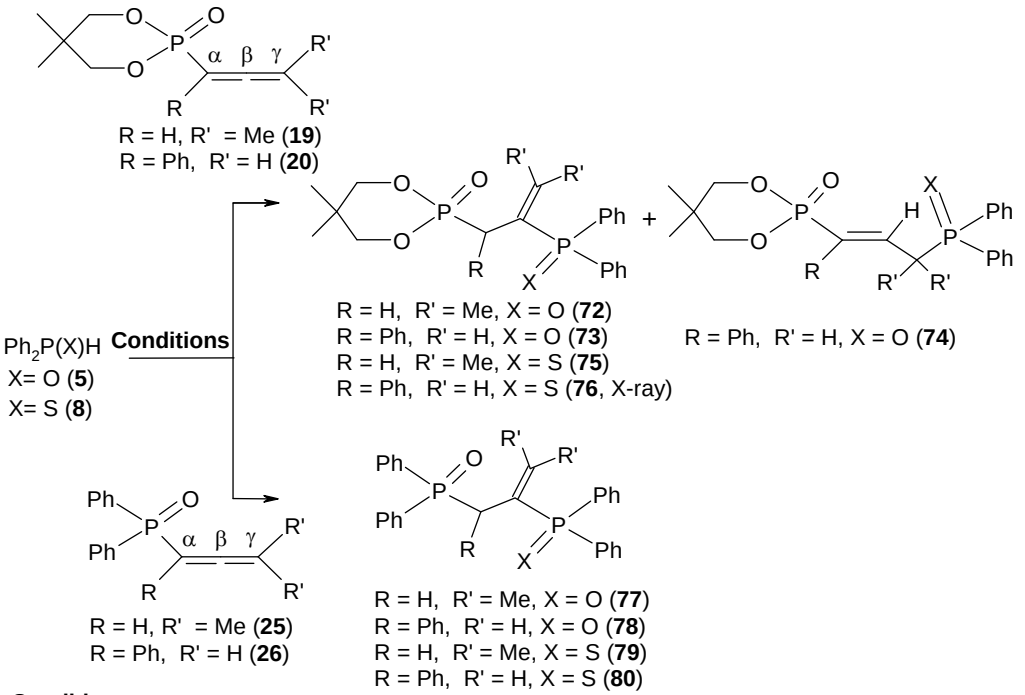
Table 4: Details on the yields and ^{31}P NMR of the products **64-71** (*cf* Scheme 18).

Entry	Substrates	Product(s)/^{31}P NMR	Yield(%)[a]
1	**5** + **18**	**64** [19.4 and 32.9 (d, J ~ 27.8 Hz)] + (*E*)-**65** [8.0 and 30.5 (d, J ~ 75.7 Hz)]	Quantitative
2	**8** + **18**	**66** [19.3 and 49.7 (d, J ~ 35.5 Hz)] + (*E*)-**67** [8.2 and 49.6 (d, J = 80.5 Hz)]	Quantitative
3	**5** + **24**	**68** [30.8 and 32.8 (d, J = 24.5 Hz)] + (*E*)-**69** [21.0 and 29.5 (d, J ~ 53.5 Hz)]	Quantitative
4	**8** + **24**	**70** [30.5 and 49.5 (d, J ~ 30.1 Hz)] + (*E*)-**71** [20.3 and 49.4 (d, J ~ 53.2 Hz)]	Quantitative

[a]Combined yield is based on ^{31}P NMR analysis.

The hydrophosphinylation reactions of $Ph_2P(X)H$ [X = O (**5**), S (**8**)] with substituted allenes **19**, **20**, **25** and **26** under solvent-free, catalyst-free conditions are less complicated (Scheme 19). In all the reactions, (β,α)-addition products (**72**-**73** and **75**-**80**, Table 5) are formed exclusively in excellent yields (>90%). A difference in the product distribution between the reactions done under neat and under Pd-catalyzed conditions was observed *only* in the hydrophosphinylation of $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**20**) with $Ph_2P(O)H$ (**5**). Under neat conditions, only one product **73** [(β,α)-addition product, 95%] was isolated whereas under Pd-catalyzed [$Pd(PPh_3)_4$ or **41**] conditions, the (γ,β)-addition product **74** (minor, 10%) was also isolated in addition to the (β,α)-addition product **73** (major, 90%). Another point of interest is that a literature method leading to the bisphosphine oxide **79** from the reaction of allenyl phosphine oxide **26** with **5** required a Ru-catalyst (Scheme 1.**40**, Chapter **1**).[57a] But we found that this reaction works well under neat conditions ***even in the absence of any catalyst*** (Table 5, entry 6).

Scheme 19



Conditions:
Neat/ 100 °C/1h or
$Pd(PPh_3)_4$ or $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**41**) (5 mol%)/ 1,4-dioxane/ 100 °C/ 1h

Table 5. Details on the yields and ^{31}P NMR of the products **72-80** (cf. Scheme 19)[a]

Entry	Substrates	Product(s)/^{31}P NMR	Yield (%)[b]
1	**5** + **19**	**72** [21.5, 31.3 (^{3}J = 7.8 Hz)]	95
2[c]	**5** + **20**	**73** [16.8, 33.3 (^{3}J = 32.8 Hz)] + **74 [**10.2, 28.5 (^{4}J = 7.0 Hz)]	90[d]
3	**8** + **19**	**75** [22.2, 44.6 (^{3}J = 8.5 Hz)]	95
4	**8** + **20**	**76** [16.4, 50.6 (^{3}J = 40.0 Hz)] (X-ray)	98
5	**5** + **25**	**77** [28.5, 31.1 (^{3}J = 5.4 Hz)]	98
6	**5** + **26**	**78** [32.6, 32.9 (^{3}J = 26.5 Hz)]	98
7	**8** + **25**	**79** [26.8, 45.1 (^{3}J = 6.5 Hz)]	95
8	**8** + **26**	**80** [32.3, 49.6 (^{3}J = 32.5 Hz)]	95

[a]All the reactions are conducted under neat or Pd-catalyzed conditions.

[b]Determined by ^{31}P NMR analysis.

[c]Under neat conditions product **73** was formed quantitatively.

[d]Under Pd-catalyzed conditions, two products **73** and **74** were formed (combined yield 90%).

Since spectroscopic data for compounds similar to **72-80** have been discussed in earlier sections, they are not elaborated here. As a means for confirmation, compound **76** was characterized by single crystal X-ray crystallography (Fig. 11). The C(6)-C(13) distance of 1.534(4) Å shows that hydrophosphinylation has occurred across this bond.

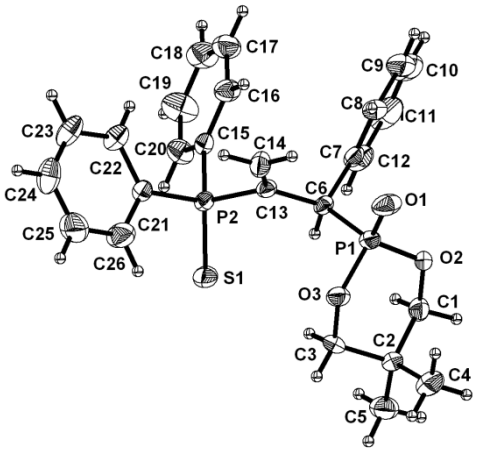


Fig. 11. An ORTEP diagram for compound **76**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(6) 1.806(3), P(2)-C(13) 1.816(3), P(2)-C(15) 1.814(4), P(2)-C(21) 1.815(4), P(2)-S(1) 1.945(1), C(6)-C(13) 1.534(4), C(13)-C(14) 1.318(4).

In order to check the relative reactivity of the allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (**19**) and allenyl phosphine oxide $Ph_2P(O)C(H)=C=CMe_2$ (**25**), we have performed their reaction with $Ph_2P(S)H$ (**8**) under solvent-free, catalyst-free conditions at 100 ^oC for 30 min in air. In the latter case [**25 + 8**] reaction was complete whereas in the former case [**19** + **8**], the reaction was incomplete as revealed by monitoring of the reaction mixture by ^{31}P NMR spectroscopy (Fig. 12). Hence we conclude that allene **19** is less reactive than allene **25** in these reactions.

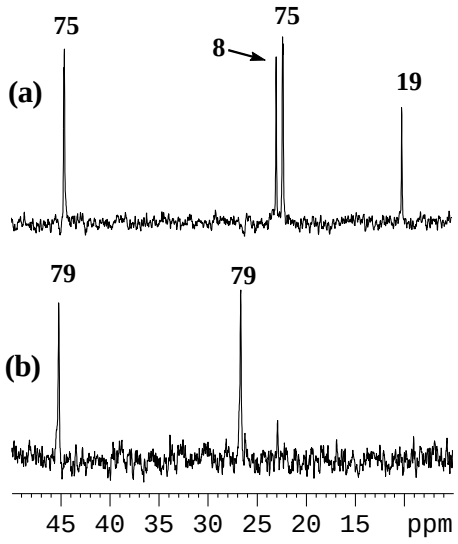


Fig. 12. A diagram showing ^{31}P NMR spectra for the reaction mixture under neat conditions at 100 ^oC/30 min for (a) allenylphosphonate **19** with $Ph_2P(S)H$ (**8**) and (b) allenyl phosphine oxide **25** with $Ph_2P(S)H$ (**8**). Compounds **75** (Table 5, entry 3) and **79** (Table 5, entry 7), respectively, are the products in the two cases.

Mechanistic pathway

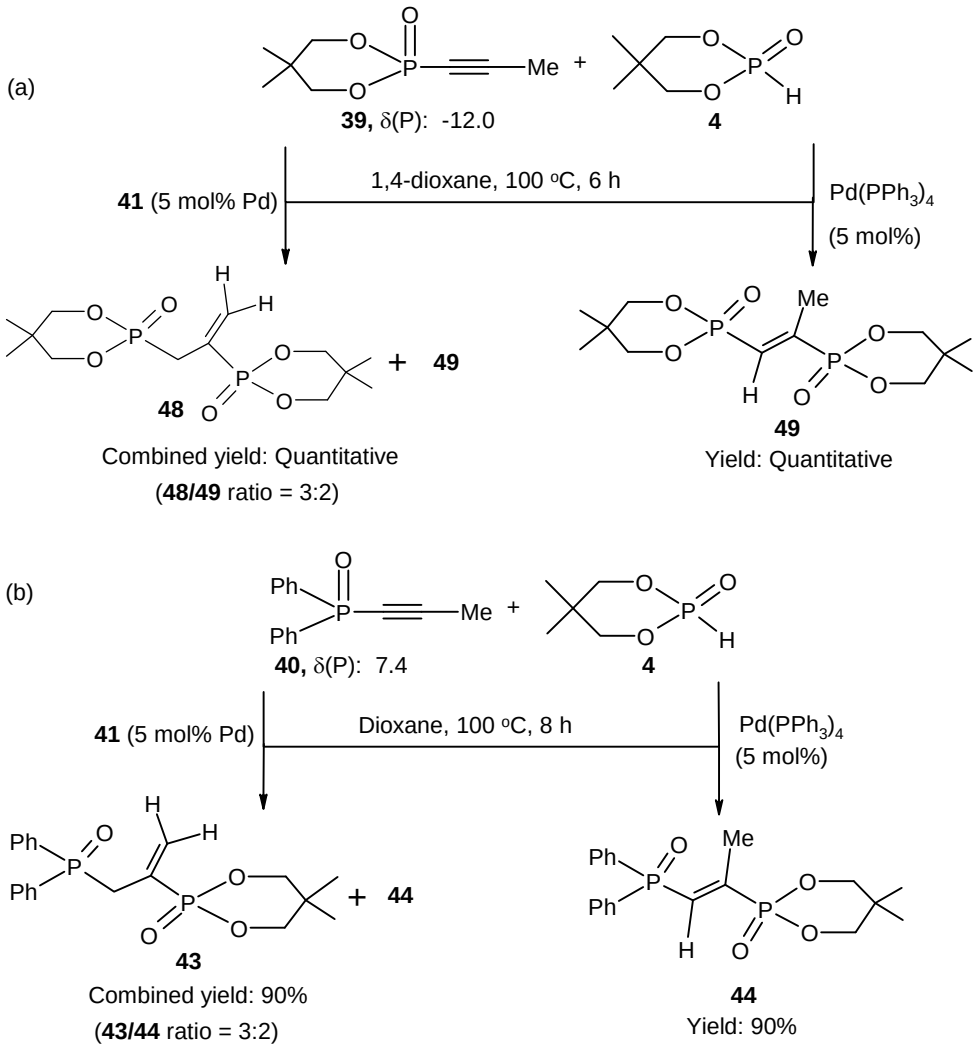
The reaction using allenes (**18-20** or **24-26**) with $Ph_2P(O)H$ (**5**) and $Ph_2P(S)H$ (**8**) under neat conditions most likely involves a radical mechanism as discussed in the literature.[37] We have conducted the reaction of $Ph_2P(S)H$ (**8**) and allene $Ph_2P(O)C(H)=C=CH_2$ (**24**) in 1,4-dioxane for 100 ^oC /1 h in the absence as well as in the presence of *p*-hydroquinone (10 mol%). In the former case, reaction was complete while in the latter case, only ~30% of allene **24** had reacted. At 80 mol% of the *p*-hydroquinone, the reaction was completely inhibited. These results also suggest a radical mechanism. The observed reactivity of the phosphonylating/phosphinylating agents $(OCH_2CMe_2CH_2O)P(O)H$ (**4**) < $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) < $Ph_2P(O)H$ (**5**) ~ $Ph_2P(S)H$ (**8**) is fairly consistent with the available literature.[36b]

2.34 Pd-catalyzed hydro(thio)phosphonylation/hydro(thio)phosphinylation of alkynes

(i) Reactions of alkynes 39-40 with 4-6 and 8

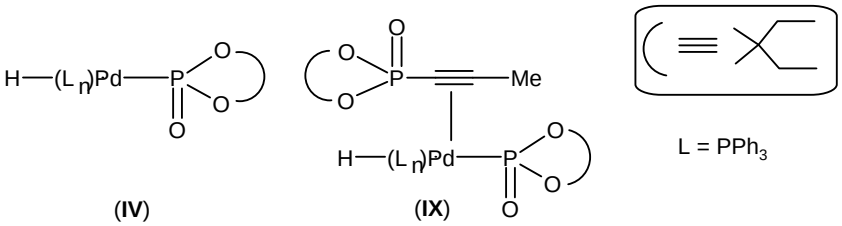
As can be seen from Scheme 9 above (section 2.31), the *alkynes* $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**39**) and $Ph_2P(O)C{\equiv}CMe$ **(40**) are the isomers of the *allenes* $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**) and $Ph_2P(O)C(H)=C=CH_2$ (**24**), respectively. What we wanted to explore in this connection was to see whether hydrophosphonylation/hydrophosphinylation of **39** and **40** will lead to products other than those obtained using the corresponding allenes **18** and **24**. Thus we extended the hydrophosphonylation/hydrophosphinylation to cover the reaction of alkynes **39** and **40** with $(OCH_2CMe_2CH_2O)P(X)H$ [X = O (**4**), S (**6**)] and $Ph_2P(X)H$ [X = O (**5**), S (**8**)]. The reaction of alkyne **39** with **4** by using Pd^I-catalyst $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**41**) afforded two products **48-49**, whereas the catalyst $Pd(PPh_3)_4$ gave the (β,α)-addition product **49** exclusively (Scheme 20a); the latter result is different from that using the corresponding allene **18**. Analogous results were obtained by using the alkyne **40** (Scheme 20b).

Scheme 20



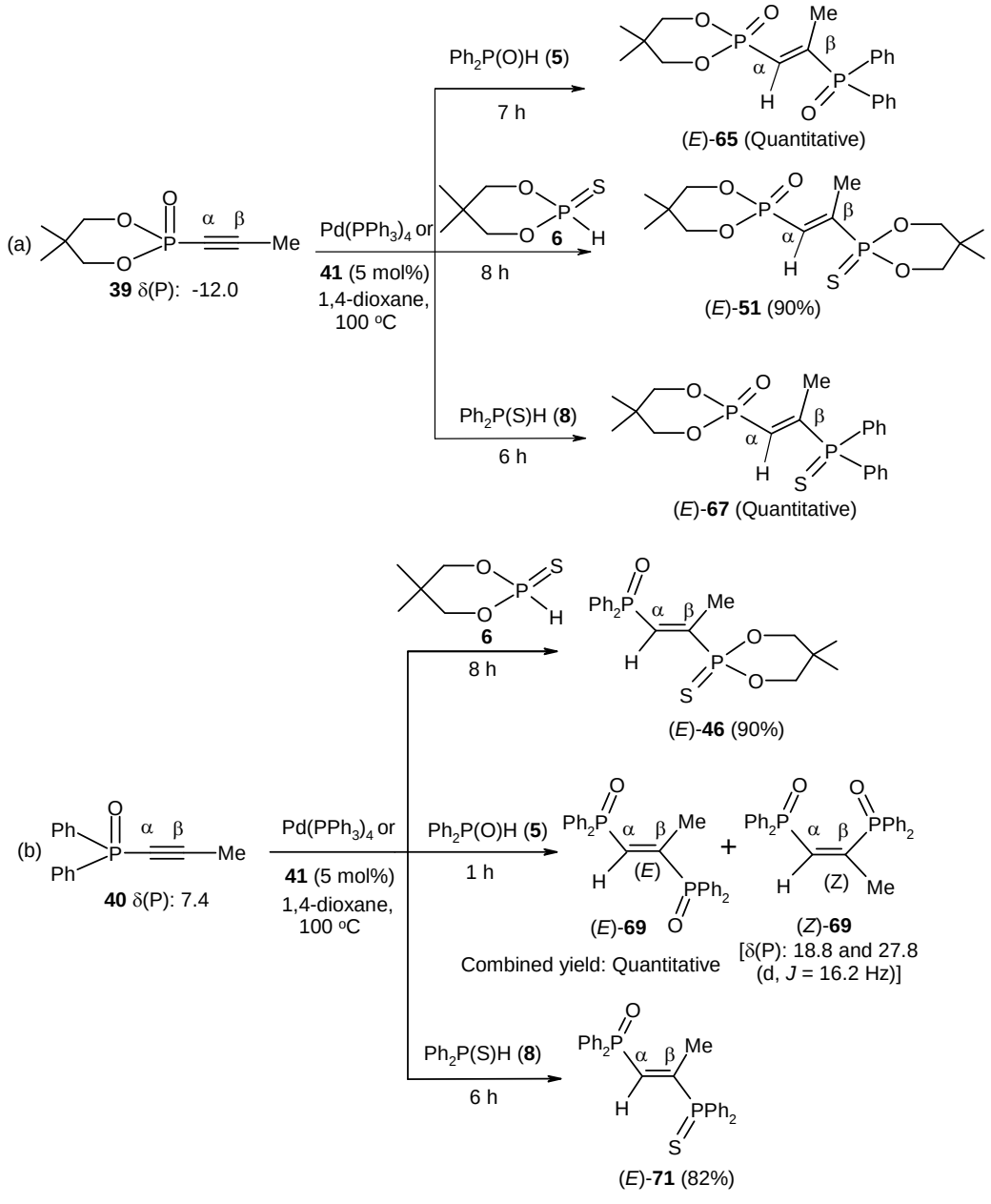
Note : Catalyst **41** is $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$

The initial step in the above phosphonylation reactions is the insertion of the P-H bond leading to a species of type (**IV**) as proposed earlier [cf. Scheme 17]. In the next step, an alkyne-Pd complex of type (**IX)** is most likely involved. Steric factors may be responsible for the formation of the *β*-phosphonylated product **48** or **49** from (**IX**).



The reactions of alkyne **39** with $Ph_2P(O)H$ (**5**), $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) or $Ph_2P(S)H$ (**8**) resulted in quantitative yields [^{31}P NMR] of (β,α)- addition products (*E*)-**65,** (*E*)-**51** or (*E*)-**67** irrespective of catalyst used (Scheme 21a). In a similar manner, the reaction of alkynyl phosphine oxide **40** with **6** or **8** also afforded single isomer (*E*)-**46** or (*E*)-**71** respectively (Scheme 21b), but, rather surprisingly, the reaction with $Ph_2P(O)H$ (**5**) afforded two isomers (*E*)-**69** and (*Z*)-**69** quantitatively (Scheme 21b); later, we realized that this reaction [alkyne **40** with **5**] works under neat conditions also.

Scheme 21

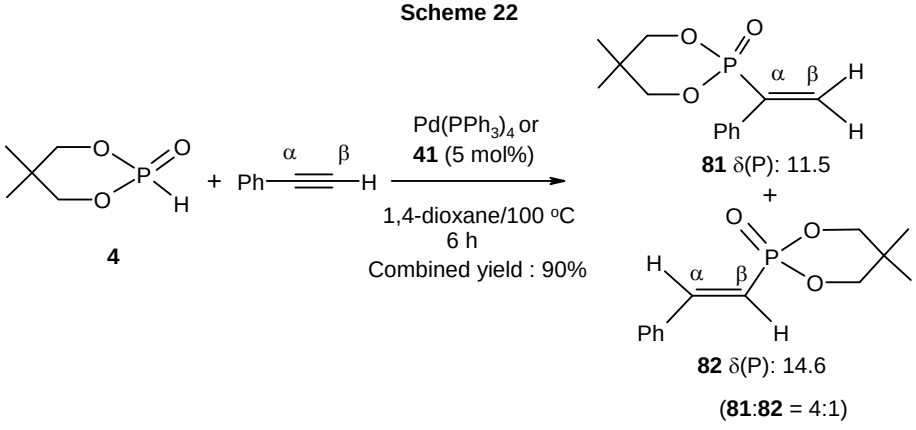


Compounds (*E*)-**69** and (*Z*)-**69** can be readily distinguished by ^{31}P NMR. The ^{31}P NMR spectrum of compound (*E*)-**69** exhibits two doublets at δ 21.0 and 29.5 with ^{3}J(P-P) ~ 53.5 Hz, while compound (*Z*)-**69** also shows two doublets at δ 18.8 and 27.8 but with a much lower ^{3}J(P-P) value of 16.2 Hz. Thus, as mentioned earlier, *trans*-^{3}J(P-P) is greater than *cis*-^{3}J(P-P). As regards the mechanism, since a Pd-complex of type **41** is involved, many possible pathways exist and hence our proposal will be too speculative. However, in most of the cases the *thiophosphinylation* takes place at the *β*-position which is similar to that for *phosphonylation* described above.

(ii) Reaction of phenyl acetylene with cyclic phosphite 4

In contrast to the reaction of $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**39**) and $Ph_2P(O)C{\equiv}CMe$ **(40**) with $(OCH_2CMe_2CH_2O)P(O)H$ (**4**) wherein the phosphite-phosphorus goes to only *β*-carbon, the reaction of phenyl acetylene (PhC≡CH) with **4** leads to both *α* and *β*- products, with the former predominating (**81**:**82** ratio 4:1) (Scheme 22). Compound **81** is new; product **82** was previously reported from our laboratory by using TBAF catalyzed reaction of PhC≡CH with **4** (Scheme 1.**7**, Chapter 1).[14]

Scheme 22

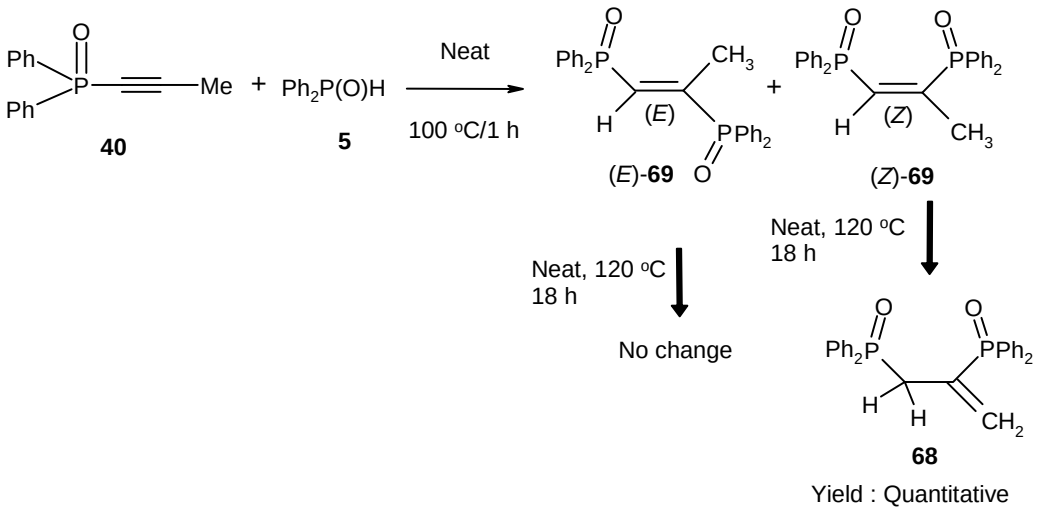


2.35 Solvent-free, catalyst-free hydrophosphinylation of alkyne $Ph_2P(O)C{\equiv}CMe$ (40) with $Ph_2P(O)H$ (5)

In a manner similar to the addition of $Ph_2P(X)H$ [X = O (**5**), S (**8**)] to allenes, we made an attempt to react $(OCH_2CMe_2CH_2O)P(X)H$ [X = O (**4**), S (**6**)] and $Ph_2P(X)H$ [X = O (**5**), S (**8**)] with alkynes $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**39**) and $Ph_2P(O)C{\equiv}CMe$ **(40**) under neat conditions. The reaction mixture of **4**, **6** or **8** with

39 or **40** gave a complicated ^{31}P NMR and starting materials remained. Only the reaction of $Ph_2P(O)H$ (**5**) with $Ph_2P(O)C{\equiv}CMe$ (**40**) worked well and within 1 h gave the (*E*)-**69** and (*Z*)-**69** isomers quantitatively (Scheme 23). More interestingly, we also found that (*Z*)-**69**, upon continuous heating [120 ^{o}C(oil bath)/ 18 h] converts to **68** [Fig 13]. To our knowledge, such isomerization has not been recorded previously in the literature. At the moment, we do not have a good rationalization for this process. We only note that the methyl group on allenes with a terminal =CR(Me) group often tends to reorganize to $-C(R)=CH_2$ with proton migration.[67a] However, compound (*E*)-**69** remains as such upon heating [^{31}P NMR]; thermodynamic factors may be responsible for its resistance to isomerization.

Scheme 23



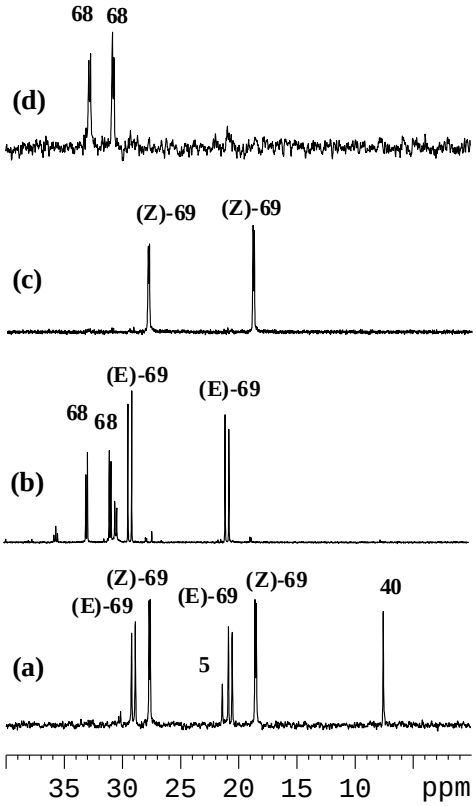


Fig. 13. ^{31}P NMR spectra of (a) **40** with $Ph_2P(O)H$ (**5**) under neat condition at 100 ^{o}C/30 min, (b) **40** with $Ph_2P(O)H$ (**5**) under neat condition at 120 ^{o}C/18 h, (c) Pure (*Z*)-**69** (d) Compound **68** obtained by heating (*Z*)-**69** at 120 ^{o}C/18 h.

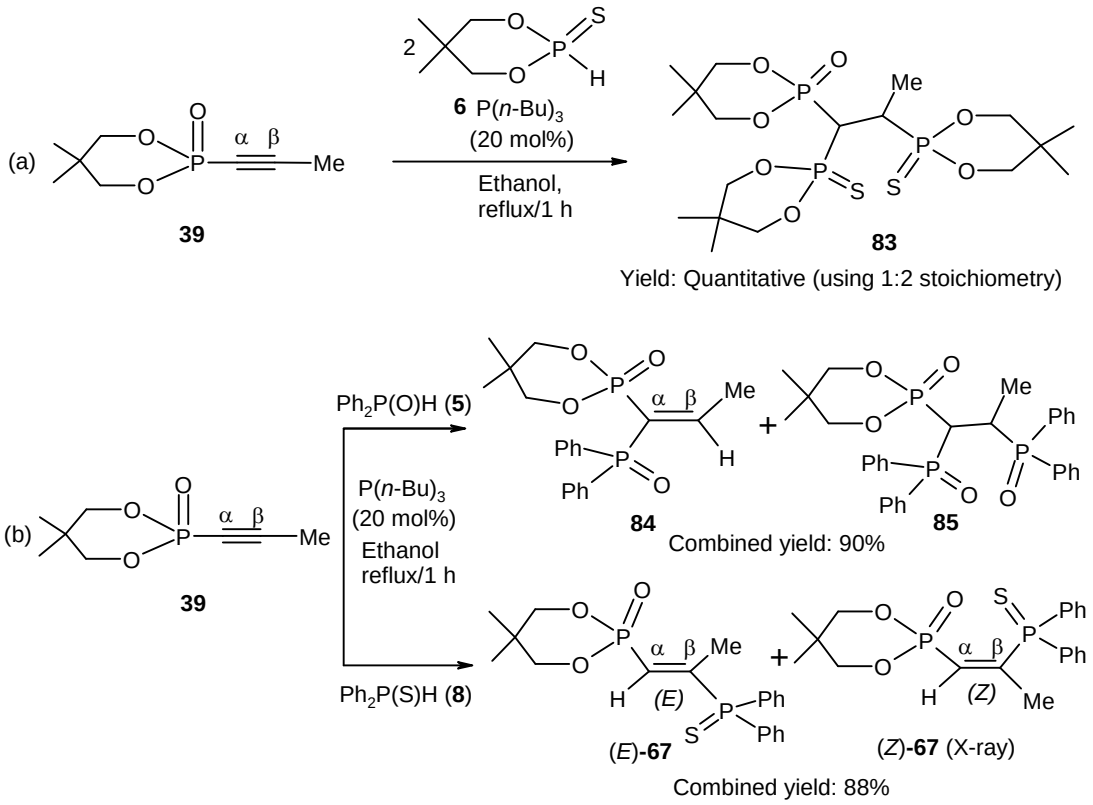
2.36 P(n-Bu)$_3$ catalyzed regioselective hydrothiophosphonylation/hydro(thio)phosphinylation of alkynes

Phosphine-catalyzed nucleophilic addition/cyclization reactions with electron deficient allenes and alkynes are well known, and many of these reactions lead to the so called 'umpolung' products.[107] In hydrophosphinylation of phosphono-alkynes, preferential formation of a geminal product [α,β-P(O)H addition] is reported.[21] However, such reports on the phosphine-catalyzed phosphonylation of allenes and alkynes, in particular phosphorylated alkynes, are rather limited.[21-22] Hence we checked the phosphonylation of allenylphosphonates (**18-20**) and allenyl phosphine oxides (**24-26**) under P(*n*-Bu)$_3$ catalyzed conditions. Thus, compounds $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**) and $Ph_2P(O)C(H)=C=CH_2$ (**24**) reacted with $(OCH_2CMe_2CH_2O)P(S)H$ (**6**), but the products (**50-52** and **45-47** respectively; section 2.32) were the same as those observed in Pd-catalyzed conditions. A similar reaction with $(OCH_2CMe_2CH_2O)P(O)H$ (**4**) led only to the isomerization to alkyne

($OCH_2CMe_2CH_2O$)P(O)C≡CMe (**39**) or Ph_2P(O)C≡CMe (**40**). Reaction of ($OCH_2CMe_2CH_2O$)P(O)CH=C=CMe_2 (**19**), ($OCH_2CMe_2CH_2O$)P(O)C(Ph)=C=CH_2 (**20**), Ph_2P(O)CH=C=CMe_2 (**25**), or Ph_2P(O)C(Ph)=C=CH_2 (**26**) with Ph_2P(O)H (**5**) and Ph_2P(S)H (**8**) led to products similar to that observed under neat conditions [see products **72-80** in Scheme 19, Section 2.33]. Then we turned our attention to phosphono/phosphino alkynes themselves (**39-40)** as substrates.

The alkyne **39** and ($OCH_2CMe_2CH_2O$)P(S)H (**6**) under P(*n*-Bu)$_3$ catalyzed conditions afforded only the bisthiophosphonylated product **83** (Scheme 24a), which is entirely different from that obtained in the Pd-catalyzed reaction (compound (*E*)-**51**; cf. Scheme 21a, Section 2.34). Hence in the 1:1 stoichiometric reaction, part of the alkyne **39** remained; quantitative conversion to **83** could be achieved readily by using 1:2 stoichiometry of **39** and **6**. There was no reaction in absence of the catalyst. The reaction of **39** with Ph_2P(O)H (**5**; 1.0 equivalent with respect to **39**) also afforded (*α,β*)-P(O)-H addition product **84** along with bisphosphinylated product **85** (Scheme 24b). Complete conversion to **85** was observed (^{31}P NMR), when 2.0 equiv of **5** was used. Rather surprisingly, the reaction of **39** with the Ph_2P(S)H (**8**) resulted in (*β,α*)-P(O)-H addition products (*E*)-**67** and (*Z*)-**67** (Scheme 24b). There was no observable bisphosphinylation. It may also be noted that in the Pd-catalyzed reaction only (*E*)-**67** was obtained (cf. Scheme 21a, Section 2.34). Distinction between (*E*)-**67** and (*Z*)-**67** could be made on the basis of the ^3J(P-P) values of 80.5 and 16.0 Hz, respectively. For further confirmation, compound (*Z*)-**67** was also characterized by single crystal X-ray crystallography (Fig. 14). Details on the yields of the products and ^{31}P NMR are given in Table 6.

Scheme 24



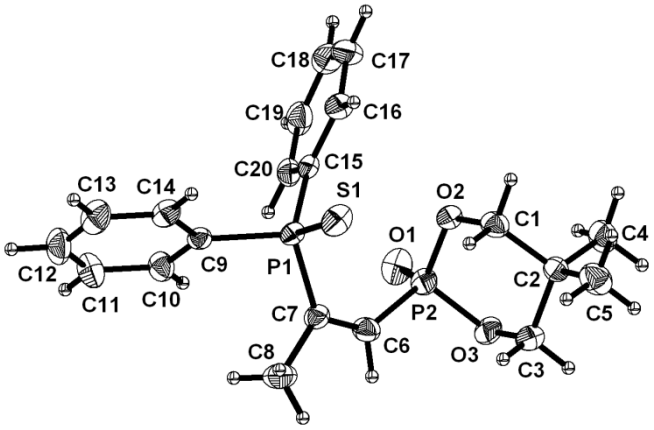


Fig. 14. An ORTEP diagram for compound (*Z*)-**67**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(7) 1.833(4), P(1)-C(9) 1.821(4), P(1)-C(15) 1.808(4), P(1)-S(1) 1.956(1), P(2)-C(6) 1.779(4), C(6)-C(7) 1.337(5), C(7)-C(8) 1.513(5).

Compounds **83-85** were characterized by analytical and spectroscopic data. For compound **83**, in the ^{1}H NMR spectrum, a characteristic doublet of doublet centered at δ 1.73 [^{3}J(P-H) = 18.0 Hz, ^{3}J(H-H) ~ 6.8 Hz] due to P(S)CHC*H*$_3$ protons was observed. Two multiplets were observed at δ 3.26-3.35 and δ 4.30-4.47 corresponding to P(S)-C*H*(Me) and P(O)-C*H*-P(S) protons, respectively. In the ^{13}C

NMR, a dd→t due to P(S)CH*C*H$_3$ carbon at δ 11.8 [$^{2,3}J$(P-C) ~ 5.1 Hz], a doublet for P(S)-*C*H carbon at δ 36.8 (d, ^{1}J(P-C) = 104.0 Hz] and a dd for (S)P*C*P(O) carbon at δ 40.3 [^{1}J(P-C) = 127.8 Hz, 90.0 Hz] were observed. The ^{31}P NMR spectrum, interestingly, shows a *singlet* for *P*(O) phosphorus at δ 9.3 and two doublets for *P*(S) phosphorus moieties at δ 90.5 and 104.7 [^{3}J(P-P) = 77.0 Hz]. Final confirmation of the structure was arrived at by comparing these spectral features with that of compound **87** discussed later.

Compound **84** was characterized only by ^{31}P NMR analysis since it contained small amounts of P(O)(*n*-Bu)$_3$ [δ(P) 50.0]. The ^{31}P NMR spectrum exhibits two doublets at δ 5.9 and 31.0 [^{3}J(P-P) ~ 42.9 Hz]. These chemical shifts are different from that of compound (*E*)-**65**, a regio-isomer of compound **84**.

In the ^{1}H NMR spectrum of compound **85** a dd at δ 1.54 [^{3}J(P-H) = 17.2 Hz, ^{3}J(H-H) = 7.2 Hz] was observed for P(O)CHC*H*$_3$ protons. In the ^{13}C NMR, a doublet due to P(O)CH*C*H$_3$ carbon [δ 13.2, ^{2}J(P-C) ~ 6.0 Hz], another doublet for P*C*HCH$_3$ [δ 32.1, ^{1}J(P-C) ~ 66.0 Hz] and a dd for P*C*HP [δ 36.7, ^{1}J(P-C) ~ 131.5 Hz, 54.5 Hz] were observed (Fig. 15). The ^{31}P NMR spectrum exhibited a singlet for (OCH$_2$CMe$_2$CH$_2$O)$_2$*P*(O) phosphorus at δ 14.5 and two doublets for Ph$_2$*P*(O) phosphorus moieties at δ 31.7 and 34.1 [^{3}J(P-P) = 34.3 Hz]. It may also be noted that, in general, *J*(P-P) values for compounds with Ph$_2$*P*(O)- group are lower than that for those with (OCH$_2$CMe$_2$CH$_2$O)*P*(O)- group [cf. compounds **83** and **85**].

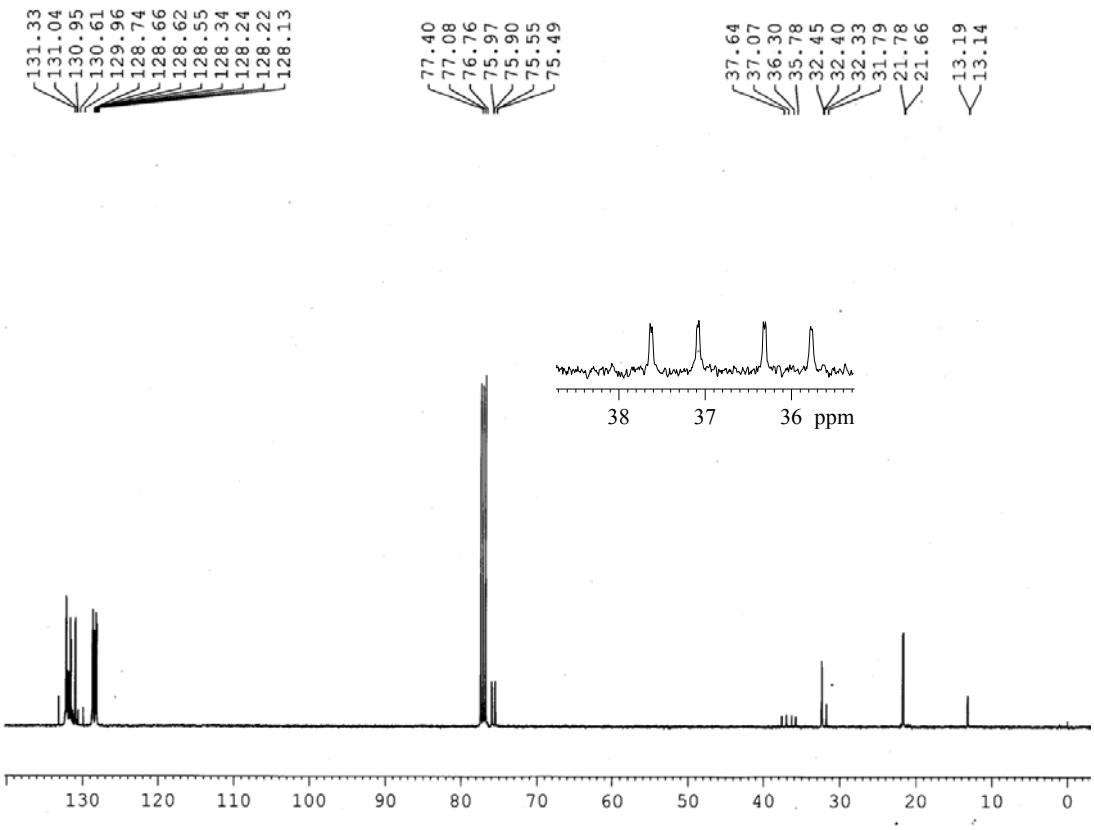


Fig. 15. ^{13}C NMR spectrum of compound **85**

Results similar to what is discussed above were obtained when $Ph_2P(O)C{\equiv}CMe$ (**40**) was used in place of alkyne $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**39**) in the P(*n*-Bu)$_3$ catalyzed reactions (Scheme 25). Thus treatment of alkyne **40** with $Ph_2P(O)H$ (**5**) gave the geminal phosphinylated product **86**, along with the bisphosphinylated derivative **87**. These products **86-87** are structurally similar to **84-85**. Addition of more $Ph_2P(O)H$ (**5)** [1.0 mol equivalents with respect to **40**] to the reaction mixture increased the yield of **87**. A literature report states that the same reaction under MW-conditions in isopropanol affords a different type of product (γ-phosphinylated product) by using alkyne **40** and $Ph_2P(O)H$ (**5**) [Scheme 1.**16**, compound 1.**62**, Chapter 1].[22] These data suggest that slight modifications in the reaction conditions could lead to the different products (or that the literature report is incorrect). As far as our work is concerned, the product **87** is characterized by single crystal X-ray crystallography (Fig. 16). Clearly, the bisphosphinylation has occurred at α and β positions.

The reaction of alkyne **40** with $Ph_2P(S)H$ (**8**) did not form the umpolung (*α,β*-P(S)-H) addition product which is similar to compound **86**. The *β,α*-P(S)-H addition

product (*E*)-**71** [similar to compound (*E*)-**67**] was isolated as a major component from this reaction (Scheme 25). Details on the yields of the products and ^{31}P NMR are shown in Table 6. From these observations, we conclude that the P(*n*-Bu)$_3$ catalyzed phosphinylation reactions with phosphono/phosphino alkynes take place differently when compared to Pd-catalyzed reactions, except in the case of $Ph_2P(S)H$ (**8**).

Scheme 25

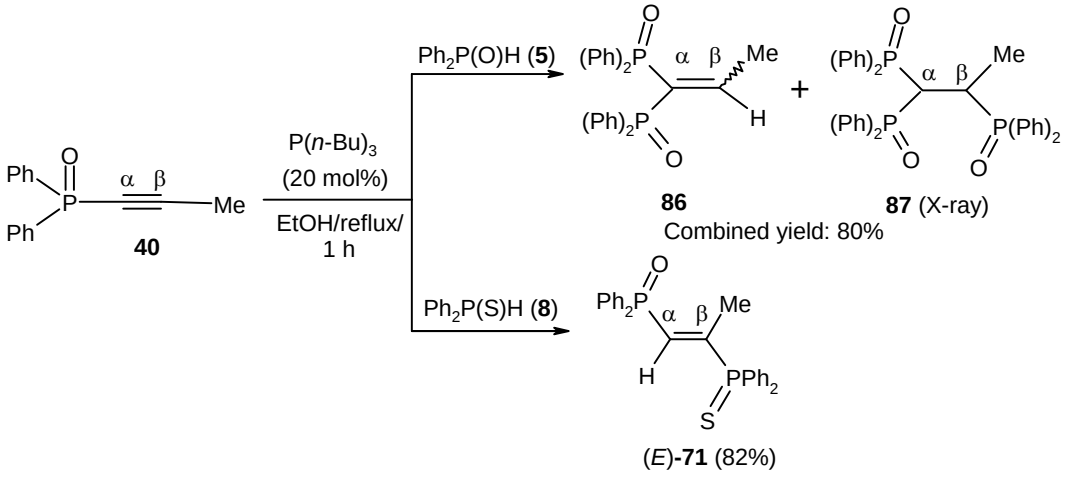


Table 6: Details on the ^{31}P NMR of the products shown in Schemes 24-25

Entry	Substrates	Product(s)	^{31}P NMR
1	**6** + **39**	**83**	9.3 (s), 90.5 and 104.7 (d, ^3J = 77.0 Hz)
2	**5** + **39**	**84**	5.9 and 31.0 (d, ^3J = 42.9 Hz)
		85	14.5 (s), 31.7 and 34.1 (d, ^3J = 34.3 Hz)
3	**8** + **39**	(*E*)-**67**	8.2 and 49.6 (d, ^3J = 80.5 Hz)
		(*Z*)-**67** (X-ray)	4.6 and 41.4 (d, ^3J = 18.5 Hz)
4	**5** + **40**	**86**	23.9 and 30.3 (d, ^3J = 38.1 Hz)
		87 (X-ray)	27.6 (s), 32.8 and 34.5 (d, ^3J = 32.6 Hz)
5	**8** + **40**	(*E*)-**71**	20.3 and 49.4 (d, ^3J ~ 53.2 Hz)

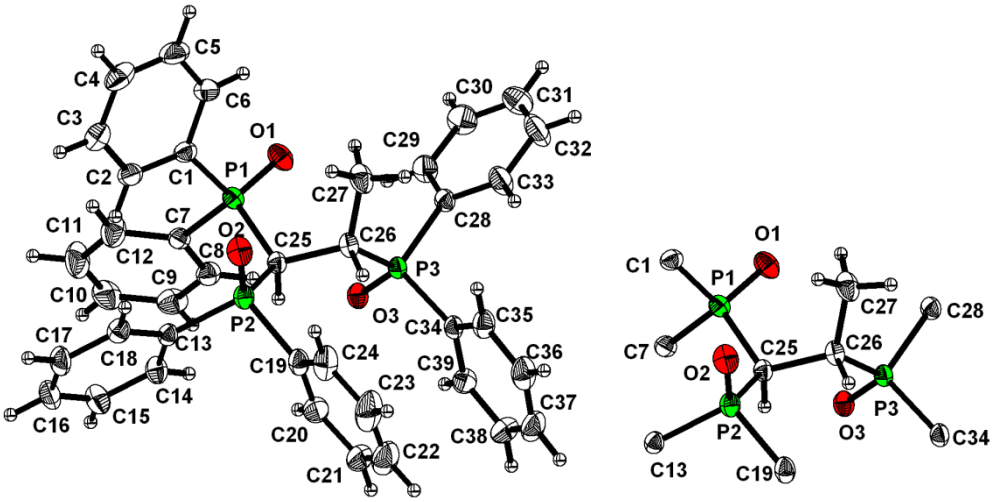
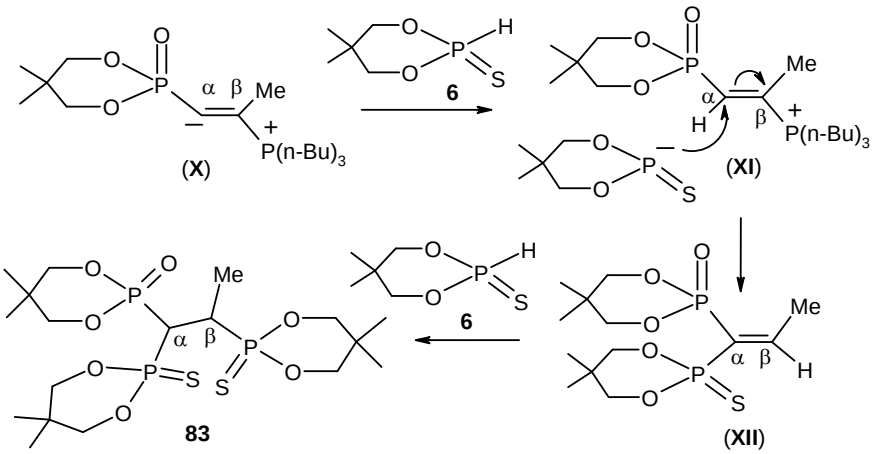


Fig. 16. An ORTEP diagram for compound **87**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(1) 1.809(2), P(1)-C(7) 1.810(2), P(1)-C(25) 1.855(2), P(2)-C(13) 1.802(2), P(2)-C(19) 1.810(2), P(2)-C(25) 1.835(2), P(3)-C(28) 1.802(2), P(3)-C(8) 1.787(3), P(3)-C(34) 1.809(2), P(3)-C(26) 1.848(2), C(25)-C(26) 1.568(3), C(26)-C(27) 1.531(3). On the right is shown selected atoms and the orientation of the three phosphorus atoms [note that one of the coupling constants, probably geminal ^{2}J(P-P), was low (<2.0 Hz) in the ^{31}P NMR spectrum]. The dihedral angles of the planes (P1, C25, C26) and (P2, C25, C26) with (P3, C26, C25) are, respectively, 85.5(1) and 41.2 (1)^{o}.

Mechanistic pathway for the formation of compound 83

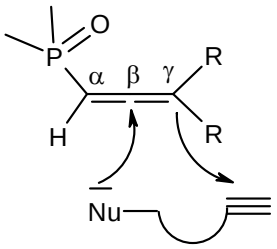
Based on the available literature, the phosphine catalyzed nucleophilic reactions of activated alkynes involve zwitterions of type **X.**[21] This species can abstract a proton from the substrate **6** leading to **XI**. Addition of phosphorus pronucleophile to **XI** at α-position gives intermediate **XII** (Scheme 26). The second phosphonylation with **6** could then occur at the β-carbon of **XII** leading to **83**. Formation of compounds **84-87** also can be explained by similarly.

