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HETEROCYCLIC CHEMISTRY

20

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20

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences, etc. Metabolism will also be included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.
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Preface

I perceive that the success of the ongoing series "Topics in Heterocyclic Chemistry" being published by Springer Verlag, under the Editorship of Prof. R. R. Gupta (who unfortunately passed away suddenly last year) motivated the publisher and the then Chief Editor to publish two volumes on Phosphorous Heterocycles as part of this series. In view of the statement of a pioneer phosphorous chemist that *phosphorus is a carbon copy of carbon*, this decision appears to be quite logical and rational. In recent years, there have been many research publications emphasizing the analogy between the classical heterocycles and their phosphorus analogs. Nevertheless, the rainbow built by the compounds of phosphorus due to its diverse coordination states and geometrical architectures thereof in various compounds apparently encompasses more colors than that created by the carbon compounds. Furthermore, the possibility of using ^{31}P NMR spectroscopy, not only for the characterization of the phosphorous compounds but also for monitoring their chemical reactions, gives a sort of thrill in its own way and makes the life of the phosphorous chemist much easier.

The then Chief Editor, the late Prof. Gupta, invited me to shoulder this responsibility as a guest editor; I accepted the invitation, with initial hesitation due to my limited experience.

I have, however, been encouraged by the warm response received from colleagues working in different corners of world agreeing to contribute articles on a wide variety of topics pertaining to organophosphorus chemistry of current interest. I would like to take this opportunity to express my sincere thanks to these colleagues, with much appreciation for their generosity.

The articles – touching quite different aspects of organophosphorus chemistry – have been selected purposely to reflect, to some extent, the wide horizon of the subject.

The first article on anellated azaphospholes presents a brief account of their synthesis, structures, and reactions.

The second article deals with the biological activity of aminophosphonic acids.

The next article describes the use of 1,2-dihydrophosphinic oxides as intermediates for the synthesis of a variety of P-heterocycles.

The fourth article presents recent developments in synthetic aspects of spirophosphoranes having phosphorus in different coordination states.

The next article includes the description of the rich chemistry of phosphinines, including azaphosphinines.

The sixth article deals with synthetic approaches to different types of 1,2-heterophosphacyclanes, including four-, five-, and six-membered P-heterocycles.

The next two articles cover the chemistry of phosphorus containing macrocycles. The phosphorus containing calixarenes have attracted much attention in recent years due to their various functions such as metal cations binding, catalysis, molecular recogination, and bioactivity. Likewise, other phosphorus-containing macrocycles, cryptands, and dendrimers find various uses in analytical chemistry and biochemistry.

We hope to include the following articles in the second volume on phosphorous heterocycles:

Diazaphospholes
Selected phosphorous heterocycles containing a stereogenic phosphorus
Heterophenes carrying phosphorus functional groups as key structures
The synthesis and chemistry of the phospholane ring system
Synthesis and bioactivity of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives
Recent developments in the chemistry of *N*-heterocyclic phosphines.

I would be failing in my duty if I do not express my sincere thanks to the people at Springer, particularly Ms. Birgit Kollmar-Thoni and Ms. Ingrid Samide, for coordinating the project with great dedication.

Jaipur, Spring 2009

Raj K. Bansal
Guest Editor

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Anellated Azaphospholes

Raj K. Bansal

Abstract Azaphospholes are five-membered 6π aromatic phosphorus heterocycles having a σ^2,λ^3-phosphorus atom and a σ^3,λ^3-nitrogen atom as the members of the ring. In this chapter the syntheses, structural determination, reactions including electrophilic substitutions, 1,2-additions and Diels-Alder reactions on >C = P– or –N = P– functionality of azaphospholes anellated to five- and six-membered nitrogen heterocycles have been reviewed.

Keywords Anellated azaphospholes, >C = P– functionality, Coordination compounds, Diels-Alder reactions, Electrophilic substitutions, –N = P– functionality

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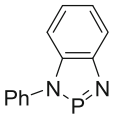
1 Introduction

Pilgram and Korte [1] can be credited with perceiving for the first time the possibility of the existence of an anellated azaphosphole when in 1963 they reported the formation of a product that was insoluble in common organic solvents and did not melt up to 350 °C, from the condensation of *N*-phenyl-1,2-diaminobenzene with triphenylphosphite at 150–180 °C. They assigned the structure **1**, namely 1,3,2-benzodiazaphosphole to the product obtained.



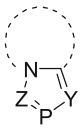
1

Structure 1

Although the actual product later turned out to be an oligomer of the proposed compound **1** [2], the suggestion was visionary, indicating the possibility of participation of the two-coordinate, tervalent phosphorus in cyclic delocalization thereby conferring aromatic stabilization. Such compounds were at that time unknown and rather unconceivable due to the energy difference between the 2p and 3p orbitals and consequent instability of the resulting >C = P– and –N = P– double bonds. In view of this, it was really daring to anticipate the existence of such a class of compounds which actually developed two decades later. During the last three decades, this field has witnessed a dramatic development leading to not only the synthesis of a large number of stable representatives of these compounds, but also their various reactions and applications in coordination chemistry that have been investigated.

Azaphospholes belong to a general class of five-membered 6π aromatic phosphorus heterocycles, known as heterophospholes, which incorporate at least one two-coordinate tervalent (σ^2,λ^3) phosphorus atom (=P–) that contributes only one electron to the aromatic sextet [3–7]. Another heteroatom such as NR, O, S (Se, Te) or even a σ^3,λ^3-phosphorus atom contributes two electrons to complete the aromatic sextet of the neutral heterophosphole ring. Azaphosphole is thus characterized by the presence of a σ^2,λ^3-phosphorus atom and a σ^3,λ^3-nitrogen atom in the five-membered ring. In view of the close analogy between carbon and phosphorus atoms [8–11], azaphospholes may be thought of as being derived from azoles by substituting one ring CH moiety by a sp^2-hybridized phosphorus atom. Likewise, anellated azaphospholes can be perceived as resulting from classical anellated azoles such as indole, indolizine, pyrazolopyridine, imidazopyridine, benzimidazole, imidazothiazole, etc. by substituting one = CH– of the five-membered ring by = P–. During the last

two decades, we have obtained independently, or in collaboration with two German research groups, a variety of anellated azaphospholes (**2**) and investigated their different reactions.



Y, Z = RC, N

2

Structure 2

In the present short review, it is intended to compile the research work on anellated azaphospholes reported during the last 10–12 years with a greater emphasis on the results obtained in our laboratories. Following the synthetic strategies documented for the anellated azoles and by using an appropriate phosphorus reagent such as PCl_3, $P(NMe_2)_3$ or $ClCH_2PCl_2$ in place of the carbon furnishing reagent, we could develop three simple methods, namely [4 + 1]cyclocondensation, [3 + 2] cyclocondensation and 1,5-electrocyclization, thereby making a variety of anellated azaphospholes accessible. Subsequently, we studied different reactions, namely electrophilic substitutions, 1,2-additions including Diels-Alder reactions on the >C = P– moiety and formation of the coordination compounds of some of the representative anellated azaphospholes. Furthermore, in recent years we have rationalized the observed diastereo- and regioselectivities in the Diels-Alder reactions by carrying out computational calculations.

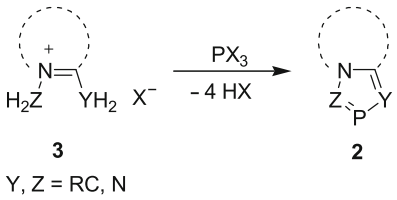
The earlier reviews on heterophospholes in general include anellated azaphospholes as well, though in a limited manner [3–6]. A comprehensive review on anellated heterophospholes covers the literature up to 1994 and includes a detailed list of the compounds and their physical data reported till then [12]. In another review, analogy between the synthetic methods and reactions of anellated heterophospholes and their non-phosphorus analogues has been highlighted [13]. A review is limited to the analogy between the synthesis of indolizines and phosphaindolizines [14]. The synthesis of anellated heterophospholes from 2-substituted cycloiminium salts forms the subject matter of two reviews [15, 16]. Some recent advances in the chemistry of anellated azaphospholes have been published in a recent review [7].

The reviews dealing primarily with the synthetic applications of phosphaalkynes include the synthesis of anellated azaphospholes as well through [3 + 2]cycloaddition [17–19]. The ^{31}P NMR chemical shifts of a large number of anellated azaphospholes find place in two reviews [12, 20].

2 Synthesis

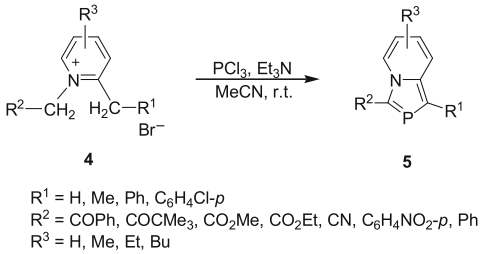
2.1 [4 + 1]Cyclocondensation

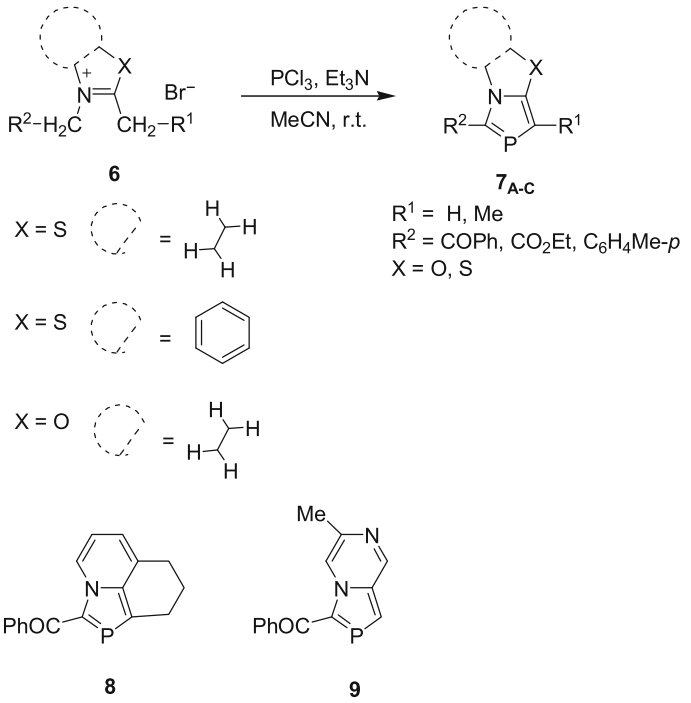
A four-membered chain, which is a part of the ring system, on reacting with an appropriate phosphorus reagent incorporates phosphorus to furnish an anellated heterophosphole [12]. Analogous to the synthesis of anellated azoles from 1,2-disubstituted cycloiminium salts through their [4 + 1]cyclocondensation with a carboxylic acid derivative, we developed a simple method for the synthesis of a variety of anellated azaphospholes using phosphorus acid derivative, such as PCl_3 or $P(NMe_2)_3$ in place of carboxylic acid derivative [15] (Scheme 1). The reaction with PCl_3 is carried out in the presence of Et_3N, but the use of $P(NMe_2)_3$ does not require an additional base.



Scheme 1 [4+1] Cyclocondensation synthesis of anellated azaphospholes

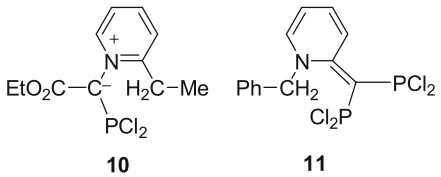
The hydrogens of the terminal groups (YH_2 and ZH_2) should be sufficiently activated, otherwise the reaction may stop at the intermediate stage. By condensing 1,2-dialkylcycloiminium salts with PCl_3 in the presence of Et_3N, we could obtain [1,3]azaphospholes anellated to pyridines, named as 2-phosphaindolizines (**5**) [21–23], thiazoline ($\mathbf{7_A}$) and benzothiazoles ($\mathbf{7_B}$) [24], oxazoline ($\mathbf{7_C}$) [25], quinoline (**8**) [21] and pyrazine (**9**) (Scheme 2) [21].





Scheme 2 Synthesis of anellated [1,3]azaphospholes

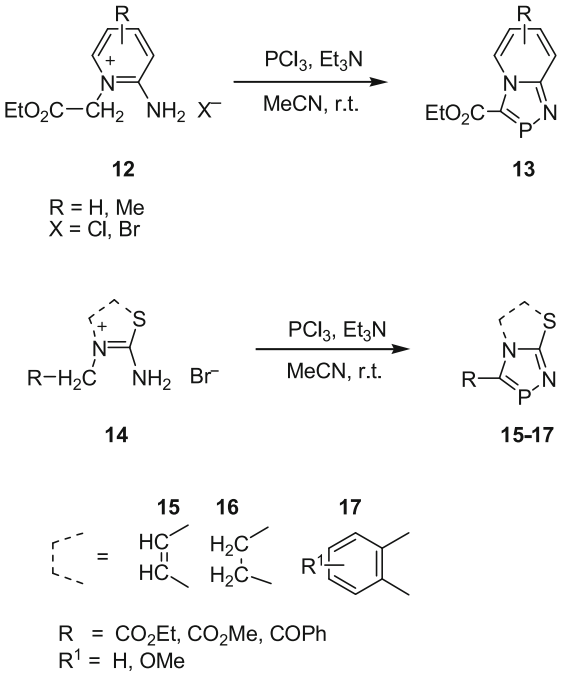
The successful isolation of the intermediate, 2-ethylpyridinium dichlorophosphino-ethoxycarbonylmethylide (**10**) on carrying out the reaction in toluene establishes initiation of the reaction at the *N*-methylene group [21]. The reaction of 1-benzyl-2-methylpyridinium bromide with PCl_3 and Et_3N, however, commences at the 2-methyl group, as evidenced by the formation of **11** that does not cyclize even on heating [26].



3

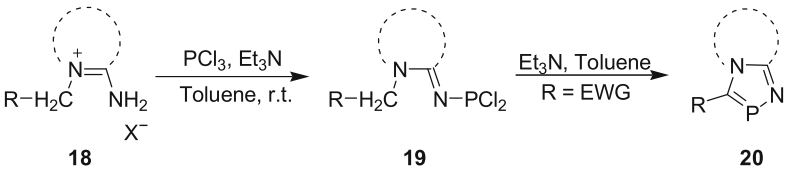
Structure 3

Likewise, we obtained [1,4,2]diazaphospholes anellated to pyridines (**13**) [27], thiazoles (**15**) and their 5,6-dihydro- (**16**) and benzo- (**17**) derivatives [28, 29] from the condensation of 1-alkyl-2-aminocycloiminium salts with PCl_3 in the presence of Et_3N (Scheme 3).



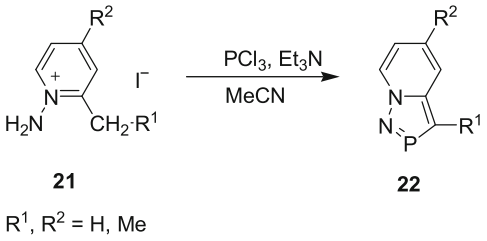
Scheme 3 Synthesis of anellated [1,4,2]diazaphospholes

In the above cases, reaction is initiated at the amino group as, on carrying out the reaction in toluene, the intermediate **19** can be isolated, which cyclizes intramolecularly to afford **20**, if the *N*-methyl group is sufficiently activated [27, 29–31] (Scheme 4).



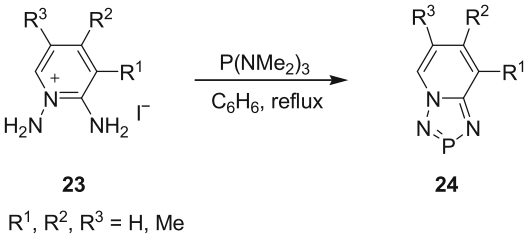
Scheme 4 Intermediate in the preparation of [1,4,2]diazaphospholes

[1,2,3]Diazaphospholo[1,5-*a*]pyridines (**22**) could be prepared in a similar manner from the condensation of 2-alkyl-1-aminopyridinium iodides [32, 33] with PCl_3 in the presence of Et_3N [34] (Scheme 5). An attempt to isolate the intermediate in this case, however, failed.



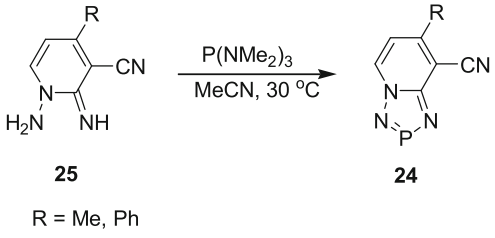
Scheme 5 Synthesis of [1,2,3]diazaphospholo[1,5-*a*]pyridines

The [4 + 1] cyclocondensation of 1,2-diaminopyridinium iodides [35], however, occurred satisfactorily with $P(NMe_2)_3$ in boiling benzene to afford [1,2,4,3] triazaphospholo[1,5-*a*]pyridines (**24**); the use of $PCl_3 + Et_3N$ in this case either gave no product at all or the yield was very poor (~10%) [36] (Scheme 6).



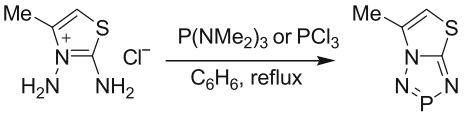
Scheme 6 Synthesis of [1,2,4,3]triazaphospholo[1,5-*a*]pyridines

Schmidpeter et al. [37] developed an alternative method for the synthesis of **24** involving condensation of 1-amino-2-imino-1,2-dihydropyridines (**25**) with $P(NMe_2)_3$ (Scheme 7).



Scheme 7 [4+1] Cyclocondensation of 1-amino-2-imino-1,2-dihydropyridines

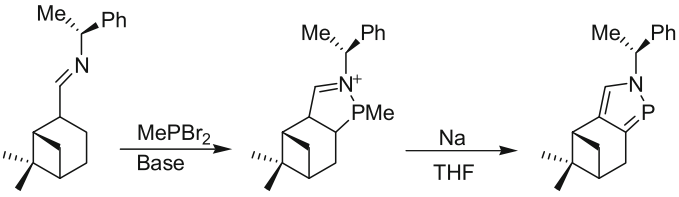
Thiazolo[2,3-*e*][1,2,4,3]triazaphosphole (**27**) was prepared from the condensation of 2,3-diaminothiazolium chloride with $P(NMe_2)_3$ or PCl_3; the use of the latter required no additional base in this case indicating high preference for the formation of the azaphosphole ring [37] (Scheme 8).



26 **27**

Scheme 8 Synthesis of thiazolo[2,3-*e*][1,2,4,3]triazaphosphole

A chiral anellated 1,2-azaphosphole (**30**) was prepared from the condensation of the Schiff base **28** with $MePBr_2$ in the presence of base followed by reduction of the resulting salt **29** with Na in THF (Scheme 9) [38]. Reduction of **29** with Mg gave a dimer found useful in the Ni-catalyzed asymmetric hydrovinylation of styrene [39, 40].

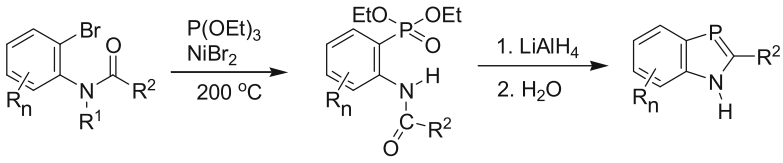


28 **29** **30**

Scheme 9 Synthesis of a chiral anellated [1,2]azaphosphole

2.2 Reductive Cyclization

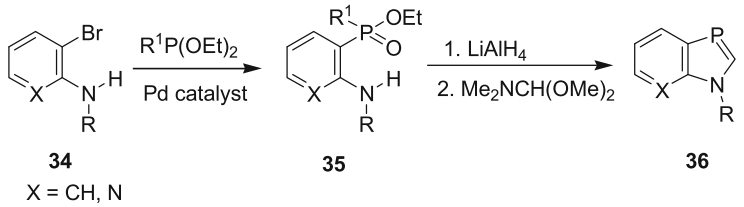
Heinicke and co-workers [41, 42] developed a two-step synthesis of 1*H*-1,3-benzazaphospholes (**33**) involving nickel-catalyzed coupling of 2-bromo- or 2-chloroanilides with triethylphosphite followed by reductive cyclization with excess $LiAlH_4$ (Scheme 10).



31 **32** **33**

Scheme 10 Synthesis of 1*H*-1,3-benzazaphospholes

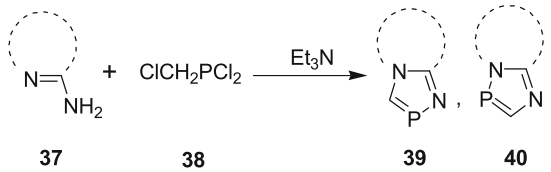
It was, however, impossible to obtain *N*-alkyl or *N*-aryl substituted 1,3-benzazaphospholes or pyrido-anellated 1,3-azaphospholes through the above route. However, palladium-catalyzed cross coupling, followed by reduction of the resulting *o*-anilino- or *o*-aminopyridophosphonates and condensation with dimethylformamide dimethylacetal led to the desired *N*-substituted benzazaphospholes (**36**, X = CH) or pyrido-anellated azaphospholes (**36**, X = N) (Scheme 11) [43–47].



Scheme 11 Synthesis of benzo- and pyrido- anellated [1,3]azaphospholes

2.3 [3 + 2]Cyclocondensation

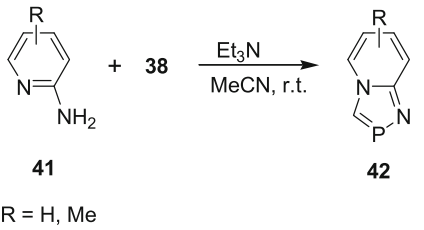
Analogous to the synthesis of anellated imidazoles [48–50], a method has been developed for the preparation of anellated [1,4,2]diazaphospholes from [3 + 2] cyclocondensation of 2-aminocycloimines with chloromethyldichlorophosphine in the presence of Et_3N (Scheme 12) [51].



Scheme 12 [3+2] Cyclocondensation synthesis of anellated [1,4,2]diazaphospholes

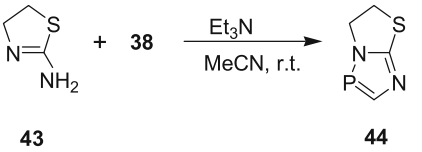
The reaction is highly regioselective and α-unsubstituted diazaphospholes are obtained in high yields. Nevertheless, it appears that the potential of the method has not been fully realized, possibly due to the cumbersome synthesis of **38** [52].

The condensation of 2-aminopyridines with **38** in the presence of Et_3N afforded [1,4,2]diazaphospholo[4,5-*a*]pyridines (**42**) with complete regioselectivity (Scheme 13) [53, 54]. It may be noted that, in contrast to [4 + 1]cyclocondensation, this method makes available α-unsubstituted products.



Scheme 13 Synthesis of [1,4,2] diazaphospholo[4,5-*a*]pyridines

A similar reaction with 2-amino-4,5-dihydrothiazole (**43**) gave 5,6-dihydrothiazolo [2,3-*e*][1,4,2]diazaphosphole (**44**), again with complete regioselectivity, though the regioorientation of **38** is reversed in this case (Scheme 14) [54].



Scheme 14 Synthesis of [2,3-*e*][1,4,2]diazaphospholes

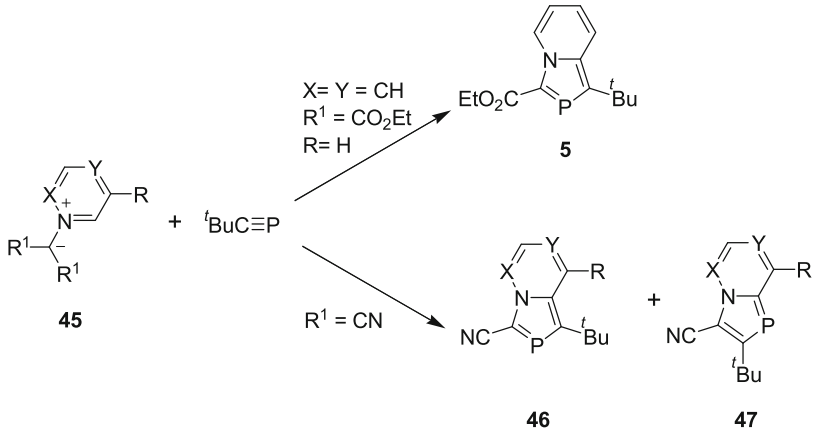
[1,4,2]Diazaphospholes anellated to thiazole, benzothiazole, pyrimidine, pyrazine and quinoline have been prepared in a similar manner. The regioselectivity in these cases varies from 67 to 100%. In the reaction with 2-aminothiazole, formation of small quantities of α-phosphinylated products was also detected by ^{31}P NMR spectroscopy [54].

2.4 [3 + 2]Cycloaddition

[3 + 2]Cycloadditions of azomethine ylides and -imines with appropriate 1,3-dipolarophiles have been employed for the preparation of anellated pyrroles and pyrazoles, respectively [49, 55–57]. In analogy, phosphaalkynes have been used as 1,3-dipolarophiles for introducing a two-coordinate phosphorus leading to a variety of anellated azaphospholes. Many such examples are included in earlier reviews [17–19]. In order to illustrate the synthetic strategy, two examples are cited here.

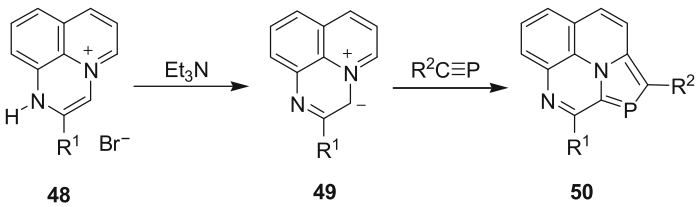
2-Phosphaindolizines (**5**) have been obtained with total regioselectivity from [3 + 2]cycloaddition of pyridinium bis(ethoxycarbonyl)methylide (**45**, X = Y = CH, R = H, R^1 = CO_2Et) with *tert*-butylphosphaethyne [58]. The reactions of *N*-dicyanomethylides of pyridine (**45**, X = Y = CH, R^1 = CN), pyridazine (**45**, X = N, Y = CH, R^1 = CN) and pyrazine (**45**, X = CH, Y = N, R^1 = CN) under these conditions, however, gave a mixture of two regioisomers (**46** and **47**) in each case.

However, on introducing a *tert*-butyl or isopropoxy group in the iminium fragment of **45** (X = Y = CH, R = ^{t}Bu or ^{i}PrO), again only one regioisomer was formed in each case (Scheme 15) [58].



Scheme 15 [3+2]Cycloaddition synthesis of anellated [1,3]azaphospholes

Likewise, isoquinoline- and phthalazine-anellated 1,3-azaphospholes have been obtained from [3 + 2]cycloaddition of the respective ylides with phosphaalkynes [59]. Similarly, ylides **49** [59] generated from deprotonation of 3*H*-pyrido[1,2,3-*de*] quinoxalinium bromides afforded azaphosphaullazines, i.e. 4,9*b*-diaza-2-phoaphacyclopenta[*c*,*d*]phenalenes (**50**) regioselectiviely through [3 + 2]cycloaddition with phosphaalkynes (Scheme 16) [60].

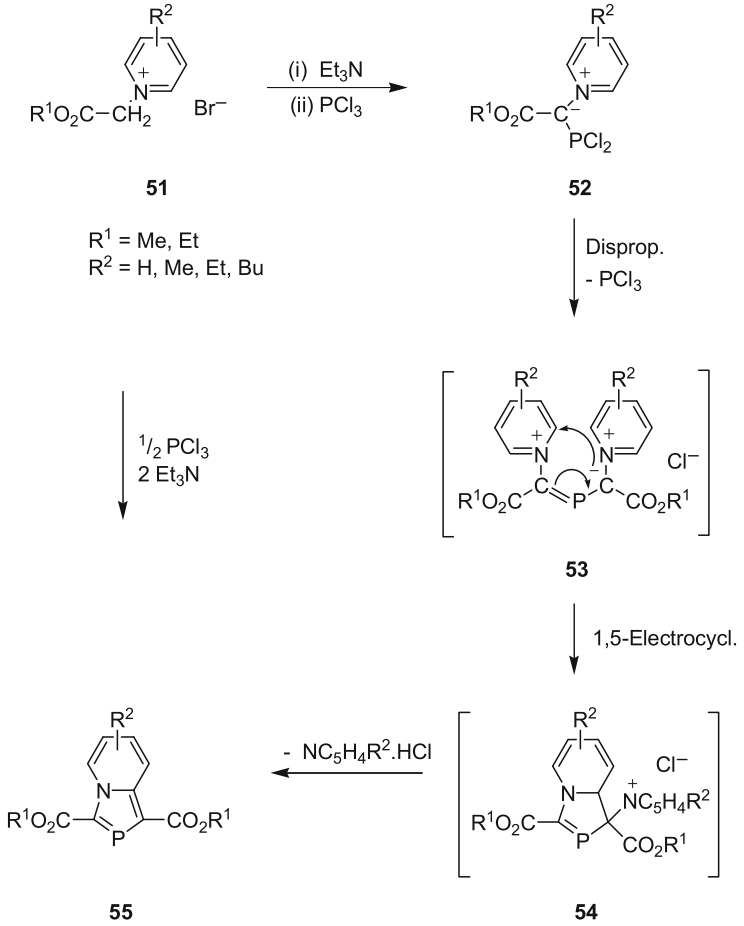


Scheme 16 Synthesis of azaphosphaullazines

2.5 1,5-Electrocyclization

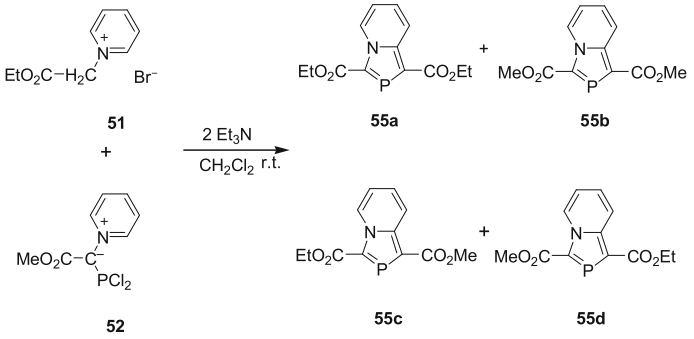
N-Cycloiminium allylides are reported to undergo intramolecular 1,5-electrocyclization followed by 1,2-elimination to afford anellated pyrroles [61]. Analogously, we succeeded in obtaining anellated 1,3-azaphospholes through this method.

Pyridinium alkoxycarbonyl-dichlorophosphinomethylides (**52**) produced from the reaction of *N*-(alkoxycarbonyl)pyridinium bromides (**51**) with Et_3N and PCl_3 undergo disproportionation to generate bis(pyridinium ylidyl)phosphenium chloride (**53**). The latter undergoes intramolecular 1,5-electrocyclization followed by 1,2-elimination to give 1,3-bis(alkoxycarbonyl)-2-phosphaindolizines (**55**) (Scheme 17) [62–64]. It may be mentioned that similar disproportionation of triphenylphosphonium dichlorophosphinomethylides has been reported by Schmidpeter and Jochem [65].



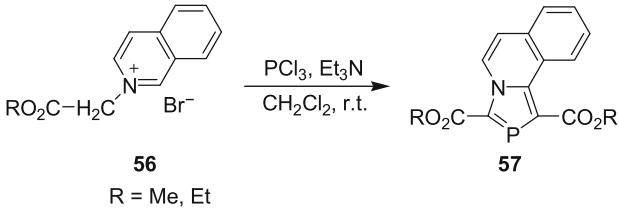
Scheme 17 1,5-Electrocyclization synthesis of 2-phosphaindolizines

The proposed mechanism of the above reaction was confirmed by carrying out a crossed reaction when all the four possible compounds were detected in the reaction product by NMR spectroscopy (Scheme 18) [62]. A one pot synthesis of **55** was subsequently developed [62–64].



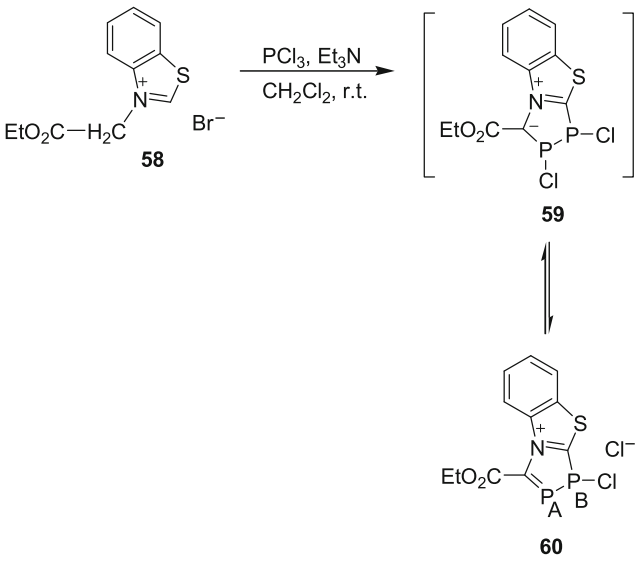
Scheme 18 2-Phosphaindolizines from a crossed reaction

The method also allows the successful synthesis of [1,3]azaphospholo[5,1-*a*] isoquinolines (**57**) (Scheme 19) [66]. The latter could be prepared in a much shorter time using a microwave irradiation technique [67]. The method, however, failed for the anellated [1,3]azaphospholo[1,5-*a*]quinolines.



Scheme 19 Synthesis of [1,3]azaphospholo[5,1-*a*]isoquinolines

The reaction of 3-(ethoxycarbonylmethyl)benzothiazolium bromide (**58**) with PCl_3 (1 equiv.) and Et_3N (2 equiv.) at room temperature yielded a dark-orange product that could not be separated from the ammonium salt. The ^{31}P NMR of the reaction mixture shows it to possess the structure, **60** (Scheme 20). The benzothiazolium methylide formed in the reaction possibly acts as the reducing agent by taking up a halogen molecule leading to the P-P bond formation [68]. A similar sequence of reactions involving dihalophosphinylation of the benzyltriphenylphosphenium bromide followed by reductive P–P bond formation has been reported by Schmidpeter et al. [69, 70].



Scheme 20 Formation of [1,3,4]azadiphospholo[5,1-*b*]benzothiazolium ion

3 Structure Determination

NMR spectroscopy (^{31}P, ^{1}H, ^{13}C) has been extensively employed for establishing structures of the anellated azaphospholes. Mass spectral fragmentation has been studied in a few cases. Single crystal X-ray diffraction studies have also been reported for a few representatives.

3.1 NMR Studies

The ^{31}P NMR chemical shifts of the anellated azaphospholes published till mid-1993 are included in a review [12]. The actual value of the ^{31}P NMR chemical shift of an anellated azaphosphole is influenced by several factors, such as the ring members adjacent to the phosphorus atom, additional nitrogen atom, size of the ring anellated, position of anellation and nature of the α-substituent. The ^{31}P NMR chemical shifts of the anellated 1,3-azaphospholes lie in the range δ 60–128 [41, 42], and with a bridging nitrogen atom in the range δ 120–202 [21–25, 62, 63, 66]. The presence of an additional nitrogen as in anellated diazaphospholes causes deshielding and the ^{31}P NMR signal lies in the range δ 184–270 [27–30, 34, 54]. The ^{31}P NMR chemical shifts of triazaphospholes anellated to pyridine or thiazole having nitrogen atoms on both sides of the phosphorus atom are more downfield and lie at δ 265–292 [36, 37].

^{1}H and ^{13}C NMR data of a large number of anellated azaphospholes have been reported [12]. The ^{13}C NMR spectra are characterized by characteristic PC couplings.

3.2 Mass Spectral Studies

Mass spectral fragmentation of a few anellated azaphospholes has been reported [23, 25, 34, 66]. In general, molecular ion peak constitutes the base peak and the basic fragmentation resembles that of the analogous non-phosphorus heterocycle.

3.3 X-Ray Crystal Structure

X-ray crystal structure determination of [1,3]azaphospholo[1,5-*a*]pyridines [23, 71] and -[5,1-*a*]isoquinoline [71] reveals the azaphosphole ring planar with the angle at phosphorus, 89.6–91.9° and the two C–P bonds lengths being almost averaged [170.8–174.7 pm] indicating an effective delocalization of 6π-electrons. The C = O group of the exocyclic ester moiety is also found to be coplanar with the azaphosphole ring revealing extended conjugation [23, 71]. Also, several crystal structures of benzazaphospholes are known, including functionally substituted representatives such as 2-lithiated, COOH, OH and bulky phosphino substituted species [43–45, 72, 73].

3.4 DFT Calculations

We have evaluated the effect of introducing a σ^2,λ^3-phosphorus atom in different positions of the pyrido anellated azole ring by carrying out theoretical calculations at the B3LYP/6–311G** level and found it to be well integrated in the aromatic sextet. NBO calculations of a few representatives further confirm preservation of the aromatic character. Furthermore, CH/P exchange causes lowering of the frontier molecular orbital energies leading to the enhanced reactivity of these compounds towards [2 + 3] and [2 + 4]cycloaddition reactions [74].

4 Reactions

The azaphosphole ring incorporates several functionalities (Fig. 1) and hence exhibits interesting reactivities towards a variety of reagents.

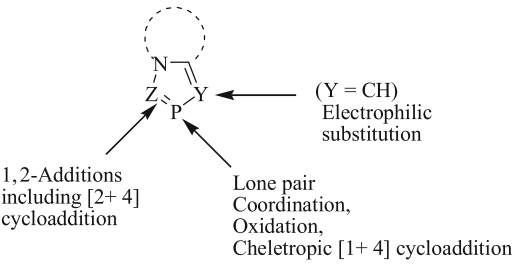
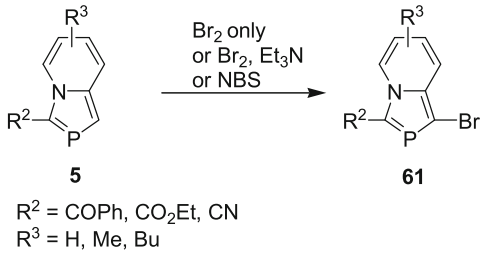


Fig. 1 Functionalities in the azaphosphole ring

4.1 Electrophilic Substitution Reactions

We have made a systematic investigation of the electrophilic substitution reactions of pyrido anellated 1,3-azaphospholes, i.e. 2-phosphaindolizines. These compounds are found to be much less reactive as compared to their non-phosphorus analogues, i.e. indolizines. In contrast to the latter, 2-phosphaindolizines do not react with acetyl chloride, benzoyl chloride or trimethylchlorosilane even on prolonged heating [75]. The reaction of 1-unsubstituted 2-phosphaindolizines with bromine, however, occurs successfully, affording 1-bromo derivatives, though in poor yields. The reaction of bromine in presence of Et_3N or using *N*-bromosuccinimide improved the yields considerably (Scheme 21) [76, 77].

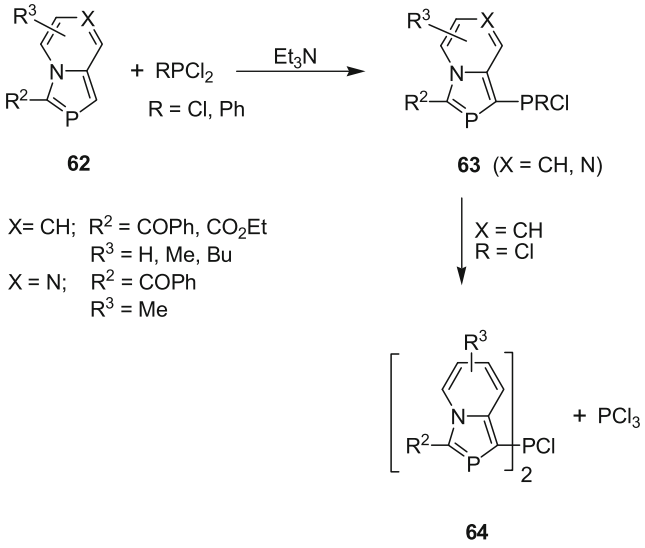


Scheme 21 Bromination of 2-phosphaindolizines

Likewise, the reaction of **5** (**62**, X = CH) and 7-aza-2-phosphaindolizine **9** (**62**, X = N) with chlorophosphines gave 1-chlorophosphino derivatives **63**. 1-Dichloro-phosphino derivatives **63** (X = CH, R = Cl) in solution show the

tendency of disproportionation producing **64**, as revealed by ^{31}P NMR (Scheme 22) [76].

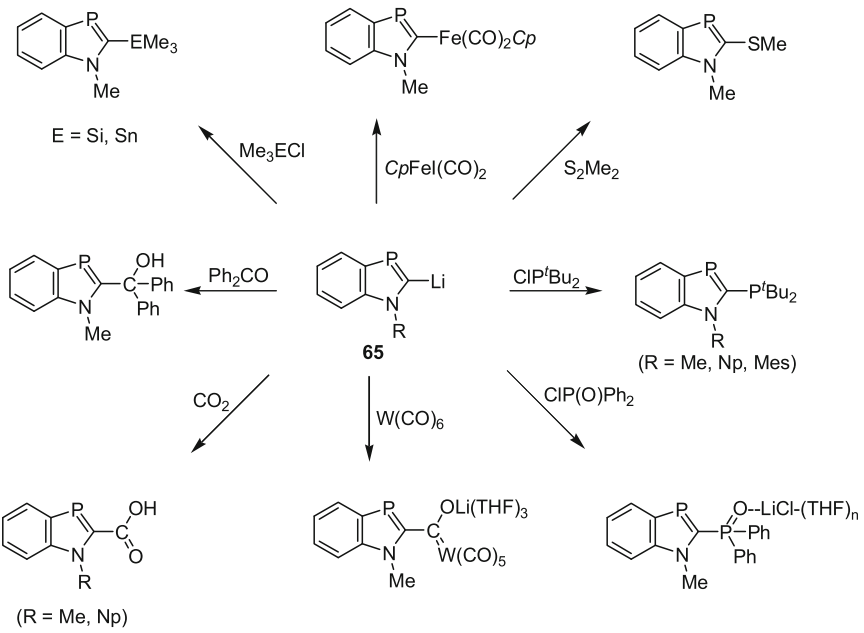
1-Dichlorophosphino substituted derivatives of [1,2,3]diazaphospholo[1,5-*a*]-pyridines [34] and 5,6-dihydro[1,3]azaphospholo[5,1-*b*]thiazole [24] were obtained directly from the reaction of the corresponding *N*-cycloiminium salt with 2 equiv. of PCl_3 in the presence of Et_3N.



Scheme 22 1-Dichlorophosphinylation of 2-phosphaindolizine

Nucleophilic substitution of two chlorine atoms of 1-dichlorophosphino moiety of **63** (X = CH) could be possible by reacting it with methanol in the presence of Et_3N. The resulting 1-dimethoxyphosphino derivative was subjected to MeI-catalyzed Arbuzov rearrangement and could be oxidized with sulfur at the exocyclic phosphorus selectively [76].

A variety of 2-functionalized 1,3-benzazaphospholes have been obtained by lithiation of 1-methyl-1,3-benzazaphosphole with ^{t}BuLi in THF or Et_2O followed by reaction with a suitable electrophilic reagent [72, 73]. 1,3-Benzazaphospholes having bulkier *N*-substituents show tendency of addition of ^{t}BuLi at the P = C bond [43–45, 72]. Lithiation of **65** (R = neopentyl) yields a mixture of both *C*-lithiated and addition products; however, in the presence of KO^{t}Bu, equilibrium shifts towards *C*-lithiation (Scheme 23).



Scheme 23 Synthesis of 2-functionalized 1,3-benzazaphospholes

4.2 Alkylation

No reaction occurs with methyl iodide; however, on reacting with Me_2SO_4, [1,4,2] diazaphospholo[4,5-*a*]pyridines [27] and [1,2,3]diazaphospholo[4,5-*a*]-pyridines [34] furnish σ^2-*N*-methylated salts. Similar behaviour is shown by thiazolo[3,2-*d*] [1,4,2]diazaphospholes [28]. However, 1,3-benzazaphospholes are alkylated at phosphorus. This allows the access to N,P-disubstituted benzazaphospholium salts, potential precursors to heterocyclic 1,3-aminophosphinocarbenes [47].

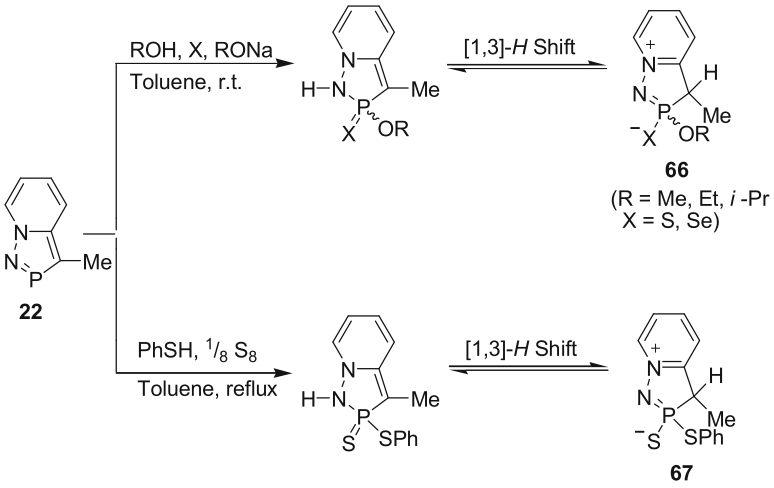
4.3 1,2-Additions to > C = P– or –N = P–

4.3.1 Addition of Protic Reagents

The >C = P– and –N = P– bonds, being polar, are attacked by protic reagents resulting in 1,2-addition, the proton being bonded to carbon or nitrogen.

Addition of water to 2-phosphaindolizine (**5**) [21] and its 1-bromo derivatives [76], [1,2,3]diazaphospholo[4,5-*a*]pyridine (**22**) [34] and [1,2,4,3]triazaphospholo-[1,5-*a*]pyridine (**24**) [36] causes hydrolysis leading to azaphosphole ring opening and formation of the pyridinium salts.

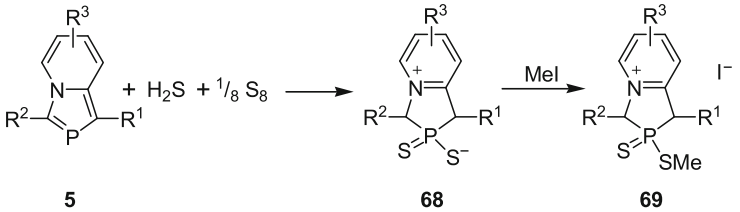
The reaction of [1,2,3]diazaphospholo[1,5-*a*]pyridine (**22**) with alcohol is completed only in the presence of sulfur or selenium and a catalytic amount of the respective sodium alkoxide to give **66**. The reaction with thiophenol also occurs in the presence of sulfur to form **67**; however no catalyst is required in this case (Scheme 24) [78].



Scheme 24 Reaction of [1,2,3]diazaphospholo[1,5-*a*]pyridine with alchohol or thiophenol

Likewise, 1,2-addition of Et_2NH to [1,2,4,3]triazaphospholo[1,5-*a*]pyridines occurs in the presence of sulfur or selenium with simultaneous oxidation of the phosphorus atom [36].

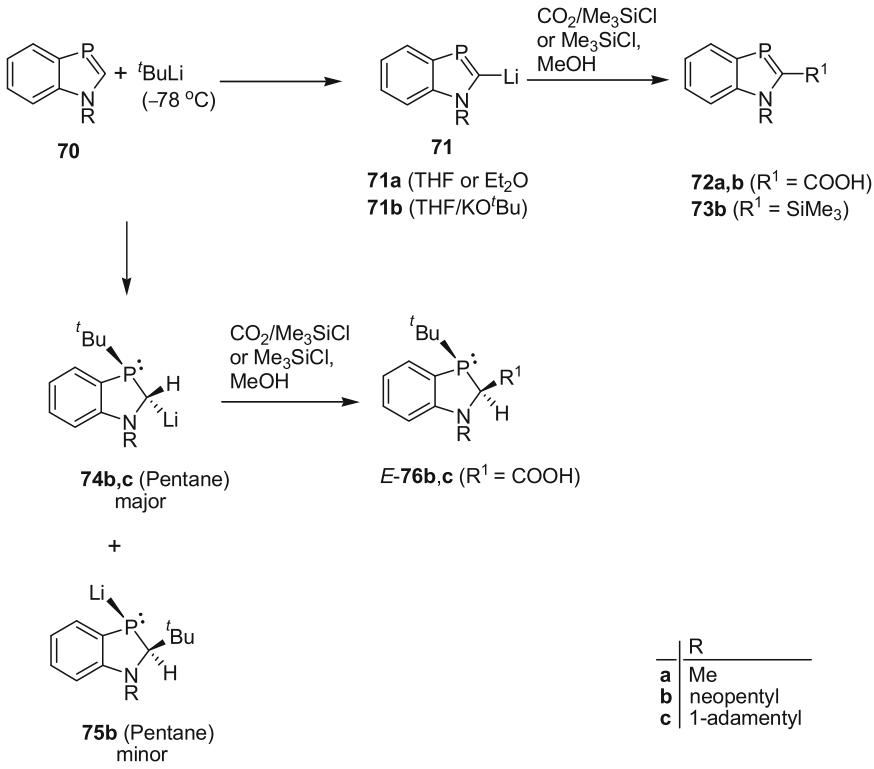
The reaction of 2-phosphaindolizines (**5**) with H_2S in the presence of sulfur leads to zwitterionic pyridinium dithiophosphinates (**68**) through 1,2-addition of H_2S on >C = P– functionality with concomitant oxidation of phosphorus atom followed by 1,3-prototropic shift. The reaction of **5** (R^1 = Me, R^2 = CO_2Me, 4-$NO_2C_6H_4$, R^3 = H) yields two diastereomers in each case, as indicated by ^{31}P NMR. In some cases the *S*-methylated products, **69**, could be obtained on reaction of **68** with MeI (Scheme 25). A selenium analogue of **69** has also been obtained [79, 80].



R^1 = H, Me
R^2 = COPh, CO_2Me, $COCMe_3$,
C_6H_4 -NO_2 -*p*
R^3 = H, Me, Et, Bu

Scheme 25 Reaction of 2-phosphaindolizine with hydrogen sulfide and sulfur

The mode of the reaction of ^{t}BuLi with P = CH–NR moiety of 1,3-benzazaphospholes (**70**) is governed by the steric bulk of the R substituent and polarity of the solvent. The reaction of **70** with small R (such as Me) in a polar solvent (THF) gives mainly *C*-lithiated product, while **70** with R = *N*-adamantyl group in a nonpolar solvent (pentane) leads to addition products (E-^{t}BuP–CHLi–NR and LiP–CH(^{t}Bu)–NR). *N*-Neopentyl group with intermediate steric demand yields mixture of both *C*-lithiated and addition products in ether, but allows switching to selective CH-lithiation in THF/KO^{t}Bu or to addition in pentane (Scheme 26) [43–45, 73].



Scheme 26 Reaction of 1,3-benzazaphosphole with *tert*-butyllithium

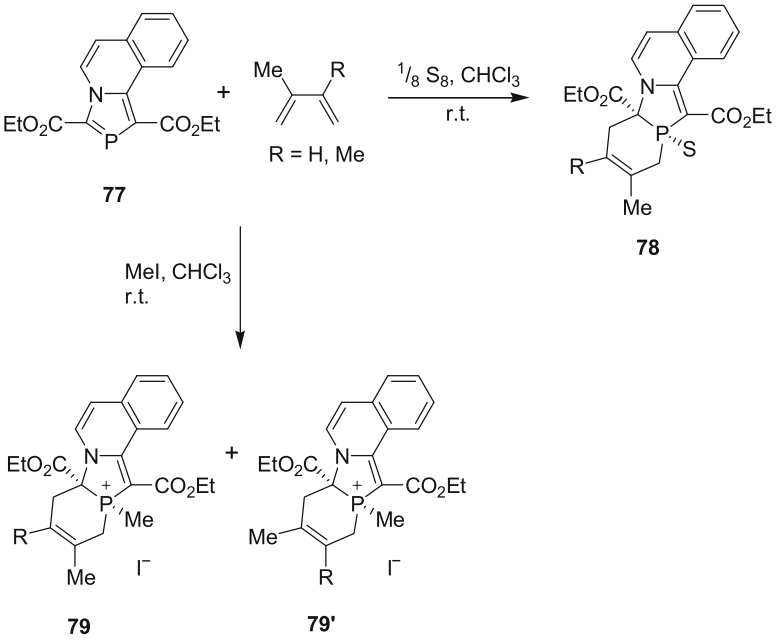
4.3.2 [2 + 4]Cycloadditions

Theoretical calculations reveal that the presence of the phosphorus atom in Diels-Alder (DA) reactant lowers the activation energy barrier relative to the analogous all-carbon system due to weaker C = P π bond as compared to the C = C π bond

[81-83]. In view of this, we have undertaken a systematic investigation of the DA reactions of a variety of anellated azaphospholes whose syntheses have been reported by our group earlier. The results of some of these reactions are included in two recent reviews dealing primarily with cycloadditions of heterophospholes [84] and DA reactions with >C = P– functionality [85].

In the azaphosphole ring, both carbon and phosphorus atoms of the >C =P– functionality are prochiral and DA reaction with it leads to the generation of two stereogenic centres. The results, however, indicate that these reactions are accompanied by high diastereo- and regioselectivity that has been rationalized in many cases by theoretical calculations [84, 85].

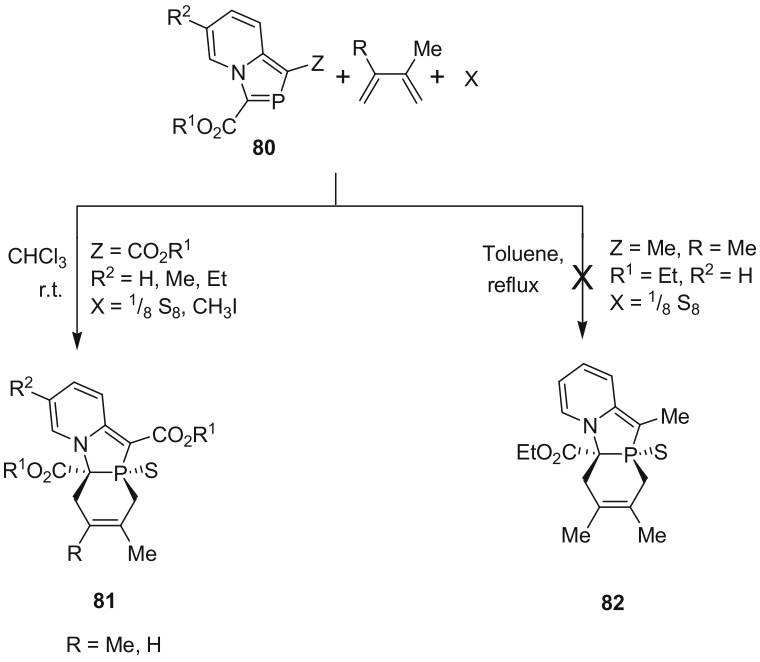
1,3-Bis(ethoxycarbonyl)-[1,3]azaphospholo[5,1-*a*]isoquinoline (**77**) undergoes [2 + 4]cycloaddition with 2,3-dimethylbutadiene (DMB) in the presence of S_8 or MeI at room temperature to give **78** (R = Me) and **79** (R = Me), respectively [66, 86]. The reaction with isoprene in the presence of sulfur proceeds with complete regioselectivity to give **78** (R = H) only, but in the presence of MeI the regioselectivity is lowered and two regioisomers **79** (R = H) (62%) and **79'** (R = H) (38%) (determined on the basis of ^{31}P NMR signal intensities) are formed (Scheme 27). The structure of **78** (R = H) was confirmed by X-ray crystal analysis [86]. The [2 + 4]cycloadditions of **77** with DMB and isoprene could be accomplished under microwave irradiation in much shorter times [67].



Scheme 27 Diels-Alder reaction of [1,3]azaphospholo[5,1-*a*]isoquinoline

In contrast to λ^3-phosphinine, wherein the reaction of sulfur with phosphorus atom precedes the DA reaction of DMB with >C = P– moiety [87–89], in the above case, it has been established that the reaction of sulfur with phosphorus atom follows the DA reaction, as **77** reacts with DMB alone also, though sluggishly, and the reaction can be completed (δ ^{31}P = 14.1) by refluxing in chloroform for 4 days [86].

It is found that the reactivity of 2-phosphaindolizine as dienophile in the DA reaction is remarkably influenced by the nature of the substituent group at C-1: 3-ethoxycarbonyl-1-methyl-[1,3]azaphospholo[1,5-*a*]pyridine (**80**) does not react with DMB even on refluxing in toluene in the presence of sulfur, whereas 1,3-bis(ethoxycarbonyl) derivative (**80**) gives [2 + 4]cycloadducts **81** at room temperature (Scheme 28). The reactions are completely diastereo- and regioselective [64, 86].

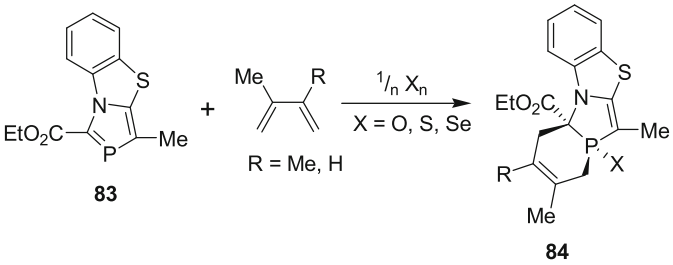


Scheme 28 Diels-Alder reaction of 2-phosphaindolizines

The diastereo- and regioselectivity as well as the relative dienophilic reactivity of **80** have been rationalized on the basis of theoretical calculations at the DFT

(B3LYP/6–311 + + G**//B3LYP/6–31G**) level. The relative stabilities of different transition structures have been explained on the basis of NBO calculations [90].

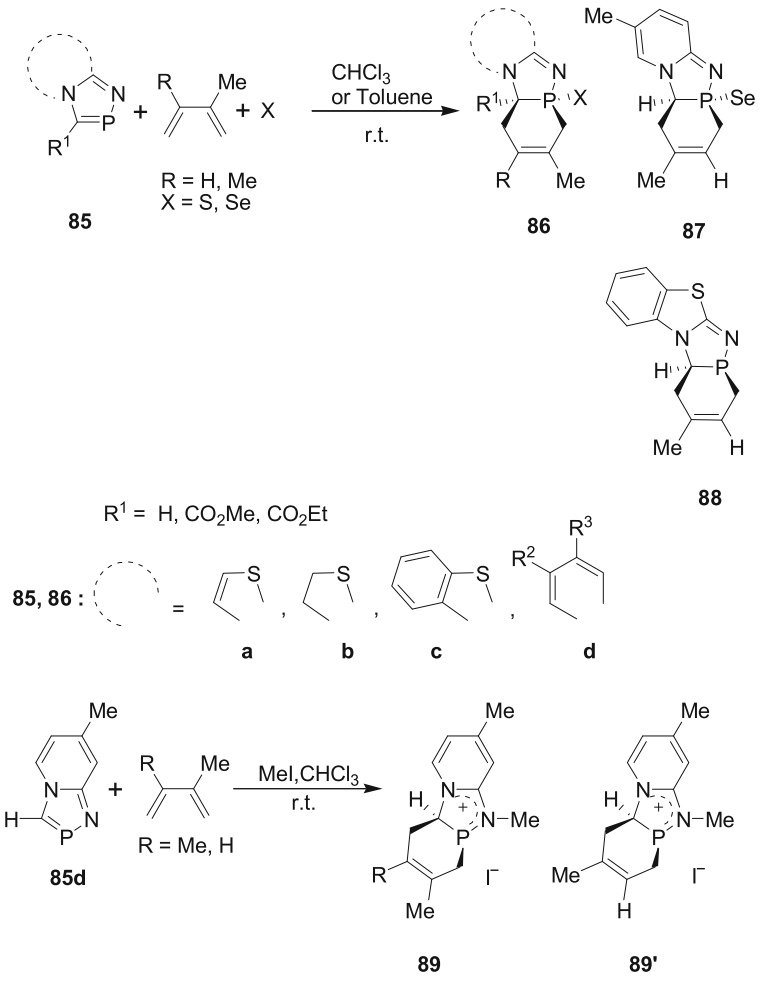
[1,3]Azaphospholo[5,1-*b*]benzothiazole (**83**) undergoes DA reaction only in the presence of an oxidizing agent such as oxygen, sulfur or selenium. The reaction with isoprene occurs with complete regioselectivity (Scheme 29) [91].



Scheme 29 Diels-Alder reaction of [1,3]azaphospholo[5,1-*b*]benzothiazole

We have also carried out the DA reactions of anellated diazaphospholes, which exhibit enhanced reactivity and can react with 1,3-dienes even in the absence of an oxidizing agent. However, the resulting [2 + 4]cycloadducts get oxidized with traces of oxygen during work-up and cannot be obtained in pure form. The cycloadditions are therefore carried out in the presence of sulfur or selenium. Thiazolo[3,2-*d*][1,4,2]diazaphospholes (**85a**) and their 5,6-dihydro (**85b**) and benzo (**85c**) derivatives [91], [1,4,2]diazaphospholo[4,5-*a*]pyridines (**85d**) [92] afford [2 + 4]cycloadducts (**86**) under these conditions (Scheme 30). The reactions occur normally with complete diastereoselectivity and high regioselectivity. The reaction of **85d** ($R^1 = R^3 = H$, $R^2 = Me$) with isoprene and selenium gives two regioisomers, **86d** (R = $R^1 = R^3 = H$, $R^2 = Me$, X = Se) and **87** in the ratio 4:1. Furthermore, the reaction of 7-methyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine (**85d**, $R^1 = R^2 = H$, $R^3 = Me$) with DMB and MeI gives **89** (R = Me), the methylation occurring at σ^2,λ^3-nitrogen atom of the cycloadduct, thereby confirming that [2 + 4]cycloaddition precedes oxidation of the phosphorus atom. The reaction with isoprene under these conditions yields a mixture of two regioisomers **89** (R = H) and **89'**, former being the major (70%) product [92].

Likewise, 3-unsubstituted [1,4,2]diazaphospholo[5,4-*b*]benzothiazole (**85c**, R^1 = H) on reaction with isoprene gives two regioisomers **86c** (R = R^1 = H, X = lone pair) and **88** in the ratio 2:1 [91].



Scheme 30 Diels-Alder reaction of anellated [1,4,2]diazaphospholes

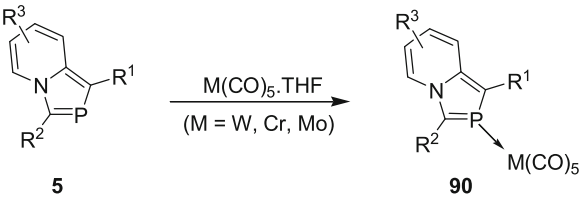
The obtained diastereo- and regioselectivities in the DA reactions of [1,4,2] diazaphospholopyridines (**85d**) have been rationalized on the basis of theoretical calculations at the DFT (B3LYP/6–311 + + G**//B3LYP/6–311G**) level [92].

Similarly, we have also investigated the diastereo- and regioselectivities of the DA reactions of thiazolodiazaphospholes and related systems theoretically at the same level. The results reveal that the reactions follow pericyclic mechanism, aromatic character of the transition structures, which are asynchronous, being confirmed by high negative nucleus independent chemical shift (NICS) values [93, 94].

4.4 Coordination Compounds

The coordinating behaviour of several anellated azaphospholes has been investigated. These compounds are found to be weak σ-donor and more efficient π-acceptor ligands.

On reacting with $M(CO)_5$.THF (M = Cr, Mo, W), 2-phosphaindolizines furnish η^1(*P*)(2-phosphaindolizine)$M(CO)_5$ complexes (Scheme 31) [95]. In one case, (2-cyclooctene)$Cr(CO)_5$ was used as the transfer reagent [21].



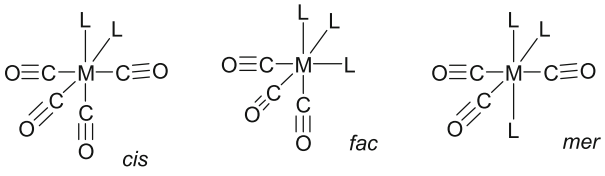
5 **90**

R^1 = H, Me, Ph
R^2 = CO_2Me, CO_2Et, COPh, $COCMe_3$, CN, $C_6H_4NO_2$-*p*
R^3 = H, Me, Bu

Scheme 31 P-Coordination of 2-phosphaindolizine to metal carbonyls

The structure of **90** (R^1 = Me, R^2 = $COCMe_3$, R^3 = H, M = Cr) has been established by X-ray crystal structure determination. The azaphosphole ring on coordination retains its planarity with a trigonal planar geometry at phosphorus atom. The pivaloyl group, however, in contrast to that in the ligand [23], acquires a staggered conformation. Furthermore, the difference in the lengths of the P-C bond decreases as compared to that in the ligand, revealing more effective delocalization in the azaphosphole ring on complexation [95].