Scheme 26



2.4 $Zn(OTf)_2$/amine catalyzed addition-cyclization reactions of propargyl alcohols with allenyl phosphine oxides

In the nucleophilic attack (say by RO^-) on allenylphosphonates, the initial attack takes place at the carbon *β*- to phosphorus.[67d] If there is a second reactive center (like –C(H)=O, C=C, C≡C etc.) on the nucleophile, further reaction leading to cyclic products can result. In the present work, we had access to a wide variety of allenylphosphonates/ allenyl phosphine oxides as well as substituted propargylic alcohols [e.g. $HC{\equiv}CR_2CH_2OH$]. Hence we wanted to explore reactions in which both the oxygen and the alkyne ends of the propargylic alcohols react with the allenes and lead to cyclized products. Such reports on the reaction of allenyl phosphonates/phosphine oxides with propargyl alcohols are not reported in the literature so far.[108] We chose $Zn(OTf)_2$ (+amine base) as a catalyst system based on a literature report that this compound catalyses the reaction of alkylidene malonate [$ArHC{=}C(CO_2Me)_2$] with propargyl alcohol; the product is a five-membered heterocycle.[109]



A diagram showing the possible reaction of nucleophile with an appended functional group

Based on the above idea, we treated the allenyl phosphine oxide $Ph_2P(O)CH=C=CH_2$ (**24**) with propargyl alcohol [$HC\equiv CCH_2OH$] by using $Zn(OTf)_2$ (10 mol%) and Et_3N (20 mol%). There was no reaction under these conditions due to the conversion of allene **24** to the corresponding alkyne $Ph_2P(O)C\equiv CMe$ (**40**). We then reacted $Ph_2P(O)CH=C=CMe_2$ (**25**) with propargyl alcohol and were delighted to get the *β,γ*-addition-cyclization product **88** (Scheme 27) in 90% yield. In this reaction, two other cyclized products **88'** (*β,α*-addition product) or **88"** are also possible but ^{31}P NMR spectrum of the reaction mixture indicated only product **88**. The reaction did not proceed even at elevated temperatures (110 ^oC) in the presence of other Zn^{II} catalysts like $ZnBr_2$, $ZnCl_2$ or $Zn(OAc)_2$. Other triflate salts like $Sc(OTf)_3$, $Cu(OTf)_2$ and $Gd(OTf)_3$ were also not effective for this transformation. After screening these catalysts, we optimized the reaction condition by changing the base (Table 7). There was no reaction in the absence of base (Table 7, entry 1) in toluene at 100 ^oC. The use of triethylamine (20 mol%) at 25 ^oC/10 h also did not give any product (entry 2), but the product readily formed when the mixture was heated at 100 ^oC for 6 h (entry 3). Use of other bases like DABCO (20 mol%), DBU (20 mol%) and K_2CO_3 (20 mol%) (Entries 4-6) also afforded the product **88**, but the reaction needed longer time for completion (10-14 h). Yield of the product was also low compared to the case in which Et_3N was used. When the amount of Et_3N was reduced from 20 mol% to 10 mol%, the reaction needed more time for completion (8 h) and the yield of the product **88** was less (80%, entry 7). We checked the role of the solvent in this reaction and found toluene was the best solvent (Table 8) compared to other solvents like THF, CH_3CN, 1,4-dioxane and DMF (Table 8, entries 2-6 respectively). Hence, we performed the remaining cyclization reactions using triethylamine as the base and toluene as the solvent. As regards characterization, compound **88** shows a signal at δ 2.4 corresponding to two protons (ring CH_2) in the ^1H NMR spectrum. Such a signal in this region is not possible for **88'** or **88"** wherein the OCH_2 protons should appear downfield to ~3.4 ppm.

Scheme 27

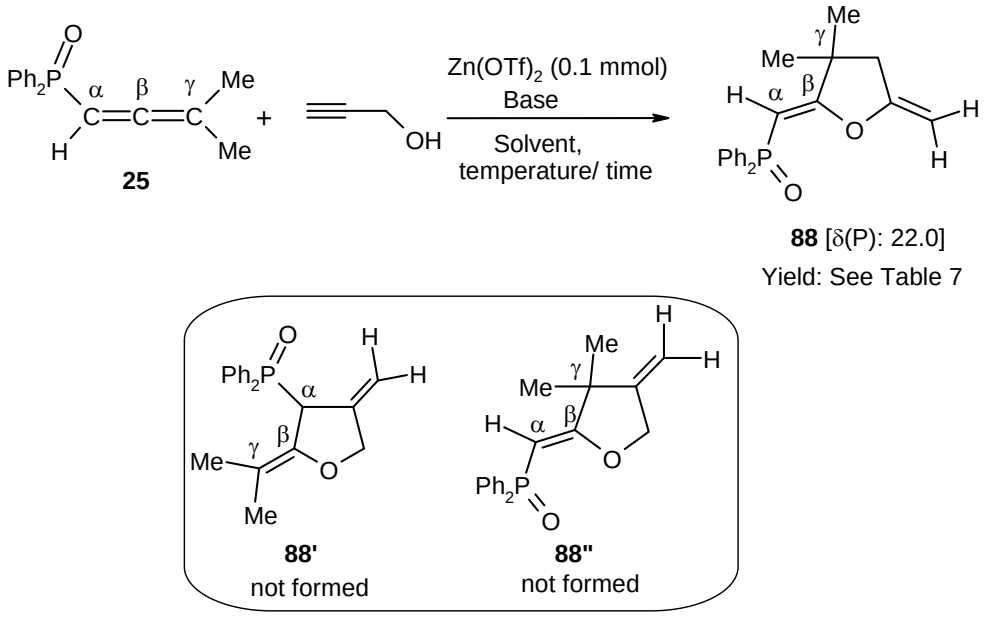


Table 7. Details on the conditions of the reaction shown in Scheme 27[a]

Entry	Base (mol%)	Temperature (^oC)	Time (h)	Yield (%)[b]
1	None	100	24	n.r
2	Et_3N (20)	25	24	n.r
3	Et_3N (20)	100	6	90
4	DABCO (20)	100	10	80
5	DBU (20)	100	9	82
6	K_2CO_3 (20)	100	14	64
7	Et_3N (10)	100	8	80

[a]Other parameters: Allene **25** (1.0 mmol), propargyl alcohol (3.0 mmol), $Zn(OTf)_2$ (0.1 mmol) in toluene (1.0 mL).

[b]Based on ^{31}P NMR analysis.

Table 8: Effect of solvent on the reaction shown in Scheme 27[a]

Entry	Solvent	Temperature (^oC)	Time (h)	Yield (%)[b]
1	Toluene	100	6	90
2	THF	60	10	84
3	CH_3CN	70	8	75
4	DCE	80	12	82

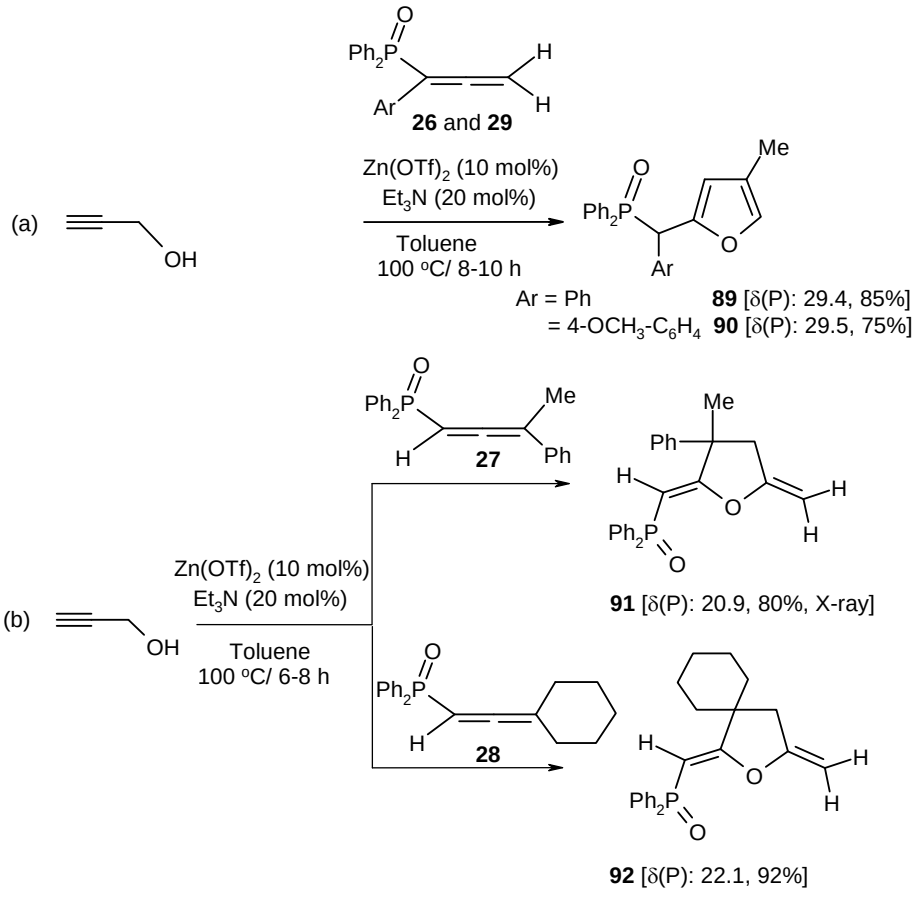
5	1,4-dioxane	100	14	64
6	DMF	90	8	56

[a]Other conditions in this reaction: Allene **25 (**1.0 mmol), propargyl alcohol (3.0 mmol), Zn $(OTf)_2$ (0.1 mmol), triethylamine (0.2 mmol).

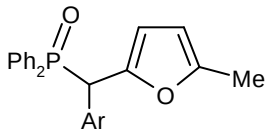
[b]Based on ^{31}P NMR analysis.

After ascertaining that the above Zn-catalyzed reaction works, we explored the reactivity of other allenyl phosphine oxides $Ph_2P(O)C(R)=C=C(R')(R'')$ [R = Ph, R' = R'' = H (**26**), R = H, R' = Me, R'' = Ph (**27**), R = H, R' = R'' = $-(CH_2)_5-$ (**28**), R = C_6H_4-*p*-OCH_3, R' = R'' = H (**29**)] with $HC\equiv CCH_2OH$ under $Zn(OTf)_2$/ Et_3N catalyzed conditions. The reaction using α-aryl substituted allenyl phosphine oxides **26** and **29** gave (*β,γ*)-addition-cyclization products **89**-**90** (Scheme 28a). In these products, the five membered ring was aromatized to lead to the furan ring. The reaction using **27**-**28** afforded products **91**-**92** (Scheme 28b) that are structurally similar to **88**. The isolated yields in all these cases are good.

Scheme 28



In the ^{1}H NMR spectrum, compound **89** shows a singlet due to CH_3 at δ 2.13, a doublet due to PC*H*(Ph) at δ 4.90 [^{2}J(P-H) = 11.6 Hz]. The furan protons appear as two sharp singlets at δ 5.82 and 6.41. In the alternative structure **89'** (see below) for the furan protons, a ^{3}J(H-H) value of at least 3.0 Hz is expected.[88] Hence the structure as given is correct. Spectroscopic data of compound **90** is similar to the compound **89**. Compound **91** is also characterized by single crystal X-ray crystallography (Fig. 17). The distances C(13)-C(14) 1.316(5) Å, C(24)-C(25) 1.308(5) Å readily identify the location of the double bonds. On this basis, the structure **92** follows.



89'

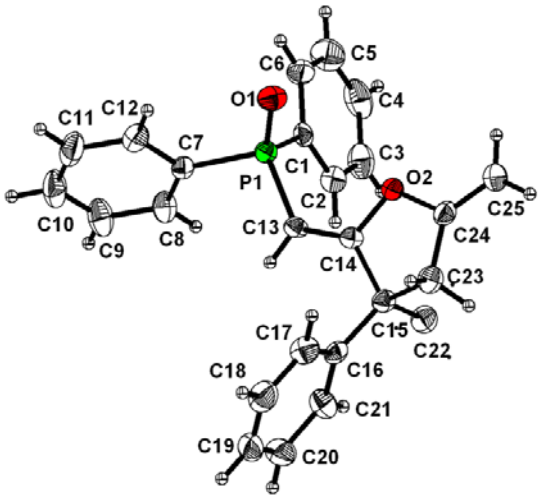
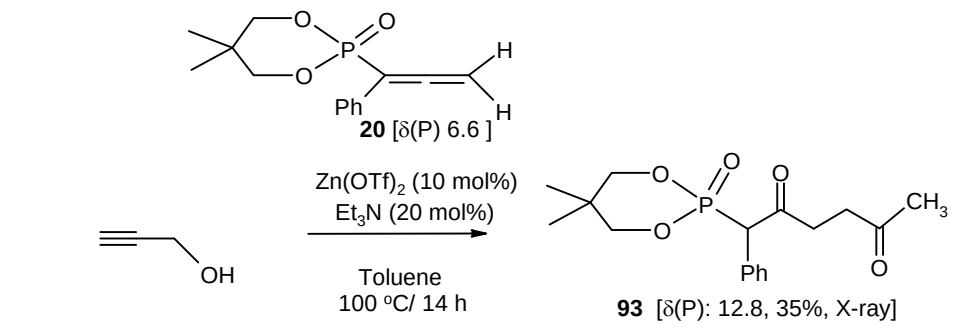


Fig. 17. An ORTEP diagram for compound **91**. Selected bond lengths [Å] with esd's in parentheses: P(1)-O(1) 1.474(3), O(1)-C(1) 1.807(4), P(1)-C(7) 1.809(4), P(1)-C(13) 1.773(4), O(2)-C(14) 1.363(4), C(13)-C(14) 1.316(5), C(15)-C(23) 1.528(5), C(24)-C(25) 1.308(5).

In contrast to the above, the reaction of allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**20**) with propargyl alcohol [$HC\equiv CCH_2OH$] surprisingly afforded a non-cyclized *β,ω*-diketophosphonate **93** (Scheme 29). This compound contains two exocyclic C(O)CH_2 groups and an additional CH_3 group as revealed by its ^{1}H NMR spectrum (Fig. 18). This compound was also characterized

by X-ray crystallography (Fig. 19). It can be noted that this product is a result of addition of a molecule of water after the propargylic group adds to the allene. Since this type of product was not of interest to us, we did not study this aspect further.

Scheme 29



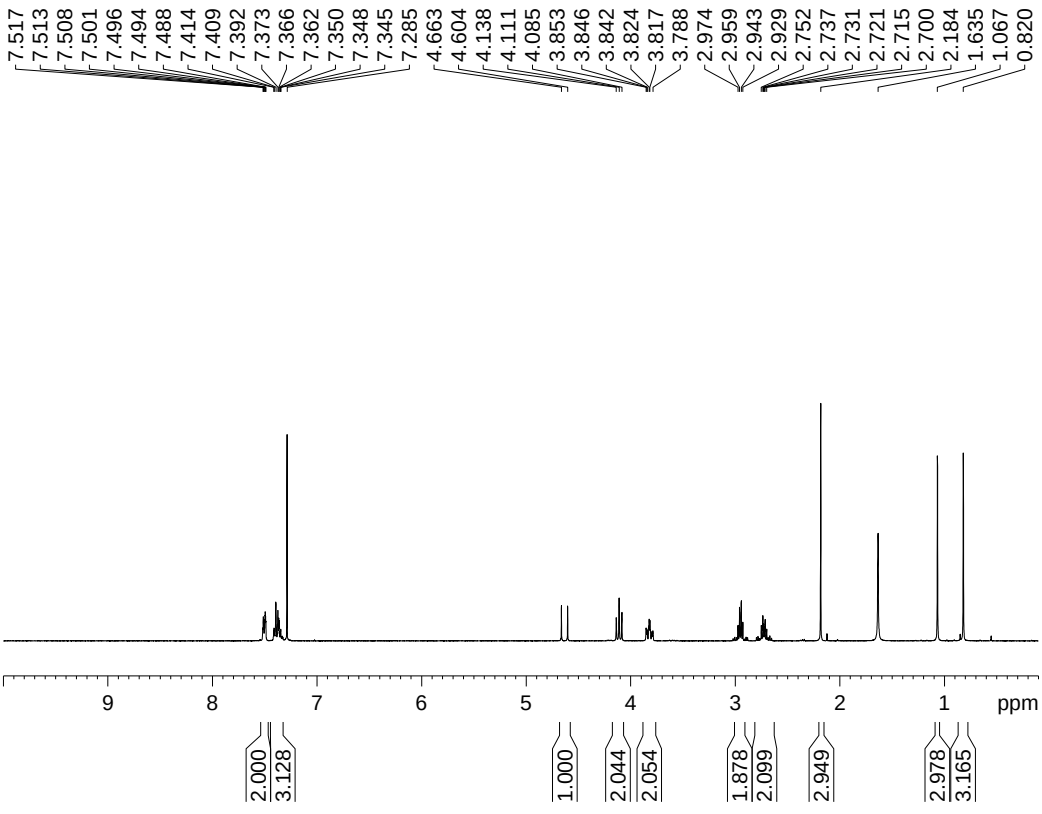


Fig 18: ^{1}H NMR spectrum of compound **93**

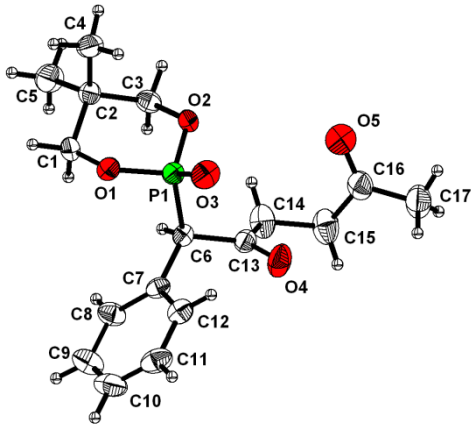
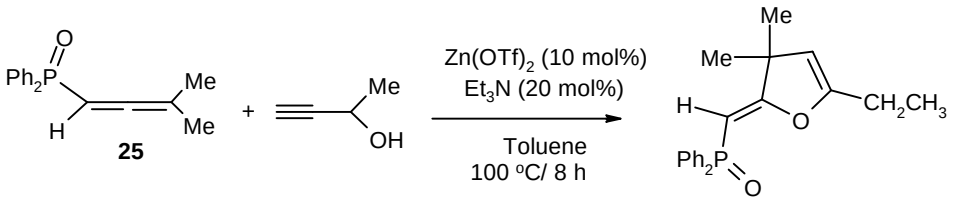


Fig. 19. An ORTEP diagram for compound **93**. Selected bond lengths [Å] with esd's in parentheses: P(1)-O(1) 1.5671(19), P(1)-O(2) 1.572(2), P(1)-O(3) 1.4593(18), P(1)-C(6) 1.818(3), O(4)-C(13) 1.202(3), O(5)-C(16) 1.220(4), C(6)-C(13) 1.534(4).

Next, we turned our attention to the reaction of allenes with methyl substituted propargyl alcohol HC≡CC(Me)(H)(OH). The allene $Ph_2P(O)CH=C=CMe_2$ (**25**) when treated with HC≡CC(Me)(H)(OH) afforded the cyclized product **94** in good yield (Scheme 29). This product is formed in a manner similar to **88**, but a proton migration from the five-membered ring to the exocyclic double bond has occurred. The newly formed CH_2CH_3 group is clearly observed in the ^{1}H NMR spectrum.

Scheme 29



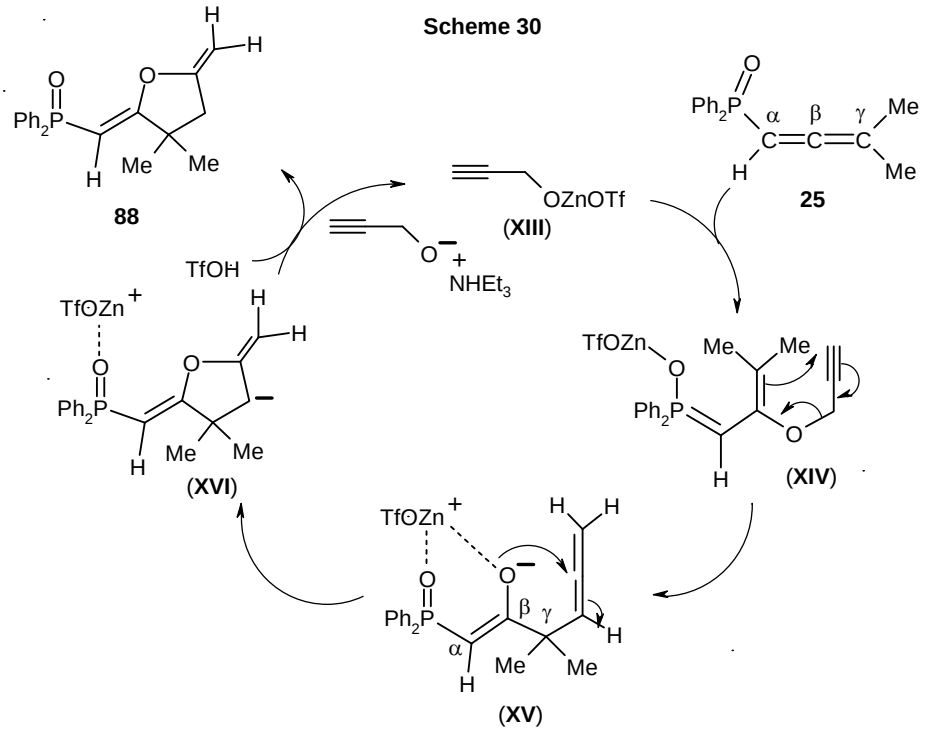
94 [δ(P): 21.3, 76%]

Plausible mechanism for the formation of 88

On the basis of the above experimental results, we propose a mechanistic rationale for the catalytic coupling reaction of propargyl alcohol with **25** (Scheme 30). First, zinc alkoxide **XIII** is formed by the exchange of propargyl alcohol with one of the triflates of $Zn(OTf)_2$. Then the zinc species **XIII** adds to the allene **25** forming species **XIV** wherein the phosphoryl oxygen coordinates to zinc. Isomerization of the species **XIV** could take place to form an allene of type **XV**. Then intramolecular cyclization takes place by the attack of oxygen connected to *β*-

carbon on the central carbon of the allene. This is followed by protonation of intermediate **XVI** furnishing product **88** and regenerates the zinc alkoxide **XIII**. Formation of the products **89-92** and **94** can also rationalized by this mechanism.

Scheme 30



SUMMARY – PART A

1) The reaction of $(OCH_2CMe_2CH_2O)PCl$ (**1**) with nitro-substituted propargyl alcohols [3-cyclohexenyl-1-(2-nitrophenyl)prop-2-yn-1-ol (**13**), 1-(2-nitrophenyl)-3-phenyl-prop-2-yn-1-ol (**15**) and 1-(2-nitrophenyl)-3-p-tolyl-prop-2-yn-1-ol (**16**)] leads to ***unusual*** seven- or five-membered heterocycles [dibenzo-azepines and *N*-hydroxy-indolinones], rather than the normally expected allenylphosphonates. These compounds are characterized by single crystal X-ray crystallography.

2) A novel and robust dinuclear Pd^I catalyst $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (**41**) has been effectively utilized in hydrophosphonylation/hydrophosphinylation of a diverse class of allenylphosphonates/allenyl phosphine oxides of types $R_2P(O)C(R')=C=CR"_2$. The efficacy of dinuclear Pd^I-catalyst **41** is comparable with $Pd(PPh_3)_4$ in these reactions. These reactions led preferentially to (β,α)-P(X)H [X = O, S] addition products. The catalyst **41** could be recovered and reused at least in two cases that we tried. The thiophosphite $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) quite often led to bisphosphonylated products.

3) Solvent-free, catalyst-free protocol for phosphonylation of allenylphosphonates and allenyl phosphine oxides with $Ph_2P(X)H$ [X = O (**5**), S (**8**)] leading to allyl-/vinyl -phosphonates/phosphine oxides in excellent yields is described. The observed reactivity of the phosphonylating/phosphinylating agents [$(OCH_2CMe_2CH_2O)P(O)H$ (**4**) < $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) < $Ph_2P(O)H$ (**5**) ~ $Ph_2P(S)H$ (**8**)] is fairly consistent with the available literature. The reactivity of the allenyl phosphine oxides is found to be more than that of allenylphosphonates.

4) Pd-catalyzed hydrophosphonylation/hydrophosphinylation of alkynes (**39-40**) cyclic phosphite (**4**), thiophosphite (**6**), $Ph_2P(O)H$ (**5**) or $Ph_2P(S)H$ (**8**) leads to vinyl- phosphonates/-phosphine oxides. More interestingly the phosphinylation of alkyne **40** with $Ph_2P(O)H$ (**5**) can be achieved under solvent-free, catalyst-free conditions leading to (*E*)-**69** and (*Z*)-**69** isomers. An interesting case of isomer conversion of a vinyl bisphosphine oxide [(*Z*)-**69**] to an allylvinyl bisphosphine oxide [**68**] is also reported.

5) P(*n*-Bu)$_3$ catalyzed hydro(thio)phosphonylation/hydro(thio)phosphinylation of alkynes (OCH$_2$CMe$_2$CH$_2$O)P(O)C≡CMe (**39**), Ph$_2$P(O)C≡CMe (**40**) with R$_2$P(X)-H [X = O, S] took place differently [(*α,β*-P(X)-H addition] compared to Pd-catalyzed reactions [(*β,α*,-P(X)-H addition], and lead to novel geminal-bis and -tris phosphorus compounds.

6) A new Zn(OTf)$_2$/NEt$_3$ catalyzed coupling reaction of allenylphosphine oxides (**25-29**) with propargyl alcohols leading to phosphino-furans is described. In the case of allenylphosphonate (OCH$_2$CMe$_2$CH$_2$O)P(O)C(Ph)=C=CH$_2$ (**20**) with HC≡CCH$_2$OH a non-cyclized *β,ω*-diketo-phosphonate [(OCH$_2$CMe$_2$CH$_2$O)P(O)C(H)(Ph)C(O)(CH$_2$)$_2$C(O)CH$_3$] (**93**) is also isolated.

EXPERIMENTAL SECTION

General: Chemicals and solvents were procured from Aldrich/ Fluka or local manufacturers. Further purification was done according to standard procedures wherever required.[110] All operations, unless otherwise specified, were carried out under dry nitrogen atmosphere using standard vacuum line techniques.[111]

Melting point: Melting points were determined using a SUPERFIT hot stage apparatus and are uncorrected.

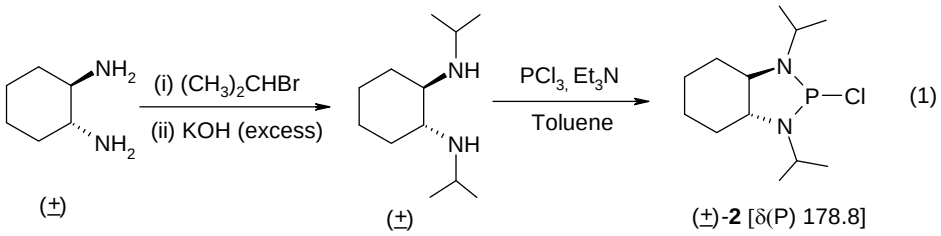
Elemental analyses: Elemental analyses were carried out on a Perkin-Elmer 240C CHN or Thermo Finnigan EA1112 CHNS analyzer.

Infrared spectroscopy: IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer.

NMR spectroscopy: ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz NMR spectrometer [field strengths: 400, 100, 162 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$) and ext. 85% H_3PO_4 (^{31}P: $\delta = 0$) respectively. All *J* values are in Hz.

LC-MS and GC-MS: LC-MS or GC-MS equipment were used to record mass spectra for isolated compounds where appropriate. LC-MS data were obtained using electrospray ionization (positive mode) on a C-18 column. GC-MS data were obtained on EI mode using ZB-1 column.

Most of the precursors are in use in the laboratory and some of them are previously known. In cases where the procedures have been modified for compounds not reported previously, full details along with the spectroscopic data are given. Compound ($OCH_2CMe_2CH_2O$)PCl [**1**, δ(P) 145.8[88]] was prepared by a literature method. (±)-*trans*-1,2-Diisopropylamino-cyclohexane and compound **2** were prepared (cf. equation 1) by slightly modifying the literature procedures.[89-90]



(1)

A mixture of (±)-*trans*-1,2-diaminocyclohexane (3.74 g, 32.4 mmol) and 2-bromopropane (20 mL) was heated at 60 ^oC for 12 h. To this stirred solution, KOH (5.53 g, 97.4 mmol) was added and heating continued for 6 h. After cooling to 25 ^oC, dichloromethane (50 mL) and then water (20 mL) were added to the reaction mixture. The organic layer was washed with saturated brine solution (20 mL), dried (Na_2SO_4) and the solvent removed to yield yellow colored oil. Upon distillation at 0.5 mm/50 ^oC, (±)-*trans*-1,2-diisopropylaminocyclohexane[89] [Yield: 68% (4.85 g, 90% purity, ^1H NMR or GC-MS evidence)] was obtained as a colorless liquid.

To a solution of (±)-*trans*-1,2-diisopropylaminocyclohexane (as prepared above; 2.93 g, ~13.3 mmol, 90% purity) and Et_3N (3.7 mL, 26.6 mmol) in toluene (30 mL), PCl_3 (1.2 mL, 13.3 mmol) was added drop-wise at 0 ^oC under nitrogen atmosphere. The reaction mixture was warmed to room temperature, and stirred for 2 h. After removal of insoluble material by filtration, the solvent was removed and pure compound **2** was distilled under vacuum as a colorless liquid. Spectroscopic data are in agreement with those previously described in literature.[90]

Yield: 3.01 g (92%).

Bp: 180 ^oC/ 0.5 mm.

^{31}P NMR: δ 178.8 [lit. 177.8[90]]

Compounds *S*(-)-($C_{20}H_{12}O_2$)PCl (**3**) [mp 88-90 ^oC; δ(P) 177.8 (lit. 177.8[91])] and ($OCH_2CMe_2CH_2O$)P(O)(H) (**4**) [bp 150^oC/ 0.5 mm; δ(P) 3.0 (lit. 2.3[88])] were prepared by following literature procedures.

3.1 Preparation of phosphine oxide/thiophosphites/phosphine sulphide

(a) Synthesis of $Ph_2P(O)H$ (5)

A modified version of literature procedure[92] was followed. To a stirred solution of K_2CO_3 (9.3 g, 67 mmol) in water (30 mL) was added Ph_2PCl (5.0 g, 22.7 mmol) at 0 ^oC over a period of 10 min and stirring continued at room temperature for 1 h. Reaction mixture was extracted with ethyl acetate (30 mL), the organic layer dried over Na_2SO_4 and analytically pure compound **5** was obtained by vacuum distillation.

Yield: 4.12 g (90%).

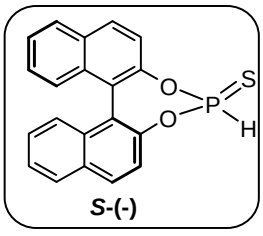
Bp: 160 ^oC (oil bath)/ 0.5 mm.

^{31}P NMR: δ 21.5 [lit. 20.0[92]].

(b) Synthesis of ($OCH_2CMe_2CH_2O$)P(S)H (6), S-(-)-($C_{20}H_{12}O_2$)P(S)H (7) and $Ph_2P(S)H$ (8)

Compound **6** [mp 78-80 ^oC; δ(P) 66.0 (lit. 65.2)[14]] was prepared by a procedure reported from our laboratory.[14] A similar procedure was adapted for compound **7** and compound **8** [mp 96-98 ^oC; δ(P) 22.8 (lit. 20.9)[112]]. The yield of **8** was 92% using 56.0 mmol of Ph_2PCl; a different procedure was used in the literature.[112]. Analytical/spectroscopic data for compound **7** are given below.

S-(-)-($C_{20}H_{12}O_2$)P(S)H (7)



Yield: 5.20 g (90%; using 16.6 mmol of **3**).

Mp: 92-94 ^oC (white solid).

IR (KBr): 2973, 2880, 2415, 1618, 1593, 1512, 1468, 1179, 1148, 816 cm^{-1}.

^{1}H NMR: δ 7.33-7.60 (m, 8H, Ar-*H*), 7.97-8.08 (m, 4H, Ar-*H*), 8.26 (d, ^{1}J(P-H) = 691.2 Hz, 1H, P(S)*H*).

^{13}C NMR: δ 119.8, 119.9, 121.6_8, 121.7_0, 122.4_3, 122.4_5, 122.5_6, 122.5_9, 125.9, 126.1, 128.5, 128.6, 131.0, 131.9, 132.0, 132.5, 144.6, 144.7, 147.9_7, 148.1_1.

^{31}P NMR: δ 80.6.

LC-MS: *m/z* 349 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{13}O_2PS$: C, 68.96; H, 3.76. Found: C, 68.85; H, 3.71.

3.2 Preparation of 1-ethynyl-1-methoxycyclohexane (9) and propargyl alcohols 10-16

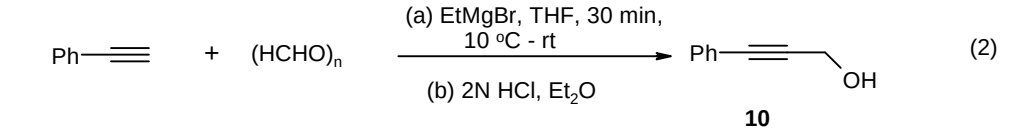
(a) 1-Ethynyl-1-methoxycyclohexane (9)

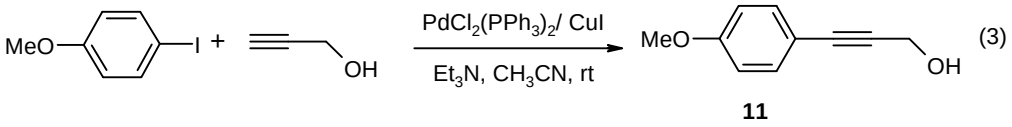
This compound was prepared by using the corresponding commercially available propargylic alcohol (1-ethynyl-1-cyclohexanol) and by slightly modifying a literature method[93] as follows:

To a solution of sodium hydride (3.35 g, 83.8 mmol, dispersed in 60% mineral oil) in THF (30 mL) was added 1-ethynyl-1-cyclohexanol (8.3 mL, 64.4 mmol) in THF (10 mL) *via* addition funnel at 0 °C and stirring continued for 30 min. To this, methyl iodide (5.20 mL, 83.8 mmol) in THF (5 mL) was added drop-wise (10 min). The resulting solution was stirred at room temperature for 1 h and quenched with water (20 mL). The upper (organic) layer was separated and the solvent was removed under vacuum. The residue was extracted with diethyl ether (2 x 40 mL). The combined organic layer was washed with water (2 x 20 mL), brine solution (20 mL), dried (Na_2SO_4), filtered and the ether was removed from the filtrate. The residue was distilled under vacuum (1.0 mm) at 25 °C to afford 1-ethynyl-1-methoxycyclohexane **(9**) as a colorless liquid [Yield: 8.12 g (91%); bp: 25 °C/1.0 mm**]**. The IR/NMR data are consistent with those reported in the literature.[93]

(b) Propargyl alcohols 10-16

Propargyl alcohols **10-11** (equations 2-3) were prepared according to the literature procedures.[94-95]

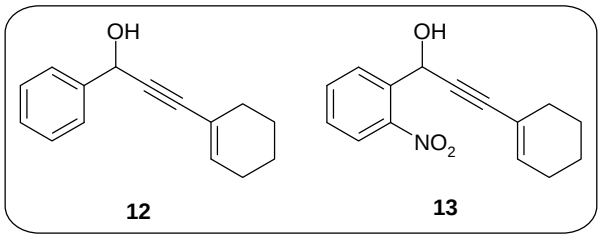




Substituted propargyl alcohols **12-16** were also prepared by the literature method (slightly modified version) as follows:[96-97]

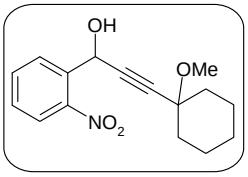
To a solution of 1-ethynyl-1-cyclohexene (3.13 g, 29.0 mmol) in anhydrous THF (20 mL), *n*-butyl lithium (15.1 mL, 46.4 mmol, 1.6M solution in hexanes) was added *via* syringe at -20 °C under nitrogen atmosphere. The resulting solution was stirred at this temperature for 30 min and then benzaldehyde (1.61 g, 14.8 mmol) in THF (5 mL) was added drop-wise. The contents were warmed to 25 ^{o}C and stirring continued for 30 min. Then the reaction mixture was quenched with saturated ammonium chloride (10 mL) solution. The solvent was removed under vacuum and the residue extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with water (2 x 10 mL), brine (5 mL), dried (Na_2SO_4) and concentrated in *vacuo*. Pure compound **12** was obtained as pale yellow liquid by passing through a short column of silica gel by eluting with ethyl acetate/hexane (1:9) mixture.

3-Cyclohexenyl-1-(phenyl)prop-2-yn-1-ol (12)[96a] **and 3-cyclohexenyl-1-(2-nitrophenyl)prop-2-yn-1-ol (13)**[96b]



These are known compounds.[96a-b]

3-(1-methylcyclohexenyl-1-(2-nitrophenyl)prop-2-yn-1-ol (14)



Yield: 3.85 g [97%; using compound **9** (3.8 g, 27.6 mmol)].

IR (Neat): 3393, 2938, 2859, 2230, 1609, 1530, 1447, 1350, 1078 cm^{-1}.

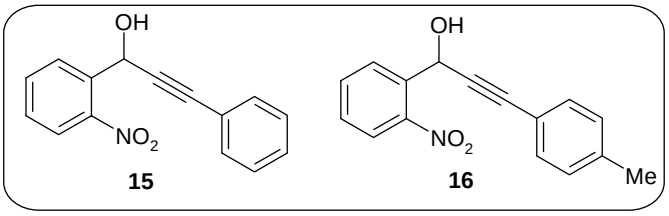
^1H NMR: δ 1.27-1.66 (m, 8H, cyclohexyl-*H*), 1.86-1.89 (m, 2H, cyclohexyl-*H*), 3.23 (s br, 1H, ArCH(O*H*)), 3.32 (s, 3H, OCH_3), 6.04 (s br, 1H, ArC*H*(OH)), 7.51 (~t, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 7.67 (~t, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 7.91 (~d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 7.96 (~d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*).

^{13}C NMR: δ 22.7, 25.3, 36.5, 50.9, 61.5, 73.9, 83.5, 88.1, 125.1, 129.3, 129.4, 133.8, 135.6, 148.1.

LC-MS: *m/z* 290 $[M+1]^+$.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.32; H, 6.71; N, 4.75.

1-(2-nitrophenyl)-3-phenyl-prop-2-yn-1-ol (15)[96b] and 1-(2-nitrophenyl)-3-p-tolyl-prop-2-yn-1-ol (16)[97]



These are known compounds.[96b,97]

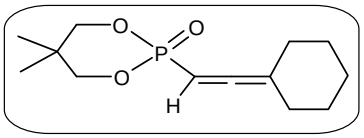
3.3 Synthesis of allenes

3.31 Synthesis of allene 17 and allenylphosphonates 18-23

Ester allene EtO_2C-C(H)=C=CH_2 (**17**; bp: 57–59 °C/ 12–14 mm) was prepared by a method previously reported from our laboratory.[98] Allenylphosphonates $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**), $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (**19**), $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**20**), $(OCH_2CMe_2CH_2O)P(O)CH=C=C(cycl\text{-}C_5H_{10})$ (**21**),

$(OCH_2CMe_2CH_2O)P(O)C(cycl\text{-}C_6H_9)=C=CH(Ph)$ (**22**) and $(OCH_2CMe_2CH_2O)P(O)C(cycl\text{-}C_6H_{10}\text{-}1\text{-}OCH_3)=C=CH(C_6H_4\text{-}2\text{-}NO_2)$ (**23**) were prepared by treating $(OCH_2CMe_2CH_2O)PCl$ (**1**) with the corresponding propargylic alcohol/ triethylamine by a standard procedure.[69] Compounds **21**-**23** are new.

Compound 21 [This compound was prepared by using 1-ethynyl-1-cyclohexanol and $(OCH_2CMe_2CH_2O)PCl$ (**1**) and purified by eluting from ethyl acetate/hexane (2:3) mixture as the eluant].



Yield: 4.71 g (85%; using 21.8 mmol of **1**).

Mp: 108-112 ^oC (white solid).

IR (KBr): 2976, 2932, 2843, 1962, 1483, 1447, 1267, 1055, 1005 cm^{-1}.

^1H NMR: δ 0.94 and 1.19 (2 s, 6H, $C(CH_3)_2$), 1.51-1.56 (m, 2H, cyclohexyl-*H*), 1.60-1.66 (m, 4H, cyclohexyl-*H*), 2.19-2.22 (m, 4H, cyclohexyl-*H*), 3.93–4.05 (m, 4H, 2 OCH_2), 5.18-5.21 (m, 1H, PC*H*).

^{13}C NMR: δ 21.1, 21.8, 25.6, 26.6, 26.7, 30.0, 30.1, 32.6 (d, ^3J(P-C) = 6.5 Hz, $C(CH_3)_2$), 76.0 (d, ^1J(P-C) = 193.7 Hz, P*C*), 76.6_6, 76.7_1, 103.7 (d, ^3J(P-C) = 16.5 Hz, PC=C=*C*), 207.8 (s br, PC=*C*).

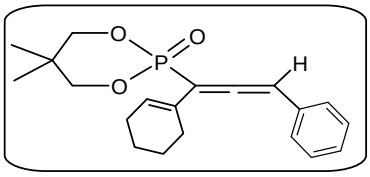
^{31}P NMR: δ 10.0.

LC-MS: *m/z* 257 $[M+1]^+$.

Anal. Calcd. for $C_{13}H_{21}O_3P$: C, 60.93; H, 8.26. Found: C, 60.85; H, 8.30.

Compound 22

[This compound was purified by column chromatography using ethyl acetate/hexane (1:1) as the eluant].



Yield: 0.90 g (74%; using 3.5 mmol of **12**).

Mp: 108-110 ^oC (white solid).

IR (KBr): 2948, 2917, 2830, 1919, 1599, 1456, 1260, 1061, 1013 cm^{-1}.

^{1}H NMR: δ 0.75 and 1.27 (2 s, 6H, C(C*H*$_3$)$_2$), 1.59-1.67 (m, 4H, cyclohexenyl-*H*), 2.04-2.19 (m, 4H, cyclohexenyl-*H*), 3.80–4.09 (m, 4H, OC*H*$_2$), 6.47-6.48 (m, 1H, PC–C=C*H*-CH$_2$), 6.65 (d, ^{4}J(P-H) = 3.1 Hz, 1H, PC=C=C*H*(Ph)), 7.25-7.28 (m, 2H, Ar-*H*), 7.32-7.37 (m, 3H, Ar-*H*).

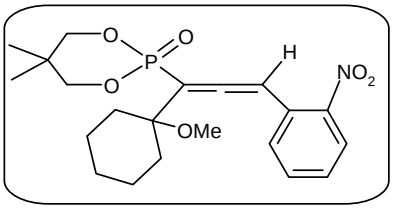
^{13}C NMR: δ 20.6, 21.8, 22.0, 22.6, 26.1, 27.2, 27.3, 32.5 (d, ^{3}J(P-C) = 7.0 Hz, *C*(CH$_3$)$_2$), 76.9 (d, ^{2}J(P-C) = 6.7 Hz, O*C*H$_2$), 77.5 (d, ^{2}J(P-C) = 7.0 Hz, O*C*H$_2$), 98.2 (d, ^{3}J(P-C) = 15.0 Hz, PC=C=*C*), 101.9 (d, ^{1}J(P-C) = 174.0 Hz, P*C*), 127.0$_9$, 127.1$_1$, 127.5 (d, ^{4}J(P-C) = 6.8 Hz, PC=C=C*C*), 128.0 (d, ^{3}J(P-C) = 1.5 Hz, PC–C=*C*H), 129.0$_2$, 129.0$_3$, 130.1, 132.4 (d, ^{2}J(P-C) = 8.2 Hz, PC–*C*=CH), 210.4 (d, ^{2}J(P-C) = 3.0 Hz, PC=*C*).

^{31}P NMR: δ 6.8.

LC-MS: *m/z* 345 [M+1]$^{+}$.

Anal. Calc. for $C_{20}H_{25}O_3P$: C, 69.75; H, 7.32. Found: C, 69.85; H, 7.23.

Compound 23 [This compound was purified by column chromatography using ethyl acetate/hexane (2:3) as the eluant]



Yield: 0.30 g (70%; using 1.0 mmol of **14**).

Mp: 118–120 ^{o}C.

IR (KBR): 2938, 2859, 1715, 1616, 1470, 1231, 1059, 1008 cm^{-1}.

^{1}H NMR: δ 0.90 and 1.13 (2 s, 6H, 2 C*H*$_3$), 1.42-1.69 (m, 8H, cyclohexyl-C*H*$_2$), 2.04-2.10 (m, 2H, cyclohexyl-C*H*$_2$), 3.19 (s, 3H, OC*H*$_3$), 3.88-4.05 (m, 4H, 2 OC*H*$_2$), 7.23 (d, ^{4}J(P-H) = 4.0 Hz, 1H, PCCC*H*Ar), 7.36 (t, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 7.54 (t, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 7.59 (d, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 7.96 (d, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*).

^{13}C NMR: δ 21.1, 21.7, 21.8, 21.9, 25.2, 32.7 (d, *J*(P-C) = 6.6 Hz, *C*(CH$_3$)$_2$), 34.6 (d, ^{3}J(P-C) = 3.8 Hz, PCC(OMe)*C*H$_2$), 34.7 (d, ^{3}J(P-C) = 3.7 Hz, PCC(OMe)*C*H$_2$), 50.4 (OCH$_3$), 76.4 (d, ^{2}J(P-C) = 6.3 Hz,

OCH_2), 77.1, 78.8 (d, ^2J(P-C) = 6.7 Hz, OCH_2), 92.7 (d, ^3J(P-C) = 15.4 Hz, PCC*C*H), 103.8 (d, ^1J(P-C) = 173.7 Hz, P*C*), 125.4, 127.5 (d, *J*(P-C) = 8.1 Hz, PCCC*C*), 128.5, 129.7, 133.7, 146.8, 211.4 (PC=*C*=CHAr).

^{31}P NMR: δ 6.6.

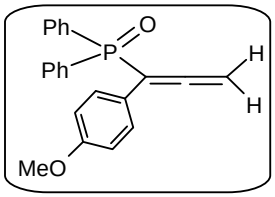
LC-MS: *m/z* 421 $[M]^+$.

Anal. Calcd. for $C_{21}H_{28}NO_6P$: C, 59.85; H, 6.70; N, 3.32. Found: C, 59.71; H, 6.75; N, 3.38.

3.32 Synthesis of allenyl phosphine oxides 24-30

Allenyl phosphine oxides $Ph_2P(O)C(H)=C=CH_2$ **(24)**, $Ph_2P(O)C(H)=C=CMe_2$ **(25)**, $Ph_2P(O)C(Ph)=C=CH_2$ (**26**), $Ph_2P(O)C(H)=C=C(Ph)(Me)$ (**27**), $Ph_2P(O)C(H)=C=C(cycl\text{-}C_5H_{10})$ (**28**), $Ph_2P(O)C(C_6H_4\text{-}p\text{-}OCH_3)=C=CH_2$ (**29**) and $Ph_2P(O)C(cycl\text{-}C_6H_9)=C=CH(Ph)$ (**30**) were prepared by a procedure similar to that for allenylphosphonates using Ph_2PCl and the corresponding propargylic alcohol/triethylamine.[69] Compounds **24-28** are known;[69] compounds **29-30** are new.

Compound 29 [This compound was purified by column chromatography using ethyl acetate/hexane (3:7) as the eluant].



Yield: 4.87 g (65%; using 22.7 mmol of **11**).

Mp: 118-112 ^oC (white solid).

IR (KBr): 3054, 2996, 1954, 1921, 1603, 1510, 1437, 1290, 1181, 1030 cm^{-1}.

^{1}H NMR: δ 3.74 (s, 3H, OCH_3), 4.85 and 4.87 (2 s, 2H, $=CH_2$; they may also be a part of closely space AB quartet, but is not investigated further), 6.79 (d, ^3J(H-H) = 8.8 Hz, 2H, Ar-*H*), 7.41-7.54 (m, 8H, Ar-*H*), 7.73-7.78 (m, 4H, Ar-*H*).

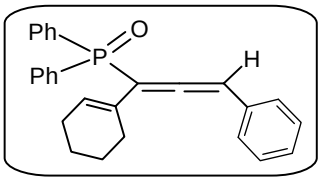
^{13}C NMR: δ 55.2, 78.5 (d, ^{3}J(P-C) = 13.0 Hz, P-C=C=*C*H$_2$), 100.2 (d, ^{1}J(P-C) = 106.4 Hz, P*C*), 114.1, 123.9, 128.2, 128.3, 129.5, 131.8, 131.9, 132.8, 159.1, 213.1 (PC=*C*=C).

^{31}P NMR: δ 29.3.

LC-MS: *m/z* 347 $[M+1]^+$.

Anal. Calcd. for $C_{22}H_{19}O_2P$: C, 76.29; H, 5.53. Found: C, 76.40; H, 5.62.

Compound 30 [This compound was purified by column chromatography by using ethyl acetate/hexane (2:3) mixture].



Yield: 2.46 g (62 %; using 10.0 mmol of **12**).

Mp: 130-132 ^{o}C (white solid).

IR (KBr): 3052, 2919, 1917, 1591, 1454, 1435, 1169, 1117 cm^{-1}.

^{1}H NMR: δ 1.55 (s br, 2H, cyclohexenyl-*H*), 1.65 (s br, 2H, cyclohexenyl-*H*), 2.07-2.17 (m, 4H, cyclohexenyl-*H*), 6.07 (d, ^{4}J(P-H) = 2.7 Hz, 1H, PC=C=C*H*(Ph)), 6.42 (s br, 1H, PC–C=C*H*), 7.03-7.15 (m, 2H, Ar-*H*), 7.05-7.53 (m, 9H, Ar-*H*), 7.66-7.71 (m, 4H, Ar-*H*).

^{13}C NMR: δ 21.8, 22.7, 26.0, 28.0 (d, ^{3}J(P-C) = 5.3 Hz, P-CC*C*H$_2$), 98.4 (d, ^{3}J(P-C) = 13.5 Hz, PC=C=*C*), 107.0 (d, ^{1}J(P-C) = 96.5 Hz, P*C*), 126.7$_0$, 126.7$_2$, 127.5, 128.0, 128.1$_0$, 128.1$_5$, 128.2, 128.4 (d, *J*(P-C) = 4.7 Hz), 128.6, 131.0 (d, *J*(P-C) = 4.2 Hz), 131.4, 131.5, 131.6, 131.7 (d, *J*(P-C) = 2.8 Hz), 132.3 (d, ^{1}J(P-C) = 53.2 Hz, P*C*), 132.4 (d, *J*(P-C) = 11.4 Hz), 133.0, 133.4, 211.7 (d, ^{2}J(P-C) = 5.8 Hz, PC=*C*=C).

^{31}P NMR: δ 30.5.

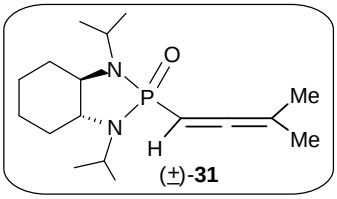
LC-MS: *m/z* 397 $[M+1]^+$.

Anal. Calcd. for $C_{27}H_{25}OP$: C, 81.80; H, 6.36. Found: C, 81.62; H, 6.41.

3.33 Synthesis of allenylphosphoramidate 31

Allenylphosphoramidate **31** was prepared by a procedure similar to that for allenylphosphonates[69] using (±)-*trans*-**2** (9.5 mmol) and propargyl alcohol/Et_3N at

room temperature (1 h reaction). This compound was purified by column chromatography by using ethyl acetate/hexane (1:1) mixture as the eluant.



(±)-**31**

Yield: 2.04 g (69%).

Mp: 78-80 ^{o}C (pale yellow solid).

IR (KBr): 2973, 2932, 2865, 1958, 1458, 1364, 1208, 1181, 1136, 1003 cm^{-1}.

^{1}H NMR: δ 1.18-1.21 (m, 6H, CH(CH_3)$_2$), 1.32-1.37 (m, 10H, cyclohexyl-*H* + CH(CH_3)$_2$), 1.74-1.75 (m, 8H, cyclohexyl-*H* + =C(CH_3)$_2$), 2.00-2.11 (m, 2H, cyclohexyl-CH_2), 2.69 (t, ^{3}J(H-H) = 8.8 Hz, 1H, PNC*H*(A)), 3.03 (t, ^{3}J(H-H) = 8.8 Hz, 1H, PNC*H*(B)), 3.42-3.50 (m, 2H, 2 C*H*(^{i}Pr)$_2$), 5.21 (s br, 1H, PC*H*).

^{13}C NMR: δ 19.3 (d, ^{3}J(P-C) = 6.3 Hz, NCH*C*H$_3$(A)CH$_3$(B)), 19.4 (d, ^{3}J(P-C) = 6.4 Hz, NCHCH$_3$(A)*C*H$_3$(B)), 20.4, 20.9, 22.0 (d, ^{3}J(P-C) = 3.4 Hz, NCH*C*H$_3$(C)CH$_3$(D)), 22.1 (d, ^{3}J(P-C) = 4.6 Hz, NCHCH$_3$(C)*C*H$_3$(D)), 24.3, 24.4, 29.9 (d, ^{3}J(P-C) = 8.0 Hz, PNCCH*C*H$_2$), 30.4 (d, ^{3}J(P-C) = 8.0 Hz, PNCCH*C*H$_2$), 44.3 (d, ^{3}J(P-C) = 5.0 Hz, PN*C*H), 44.8 (d, ^{3}J(P-C) = 3.1 Hz, PN*C*H), 59.5 (d, ^{2}J(P-C) = 6.3 Hz, PNC*C*H), 60.6 (d, ^{2}J(P-C) = 7.7 Hz, PNC*C*H), 85.2 (d, ^{1}J(P-C) = 157.5 Hz, P*C*), 95.0 (d, ^{3}J(P-C) = 15.0 Hz, PC=C=*C*), 209.7 (s br, PC=*C*).

^{31}P NMR: δ 25.0.

LC-MS: *m/z* 311 [M+1]$^{+}$.

Anal. Calcd. for $C_{17}H_{31}N_2OP$: C, 65.78; H, 10.07; N, 9.02. Found: C, 65.32; H, 10.05; N, 9.03.

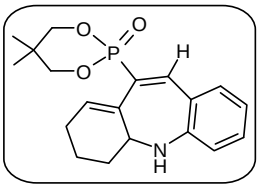
3.4 Synthesis of phosphorus-containing dibenzo-azepines 33-35 and *N*-hydroxy indolinone derivatives 36-38

(i) Dibenzo-azepines

Phosphorus-based dibenzo-azepines (**33-35**) were obtained by using a procedure similar to that for allenylphosphonates by treating propargyl alcohol **13**

/triethylamine with ($OCH_2CMe_2CH_2O$)PCl (**1**) or Ph_2PCl (molar stoichiometry 1:1) for 12 h at 60 ^oC. Compound **33** was purified by column chromatography (silica gel 100/200 mesh) by using ethyl acetate/hexane (3:2) mixture as the eluant. Crystallization was done at 25 ^oC using chloroform (2 mL/0.2 g of compound) as the solvent.

Compound 33



Yield: 1.21 g (60%; using 5.83 mmol of **1**).

Mp: 182-184 ^oC (yellow solid).

IR (KBr): 3353, 2936, 2882, 1605, 1487, 1240, 1059, 1011, 748 cm^{-1}.

^1H NMR: δ 1.01 and 1.18 (2 s, 6H, 2 C*H*$_3$), 1.66-1.73 (m, 4H, cyclohexenyl-*H*), 1.95-2.29 (m, 3H, cyclohexenyl-*H*+N*H*), 3.60 (s br, 1H, C*H*NHAr), 3.84-3.95 and 4.12-4.18 (2 m, 4H, 2 OC*H*$_2$), 6.57 (s br, 1H, PCCC*H*(cyclohexenyl)), 6.62 (d, ^3J(H-H) = 7.5 Hz, 1H, Ar-*H*), 6.74 (t, ^3J(H-H) ~ 7.5 Hz, 1H, Ar-*H*), 7.08-7.12 (m, 1H, Ar-*H*), 7.14 (d, ^3J(P-H) ~ 26.4 Hz, 1H, PC=C*H*(cis)), 7.22 (d, ^3J(H-H) = 7.5 Hz, 1H, Ar-*H*). This spectrum is illustrated in Fig. 20.

^{13}C NMR: δ 18.0, 21.5, 21.9, 26.1, 30.3, 32.6 (d, ^3J(P-C) = 5.9 Hz, *C*Me$_2$), 51.3 (d, ^3J(P-C) = 12.4 Hz, P-CC*C*HNH), 75.7 and 76.2 (2 d, ^2J(P-C) = 6.3 Hz, 2 O*C*H$_2$), 116.9, 118.4, 120.7 (d, ^2J(P-C) = 23.4 Hz, PC-*C*=C), 125.1 (d, ^1J(P-C) = 175.0 Hz, P*C*), 127.8 (d, ^3J(P-C) = 3.7 Hz, PCC*C*(cyclohexenyl)), 130.4, 134.4 (d, ^3J(P-C) = 8.6 Hz, PCC*C*), 135.8, 141.0 (d, ^2J(P-C) = 10.8 Hz, PC=*C*H(*cis*)Ar), 149.5.

^{31}P NMR: δ 16.1.

LC-MS: *m/z* 346 $[M+1]^+$

Anal. Calcd. for $C_{19}H_{24}NO_3P$: C, 66.07; H, 7.00; N, 4.06. Found: C, 66.21; H, 6.89; N, 4.15.

This compound was crystallized from chloroform (2 mL/0.2 g). X-ray structure was determined for this sample.

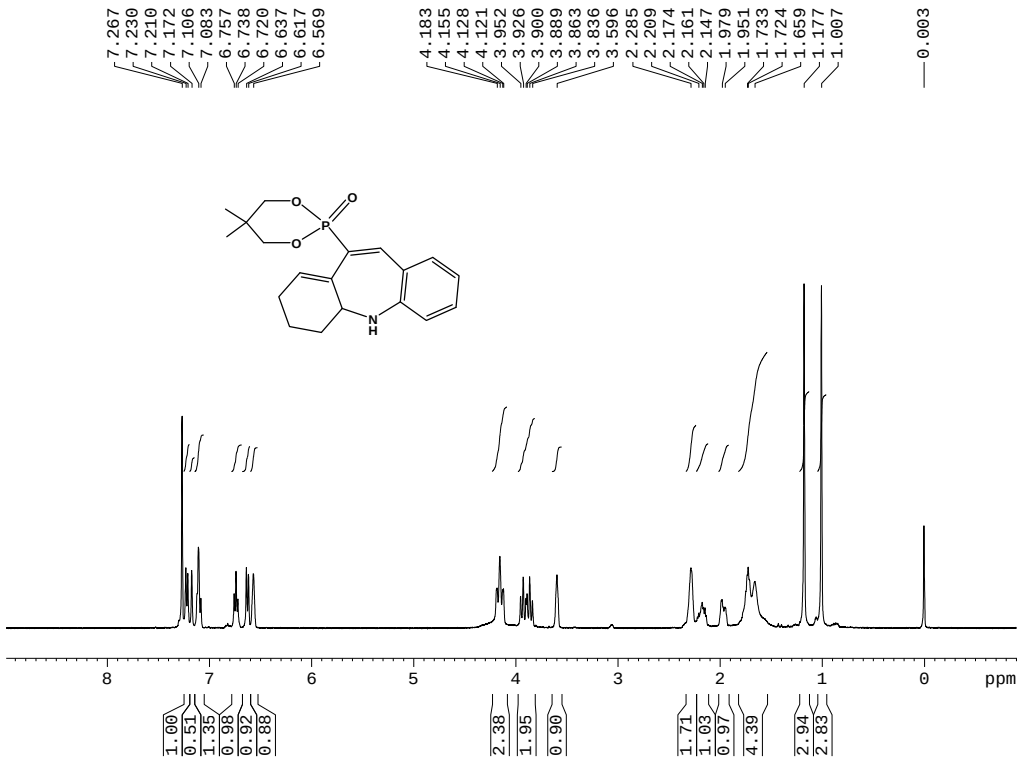
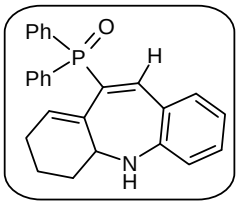


Fig. 20 ^{1}H NMR spectrum of compound **33**

(*E*)-11-(diphenylphosphoryl)-3,4,4a,5-tetrahydro-2H-dibenzo[b,f]azepine (34)



This compound was eluted by using ethyl acetate/hexane (4:1) mixture after eluting compound **35**.

Yield: 0.80 g (52%; using 3.90 mmol of Ph_2PCl).

Mp: 132–136 ^{o}C (brown solid).

IR (KBr): 3272, 3056, 2930, 1715, 1605, 1485, 1437, 1159, 1098, 748 cm^{-1}.

^{1}H NMR: δ 1.43-1.68 (m, 4H, cyclohexenyl-*H*), 1.92-2.08 (m, 3H, cyclohexenyl-*H* + N*H*), 3.60 (br, 1H, C*H*NHAr), 6.32 (s, br, 1H, PCCC*H*(cyclohexenyl)), 6.55-6.64 (m, 2H, P-CC*H*(cis) + Ar-*H*), 6.82 (d, ^{3}J(H-H) ~ 7.5 Hz, 1H, Ar-*H*), 7.05 (t, ^{3}J(H-H) ~ 7.5 Hz, 1H, Ar-*H*), 7.35-7.48 (m, 4H, Ar-*H*), 7.53-7.68 (m, 7H, Ar-*H*).

^{13}C NMR: δ 17.7, 26.0, 30.0, 51.4 (d, ^{3}J(P-C) = 8.6 Hz, P-CC*C*HN), 116.9, 117.9, 120.2 (d, ^{2}J(P-C) = 19.7 Hz, PC-*C*), 126.2, 128.4, 128.5, 129.0_0, 129.0_4, 130.2, 131.2, 131.6, 131.9, 132.0, 132.1, 132.8 (d,

^{1}J(P-C) = 101.8 Hz, P*C*), 133.2 (d, ^{1}J(P-C) = 103.7 Hz, P*C*=CH), 134.8 (d, *J*(P-C) = 7.6 Hz), 142.3 (d, *J*(P-C) = 14.1 Hz), 149.0.

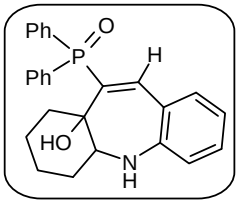
^{31}P NMR: δ 35.4.

LC-MS: *m/z* 398 $[M+1]^{+}$.

HRMS: Calcd. for $C_{26}H_{24}NOP$: m/z 397.1596. Found: *m/z* 398.1675 $[M+H]^{+}$.

Anal. Calcd. for $C_{26}H_{24}NOP$: C, 78.57; H, 6.09; N, 3.52. Found: C, 78.41; H, 6.22; N, 3.63.

(*E*)-11-(diphenylphosphoryl)-2,3,4,4a,5,11a-hexahydro-1H-dibenzo[b,f]azepine-11a-ol (35)



This compound was purified by column chromatography using ethyl acetate/hexane (1:1) mixture. This compound surprisingly eluted before compound **34**.

Yield: 0.080 g (5%; using 3.90 mmol of Ph_2PCl).

Mp: 180–182 ^{o}C (white solid).

IR (KBr): 3310, 3055, 1611, 1491, 1437, 1146, 748 cm^{-1}

^{1}H NMR: δ 1.37-2.41 (m, 8H, cyclohexyl-*H*), 3.14 (s br, 1H, C*H*NH), 4.03 (br, 1H, N*H*), 6.12 (s br, 1H, O*H*)), 6.45 (d, ^{2}J(P-H) = 22.4 Hz, 1H, PC=C*H*(*cis*)), 6.70-6.73 (m, 2H, Ar-*H*), 6.86 (d, ^{3}J(H-H) ~ 7.5 Hz, 1H, Ar-*H*), 7.13 (t, ^{3}J(H-H) ~ 7.5 Hz, 1H, Ar-*H*), 7.44-7.65 (m, 8H, Ar-*H*), 7.73-7.78 (m, 2H, Ar-*H*).

^{13}C NMR: δ 19.8, 20.8, 28.8, 35.1, 58.6 (d, ^{3}J(P-C) = 8.4 Hz, P-CC*C*HNH), 77.1, 117.2, 119.0, 120.4 (d, ^{2}J(P-C) = 21.0 Hz, PC-*C*), 128.5, 128.6_1, 128.6_5, 128.7, 130.5, 131.8, 131.9, 132.0, 132.1, 132.2, 133.7 (d, ^{1}J(P-C) = 96.1 Hz, P*C*), 135.2, 135.8 (d, ^{1}J(P-C) = 95.5 Hz, P*C*), 140.1 (d, ^{2}J(P-C) = 14.0 Hz, PC=*C*H(*cis*)), 149.4.

^{31}P NMR: δ 42.5.

LC-MS: *m/z* 416 $[M+1]^{+}$.

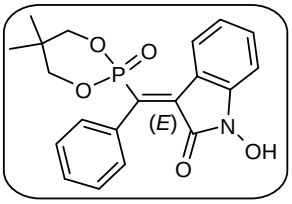
Anal. Calcd. for $C_{26}H_{26}NO_2P$: C, 75.16; H, 6.31; N, 3.37. Found: C, 75.06; H, 6.39; N, 3.29.

This compound was crystallized from ethyl acetate (2 mL). X-ray structure was determined for this compound.

(ii) N-hydroxy-indolinones 36-38

A procedure similar to dibenzo-azepines preparation was used for the synthesis of phosphorus-based *N*-hydroxy indolinones by treating **1** or Ph_2PCl (3.24 mmol) with propargyl alcohols **15** or **16** (3.24 mmol)/triethylamine (3.24 mmol) at 60 ^oC for 2 h.

Compound 36



This compound (red color) was obtained by using **1** and propargyl alcohol **15** and purified by column chromatography using ethyl acetate/hexane (1:1) mixture as the eluant.

Yield: 0.75 g (60%).

Mp: 226-228 ^oC.

IR (KBr): 3250 (br), 3092, 2935, 1726, 1618, 1462, 1248, 1047, 1011 cm^{-1}.

^1H NMR: δ 0.64 and 1.20 (2 s, 6H, 2 CH_3), 3.39-3.43 and 3.75-3.82 (2 m, 4H, 2 OCH_2), 6.51 (d, ^3J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 6.84 (t, ^3J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 7.04 (t, ^3J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 7.15-7.17 (m, 2H, Ar-*H*), 7.25-7.29 (m, 2H, Ar-*H*), 7.37-7.39 (m, 1H, Ar-*H*), 8.10 (d, ^3J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 9.75 (s br, 1H, N-O*H*). This spectrum is illustrated in Fig. 21.

^{13}C NMR: δ 20.5, 21.9, 32.4 (d, ^3J(P-C) = 8.0 Hz, C(*C*H_3)$_2$), 77.4, 77.6, 107.6, 116.1 (d, ^3J(P-C) = 8.0 Hz, PCC*C*), 121.9, 126.3, 128.0 (d, ^2J(P-C) = 35.0 Hz, PC(Ph)*C*), 129.3 (d, ^3J(P-C) = 6.0 Hz, PC(Ph)C*C*), 131.9, 134.8 (d, ^3J(P-C) = 11.0 Hz, PC(Ph)C*C*), 135.1 (d, ^3J(P-C) = 5.0 Hz, PC(Ph)C*C*), 137.1 (d, ^1J(P-C) = 168.0 Hz, P*C*(Ph)), 142.5, 161.7 (d, ^3J(P-C) = 26.0 Hz, PC(Ph)C*C*(O)).

^{31}P NMR: δ 4.7.

LC-MS: *m/z* 386 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{20}NO_5P$: C, 62.34; H, 5.23; N, 3.63. Found: C, 63.28; H, 5.19; N, 3.72.

This compound was crystallized from dichloromethane (2 mL). X-ray structural analysis was performed on this sample.

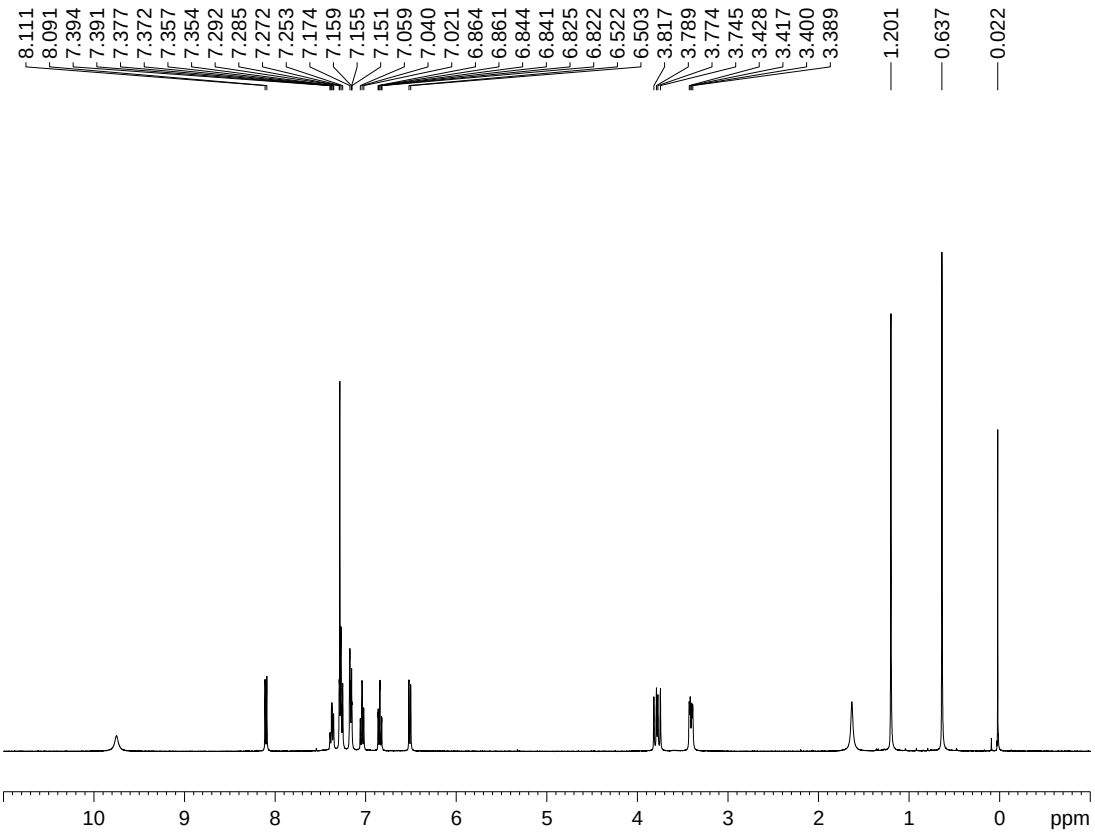
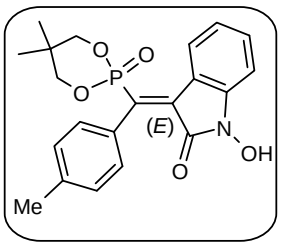


Fig. 21 ^{1}H NMR spectrum of compound **36**

Compound 37



This compound (red color) was obtained by using **1** (3.00 mmol) and propargyl alcohol **16** (3.00 mmol) and purified by column chromatography using ethyl acetate/hexane (1:1) mixture as the eluant.

Yield: 0.74 g (62%).

Mp: 236–238 ^{o}C.

IR (KBr): 3100, 2971, 2930, 1726, 1616, 1462, 1323, 1250, 1067 cm^{-1}.

^{1}H NMR: δ 0.63 and 1.19 (2 s, 6H, 2 CH_3), 2.42 (s, 3H, CH_3), 3.41-3.44 and 3.71-3.79 (2 m, 4H, 2 OCH_2), 6.49 (d, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 6.83 (t, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 7.02 (s br, 5H, Ar-*H*), 8.08 (d, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 9.79 (s br, 1H, N-O*H*).

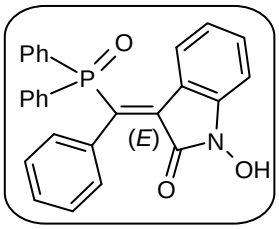
^{13}C NMR: δ 20.6, 21.6, 22.0, 32.4 (d, ^{3}J(P-C) = 8.0 Hz, C(*C*H_3)$_2$), 76.8, 77.1, 107.6, 116.2 (d, ^{3}J(P-C) = 8.0 Hz, PCC*C*), 121.9, 126.3, 128.9, 129.1, 129.2, 131.7, 132.0 (d, *J*(P-C) = 5.3 Hz), 134.7 (d, *J*(P-C) = 11.3 Hz), 137.5 (d, ^{1}J(P-C) = 167.0 Hz, P*C*), 137.6, 142.5, 161.8 (d, ^{3}J(P-C) = 25.8 Hz, PC(Ph)C*C*(O)).

^{31}P NMR: δ 4.9.

LC-MS: *m/z* 400 $[M+1]^{+}$.

Anal. Calcd. for $C_{21}H_{22}NO_5P$: C, 63.15; H, 5.55; N, 3.51. Found: C, 63.32; H, 5.47; N, 3.61.

(*E*)-3-((diphenylphosphoryl)(phenyl)methylene)-1-hydroxyindolin-2-one (38)



This compound (red color) was obtained by using Ph_2PCl (3.50 mmol) and propargyl alcohol **15** (3.50 mmol) and purified by column chromatography using ethyl acetate/hexane (1:1) mixture as the eluant.

Yield: 0.78 g (50%).

Mp: 200-202 ^{o}C.

IR (KBr): 3056, 2922, 2780, 1721, 1616, 1437, 1159, 1049, 739, 693 cm^{-1}.

^{1}H NMR: δ 6.42 (d, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 6.56 (t, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 6.70 (s br, 2H, Ar-*H*), 6.83-6.89 (m, 4H, Ar-*H*), 6.94-6.98 (m, 1H, Ar-*H*), 7.26 (s br, 4H, Ar-*H*), 7.39-7.43 (m, 2H, Ar-*H*), 7.50 (s br, 3H, Ar-*H*), 7.71 (d, ^{3}J(H-H) ~ 7.6 Hz, 1H, Ar-*H*), 11.1 (s br, 1H, N-O*H*).

^{13}C NMR: δ 107.7, 116.2, 121.4, 126.6, 127.8, 127.9, 128.4, 128.6, 128.8, 129.9, 131.6, 132.2, 132.3, 136.5 (d, ^{1}J(P-C) = 64.0 Hz, P*C*(Ph)), 141.7, 142.5, 143.1, 161.7 (d, ^{3}J(P-C) = 18.4 Hz, *C*=O).

^{31}P NMR: δ 34.4.

LC-MS: *m/z* 437 $[M]^+$

Anal. Calcd. for $C_{27}H_{20}NO_3P$: C, 74.14; H, 4.61; N, 3.20. Found: C, 74.05; H, 4.71; N, 3.31.

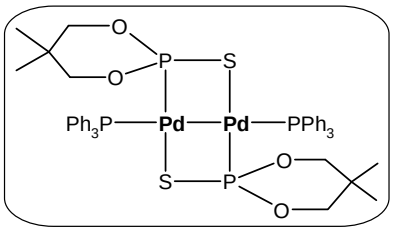
3.5 Synthesis of alkynes 39-40

Alkynylphosphonate $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**39)** and alkynyl phosphine oxide $Ph_2P(O)C{\equiv}CMe$ (**40**) were prepared according to the literature procedures by isomerization of allenes **18** and **24** respectively.[67a,103]

3.6 Preparation of dinuclear Pd^I-complexes $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (41) and *S,S*-(-)-$[(C_{20}H_{12}O_2)P\text{-}S\text{-}Pd(PPh_3)_2]_2$ (42)

A solution of $Pd(PPh_3)_4$ (0.46 g, 0.40 mmol) and $(OCH_2CMe_2CH_2O)P(S)H$ (**6)** (0.066 g, 0.40 mmol) in 1,4-dioxane (2 mL) was heated at 60 ^oC for 2 h. Progress of the reaction was monitored by ^{31}P NMR. When there was no starting material (thiophosphite), reaction mixture was cooled to room temperature (25 ^oC), the red crystals formed were filtered and then dried *in vacuo*.

$[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$ (41)



Yield: 0.20 g (95%).

Mp: 220 ^oC (charring, yellow solid after removal of solvent).

IR (KBr): 3056, 2957, 2853, 1433, 1252, 1119, 1040, 978, 748 cm^{-1}.

^{1}H NMR: δ 0.30 and 0.52 (2 s, 12H, 4 C*H*$_3$), 3.05-3.13 (m, 4H, 2 OC*H*$_2$), 3.71 (s, 16H, dioxane-*H*), 4.36 (m, 4H, 2 OC*H*$_2$), 7.34-7.35 (m, 18H, Ar-*H*), 7.55 (s br, 12H, Ar-*H*).

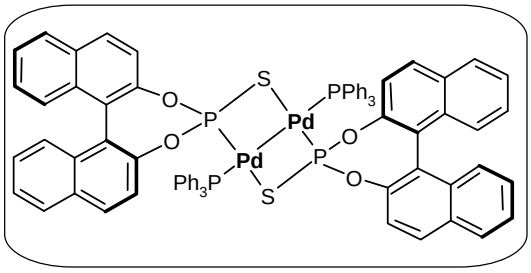
^{13}C NMR: δ 21.9, 22.5, 33.1 (s br, *C*Me$_2$), 67.1 (dioxane-OCH$_2$), 72.2 (s br, OCH$_2$), 127.8, 127.9, 129.4, 133.1 (dd→t, $^{2,3}J$(P-C) ~ 17.0 Hz), 134.7 (dd→t, $^{2,3}J$(P-C) ~ 17.0 Hz).

^{31}P NMR: δ 15.3 and 148.0 (2 d, ^2J(P-P) ~ 12.2 Hz each).

Anal. Calcd. for $C_{46}H_{50}O_4P_4Pd_2S_2$ (after drying): C, 51.74; H, 4.72. Found: C, 51.62; H, 4.83.

This compound was crystallized from 1,4-dioxane (1 mL). X-ray structural analysis was performed on this sample.

***S,S*-(-)-[$(C_{20}H_{12}O_2)$P-S-Pd(PPh_3)]$_2$ (42)**



A procedure similar to that for **41** was adapted for this compound by treating *S*-(-)-$(C_{20}H_{12}O_2)$P(S)H (**7**) with $Pd(PPh_3)_4$ in toluene (3 mL).

Yield: 0.15 g (90%; using 0.20 mmol of **7**).

Mp: 250-254 ^oC (yellow solid).

IR (KBr): 3052, 1620, 1586, 1433, 1324, 1221, 941, 746, 691 cm^{-1}.

^1H NMR (DMSO-d_6): δ 7.01-7.07 (m, 20H, Ar-*H*), 7.23-7.64 (m, 16H, Ar-*H*), 7.96-8.05 (m, 6H, Ar-*H*), 8.32 (s br, 12H, Ar-*H*).

^{31}P NMR (DMSO-d_6): δ 17.2 and 191.8 (2 dd, ^2J(P-P) ~ 30.4 Hz and ^4J(P-P) ~ 6.8 Hz each).

The compound had a low solubility in $CDCl_3$ and DMSO-d_6 hence ^{13}C NMR spectrum was not recorded.

Anal. Calcd. for $C_{76}H_{54}O_4P_4Pd_2S_2$: C, 63.74; H, 3.80. Found: C, 63.55; H, 3.89.

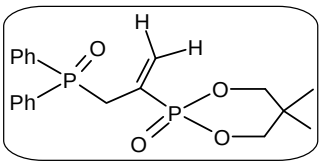
3.7 Pd-catalyzed and solvent-free, catalyst-free, hydro(thio)phosphonylation/hydro(thio)phosphinylation of allenes

3.71 Pd-catalyzed hydrophosphonylation/hydrothiophosponylation of allenes: Synthesis of compounds 43-63

Representative procedure for 43-44*:* A mixture of $(OCH_2CMe_2CH_2O)P(O)H$ (**4**) (1.05 mmol), allenyl phosphine oxide $Ph_2P(O)C(H)=C=CH_2$ (**24**) and $Pd(PPh_3)_4$ or dinuclear Pd^I-complex (**41**) (5.0 mol%) in 1,4-dioxane (2 mL) was heated at 100 ^oC for 4-12 h. The reaction mixture was cooled to room temperature, quenched with distilled water (2 mL) and extracted

with ethyl acetate (2 x 10 mL). The organic layer was dried (Na_2SO_4), removed the solvent under reduced pressure and the residue containing **43** and **44** was subjected to silica gel (100/200 mesh) column chromatography. Pure compounds were isolated by using ethyl acetate/hexane mixture. Details on the solvent combination (eluant system) used for the isolation of individual compounds are given below.

(a) Compounds 43 and (*E*)-44



43

The eluant used was ethyl acetate; compound **43** eluted before compound **44**.

Yield: 80% by NMR [**43**+**44**]; 0.14 g (isolated, 45%, **43**).

Mp: 138-140 ^{o}C.

IR (KBr): 3054, 2969, 1437, 1264, 1194, 1059, 1007 cm^{-1}.

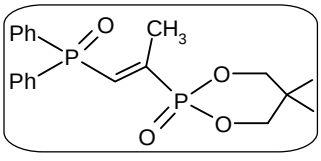
^{1}H NMR: δ 0.87 and 1.06 (2 s, 6H, 2 CH_3), 3.32 (dd→t, $^{2,3}J$(P-H) ~ 12.1 Hz, 2H, PCH_2), 3.70 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 10.0 Hz, 2H, OCH_2(A)), 3.90 (dd, ^{3}J(P-H) = 13.3 Hz, ^{2}J(H-H) = 11.4 Hz, 2H, OCH_2(B)), 6.10 (d, ^{3}J(P-H) = 23.2 Hz, 1H, =CH_A(*cis*)), 6.38 (d, ^{3}J(P-H) = 48.5 Hz, 1H, =CH_B(*trans*)), 7.44-7.49 (m, 6H, Ar-*H*), 7.72-7.77 (m, 4H, Ar-*H*).

^{13}C NMR: δ 21.1, 21.5, 30.7 (dd, ^{1}J(P-C) = 67.1 Hz, ^{2}J(P-C) = 11.6 Hz, PCH_2), 32.4 (d, ^{3}J(P-C) = 6.2 Hz, *C*Me$_2$), 76.2, 76.3, 126.9 (d, *J*(P-C) = 7.0 Hz), 128.6, 128.8, 130.9, 131.0, 132.1, 132.2 (d, ^{1}J(P-C) = 100.2 Hz, P*C*), 134.5 (dd→t, $^{2,3}J$(P-C) ~ 7.0 Hz, PC=*C*H$_2$).

^{31}P NMR: δ 11.7 and 29.8 (2 d, ^{3}J(P-P) = 26.0 Hz each).

LC-MS: *m/z* 391 [M+1]$^{+}$.

Anal. Calcd. for $C_{20}H_{24}O_4P_2$: C, 61.54; H, 6.20. Found: C, 61.50; H, 6.24.



(*E*)-44

The eluant used was ethyl acetate-methanol (20:1) after eluting compound **43**.

Yield: 80% by NMR [**43**+**44**]; 0.060 g (isolated, 15%, **44**).

Mp: 170-172 ^{o}C.

IR (KBr): 2967, 1597, 1437, 1271, 1194, 1051 cm^{-1}.

^{1}H NMR: δ 1.00 and 1.06 (2 s, 6H, 2 CH_3), 2.34 (ddd→td, ^{3}J(P-H) = 15.8 Hz, ^{4}J(P-H) ~ ^{4}J(H-H) = 2.0 Hz, 3H, CH_3), 3.81 (~dd, ^{3}J(P-H) = 13.6 Hz, ^{2}J(H-H) = 11.2 Hz, 2H, OCH_2(A)), 4.18 (~t, ^{3}J(P-H) ~ ^{2}J(H-H) ~ 10.0 Hz, 2H, OCH_2(B)), 7.09 (dd, ^{2}J(P-H) = 29.2 Hz, ^{3}J(P-H) = 24.4 Hz, 1H, C*H*), 7.41-7.51 (m, 6H, Ar-*H*), 7.65-7.70 (m, 4H, Ar-*H*).

^{13}C NMR: δ 16.0 (~t, $^{2,3}J$(P-C) ~ 8.0 Hz, =C(*C*H$_3$)P), 21.5, 21.6, 32.6 (d, ^{3}J(P-C) = 6.0 Hz, *C*Me$_2$), 75.6, 75.7, 128.8, 128.9, 130.9, 131.0, 132.2, 132.6 (d, ^{1}J(P-C) = 104.0 Hz, P*C*), 135.7 (dd, ^{1}J(P-C) = 90.0 Hz, ^{2}J(P-C) = 6.0 Hz, P*C*H), 147.2 (d, ^{1}J(P-C) = 164.0 Hz, ^{2}J(P-C) = 4.1 Hz, P*C*(CH$_3$)).

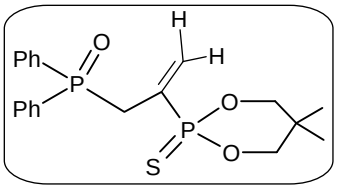
^{31}P NMR: δ 11.9 and 20.8 (2 d, ^{3}J(P-P) = 73.2 Hz each).

LC-MS: *m/z* 391 [M+1]$^{+}$.

Anal. Calcd. for $C_{20}H_{24}O_4P_2$: C, 61.54; H, 6.20. Found: C, 61.66; H, 6.18.

This compound was crystallized from ethyl acetate (1 mL). X-ray structural analysis was performed on this sample.

(b) Compounds 45, (*E*)-46 and 47



45

This compound was prepared by using thiophosphite ($OCH_2CMe_2CH_2O$)P(S)H (**6**) with allenyl phosphine oxide $Ph_2P(O)C(H)=C=CH_2$ (**24**). The eluant used was ethyl acetate/hexane (1:1) for compound **45** (highest R_f, eluted first).

Yield: 90% by NMR [**45**+**46**+**47**]; 0.17 g (isolated, 40%, **45)**.

Mp: 138-140 ^{o}C.

IR (KBr): 3055, 2967, 2201, 1437, 1192, 1119, 1047 cm^{-1}.

^{1}H NMR: δ 0.98 and 1.00 (2 s, 6H, 2 CH_3), 3.41 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 12.0 Hz, 2H, OCH_2), 3.69 (dd, $^{2,3}J$(P-H) = 14.8 and 11.2 Hz, 2H, PCH_2), 4.14 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 11.2 Hz, 2H, OCH_2), 6.26

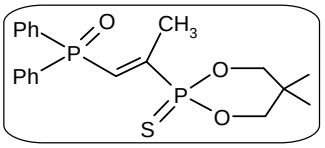
(dd, $^{3,4}J$(P-H) = 24.8 and 2.8 Hz, 1H, =CH_A(*cis*)), 6.51 (dd, $^{3,4}J$(P-H) = 50.4 and 1.2 Hz, 1H, =CH_B(*trans*)), 7.43-7.53 (m, 6H, Ar-*H*), 7.74-7.80 (m, 4H, Ar-*H*).

^{13}C NMR: δ 21.6, 22.0, 30.4 (dd, ^{1}J(P-C) = 67.0 Hz, ^{2}J(P-C) ~ 12.7 Hz, P*C*H$_2$), 32.9 (d, ^{3}J(P-C) = 6.1 Hz, *C*Me$_2$), 75.2, 75.3, 128.7, 128.8, 128.9, 131.0, 131.1, 131.3, 131.9, 132.1, 132.4, 132.7, 132.9, 133.5.

^{31}P NMR: δ 29.6 and 82.5 (2 d, ^{3}J(P-P) ~ 29.5 Hz each).

LC-MS: *m/z* 407 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{24}O_3P_2S$: C, 59.11; H, 5.95. Found: C, 59.05; H, 5.91.



(*E*)-46

The eluant used was ethyl acetate/hexane (3:2) [middle R_f; after eluting compound **45**].

Yield: 90% by NMR [**45**+**46**+**47**]; 0.07 g (isolated, 15%, **46**).

Mp: 156-158 ^{o}C.

IR (KBr): 3054, 2967, 2886, 1593, 1472, 1437, 1194, 1046, 997 cm^{-1}.

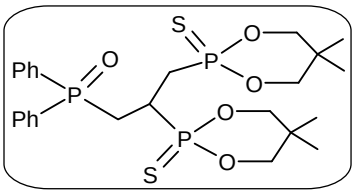
^{1}H NMR: δ 0.98 and 1.17 (2 s, 6H, 2 C*H*$_3$), 2.46 (ddd, $^{3,4}J$(P-H) = 15.8 and 2.8 Hz, ^{4}J(H-H) ~ 1.6 Hz Hz, 3H, C*H*$_3$), 3.77 (dd, $^{2,3}J$(P-H) = 18.0 and 10.0 Hz, 2H, OC*H*$_2$), 4.37 (dd, $^{2,3}J$(P-H) = 12.0 and 8.0 Hz, 2H, OC*H*$_2$), 7.27-7.56 (m, 6H, PC*H* + Ar-*H*), 7.69-7.74 (m, 5H, Ar-*H*).

^{13}C NMR: δ 15.2, 21.5, 22.3, 33.2 (d, ^{3}J(P-C) ~ 6.2 Hz, *C*Me$_2$), 74.8, 74.9, 128.8, 128.9, 130.9, 131.0, 132.1, 133.3, 135.9 (dd, ^{1}J(P-C) ~ 100.0 Hz, ^{2}J(P-C) ~ 4.5 Hz, P*C*H), 151.1 (d, ^{1}J(P-C) ~ 122.0 Hz, P*C*CH$_3$).

^{31}P NMR: δ 20.9 and 84.8 (2 d, ^{3}J(P-P) ~ 75.0 Hz each).

LC-MS *m/z* 407 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{24}O_3P_2S$: C, 59.11; H, 5.95. Found: C, 59.21; H, 6.05.



47

The eluant used was ethyl acetate/hexane (3:2) [lowest R_f; after eluting compound **46**].

Yield: 90% by NMR [**45**+**46**+**47**]; 0.46 g (isolated, 20%, **47**).

Mp: 88-90 ^{o}C.

IR (KBr): 3056, 2963, 2880, 1437, 1194, 1121, 1049 cm^{-1}.

^{1}H NMR: δ 0.88, 0.94, 1.06 and 1.10 (4 s, 12H, 4 C*H*$_3$), 2.66–2.92 (m, 4H, PC*H*$_2$), 3.48-3.51 (m, 1H, PC*H*), 3.70–3.90 (m, 4H, OC*H*$_2$), 3.95–4.12 (m, 2H, OC*H*$_2$), 4.22-4.27 (m, 2H, OC*H*$_2$), 7.47-7.54 (m, 6H, Ar-*H*), 7.74-7.78 (m, 2H, Ar-*H*), 7.83-7.88 (m, 2H, Ar-*H*).

^{13}C NMR: δ 21.5, 21.9, 22.3, 29.0, 29.5, 29.9, 30.2 (many lines due to P*C*H + P*C*H$_2$), 32.5 (d, ^{3}J(P-C) = 6.0 Hz, *C*(CH$_3$)$_2$), 33.1 (d, ^{3}J(P-C) = 6.1 Hz, *C*(CH$_3$)$_2$), 74.4 (d, ^{3}J(P-C) = 6.1 Hz, O*C*H$_2$), 75.9 (d, ^{2}J(P-C) = 7.5 Hz, O*C*H$_2$), 76.2 (d, ^{2}J(P-C) = 7.6 Hz, O*C*H$_2$), 128.6, 128.7, 130.6, 130.7, 131.3, 131.4, 131.9, 132.8 (d, ^{1}J(P-C) = 64.9 Hz, P*C*).

^{31}P NMR: δ 30.0 (d, ^{3}J(P-P) = 36.8 Hz, P(O)), 96.3 and 96.7 (m, AB part of the ABX spectrum; X = P(O)).

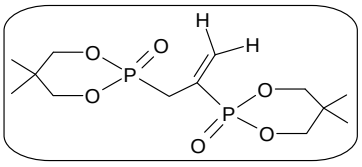
LC-MS: *m/z* 573 [M+1]$^{+}$.

Anal. Calcd. for $C_{25}H_{35}O_5P_3S_2$: C, 52.44; H, 6.16. Found: C, 52.35; H, 6.21.

When allene $Ph_2P(O)C(H)=C=CH_2$ (**24**) (1 mmol) was treated with thiophosphite **6** (2 mmol), we were able to isolate **47** as a single product.

Yield: 90% by NMR, 0.43 g, (isolated, 75%).

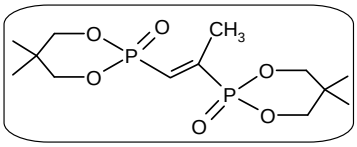
(c) Compounds 48 and (*E*)-49



48

This compound was synthesized by using allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**) and phosphite **4** and isolated by using ethyl acetate/hexane (3:2) as the eluant.

Yield: Quantitative by NMR [**48**+**49]**; 0.11 g (isolated, 32%, **48**). This is a known compound.[106]

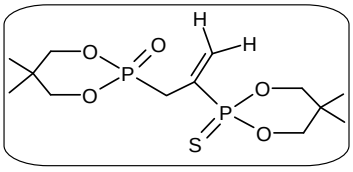


(*E*)-49

The eluant used was ethyl acetate/hexane (4:1); compound **49** eluted after compound **48**.

Yield: Quantitative by NMR [**48**+**49]** (ratio 2:3); 0.14 g (isolated, 42%, **49**). This is a known compound.[106]

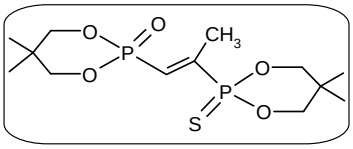
(d) Compounds 50, (*E*)-51 and 52



50

The eluant used was ethyl acetate- hexane (2:3); compound **50** eluted before **51/52**.

Yield: Quantitative by NMR [**50+51**+**52**]; 0.15 g (isolated, 42%, **50**). This is a known compound.[106]



(*E*)-51

It was a minor product (5%) by using this procedure, and hence was isolated only by using the procedure given in section 3.81(i) below. The eluant used was ethyl acetate/hexane (1:1) mixture.

Mp: 138–142 ^{o}C.

IR (KBr): 2967, 2893, 1618, 1470, 1250, 1047, 990 cm^{-1}.

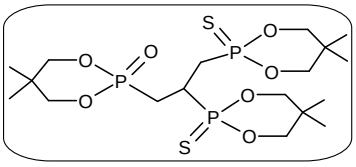
^{1}H NMR: δ 0.89, 0.96, 1.13 and 1.18 (4 s, 12H, 4 C*H*$_3$), 2.37 (dd, $^{3,4}J$(P-H) = 15.6 and 1.8 Hz, 3H, =CC*H*$_3$), 3.77–3.91 (m, 4H, OC*H*$_2$), 4.03–4.09 (m, 2H, OC*H*$_2$), 4.30–4.35 (m, 2H, OC*H*$_2$), 6.62 (dd, $^{2,3}J$(P-H), = 31.4 and 19.9 Hz, 1H, =C*H*).

^{13}C NMR: δ 16.0 (dd→t, $^{2,3}J$(P-C) ~ 8.8 Hz, C=C*C*H$_3$), 21.0, 21.5, 21.6 and 22.1 (4 s, *C*H$_3$), 32.5 (d, ^{3}J(P-C) = 6.2 Hz, *C*(CH$_3$)$_2$), 33.2 (d, ^{3}J(P-C) = 5.7 Hz, *C*(CH$_3$)$_2$), 75.1 (d, ^{2}J(P-C) = 6.4 Hz, O*C*H$_2$), 76.3 (d, ^{2}J(P-C) = 5.8 Hz, O*C*H$_2$), 128.1 (dd, ^{1}J(P-C) = 171.0 Hz and ^{2}J(P-C) ~ 11.8 Hz, P-*C*H), 151.8 (dd, ^{1}J(P-C) = 162.3 Hz and ^{2}J(P-C) = 7.1 Hz, P*C*):

^{31}P NMR: δ 7.6 and 83.0 (2 d, ^{3}J(P-P) = 102.9 Hz each).

LC-MS: *m/z* 355 [M+1]$^{+}$.

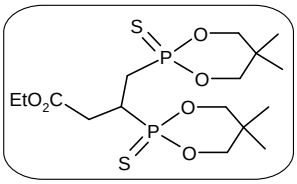
Anal. Calcd. for $C_{13}H_{24}O_5P_2S$: C, 44.06; H, 6.83. Found: C, 44.15; H, 6.78.



52

Yield: Quantitative by NMR [**50**+**51**+**52**]; 0.10 g (isolated, 20%, **52**). The eluant used was ethyl acetate/hexane (2:3). Compound **52** elutes after compound **50/51**. This compound was also reported by my colleague.[106]

(e) Compound 53



This compound was prepared by reacting allene EtO_2C-C(H)=C=CH_2 (**17**) (1.0 mmol) with thiophosphite **6** (2.0 mmol) by adapting procedure (see section 3.71) and isolated by using ethyl acetate/hexane (2:3) mixture as eluant.

Yield: 95% by NMR; 0.36 g (isolated, 80%).

Mp: 122–124 ^{o}C.

IR (KBr): 2965, 2882, 1736, 1472, 1372, 1209, 1047 cm^{-1}.

^{1}H NMR: δ 0.95, 1.06, 1.12 and 1.21 (4 s, 12H, 4 CH_3), 1.27 (t, ^{3}J(H-H) = 8.0 Hz, 3H, OCH_2CH_3), 2.42-2.48 (m, 1H, PCH_AH_B), 2.64-2.68 (m, 1H, PCH_AH_B), 2.91-3.01 (m, 2H, CH_2CO_2Et), 3.38-3.53 (m, 1H, P(S)C*H*), 3.73-3.84 (m, 2H, OCH_2), 3.91-4.01 (m, 2H, OCH_2), 4.13-4.28 (m, 4H, 2 OCH_2), 4.37-4.43 (m, 2H, OCH_2CH_3).

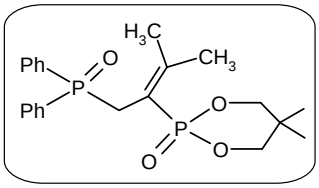
^{13}C NMR: δ 14.2 (OCH_2CH_3), 21.4, 21.7, 22.1 and 22.4 (4 CH_3), 31.9 (dd, ^{1}J(P-C) = 99.7 Hz and ^{2}J(P-C) ~ 3.0 Hz, P(S)CH_2), 32.1 (d, ^{1}J(P-C) = 97.5 Hz P-*C*H), 33.0 (d, ^{3}J(P-C) = 6.0 Hz, $C(CH_3)_2$), 33.2 (d, ^{3}J(P-C) = 5.7 Hz, $C(CH_3)_2$), 33.9, 61.0 (OCH_2CH_3), 74.0 and 74.1 (2 d, ^{2}J(P-C) ~6.1 Hz, OCH_2), 75.1 and 75.2 (2 d, ^{2}J(P-C) ~7.0 Hz, OCH_2), 177.7 (d, ^{3}J(P-C) = 4.1 Hz *C*(O)).

^{31}P NMR: δ 97.3 and 98.8 (2 d, ^{3}J(P-P) = 80.2 Hz each).

LC-MS: *m/z* 443 $[M-1]^{+}$.

Anal. Calcd. for $C_{16}H_{30}O_6P_2S_2$: C, 43.23; H, 6.80. Found: C, 43.28; H, 6.73.

(f) Compound 54



This compound was isolated by using ethyl acetate as eluant.

Yield: 95% by NMR; 0.37 g (isolated, 90%).

Mp: 158-160 ^{o}C.

IR (KBr): 3054, 2965, 2913, 1616, 1470, 1439, 1252, 1177, 1069 cm^{-1}.

^{1}H NMR: δ 0.87 and 0.96 (2 s, 6H, 2 CH_3), 1.62 and 2.09 (br 2 s, 6H, C=C(CH_3)$_2$), 3.46 (dd→t, $^{2,3}J$(P-H) ~ 15.0 Hz, 2H, PCH_2), 3.73 (dd, ^{3}J(P-H) = 14.0 Hz, ^{2}J(H-H) ~ 11.2 Hz, 2H, OCH_2), 4.01 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 9.6 Hz, 2H, OCH_2), 7.39-7.44 (m, 6H, Ar-*H*), 7.73-7.77 (m, 4H, Ar-*H*).

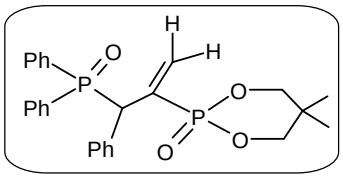
^{13}C NMR: δ 21.7, 22.3, 24.3-25.6 (m, 2 *C*H$_3$), 32.5 (d, ^{3}J(P-C) ~ 5.4 Hz, *C*Me$_2$), 32.8 (dd, ^{1}J(P-C) ~70.0 Hz and ^{2}J(P-C) ~ 13.1 Hz, P*C*H$_2$), 74.6, 74.7, 113.1 (dd, ^{1}J(P-C) = 187.2 Hz and ^{2}J(P-C) ~ 9.8 Hz, (P)*C*=CMe$_2$), 128.3, 128.5, 131.1, 131.2, 131.7, 133.1 (d, ^{1}J(P-C) = 98.2 Hz, P*C*), 158.2 (dd→t, $^{2,3}J$(P-C) ~ 9.5 Hz, =*C*(Me)$_2$).

^{31}P NMR: δ 16.4 and 28.6 (2 d, ^{3}J(P-P) ~ 6.6 Hz each).

LC-MS: *m/z* 419 [M+1]$^{+}$.

Anal. Calcd. for $C_{22}H_{28}O_4P_2$: C, 63.15; H, 6.75. Found: C, 63.28; H, 6.70.

(g) Compound 55



The eluant used was ethyl acetate/hexane (3:2).

Yield: 80% by NMR; 0.33 g (isolated, 70%).

Mp: 188-190 ^{o}C.

IR (KBr): 2961, 1591, 1474, 1437, 1269, 1188, 1071, 817 cm^{-1}.

^{1}H NMR: δ 0.73 and 1.09 (2 s, 6H, 2 CH_3), 2.99 (dd, ^{3}J(P-H) = 11.2 Hz, ^{2}J(H-H) = 6.8 Hz, 1H, OCH_AH$_B$), 3.45 (dd, ^{3}J(P-H) = 16.5 Hz, ^{2}J(H-H) =

13.1 Hz, 1H, OCH_AH_B), 3.71 (dd, ^3J(P-H) = 11.2 Hz, ^2J(H-H) = 6.8 Hz, 1H, OCH_AH_B), 3.93 (dd, ^3J(P-H) = 16.5 Hz, ^2J(H-H) = 13.1 Hz, 1H, OCH_AH_B), 4.55 (dd, $^{2,3}J$(P-H) = 13.8 and 8.6 Hz, 1H, PC*H*(Ph)), 6.10 (dd, ^3J(P-H) = 22.8 Hz, ^2J(H-H) = 1.2 Hz, 1H, $=CH_A$(cis)), 7.10-7.24 (m, 8H, Ar-*H* + $=CH_B$(trans)), 7.31-7.36 (m, 3H, Ar-*H*), 7.53–7.54 (m, 3H, Ar-*H*), 8.03-8.08 (m, 2H, Ar-*H*).