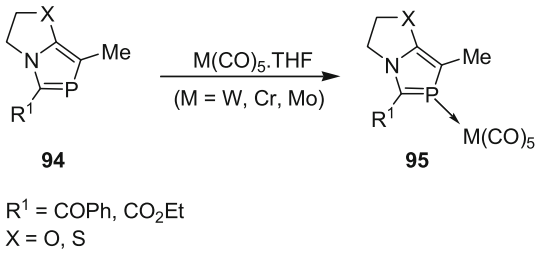
An attempt to obtain π-complexes from the reaction of **5** with (cycloheptatriene) $Mo(CO)_3$ or (mesitylene)$W(CO)_5$ failed; instead a variety of complexes of the types $L_2M(CO)_4$ or $L_3M(CO)_3$ (**91–93**) were formed [95].



91 (M =Cr) **92** (M = Mo, W) **93** (M = Mo)

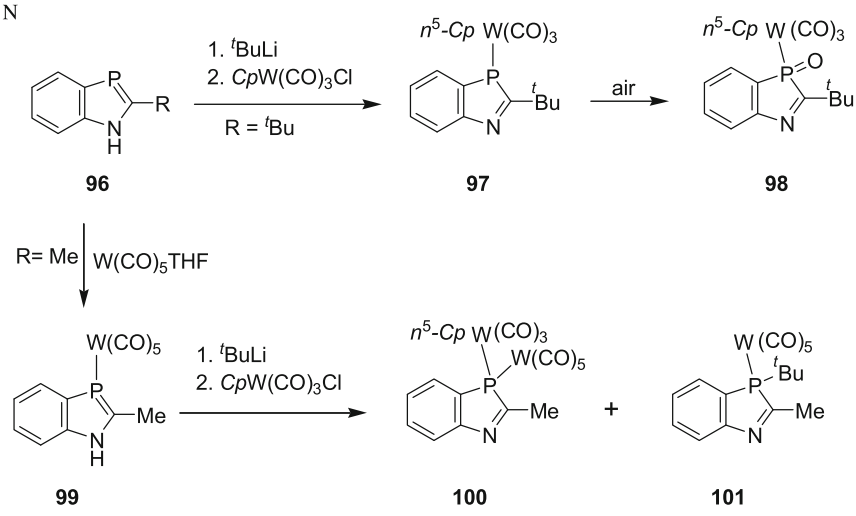
Structure 4

Likewise, $\eta^1(P)$(1,3-azaphospholooxazoline/-thiazoline)$M(CO)_5$ complexes **95** have been prepared (Scheme 32) [96].



Scheme 32 P-Coordination of [1,3]azaphospholooxazoline/thiazoline to metal carbonyls

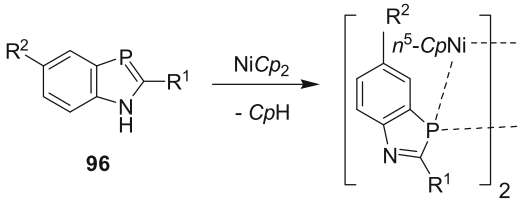
Lithium benzazaphospholide generated from lithiation of 1,3-benzazaphosphole with BuLi on reacting with ($CpW(CO)_3Cl$) affords η^1-(benzazaphospholide-*P*) W(II) complex **97**. The latter on air oxidation yields *P*-oxo-benzazaphospholide complex **98** whose structure has been confirmed by X-ray crystal analysis. On the other hand, η^1-(*P*)-(1,3-benzazaphosphole)$W(CO)_5$ complex (**99**) obtained from the reaction of **96** with [$W(CO)_5$.THF] on successive reactions with ^{t}BuLi and [$CpW(CO)_3Cl$)] affords mixed valence bimetallic W(II)-W(0) complex **100**. A small quantity of the side product **101** is also formed (Scheme 33) [97, 98].



Scheme 33 Coordination of lithium benzazaphospholide

A η^1-(*P*)-$W(CO)_5$ complex of 2-stannyl-1,3-benzazaphosphole accessible from the reaction of 2-stannyl derivative (see Scheme 23) with $W(CO)_5THF$ decomposes slowly with formal loss of Me_2SnCH_2 on repeated crystallization [99].

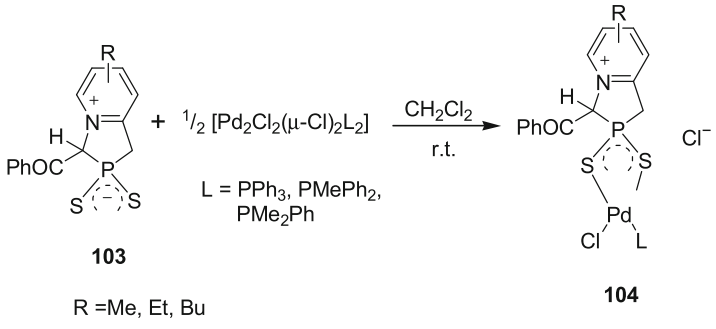
1,3-Benzazaphospholes (**96**) on heating with nickelocene directly provide the benzazaphospholide complexes **102**. NMR and MS data are consistent with a dimer structure and μ-*P* coordination of the Ni*Cp* fragment which is confirmed by a crystal analysis of **102** (R^1 = ^{t}Bu, R^2 = Me) (Scheme 34) [100].



102	a	b	c	d	e	f
R^1	Me	^{t}Bu	Ph	Me	^{t}Bu	Ph
R^2	H	H	H	Me	Me	Me

Scheme 34 μ-P-Coordination of 1,3-benzaazaphospholes to nickel

Mononuclear complexes of the type $[Cp^*RhCl_2(L)]\cdot H_2O$ and $[Ru(cymene)Cl_2(L)]\cdot H_2O$ have been obtained from the reaction of anellated azaphospholes (L = 2-phosphaindolizine and 1,3-azaphospholo[5,1-*a*]isoquinoline) with $[\eta^5\text{-}Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) and $[Ru[\eta^6\text{-cymene})Cl_2]_2$, respectively. NMR studies reveal a dynamic equilibrium between covalent and ionic forms of the complexes in solution [101]. The zwitterionic pyridinodithiophosphinates (**103**), obtained from the reaction of 2-phosphaindolizines with H_2S/S_8, have been used as chelating ligands to obtain $[PdCl(L)]^+ Cl^-$ type complexes (Scheme 35) [102].



Scheme 35 Coordination of pyridodithiophosphinates

5 Concluding Remarks

A variety of anellated azaphospholes have become accessible through facile methods. These compounds have appreciable stability and incorporate several functionalities. In view of this, starting with these compounds, a variety of organophosphorus compounds including their transition metal complexes can be synthesized. Some promising results have already been obtained and it is hoped that this brief report will stimulate further work in this field.

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References

1. Pilgram K, Korte F. (1963) *Tetrahedron* 19:137
2. Nitchen SK, Malavaud C. (1993) *Tetrahedron* 49:4651
3. Schmidpeter A, Karaghiosoff K. (1990) In: Regitz M, Scherer OJ (eds) Multiple bonds and low coordination in phosphorus chemistry. Thieme, Stuttgart, p 258
4. Schmidpeter A. (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II, vol 4. Pergamon, Oxford, p 771
5. Schmidpeter A. (2001) In: Mathey F (ed) Phosphorus-carbon heterocyclic chemistry: the rise of a new domain. Elsevier, Oxford, p 363
6. Bansal RK, Gupta N. (2004) In: Storr RC, Gilchrist TL (eds) Science of synthesis: methods of molecular transformations (Houben-Weyl), vol 13. Thieme, Stuttgart, pp 647, 689, 743
7. Bansal RK, Gupta N, Kumawat SK. (2007) *Current Org Chem* 11:33
8. Mathey F. (1992) *Acc Chem Res* 25:90
9. Dillon KB, Mathey F, Nixon JF. (1998) Phosphorus: the carbon copy, Wiley, New York
10. Nyulaszi L, Veszpremi T, Reffy J. (1993) *J Phys Chem* 97:4011
11. Schmidpeter A. (1999) *Heteroat Chem* 10:529
12. Bansal RK, Karaghiosoff K, Schmidpeter A. (1994) *Tetrahedron* 50:7675
13. Bansal RK, Heinicke J. (2001) *Chem Rev* 101:3549
14. Bansal RK, Gupta N, Surana A. (1998) *J Indian Chem Soc* 75:648
15. Bansal RK, Karaghiosoff K, Gandhi N, Schmidpeter A. (1995) Synthesis 361
16. Bansal RK, Mahnot R, Pandey G, Gupta R. (1994) *J Indian Chem Soc* 71:415
17. Regitz M, Binger P. (1998) *Angew Chem Int Ed Engl* 27:1484
18. Regitz M. (1990) *Chem Rev* 90:191
19. Regitz M. (1990) In: Regitz M, Scherer OJ (eds) Multiple bonds and low coordination in phosphorus chemistry. Thieme, Stuttgart, p 58
20. Karaghiosoff K, Schmidpeter A. (1988) *Phosphorus Sulfur* 36:217
21. Bansal RK, Karaghiosoff K, Gupta N, Schmidpeter A, Spindler C. (1991) *Chem Ber* 124:475
22. Bansal RK, Kabra V, Gupta N. (1992) *Indian J Chem* 31B:254
23. Gupta N, Jain CB, Heinicke J, Bharatiya N, Bansal RK, Jones PG. (1998) *Heteroat Chem* 9:333
24. Bansal RK, Mahnot R, Sharma DC, Karaghiosoff K, Schmidpeter A. (1992) *Heteroat Chem* 3:351
25. Bansal RK, Jain CB, Gupta N, Karaghiosoff K, Schmidpeter A. (1994) *Phosphorus Sulfur Silicon* 86:139

26. Bansal RK, Gupta N, Gupta R, Pandey G, Agarwal M. (1996) *Phosphorus Sulfur Silicon* 112:121
27. Karaghiosoff K, Bansal RK, Gupta N. (1992) *Z Naturforsch* 47B:373
28. Bansal RK, Mahnot R, Sharma DC, Karaghiosoff K. (1992) Synthesis 267
29. Bansal RK, Kabra V, Munjal R, Gupta N. (1994) *Indian J Chem* 33B:992
30. Bansal RK, Sharma DC, Mahnot R. (1991) *Tetrahedron Lett* 32:6433
31. Bansal RK, Kabra V, Munjal R, Gupta N. (1994) *Phosphorus Sulfur Silicon* 97:141
32. Gösl R, Meuwsen A. (1959) *Chem Ber* 92:2521
33. Okamoto T, Hirobe M, Ohsawa A. (1966) *Chem Pharm Bull* 14:518
34. Bansal RK, Pandey G, Gupta R, Karaghiosoff K, Schmidpeter A. (1995) Synthesis 173
35. Okamoto T, Hirobe M, Tamai Y, Yabe E. (1966) *Chem Pharm Bull* 14:506
36. Bansal RK, Gandhi N, Karaghiosoff K, Schmidpeter A. (1995) *Z Naturforsch* 50b:558
37. Schmidpeter A, Steinmüller F, Zabotina EY. (1993) *J Prakt Chem* 335:458
38. Angermund K, Eckerle A, Monkiewicz J, Krüger C, Wilke G. (1998) *Inorg Chim Acta* 270:273
39. Angermund K, Eckerle A, Frank L. (1995) *Z Naturforsch* 270B:488
40. Wilke G, Monkiewicz J, Kuhn H (Studiengesellschaft Kohle m.b. H) (1986) Patent DE 3618169
41. Bansal RK, Gupta N, Heinicke J, Nikonov GN, Saguitova F, Sharma DC. (1999) Synthesis 264
42. Heinicke J, Gupta N, Surana A, Peulecke N, Witt B, Steinhauser K, Bansal RK, Jones PG. (2001) *Tetrahedron* 57:9963
43. Aluri BR, Kindermann MK, Jones PG, Dix I, Heinicke JW. (2008) *Inorg Chem* 47:6900
44. Adam MSS, Kühl O, Kindermann MK, Heinicke JW, Jones PG (2008) *Tetrahedron* 64:7960
45. Heinicke J, Aluri BR, Adam MSS, Jones PG. (2008) *Phosphorus Sulfur Silicon* 183:779
46. Heinicke J, Aluri BR, Adam MSS, Ullah F. (2008) Phosphorus Sulfur Silicon (in press)
47. Aluri BR. (2008) PhD thesis, University Greifswald (Germany)
48. Montgomery JA, Secrist JA III. (1984) In: Katritzky AR, Rees CW (eds) Comprehensive heterocyclic chemistry I, vol. 5. Pergamon, Oxford, p 607
49. Pilgram KH. (1984) In: Katritzky AR, Rees CW (eds) Comprehensive heterocyclic chemistry I, vol 6. Pergamon, Oxford, p 973
50. Abarca B, Ballesteros R. (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II, vol 8. Pergamon, Oxford, p 25
51. Karaghiosoff K, Cleve C, Schmidpeter A. (1986) *Phosphorus Sulfur* 28:289
52. Karaghiosoff K, Schmidpeter A, Mayer P. (1996) In: Herrmann WA (ed) Synthetic methods of inorganic and organometallic chemistry; Group 15: Phosphorus and organometallic chemistry, vol 3. Thieme, Stuttgart, p 52
53. Litvinov IA, Karaghiosoff K, Schmidpeter A, Zabotina EY, Dianova EN. (1991) *Heteroat Chem* 2:369
54. Karaghiosoff K, Mahnot R, Cleve C, Gandhi N, Bansal RK, Schmidpeter A. (1995) *Chem Ber* 128:581
55. Flitsch W. (1984) In: Katritzky AR, Rees CW (eds) Comprehensive heterocyclic chemistry-I, vol 4. Pergamon, Oxford, p 443
56. Flitsch W. (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry-II, vol 8. Pergamon, Oxford, p 237
57. Greenhill JV. (1984) In: Katritzky AR, Rees CW (eds) Comprehensive heterocyclic chemistry-I, vol 5. Pergamon, Oxford, p 305
58. Bergsträβer U, Hoffmann A, Regitz M. (1992) *Tetrahedron Lett 33*:1049
59. Kanemasa S, Kobira S, Kujigaeshi S. (1980) *Heterocycles* 14:1107
60. Bergsträβer U, Stannek J, Regitz M. (1994) J Chem Soc Chem Commun 1121
61. Taylor EC, Turchi IJ. (1979) *Chem Rev* 79:181
62. Bansal RK, Surana A, Gupta N. (1999) *Tetrahedron Lett* 40:1565
63. Bansal RK, Gupta N, Baweja M, Hemrajani L, Jain VK. (2001) *Heteroat Chem* 12:602
64. Bansal RK, Gupta N, Kumawat SK, Dixit G. (2008) *Tetrahedron* 64:6395
65. Schmidpeter A, Jochem, G. (1992) *Tetrahedron Lett* 33:471

66. Bansal RK, Hemrajani L, Gupta N. (1999) *Heteroat Chem* 10:598
67. Bansal RK, Dandia A, Gupta N, Jain D. (2003) *Heteroat Chem* 14:560
68. Bansal RK, Heinicke J. (2001) *Unpublished results, reported preliminarily in the Review. Chem Rev* 101:3549
69. Jochem G, Schmidpeter A, Thomann M, Nöth H. (1994) *Angew Chem Int Ed Engl* 33:663
70. Jochem G, Schmidpeter A, Kulzer F, Dick S. (1995) *Chem Ber* 128:1015
71. Bansal RK, Gupta N, Gupta N, Karaghiosoff K. (results to be published)
72. Heinicke J, Steinhauser K, Peulecke N, Spannenberg A, Mayer P, Karaghiosoff K. (2002) *Organometallics* 21:912
73. Aluri BR, Kindermann MK, Jones PG, Heinicke J. (2008) *Chem Eur J* 14:4328–;4335
74. Gupta N, Bansal RK. (2003) *J Indian Chem Soc* 80:997
75. Bansal RK, Gupta N (results to be published)
76. Bansal RK, Gupta N, Kabra V, Spindler C, Karaghiosoff K, Schmidpeter A. (1992) *Heteroat Chem* 3:359
77. Schmidpeter A, Bansal RK, Karaghiosoff K, Steinmüller F, Spindler C. (1990) *Phosphorus Sulfur Silicon* 49/50:349
78. Bansal RK, Pandey G (results to be published)
79. Karaghiosoff K, Hackenbracht G, Schmidpeter A, Bansal RK, Gupta N, Sharma DC, Mahnot R, Kabra V. (1993) *Phosphorus Sulfur Silicon* 77:235
80. Bansal RK, Gupta N, Bharatiya N, Gupta G, Surana A, Hackenbracht G, Karaghiosoff K. (1998) *Heteroat Chem* 9:445
81. Bachrach SM, Liu M. (1992) *J Org Chem* 57:6736
82. Bachrach SM. (1997) *J Org Chem* 62:5801
83. Wannere CS, BansalRK, SchleyerPvR. (2002) *J Org Chem* 67:9162
84. Bansal RK, Gupta N, Gupta N. (2004) *Heteroat Chem* 15:271
85. Bansal RK, Kumawat SK. (2008) Tetrahedron (in press)
86. Bansal RK, Jain VK, Gupta N, Gupta N, Hemrajani L, Baweja M, Jones PG. (2002) *Tetrahedron* 58:1573
87. Floch PL, Carmichael D, Mathey F. (1991) *Organometallics* 10:2432
88. Mathey F, Alcaraz JM. (1984) J Chem Soc Chem Commun 508
89. Bansal RK, Gupta N, Kumawat SK. (2008) *Z Naturforsch* 63B:321
90. Bansal RK, Gupta N, Kumawat SK, Dixit G J Phys Org Chem (in press)
91. Bansal RK, Karaghiosoff K, Gupta N, Kabra V, Mahnot R, Sharma DC, Munjal R, Kumawat SK. (2005) *Z Naturforsch* 60B:7
92. Bansal RK, Karaghiosoff K, Gupta N, Gandhi N, Kumawat SK. (2005) *Tetrahedron* 61:10521
93. Bansal RK, Gupta N, Kumawat SK. (2006) *Tetrahedron* 62:1548
94. Bansal RK, Gupta N, Kumawat SK. (2006) *Heteroat Chem* 17:402
95. Gupta N, Jain CB, Heinicke J, Bansal RK, Jones PG. (1998) Eur J Inorg Chem 1079
96. Jain CB, Sharma DC, Gupta N, Heinicke J, Bansal RK. (1999) *J Organomet Chem* 577:337
97. Heinicke J, Surana A, Peulecke N, Bansal RK, Murso A, Stalke D. (2001) Eur J Inorg Chem 2563
98. Surana A, Singh S, Bansal RK, Peulecke N, Spannenberg A, Heinicke J. (2002) *J Organomet Chem* 646:113
99. Heinicke J, Steinhauser K, Peuleuke N, Spannenberg A, Mayer P, Karaghiosoff K. (2002) *Organometallics* 21:912
100. Heinicke J, Gupta N, Singh S, Surana A, Bansal RK, Kühl O, Bansal RK, Karaghiosoff K, Vogt M. (2002) *Z Anorg Allg Chem* 628:2869
101. Jain VK, Hemrajani L, Bansal RK. (2002) *Indian J Chem* 41A:506
102. Jain VK, Hemrajani L, Bansal RK. (2002) *Indian J Chem* 41A:550

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Biological Activity of Aminophosphonic Acids and Their Short Peptides

Barbara Lejczak and Pawel Kafarski

Abstract The biological activity and natural occurrence of the aminophosphonic acids were described half a century ago. Since then the chemistry and biology of this class of compounds have developed into the separate field of phosphorus chemistry. Today it is well acknowledged that these compounds possess a wide variety of promising, and in some cases commercially useful, physiological activities. Thus, they have found applications ranging from agrochemical (with the herbicides glyphosate and bialaphos being the most prominent examples) to medicinal (with the potent antihypertensive fosinopril and antiosteoporetic bisphosphonates being examples).

Keywords Aminophosphonates, Bisphosphonates, Drug design and development, Enzyme inhibitors, Phosphono peptides, Structural analogues, Transition state analogues

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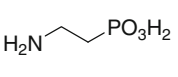
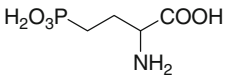
1 Introduction

Half a century ago, two important research papers were published: one by Horiguchi and Kandatsu [1], who identified 2-aminoethanephosphonic acid (ciliatine, **1**) in ciliated sheep rumen protozoa, and the second by Mastalerz [2], who described the phosphonic acid analogue **2** of glutamic acid as an inhibitor of avian brain glutamine synthetase. It is worth noting that aminophosphonates as possible constituents of living matter and effectors of biological systems were considered by Chavane [3] in the early 1940s, and his findings first published after World War II.



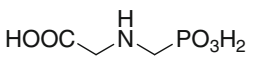
ciliatine (**1**)



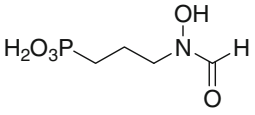
inhibitor of glutamine synthetase (**2**)

These research papers constituted a starting point of the chemistry and biology of aminoalkanephosphonic acids, which till 1959 were almost unknown. Today these compounds and their derivatives are the subject of more than 7000 papers, with five to seven papers on the biological activity of aminoalkanephosphonic acids and their short peptides (excluding papers describing the activity of bisphosphonates and herbicide glyphosate) appearing every week.

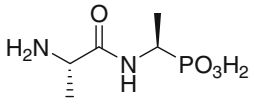
A new dimension to the studies on biologically active aminophosphonates was added by discoveries of an extremely effective non-systemic herbicide glyphosate (**3**) [4], the antibacterials fosmidomycin (**4**) [5] and alafosfalin (**5**) [6], antihypertensive fosinopril (**6**) [7], and antiosteoporetic bisphosphonates (**7**) [8].



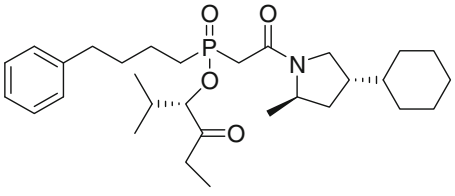
glyphosate (**3**)



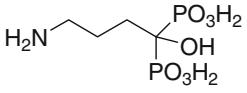
fosmidomycin (**4**)



alafosfalin (**5**)



fosinopril (**6**)



alendronate (**7**)

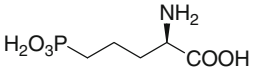
In addition to the book of Kukhar and Hudson [9], which describes various aspects of the chemistry and biology of aminophosphonic acids and their peptides, a number of excellent reviews on various aspects of the biological activity of these compounds have been published [10–16]. We therefore limit our review to the latest achievements in this field.

2 Aminoalkanephosphonic Acids as Structural Analogues of Amino Acids

Aminophosphonic acids are broadly defined as analogues of amino acids, in which the carboxylic group is replaced by phosphonic acid or related function (mostly a phosphonous or phosphinic acid group). Their negligible mammalian toxicity and the fact that they efficiently mimic amino acids make them important metabolites, which compete with their carboxylic counterparts for the active sites of the enzymes and other cell receptors. However, carboxylic and phosphonic acid moieties are different in shape (tetrahedral phosphonic versus flat carboxylic), acidity (with phosphonic acid being significantly more acidic), and steric bulk (phosphorus atom has bigger radius than carbon atom) and this defies the intuitive understanding of structural analogy.

This approach has been most widely used for the preparation of neuroactive analogues of the central nervous system neurotransmitters glutamic and γ-aminobutyric acids [17].

Glutamic acid is the neurotransmitter of most excitatory synapses in the mammalian central nervous system. It is thus involved in numerous physiological brain functions, as well as pathologies and disorders including Parkinson's, Huntington's and Alzheimer's diseases. The isosteric replacement of the ω-carboxylate moiety of glutamic acid, or its homologues, by a ω-phosphonate group has not resulted in new drugs but it represents a productive strategy for differentiating subtypes of excitatory amino acid receptors; it appears a useful tool for studies on neurotransmission. For example, extended L-glutamic acid derivatives of D configuration, exemplified by D-AP5 (**8**) and D-AP7 (**9**) have been characterized as potent and selective NMDA competitive antagonists, while L-AP4 (formal analogue of glutamic acid, **10**) has been characterized as a selective group III metabotropic glutamate receptor agonist [18]. It is worth noting that replacement of the phosphonic group of the latter by a phosphinic function (**11**) resulted in the loss of activity [19].



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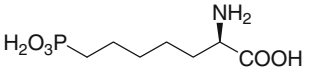

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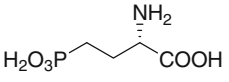

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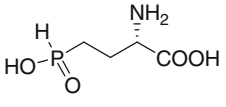
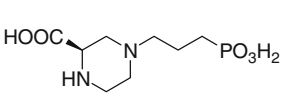


11

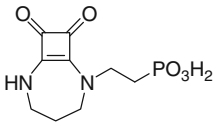
As shown by molecular modeling, quite small changes in the structure of these mimetics reflect in their significantly different mode of binding by NR2A and NR2B subunits of NMDA receptors [20,21]. For example, the phosphonate moiety of D-AP5 forms salt bridges with lysines 488 and 485 and arginine-519, and a hydrogen bond with serine-690 of the NR2B receptor, whereas the γ-carboxylate group of L-glutamic acid binds with serine-690 and threonine-691 of the same.

Therefore, it is not surprising that the search for subtype selective ligands has been based on conformational constraining ω-phosphonate analogues by embedding their skeleton into cyclic rigid structures. Although some of these attempts were successful if considering antagonistic activity [22–26], most have substantially failed if considering the search for new agonists [22,27].

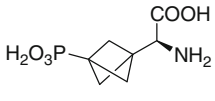
Reperesentative constrained antagonists of NMDA receptors



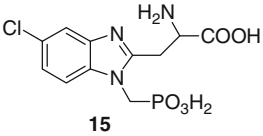
CPP, **12**



perzinfotel, **13**



RBPG, **14**



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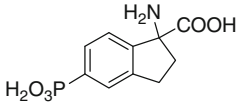
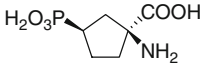


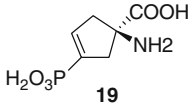
16

Representative constrained agonists of NMDA receptors

CPrAP4, **17**



ACPC, **18**



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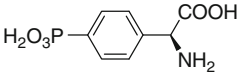
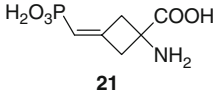
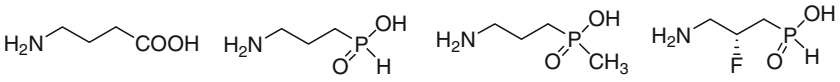


PPG, **20**



21

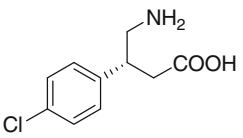
γ-Aminobutyric acid (GABA, **22**) is the major inhibitory neurotransmitter in the central nervous system, being present in some 40% of all neurons. It activates three major classes of receptors identified so far. $GABA_A$ and $GABA_C$ receptor are chloride channels, whereas the $GABA_B$ receptor is a metabotropic one and activates the second messenger systems phospholipase C and adenylate cyclase, followed by activation of K^+ and Ca^{2+} ion channels via G-coupled proteins. Effectors of these receptors (agonists, antagonist, and allosteric regulators) are an important class of pharmaceutical and pharmacological probes [28]. Phosphonic and phosphinic analogues of GABA are not only potent effectors of these receptors but are also extremely selective ones. For example, 3-aminopropylphosphinic acid (**23**), a simple analogue of GABA, exhibits high affinity towards the $GABA_B$ receptor (1 nM) and very low affinity to the $GABA_A$ receptor (4500 nM), thus being a selective agonist of the first [29]. Its close analogue, 3-aminopropyl(methyl)phosphinic acid (SK 97541, **24**), appears to be an agonist of the $GABA_B$ receptor and simultaneously antagonistic towards the $GABA_C$ receptor [30]. Introduction of hydroxy- or fluoro- substituent into the chain of compounds **23** and **24** resulted in even stronger antagonists, with compound **25** being the most active [31].



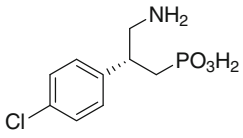
GABA, **22** **23** **24** **25**

GABA is a highly flexible molecule and thus can attain many low-energy conformations that bind to different GABA receptors, exhibiting either agonistic or antagonistic activity. Aminophosphinic and aminophosphonic acids have been found to be the most prominent class of antagonists, with phaclofen (**27**) being the first one selective towards $GABA_B$ receptors [32]. It was obtained by replacing the carboxylic moiety of baclofen (**26**, a popular drug used to treat spasmacity) by a phosphonic group. Since its discovery, many antagonists of variable structures and considerable selectivity have been obtained. Thus, CGP 54626 (**28**) and CGP 35348 (**29**) rank amongst the most potent antagonists of $GABA_B$ receptors [33], and TPMPA (**30**), the phosphinic analogue of isonipecotic acid (**31**), imidazole methylphoshinic acids (**32**), and CGP 44533 (**33**) are antagonists of $GABA_C$ receptors [34–37]. There are no good antagonists for $GABA_A$ receptors.

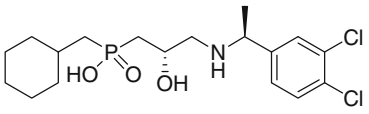
Although a number of aminophosphonate effectors of GABA receptors are quite impressive, only few exceed the potency of baclofen and none of them have been applied successfully in medicine. It is also impossible to draw any meaningful structure–activity relationship between the chemical structure of agonists or antagonists and the observed activity, partly because the molecular modeling of ligand-gated channels is challenging [38].



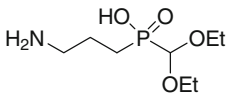
baclofen, **26**



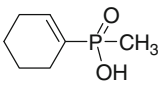
phaclofen, **27**



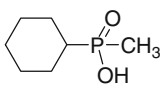
CGP 54626, **28**



CGP 35348, **29**



TPMPA, **30**



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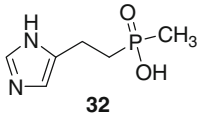

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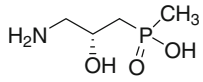
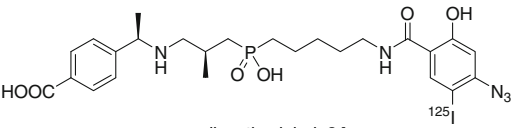
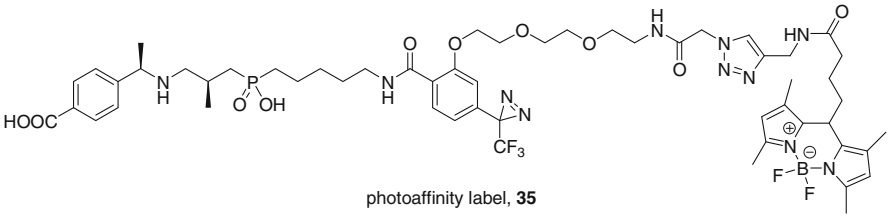


CGP 44533, **33**

Anyway, a number of phosphinic acids structurally related to CGP 54626, were modified in order to obtain radioactive [39] or photoaffinity [40] labels as valuable probes for studying the localization and function of $GABA_B$ receptors in the living cells.

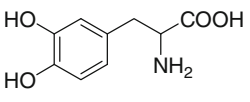


radioactive label, **34**

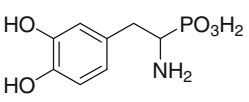


photoaffinity label, **35**

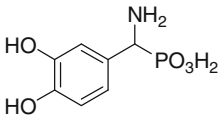
The use of aminophosphonates seems to be an obvious means of constructing false substrates or inhibitors of enzymes involved in amino acid metabolism. One of the first examples was the finding that phosphonic analogues of tyrosine and 3,4-dihydroxyphenylalanine **37** (dopa, **36**) are oxidized by tyrosinase in an identical manner as the substrates [41,42]. Interestingly **38,** an analogue of 3,4-dihydroxyphenylglycine, appeared to be strongly inhibitory [41]. The careful examination of its mechanism of action revealed that this compound is also oxidized by tyrosinase. The product of oxidation is unstable and spontaneously decomposes, causing reversal of the non-enzymatic reactions that follow enzymatic oxidation of the natural substrate and thus protecting the substrate from being oxidized by the enzyme [43]. Under biochemical assay conditions it is seen as inhibition.



dopa, **36**



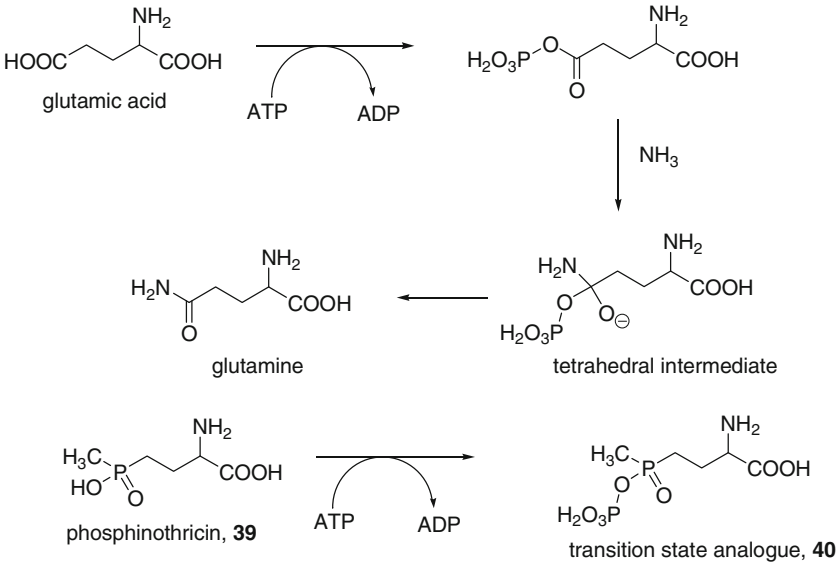
37 analogue of dopa



38 analogue
of 3,4-dihydroxyphenylglycine

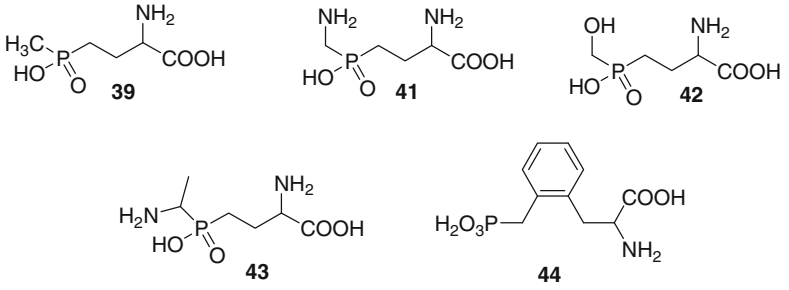
Phosphinothricin (**39**), a phosphinic acid mimetic of glutamic acid produced by various strains of *Streptomycete* species, is a potent inhibitor of glutamine synthetase [44,45] and a commercial herbicide known as glufosinate. This enzyme catalyzes a reaction of central importance in nitrogen metabolism, namely the first step in nitrogen assimilation – ATP-dependent conversion of L-glutamic acid to L-glutamine. However, identically to the natural substrate, phosphinothricin is phosphorylated, which generates an isostere of the presumed reaction intermediate, the unstable adduct between phosphorylated glutamic acid and ammonia [46]. Thus, phosphorylated phosphinothricin (**40**) acts as a real inhibitor of the enzyme (Scheme 1).

A new promising perspective for glutamine synthetase inhibition studies is the design and synthesis of novel antibacterials against *Mycobacterium turberculosis*, a leading cause of deaths due to a single infectious agent. Thus, based on available crystal structures of the inhibitor–enzyme complex [47,48], the mechanism of glutamine synthetase by phosphinothricin and its analogues was studied in some



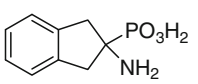
Scheme 1 Mechanism of action of glutamine synthetase and mechanism of suicidal inhibition of this enzyme by phosphinothricin

detail using molecular modeling methods [13,49]. This enabled the design and synthesis of new inhibitors of the enzyme (**41**–**43**), which proved to be nearly equipotent with phosphinothricin. However, they exhibit different kinetics of inhibition, which may suggest that they are not phosphorylated in the enzyme active site and thus act as simple structural analogues [50]. In contrast to the studies on neuroeffectors, introduction of the strain into the molecule skeleton of a phosphonic analogue of glutamic acid (e.g., as in the case of **44**) did not result in improved inhibitory activity [51].

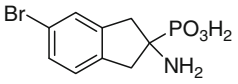


2-Aminoindane-2-phosphonic acid (AIP, **45**) is perhaps the most successful example of the implementation of the concept of structural analogy between carboxylic and phosphonic moieties. It is a constrained analogue of L-phenylalanine, a substrate for phenylalanine ammonia-lyase and a potent inhibitor of this enzyme [52,53]. This compound is commonly used as a tool for studying various aspects of biosynthesis of

aromatic compounds, including as important an issue as lignin biosynthesis. Although a number of its analogues have been synthesized and evaluated as inhibitors of this enzyme [54–56] none of them appeared to be competitive with AIP, with its bromo- and methyl-substituted derivatives (**46** and **47**, respectively) being the most active.



AIP, **45**



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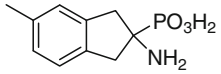
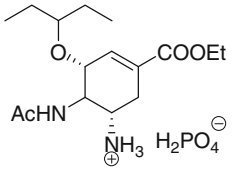
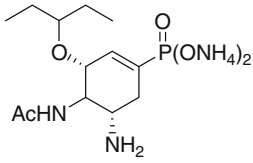


47

Replacement of the carboxylic group of an analogue of oseltamvir (**48**, a potent antiinfluenza drug known as Tamiflu) by a phosphonic moiety led to Tamiphosphor (**49**), a promising antiviral agent and extremely potent inhibitor of influenza virus neuraminidase (K_i = 0.15 nM against A/WSN/1933 virus). Replacing the amino group of Tamiphosphor with a guanidine moiety resulted in enhanced inhibition (K_i = 0.06 nM) and significant antiflu activity [57]. The guanidinium group most likely exerts strong electrostatic interactions with viral neuraminidasae acidic amino acids, namely Glu-119, Asp-115, and Glu-227.

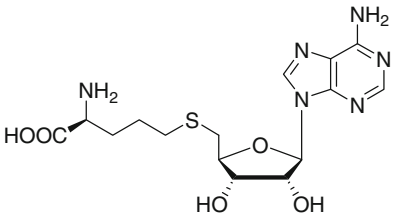


Tamiflu, **48**

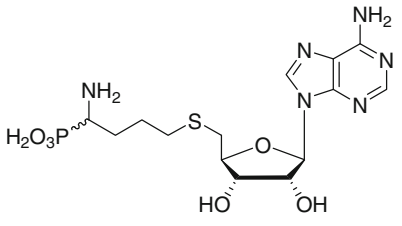


Tamiphosphor, **49**

S-Adenosyl-L-methionine serves as methyl donor for a variety of transmethylation reactions. These methyl transfer reactions are indirectly controlled by the cellular level of *S*-adenosyl-L-homocysteine (**50**). In eukaryotes, the intracellular ratio of both compounds is regulated by hydrolysis of *S*-adenosyl-L-homocysteine to adenosine and homocysteine. Consequently, this enzyme has become an attractive target for drug design since its inhibitors have been shown to exhibit antiviral, antiparasitic, antiarthritic, and immunosuppressive effects. Both enantiomers of phosphonic analogue **51** of *S*-adenosyl-L-homocysteine appear to be irreversible inhibitors of the hydrolase; however, each presented distinct kinetic characteristics [58].



S-adenosyl-*L*-homocysteine, **50**



51

In some cases, simple replacement of a carboxylic group by a phosphonic one does not result in simple structural analogues. Indeed, some of these compounds act

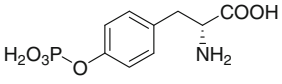
rather as transition state analogues. This is well seen when considering a phosphonic acid analogue of leucine as an inhibitor of leucine aminopeptidase [59,60]. As demonstrated by both crystal structure [61,62] and molecular modeling [63–65], the tetrahedral phosphonic group resembles a high-energy transition state of peptide bond hydrolysis. Additionally, the phosphonic acid moiety strongly complexes two zinc ions present in the enzyme active site [65].

3 Compounds in Which the Phosphate Fragment of the Molecule is Replaced by Its Non-hydrolyzing Methylenephosphonate and Related Moieties

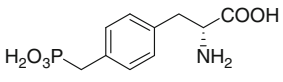
A phosphate moiety is the common structural motif of a wide range of natural biologically active compounds, which play important roles as metabolic intermediates, as common regulatory switches for proteins, and as the backbone of genetic information. Phosphate esters are subjected to ready cleavage by phosphatases. Unlike a phosphate group, the phosphonate carbon-to-phosphorus linkage is resistant to hydrolysis and this property has made these compounds attractive as phosphate analogues in numerous applications.

Phosphorylation of tyrosine residues in proteins is responsible for control in cellular signaling pathways. Given the complexity of cellular signaling and the large number of phosphoproteins in the cell, it is likely that a single protein-tyrosine phosphatase may be involved in the regulation of multiple signaling pathways, and that multiple protein-tyrosine phosphatases may act cooperatively to regulate a particular pathway. A major goal in the research concentrating on these enzymes is to establish the precise functional roles for individual protein-tyrosine phosphatases, both in normal cellular physiology and in pathogenic conditions.

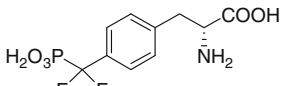
Much of the interest in phospho-L-tyrosine (**52**) has centered around non-hydrolyzable phosphonic acids such as phosphonomethylphenylalanine (**53**, PmP) due to its ability to faithfully replicate several biological interactions of native phospho-L-tyrosine residues [66,67]. Progress on these analogues is based on preparation of phospho-L-tyrosine isostere containing a difluoromethyl moiety in the place of an oxygen atom (**53**, F_2Pmp). It is an efficient inhibitor of tyrosine phosphatases because of its lower pK_a value relative to Pmp and because the difluoromethyl group is still capable of acting as a hydrogen bond acceptor, being isoelectronic with the oxygen atom [68]. Synthetic studies allowed the elaboration of methods for facile introduction of these mimetics into a variety of peptides using standard protocols of solid-phase peptide synthesis, and thus the synthesis of potent inhibitors of various protein-tyrosine phosphatases [69–72]. Syntheses of the effective inhibitors are frequently based on the determination of crystal structures of these enzymes in complexes with their inhibitors [73–75].



phospho-tyrosine, **52**

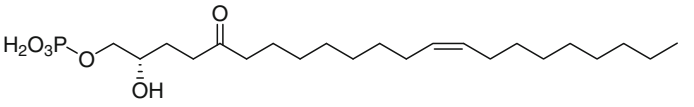


Pmp, **53**

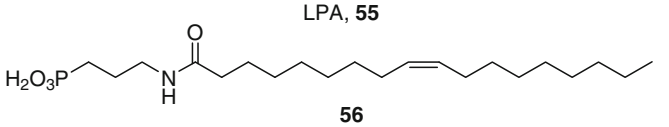


F2Pmp, **54**

The same approach was applied to the synthesis of non-hydrolyzing phospholipid analogues. An analogue of lysophosphatidic acid (LPA, **55**) may serve as an example. This phospholipid is an intracellular signaling molecule that induces an array of receptor-mediated biological effects. However, it is fast deactivated by lipid phosphate-phosphatase. Structurally related phosphonic (**56** and **57**) acids were considered as stable agents that may modulate lysophosphatidic acid signaling. Quite surprisingly, the compound in which the keto moiety replaces the phosphate oxygen atom appeared to be the best antagonist of the LPA receptor, being additionally quite selective towards one of the three receptor subtypes, namely LPA_1 receptor [76].



LPA, **55**



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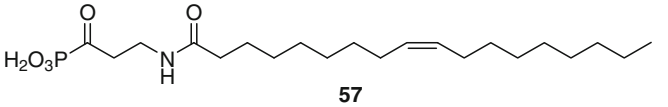
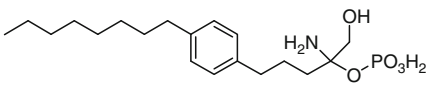
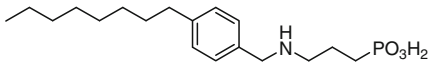


57

Sphingosine 1-phosphate receptors are integral membrane G-protein-coupled receptors, which are referred to as endothelial differentiation gene receptors. These receptors provide a control over numerous aspects of cellular physiology when activated by endogenous sphingosine 1-phosphate (S1P). Particular attention has been paid to the role of these receptors in regulating the immune system since discovery of their antagonist FTY720, which inhibits the egress of T-lymphocytes from secondary lymphoid tissues and is thus thought to directly affect T-cells away from sites of inflammation. FTY720 is activated in vivo when phosphorylated by kinase type 2 yielding intermediate **58**. Designing analogues of **58** gave a series of phosphonic acids (**59** and **60**), which not only resemble the phosphorylated drug but are also conformationally less flexible because of the presence of an aromatic ring in their structure. These second-generation analogues appear to be potent antagonists of $S1P_1$ and $S1P_5$ receptors [77,78].



phosphorylated FTY720, **58**



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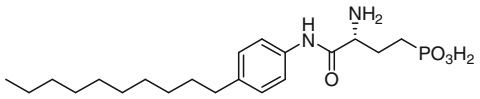
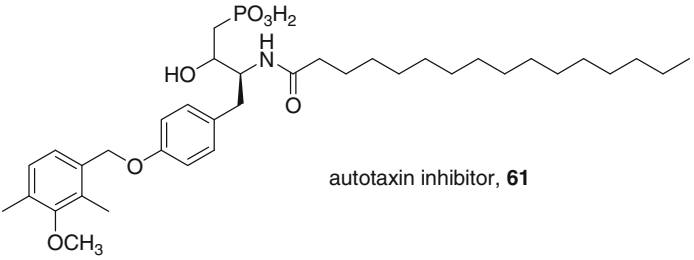


60

Replacement of phosphate by methylenephosphonate or related moieties has also been frequently applied to the synthesis of inhibitors of various enzymes. This

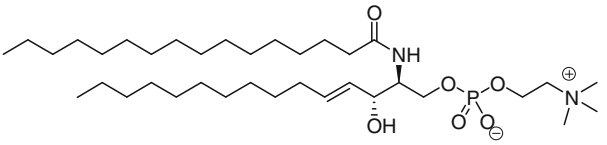
may be achieved by design of analogues of either the enzyme substrate, product or its high-energy intermediate.

The autocrine mobility factor autotaxin (ATX) is a glycoprotein isolated from melanoma cell supernatant. In vivo, a well-documented experiment is the forced expression of ATX, which augments tumor cell invasion and metastasis and also promotes angiogenesis, a process essential for tumor growth. ATX belongs to the nucleotide pyrophosphatase and phosphodiesterase family of enzymes. Interest in that enzyme was stimulated by finding that it acts as an elusive plasma lysophospholipase by cleavage of the choline group from lysophophatidyl choline. This is a major path of biosynthesis of lysophosphatidic acid (LPA). A lead towards the development of inhibitors of this enzyme was provided by the discovery that it is inhibited by the product. Thus, a series of modifications of the structure of LPA provided potent aminophosphonate inhibitors of ATX, with **61** as the representative. Their structure is somewhat similar to the LPA receptor antagonists mentioned earlier [79,80].

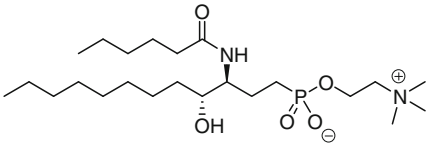


autotaxin inhibitor, **61**

Sphingomyelin is a substrate of sphingomyelinases, a class of enzymes that, depending on their localization and source, play an essential role in many physiologic processes, such as apoptosis, lipopolysaccharide-induced inflammatory response, stimulation of tumor necrosis factor production, and others. Introduction of methylene or difluoromethylene moieties in place of the phosphate oxygen of sphingomyelin led to potent inhibitors of the enzyme from *Bacillus cereus* [81].



sphingomyelin **62**



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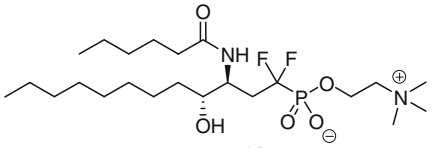
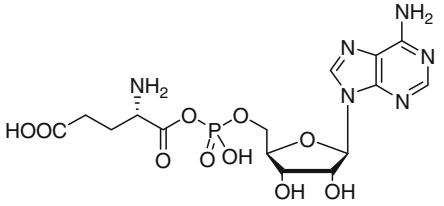


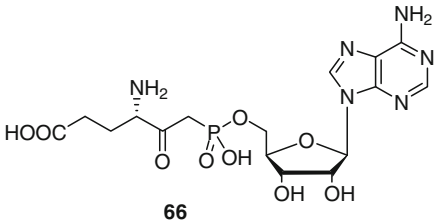
64

In many enzymatic reactions carboxylic acids are activated by their transformation into anhydrides by phosphorylation of the carboxylic moiety with the action of ATP.

Since phosphate is a good leaving group, nucleophiles react with such anhydrides providing final products that may be esters, amides, or aldehydes. Thus, introduction of a non-hydrolyzable group in place of the anhydride oxygen of such high-energy intermediates of enzymatic reaction is thought to be an approach to production of potent enzyme inhibitors. However, this reasoning is frequently unsuccessful, as shown in the case of inhibitors of glutamine synthetase [45] and bacterial aspartate semialdehyde dehydrogenase [82]. Similar results were obtained when β-ketophosphonate analogues **66** of glutaminyl adenylate (**65**) were studied, in which a β-ketophosphonate function served as surrogate of the reactive acylphosphate subunit in inhibitors of glutamyl- and glutaminyl-tRNa synthetases [83]. It is worth noting that these inhibitors, although of moderate potency, are selective towards *Escherichia coli* enzymes, being 150 times more effective than for the bovine liver enzyme.

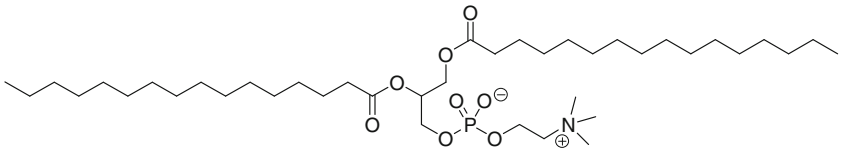


glutamyladenylate, **65**

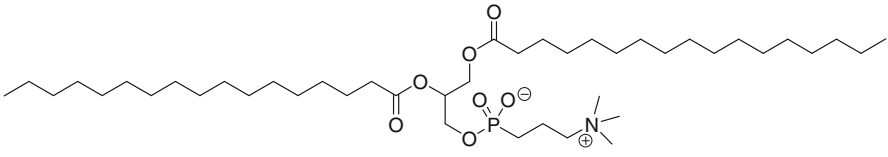


66

A life-threatening deficiency in pulmonary surfactants is the cause of neonatal respiratory distress syndrome in premature infants. In addition, dysfunction of pulmonary surfactants is a major contributor to the pathophysiology of clinical acute lung injury and acute respiratory distress syndrome. Exogenous surfactant replacement therapy appears to be a tremendous success, although it is complicated and requires application of exogenous surfactants having maximal surface activity and being resistant to inactivation. A promising alternative to natural phospholipids (such as 1,2-dipalmitoyl-*sn*-3-phosphatidylcholine, DPPC, **67**) is the use of their phosphonic analogues, such as the intensively studied compound **68** (named DEPN-8) [84] that appeared to be very effective when studied in rat models [85].



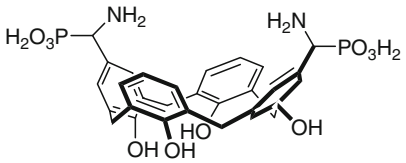
DPPC, **67**



DEPN-8, **68**

Quite unusual and curious is the finding that calixarenes modified with the aminomethyphosphonic acid moiety (a compound of complex chemical structure unrelated

to any natural product) exhibited moderate activity as inhibitors of kidney alkaline phosphatase, with isomer *R*,*R* of **69** being 50 times as potent as the *S*,*S* isomer [86].

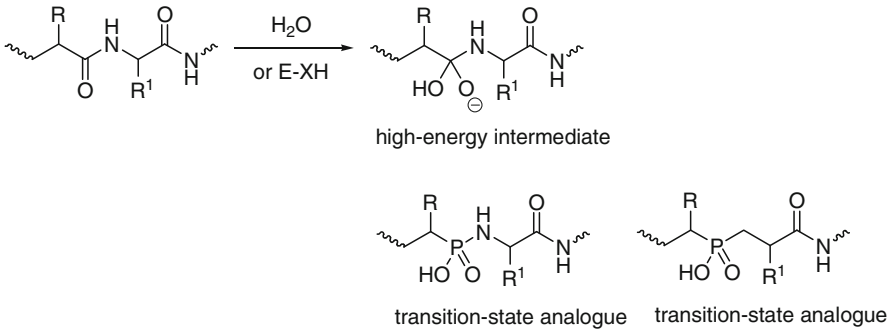


69

4 Aminophosphonates and Phosphono Peptides as Transition State Analogues of Enzymatic Reactions

The application of phosphonic, phosphonamidate, or phosphinic analogues of amino acids and peptides as inhibitors of hydrolytic enzymes, especially proteases, is based on the concept of the resemblance of the phosphorus moiety to the high-energy tetrahedral transition state of ester or amide bond hydrolysis (Scheme 2) [10,11]. This approach appeared to be most successful in the case of metalloproteases, for which a wide variety of such inhibitors have been described. This is because the presence of the organophosphorus moiety in the active site of metalloprotease additionally causes strong chelation of active-site metal ions.

Simple phosphonic acid analogues of amino acids acting via this mechanism rank amongst the potent inhibitors of metalloproteaseses, with leucine aminopeptidase, aminopeptidase N, and malarial aspartyl aminopeptidase [65,87–92] being described most recently in some detail. Crystallography and molecular modeling have shown that potent inhibitory activities result from both: (i) the resemblance of the tetrahedral organophosphorus fragment of the molecule to a transition state, and (ii) the strong electrostatic binding formed between positively charged metal ions and the negatively charged phosphonic acid group [64,93,94]. This is well represented by the binding mode of a phosphonic analogue of leucine (**70**) to the active site of leucine aminopeptidase (Fig. 1).



Scheme 2 Phosphonamidates and phoshinates as transition state analogues of peptide bond hydrolysis

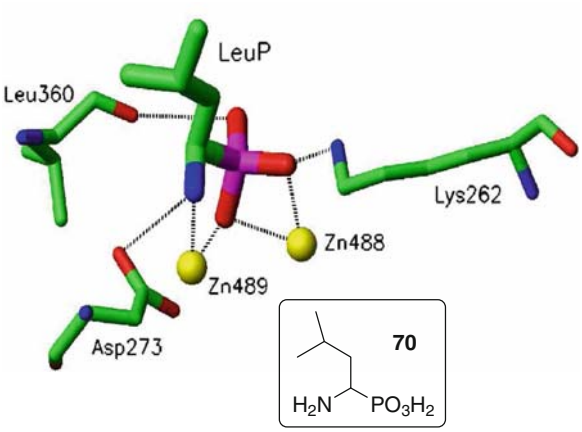
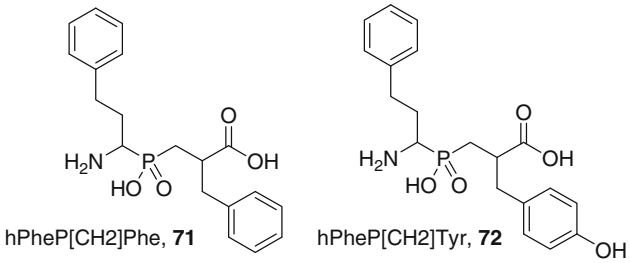


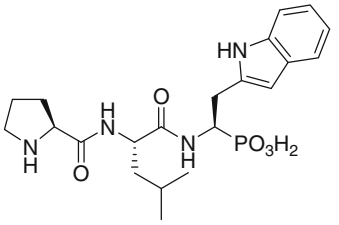
Fig. 1 Mode of binding of phosphonic analogue of leucine in the active site of leucine aminopeptidase

Leucine aminopeptidase is an enzyme for which the most systematic and detailed computational studies regarding enzyme–inhibitor interactions have been performed [63–65]. These studies have shown that phosphonamidate peptides seem to be the closest analogues of the transition state; however, their susceptibility to hydrolysis in aqueous media strongly limits their usefulness [95]. Thus, the phosphinic acids, mimicking transition state analogues of the scissile amide bond hydrolysis, appear to be the inhibitors of choice. Molecular modeling enabled the choice of two such compounds, namely analogues of homophenylalanylphenylalanine (hPheP[CH_2]Phe, **71**) and homophenylalanyltyrosine (hPheP[CH_2] (Tyr, **72**), as the most active ones [65]. These compounds were additionally found to act as potent inhibitors of *Plasmodium falciparum* M17 leucine aminopeptidase, an enzyme responsible for partial digestion of host cell hemoglobin, which serves as a source of amino acids for its own protein synthesis [96]. The compound, hPheP[CH_2]Phe also appeared to have antimalarial activity, effectively reducing parasitemia in mice infected with *Plasmodium chabaudi* [90] and being equipotent with the commonly used antimalarial drug chloroquinone.

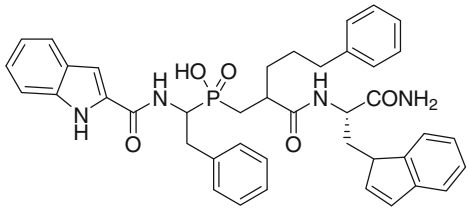


Transition state analogy provided by phosphinic and phosphonic acids were also successfully applied to the discovery of potent and selective inhibitors of matrix metalloproteinases [97–104]. This family of zinc endopeptidases degrades virtually

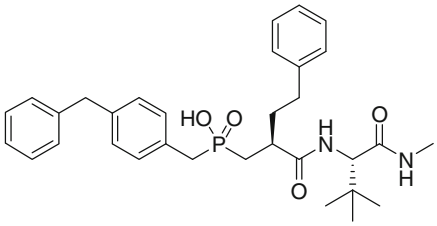
all the constituents of the extracellular matrix and is necessary for normal tissue remodeling, being particularly implicated in ovulation, embryogenic growth, angiogenesis, and differentiation and healing. Overexpression or an inadequate level of matrix metalloproteinases can contribute to the pathophysiology of a variety disease states. The angiogenetic process favored by these enzymes is essential for the vascoularization and growth of tumors. Thus, they are considered to be an excellent target for new anticancer therapeutics. The development of their inhibitors (with **73–75** being representative examples) has relied on the use of peptide sequences recognized by the target proteases, to which have been grafted phosphinic or phosphonic functionalities able to interact with the zinc ions present in the active sites of these enzymes. Selectivity of the inhibitors had been reached by variation of the peptide scaffold by means of combinatorial pseudopeptide synthesis [98,99,103,105–107] or by application of molecular modeling based on crystallographic studies of these enzymes [101,108–110].



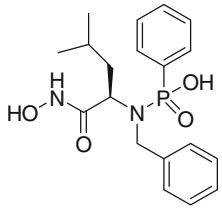
inhibitor of MMP-8, **73**



inhibitor of MMP-11, **74**



inhibitor of MMP-13, **75**



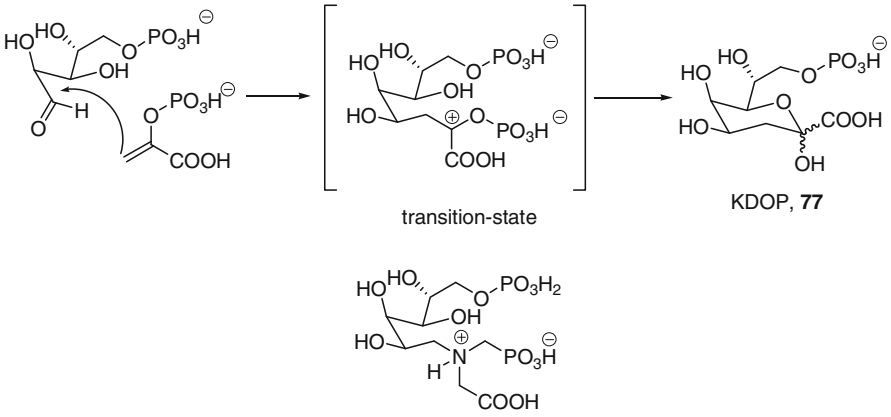
inhibitor of MMP-3, **76**

A similar approach has been recently applied to the design and synthesis of novel potent inhibitors of various metalloenzymes, including carboxypeptidases [111,112], aminopeptidase N [113], metallo-β-lactamase [114], renal dipeptidase [115], peptide deformylase [116], sortase [117], angiotensin-converting enzymes [118,119], and antifolates [120–122]. All of these enzymes are medicinally important and thus the development of these inhibitors into promising drugs might be expected.

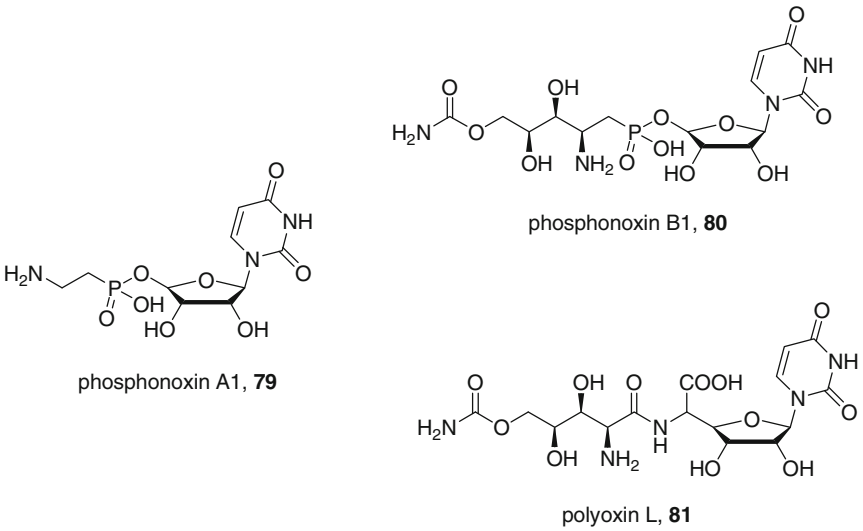
The use of phosphinic acids as inhibitors of other classes of enzymes is less developed. The representative examples of potent inhibitors of enzymes of medical interest include aspartyl proteases [123,124], bacterial amino acid-adding enzymes (Mur enzymes) [125,126], bacterial alanyl tRNA ligase [127], human cyclophilin [128], antigen 85C [129,130], and γ-glutamyl transpeptidases [131]. A similar approach applied to cathepsin C has shown that phosphinic acids, although being moderate inhibitors, do not act as transition-state analogues of cysteine protease [132].

Aminophosphonates, with a positively charged amino group mimicking the carbocationic high-energy intermediate of S_N1 reactions, are rarely used in inhibitor design. A good example is the design and synthesis of **78**, an inhibitor of 3-deoxy-D-*manno*-2-oculosonate-8-phosphate (KDOP, **77**) synthase. This enzyme plays an essential role in the assembly process of the lipopolysachcharides of most Gram-negative bacteria, and is therefore an attractive target for the design of novel antibacterial drugs [133] (Scheme 3).

A similar approach, although less obvious, was also applied to the preparation of inhibitors of UDP-galactopyranose [134] and chitin synthetases (**79** and **80**, respectively) [135,136]. The inhibitors of chitin synthetases are formal analogues of polyoxins (representative compound **81**), natural antifungal antibiotics produced by *Pseudomonas* and *Actinomycetes*.



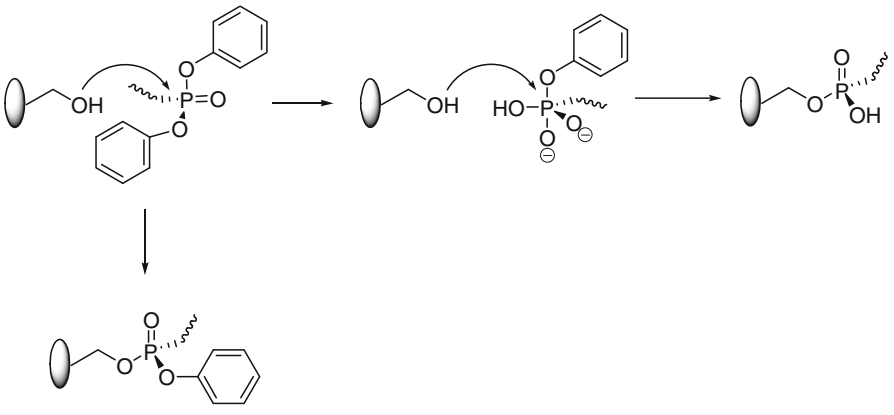
Scheme 3 Mechanism of reaction in the active site of KDOP synthase and resemblance between transition state of this reaction and inhibitor **78**



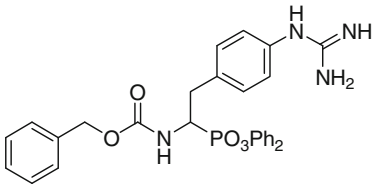
5 Aminophosphonate Derivatives Phosphonylating Active Site Serine

Serine proteases are a group of enzymes with a wide range of activity involved in many physiological states of pathological disorders. Their uncontrolled activity often leads to serious diseases like emphysema, cystic fibrosis, or cancer development and progression. Reactive phosphonate- and peptidyl-phosphonate diphenyl esters have been applied successfully to covalently modify members the of serine hydrolase superfamily [9,137]. They act as active-site directed irreversible inhibitors, which after formation of the normal enzyme–substrate complex, covalently phosphonylate the active site serine. The mechanism of action of these inhibitors presumably involves nucleophilic attack of serine hydroxyl at the phosphorus atom, which results in the formation of phosphonylated enzyme. In this complex, the phosphorus atom resembles the tetrahedral intermediate formed during the hydrolysis of the peptide bond. Single diphenyl phosphonates are usually weak inhibitors and enhancement of their activity is achieved by their introduction into the peptide chain. The composition of the peptide chain also ensures their selectivity towards the chosen enzyme. Studies on inhibitors of human α-thrombin [138], a protease affecting the coagulation cascade and target for the search for anticoagulating drugs, revealed the detailed mechanism of inhibition. Thus, crystallographic studies using potent tripeptide inhibitor of this enzyme have shown that the reaction proceeds via an addition–elimination mechanism that involves a pentacoordinate intermediate (Scheme 4).