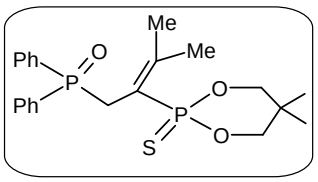
^{13}C NMR: δ 20.9, 21.8, 32.1 (d, ^3J(P-C) = 6.5 Hz, CMe_2), 46.6 (dd, ^1J(P-C) = 63.4, ^2J(P-C) = 11.5 Hz, PCH(Ph)), 75.2, 75.3, 127.4, 128.0, 128.1, 128.7, 128.8, 130.4 (d, J(P-C) = 5.2 Hz), 130.9, 131.0, 131.5, 131.7, 131.8, 132.0, 133.0, 133.4 (d, J(P-C) = 5.2 Hz), 133.7 (d, J(P-C) = 7.4 Hz), 134.8 (dd, ^1J(P-C) = 170.0 Hz and ^2J(P-C) ~5.0 Hz, $PC=CH_2$).

^{31}P NMR: δ 11.6 and 32.8 (2 d, ^3J(P-P) = 37.6 Hz each).

LC-MS: *m/z* 466 $[M]^+$.

Anal. Calcd. for $C_{26}H_{28}O_4P_2$: C, 66.95; H, 6.05. Found: C, 66.85; H, 6.12.

(h) Compound 56



The eluant used was ethyl acetate/hexane (3:2).

Yield: 85% by NMR; 0.31 g (isolated, 72%).

Mp: 142-144 °C.

IR (KBr): 2963, 2924, 2874, 2475, 1437, 1196, 1119, 1047, 995 cm^{-1}.

^{1}H NMR: δ 0.85 and 0.95 (2 s, 6H, 2 CH_3), 1.70 and 2.16 (2 s, 6H, $C=C(CH_3)_2$), 3.54-3.62 (m, 4H, PCH_2+OCH_2), 4.14-4.22 (br m, 2H, OCH_2), 7.43 (s br, 6H, Ar-*H*), 7.78-7.83 (m, 4H, Ar-*H*).

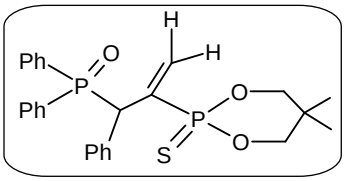
^{13}C NMR: δ 21.6, 22.5, 24.6, 24.7, 30.7 (dd, ^1J(P-C) = 67.0 Hz and ^2J(P-C) = 3.8 Hz, PCH_2), 32.9 (d, ^3J(P-C) = 5.6 Hz, CMe_2), 73.8, 73.9, 118.3 (dd, ^1J(P-C) = 146.5 Hz and ^2J(P-C) = 9.4 Hz, PCH), 128.4, 128.5, 131.1, 131.2, 131.7, 132.0, 132.1, 132.9, 133.1, 134.0, 155.3 (dd, $^{2,3}J$(P-C) = 10.8 and 8.7 Hz, $PCH=CMe_2$).

^{31}P NMR: δ 27.4 and 83.4 (2 d, ^3J(P-P) ~ 7.3 Hz each).

LC-MS: *m/z* 435 $[M+1]^+$.

Anal. Calcd. for $C_{22}H_{28}O_3P_2S$: C, 60.82; H, 6.50. Found: C, 60.75; H, 6.54.

(i) Compounds 57 and 58



57

The eluant used was ethyl acetate/hexane (2:3) for compound **57** which eluted first.

Yield: 80% by NMR [**57**+**58**]; 0.29 g (isolated, 60%, **57**).

Mp: 182-184 ^oC.

IR (KBr): 2961, 2882, 1435, 1190, 1047, 991 cm^{-1}.

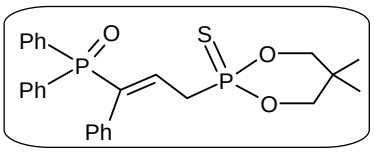
^1H NMR: δ 0.82 and 1.00 (2 s, 6H, 2 C*H*$_3$), 3.03 (dd→t, ^3J(P-H) = ^2J(H-H) ~ 12.0 Hz, 1H, OC*H*$_A$H$_B$), 3.63-3.71 (m, 2H, OC*H*$_2$), 4.07 (dd→t, ^3J(P-H) = ^2J(H-H) ~ 12.0 Hz, 1H, OCH$_A$*H*$_B$), 4.80 (dd, $^{2,3}J$(P-H) ~ 15.2 Hz and 8.4 Hz, 1H, PC*H*(Ph)), 6.22 (dd, ^3J(P-H) = 24.4 Hz, ^2J(H-H) = 1.2 Hz, 1H, =C*H*$_A$), 7.10-7.16 (m, 4H, =C*H*$_B$(*trans*) + Ar-*H*), 7.21-7.26 (m, 3H, Ar-*H*), 7.33-7.41 (m, 3H, Ar-*H*), 7.46-7.53 (m, 4H, Ar-*H*), 8.06-8.11 (m, 2H, Ar-*H*).

^{13}C NMR: δ 21.7, 21.8, 32.5 (d, ^3J(P-C) = 6.3 Hz, *C*Me$_2$), 46.6 (dd, ^1J(P-C) = 63.0 Hz and ^2J(P-C) ~ 13.2 Hz, P*C*H(Ph)), 75.0 (d, ^2J(P-C) = 7.0 Hz, O*C*H$_2$), 76.1 (d, ^2J(P-C) = 7.4 Hz, O*C*H$_2$), 127.4, 128.1, 128.2, 128.6, 128.7, 130.5, 130.6, 130.7, 130.9, 131.0, 131.5, 131.7, 131.8, 132.0, 132.7 (dd→t, $^{2,3}J$(P-C) ~ 8.2 Hz, C=*C*H$_2$), 133.4, 137.7 (d, ^1J(P-C) = 127.1 Hz, P*C*=CH$_2$).

^{31}P NMR: δ 32.2 and 82.1 (2 d, ^3J(P-P) = 39.1 Hz each).

LC-MS: *m/z* 483 $[M+1]^+$.

Anal. Calcd. for $C_{26}H_{28}O_3P_2S$: C, 64.72; H, 5.85. Found: C, 64.55; H, 5.92.



58

The eluant used was ethyl acetate/hexane (1:1); compound **58** eluted after compound **57**.

Yield: 90% by NMR [**57**+**58**]; 0.024 g (isolated, 5%, **58**).

Mp: 170-172 ^{o}C.

IR (KBr): 2928, 2878, 1613, 1435, 1177, 1117, 1045, 991 cm^{-1}.

^{1}H NMR: δ 0.90 and 1.11 (2 s, 6H, 2 C*H*$_3$), 3.05 (dd, ^{2}J(P-H) = 20.0 Hz, ^{3}J(H-H) = 6.8 Hz, 2H, P(S)C*H*$_2$), 3.63-3.71 (m, 2H, OC*H*$_2$), 4.36-4.41 (m, 2H, OC*H*$_2$), 6.64-6.75 (m, 1H, P(S)CH$_2$C*H*), 7.07 (s br, 2H, Ar-*H*), 7.22 (s br, 3H, Ar-*H*), 7.42-7.44 (m, 3H, Ar-*H*), 7.50-7.54 (m, 3H, Ar-*H*), 7.68-7.73 (m, 4H, Ar-*H*)

^{31}P NMR: δ 27.8 and 91.8 (2 d, ^{4}J(P-P) ~ 8.0 Hz each).

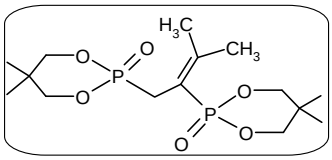
LC-MS: *m/z* 483 [M+1]$^{+}$.

Anal. Calcd. for $C_{26}H_{28}O_3P_2S$: C, 64.72; H, 5.85. Found: C, 64.88; H, 5.79.

The sample amount was too low to obtain a decent ^{13}C NMR spectrum.

This compound was crystallized from dichloromethane/hexane mixture (2 + 1 mL). X-ray structure was obtained on this sample.

(j) Compound 59

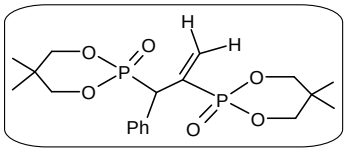


The eluant used was ethyl acetate/hexane (9:1).

Yield: 90% by NMR; 0.28 g (isolated, 77%).

This is a known compound.[106]

(k) Compound 60

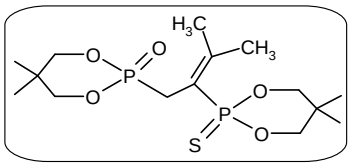


The eluant used was ethyl acetate/hexane (1:1).

Yield: 90% by NMR; 0.33 g (isolated, 80%).

This is a known compound.[106]

(l) Compound 61

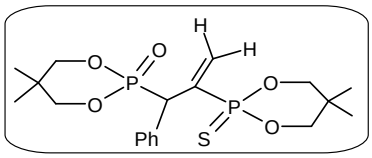


The eluant used was ethyl acetate/hexane (1:1).

Yield: 85% by NMR Yield 0.30 g (isolated, 78%).

This is a known compound.[106]

(m) Compound 62

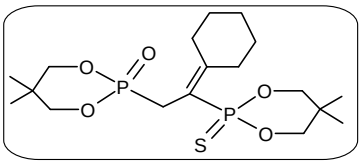


The eluant used was ethyl acetate/hexane (1:1).

Yield: 89% by NMR; 0.36 g (isolated, 85%).

This is a known compound.[106]

(n) Compound 63



The eluant used was ethyl acetate/hexane (1:1).

Yield: 90% by NMR; 0.30 g (isolated, 70%).

Mp: 148-150 ^{o}C.

IR (KBr): 2967, 2930, 2890, 1609, 1476, 1246, 1053, 984 cm^{-1}.

^{1}H NMR: δ 0.93, 0.99, 1.13 and 1.17 (4 s, 12H, 4 CH_3), 1.59-1.68 (m, 6H, cyclohexyl-*H*), 2.36 (s br, 2H, cyclohexyl-*H*), 2.77 (s br, 2H, cyclohexyl-*H*), 3.13 (dd, $^{2,3}J$(P-H) = 21.6 and 16.0 Hz, 2H, PCH_2), 3.77 (dd, ^{3}J(P-H) = ^{2}J(H-H) ~ 20.9 and 10.9 Hz, 2H, OCH_ACH$_B$), 3.91 (dd, ^{3}J(P-H) = ^{2}J(H-H) ~ 20.9 and 10.9 Hz, 2H, OCH_ACH$_B$),

4.17 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 9.8 Hz, 2H, OCH_ACH_B), 4.45 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 9.8 Hz, 2H, OCH_ACH_B).

^{13}C NMR: δ 21.5$_7$, 21.5$_9$, 21.9 and 22.6 (4 CH_3), 25.4 (dd, ^{1}J(P-C) = 138.0 Hz and ^{2}J(P-C) = 13.8 Hz, PCH_2), 25.9, 27.5, 27.6, 32.7 (d, ^{3}J(P-C) = 6.2 Hz, CMe_2), 33.2 (d, ^{3}J(P-C) = 5.1 Hz, CMe_2), 33.3, 33.5, 34.9, 35.0, 73.8 (d, ^{2}J(P-C) = 6.0 Hz, OCH_2), 75.1 (d, ^{2}J(P-C) = 6.0 Hz, OCH_2), 115.3 (dd, ^{1}J(P-C) = 148.1 Hz and ^{2}J(P-C) ~ 11.6 Hz, PC), 162.4 (dd→t, $^{2,3}J$(P-C) = 11.0 Hz, PC=C).

^{31}P NMR: δ 22.8 and 83.0 (2 d, ^{3}J(P-P) ~ 9.8 Hz each).

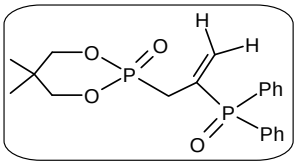
LC-MS: *m/z* 423 $[M+1]^+$.

Anal. Calcd. for $C_{18}H_{32}O_5P_2S$: C, 51.18; H, 7.63. Found: C, 51.25; H, 7.71.

3.72 Solvent free, catalyst-free hydro(thio)phosphinylation of allenes: Synthesis of compounds 64-80

General procedure for 64 and (E)-65: In a 25 mL round bottom flask a mixture of $(OCH_2CMe_2CH_2O)P(O)C(H)=C=CH_2$ (**18**) (1.00 mmol) and $Ph_2P(O)H$ (**5**) (1.05 mmol) was heated at 100 ^{o}C (oil bath temperature) for one hour in air. Progress of the reaction was monitored by TLC or ^{31}P NMR. Analytically pure compounds **64** and (*E*)-**65** were obtained by passing them through a short column (silicagel; ethylacetate/hexane).

(a) Compounds 64 and (*E*)-65



64

The eluant used was ethyl acetate/hexane (7:3) for compound **65** which eluted first; this was followed by compound **64** using ethyl acetate/hexane (4:1) mixture.

Yield: Quantitative by NMR [**64**+**65**]; 0.29 g (isolated, 75%, **64**).

Mp: 134-136 ^{o}C.

IR (KBr): 3052, 2969, 2886, 1478, 1439, 1277, 1180, 1119, 1059, 1009 cm^{-1}.

^{1}H NMR: δ 0.90 and 1.13 (2 s, 6H, 2 CH_3), 3.00 (dd, $^{2,3}J$(P-H) = 20.4 and 9.6 Hz, 2H, PCH_2), 3.87-3.95 (m, 4H, 2 OCH_2), 5.71 (dd, $^{3,4}J$(P-H) =

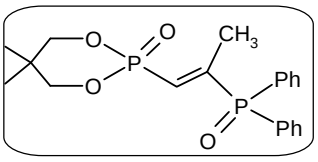
23.2 and 4.8 Hz, 1H, =CH_A(*cis*)), 6.38 (d, ^3J(P-H) = 48.5 Hz, 1H, =CH_B(*trans*)), 7.44-7.49 (m, 6H, Ar-*H*), 7.72-7.77 (m, 4H, Ar-*H*).

^{13}C NMR: δ 21.0, 21.5, 24.4 (dd, ^1J(P-C) = 132.1 Hz, ^2J(P-C) = 11.0 Hz, P*C*H$_2$), 32.5 (d, ^3J(P-C) = 7.0 Hz, *C*Me$_2$), 76.3, 76.4, 128.6, 128.7, 130.3 (d, ^1J(P-C) = 104.0 Hz, P*C*), 131.4, 132.0, 132.1, 132.3, 134.5.

^{31}P NMR: δ 19.4 and 32.9 (2 d, ^3J(P-P) ~ 27.8 Hz each).

LC-MS: *m/z* 391 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{24}O_4P_2$: C, 61.54; H, 6.20; Found: C, 61.72; H, 6.26.



(*E*)-65

The eluant used was ethyl acetate/hexane (7:3) for compound **65** which eluted first.

Yield: Quantitative by NMR [**64**+**65**]; 0.022 g (isolated, 5%, **65**).

IR (KBr): 3059, 2971, 2884, 1472, 1437, 1273, 1190, 1119, 1057 cm^{-1}.

^{1}H NMR: δ 0.99 and 1.16 (2 s, 6H, 2 C*H*$_3$), 2.25 (ddd, $^{3,4}J$(P-H) = 13.2 and 3.0 Hz, ^4J(H-H) ~ 1.6 Hz, 3H, C*H*$_3$), 3.88-3.93 (m, 2H, OC*H*$_2$), 4.01-4.08 (m, 2H, OC*H*$_2$), 7.09 (dd, $^{2,3}J$(P-H) ~ 22.0 Hz, 1H, C*H*), 7.48-7.51 (m, 4H, Ar-*H*), 7.56-7.60 (m, 2H, Ar-*H*), 7.66-7.76 (m, 4H, Ar-*H*).

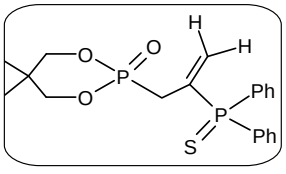
^{13}C NMR: δ 17.3, 21.4, 21.7, 32.5 (d, ^3J(P-C) = 7.6 Hz, C(*C*H$_3$)$_2$), 76.1, 76.2, 128.7, 128.9, 129.0, 132.1, 132.2, 132.5, 132.6, 132.7, 154.6 (d, ^1J(P-C) = 81.3 Hz, P*C*).

^{31}P NMR: δ 8.0 and 30.5 (2 d, ^3J(P-P) ~ 75.7 Hz each).

LC-MS: *m/z* 391 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{24}O_4P_2$: C, 61.54; H, 6.20. Found: C, 61.45; H, 6.26.

(b) Compounds 66 and (*E*)-67 [Using 1.0 mmol of allene **18**]



66

The eluant used was ethyl acetate/hexane (1:1) for compound **66** which eluted first.

Yield: Quantitative by NMR [**66**+**67]**; 0.32 g (isolated, 80%, **66**).

Mp: 152-154 ^{o}C.

IR (KBr): 3054, 2967, 2884, 1478, 1439, 1283, 1180, 1105, 1059, 1005 cm^{-1}.

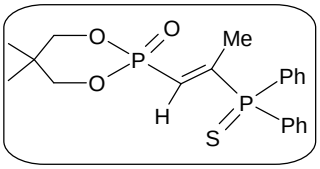
^{1}H NMR: δ 0.90 and 1.15 (2 s, 6H, 2 CH_3), 3.14 (dd, $^{2,3}J$(P-H) = 19.8 and 10.2 Hz, 2H, PCH_2), 3.85-3.92 and 3.97-4.02 (2 m, 4H, 2 OCH_2), 5.56 (dd, $^{3,4}J$(P-H) = 21.2 and 3.6 Hz, 1H, =CH_A(*cis*)), 6.59 (d, ^{3}J(P-H) = 44.0 Hz, 1H, =CH_B(*trans*)), 7.48-7.54 (m, 6H, Ar-*H*), 7.79-7.84 (m, 4H, Ar-*H*).

^{13}C NMR: δ 21.0, 21.8, 24.3 (dd, ^{1}J(P-C) = 132.0 Hz, ^{2}J(P-C) ~ 13.1 Hz, P*C*H_2), 32.5 (d, ^{3}J(P-C) = 6.5 Hz, *C*Me_2), 76.5, 76.6, 128.6, 128.8, 129.8 (d, ^{1}J(P-C) = 83.1 Hz, P*C*), 132.1, 132.3, 132.4, 132.7, 132.8, 133.3, 133.4.

^{31}P NMR: δ 19.3 and 49.7 (2 d, ^{3}J(P-P) ~ 35.5 Hz each).

LC-MS: *m/z* 407 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{24}O_3P_2S$: C, 59.11; H, 5.95. Found: C, 59.25; H, 5.83.



(*E*)-67

The eluant used was ethyl acetate/hexane (3:2) after eluting compound **66**.

Yield: Quantitative by NMR [**66+67**]; 0.020 g (isolated, 5%, **67**).

IR (KBr): 2965, 2928, 1601, 1474, 1437, 1277, 1059, 1007 cm^{-1}.

^{1}H NMR: δ 0.88 and 1.15 (2 s, 6H, 2 CH_3), 2.31-2.34 (m, 3H, (S)PC(CH_3)), 3.78-3.80 and 4.02-4.05 (2 m, 4H, 2 OCH_2), 6.35-6.46 (br m, 1H, (O)PC*H*), 7.48-7.52 (m, 6H, Ar-*H*), 7.76 (s br, 4H, Ar-*H*).

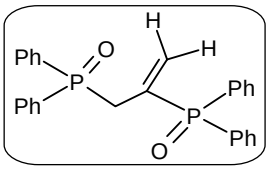
^{13}C NMR: δ 17.3 (dd→t, $^{2,3}J$(P-C) ~ 15.3 Hz, (S)PC(*C*H_3)), 21.2, 21.6, 32.5 (d, ^{3}J(P-C) = 5.9 Hz, C(*C*H_3)$_2$), 76.2, 76.3, 127.6 (dd, ^{1}J(P-C) = 152.2, ^{2}J(P-C) ~ 13.1 Hz), 128.5, 128.6, 128.8, 128.9, 129.7 (d, ^{1}J(P-C) = 84.3 Hz, PC), 132.1, 132.2, 154.2 (d, ^{1}J(P-C) = 63.1 Hz, P*C*).

^{31}P NMR: δ 8.2 and 49.6 (2 d, ^{3}J(P-P) = 80.5 Hz each).

LC-MS: *m/z* 407 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{24}O_3P_2S$: C, 59.11; H, 5.95; Found: C, 59.25; H, 5.91.

(c) Compounds 68 and (*E*)-69 [Using 1.0 mmol of allene **24**]



68

The eluant used was ethyl acetate/hexane (3:2) for compound **68** which eluted first.

Yield: Quantitative by NMR [**68**+**69**]; 0.33 g (isolated, 75%, **68**).

IR (KBr): 3056, 2978, 1483, 1437, 1192, 1119, 1071 cm^{-1}.

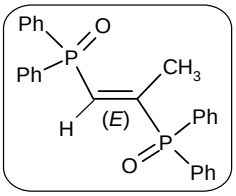
^{1}H NMR:): δ 3.44 (dd, $^{2,3}J$(P-H) = 12.0 and 8.0 Hz, 2H, PCH_2)), 5.54 (d, ^3J(P-H) = 20.0 Hz, 1H, =CH_A(*cis*)), 6.79 (d, ^3J(P-H) = 40.0 Hz, 1H, =CH_B(trans)), 7.41-7.56 (m, 12H, Ar-*H*), 7.70-7.78 (m, 8H, Ar-*H*).

^{13}C NMR: δ 29.6 (dd, ^1J(P-C) = 67.8 Hz, ^2J(P-C) = 9.9 Hz, P*C*H_2), 128.6, 128.7, 128.9, 130.1 (d, ^1J(P-C) = 102.5 Hz, (P)*C*=CH_2), 131.0, 131.1, 131.8, 131.9, 132.0, 132.2, 132.8, 133.7, 133.8, 134.7 (dd→t, ^1J(P-C) ~ 7.5 Hz, PC=*C*H_2).

^{31}P NMR: δ 30.8 and 32.8 (2 d, ^3J(P-P) = 24.5 Hz each).

LC-MS: *m/z* 441 $[M-1]^+$.

Anal. Calcd. for $C_{27}H_{24}O_2P_2$: C, 73.30; H, 5.47. Found: C, 73.45; H, 5.41.



(*E*)-69

It was isolated by using the procedure from section 3.81a, since it was a minor (5%) product by using this method. The eluant used was ethyl acetate/hexane (4:1).

Mp: 144-146 ^oC.

IR (KBr): 3056, 2967, 1736, 1589, 1435, 1264, 1190, 1117 cm^{-1}.

^{1}H NMR: δ 2.26 (ddd, $^{3,4}J$(P-H) = 13.6 and 2.8 Hz, ^4J(H-H) = 1.0 Hz, 3H, CH_3), 7.20-7.32 (m, 1H, PC*H*), 7.42-7.57 (m, 12H, Ar-*H*), 7.64-7.72 (m, 8H, Ar-*H*).

^{13}C NMR: δ 16.8 (dd→t, $^{2,3}J$(P-C) = 9.0 Hz, =C(*C*H_3)), 128.7, 128.9, 129.6 (d, ^1J(P-C) = 102.0 Hz, P*C*), 130.8, 130.9, 132.0, 132.1, 132.5, 133.0 (d, ^1J(P-C) = 103.9 Hz, P*C*), 135.3 (dd, ^1J(P-C) = 88.7 Hz, ^2J(P-C) = 4.5

Hz, P*C*H), 153.6 (d, ^{1}J(P-C) = 78.0 Hz, P*C*(CH_3)). This spectrum is illustrated in Fig. 22.

^{31}P NMR: δ 21.0 and 29.5 (2 d, ^{3}J(P-P) ~ 53.5 Hz each).

LC-MS: *m/z* 441 $[M-1]^+$.

Anal. Calcd. for $C_{27}H_{24}O_2P_2$: C, 73.30; H, 5.47. Found: C, 73.48; H, 5.41.

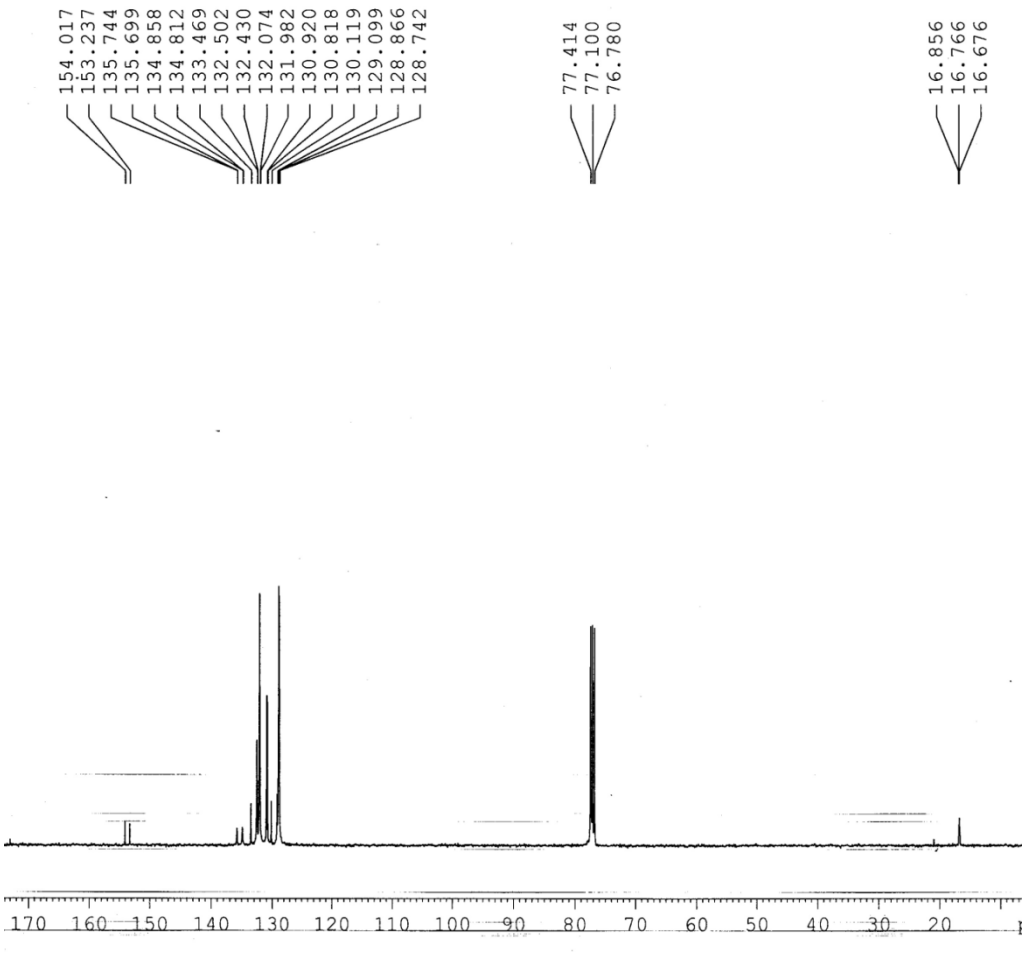
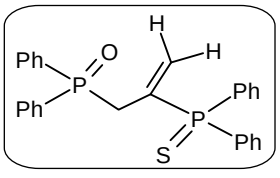


Fig. 22. ^{13}C NMR spectrum of compound (***E***)-**69**

(d) Compounds 70 and (*E*)-71 [Using 1.0 mmol of allene **24**]



70

The eluant used was ethyl acetate/hexane (3:2) for compound **71** which eluted first; this was followed by compound **70** using ethyl acetate/hexane (7:3).

Yield: Quantitative by NMR [**70**+**71**]; 0.23 g (isolated, 50%, **70**).

Mp: 144-146 ^{o}C.

IR (KBr): 3056, 2921, 1612, 1481, 1437, 1188, 1103 cm^{-1}.

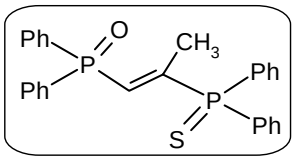
^{1}H NMR: δ 3.53 (dd, $^{2,3}J$(P-H) = 12.4 and 9.2 Hz, 2H, PCH_2), 5.43 (d, ^{3}J(P-H) = 22.0 Hz, 1H, =CH_A(*cis*)), 6.76 (d, ^{3}J(P-H) = 44.0 Hz, 1H, =CH_B(trans)), 7.41-7.52 (m, 12H, Ar-*H*), 7.67-7.72 (m, 4H, Ar-*H*), 7.77-7.81 (m, 4H, Ar-*H*).

^{13}C NMR δ 29.9 (dd, ^{1}J(P-C) = 67.1 Hz, ^{2}J(P-C) ~ 12.4 Hz, P*C*H$_2$), 128.6, 128.7, 128.9, 130.0 (d, ^{1}J(P-C) = 83.4 Hz), 130.8, 130.9, 131.9, 132.0, 132.2, 132.3, 133.0, 133.1, 134.2 (dd, ^{1}J(P-C) = 73.9 Hz, ^{2}J(P-C) ~ 6.0 Hz).

^{31}P NMR: δ 30.5 and 49.5 (2 d, ^{3}J(P-P) ~ 30.1 Hz each).

LC-MS: *m/z* 459 [M+1]$^{+}$.

Anal. Calcd. for $C_{27}H_{24}OP_2S$: C, 70.73; H, 5.28. Found: C, 70.85; H, 5.21.



(*E*)-71

Yield: Quantitative by NMR [**70**+**71**]; 0.020 g (isolated, 5%, **71**).

Mp: 124-128 ^{o}C.

IR (KBr): 2919, 2853, 1607, 1435, 1196, 1117 cm^{-1}.

^{1}H NMR: δ 2.35 (dd, $^{2,3}J$(P-H) = 14.4 and 0.8 Hz, 3H, =CCH_3), 7.17-7.26 (m, 1H, P(O)C*H*), 7.46-7.54 (m, 10H, Ar-*H*), 7.65-7.80 (m, 10H, Ar-*H*).

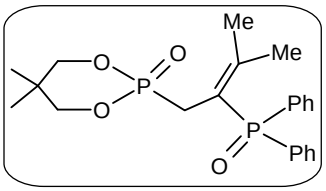
^{13}C NMR: δ 16.9 (dd→t, ^{2}J(P-C) = 9.8 Hz, ^{3}J(P-C) ~ 7.6 Hz, =C*C*H$_3$), 128.5, 128.6, 128.8, 128.9, 130.2 (d, ^{1}J(P-C) = 83.4 Hz, P*C*), 130.6, 130.8, 131.9, 131.0, 132.0, 132.1, 132.2, 133.0, 133.2 (d, ^{1}J(P-C) = 104.5 Hz, P*C*), 135.1 (dd, ^{1}J(P-C) = 88.5 Hz, ^{2}J(P-C) ~ 7.0 Hz, P(O)*C*H), 153.9 (d, ^{1}J(P-C) = 61.1 Hz, =C(P)CH$_3$).

^{31}P NMR: δ 20.3 and 49.4 (2 d, ^{3}J(P-P) ~ 53.2 Hz each).

LC-MS: *m/z* 459 [M+1]$^{+}$.

Anal. Calcd. for $C_{27}H_{24}OP_2S$: C, 70.73; H, 5.28. Found: C, 70.85; H, 5.21.

(e) Compound 72 [Using 1.0 mmol of allene **19**]



The eluant used was ethyl acetate.

Yield: 95% by NMR; 0.33 g (isolated, 80%).

Mp: 156-158 ^{o}C.

IR (KBr): 3050, 2876, 1472, 1437, 1260, 1190, 1113, 1047, 995 cm^{-1}.

^{1}H NMR: δ 0.89 and 1.05 (2 s, 6H, 2 CH_3), 1.71-1.73 and 2.12-2.13 (2 m, 6H, C=C(CH_3)$_2$), 3.14 (dd, $^{2,3}J$(P-H) = 21.0 and 7.0 Hz, 2H, PCH_2), 3.91 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 12.8 Hz, 2H, OCH_2), 4.02 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 10.4 Hz, 2H, OCH_2), 7.44-7.53 (m, 6H, Ar-*H*), 7.74-7.79 (m, 4H, Ar-*H*).

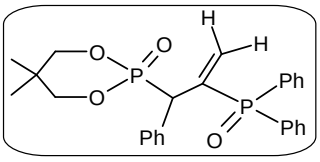
^{13}C NMR: δ 21.2, 21.7, 24.9 (dd, $^{3,4}J$(P-C) = 11.9 and 2.8 Hz, PC=C*C*H$_3$(A)CH$_3$(B)), 26.0 (dd, ^{1}J(P-C) = 136.4 Hz, ^{2}J(P-C) ~ 12.2 Hz, P*C*H$_2$), 26.1 (dd, $^{3,4}J$(P-C) = 8.8 and 3.1 Hz, PC=CCH$_3$(A)*C*H$_3$(B)), 32.5 (d, ^{3}J(P-C) = 6.9 Hz, *C*Me$_2$), 75.8, 75.9, 116.4 (dd, ^{1}J(P-C) = 102.2 Hz, ^{2}J(P-C) ~ 11.2 Hz, P*C*H=), 128.5, 128.6, 131.7, 131.8, 131.9, 133.2 (d, ^{1}J(P-C) = 99.1 Hz, P*C*), 156.6 (dd→t, $^{2,3}J$(P-C) ~ 8.4 Hz, =*C*Me$_2$).

^{31}P NMR: δ 21.5 and 31.3 (2 d, ^{3}J(P-P) ~ 7.8 Hz each).

LC-MS: *m/z* 419 [M+1]$^{+}$.

Anal. Calcd. for $C_{22}H_{28}O_4P_2$: C, 63.15; H, 6.75. Found: C, 63.31; H, 6.62.

(f) Compounds 73 and 74 [Using 1.0 mmol of allene **20**]



73

The eluant used was ethyl acetate/hexane (3:2) for compound **73** which eluted first.

Yield: 90% by NMR [**73**+**74**; using 5 mol% of Pd(PPh$_3$)$_4$ or **41** as catalyst]; 0.27 g (isolated, 58%, **73**).

Mp: 170-172 ^{o}C.

IR (KBr): 3054, 2969, 1437, 1264, 1194, 1059, 1007 cm^{-1}.

^{1}H NMR: δ 0.82 and 1.15 (2 s, 6H, 2 CH_3), 3.80-3.90 and 4.14-4.17 (2 m, 4H, OCH_2), 4.78 (dd, $^{2,3}J$(P-H) = 21.0 and 12.1 Hz, 1H, PCH_2), 5.80 (dd, $^{3,4}J$(P-H) = 20.4 and 10.0 Hz, 1H, =CH_A(*cis*)), 7.00 (dd, $^{3,4}J$(P-H) = 42.4 and 4.3 Hz, 1H, =CH_B(*trans*)), 7.14-7.15 (m, 3H, Ar-*H*), 7.27-7.53 (m, 10H, Ar-*H*), 7.59-7.64 (m, 2H, Ar-*H*).

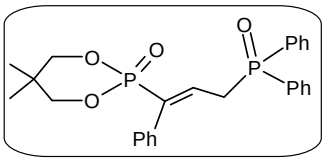
^{13}C NMR: δ 20.7, 21.8, 32.4 (d, ^{3}J(P-C) = 12.3 Hz, *C*Me$_2$), 40.5 (dd, ^{1}J(P-C) = 130.8 Hz, ^{2}J(P-C) = 15.5 Hz, P*C*H(Ph)), 75.6, 76.7, 127.4, 128.3, 128.4, 128.5, 129.4, 129.5, 129.8, 130.2, 130.8, 131.2, 132.0, 132.1, 132.2, 132.3, 134.5, 134.7, 134.8, 138.1.

^{31}P NMR: δ 16.8 and 33.3 (2 d, ^{3}J(P-P) ~ 32.8 Hz each).

LC-MS: *m/z* 467 $[M+1]^+$.

Anal. Calcd. for $C_{26}H_{28}O_4P_2$: C, 66.95; H, 6.05. Found: C, 66.85; H, 6.12.

Under solvent-free, catalyst-free conditions the yield of **73** was 95% [by NMR]; isolated yield in this case was 0.40 g (85%) by using ethyl acetate/hexane (3:2) mixture as the eluant.



74

Yield: 90% by NMR [**73**+**74**; using 5 mol% of $Pd(PPh_3)_4$ or **41** as catalyst]; 0.05 g (isolated, 10%, **74**).

Mp: 176-178 ^{o}C.

IR (KBr): 3059, 2969, 1435, 1252, 1204, 1051, 1010 cm^{-1}.

^{1}H NMR: δ 0.73 and 1.05 (2 s, 6H, 2 CH_3), 3.32 (ddd, ^{2}J(P-H) = 14.0 Hz, ^{3}J(H-H) and ^{4}J(P-H) ~ 7.8 and 1.6 Hz, 2H, PCH_2), 3.68 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 10.4 Hz, 2H, OCH_2), 3.96 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 12.8 Hz, 2H, OCH_2), 6.79-6.86 (m, 1H, =C*H*CH$_2$), 7.10 (s br, 2H, Ar-*H*), 7.30-7.31 (m, 3H, Ar-*H*), 7.46-7.58 (m, 6H, Ar-*H*), 7.64-7.68 (m, 4H, Ar-*H*).

^{13}C NMR: δ 20.9, 21.7, 32.3 (d, ^{3}J(P-C) = 7.3 Hz, *C*Me$_2$), 33.0 (dd, ^{1}J(P-C) = 66.3 Hz, ^{2}J(P-C) ~ 19.7 Hz, P*C*H$_2$), 76.2, 76.3, 128.2, 128.6, 128.8, 128.9, 129.3, 129.4, 130.9, 131.1, 132.0 (d, ^{1}J(P-C) = 101.3 Hz, P*C*),

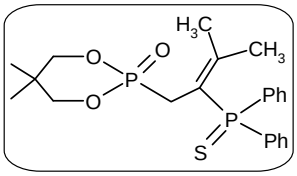
132.3, 132.5, 133.2, 133.3, 135.2 (dd, ^{1}J(P-C) = 169.8 Hz, ^{2}J(P-C) ~ 9.6 Hz, P*C*(Ph)), 137.1 (~dd, ^{2}J(P-C) = 11.0 and 8.2 Hz, =*C*HCH$_2$P).

^{31}P NMR: δ 10.2 and 28.5 (2 d, ^{4}J(P-P) = 7.0 Hz each).

LC-MS: *m/z* 467 $[M+1]^+$.

Anal. Calcd. for $C_{26}H_{28}O_4P_2$: C, 66.95; H, 6.05. Found: C, 66.98; H, 6.12.

(g) Compound 75 [Using 1.0 mmol of allene **19**]



The eluant used was ethyl acetate/hexane (3:2).

Yield: 95% by NMR; 0.37 g (isolated, 85%).

Mp: 136-138 °C.

IR (KBr): 3057, 2963, 2874, 1474, 1437, 1281, 1100, 1061, 1011 cm^{-1}.

^{1}H NMR: δ 0.92 and 0.98 (2 s, 6H, 2C*H*$_3$), 1.77 and 2.11 (2s br, 6H, C=C(C*H*$_3$)$_2$), 3.13-3.22 (m, 2H, PC*H*$_2$), 3.82-3.94 (m, 4H, 2 OC*H*$_2$), 7.46 (s br, 6H, Ar-*H*), 7.93-7.94 (m, 4H, Ar-*H*).

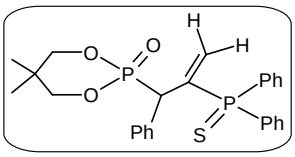
^{13}C NMR: δ 21.5, 21.6, 25.4 (d, ^{3}J(P-C) = 13.0 Hz, =C*C*H$_3$(A)), 26.5 (d, ^{3}J(P-C) = 13.0 Hz, =C*C*H$_3$(B)), 27.8 (dd, ^{1}J(P-C) = 134.5 Hz, ^{2}J(P-C) = 16.0 Hz, P*C*H$_2$), 32.5 (d, ^{3}J(P-C) = 8.0 Hz, *C*Me$_2$), 75.3, 75.4, 116.9 (dd, ^{1}J(P-C) = 81.0 Hz, ^{2}J(P-C) = 10.0 Hz, P*C*=), 128.5, 128.6, 131.2, 132.1, 132.2, 133.1, 133.9, 155.6 (dd→t, $^{2,3}J$(P-C) ~ 9.2 Hz, =*C*Me$_2$).

^{31}P NMR: δ 22.2 and 44.6 (2 d, ^{3}J(P-P) ~ 8.5 Hz each).

LC-MS: *m/z* 435 $[M+1]^+$.

Anal. Calcd. for $C_{22}H_{28}O_3P_2S$: C, 60.82; H, 6.50. Found: C, 60.75; H, 6.59.

(h) Compound 76 [Using 1.0 mmol of allene **20**]



This compound was precipitated from ethyl acetate solution (4 mL) at 30 °C as a white solid.

Yield: 98% by NMR: 0.42 g (isolated, 88%).

Mp: 192-194 ^{o}C.

IR (KBr): 2967, 2876, 1476, 1435, 1285, 1061, 1011 cm^{-1}.

^{1}H NMR: δ 0.88 and 1.19 (2 s, 6H, 2 CH_3), 3.82-3.90 (m, 2H, OCH_ACH_B), 3.98-4.01 (m, 1H, OCH$_A$$H_B$), 4.41-4.45 (m, 1H, OC$H_AH_B$), 5.30 (dd, $^{2,3}J$(P-H) = 20.4 and 15.4 Hz, 1H, PC*H*(Ph)), 5.68 (dd, $^{3,4}J$(P-H) = 21.2 and 4.8 Hz, 1H, =C*H*(*cis*)), 6.98-7.11 (m, 4H, =C*H*(*trans*) + Ar-*H*), 7.19-7.23 (m, 2H, Ar-*H*), 7.31-7.57 (m, 8H, Ar-*H*), 7.69-7.74 (m, 2H, Ar-*H*).

^{13}C NMR: δ 20.8, 22.0, 32.5 (d, ^{3}J(P-C) = 7.0 Hz, *C*Me$_2$), 40.4 (dd, ^{1}J(P-C) = 128.4 Hz, ^{2}J(P-C) = 13.6 Hz, P*C*H(Ph)), 76.8, 127.4, 128.0, 128.2, 128.4, 128.5, 128.6, 129.4, 129.5, 129.8 (d, ^{1}J(P-C) = 83.0 Hz, P*C*), 130.8 (d, ^{1}J(P-C) = 84.6 Hz, P*C*), 131.5, 131.9, 132.3, 132.4, 132.5, 133.1 (dd→t, $^{2,3}J$(P-C) ~ 6.8 Hz, C=*C*H$_2$), 134.5, 138.1 (dd, ^{1}J(P-C) = 75.8 Hz, ^{2}J(P-C) = 13.6 Hz, *C*=CH$_2$).

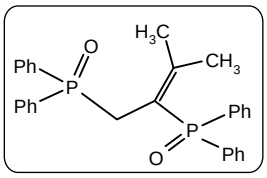
^{31}P NMR: δ 16.4 and 50.6 (2 d, ^{3}J(P-P) ~ 40.0 Hz each).

LC-MS: *m/z* 483 [M+1]$^{+}$.

Anal. Calcd. for $C_{26}H_{28}O_3P_2S$: C, 64.72; H, 5.85. Found: C, 64.85; H, 5.80.

This compound was crystallized from ethyl acetate (2 mL). X-ray structure analysis was performed on this sample.

(i) Compound 77 [Using 1.0 mmol of allene **25**]



The eluant used was ethyl acetate/hexane (4:1).

Yield: 98% by NMR; 0.42 g (isolated, 90%).

IR (KBr): 3056, 2913, 1717, 1611, 1483, 1447, 1167, 1117, 1028 cm^{-1}.

^{1}H NMR: δ 1.64-1.65 and 1.99-2.04 (2 m, 6H, C=C(CH_3)$_2$), 3.74 (dd→t, $^{2,3}J$(P-H) ~ 13.6 Hz, 2H, PCH_2), 7.27-7.40 (m, 12H, Ar-*H*), 7.53-7.57 (m, 4H, Ar-*H*), 7.70-7.78 (m, 4H, Ar-*H*).

^{13}C NMR: δ 25.5 (d, ^{3}J(P-C) = 11.8 Hz, =C*C*H$_3$(A)CH$_3$(B)), 26.2 (d, ^{3}J(P-C) = 7.3 Hz, PC=CCH$_3$(A)*C*H$_3$(B)), 32.3 (dd, ^{1}J(P-C) = 67.0 Hz, ^{2}J(P-C) ~

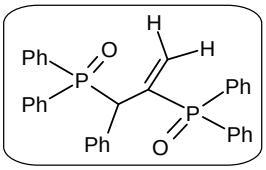
12.2 Hz, P*C*H$_2$), 117.5 (dd, ^1J(P-C) = 100.5 Hz, ^2J(P-C) ~ 9.6 Hz, *C*=C(CH$_3$)$_2$), 128.3, 128.4, 131.0, 131.3, 131.6, 131.7, 131.8, 132.8, 132.9, 133.8, 133.9, 156.6 (dd→t, $^{2,3}J$(P-C) ~ 7.6 Hz, =*C*(Me)$_2$).

^{31}P NMR: δ 28.5 and 31.1 (2 d, ^3J(P-P) ~ 5.4 Hz each).

LC-MS: *m/z* 471 [M+1]$^+$.

Anal. Calcd. for $C_{29}H_{28}O_2P_2$: C, 74.03; H, 6.00. Found: C, 74.18; H, 6.11.

(j) Compound 78 [Using 1.0 mmol of allene **26**]



Compound **78** was precipitated from ethyl acetate solution (4 mL) at 30 ^{o}C as white solid.

Yield: 98% by NMR, 0.49 g (isolated, 95%).

Mp: 188-190 ^{o}C [lit. 192-195 ^{o}C[57a]].

IR (KBr): 3056, 2965, 1437, 1181, 1117, 1098 cm^{-1}.

^{1}H NMR: δ 5.14 (dd, $^{2,3}J$(P-H) = 11.0 and 7.4 Hz, 1H, PC*H*(Ph)), 5.46 (d, ^3J(P-H) = 19.2 Hz, 1H, =CH_A(cis)), 6.91-6.99 (m, 3H, =CH_B(*trans*) + Ar-*H*), 7.13-7.57 (m, 21H, Ar-*H*), 8.18-8.22 (m, 2H, Ar-*H*).

^{13}C NMR: δ 44.7 (dd, ^1J(P-C) = 58.5 Hz, ^2J(P-C) ~ 14.4 Hz, P*C*H(Ph)), 126.9, 127.9, 128.0, 128.3, 128.4, 128.6, 128.7, 129.1, 130.2, 130.6, 130.9, 131.3, 131.9, 133.1, 134.0, 140.9 (d, ^1J(P-C) = 86.9 Hz, P*C*).

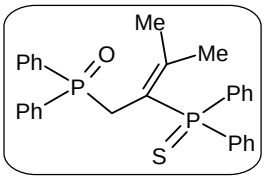
^{31}P NMR: δ 32.6 and 32.9 (2 d, ^3J(P-P) ~26.5 Hz each).

LC-MS: *m/z* 517 [M-1]$^+$.

Anal. Calcd. for $C_{33}H_{28}O_2P_2$: C, 76.44; H, 5.44. Found: C, 76.25; H, 5.36.

This compound is reported in literature.[57a]

(k) Compound 79 [Using 1.0 mmol of allene **25**]



The eluant used was ethyl acetate/hexane (3:2).

Yield: 95% by NMR; 0.41 g (isolated, 84%).

Mp: 130-132 ^{o}C.

IR (KBr): 3054, 2919, 2851, 1601, 1435, 1192, 1098 cm^{-1}.

^{1}H NMR: δ 1.66-1.68 and 1.88-1.89 (2 m, 6H, 2 CH_3, =C(CH_3)$_2$), 3.82 (dd, $^{2,3}J$(P-H) = 16.4 and 13.2 Hz, 2H, PCH_2), 7.24-7.38 (m, 12H, Ar-*H*), 7.62-7.67 (m, 4H, Ar-*H*), 7.75-7.81 (m, 4H, Ar-*H*).

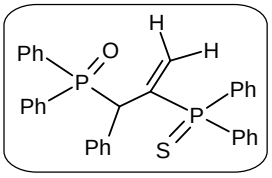
^{13}C NMR: δ 26.3 (d, ^{3}J(P-C) = 12.3 Hz, =C*C*H$_3$(A)), 26.6 (d, ^{3}J(P-C) = 8.7 Hz, =C*C*H$_3$(B)), 33.3 (dd, ^{1}J(P-C) = 65.9 Hz, ^{2}J(P-C) = 14.4 Hz, P*C*H$_2$), 117.4 (dd, ^{1}J(P-C) = 82.6 Hz, ^{2}J(P-C) = 9.0 Hz, (P)*C*=CMe$_2$), 128.3, 128.4, 130.6, 130.7, 130.8, 130.9, 131.0, 131.1, 131.3, 131.5, 131.6, 131.7, 131.9, 132.0, 133.5 (d, ^{1}J(P-C) = 85.6 Hz, P*C*), 134.0 (d, ^{1}J(P-C) = 94.3 Hz, P*C*), 155.7 (dd, $^{2,3}J$(P-C) = 15.3 and 7.0 Hz, PC=*C*Me$_2$).

^{31}P NMR: δ 26.8 and 45.1 (2 d, ^{3}J(P-P) = 6.5 Hz each).

LC-MS: *m/z* 487 [M+1]$^{+}$.

Anal. Calcd. for $C_{29}H_{28}OP_2S$: C, 71.59; H, 5.80. Found: C, 71.45; H, 5.86.

(l) Compound 80 [Using 1.0 mmol of allene **26**]



This compound was precipitated from ethyl acetate solution (4 mL) at 30 ^{o}C.

Yield: 95% by NMR; 0.43 g (isolated, 80%).

Mp: 194-196 ^{o}C (white solid).

IR (KBr): 3056, 2868, 1491, 1435, 1186, 1100 cm^{-1}.

^{1}H NMR: δ 5.43 (d, ^{2}J(P-H) = 21.6 Hz, 1H, =CH_A(cis)), 5.71 (dd, $^{2,3}J$(P-H) = 14.6 and 8.5 Hz, 1H, PC*H*(Ph)), 6.90-6.92 (m, 3H, Ar-*H*), 7.10-7.57 (m, 21H, =CH_B(*trans*) + Ar-*H*), 8.24-8.28 (m, 2H, Ar-*H*).

^{13}C NMR: δ 45.0 (dd, ^{1}J(P-C) = 64.1 Hz, ^{2}J(P-C) ~ 12.0 Hz, P*C*H(Ph)), 127.0, 127.8, 127.9, 128.1, 128.4$_2$, 128.4$_9$, 128.5, 128.6, 128.8 (d, ^{1}J(P-C) = 110.0 Hz, P*C*), 129.3, 130.5, 130.6, 130.9, 131.0, 131.3, 131.5, 131.9, 132.0, 132.1, 132.2, 132.4, 132.7, 133.1, 133.6, 139.6 (d, ^{1}J(P-C) = 67.7 Hz, *C*=CH_2).

^{31}P NMR: δ 32.3 and 49.6 (2 d, ^{3}J(P-P) ~ 32.5 Hz each).

LC-MS: *m/z* 535 $[M+1]^+$.

Anal. Calcd. for $C_{33}H_{28}OP_2S$: C, 74.14; H, 5.28. Found: C, 74.31; H, 5.21.

3.8 Pd-catalyzed and solvent-free, catalyst-free hydro(thio)phosphonylation/hydro(thio)phosphinylation of alkynes

3.81 Pd-catalyzed hydro(thio)phosphonylation/hydro(thio)phosphinylation of alkynes

(i) Reactions of alkynes 39-40 with 4-6 and 8: Synthesis of vinyl-phosphonates/-phosphine oxides

General procedure for 48 and (*E*)-49: A mixture of the alkyne $(OCH_2CMe_2CH_2O)PC{\equiv}CMe$ (**39**) (1.0 mmol), $(OCH_2CMe_2CH_2O)P(O)H$ (**4**) (1.05 mmol) and $Pd(PPh_3)_4$ or **41** (5.0 mol%) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C for 6-18 h. The reaction mixture was cooled to room temperature, quenched with distilled water (2 mL) and extracted with ethyl acetate (2 x 10 mL). The organic layer was dried (Na_2SO_4), solvent removed under reduced pressure and the pure compounds **48** and (*E*)-**49** were purified by column chromatography (silica gel; hexane-ethyl acetate).

Products **43**, (*E*)-**44**, (*E*)-**46**, **48**, (*E*)-**49**, (*E*)-**51**, (*E*)-**65**, (*E*)-**67**, (*Z*)-**67**, (*E*)-**69** and (*E*)-**71** were also synthesized by this method. Among these, compounds **48** and (*E*)-**49** are known.[106] Data for other compounds, as appropriate, are already given above.

(a) Reaction of alkyne 39 with cyclic phosphite 4

Compound 48

Yield [using **41**]: Quantitative by NMR [(**48**+**49)** (ratio 3:2)]; 0.12 g (isolated, 35%). This is a known compound[106]

Compound (*E*)**-49**

Yield [using **41**]: Quantitative by NMR [(**48**+**49)** (ratio 3:2)]; 0.09 g (isolated, 25%). Yield [using $Pd(PPh_3)_4$]: Quantitative by NMR [(*E*)**-49]**; 0.24 (isolated, 70%,). This is a known compound[106]

(b) Reaction of alkyne 40 with cyclic phosphite 4

Compound 43 [Spectroscopic and analytical data in section 3.71]

Yield [using **41**]: 90% by NMR [(**43+44)**; (ratio 3:2)] 0.20 g (isolated, 50%)]

Compound (*E*)**-44** [Spectroscopic and analytical data in section 3.71]

Yield [using **41**]: 90% by NMR [(**43+44), (**ratio 3:2)]; 0.090 g (isolated, 22%)]. Yield [using $Pd(PPh_3)_4$]: 90% by NMR [(*E*)**-44]**; 0.28 g (isolated, 72%].

(c) Reaction of alkyne 39 with $Ph_2P(O)H$ (5)

Compound (*E*)**-65** [Spectroscopic and analytical data in section 3.71]

Yield: Quantitative by NMR; 0.25 g (isolated, 73%).

(d) Reaction of alkyne 39 with $(OCH_2CMe_2CH_2O)P(S)H$ (6)

Compound (*E*)**-51** [Spectroscopic and analytical data in section 3.71]

Yield: 90% by NMR; 0.27 g (isolated, 75%).

(e) Reaction of alkyne 39 with $Ph_2P(S)H$ (8)

Compound (*E*)**-67** [Spectroscopic and analytical data in section 3.71]

Yield: Quantitative by NMR; 0.32 g (isolated, 78%).

(f) Reaction of alkyne 40 with $(OCH_2CMe_2CH_2O)P(S)H$ (6)

Compound (*E*)**-46** [Spectroscopic and analytical data in section 3.71]

Yield: 90% by NMR; 0.32 g (isolated, 80%).

(g) Reaction of alkyne 40 with $Ph_2P(S)H$ (8)

Compound (*E*)-**71** [Spectroscopic and analytical data in section 3.71]

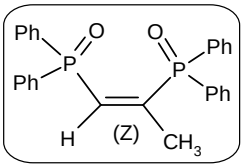
Yield: 82% by NMR; 0.13 g (isolated, 68%).

(h) Reaction of alkyne 40 with $Ph_2P(O)H$ (5)

Compound (*E*)-**69** [Spectroscopic and analytical data in section 3.71]

Yield: Quantitative by NMR [(*E*)-**69**+(*Z*)-**69**, ratio 3:2]; 0.19 g (isolated 42%, (*E*)-**69**). The eluant used was ethyl acetate/hexane (4:1).

Compound (*Z*)-**69**



The eluant used was ethyl acetate, after eluting compound (*E*)-**69**.

Yield: Quantitative by NMR [(*E*)-**69**+(*Z*)-**69**]; 0.18 g (isolated 40%, (*Z*)-**69**).

IR (Neat): 3055, 2922, 2849, 1713, 1437, 1198, 1119 cm^{-1}.

^1H NMR: δ 2.21 (d, ^3J(P-H) = 11.2 Hz, 3H, =CC*H*$_3$), 7.04 (dd, $^{2,3}J$(P-H) = 17.4 and 37.8 Hz, 1H, =C*H*), 7.31-7.44 (m, 12H, Ar-*H*), 7.59-7.71 (m, 8H, Ar-*H*).

^{13}C NMR: δ 26.5 (dd, ^2J(P-C) = 16.6 Hz, ^3J(P-C) = 11.9 Hz, =C*C*H$_3$), 128.1$_0$, 128.1$_6$, 128.2, 128.3, 130.3, 130.8, 130.9, 131.3, 131.9, 132.1, 132.3, 134.0 (d, ^1J(P-C) = 106.8 Hz, P*C*), 137.8 (dd, ^1J(P-C) = 96.5 Hz, ^2J(P-C) = 8.1 Hz, (P)*C*H=C(P)Me), 153.0 (d, ^1J(P-C) = 84.8 Hz, P*C*CH$_3$). This spectrum is illustrated in Fig. 23.

^{31}P NMR: δ 18.8 and 27.8 (2 d, ^3J(P-P) ~ 16.2 Hz each).

LC-MS: *m/z* 441 $[M-1]^+$.

Anal. Calcd. for $C_{27}H_{24}O_2P_2$: C, 73.30; H, 5.47. Found: C, 73.15; H, 5.56.

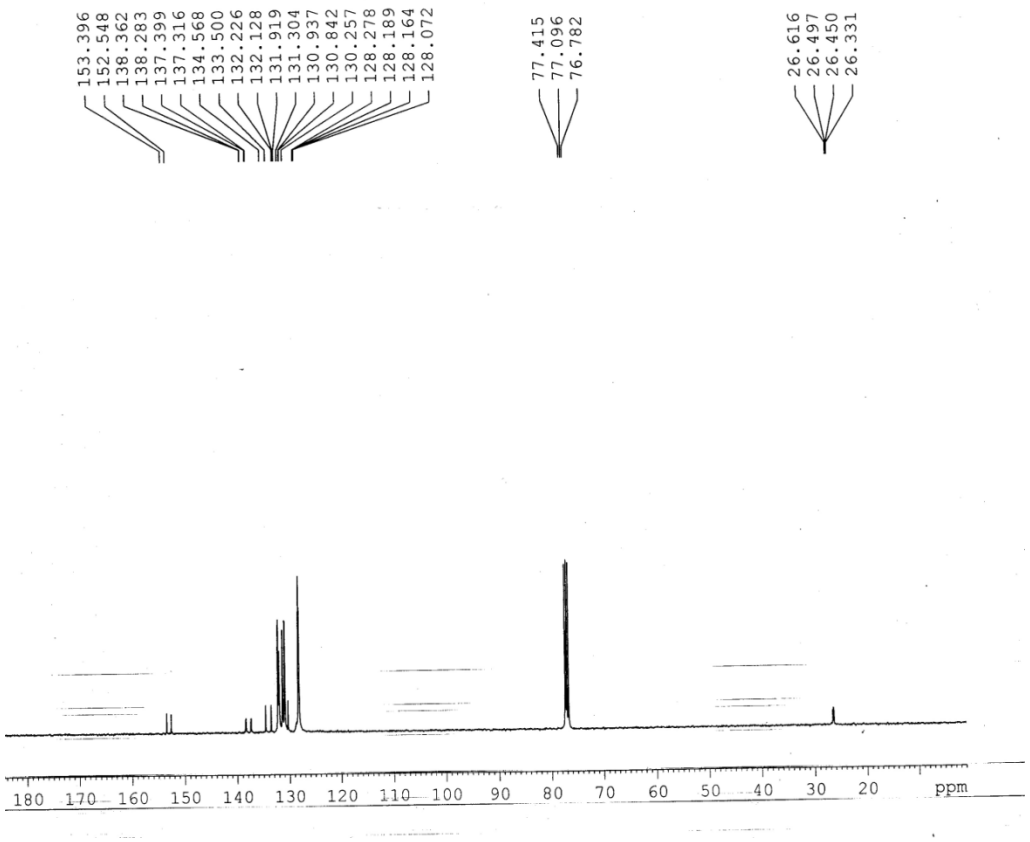
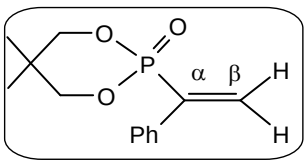


Fig. 23. ^{13}C NMR spectrum of compound (*Z*)-**69**

(ii) Reaction of PhC≡CH with (OCH$_2$CMe$_2$CH$_2$O)P(O)(H) (**4**)*: Synthesis of 81-82*

These compounds (**81-82**) were prepared by using PhC≡CH (1.0 mmol) and cyclic phosphite **4** (1.05 mmol) in a manner similar to the reactions described in section 3.81(i). The reaction mixture contained products **81** and **82** in the ratio 4:1 (^{31}P NMR).

Compounds 81 and 82



81

This compound was eluted after **82** by using ethyl acetate/hexane (2:3) mixture.

Yield: 90% by NMR; 0.19 g (isolated, 75%).

Mp: 140-142 ^{o}C.

IR (KBr): 3057, 2965, 2886, 1493, 1480, 1262, 1057, 1003 cm$^{-1.}$

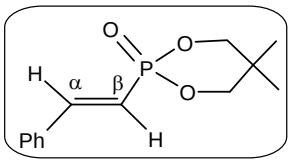
^{1}H NMR: δ 0.90 and 1.14 (2 s, 6H, 2 CH_3), 3.83 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 10.4 Hz, 2H, OCH_2), 4.10 (dd→t, ^{3}J(P-H) = ^{2}J(H-H) ~ 13.0 Hz, 2H, OCH_2), 6.20 (d, ^{3}J(P-H) = 45.6 Hz, 1H, =CH_A(trans)), 6.30 (d, ^{3}J(P-H) = 20.0 Hz, 1H, =CH_B(cis)), 7.36-7.37 (m, 3H, Ar-*H*), 7.55-7.57 (m, 2H, Ar-*H*).

^{13}C NMR: δ 21.3, 21.8, 32.6 (d, ^{3}J(P-C) = 6.5 Hz, C(*C*H_3)$_2$), 76.2, 76.3, 127.6, 127.7, 128.6, 131.7, 131.9. The doublet due to the ^{1}J(P-C) was not clear.

^{31}P NMR: δ 11.5.

LC-MS: *m/z* 253 $[M+1]^+$.

Anal. Calcd. for $C_{13}H_{17}O_3P$: C, 61.90; H, 6.79. Found: C, 61.82; H, 6.88.



82

This compound was eluted from ethyl acetate/hexane (3:7) mixture.

Yield: 90% by NMR; 0.09 g (isolated, 5%).

^{31}P NMR: δ 15.5 [lit: 14.6[14]]. This is a known compound.[14]

3.82 Solvent-free, catalyst-free hydrophosphinylation reaction of $Ph_2P(O)C{\equiv}CMe$ (40) with $Ph_2P(O)H$ (5): Synthesis of (Z)-69 and (E)-69 isomers

A mixture of alkyne **40** (0.24 g, 1.0 mmol) and $Ph_2P(O)H$ (**5**) (0.212 g, 1.05 mmol) was heated at 100 ^{o}C for one hour in air. Progress of the reaction was monitored by ^{31}P NMR and TLC. Analytically pure compounds [(*Z*)-**69** and (*E*)-**69**)] were separated by column chromatography (ethyl acetate/hexane). When the reaction mixture was heated further at 120 ^{o}C for 18 h, isomer (*E*)-**69** was remaining in the reaction mixture but isomer (*Z*)-**69** was fully converted to **68**.

Compound (*E*)-**69** [Spectroscopic and analytical data in section 3.71]

The eluant used was ethyl acetate/hexane (4:1).

Yield: Quantitative by NMR [(*E*)-**69**+(*Z*)-**69**, ratio 3:2]; 0.19 g (isolated 42%, (*E*)-**69**).

Compound (*Z*)-**69** [Spectroscopic and analytical data in section 3.81(i)]

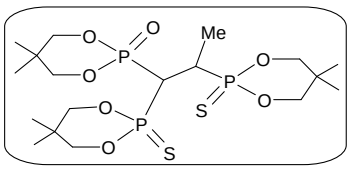
The eluant used was ethyl acetate, after eluting compound (*E*)-**69**.

Yield: Quantitative by NMR [(*E*)-**69**+(*Z*)-**69**, ratio 3:2]; 0.18 g (isolated 40%, (*Z*)-**69**).

3.9 P(*n*-Bu)$_3$ catalyzed hydrothiophosphonylation/hydro(thio)phosphinylation reactions of alkynes: Synthesis of compounds 83-87

General procedure for 83: A mixture of $(OCH_2CMe_2CH_2O)P(O)C{\equiv}CMe$ (**39)** (1.0 mmol) and $(OCH_2CMe_2CH_2O)P(S)H$ (**6**) (2.0 mmol) and P(*n*-Bu)$_3$ (20 mol%) in ethanol (3 mL) was heated under reflux for 1 h. Solvent was removed *in vacuo* and the pure compound **83** was isolated by passing through the silica gel column (ethyl acetate/hexane).

(a) Compound 83



The eluant used was ethyl acetate/hexane (3:2).

Yield: Quantitative by NMR; 0.30 g (isolated, 58%).

Mp: 168-172 ^{o}C.

IR (KBr): 2967, 2924, 2886, 1472, 1372, 1269, 1154, 1047 cm^{-1}.

^{1}H NMR: δ 0.85, 0.93, 1.01, 1.19. 1.25 (5 s, 18H, 6 C*H*$_3$), 1.73 (dd, ^{3}J(P-H) = 18.0 Hz, ^{3}J(H-H) ~ 6.8 Hz, 3H, (S)PCH(C*H*$_3$)), 3.26-3.35 (m, 1H, (S)PC*H*(CH$_3$)), 3.73-4.22 (m, 8H, 4 OC*H*$_2$), 4.30-4.47 (m, 5H, (O)PC*H* + 2 OC*H*$_2$).

^{13}C NMR: δ 11.8 (dd→t, $^{2,3}J$(P-C) ~ 5.1 Hz, (S)PCH(*C*H$_3$)), 21.0, 21.3, 22.0, 22.3 and 22.7 (5 s, 6 *C*H$_3$), 32.5 (d, ^{3}J(P-C) = 7.7 Hz, *C*(CH$_3$)$_2$), 33.2-33.3 (m, *C*(CH$_3$)$_2$), 36.8 (d, ^{1}J(P-C) = 104.0 Hz, (S)P*C*H(CH$_3$)), 40.3 (dd, ^{1}J(P-C) = 127.8 Hz and 90.0 Hz, (S)P*C*HP(O)), 73.8 (d, ^{2}J(P-C) = 6.8 Hz, O*C*H$_2$), 74.2 (d, ^{2}J(P-C) = 5.6 Hz, O*C*H$_2$), 75.3 (d, ^{2}J(P-C) = 6.8 Hz, O*C*H$_2$), 75.8 (d, ^{2}J(P-C) = 6.7 Hz, O*C*H$_2$), 77.7 (d, ^{2}J(P-C) = 7.3 Hz, O*C*H$_2$). This spectrum is illustrated in Fig. 24.

^{31}P NMR: δ 9.3 (s), 90.5 and 104.7 (2 d, ^{3}J(P-P) = 77.0 Hz each).

LC-MS: *m/z* 521 [M+1]$^{+}$.

Anal. Calcd. for $C_{18}H_{35}O_7P_3S_2$: C, 41.53; H, 6.78. Found: C, 41.65; H, 6.71.

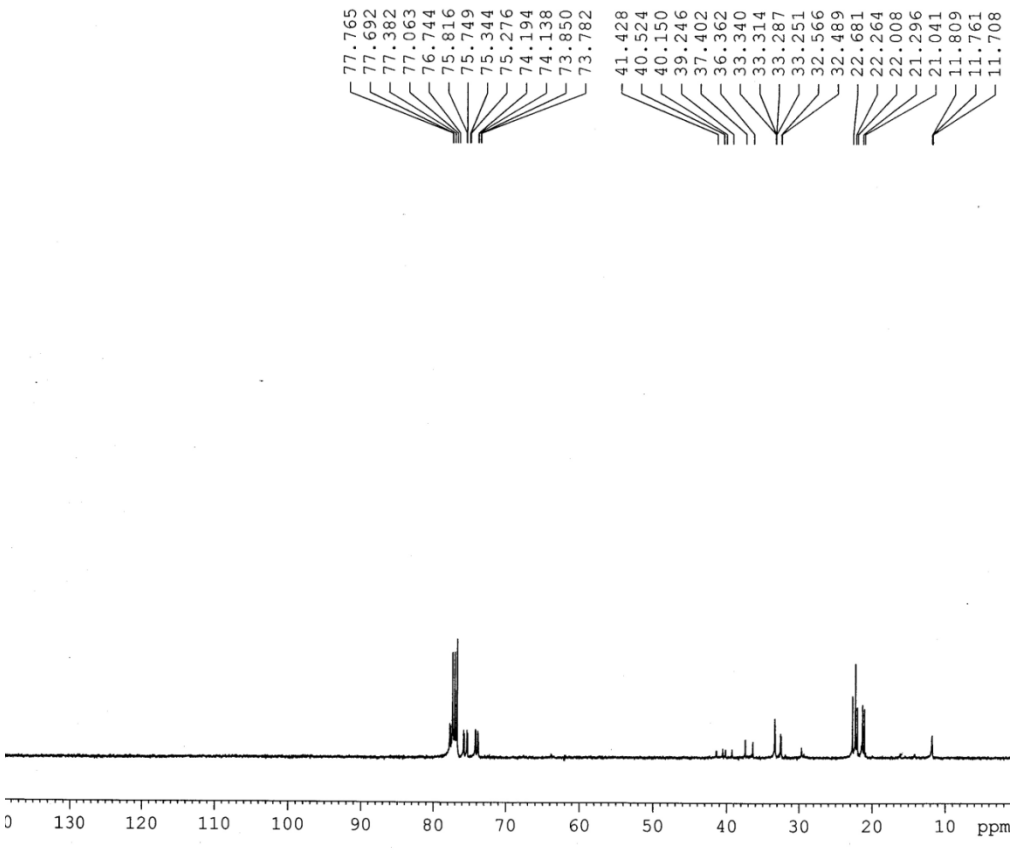
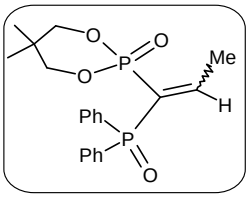


Fig.24. ^{13}C NMR spectrum of compound **83**

(b) Compounds 84 and 85 [Using **39 (**1.0 mmol) and $Ph_2P(O)H$ (**5**) (2.0 mmol)]



84

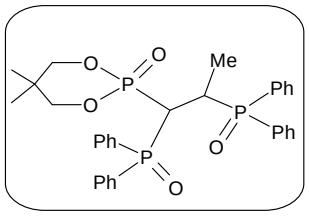
Compound **85** (0.30 g) was precipitated from ethyl acetate solution (3 mL) at -5 ^{o}C. The residue was chromatographed using ethyl acetate/hexane (1:1) to obtain compound **84.**

Yield: 90% by NMR [**84+85**]; 0.080 g (isolated along with $(n\text{-Bu})_3P(O)$, 20%, **84**).

^{31}P NMR: δ 5.9 and 31.0 (2 d, ^{3}J(P-P) ~ 42.9 Hz each).

LC-MS: *m/z* 391 $[M+1]^{+}$.

The ^{1}H and ^{13}C NMR spectra were complicated because of the signals due to $(n\text{-Bu})_3P(O)$.



85

Compound **85** was precipitated from ethyl acetate solution (3 mL) at -5 ^{o}C.

Yield: 90% by NMR [**84**+**85**]; 0.30 g (isolated, 50%, **85**).

Mp: 154-160 ^{o}C.

IR (KBr): 3057, 2975, 2876, 1647, 1474, 1439, 1273, 1206, 1171, 1115, 1061, 1015 cm^{-1}.

^{1}H NMR: δ 0.85, 0.93, (2 s, 6H, 2 CH_3), 1.54 (dd, ^{3}J(P-H) = 17.2 Hz, ^{3}J(H-H) = 7.2 Hz, 3H, (O)PCH(CH_3)), 3.36-3.64 (m, 3H, (S)PCH(CH_3) + OCH_2(A)), 3.70-3.75 (m, 2H, OCH_2(B)), 3.98-4.11 (m, 1H, (O)PCH), 7.36-7.45 (m, 12H, Ar-H), 7.56-7.60 (m, 2H, Ar-H), 7.78-7.90 (m, 4H, Ar-H), 8.06-8.11 (m, 2H, Ar-H).

^{13}C NMR: δ 13.2 (dd→t, $^{2,3}J$(P-C) ~ 5.1 Hz, (S)PCH(*C*H$_3$)), 21.7, 21.8, 32.1 (d, ^{1}J(P-C) ~ 66.0 Hz, (O)P*C*H(CH$_3$)), 32.4 (d, ^{3}J(P-C) ~ 7.0 Hz, *C*(CH$_3$)$_2$), 36.7 (dd, ^{1}J(P-C) ~ 131.5 Hz, 54.5 Hz, (O)P*C*HP(O)), 75.5 (d, ^{2}J(P-C) = 6.0 Hz, O*C*H$_2$), 76.0 (d, ^{2}J(P-C) = 7.0 Hz, O*C*H$_2$), 128.1, 128.2 (d, J = 2.0 Hz), 128.3, 128.5, 128.6 (d, J(P-C) = 4.0 Hz), 128.7, 130.3 (d, ^{1}J(P-C) = 65.0 Hz, P*C*), 130.9, 131.0, 131.3, 131.5, 131.6, 131.7, 131.8$_1$ (dd, ^{1}J(P-C) = 102.0 Hz, J(P-C) = 6.0 Hz, P*C*), 131.8$_3$ (d, J(P-C) = 3.0 Hz), 131.9 (d, J(P-C) = 3.0 Hz), 132.1 (d, J(P-C) = 3.0 Hz), 132.2 (d, J(P-C) = 2.0 Hz), 132.3, 132.4, 133.1.

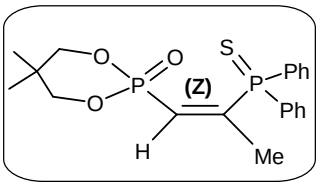
^{31}P NMR: δ 14.5 (s), 31.7 and 34.1 (2 d, ^{3}J(P-P) = 34.3 Hz each).

LC-MS: *m/z* 391 [M-202+1]$^{+}$.

Anal. Calcd. for $C_{32}H_{35}O_5P_3$: C, 64.86; H, 5.95. Found: C, 64.72; H, 5.91.

(c) Compounds (*E*)-**67** and (*Z*)-**67** [Using **39** (1.0 mmol) and $Ph_2P(S)H$ (**8**) (2.0 mmol)] [Spectroscopic and analytical data in section 3.71]

Yield: 88% by NMR [(*E*)-**67**+(*Z*)-**67**]; 0.13 g (isolated, 32%, (*E*)-**67**).



(*Z*)-**67**

Compound (*Z*)-**67** was precipitated from ethyl acetate solution (2 mL) at -5 ^{o}C.

Yield: 88% by NMR [(*E*)-**67**+(*Z*)-**67**]; 0.16 g (isolated, 40%, (*Z*)-**67**).

Mp: 150-154 ^{o}C.

IR (KBr): 3057, 2965, 1630, 1474, 1439, 1275, 1250, 1100, 1057, 1005 cm^{-1}.

^{1}H NMR: δ 0.90, 1.03 (2 s, 6H, 2 C*H*$_3$), 2.13 (d, ^{3}J(P-H) = 12.4 Hz, 3H, (S)PC(C*H*$_3$)), 3.71-3.78 and 3.96-4.01 (2 m, 4H, 2 OC*H*$_2$), 6.37 (dd, $^{2,3}J$(P-H) = 40.6 and 11.0 Hz, 1H, (O)PC*H*)), 7.46-7.48 (m, 6H, Ar-*H*), 7.98-8.03 (m, 4H, Ar-*H*).

^{13}C NMR: δ 21.1, 21.7, 27.3 (dd, $^{2,3}J$(P-C) = 21.9 and 13.8 Hz, (S)PC(*C*H$_3$)), 32.3 (d, ^{3}J(P-C) = 6.2 Hz, C(*C*H$_3$)$_2$), 76.4$_0$, 76.4$_3$, 127.7 (dd, ^{1}J(P-C) = 183.5 Hz, ^{2}J(P-C) ~ 8.3 Hz (O)PC), 128.3, 128.4, 128.8, 129.0, 130.8 (d, ^{1}J(P-C) = 83.7 Hz, P*C*), 131.9$_2$, 131.9$_5$, 132.1, 132.2, 132.4, 153.2 (dd, ^{1}J(P-C) = 68.4 Hz, ^{2}J(P-C) = 4.5 Hz, P*C*CH$_3$).

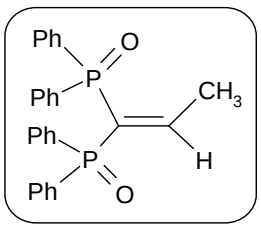
^{31}P NMR: δ 4.6 and 41.4 (2 d, ^{3}J(P-P) = 18.5 Hz each).

LC-MS: *m/z* 405 [M-1]$^{+}$.

Anal. Calcd. for $C_{20}H_{24}O_3P_2S$: C, 59.11; H, 5.95. Found: C, 59.32; H, 5.88.

X-ray structure analysis was performed on the sample crystallized from ethyl acetate/hexane (4:1) mixture.

(d) Compounds 86 and **87** [Using **40 (**1.0 mmol) and $Ph_2P(O)H$ (**5**) (2.0 mmol)]



86

Compound **87** (0.30 g) was precipitated from ethyl acetate solution (3 mL) at -5 ^{o}C. The residue was chromatographed using ethyl acetate/hexane (1:1) to obtain compound **86** (R_f is higher than that for compound **87**).

Yield: 80% by NMR [**86**+**87**]; 0.050 g (isolated 10%, **86**).

IR (KBr): 3056, 2975, 2884, 2211, 1601, 1472, 1437, 1279, 1101 cm^{-1}.

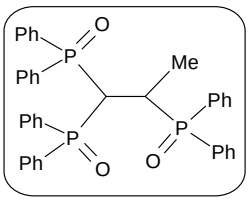
^{1}H NMR: δ 2.06 (s br, CH_3), 6.85-7.02 (m, 1H, =CHCH$_3$), 7.25-7.43 (m, 12H, Ar-*H*), 7.54-7.59 (m, 4H, Ar-*H*), 7.74-7.79 (m, 4H, Ar-*H*).

^{13}C NMR: δ 19.3 (dd, $^{2,3}J$(P-C) = 15.9, 8.3 Hz, =CH(*C*H$_3$)), 127.8, 127.9, 128.4, 128.5, 131.3 (d, ^{1}J(P-C) = 105.9 Hz, P*C*), 131.6, 131.7, 132.3, 132.4, 132.5, 162.7 (d, ^{2}J(P-C) = 3.8 Hz, =*C*(CH$_3$)).

^{31}P NMR: δ 23.9 and 30.3 (2 d, ^{2}J(P-P) ~ 38.1 Hz each).

LC-MS: *m/z* 441 [M-1]$^{+}$.

Anal. Calcd. for $C_{27}H_{24}O_2P_2$: C, 73.30; H, 5.47. Found: C, 73.45; H, 5.42.



87

Compound **87** was precipitated from ethyl acetate solution (3 mL) at -5 ^{o}C.

Yield: 80% by NMR [**86**+**87**]; 0.27 g (isolated, 60%, **87**).

Mp: 238-240 ^{o}C.

IR (KBr): 3054, 2955, 2928, 2876, 1588, 1481, 1435, 1184, 1115 cm^{-1}.

^{1}H NMR: δ 1.41 (dd, ^{3}J(P-H) = 17.6 Hz, ^{3}J(H-H) = 7.6 Hz, 3H, PCH(CH_3)), 3.49-3.65 (m, 1H, PCH(CH$_3$)), 4.89-5.01 (m, 1H, PCHP), 7.11-7.44 (m, 18H, Ar-*H*), 7.50-7.57 (m, 4H, Ar-*H*), 7.75-7.81 (m, 8H, Ar-*H*).

^{13}C NMR: δ 14.5 (d, ^{2}J(P-C) = 6.7 Hz, (O)PCH(*C*H$_3$)), 33.5 (dd, ^{1}J(P-C) = 67.0 Hz, ^{2}J(P-C) ~ 2.2 Hz, (O)P*C*H(CH$_3$)), 41.5 (ddd, ^{1}J(P-C) ~ 58.4 Hz and 52.1 Hz, ^{2}J(P-C) ~ 2.8 Hz, (O)P*C*P(O)), 127.8, 127.9, 128.1, 128.2, 128.3, 128.4$_0$, 128.4$_4$, 128.5, 130.4, 130.6, 130.8, 130.9, 131.0, 131.1, 131.2$_9$, 131.3$_2$, 131.4, 131.5, 131.5$_4$, 131.5$_7$, 131.6, 131.9, 132.1, 132.1$_2$, 132.1$_5$, 132.2, 132.3, 132.5 (d, ^{3}J(P-C) = 4.1 Hz, P*C*), 133.0. (d, ^{1}J(P-C) = 43.9 Hz, P*C*), 134.0. (d, ^{1}J(P-C) = 38.9 Hz, P*C*), 134.5.

^{31}P NMR: δ 27.6 (s), 32.8 and 34.5 (2 d, ^{3}J(P-P) ~ 32.6 Hz each).

LC-MS: *m/z* 441 [M-202-1]$^{+}$.

Anal. Calcd. for $C_{39}H_{35}O_3P_3$: C, 72.67; H, 5.47. Found: C, 72.55; H, 5.41.

This compound was crystallized from ethyl acetate (2 mL). X-ray structure was determined for this sample.

(e) Compound (*E*)**-71** [Using **40 (**1.0 mmol) and $Ph_2P(S)H$ (**8**) (2.0 mmol)] [Spectroscopic and analytical data in section 3.71]

This compound was isolated by using ethyl acetate/hexane (3:2) mixture as the eleuant.

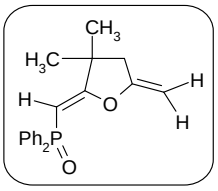
Yield: 82% by NMR; 0.13 g (isolated, 68%, (*E*)-**71**).

3.10 $Zn(OTf)_2/Et_3N$ catalyzed addition-cyclization reactions of propargyl alcohols with allenes: Synthesis of compounds 88-94

(i) Reaction of propargyl alcohol ($HC\equiv CCH_2OH$) with allenyl phosphine oxides 25-29 and allenylphosphonate 20: Synthesis of phosphino-dihydrofurans and furans (88-92) as well as a β,ω-diketophosphonate 93

General procedure for compound 88: A mixture of $Ph_2P(O)C(H)=C=CMe_2$ (**25**) (0.27 g, 1.0 mmol), $HC\equiv CCH_2OH$ (0.80 mL, 3.0 mmol), $Zn(OTf)_2$ (0.036 g, 0.1 mmol) and triethylamine (0.01 g, 0.2 mmol) in toluene (2 mL) was heated at 100 ^oC for 6-8 h. Progress of the reaction was monitored by TLC and ^{31}P or ^1H NMR. When there was no starting material present, reaction mixture was cooled to 25 ^oC, quenched with distilled water (5 mL) and extracted with ethyl acetate (2 x 10 mL). The organic layer was dried (Na_2SO_4), solvent removed under reduced pressure and the compound **88** was purified by column chromatography (silica gel; hexane-ethyl acetate).

Compound 88



The eluant used was ethyl acetate: hexane (3:2).

Yield: 0.29 g (90%).

Mp: gummy liquid.

IR (Neat): 3056, 2967, 2930, 2876, 1634, 1437, 1186, 1030 cm^{-1}.

^1H NMR: δ 1.29 (s, 6H, 2 C*H*$_3$), 2.40 (s, 2H, C*H*$_2$), 4.07 (s, 1H, C=C*H*$_A$CH$_B$), 4.31 (s, 1H, C=CH$_A$C*H*$_B$), 4.97 (d, ^2J(P-H) = 9.6 Hz, 1H, PC*H*), 7.44-7.50 (m, 6H, Ar-*H*), 7.75-7.80 (m, 4H, Ar-*H*).

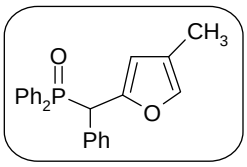
^{13}C NMR: δ 27.0, 41.2, 42.7 (d, ^{3}J(P-C) = 8.8 Hz, PC=C*C*), 85.6 (d, ^{1}J(P-C) = 108.3 Hz, P*C*H), 86.6, 128.1, 128.3, 130.0, 131.2, 131.4, 131.8, 134.4 (d, ^{1}J(P-C) = 106.4 Hz), 157.9, 178.6 (d, ^{2}J(P-C) = 3.3 Hz, PC=*C*).

^{31}P NMR: δ 22.0.

LC-MS: *m/z* 324 $[M+1]^{+}$.

Anal. Calcd. for $C_{20}H_{21}O_2P$: C, 74.06; H, 6.53. Found: C, 74.15; H, 6.48.

Compound 89



This compound was prepared by using allene $Ph_2P(O)C(Ph)=C=CH_2$ **(26)** and propargyl alcohol $HC\equiv CCH_2(OH)$ using the same molar stoichiometry as above. The eluant used was ethyl acetate/hexane (3:7) mixture.

Yield: 0.32 g (85%).

Mp: 152-156 ^{o}C

IR (KBr): 3057, 2961, 1698, 1485, 1439, 1264, 1179, 1101, 797 cm^{-1}.

^{1}H NMR: δ 2.13 (s, 3H, C*H*$_3$), 4.90 (d, ^{2}J(P-H) = 11.6 Hz, 1H, PC*H*(Ph)), 5.82 (s, 1H, Furan-*H*), 6.41 (s, 1H, Furan-*H*), 7.17-7.30 (m, 5H, Ar-*H*), 7.35-7.52 (m, 4H, Ar-*H*), 7.74-7.79 (m, 6H, Ar-*H*).

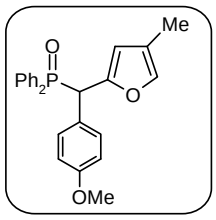
^{13}C NMR: δ 13.5, 48.4 (d, ^{1}J(P-C) = 65.6 Hz, P*C*H(Ph), 106.9, 110.6, 127.3, 128.1, 128.2, 128.3, 128.4, 130.0, 131.3, 131.4, 131.5, 131.6, 131.7, 134.3, 147.7, 151.3.

^{31}P NMR: δ 29.4.

LC-MS: *m/z* 373 $[M+1]^{+}$.

Anal. Calcd. for $C_{24}H_{21}O_2P$: C, 77.41; H, 5.68. Found: C, 77.31; H, 5.75.

Compound 90



This compound was prepared by using allene $Ph_2P(O)C(C_6H_4$-*p*-$OCH_3)=C=CH_2$ **(29)** and propargyl alcohol $HC\equiv CCH_2(OH)$ using the same molar stoichiometry as above. The eluant used was ethyl acetate/hexane (2:3) mixture.

Yield: 0.30 g (75%).

Mp: 180-182 ^oC.

IR (KBr): 3057, 2961, 1698, 1485, 1439, 1264, 1179, 1101, 797 cm^{-1}.

^1H NMR: δ 2.12 (s, 3H, C*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 4.86 (d, ^2J(P-H) = 12.0 Hz, 1H, PC*H*(Anis)), 5.81 (s, 1H, Furan-*H*), 6.36 (s, 1H, Furan-*H*), 6.73 (d, ^3J(H-H) = 8.1 Hz, 2H, Ar-*H*), 7.21 (d, ^3J(H-H) = 8.1 Hz, 2H,Ar-*H*), 7.32-7.53 (m, 8H, Ar-*H*), 7.72-7.77 (m, 2H, Ar-*H*).

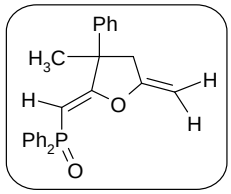
^{13}C NMR: δ 13.4, 46.9 (d, ^1J(P-C) = 66.7 Hz, P*C*H(anis)), 55.2 (O*C*H$_3$), 106.8, 110.3, 113.7, 126.2, 128.1, 128.2, 128.3, 130.9, 131.3, 131.4, 147.9, 151.2, 158.8.

^{31}P NMR: δ 29.5.

LC-MS: *m/z* 403 $[M+1]^+$.

Anal. Calcd. for $C_{25}H_{23}O_3P$: C, 74.62; H, 5.76. Found: C, 74.45; H, 5.81.

Compound 91



This compound was prepared by using $Ph_2P(O)C(H)=C=C(Ph)(Me)$ **(27)** and propargyl alcohol $HC\equiv CCH_2(OH)$ using the same molar stoichiometry as above. The eluant used was ethyl acetate/hexane (3:2) mixture.

Yield: 0.31 g (80%).

Mp: 128-130 ^oC

IR (KBr): 2967, 2917, 1628, 1435, 1225, 1190, 1065, 694 cm^{-1}.

^{1}H NMR: δ 1.73 (s, 3H, CH_3), 2.75 and 2.95 (2 d, ^{2}J(H-H) ~ 15.8 Hz, 2H, C$H_A H_B$), 4.10-4.11 (m, 1H, C=CH_ACH$_B$), 4.38-4.39 (m, 1H, C=CH$_A$CH_B), 4.90 (d, ^{2}J(P-H) = 10.0 Hz, 1H, PC*H*), 7.29-7.38 (m, 5H, Ar-*H*), 7.41-7.51 (m, 6H, Ar-*H*), 7.71-7.79 (m, 4H, Ar-*H*).

^{13}C NMR: δ 13.0, 25.7, 43.9, 50.5 (d, ^{3}J(P-C) = 9.1 Hz, PCC*C*(Ph)), 86.7, 89.4 (d, ^{1}J(P-C) = 106.3 Hz, P*C*), 109.6, 126.0, 127.3, 128.1, 128.2, 128.2_7, 128.3_1, 128.6, 128.7, 130.9, 131.0, 131.1_0, 131.1_1, 131.1_3, 131.2, 131.3, 134.0 (d, *J*(P-C) = 14.5 Hz), 135.1 (d, *J*(P-C) = 14.5 Hz, PCC), 143.8, 157.8, 177.2.

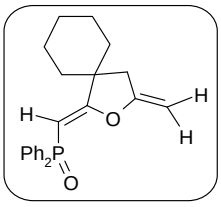
^{31}P NMR: δ 20.9.

LC-MS: *m/z* 387 $[M+1]^+$.

Anal. Calcd. for $C_{25}H_{23}O_2P$: C, 77.70; H, 6.00. Found: C, 77.65; H, 6.10.

This compound was crystallized from ethyl acetate/hexane (1+1 mL). X-ray structure was determined for this sample.

Compound 92



This compound was prepared by using allene $Ph_2P(O)C(H)=C=C(cycl\text{-}C_5H_{10})$ (**28**) and propargyl alcohol HC≡CCH_2(OH) using the same molar stoichiometry as above. The eluant used was ethyl acetate/hexane (3:2) mixtrure.

Yield: 0.68 g (92%).

Mp: 110-112 ^{o}C

IR (KBr): 3050, 2926, 2853, 1698, 1437, 1231, 1190, 1046, 698 cm^{-1}.

^{1}H NMR: δ 1.24-1.30 (m, 4H, cyclohexyl-*H*), 1.46-1.52 (m, 2H, cyclohexyl-*H*), 1.66-1.70 (m, 4H, cyclohexyl-*H*), 2.51 (s, 2H, OCH_2), 4.04 (d, ^{2}J(H-H) = 1.6 Hz, 1H, C=CH$_A$CH_B), 4.25 (d, ^{2}J(H-H) = 1.6 Hz, 1H, C=CH$_A$CH_B), 4.95 (d, ^{2}J(P-H) = 10.0 Hz, 1H, PC*H*), 7.39-7.48 (m, 6H, Ar-*H*), 7.72-7.76 (m, 4H, Ar-*H*).

^{13}C NMR: δ 22.8, 25.3, 35.7, 36.5, 47.4 (d, ^{3}J(P-C) = 8.6 Hz, PCC*C*), 86.2, 86.3 (d, ^{1}J(P-C) = 107.9 Hz, P*C*), 128.1, 128.3, 131.1, 131.2_0, 131.2_2,

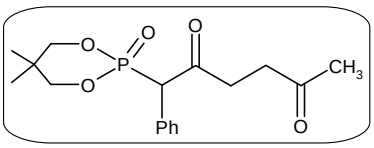
134.7 (d, ^{1}J(P-C) = 107.0 Hz, P*C*), 158.3, 178.7 (d, ^{2}J(P-C) = 4.1 Hz, PC=*C*).

^{31}P NMR: δ 22.1.

LC-MS: *m/z* 365 $[M+1]^{+}$.

Anal. Calcd. for $C_{23}H_{25}O_2P$: C, 75.81; H, 6.91. Found: C, 75.89; H, 6.85.

Compound 93



This compound was prepared by using $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**20**), and propargyl alcohol $HC\equiv CCH_2(OH)$. The eluant used was ethyl acetate/hexane (3:2) mixture.

Yield: 0.13 g (35%; using 1.1 mmol of **20**).

Mp: 176-178 ^{o}C.

IR (KBr): 2967, 2915, 1719, 1628, 1360, 1265, 1055, 1007, 794 cm^{-1}.

^{1}H NMR: δ 0.82 and 1.07 (2 s, 6H, 2 C*H*$_3$), 2.18 (s, 3H, C(O)C*H*$_3$), 2.71-2.75 (m, 2H, C*H*$_2$), 2.93-2.99 (m, 2H, C*H*$_2$), 3.78-3.85 (m, 2H, OC*H*$_2$), 4.11 (dd → t, ^{3}J(P-H) = ^{2}J(H-H) ~10.7 Hz, 2H, OC*H*$_2$), 4.63 (d, ^{3}J(P-H) = 23.6 Hz, 1H, PC*H*(Ph)), 7.33-7.41 (m, 3H, Ar-*H*), 7.49-7.52 (m, 2H, Ar-*H*).

^{13}C NMR: δ 21.1 and 21.7 (2 *C*H$_3$), 29.9 (C(O)*C*H$_3$), 32.6 (d, ^{3}J(P-C) = 7.2 Hz, C(C*H*$_3$)$_2$), 37.0$_8$, 37.1$_4$ (d, ^{3}J(P-C) = 3.7 Hz, C(O)*C*H$_2$), 58.4 (d, ^{1}J(P-C) = 129.2 Hz, P*C*H(Ph)), 76.2 (O*C*H$_2$), 76.3 (O*C*H$_2$), 128.2 (d, *J*(P-C) = 2.9 Hz), 128.9 (d, *J*(P-C) = 2.2 Hz), 129.9, 130.0, 130.3, 130.4, 201.8 (d, ^{2}J(P-C) = 4.6 Hz, PC*C*(O)), 206.7 (*C*(O)CH$_3$).

^{31}P NMR: δ 12.8.

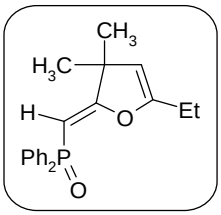
LC-MS: *m/z* 339 $[M+1]^{+}$.

This compound was crystallized from ethyl acetate/hexane (1:1) mixture. X-ray structure was determined for this compound.

(ii) Reaction of HC≡CCHMe(OH) with allene $Ph_2P(O)C(H)=C=CMe_2$ (25): Synthesis of compound 94

The above procedure [section 3.10(i)] was followed by using $Ph_2P(O)C(H)=C=CMe_2$ (**25**) (1.0 mmol) and HC≡CC(Me)H(OH) in the same molar ratio. The eluant used was ethyl acetate: hexane (3:2).

Compound 94



Yield: 0.26 g (76%).

Mp: Gummy liquid

IR (Neat): 3057, 2969, 2926, 1709, 1634, 1437, 1121 cm^{-1}.

^{1}H NMR: δ 0.82 (t, ^3J(H-H) ~ 7.4 Hz, 3H, CH_2CH_3), 1.29 (s, 6H, 2 CH_3), 2.00 (q, ^3J(H-H) ~ 7.4 Hz, 2H, CH_2CH_3), 4.81 (s, 1H, Furan-C*H*), 5.04 (d, ^2J(P-H) = 9.6 Hz, 1H, PC*H*), 7.43-7.48 (m, 6H, Ar-*H*), 7.76-7.80 (m, 4H, Ar-*H*).

^{13}C NMR: δ 10.3, 20.6, 28.9, 31.0, 48.4 (d, ^3J(P-C) = 8.9 Hz, PC=C-*C*$(CH_3)_2$), 85.7 (d, ^1J(P-C) = 109.4 Hz, P*C*H), 107.7, 128.2, 128.3, 131.1, 131.2, 134.8 (d, ^1J(P-C) = 107.0 Hz, P*C*)), 156.7, 181.4, 207.1.

^{31}P NMR: δ 21.3.

Anal. Calcd. for $C_{21}H_{23}O_2P$: C, 74.54; H, 6.85. Found: C, 74.45; H, 6.91.

3.11 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **33**.$CHCl_3$, **35**, **36.**CH_2Cl_2, **41.**$2C_4H_8O_2$, **44**, **58**, (*Z*)-**67**, **76**, **87**, **91** and **93**) and X-ray data were collected at 293 K on a Bruker AXS-SMART or on an OXFORD diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using standard methods.[113] Absorption corrections were done using SADABS program, where applicable. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were fixed by geometry or located by a Difference Fourier and refined isotropically. Crystal data are summarized in Tables 9-11.

Table 9. Crystal data for compounds **33**.$CHCl_3$, **35**, **36.**CH_2Cl_2 and **41.**$2C_4H_8O_2$[a]

Compound	**33**.$CHCl_3$	**35**	**36.**CH_2Cl_2	**41.**$2C_4H_8O_2$
Emp. formula	$C_{20}H_{25}NO_3PCl_3$	$C_{26}H_{26}NO_2P$	$C_{41}H_{42}N_2O_{10}P_2Cl_2$	$C_{54}H_{66}O_8P_4Pd_2S_2$
Formula weight	464.73	415.45	855.61	1243.87
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P2(1)/c*	*P2(1)/c*	*P2(1)/c*	*P2(1)/n*
a /Å	10.0813(12)	8.973(4)	23.992(9)	11.0267(14)
b /Å	10.0455(12)	15.480(6)	14.574(6)	25.600(3)
c /Å	22.053(3)	17.629(6)	11.636(5)	21.858(3)
α/deg	90	90	90	90
β/deg	98.363(2)	117.171(16)	92.284(6)	92.380(2)
γ/deg	90	90	90	90
V /Å^3	2209.6(5)	2178.5(15)	4065(3)	6164.9(14)
Z	4	4	4	4
D_{calc} /g cm^{-3}]	1.397	1.267	1.398	1.340
μ /mm^{-1}	0.508	0.149	0.299	0.801
F(000)	968	880	1784	2552
Data/ restraints/ parameters	3871/0/255	3829/0/271	7050/0/520	14749/11/689
S	1.091	1.034	0.991	1.055
R1 [I>2σ(I)]	0.0689	0.0479	0.0585	0.0555
wR2 [all data]	0.1702	0.1116	0.1562	0.1938
Max./min. residual electron dens. [eÅ^{-3}]	0.729/-0.559	0.336/-0.262	0.711/-0.519	1.085/-0.487

[a]$R1 = \Sigma||F_O| - |F_C||/\Sigma|F_O|$ and $wR2 = [\Sigma w(F_O^2-F_C^2)^2/\Sigma wF_O^4]^{0.5}$

Table 10. Crystal data for compounds **44**, **58**, (*Z*)-**67**, **76**[a]

Compound	**44**	**58**	(*Z*)-**67**	**76**
Emp. formula	$C_{20}H_{24}O_4P_2$	$C_{26}H_{28}O_3P_2S$	$C_{20}H_{24}O_3P_2S$	$C_{26}H_{28}O_3P_2S$
Formula weight	390.33	482.49	406.40	482.48
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P2(1)/c*	*P2(1)/c*	*C2/c*	*P2(1)/c*
a /Å	12.4520(7)	11.3638(9)	26.735(3)	14.248(4)
b /Å	10.8216(7)	9.3652(7)	10.2135(10)	15.981(3)
c /Å	18.3965(8)	24.1817(19)	16.800(2)	11.547(3)
α/deg	90	90	90	90
β/deg	126.803(3)	103.1310(10)	114.155(15)	99.62(3)
γ/deg	90	90	90	90
V /Å^3	1984.88(19)	2506.2(3)	1762.8(13)	2592.3(10)
Z	4	4	8	4
D_{calc} /g cm^{-3}]	1.306	1.279	1.290	1.236
μ /mm^{-1}	0.241	0.282	0.324	0.272
F(000)	824	1016	1712	1016
Data/ restraints/ parameters	3499/0/238	4413/0/291	3572/0/238	4554/0/291
S	1.109	1.032	1.110	0.773
R1 [I>2σ(I)]	0.0389	0.0397	0.0521	0.0513
wR2 [all data]	0.0942	0.1082	0.1499	0.1131
Max./min. residual electron dens. [eÅ^{-3}]	0.437/-0.329	0.210/-0.329	0.432/-0.263	0.285/-0.335

[a]$R1 = \Sigma||F_O| - |F_C||/\Sigma|F_O|$ and $wR2 = [\Sigma w(F_O^2-F_C^2)^2/\Sigma wF_O^4]^{0.5}$

Table 11. Crystal data for compounds **87**, **91**, **93**[a]

Compound	**87**	**91**	**93**
Emp. formula	$C_{39}H_{35}O_3P_3$	$C_{25}H_{23}O_2P$	$C_{17}H_{23}O_5P$
Formula weight	644.58	386.40	338.32
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P2(1)/c*	*P2(1)/c*	*P2(1)/c*
a /Å	12.6505(14)	19.112(8)	9.975(5)
b /Å	14.123(3)	6.357(3)	16.638(5)
c /Å	18.442(3)	17.348(7)	11.202(5)
α/deg	90	90	90
β/deg	98.311(12)	103.677(7)	108.52(6)
γ/deg	90	90	90
V /Å^3	3260.3(9)	2047.9(15)	1762.8(13)
Z	4	4	4
D_{calc} /g cm^{-3}]	1.313	1.253	1.275
μ /mm^{-1}	0.221	0.152	0.178
F(000)	1352	816	720
Data/ restraints/ parameters	5692/0/407	3607 /0/ 254	3099 / 0 / 211
S	0.968	1.044	0.836
R1 [I>2σ(I)]	0.0390	0.0795	0.0469
wR2 [all data]	0.0921	0.1720	0.1103
Max./min. residual electron dens. [eÅ^{-3}]	0.253/-0.280	0.334/-0.192	0.169/-0.164

[a]$R1 = \Sigma||F_O| - |F_C||/\Sigma|F_O|$ and $wR2 = [\Sigma w(F_O^2-F_C^2)^2/\Sigma wF_O^4]^{0.5}$

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PART B

SYNTHETIC STUDIES ON 9-CHLOROACRIDINES

INTRODUCTION

4.1 General Introduction: Acridines

Acridine is a tricyclic aromatic hydrocarbon, structurally related to anthracene with one of the central CH group is replaced by nitrogen (Fig 4.1). It is a pale yellow solid, first isolated from coal tar. It is a raw material used for the production of dyes and some valuable drugs.