Although diphenyl phosphonates were most commonly applied in the last decade of the twentieth century, several interesting inhibitors of serine proteases have also been described recently. The representative examples are inhibitors of urokinase-type plasminogen activator (**82**), designed as potential anticancer agents [139–141]; of seprase (**83**), studied as antimelanotic agents [142]; and of dipeptidyl peptidases (**84** and **85**), acting as drugs for the treatment of type 2 diabetes [143–146]. In the case of urokinase inhibition, binding of the inhibitors was additionally studied by



Scheme 4 Mechanism of deactivation of serine proteases by diphenyl aminophosphopnates and phosphonopeptides



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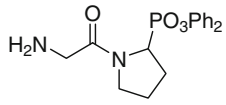

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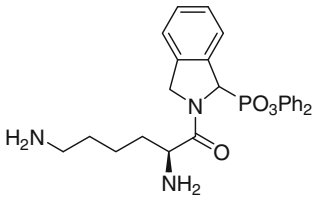
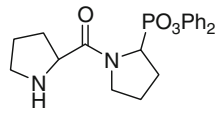


inhibitor of DPP 8, **84**



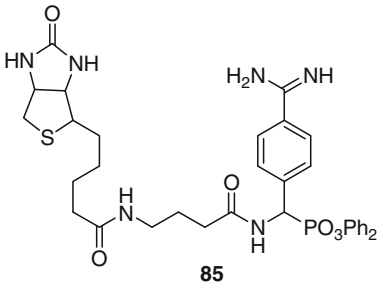
inhibitor of DPP IV, **85**

means of flexible docking calculations and rigorous ab initio study of binding energy [146]. Availability of the experimental inhibitory activities and comparison with theoretical binding energy allowed for validation of theoretical models of inhibition, as well as prediction of binding affinity compounds yet to be synthesized.

Antibodies with proteolytic activity, specific for certain pathological states, represent a broad platform from which a new generation of therapeutics can be potentially developed. Suitable targets for such antibodies include endogenous polypeptides that play a critical role in the pathogenesis of autoimmune and metabolic disorders, and those that allow cancer and microbial cells to survive and multiply. Since the immune system exhibits a tendency to synthesize such antibodies upon pathological states, these antibodies are naturally available. However, their isolation and characterization is challenging and cumbersome.

Biotinylated diphenyl phosphonates (e.g., **85**–**87**) appear to be a class of good selectors for the catalytic antibodies containing catalytically active serine in the newly formed catalytic center. These compounds were applied to select catalytic antibodies from the heavy and light chain subunits of immunoglobulins obtained from lupus patients. These antibodies were able to hydrolyze the CD4 binding site of gp120, a protein responsible for selective recognition of infected cells by human immunodeficiency virus [147]. Interestingly, diphenyl phosphonates acted as irreversible, while monophenyl phosphonates as reversible, transition-state analogue inhibitors. A similar approach was also applied to the selection of antibodies able to inactivate hepatitis C virus [148], Kaposi's sarcoma-associated herpesvirus [149], and some cancer cells [150]. Additionally, the ability of these phosphonates to be bound by structurally variable proteins devoid of catalytic activity may serve as a means for construction of diagnostic tools directed towards identification of marker proteins [151].

N-Blocked aminophosphonate monoesters **88** and **89** appear to act as irreversible inhibitors of class C and class D β-lactamases [152,153], compounds designed to overcome β-lactam resistance in bacteria. The active site serine present in the active



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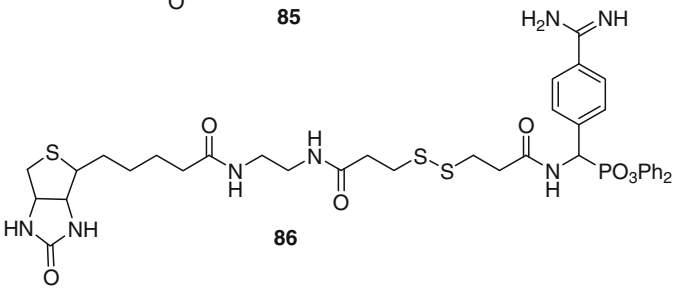

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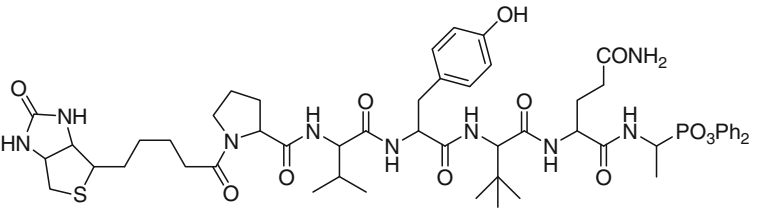
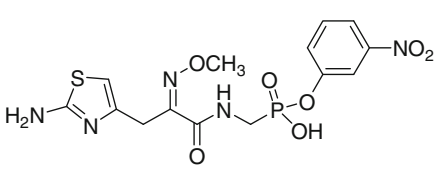
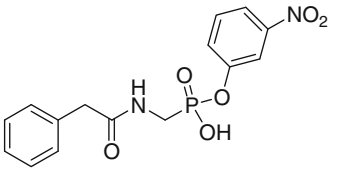


87

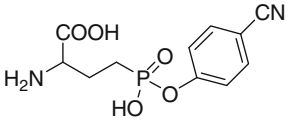
sites of these enzymes, in contrast to the serine proteases, is readily and irreversibly phosphonylated. A similar approach was also applied to the inhibition of γ-glutamyl transpeptidase (representative inhibitor **90** [154]), an enzyme that catalyzes the first step in glutathione metabolism and is overexpressed in human tumors.



class C β-lactamase inhibitor **88**



class D β-lactamase inhibitor **89**

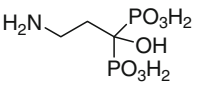


γ-glutamyltranspeptidase inhibitor **90**

6 Bisphosphonates

Bisphosphonic acids are hydrolytically stable analogues of pyrophosphate and are characterized by a common P–C–P fragment, in which the carbon-to-phosphorus bond replaces the oxygen-to-phosphorus bond. Simple bisphosphonates were primarily used in the early days as antiscaling and anticorrosive agents. However, it was only in the 1960s that their potential for the treatment of various bone diseases was realized after Fleisch and coworkers [155] discovered that bisphosphonates impaired the formation and dissolution of calcium phosphate crystals in vitro. Bisphosphonates have now been employed as therapeutic agents for treatment of bone disorders, hypocalcaemia of malignancy, and osteoporosis for over three decades [156–158] and are also routinely used as ^{99}Tc complexes in skeletal scintigraphy [159].

Low bone density and osteoporosis represent major health threats for millions of people worldwide. Significant efforts devoted to prevention, treatment and impediment of osteoporosis yielded a class of highly effective bisphosphonate drugs with nitrogen-containing bisphosphonates such as pamidronate (**91**) (Aredia), alendronate (**92**) (Fosamax), zoledronate (**93**) (Zometa) and risedronate (**94**) (Actonel), being the current drugs of choice.



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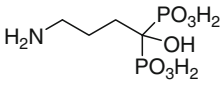

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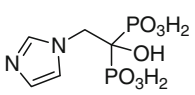

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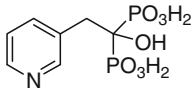


94

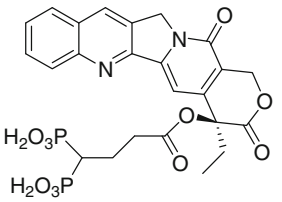
These drugs exhibit very high affinity for bone tissue, being rapidly adsorbed at bone surface, binding irrotationally to bone, and displacing orthophosphate from the bone mineral matrix [160]. They act on bone metabolism, most likely by blocking farnesylpyrophosphate synthase within osteoclasts, the cells responsible for bone resorption. This causes the disruption of prenylation of Ras, Rho, and Rac regulatory proteins and thus affects osteoclastogenesis, cell survival, and cytoskeletal dynamics [161–170]. Therefore, it is not surprising that their binding to the active site of this enzyme is intensively studied by means of crystallography [171–174] and computational methods [162,173,175,176]. Quite interestingly, metabolic profiling of urine from preclinical studies on the action of zoledronate in rats revealed the presence of *N*-acteylfelinine, a precursor of a cat-specific pheromone, felinine, a unique sulfur-containing amino acid found in the urine of domestic cats [177]. This shows that zoledronate, by inhibition of farnesylpyrophosphate synthase, causes an increase in the isoprenoid pool and, in consequence, stimulates the biosynthesis of this unusual compound.

One of the shortcomings of bisphosphonates is their exceptionally low bioavailability [178,179]. This problem may be dealt with by administering functionalized

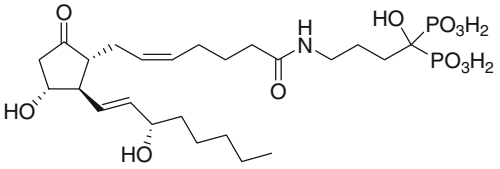
active compound (a prodrug) that would release the bisphosphonate upon metabolism and such an approach was quite successfully applied to aledronate by its conversion into *N*-myristoylalendronic acid [180]. Another solution is controlled release of the drug from porous materials. For example, the use of hexagonally ordered mesoporous silica caused an increase of the intake rate of alendronate from 1% up to 40% [181].

A far more serious problem in of the use of bisphosphonates is the finding that they cause jaw osteonecrosis when used to cure osteoporosis, bone metastases resulting from other types of cancers, and bone lesions of multiple myeloma [182–185]. The majority of cases involved intravenous application of bisphophonates. The cause of this side effect has not been determined yet. This also shows that the search for new, structurally diverse bisphosphonates without this effect is strongly required.

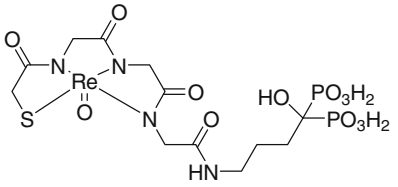
Because bisphosphonates are specifically targeted to bone and exhibit significant binding capability to hydroxyapatite, their actions become limited to osseous tissue. This property was used to target known chemotherapeutic agents to bone after their conjugation with bisphosphonates through hydrolyzable linkage (**95**–**97** are representative examples). This concept is called the *osteoporetic drug delivery system*. Thus, they were used to target radioisotopes, antineoplastic agents, antiinflammatory agents, agents for augmentation of bone mass, and proteins [186–189].



conjugate **95** with Camphotecin
anticancer agent



conjugate **96** with prostaglandin E_2
for prevention of systematic bone loss



conjugate **97** with radioisotope
for metastaic bone pain pallination

Protozoa are causative agents of a wide range of diseases including malaria (caused by *Plasmodium* spp.), sleeping sickness (caused by *Trypanosoma brucei*), Chagas disease (caused by *Trypanosoma cruzi*), and leishmaniasis (caused by *Leishmania* species). These are widespread and dangerous infectious diseases. For example, there are over 500 million cases of malaria and it causes the death of one to three million people annually. Over 350 million people are exposed to the risk of infection by leishmaniasis. Bisphosphonates have been found to exhibit strong

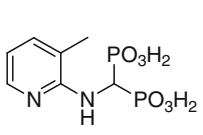
action against the in vitro proliferation of several protozoan parasites [190–194]. A parasitological cure of these tropical diseases has also been recently documented in mouse models of the diseases, although there is still a lack of a reliable structure–activity relationship [195–197].

The antiparasitic activity of these compounds has been attributed to the inhibition of farnesyl pyrophosphate synthetases [160,196,198–201], enzymes of the protozoal mevalonic acid pathway. However, other targets, such as protozoan hexokinase [202], exopolyphosphatase [203], or purine transferase [204] are also taken into consideration.

As shown above, bisphosphonates reveal variable physiologic activity. They were also found to have antibacterial [166,205] and anticancer properties [206–213] and to stimulate γ,δ,T cells of the immune system [205,214–217], drawing interest in their application for cancer immunotherapy.

A subclass of bisphosphonates, derivatives of aminomethylenebisphosphonic acid, also exhibits interesting herbicidal activities, with compounds **98**–**100** being the most active. The main phytotoxic effects are browning and swelling of the shoots and strong hypocotyls chlorosis. Growth is slowed down substantially a few days after application, and desiccation of plant tissues becomes pronounced after 2 weeks [218–229].

Also in this case, inhibition of farnesyl pyrophosphate synthase was considered to be a primary site of action of these herbicides [222,224]. This was supported by finding that these derivatives significantly decrease carotenoid and chlorophyll synthesis. However, further studies have indicated that derivatives of aminomethylenebisphosphonic acid should be considered as a heterogenous group of herbicides with various molecular modes of action. They were found to also inhibit glutamine synthetase [227,228], 3-deoxy-D-*arabino*-heptulosonate-7-phosphate synthase [228], pyrophosphatase [229,230], and δ^1-pyrroline-5-carboxylate reductase [231,232]. All these enzymes are metal-dependent; the strong complexing properties of bisphosphonates [233] may be of vital importance for their inhibition.



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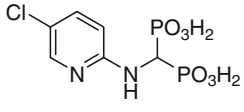

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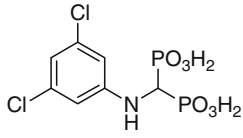
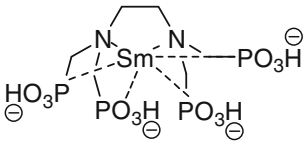


100

The complexing property of the phosphonate moiety was a basis for the construction of bone radiodiagnostic agents and magnetic resonance imaging (MRI) contrast agents. Radiodiagnosis relies on γ-ray scanning using complexes of radioactive metals such as ^{99m}Tc, ^{153}Sm, ^{161}Tb, ^{166}Ho, ^{177}Lu, or ^{140}Ln with polyamino polyphosphonates representing a variety of chemical structures [234–239]. For example, sammarium(III) complexed with most popularly used ethylenediaminetet

rakis(methylene-phosphonic acid) (**101**, Quadramet) concentrates in areas of bone turnover in association with hydroxyapatite and selectively accumulates in osteoblastic lesions [240]. Quite interestingly, most of these complexes (e.g., **102**) actively relieve the pain of bone metastases [239,241–244] although the mechanism of their action is not fully understood.



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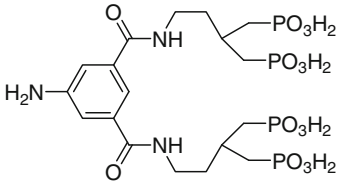
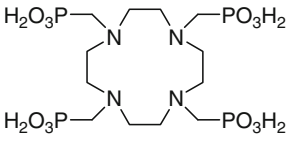


102

A major field of application of MRI contrast agents is in diagnosis of carcinoma in soft tissues. However, it is known that metastasis of almost all types of cancer may affect bones. Therefore, bone-targeted contrast agents based on ligands containing phosphonic acid groups are also of interest, with the most intensively studied analogues being **103** and **104** of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA, **105**) [238,245–247].



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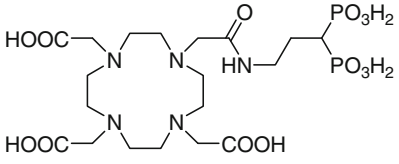

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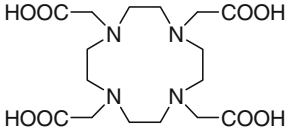
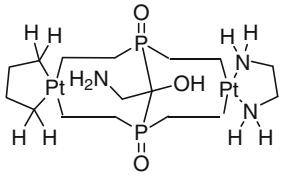


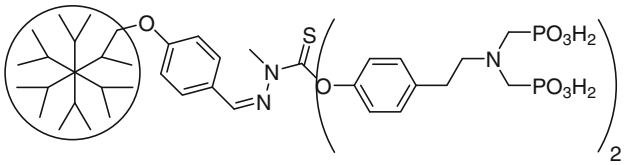
105

Aminopolyphosphonates have also been used as analogues of cisplatin, in which phosphonate units target this anticancer drug to bone tissues [248]. The analogue **106** exhibits activity superior to cisplatin and its availability was improved by encapsulating the drug into silica xerogels [249].



106

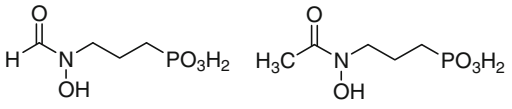
There are single reports on the use of bis- [250] and poly-phosphonates [251] for the removal of uranyl ions from blood and papers, showing that phosphorus-containing dendrimers (such as **107**) functionalized at the surface with 16 aminobismethylene phosphonic acid groups promoted fully functional NK cells and provided the activation of monocytes from healthy human blood mononuclear cells in culture [252–254], thus exhibiting immunostimulating properties.



107

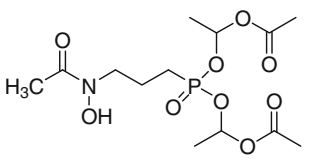
7 Modifications of Natural Aminophosphonic Acids

Fosmidomycin (**108**) was isolated, alongside its three structural analogues, from a culture broth of *Streptomyces lavendulae* and *Strepromyces rubellomurinus* as an antibiotic active against Gram-negative bacteria [255,256]. Its mechanism of action is based on inhibition of 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DOXP reductoisomerase), an enzyme involved in the 2*C*-methyl-D-erythritol 4-phosphate pathway for the biosynthesis of isoprenoids [257,258]. This enzyme is present in most bacteria, green algae, and the plastids of higher plants, while it is absent in humans [259,260]. Fosmidomycin and its more active acetyl congener FR900098 (**109**) are potent inhibitors of protozoan DOXP reductoisomerase [258] and are active against *Plasmodium palcifarum* in vitro and *Plasmodium vinckei* in a mouse model [258,259]. However, oral bioavailability of both compounds is only moderate, with a resorption rate of approximately 30% [261]. Fosmidomycin has received considerable attention, and clinical trials conducted in Gabon and Thailand confirmed its potential as an antimalarial drug [262,263]. It has advantages in being remarkably nontoxic and in exhibiting activity against multiresistant parasite strains.

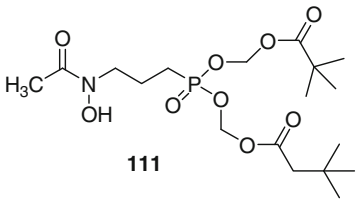


108 **109**

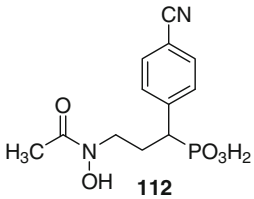
Fosmidomycin represents a valuable lead for further modifications. In most cases, prodrugs of this antibiotic are produced in the hope of increasing drug resorption rate (representative compounds **110** and **111**) [264–267]. Also, the insertion of substituents in the α-position of the propyl chain of the molecule (see **112** and **113**) [267–269], as well as introduction of the retrohydroxamate moiety (**114**) [270–272], seem to be promising. Modified analogues of fosmidomycin were found to inhibit accumulation of ajmalicine, a marker of monoterpenoid indole alkaloids production in cells of *Catharanthus roseus* [273].



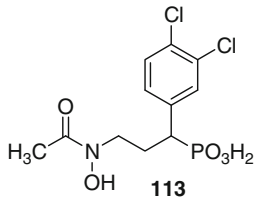
110



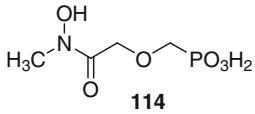
111



112

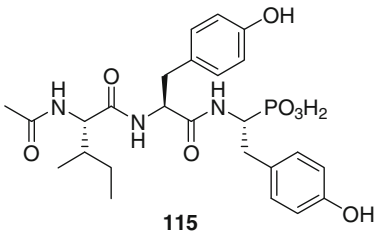


113

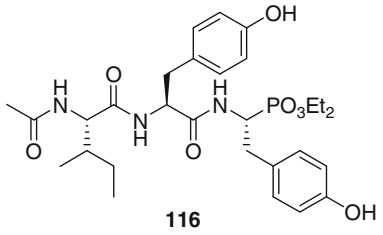


114

K-26 (**115**) was initially discovered via angiotensin-converting enzyme (ACE) bioactivity-guided fractionation of the extracts of a soil-dwelling prokaryote, actinomycete strain K-26 [274]. It has been reported to possess ACE inhibitory activity, comparable to the widely prescribed antihypertensive drug Captopril. Analogues of K-26 were also found to markedly inhibit ACE activity [275]. In order to ascertain the structure–activity relationship in this class of peptidyl antibiotics, eight analogues of K-26 were synthesized and evaluated towards this enzyme. Esterification of the phosphonic moiety was found to be the critical determinant of activity, resulting in compound **116** with 1500-fold increased ACE inhibition as compared to carboxyl analogues [276].



115



116

References

1. Horiguchi M, Kandatsu M (1959) Nature 184:901
2. Mastalerz P (1959) Archiv Immun Ter Dosw 7(20):1. Chem Abst 53:18879b
3. Chavane V (1949) Gen Ann Chim 4:352. Chem Abst 45:7516g
4. Franz JE, Mao MK, Sikorski JA (1997) Glyphosate:a unique global herbicide. Monograph 189. American Chemical Society, Washington DC
5. Okuhara M, Kuroda Y, Goto T, Okamoto M, Terano H, Kohsaka M, Aoki H, Imanaka H (1980) J Antibiot 33:13

6. Allen JG, Atherton FR, Hall MJ, Hassall CH, Holmes SW, Lambert RW, Nisbet LJ, Ringrose PS (1978) Nature 272:56
7. Karanewsky DS, Badia MC, Cushman DW, De Forrest JM, Dejneka T, Loots MJ, Pern MG, Petrillo Jr RD, Powell RJ (1988) J Med Chem 31:204
8. Russell RGG (2006) Ann NY Acad Sci 1068:367–401
9. Kukhar VP, Hudson HR (eds) (2000) Aminophosphonic and aminophosphinic acids: chemistry and biological activety. Wiley, Chichester
10. Kafarski P, Lejczak B (1991) Phosphorus Sulfur Silicon 63:193
11. Collinsova M, Jiracek J (2000) Curr Med Chem 7:629
12. Kafarski P, Lejczak B (2001) Curr Med Chem – Anti-Cancer Agents 1:301
13. Berlicki Ł, Kafarski P (2005) Curr Org Chem 9:1829
14. Romanenko VD, Kukhar VP (2006) Chem Rev 106:3868
15. Wardle NJ, Bligh SWA, Hudson HR (2007) Curr Org Chem 11:1635
16. Hecker SJ, Erion MD (2008) J Med Chem 51:2328
17. Macciarulo A, Pellicciari R (2007) J Mol Graph Model 26:728
18. Dingledine R, Borges K, Bowie D, Traynelis SF (1999) Pharmacol Rev 51:7
19. Selvam C, Goudet C, Ouselatti N, Pin J-P, Acher FC (2007) J Med Chem 50:4656
20. Tikhonova IG, Baskin II, Palyulin VA, Zefirov NS, Bachurin SO (2002) J Med Chem 45:3836
21. Grazioso G, Moretti L, Scapozza L, de Amici M, de Micheli C (2005) J Med Chem 48:5489
22. Schoepp DD, Jane DE, Monn JA (1999) Neuropharmacology 38:1431
23. Baudy RB, Fletcher III H, Yardley JP, Zaleska MM, Bramlett RD, Tasse RP, Kowal DM (2001) J Med Chem 44:1516
24. Brandt MR, Cummons TA, Potestio L, Sukoff SJ, Rozenzweig-Lipson S (2005) J Pharm Exp Ther 313:1379
25. Feng B, Morley RM, Jane DE, Monaghan DT (2005) Neuropharm 48:354
26. Filosa R, Marinozzi M, Constantino G, Hermit MB, Thomsen C, Pellicciari R (2006) Bioorg Med Chem 14:3811
27. Amori L, Constantino G, Marinozzi M, Pellicciari R, Gasparini F, Flor PJ, Kuhn R, Vranesic I (2000) Bioorg Med Chem Lett 10:1447
28. Bettler B, Kaupman K, Mosbacher J, Gassman M (2004) Physiol Rev 84:835
29. Ong J, Kerr DIB (2005) CNS Drug Rev 11:317
30. Bon C, Galvan M (1996) Brit J Pharmacol 118:961–967
31. Alstermark C, Amin K, Dinn SR, Elbering T, Fjellström O, Fitzpatrick K, Geiss WB, Gottfries J, Guzzo PR, Harding JP, Holmén A, Kothare M, Lehmann A, Mattsson JP, Nilsson K, Sundén G, Swanson M, von Unge S, Woo AM, Wyle MJ, Zheng X (2008) J Med Chem 51:4315
32. Kerr DI, Ong J, Prager RH, Gynther BD, Curtis GR (1987) Brain Res 495:150
33. Bowery NG, Enna SJ (2000) J Pharmacol Exp Ther 292:2
34. Murata Y, Woodward RM, Miledi R, Overmann LE (1996) Bioorg Med Chem Lett 6:2073
35. Krehan D, Frolund B, Krogsgaard-Larsen P, Kehler J, Johnston GAR, Chebib M (2003) Neurochem Int 42:561
36. Orain D, Mattes H (2006) Tetrahedron Lett 47:1253
37. Hinton T Chebib M, Johnston GAR (2008) Bioorg Med Chem Lett 18:402
38. Bertaccini E, Trudel JR (2001) Int Rev Neurobiol 48:141
39. Bowery NG, Bettler B, Froestl W, Gallagher JP, Marshall F, Raiteri M, Bonner TI, Enna SJ (2003) 54:247
40. Li X, Cao J-H, Li Y, Ronard P, Zhang Y, Yi P, Liu J-F, Nan F-J (2008) J Med Chem 51:3057
41. Iron A, Monique R, Duboy J-P, Beranger M, Cassaigne A, Neuzil E (1981) Biochem Soc Trans 9:246
42. Lejczak B, Kafarski, P, Makowiecka E (1987) Biochem J 242:81
43. Gąsowska B, Wojtasek H, Jurek J, Drąg M, Nowak K, Kafarski P (2002) Eur J Biochem 269:4098
44. Evsigneeva ZG, Solovieva NA, Sidelnikova LI (2003) Prikl Biokhim Mikrobiol 39:613
45. Berlicki Ł (2008) Mini Rev Med Chem 8:869
46. Logusch EW, Walker DM, McDonald JF, Franz JE (1989) Biochemistry 29:3034
47. Gill HS, Eisenberg D (2001) Biochemistry 40:1903

48. Krajewski WW, Jones AT, Mowbray SL (2005) Proc Natl Acad Sci USA 102:10499
49. Berlicki Ł, Obojska A, Forlani G, Kafarski P (2006) J Med Chem 48:6340
50. Forlani G, Obojska A, Berlicki Ł, Kafarski P (2006) J Agric Food Chem 54:796
51. Nordqvist A, Nilsson MT, Röttger S, Odeli LR, Krajewski WW, Andersson CE, Larhed M, Mowbray SL, Karlen A (2008) Bioorg Med Chem 16:5501
52. Zoń J, Amrhein N (1992) Liebigs Ann Chem 625
53. Appert C, Zoń J, Amrhein N (2003) Phytochemistry 62:415
54. Zoń J, Szefczyk B, Sawka-Dobrowolska W, Gancarz R, Kucharska-Zoń M, Latajka R,Amrhein N, Miziak P, Szczepanik W (2004) New J Chem 28:1048
55. Zoń J. Miziak P, Amrhein N, Gancarz R (2005) Chem Biodiv 2:1187
56. Miziak P, Zoń J, Amrhein N, Gancarz R (2007) Phytochemistry 68:407
57. Shie J-J, Fang J-M, Wang S-Y, Tsai K-C, Cheng Y-SE, Yang A-S, Hsiao S-C, Su C-Y, Wong C-H (2007) J Am Chem Soc 129:11892
58. Steere JA, Sampson PB, Honek JF (2002) Bioorg Med Chem Lett 12:457
59. Giannousis PP, Bartlett PA (1987) J Med Chem 30:1603
60. Lejczak B, Kafarski P, Zygmunt J (1989) Biochemistry 28:3549
61. Kim H, Lipscomb WN (1994) Adv Enzymol Relat Areas Mol Biol 68:153
62. Strater N, Lipscomb WN (1995) Biochemistry 34:9200
63. Grembecka J, Sokalski WA, Kafarski P (2000) J Comput-Aided Mol Design 14:531
64. Grembecka J, Sokalski WA, Kafarski P (2001) Int J Quant Chem 84:302
65. Grembecka J, Mucha A, Cierpicki T, Kafarski P (2003) J Med Chem 46:2641
66. Zhang Z-Y (2002) Ann Rev Pharmacol Toxicol 42:202
67. Tautz L, Pellechia M, Mustelin T (2006) Exp Opin Therapeut Agents 10:157
68. Burke Jr TR (2006) Curr Top Med Chem 6:1465
69. Oishi S, Karki RG, Shi Z-D, Worthy KM, Bindu L, Chertov O, Esposito D, Frank P, Gilette WK, Maderia M, Hatley J, Nicklaus MC, Barchi Jr JJ, Fisher RJ, Burke Jr TR (2005) Bioorg Med Chem 13:2431
70. Boutselis IG, Yu XS, Zhang Z-Y, Borch RF (2007) J Med Chem 50:856
71. Dourlat J, Valentin B, Liu W-Q, Garbay C (2007) Bioorg Med Che. Lett 17:3943
72. Shen K (2007) Methods 42:234
73. Johnson TO, Ermolieff J, Jarousek MR (2002) Nat Drug Discovery 1:696
74. Kumar S, Zhou B, Liang F, Wang W-Q, Huang Z, Zhang Z-Y (2004) Proc Natl Acad Sci USA 101:7943–7948
75. Walchi S, Espanel X, Harrenga A, Rossi M, Cesareni G, van Huijduijnen (2004) J Biol Chem 279:311–318
76. Santos WL, Heasly BH, Jarosz R, Carter KM, Lynch KR, Macdonald TL (2004) Bioorg Med Chem Lett 14:3473
77. Hale JJ, Doherty G, Toth L, Mills SG, Hajdu R, Keohane CA, Rosenbach M, Milligan J, Shei G-J, Chrebet G, Bergstrom J, Card D, Forrest M, Sun S-Y, West S, Xie H, Nomura N, Rosen H, Mandala S (2004) Bioorg Med Chem Lett 14:3501
78. Foss Jr FW, Snyder AH, Davis MD, Rouse M, Okusa MD, Lynch KR, Macdonald TL (2007) Bioorg Med Chem 15:663
79. Cui P, Tomsig JL, McCalmont WF, Lee S, Becker CJ, Lynch KR, Macdonald TL (2007) Bioorg Med Chem Lett 17:1634
80. Cui P, McCalmont WF, Tomsig JL, Lynch KR, Macdonald TL (2008) Bioorg Med Chem 16:2212
81. Hakogi T, Yamamoto T, Fujii S, Ikeda K, Katsumura S (2006) Tetrahedron Lett 47:2627
82. Cox RJ, Gibson JS, Hadfield AT (2005) Chem BioChem 2255
83. Balg C, Blais SP, Bernier S, Hout JL, Couture M, Lapointe J, Chênevert R (2007) Bioorg Med Chem 15:295
84. Notter RH, Wang Z, Wang Z, Davy AD, Schwan AL (2007) Bioorg Med Chem Lett 17:113
85. Wang Z, Chang Y, Schwan AL, Notter RH (2007) Am J Resp Cell Mol Biol 37:387
86. Cherenok S, Vovk A, Muravyova I, Shivanyuk A, Kukhar V, Lipokowski J, Kalchenko V (2006) WOrg Lett 8:549

87. Drag M, Grembecka J, Pawelczak M, Kafarski P (2005) Eur J Med Chem 40:764
88. Mucha A, Kunert A, Grembecka J, Pawelczak M, Kafarski P (2006) Eur J Med Chem 41:768
89. Drag M, Grzywa R, Oleksyszyn J (2007) Bioorg Med Chem Lett 17:1516
90. Skinner-Adams TS, Lowther J, Teuscher F, Stack CM, Grembecka J, Mucha A, Kafarski P, Treholme TR, Dalton JP, Gardiner DL (2007) J Med Chem 50:602
91. Teuscher F, Lowther J, Skinner-Adams TS, Spielmann T, Dixon MWA, Stack CM, Donelly S, Mucha A, Kafarski P, Vassiliou S, Gardiner DL, Dalton JP, Trenholme KR (2007) J Biol Chem 282:30817
92. Vassiliou S, Xeilari M, Yiotakis A, Grembecka J, Pawelczak M, Kafarski P, Mucha A (2007) Bioorg Med Chem Lett 15:3187
93. Holz RC (2002) Coord Chem Rev 232:5
94. Berlicki L, Grembecka J, Dyguda-Kazimierowicz E, Kafarski P, Sokalski WA (2007) In: Sokalski WA Molecular materials with specific interactions – modeling and design. Challenges and advances in computational chemistry and physics, vol 4. Springer, Dordrecht, pp 365–398
95. Mucha A, Grembecka J, Cierpicki T, Kafarski P (2003) Eur J Org Chem 4797
96. Stack CM, Lowther J, Cunningham E, Donelly S, Gardiner DL, Treholme KR, Skinner-Adams TS, Teuscher F, Grembecka J, Mucha A, Kafarski P, Lua L, Bell A, Dalton JP (2007) J Biol Chem 282:2069
97. Reiter LA, Mitchell PG, Martinelli GJ, Lopresti-Morrow LL, Yocum SA, Eskra JD (2003) Bioorg Med Chem Lett 13:2331
98. Dive V, Georgiadis D, Matziari M, Makaritis A, Beau F, Cuniasse P, Yiotakis A (2004) Cell Mol Life Sci 61:2010
99. Matziari M, Beau F, Cuniasse P, Dive V, Yiotakis A (2004) J Med Chem 47:325
100. Agamemnone M, Campestre C, Preziuso S, Consalvi V, Crucianelli M, Mazza F, Politi V, Ragno R, Tortorella P, Gallina C (2005) Eur J Med Chem 40:271
101. Bianchi G, Aschi M, Cavicchio G, Crucianelli M, Prezusio S, Gallina C, Nastari A, Gavuzzo E, Mazza F (2005) Bioorg Med Chem 13:4740
102. Lauer-Fields J, Brew K, Whitehead JK, Li S, Hammer RP, Fields GB (2007) J Am Chem Soc 129:10408
103. Matziari M, Dive V, Yiotakis A (2007) Med Res Rev 27:528
104. Verma RP, Hansch C (2007) Bioorg Med Chem 15:2223
105. Gall A-L, Ruff M, Kannan R, Cuniasse P, Yiotakis A, Dive V, Rio M-C, Basset P, Moras D (2001) J Mol Biol 307:577
106. Makaritis A, Georgiadis D, Dive V, Yiotakis A (2003) Chem Eur J 9:2079
107. Manzenrieder F, Frank AO, Kessler H (2008) Angew Chem Int Ed 47:2608
108. Burchardt JU, Schiødt CB, Krog-Jensen C, Delaisse J-M, Foged NT, Meldal M (2000) J Comb Chem 2:624
109. Devel L, Rogakos V, David A, Makartis A, Beau F, Cuniasse P, Yiotakis A, Dive V (2006) J Biol Chem 281:11152
110. Aschi M, Besker N, Re N, Pochetti G, Coletti C, Mazza F (2007) J Med Chem 30:211
111. Mallari JP, Choy CJ, Hu Y, Martinez AR, Hosaka M, Toriyabe Y, Maung J, Blecha JE, Pavkovic SF, Berkman CE (2004) Bioorg Med Chem 12:6011
112. Adler M, Buckman B, Bryant J, Chang Z, Chu K, Emayan K, Hrvatin P, Islam I, Morser J, Sukovich D, West C, Yuan S, Whitlow M (2008) Acta Crystallogr D64:149
113. Grzywa R, Oleksyszyn J (2008) Bioorg Med Chem Lett 18:3734
114. Payne DJ, Du W, Bateson JH (2000) Exp Opin Invest Drugs 9:247
115. Gurulingappa H, Buckhalts P, Kinzler KW, Vogelstein B, Khan SR (2004) Bioorg Med Chem Lett 14:3531
116. Smith HK, Beckett RP, Clements JM, Doel S, East SP, Launchbury SB, Pratt LM, Spavold ZM, Thomas W, Todd RS, Whittaker M (2002) Bioorg Med Chem Lett 12:3595
117. Kruger RG, Barkallah S, Frankel BA, McCafferty DG (2004) Bioorg Med Chem 12:3723
118. Corradi HR, Chitapi I, Sewell BT, Georgiadis D, Dive V, Sturrock ED, Acharya KR (2007) Biochemistry 46:5473

119. Mores A, Matziari M, Beau F, Cuniasse P, Yiotakis A, Dive V (2008) J Med Chem 51:2216
120. Bartley DM, Coward JK (2005) J Org Chem 70:6757
121. Feng Y, Coward JK (2006) J Med Chem 49:770–788
122. Yang Y, Coward JK (2007) J Org Chem 72:5748
123. Vidossich P, Carloni P (2006) J Phys Chem B 110:1437
124. Manzenrieder F, Frank AO, Huber T, Dorner-Ciossek C, Kessler H (2007) Bioorg Med Chem 15:4136
125. Štrancar K, Blanot D, Gobec S (2006) Bioorg Med Chem Lett 16:343
126. Štrancar K,Boniface A, Blanot D, Gobec S (2007) Arch Pharm Chem Life Sci 340:127
127. Cressina E, Lloyd AJ, De Pascale G, Roper DI, Dowson CG Bugg TDH (2007) Bioorg Med Chem Lett 17:4654
128. Demange L, Dugave C (2001) Tetrahedron Lett 42:6295
129. Gobec S, Plantan I, Mravljak J, Wilson RA, Besra GS, Kikelj D (2004) Bioorg Med Chem Lett 14:3559
130. Gobec S, Plantan I, Mravljak J, Švajger U, Wilson RA, Besra GS, Soares SL, Appelberg R, Kikelj D (2007) Eur J Med Chem 42:54
131. Han L, Hiratake J, Kamiyama A, Sakata K (2007) Biochemistry 46:1432
132. Mucha A, Pawelczak M, Hurek J, Kafarski P (2004) Bioorg Med Chem Lett 14:3113
133. Asojo O, Friedman J, Adir N, Belakhov V, Shoham Y, Baasov T (2001) Biochemistry 40:6326
134. Pan W, Ansiaux C, Vincent SP (2007) Tetrahedron Lett 48:4353
135. Suk D-H, Rejman D, Dykstra CC, Pohl R, Pankiewicz KW, Patterson SE (2007) Bioorg Med Chem Lett 17:2811
136. Zhou D, Staake M, Patterson S (2008) Org Lett 10:2179
137. Oleksyszyn J, Powers JC (1994) Amino acid and peptide phosphonate as specific inhibitors of serine peptidases. In: Barret AJ Methods in enzymology, vol 244. Academic, San Diego, pp 423–441
138. Skordalakes E, Dodson GG, St Clair Green D, Goodwin GA, Scully MF, Hudson HR, Kakkar VV, Deadman JJ (2001) J Mol Biol 311:549
139. Sienczyk M, Oleksyszyn J (2004) Tetrehedron Lett 45:7251
140. Joossens J, Van der Veken P, Surpateanu G, Lambeir A-M, El-Sayed I, Ali OM, Augustyns K, Haemers A (2006) J Med Chem 49:5785
141. Joossens J, Ali OM, El-Sayed I, Surpateanu G, Van der Veken P, Lambeir A-M, Setyono-Han B, Foeskens JA, Schneider A, Schmalix W, Haemers A, Augustyns K (2007) J Med Chem 50:6638
142. Gilmore BF, Lynas JF, Scott CJ, McGoohan C, Martin L, Walker B (2006) Biochem Biophys Res Commun 346:436
143. Augustyns K, Van der Veken P, Haemers A (2005) Curr Med Chem 12:971
144. Gilmore BF, Carson L, McShane LL, Quinn D, Coulter WA, Walker B (2006) Biochem Biophys Res Commun 347:373
145. Van der Veken P, Soroka A, Brandt I, Chen Y-S, Maes M-B, Lambeir A-M, Chen X, Haemers A, Scharpé S, Augustyns K, De Meester I (2007) J Med Chem 50:5568
146. Grzywa R, Dyguda-Kazimierowicz E, Sieńczyk M, Feliks M, Sokalski WA, Oleksyszyn J (2007) J Mol Model 13:677
147. Zhou Y-X, Karle S, Tagiuchi H, Planque S, Nishiyama Y, Paul S (2002) J Immunol Meth 269:257–268
148. Taguchi H, Keck Z, Foung SKH, Paul S, Nishiyama Y (2004) Bioorg Med Chem Lett 14:4529
149. Marnett AB, Nomura AM, Shimba N, Ortiz de Montellano PR, Craik CS (2004) Proc Natl Acad Sci USA 101:6870
150. Planque S, Bangale Y, Song X-T, Karle S, Taguchi H, Poindexter B, Bick R, Edmundson A, Nishiyama Y, Paul S (2004) J Biol Chem 279:14024
151. Nishiyama Y, Mitsuda Y, Taguchi H, Planque S, Hara M, Karle S, Hanson CV, Uda T, Paul S (2005) J Mol Recogn 18:295

152. Nukaga M, Kumar S, Nukaga K, Pratt RF, Knox JR (2004) J Biol Chem 279:9344
153. Adediran SA, Nukaga M, Baurin S, Pratt RF (2005) Antimicrob Agents Chemother 49:4410
154. Han L, Hiratake J, Kamiyama A, Sakata K (2007) Biochemistry 46:1432
155. Fleisch H, Russel RGG, Staruman F (1966) Nature 212:901
156. Green JR (2004) Oncologist 9:4
157. Licata AA (2005) Ann Pharmacother 39:668
158. Russell RGG (2006) Ann NY Acad Sci 1068:367
159. Ogawa K, Mukai T, Ararno Y, Ono M, Hanaoka H, Ishino S, Hashimoto K, Nishimura H, Saji H (2005) Bioconjugate Chem 16:751
160. Mukherjee S, Song Y, Oldfield E (2008) J Am Chem Soc 130:1264
161. Shipman CM, Croucher PI, Russell RGG, Rogers MJ (1998) Cancer Res 58:5294
162. Ebetino FH, Roze CN, McKenna CE, Barnett CL, Dunfors JE, Russell RGG, Mielig GE, Rogers MJ (2005) J Organometal Chem 690:2679
163. Sanders JM, Song Y, Chan JMW, Zhang Y, Jennings S, Kosztowski T, Odeh S, Flessner R, Schwerdtfeger C, Kotsikorou E,Meints GA, Ortiz Gomaes A, Gonzales-Pacanowska D, Raker AM, Wang H, van Beek ER, Papapoulos SE, Morita CT, Oldfield E (2005) J Med Chem 48:2957
164. Dunford JE, Rogers MJ, Ebetino FH, Pipps RJ, Coxon FP (2006) J Bone Miner Res 21:684
165. Kavanagh KL, Guo K, Dunford JE, Wu X, Knapp S, Ebetino FH, Rogers MJ, Russell RGG, Oppermann U (2006) Proc Natl Acad Sci USA 103:7829
166. Leon A, Liu L, Yang Y, Hidock MP, Hall P, Yin F, Studer D, Puan K-J, Morita CT, Oldfield E (2006) J Med Chem 49:7331
167. Yin F, Cao R, Goddard A, Zhang Y, Oldfield E (2006) J Am Chem Soc 128:3524
168. Guo R-T, Cao R, Liang P-H, Ko T-P, Chang T-H, Hudock MP, Jeng W-J, Chen CK-M, Zhang Y, Song Y, Kuo C-J, Yin F, Oldfield E, Wang A H-J (2007) Proc Natl Acad Sci USA 104:10022
169. Wiemer AJ, Tong H, Swanson KM, Hohl RJ (2007) Biochem Biophys Res Commun 353:921
170. Dunford JE, Kwaasi AA, Rogers MJ, Barnett BL, Ebetino FH, Russell RGG, Opperman U, Kavanagh KL (2008) J Med Chem 51:2187
171. Hosfield DJ, Zhang Y, Dougan DR, Broun A, Tari LW, Swanson RV, Finn J (2004) J Biol Chem 279:8526
172. Mao J, Gao Y-G, Odeh S, Robinson H, Montavetti A, Docampo R, Oldfield E (2004) Acta Crystallogr D60:1863
173. Mao J, Mukherjee, Zhang Y, Cao R, Sanders JM, Song Y, Zhang Y, Meints GA, Mukkamala D, Hudock MP, Oldfield E (2006) J Am Chem Soc 128:14485
174. Rondeau JM, Bitsch F, Bourgier E, Geiser M, Hemming R, Kroemer M, Lehman S, Ramage P, Riffel S, Strauss A, Green JR, Jahnke W (2006) ChemMedChem 1:267
175. Martin MB, Arnold W, Heath III HT, Urbina JA, Oldfield E (1999) Biochem Biophys Res Commun 263:754
176. Berlicki L, Kafarski P (2002) Pestic Biochem Physiol 73:94
177. Dieterle F, Scglotterbeck G, Binder M, Ross A, Suter L, Senn H (2007) Chem Res Toxicol 20:1291
178. Gertz BJ, Holland SD, Kline WF, Matuszewski BK, Freeman A, Quan H, Lasseter KC, Mucklow JC, Porras AG (1995) Clin Pharmacol Therapeut 58:288
179. Hoffman A, Stepensky D, Ezra A, Van Gelder JM, Golomb G (2001) Int J Pharm 220:1
180. Vachal P, Hale JJ, Lu Z, Streckfuss EC, Mills SG, MacCoss M, Yin DH, Algayer K, Manser K, Kesisoglou F, Ghosh S, Alani LL (2006) J Med Chem 49:3060
181. Balas F, Manzano M, Horcjada P, Vallet-Regi M (2006) J Am Chem Soc 128:8116
182. Leite AF, Figueiredo PT, Melo NS, Acevedo AC, Paraiso Cavalcanti MG, Paula LM, Paula AP, Silva Guerra EN (2006) Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:14
183. Dannemann C, Grätz KW, Riener MO, Zwahlen RA (2007) Bone 40:828
184. Hess LM, Jeter JM, Benham-Hutchins M, Albers DS (2008) Am J Med 121:475
185. Subramaniam RM, Miller GM (2008) Eur J Radiol 66:e9

186. Uludag H (2002) Curr Pharm Des 8:99
187. Ogawa K, Mukai T, Ararno Y, Ono M, Hanaoka H, Ishino S, Hashimoto K, Nishimura H, Saji H (2005) Bioconj Chem 16:751
188. Ehrick RS, Capaccio M, Puelo DA, Bachas LG (2008) Bioconj Chem 19:315
189. Erez R, Ebner S, Attali B, Shabat D (2008) Bioorg Med Chem Lett 18:816
190. Urbina JA, Moreno B, Vierkotter S, Oldfield E, Payares G, Sanoja C, Bailey BN, Yan W, Scott DA, Moreno SNJ, Docampo R (1999) J Biol Chem 274:33609
191. Martin MB, Grimley JS, Lewis JC, Heath III HT, Bailey BN, Kendrick H, Yardley V, Caldera A, Lira R, Urbina JA, Moreno SNJ, Docampo R, Croft SL, Oldfield E (2001) J Med Chem 44:909
192. Martin MB, Sanders JM, Kendrick H, de Luca-Fradley K, Lewis JC, Grimley JS, van Brussel EM, Olsen JR, Meints GA, Burzyńska A, Kafarski P, Croft SL, Oldfield E (2002) J Med Chem 45:2904
193. Szajnman SH, Bailey BN, Docampo R, Rodriguez JB (2001) Bioorg Med Chem Lett 11:789
194. Bouzahzah B, Jelicks LA, Morris SA, Weiss LM, Tarnowitz HB (2005) Parazitol Res 96:184
195. Rodriguez N, Bailey BN, Martin MB, Oldfield E, Urbina JA, Docampo R (2002) J Infect Dis 186:138
196. Yardley V, Khan AA, Martin MB, Slifer TR, Araujo FG, Moreno SN, Docampo R, Croft SL, Oldfield E (2002) Animicrob Agent Chemother 46:929
197. Garzoni LR, Waghabi MC, Baptista MM, de Castro SL, Meirelles MNL, Britto CC, Docampo R, Oldfield E, Urbina JA (2004) Int J Antimicrob Agents 23:286
198. Montalvetti A, Bailey BN, Martin MB, Severin GW, Oldfield E, Docampo R (2001) J Biol Chem 276:33930
199. Sanders JM, Gomes AO, Mao J, Meints GA, Van Brussel EM, Burzynska A, Kafarski P, Gonzales-Pacanowska D, Oldfield E (2003) J Med Chem 46:5171
200. Szajnman SH, Montalvetti A, Wang Y, Docampo R, Rodriguez JB (2003) Bioorg Med Chem Lett 13:3231
201. Szajnman SH, Ravaschino EL, Docampo R, Rodriguez JB (2005) Bioorg Med Chem Lett 15:4685
202. Hudock MP, Sanz-Rodriguez CE, Song Y, Chan JMW, Zhang Y, Odeh S, Kosztowski T, Leonrossell A, Cóncepcion JL, Yardely V, Croft SL, Urbina JA, Oldfield E (2006) J Med Chem 49:215
203. Kotsikorou E, Song Y, Chan JMW, Faelens S, Tovian Z, Broderick E, Bakalara N, Docampo R, Oldfield E (2005) J Med Chem 48:6128
204. Fernández D, Wenck MA, Craig III SP, Delfino JM (2004) Bioorg Med Chem Lett 14:4501
205. Wang L, Kamath A, Das H, Li L, Bukowski J (2001) J Clin Invest 108:1349
206. Verdijk R, Franke H, Vermes I (2003) Cancer Lett 246:308
207. Milner RJ, Farese J, Henry CJ, Selring K, Fan TM, de Lorimier L-P (2004) J Vet Intern Med 18:594
208. Fromigue O, Lagneaux L, Body JJ (2000) J Bone Miner Res 15:2211
209. Chuah C, Barnes DJ, Kwok M, Corbin A, Deininger MWN, Druker BJ, Melo JV (2005) Leukemia 19:1896
210. Segawa H, Kimura S, Kuroda J, Sato K, Nogawa M, Yuasa T, Yakota A, Hodohara K, Fujiyama Y, Maekawa T (2005) Leukemia Res 29:451
211. Roelofs AJ, Hulley PA, Meijer A, Ebetino FH, Russell RGG, Shipman CM (2006) Int J Cancer 119:1254
212. Horie N, Murata H, Kimura S, Takeshita H, Sakabe T, Matsui T, Kubo T, Fushiki S (2007) Brit J Cancer 96:255
213. Silva KL, Vasconcellos DV, Delfraro de Paula Castro E, da Cunha Vasconcelos F, Bigni R, Maia RC (2008) Cancer Chemo Pharmacol 62:165
214. Kunzmann V, Bauer E, Wilhelm N (1999) N Engl J Med 340:737
215. Wilhelm M, Kunzmann V, Eckstein S, Reimer P, Weissinger F, Ruedinger T, Tony H-P (2003) Blood 102:200
216. Sanders JM Ghosh S, Chan JMW, Meints GA, Wang H, Raker AM, Song Y, Colantino A, Burzynska A, Kafarski P, Morita CT, Oldfield E (2004) J Med Chem 47:375

217. Bukowski JF, Dascher CC, Das H (2005) Biochem Biophys Res Commun 328:746
218. Suzuki F, Fujikawa Y, Yamamoto S, Mizutani H, Ohya T, Ikai T, Oguchi T (1979) Ger Offen 2,831,578
219. Lejczak B, Boduszek B, Kafarski P, Forlani G, Wojtasek H, Wieczorek P (1996) J Plant Growth Regul 15:109
220. Forlani G, Kafarski P, Lejczak B, Wieczorek P (1997) J Plant Growth Regul 16:147
221. Kafarski P, Lejczak B, Forlani G, Gancarz R, Torreilles G, Grembecka J, Ryczek A, Wieczorek P (1997) J Plant Growth Regul 16:153
222. Oberhauser V,Gaudin J, Fonne-Pfister R, Schär H-P (1998) Pestic Biochem Physiol 60:111
223. Chuiko L, Lozinsky MO, Jasicka-Misiak I, Kafarski (1999) J Plant Growth Regul 18:171
224. Cromartie TH, Fisher KJ, Grossman JN (1999) Pestic Biochem Physiol 63:114
225. Kafarski P, Lejczak B, Forlani G (2000) Heteroatom Chem 11:449
226. Forlani G, Lejczak B, Kafarski P (2000) Aust J Plant Physiol 27:639
227. Obojska A, Berlicki L, Kafarski P, Lejczak B, Chicca M, Forlani G (2004) J Agric Food Chem 52:333
228. Forlani G, Lejczak B, Kafarski P (1999) J Plant Growth Regul 18:73
229. Gordon-Weeks R, Parmar S, Davies TGE, Leigh RA (1999) Biochem J 337:373
230. Szabo CM, Oldfield E (2001) Biochem Biophys Res Commun 287:468
231. Forlani G, Gilberti S, Berlicki Ł, Petrollino D, Kafarski P (2007) J Agric Food Chem 55:4340
232. Forlani G, Occhipinti A, Berlicjki Ł, Dziedziola G, Wieczorek A (2008) J Agric Food Chem 56:3193
233. Matczak-Jon E, Adrabińska-Videnowa V (2005) Coord Chem Rev 249:2458
234. Caravan P, Ellison JJ, McMurry TJ, Lauffer RB (1999) Chem Rev 99:2293
235. Volkert WA, Hoffman TJ (1999) Chem Rev 99:2269
236. Mondry A, Janicki R (2006) Dalton Trans 4702
237. Panwar P, Kumar N, Singh S, Rawat H, Mishra AK (2007) Bioorg Med Chem 15:1138
238. Vitha T, Kubićek V, Hermann P, Vander elst L, Muller RN, Kolar ZI, Wolterbeek HT, Breeman WAP, Lukeš I, Peters JA (2008) J Med Chem 51:677
239. Djokić DD, Janković DL, Nikolić NS (2008) Bioorg Med Chem 16:4457
240. Goel A, Dispenzieri A, Witzig TE, Russell SJ (2006) Drug Discov Today Dis Mech 3:515
241. Arano Y, Mukai T, Uezono T, Wakisaka K, Motonari H, Akizawa H, Taoka Y, Yokoyama AQ (1994) J Nucl Med 35:890
242. Menda J, Bushnell DL, Williams RD, Miller SNR, Thomas MO (2000) Clin Nucl Med 25:698
243. Sapienza MT, Ono CR, Cury Guimarães MI, Watanabe T, Costa PA, Buchpiguel CA (2004) Rev Hop Clin FAc Med S Paulo 59:321
244. Tripathi M, Singhal T, Chandrasekhar N, Kumar P, Bal C, Jhulka PK, Bandopadhyaya G, Malhorta A (2006) Indian J Cancer 43:86
245. Adzamli IK, Gries H, Johnson D, Blau M (1989) J Med Chem 32:139
246. Alves FC, Donato P, Sherry AD, Zaheer AD, Zhand S, Lubag AJM, Merritt ME, Lenkinski RE, Frangioni JV, Neves M, Prata MIM, Santos AC, de Lima JJP, Geraldes CFGC (2003) Invest Radiol 38:750
247. Kubiček V, Rudowsky J, Kotek J, Herman P, Vander Elst L, Muller RN, Kolar ZI, wolterbeek HT, Peters JA, Lukes IA (2005) J Am Chem Soc 127:16477
248. Klenner T, Valenzuela P, Keppler BK, Scherf HR (1990) J Cancer Res Clin Oncol 116:453
249. Margiotta N, Ostuni R, Teoli D, Morpu rgo M, Realdon R, Palazzo B, Natali G (2007) Dalton Trans 3131
250. Wang L, Yang Z, Gao J, Xu K, Gu K, Zhang B, Zhang X, Xu B (2006) J Am Chem Soc 128:13358
251. Chaleix V, Lecouvey M (2007) Tetrahedron Lett 48:703
252. Poupot M, Griffe L, Marchand P, Maraval A, Rolland O, Martinet L, Turrin C-O, Caminade V, Fournie J-J, Majoral J-P, Poupot R (2006) FASEB J 20:2339
253. Griffe L, Poupot P, Marchand P, Marval O, Turrin C-O, Rolland O, Métivier P, Bacquet G, Fournié J-J, Caminade A-M, Poupot R, Majoral J-P (2007) Angew Chem Int Ed 46:2523

254. Rolland O, Griffe L, Poupot M, Maraval A, Ouali A, Coppel Y, Fournié J-J, Bacquet G, Turrin C-O, Caminadse A-M, MAjoral J-P, Poupot R (2008) Chem Eur J 14:4836
255. Kamiya T, Hemmi H, Takeno H, Hashimoto M (1980) Tetrahedron Lett 21:95
256. Hashimoto M, Hemmi K, Takeno H, Kamiya T (1980) Tetrahedron Lett 21:99
257. Kuzuyama T, Shimizu T, Takahashi S, Seto H (1998) Tetrahedron Lett 39:7913
258. Jomaa H, Wiesner J, Sanderbrand S, Altincicek B, Weidemeyer C, Hintz M, Turbachova I, Eberl M, Zeidler J, Lichtenthaler HK, Soldati D, Beck E (1999) Science 285:1573
259. Kuzuyama T, Takahashi S, Tagaki M, Seto H (2000) J Biol Chem 275:19928
260. Eisenreich W, Rohdich F, Bacher A (2001) Trends Plant Sci 6:78
261. Wiesner J, Seeber F (2005) Expert Opin Ther Targest 9:23
262. Missinou MA, Borrmann G, Schindler A, Issifou S, Adegnika AA, Matsiegui PB, Binder R, Lell B, Wiesner J, Baranek T, Jomaa H, Kremsner PG (2002) Lancet 360:1941
263. Lell B, Ruangweerayut R, Wiesner J, Missinou MA, Schindler A, Baranek T, Hintz M, Hutchinson D, Jomaa H, Kremsner PG (2003) Antimicrob Agents Chemother 47:735
264. Reichenberger A, Wiesner J, Weidemeyer C, Dreiseidler E, Sanderbrand S, Altincicek B, Beck E, Schlitzer M, Jomaa H (2001) Bioorg Med Chem Lett 11:833
265. Ortmann R, Wiesner J, Reichenberg A, Henschker D, Beck E, Jomaa H, Schilzer M (2005) Arch Pharm Life Sci 338:305
266. Kurz T, Schülter K, Kaula U, Bergmann B, Walter RD, Geffken D (2006) Bioorg Med Chem 14:5121
267. Schülter K, Walter RG Bergmann B, Kurz T (2006) Eur J Med Chem 41:1385
268. Haemers T, Wiesner J, Van Poecke S, Goeman J, Henschker D, Beck E, Jomaa H, Van Calenbergh S (2006) Bioorg Med Chem Lett 16:1888
269. Devreux V, Wiesner J, Jomaa H, Rozenski J, Van der Eycken J, Van Calenbergh S (2008) J Org Chem 72:3783
270. Courtois M, Mincheva Z, Andreu F, Rideau M, Viaud-Massuard MC (2004) J Enzyme Inhib Med Chem 19:559
271. Kuntz L, Trisch D,Grosdemange-Billiard C, Hemmerlin A, Willem A, Bach TJ, Rohmer M (2005) Biochem J 386:127
272. Haemers T, Wiesner J, Giesmann D, Verbrugghen T, Hillaert U, Ortmann R, Jomaa H, Link A, Schilzer M, Van Calenbergh S (2008) Bioorg Med Chem 16:3361
273. Mincheva Z, Courtois M, Andreu F, Rideau M, Viaud-Massuard M-C (2005) Phytochemistry 66:1797
274. Seto H, Kuzuyama T (1999) Nat Prod Rep 16:589
275. Yamato M, Koguchi T, Okachi R, Yamada K, Nakayama K, Kase H, Karasawa A, Shuto K (1986) J Antibiot 39:44
276. Ntai I, Bachmann B (2008) Bioorg Med Chem Lett 18:3068

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Phosphinine Derivatives and their Use as Versatile Intermediates in P-Heterocyclic Chemistry

György Keglevich

Abstract The simplest preparation of 1,2-dihydrophosphinine oxides is based on ring enlargement of 2,5-dihydro-1*H*-phosphole oxides involving the addition of dichlorocarbene on the double-bond of the dihydrophosphole oxide that is followed by the opening of the cyclopropane ring so formed. Variation of the substitution pattern and the extent of saturation of the hetero ring made available a variety of six-membered P-heterocycles, such as 1,4-dihydrophosphinine oxides, 1,2,3,6-tetrahydrophosphinine oxides and 1,2,3,4,5,6-hexahydrophosphinine oxides. 3-P(O)Y_2-Substituted 1,2,3,6-tetrahydrophosphinine oxides obtained by the Michael reaction of 1,2-dihydrophosphinine oxides form another representative group. The 3-P(O)Y_2-tetrahydrophosphinine oxides, along with their saturated derivatives may be useful precursors of bidentate P-ligands. Novel intramolecular interactions were found to determine the conformation of the 3-substituted tetrahydrophosphinine oxides.

The Diels-Alder reaction of 1,2-dihydrophosphinine oxides with dienophiles, such as acetylenic derivatives and maleic acid derivatives affords 2-phosphabicyclo [2.2.2]octadiene and 2-phosphabicyclo[2.2.2]octene 2-oxides that may be regarded as the precursors of low-coordinate, methylenephosphine oxides that are useful in the phosphorylation of O- and N-nucleophiles. It was observed that the photochemically induced fragmentation-related phosphorylation may follow a novel addition–elimination mechanism instead of the "classical" elimination–addition protocol.

The unexpected observation that the interaction of 1-(2,4,6-triisopropylphenyl-1, 2-dihydrophosphinine oxide and dimethyl acetylenedicarboxylate resulted in a

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β-oxophosphorane instead of the expected Diels-Alder cycloadduct prompted us to recognise a new reaction that follows a novel inverse Wittig type protocol. The reaction was found to be of general value, and hence was extended to other 1-aryl substituted P-heterocycles. The mechanism involving an oxaphosphete intermediate was studied by quantum chemical calculations. Application of the microwave technique in the synthesis of β-oxophosphoranes led to neat reactions and high yields of the β-oxophosphoranes.

Keywords 1,2-Dihydrophosphinine oxide, 1,2,3,4,5,6-Hexahydrophosphinine oxide, β-Oxophosphoranes, 2-Phosphabicyclo[2.2.2]octene derivative, 1,2,3,6-Tetrahydrophosphinine oxide,

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1 Introduction

In the last 10–12 years, the importance of the heterocyclic discipline within the organophosphorus chemistry has increased continuously. This is well demonstrated by the book “Phosphorus-Carbon Heterocyclic Chemistry: The Rise of a New Domain” edited by Mathey [1] and by the II and III series of “Comprehensive Heterocyclic Chemistry” published in 1996 and 2008, respectively[2,3], which incorporate a significant segment of P-heterocyclic chemistry.

The research group at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics has been dealing with P-heterocycles for more than two decades. During our work five- and six-membered derivatives (phospholes and phosphinines) were in the focus[4–6]. On the one hand they serve as valuable starting materials in synthetic organic chemistry;

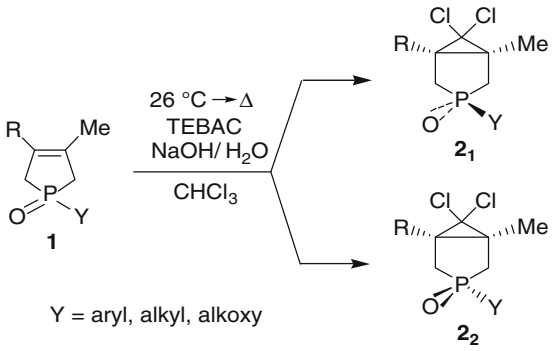
on the other hand their P(III) derivatives may be ligands in transition metal complexes that are potential catalysts in homogeneous catalysis. The seven- and eight-membered bridged P-heterocycles based on phosphole and phosphinine derivatives may be regarded to be precursors of low-coordinated fragments that can be used in phosphorylations[7, 8]. A variety of special P-heterocycles bearing a 2,4,6-trialkylphenyl substituent on the P atom entered into a novel type of inverse Wittig reaction [8, 9]. All the relevant results mentioned above will be discussed in this paper.

An overview is given on the synthesis, reactivity, and properties of six-membered P-heterocycles, such as 1,2-dihydro-, 1,2,3,6-tetrahydro- and 1,2,3,4,5,6-hexahydrophosphinine oxides, as well as bridged P-heterocycles, such as phosphabicyclo[2.2.2]octene derivatives and finally heterocyclic β-oxophosphoranes.

2 Six-Membered P-Heterocycles (Phosphinine Derivatives)

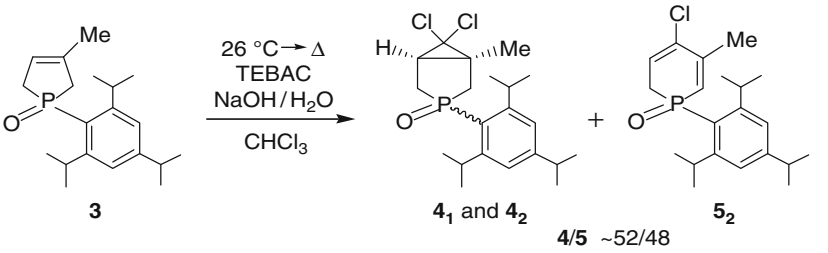
2.1 Ring Expansion of 2,5-Dihydro-1H-Phosphole Oxides to 1,2-Dihydro- and 1,2,3,6-Tetrahydrophosphinine Oxides

Easily available 2,5-dihydro-1*H*-phosphole oxides (**1**) served as excellent starting materials for six-membered P-heterocycles when subjected to ring enlargement. In the first step, dichlorocarbene was added on their double-bond to afford the phosphabicyclohexanes (2), in most cases, as a mixture of two diastereomers ($\mathbf{2}_1$ and $\mathbf{2}_2$) (Scheme 1)[10, 11, 12, 13, 14, 15, 16, 17].



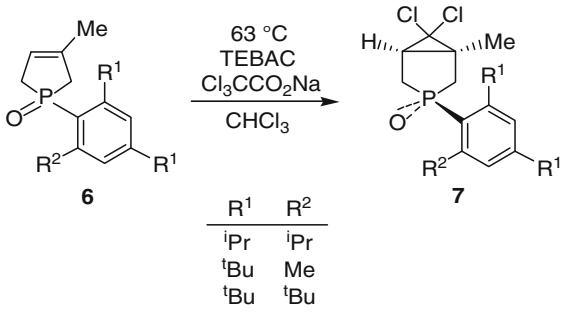
Scheme 1

It was quite interesting that in the case of **3** having a 2,4,6-triisopropylphenyl substituent on the phosphorus atom, partial opening of the cyclopropane ring of the initially formed phosphabicyclohexanes ($\mathbf{4}_1$ and $\mathbf{4}_2$) resulted in the corresponding 1,2-dihydrophosphinine oxide ($\mathbf{5}_2$) (Scheme 2) [18].



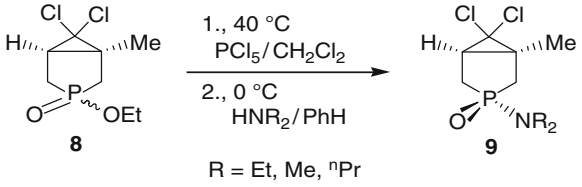
Scheme 2

In the above cases, dichlorocarbene was generated from chloroform under liquid–liquid phase transfer catalytic conditions. Alternatively, sodium trichloroacetate was also used as the precursor of dichlorocarbene as shown by the **6** → **7** transformation (Scheme 3)[16, 18].



Scheme 3

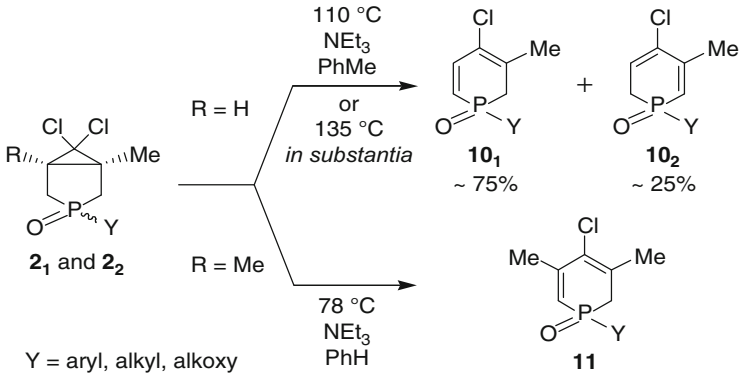
Change in the functional group of phosphinic ester **8** led to phosphinic amide **9** (Scheme 4) [14].



Scheme 4

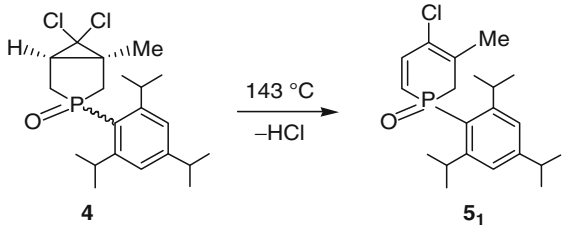
The second step of the ring-enlargement involves opening of the cyclopropane ring of the dichlorocarbene adducts (e.g. $\mathbf{2}_1$ and $\mathbf{2}_2$) simply by heating to afford

1,2-dihydrophosphinine oxides (**10** or **11**) (Scheme 5). The monomethylphosphabicyclohexane oxides (**2**, R = H) can be converted to the 6-ring P-cycles at 110–135 °C, while the dimethyl derivatives (**2**, R = Me) require only heating at 78 °C. Another difference is that in the former case the product is formed as a mixture of double-bond isomers ($\mathbf{10_1}$ or $\mathbf{10_2}$), while in the latter instance there is only one isomer (**11**) (Scheme 5)[12, 13, 15, 16, 17].



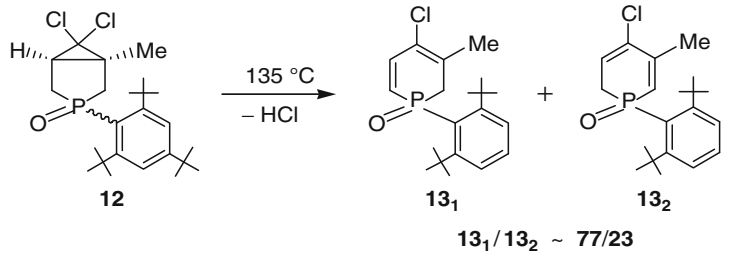
Scheme 5

Again, a peculiarity was observed with the triisopropylphenyl-substituted model compound (**4**): thermolysis of the diastereomeric mixture of **4** gave only a single 1,2-dihydrophospninine oxide ($\mathbf{5_1}$) that was different from the isomer formed during the dichlorocarbene addition shown in Scheme 2 (Scheme 6) [18].



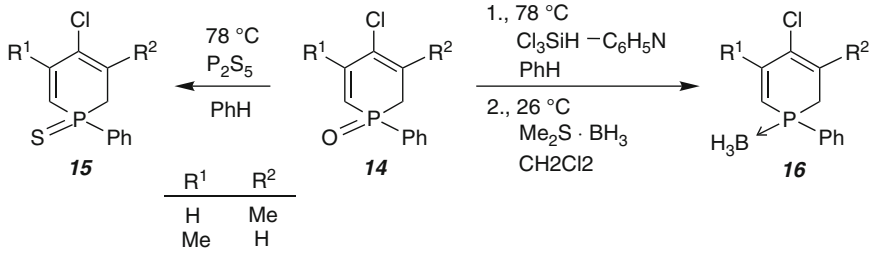
Scheme 6

Thermolysis of the tri-*tert*-butylphenyl phosphabicyclohexane (**12**) led to dihydrophosphinine oxides $\mathbf{13_1}$ and $\mathbf{13_2}$. As can be seen, the opening of the cyclopropane ring was accompanied by the loss of the *tert*-butyl group in position **4** (Scheme 7) [16].



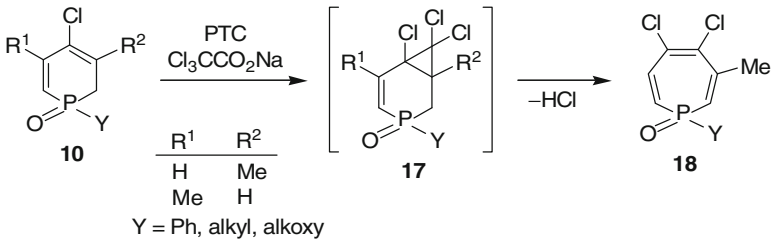
Scheme 7

Changes in the P-functionality of the dihydrophosphinine oxides (**14**) made available phosphine sulfides and phosphine boranes (**15** and **16**, respectively) (Scheme 8)[19, 20].

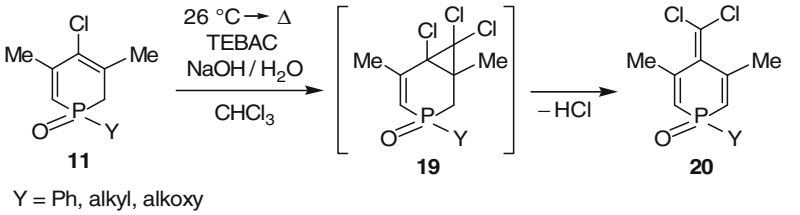


Scheme 8

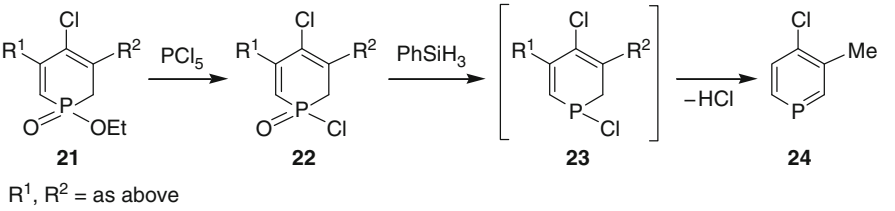
The 1,2-dihydrophosphinine oxides could be further utilized in the synthesis of phosphepine oxides (**18**), 4-dichloromethylene-1,4-dihydrophosphinine oxides (**20**) and aromatic phosphinines (**24**). In the first case, the six-membered ring is expanded further to a seven-membered P-heterocycle (Scheme 9) [21]. In the second instance, where a dimethyl-dihydrophosphinine oxide (**11**) is the starting material, the interaction with a dichlorocarbene unit results in, interestingly, the formation of a dichloromethylene group in position 4 rather than an expansion of the ring (Scheme 10) [17, 22]. To obtain a phosphinine from 1,2-dihydrophosphinine oxides **21**, a three-step aromatization process was elaborated (Scheme 11) [23].



Scheme 9

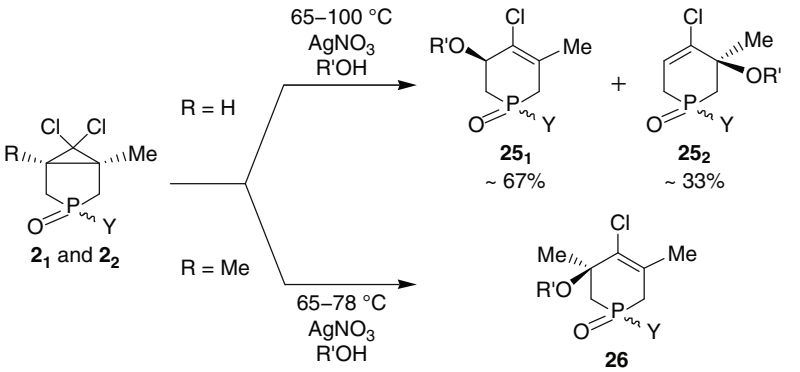


Scheme 10



Scheme 11

Beside the thermal cyclopropane ring opening, another possibility is the solvolytic ring opening in the presence of electrophiles such as silver salts, to afford 3-alkoxy- or 3-hydroxy-1,2,3,6-tetrahydrophosphinine oxides (**25** and **26**, respectively) (Scheme 12)[17, 24]. The monomethyl-tetrahydrophosphinine oxides (**25**) were formed as a mixture of two regioisomers, while the dimethyl derivatives (**26**) were formed as a single regioisomer. All regioisomers mentioned consisted of two diastereomers.



Scheme 12

2.2 Conformation of 1,2,3,6-Tetrahydrophosphinine Oxides

The conformational situation of the tetrahydrophosphinine oxides **25**$_1$ was evaluated on the basis of stereospecific $^3J_{PH}$ NMR coupling constants. In the case of the major regioisomer (**25**$_1$), an equilibrium mixture of two *half-chair* forms was substantiated (Fig. 1) [24].

The conformational situation of the other regioisomer (**25**$_2$) was established in a similar way, but utilising $^3J_{PC}$ coupling constants suggesting an equilibrium shifted towards the *half-chair*$_2$ conformer (Fig. 2) [24].

Conformation of the 1-alkoxy-tetrahydrophosphinine oxides (**25**, Y = alkoxy) was the subject of a separate study. Stereospecific couplings suggested that regioisomers **25**$_1$ and **25**$_2$ adopt the *half-chair*$_2$ conformation. It is quite surprising that the dimethyl derivatives (**26**) exist in the *boat*$_1$ conformation (Fig. 3) [17].

It can be seen that the conformational situation of 1,2,3,6-tetrahydrophosphinine oxides is highly sensitive towards substitution effects.

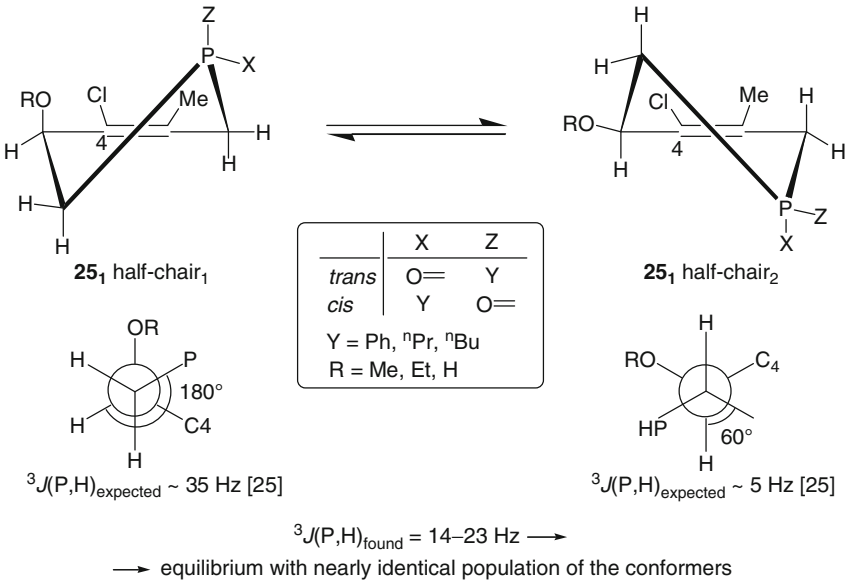


Fig. 1 Conformational equilibrium for tetrahydrophosphinine oxides *25*$_1$

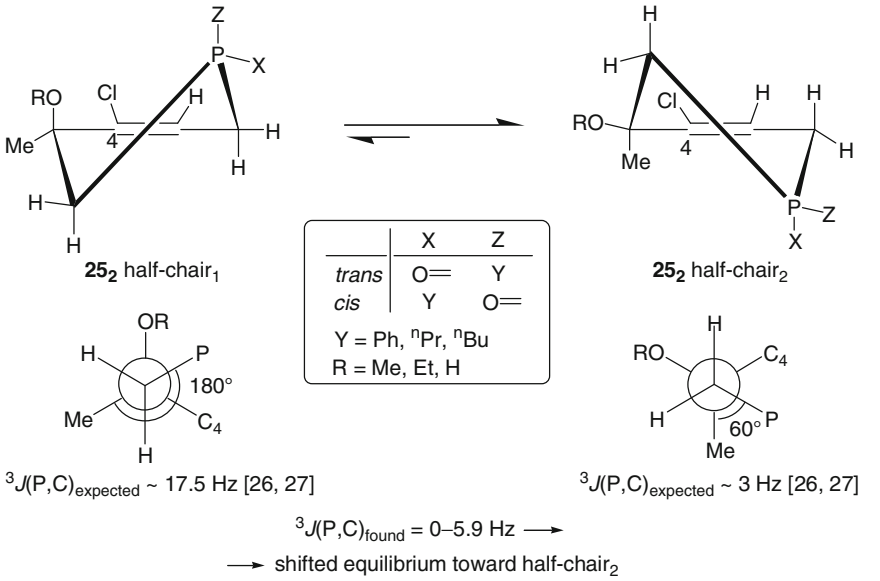


Fig. 2 Conformational equilibrium for tetrahydrophosphinine oxides 25_2

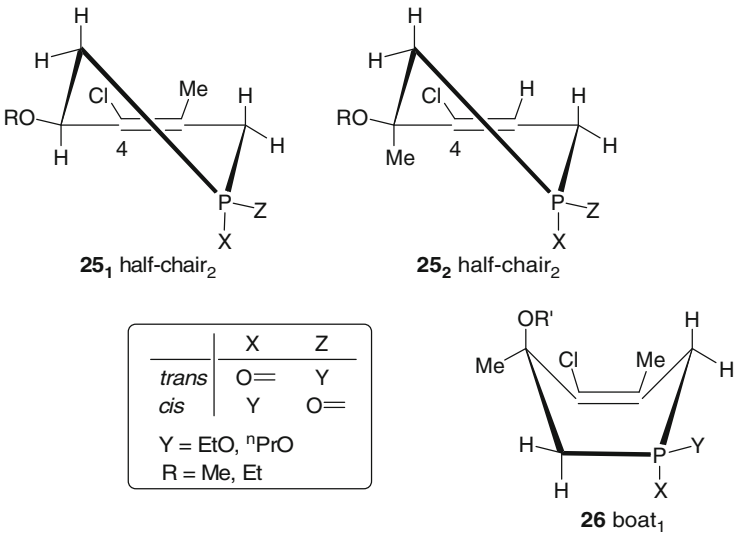
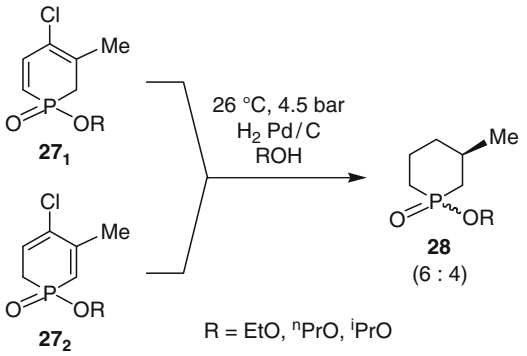


Fig. 3 Conformation of 1-alkoxy-tetrahydrophosphinine oxides 25_1, 25_2 and *26*

2.3 1,2,3,4,5,6-Hexahydrophosphinine- and 1,2,3,6-Tetrahydrophosphinine Oxides by Reductive Approaches

1,2-Dihydrophosphinine oxides served as excellent starting materials to more saturated derivatives. First of all, the dihydrophosphinine oxides (**27**) were subjected to catalytic hydrogenation to furnish diastereomeric mixtures of 1,2,3,4,5,6-hexahydrophosphinine oxides (**28**). The reaction involves reduction of the double-bond and hydrogenolysis of the C–Cl bond (Scheme 13) [28].



Scheme 13

A shifted equilibrium toward the *chair*$_1$ conformer having its skeletal methyl group in the equatorial position was substantiated (Fig. 4) [28].

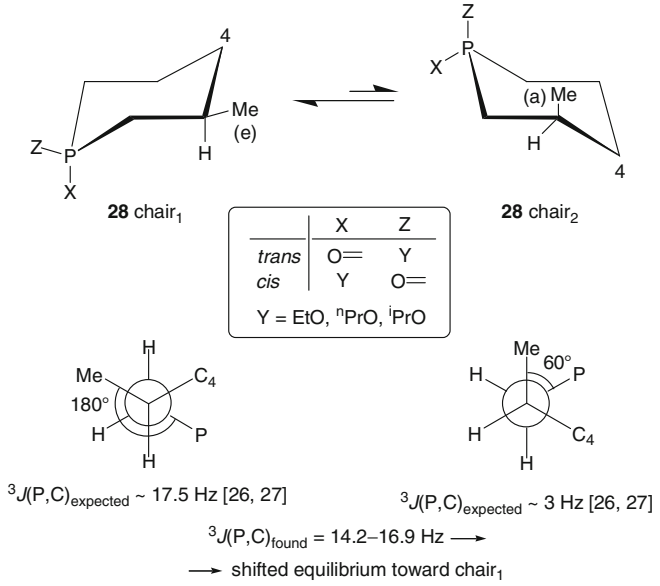
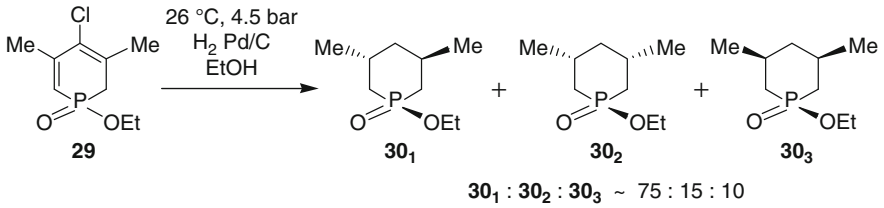


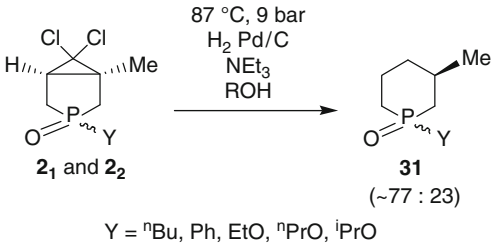
Fig. 4 Conformational equilibrium for hexahydrophosphinine oxides *28*

Catalytic hydrogenation of dimethyl-dihydrophosphinine oxide **29** gave dimethyl-hexahydrophosphinine oxide **30** as a mixture of three isomers ($\mathbf{30}_1$, $\mathbf{30}_2$ and $\mathbf{30}_3$) (Scheme 14) [28].



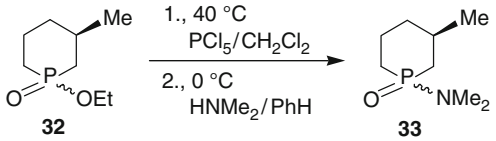
Scheme 14

It is recalled that the dihydrophosphinine oxides (e.g. **10**) are obtained by the thermolysis of phosphabicyclohexane oxides (e.g. **2**). It was also possible to obtain hexahydrophosphinine oxides (**31**) directly from the phosphabicyclohexane oxides (**2**), but somewhat more forcing conditions had to be applied during the hydrogenation (Scheme 15) [29].



Scheme 15

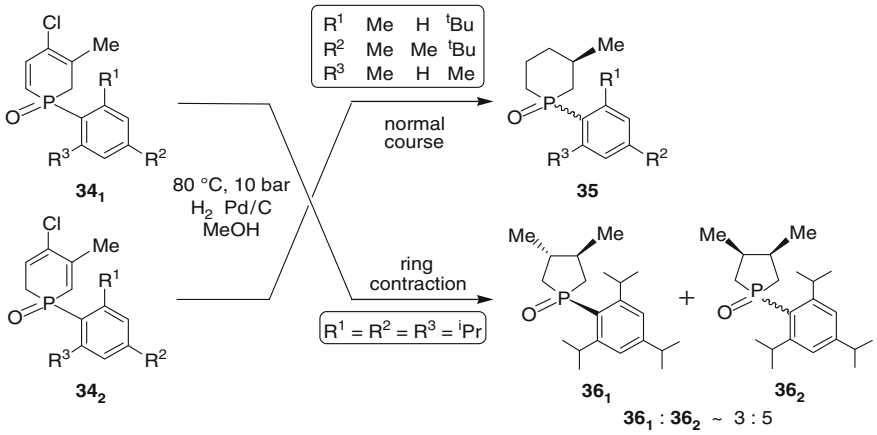
The phosphinic ester (**32**) so obtained was easily converted to an amide derivative **33** (Scheme 16) [28].



Scheme 16

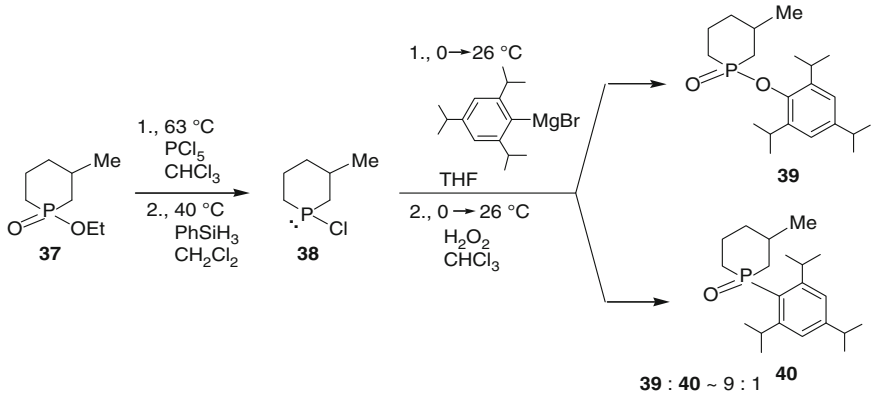
Catalytic hydrogenation of 2,4,6-trialkylphenyl- and 4-alkylphenyl-1,2-dihydrophosphinine oxides (**34**) afforded, in most cases, the expected hexahydrophosphinine oxides (**35**). However, hydrogenation of the triisopropylphenyl starting

material (**34**, $R^1 = R^2 = R^3 = {}^iPr$) gave, surprisingly, a mixture of two dimethylphospholane oxides (**36**$_1$ and **36**$_2$) formed via an unexpected ring contraction reaction (Scheme 17) [16].



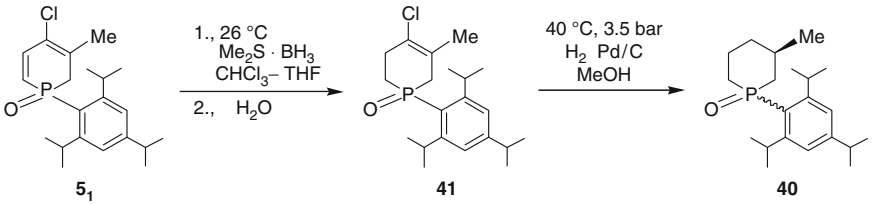
Scheme 17

The preparation of the triisopropylphenyl-hexahydrophosphinine oxide (**40**) required alternative synthetic methods. In the first approach, introduction of the aryl group was attempted by substitution at the phosphorus atom. The 6-ring phosphinate (**37**) was converted to the corresponding phosphinous chloride (**38**) in two steps, whose reaction with the Grignard reagent followed by oxidation led, surprisingly, to a 9:1 mixture of an O-inserted species (**39**) and the desired product (**40**) (Scheme 18) [30].



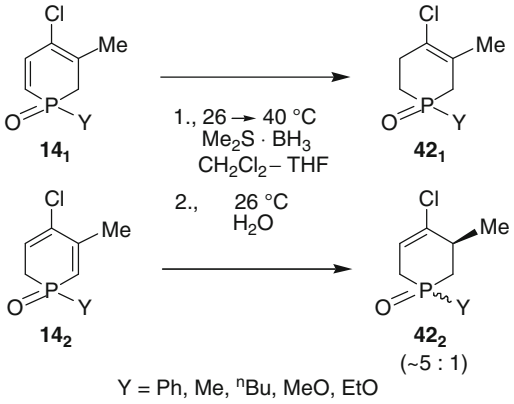
Scheme 18

According to another protocol, the double-bonds of the aryl-dihydrophosphinine oxide (**5**$_1$) were subjected to a stepwise saturation. In the first step, the electron-poor α,β-double-bond of the starting material (**5**$_1$) was reduced via hydroboration. The remaining unsaturation and the chlorine atom in **41** were removed by catalytic hydrogenation. This method was found to be more suitable for the preparation of the triisopropylphenyl-hexahydrophosphinine oxide (**40**) (Scheme 19) [30].



Scheme 19

The 1,2-dihydrophosphinine oxide (**5**$_1$) → 1,2,3,6-tetrahydrophosphinine oxide (**41**) transformation shown in Scheme 19 was found to be of general applicability. A variety of P-substituted dihydrophosphinine oxides (**14**) were converted to tetrahydrophosphinine oxides (**42**) by the addition of borane to the reactive α,β-double-bond followed by hydrolysis of the boryl intermediate so obtained (Scheme 20) [31].



Scheme 20

Product **42**$_1$ (Y = Ph) exists in a *half-chair* conformation, in which the phenyl group is quasi-equatorial (Fig. 5) [31].

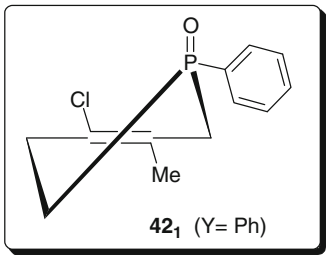
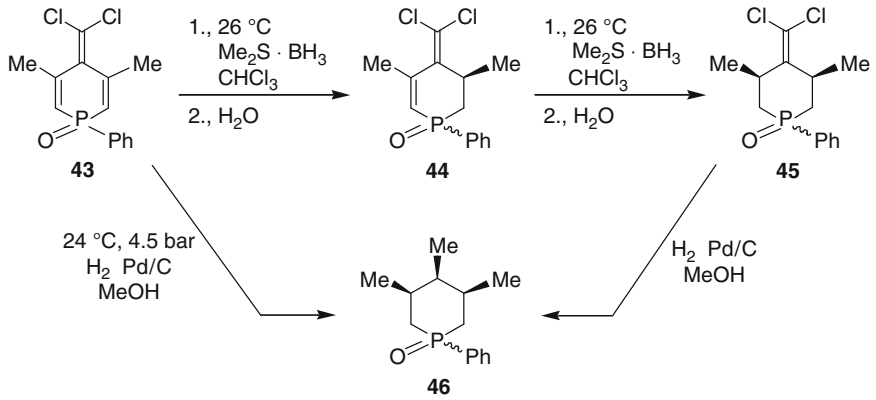


Fig. 5 Conformation of tetrahydrophosphinine oxide 42_1 (Y=Ph)

Selective reduction of electron-poor double-bonds was also extended to a 4-substituted-1,4-dihydrophosphinine oxide (**43**). Its α,β-double-bonds could be reduced step by step to give eventually the 4-substituted hexahydrophosphinine oxide (**45**) that, on catalytic hydrogenation, afforded the corresponding trimethyl-hexahydrophosphinine oxide (**46**). The latter could also be obtained directly from **43** by catalytic hydrogenation (Scheme 21) [32].



Scheme 21

In the chair conformation of **46**, the P-phenyl and the 4-methyl substituents are axial (Fig. 6) [32].

2.4 1,2,3,6-Tetrahydrophosphinine- and 1,2,3,4,5,6-Hexahydrophosphinine Oxides with an Exocyclic P-Moiety

A series of 3-phosphinoxido- and 3-phosphono-1,2,3,6-tetrahydrophosphinine oxides (**47**) was synthesized by the addition of diphenylphosphine oxide and dialkyl phosphites on the electron-poor α,β-double-bond of 1,2-dihydrophosphinine

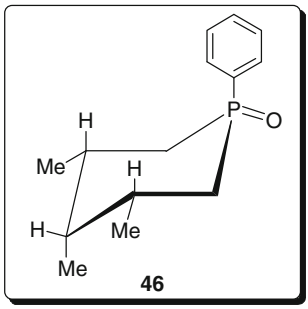
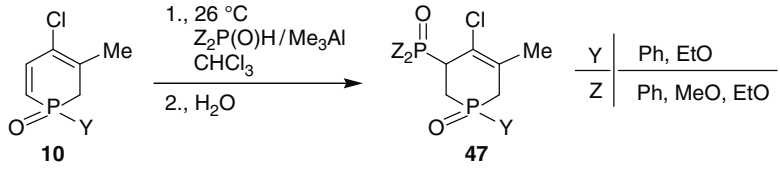


Fig. 6 Conformation of hexahydrophosphinine oxide *46*

oxides (**10**). As a matter of fact, it is the >P(O)$^-$ anion generated from the reagents by trimethylaluminum which adds on the Michael-acceptor. It is noteworthy that the reaction was diastereoselective (Scheme 22)[33, 34].



Scheme 22

Conformation of the 3-P(O)Z_2-tetrahydrophosphinine oxides (**47**) was evaluated, in the first approach, by high level quantum chemical calculations, suggesting that these P-heterocycles prefer adopting one of the *twist-boat* conformations (in the first place *trans*$_1$ or perhaps *cis*$_1$) (Fig. 7) [34].

Weak intramolecular interactions of unusual type were found to stabilize the *twist-boat* conformations. In the 3-diphenylphosphinoxido-1-phenyl-tetrahydrophosphinine oxide (**48**), an interaction between the oxygen atom of the exocyclic P = O-moiety and the suitable hydrogen atom of the C(6)H_2 unit could be observed (marked "A_1"). The same P = O group also interacted with a suitable proton of the P(1)-phenyl substituent (marked "D") (Fig. 8) [34].

The 3-dimethylphosphono-1-phenyl-tetrahydrophosphinine oxide (**49**) is a good example to show two P = O – HC interactions of similar type at the same time. Beside the A_1 interaction, similar to that shown in Fig. 8, there is a similar interaction between the oxygen of the ring P = O and the suitable CH unit of the exocyclic dimethylphosphono moiety (A_2) (Fig. 9) [34].

In this context the most interesting model compound was 3-diethylphosphono-1-ethoxy-tetrahydrophosphinine oxide (**50**), as three different kind of stabilizing

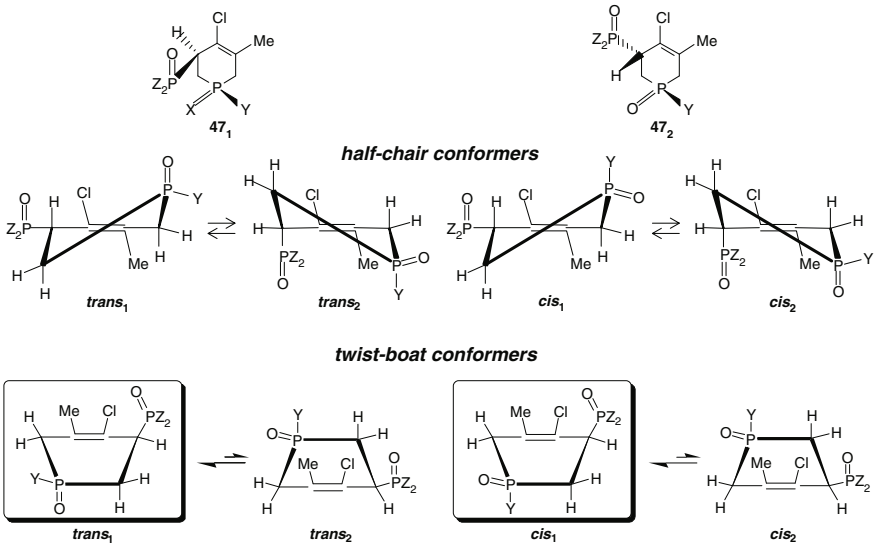


Fig. 7 Possible conformational equilibriums for tetrahydrophosphinine oxides 47_1 and 47_2

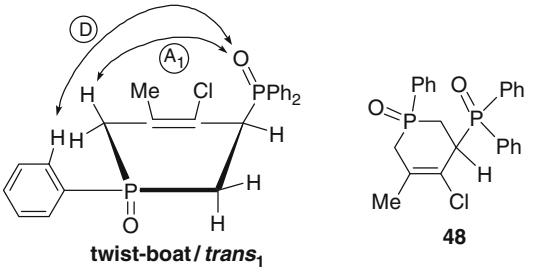


Fig. 8 Intramolecular interactions in tetrahydrophosphinine oxide *48*

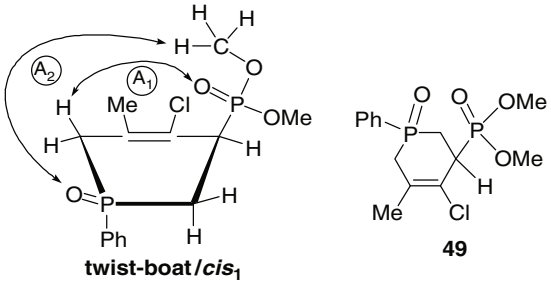


Fig. 9 Intramolecular interactions in tetrahydrophosphinine oxide *49*

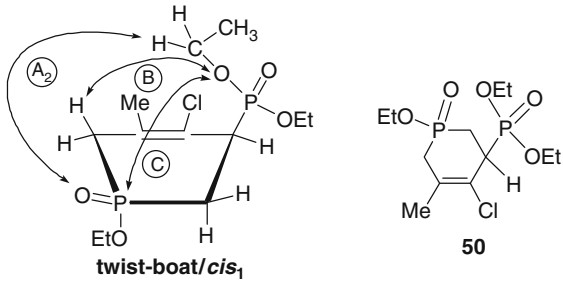
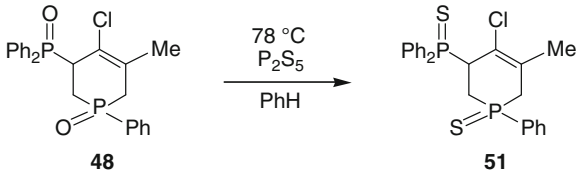


Fig. 10 Intramolecular interactions in tetrahydrophosphinine oxide *50*

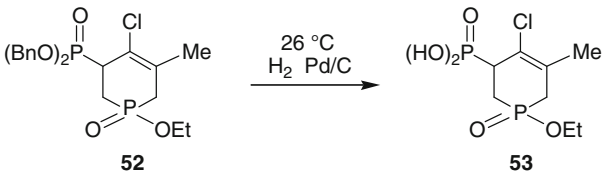
interactions are present in the molecule at the same time. The first is the interaction of A_2 type, while the second and the third are the interactions between the oxygen atom of the alkoxy group of the exocyclic phosphono moiety and a suitable hydrogen of the C(6)H_2 group (B) and the phosphorus atom of the ring P = O (C), respectively (Fig. 10) [34].

The bis(phosphine oxide) (**48**) was useful in the synthesis of 3-diphenylphosphinsulfido-tetrahydrophosphinine sulfide (**51**) in which the same kind of intramolecular interactions found in the analogous dioxide derivative could be established (Scheme 23) [34].



Scheme 23

The dibenzylphosphono-tetrahydrophosphinine oxide (**52**) was transformed into the free phosphonic acid (**53**) by debenzylation that was found to exist in a *half-chair* conformation stabilized by an intramolecular H-bonding (Scheme 24, Fig. 11) [34].



Scheme 24

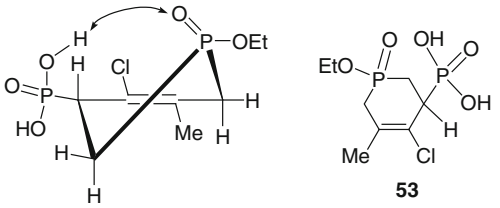


Fig. 11 Intramolecular interaction in tetrahydrophosphinine oxide *53*

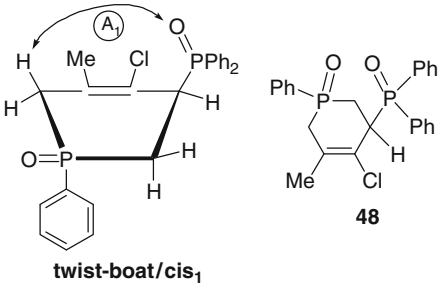
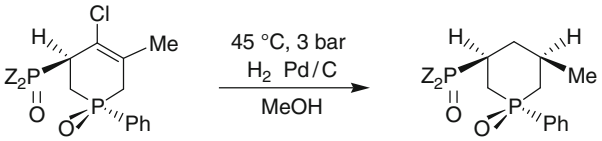


Fig. 12 Intramolecular interaction in the X-ray structure of tetrahydrophosphinine oxide *48*

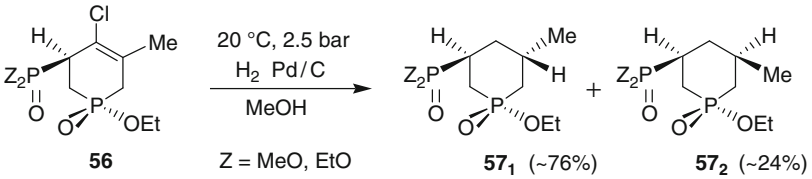
The diphenylphosphinoxido-phenyl-tetrahydrophosphinine-oxide (**48**) was also investigated by single crystal X-ray analysis. The P-heterocycle contained one molecule of crystalline water that served as an intramolecular pincer. The intramolecular H-bonding between the exocyclic P = O and a suitable hydrogen atom of the $C(6)H_2$ suggested by quantum chemical calculations could also be proved experimentally (Fig. 12) [35].

It was found that, on the basis of the configuration of the ring-P atom, the stereostructure corresponds to cis_1 as shown in Fig. 7. Intermolecular interactions holding the tetrahydrophosphinine oxide units together in the crystal could also be observed in the packing diagram.

Catalytic hydrogenation of 1,2,3,6-tetrahydrophosphinine oxides with an exocyclic P-functionality afforded a variety of 3-substituted 1,2,3,4,5,6-hexahydrophosphinine oxides. Saturation of the double-bond and hydrogenolysis of the C–Cl bond took place under unusually mild conditions. The reductions were found to be diastereoselective. Hydrogenation of the 1-phenyl starting materials (**54**) gave the 3-substituted hexahydrophosphinine oxides (**55**) as single diastereomers (Scheme 25). At the same time, reduction of the 1-ethoxy starting P-heterocycle (**56**) furnished the product as a mixture of a major ($\mathbf{57}_1$) and a minor ($\mathbf{57}_2$) stereoisomer (Scheme 26) [36].



Scheme 25



Scheme 26

Stereostructure and conformation of the products (*55* and 57_1) were evaluated on the basis of stereospecific NMR couplings. Regarding the chair conformers, the skeletal-Me of the triphenyl product must be equatorial, while that of the major isomer of the triethoxy product is probably axial (Fig. 13) [36]. Due to the preserved configuration of the C(3)-centre, the 3-P substituent occupies the more favourable equatorial position.

High level theoretical calculations were also carried out to study the possible conformations. On one hand, the above conclusions were confirmed, while on the other hand, position of the P(1)-substituents was also substantiated (Fig. 14) [37].

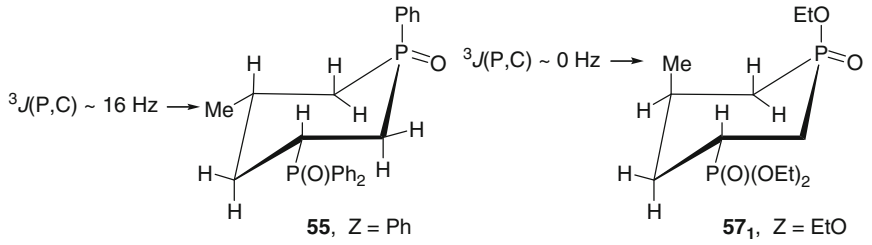


Fig. 13 Conformation of hexahydrophosphinine oxides *55* and 57_1

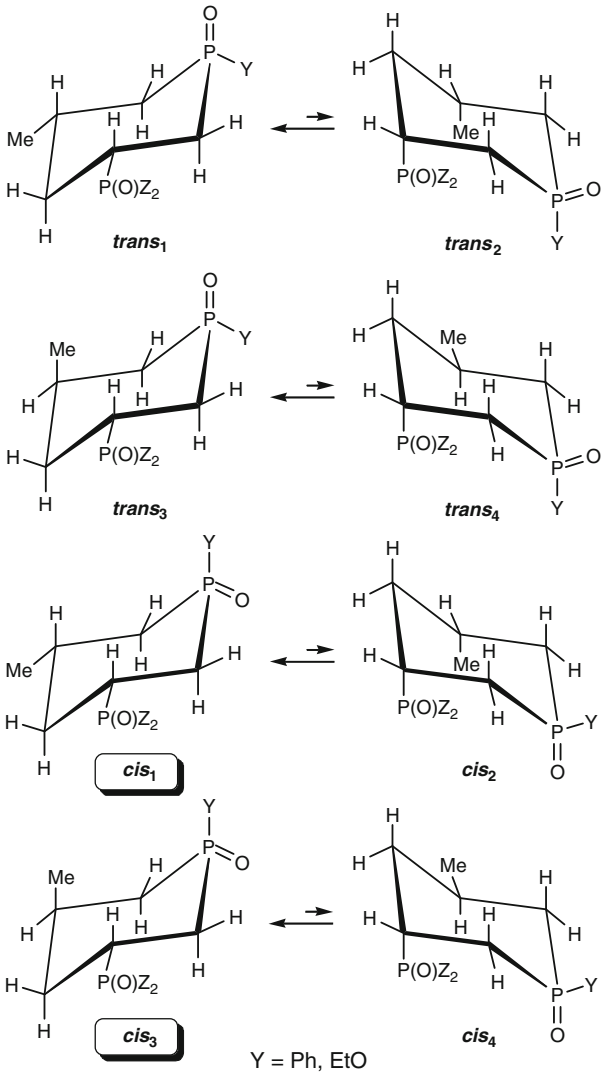


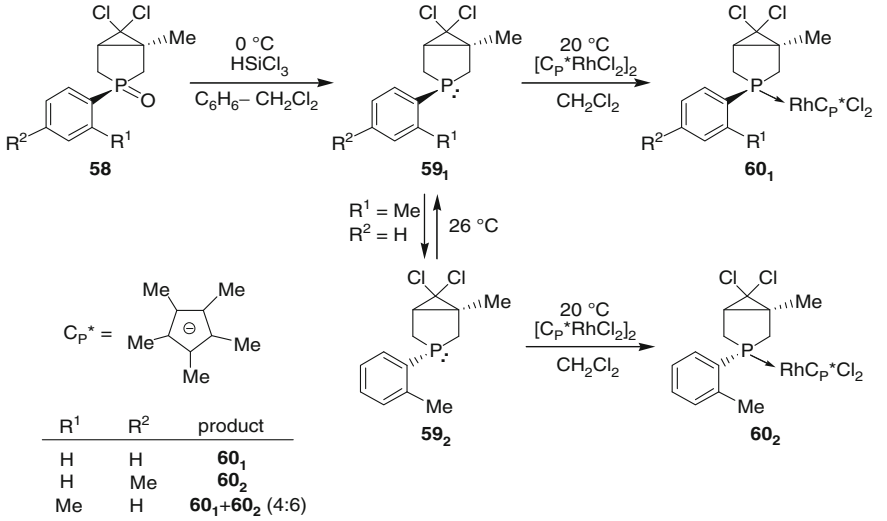
Fig. 14 Conformational possibilities for hexahydrophosphinine oxides *55* and *57*

2.5 P-Heterocycles Within the Coordination Sphere of Transition Metals

Phosphine ligands, including P-heterocyclic entities, are often used in transition metal complexes. The phosphole derivatives are the most widely used heterocyclic P-ligands. In this part the less known transition metal complexes with 6-ring phosphines are summarized.

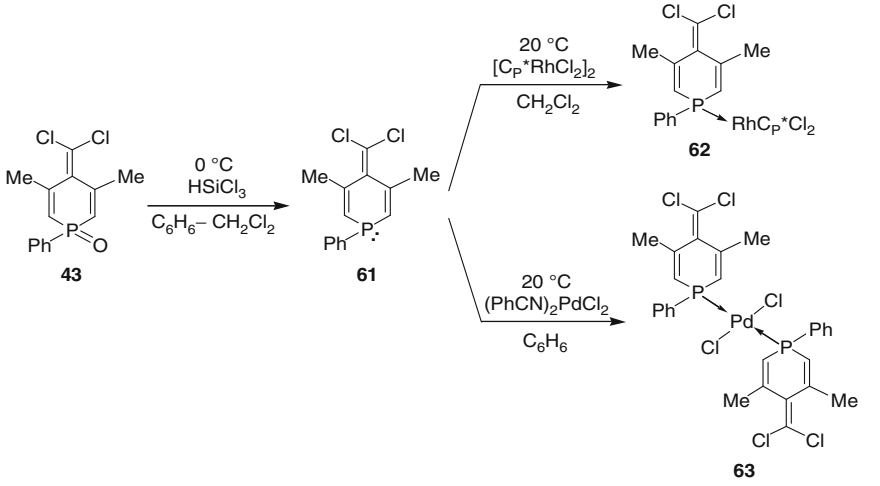
Several aryl phosphabicyclohexane oxides (**58**) were readily deoxygenated to the corresponding phosphines (**59**) with retention of P-configuration. In one case

(**58**, R^1 = Me, R^2 = H), however, an unexpected inversion took place to afford a mixture of two phosphines (**59$_1$** and **59$_2$**). The phosphines (**59$_1$** and **59$_2$**) were reacted with bis[(pentamethylcyclopentadienyl)rhodium dichloride to furnish the corresponding rhodium(III) complexes (**60$_1$** and **60$_2$**) (Scheme 27) [38].



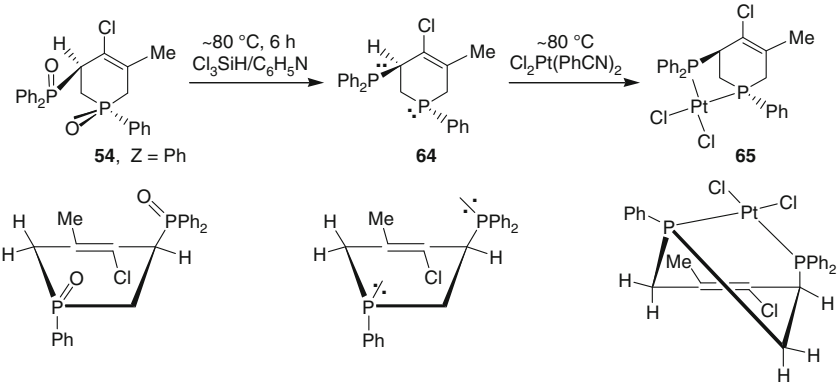
Scheme 27

4-Dichloromethylene-1,4-dihydrophosphinine oxide (**43**) was subjected to a similar sequence of reactions to afford the analogous Rh(III) complex (**62**). In this particular case, the phosphine (**61**) was also utilized in the preparation of a palladium(II) complex (**63**) (Scheme 28. The complexes were tested in the hydroformylation of styrene [38].



Scheme 28

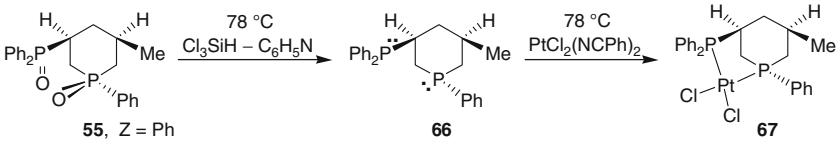
A novel bidentate P-ligand was prepared from the 3-diphenylphosphinoxido-1-phenyl-tetrahydrophosphinine oxide (**54**, Z = Ph) by double deoxygenation. Reaction of the bisphosphine (**64**) so obtained with dichlorodibenzonitrileplatinum (II) afforded *cis* chelate complex **65** (Scheme 29) [39].



Scheme 29

Stereostructures of the bisphosphine (**64**) and the *cis* chelate complex (**65**) were evaluated by quantum chemical calculations.

The 3-diphenylphosphonoxido-1-phenyl-hexahydrophosphinine oxide (**55**, *Z* = Ph) was subjected to a similar sequences of reaction. The *cis* chelate complex (**67**) was obtained in a better yield as the consequence of the more flexible hexahydrophosphinine ring (Scheme 30) [40]. Stereostucture of the diphosphines and the possible complexes was evaluated by calculations.



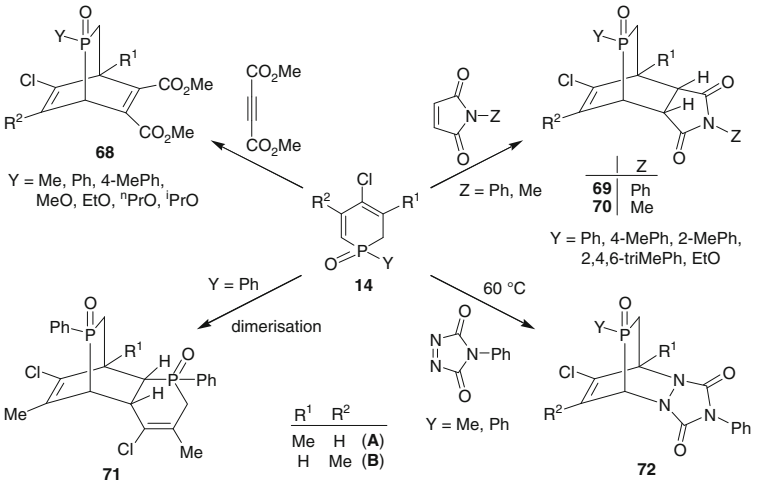
Scheme 30

3 Bridged P-Heterocycles

3.1 Synthesis of Phosphabicyclo[2.2.2]octadiene- and Phosphabicyclo[2.2.2]octene Derivatives

The dihydrophosphinine oxides (**14**) could easily be involved in Diels-Alder reactions with different dienophiles, such as dimethyl acetylenedicarboxylate (DMAD) and maleic derivatives, like *N*-phenylmaleimide to give the corresponding

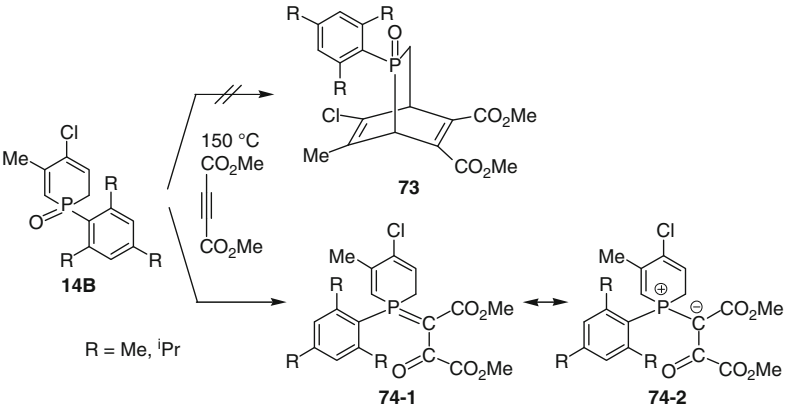
phosphabicyclo[2.2.2]octadienes (**68**)[41, 42, 43] or phosphabicyclooctenes (**69** and **70**)[41, 44, 45], respectively. The cycloadducts were obtained as a mixture of double-bond (**A** and **B**) and P-configurational isomers (Scheme 31).



Scheme 31

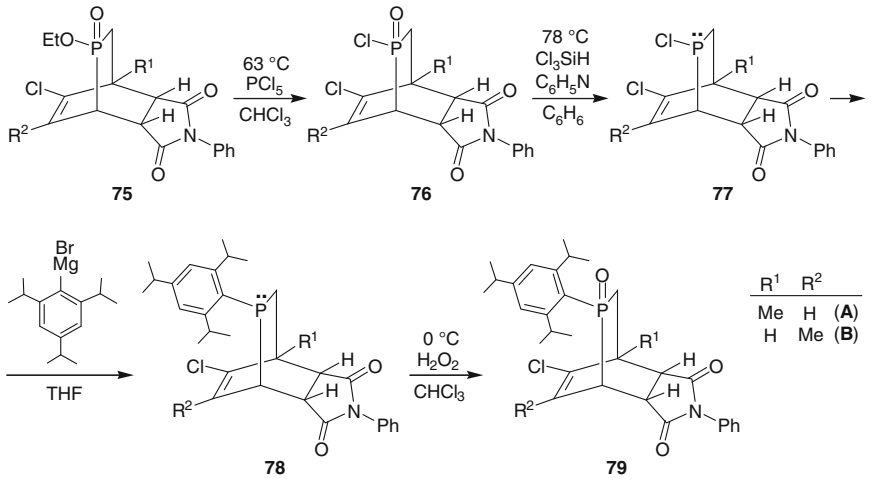
Another unit of the dihydrophosphinine oxide (**14**) was applied as the dienophile in the [4 + 2] cycloaddition yielding dimer **71**[46, 47] (Scheme 31). Reaction of the dihydrophosphinine oxides with 4-phenyl-1,2,4-triazoline-3,5-dione gave 7,8-diazaphosphabicyclo[2.2.2]octenes (**72**) as the first examples of this family of compound (Scheme 31)[45, 48].

It is noteworthy that the trialkylphenyldihydrophosphinine oxide **14B** (R = ^{i}Pr) did not react with DMAD in a [4 + 2] fashion to afford the corresponding phosphabicyclooctadiene (**73**); rather, an isomeric product, phosphorane/ylide **74**, was formed. This novel transformation can be regarded as an inverse Wittig-protocol (Scheme 32)[49, 50].



Scheme 32

Due to steric hindrance in the Diels-Alder reaction, it seemed to be more appropriate to synthesize the P-triisopropylphenyl phosphabicyclooctene (**79**) by an alternative approach involving substitution at the phosphorus atom. The P-ethoxy bridged compound (**75**) was converted to the corresponding phosphinic chloride (**76**) by reaction with phosphorus pentachloride. The oxygen atom of the P = O group was then removed by trichlorosilane to afford phosphinous chloride **77**. Then an aryl group was introduced by Grignard reaction and the phosphine (**78**) so obtained was oxidized to the corresponding phosphine oxide (**79**) (Scheme 33) [45].

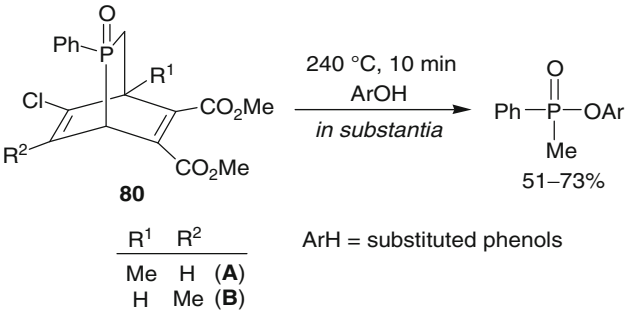


Scheme 33

3.2 Fragmentation-Related Phosphorylations

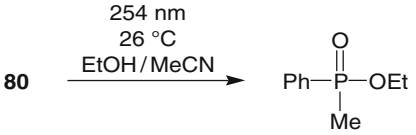
Mathey discovered in 1984 that the phosphabicyclooctadienes acted as precursors for methylenephosphine derivatives [51]. Later on, Quin and Keglevich synthesized series of phosphabicyclooctene oxides and evaluated their fragmentation ability. Thermal examinations revealed that the phosphabicyclooctadiene oxides (**68**) underwent retro-cycloaddition in the range 190–290 °C [52], while the phosphabicyclooctene analogs were fragmented (**69**) in the range 320–440 °C [53]. The higher thermostability of the phosphabicyclooctenes (**69**) is the consequence of their lower ring strain, as compared to that of bicyclooctadienes (**68**).

As thermal examinations suggested, the phosphabicyclo[2.2.2]octadienes were used in thermo-induced fragmentation-related phosphorylations. It was possible to phosphinylate non-volatile phenol and naphthol derivatives by heating their sample with precursor **80** at 240 °C in the absence of any solvent. The esters (PhP(O)(OAr)Me) were obtained in 51–73% yield after chromatography [54] (Scheme 34).



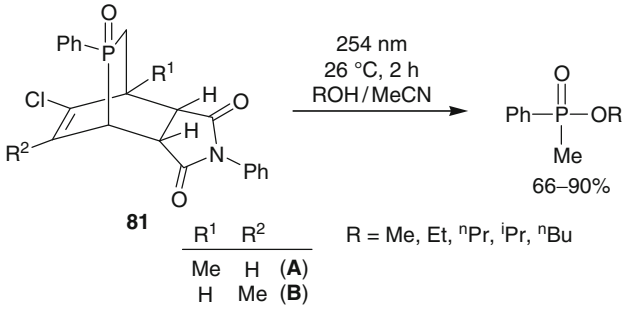
Scheme 34

Under photochemical conditions, the phosphinylated products could be obtained at room temperature. Irradiation of the acetonitrile solution of phosphabicyclooctadiene **80** in the presence of ethanol led to the formation of PhP(O)(OEt)Me (Scheme 35) [43].



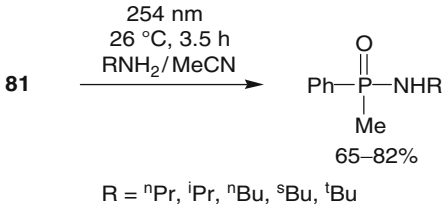
Scheme 35

It was more appropriate to phosphinylate simple alcohols using phosphabicyclo[2.2.2]octene **81** under photochemical conditions (Scheme 36) [44] as the procedure is simple, convenient and gives the phosphinic esters efficiently.



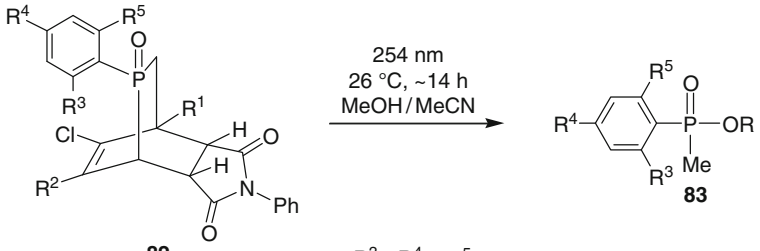
Scheme 36

The above procedure could be extended to the phosphinylation of primary amines using precursor **81**. The phosphinic amides (PhP(O)NHR)Me) were obtained in 65–82% yield after irradiation and purification (Scheme 37) [55]. The secondary amines could be phosphinylated only in low (6–11%) yields that is presumably due to the steric hindrance (see the paragraph on the mechanism below) [55].



Scheme 37

The utilisation of the P-aryl phosphabicyclooctenes in the preparation of the corresponding aryl(methyl)phosphinates (ArP(O)(OR)Me) was of special interest, as these species were mostly new. The *para*- and *ortho*-methylphenyl precursors **82** (R^3 or R^4 = Me, the others H) could well be used in the photoinduced phosphinylation of methanol. The trimethylphenyl- and especially the triisopropylphenyl(methyl) phosphinate was obtained in lower yields after a prolonged reaction time as a consequence of steric hindrance (see the paragraph on the mechanism below) (Scheme 38)[41, 45].



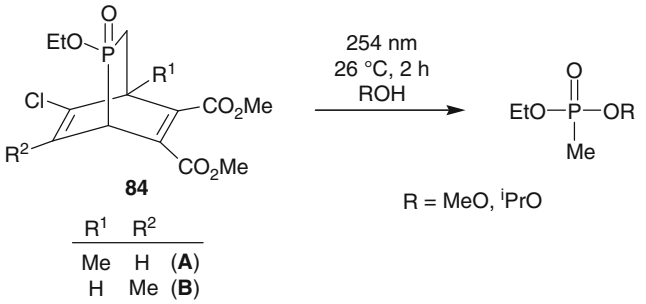
R^1	R^2	
Me	H	(**A**)
H	Me	(**B**)

R^3	R^4	R^5	tr [h]	Yield of **83** [%]
H	Me	H	2	91
Me	H	H	2	87
Me	Me	Me	7	40
iPr	iPr	iPr	14	15

Scheme 38

It is worthy of mention that both the phosphabicyclooctadienes (**68**) and the phosphabicyclooctenes (**69–71**) were used as the mixture of double-bond isomers (**A** and **B**) consisting of P-configurational isomers. The isomeric composition of the precursors (**68–71**) did not, however, affect the outcome of the phosphinylations, as under the conditions of the thermolysis or the photolysis, all four isomers were utilized.

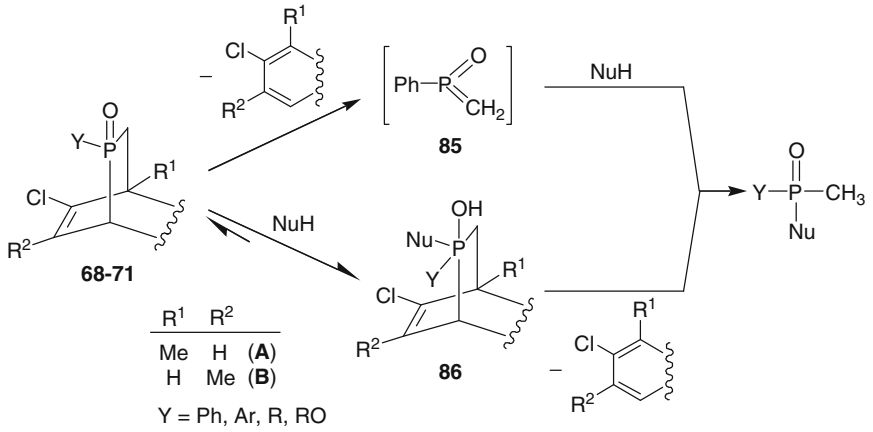
It was a challenge for us to examine the photolysis of the P-ethoxy precursor (**84**) in the presence of alcohols other than ethanol. These reactions provided the corresponding alkyl ethyl methylphosphonate neatly. No alcoholysis was observed to have taken place (Scheme 39) [56].



Scheme 39

3.3 Mechanism of the Fragmentation-Related Phosphorylations

Experimental evidence suggested that, beside the elimination–addition (EA) mechanism involving methylenephosphine oxide (**85**) as the intermediate, another route, an addition–elimination (AE) mechanism, can also be realised in the fragmentation-related phosphorylation of precursors **68–71**. According to this, an intermediate with a pentavalent, pentacoordinated phosphorus atom (**86**) is formed in the rate-determining step by the attack of the nucleophilic agent on the phosphoryl group (Scheme 40) [44].