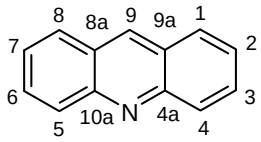


Fig. 4.1 Acridine and its IUPAC numbering

Various substituted acridines[1] exhibit important biological activities, including activity against cancer,[2] due to their ability to intercalate into DNA and disrupt unwanted cellular processes.[3] This unique property of acridines has been exploited in many areas of medicine. As a result, significant biological activity toward viruses,[4] bacteria,[5] parasites,[6] fungus,[7] Alzheimer's disease,[8] and HIV/AIDS[9] has also been reported.

Amsacrine [*N*-(4-(acridin-9-ylamino)-3-methoxyphenyl) methanesulfonamide, 4.**1**] is the best-known compound of 9-anilinoacridines series and drug used in acute *lymphoblastic leukemia.* It was one of the first DNA-intercalating agents to be considered as a topoisomerase II inhibitor.[10a] Antiseptic agent, proflavine [3,6-acridinediamine, 4.**2**] used effectively during world war II for deep wound dressing, has been studied extensively as a novel RNA-targeted antiviral drug and as an intercalator in cancer treatments. It was the CAS molecule of the week (September 2005). Nitracrine (4.**3**) is an anti-tumor agent.[10b] Acridine orange [3,6-dimethylaminoacridine, 4.**4**] is a nucleic acid-selective metachromatic stain useful for cell cycle determination. Quinacrine (4.**5**) is an anti-prion agent. The structures of compounds 4.**1**-4.**5** are shown in Fig. 4.2.

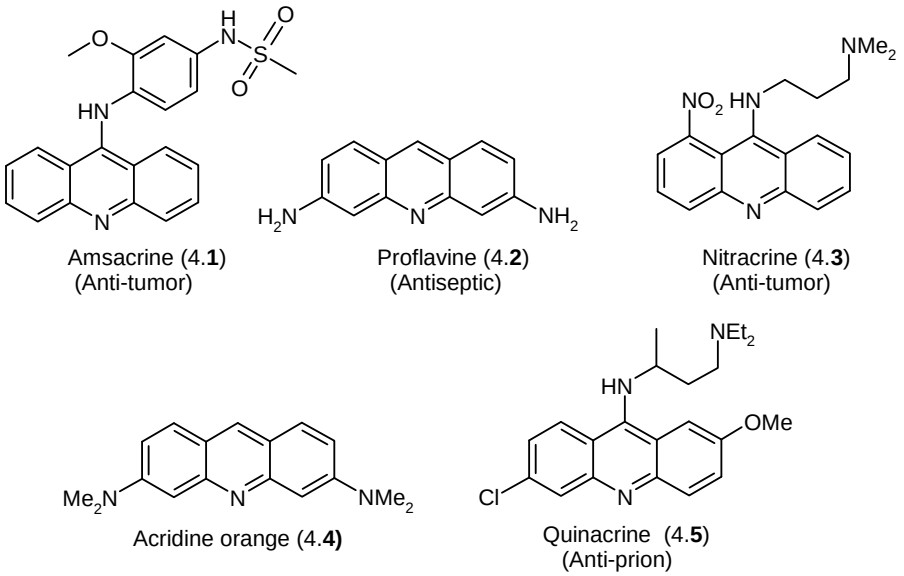


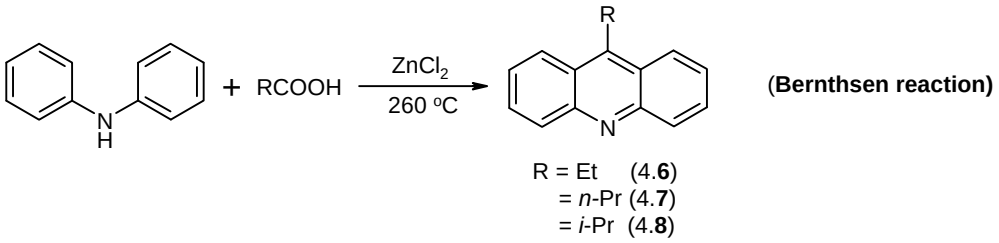
Fig. 4.2 Some of the biologically important acridine derivatives.

4.2 Synthesis of acridine derivatives

4.21 9-Alkyl or 9-aryl acridines and acridones

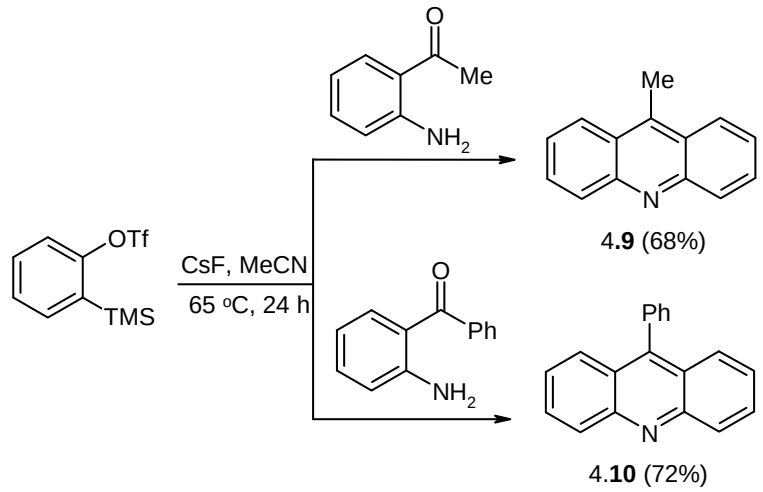
Many synthetic processes are known for the production of acridine and its derivatives. Traditional synthetic methods involve condensing diarylamines with aryl or alkyl carboxylic acids[11] (Bernthsen acridine synthesis) leading to 9-alkyl or 9-aryl acridine derivatives 4.**6**-4.**8** (Scheme 4.1).

Scheme 4.1



Recently, Larock *et al.* reported the synthesis of 9-substituted acridine derivatives by the reaction of 2-aminoaryl ketones and arynes generated by the treatment of various o-(trimethylsilyl)aryl triflates with CsF that results in [4+2] annulation (Scheme 4.2).[12]

Scheme 4.2

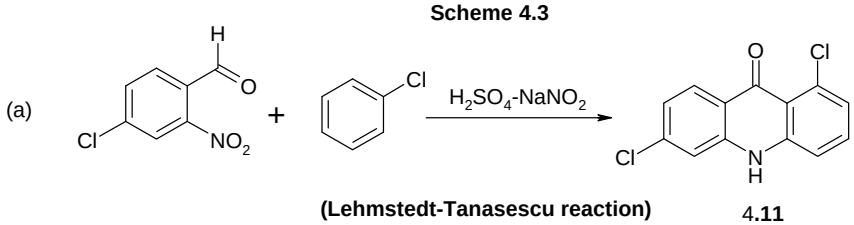


4.**9** (68%)

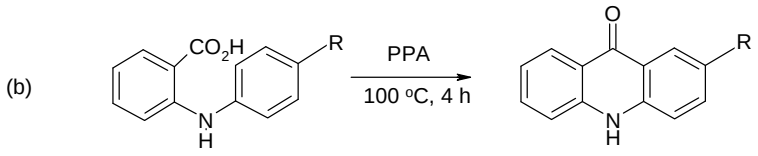
4.**10** (72%)

Acridone derivatives were synthesized by treating *o*-nitrobenzaldehyde with arenes in presence of H_2SO_4-$NaNO_2$ mixture[13] (Lehmstedt-Tanasescu reaction) (Scheme 4.3a). Another method involves the condensation of *N*-phenylanthralinic acid derivatives in the presence of polyphosphoric acid (Scheme 4.3b).[14]

Scheme 4.3



(Lehmstedt-Tanasescu reaction) 4.**11**

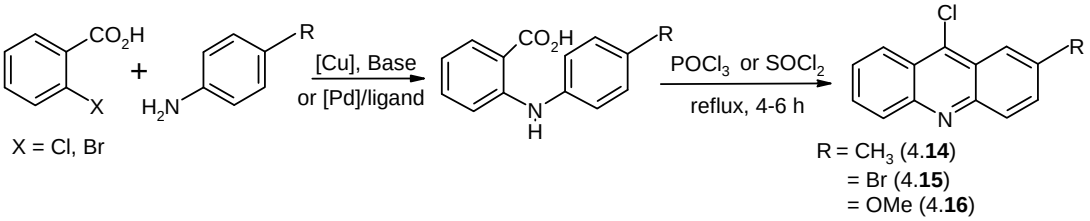


R = Me (4.**12**)
= OMe (4.**13**)

4.22 9-Chloroacridines

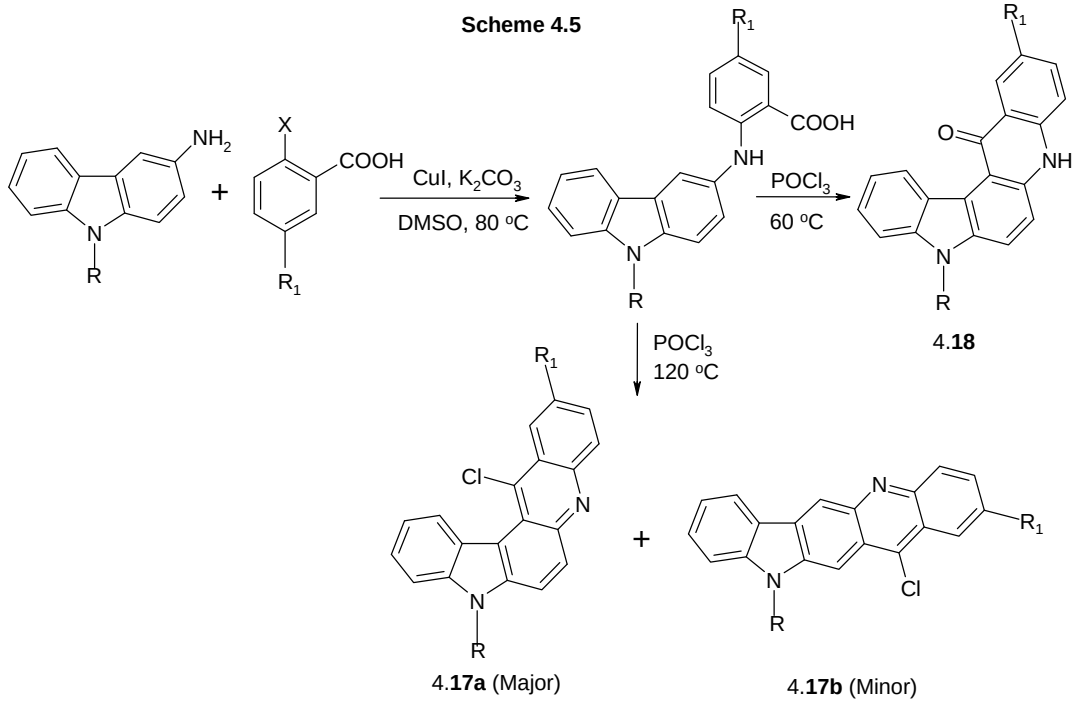
Among the acridine derivatives, 9-chloroacridines belong to a sub-class of compounds which can be converted to many synthetically and biologically important molecules. Csuk and co-workers reported the preparation of functionalized 9-chloroacridines by condensing *o*-halobenzoic acids with functionalized anilines[15] followed by the cyclization of *N*-phenylanthranilic acids (Scheme 4.4).

Scheme 4.4



Recently, Nagarajan and co-workers reported a convenient synthesis of 9-chloroacridine derivatives 4.**17a-b** *via* Ullmann-Goldberg condensation of 9-aminocarbazole with *o*-halobenzoic acids followed by cyclization with $POCl_3$ at 120 ^oC (Scheme 4.5).[16] Acridone derivative 4.**18** was also formed at 60 ^oC (low temperature).

Scheme 4.5



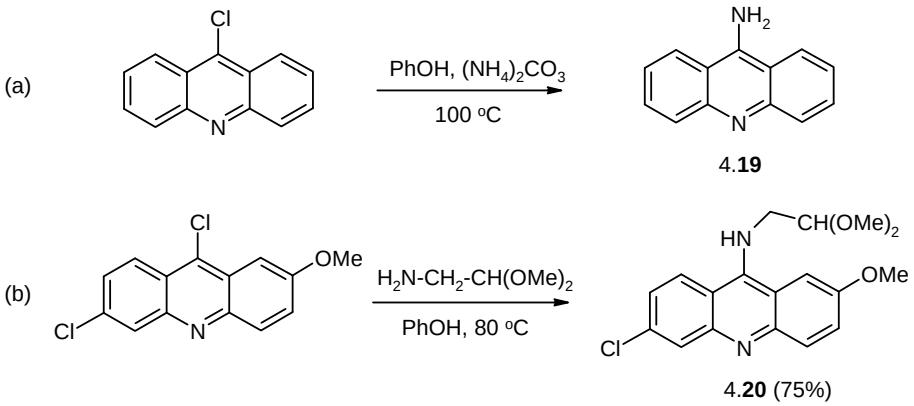
4.3 Nucleophilic addition/substitution reactions of acridine derivatives at 9th position

Position 9 of acridine is particularly electrophilic because of the presence of nitrogen at the *para*-position of the central ring. Its reactivity was reviewed in 1977 by Skonieczny.[17]

4.31 Addition of amines

Nucleophilic addition of amine to 9-chloroacridine in the presence of PhOH/$(NH_4)_2CO_3$ mixture produces 9-aminoacridine in 84% yield (Scheme 4.6a).[18] This is a highly fluorescent dye used clinically as a topical antiseptic. A long chain containing 9-aminoacridine derivative 4.**20** is also prepared by heating 6,9-dichloro-2-methoxyacridine in phenol with corresponding amine (Scheme 4.6b).[19a] A variety of 9-aminoacridine derivatives which are under biological activity evaluation are also reported in the literature.[19b-i]

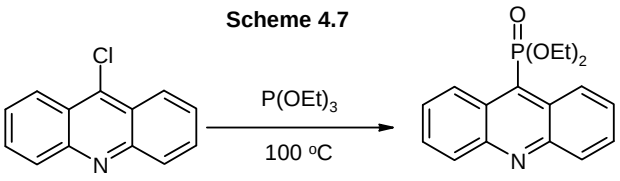
Scheme 4.6



4.32 Addition of phosphorus nucleophiles

Reaction of $P(OEt)_3$ with 9-chloroacridine was first reported by Kosolapoff and his group in 1947.[20] In this Michaelis-Arbuzov reaction, the product obtained, as per the authors, was diethyl acridyl-9-phosphonate 4.**21** (Scheme 4.7).[20]

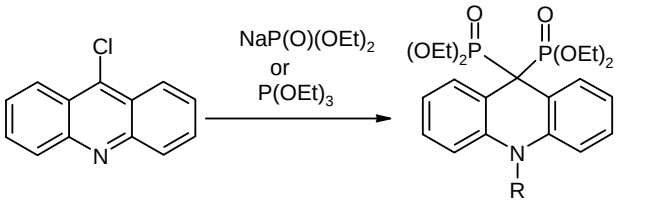
Scheme 4.7



4.**21**

The same reaction was repeated by Redmore, but only the bisphosphonate **4.22a** could be isolated in 34% yield (Scheme 4.8).[21] No product corresponding to that described by Kosolapoff was formed by this route. This compound was characterized by IR, ^{1}H NMR and mass spectroscopy. The compound is readily acetylated to produce the acetate 4**.22b** which exhibits spectral data in complete accord with the structure (Scheme 4.8). We do expect the monophosphonylated product also in this reaction and hence it is worthwhile to investigate this aspect using different P^{III} precursors.

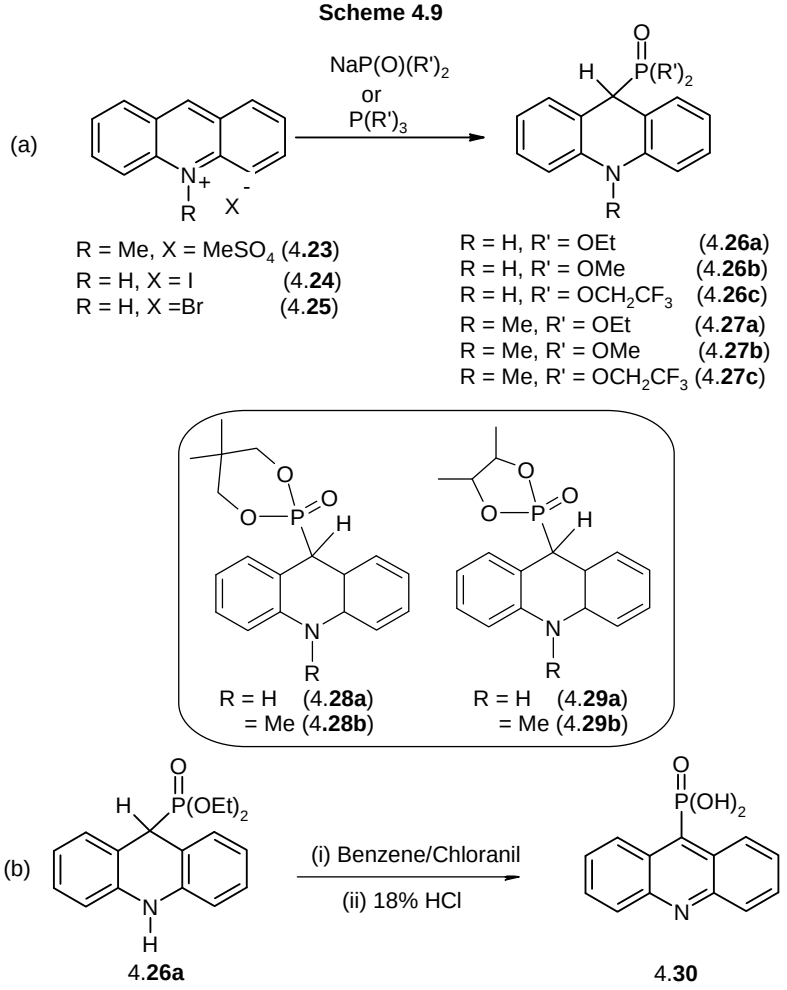
Scheme 4.8



R = H (4.**22a**)
= C(O)Me (4.**22b**)

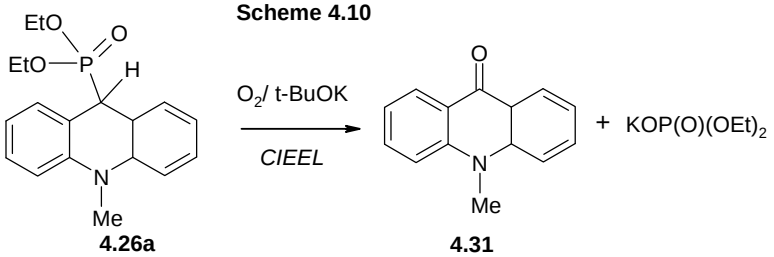
The 1,4- addition of diethylphosphite or dialkyl sodium phosphonate to acridinium salts (4.**23**-4.**25**) leads to the formation of dihydroacridylphosphonates (4.**26**-4.**29**) in quantitative yield (Scheme 4.9a).[21] Dehydrogenation of 4.**26a** was achieved upon heating in benzene with chloranil to yield 4.**21** and subsequent hydrolysis resulted in acridyl-9-phosphonic acid 4.**30** (Scheme 4.9b).

Scheme 4.9



While investigating the chemiluminescence in autoxidation of phosphonate carbanions, Motoyoshiya *et al*. also prepared weakly fluorescent 9-phosphonoacridines such as 4.**26**-4.**29** in good yields (41-70%).[22] The autoxidation of phosphonate carbanions derived from 9-phosphono-10-hydroacridanes (**4.26a**) and *t*-BuOK in aprotic solvents provided chemiluminescence that was long enough to be spectroscopically detected, and whose emission spectra were in complete agreement with the fluorescence spectrum of the anion of acridone **4.31** independently generated under basic conditions (Scheme 4.10).

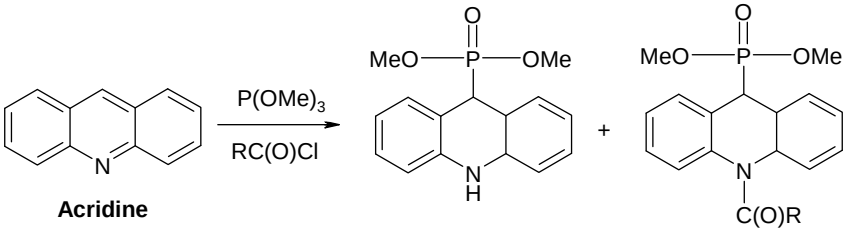
Scheme 4.10



(*CIEEL* = chemically induced electron exchange luminiscence)

Reissert-like reaction with $P(OMe)_3$ and various acyl or sulfonyl chlorides begins with the formation of an intermediate *N*-acylacridinium that activates 9th position of acridine towards $P(OMe)_3$. The resulting products are dimethyl-(9-acridane) phosphonate 4.**26b** and dimethyl(*N*-acyl-9-acridane)phosphonate 4.**32a** (Scheme 4.11).[23]

Scheme 4.11



Acridine

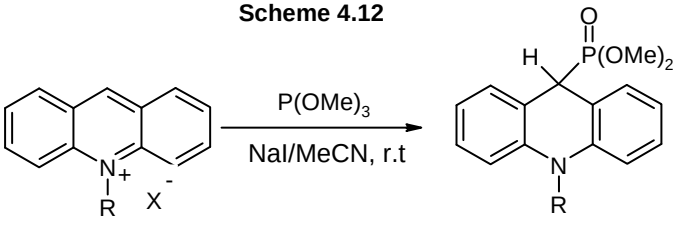
4.**26b** (3-70%)

4.**32** (2-32%)

R = Me (4.**32a**)
Et (4.**32b**)
Ph (4.**32c**)

Akiba *et al.* treated acridinium cations with trimethyl phosphite in the presence of sodium iodide in acetonitrile (Scheme 4.12).[24] This Michaelis-Arbuzov reaction took place at room temperature and gave the corresponding phosphonates 4.**33** in high yields.

Scheme 4.12



R = H, Me, Et, Bn
X = Cl, Br, $MeSO_4$, $EtSO_4$

4.**33** (76-92%)

Due to the fact that acridine derivatives (4.**1**-4.**5**) as well as bisphosphonates (cf. 4.**22a-b**) have some therapeutic value, it is deemed worthwhile to begin exploring acridine chemistry and later introduce phosphonate group in favorable cases in the present work.

OBJECTIVES OF THE PRESENT WORK - PART B

The main objective of this part of the work is to develop simple routes to new acridine based organophosphonates and to find utility of the products [e.g. as anti-leukemia agents]. Specifically, it is intended to explore

(i) Phosphonylation of 9-propargyl acridines [prepared from 9-chloroacridines] to synthesize phosphono-acridines and to check their biological (anti-leukemia) activity,

(ii) Nucleophilic substitution reactions of 9-chloroacridines with dimethyl malonate for the synthesis of malono-acridines,

(iii) Synthesis of 9-vinyl acridine-based organophosphonates by using allenylphosphonate/allenyl phosphine oxide.

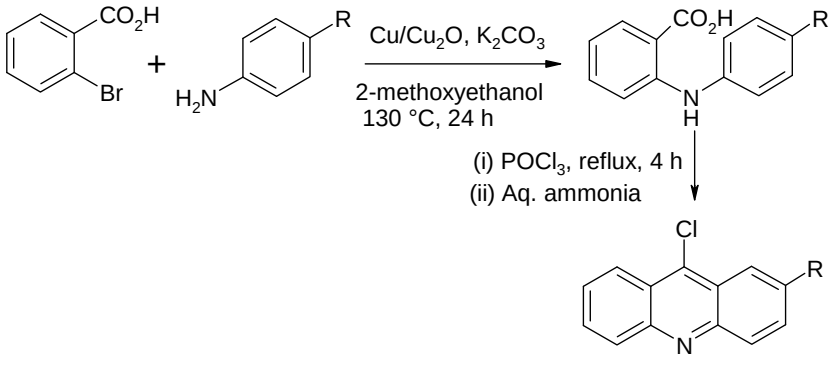
RESULTS AND DISCUSSION

Cyclic phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1**) [compound **5** in Chapter 3], allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (**2**) [compound **19** in Chapter 3] and allenyl phosphine oxide $Ph_2P(O)C(H)=C=CMe_2$ (**3**) [compound **25** in Chapter 3] were prepared by literature methods.[25-26]

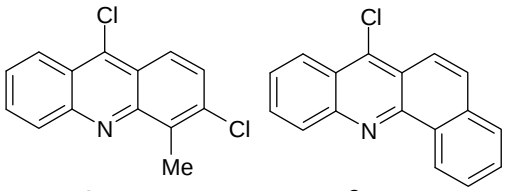
5.1 Synthesis of 9-chloroacridines 4-9 and the 9-prop-2-ynyloxy-acridine (10)

Treatment of anthranilic acids [prepared in 70-80% yield by coupling aromatic amines with *o*-bromobenzoic acid in the presence of Cu/Cu_2O[27]] with phosphorus oxychloride ($POCl_3$) at 130 °C for 2-4 h[28] afforded the corresponding 9-chloroacridine derivatives [9-chloroacridine (**4**), 9-chloro-2-methylacridine (**5**), 2-bromo-9-chloroacridine (**6**), and 9-chloro-2-nitroacridine (**7**)] (Scheme 1). Compounds 3,9-dichloro-4-methylacridine (**8**) and 7-chloro-benzo[c]acridine (**9**) were also synthesized in a manner similar to the preparation of the compounds **4**-**7**. Among these compounds **6-9** are new. These compounds were characterized by IR, NMR (^1H, ^{13}C), LC-MS and CHN analyses. These chloroacridines are moderately sensitive to the atmospheric moisture and hence need to be preserved in a moisture-free atmosphere.

Scheme 1



R = H (**4**), Me (**5**), Br (**6**), NO_2 (**7**)
Yields: 50-75%

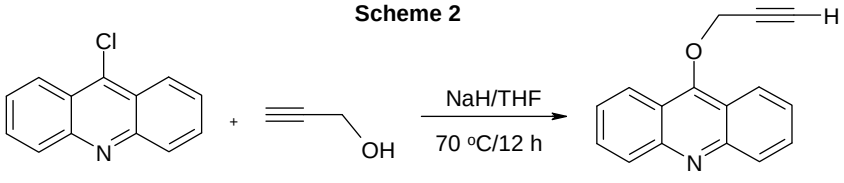


8 **9**

Yield: 75% 60%

We have utilized 9-chloroacridine (**4**) for the preparation of **9**-prop-2-ynyloxy-acridine (**10**) by substituting propargyl group at the 9th position of the 9-chloroacridine (Scheme 2). The spectroscopic (^{1}H and ^{13}C NMR) and analytical (LC-MS/CHN) data are in agreement with the structure. The main purpose of synthesizing this compound was to use it as a precursor for phosphono-substituted acridines in transition-metal catalyzed phosphonylation reactions.

Scheme 2



4 **10** (60%)

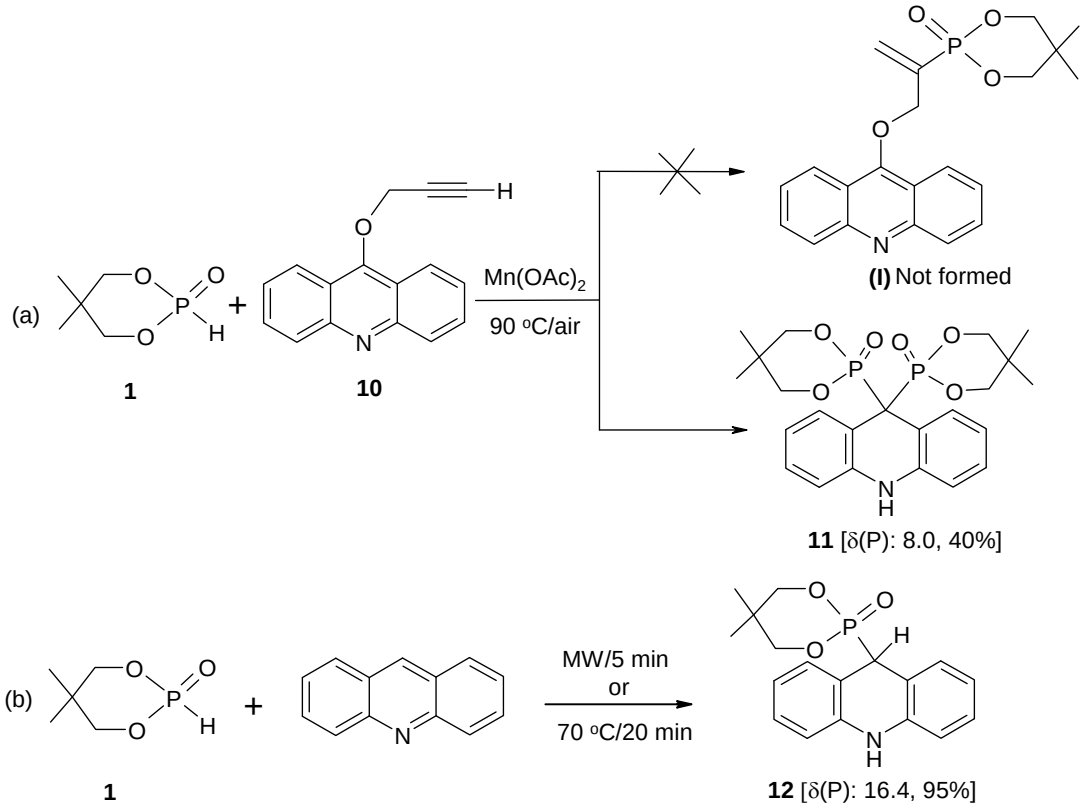
5.2 Hydrophosphonylation of acridine derivatives

(a) Synthesis of phosphono-acridines

As mentioned above, we made an attempt to prepare the compound of type **I** by phosphonylating the 9-propargyloxy-acridine (**10**) with $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1**) using $Mn(OAc)_2$[29] as the catalyst (Scheme 3a). Surprisingly, this reaction did not give the expected product **I** but led only to the bisphosphonylated compound **11**. This compound showed a band at 3260 cm^{-1} in the IR spectrum corresponding to ν(NH). In the ^{1}H NMR spectrum, a broad signal at δ 7.90 (N*H* proton) was present. The integrated intensity ratio of the 1,3,2-dioxaphosphorinane ring protons to the aromatic protons was in agreement with the presence of two 1,3,2-dioxaphosphorinane rings to one acridane (reduced form of acridine) residue. In the ^{13}C NMR spectrum, it exhibited a low intensity *triplet* at the aliphatic carbon region with δ 51.8 and *J*(P-C) = 132.1 Hz, indicating that this carbon is attached to two phosphorus atoms. All these data are consistent with the bisphosphonate structure **11** for the compound; this analysis was proven by means of

single crystal X-ray crystalligraphy also (Fig. 1). The two P-C bond distances [P(1)-C(9) 1.851(5), P(2)-C(9) 1.853(5)] are in the range expected for P-C single bond; the C(9)-C(10) as well as C(9)-C(13) distances are also consistent with C-C single bonds.[30] Following this result, we wanted to check whether phosphonylation occurs with simple acridine or not. In this case, however, we obtained the known monophosphonate (**12**)[22a] quantitatively from the direct addition of cyclic phosphite **1** to acridine under conventional heating or microwave (MW) conditions for 20 min (Scheme 3b). Thus realizing the potential for utilizing the 9th position of the acridines, we turned our attention to the more readily accessible 9-chloroacridines **4-9** as precursors in the phosphonylation reactions.

Scheme 3



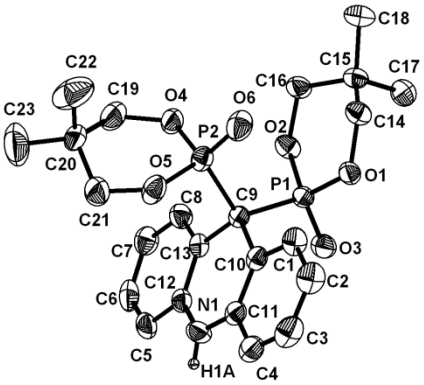
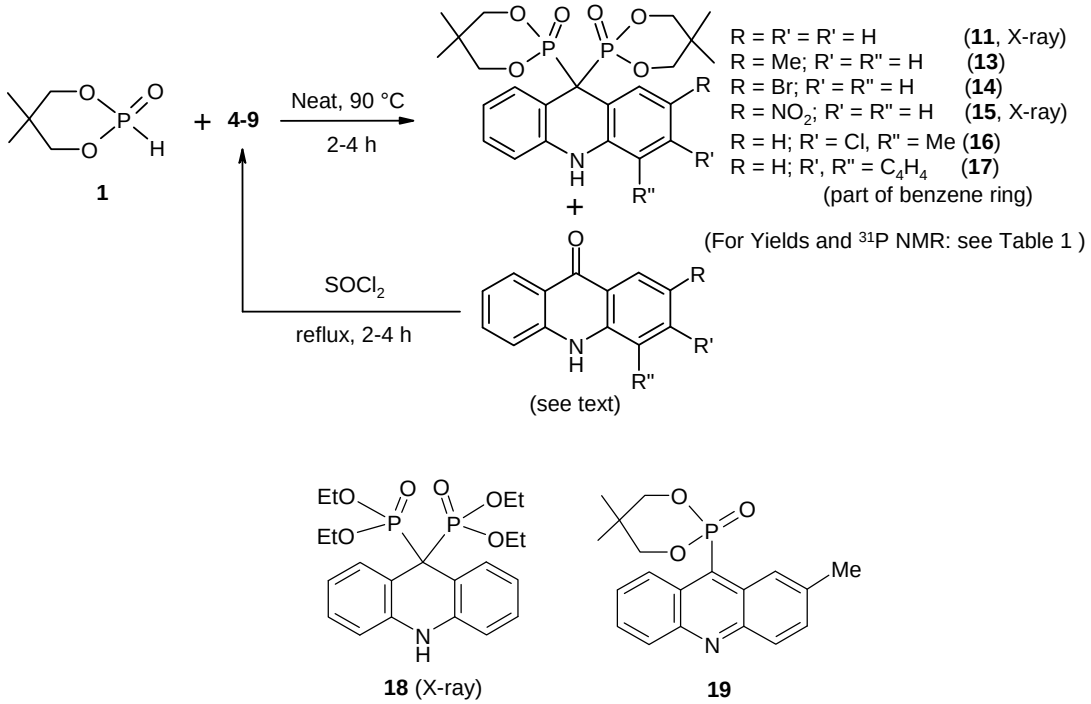


Fig. 1. An ORTEP diagram of the compound **11**.CH_3CN. Solvent molecule and hydrogen atoms (except N-*H*) are omitted for clarity. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(9) 1.851(5), P(2)-C(9) 1.853(5), N(1)-C(11) 1.368(7), N(1)-C(12) 1.381(7), C(9)-C(10) 1.554(7), C(9)-C(13) 1.555(7).

When the 9-chloroacridines **4-9** were treated with the cyclic phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1**) under neat conditions at 90 °C for 2-4 h, bisphosphonates **11** and **13-17** were formed along with the corresponding acridones (Scheme 4). Though the yield of the compounds is only moderate (reaction mixture showed single phosphonate product by ^{31}P NMR, yield in the reaction mixtures 50-60%; isolated yield of pure compounds 15-30%) formation of these compounds represents an easy access to bisphosphonylated acridone derivatives. We made an attempt to increase the yield of **11** by changing the reaction conditions; however, we always ended up in having acridone (30-40%) by-product, probably because of a competing –OH to -Cl exchange between 9-chloroacridine and phosphite. However, this problem could be circumvented since the acridone formed was readily converted back to the 9-chloroacridine by simple treatment with thionyl chloride.[28] It may also be noted that the isolation of **11** and **13-17** is fairly straightforward. The structures of the bisphosphonates **15** and **18** are confirmed by single crystal X-ray crystallography (Fig. 2). An analogous reaction of 9-chloroacridine (**4)** with diethyl phosphite afforded the corresponding bisphosphonate **18**; this compound, however is known in the literature.[21] Considering that the byproduct acridone could be quantitatively converted to the corresponding chloroacridines, the effective yield is very good. Use of different solvents (THF and toluene) did not alter the yield significantly. Employing more than two mole equivalents of phosphite **1** did not significantly alter the yields, and even the use of less than one mole equivalents of **1**

led mostly to the bisphosphonate as the only solid phosphorus product (^{31}P NMR). By using a lower stoichiometry of phosphite **1** in its reaction with 9-chloro-2-methylacridine (**5**), the monophosphonate **19** could also be isolated.

Scheme 4



18 (X-ray)

19

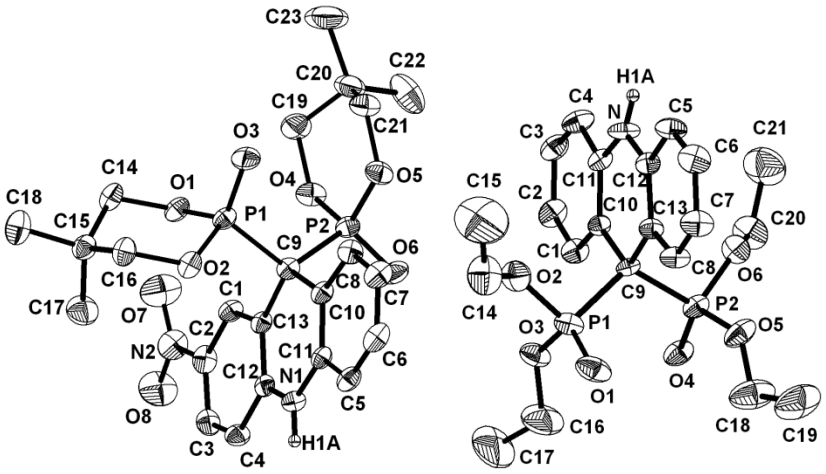


Fig. 2. ORTEP diagrams for compounds **15**.OC_4H_8 (left) and **18** (right). Selected bond lengths [Å] with esd's in parentheses: Compound **15**.OC_4H_8: P(1)-C(9) 1.864(5), P(2)-C(9) 1.849(5). Compound **18**: P(1)-C(9) 1.829(5), P(2)-C(9) 1.848(5).

Table 1. Details on the yields and ^{31}P NMR chemical shifts for the compounds **11** and **13-19**.

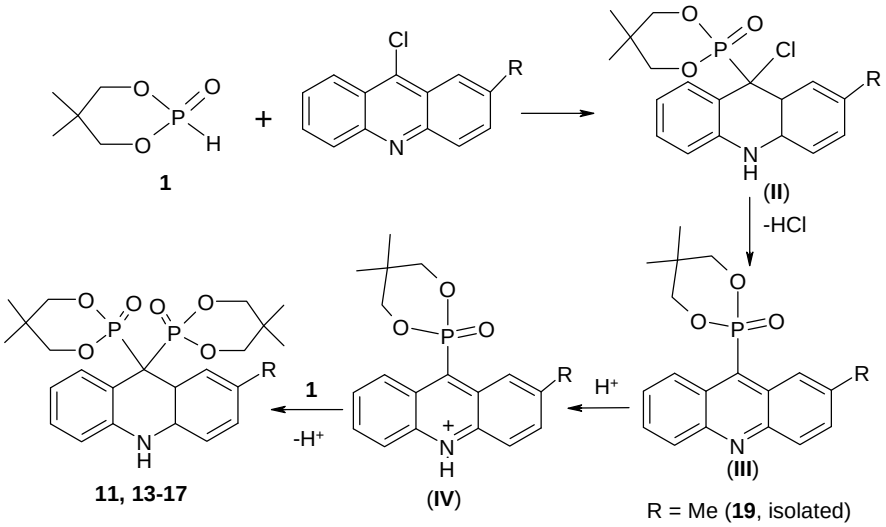
Entry	Compound	Yield (%)[a]	δ(P)
1	**11**	55	8.0
2	**13**	52	8.1
3	**14**	58	7.3
4	**15**	50	7.1
5	**16**	54	8.0
6	**17**	52	8.0
7	**18**	60	15.9
8	**19**	20	10.6

[a]Yields are determined by ^{31}P NMR analysis.

(b) Mechanistic pathway

A possible pathway for the formation of bisphosphonates, synthesized as described above, is shown in Scheme 5. The monophosphonate of type (**II**) could undergo elimination of a molecule of HCl to afford the 9-phosphono-acridine (**III**). Since the nitrogen site is basic, it can take up the available proton from the acid to lead to a species like (**IV**), in which the double bond attached to the phosphonate group is activated to accept a second phosphonate entity to lead to the bisphosphonates **11**, **13-15** (or **16-17**). It is also possible that species (**III**) can simply reorganize to the amine salt (**IV**) with chloride as the counter-ion, prior to the addition of the second molecule of **1**. Evidence for the involvement of (**III**) comes from the fact that in one case, we could isolate **19**, albeit in modest yields.

Scheme 5



(c) Biological (anti-leukemia) activity of compound 13

Cytotoxicity (IC_{50} in μM) for compound **13** with cell lines HepG2 and HeLa were found to be 150 and 79, respectively.[31] These data suggest that our compounds are fairly active and efforts are under way to obtain the corresponding bisphosphonic acids and check their activity [These data were provided to us by Mr. Jyothi Manohar, Prof. Reddana's lab, School of Life sciences, University of Hyderabad].

(d) A brief discussion of the hydrogen bonding interaction in the X-ray structures of 11.CH_3CN, 15.OC_4H_8 and 18

As can be seen from the structural drawings, an N-H group is present in the structure of the **11.**CH_3CN, **15**.OC_4H_8 and **18**, there is clear-cut hydrogen bonding interaction between the N*H* of the acridane residue and one of the P=O groups of the phosphonate group in all the three compounds. This is exhibited by the formation of dimeric units in **11.**CH_3CN and **15**.OC_4H_8. However, in the ethyl compound **18** the preference is in favor of a hydrogen bonded chain rather than dimer formation. Interestingly, compound **11.**CH_3CN crystallizes in the trigonal space group R-3 which appears to be a manifestation of additional C-H…O hydrogen bonding interactions between the three protons of the solvent acetonitrile and an oxygen atom of 1,3,2-dioxaphosphorinane of the ring as shown in Fig. 3. Involvement of acetonitrile hydrogen atoms in C-H…O interaction has been observed by us before.[32]

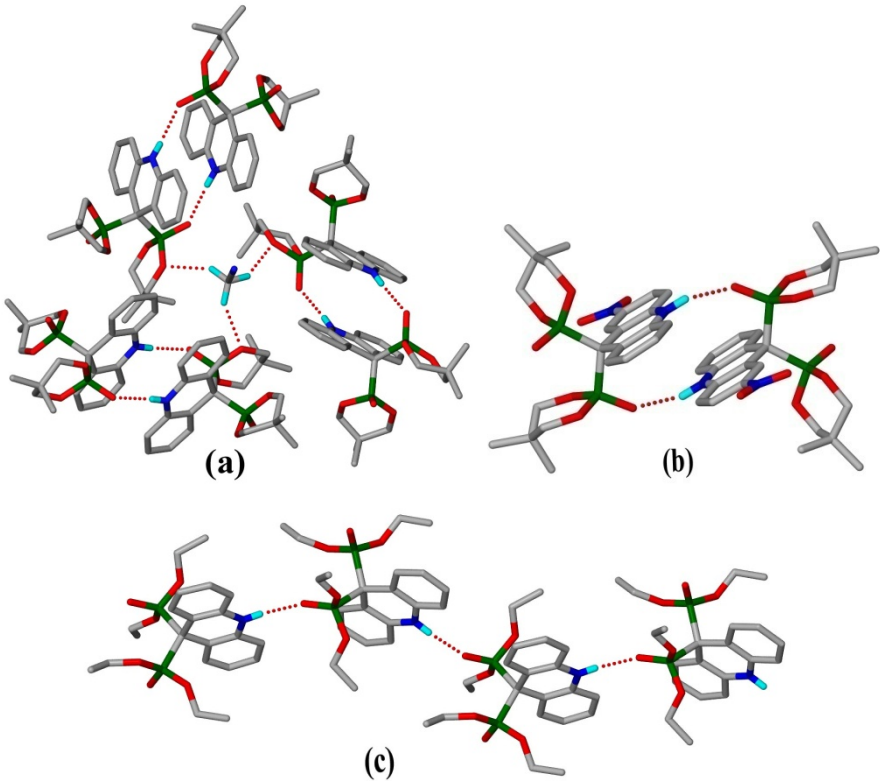


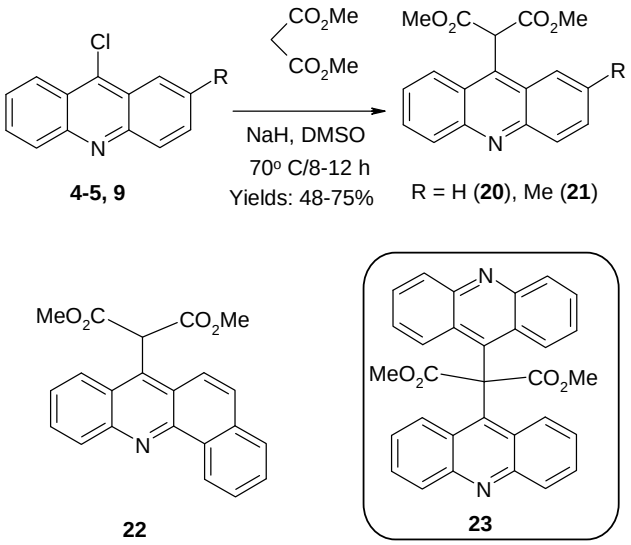
Fig. 3. Drawings showing hydrogen bonding interactions in (a) **11.**CH_3CN, (b) **15.**OC_4H_8 and (c) **18**. Hydrogen bonding interactions: Compound **11.**CH_3CN (Å, °): N(1)-H(1A)…O(3') 0.77(4), 2.18(4), 2.952(7), 176(4); C(25)-H(25A)…O(2) 1.07(7), 2.41(8), 3.361(8), 147(6). Symm. Equiv.: 5/3-x, 4/3-y, 1/3-z. Compound **15.**OC_4H_8 N(1)-H(1A)…O(6') 0.86, 1.99, 2.820(6) 162.5. Symm. Equiv.: 2-x, 1-y, -z. Compound **18** N-H(1A)…O(4') 0.78(5), 2.18(5), 2.910(6), 155(5). Symm. Equiv.: 2-x, 0.5+y, -z.

5.3 Nucleophilic substitution reactions of 9-chloroacridines with dimethyl malonate: Synthesis of malono-acridines 20-22 and bis(acridinyl)malonate 23

The reaction discussed above differs from normal nucleophilic substitution reactions of chloroacridines that lead to monosubstituted products.[33] In a manner similar to the phosphonylation reaction of 9-choloroacridines, we wanted to check reactions using dimethyl malonate/base for C-C bond formation at 9th position of 9-chloroacridine. In this context, in addition to the propargyloxy compound **10**, we have prepared monosubstituted acridines **20-22** by reacting dimethyl malonate/NaH with 9-chloroacridines **4-5** and **9** (Scheme 6).[34] These results show that a large number of 9-*C*-substituted acridines should be accessible *via* chloroacridines and the

plethora of available routes for C-C bond forming reactions. All these products [**20-22**] are well defined air-stable solids and have been characterized by NMR spectroscopy and analytical data. Perhaps more interesting is that in addition to these mono-substituted products, we also obtained a small amount of the compound **23** that has malonate with two acridine residues. This compound also had satisfactory analytical data. Utilization of these products for further reactions is being currently pursued in the laboratory.

Scheme 6



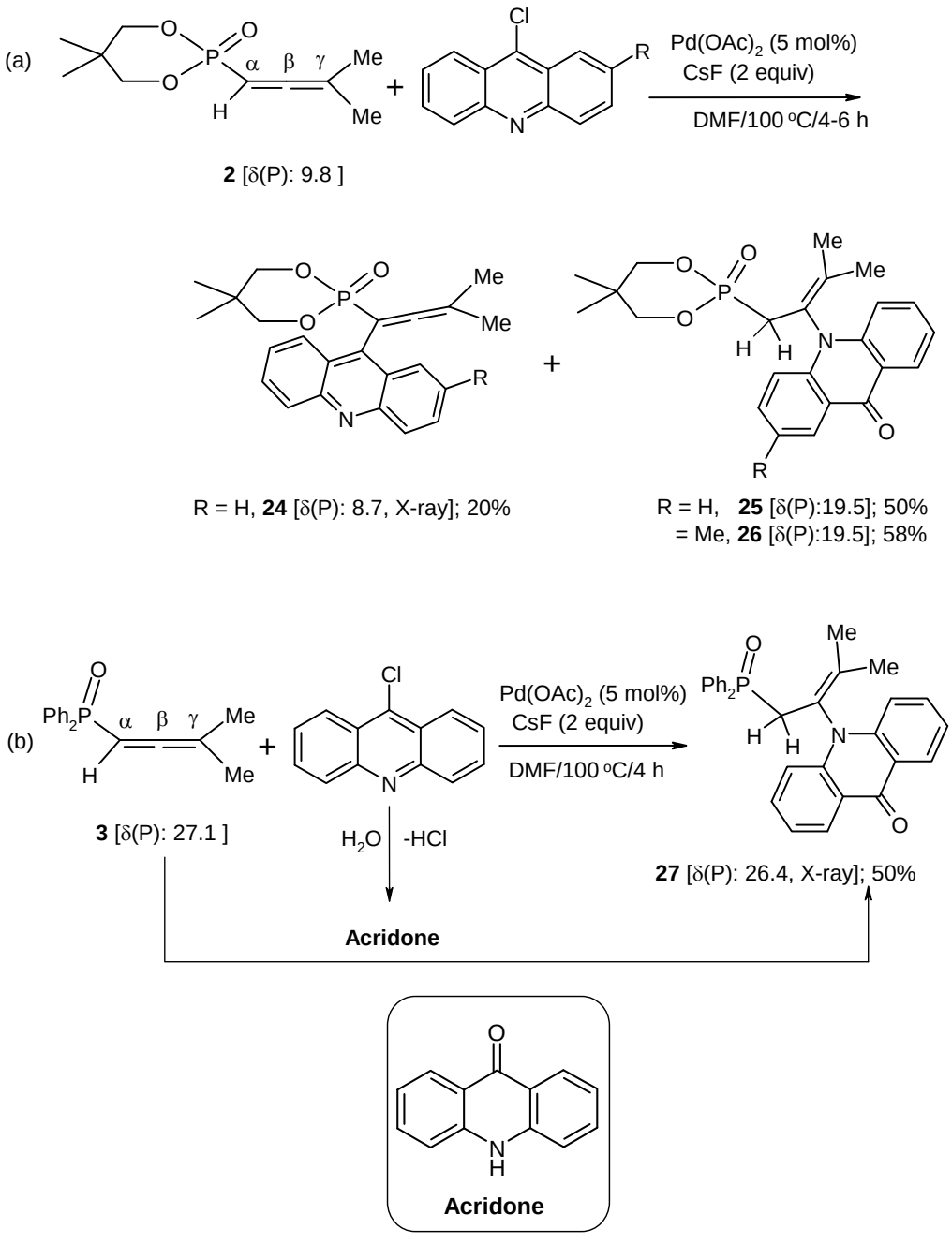
5.4 Attempted Heck-coupling reaction of $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (2) and $Ph_2P(O)C(H)=C=CMe_2$ (3) with 9-chloroacridines (4-5)

(a) Synthesis and characterization of phosphono-acridine derivatives 24-26 and the acridonyl phosphine oxide 27

In connection with the synthesis of acridine based organophosphonates, we planned to utilize 9-chloroacridines in Pd-catalyzed Heck-coupling reactions with allenylphosphonate $(OCH_2CMe_2CH_2O)P(O)C(H)=C=Me_2$ (**2**) and allenyl phosphine oxide $Ph_2P(O)C(H)=C=Me_2$ (**3**). This had the precedence in our laboratory, wherein my colleagues had used functionalized iodoarenes and allenes to obtain numerous heterocyclic products.[35] Thus we made an attempt to prepare vinyl acridines by coupling allenylphosphonate **2** [and allenyl phosphine oxide **3**] with 9-chloroacridine (**4**). Interestingly, a rather unusual arylation at the α-position [instead

of *β*-position][36] of allene **2** occurred, leading to the α-acridyl allene product **24** (Scheme 7a). Another product **25** was also isolated along with **24**. Although ^{31}P NMR spectrum of the reaction mixture of 9-chloro-2-methylacridine (**5)** with allene **2** showed the peak [δ(P): 8.3] corresponding to a product similar to **24**, it could not be isolated (Scheme 7a). Here only the acridone-addition product (**26**) that is similar to compound **25** was isolated. The reaction of allene **3** with 9-chloroacridine (**4**) gave only the acridone-addition product **27** (Scheme 7b).