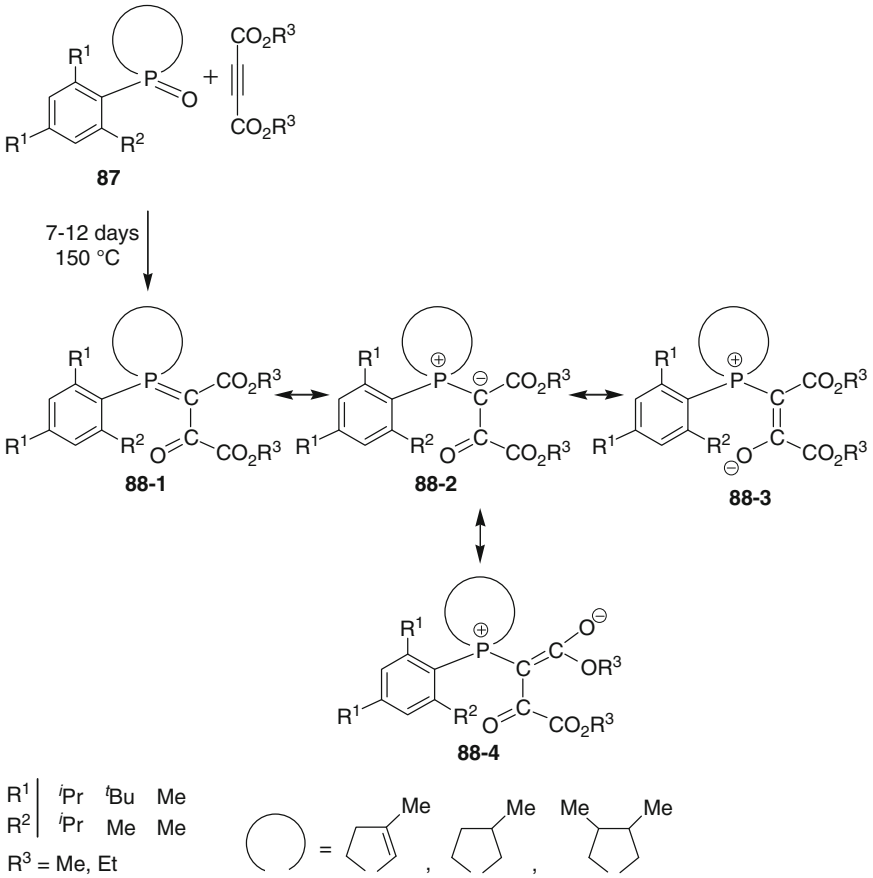
Scheme 40

The novel mechanism was proved by concurrent reactions applying equimolar mixtures of different alcohol pairs. A significant selection in favour of the more nucleophilic species was observed [57].

The results of the photolysis with the phosphabicyclooctenes having sterically demanding trialkylphenyl substituent on the phosphorus atom (**82**) were also consistent with the involvement of a pentacoordinated intermediate. The high sensitivity toward the steric factors underlines the role of the AE mechanism [45].

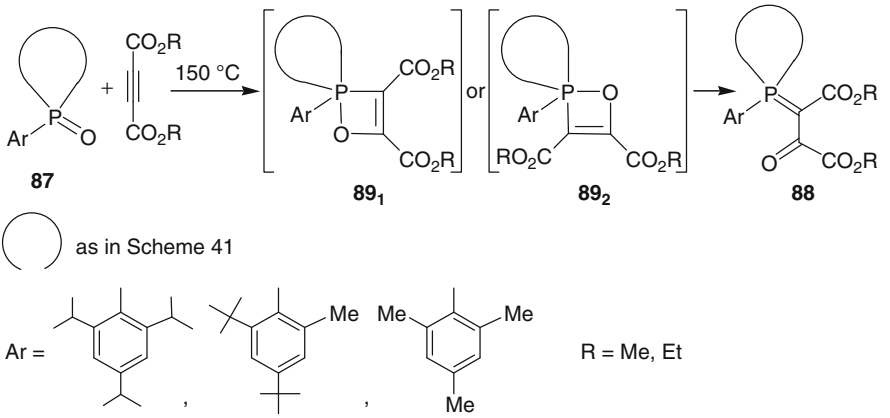
4 β-Oxophosphoranes/Ylides Based on P-Heterocycles

It was found that the interaction of 1,2-dihydrophosphinine oxide **14B** bearing a 2,4,6-trialkylphenyl substituent on the phosphorus atom with dimethyl acetylenedicarboxylate (DMAD) gave, surprisingly, a β-oxophosphorane that can be regarded as a stabilised phosphonium ylide (**74**) (Scheme 32). The reaction proved to be general and took place with 2,3-dihydro- and 2,3,4,5-tetrahydro-1H-phosphole oxides (**87**) as well affording the corresponding β-oxophosphoranes/ylides (**88**, R^3 = Me) (Scheme 41)[58, 59, 60, 61, 62, 63]. As can be seen, the products (**88**) may bear a 2,4,6-triisopropylphenyl-, a 2,4-di-*tert*-butyl-6-methylphenyl-, or a trimethylphenyl group on the phosphorus atom. It was possible to use diethyl acetylenedicarboxylate (DEAD) instead of DMAD as the acetylenic component to furnish bis(diethyl) esters (**88**, R^3 = Et). The bis(alkoxycarbonyl)-β-oxo products (**88**) may exist under four resonating structures, such as phosphorane **88**–**1**, ylide **88**–**2**, enolate **88**–**3** and stabilized ylide **88**–**4**.



Scheme 41

The reaction of cyclic phosphine oxides bearing a 2,4,6-trialkylphenyl substituent on the phosphorus atom (**87**) with DMAD affording phosphorane/ylide **88** was assumed to involve an intermediate of oxaphosphete type (**89**) formed by the [2 + 2] cycloaddition of the P = O group and the acetylenic moiety. Ring opening of the strained oxaphosphete (**89**), that may adopt different conformations (see below), may give the phosphorane/ylide (**88**) (Scheme 42)[60, 61]. This kind of reaction has been observed for the first time by Keglevich et al.



Scheme 42

A careful evaluation by PM3 quantum chemical calculations [64] revealed that the trigonal bipyramid (TBP) around the pentavalent pentacoordinated phosphorus atom of the oxaphosphetes (**89**) was considerably distorted [65]. Two kinds of intermediate could be found; in $\mathbf{89}_1$ the oxygen atom occupies an axial position, while in $\mathbf{89}_2$ the oxygen is equatorial. In both structures ($\mathbf{89}_1$ and $\mathbf{89}_2$), the sterically demanding aryl substituent is in the equatorial position, while both the four-membered and the other hetero ring adopt an apical–equatorial orientation. Possible intermediates $\mathbf{89a}_1$, $\mathbf{89a}_2$, $\mathbf{89b}_1$ and $\mathbf{89b}_2$ are shown in Fig. 15. The heat of formation (H_f) values for the $\mathbf{89b}_1/\mathbf{89b}_2$ pair of conformers obtained by PM3 calculations suggested that the species with an axial oxygen atom ($\mathbf{89b}_1$) is more unstable than the isomer with an equatorial oxygen atom ($\mathbf{89b}_2$). For this, oxaphosphetes $\mathbf{89}_2$ were at first assumed to be the intermediates during the **1**→**2** transformation [9]. In one instance, it was possible to calculate a spirocyclic oxaphosphete by HF/6–31G* ab initio calculations. The possible formation of the oxaphosphetes of type **89** was studied in detail [66]. Factors stabilizing and destabilizing the heterophosphete intermediates were also investigated in general[67, 68]. Applying the B3LYP level of theory, it was found that the oxaphosphetes of type $\mathbf{89}_2$ were destabilized by the effect of antiaromaticity. Hence, oxaphosphetes with an axial oxygen atom ($\mathbf{89}_1$) were assumed to be the real intermediates of the reaction under discussion.

The novel reaction of the trialkylphenyl cyclic phosphine oxides with DMAD via a 1,2-oxaphosphete intermediate can be regarded as an inverse Wittig reaction.

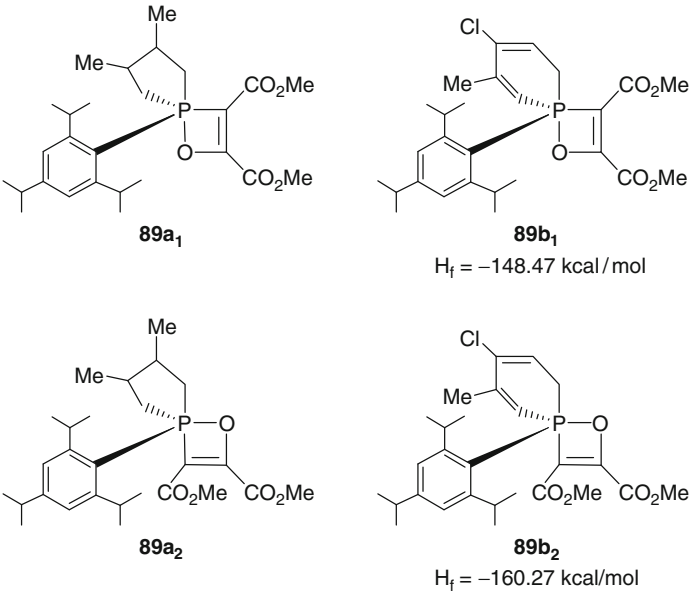


Fig. 15 Possible intermediates in the reaction of cyclic phosphine oxides and dimethyl acetylenedicarboxylate

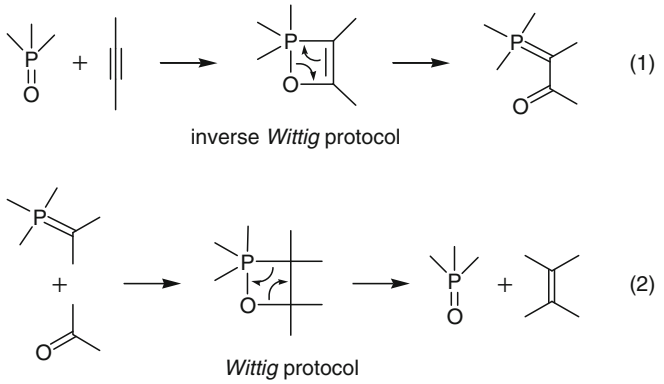


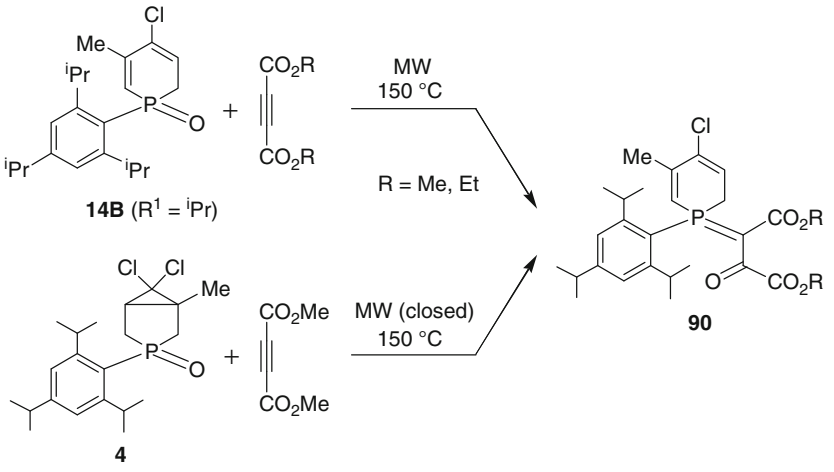
Fig. 16 Comparison of the inverse wittig protocol and the Wittig protocol

Stabilization of the oxaphosphete formed by the cycloaddition of the P = O group and the acetylene moiety involves formally the rupture of the P–O bond and the formation of a P = C and a C = O double-bond (Fig. 16). It is recalled that a Wittig reaction follows the opposite direction; the cycloaddition of a P = C and O = C unit gives a 1,2-oxaphosphetane that is opened up to furnish a phosphine oxide and an olefin (Fig. 16).

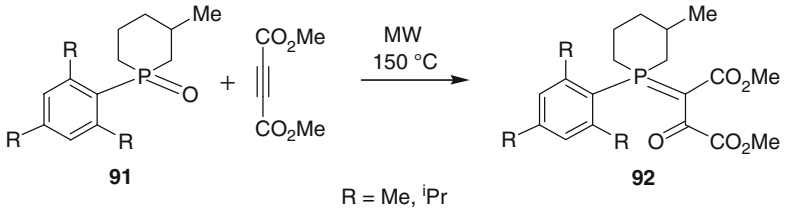
The energy requirement for the opening of the oxaphosphete ring involving the rupture of a P–O bond is considerable (ca 98kcal mol^{-1} bond energy). The driving force for the rearrangement is the relief of the ring strain and the extended delocalisation in the phosphorane/ylide formed.

The 1,2-oxaphosphetes are the unsaturated derivatives of 1,2-oxaphosphetanes, intermediates of the Wittig reaction. Generally, the oxaphosphetanes can only be observed at low temperatures [69].

The prolonged reaction times of 10–14 days at 150 °C could be avoided by the use of the microwave (MW) technique [70]. On MW irradiation, the inverse Wittig type reactions of P-(2,4,6-triisopropylphenyl) cyclic phosphine oxides and dialkyl acetylenedicarboxylates were complete in 3h. Under such conditions, the yield was better and the polymerization side-reactions of the reactants were suppressed. This is exemplified by the inverse Wittig reaction of the corresponding 1,2-dihydrophosphinine oxide (**14B**, R^1 = ^{i}Pr) or 1,2,3,4,5,6-hexahydrophosphinine oxide (**91**, R = ^{i}Pr) to afford β-oxophosphoranes **90** and **92** (R = ^{i}Pr), respectively (Schemes 43 and 44). It was also possible to get product **90** using the phosphabicyclohexane oxide (**4**) as the starting material (Scheme 43). In this case, the opening of the cyclopropane ring preceded the main reaction. The use of the MW technique also made possible the conversion of P-(2,3,6-trimethylphenyl) derivatives (e.g. **91**, R = Me) to the respective β-oxophosphoranes (e.g. **92**, R = Me) (Scheme 44). The trimethylphenyl cyclic phosphine oxides are otherwise unreactive under thermal conditions.



Scheme 43



Scheme 44

References

1. Mathey F, (ed) (2001) Phosphorus-carbon heterocyclic chemistry: the rise of a new domain. Pergamon/Elsevier, Amsterdam
2. Katritzky AR, Rees CW,Scriven EFV (eds) (1996) Comprehensive heterocyclic chemistry II, vols 1–6, 9. Pergamon/Elsevier, Oxford
3. Katritzky AR, (ed) (2008) Comprehensive heterocyclic chemistry III, vol 7. Pergamon/Elsevier, Amsterdam
4. Keglevich G, (1993) Synthesis 931
5. Keglevich G, (1996) Rev Heteroatom Chem 14:119
6. Keglevich G, (2006) Current Org Chem 10:93
7. Keglevich G, Szelke H, Kovács J. (2004) Current Org Synth 1:377
8. Keglevich G, (2002) Current Org Chem 6:891
9. Keglevich G, Forintos H, Körtvélyesi T. (2004) Current Org Chem 8:1245
10. Keglevich G, Petneházy I, Miklós P, Almásy A, Tóth G, Tőke L, Quin LD (1987) J Org Chem 52:3983
11. Keglevich G, Janke F, Fülöp V, Kálmán A, Tóth G, Tőke L (1990) Phosphorus Sulfur Silicon Relat Elem 54:73
12. Keglevich G, Androsits B, Tőke L. (1988) J Org Chem 53:4106
13. Keglevich G, Brlik J, Janke F, Tőke L. (1990) Heteroatom Chem 1:419
14. Keglevich G, Kovács A, Tőke L, Újszászy K, Argay G Czugler M, Kálmán A (1993) Heteroatom Chem 4:329
15. Keglevich G, Vaskó áGy, Dobó A, Ludányi K, Tőke L. (2001) J Chem Soc Perkin Trans 1: 1062
16. Keglevich G, Forintos H, Sipos M, Dobó A, Ludányi K, Vékey K, Tungler A, Tőke L (2001) Heteroatom Chem 12:528
17. Keglevich G, Tőke L, Kovács A, Tóth G, Újszászy K. (1993) Heteroatom Chem 4:61
18. Keglevich G, Keser GyM, Forintos H, Szöll sy á, Ludányi K, Tőke L (1999) J Chem Soc Perkin Trans 1: 1801
19. Keglevich G, Tőke L, Lovász Cs, Újszászy K, Szalontai G. (1994) Heteroatom Chem 5:395
20. Keglevich G, Újszászy K, Szöllősy á, Ludányi K, Tőke L (1996) J Organomet Chem 516:139
21. Keglevich G, Janke F, Brlik J, Petneházy I, Tóth G, T ke L (1989) Phosphorus Sulfur 46:69
22. Keglevich G, Szöllősy á, Tőke L, Fülöp V, Kálmán A (1990) J Org Chem 55:6361
23. Keglevich G, Újszászy K, Kovács A, Tőke L (1993) J Org Chem 58:977
24. Keglevich G, Tóth G, Petneházy I, Miklós P, Tőke L (1987) J Org Chem 52:5721
25. Benezra C, (1973) J Am Chem Soc 95:6890
26. Adiwidjaja G, Meyer B, Thiem J. (1979) Z Naturforsch B Anorg Chem Org Chem 34:1547
27. Quin LD, Gallagher MI, Cuncle GT, Chesnut DB (1980) J Am Chem Soc 102:3136

28. Keglevich G, Kovács A, Újszászy K, Tungler A, Tóth G, Tőke L (1992) Phosphorus Sulfur 70:219
29. Keglevich Gy, Tungler A, Novák T, Tőke L (1996) J Chem Res (S) 528
30. Keglevich G, Sipos M, Lengyel D, Forintos H, Körtvélyesi T, Imre T, Tőke L (2004) Synth Commun 34:4159
31. Keglevich Gy, Böcskei Zs, Újszászy K, Tőke L (1997) Synthesis 1391
32. Keglevich G, Fekete M, Chuluunbaatar T, Dobó A, Böcskei Zs, Tőke L (2000) Synth Commun 30:4221
33. Keglevich G, Sipos M, Imre T, Ludányi K, Szieberth D, Tőke L (2002) Tetrahedron Lett 43:8515
34. Keglevich G, Sipos M, Szieberth D, Nyulászi L, Imre T, Ludányi K, Tőke L. (2004) Tetrahedron 60:6619
35. Czugler M, Körtvélyesi T, Fábián L, Sipos M Keglevich G.y (2007) Cryst Eng Comm 9:561
36. Keglevich G, Sipos M, Körtvélyesi T, Imre T, Tőke L. (2005) Tetrahedron Lett 46:1655
37. Sipos M, Körtvélyesi T, Ujj V, Ludányi K, Vékey K, Tőke L, Keglevich G (2007) Heteroatom Chem 18:747
38. Odinets IL, Vinogradova NM, Lyssenko KA, Golovanov DG, Petrovskii PV, Mastryukova TA, Szelke H, Balázsdi Szabó N, Keglevich G.y (2005) J Organomet Chem 690:704
39. Keglevich G, Sipos M, Szieberth D, Petőcz G Kollár L (2004) J Organomet Chem 689:3158
40. Keglevich G, Sipos M, Ujj V, Körtvélyesi T (2005) Lett Org Chem 2:608
41. Keglevich G, Szelke H, Bálint À, Imre T, Ludányi K, Nagy Z, Hanusz M, Simon K, Harmat V, Tőke L. (2003) Heteroatom Chem 14:443
42. Quin LD, Tang J-S, Keglevich G (1991) Heteroatom Chem 2:283
43. Quin LD, Tang J-S, Quin GyS, Keglevich G (1993) Heteroatom Chem 4:189
44. Keglevich G, Steinhauser K, Ludányi K, Tőke L. (1998) J Organomet Chem 570:49
45. Keglevich G, Szelke H, Tamás A, Harmat V, Ludányi K, Vaskó ÁG Tőke L (2002) Heteroatom Chem 13:626
46. Keglevich G, Kovács J, Ludányi K, Tőke L. (2002) Heterocyclic Commun 8:31
47. Keglevich G, Kovács J, Körtvélyesi T Parlagh Gy, Imre T, Ludányi K, Hegedűs L, Hanusz M, Simon K, Márton A, Marosi Gy, Tőke L. (2004) Heteroatom Chem 15:97
48. Keglevich G, Szelke H, Tőke L. (2001) Heterocyclic Commun 7:365
49. Keglevich G, Körtvélyesi T, Forintos H, Vaskó ÁG Izvekov V, Tőke L (2002) Tetrahedron 58:3721
50. Keglevich G, Forintos H, Körtvélyesi T, Tőke L (2002) J Chem Soc Perkin Trans 1:, 26
51. Deschamps E, Mathey F (1984) J Chem Soc Chem Commun 1214
52. Keglevich G, Újszászy K,Quin LD; Quin GS (1993) Heteroatom Chem 4:559
53. Keglevich G, Steinhauser K, Keserű GM, Böcskei Zs, Újszászy K, Marosi G Ravadits I, Tőke L. (1999) J Organomet Chem 597:182
54. Keglevich G, Szelke H, Dobó A, Nagy Z, Tőke L (2001) Synth Commun 31:119
55. Keglevich G, Szelke H, Nagy Z, Dobó A, Novák T, Tőke L J. (1999) Chem Res 581
56. Szelke H, Ludányi K, Imre T, Nagy Z, Vékey K, Tőke L, Keglevich G.y (2004) Synth Commun 34:4171
57. Jankowski S, Rudzinski J, Szelke H, Keglevich G (2000) J Organomet Chem 595:109
58. Keglevich G, Vaskó ÁG Dobó A, Ludányi K, Tőke L. (2001) J Chem Soc Perkin Trans 1:, 1062
59. Keglevich G, Körtvélyesi T, Forintos H, Tamás A, Ludányi K, Izvekov V, Tőke L. (2001) Tetrahedron Lett 42:4417
60. Keglevich G, Forintos H, Körtvélyesi T, Tőke L. (2002) J Chem Soc Perkin Trans 1:, 26
61. Keglevich G, Körtvélyesi T, Forintos H, Vaskó ÁGy Izvekov V, Tőke L (2002) Tetrahedron 58:3721
62. Keglevich G, Forintos H, Szelke H, Tamás A, Vaskó ÁG Kovács J, Körtvélyesi T, Kollár L, Tőke L. (2002) Phosphorus Sulfur Silicon Relat Elem 177:1681
63. Keglevich Gy, Forintos H, Ujvári A, Imre, T, Ludányi K, Nagy Z, Tőke L (2004) J Chem Res 432
64. Stewart JJP (1995) MOPAC93 (Revision V. 2), Fujitsu Ltd., Tokyo

65. Keglevich G, Körtvélyesi T, Forintos H, Lovas S (2002) J Chem Soc Perkin Trans 2:, 1645
66. Keglevich G, Körtvélyesi T, Ujvári A, Dudás E (2005) J Organomet Chem 690:2497
67. Mucsi Z, Körtvélyesi T, Viskolcz B, Csizmadia IG, Novák T, Keglevich G (2007) Eur J Org Chem 2007:1759
68. Mucsi Z, Hermecz I, Viskolcz B, Csizmadia I G, Keglevich G (2008) Tetrahedron 64:1868
69. Vedejs E, Marth CF (1994) In: Quin LD,Verkade JG (eds) Phosphorus-31 NMR spectral properties in compound characterization and structural analysis. VCH, New York, Chap. 23, p 297
70. Keglevich G, Dudás E, Sipos M, Lengyel D, Ludányi K (2006) Synthesis 1365

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Spiro- and Tricyclic Phosphoranes with Six- and Higher-Membered Rings

K.C. Kumara Swamy, M. Phani Pavan, and Venu Srinivas

Abstract This article presents developments in synthetic and structural aspects of tetra-, penta-, and hexacoordinate spirocyclic phosphoranes that involve primarily a 1,3,2-dioxaphosphorus heterocyclic skeleton and lie at the border between traditional organic and inorganic chemistry. Studies on these systems have made us rethink the traditional tenets on structural preferences in pentacoordinate phosphorus chemistry. Some compounds have a bearing on the mechanism of the Mitsunobu reaction while others are useful as chiral resolving agents or strong phosphazenic bases.

Keywords Hypervalency, Mitsunobu reaction, Pentacoordinate phosphoranes, Phosphazenic base, Spirocyclic

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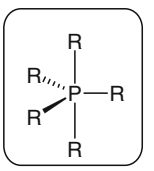
1 Introduction

According to Corbridge [1], compounds with five ligands around P atom (e.g., **1**) are generally called phosphoranes, and anionic hexacoordinate phosphorus compounds are called phosphorides or phosphates. Many neutral pentavalent tri- or tetracoordinate compounds (e.g., **2–6**) are also often given the name phosphoranes [2–6]. In this review, we restrict ourselves to cyclic phosphorus heterocycles possessing the general structures **7–9.** Relative to acyclic systems, cyclic compounds are generally more stable and hence are more amenable for detailed studies. Although numerous compounds with phosphorus as a part of a five-membered ring have been known for a long time, structural and conformational studies on those possessing six- and higher-membered rings are restricted mostly to the past two decades. Such knowledge has greatly enhanced our understanding of pentacoordinate molecules, with a necessity to modify some of the proposed tenets on ligand (group) preferences in trigonal bipyramidal geometry. The latter studies have some significance since numerous chemical and biochemical reactions (e.g., action of cyclic AMP) centered at phosphorus take place via pentacoordination. Since phosphonium salts are the ionic isomers of the pentacoordinate phosphoranes, we believe that inclusion of tetracoordinate spirocyclic compounds is in order and hence they are briefly discussed. Furthermore, if there is a donor atom on the ring, phosphorus can increase its coordination number to six; therefore, spirocyclic phosphoranes of this type are also discussed in this presentation.



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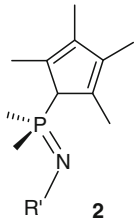
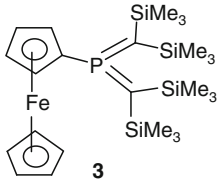


2

P-cyclopentadienyl-iminophosphorane



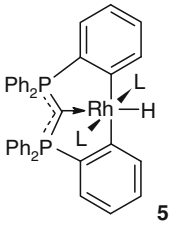
3

Ferrocenylbis(ylene) phosphorane

n-$Bu_3P{=}C(CO_2Me)_2$

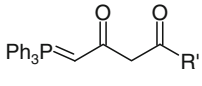
4

Dimethylmalonyl tributylphosphorane



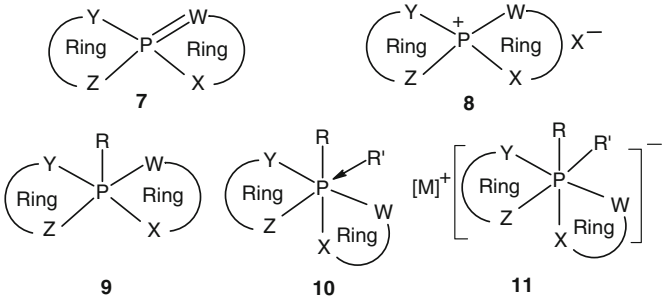
5

Rhodium hexaphenylcarbodiphosphorane complex



6

(2,4-Dioxobutylidine) phosphorane

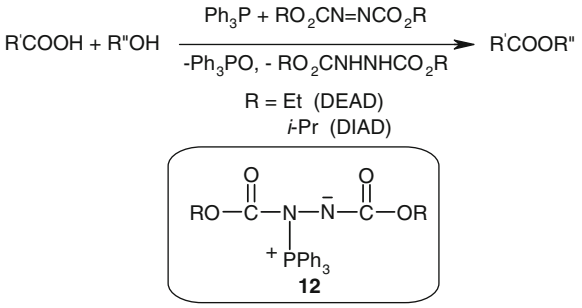


[Criterion: Size of at least one ring ⩾6]

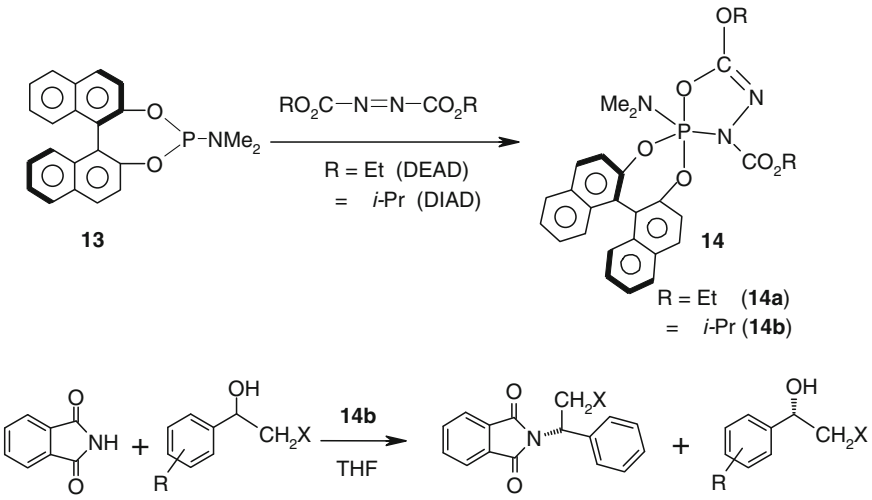
Anionic tricyclic phosphoranes (also called phosphates) are not too large in number, but are included for the sake of comparison with their neutral analogs. As pointed out by Holmes, the coordination tendencies of phosphorus to form a hexacoordinate state from a pentacoordinate state might assist in describing the mechanistic action of phosphoryl transfer enzymes [7]. Synthesis of a large number of cyclic phosphoranes most often involves oxidative addition to a P^{III} precursor and only in a few cases is a direct substitution reaction using PX_5 involved. The discussion herein is primarily related to synthetic and structural features and wherever possible the relevance of the compounds to existing methodologies or concepts will be highlighted.

2 Reaction of Cyclic P^{III} Compounds with Azodicarboxylates: a Convenient Route to Spirophosphoranes

The triphenylphosphine (Ph_3P)-diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD)-mediated esterification of an acid with clean inversion of configuration for asymmetric alcohols, known as the Mitsunobu reaction, has been widely used in a variety of synthetic applications (Scheme 1) [8, 9]. The accepted mechanism for this reaction involves the Morrison–Brunn–Huisgen (MBH) betaine **12** as a key intermediate. Recently, this betaine has also been exploited for the generation of a wide variety of pyrazole heterocycles [10–12]. However, earlier reports also suggested that species other than **12**, in particular pentacoordinate phosphoranes, were formed when the P^{III} substrates were different [13, 14]. For example, it was shown that binaphthol-derived precursor **13** reacted with DEAD/DIAD to yield the pentacoordinate phosphorane **14**, and not the betaine **12** (Scheme 2) [15, 16]. It was also shown that compound **14** participated in the Mitsunobu coupling between alcohol and a nucleophile such as an acid or phthalimide.

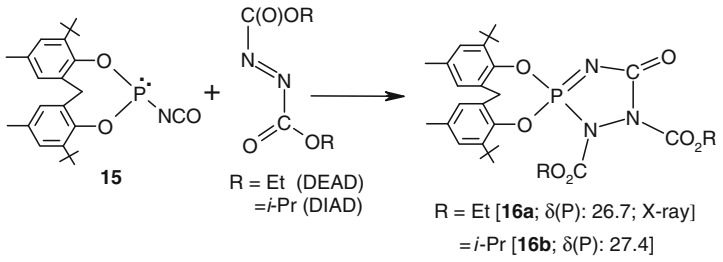


Scheme 1 Mitsunobu esterification reaction



Scheme 2 Involvement of pentacoordinate phosphorane in Mitsunobu reaction

Thus, it is apparent that the reaction of P^{III} compounds with DIAD/DEAD depends on the substituents present on the phosphorus. To uncover the structural details of species of type **12**, as well as to find alternatives to Ph_3P, a lot of effort has been put in during the last few years using a phosphocin–heterocyclic P^{III} system that tends to give fairly stable crystalline products. In one such example, the isocyanate, CH_2(6-*t*-Bu–4-Me–$C_6H_2O)_2$P–NCO (**15**) was treated with DEAD/DIAD. The resulting compounds were spirocyclic iminophosphoranes **16a–b** (Scheme 3), whose structures are different from either **12** or **14** [17].



Scheme 3 Formation of five-membered heterocycles **16a-b**

The ^{31}P NMR spectra of the reaction leading to **16b** recorded over a period of time revealed interesting features (Fig. 1). After 15 min of the addition of DIAD to a solution of **15** in C_6D_6, a peak at δ(P) –64.9 in the pentacoordinate region was observed along with the peak at δ(P) 28.6 in the tetracoordinate region [18][1]. After 25 min, the intensity of the downfield peak at δ(P) 28.6 increased at the cost of the upfield peak; after 35 min, the downfield peak at δ(P) 28.6 corresponding to **16b** was the most dominant one. The slight difference in δ(P) values in $CDCl_3$ (δ 27.4) and C_6D_6 (δ 28.6) is likely to be due to solvent effects. These results suggested that a pentacoordinate intermediate may also have been involved in the formation of **16b** (Scheme 4). This statement is also corroborated by the isolation of pentacoordinate

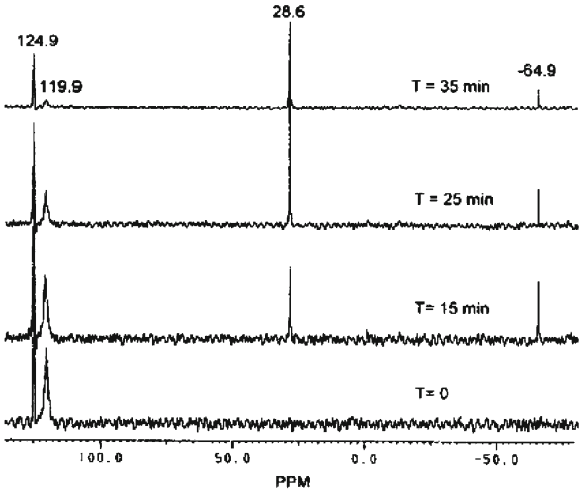
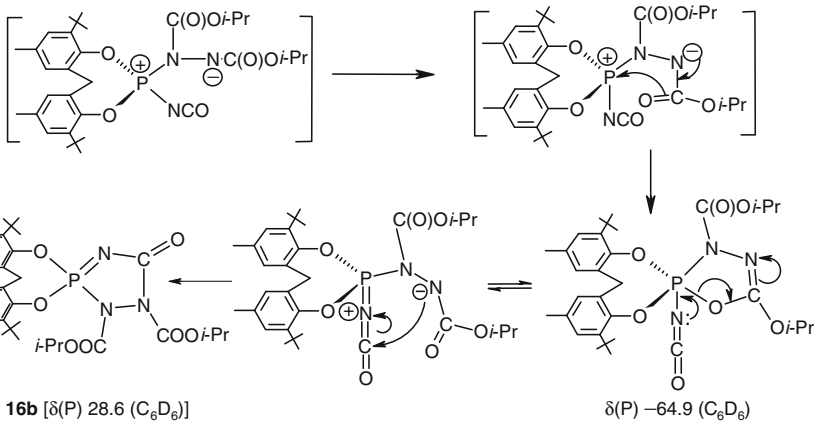


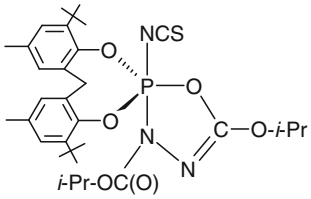
Fig. 1 ^{31}P NMR spectra recorded over a period of time during the formation of **16b** in benzene–d_6 (two signals for the precursor **15** are likely due to isomers)

[1] The P^{III} precursor **15** showed two peaks at 119.9 (broad, major) and 124.9 (sharp, minor) in solution probably due to isomers resulting from different conformations of the eight-membered phosphocin ring.



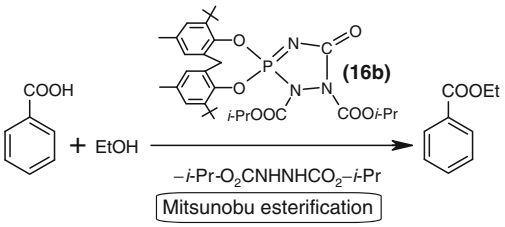
Scheme 4 Possible pathway for the formation of the heterocycle **16b**

isothiocyanate compound, [CH_2(6-*t*-Bu–4-Me–C_6H_2O)$_2$P{N(CO_2-*i*-Pr)NC(O-*i*-Pr)O}]-(NCS) (**18**) from analogous reaction of CH_2(6-*t*-Bu–4-Me–C_6H_2O)$_2$P–NCS (**17**) with DIAD [19]. The difference in the reactivity of this isothiocyanate and of the isocyanate probably stems from a better charge separation at the C=O end in the latter compared to the C=S end in the former.



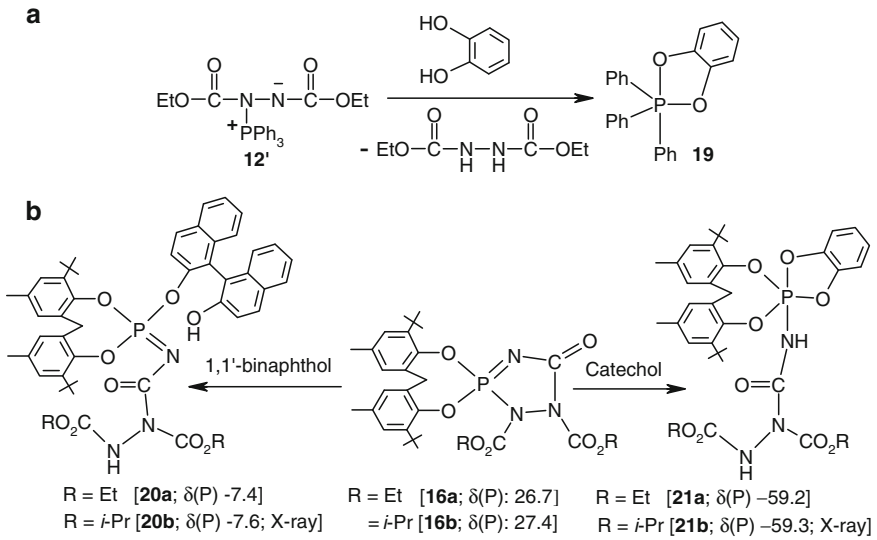
18

Interestingly, despite having a structure different from the betaine **12**, compound **16b** does participate in the Mitsunobu coupling between ethanol and benzoic acid (Scheme 5) [19], suggesting that the five-membered heterocycle is in equilibrium with the betaine form.



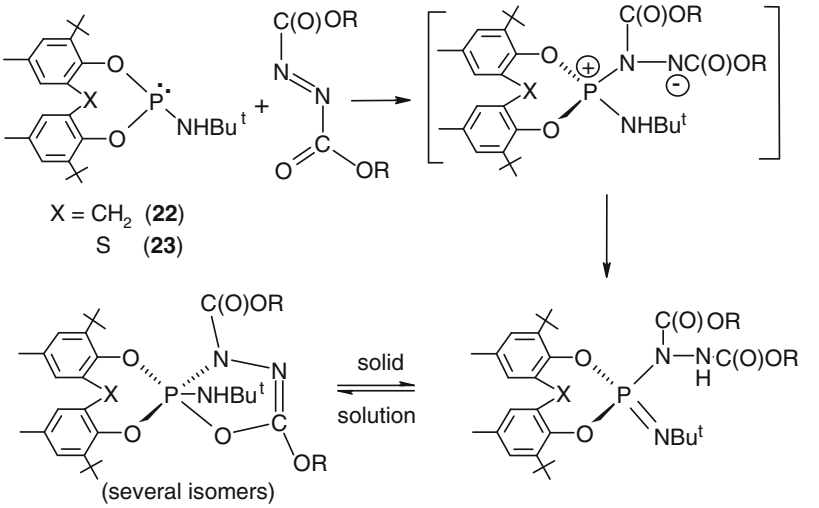
Scheme 5 Involvement of **16b** in the Mitsunobu reaction

In an earlier work, Trippett and coworkers used the betaine **12′** as a precursor to various pentacoordinate phosphoranes (see Scheme 6) [20]. In these reactions, DEAD was converted to the hydrazine derivative $EtO_2CNHNHCO_2Et$ and the pentacoordinate compound $Ph_3P(1,2\text{-}O_2C_6H_4)$ (**19**) was formed. By contrast, compounds **16a–b** underwent a two-step addition depending on the diol [17]. First, the P–N single bond was cleaved and then addition across the P=N double bond took place. When 1,1′-bi-2-naphthol was used, the reaction stopped at the first stage to lead to tetracoordinate compounds **20a–b**. When catechol was used, the addition across the P=N bond also took place to lead to the spirocyclic pentacoordinate phosphoranes **21a–b**. These reactions are shown in Scheme 6b. The structures of **20b** and **21b** were confirmed by X-ray crystallography. The ^{31}P NMR spectra of **20a–b** and **21a–b** were, respectively, in the expected tetra- and pentacoordinate regions.



Scheme 6 Comparison of the reactivity of **12** with that of **16a-b**

The reaction of *t*-butylamino phosphorimidite $X(6\text{-}t\text{-}Bu\text{-}4\text{-}Me\text{-}C_6H_2O)_2PNH\text{-}t\text{-}Bu$ [X = CH_2 (**22**), S (**23**)] with DEAD and DIAD afforded compounds with composition $[X(6\text{-}t\text{-}Bu\text{–}4\text{-}Me\text{–}C_6H_2O)_2P(N\text{-}t\text{-}Bu)\{N(CO_2R)NH(CO_2R)\}]$ [X = CH_2, R = Et (**24a**), *i*-Pr (**24b**); X = S, R = Et (**25**)] (Scheme 7) as shown by ^1H and ^{31}P (solution and solid) NMR as well as elemental analyses [17]. Compound **25** was characterized by X-ray crystallography, which clearly showed (i) a strong P=N(*t*-Bu) bond [P–N 1.464(4) Å], and (ii) the carbamate-type linkage –NH–C(O) OR as a hydrogen-bonded dimer through the NH and the C=O moieties. The ^{31}P NMR [$C_6D_5CD_3$] chemical shifts of compounds **24a–b** and **25** are, however, in the pentacoordinate region. What is more, the low temperature ^{31}P NMR spectra of **24a**

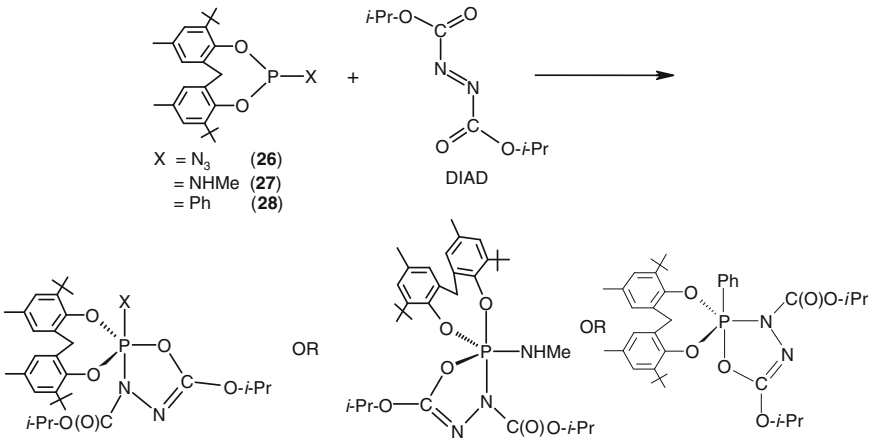


X = CH_2, R = Et [**24a**; δ(P) –56.4 (room temp.), –48.4,–50.3,–53.4, –54.2 (242 K)]
X = CH_2, R = *i*-Pr [**24b**; δ(P) –57.6 (room temp.)]
X = S, R = Et [**25**; δ(P) –56.3 (room temp.),–10.5, –53.5, –55.7, –56.9 (255 K)] (X-ray)

Scheme 7 Formation of compounds **24a-b** and **25**

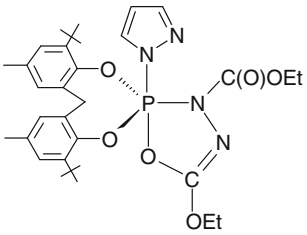
and **25** showed four different signals [**24a** (242 K): δ –48.0, –50.3, –53.4, –54.2; **25** (255 K) –50.5, –53.0, –55.7, –56.9; reversible to single broad peak at room temperature], suggesting the presence of four distinct isomers. Such isomerism is possible only for spirocyclic pentacoordinate isomers (shown in Scheme 7). This is the first ever observation of four distinct phosphoranes in solution.

In contrast to the above, the more commonly isolated products are the pentacoordinate spirocyclic phosphoranes **29–32** if one uses P^{III} precursors **26–28** with at least two oxygen atoms connected to phosphorus (Scheme 8). In the structures of **18** and **29,** the eight-membered ring spans diequatorial positions and the five-membered ring spans apical–equatorial, allowing the fifth acyclic group to occupy the remaining apical position. In **30**, the NHMe occupies an equatorial position with both the eight- and the five-membered rings spanning apical–equatorial positions. In the phenyl compound **31**, although the phenyl group is apical, the eight-membered ring is diequatorial and the five-membered ring occupies apical–equatorial orientation with the nitrogen (of the five-membered ring) in an apical position. This nitrogen was equatorial in **18** and **29**. Thus, the less-electronegative nitrogen atom rather than the oxygen atom in the five-membered ring occupies the apical position in **18**, **29**, and **30**. In **31**, a carbon occupies an apical position in preference to an oxygen atom of the eight-membered ring. Compound **32,** prepared by a similar route, also has the pyrazolyl nitrogen at the apical position. Thus, all these compounds show the phenomenon of "reversed apicophilicity" for trigonal bipyramidal molecules.



Scheme 8 Formation of pentacoordinate phosphoranes **29**-**31**

These observations are in contrast to Bent's rule or the 3c–4e bonding picture for the apical bonds, according to which the more electronegative substituents are expected to prefer apical sites [21–23]. The conformation of the heterocyclic phosphocin ring is different when it is located in diequatorial or apical-equatorial positions in the above compounds (Sect. 3).

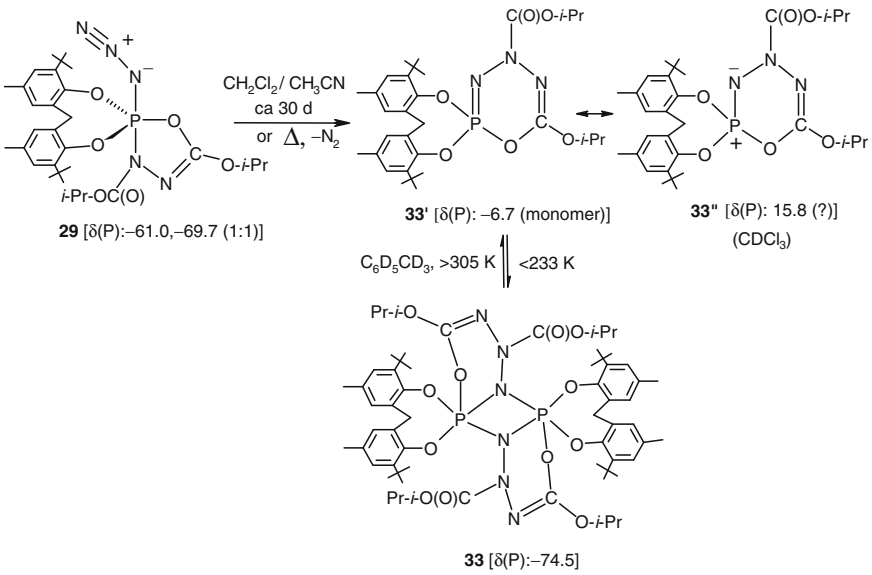


32 [δ(P): –72.9; X-ray]

The room temperature solution state ^{31}P NMR chemical shifts of these compounds are clearly in the pentacoordinate region. Also noteworthy is the point that the structural characterization of three different types (**18/29, 30, 31/32**) lends credence to the rationalization of several signals observed in low temperature ^{31}P NMR spectra of these phosphoranes. This feature also shows that the difference in energy among the various isomers is small.

Compound **29** is thermally unstable and upon heating in toluene showed mainly two peaks in the ^{31}P NMR [δ 13.7 (br, 60%) and –6.9 (sharp, 35%)] in solution. The compound corresponding to the latter could be isolated as a crystalline solid when

29 was kept in solution for a period of over 30 days. An X-ray structure of this compound revealed that it is **33**, a fused cyclodiphosphazane, wherein the phosphorus is still pentacoordinate (Scheme 9) [17, 24]. The apparent anomaly between the room temperature solution NMR [δ(P) −6.9 in toluene-d_8] and the solid state X-ray structure was resolved by recording low temperature ^{31}P NMR spectra (Fig. 2). Indeed, at 233 K the expected peak in the pentacoordinate region [δ(P) −74.5 in



Scheme 9 Formation of the cyclodiphosphazane **33**

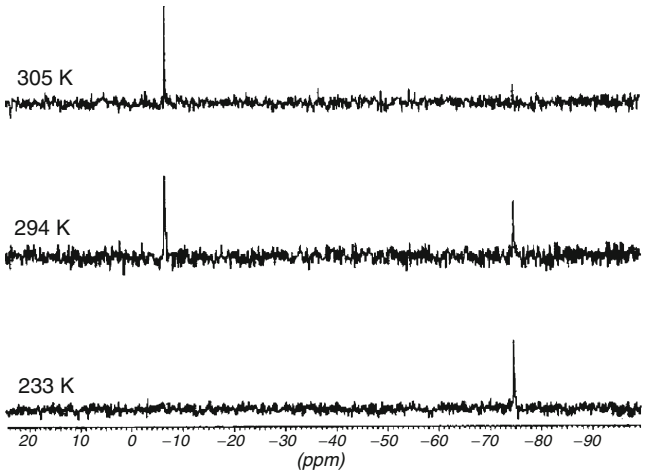
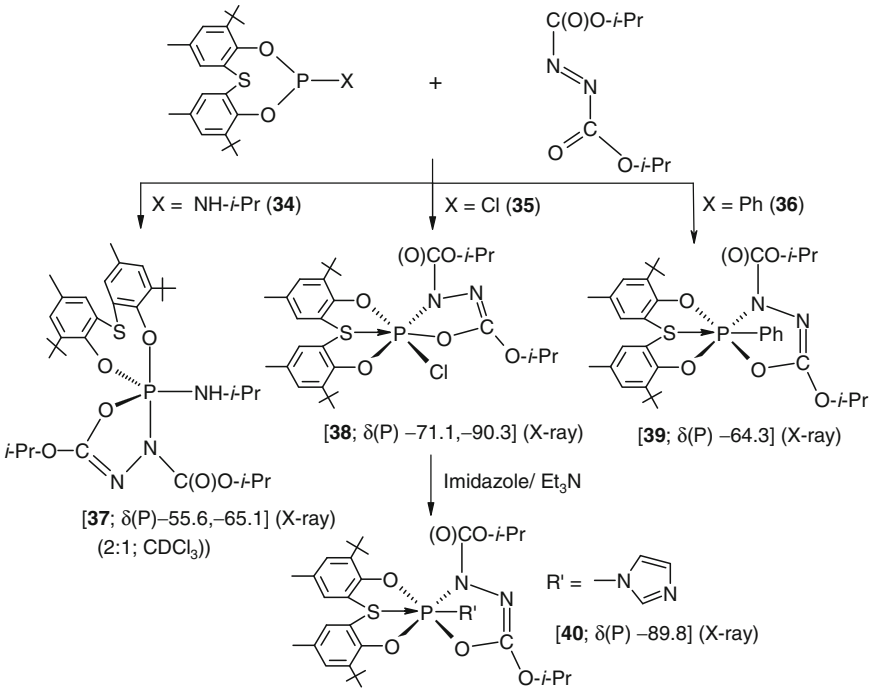


Fig. 2 Variable-temperature ^{31}P NMR spectra for **33**

toluene-d_8] was observed. The difference in the room temperature chemical shifts in toluene and chloroform is attributed to the phosphonium ion–iminophosphorane conversion. Formation of **33′** (and hence **33**) occurs through N_2 elimination from **29** followed by rearrangement (Scheme 9); this is analogous to the formation of isocyanates from acid azides via Curtius rearrangement. Thus, identification of the monomer **32′** in addition to the structural characterization of **33** gives a nice example of Curtius-type rearrangement involving spirophosphorane.

It has been mentioned above that if there is an internal donor atom in the ring containing phosphorus, hexacoordination may result. In the examples cited in Scheme 10, while the isopropylamino precursor **34** reacted with DIAD to give a spirocyclic pentacoordinate phosphorane **37**, the chloro and the phenyl precursors **35–36** led to tricyclic hexacoordinate phosphoranes **38**–**39**, in which there is intramolecular S → P coordination [25]. Treatment of **39** with imidazole resulted in the tricyclic phosphorane **40**. Thus, while the *t*-butylamino compound **25** exists as an iminophosphorane in the solid state, the isopropylamino compound **37** prefers pentacoordination (P···S distance is 3.287 Å), but the chloro (P···S 2.317 Å) or imidazolyl (P···S 2.422 Å) compounds go for six-coordination. Also, it may be noted that the geometrical disposition of the substituents in the hexacoordinate compounds **38** and **39** is different. While the chlorine is *cis* to sulfur in **38**, the phenyl group is *trans* to sulfur in **39** in the solid state. Thus, two signals in the solution state ^{31}P NMR spectrum of **38** is indicative of the existence of isomeric hexacoordinate



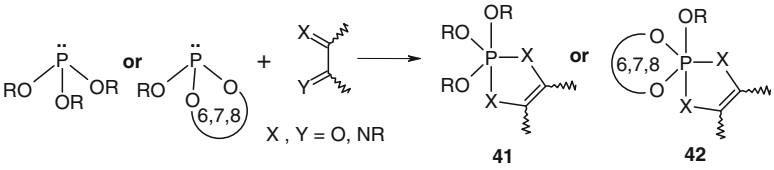
Scheme 10 Formation of hexacoordinate phosphoranes **37–40**

species in solution, one observed in the solid state and the other with geometry similar to that of **40**.

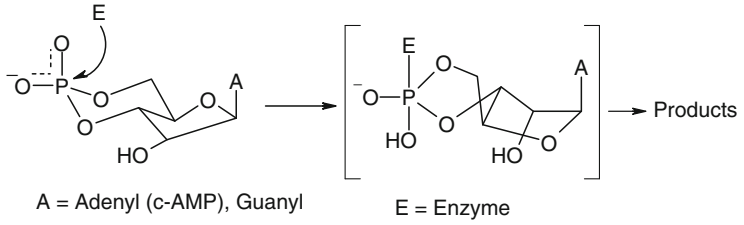
The above results, in addition to providing new spirocyclic phosphoranes of conceptual significance, could perhaps help in designing new reagent systems for Mitsunobu chemistry.

3 Phosphoranes from the Reaction of P^{III} Compounds with Activated Ketones/Diketones

The lone pair of electrons present on the phosphorus atom can be involved in (4 + 1) cycloaddition with reactants like 1,2-diketones, ketoimines, or other α,β-unsaturated compounds (Scheme 11) [26]. The final products formed are, in general, pentacoordinate phosphoranes **41/42** [27, 28] and hence these reactions are called oxidative addition reactions, wherein the reactants oxidatively add on to the phosphorus atom. Four atoms from the diketone/ketoimine and the phosphorus atom of the phosphite take part in this [4 + 1] cycloaddition. Some of the reactions discussed in Sect. 2 are actually a subset of this system. To obtain spirocyclic phosphoranes with ring sizes other than five, we need to have the required ring in the P^{III} precursor itself. Because of the simplicity in conducting the reaction, it has been widely exploited by numerous workers, and hence is discussed in more detail herein. Pentacoordinate phosphorus compounds thus obtained have a unique place in phosphorus chemistry and biochemistry as they serve as models in numerous reactions at the tetracoordinate P^{V} center [27–31]. For example, cAMP action with protein kinases was supposed to proceed via diequatorial (e–e) ring placement in a TBP activated state (Scheme 12) [32]. Evidently, the nature of the products depends upon the disposition of the substituents



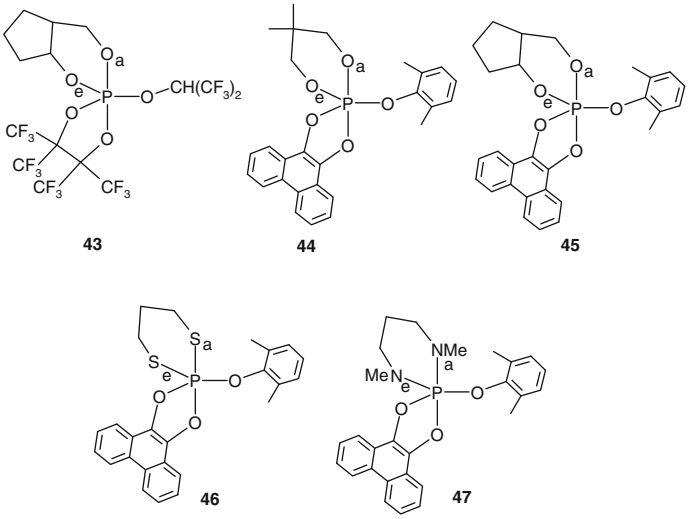
Scheme 11 Reactions of P^{III} compounds with diketones, keto-imines etc.



Scheme 12 Formation of a proposed activated state for the action of cAMP

in the transition state, which would perhaps relate to their relative apicophilicities [33–35] in the most commonly observed trigonal bipyramidal geometry.

The spirocyclic phosphorane **43** was obtained by the oxidative addition of hexafluoroacetone to the corresponding P^{III} precursor while compounds **44–47** were prepared by reacting 9,10-phenanthrene quinone with the corresponding cyclic phosphite [36–38]. A few other compounds with phosphorus as a part of six-membered ring were known earlier [39, 40], but generalization of the structural preferences was not possible due to limited data. In all the compounds **43–47**, the saturated six-membered ring at phosphorus spans an apical–equatorial position. Such a result, therefore, suggests that the diequatorial disposition proposed as per Scheme 12 [32] may not be correct. Another feature of interest in these compounds is the conformation of the saturated 1,3,2-dioxa- (or dithia/diaza) phosphorinane heterocycle. In contrast to the *chair* conformation observed in most of the tri- or tetracoordinate compounds, the six-membered phosphorinane ring adapts a *boat* conformation with apical oxygen and the carbon atom opposite it at the prow and the stern positions, respectively. Compounds **48**–**49** illustrate this feature nicely (Fig. 3) [41]. Compounds **50** [42] and **51** [43], wherein the six-membered ring occupies diequatorial positions, are exceptions.



A system in which the apical–equatorial and diequatorial dispositions for the ring are feasible, depending on the other substituents, involves the sterically hindered eight-membered ring present in **52–67** [31, 44–49]. Structural studies on these compounds showed that a secondary amino group (–NMe_2, –NMePh, –N-*i*-Pr_2) is more apicophilic than a primary amino (–NHMe) or –NH_2 group. This is rather surprising because the –NMe_2 group is certainly bulkier than the –NHMe group. In addition, the –NMe_2 group can be expected to have lower (group) electronegativity (Mulliken electronegativity: –NHMe 8.5; –N(Me)Et 8.4 [49]) and hence be less apicophilic. However, more investigations are necessary to confirm this finding. Perhaps more

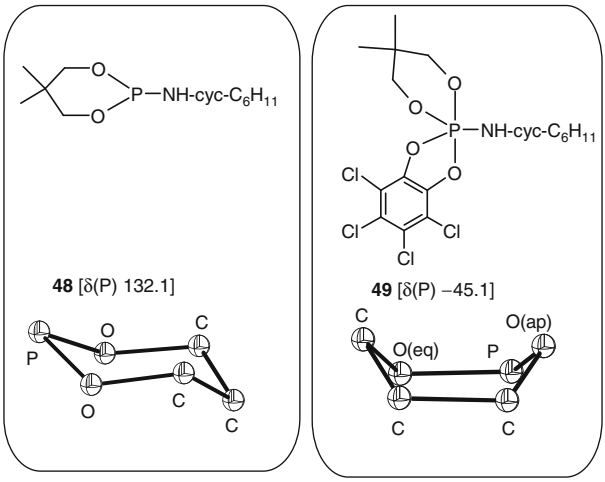
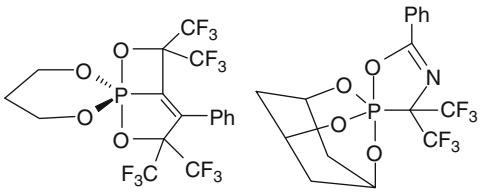
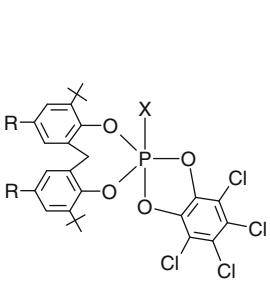
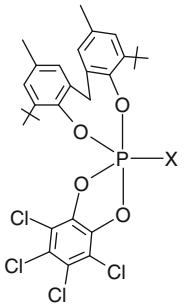


Fig. 3 Conformation (based on X-ray crystal structure) of the 1,3,2-dioxaphosphorinane ring in **48** (*left*) and **49** (*right*)



50 **51**





52 [R = *t*-Bu, X = Ph]
53 [R = *t*-Bu, X = Et]
54 [R = Me, X = Cl]
55 [R = Me, X = N_3]
56 [R = Me, X = Ph]
57 [R = Me, X = NMe_2]
58 [R = Me, X = N-*i*-Pr_2]
59 [R = Me, X = N(Me)Ph]
60 [R = Me, X = -SC_6H_4Cl]
61 [R = Me, X = *t*-Bu]
62 [R = Me, X = Et]

63 [X = Me]
64 [X = NH_2]
65 [X = NHMe]
66 [X = NHPh]
67 [X = N=PPh_3]

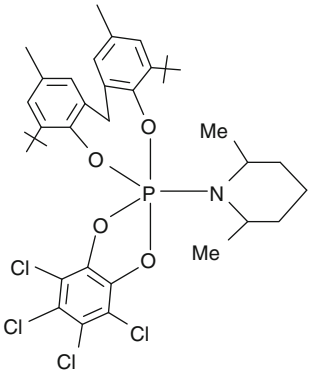
(substituent dispositions based on **X-ray** structures)

dramatic is the fact that the sterically very crowded *t*-butyl group in compound **61** is at the apical site while the much smaller methyl group in **63** is at the equatorial site [47]. The apical disposition of the ethyl group in **62** is also significant because it shows that even minor changes in the substituents can tilt the balance to favor a different placement for the eight-membered ring. Results such as these have certainly made us have second thoughts about the general tenets put forth earlier about the site preferences in trigonal bipyramidal phosphorus [31].

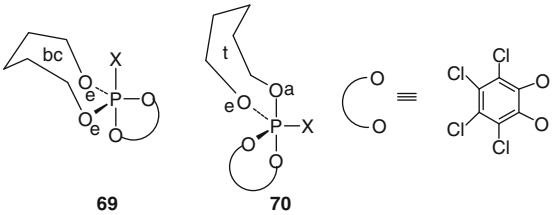
The crucial role of subtle and remote steric effects is also illustrated in the structure of **68** that, unlike the compounds **58–59**, has the bulky secondary amino group at the equatorial position [50]. This structure is different from that proposed earlier for this compound [46]. However, there is a very significant distortion of the geometry at phosphorus with the O_{apical}–P–O_{apical} angle being 166°, which is quite far from the expected 180°. This molecule does not show the "reversed apicophilicity" phenomenon discussed above, but the significant distortion of geometry at the phosphorus is an indication that there are additional factors, like the two methyl groups of the 2,6-lupetidine group projecting in the same direction, that could distort the geometry.

One of the other interesting features in this system relates to the conformation of the eight-membered ring, which is essentially a boat–chair (symmetrical *anti*) when the phosphocin ring is located diequatorially (e.g., **52–62**), or tub when the same ring is located apical–equatorial (e.g., **63–67**) in a trigonal bipyramid. This is diagrammatically shown in **69–70**. The actual disposition in the trigonal bipyramid for **56** and **63** are shown in Fig. 4**.**

In the solid state, compound **62** obtained from the reaction mixture showed a major signal in the ^{31}P NMR at δ −10.6 (~90%) along with a minor signal at δ −25.0 (~10%), suggesting that two isomers had been formed; however, only the one with an apical ethyl group crystallized. In toluene-d_8 solution at room temperature, there were two signals at δ −18.5 (sharp) and −25.3 (broad), but at 246 K, there were three fairly sharp signals at δ −14.2, −18.7, and −25.3. Multiple signals were also observed for many other phosphoranes including **57**, **63**, and **65**. These data clearly show the existence of many isomeric phosphoranes in solution.

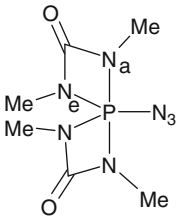


68 [δ(P): –40.0] (X-ray)



69 **70**

bc ≡ boat-chair conformation; t ≡ tub conformation
a ≡ apical; e ≡ equatorial



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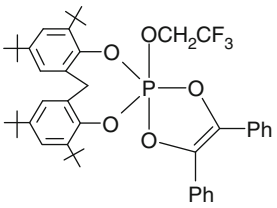

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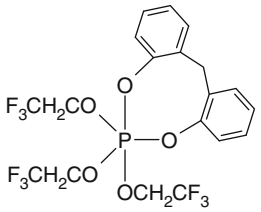

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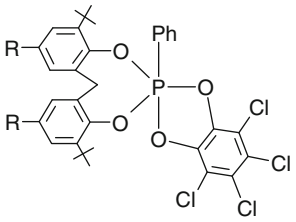
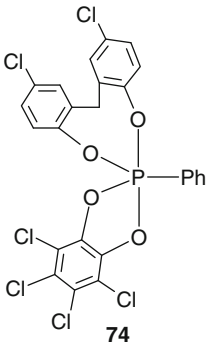


R = *t*-Bu (**52**), Me (**56**)



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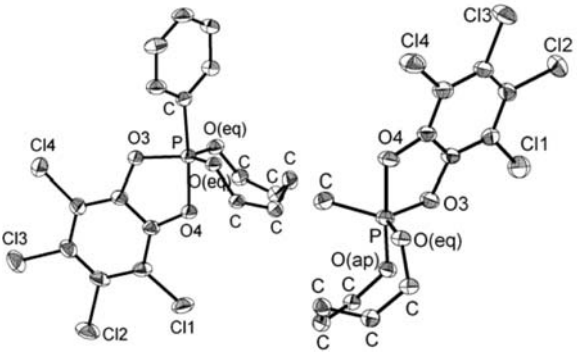
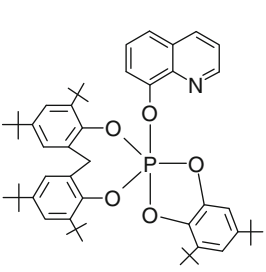


Fig. 4 ORTEP drawings of **56** (*left*) and **63** (*right*) showing selected atoms. Note the change in the conformation of the eight-membered ring in the two cases

It is also clear that the phenyl group **56** is definitely more apicophilic than the methyl group **63**. This observation is consistent with Trippett's prediction [34], but contradicts that of Corbridge [33]. A structural proof for the high apicophilicity of an *S*-aryl group is also provided through compound **60** [46]. In this compound, the *p*-chlorothiophenoxy group occupies the apical position. Although the dicoordinated nitrogen in **67** should be more electronegative than the tricoordinated nitrogen in **59**, it is less apicophilic clearly because of the steric factors. By contrast, the dicoordi-

nated nitrogen connected to P in the azido-phosphorane **55** is apical, because of lower steric constraints and higher group electronegativity. The role of the eight-membered ring in placing the azido group apical is also important; since in the azido phosphorane $[MeNC(O)NMe]_2P(N_3)$ (**71**) (which contains only four-membered rings at phosphorus), the azido group is placed equatorially [51]. Steric effects seem to play a role in occupancy of the eight-membered ring at the TBP phosphorus center. This is evident in compounds **72–73**. The eight-membered ring spans the diequatorial sites of a TBP in **72** [52]; by way of contrast, when alkyl substituents on the aryl components of the rings are removed as in **73** [53], the TBP structures have the rings occupying apical–equatorial sites. Also, the eight-membered ring spans the diequatorial sites of a TBP in **52** and **56** [44, 45]; by way of contrast, when alkyl substituents on the aryl components of the rings are removed as in **74** [44, 52], the TBP structure has the same ring occupying apical–equatorial sites.

Electronegativity effects are perhaps seen more clearly in spirophosphoranes **75** [54] and **76** [41]. The oxinato group, which is more electronegative than the cylcohexylamino group, spans the apical position as expected, thus forcing the eight-membered ring to span diequatorial positions at the TBP center.



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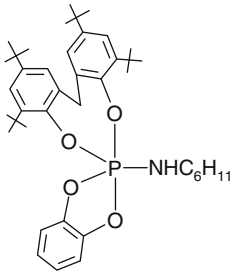
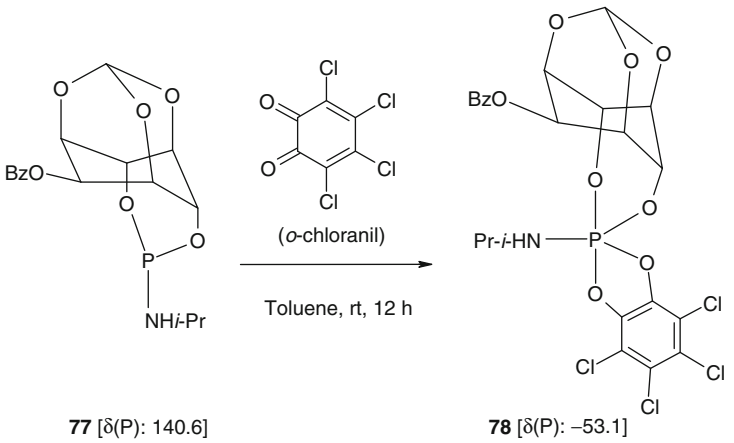


76

Phosphorylated myo-inositol derivatives are important in cellular signal transduction [55]. Pentacoordinate phosphorus is involved in the corresponding phosphoryl transfer reactions. However, not much structural information is available about the inositol-based cyclic phosphites/phosphates. In the only example known, compound **77** was treated with *o*-chloranil to lead to the pentacoordinate phosphorane **78** (Scheme 13) [56]. Here, the more electronegative oxygen atoms occupy the apical positions while the less electronegative nitrogen is equatorial in the TBP structure, as expected from Bent's rule. The six-membered ring in **77** has a boat conformation (Fig. 5a), but this conformation is actually different from that observed in other pentacoordinate compounds in that for the latter, one oxygen and a CH_2 carbon are above the mean plane of the other four atoms (e.g., **49**; Fig. 5b) [41]. In **78**, the phosphorus and a carbon atom of the inositol residue are above the mean plane of the remaining four atoms.

The bicyclic sulfur-containing tetraoxyphosphorane **79**, with an NMe_2 group as the fifth substituent, did not show S → P coordination even though the rings are in



Scheme 13 Formation of pentacoordinate phosphorane **78**

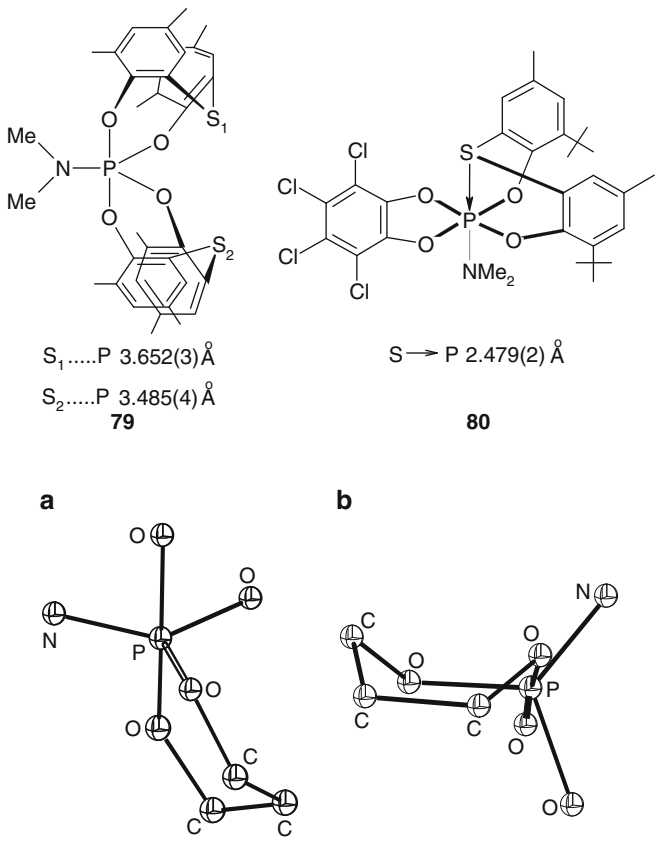
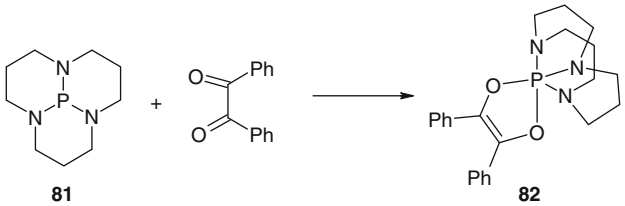


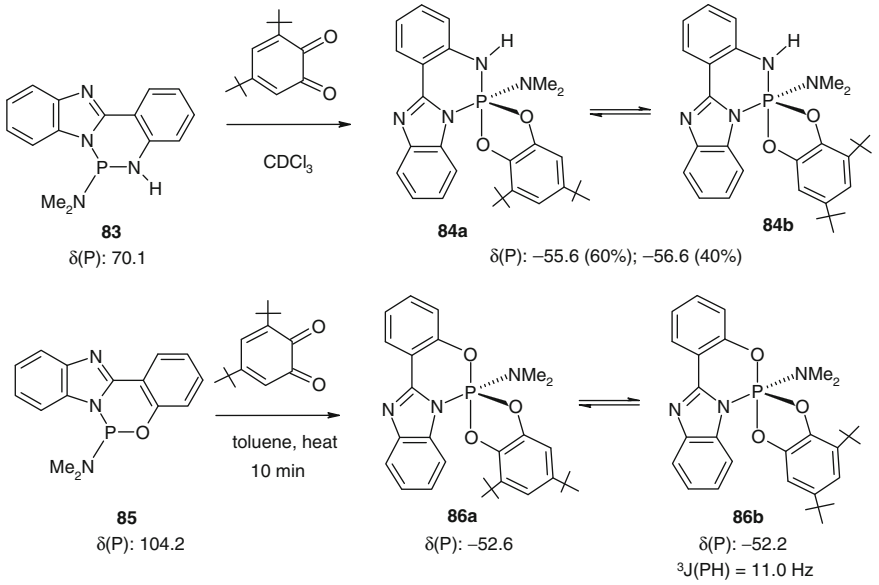
Fig. 5 Plots showing the conformation (based on X-ray crystal structure) of the six-membered ring in **a** compound **78**, and **b** compound **49**; note the difference in the location of phosphorus atom in the boat

the favorable tub conformation [57]. The authors ascribe the lack of sulfur donor action to the P–N π back-bonding that reduces the electrophilicity of phosphorus to prevent additional coordination. In contrast, the presence of a more electron-withdrawing tetrachlorocatecholate ligand in the analogous cyclic tetraoxyphosphorane (**80**) increases the Lewis acidity of phosphorus to allow hexacoordination. Thus, the tendency to go for hexacoordination is enhanced by a more electronegative group but decreased by the π back-bonding (P to N) at phosphorus.

There are also some earlier examples that involve the addition of a diketone to a P^{III} compound bearing a six- or higher-membered ring. Synthesis of the fused spirocycle **82** by starting with **81** and benzil was reported by Denney et al. (Scheme 14) [58]. Reactions of P^{III} compounds with 3,5-di-*t*-butyl-1,2-benzoquinone offer the opportunity to explore isomeric phosphoranes, since the two quinone oxygen atoms are in slightly different environments. Thus, the use of cyclic aminophosphine **83** or phosphite **85** leads to isomeric spirocyclic phosphoranes **84a–b** or **86a–b**



Scheme 14 Formation of pentacoordinate phosphorane **82**

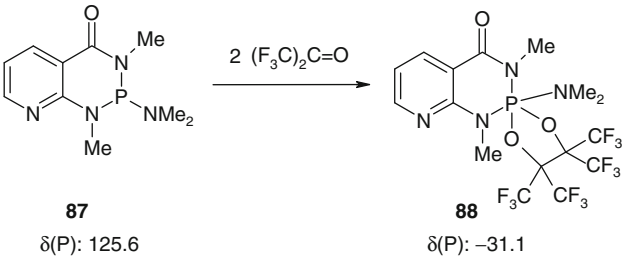


Scheme 15 Formation of aminophosphoranes **84a-b** and **86a-b**

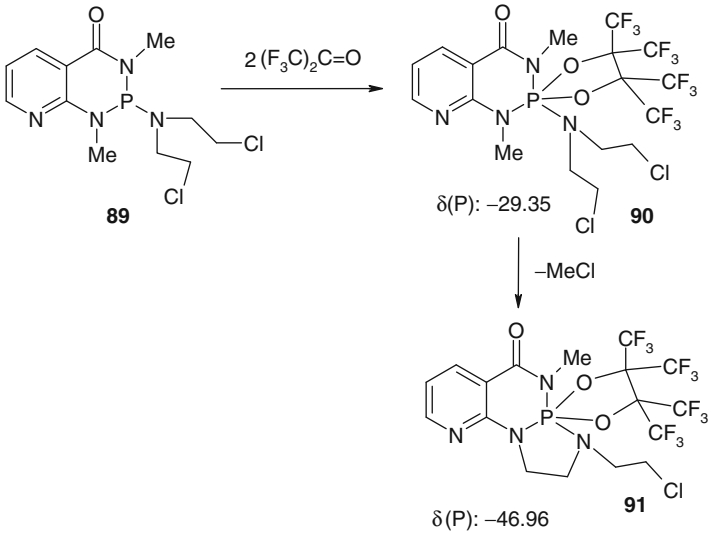
(Scheme 15) [59, 60]. The two isomers in each case differ with respect to the location of the two slightly different oxygen atoms of the five–membered ring in the trigonal bipyramidal geometry (apical or equatorial). The ^{31}P NMR spectrum distinguishes these two possibilities.

Schmutzler and coworkers have utilized the ring system present in **87** for the synthesis of the pentacoordinate phosphorane **88** (Scheme 16) [61]. Unlike the reaction with diketones discussed above, a reactive monoketone is utilized in this case and there is a C–C bond formation. Here also, the six-membered diazaphosphorinane ring spans an apical–equatorial disposition in a distorted trigonal bipyramid.

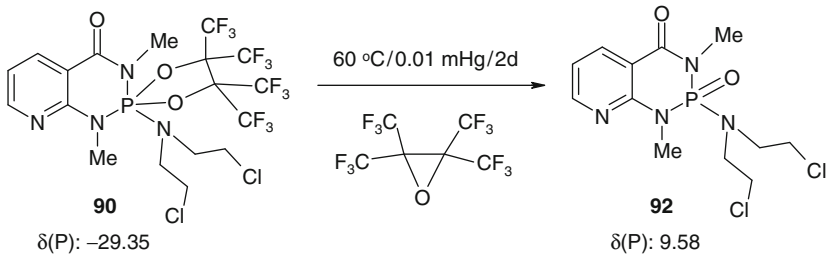
More interesting chemistry has been developed by the same group by replacing the $-NMe_2$ group by the $-(CH_2CH_2Cl)_2$ group [62]. Thus, although compound **90** obtained by starting with **89** is similar to **88**, it undergoes elimination of a molecule of chloromethane to afford the tricyclic phosphorane **91** (Scheme 17), which has a slightly distorted



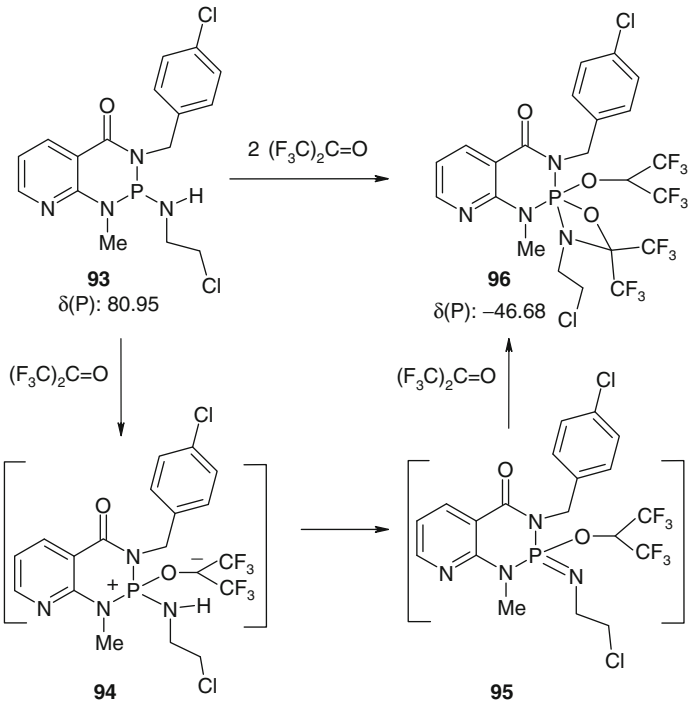
Scheme 16 Formation of spirocyclic phosphorane **88**



Scheme 17 Formation of tricyclic phosphorane **91**



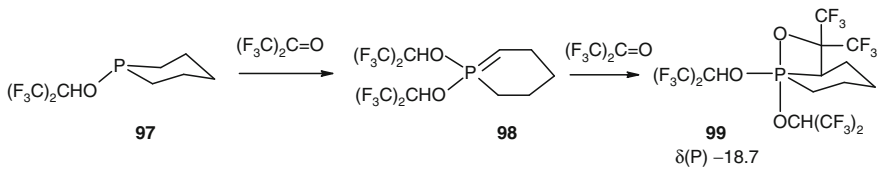
Scheme 18 Thermal degradation of phosphorane **90** to compound **92**



Scheme 19 Formation of the spirocyclic phosphorane **96**

trigonal bipyramidal structure with an oxygen of the five-membered ring and the nitrogen directly connected to the aromatic residue at the apical positions. Many other similar tricyclic phosphoranes have been synthesized by the same group [63]. Compound **90** upon heating in vacuum undergoes elimination of the tetrakis(trifluoromethyl)oxirane to lead to the tetracoordinate heterocycle **92** (Scheme 18) [64].

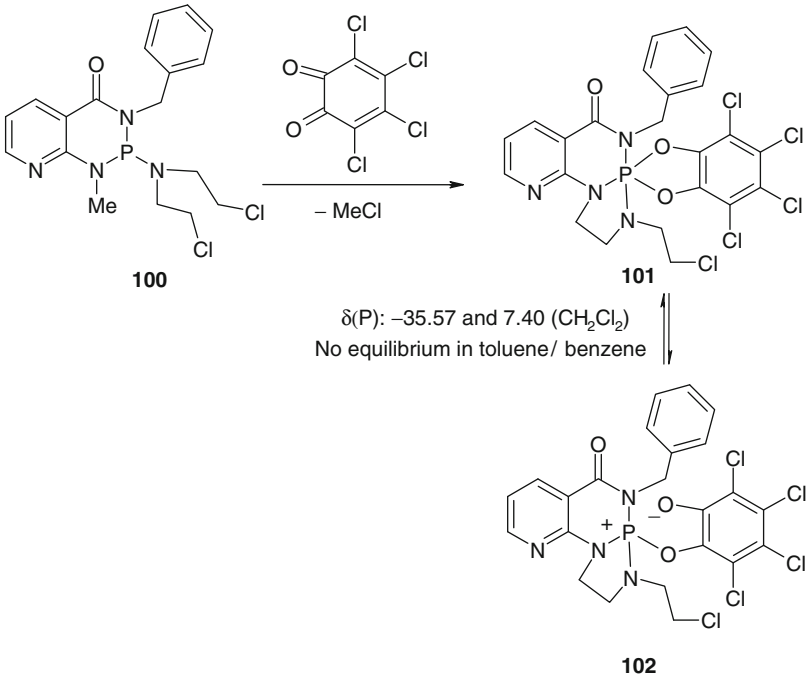
If the $-N(CH_2CH_2Cl)_2$ group is replaced by $-NH(CH_2CH_2Cl)$ in the above system (as in **93**) a different type of heterocycle arises, as reported by Schmutzler's group [65]. A four-membered oxazaphosphetidene ring is newly formed in this case to lead to the bicyclic phosphorane **96**, most likely via the phosphonium zwitterion **94** and the iminophosphorane **95** (Scheme 19). A somewhat analogous reaction



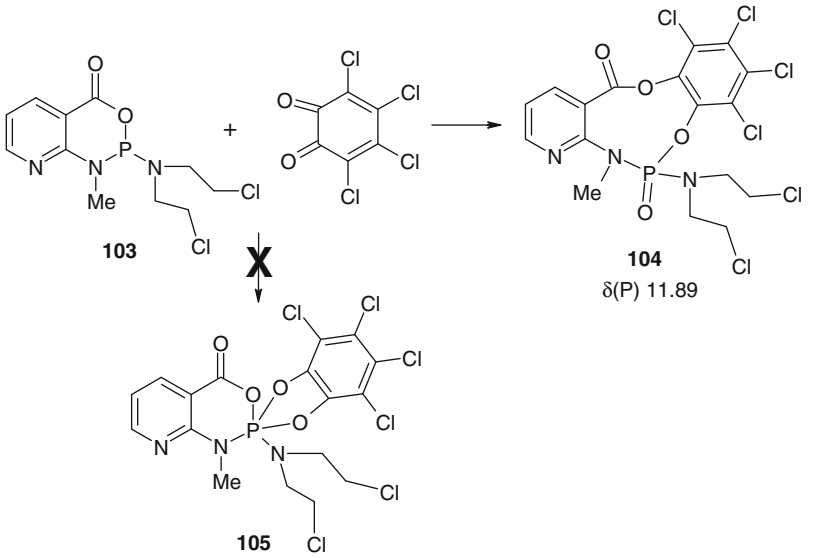
Scheme 20 Formation of the phosphorane **99**

using 1-alkoxyphosphorinane **97** reported by Röschenthaler is shown in Scheme 20 [66]. Instead of the imine (e.g., **95**), a P=C bonded species is formed initially, which upon further addition of hexafluoroacetone leads to the phosphorane **99** via **98**. The net result here is the formation of a 1,2$\lambda^5\sigma^5$-oxaphosphetane ring.

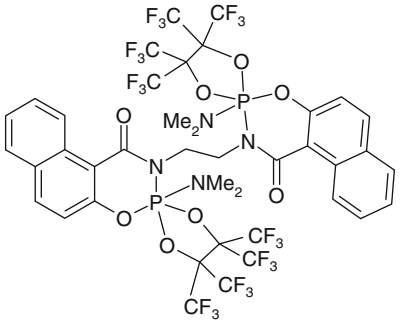
In the synthesis of tricyclic compound **101** from **100** and *o*-chloranil, both the oxidative addition and MeCl elimination (from N*Me* and NCH_2CH_2*Cl*) occur as shown (Scheme 21) [65]. Although the structure of this compound is retained in toluene solution, equilibrium between the pentacoordinate phosphorane **101** and the tetracoordinate phosphonium form **102** is indicated in dichloromethane solution. Thus, two ^{31}P NMR signals at δ –35.57 and 7.40 are observed when the spectrum is recorded in dichloromethane. Interestingly, in contrast to these results, reaction of the oxazaphosphorinane precursor **103** with *o*-chloranil proceeded in a



Scheme 21 Formation of the tricyclic phosphorane **101** and its zwitterionic form **102**



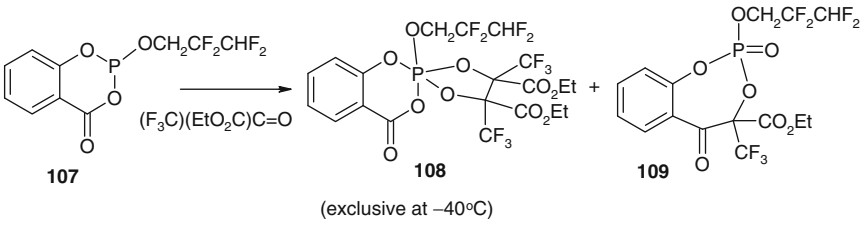
Scheme 22 Ring enlargement reaction of **103** leading to **104**



106 [δ(P) −47.12, −47.89]

different manner and the ring-expanded product **104**, instead of the spirocyclic phosphorane **105**, was obtained (Scheme 22) [67]. It was, however, possible to synthesize bisphosphoranes (e.g., **106**) using the reaction of appropriate P^{III} precursors with hexafluoroacetone [68]. Two signals were observed in the ^{31}P NMR spectrum of this compound. Since the solubility was rather poor, further investigations into this aspect were not conducted.

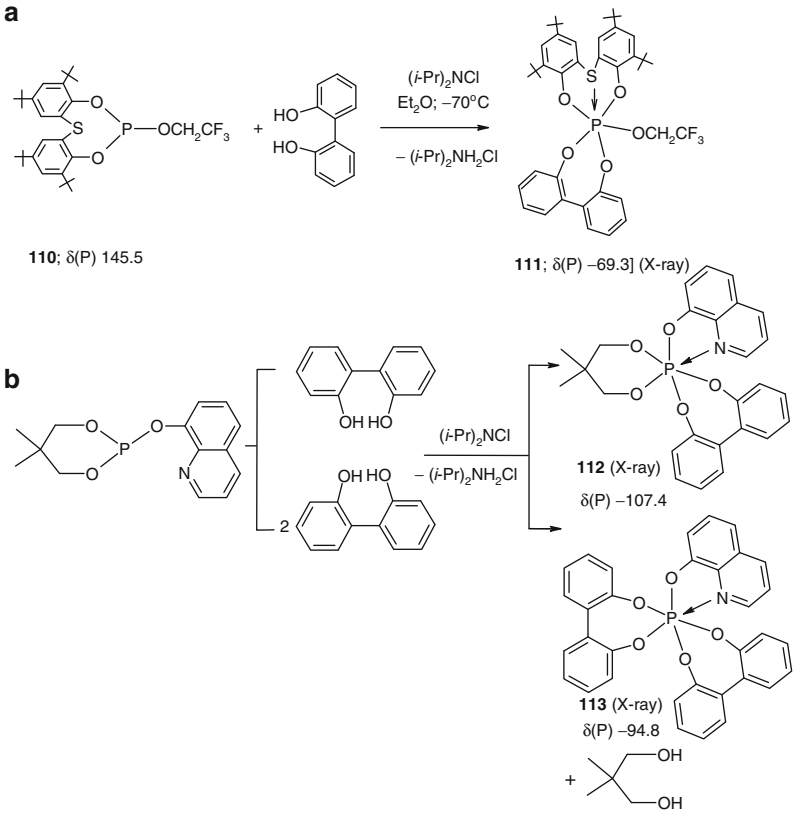
The salicylic acid derivative **107** undergoes exclusive oxidative addition with $(F_3C)(EtO_2C)C{=}O$ to lead to the pentacoordinate phosphorane **108** at low temperatures, but a mixture of **108** and the ring-expanded product **109** are obtained at higher temperatures (Scheme 23) [69]. However, unlike the case of **104**, wherein ring expansion is from six to eight, here it is from six- to seven-membered**.** The precursor with the $–OCH_2CF_3$ group in place of $–OCH_2CF_2CHF_2$ underwent spirocyclization with $(EtO_2C)_2C{=}O$, to lead to a compound similar to **108** that on thermolysis led to the ring-expansion product analogous to **109** in high yield [70].



Scheme 23 Formation of phosphorane **108** along with the ring-enlarged product **109**

4 Phosphoranes from the Reaction of *N*-Chloro-diisopropylamine and Diol with P^{III} Compounds

The most useful and straightforward route to spirocyclic phosphoranes with six- and higher-membered rings is the reaction of a P^{III} precursor with *N*-(chloro)diisopropylamine followed by addition of the appropriate diol. This route is effective both for penta- and hexacoordinate compounds. Two such reactions affording **111–113** are given in Scheme 24 [54, 71]. In the case of compounds containing the bridgehead



Scheme 24 Formation of hexacoordinate phosphoranes **111-113**

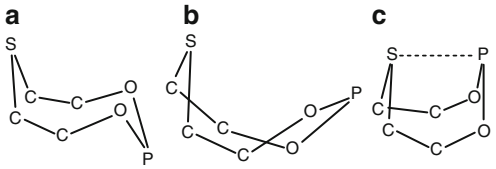
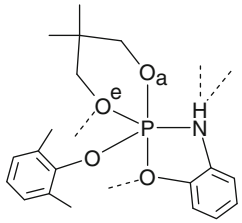


Fig. 6 **a** Boat–chair (symmetrical *anti*; similar to that in compound **56**), **b** tub without S→P interaction (e.g., compound **37/79**), and **c** tub with S/P coordinate bond (as in **38/39/111**) for the phosphocin ring, as revealed by X-ray crystallography

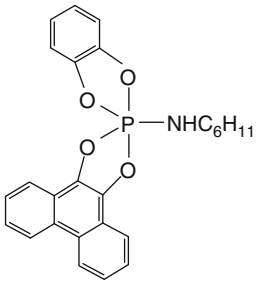
sulfur, formation of the donor–acceptor S → P bond leading to hexacoordination depends upon the other substituents present on phosphorus. In **111**, the P···S distance of 2.375 (3) Å as well as the near-octahedral geometry at phosphorus both support P–S bond formation. The flexibility of this eight-membered ring to adapt different conformations like boat–chair (symmetrical *anti*) or tub is also evident; here, it adapts a tub conformation to accommodate P···S interaction (Fig. 6), while a boat–chair is seen when a similar ring is present diequatorially in a trigonal bipyramidal phosphorus [25, 57]. The seven-membered phosphepin ring used in these systems is rather rigid and adapts essentially arrow–boat conformation in all the cases studied (see below), be it tetra-, penta- or hexacoordinate phosphorus [54].

The reaction shown in Scheme 24b illustrates another facet of the reactions of hypervalent phosphorus compounds [54]. While **112** is the expected product, the reaction also affords the ring-exchanged product **113**; when the stoichiometry of the biphenol in the reaction was changed from 1:1 to 1:2, the latter product was dominant. This paper also reports the effects of ring size on the ^{31}P NMR chemical shifts; it can be noted that the replacement of the six-membered saturated ring in **112** by the seven-membered phosphepin ring in **113** moves the ^{31}P NMR chemical shift downfield. This effect is similar to the downfield shifts observed in the case of compounds with five-membered rings at the phosphorus.

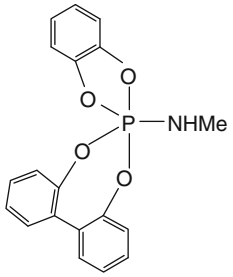
The compound **114** was readily prepared by treating the required precursor with *N*-chlorodiisopropylamine followed by *o*-aminophenol. Interestingly, a chair conformation for the six-membered 1,3,2-dioxaphosphorinane ring with the involvement of hydrogen bonding was detected [72]. This can be contrasted with the boat conformation found when this ring is located apical–equatorially in a trigonal bipyramid, as discussed above. Further studies on hydrogen bonding effects on



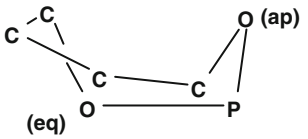
114



115 [δ(P): –28.2; X-ray]



116 [δ(P): –34.6; X-ray]

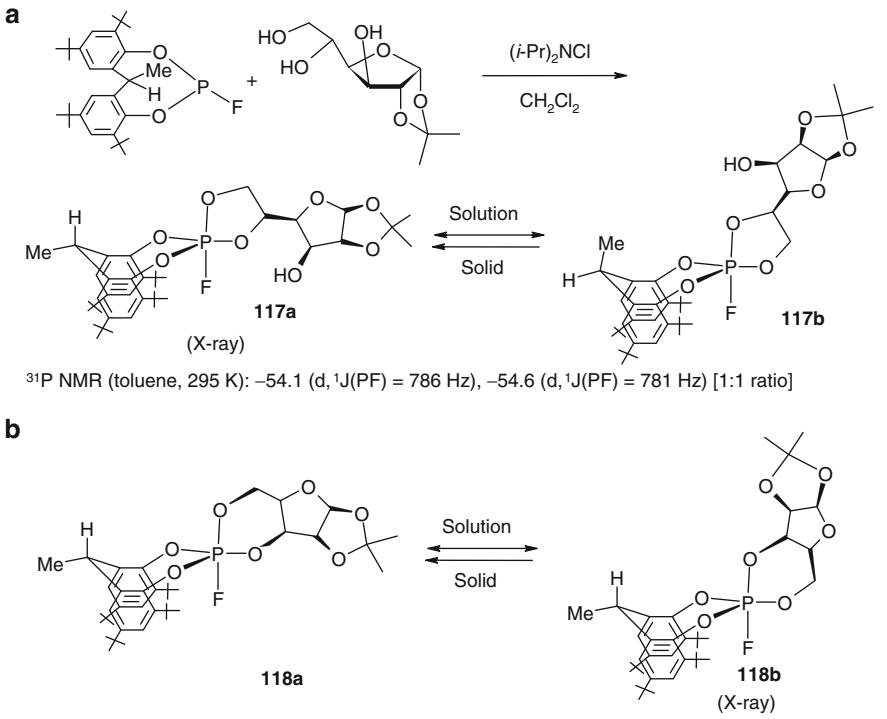


arrow-boat conformation of the phosphepin ring in **116**

phosphoranes bearing a 1,3,2-dioxaphosphorinane ring have revealed that the incorporation of hydrogen bonding via NH groups may also make use of donor functions attached to five-membered rings of tetraoxyphosphoranes, rather than the use of P–O ring-bound oxygen atoms [73]. In both the cases, chain and dimer formations were observed with the rings situated apical–equatorially in trigonal bipyramidal geometry. Overall, hydrogen bonding gave either boat or chair conformation for the six-membered ring, suggesting that the difference in energy between the two is rather small. The implication of these results is that for the formation of phosphorane activated states with diequatorial disposition of similar six-membered rings (of cAMP) in the interaction of protein kinases with cAMP [74], a combination of active-site constraints would be required [73].

Recently, primary amino-substituted phosphoranes **115–116** were synthesized and their molecular structures determined [75]. While **115** was prepared by the oxidative addition using 9,10-phenanthrenequinone, the *N*-chlorodisopropylamine route was adapted for **116**. In the spirophosphorane **115**, molecules organize themselves as weakly hydrogen-bonded dimers with one of the *apical* oxygen atoms of the catecholate residue involved in hydrogen bonding with the NH proton. Here again, the apical–equatorial placement of the six- or seven-membered rings is unaffected due to the hydrogen bonding. These hydrogen-bonding studies are perhaps useful in arriving at a probable transition state pentacoordinate species in the nucleophilic substitution reactions of phosphate esters; however, the effects are not strong enough to change the apicophilicity of the substituents.

Structural investigations on biologically relevant phosphoranes are generally hard to come by. Only recently have some major successes been achieved in this direction [76, 77]. Cyclic oxyphosphoranes offer a better chance of success [56, 78–82]. The phosphorane **78** with an inositol residue has been discussed above [56]. Several carbohydrate-based phosphoranes were synthesized by reacting 2,2′-ethylidene-bis(4,6-di-*t*-butylphenyl)-fluorophosphite with 1,2-*O*-isopropylidene-*R*-D-glucofuranose, β-chloralose, and 1,2-isopropylidene-*R*-D-xylofuranose to form the phosphoranes in the presence of *N*-chlorodiisopropylamine. In the two examples shown in Scheme 25, the solid state structure shows a well-defined geometry, but in solution, two isomers [**117a/b** and **118a/b**] are clearly seen [81]. These isomers were distinguished clearly in both ^{31}P and ^{19}F NMR. A drawing showing the conformation of the eight-membered ring in **117a/b** and of the six-membered ring



Scheme 25 Formation of isomeric mixtures of **117a-b** and **118a-b**

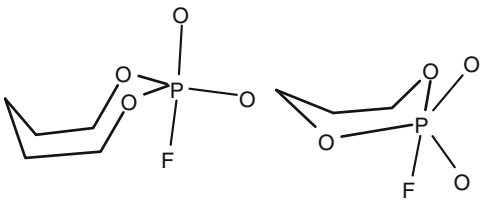
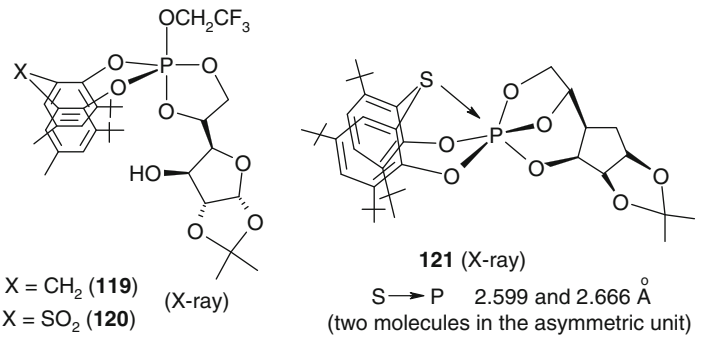


Fig. 7 Drawing (based on X-ray structure) showing the conformation of **a** eight-membered ring in **117a/b**, and **b** six-membered ring in **118b**

in **118b**, as revealed by X-ray crystallography, is shown in Fig. 7. While the eight-membered ring has an *anti* (boat–chair) conformation, the six-membered ring shows a boat conformation. In another paper, Holmes and coworkers have reported structural characterization of several other phosphoranes (e.g., **119–120**) that are analogous to **117b** [82]. However, unlike the case of **117a–b**, only one isomer was



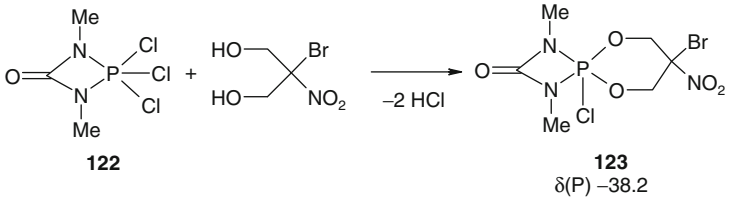
observed in the solution as well as in the solid state. The hexacoordinate fused ring system **121** with S → P coordinate bond was also synthesized by the *N*-chloro-diisopropylamine route and characterized by X-ray crystallography.

5 Exchange Reactions of Pentavalent Phosphorus Compounds

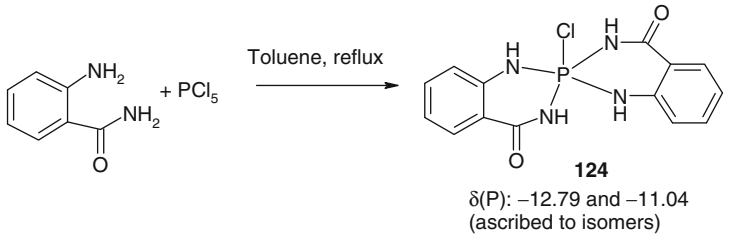
5.1 Pentacoordinate Spirophosphoranes

An example involving the reaction of the pentacoordinate precursor **122** pertains to the urea derivative **123**, as reported by Neda et al. (Scheme 26) [83]. This is a simple but general reaction to obtain a large number of spirocyclics containing varying ring sizes, with one four-membered ring on phosphorus. The reaction of PCl_5 with several *ortho*-substituted benzenes is also reported to afford cyclic chlorophosphoranes, an example (**124**) of which is given in Scheme 27 [84].

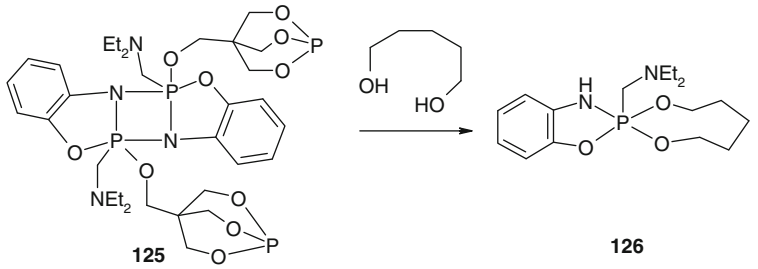
An interesting route to the introduction of a higher-membered ring via an exchange reaction utilizing a cyclodiphosph^{V}azane has been reported by Pudovik et al. (Scheme 28) [85]. The cyclophosphazane ring in **125** is cleaved in its reaction with 1,5-pentanediol leading to the spirophosphorane **126** that contains an eight-membered



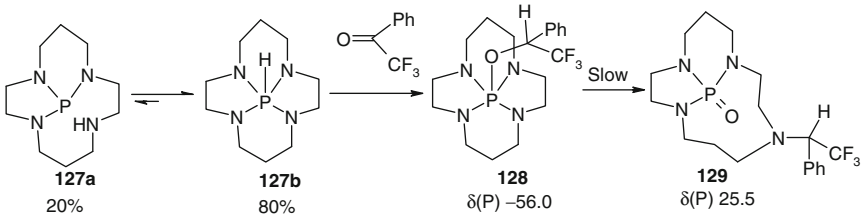
Scheme 26 Synthesis of the spirocyclic chlorophosphorane **123**



Scheme 27 Synthesis of the spirocyclic chlorophosphorane **124**



Scheme 28 A ring cleavage reaction leading to phosphorane **126**



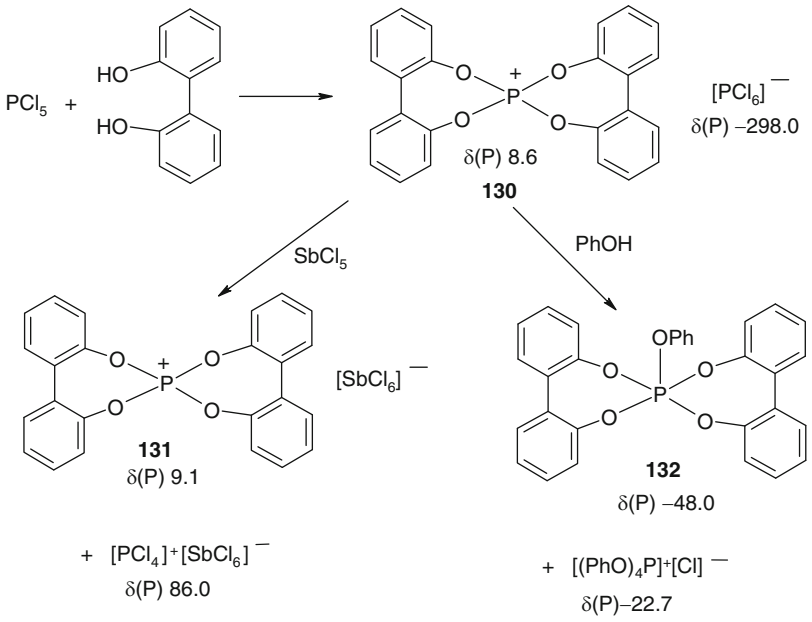
Scheme 29 Formation of phosphorane **128** and its conversion to compound **129**

ring. Another reaction of a pentacoordinate phosphorane **127b** that is in equilibrium with its tricoordinate counterpart **127a** is shown in Scheme 29 [86]. The ^{31}P NMR spectrum of the resulting compound **128** exhibits a signal at δ −56.0 in toluene. When this solution was left at −30°C in a sealed tube, it converted, slowly but completely, to its tetracoordinate isomer **129** that showed a singlet at 25.5 ppm in its ^{31}P NMR spectrum. The latter chemical shift is in the expected region for a tris(dialky1amino)phosphine oxide.

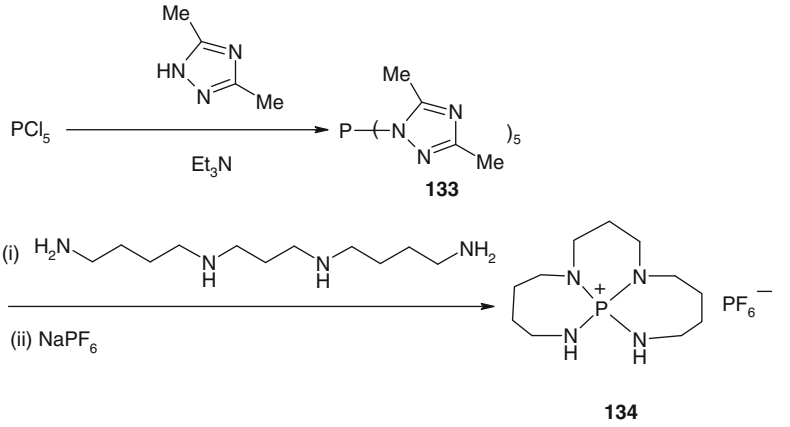
5.2 Phosphonium Salts and Iminophosphoranes

A set of compounds wherein changes in the substituents on phosphorus lead to either spirophosphonium salt (**131**) or spirophosphorane (**132**) via the species **130** was reported by Gloede et al. (Scheme 30) [87]. Formation of the phosphorane and the phosphonium salt could be readily inferred from the ^{31}P NMR data. The hydrolyzed product containing one of the seven-membered rings could be isolated. Phosphonium salts analogous to **130–131** with a BINOL residue were also identified in the same work.

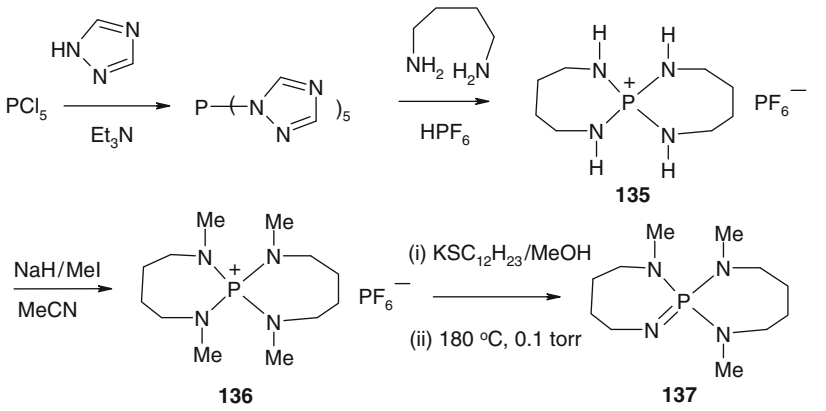
In connection with the synthesis of strong uncharged auxiliary bases useful for various organic applications, Schwesinger and coworkers synthesized the spirophosphorus compound **134**, that contains both six- and seven-membered rings around phosphorus, via the phosphorane **133** (Scheme 31) [88]. A similar strategy was used to prepare the spirophosphonium salt **135**, which was finally converted to the spiro-iminophosphorane **137** via the methylated product **136** (Scheme 32). Compounds such as **137** are very strong bases with pK_{BH}+ (MeCN) of 28.38 (the corresponding value for DBU is 24.33); this base underwent only 10% alkylation with *i*-PrBr.



Scheme 30 Formation of phosphonium salts **130-131** and phosphorane **132**



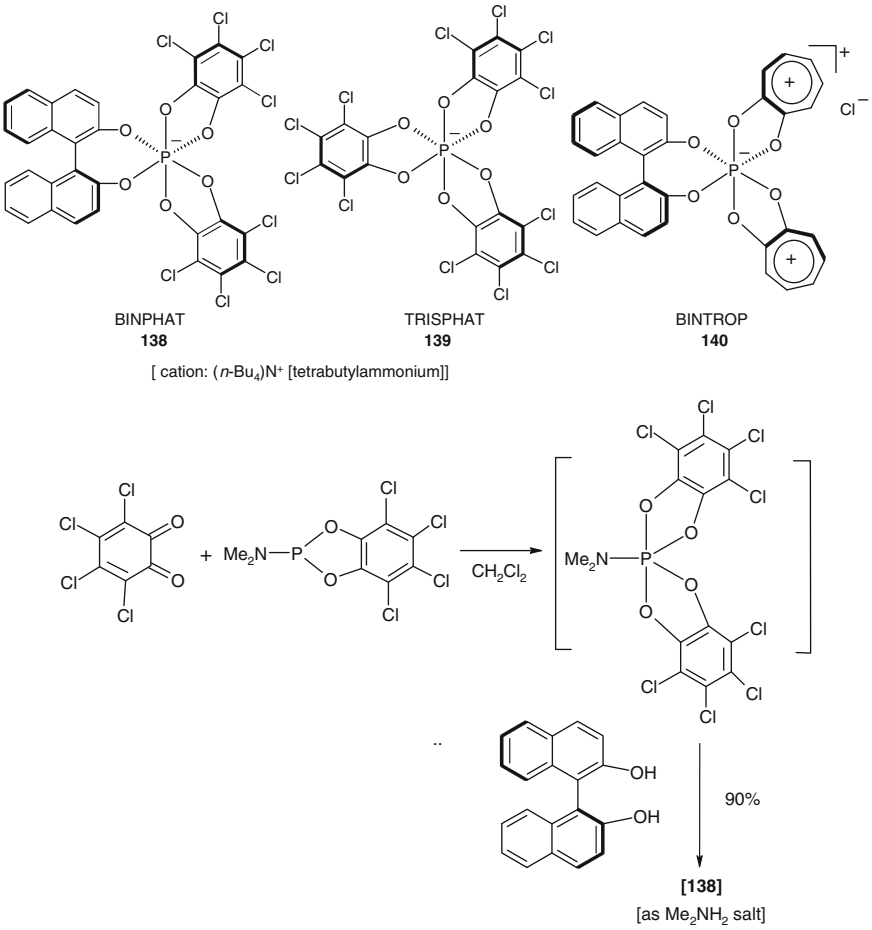
Scheme 31 Formation of the tricyclic phosphonium salt **134**



Scheme 32 Synthesis of the iminophosphorane **137**

5.3 Anionic and Cationic Hexacoordinate Phosphorus Compounds

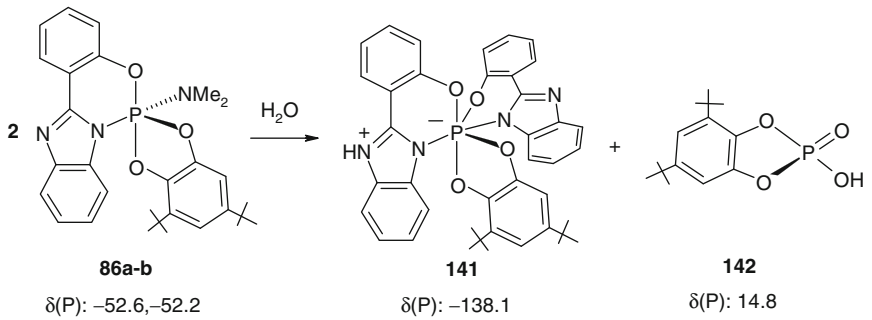
There are quite a number of cyclic anionic hexacoordinate phosphorus compounds described in the literature [89–93]. Among recent examples, the chiral hexacoordinate phosphate anion, (Λ,*R*)-BINPHAT [bis(tetrachlorobenzenediolato) mono([1,1′]binaphthalenyl-2,2′-diolato)phosphate^{v}] (**138**) as its tetrabutylammonium salt is a very efficient NMR chiral shift agent for quaternary ammonium cations, e.g., PhCH(Me)NMe_3^+. This species gives rise to large separations (ΔΔδ up to



Scheme 33 Synthesis of the cyclic phosphate salt $[Me_2NH_2]^+[\mathbf{138}]^-$

0.29 ppm) of the proton signals of the enantiomers [94, 95] and is better than (Δ)-TRISPHAT [tris-(tetrachlorobenzenediolato)phosphate^{v}] (**139**). Compound **138** is now commercially available and its synthetic route via an exchange reaction is shown in Scheme 33 [96]. There are also a few studies on cationic hexacoordinate compounds. With regard to those with higher-membered rings, Lacour and coworkers have shown recently that tropolone, binaphthol, and PCl_5 react in one step to give C_2-symmetric hexacoordiante phosphorus cation **140** (chloride is the anion), which also acts as an efficient NMR chiral shift reagent for chiral phosphate and borate anions [97].

Synthesis of phosphoranes **86a–b** was discussed above. When a $CDCl_3$ solution of the isomeric mixture of **86a–b** was left aside for 10 days, two new signals appeared at δ(P) 14.8 and −138.1 (1:1 ratio) with concomitant disappearance of the



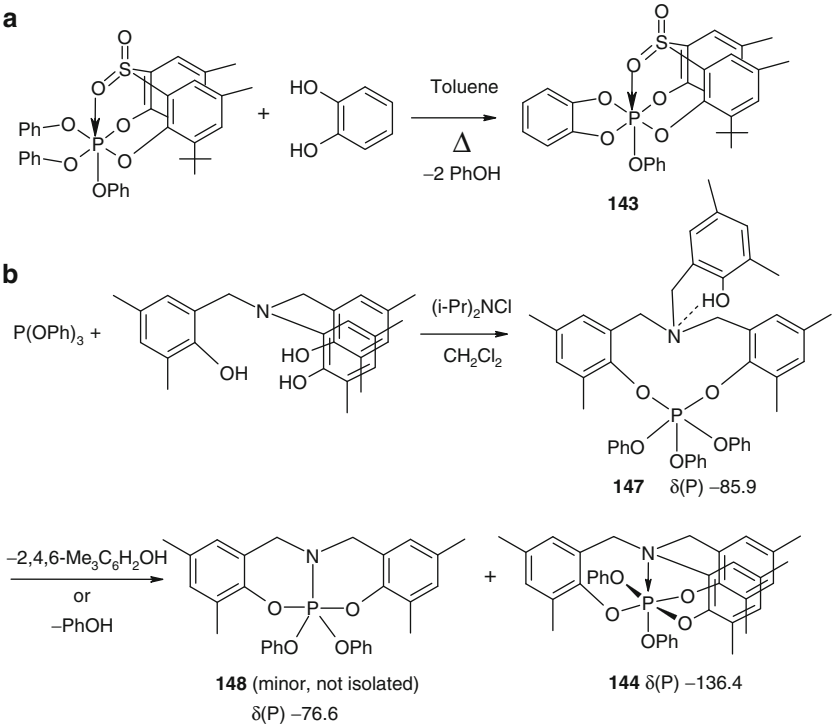
Scheme 34 Formation of compounds **141** and **142**

original signals [60]. The latter signal is in the hexacoordinate region that corresponds to the anion **141**, while the former corresponds to the phosphate **142** (Scheme 34). These compounds result from the hydrolysis/reorganization of the ligands around phosphorus.

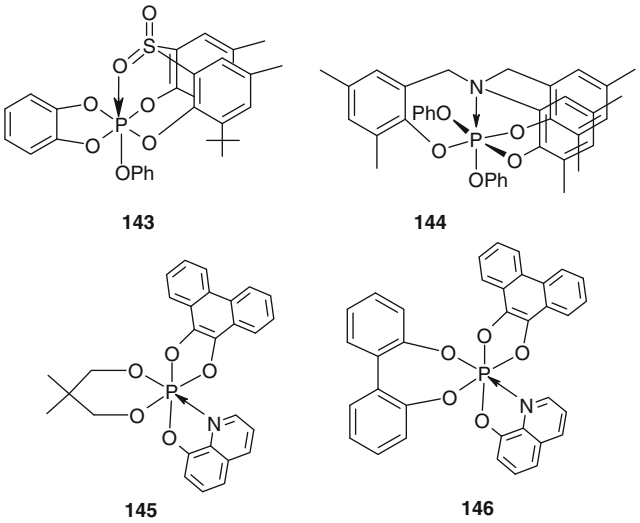
5.4 Neutral Hexacoordinate Phosphorus Compounds

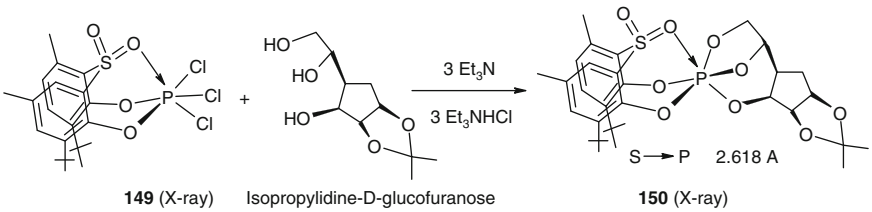
The simplest route to a neutral hexacoordinate phosphorus center is to use the Lewis acidity of the P^{v} compounds in combination with simple Lewis base donors. In most cases, the donor atoms are nitrogen and oxygen bases although several sulfur and a few P^{III} donors have also been used [98–100]. Thus, neutral hexacoordinate P^{v} compounds utilizing the chelating effect of one monovalent bidentate ligand to form a four-, five- (oxyquinolates), or six-membered (acetyl acetonate) chelate ring are known. In most cases, formation of the hexacoordinate P^{v} center is stabilized by rendering it highly acidic using an electron-withdrawing substituent such as F, Cl, or CF_3. Several studies have shown that sulfur, oxygen, and nitrogen atoms incorporated into flexible ring systems can also act as donor atoms and increase the coordination number on phosphorus [99]. Numerous such donor–acceptor hexacoordinate complexes with five-membered rings (as a part of the donor ring or as a separate entity) are known [101–103] but, relatively speaking, those with larger rings are much less in number. Hexacoordinate compounds **143–146** are examples of compounds formed by the donor action of sulfur and oxygen that contain at least one larger ring [54, 104, 105].

Compound **143** was prepared by an exchange reaction shown in Scheme 35a, with introduction of the sulfonated ring in the previous step being accomplished by reacting $P(OPh)_3$ with the diol in the presence of $(i\text{-Pr})_2NCl$ [104]. The phosphorane–atrane **144** was obtained as a major product along with **148** (not isolated), as shown in Scheme 35b. The same reaction also produced a cyclic phosphorane **147** with an unusually large ten-membered ring as an intermediate. A derivative similar to the atrane–phosphorane **144** with different substituents on the aromatic ring has also been reported by the same group [106].

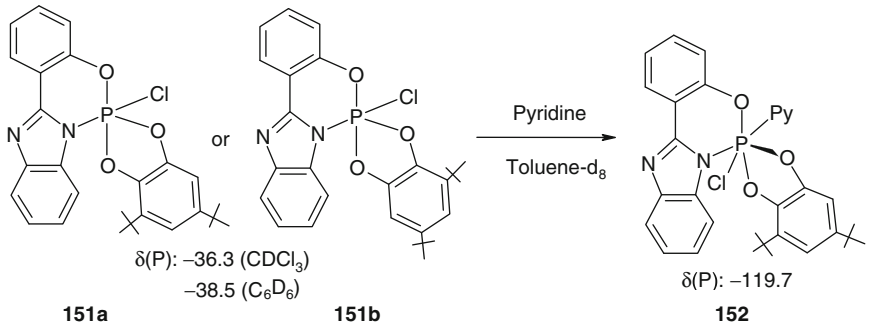


Scheme 35 Formation of hexacoordinate products **143-144**





Scheme 36 Formation of the hexacoordinate compound **150**



Scheme 37 Synthesis of the pyridine adduct **152**

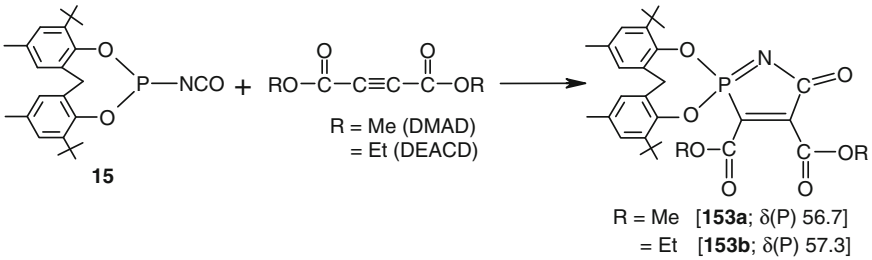
Another compound of interest is **150**, prepared by the reaction of the trichlorophosphorane **149** with isopropylidine-D-glucofuranose in the presence of a base (Scheme 36). In this compound, there is a fairly strong O→P coordination. Thus, this system has given a diverse range of structurally different cyclic penta- and hexacoordinate phosphorus compounds [82].

When the $-NMe_2$ group present in **86a–b** (discussed above) was replaced by a –Cl group, the resulting isomeric phosphorane **151a/b** showed pronounced Lewis acidic character [60]. In fact, upon addition of pyridine, the original signals in the ^{31}P NMR disappeared and a new peak at −119.7 ppm, corresponding to the hexacoordinate species **152**, appeared (Scheme 37). Interestingly, the authors observed that the room temperature ^{31}P NMR resonance at −119.7 was split into five other signals at −90 °C (δ −118.9, −120.4, −122.2, −123.8 and −124.8), all of which correspond to hexacoordinate species.

6 Reactions of Functionalized P^{III} Compounds with Activated Alkynes

A large number of synthetic applications for diverse organic transformations utilize triphenylphosphine–dimethyl acetylenedicarboxylate (Ph_3P–DMAD) or the combination of a P^{III} compound and electron-deficient alkene/alkyne [107–109]. The key

intermediate in the reaction utilizing the Ph_3P–DMAD combination is assumed to be $Ph_3P^+C(CO_2Me)=C^-(CO_2Me)$. Hence it was of some interest to study the reactivity of cyclic phosphites with alkynes in order to explore whether other modes of reactivity were possible. Thus, the reaction of $CH_2(6\text{-}t\text{-Bu–4-Me–}C_6H_2O)_2P$–NCO (**15**) with dipolarophiles like dimethyl acetylenedicarboxylate (DMAD) and diethyl acetylenedicarboxylate (DEACD) yielded spirocyclic products **153a–b** (Scheme 38, Fig. 8) [110]. The structure of **153a** was unambiguously proved by X-ray crystallography. This gave a convincing demonstration of the 1,3-(P,C) dipolar nature of P^{III} isocyanates. It is also interesting to note that this iminophosphorane is similar to the spirocyclic phosphorane **16a** obtained in the reaction with dialkyl azodicarboxylates $RO_2CN{=}NCO_2R$ [17]. By contrast, treating an organic isocyanate R-NCO



Scheme 38 Synthesis of the heterocyclic iminophosphoranes **153a-b**

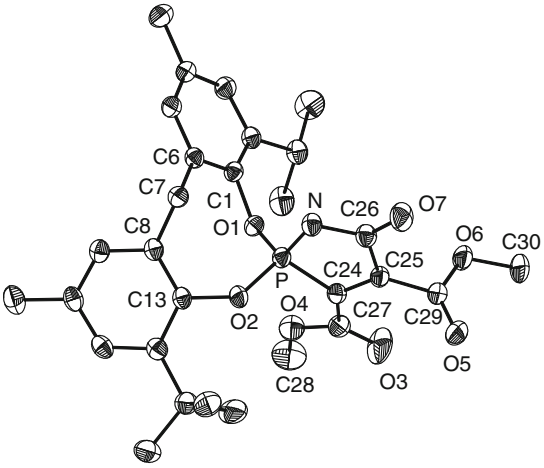
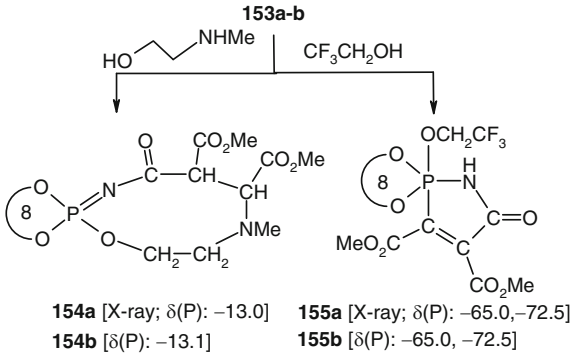


Fig. 8 Molecular structure of **153a**. Only non-hydrogen atoms are shown, with labeling on selected atoms. Selected bond parameters: P–O(1) 1.542(2), P–O(2) 1.549(2), P–N 1.558(2), P–C(24) 1.773(2), N–C(26) 1.359(3), C(24)–C(25) 1.321(4), C(25)–C(26) 1.521(4) Å. ORTEP was redrawn from supporting material given in [111]

with DMAD could, logically, lead to six-membered pyridone rings through a [2 + 2 + 2] cycloaddition, possibly via the unstable azetones [111].

A rather unique and unprecedented ring expansion (from five- to nine-membered) occurs upon addition of 2-(methylamino)ethanol to **153a–b**, to yield the



Scheme 39 Synthesis of iminophosphoranes **154a-b** and pentacoordinate phosphoranes **155a-b**

heterocyclic iminophosphorane **154a–b** (Scheme 39) [110]. A part of the X-ray structure of **154a** showing the conformation of the two large rings is shown in Fig. 9. A Michael-type [1, 4] addition in which the amine attacks at the carbon adjacent to phosphorus is the key step; cleavage of the P–C bond occurs during subsequent

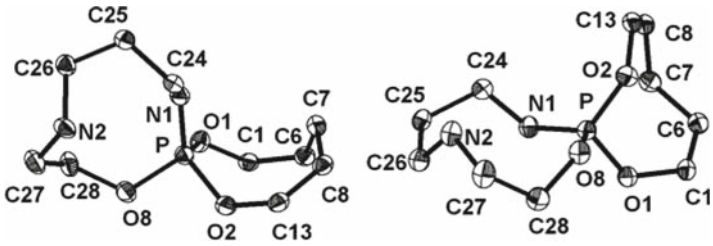
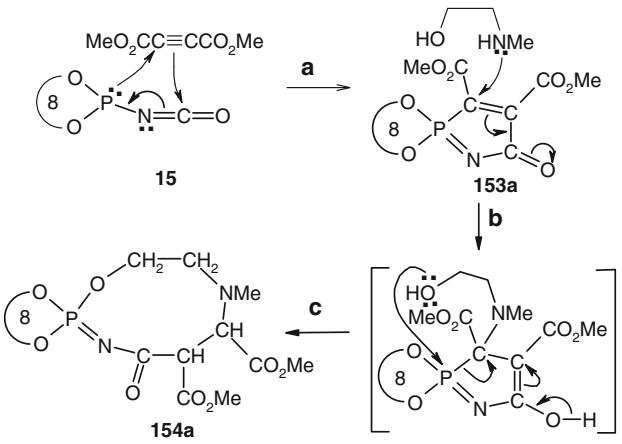


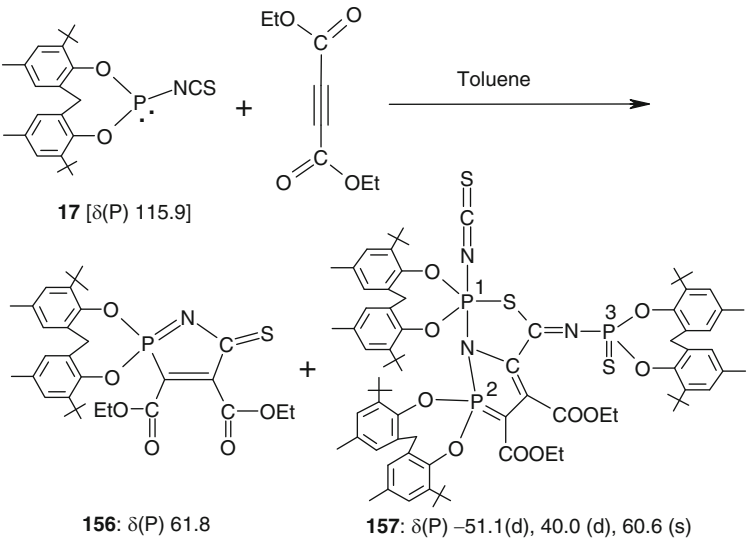
Fig. 9 Two views of the iminospirophosphorane **154a** showing the conformations of the eight- (*left*) and nine- (*right*) membered rings. Only selected atoms are shown

attack by the hydroxy group on phosphorus (Scheme 40). This reaction contrasts with the addition of 2,2,2-trifluoroethanol across the P=N bond of **153a–b** resulting in the spirocyclic pentacoordinate phosphoranes **155a–b** (Scheme 39). The ^{31}P NMR spectra of these latter compounds in $CDCl_3$ solution exhibit two signals suggesting the presence of isomeric phosphoranes in solution.