Scheme 7



In the ^{1}H NMR spectrum of compound **24**, the signal due to α-proton [that was present in the precursor **2**] is missing and the integrated intensities match with the structure as given. LC-MS data and CHN analyses are also consistent. Since α-arylation on allenylphosphonates is not common, we have also determined the X-ray structure of compound **24** (Fig. 4). The bond distances of C(6)-C(20) [1.312(3)Å] and C(20)-C(21) [1.299(3)Å] confirm that the allene moiety is intact.

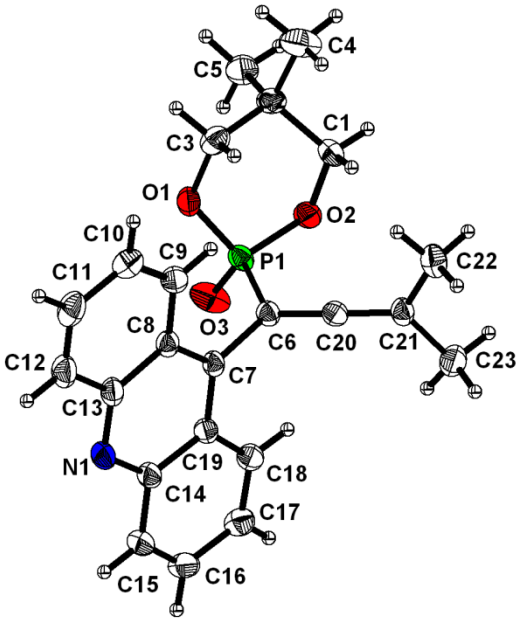


Fig. 4. An ORTEP diagram of compound **24**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(6) 1.7974(19), C(6)-C(7) 1.508(2), C(6)-C(20) 1.312(3), C(20)-C(21) 1.299(3).

The formation of unexpected products **25-27** may be due to the addition of the acridones [formed *via* water (adventitious) addition to the 9-chloroacridines (**4** or **5)** in the reaction mixture] to the allenes **2** or **3**. This assertion is confirmed by treating acridone directly with the allene (**2**) in the presence of CsF which led only to the product **25**. In a similar manner, other products **26-27** are also formed. All these compounds show the P(O)-CH_2 doublet at δ 3.0 [^{2}J(P-H) ~ 21.5 Hz for compounds **25-26**] and δ 3.5 [^{2}J(P-H) = 12.8 Hz for compound **27**]. The structure of compound **27** is confirmed by single crystal X-ray data (Fig. 5).

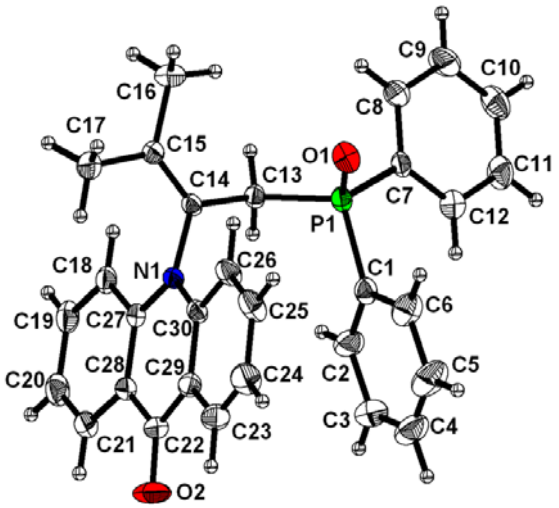


Fig. 5. An ORTEP diagram of compound **27**. Selected bond lengths [Å] with esd's in parentheses: P(1)-C(13) 1.813(3), O(2)-C(22) 1.225(4), N(1)-C(14) 1.451(4), N(1)-C(27) 1.382(4), N(1)-C(30) 1.391(4), C(13)-C(14) 1.515(4), C(21)-C(28) 1.406(6), C(14)-C(15) 1.326(4), C(22)-C(29) 1.457(6).

It may be noted that compounds **25-27** are enamines. Since normal enamines are hydrolytically unstable, we ascribe the stability of **25-27** to steric factors. For example, a diethylamino group (-NEt_2) in place of acridone residue in **25** hydrolyzes readily to give *β*-ketophosphonate $(OCH_2CMe_2CH_2O)P(O)CH_2C(O)CHMe_2$.[37] However our compounds **25-27** are fairly stable to moisture.

(b) UV-Visible and Fluorescence spectra of compounds 25-27

Acridone and its derivatives are reported to have characteristic fluorescence spectra.[22] Therefore, we have recorded the absorption and fluorescence spectra of acridone compounds **25-27** [1.0 μM/CH_3CN]. The data are summarized in Table 2. Compounds **25** and **26** showed two bands (368 and 397 nm) in the absorbance spectra due to the acridone moiety (Fig. 6). But the absorbance spectrum of compound **27** displayed additional bands at 291 and 303 nm due to the phenyl rings, along with the bands at 377 and 392 nm. The emission spectrum of **25** gave two bands at 402 and 426 nm (Fig. 6). In a similar manner compounds **26-27** also displayed two bands in the emission spectra. The details are given in Table 2. Synthesis and photochemical properties of this kind of derivatives are currently in progress in our laboratory.

Table 2. UV-Visible and Fluorescence spectral details for compounds **25-27**

Compound	λ_{max}^{abs}	λ_{max}^{fluo}
25	369, 390	404, 426
26	367, 397	413, 435
27	291, 303, 377, 392	406, 428

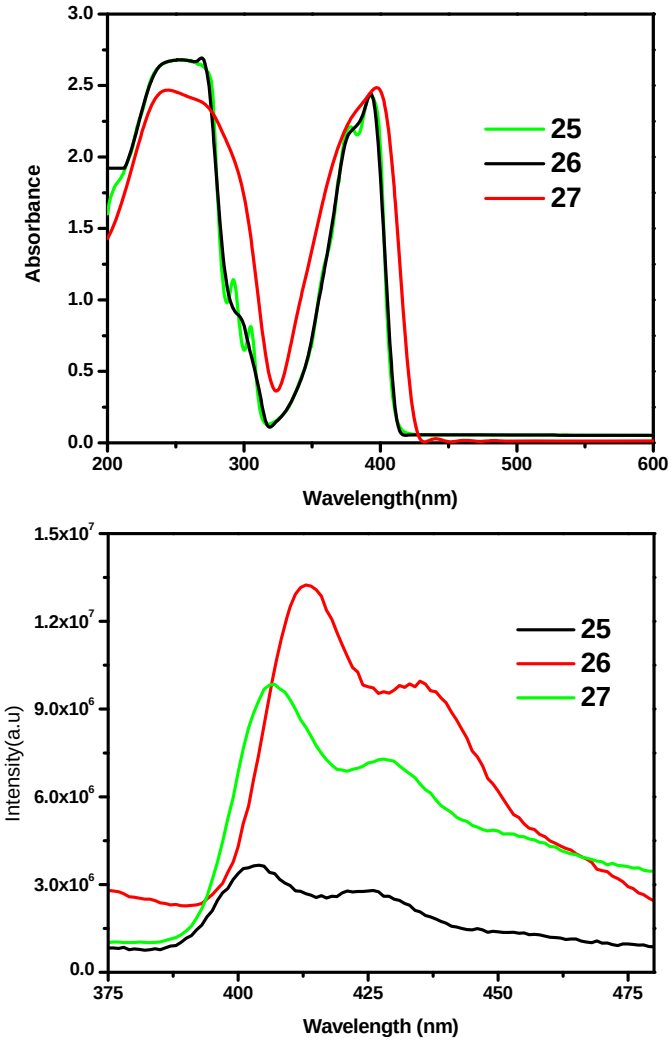


Fig. 6. Absorption (top) and emission (bottom) spectra for compounds **25-27** in CH_3CN

SUMMARY – PART B

1) Synthesis of phosphono-acridanes *via* phosphonylation of 9-chloroacridines with $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1**) is accomplished. Since the by-product acridones can be readily converted back to the 9-chloroacridines, the overall yield is quite good. The preliminary cytotoxic data for **13** is encouraging to do further work on this aspect.

2) Dimethyl malonyl-acridines were readily prepared by a simple nucleophilic displacement reaction of C-Cl bond in 9-chloroacridines. These reactions can also lead to the bis(acridinyl)malonates as demonstrated by the isolation of the compound **23**.

3) The reaction of allene $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (**2**) with 9-chloroacridine (**4**) resulted in the α-arylated product $(OCH_2CMe_2CH_2O)P(O)C(9\text{-acridinyl})=C=CMe_2$ (**24**). This type of α-arylation is rather uncommon in allene chemistry. The simple nucleophilic addition reaction of corresponding acridones with allenes $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ (**2**) and $Ph_2P(O)C(H)=C=CMe_2$ **(3)** afforded fairly stable enamino phosphonates **25-27**.

EXPERIMENTAL SECTION

Absorbance and Fluorescence Spectroscopy: Steady state absorption and fluorescence spectra were recorded on UV-Vis-NIR scanning spectrophotometer (Shimadzu, model no. UV-3101PC) and SPEX FLUOROMAX-3 spectrofluorometer, respectively.

Details of the other instruments, standards etc. are already given in Chapter 3.

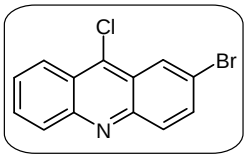
Cyclic phosphite ($OCH_2CMe_2CH_2O$)P(O)(H) [**1**, δ(P) 2.3] [Compound **7** in Part-A] was prepared by following a method previously reported from our laboratory.[25] Allenylphosphonate ($OCH_2CMe_2CH_2O$)P(O)CH=C=CMe_2 [**2**, δ(P) 9.8] and allenyl phosphine oxide Ph_2P(O)C(H)=C=CMe_2 [**3**, δ(P) 27.1] [labelled as **19** and **25** in Part-A] prepared by literature methods.[26]

6.1 Preparation of 9-chloroacridine derivatives 4-9 and 9-prop-2-ynyloxy-acridine (10)

(i) 9-Chloroacridines 4-9

The appropriate anthranilic acid (6.7 mmol) was dissolved in $POCl_3$ (10 mL) and the solution heated under reflux for 4 h. After cooling to room temperature, excess of $POCl_3$ was distilled off and the mixture was added very carefully with vigorous stirring to a mixture containing crushed ice, aq. ammonia (10 mL) and chloroform (30 mL) making sure that the solution was always basic. The aqueous layer was extracted with chloroform (2 x 30 mL) and combined with the original organic layer, then dried [$CaCl_2$]. The solvent was removed to yield the crude product. Analytically pure samples were obtained after flash-chromatography. 9-Chloroacridine (**4**) and 9-chloro-2-methylacridine (**5**) are known.[28] Data for the new compounds **6-9** are given below.

(a) 9-Chloro-2-bromoacridine (6)



This compound was isolated by using ethyl acetate/hexane (1:20) mixture.

Yield: 1.38 g (71%).

Mp: 160-162 ^{o}C (grey solid).

IR (KBr): 3123, 3088, 2980, 1636, 1595, 1524, 1466, 1346, 754 cm^{-1}.

^{1}H NMR: δ 7.92 (t, 1H, ^{3}J(H-H) ~ 7.8 Hz, Ar-*H*), 8.14-8.18 (m, 2H, Ar-*H*), 8.60 (d, 1H, ^{3}J(H-H) = 8.8 Hz, Ar-*H*), 8.76 (d, 1H, ^{3}J(H-H) = 1.5 Hz, Ar-*H*), 8.93 (d, 1H, ^{3}J(H-H) ~ 9.0 Hz, Ar-*H*), 8.98 (d, 1H, ^{3}J(H-H) ~ 9.0 Hz, Ar-*H*).

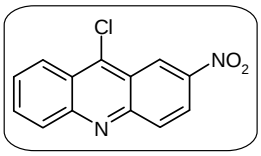
^{13}C NMR: δ 121.6, 124.5, 124.7, 125.0, 126.6, 127.7, 129.6, 131.1, 131.2, 134.5, 146.8, 148.6;

LC-MS: *m/z* 294 $[M+1]^{+}$.

Anal. Calcd. for $C_{13}H_7BrClN$: C, 53.37; H, 2.41; N, 4.79. Found: C, 53.41; H, 2.41; N, 4.74.

(b) 9-Chloro-2-nitroacridine (7)

This compound was isolated by using ethyl acetate/hexane (1:9) mixture.



Yield: 0.87 g (50%).

Mp: 172-174 ^{o}C (yellow solid).

IR (KBr): 3088, 2919, 2847, 1935, 1634, 1520, 1354, 764 cm^{-1}.

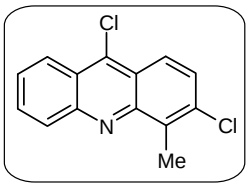
^{1}H NMR: δ 7.63 (td, 1H, ^{3}J(H-H) ~ 8.0 Hz, ^{4}J(H-H) ~ 2.0 Hz, Ar-*H*), 7.75 (~t, 1H, ^{3}J(H-H) ~ 8.0 Hz, Ar-*H*), 8.25 (d, 1H, ^{3}J(H-H) ~ 8.8 Hz, Ar-*H*), 8.33 (d, 1H, ^{3}J(H-H) = 9.5 Hz, Ar-*H*), 8.47 (d, 1H, ^{3}J(H-H) = 8.8 Hz, Ar-*H*), 8.48-8.52 (m, 1H, Ar-*H*), 9.41 (d, 1H, ^{4}J(H-H) = 2.0 Hz, Ar-*H*).

^{13}C NMR: δ 122.8, 123.7, 125.1, 128.5, 130.0, 131.9, 133.1, 145.1, 145.7, 149.2, 150.7.

LC-MS: *m/z* 259 $[M+1]^+$.

Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.73; N, 10.83. Found: C, 60.48; H, 2.69; N, 10.96.

(c) 3,9-Dichloro-4-methylacridine (8)



This compound was isolated by using ethyl acetate/hexane (1:9) mixture.

Yield: 1.30 g (75%).

Mp: 150-152 ^oC (yellow solid).

IR (KBr): 2966, 1601, 1549, 1520, 1454, 1395, 1314, 1009, 752 cm^{-1}.

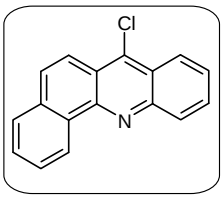
^1H NMR: δ 2.98 (s, 3H, CH_3), 7.53 (d, 1H, ^3J(H-H) = 9.3 Hz, Ar-*H*), 7.62 (~t, 1H, ^3J(H-H) ~ 7.6 Hz, Ar-*H*), 7.78 (~t, 1H, ^3J(H-H) ~ 7.6 Hz, Ar-*H*), 8.18 (d, 1H, ^3J(H-H) = 9.3 Hz, Ar-*H*), 8.22 (d, 1H, ^3J(H-H) = 8.8 Hz, Ar-*H*), 8.36 (d, 1H, ^3J(H-H) = 8.8 Hz, Ar-*H*).

^{13}C NMR: δ 15.0, 122.7, 123.0, 123.8, 124.5, 127.1, 128.5, 130.4, 130.5, 134.9, 135.5, 144.2, 148.3, 148.5.

Anal. Calcd. for $C_{14}H_9Cl_2N$: C, 64.15; H, 3.46; N, 5.34. Found: C, 64.22; H, 3.47; N, 5.24.

(d) 7-Chloro-benzo[c]acridine (9)

This compound was isolated by using ethyl acetate/hexane (1:9) mixture.



Yield: 1.17 g (60%).

Mp: 144-146 ^oC (yellow solid).

IR (KBr): 3036, 1624, 1557, 1493, 1470, 1393, 1304, 1238, 742 cm^{-1}.

^1H NMR: δ 7.70 (~t, 1H, ^3J(H-H) ~ 8.0 Hz, Ar-*H*), 7.75-7.82 (m, 3H, Ar-*H*), 7.85-7.90 (m, 2H, Ar-*H*), 8.21 (d, 1H, ^3J(H-H) = 9.3 Hz, Ar-*H*), 8.40

(d, 1H, ^3J(H-H) = 8.6 Hz, Ar-*H*), 8.46 (d, 1H, ^3J(H-H) = 8.6 Hz, Ar-*H*), 9.50 (d, 1H, ^3J(H-H) = 7.9 Hz, Ar-*H*).

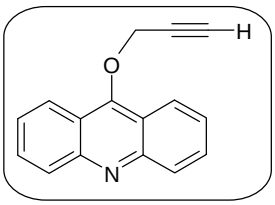
^{13}C NMR: δ 121.8, 122.7, 124.5, 124.9, 125.7, 127.0, 127.7, 128.0, 129.1, 129.5, 130.1, 130.2, 131.4, 133.6, 140.1, 147.6, 147.9.

LC-MS: *m/z* 264 $[M+1]^+$.

Anal. Calcd. for $C_{17}H_{10}ClN$: C, 77.42; H, 3.82; N, 5.31. Found: C, 77.41; H, 3.84; N, 5.53.

(ii) 9-Prop-2-ynyloxy-acridine (10)

To a suspension of NaH (0.48 g, 2.0 mmol) in THF (10 mL) was added propargyl alcohol (0.06 g, 1.2 mmol) at room temperature under nitrogen atmosphere and the mixture stirred for 10 min. To this solution, 9-chloroacridine (**4**) (0.21 g, 1.0 mmol) was added at once and stirring continued at 70 ^oC for 12 h. The reaction mixture was quenched with cold water (5 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with water (2 x10 mL), brine solution (10 mL), dried (Na_2SO_4) and then the solvent removed to obtain a solid. Pure compound **10** was isolated by column chromatography [ethyl acetate/hexane (1:9)].



Yield: 0.14 g (60%).

Mp: 152-154 ^oC (pale yellow solid)

IR (KBr): 3160, 2114, 1618, 1557, 1414, 1337, 1092, 758 cm^{-1}.

^{1}H NMR: δ 2.60 (t, 1H, ^4J(H-H) = 2.3 Hz, C≡C*H*), 5.04 (d, 2H, ^4J(H-H) = 2.3 Hz, OCH_2), 7.54-7.58 (m, 2H, Ar-*H*), 7.77-7.81 (m, 2H, Ar-*H*), 8.24 (d, 2H, ^3J(H-H) = 8.6 Hz, Ar-*H*), 8.35 (d, 2H, ^3J(H-H) = 8.6 Hz, Ar-*H*).

^{13}C NMR: δ 63.7, 77.8, 78.2, 120.6, 122.7, 125.5, 129.7, 130.5, 150.5.

LC-MS: *m/z* 234 $[M+1]^+$.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.21; H, 4.71; N, 6.18.

6.2 Hydrophosphonylation of acridine derivatives

6.21 Hydrophosphonylation of 10 with $(OCH_2CMe_2CH_2O)P(O)(H)$ (1)

A mixture of 9-prop-2-ynyloxy-acridine (**10**) (1.17 g, 5.0 mmol), phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1)** (2.25 g, 15.0 mmol) and $Mn(OAc)_2$ (0.68 g, 0.25 mmol) were heated at 90 ^oC under nitrogen for 4 h. Ethyl acetate (20 mL) was added to the mixture and the resulting solution washed with water (10 x 20 mL), brine solution, dried (Na_2SO_4) and concentrated to yield a brown colored gummy solid. Pure compound **11** was isolated using column chromatography (ethyl acetate/hexane-4:1) as a pale yellow solid.

Yield: by NMR (40%); 0.36 g (15%, isolated).

This compound was recrystallized from acetonitrile (3 mL). For spectroscopic and analytical data please see section 6.23 below.

6.22 Hydrophosphonylation of acridine with $(OCH_2CMe_2CH_2O)P(O)(H)$ (1): Synthesis of compound 12

Acridine (0.18 g, 1.0 mmol) and phosphite $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1**) (0.18 g, 1.2 mmol) were irradiated in microwave [180 °C; 160 W] for 5 min or heated at 70 ^oC for 20 min. Ethyl acetate (10 mL) was added and the organic layer washed with water (3 x 10 mL) and brine solution (10 mL), then dried (Na_2SO_4). The solvent was removed to yield brown colored solid. Pure compound **12** was obtained by column chromatography (ethyl acetate/hexane-4:1).

Yield: 0.31 g (95%).

Mp: 190-192 ^oC [lit. 187-188 ^oC[22]]

^{31}P NMR: δ 16.4 [lit. 16.7[22]]

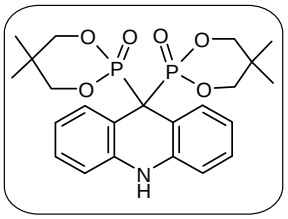
^1H and ^{13}C NMR spectra were identical to that reported before.[22]

6.23 Hydrophosphonylation of 9-chloroacridines with $(OCH_2CMe_2CH_2O)P(O)(H)$ (1) and $(EtO)_2P(O)(H)$: Preparation of 11 and 13-18

In a 25 mL round bottom flask, 9-chloroacridine (**4**, 1.07 g, 5.0 mmol) and phosphite **1** (1.50 g, 10.0 mmol) were heated at 90 ^oC under nitrogen for 4 h. At this stage, only one phosphorus signal due to the product was observed. When there was no 9-chloroacridine left (TLC), ethyl acetate (20 mL) was added to the reaction

mixture followed by saturated sodium bicarbonate solution. The organic layer was separated and aqueous layer extracted thrice (3 x 10 mL) with ethyl acetate. The combined organic part was washed with water (5 x 20 mL), brine solution, dried (Na_2SO_4) and concentrated to yield a brown colored gummy solid. Pure 9,9-bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-9,10-dihydro-acridine (**11**) was isolated by column chromatography (ethyl acetate/hexane-4:1) as a white solid. Other compounds **13-18** were prepared similarly. The reaction mixture showed a single phosphonate product in most cases, in ca 50-60% (^{31}P NMR). We could also recover the corresponding acridone formed as a byproduct, and convert it back to 9-chloroacridine in nearly quantitative yields by treatment with thionyl chloride ($SOCl_2$).

9,9-Bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl) 9,10-dihydro-acridine (11)



Pure compound was isolated by using ethyl acetate/hexane (9:1) as eluant.

Yield: by NMR (55%), 0.50 g (isolated, 20%).

Mp: 248-250 ^{o}C.

IR (KBr): 3266, 2965, 1613, 1530, 1491, 1344, 1250, 1064 cm^{-1}.

^{1}H NMR: δ 0.71 (s, 6H, 2 CH_3), 1.22 (s, 6H, 2 CH_3), 3.91-3.97 (m, 4H, 2 OCH_2), 4.15-4.17 (m, 4H, 2 OCH_2), 6.03 (d, 2H, ^3J(H-H) = 7.6 Hz, Ar-*H*), 6.64 (~t, 2H, ^3J(H-H) ~ 7.6 Hz, Ar-*H*), 6.71 (~t, 2H, ^3J(H-H) ~ 7.6 Hz, Ar-*H*), 7.80 (d, 2H, ^3J(H-H) = 7.6 Hz, Ar-*H*), 7.96 (s, 1H, N*H*).

^{13}C NMR: δ 20.7, 22.5, 32.4 and 32.5 (2 d, ^3J(P-C) ~ 4.4 Hz, *C*Me$_2$), 51.8 (t, ^1J(P-C) = 132.1 Hz, P-*C*-P), 78.3, 110.0 and 110.1 (2 d, *J*(P-C) ~ 7.2 Hz), 115.0, 118.4, 129.4, 131.7, 139.0 and 139.2 (2 d, *J*(P-C) ~ 5.5 Hz).

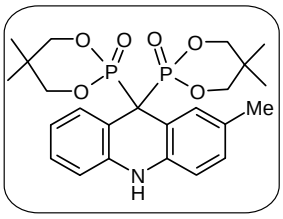
^{31}P NMR: δ 8.0.

LC-MS: *m/z* 478 [M+1]$^+$.

Anal. Calcd. for $C_{23}H_{29}NO_6P_2$: C, 57.86; H, 6.12; N, 2.93. Found: C, 58.04; H, 6.10; N, 2.84.

This compound was crystallized from acetonitrile (2 mL). Single crystal X-ray structure analysis was performed on this compound.

9,9-Bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2-methyl-9,10-dihydro-acridine (13)



Pure compound was isolated by using ethyl acetate as eluant.

Yield: by NMR (52%), 0.74 g (isolated, 30%).

Mp: 262-264 ^oC.

IR (KBr): 3272, 2963, 2926, 1615, 1495, 1343, 1256, 1066 cm^{-1}.

^1H NMR: δ 0.71 (s, 6H, 2 CH_3), 1.22 (s, 6H, 2 CH_3), 2.25 (s, 3H, CH_3), 3.92-3.98 (m, 4H, 2 OCH_2), 4.13-4.16 (m, 4H, 2 OCH_2), 6.00 (d, 1H, ^3J(H-H) = 7.6 Hz, Ar-*H*), 6.05 (d, 1H, ^3J(H-H) = 7.9 Hz, Ar-*H*), 6.53 (d, 1H, ^3J(H-H) = 7.9 Hz, Ar-*H*), 6.64 (~t, 1H, ^3J(H-H) ~ 7.6 Hz, Ar-*H*), 6.72 (~t, 1H, ^3J(H-H) ~ 7.6 Hz, Ar-*H*), 7.61 (s, 1H), 7.82 (d, 1H, ^3J(H-H) = 7.6 Hz, Ar-*H*), 7.86 (s, 1H).

^{13}C NMR: δ 20.7, 21.1, 22.4, 32.4 and 32.5 (2 d, ^3J(P-C) ~ 4.2 Hz, *C*Me$_2$), 51.8 (t, ^1J(P-C) = 132.4 Hz, P-*C*-P), 78.2, 109.7 and 109.8 (2 d, *J*(P-C) ~ 9.2 Hz), 114.7 and 114.8 (2 d, *J*(P-C) ~ 7.9 Hz), 118.2, 127.3, 129.2, 130.1, 131.9 (t, *J*(P-C) = 3.6 Hz), 136.7, 139.4. This spectrum is shown in Fig. 7.

^{31}P NMR: δ 8.1.

LC-MS: *m/z* 492 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{31}NO_6P_2$: C, 58.65; H, 6.36; N, 2.85. Found : C, 58.64; H, 6.36; N, 2.86.

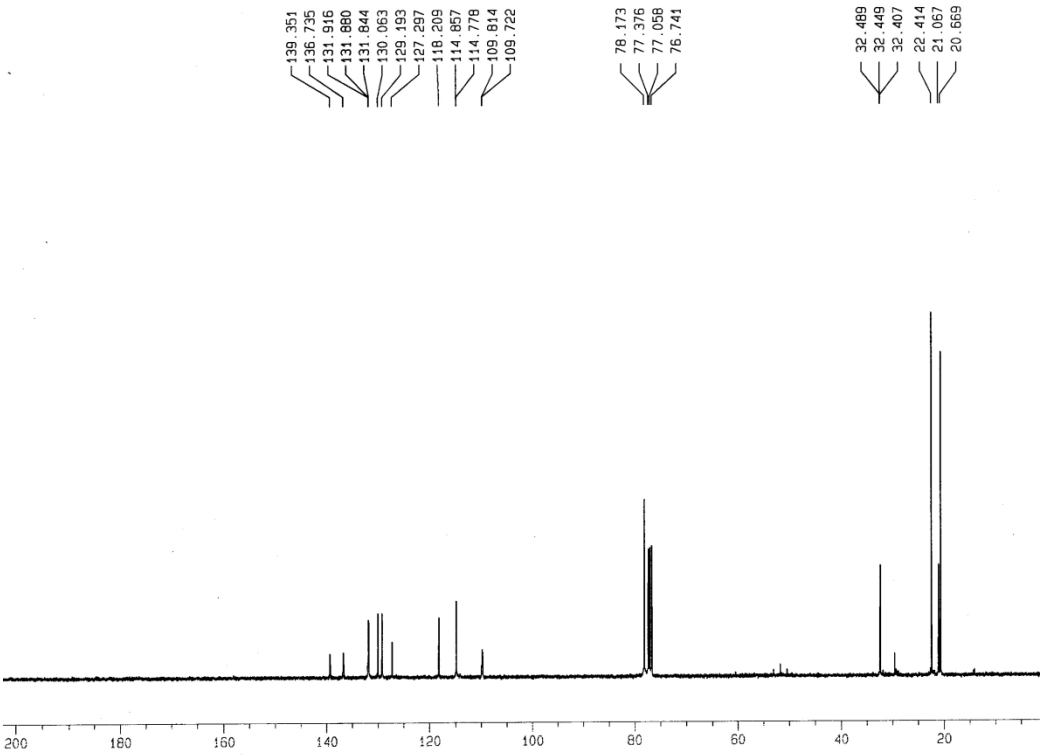
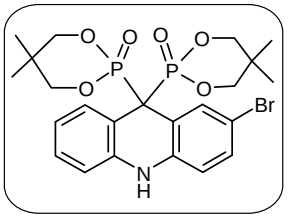


Fig. 7. ^{13}C NMR spectrum of compound **13**

2-Bromo-9,9-bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl) 9,10-dihydro-acridine (14)



Pure compound was isolated by using ethyl acetate/hexane (9:1) as the eluant.

Yield: by NMR (58%), 0.72 g (isolated, 26%).

Mp: 268-270 ^{o}C.

IR (KBr): 3254, 3177, 2967, 1615, 1489, 1244, 1069, 1028 cm^{-1}.

^{1}H NMR: δ 0.75 (s, 6H, 2 CH_3), 1.26 (s, 6H, 2 CH_3), 4.01 (not resolved, 4H, 2 OCH_2), 4.22 and 4.24 (~2 d, 4H, ^2J(H-H) ~ ^3J(P-H) ~7.1 Hz, 2 OCH_2), 5.92-5.98 (m, 2H, Ar-*H*), 6.68-6.77 (m, 3H, Ar-*H*), 7.78 (d, 1H, ^3J(H-H) = 6.6 Hz, Ar-*H*), 7.86 (s, 1H), 8.39 (s, 1H).

^{13}C NMR: δ 20.6, 22.4, 32.4 and 32.5 (2 d, ^3J(P-C) ~ 4.0 Hz, *C*Me$_2$), 51.6 (t, ^1J(P-C) = 131.0 Hz, P-*C*-P), 78.5 and 78.6 (2 d, ^2J(P-C) ~ 11.0 Hz,

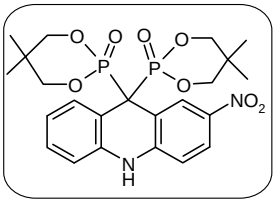
O*C*H$_2$), 109.5 and 109.6 (2 d, *J*(P-C) ~ 8.0 Hz), 109.9, 111.9, 115.2, 116.3, 118.8, 129.6, 131.5, 132.1, 134.0, 138.6, 138.8.

^{31}P NMR: δ 7.3.

LC-MS: *m/z* 556 $[M]^+$.

Anal. Calcd. for $C_{23}H_{28}BrNO_6P_2$: C, 49.66; H, 5.07; N, 2.52. Found: C, 49.61; H, 5.12; N, 2.70.

9,9-Bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2-nitro-9,10-dihydro-acridine (15)



Pure compound was isolated by using ethyl acetate as eluant.

Yield: by NMR (50%), 0.39 g (isolated, 15%).

Mp: 272-274 ^oC (yellow solid)

IR (KBr): 2963, 2924, 2855, 1624, 1491, 1262, 1092, 1020, 800 cm^{-1}.

^{1}H NMR: δ 0.76 (s, 6H, 2 C*H*$_3$), 1.28 (s, 6H, 2 C*H*$_3$), 4.04-4.13 (m, 4H, 2 OC*H*$_2$), 4.24-4.28 (not resolved, 4H, 2 OC*H*$_2$), 5.98 and 6.00 (2 closely spaced d, 2H, Ar-*H*), 6.71 (~t, 1H, ^{3}*J*(H-H) ~ 7.8 Hz, Ar-*H*), 6.82 (~t, 1H, ^{3}*J*(H-H)~ 7.8 Hz, Ar-*H*), 7.47 (d, 1H, ^{3}*J*(H-H)= 8.8 Hz, Ar-*H*), 7.83 (d, 1H, ^{3}*J*(H-H)= 7.8 Hz, Ar-*H*), 8.76 (d, 1H, ^{3}*J*(H-H)= 1.9 Hz, Ar-*H*), 9.27 (s, 1H, N*H*).

^{13}C NMR: δ 20.6, 22.2, 32.6 and 32.7 (2 d, ^{3}*J*(P-C) ~ 4.2 Hz, *C*Me$_2$), 52.1 (t, ^{1}*J*(P-C) ~ 132.2 Hz, P-*C*-P), 78.6, 110.0 and 110.7 (2 d, *J*(P-C) ~ 8.0 Hz), 114.1, 115.7, 121.0, 125.3, 129.2, 129.8, 131.6, 137.2 (d, *J*(P-C) ~ 5.3 Hz), 139.0, 144.8 (d, *J*(P-C) ~ 4.3 Hz).

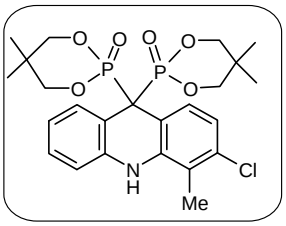
^{31}P NMR: δ 7.1.

LC-MS: *m/z* 522 $[M]^+$.

Anal. Calcd. for $C_{23}H_{28}N_2O_8P_2$: C, 52.88; H, 5.40; N, 5.36. Found: C, 52.79; H, 5.45; N, 5.45.

This compound was crystallized from dichloromethane (3 mL) containing traces of THF; X-ray structural analysis was performed on this sample.

3-Chloro-9,9-bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-4-methyl-9,10-dihydro-acridine (16*)*



Pure compound was isolated by using ethyl acetate as eluant.

Yield: by NMR (54%), 0.52 g (isolated, 20%).

Mp: 280-282 ^{o}C.

IR (KBr): 3285, 2965, 1611, 1470, 1258, 1061 cm^{-1}.

^{1}H NMR: δ 0.73 (s, 6H, 2 C*H*$_3$), 1.17 (s, 6H, 2 C*H*$_3$), 1.90 (s, 3H, C*H*$_3$), 3.98-4.02 (m, not resolved, 4H, 2 OC*H*$_2$), 4.08-4.11 (m, 4H, 2 OC*H*$_2$), 6.53 (d, 1H, ^{3}*J*(H-H) = 7.8 Hz, Ar-*H*), 6.72-6.83 (m, 3H, Ar-*H*), 6.93 (s, 1H, N*H*), 7.74 (d, 1H, ^{3}*J*(H-H) = 8.7 Hz, Ar-*H*), 7.85 (d, 1H, ^{3}*J*(H-H) = 7.8 Hz, Ar-*H*).

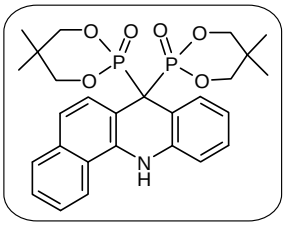
^{13}C NMR: δ 13.5, 20.8, 22.3, 32.4 and 32.5 (2 d, ^{3}*J*(P-C) ~ 3.1 Hz, *C*Me$_2$), 52.0 (t, ^{1}*J*(P-C)= 132.0 Hz, P-*C*-P), 77.9 and 78.0 (2 d, ^{2}*J*(P-C)~ 4.0 Hz, O*C*H$_2$), 109.4 and 110.3 (2 d, *J*(P-C)~ 7.0 Hz), 115.5, 119.4, 119.8, 120.0, 129.4, 130.5, 132.0, 135.2, 138.2, 138.4.

^{31}P NMR: δ 8.0.

LC-MS: *m/z* 525 [M-1]$^{+}$.

Anal. Calcd. for $C_{24}H_{30}ClNO_6P_2$: C, 54.81; H, 5.75; N, 2.66. Found: C, 54.88; H, 5.71; N, 2.69.

7,7-Bis-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-7,12-dihydro-benzo[c]acridine (17)



Pure compound was isolated by using ethyl acetate as eluant.

Yield: By NMR (52%), isolated 0.26 g (15%).

Mp: 298-300 ^{o}C.

IR (KBr): 3295, 3061, 2963, 1607, 1535, 1495, 1414, 1262, 1061, 745 cm^{-1}.

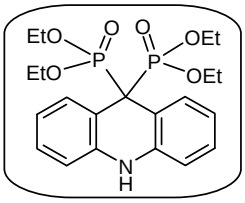
^{1}H NMR δ 0.66 (s, 6H, 2 C*H*$_3$), 1.21 (s, 6H, 2 C*H*$_3$), 3.91-3.99 (m, 4H, 2 OC*H*$_2$), 4.13 (m, not resolved, 4H, 2 OC*H*$_2$), 6.40-6.43 (m, 1H, Ar-*H*), 6.53 (~t, 2H, ^{3}J(H-H) ~ 7.2 Hz, Ar-*H*), 7.09-7.15 (m, 2H, Ar-*H*), 7.24-7.27 (m, 1H, Ar-*H*), 7.45 (d, 1H, ^{3}J(H-H) = 7.8 Hz, Ar-*H*), 7.73-7.79 (m, 2H, Ar-*H*), 7.92 (d, 1H, ^{3}J(H-H) = 8.8 Hz, Ar-*H*), 8.02 (s, 1H, N*H*).

^{13}C NMR: δ 20.8, 22.5, 32.5 and 32.6 (2 d, ^{3}J(P-C) ~ 4.4 Hz, *C*Me$_2$), 52.7 (t, ^{1}J(P-C) = 136.2 Hz, P-*C*-P), 78.1, 115.5, 118.6, 119.8, 121.2, 122.0, 125.1, 126.0, 127.5, 128.8, 129.0, 131.0, 132.6, 134.8, 138.6.

^{31}P NMR: δ 8.0.

Anal. Calcd. for $C_{27}H_{31}NO_6P_2$: C, 61.48; H, 5.92; N, 2.66. Found: C, 61.42; H, 5.96; N, 2.73.

[9-(Diethoxy-phosphoryl)-9,10-dihydro-acridin-9-yl]-phosphonic acid diethyl ester (18)



Pure compound was isolated by using ethyl acetate:hexane (4:1) mixture as the eluant.

Yield: by NMR (60%), 0.60 g (isolated, 25%)

Mp: 214-216 ^{o}C

IR (KBr): 3266, 2963, 2894, 1613, 1530, 1491, 1344, 1250, 743 cm^{-1}.

^{1}H NMR: δ 1.16 (t, 12H, ^{3}J(H-H) = 7.2 Hz, 4 OCH$_2$C*H*$_3$), 4.00-4.10 (m, 8H, 4 OC*H*$_2$CH$_3$), 6.12 (s, 1H, N*H*), 6.47 (d, 2H, ^{3}J(H-H) = 7.6 Hz, Ar-*H*), 6.78 (~t, 2H, ^{3}J(H-H) = 7.6 Hz, Ar-*H*), 7.07 (~t, 2H, ^{3}J(H-H) ~ 7.6 Hz, Ar-*H*), 8.16 (d, 2H, ^{3}J(H-H) = 7.6, Ar-*H*).

^{13}C NMR: δ 16.2 and 16.3 (2 d, ^{3}J(P-C) ~ 2.7 Hz, OCH$_2$*C*H$_3$), 50.5 (t, ^{1}J(P-C) = 132.5 Hz, P-*C*-P), 63.8 and 63.9 (2 d, ^{2}J(P-C)~ 3.5 Hz, OCH$_2$CH$_3$),

112.0 (t, *J*(P-C) = 8.2 Hz), 114.0, 118.8, 129.0, 133.3, 138.7 (t, *J*(P-C) = 5.5 Hz)

^{31}P NMR: δ 15.9.

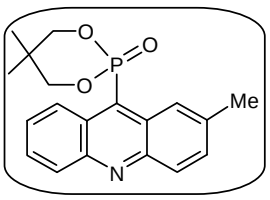
LC-MS: *m/z* 453 $[M]^+$.

Anal. Calcd. for $C_{21}H_{29}NO_6P_2$: C, 55.63; H, 6.45; N, 3.09. Found: C, 55.71; H, 6.41; N, 3.12.

This is a known compound.[21] In the present work, this compound was crystallized from ethyl acetate/hexane (4 + 1 mL) mixture; X-ray structural analysis was performed on this sample.

6.24 Synthesis of monophosphonate 19

A mixture of 9-chloro-2-methylacridine (**5**, 1.14 g, 5 mmol) and $(OCH_2CMe_2CH_2O)P(O)(H)$ (**1**) (0.60 g, 4 mmol) was heated at 90 ^oC under nitrogen for 4 h. Ethyl acetate (20 mL) followed by saturated sodium bicarbonate solution were added to the reaction mixture. The organic layer was separated and aqueous layer extracted thrice (3 x 10 mL) with ethyl acetate. The combined organic layer was washed with water (5 x 20 mL), brine solution, dried (Na_2SO_4) and concentrated to yield brown colored gummy solid. Pure 9-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-acridine (**19**) was isolated from column chromatography (ethyl acetate/hexane-2:3) as a pale yellow solid.



19

Yield: by NMR (20%); 0.17 g (isolated 10%).

Mp: 182-184 ^oC.

IR (KBr): 2974, 2924, 1634, 1474, 1262, 1051, 1009 cm^{-1}.

^{1}H NMR: δ 0.67 and 1.44 (2 s, 6H, 2 C*H*$_3$), 2.63 (s, 3H, C*H*$_3$), 3.59-3.63 (m, 2H, OC*H*$_2$), 3.99-4.07 (m, 2H, OC*H*$_2$), 7.63-7.83 (m, 3H, Ar-*H*), 8.22 (d, 1H, ^{3}*J*(H-H) = 8.8 Hz, Ar-*H*), 8.30 (d, 1H, ^{3}*J*(H-H) = 7.6 Hz, Ar-*H*), 8.57 (s, 1H, Ar-*H*); 8.80 (d, 1H, ^{3}*J*(H-H) = 8.8 Hz, Ar-*H*)

^{13}C NMR: δ 20.4, 22.2, 22.5, 32.1 (d, ^{3}J(P-C) = 6.0 Hz, *C*Me$_2$), 76.8, 76.9, 124.3 (d, *J*(P-C) = 5.8 Hz), 126.0 (d, *J*(P-C) = 5.7 Hz), 126.8, 127.1, 127.2, 127.8, 129.5, 130.2, 130.6, 133.0, 138.2 [the doublet due to ^{1}J(P-C) was not clear].

^{31}P NMR: δ 10.6.

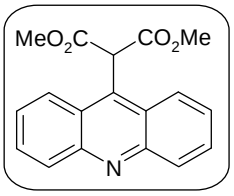
LC-MS: *m/z* 342 $[M+1]^+$.

Anal. Calcd. for $C_{19}H_{20}NO_3P$: C, 66.85; H, 5.91; N, 4.10. Found: C, 66.81; H, 5.86; N, 4.18.

6.3 Reaction of 9-chloroacridines (4-5 and 9) with dimethyl malonate: Synthesis of compounds 20-23

Typical procedure for 20: To a suspension of NaH (0.48 g, 2.0 mmol) in DMSO (5 mL), dimethyl malonate (0.16 g, 1.2 mmol) was added at room temperature under nitrogen atmosphere and the mixture stirred for 10 min. To the resulting solution, 9-chloroacridine (0.21 g, 1.0 mmol) was added all at once and stirring continued at 70 ^{o}C for 12 h. The reaction mixture was quenched with cold water (5 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with water (2 x 10 mL), brine solution (10 mL), dried (Na_2SO_4) and then the solvent removed to obtain compound **20** as an yellow solid. Pure compound was crystallized from dichloromethane/hexane (4:1).

2-Acridin-9-yl-malonic acid dimethyl ester (20)



Pure compound was isolated by using ethyl acetate:hexane (1:9) mixture as light yellow solid.

Yield: 0.20 g (65%).

Mp: 150-152 ^{o}C.

IR (KBr): 2953, 2859, 1738, 1634, 1558, 1437, 1325, 1146, 764 cm^{-1}.

^{1}H NMR: δ 3.74 (s, 6H, 2 CO_2CH_3), 6.08 (s, 1H, C*H*CO_2Me), 7.61 (d, 2H, ^{3}J(H-H) = 7.8, Hz, Ar-*H*), 7.79 (d, 2H, ^{3}J(H-H) = 7.6 Hz, Ar-*H*), 8.23-8.29 (m, 4H, Ar-*H*).

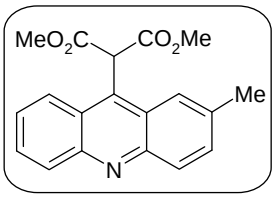
^{13}C NMR δ 51.2, 53.2, 124.2, 125.3, 126.8, 129.8, 130.7, 135.6, 149.0, 168.1.

LC-MS: *m/z* 310 $[M+1]^+$.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.78; H, 4.93; N, 4.65.

This compound was crystallized from dichloromethane and hexane (4 + 1 mL). X-ray structural analysis was performed for this compound.[34]

2-(2-Methyl-acridin-9-yl)-malonic acid dimethyl ester (21)



Pure compound was isolated by using ethyl acetate:hexane (1:9) mixture as light yellow solid.

Yield: 0.19 g (60%; using 1.0 mmol of compound **5**).

Mp: 160-162 ^{o}C.

IR(KBr): 2957, 2919, 2855, 1738, 1634, 1555, 1435, 1325, 1024, 814 cm^{-1}.

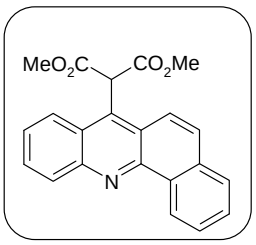
^{1}H NMR: δ 2.61 (s, 3H, C*H*$_3$), 3.74 (s, 6H, 2 CO_2CH_3), 6.05 (s, 1H, C*H*CO_2Me), 7.57-7.77 (m, 3H Ar-*H*), 7.95 (s, 1H, Ar-*H*), 8.15-8.25 (m, 3H, Ar-*H*).

^{13}C NMR: δ 22.5, 51.2, 53.2, 122.1, 124.4, 125.5, 126.7, 129.4, 130.4, 130.6, 132.8, 134.4, 137.0, 148.0, 148.5, 168.3.

LC-MS: *m/z* 324 $[M+1]^+$.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.65; H, 5.24; N, 4.52.

2-Benzo[*c*]acridin-7-yl-malonic acid dimethyl ester (22)



Pure compound was isolated by using ethyl acetate/hexane (1:9) mixture as a light yellow solid.

Yield: 0.17 g (48%; using 1.0 mmol of compound **9**).

Mp: 168-170 ^{o}C.

IR (KBr): 3117, 2922, 1717, 1651, 1541, 1474, 1325, 1150, 1041 cm^{-1}.

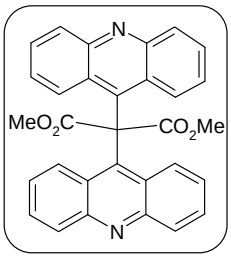
^{1}H NMR: δ 3.74 (s, 6H, 2 CO_2CH_3), 6.06 (s, 1H, $CHCO_2Me$), 7.66-7.87 (m, 7H, Ar-*H*), 8.26 (d, 1H, ^{3}J(H-H) = 8.3 Hz, Ar-*H*), 8.42 (d, 1H, ^{3}J(H-H) = 8.3 Hz, Ar-*H*), 9.55 (d, 1H, ^{3}J(H-H) = 7.4 Hz, Ar-*H*).

^{13}C NMR: δ 51.4, 53.3, 121.8, 123.9, 124.1, 125.7, 126.9, 127.7, 127.8, 128.9, 129.3, 131.2, 132.0, 133.2, 134.7, 147.6, 147.8, 168.3.

LC-MS: *m/z* 360 $[M+1]^{+}$.

Anal. Calcd. for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.65; H, 4.72; N, 3.98.

2,2-Di-acridin-9-yl-malonic acid dimethyl ester (23)



This compound was obtained in the same reaction as that for **20**. Pure compound **23** was eluted from ethyl acetate/hexane (1:9) mixture after eluting compound **20**.

Yield: 0.05 g (10%; using 1.0 mmol of compound **4**).

Mp: ~300 ^{o}C.

IR (KBr): 2924, 1717, 1636, 1541, 1522, 1474, 1339, 1020 cm^{-1}.

^{1}H NMR: δ 4.26 (s, 6H, 2 CO_2CH_3), 7.54 (~t, 2H, ^{3}J(H-H) ~8.0 Hz, Ar-*H*), 7.78 (~t, 2H, ^{3}J(H-H) ~ 8.0 Hz, Ar-*H*), 8.23 (d, 2H, ^{3}J(H-H) ~ 8.0 Hz, Ar-*H*), 8.30 (d, 2H, ^{3}J(H-H) ~ 8.0 Hz, Ar-*H*).

^{13}C NMR: δ 52.4, 62.2, 121.4, 124.2, 125.6, 127.4, 128.7, 131.4, 133.2, 147.6, 147.8, 168.8. The extra peaks are likely to be due to slight asymmetry in the compound.

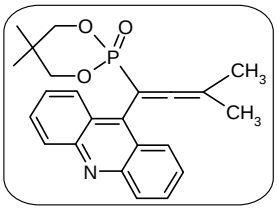
LC-MS: *m/z* 486 $[M]^{+}$.