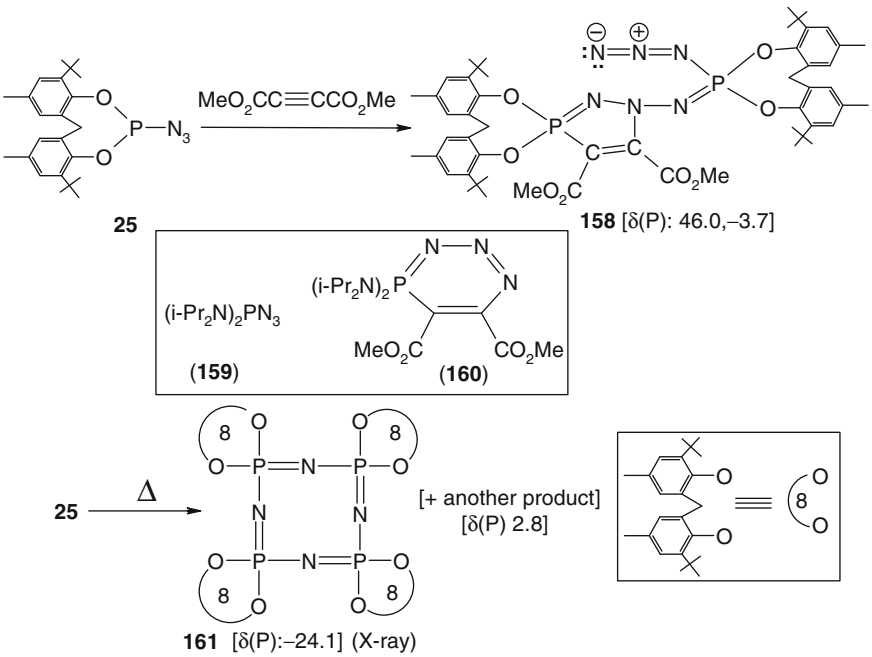


Scheme 40 Possible pathway leading to compound **154a**

The reaction of the isothiocyanate compound **17** with DEAD also afforded a spirocyclic heterocycle **156** analogous to **154a–b** but, in addition, a very unusual tricyclic pentacoordinate phosphorane **157** was obtained (Scheme 41) [112]. Stoichiometrically, compound **157** can be construed an addition product of two



Scheme 41 Formation of the heterocycle **156** and phosphorane **157**



Scheme 42 Formation of the iminophosphorane **158** and the cyclophosphazene **161**; structures of the azide **159** and the imino compound **160** are also shown.

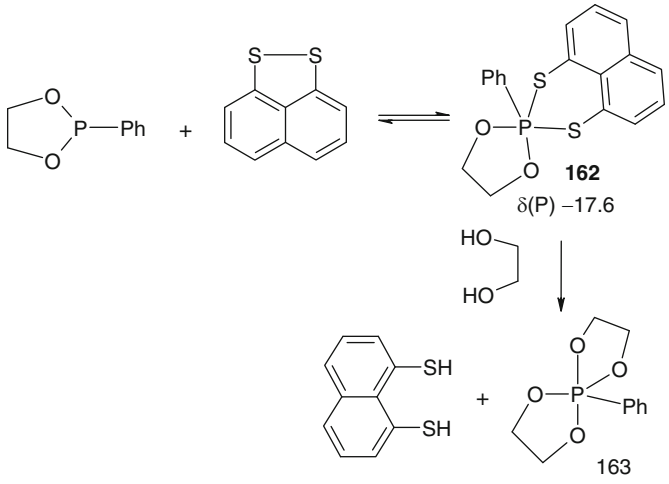
molecules of **17** with a molecule of **156**. Isolation of such a species also points towards the diverse reaction chemistry of functionalized P^{III} derivatives. Spirocyclic iminophosphorane **156** undergoes addition of 2,2,2-trifluoroethanol in a manner similar to **154a** to lead to an isolatable phosphorane analogous to **155a**.

The reaction of the cyclic P^{III} azide $CH_2(6\text{-}t\text{-Bu–}4\text{-Me–}C_6H_2O)_2P\text{–}N_3$ (**25**) with DMAD also afforded a heterocycle **158**, but with two phosphorus residues per DMAD (Scheme 42) [110]. This reaction pathway is completely different from that observed for $[(i\text{-Pr})_2N]_2PN_3$ (**159**) [113] or for the organic azide PhN_3 [114]. In the reaction using **159**, the six-membered heterocycle **160** was formed. An attempted extension of this reaction to less reactive acetylenes was not successful because the precursor azide **25** was thermally unstable and led to a mixture of cyclophosphazene derivatives from which $[CH_2(6\text{-}t\text{-Bu–}4\text{-Me–}C_6H_2O)_2P{=}N]_4$ (**161**) could be isolated [115]. Although spirocyclic cyclophosphazenes can in principle be considered under iminophosphoranes, they themselves should be a topic for full discussion [116] and hence are not discussed further.

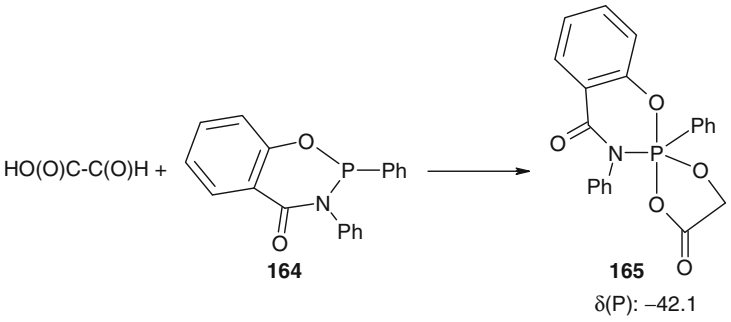
7 Miscellaneous Reactions Leading to Spirophosphoranes

An interesting oxidative addition reaction involves the addition of cyclic disulfides to a P^{III} precursor. Although exploited only to a limited extent, the reaction offers a nice route to dithiaphosphoranes [117, 118]. The example **162** cited in Scheme 43 gives a phosphorane with a six-membered 1,3,2-dithiaphosphorin ring system. The dithia moiety can be replaced by reacting **162** with 1,2-ethanediol to lead to the phospholane derivative **163**.

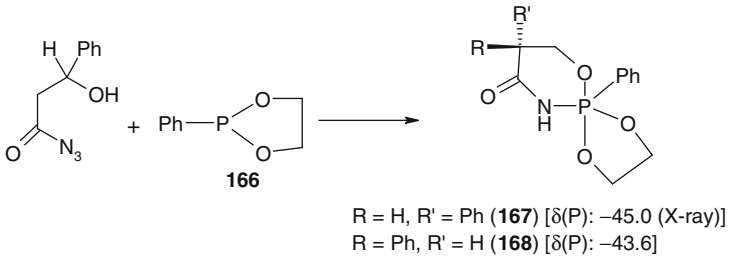
Anhydrous glyoxylic (oxoacetic) acid reacts with several P^{III} compounds leading to pentavalent species with the acid proton shifted to a carbon atom, as shown in Scheme 44 [119]. Thus, it can be noted that in the formation of **165** from **164**, the



Scheme 43 Synthesis of the phosphoranes **162-163**



Scheme 44 Synthesis of the spirocyclic phenylphosphorane **165**

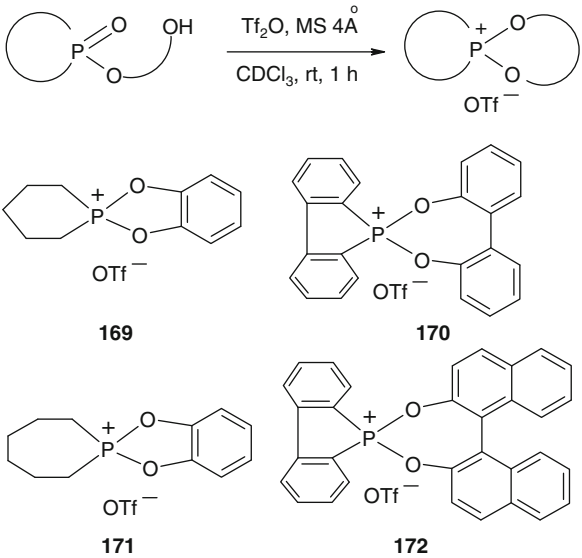


Scheme 45 Synthesis of the spirocyclic phosphoranes **167-168**

carboxylic acid proton has moved to the aldehydic carbon. Despite its novelty and simplicity, this reaction does not seem to have been utilized much in the literature.

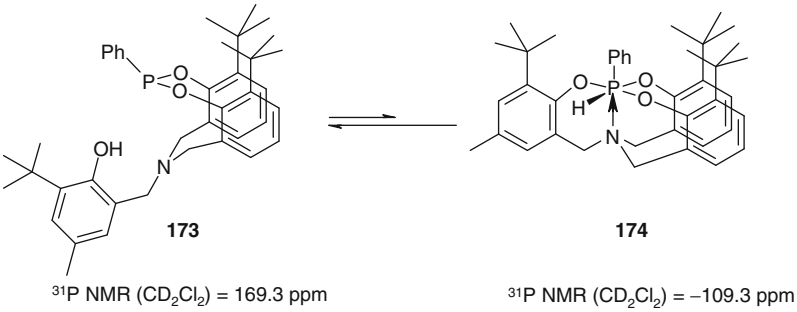
A unique reaction using acyl azides and P^{III} precursors is also known to afford pentacoordinate phosphoranes; examples that lead to the formation of six-membered ring at phosphorus are shown in Scheme 45 [120]. It is likely that this reaction takes place via the formation of iminophosphorane resulting from the reaction of the azide with the P^{III} compound.

Several spirocyclic phosphonium triflate salts [**169–172**] have been prepared by Terada and Kouchi by the route shown in Scheme 46 for metal-free Lewis acid catalysis in Diels–Alder reaction [121]. It may be noted that these compounds are

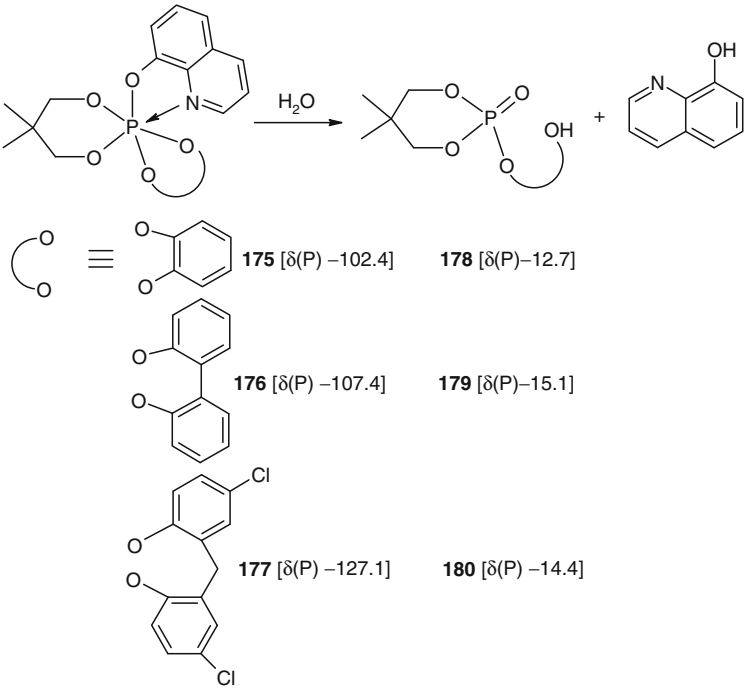


Scheme 46 Synthesis of the phosphonium triflate salts **169-172**

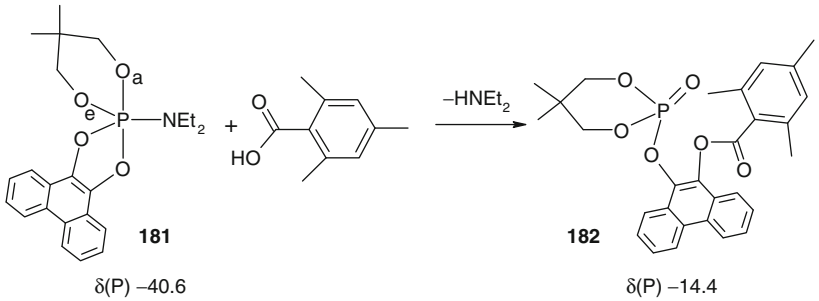
the ionic isomers of the pentacoordinate phosphoranes. The triflate anion is perhaps responsible for the prevalence of the phosphonium form over the phosphorane. The authors reported that the compounds containing five-membered dioxaphosphacycles **169–170** were quite effective, while those containing the seven-membered rings as in **171–172** were inactive as catalysts.



Scheme 47 Equilibrium between the tricoordinate species **173** and the hexacoordinate compound **174**



Scheme 48 Hydrolysis of spirophosphoranes **175-177** leading to **178-180**



Scheme 49 Reaction of phosphorane **181** with 2,4,6-trimethylbenzoic acid

The first example of conversion of tricoordinate to hexacoordinate phosphorus was also reported by Holmes and coworkers [105]. It was shown that $PhPCl_2$ upon treatment with tris(2-hydroxy-3,5-dimethylbenzyl)amine led to the tricoordinate phosphorus compound **173** (X-ray), which in solution underwent structural change to hexacoordinate species **174** (Scheme 47).

As regards the reactivity of spirophosphoranes, hydrolysis is of some interest since this gives an idea of the reactivity of different types of rings around phosphorus in penta- or hexacoordinate phosphorus. In one such study, hexacoordinate phosphoranes **175–177** were treated with water (Scheme 48) [122]. It was always found that the saturated six-membered ring (compounds **178–180**) remained intact. The oxinate group was cleaved off readily while the other unsaturated ring underwent partial opening to lead to the phosphate esters. A somewhat related reaction is that of the pentacoordinate phosphorane **181** with 2,4,6-trimethylbenzoic acid, wherein the tetracoordinate compound **182** was isolated (Scheme 49) [54].

8 Concluding Remarks

In this chapter, we have surveyed methods of generating spirocyclic (heterocyclic) phosphorus compounds with the phosphorus bearing a ring that is at least one larger than five-membered. Reactivity of such compounds, wherever appropriate, was also discussed. The advances made in this area have helped us in understanding (i) the diversity involved in species other than Morrison–Brunn–Huisgen intermediates that are relevant to the first stage of the Mitsunobu reaction, and (ii) structural and conformational preferences for six- (and higher) membered heterocycles in trigonal bipyramidal phosphorus that have implications for the apicophilicity rules as well as for cAMP action. Some applications that include resolving agents like BINPHAT (**138**), strong phosphazenic bases like the iminophosphorane **137**, and spirocyclic phosphonium triflates like **169** as organocatalysts for Diels–Alder reactions are worth-noting, although more of such uses are desirable. The expansion of

hexacoordinate phosphorus chemistry and its varied facets is also a remarkable achievement, although its application needs to be developed further.

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References

1. Corbridge DEC (2000) Phosphorus 2000: chemistry, biochemistry and technology, 4th edn. Elsevier, Amsterdam, p 361–370
2. Petrov AR, Rufanov KA, Ziemer B, Neubauer P, Kotov VV, Sundermeyer J (2008) Dalton Trans 909
3. Pietschnig R, Nieger M, Niecke E, Airola K (1997) J Organomet Chem 541:237
4. McNulty J, Capretta A, Laritchev V, Dyck J, Robertson A (2003) J Org Chem 68:1597
5. Jones ND, Cavell RG (2005) J Organomet Chem 690:5485
6. Mross G, Holtz E, Langer P (2006) J Org Chem 71:8045
7. Holmes RR (2004) Acc Chem Res 37:746
8. Jenkins ID, Mitsunobu O (1995) In: Paquette LA (ed) Encyclopedia of reagents for organic synthesis, vol 8. Wiley, New York, p 5379
9. But TYS, Toy PH (2007) Chem Asian J 2:1340
10. Nair V, Mathew SC, Biju AT, Suresh E (2007) Angew Chem Int Ed 46:2070
11. Otte RD, Sakata T, Guzei LA, Lee D (2005) Org Lett 7:495
12. Chakravarty M, Bhuvan Kumar NN, Sajna KV, Kumara Swamy KC (2008) Eur J Org Chem 4500
13. Arbuzov BA, Polezhaeva NA, Vinogradova VS (1968) Izv Akad Nauk SSSR Ser Khim 2525; Chem Abst (1969) 70:87682
14. Gonclaves H, Domroy JR, Chapleur Y, Castro B, Faudet H, Burgada R. (1980) Phosphorus Sulfur 147
15. Hulst R, Van Basten A, Fitzpatrick K, Kellogg RM (1995) J Chem Soc Perkin Trans 1 2961
16. Li Z, Zhou Z, Wang L, Zhou Q, Tang C (2002) Tetrahedron Asymmetry 13:145
17. Satish Kumar N, Praveen Kumar K, Pavan Kumar KVP, Kommana P, Vittal JJ, Kumara Swamy KC (2004) J Org Chem 69:1880
18. Satish Kumar N (2004) Studies on the synthesis, reactivity and utility of cyclic phosphorus(III) compounds and organophosphonates, Ph D thesis, University of Hyderabad, Hyderabad
19. Satish Kumar N, Kommana P, Vittal JJ, Kumara Swamy KC (2002) J Org Chem 67:6653
20. Bone SA, Trippett S (1976) J Chem Soc Perkin 1 156
21. Huheey JE, Keiter EA, Keiter RL (1993) Inorganic chemistry – principles of structure and reactivity, 4th edn. Addison-Wesley (Harper Collins), New York, p 227
22. Wulfsberg G (2000) Inorganic chemistry. University Science Books, Sausalito, CA, p 110
23. Lattman M (1994) Hypervalent compounds. In: King RB (ed) Encyclopedia of inorganic chemistry, vol 3. Wiley, Chichester, p 1496
24. Kommana P (2002) Studies on the reactivity of amino, azido and chloro-phosphorus(III) compounds, Ph D thesis, University of Hyderabad
25. Pavan Kumar KVP, Satish Kumar N, Kumara Swamy KC (2006) New J Chem 30:717
26. Osman FH, El-Samahy FA (2002) Chem Rev 102:629
27. Sheldrick WS (1978) Top Curr Chem 73:1
28. Holmes RR, Day RO, Deiters JM, Kumara Swamy KC, Holmes JM, Hans J, Burton SD, Prakasha TK (1992) In: Walsh EN, Griffith EJ, Parry RW, Quin LD, (Eds.) Phosphorus chemistry-development in American science. ACS Symposium Series 486, Chapter 2
29. Kumara Swamy KC, Burton SD, Holmes JM, Day RO, Holmes RR (1990) Phosphorus Sulfur Silicon 53:437

30. Skordalakes E, Dodson GG, St Clair Green D, Goodwin CA, Scully MF, Hudson HR, Kakkar VV, Deadman JJ (2001) J Mol Biol 311:549
31. Kumara Swamy KC, Satish Kumar N (2006) Acc Chem Res 39:324
32. Gorenstein DG (1987) Chem Rev 87:1047
33. Corbridge DEC (2000) Phosphorus 2000: chemistry, biochemistry and technology, 4th edn. Elsevier, Amsterdam,See Ref. 1 (2000) pp 1134-–1135
34. Trippett S (1976) Phosphorus Sulfur 1:89
35. Nakamoto M, Kojima S, Matsukawa S, Yamamoto Y, Akiba K-Y (2002) J Organomet Chem 441:643
36. Yu JH, Arif AM, Bentrude WG (1990) J Am Chem Soc 112:7451
37. Holmes RR, Kumara Swamy KC, Holmes JM, Day RO (1991) Inorg Chem 30:1052
38. Kumara Swamy KC, Holmes JM, Day RO, Holmes RR (1990) J Am Chem Soc 112:6092
39. Barlow JH, Bone SA, Russell DR, Trippett S, Whittle PJ (1976) J Chem Soc Chem Commun 1031
40. Schomburg D, Hacklin H, Röschenthaler G-V (1988) Phosphorus Sulfur 35:241
41. Said MA, Pülm M, Herbst-Irmer R, Kumara Swamy KC (1997) Inorg Chem 36:2044
42. Huang Y, Arif AM, Bentrude WG (1991) J Am Chem Soc 113:7800
43. Carrell HL, Berman HM, Ricci JS, Hamilton WC, Ramirez F, Maracek JF, Kramer L, Ugi I (1975) J Am Chem Soc 97:38
44. Timosheva NV, Prakasha TK, Chandrasekaran A, Day RO, Holmes RR (1995) Inorg Chem 34:4525
45. Kumaraswamy S, Muthiah C, Kumara Swamy KC (2000) J Am Chem Soc 122:964
46. Kommana P, Kumaraswamy S, Vittal JJ, Kumara Swamy KC (2002) Inorg Chem 41:2356
47. Kommana P, Satish Kumar N, Vittal JJ, Jayasree EG, Jemmis ED, Kumara Swamy KC (2004) Org Lett 6:145
48. Timosheva NV, Chandrasekaran A, Prakasha TK, Day RO, Holmes RR (1996) Inorg Chem 35:6552
49. Bergmann D, Hinze J (1987) In: Sen KD, Jørgensen CK Structure and bonding, electronegativity, vol 66. Springer, Heidelberg, p 145
50. Pavan Kumar KVP (2006) Investigations on the reactivity of P(III) compounds with dialkyl azodicarboxylates and utility of organophosphonates PhD Thesis, University of Hyderabad, Hyderabad
51. Wunderlich H, Mootz D, Schmutzler R, Wieber M (1974) Z Naturforsch B29:32
52. Prakasha TK, Chandrasekaran A, Day RO, Holmes RR (1995) Inorg Chem 34:1243
53. Prakasha TK, Day RO, Holmes RR (1992) Inorg Chem 31:1913
54. Said MA, Pülm M, Herbst-Irmer R, Kumara Swamy KC (1996) J Am Chem Soc 118:9841
55. Potter BVL, Lampe D (1995) Angew Chem Int Ed Engl 34:1933
56. Pavan Kumar KVP, Kumara Swamy KC (2007) Carbohydrate Res 342:1182
57. Prakasha TK, Day RO, Holmes RR (1994) Inorg Chem 33:93
58. Denney DB, Denney DZ, Hammond PJ, Tseng K-S (1981) J Am Chem Soc 103:2054
59. Hernández-Díaz J, Flores-Parra A, Contreras R (2004) Heteroat Chem 15:321
60. Hernández-Díaz J, Flores-Parra A, Contreras R (2004) Heteroat Chem 15:307
61. Sonnenburg R, Neda I, Fischer A, Jones PG, Schmutzler R (1995) Chem Ber 128:627
62. Sonnenburg R, Neda I, Thönnensen H, Jones PG, Schmutzler R (2000) Z Anorg Allg Chem 626:412
63. Neda I, Melnicky C, Vollbrecht A, Schmutzler R (1996) Synthesis 4:473
64. Plinta H-J, Neda I, Schmutzler R (1994) J Fluorine Chem 69:51
65. Neda I, Melnicky C, Vollbrecht A, Fisher A, Jones PG, Schmutzler R (1996) Z Anorg Allg Chem 622:1047
66. Hacklin H, Röschenthaler G-V (1988) Z Anorg Allg Chem 561:49
67. Vollbrecht A, Neda I, Fisher A, Jones PG, Schmutzler R (1995) Phosphorus Sulfur Silicon 107:69
68. Lu Y, Freytag M, Jones PG, Schmutzler R (2003) Z Anorg Allg Chem 629:1953
69. Mironov VF, Burnaeva LA, Krokhalev VM, Salontin VI, Konovalova IV, Mavleev RA, Chernov PP (1992) Zh Obsh Khim 62:1425; Chem Abst (1993) 118:102081

70. Mironov VF, Burnaeva LA, Konovalova IV, Khlopushina GA, Mavleev RA, Chernov PP, Pudovik AN (1993) *Zh Obshch Khim 63:25; Chem Abst (1993)* 119:72706
71. Prakasha TK, Day RO, Holmes RR (1992) Inorg Chem 31:3391
72. Day RO, Kumara Swamy KC, Fairchild L, Holmes JM, Holmes RR (1991) J Am Chem Soc 113:1627
73. Hans J, Day RO, Holmes RR (1991) Inorg Chem 30:3928
74. Broeders NLHL, Koole LH, Buck HM (1990) J Am Chem Soc 112:7475
75. Muthiah C, Said MA, Pülm M, Herbst-Irmer R, Kumara Swamy KC (2000) Polyhedron 19:63
76. Lahiri SD, Zhang G, Dunaway-Mariano D, Allen KN (2003) Science 299:2067
77. Tremblay LW, Zhang G, Dai J, Dunaway-Mariano D, Allen KN (2005) J Am Chem Soc 127:5298
78. Sychev VA, Koroteev MP, Dzgoeva ZM, Nifant'ev EE (2001) Russ J Gen Chem 71:188
79. Katalenic D, Skaric V, Klaic B (1994) Tetrahedron Lett 35:2743
80. Timosheva NV, Chandrasekaran A, Holmes RR (2005) J Am Chem Soc 127:12474
81. Timosheva NV, Chandrasekaran A, Holmes RR (2006) Inorg Chem 45:3113
82. Timosheva NV, Chandrasekaran A, Holmes RR (2006) Inorg Chem 45:10836
83. Neda I, Kaukorat T, Fischer A, Jones PG (1993) Phosphorus Sulfur Silicon 85:153
84. Anand BN, Rajwant B, Kussum A, Kumari U (1991) Ind J Chem Sect A 30:862
85. Pudovik MA, Terent'eva SA, Pudovik AN (1996) Zh Obsh Khim 66:366; Chem Abst (1996) 126:8215
86. Bouvier F, Vierling P, Dupart J-M (1988) Inorg Chem 27:1099
87. Gloede J, Piepera U, Habicherb WD, Schneider M (2002) Z Anorg Allg Chem 628:480
88. Schwesinger R, Willaredt J, Schlemper H, Keller M, Schmitt D, Fritz H Chem Ber (1994) 127:2435
89. Constant S, Lacour J (2005) Top Curr Chem 250:1
90. Lacour J, Hebbe-Viton V (2003) Chem Soc Rev 32:373
91. Koenig M, Klaebe A, Munoz A, Wolf R (1979) J Chem Soc Perkin Trans 2, p 40
92. Hellwinkel D, Lindner W, Wilfinger HJ (1974) Chem Ber 107:1428
93. Shevchenko IV, Fischer A, Jones PG, Schmutzler R (1992) Chem Ber 125:1325
94. Lacour J, Vial L, Herse C (2002) Org Lett 4:1351
95. Hebbe V, Londez A, Goujon-Ginglinger C, Meyer F, Uziel J, Juge S, Lacour J (2003) Tetrahedron Lett 44:2467
96. Lacour J, Londez A, Goujon-Ginglinger C, Buss V, Bernardinelli G (2000) Org Lett 2:4185
97. Lacour J, Vial L, Bernardinelli G (2002) Org Lett 4:2309
98. Wong CY, Kennepohl DK, Cavell RG (1996) Chem Rev 96:1917
99. Holmes RR (1998) Acc Chem Res 31:535
100. Kumara Swamy KC, Kumaraswamy S, Said MA, Krishna Kishore RS, Herbst-Irmer R, Pülm M (2000) Curr Sci 78:473
101. Wong CY, McDonald R, Cavell RG, (1996) Inorg Chem 35:325
102. Sherlock DJ, Chandrasekaran A, Day RO, Holmes RR (1997) J Am Chem Soc 119:1317
103. Sood P, Chandrasekaran A, Day RO, Holmes RR (1998) Inorg Chem 37:6329
104. Chandrasekaran A, Day RO, Holmes RR (1997) J Am Chem Soc 119:11434
105. Timosheva NV, Chandrasekaran A, Holmes RR (2004) Inorg Chem 43:7403
106. Timosheva NV, Chandrasekaran A, Holmes RR (2005) Z Anorg Allg Chem 631:1
107. Lu X, Zhang C, Xu Z (2001) Acc Chem Res 34:535
108. Valentine Jr DH, Hillhouse JH (2003) Synthesis, p 317
109. Nair V, Rajesh C, Vinod AU, Bindu S, Sreekanth AR, Mathen JS, Balagopal L (2003) Acc Chem Res 36:899
110. Kumaraswamy S, Kommana P, Satish Kumar N, Kumara Swamy KC (2002) Chem Commun 40
111. Storzer W, Schomburg D, Röschenthaler GV (1981) Z Naturforsch B 36:1071
112. Kumaraswamy S, Senthil Kumar K, Satish Kumar N, Kumara Swamy KC (2005) Dalton Trans 1847

113. Bieger K, Tejeda J, Rèau R, Dahan F, Bertrand G (1994) J Am Chem Soc 116:8087
114. Padwa A (1991) In: Trost BM, Fleming I Comprehensive organic synthesis, vol 4. Pergamon, Oxford, p 1069
115. Kommana P, Kumaraswamy S, Kumara Swamy KC (2003) Inorg Chem Commun 6:394
116. Bhuvan Kumar NN, Kumara Swamy KC (2008) Chirality 20:781
117. Kimura Y, Kokura T, Saegusa T (1983) J Org Chem 48:3815
118. For earlier work, see: De''Ath NJ, Denney, DB (1972) J Chem Soc Chem Commun 395
119. Kobayashi S, Narukawa Y, Saeusa T (1982) Synth Commun 12:539
120. Poechlauer P, Petter W, Peringer P, Mueller EP (1985) J Chem Soc Chem Commun 1764
121. Terada M, Kouchi M (2006) Tetrahedron 62:401
122. Kumara Swamy KC, Said MA, Kumaraswamy S, Herbst-Irmer R, Pülm M (1998) Polyhedron 17:3643

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The Chemistry of Phosphinines

Pascal Le Floch

Abstract Recent developments in the chemistry of phosphinines are reported. This chapter presents and discusses the most important breakthroughs achieved during the last decade. New synthetic approaches allowing the synthesis of polyfunctional phosphinines as well as improvements of well known methods are reported. The use of phosphinines in coordination chemistry is also presented with particular emphasis on their use in the stabilization of low valent and highly reduced transition metal complexes. Another aim of this review is to discuss recent applications of phosphinines, and structures derived directly from phosphinines such as phosphacyclohexadienyl anions and phosphabarrelenes, as ligands in homogeneous catalysis.

Keywords Coordination complexes, Heterocycles, Homogeneous catalysts, Phosphinines, Phosphorus compounds.

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1 Introduction

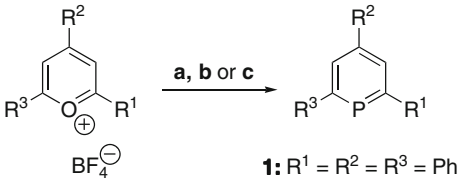
Phosphinines, the phosphorus equivalents of pyridines, whose synthesis was first achieved by Märkl in 1966, have long been considered as chemical curiosities for phosphorus chemists [1]. Until the 1980s, most studies essentially focused on their synthesis and the understanding of their reactivity. Several important reviews, covering different periods and different areas of the chemistry of phosphinines (synthesis and reactivity [2–5], coordination chemistry [6], and catalysis [7, 8]), have already been devoted to this important class of phosphorus heterocycles. Significant advances have been made over the last decade thanks to the development of new synthetic approaches (or the improvement of older methods) that henceforth allow the preparation of polyfunctional derivatives and sophisticated edifices on significant scales. The rapid developments of theoretical methods (DFT, ab initio methods) also strongly contributed to confirm that phosphinines constitute a very peculiar class of aromatic phosphorus ligands whose electronic properties differ markedly from those of classical tertiary phosphines and other unsaturated acyclic and heterocyclic phosphorus compounds. Thus, it has been clearly demonstrated, and illustrated through many examples, that the most significant electronic feature of phosphinines is their important π-accepting capacity. This property, which results from the presence of a low lying LUMO, makes them suitable precursors for the synthesis of stable radical anions and dianions featuring unusual bonding and structures. Importantly, this property also renders them very attractive ligands for the stabilization of electron rich metal centres or metal surfaces. Significant efforts have therefore been made to exploit the original structure of phosphinines in homogeneous catalysis where there is a great demand for strong π-acceptor ligands. As will also be seen, though the reactivity of the highly electrophilic character of phosphinines hampers their use in some catalytic processes, some interesting applications have been developed. Furthermore, recent studies have shown that the phosphinine skeleton provides a powerful entry to the synthesis of new classes of ligands featuring an sp^3-hybridized phosphorus atom such as 1-phosphabarrelenes and 1*R*-phosphacyclohexadienyl anions. All these developments will be discussed in this review. Note that this review deals exclusively with the chemistry of monophosphinines. The chemistry of di- and triphosphinines will not be discussed here.

2 Synthetic Approaches Towards Phosphinines

2.1 Classical O^+ /P Exchange

The O^+ /P exchange from pyrilium salt using a source of PH_3 is the classical procedure that allowed the synthesis of the first phosphinine, the ubiquitous 2,4,6-triphenylderivative **1** reported by Märkl in 1966. This straightforward approach which relies on the use of easily available and inexpensive compounds

has recently been widely exploited by the groups of Breit [9, 10], BASF [11] and Müller [8] for the synthesis of polyfunctional derivatives. The general scheme of this synthetic approach is presented in the following (scheme 1).

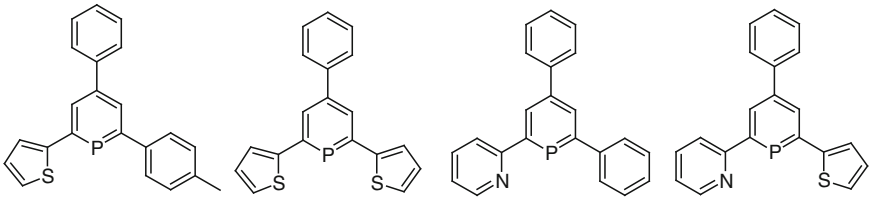


Scheme 1 (**a**) $PTMS_3$, MeCN, reflux; (**b**) PH_3, *n*-butanol, 110°C; (**c**) $P(CH_2OH)_4$, C_5H_5N, 8°C

This methodology has also been extended to the synthesis of a new class of polyheterocyclic derivatives such as compounds **2–5** featuring thiophene or pyridine as ancillary substituents (Fig. 1) [12, 13].

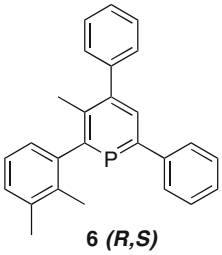
Most importantly, this O^+/P exchange proved to be very appropriate for the synthesis of atropoisomeric phosphinines. Müller and his group shown that phosphinine **6** could be obtained as a 1:1 mixture of enantiomers and that separation could be successfully achieved by analytical HPLC (Fig. 2) [14]. A rotational barrier of $D G^{\#} = 116$ kJ mol^{-1} for enantiomerization of **6** was predicted by means of DFT calculations, indicating that **6** is expected to be configurationally stable at room temperature [15].

The methoxy derivative was obtained using the same procedure. Conversion of this compound into the hydroxyl derivatives **7** and **8** afforded a nice entry to a new



2 **3** **4** **5**

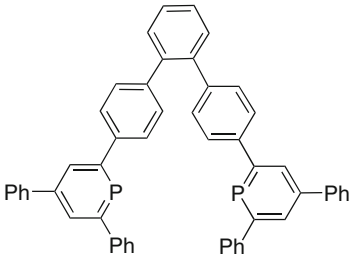
Fig. 1 Polyheterocyclic phosphinines featuring thiophenes or pyridines



6 ***(R,S)***

separated by chiral HPLC

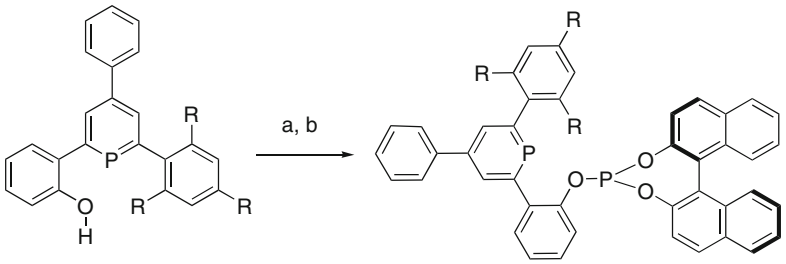
Fig. 2 A configurationally stable phosphinine



11

Fig. 3 A bis-phosphinine with a wide bite angle

class of chiral bidentate phosphinine-based ligands. Thus reaction of **7** and **8** with the (*S*)-BINOL-PCl derivative afforded the bidentate ligands **9** and **10** in good yields (Scheme 2) [16].



7: R = H
8: R = Me

9: R = H
10: R = Me

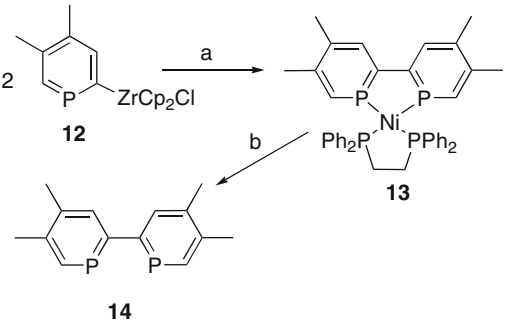
Scheme 2 **a** BBr_3/CH_2Cl_2; **b** (*S*)-Binol-PCl, Et_3N, toluene

Finally, wide bite-angle bis-phosphinines such as **11** were also obtained using the same approach (Fig. 3). Calculations carried out at the MM2 level revealed that the P–P distance in the most stable conformation is about 4.64 Å, thus showing that this ligand can achieve *trans* coordination on metal centres [17].

2.2 2-Halogenophosphinines as Precursors

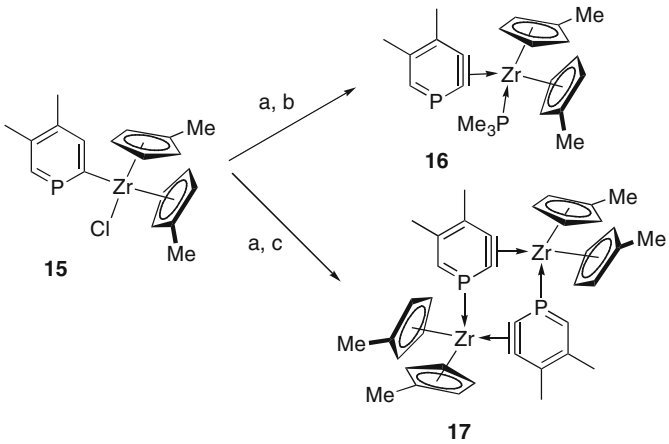
2-Halogeno- and 2,6-dihalogenophosphinines already proved to be suitable synthons for the elaboration of 2,6-disubstituted phosphinines through different derivatization methods including transition metals such as Pd and Ni or organometallic derivatives such as Li [18] and Zn [19]. Most recent developments focused on the use of zirconocene(IV) derivatives which can be directly prepared from the reaction of 2-halogenophosphinines (X = Cl, Br) with the 14 VE fragment $[ZrCp_2]$

[20]. Zirconium(IV) complexes such as **12** were successfully employed for the synthesis of 2,2'-biphosphinines upon reaction with the [Ni(dppe)Cl_2] complex [21]. This process relies on a C-Zr to C-Ni bond metathesis leading to the nickel (0) biphosphinine complex **13**. Release of the 2,2-biphosphinine ligand **14** from nickel was achieved in a second step upon oxidation with hexachloroethane (Scheme 3).



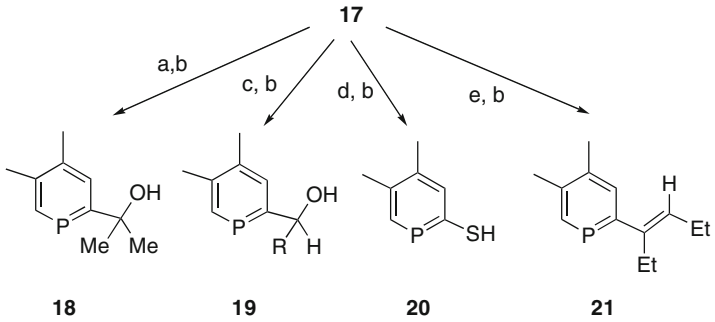
Scheme 3 **a** [Ni(dppe)Cl2], THF, 70 °C; **b** C_2Cl_6, toluene, RT

Zirconium(IV) complexes such as **15** also could be converted to the η^2-phosphabenzyne zirconocene complexes which can be isolated either as the PMe_3 adduct **16** [22] or as the corresponding dimer **17** (Scheme 4) in which the phosphine ligand acts as a 4 e donor (2 e being given by the lone pair at P to Zr and 2 e being given at zirconium by the pseudo benzyne ligand) [23, 24]. The X-ray crystal structure of **17** revealed that the C–C bond distance at 1.361(2) Å is closer to a double bond than to a genuine triple bond. Therefore, it was concluded that these η^2-phosphabenzyne complexes must be regarded as Zr(IV) complexes like their well-known carbon counterparts.



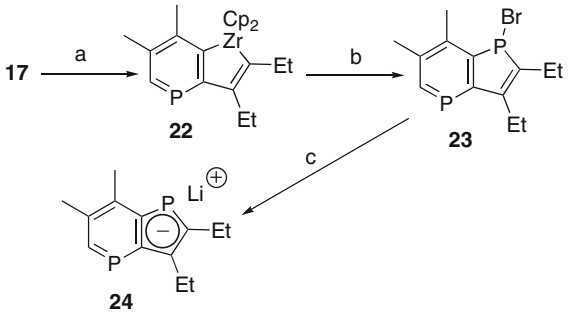
Scheme 4 **a** MeLi, THF, −80 °C; **b** 50 °C toluene, PMe_3; **c** 50 °C toluene

Not surprisingly, there is a strong analogy between the reactivity of these phosphabenzyne complexes and that of their benzene analogs. They react with ketones and aldehydes to yield the corresponding alcohols **18** and **19** after hydrolysis. Interestingly, the polarization induced by the presence of the phosphorus atom makes these transformations regioselective, the incoming functional group being grafted at the C2 position (α-position at phosphorus). This approach was also exploited to prepare the first 2-thio-phosphinine **20** (through reaction with elemental sulphur) and the vinyl derivative **21**, when 3-hexyne was used as partner (Scheme 5).



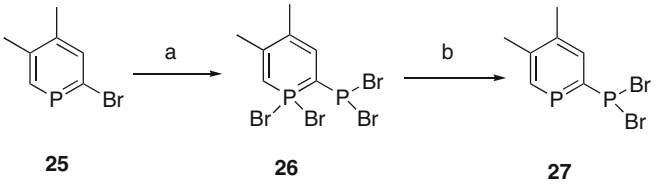
Scheme 5 **a** Me_2CO, toluene, 80 °C; **b** H_3O^+, RT; **c** RCHO, THF, 80 °C; **d** 1/8 S_8; **e** EtCCEt, toluene 80 °C

Interestingly, it was also shown that these η^2-phosphabenzyne zirconocene complexes with alkyne also provide a direct entry to 1,4-diphosphaindenes through a Zr-C to Zr-P bond metathesis upon reaction of the zirconacyclophosphaindene **22** with PBr_3 [25]. These new heterocycles were also characterized as their bromo **23** and monoanionic derivative **24**, the negative charge residing on the phospholide unit (Scheme 6).



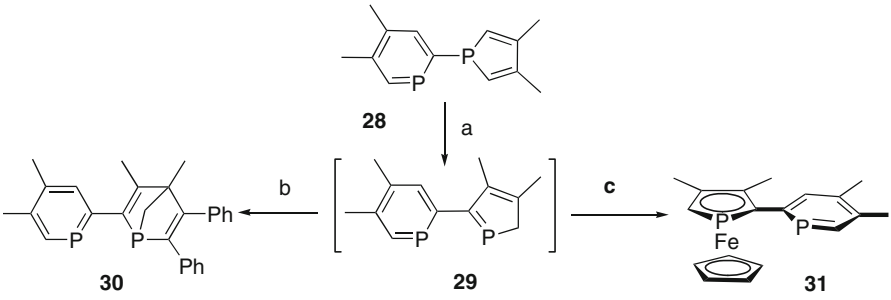
Scheme 6 **a** EtCCEt, toluene, 80 °C; **b** PBr_3, CH_2Cl_2; **c** Li, THF, RT

Noteworthy, 2-bromophosphinines have also found an interesting application in the synthesis of a new class of phosphinine-based bidentate ligands featuring either a phosphine or a phosphorus heterocycle like phosphirene or 1,2-dihydrophosphete. Reaction of phosphorus tribromide with 2-bromophosphinine **25** afforded the 2-dibromophosphinophosphinine **27** which in turn could be converted to functional derivatives either through nucleophilic or electrophilic reaction at the P–Br bonds. The mechanism of this phosphination process was shown to involve the transient formation of the λ^5-dibromophosphinine **26** (Scheme 7) [26].



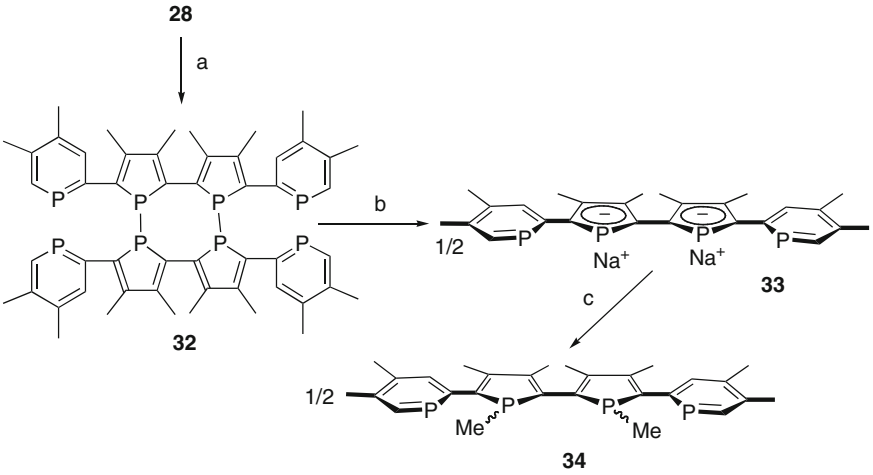
Scheme 7 **a** PBr_3, neat, RT; **b** $P(CH_2CH_2CN)_3$, CH_2Cl_2, RT

Cross-coupling reactions between phospholide anions and bromophosphinines were also thoroughly exploited to prepare a new class of bi- and polydentate ligands featuring a phosphinine and a phosphole, a phosphaferrocene, or a phosphanorbornadiene unit. It was shown that the thermal reaction of the 2-phosphininyl-1*H*-phosphole **28** affords the transient phosphinine-2*H*-phosphole **29** which results from a classical [1, 5]sigmatropic shift of the substituent (here the C2-phosphininyl radical) around the phosphole nucleus. Trapping reaction of this very reactive intermediate with diphenylacetylene and the $[FeCp(CO)_2]_2$ dimer respectively afforded the bidentate phosphinine-phosphanorbornadiene ligand **30** and the phosphinine- phosphaferrocene derivative **31** (Scheme 8) [27].



Scheme 8 **a** 130 °C toluene; **b** PhCCPh, 130 °C, toluene; **c** $[FeCp(CO)_2]_2$, CO, 90 °C

A similar strategy was employed to assemble the tetramer **32** which features four central phosphole units and four peripheral phosphinine rings. Importantly, reduction of this oligomer with 4 equiv. of sodium naphthalenide sodium resulted in the cleavage of the two P–P bonds and formation of the phospholide anions. This dianionic species was found to be sufficiently stable to be characterized. Trapping reaction of dianion **33** with methyl iodide afforded the tetradentate ligand **34** (Scheme 9).

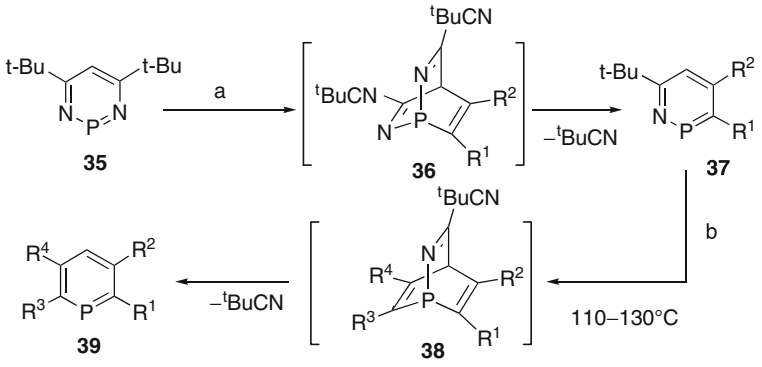


Scheme 9 **a** 130 °C toluene; **b** 4 $C_{10}H_8Na$, THF, RT; **c** MeI, THF, RT

2.3 Chemistry of 1,3,2-Diazaphosphinines

1,3,5-Diazaphosphines were first employed by Märkl to generate phosphinines through a [4 + 2] cycloaddition/cycloreversion sequence with functional alkynes [28, 29]. Unfortunately, this approach proved to be quite limited due to the poor availability of diazaphosphinines from the corresponding diazapyrilium salts. However, 1,2-aza- and 1,3,2-diazaphosphinines that can be straightforwardly prepared through a Ti-N to N-P bond metathesis from the corresponding diazatitanacycles proved to be more easily accessible and therefore were extensively employed for the synthesis of tetrafunctional phosphinines and sophisticated edifices [30, 31]. In general, 1,3,2-diazaphosphinines such as **35** undergo a first cycloaddition with alkynes around 80–90 °C to yield transiently a diazaphosphabarrelene **36**. DFT calculations have clearly shown that these diazaphosphabarrelenes are thermally unstable and decompose as soon as they are formed to yield 1,2-azaphosphinine derivatives **37**. NICS (nucleus independent chemical shift) calculations, which were carried out on theoretical optimized structures, have clearly shown that 1,2-azaphosphinines are more aromatic than their diaza congeners [32]. These monoazaphosphinine derivatives are still sufficiently reactive to undergo a second

Diels-Alder reaction at higher temperature (around 110–120 °C) to give azaphosphabarrelenes **38** which finally decompose to yield the expected 2,3,5,6-tetrafunctional phosphinines **39**. Importantly, the difference of reactivity between diaza and mono aza-phosphinine derivatives allows the successive use of two different alkynes. The general principle of this synthetic approach is presented in Scheme 10. It is important to mention that all these cycloaddition/cycloreversion sequences can be performed in the same flask and there is no need to isolate the 2-zaphosphinine formed after the first Diels-Alder reaction.



Scheme 10 **a** R_1CCR_2, toluene 80–90 °C; **b** R_3CCR_4, toluene, 110–120 °C

The following figure presents some of the symmetrically and unsymmetrically substituted 2,3,5,6-tetrafunctional compounds that were prepared using this methodology. As can be seen, silyl substituted alkynes were often employed as substrate since their cycloadditions with diazaphosphinines proceed with a very good regioselectivity, the silyl group being always located at the C2 or at the C6 position in the formed phosphinine. Thus, for example, compound **40**, **41** and **42** respectively result from the reaction of diazaphosphinine **35** with 2 equiv. of ethynylpyridine, $PhCCSiMe_2CCPh$ or bis(diphenylphosphino)acetylene. Compound **43** results from the reactions of diazaphosphinine **35** with $(Cp_2Fe)CC\text{-}SiMe_3$ followed by the reaction of the corresponding monoazaphosphinine formed with $HCC\text{-}SiMe_3$. Phosphinine **44** was built by first reacting diazaphosphinine **35** with $MeCCCH(OEt)_2$ and then by condensing phenylacetylene on the monoazaphosphinine formed in a second step (Fig. 4).

However, most efforts focused on the elaboration of polydentate ligands using 1,4 and 1,6-diynes as substrates. Bi-, tri- and tetradentate ligands such as **45**–**48** were thus successively prepared and structurally characterized. This approach was also successfully extended to the preparation of the first mixed phosphinine ether macrocycles such as **49** [33]. Mixed tridentate species featuring phosphole, phospholide or phosphaferrocene moieties were also prepared from the condensation of diazaphosphinine **35** with the corresponding bis(dimethylsilyl) alkynyl derivatives (Fig. 5) [34].

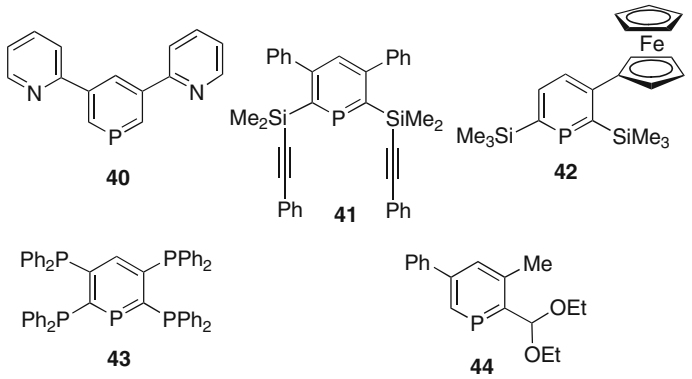


Fig. 4 Some functional phosphinines synthesized through the reaction of diazaphosphinine **35** with alkynes

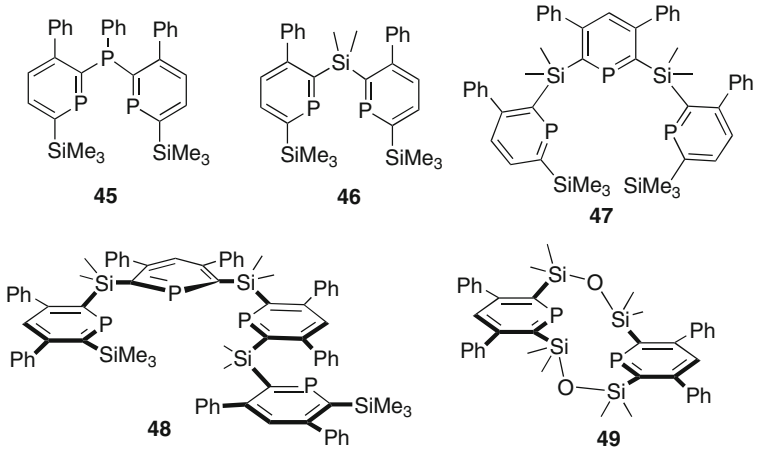


Fig. 5 Some polydentate phosphinines ligands synthesized through the reaction of diazaphosphinine **35** with diynes

A significant breakthrough was achieved with the synthesis of the first phosphorus macrocycles featuring sp^2-hydridized phosphorus atoms – silacalix-[*n*]-phosphinines (*n* indicating the number of phosphinines units contained in the macrocycle) [35]. Compounds **50** (*n* = 4) and **51** (*n* = 3) were obtained in modest to good yields using a two-step procedure which relies on the reaction of a 2,6-bis(dimethylsilylalkynyl)phosphinine with diazaphosphinine **35**. Mixed derivatives featuring two thiophene **52** and furan **53** moieties could also be prepared following the same strategy (Fig. 6). All these macrocycles were isolated as very air stable and moderately soluble powders that can be purified and handled without any difficulties. Combination of NMR data and X-ray crystallography reveal that these compounds are fluxional in solution [36]. As will be seen further, in

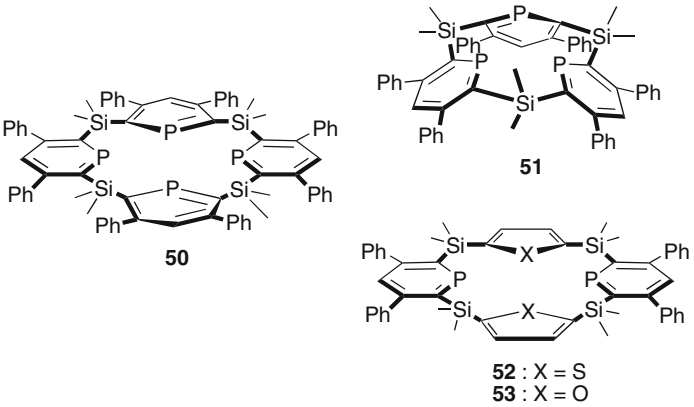
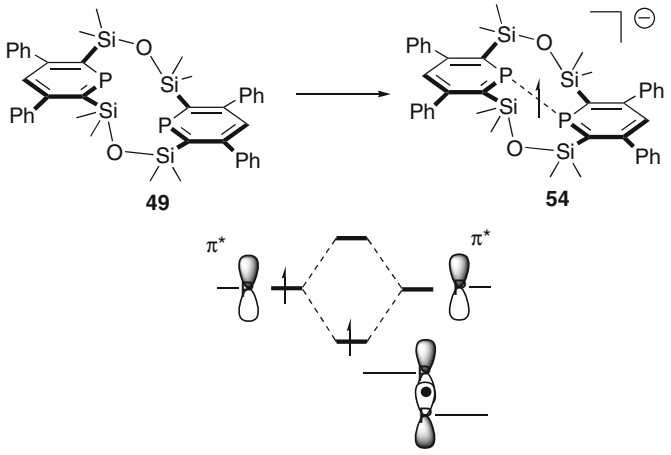


Fig. 6 Some phosphinine-based macrocycles

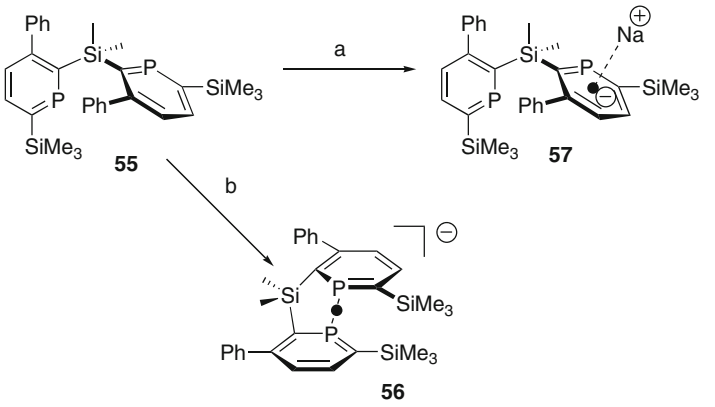
the following section dealing with the coordination chemistry of phosphinines, these macrocycles have found interesting applications in the stabilization of reduced transition metal centres.

Reduction processes of the bis-phosphinine **49** was thoroughly investigated by a combination of EPR spectroscopy and DFT calculations. It was shown that the monoelectronic reduction of **49** with sodium naphthalenide at low temperature affords the corresponding radical anion **54** in which the odd electron is localized in a one-electron P–P bond 2.763 vs 3.256 Å in the neutral molecule) [37]. DFT calculations suggest that formation of this bond results from the in-phase combinations of the LUMOs of phosphinine which exhibit a large coefficient at phosphorus (π^* orbital) (Scheme 11). Unfortunately, anion radical **54** could not be crystallized but the X-ray crystal structure of the corresponding dianionic species was recorded.



Scheme 11 $NaC_{10}H_8$, THF, −80 °C

Further studies on the reduction of bisphosphinine **55** showed that the existence of a rigid structure is not a prerequisite to the formation of a one electron P–P bond [38]. Combination of EPR spectroscopy and DFT calculations indicates that a loose P–P bond (3.479 vs .5.8 Å in the neutral molecule) is formed upon reduction with one electron (compound **56**). Additional experiments carried out with (or without) cryptands at various temperatures showed that the formation of a tight ion-pair can stabilize compound **57** in which the odd electron is exclusively localized on a single phosphinine ring (Scheme 12).

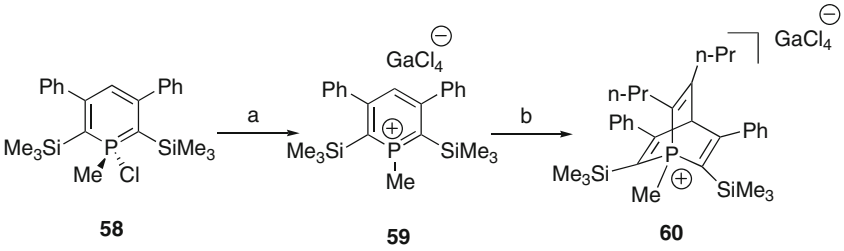


Scheme 12 **a** Reduction carried out without cryptand. **b** In the presence of cryptand

2.4 Miscellaneous Reactions

As could be noted in the previous section, 2-silylsubstitued derivatives have significantly contributed to the chemistry of phosphinines either in allowing the synthesis of sophisticated structures and edifices or in providing a significant kinetic stabilization (reduced species). Another additional example of their utility was given with the synthesis of the first stable methylphosphininium cation. Though phosphininium cations have been proposed as intermediates in various synthetic transformations, they were never isolated as discrete species nor fully characterized. In 2003 it was shown that the reaction of λ^5–1-methyl-chlorophosphinine **58** in the presence of $GaCl_3$ as chloride abstractor afforded the 1-methylphosphininium cation **59** which was structurally characterized [39]. Interestingly, DFT calculations suggest that the aromatic character (ASE aromatic stabilization energy computed at the B3LYP/6–311 + G** level of theory) of this reactive cationic species compares with that of phosphinine. Cation **59** proved to be very sensitive towards nucleophilic attack to form λ^5-phosphinine derivatives. Despite their high aromatic character, phosphininium cations easily react with alkynes through a [4 + 2] cycloaddition process to yield phosphabarrelenium salts such as **60** (Scheme 13). Indeed, DFT calculations carried out at the MP2/6–311 + G** level of theory have shown that

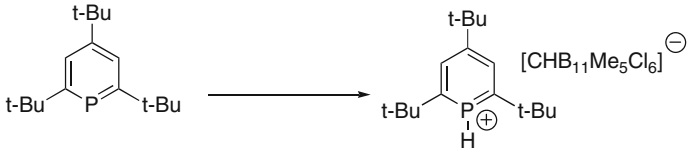
introduction of a methyl cation at the phosphorus atom of phosphinine results in a dramatic lowering of the HOMO which facilitates the Diels Alder reaction.



58 **59** **60**

Scheme 13 **a** $GaCl_3$, CH_2Cl_2, RT; **b***n*-PrCC*n*-Pr, CH_2Cl_2, RT

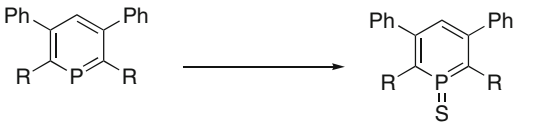
In 2008, protonation of 2,4,6-tri-ter-butylphosphinine **61** (as well as the methylation and silylation of 1,3,5 triphosphabenzene) was achieved by using the toluenium salt of a carborane anion [40]. The X-ray crystal structure of the corresponding phosphininium salt **62** has been recorded and it was shown that, upon protonation, the phosphorus atom gains an hypervalent character (Scheme 14).



61 **62**

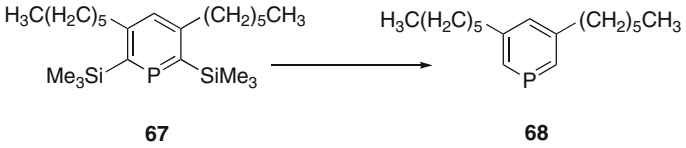
Scheme 14 $[C_7H_8][CHB_{11}Me_5Cl_6]$, C_6H_6, RT

For a long time, phosphinine sulphides eluded isolation but finally the stable phosphinine sulphides **65** and **66** were reported in 2007 [41]. Both compounds were respectively obtained by reaction of phosphinines **63** and **64** with elemental sulphur and structurally characterized (Scheme 15). DFT calculations reveal that phosphinine sulphides (as well as their oxide counterparts) are aromatic compounds. In sulphides, the sulphur atom lone pairs are efficiently stabilized by two σ*(P–C) orbitals and the π* system of the phosphinine through negative hyperconjugation. Oxidation of the phosphinine leads to a complete rehybridization at phosphorus. The variations observed across the series follow Bent's rule and are in excellent agreement with the experimental data.



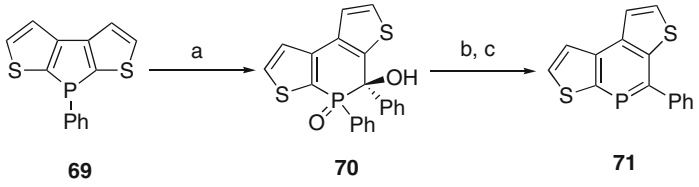
Scheme 15 1/8 S_8, toluene, 5–7 days, 90 °C

A synthetic approach toward 3,5-disubstituted phosphinines such as **68** was reported in 2008 [42]. This simple approach relies on the protodesylilation of 2,6-bis(trimethylsilyl)phosphinines (such as **67**) with HCl in ether (Scheme 16). A DFT study revealed that protonation first takes place at the phosphorus atom and that a chloro-1,2-dihydrophosphinine is involved as intermediate.