Anal. Calcd. for $C_{31}H_{22}N_2O_4$: C, 76.53; H, 4.56; N, 5.76. Found: C, 76.65; H, 4.51; N, 5.82.

6.4 Synthesis of phosphono/phosphino-acridine derivatives 24-27

Representative procedure for 24-25: A mixture of allene $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$ **(2)** (0.216 g, 1.0 mmol), 9-chloroacridine (**4**, 0.213 g, 1.0 mmol), $Pd(OAc)_2$ (0.006 mmol, 5 mol%), CsF (0.21 g, 4.0 mmol) in DMF (5 mL) was heated at 100 ^oC for 4-6 h. When there was no starting material present (^{31}P NMR or TLC), the solvent was removed, reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with water (2 x 10 mL), brine solution (10 mL), dried (Na_2SO_4) and then the solvent removed to obtain the crude material containing the mixture of **24** and **25** (^{31}P NMR) as a green colored gummy solid.

(a) Compounds 24 and 25



24

Pure compound was eluted by using ethyl acetate as pale yellow solid after eluting compound **25**.

Yield: 0.08 g (20%).

Mp: 184-186 ^oC.

IR (KBr): 2946, 2907, 1958, 1634, 1601, 1485, 1458, 1265, 1061, 1011 cm^{-1}.

^1H NMR: δ 0.47 and 0.88 (2 s, 6H, 2 CH_3), 1.91-1.93 (m, 6H, =C(CH_3)$_2$), 3.57-3.61 (m, 2H, OCH_2), 4.12-4.18 (m, 2H, OCH_2), 7.61 (d, 2H, ^3J(H-H) ~ 7.8 Hz, Ar-*H*), 7.82 (d, 2H, ^3J(H-H) ~ 7.8 Hz, Ar-*H*), 8.27 (~t, 2H, ^3J(H-H) ~7.8 Hz, Ar-*H*), 8.38 (~t, 2H, ^3J(H-H) ~7.8 Hz, Ar-*H*).

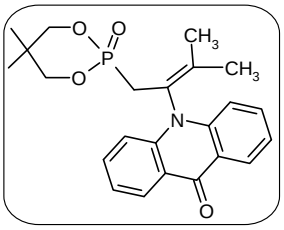
^{13}C NMR: δ 19.0, 19.1, 20.8, 21.3, 32.2 (d, ^3J(P-C) = 6.0 Hz, *C*Me$_2$), 75.7, 75.8, 88.8 (d, ^1J(P-C) = 199.1 Hz, P-*C*=C=C), 99.3 (d, ^3J(P-C) = 16.0 Hz, P-C=C=*C*), 125.2, 125.3, 126.0, 126.5, 129.8, 130.1, 138.5, 148.9, 211.4.

^{31}P NMR: δ 8.7.

LC-MS: *m/z* 394 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{24}NO_3P$: C, 70.22; H, 6.15 N, 3.56. Found: C, 70.12; H, 6.10; N, 3.61.

This compound was crystallized from ethyl acetate (2 mL) at room temperature. X-ray structure was determined for this sample.



25

This compound was isolated from the same reaction mixture which is containing **24**. Pure compound was eluted by using ethyl acetate/hexane (3:2) mixture before **24**.

Yield: 0.20 g (50%).

Mp: 170-172 ^oC.

IR (KBr): 3069, 2957, 1634, 1601, 1485, 1458, 1264, 1063, 1017 cm^{-1}.

^1H NMR: δ 0.73 and 0.91 (2 s, 6H, 2 CH_3), 1.52 (d, 3H, *J*(P-H) = 5.8 Hz, =CCH_3(A)), 2.24 (d, 3H, *J*(P-H) = 4.5 Hz, =CCH_3(B)), 3.00 (d, 2H, ^2J(P-H) = 21.1 Hz, PCH_2), 3.34 (dd→t, 2H, ^3J(P-H) = ^2J(H-H) ~ 11.2 Hz, OCH_2), 3.78 (dd→t, 2H, ^3J(P-H) = ^2J(H-H) ~ 11.6 Hz, OCH_2), 7.32 (t, 2H, ^3J(H-H) = 7.4 Hz, Ar-*H*), 7.48 (d, 2H, ^3J(H-H) = 8.8 Hz, Ar-*H*), 7.68-7.72 (m, 2H, Ar-*H*), 8.56-8.58 (m, 2H, Ar-*H*). This spectrum is illustrated in Fig. 8.

^{13}C NMR: δ 20.3, 20.8, 21.3, 21.4, 27.6 (d, ^1J(P-C) = 135.1 Hz, P*C*H_2), 32.4 (d, ^3J(P-C) = 6.0 Hz, *C*(Me)$_2$), 75.4, 75.5, 116.9, 119.6, 121.9, 122.2, 127.6, 133.8, 140.6, 178.2 (*C*=O).

^{31}P NMR: δ 19.5.

LC-MS: *m/z* 412 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{26}NO_4P$: C, 67.14; H, 6.37; N, 3.40. Found: C, 66.95; H, 6.45; N, 3.56.

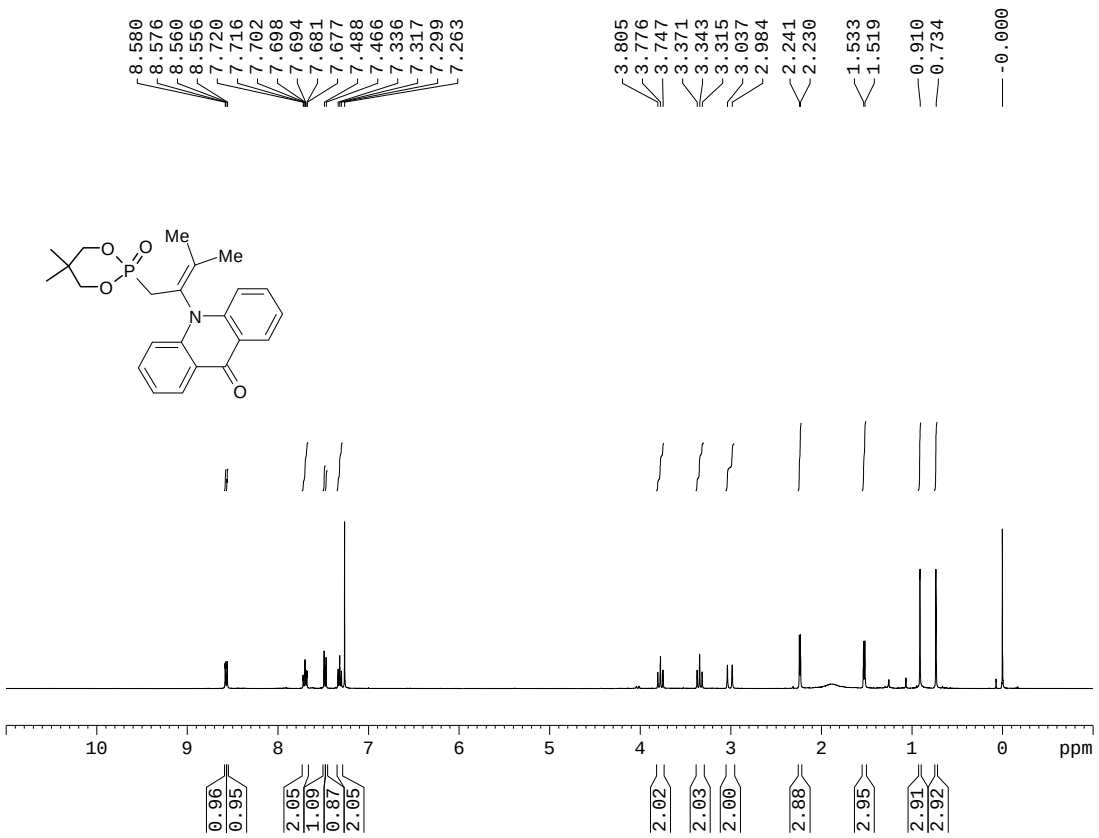
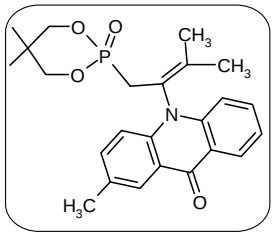


Fig. 8. ^{1}H NMR spectrum of compound **25**

(b) Compound 26



The reaction conducted in a manner similar to that for compound **24** using same molar quantities of allene **2** and 9-chloro-2-methylacridine **5**. Pure compound was isolated as a green solid by using ethyl acetate/hexane (3:2) mixture as the eluant.

Yield: 0.25 g (58%).

Mp: 172-176 ^{o}C.

IR (KBr): 3071, 2973, 1632, 1601, 1495, 1480, 1271, 1059, 1007 cm^{-1}.

^{1}H NMR: δ 0.74 and 0.94 (2 s, 6H, 2 CH_3), 1.52 (d, 3H, J(P-H) = 5.6 Hz, =CCH_3(A)), 2.24 (d, 3H, J(P-H) = 4.4 Hz, =CCH_3(B)), 2.50 (s, 3H, Ar-CH_3), 3.00 (d, 2H, ^{2}J(P-H) = 20.8 Hz, PCH_2), 3.33-3.38 (m, 2H, OCH_2), 3.35-3.80 (m, 2H, OCH_2), 7.31 (t, 1H, ^{3}J(H-H) = 7.6 Hz, Ar-

H), 7.40 (d, 1H, ^{3}J(H-H) = 8.8 Hz, Ar-*H*), 7.46 (d, 1H, ^{3}J(H-H) = 8.4 Hz, Ar-*H*), 7.52-7.55 (m, 1H, Ar-*H*), 7.68-7.71 (m, 1H, Ar-*H*), 8.37 (s br, 1H, Ar-*H*), 8.57-8.59 (m, 1H, Ar-*H*).

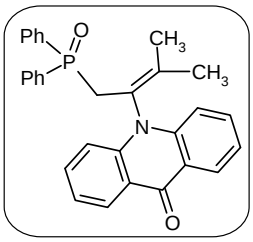
^{13}C NMR: δ 20.3 (d, ^{4}J(P-C) = 3.0 Hz, C=C*C*H$_3$), 20.7 (d, ^{4}J(P-C) = 3.0 Hz, C=C*C*H$_3$), 20.8, 21.2, 21.4, 27.4 (d, ^{1}J(P-C) = 135.0 Hz, P*C*H$_2$), 32.3 (d, ^{3}J(P-C) = 6.0 Hz, *C*(Me)$_2$), 75.4, 75.5, 116.8 (d, ^{3}J(P-C) = 12.4 Hz, PC*C*=CMe$_2$), 119.7, 119.8, 121.6, 122.0 (d, *J*(P-C) = 2.0 Hz), 126.7, 127.5, 131.5, 133.5, 135.2, 138.6, 140.4, 142.1, 142.2, 178.0 (*C*=O).

^{31}P NMR: δ 19.5.

LC-MS: *m/z* 426 $[M]^+$.

Anal. Calcd. for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found: C, 67.85; H, 6.54; N, 3.41.

(c) Compound 27



The procedure was the same as that for compound **24** using same molar quantities of allene **3** and 9-chloroacridine **4**. Pure compound was isolated by using ethyl acetate/hexane (1:1) mixture as brown colored solid.

Yield: 0.23 g (50%).

Mp: 192-194 ^{o}C.

IR (KBr): 3057, 2957, 2905, 1634, 1601, 1483, 1433, 1265, 1167, 1117 cm^{-1}.

^{1}H NMR: δ 1.52 (d, 3H, *J*(P-H) = 4.4 Hz, =CC*H*$_3$(A)), 2.24 (d, 3H, *J*(P-H) = 4.8 Hz, =CC*H*$_3$(B)), 3.60 (d, 2H, ^{2}J(P-H) = 12.8 Hz, PC*H*$_2$), 7.10-7.14 (m, 4H, Ar-*H*), 7.18-7.22 (m, 2H, Ar-*H*), 7.25-7.35 (m, 6H, Ar-*H*), 7.43 (d, ^{3}J(H-H) = 8.4 Hz, 2H, Ar-*H*), 7.56-7.60 (m, 2H, Ar-*H*), 8.36-8.39 (m, 2H, Ar-*H*).

^{13}C NMR: δ 20.5, 20.9, 34.0 (d, ^{1}J(P-C) = 67.7 Hz, P*C*H$_2$), 117.1, 120.9 (d, ^{3}J(P-C) = 9.1 Hz, PC*C*=CMe$_2$), 121.5, 122.1, 127.5, 128.3, 128.4, 131.7,

132.5 (d, ^{1}J(P-C) = 99.5 Hz, P*C*), 133.6, 140.3, 142.1 (d, *J*(P-C) = 8.7 Hz), 177.8 (*C*=O).

^{31}P NMR: δ 26.4.

LC-MS: *m/z* 464 $[M+1]^{+}$.

Anal. Calcd. for $C_{30}H_{26}NO_2P$: C, 77.74; H, 5.65; N, 3.02. Found: C, 77.63; H, 5.58; N, 3.12.

This compound was crystallized from ethylacetate/hexane (2 + 1 mL) mixure at 25 ^{o}C for one day. X-ray structural analysis was performed on this sample.

6.5 Cytotoxic report for synthetic compound 13

Cytotoxic data[31] for compound **13** on three different cell lines are checked by Mr. Jyoti Manohar from Prof. Reddanna's lab (School of Life Sciences, UoH). The data is given below in Table 3.

Materials: Cell lines used in this study were Hep-G2 (human liver), Hela, HL-60 (human promyelocytic leukemia). These cell lines were obtained from National Center for Cell science (NCCS), Pune, India. DMEM (Dulbeccos Modified Eagles Medium), RPMI-1640, MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide], Trypsin, EDTA were purchased from Sigma Chemicals Co (st.Louis, MO), Fetal bovine serum were purchased from Arrow labs, 96 well flat bottom tissue culture plates were purchased from Tarson.

Table 3: Cytotoxic data for compound **13** with **HepG2**, **HeLa** and **HL-60** cell lines

	HepG2 cell line						
Concn (µg)	**OD**	**%Inhibition**	**IC50 (µg)**				**OD**
10	0.6041	19.1406773	**74.01934**			Control	0.837
50	0.47135	36.9093829				Control+DMSO	0.747
100	0.15505	79.2464195					
200	0.086067	88.4799001					
	HeLa cell line						
Concn (µg)	**OD**	**%Inhibition**	**IC50 (µg)**				**OD**

10	0.5718	44.266	**38.92**			Control	1.414833
50	0.2194	78.619				Control+DMSO	1.026033
100	0.0449	95.621					
200	0.0150	98.540					
	HL-60 cell line						
Concn (µg)	**OD**	**%Inhibition**	**IC50 (µg)**				**OD**
10	0.535	8.614	**540.4329**			Control	0.602733
50	0.534	8.804				Control+DMSO	0.585533
100	0.528	9.815					
200	0.446	23.757					

The results indicate that our compound **13** effectively inhibits the HeLa and HepG2 cell lines.

6.6 X-ray crystallography

The methodology was similar to that given in Chapter 3.[38] Data quality was not good in the case of **15.**OC_4H_8 and hence the R values are rather high due to the disordered solvent; for **18**, the terminal ethyl groups were disordered and hence the thermals were high. Crystal data are summarized in Tables 4-5.

Table 4. Crystal data for compounds **11.**CH_3CN, **15.**OC_4H_8, **18** and **24**[a]

Compound	**11.**CH_3CN	**15.** OC_4H_8	**18**	**24**
Emp. formula	$C_{71}H_{90}N_4O_{18}P_6$	$C_{27}H_{36}N_2O_9P_2$	$C_{21}H_{29}NO_6P_2$	$C_{23}H_{24}NO_3P$
Formula weight	1473.29	594.52	453.39	393.40
Crystal system	Trigonal	Monoclinic	Monoclinic	Monoclinic
Space group	*R-3*	*P2(1)/c*	*P2(1)/c*	*P2/c*
a /Å	21.029(3)	15.240(5)	8.096(6)	16.405(7)
b /Å	21.029(3)	10.453(3)	15.300(11)	6.307(3)
c /Å	28.896(7)	21.548(7)	19.538(7)	19.989(8)
α/deg	90	90	90	90
β/deg	120	100.909(5)	96.211(13)	96.214(7)
γ/deg	90	90	90	90
V /Å^3	11067 (3)	3370.6(19)	1174.5(15)	2056.0(16)
Z	6	4	2	4
D_{calc} /g cm^{-3}]	1.326	1.172	1.282	1.271
μ /mm^{-1}	0.217	0.176	0.220	0.157
F(000)	4668	1256	480	832
Data/ restraints/ parameters	4237/0/311	5928/0/410	4011/1/279	3624/0/257
S	0.965	1.076	1.038	1.100
R1 [I>2σ(I)]	0.0785	0.1013	0.0681	0.0469
wR2 [all data]	0.1638	0.2839	0.1252	0.1201
Max./min. residual electron dens. [eÅ^{-3}]	0.628 / -0.243	0.918 / -0.417	0.242 / -0.204	0.293/-0.284

[a]$R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma wF_o^4]^{0.5}$

Table 5. Crystal data for compound **27**[a]

Compound	**27**
Emp. formula	$C_{26}H_{26}NO_2P$
Formula weight	594.52
Crystal system	Monoclinic
Space group	*P2(1)/c*
a /Å	11.072(2)
b /Å	16.360(3)
c /Å	15.858(4)
α/deg	90
β/deg	121.423(15)
γ/deg	90
V /Å^3	2451.2(9)
Z	4
D_{calc} /g cm^{-3}]	1.256
μ /mm^{-1}	0.140
F(000)	976
Data/ restraints/ parameters	4301/0/309
S	0.887
R1 [I>2σ(I)]	0.0626
wR2 [all data]	0.1858
Max./min. residual electron dens. [eÅ^{-3}]	0.448/ -0.603

[a]$R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma wF_o^4]^{0.5}$

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34) An X-ray structure of **20** is available (Fig. 9), but the full set of data (data completeness 90%) could not be collected although the data to parameter ratio is >10. *Crystal data* **20**: $C_{18}H_{15}NO_4$, M = 309.31, Triclinic, Space group *P-(1), a* = 7.646(1), b = 9.685(1), c = 10.937(1) Å, α= 101.538(2), β = 101.467(2)°, γ = 95.689(2)°, V = 769.52(17) Å^3, Z = 2, μ = 0.095 mm^{-1}, data/restraints/parameters: 2701/0/211, R indices ($I > 2\sigma(I)$): R1 = 0.0453, *wR*2 (all data) = 0.1262. Max./min. residual electron density (eÅ^{-3}) 0.207 / -0.207.

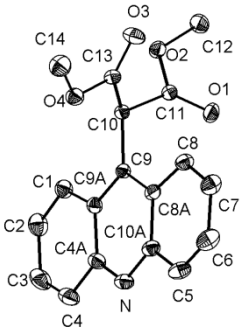

Fig. 9. An ORTEP diagram of compound **20** [C(9)-C(10) 1.521(2)Å]

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Publication numbers and atomic coordinates for X-ray structures reported in this thesis

I. Publication numbers for the published compounds

PART B: Compounds 11.CH_3CN**, 15.**OC_4H_8 **and 18: Publication no. 1 (Contents, p. xi)**

II. Selected atomic coordinates for compounds 33.$CHCl_3$, 35, 36.CH_2Cl_2, 41.$2C_4H_8O_2$, 44, 58, (*Z*)-67, 76, 87, 91 and 93 from PART A and for compounds 24 and 27 from PART B

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 4. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

PART A

Compound 33.$CHCl_3$

Atom	x	y	z	U(eq)
P	-7(1)	10083(1)	1659(1)	37(1)
O(1)	478(2)	11190(3)	2143(1)	38(1)
O(2)	196(3)	8741(3)	2023(1)	44(1)
O(3)	-1420(3)	10290(4)	1411(1)	65(1)
N(1)	2393(3)	9840(4)	-62(1)	44(1)
C(1)	1673(4)	10975(4)	2592(2)	37(1)
C(2)	1622(4)	9654(4)	2916(2)	35(1)
C(3)	1444(4)	8557(4)	2439(2)	41(1)
C(4)	2968(4)	9444(6)	3327(2)	57(1)
C(5)	480(4)	9643(5)	3301(2)	46(1)
C(6)	1111(3)	10107(4)	1096(2)	28(1)
C(7)	1755(3)	11265(4)	1045(2)	32(1)
C(8)	2575(4)	11772(4)	604(2)	36(1)
C(9)	3087(4)	13068(4)	703(2)	53(1)
C(10)	3707(5)	13725(5)	265(3)	67(2)
C(11)	3828(5)	13089(6)	-276(3)	67(2)
C(12)	3372(4)	11837(6)	-381(2)	59(1)
C(13)	2771(4)	11123(4)	55(2)	40(1)
C(14)	2447(4)	8876(4)	418(2)	41(1)
C(15)	2688(5)	7466(5)	186(2)	56(1)
C(16)	1445(5)	6857(5)	-129(2)	58(1)
C(17)	436(4)	6703(4)	306(2)	45(1)
C(18)	325(4)	7933(4)	676(2)	40(1)
C(19)	1222(3)	8902(4)	730(2)	29(1)
Cl(2)	4821(1)	6006(1)	3355(1)	50(1)
Cl(3)	4543(1)	3314(1)	2930(1)	69(1)
Cl(4)	3421(1)	5477(2)	2146(1)	63(1)
C(20)	3771(4)	4885(4)	2908(2)	45(1)

Compound 35

Atom	x	y	z	U(eq)
P(1)	2846(1)	7194(1)	2726(1)	18(1)
O(1)	4226(2)	7821(1)	2884(1)	23(1)
O(2)	5431(2)	6746(1)	2084(1)	24(1)
N(1)	4089(2)	4491(1)	1873(1)	21(1)
C(1)	2927(3)	6872(1)	3731(1)	20(1)
C(2)	3816(3)	7387(2)	4437(2)	25(1)
C(3)	3946(3)	7164(2)	5225(2)	32(1)
C(4)	3203(3)	6418(2)	5312(2)	33(1)
C(5)	2320(3)	5896(2)	4614(2)	34(1)
C(6)	2172(3)	6119(2)	3824(2)	29(1)
C(7)	829(3)	7665(1)	2070(1)	19(1)
C(8)	-290(3)	7903(2)	2377(2)	26(1)
C(9)	-1724(3)	8355(2)	1861(2)	31(1)
C(10)	-2072(3)	8569(2)	1036(2)	27(1)
C(11)	-975(3)	8323(2)	720(2)	27(1)
C(12)	465(3)	7876(1)	1235(1)	23(1)
C(13)	3022(3)	6231(1)	2200(1)	17(1)
C(14)	1590(3)	5801(1)	1729(1)	19(1)
C(15)	1197(3)	4960(1)	1311(1)	18(1)
C(16)	-493(3)	4755(1)	841(1)	20(1)
C(17)	-1025(3)	3947(1)	504(1)	23(1)
C(18)	175(3)	3317(1)	644(1)	23(1)
C(19)	1844(3)	3500(1)	1082(1)	21(1)
C(20)	2401(3)	4326(1)	1419(1)	19(1)
C(21)	4787(3)	5297(1)	1741(2)	22(1)
C(22)	6566(3)	5135(2)	1873(2)	27(1)
C(23)	7747(3)	4906(2)	2793(2)	30(1)
C(24)	7729(3)	5599(2)	3402(2)	29(1)
C(25)	5955(3)	5781(2)	3268(1)	24(1)
C(26)	4792(3)	6012(1)	2344(1)	19(1)

Compound 36.CH_2Cl_2

Atom	x	y	z	U(eq)
P(1)	3891(1)	6710(1)	4552(1)	16(1)
O(1)	4153(1)	5961(2)	3941(2)	23(1)
O(2)	3741(1)	7526(2)	3722(2)	19(1)
O(3)	4300(1)	7112(2)	5520(2)	18(1)
O(4)	2219(1)	5649(2)	6259(2)	23(1)
O(5)	2447(1)	4152(2)	7762(2)	29(1)
N(1)	2825(1)	4608(2)	7104(2)	19(1)
C(1)	3680(2)	8468(2)	4135(3)	20(1)
C(2)	4136(2)	8735(3)	5020(3)	21(1)
C(3)	4171(2)	8017(3)	5972(3)	20(1)
C(4)	4699(2)	8808(3)	4450(3)	26(1)
C(5)	3978(2)	9642(3)	5552(4)	32(1)
C(6)	3256(1)	6391(2)	5246(3)	15(1)
C(7)	3239(1)	5667(2)	5965(3)	14(1)
C(8)	3668(1)	5037(2)	6454(3)	15(1)
C(9)	4241(1)	4970(2)	6413(3)	18(1)
C(10)	4526(2)	4291(3)	7039(3)	20(1)
C(11)	4239(2)	3686(3)	7717(3)	20(1)
C(12)	3665(2)	3748(3)	7804(3)	21(1)
C(13)	3392(1)	4418(2)	7158(3)	17(1)
C(14)	2689(1)	5352(2)	6442(3)	16(1)
C(15)	2774(1)	7022(2)	5029(3)	16(1)
C(16)	2490(1)	7071(3)	3961(3)	20(1)
C(17)	2092(2)	7744(3)	3764(3)	26(1)
C(18)	1977(2)	8375(3)	4605(3)	29(1)

C(19)	2250(2)	8314(3)	5681(3)	26(1)
C(20)	2645(2)	7642(3)	5886(3)	22(1)
P(2)	1566(1)	3191(1)	5091(1)	18(1)
O(6)	1764(1)	3289(2)	6298(2)	25(1)
O(7)	1540(1)	2156(2)	4734(2)	19(1)
O(8)	954(1)	3556(2)	4908(2)	21(1)
O(9)	2815(1)	4911(2)	2764(2)	23(1)
O(10)	3935(1)	4307(2)	3228(2)	28(1)
N(2)	3465(1)	4049(2)	3792(2)	18(1)
C(21)	1200(2)	1896(3)	3709(3)	22(1)
C(22)	598(2)	2204(3)	3805(3)	20(1)
C(23)	589(2)	3240(3)	3944(3)	23(1)
C(24)	326(2)	1726(3)	4800(3)	22(1)
C(25)	281(2)	1970(3)	2670(3)	28(1)
C(26)	2000(1)	3806(2)	4102(3)	15(1)
C(27)	2554(1)	3678(2)	4115(3)	16(1)
C(28)	2934(1)	3042(2)	4755(3)	16(1)
C(29)	2856(2)	2279(3)	5433(3)	20(1)
C(30)	3316(2)	1814(3)	5892(3)	21(1)
C(31)	3851(2)	2109(3)	5689(3)	20(1)
C(32)	3946(2)	2858(3)	4998(3)	19(1)
C(33)	3484(1)	3299(2)	4535(3)	17(1)
C(34)	2935(2)	4301(3)	3447(3)	19(1)
C(35)	1700(1)	4457(2)	3304(3)	17(1)
C(36)	1617(2)	4223(3)	2147(3)	20(1)
C(37)	1308(2)	4797(3)	1412(3)	22(1)
C(38)	1073(2)	5594(3)	1818(3)	25(1)
C(39)	1158(2)	5825(3)	2967(3)	24(1)
C(40)	1469(2)	5259(3)	3706(3)	20(1)
Cl(1)	9408(1)	701(1)	6905(1)	39(1)
Cl(2)	8986(1)	1709(1)	8855(1)	33(1)
C(41)	8997(2)	650(3)	8132(4)	36(1)

Compound 41. $2C_4H_8O_2$

Atom	x	y	z	U(eq)
Pd(1)	6992(1)	2146(1)	7410(1)	47(1)
Pd(2)	7007(1)	2706(1)	6414(1)	47(1)
P(1)	7490(1)	1664(1)	6619(1)	53(1)
P(2)	7479(1)	3196(1)	7220(1)	48(1)
P(3)	6580(1)	3304(1)	5639(1)	47(1)
P(4)	6608(1)	1556(1)	8186(1)	48(1)
S(1)	6760(2)	1931(1)	5817(1)	77(1)
S(2)	6733(1)	2932(1)	7988(1)	68(1)
O(1)	7158(3)	1049(1)	6670(2)	73(1)
O(2)	8928(3)	1632(1)	6573(2)	66(1)
O(3)	8920(3)	3242(1)	7354(2)	58(1)
O(4)	7112(3)	3804(1)	7128(2)	61(1)
C(1)	7661(6)	709(2)	6208(3)	89(2)
C(2)	9008(6)	722(2)	6217(3)	79(2)
C(3)	9418(5)	1284(2)	6124(3)	81(2)
C(4)	9500(9)	499(4)	6818(4)	144(4)
C(5)	9450(7)	388(3)	5689(3)	107(2)
C(6)	9354(5)	3616(2)	7815(2)	66(1)
C(7)	8944(5)	4166(2)	7662(2)	65(1)
C(8)	7568(5)	4173(2)	7592(2)	68(1)
C(9)	9493(6)	4349(2)	7068(3)	84(2)
C(10)	9328(7)	4541(2)	8184(3)	92(2)
C(11)	7872(4)	1105(2)	8326(2)	52(1)
C(12)	7734(5)	583(2)	8437(2)	67(1)
C(13)	8758(6)	267(2)	8535(3)	83(2)
C(14)	9891(6)	491(3)	8528(3)	82(2)

C(15)	10045(5)	1003(3)	8423(3)	83(2)
C(16)	9030(4)	1310(2)	8303(3)	71(1)
C(17)	6410(4)	1874(2)	8922(2)	54(1)
C(18)	5424(6)	2197(2)	8981(3)	71(1)
C(19)	5220(7)	2464(3)	9509(3)	87(2)
C(20)	6047(8)	2418(3)	10000(3)	98(2)
C(21)	7043(7)	2093(3)	9957(3)	98(2)
C(22)	7219(5)	1831(2)	9410(2)	73(1)
C(23)	5267(4)	1141(2)	8112(2)	51(1)
C(24)	4675(5)	959(2)	8613(3)	68(1)
C(25)	3648(5)	649(2)	8536(3)	81(2)
C(26)	3219(5)	527(3)	7965(4)	88(2)
C(27)	3786(5)	698(3)	7461(3)	85(2)
C(28)	4803(4)	1006(2)	7526(2)	68(1)
C(29)	6328(4)	3020(2)	4881(2)	56(1)
C(30)	5321(6)	2699(2)	4792(3)	75(2)
C(31)	5086(7)	2471(3)	4220(3)	91(2)
C(32)	5843(8)	2551(3)	3754(3)	98(2)
C(33)	6856(7)	2863(3)	3836(3)	94(2)
C(34)	7094(6)	3095(2)	4403(2)	74(1)
C(35)	5248(4)	3706(2)	5708(2)	53(1)
C(36)	4744(5)	3988(2)	5214(2)	70(1)
C(37)	3737(6)	4310(2)	5277(3)	88(2)
C(38)	3207(5)	4333(2)	5844(4)	89(2)
C(39)	3679(5)	4070(3)	6320(3)	86(2)
C(40)	4722(4)	3753(2)	6271(3)	67(1)
C(41)	7820(4)	3757(2)	5548(2)	50(1)
C(42)	8987(4)	3563(2)	5579(2)	63(1)
C(43)	9963(5)	3890(3)	5519(3)	80(2)
C(44)	9801(5)	4414(2)	5459(3)	80(2)
C(45)	8664(5)	4621(2)	5434(3)	75(2)
C(46)	7675(5)	4292(2)	5471(2)	67(1)
O(5)	3400(20)	4097(11)	8206(8)	292(14)
O(6)	3210(30)	3679(11)	9189(10)	320(17)
C(47)	4129(11)	3815(8)	9221(8)	123(7)
C(48)	4323(12)	3877(10)	8547(9)	200(13)
C(49)	2341(12)	3814(9)	8342(7)	133(7)
C(50)	2134(11)	3842(9)	9014(8)	147(8)
O(7)	6197(9)	2577(5)	1881(7)	266(7)
O(8)	8525(9)	2608(7)	1883(7)	287(7)
C(51)	6828(17)	2082(5)	1918(8)	237(8)
C(52)	7910(15)	2267(6)	2300(8)	275(12)
C(53)	7720(20)	3069(4)	1904(9)	306(13)
C(54)	6885(12)	2838(5)	1422(5)	201(7)
O(9)	8140(40)	3843(13)	-389(7)	327(19)
O(10)	8440(40)	4078(18)	633(11)	370(30)
C(55)	9140(20)	3942(12)	-275(15)	210(20)
C(56)	9060(40)	4367(13)	200(20)	310(30)
C(57)	7760(20)	4091(10)	630(11)	162(14)
C(58)	7350(20)	3794(10)	54(13)	200(13)

Compound 44

Atom	x	y	z	U(eq)
P(1)	-616(1)	5298(1)	6778(1)	15(1)
P(2)	3665(1)	4665(1)	7902(1)	17(1)
O(1)	-1018(1)	6527(1)	6330(1)	21(1)
O(2)	4312(1)	5621(1)	7619(1)	21(1)
O(3)	4145(1)	5082(1)	8876(1)	19(1)
O(4)	4036(1)	3396(1)	7880(1)	27(1)
C(1)	-1441(2)	4047(2)	5971(1)	16(1)
C(2)	-909(2)	2865(2)	6137(1)	21(1)
C(3)	-1615(2)	1943(2)	5492(1)	25(1)
C(4)	-2866(2)	2196(2)	4690(1)	21(1)
C(5)	-3402(2)	3370(2)	4527(1)	21(1)

C(6)	-2690(2)	4298(2)	5161(1)	19(1)
C(7)	-1039(2)	5105(2)	7551(1)	16(1)
C(8)	-537(2)	4129(2)	8172(1)	20(1)
C(9)	-887(2)	4041(2)	8759(1)	25(1)
C(10)	-1733(2)	4914(2)	8723(2)	29(1)
C(11)	-2258(2)	5864(2)	8094(1)	25(1)
C(12)	-1913(2)	5962(2)	7507(1)	19(1)
C(13)	1166(2)	4991(2)	7460(1)	16(1)
C(14)	1877(2)	4937(2)	7135(1)	17(1)
C(15)	1303(2)	5040(2)	6151(1)	29(1)
C(16)	4213(2)	6929(2)	7771(1)	22(1)
C(17)	4831(2)	7191(2)	8765(1)	21(1)
C(18)	4133(2)	6400(2)	9054(1)	20(1)
C(19)	6341(2)	6938(2)	9374(1)	27(1)
C(20)	4546(2)	8543(2)	8829(2)	28(1)

Compound 58

Atom	x	y	z	U(eq)
S(1)	749(1)	588(1)	1317(1)	109(1)
P(1)	4943(1)	2549(1)	3766(1)	41(1)
P(2)	1877(1)	1638(1)	1875(1)	52(1)
O(1)	5205(1)	3831(1)	3457(1)	57(1)
O(2)	1319(1)	2375(2)	2349(1)	66(1)
O(3)	2496(1)	2930(2)	1633(1)	53(1)
C(1)	6299(2)	1834(2)	4222(1)	44(1)
C(2)	7349(2)	2625(2)	4269(1)	58(1)
C(3)	8412(2)	2165(3)	4625(1)	73(1)
C(4)	8431(2)	919(3)	4922(1)	76(1)
C(5)	7405(2)	116(3)	4875(1)	68(1)
C(6)	6330(2)	575(2)	4529(1)	53(1)
C(7)	3916(2)	2932(2)	4216(1)	44(1)
C(8)	4318(2)	3229(2)	4789(1)	61(1)
C(9)	3526(2)	3690(3)	5107(1)	79(1)
C(10)	2319(2)	3838(3)	4859(1)	77(1)
C(11)	1904(2)	3540(2)	4294(1)	66(1)
C(12)	2693(2)	3098(2)	3972(1)	52(1)
C(13)	4204(1)	1169(2)	3285(1)	41(1)
C(14)	3954(2)	-289(2)	3479(1)	40(1)
C(15)	4627(2)	-1420(2)	3356(1)	62(1)
C(16)	4399(2)	-2793(2)	3503(1)	73(1)
C(17)	3515(2)	-3062(2)	3776(1)	70(1)
C(18)	2833(2)	-1963(2)	3904(1)	74(1)
C(19)	3055(2)	-573(2)	3757(1)	61(1)
C(20)	3885(2)	1548(2)	2743(1)	48(1)
C(21)	3134(2)	662(2)	2279(1)	53(1)
C(22)	552(2)	3608(3)	2161(1)	76(1)
C(23)	1214(2)	4773(2)	1923(1)	62(1)
C(24)	1720(2)	4165(2)	1448(1)	61(1)
C(25)	303(3)	5946(3)	1667(1)	89(1)
C(26)	2215(3)	5399(3)	2387(1)	102(1)

Compound (*Z*)-67

Atom	x	y	z	U(eq)
S(1)	2062(1)	1757(1)	2624(1)	60(1)

P(1)	1428(1)	1671(1)	1500(1)	39(1)
P(2)	643(1)	-1449(1)	1366(1)	45(1)
O(1)	312(1)	-1751(3)	451(2)	65(1)
O(2)	1264(1)	-1792(2)	1664(2)	44(1)
O(3)	452(1)	-2255(3)	1995(2)	53(1)
C(1)	1617(1)	-1910(4)	2589(3)	51(1)
C(2)	1379(1)	-2800(4)	3067(2)	44(1)
C(3)	815(2)	-2287(4)	2921(3)	55(1)
C(4)	1345(2)	-4219(4)	2748(3)	66(1)
C(5)	1756(2)	-2732(5)	4046(3)	70(1)
C(6)	564(1)	196(4)	1643(3)	48(1)
C(7)	805(1)	1353(4)	1674(2)	43(1)
C(8)	593(2)	2548(4)	1969(3)	74(1)
C(9)	1286(1)	3220(3)	912(2)	38(1)
C(10)	779(2)	3463(4)	244(3)	52(1)
C(11)	677(2)	4652(4)	-189(3)	68(1)
C(12)	1078(2)	5593(5)	37(3)	73(1)
C(13)	1585(2)	5359(4)	684(3)	67(1)
C(14)	1692(2)	4180(4)	1128(3)	49(1)
C(15)	1493(1)	495(4)	743(2)	40(1)
C(16)	2002(2)	-69(4)	931(3)	56(1)
C(17)	2074(2)	-896(5)	338(4)	75(2)
C(18)	1639(3)	-1193(5)	-431(4)	76(2)
C(19)	1130(2)	-682(4)	-614(3)	64(1)
C(20)	1058(2)	181(4)	-33(3)	48(1)

Compound 76

Atom	x	y	z	U(eq)
C(14)	4135(3)	5521(2)	1805(3)	56(1)
P(2)	2491(1)	5615(1)	2713(1)	41(1)
P(1)	3620(1)	3737(1)	656(1)	46(1)
S(1)	1796(1)	4718(1)	3351(1)	57(1)
O(2)	3011(2)	3083(1)	-181(2)	53(1)
O(3)	3855(2)	3286(1)	1893(2)	50(1)
O(1)	4473(2)	3984(1)	218(2)	72(1)
C(2)	2732(2)	2118(2)	1395(3)	43(1)
C(15)	1710(3)	6364(2)	1853(3)	42(1)
C(6)	2811(2)	4581(2)	823(3)	37(1)
C(13)	3264(2)	5226(2)	1731(3)	37(1)
C(7)	2370(3)	4959(2)	-358(3)	45(1)
C(21)	3250(2)	6201(2)	3848(3)	44(1)
C(8)	2929(3)	5330(2)	-1080(3)	63(1)
C(1)	2320(3)	2568(2)	248(3)	52(1)
C(3)	3131(3)	2780(2)	2295(3)	51(1)
C(4)	3503(3)	1505(2)	1218(4)	75(1)
C(20)	819(3)	6510(3)	2095(3)	64(1)
C(16)	1999(3)	6810(2)	945(3)	57(1)
C(26)	3703(3)	5800(3)	4838(4)	77(1)
C(22)	3405(3)	7053(2)	3737(4)	58(1)
C(23)	4007(3)	7474(3)	4619(4)	71(1)
C(24)	4451(3)	7070(3)	5590(4)	78(1)
C(12)	1401(3)	4944(2)	-713(4)	66(1)
C(17)	1402(4)	7385(3)	302(4)	71(1)
C(18)	518(4)	7525(3)	555(4)	80(1)
C(19)	227(3)	7084(3)	1442(4)	90(2)
C(10)	1545(6)	5671(3)	-2470(5)	109(2)
C(9)	2501(5)	5688(3)	-2135(4)	91(2)
C(5)	1916(3)	1666(2)	1825(3)	71(1)
C(11)	975(4)	5308(3)	-1775(5)	99(2)
C(25)	4310(4)	6237(3)	5708(4)	92(2)

Compound 87

Atom	x	y	z	U(eq)
P(1)	2364(1)	2889(1)	4811(1)	34(1)
P(2)	1796(1)	847(1)	4100(1)	36(1)
P(3)	4612(1)	2351(1)	3779(1)	31(1)
O(1)	3381(1)	3383(1)	5078(1)	48(1)
O(2)	1857(1)	269(1)	4774(1)	50(1)
O(3)	3946(1)	3093(1)	3364(1)	39(1)
C(1)	1742(2)	2414(1)	5557(1)	37(1)
C(2)	706(2)	2070(2)	5485(1)	44(1)
C(3)	303(2)	1703(2)	6078(1)	54(1)
C(4)	933(3)	1657(2)	6743(1)	62(1)
C(5)	1963(2)	1987(2)	6830(1)	61(1)
C(6)	2365(2)	2381(2)	6239(1)	50(1)
C(7)	1422(2)	3673(1)	4277(1)	35(1)
C(8)	1790(2)	4132(1)	3699(1)	44(1)
C(9)	1174(2)	4809(2)	3294(1)	57(1)
C(10)	185(2)	5029(2)	3455(2)	66(1)
C(11)	-186(2)	4591(2)	4026(2)	79(1)
C(12)	433(2)	3922(2)	4442(2)	62(1)
C(13)	450(2)	1188(1)	3738(1)	33(1)
C(14)	201(2)	1874(2)	3196(1)	47(1)
C(15)	-849(2)	2083(2)	2930(1)	55(1)
C(16)	-1661(2)	1603(2)	3190(1)	54(1)
C(17)	-1431(2)	922(2)	3718(1)	51(1)
C(18)	-387(2)	722(1)	3993(1)	41(1)
C(19)	2289(2)	194(2)	3374(1)	42(1)
C(20)	2400(2)	570(2)	2696(1)	55(1)
C(21)	2804(2)	31(2)	2169(2)	71(1)
C(22)	3092(2)	-889(3)	2322(2)	86(1)
C(23)	2990(2)	-1269(2)	2992(2)	87(1)
C(24)	2591(2)	-737(2)	3518(2)	62(1)
C(25)	2633(2)	1913(1)	4191(1)	31(1)
C(26)	3830(2)	1588(1)	4318(1)	35(1)
C(27)	4311(2)	1385(2)	5113(1)	53(1)
C(28)	5750(2)	2844(1)	4356(1)	35(1)
C(29)	5712(2)	3789(2)	4549(1)	49(1)
C(30)	6591(2)	4211(2)	4948(2)	68(1)
C(31)	7496(2)	3698(2)	5170(2)	75(1)
C(32)	7544(2)	2772(2)	4996(2)	75(1)
C(33)	6670(2)	2333(2)	4584(1)	57(1)
C(34)	5125(2)	1550(1)	3149(1)	35(1)
C(35)	5498(2)	642(2)	3329(1)	49(1)
C(36)	5831(2)	67(2)	2806(2)	64(1)
C(37)	5785(2)	377(2)	2098(2)	73(1)
C(38)	5426(2)	1263(2)	1910(2)	67(1)
C(39)	5095(2)	1852(2)	2432(1)	49(1)

Compound 91

Atom	x	y	z	U(eq)
P(1)	2936(1)	9821(2)	2025(1)	37(1)
O(1)	2704(1)	12038(4)	1982(2)	54(1)
O(2)	1291(1)	9220(4)	1740(2)	45(1)
C(1)	3123(2)	8799(6)	3025(2)	39(1)
C(2)	2995(2)	6761(7)	3219(2)	53(1)
C(3)	3156(2)	6143(8)	4006(3)	69(1)
C(4)	3437(3)	7554(10)	4588(3)	79(2)
C(5)	3573(3)	9546(10)	4399(3)	83(2)
C(6)	3414(2)	10189(7)	3624(2)	61(1)
C(7)	3770(2)	9514(6)	1716(2)	37(1)

C(8)	4166(2)	7696(7)	1836(2)	53(1)
C(9)	4800(2)	7538(9)	1593(3)	72(1)
C(10)	5040(2)	9187(10)	1232(3)	79(2)
C(11)	4660(3)	11013(9)	1117(3)	75(2)
C(12)	4026(2)	11196(7)	1361(2)	57(1)
C(13)	2347(2)	7982(6)	1433(2)	41(1)
C(14)	1647(2)	7852(5)	1363(2)	36(1)
C(15)	1121(2)	6192(6)	946(2)	40(1)
C(16)	1311(2)	5368(6)	198(2)	40(1)
C(17)	1234(2)	6572(7)	-465(3)	60(1)
C(18)	1393(3)	5833(9)	-1135(3)	74(1)
C(19)	1637(2)	3865(9)	-1179(3)	69(1)
C(20)	1726(3)	2592(8)	-534(3)	75(1)
C(21)	1571(2)	3350(7)	172(3)	59(1)
C(22)	1097(2)	4470(6)	1561(3)	57(1)
C(23)	415(2)	7414(7)	815(2)	53(1)
C(24)	547(2)	8861(6)	1498(2)	44(1)
C(25)	103(2)	9759(7)	1867(3)	60(1)

Compound 93

Atom	x	y	z	U(eq)
P(1)	5863(1)	2599(1)	2694(1)	47(1)
O(1)	5222(2)	3461(1)	2363(2)	50(1)
O(2)	7440(2)	2664(1)	2709(2)	50(1)
O(3)	5755(2)	2316(1)	3894(2)	69(1)
O(4)	5252(2)	636(1)	2254(2)	86(1)
O(5)	8909(3)	542(2)	3094(3)	107(1)
C(1)	5612(3)	3956(2)	1453(3)	52(1)
C(2)	7203(3)	4023(2)	1767(2)	50(1)
C(3)	7796(3)	3179(2)	1790(3)	54(1)
C(4)	7880(3)	4436(2)	3034(3)	65(1)
C(5)	7500(4)	4500(2)	701(3)	82(1)
C(6)	4957(3)	1958(2)	1368(2)	43(1)
C(7)	3359(3)	1994(2)	1081(2)	48(1)
C(8)	2519(3)	2338(2)	-28(2)	63(1)
C(9)	1066(4)	2376(2)	-316(3)	83(1)
C(10)	424(4)	2059(2)	479(4)	84(1)
C(11)	1215(4)	1711(2)	1577(3)	73(1)
C(12)	2696(4)	1681(2)	1897(3)	62(1)
C(13)	5580(3)	1108(2)	1583(3)	51(1)
C(14)	6621(4)	884(2)	933(3)	74(1)
C(15)	7219(4)	43(2)	1253(3)	86(1)
C(16)	8209(4)	-33(2)	2565(3)	71(1)
C(17)	8320(4)	-825(2)	3183(4)	97(1)

PART B

Compound 24

Atom	x	y	z	U(eq)
P(1)	3223(1)	3600(1)	5371(1)	42(1)
O(1)	3969(1)	4808(2)	5118(1)	49(1)
O(2)	3300(1)	3970(2)	6151(1)	49(1)
O(3)	3222(1)	1362(2)	5199(1)	72(1)
N(1)	1737(1)	3866(3)	2878(1)	49(1)
C(1)	3617(1)	5947(4)	6447(1)	56(1)
C(2)	4415(1)	6617(3)	6187(1)	49(1)
C(3)	4256(1)	6797(4)	5428(1)	52(1)
C(4)	4628(2)	8835(4)	6463(2)	83(1)
C(5)	5103(1)	5048(4)	6394(1)	62(1)

C(6)	2303(1)	4917(3)	5021(1)	38(1)
C(7)	2071(1)	4650(3)	4275(1)	37(1)
C(8)	2359(1)	6044(3)	3807(1)	39(1)
C(9)	2796(1)	7945(3)	3989(1)	47(1)
C(10)	3060(1)	9224(4)	3512(1)	57(1)
C(11)	2915(2)	8688(4)	2825(1)	63(1)
C(12)	2488(1)	6932(4)	2628(1)	58(1)
C(13)	2180(1)	5555(3)	3107(1)	44(1)
C(14)	1436(1)	2593(3)	3330(1)	43(1)
C(15)	957(1)	812(4)	3091(1)	54(1)
C(16)	653(1)	-560(4)	3515(1)	57(1)
C(17)	800(1)	-253(4)	4216(1)	55(1)
C(18)	1250(1)	1420(3)	4471(1)	46(1)
C(19)	1589(1)	2910(3)	4043(1)	39(1)
C(20)	1839(1)	5838(3)	5431(1)	40(1)
C(21)	1410(1)	6648(3)	5877(1)	43(1)
C(22)	1534(2)	8876(3)	6126(1)	57(1)
C(23)	769(1)	5340(4)	6178(1)	58(1)

Compound 27

Atom	x	y	z	U(eq)
P(1)	2073(1)	9737(1)	2500(1)	48(1)
O(1)	658(3)	9720(1)	1585(2)	66(1)
O(2)	6526(4)	7157(2)	2302(3)	107(1)
N(1)	4205(3)	9252(1)	1523(2)	44(1)
C(1)	2711(4)	8738(2)	3024(3)	54(1)
C(2)	4112(5)	8574(2)	3711(4)	83(1)
C(3)	4534(6)	7797(3)	4118(4)	100(2)
C(4)	3552(8)	7197(2)	3847(4)	99(2)
C(5)	2169(8)	7349(2)	3184(5)	107(2)
C(6)	1754(5)	8119(2)	2777(3)	81(1)
C(7)	2056(4)	10333(2)	3455(3)	48(1)
C(8)	1531(5)	11110(2)	3228(3)	70(1)
C(9)	1387(6)	11582(3)	3903(4)	90(2)
C(10)	1813(5)	11273(3)	4818(4)	86(1)
C(11)	2339(5)	10509(3)	5056(3)	78(1)
C(12)	2490(4)	10036(2)	4389(3)	65(1)
C(13)	3416(4)	10222(2)	2344(2)	46(1)
C(14)	3415(4)	9993(2)	1418(3)	42(1)
C(15)	2820(4)	10413(2)	581(3)	47(1)
C(16)	1967(4)	11171(2)	418(3)	67(1)
C(17)	2927(5)	10163(2)	-289(3)	68(1)
C(18)	6355(4)	10059(2)	2277(3)	56(1)
C(19)	7794(5)	10099(3)	2746(3)	71(1)
C(20)	8607(5)	9393(3)	2988(3)	79(1)
C(21)	7959(5)	8657(3)	2753(3)	75(1)
C(22)	5820(5)	7784(2)	2030(3)	66(1)
C(23)	3542(6)	7034(2)	1094(3)	75(1)
C(24)	2123(6)	7009(2)	533(4)	84(1)
C(25)	1353(5)	7732(2)	276(3)	74(1)
C(26)	2036(4)	8470(2)	599(3)	61(1)
C(27)	5664(4)	9296(2)	2022(2)	46(1)
C(28)	6478(4)	8587(2)	2264(3)	54(1)
C(29)	4279(5)	7777(2)	1431(3)	58(1)
C(30)	3509(4)	8508(2)	1187(3)	46(1)