Scheme 16 HCl (3 equiv.), Et_2O, RT

Little attention has been paid over the last decadeto the synthesis of fused phosphinines. However, in 2008, the preparation of a dithienophosphinine was reported. Compound **71** was obtained in three steps from dithienophosphole **70** by reaction successively with acetyl chloride, triethylamine and water [43]. This transformation involves the transient formation of the oxide **69** (Scheme 17). DFT calculations reveal that the fused derivative is less aromatic than the parent compound C_5H_5P and suggest that a substantial electronic delocalization takes place within the three rings. Both the HOMO and the LUMO are localized on the P = C-Ph double bond and thus resemble those of a phosphaalkene derivative.



Scheme 17 **a** PhCOCl, Et_3N, toluene. **b** $(ArPS_2)_2$, toluene, 120 °C; **c** Ni, 250 °C, 5 days

3 Coordination Chemistry of Phosphinines

3.1 Classical Complexes

In contrast to classical phosphanes, phosphinines can adopt various coordination modes depending on the nature of the metal and its oxidation state. Bonding modes are also strongly dependant on the substitution scheme of the ring. Four main bonding modes are known: the η^6-bonding mode in which coordination takes place through the π-system of the ring (6 e donor ligand), classical η^1-bonding mode in which phosphinine behaves as a two electron donor through the lone pair at phosphorus, the mixed η^1, η^6 bonding mode which results from the combination of the two first modes (8 e donor ligand) (Fig. 7), and finally, a μ^2 bonding mode in which phosphinine behaves as a two electron donor ligand which has also been evidenced in some clusters and dimetallic complexes.

Many new complexes have been characterized over the last 10 years and an exhaustive presentation will largely exceed the scope of this review. Only complexes that merit comments because of their structural or electronical originality will be presented. An arbitrary separation has also been made between classical complexes that obey the usual electron counting rules, more exotic species such as electron excessive transition metal species and new species derived from the structure of phosphinines such as π^4-phosphacyclohexadienyl anions.

The tendency to form π-complexes on going from right to left of the Periodic Table has been confirmed by the isolation of the titanium complex **72**. Indeed, as previously reported by Elschenbroich and coworkers [44, 45], the presence of bulky groups at the periphery precludes η^1-coordination at the phosphorus atom lone pair. Not surprisingly, trimethylsilyl derivatives of phosphinines were employed to synthesize new π-complexes. The Fe(0) complex **73** was obtained through metal atom ligand condensation at 77 K [46–48]. Complexes **74–76** were more conventionally prepared through displacement reactions with the appropriate transition metal precursors ([RuCp*(η^4-C_4H_{10})Cl] [49] for the synthesis of **74** and $[M(COD)_2]^+$ (COD = 1,5-cyclooctadiene) cationic complexes for **75** and **76**) (Fig. 8) [50].

The η^1-bonding appears to be the most widespread and a lot of new complexes have been synthesized over the last decade. Due to their activity in the catalyzed hydroformylation of olefins, many new Rh(I) complexes have been synthesized and characterized. Some of these are presented in Fig. 9. Despite the presence of one methyl and one phenyl group at the C2 and C6 positions, the 2-methyl-4–6-diphe-

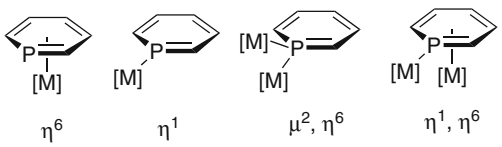


Fig. 7 Main bridging modes of phosphinines

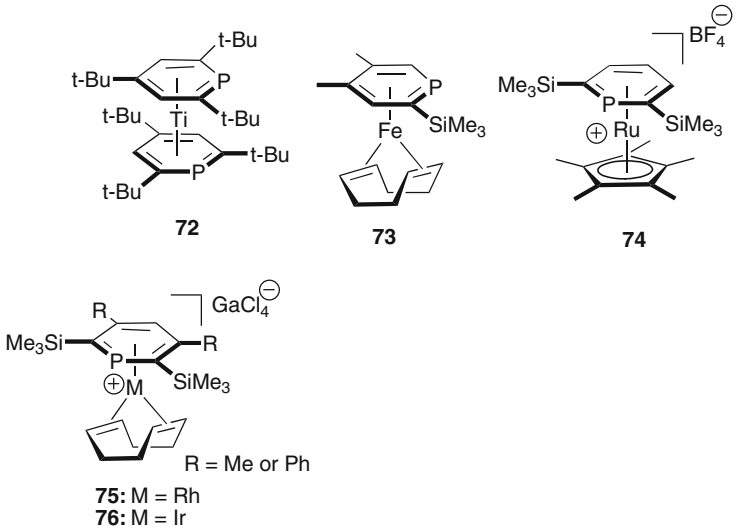


Fig. 8 Some η^6-complexes of phosphinines

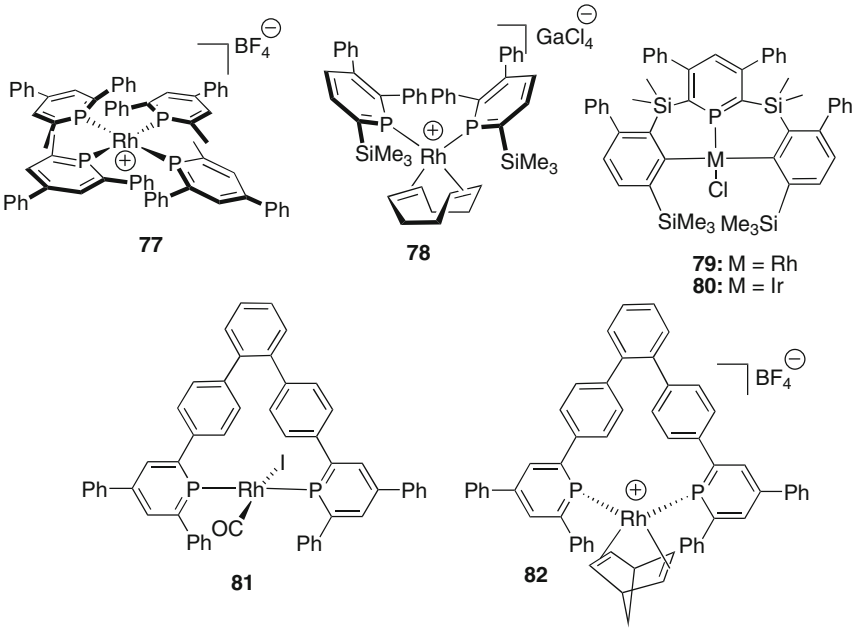


Fig. 9 Some group 9 metal complexes of phosphinines

nylphosphinine reacts with the cationic $[Rh(COD)]_2[BF_4]$ complex to afford the corresponding homoleptic complex **77** [51, 52]. Introduction of a bulkier substituent, such as trimethylsilyl, prevents the formation of the homoleptic species and yields complex **78** in which the COD ligand remains bound to the metal. Studies were not limited to monodentate ligands and bis- and trisphosphinines were also reacted with group 9 metal precursors. Thus, in 1998, Rh(I) **79** and Ir(I) **80** complexes of a trisphosphinine were isolated and structurally characterized [53]. Much more recently, the groups of Müller and van Leeuwen reported on the synthesis of Rh(I) complexes of a bisphosphinine ligand featuring a wide bite angle [17]. Interestingly, they showed that this ligand can either be coordinated in a *cis* (complex **81**) or a *trans* (complex **82**) fashion depending on the other ligand present at the rhodium centre (Fig. 9). Thus reaction of the ligand with $[Rh(nbd)_2][BF_4]$ (nbd = norbornadiene) results in the formation of several species at low temperature to which unsymmetrical *cis* structures could be attributed.

The chemistry of group 10 and group 11 metals has also been re-explored. Thus, a cationic Au(I) homoleptic complex **83** of 2,6-bis(trimethylsilyl) phosphinine has been characterized [54]. More intriguing results were obtained while studying the reactivity of monophosphinines towards group 10 metal centres. During an attempt to isolate a Pd(0) homoleptic complex by reacting the 2,4,6-triphenylphosphinine with $[Pd(OAc)_2]$, an unknown dimeric structure was formed Trapping reaction of this species with PEt_3 afforded the interesting triangular Pd_3 cluster **84** in which each ligand adopts an unusual μ^2 bonding mode (Fig. 10) [55]. A theoretical study (DFT) indicated a low3 bond order of Pd–Pd bonds (0.11) and that coordination of the ligand to the Pd_3 core involve *s* and π orbitals of phosphinine.

Some complexes of 2-phosphinophosphinines were also synthesized. In most cases, these types of ligands, which can be regarded as the phosphinine equivalents of the ubiquitous dppm (bis(diphenylphosphino)methane), bridge two metal centres. Complexes of the $[Mn(CO)_4]_2$, $[FeCp(CO)]_2$ and $[MoCp(CO)_2]$ fragments were synthesized and identified [56]. The combination of a phosphinine and a

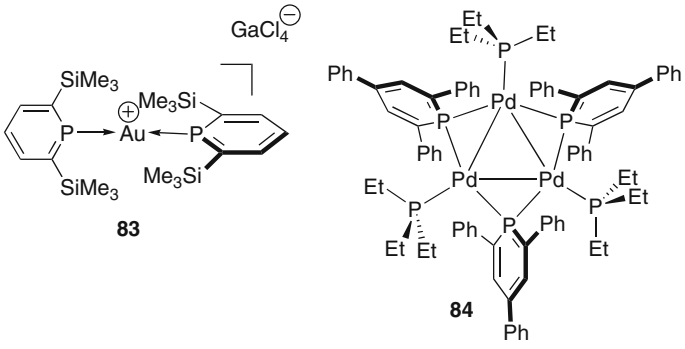


Fig. 10 A homoleptic cationic Au(I) complex and a Pd_3 cluster featuring three μ^2-bridging phosphinines

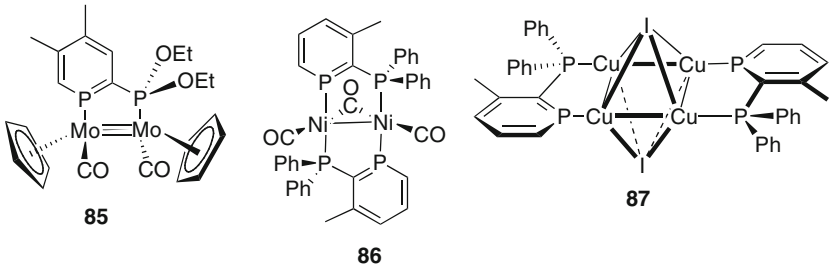
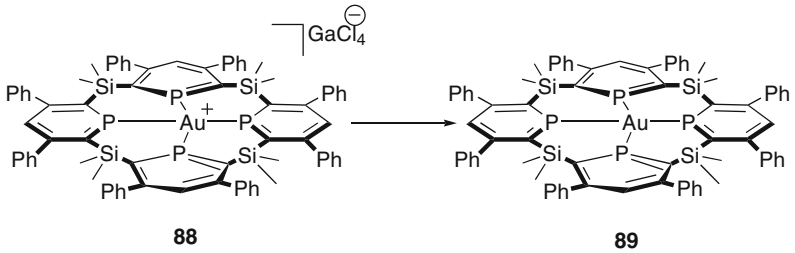


Fig. 11 2-Phosphinophosphinines as bridging ligands

phosphate ligand proved to be well adapted to stabilize the Mo≡Mo triple bonded complex **85**. Interestingly, the Ni complex **86** of a diphenylphosphinophosphinne was electrochemically reduced to form the corresponding 19 VE species. In the same study, this ligand was also used to form the tetranuclear Cu(I) complex **87** in which the iodine is μ^4-face bridged onto the Cu_4 core (Fig. 11) [57].

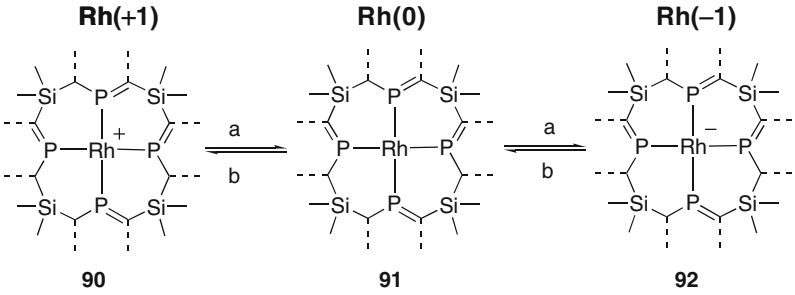
3.2 Reduced Complexes

The strong π-accepting capacity of phosphinines makes them suitable ligand for the stabilization of low-valent transition metal complexes and electron excessive species, contrary to most of classical tertiary phosphines and most of nitrogen ligands. Therefore, much efforts focused on the use of ligands such as polyphosphinines and 2,2'-biphosphinines which were used as phosphorus equivalents of the CO ligand. The silacalix-[4]-phosphinine macrocycle **50** was successfully employed to stabilize an Au(0) complex **89** which exhibited a relatively good thermal stability (stable up to 243 K) (Scheme 18) [58] contrary to its CO analogs $(CO)_n$ (n = 1 or 2) which decompose rapidly and were characterized in matrices at low temperature (77 K). This species, which was obtained by reduction of the corresponding cationic complex **88** with sodium naphthalenide at –80 °C, was fully characterized by EPR spectroscopy. The EPR signal which consists of 20 lines was in good agreement with the structure proposed with four phosphorus atoms interacting with the gold nucleus. A comparison of the ^{197}Au and ^{31}P isotropic coupling constants with the corresponding atomic parameters reveals that 24% of the spin is localized in a gold *s* orbital.



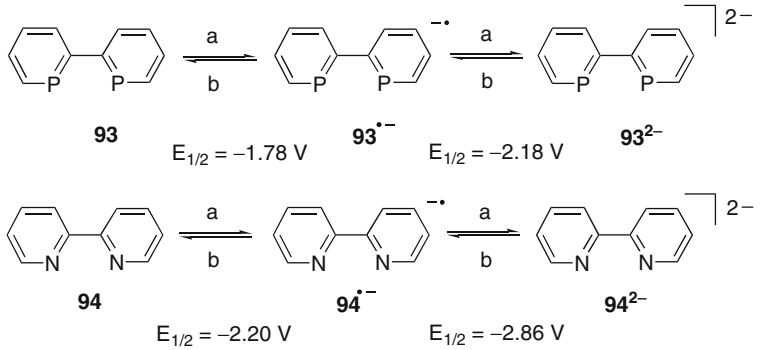
Scheme 18 $C_{10}H_8Na$ (1 equiv.), THF, –80 °C

The same ligand was employed for the stabilization of 17 VE Rh(I) and 18 VE Rh(0) complexes. An electrochemical study revealed that complex **90** could undergo two monoelectronic reduction to yield the two complexes **91** and **92** respectively. EPR measurements and DFT calculations ware carried out on the paramagnetic species **91** (Scheme 19) [59]. Combination of these data suggests that the complex adopts as slightly distorted square planar geometry like its cationic precursor, the odd electron being mainly delocalized over the four phosphorus atoms (only 10% of the electron density residing on Rh). Similar experiments were also undertaken with the macrocycle featuring two thiophenes in place of two phosphinines. As expected, EPR measurements and DFT data confirmed that the replacement of two phosphinine units results in an increase of the electron density on the rhodium atom (35%).



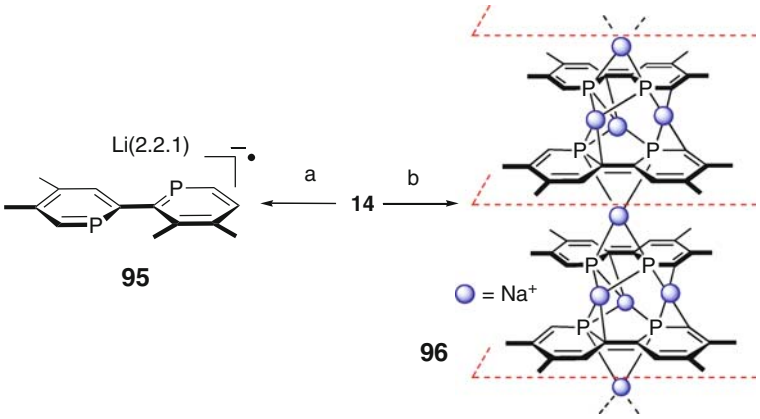
Scheme 19 **a** Electrochemical monoelectronic reduction. **b** Electrochemical monoelectronic oxidation

Phosphorus analogs of 2,2'-bipyridines were extensively used to stabilize highly electron rich and excessive metal complexes. Interestingly, these 2,2'- biphosphinine ligands possess a low lying π*-LUMO which is mainly localized on the phosphorus atom. Though the symmetry and shape of the LUMO are similar to in bipyridines, the most important coefficients are localized over the carbon atoms of the ring. Therefore, it was proposed that 2,2'-biphosphinines could behave stronger acceptor ligands. This hypothesis was confirmed by an electrochemical study which revealed that the phosphorus ligands are much more easily reduced than their nitrogen analogs [60]. Thus, in the case of the parent biphosphinine, $C_{10}H_8P_2$**93**, the first monoelectronic reduction yielding the anion radical **93**$^{-}$ takes place at $E_{1/2} = -1.78$ V (vs SCE) vs $E_{1/2} = -2.20$ V (vs SCE) for the bipyridine **94** (Scheme 20).



Scheme 20 **a** Electrochemical monoelectronic reduction. **b** Electrochemical monoelectronic oxidation

The X-ray crystal structure of the anion radical **95**, as well as that of the dianionic species **96** of the tmbp ligand **14** (4,4',5,5'-tetramethylbiphosphinine), were recorded. Compound **95** was obtained by reduction with lithium metal in the presence of Li (2.1.1) (2.2.1 = 4,7,13,16,21 pentaoxa-1,10-dizabicyclo[8.8.5]tricosane) cryptand whereas compound 96 was prepared by reduction with sodium metal in the presence of DME as solvent (Scheme 21). Whereas **95** was obtained as a monomeric species, **96** was structurally characterized as a polymeric chain. In both anions, the internal C–C bond distance connecting the two phosphinine rings was found to be significantly shortened with regards to that of the free ligand, indicating that most of the negative charge resides on the P–C–C–P bridge [61].



Scheme 21 **a** Li (2.2.1), THF, RT. **b** 2 Na, DME, RT

The coordination chemistry of the tetramethyl derivative **14** was widely explored. Classical complexes with Ru(II) [62] (P analog of the $[Ru(bpy)_3]^{2+}$ complex) and Pt(II) [63] centres were prepared but their stability was found to be highly dependant on the electron richness of the metal fragment. Thus, in the case of electron deficient metal fragments, 2,2'-biphosphinines complexes were found to be very sensitive towards nucleophilic attacks of water and alcohols. In contrast, in the case of electron rich metal fragments, complexes were found to be perfectly stable towards air and moisture. Some of these complexes are presented in Fig. 13. The Ru(II) complex **97** [64] was found to be a good precursor of the anionic Ru(0) complex **98** which in turn, upon oxidation, yielded the dimeric Ru(I) complex **99** [65]. An osmium(0) cluster **100**, which contrary to its bipyridine analog proved to be photostable, was also prepared and structurally characterized [66, 67]. Reactions of ligand **14** with manganese complexes yielded different results depending on the nature of the precursor. Whereas reaction with $[Mn(CO)_5Br]$ afforded the classical complex **201** [68], reaction with $[Mn_2(CO)_{10}]$ gave the dinuclear species **202** (Fig. 12) [69]. Interestingly, in this complex the biphosphinine ligand behaves as 8 electron donor, two electrons being given by the two phosphorus atom lone pairs

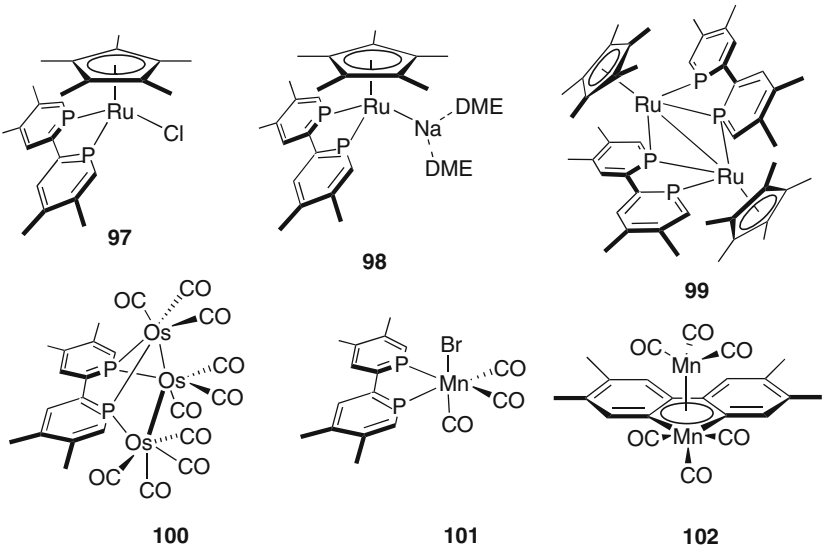


Fig. 12 Some biphosphinine complexes

and four electrons being added by the two P = C double bonds. Complex **202** can thus be regarded as an anionic diphosphamanganacycle coordinated in a η^5-fashion to a $[Mn(CO)_3]^+$ metal fragment.

The most striking results were obtained with homoleptic complexes of electron rich metal fragments which cannot exist when classical ligands such as bipyridines and chelating diphosphines are employed. Two synthetic approaches were developed to prepare such species. The first, which is the most traditional, involves the classical reduction of a preformed complex. The second approach relies on the reaction of the reduced ligand such as monoanion **95** or dianion **96** with the appropriate transition metal precursor. This methodology was employed for the synthesis of the dianionic complexes of group 4 metals **103–105** [70]. Though they adopt a formal d^6 electronic configuration, theses complexes, as well as their group 6 neutral analogs **106–108**, adopt a trigonal prismatic geometry [71]. Theoretical calculations revealed that a pronounced electronic transfer takes place in all complexes and that a formal d^6 electron configuration is purely formal. A comparison with bipyridine analogs allowed to conclude that the phosphorus and the nitrogen ligands accommodate excess of electron density for the metal in different ways. In phosphorus complexes, the HOMO is mainly metal localized whereas in bipyridine complexes this HOMO describes the π^*system of the ligand. The energetic evolution of the LUMO allowed rationalization of the progressive change from the trigonal prismatic geometry to the octahedral one in these formal d^6 complexes [72]. Dianionic complexes of Ru(−II) and Fe(−II) were also synthesized using the second approach [73]. The X-ray crystal structure of the Ru **109** complex suggests

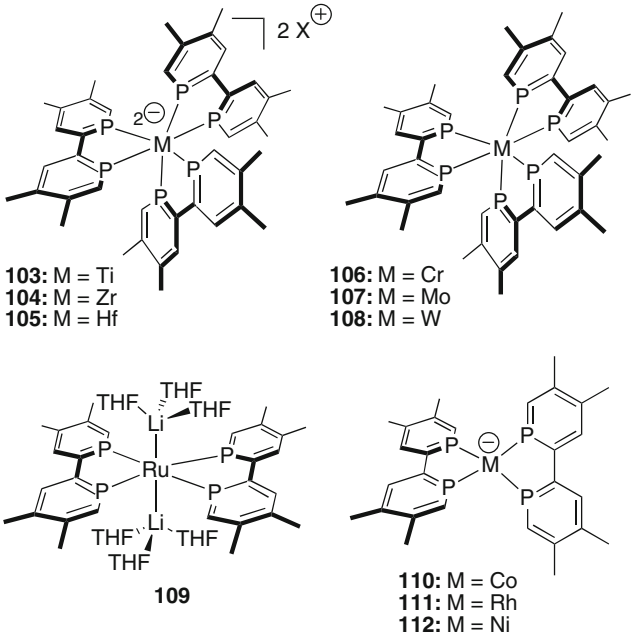
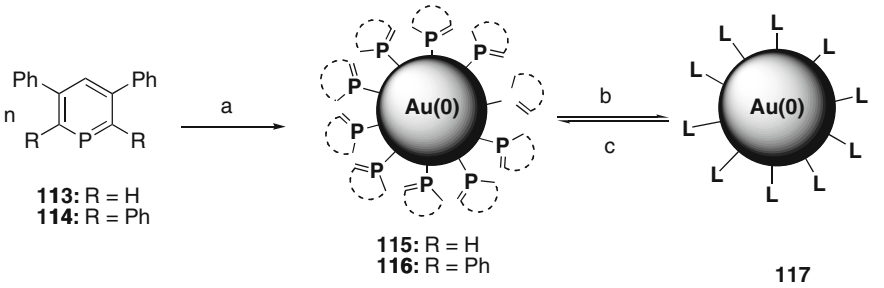


Fig. 13 Reduced biphosphinine complexes

that the complex cannot be described as a pure d^{10} complex since a significant part of the electron density resides on the ligands. Anionic complexes of group 9 metals were also prepared with Co (**110**) and Rh (**111**) [74] as well as the 19 electron Ni complex **112** which was electrochemically generated (Fig. 13) [75, 76]. Theoretical calculations were undertaken to rationalize geometries of these $[M(biphosphinine)_2]^{n-}$ –d^{10} complexes which present either a square planar or a tetrahedral arrangement of the ligand around the metal. It was found that the lower the d orbitals on the metal centre (Ni < Co(–I) < Pt < Rh (–I) < Ru (–II)), the less favoured the square planar conformation.

Finally, it must be mentioned that phosphinines were also recently employed to stabilize gold nanoparticles (NPs). Reduction of the $[AuCl(SMe_2)]$ precursor with a substoichiometric amount of ligands such as **114** and **115** afforded particles of 8.5 ± 2 nm diameter [77]. Importantly, it was observed that grafting of phosphinines at the surface of theses Au NPs induces a significant shift of the plasmon band (from 520 nm for classical sp^3 hybridized phosphines to 580 with **115** and **116**). It was proposed that this red shift may result from a decrease of the electron density within the NPs induced by the strong π-accepting capacity of phosphinines. This optical property was exploited for the detection of small phosphines and thiols through UV-vis spectroscopy. Thus, Au NPs **115** were immobilized in periodically organized mesoporous silica thin films using the evaporation induced self assembly (EISA) method. The resulting systems proved to be very efficient for the detection of posphines such as PPh_3 and PMe_3 using 5 ppm solutions (about 1000 equiv. with

regard to the phosphinine ligand) [78]. After displacement of phosphinine by the incoming ligand (formation of Au NPs **117**) and UV-vis detection, the sensor could be regenerated using H_2 (3 atm) and the appropriate phosphinine (Scheme 22). Importantly, the phosphinine-based nanoparticles were also employed to generate Janus-type nanoparticles upon reaction with thiols [79].



113: R = H
114: R = Ph

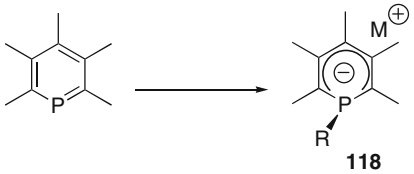
115: R = H
116: R = Ph

117

Scheme 22 **a** [$AuCl(SMe)_2$], $C_{10}H_8Na$, THF, RT. **b** L = ligand (RSH, PMe_3, PPh_3). **c** Phosphinine, H_2 (3 atm)

3.3 Phosphacyclohexadienyl Complexes

The high electrophilic character of the phosphorus atom of phosphinines was also exploited to devise a new class of anionic ligands. Thus, as previously shown by Märkl [80], Ashe [81] and Dimroth [82], upon reaction with nucleophiles, 1-P-R-phosphacyclohexadienyl anions of general formula **118** are formed (Scheme 23). Note that these anions were extensively used in the past for the synthesis of various λ^5-phosphinine derivatives, 1,2-and 1,4-dehydrophosphinines and π-complexes. The structure of the lithium derivative **119** was recently reported and electronic structures of these anions were studied through DFT calculations (Fig. 14) [83]. As suggested by the coordination mode of the lithium cation, these DFT studies revealed that negative charge is delocalized over the pentadienyl part of the ring with a predominance on the two a-carbon atoms. An analysis of the charge distribution strongly suggests that the electronic structure of these phosphacyclohexadienyl anions is closer to that of classical pentadienyl anions than to that their carbon analogs, the cyclohexadienyl anions. Therefore in these anions, the phosphorus atom possesses electronic properties that are very similar to that of classical tertiary phosphines.



118

Scheme 23 RM (M = Li, Na, K)

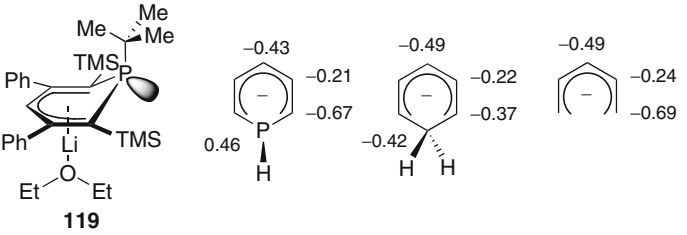
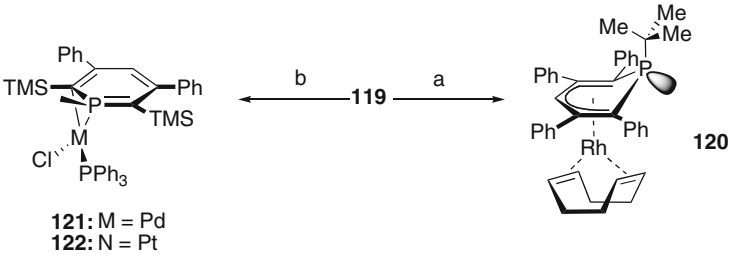


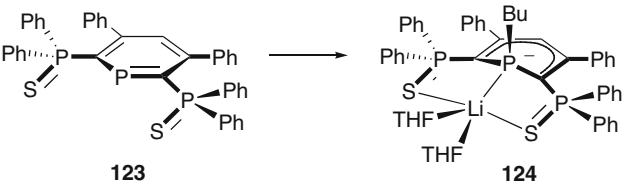
Fig. 14 Lithium-π complex of a cyclophosphacyclohexadienyl anion

Interestingly, it was shown that the coordination mode of these anions varies depending on the nature of the transition metal fragment. Thus reactions of anion **119** with $[Rh(COD)Cl]_2$ afforded very stable complex **120** in which only the pentadienyl part of the ring is coordinated [84]. In contrast, reactions with dichloropalladium and platinum (II) precursors yielded the hitherto unknown η^2-complex **121** and **122** (Scheme 24) [85]. A combination of NMR experiments and DFT calculations revealed that these complexes are in equilibrium with the l^5-phosphinine complexes in which the ligand is η^1-coordinated through the phosphorus atom.



Scheme 24 **a** ½ $[Rh(COD)Cl]_2$, THF, RT. **b** $[M(PPh_3)_2Cl_2]$, THF, RT

The coordinating behaviour of these anions also proved to be very dependant on the substitution scheme of the phosphinine ring. Thus, adjunction of two ancillary phosphinosulphide ligands, such as in phosphinine **123**, resulted in the formation of anions (such as **124**) in which the counter cation is coordinated both to the phosphorus atom and the sulphur atoms (Scheme 25). The preference for η^1-coordination in theses S~P~S pincer ligands can be explained by the destablization of the phosphorus atom lone pair by the lone pairs at sulphur atoms [86]. Thus, in these S~P~S anionic ligands, the HOMO does not describe the *p*-pentadienyl system, but instead the lone pair at phosphorus. Not surprisingly, reactions of these anions with transition metal precursors afforded the corresponding η^1-complexes in which the S~P or S~P~S ligands behave as 4 or 6 electrons donor ligands. Various complexes were prepared with group 8–11 metals. Some of these complexes (**125–130**) are presented in Fig. 15 in the case of Ni, Pd, Pt, [87, 88] Ru, [89]Au and Cu [90] .



Scheme 25 *n*-BuLi, THF, RT

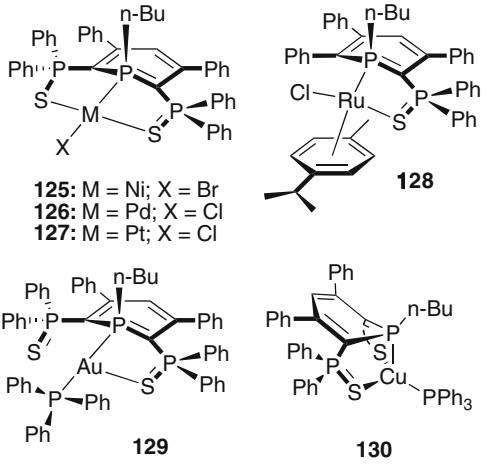


Fig. 15 η^1-Complexes of S~P and S~P~S anionic ligands

Rhodium complexes of these anionic S~P~S ligands were shown to exhibit an interesting reactivity and important electronic properties [91, 92]. Thus complex **131** proved to be highly reactive towards O_2, CS_2, CO_2, SO_2 to afford the corresponding Rh(III) species. Interestingly, all additions onto the rhodium centre were found to be regioselective, reactions always taking place at the *syn* face of the complex. Theoretical calculations carried out within the DFT framework led to the conclusion that this *syn* addition is favoured both by a low energetic barrier needed to form a distorted structure in the triplet state and by the nature of the Rh-A bond formed (A = C, O or S) [93–95]. On the other hand, the cationic 18 VE homoleptic complex **132** was synthesized through the reaction of 2 equiv. of the S~P~S anionic ligand with the $[RhCl_3(tht)_3]$ (tht = tetrahydrothiophene). It was shown that chemical reduction of this complex with Zn afforded the corresponding stable 19 VE Rh(II) complex (Fig. 16). A combination of EPR spectroscopy and theoretical calculations revealed that the odd electron is delocalized over the rhodium atom and the ancillary axial P = S ligands [96].

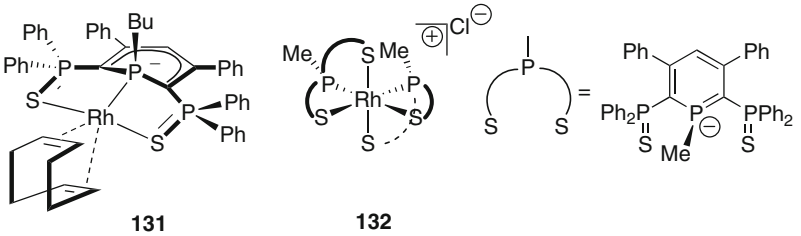


Fig. 16 Rhodium(I) and (III) complexes of an S~P~S anionic ligand

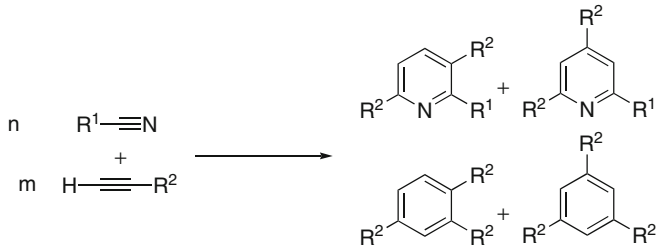
Finally, it must also be mentioned that preliminary studies have shown that these S~P~S anionic ligands can strongly stabilize lanthanides (III) such as Ce and Nd and uranium(IV) [97].

4 Phosphinines in Homogeneous Catalysis

4.1 Phosphinines

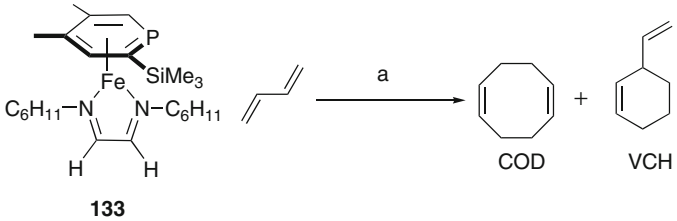
Evaluation of the activity of phosphinine complexes in homogeneous catalysis only began during the last decade, probably due to the lack of synthetic methods allowing the synthesis of functional derivatives which hampered the chemistry of the ring for a long time. A second reason that may explain this lack of interest concerns the high reactivity of phosphinines towards nucleophiles. Indeed, as shown previously, the stability of the ring upon coordination proved to be dramatically dependant on the oxidation state of the complex and complexes of metal bearing important oxidation states were found to be kinetically unstable. Therefore, it is not really surprising to see that most studies focused on electron-rich metal complexes. So far only a few applications have been reported but, as will be seen in the following pages, the results obtained can be considered as relatively significant.

The first application of phosphinines in catalysis was reported by Zenneck et al. in 1996 in the case of η^6-Fe complexes [46, 98]. It was shown that complex **73** could catalyse the cyclotrimerization of dimethyl acetylenedicarboxylate as well as the formation of pyridines from alkynes and nitriles. Importantly, the catalytic activity of this complex was found to be superior to that of the corresponding benzene [Fe(η^6-C_6H_6)(COD)] complex. Reactions of methylpropargyl ether with butyronitrile in the presence of complex **73** as catalyst in a ratio: 620:2,720:1 afforded a mixture of functional benzenes and pyridines. Turn over numbers (TON) for the conversion into pyridines reached 160 and those for the formation of functional benzenes reached 326, thus corresponding to a chemoselectivity of 0.49 (Scheme 26).



Scheme 26 Complex **73** as catalyst, 20 °C, 48–96 h

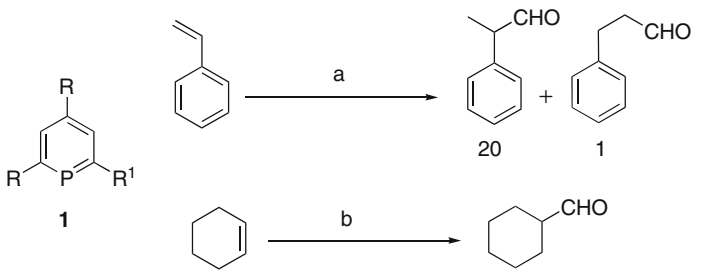
Additional experiments were also carried out with complex **133** which results from the substitution of the COD ligand in **73** by a 1,4-diaza-1,3-diene (DAD) [48]. The catalytic activity of **133** in the cyclodimerization of 1,3-butadiene was compared to that of its carbon counterpart the [Fe(η^6-toluene)(DAD)] complex. In this case, the toluene complex proved to be 10 times more efficient and yielded better TON than the phosphinine-based complex for the formation of COD (1,5-cyclooctadiene) and VCH (vinylcyclohexene). This lack of activity was ascribed to the stronger affinity of phosphinine ligands towards Fe(0) thus limiting the generation of the 12 VE [Fe(DAD)] complex which is the genuine catalytic active species (Scheme 27).



Scheme 27 **a** 120 °C, 9 bars

The most significant results were obtained by the group of Breit who demonstrated that phosphinine rhodium(I) complexes behave as very efficient catalysts. In the first two reports, most efforts focused on the hydroformylation of styrene and important conversion yields and interesting selectivities in favour of the branched aldehyde were obtained by using derivatives of 2,4,6-triphenylphosphinine **1** [51]. Importantly, reactions could be carried out under mild conditions in toluene at 25 °C using [Rh(acac)$(CO)_2$] complex as catalytic precursor with a Rh:phosphinine:substrate ratio of 1:5:280 and a CO/H_2 (1:1) pressure of 20 bars. With the triphenyl derivative, a Turn Over Frequency (TOF) of 28.7 mol substrate/mol catalyst/h was obtained, the conversion yield reaching 30.8%. Theses

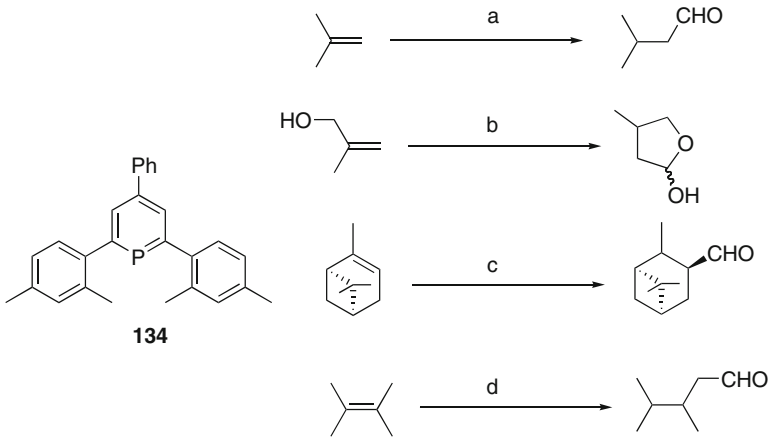
performances were found significantly higher than that of the classical [Rh(acac)$(CO)_2$]/PPh_3 catalyst (TOF = 7.5) [99]. The conversion of internal aldehydes was also successfully investigated. The conversion of cyclohexene into cyclohexylcarbaldehyde was achieved at 90 °C in toluene using a Rh:phosphinine:substrate ratio of 1:10:570 and an initial pressure of CO/H_2 of 20 bars (Scheme 28). A remarkable TOF of 214 substrate/mol catalyst/h was obtained under these experimental conditions.



Scheme 28 **a** [Rh(acac)$(CO)_2$] + **1**, CO/H_2 20 bars, toluene, 25 °C. **b** Rh(acac)$(CO)_2$] + **1**, CO/H_2 20 bars, toluene, 90 °C

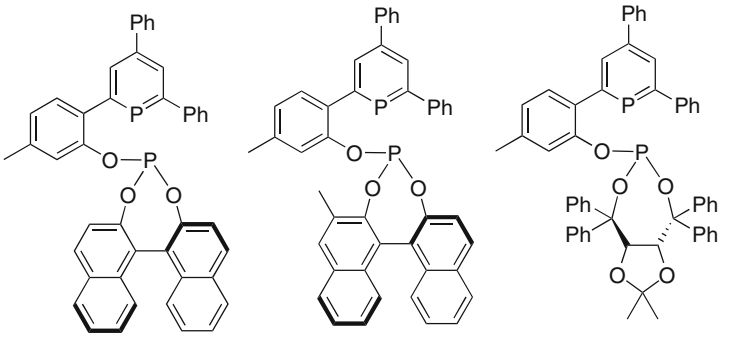
The influence of steric factors on the phosphinine ligand was also examined in a following report by the same group [9]. In this study, the conversion of oct-1-ene was chosen as a model reaction. The more satisfying results were obtained with the triarylsubstituted derivative **134** which features two xylyl groups at the a-positions of phosphorus. High TOF (45,370 substrate/mol catalyst/h) were obtained when the reaction was carried out at 130 °C with a complete consumption of the starting material within 30 min. Additional experiments emphasized the remarkable catalytic activity of the combination of ligand **134** with the [Rh(acac)$(CO)_2$] complex. A TOF of 3132 substrate/mol catalyst/h was obtained in the conversion of methylpropene when the reaction was carried out at 80 °C. Comparatively, the PPh_3-based catalyst proved to be 100 times slower. The conversion of methyl alcohol into the corresponding lactol was also investigated as well as the hydroformylation of tri- and tetrasubstituted olefins. Thus, α-pinene was successfully converted into the corresponding aldehyde with a very good regio- and diastereoselectivity using 60 bars of CO/H_2 in toluene at 80 °C. Note that the corresponding PPh_3 catalyst failed to provide any aldehyde under these conditions. Conversion of tetramethylethylene into 3,4-dimethylpentanal was shown to proceed through a two-step process that involves the an isomerization of the substrate into 2,3-dimethybut-1-ene. Though the conditions used were relatively drastic (100 °C under a CO/H_2 pressure of 60 bars), it is worth mentioning that only cobalt-based systems can achieve this type

of transformation (also under drastic conditions) (Scheme 29). NMR experiments were carried out with ligand **134** to determine the nature of the active species but no definitive formulation could be established on the basis of ^{31}P NMR data. A parallel experiment using [Ir(acac)$(CO)_2$] precursor under the same conditions than that used in the catalysis allowed to propose that a pentaccordinated hydrido-iridium complex could be formed.



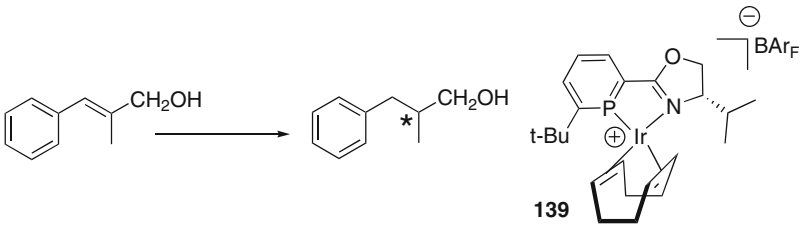
Scheme 29 **a** [Rh(acac)$(CO)_2$] + **134**, CO/H_2 30 bars, toluene, 80 °C. **b** Rh(acac)$(CO)_2$] + **134**, CO/H_2 20 bars, toluene, 80 °C. **c** [Rh(acac)$(CO)_2$] + **134**, CO/H_2 60 bars, toluene, 80 °C. **d** Rh(acac)$(CO)_2$] + **134**, CO/H_2 20 bars, toluene, 100 °C

Note that phosphinine **134** was also employed by Reetz et al. in combinatorial homogeneous catalysis for the rhodium(I)-catalyzed asymmetric hydrogenation of acetamidoacrylate [100]. The heterocombination of *(R)*-BINOL and **9** leads to an enantiomeric excess of 58.6% (*R* enantiomer formed). Quite recently, the group of Müller shown that phosphinine Rh(I) complexes could be employed in the asymmetric hydrogenation of dimethyl itaconate [8]. BINOL (**9** and **135**) and TADDOL (**136**) derivatives of the 2,4,6 triphenyl derivative were thus prepared and evaluated. The *(S)*-BINOL-based ligand **9** proved to be the most efficient and a TOF of 2500 h^{-1} with an enantioselectivity of ee = 79% were obtained when the reaction was carried out at 25 °C using 0.1 mol% of catalyst. Ligand **135** (TOF = 2040 h^{-1}, ee = 65%) and **136** (TOF = 976 h^{-1}, ee = 52%) were found to be less efficient. Performances of the rhodium catalyst featuring **9** as ligand were also evaluated in the hydrogenation of methyl 2-(*N*-acetylamino)cinnamate (TOF = 1030 h^{-1} at 20% conversion, ee = 62%) (Scheme 30).



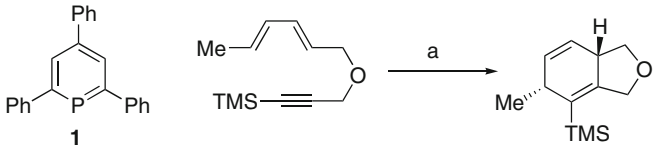
Scheme 30 For substrate **137**, 0.1 mol% catalyst, CH_2Cl_2, RT, H_2 (10 bars); for substrate **138**, 1 mol% catalyst, CH_2Cl_2, 40 °C, H_2 (10 bars)

Finally, to complete this overview of the chemistry of group 9 phosphinine-based catalysts, it must also be mentioned that Neumann and Pfaltz also investigated the use of mixed phosphinine-oxazoline ligands, initially synthesized by Breit, in the Ir(I)-catalysed hydrogenation of several highly substituted unfunctionalized and functionalized alkenes and imines as well as in the hydrogenation of acetophenone [101]. The most significant results were obtained in the hydrogenation of 2-methyl-3-phenyl-prop-2-en-1-ol which was achieved with a full conversion and a high ee of 92% using complex **139** (Scheme 31). However, nature of the catalyst was not definitely identified in these different hydrogenation processes and it was not confirmed that the structure of the phosphinine was preserved during the catalytic cycle.



Scheme 31 Catalyst 139, H_2 (50 bars), CH_2Cl_2, RT, 3 h

A last interesting application deals with the chemistry of Ni(0) phosphinine complexes. Some phosphinine ligands were successfully employed as ligands in the intramolecular Wender's [4 + 2] cycloaddition [102]. It was proposed that the strong π-accepting capacity of phosphinines tends to favour the reductive elimination process which turns out to be the rate determining step of this transformation. The most significant results were obtained with the ubiquitous 2,4,6-triphenyl derivative **1** (Scheme 32). However, in order to ensure a nearly full conversion (92%), high loading of catalyst was needed and, in a typical experiment, 10 mol% of [Ni(COD)$_2$] and 20 mol% of the phosphinine ligand were employed.

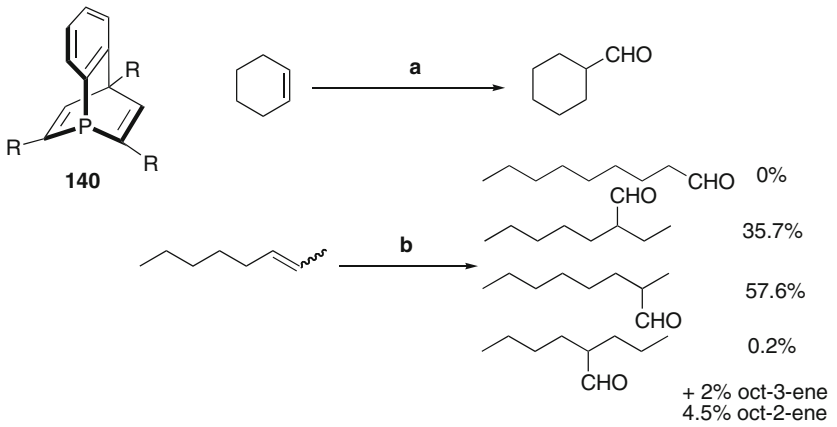


Scheme 32 **a** [Ni(COD)$_2$] (10 mol%), **1** (20 mol%), cyclohexane, 80 °C, 5 h

4.2 Phosphinine Derivatives

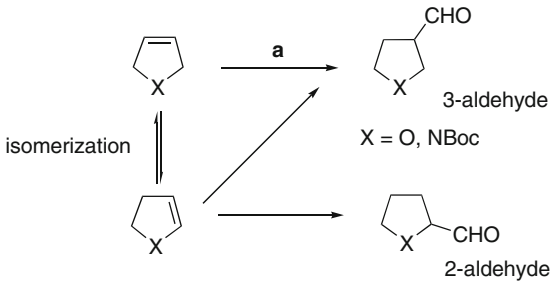
As previously explained, the phosphinine skeleton can be exploited to elaborate new classes of ligands. Two electronic properties of the ring were intensively used for this purpose. First, the high electrophilicity of the phosphorus atom was employed to synthesize phosphacyclohexadienyl anions. Second, the polarization of the π system, induced by the introduction of phosphorus atom, makes phosphinines relatively good partners for [4 + 2] cycloaddition with activated alkynes to form 1-phosphabarrelenes. These original bicyclic molecules behave as relatively modest σ-donor and strong π-acceptor ligands because of the important 3s character in the phosphorus atom lone pair (56.3% given by NBO calculations at the B3LYP/6–31G* level of theory on the parent compound C_7H_7P) [103] and to the presence of low lying σ*-orbitals resulting from the vinylic substitution but their σ-donating capacity can be easily tuned up by playing with substituents at the α-postions at phosphorus. The first investigations on the catalytic behaviour of phosphabarrelenes were made by Breit et al. in the case of the Rh-catalyzed hydroformylation of olefins [104–106]. Phosphabarrelenes such as **140** were prepared, according to a procedure reported by Märkl, by reacting the corresponding phosphinines with benzyne. Combination of **140** and [Rh(acac)(CO)$_2$] proved to be much more efficient for the conversion of cyclohexene into cyclohexylcarbaldehyde compared to the industrial process involving Rh/PPh$_3$ (1000 times slower). Thus a conversion of 49% was obtained using 10 bars of CO/H$_2$ at 120 °C in toluene and 2 equiv. of ligand per equiv. of the catalytic precursor. More strikingly, the same system was used to achieve the hydroformylation of internal olefins without

provoking an isomerization to the corresponding α-olefin. A nice illustration was provided by the hydroformylation oct-2-ene (*E/Z*= 77/23) which exclusively yielded branched aldehydes (Scheme 33).



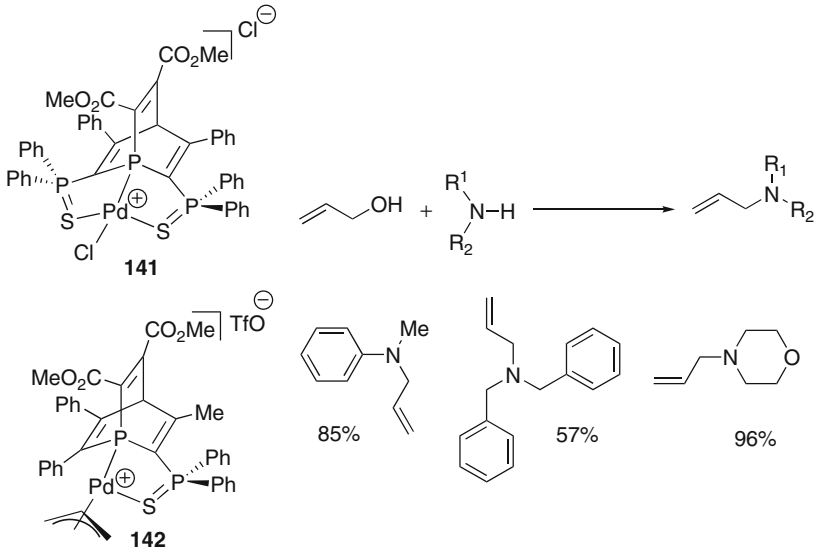
Scheme 33 **a** [Rh(acac)$(CO)_2$], **140** (2 equiv./Rh atom), CO/H_2 (10 bars) toluene, 120 °C. **b** [Rh(acac)$(CO)_2$], **140** (2 equiv./Rh atom), CO/H_2 (10 bars) toluene, 70 °C

Importantly, a similar result was obtained with heterocyclic alkenes such as 2,5-dihydrofuran and N-Boc-pyrroline which were converted to the corresponding 3-aldehyde. It must be noted that the P[O(2,4-di-*t*BuC_6H_3)]$_3$ rhodium-based catalyst, which is one of the most active catalyst for this type of transformation, also furnished the 2-aldehyde derivative resulting from the hydroformylation of the 2,3-dihydroheterocyclopentenes (Scheme 34).



Scheme 34 **a** [Rh(acac)$(CO)_2$], **140,** CO/H_2 (10 bars), 50 °C

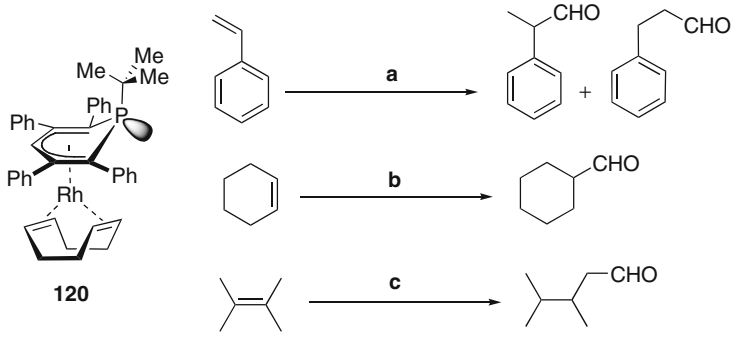
Note that very recently the group of Müller also reported on the synthesis of an enantiomerically pure phosphabarrelene ligand which was obtained through cycloaddition of benzyne with a prochiral phosphinine. This new ligand as well as chiral phosphabarrelene phosphite ligands, prepared by Breit, were evaluated in the Rh-catalyzed asymmetric hydroformylation of prochiral olefins and in the Rh-catalyzed hydrogenation of olefins [14]. Phosphabarrelenes were also incorporated into bi- and tridentate ligands featuring ancillary phosphinosulphides as ancillary ligands. The palladium complex **141** proved to be very efficient in the Suzuki-Myaura coupling to form biphenyl derivatives (TON about 95,000). More importantly, complex **142** which only features one phosphinosulphide group found an interesting application in the Pd-catalyzed allylation of primary and secondary amines with allylic alcohols (Scheme 35). In contrast to most catalysts, the transformation did not stop after the first allylation and diallylamines were also formed in significant amounts [107].



Scheme 35 Complex **142** (2 mol%), THF, 70°C, 24 h

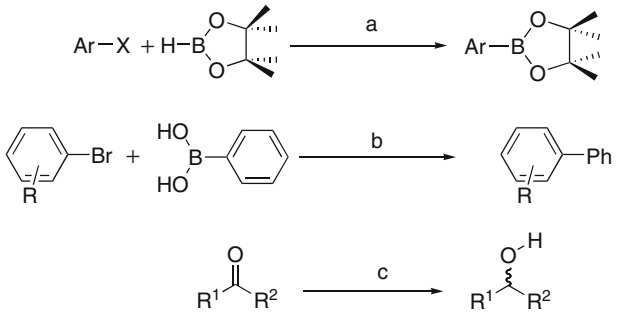
The use of phosphacyclohexadienyl anions as ligands in homogeneous catalysis was also explored. As previously seen, either π- or σ-complexes can be formed upon reaction with transition metal precursors depending on the substitution scheme of the phosphinine nucleus. Only one report deals with the catalytic activity of π-complexes. In 2005, it was shown that the η^5-Rh(I) complex **120** displays a very good catalytic activity in the hydroformylation of terminal and internal olefins. Very high conversion yields and TON were obtained in the hydroformylation of

substrates such as styrene and cyclohexene under mild conditions with a low loading of catalyst. Thus, conversion of styrene took place at 40 °C using a CO/H_2 pressure of 20 bars with 0.5% of catalyst. These results compare with those obtained by Breit with phosphinines since only 1 equiv. of ligand is consumed vs 20 equiv. in the case of phosphinines (with a lower amount of Rh). Hydroformylation of cyclohexene proceeded using an initial H_2/CO pressure of 20 bars using a catalyst:substrate ratio of 1:1460 (62% of conversion). Like the phosphinine-based catalysts developed by Breit, catalyst **120** could also convert 2,3-dimethylbutene into 3,4-dimethylpentanal using an initial CO/H_2 pressure of 20 bars with a catalyst loading of 0.1 mol% at 90 °C in toluene (Scheme 36).



Scheme 36 **a** CO/H_2 (20 bars), toluene, RT, 20 h. **b** CO/H_2 (20 bars), toluene, 90 °C, 4 h. **c** CO/H_2 (20 bars), toluene, 90 °C, 10 h

More attention has been paid so far to the use of η^1 metal-complexes of these phosphacyclohexadienyl ligands. The first initial report dealt with the use of S~P~S pincer palladium complex **126** which was employed in the formation of arylboronic esters from halogenoarenes and pinacol borane [88]. Relatively high TON numbers (between 5×10^3 and 10×10^3) were obtained when the transformation was carried out in dioxane using NEt_3 as a base. The activity of this catalyst was also evaluated in the classical Heck reaction between methylacrylate and iodobenzene to afford *trans*-cinnamate. In a second report, it was shown that the Pd-allyl complex **142** was an efficient catalyst for the classical Suzuki-Myaura coupling of bromoarenes with phenylboronic acids [107]. Thus in the conversion of 4-bromoacetophenone, a TON of 799×10^3 was recorded when the reaction was carried out in toluene under reflux using K_2CO_3 as base. Finally, an article published in 2007 reports on the catalytic activity of the cationic derivative of **126** in the palladium-catalysed allylation of aldehydes with allyltributyltin as reagent [108]. Note also that the ruthenium complex **128** was employed in the transfer hydrogenation of ketones using isopropanol as solvent and KOH as base but conversion yields were found to be modest with regard to the most efficient catalytic systems such as those developed by Noyori (Scheme 37) [89].



Scheme 37 **a** Complex **126** (catalyst), dioxane, Et_3N, 80 °C, 15 h 5 days. **b** Complex **142** (catalyst), toluene, K_2CO_3, 110 °C, 24 h. **c** Complex **128** (catalyst), KOH (0.1 M) *i*-PrOH, 80 °C

Finally, a last possible use of phosphinines as precursors of phosphines for homogeneous catalysis deals with their transformation into phosphinane. The BASF group showed that alkylation of the phosphorus atom followed by a complete hydrogenation of the ring afforded phosphinanes that showed remarkable activity in the Rh-catalyzed hydroformylation of olefins [109, 110].

5 Conclusion

As can be seen throughout this review, the chemistry of phosphinines has reached over the last decade a significant maturity and this class of heterocycle can now really be considered to be a very useful tool in different areas such as organophosphorus chemistry, coordination chemistry and, more recently, in homogeneous catalysis. A large variety of polyfunctional systems are henceforth available and recent synthetic developments allow henceforth their preparation on relatively important scales. Applications forecasting is always difficult, especially in chemistry, but one may now be relatively confident about promising developments in this area of heterocyclic phosphorus chemistry. Indeed it is now well established that phosphinines exhibit electronic properties that make them remarkably different from classical phosphines as well as from their nitrogen analogs, the pyridines. Among possible ways of developments one may quote their use for the elaboration of catalysts that can stand the presence of strong reducing media or that act as themselves as reducing agents through electronic transfer to substrates. More classical developments can also be accepted in traditional catalysis where ligands possessing a strong π-accepting capacity and tunable steric properties are still particularly attractive. Another possible rewarding field of investigation undoubtedly concerns their use as ligands for metal surfaces (colloids or nanoparticles) in the elaboration of catalysts, sensors, or materials exhibiting specific electronic or optical properties. In conclusion, the field is therefore still widely open and only time will tell whether this will be sustained in the future.

References

1. Märkl G (1966) *Angew Chem Int Ed Engl* 5:846
2. Märkl G (1990) Multiple bonds and low coordination in phosphorus chemistry,. Georg Thieme Verlag, New York, p 220
3. Le Floch P (2001) Phosphorus-carbon heterocyclic chemistry : Tthe rise of a new domain., Pergamon, p 485
4. Dillon KB, Mathey F, Nixon JF (1998) Phosphorus: Tthe carbon copy. Wiley, Chichester
5. Mathey F, Le Floch P (2004) Science of synthesis, vol. 15, Thieme Verlag, p. 1097
6. Le Floch P (2006) *Coord Chem Rev* 250:627
7. Weber L (2002) *Angew Chem Int Ed* 41 :653
8. Müller C, Vogt D (2007) *Dalton Trans* 47:5505
9. Breit B, Winde T, Mackewitz T, Paciello R, Harms K (2001) *Chem Eur J* 7:3106
10. Paciello R, Zeller E, Breit B, Röper M (1999) BASF patent: DE 197 43 197 A1
11. Mackewitz T, Röper M (2000) BASF patent: 1 036 796 A1
12. Müller C, Wasserber D, Weemers J, Pidko AA,Hoffmann S, Lutz M, Spek AL, Meskers SCJ, Jamssen RAJ, van Santen RA, Vogt D (2007) *Chem Eur J* 13 :4548
13. Müller C, Lutz M, Spek AL, Vogt D, (2006) *Journal of Chemical Crystallogr*aphy 36:869.
14. Müller C, Pidko EA, Totev D, Lutz M, Spek AL, van Santen RA, Vogt D (2007) Dalton Trans 5372.
15. Müller C, Pidko EA, Staring AJPM, Lutz M, Spek AL, van Santen RA, Vogt D (2008) *Chem Eur J* 14:4899.
16. Müller C, Lopez LG, Kooijman H, Spek AL, Vogt D (2006) *Tetrahedron Lett* 47:2017.
17. Müller C, Freixa Z, Lutz M, Spek AL, Vogt D, van Leeuwen PWNM (2008) *Organometallics* 27:834.
18. Le Floch P, Carmichael D, Mathey F (1991) *Organometallics* 10:2432.
19. Teunissen HT, Bickelhaupt F (1992) *Tetrahedron Lett* 33:3537.
20. Le Floch P, Mathey F (1993) *J Chem Soc, Chem Commun* 1295
21. Rosa P, Mézailles N, Mathey F, Le Floch P (1998) *J Org Chem* 63:4826.
22. Le Floch P, Kolb A, Mathey F (1994) *J Chem Soc, Chem Commun* 2065
23. Rosa P, Le Floch P, Ricard L, Mathey F (1997) *J Am Chem Soc* 119:9417.
24. Avarvari N, Rosa P, Mathey F, Le Floch P (1998) *J Organomet Chem* 567:151.
25. Rosa P, Ricard L, Mathey F, Le Floch P (1999) *J Chem Soc, Chem Commun* 537.
26. Waschbüsch K, Le Floch P, Mathey F (1996) *Organometallics* 15:1597.
27. Waschbüsch K, Le Floch P, Mathey F (1996) *Bull Soc Chim Fr* 132:910.
28. Märkl G, Dorfmeister G (1987) *Tetrahedron Lett* 28:1093.
29. Märkl G, Dorsch S (1995) *Tetrahedron Lett* 36 :3839.
30. Avarvari N, Le Floch P, Mathey F (1996) *J Am Chem Soc* 118:11978.
31. Avarvari N, Le Floch P, Ricard L, Mathey F (1997) *Organometallics* 16:4089.
32. Frison G, Sevin A, Avarvari N, Mathey F, Le Floch P (1999) *J Org Chem* 64:5524.
33. Mézailles N, Maigrot N, Hamon S, Ricard L, Mathey F, Le Floch P (2001) *J Org Chem* 66: 1054.
34. Sava X, Mézailles N, Maigrot N, Nief F, Ricard L, Mathey F (1999) *Organometallics* 18:4205.
35. Avarvari N, Mézailles N, Ricard L, Le Floch P, Mathey F (1998) *Science* 280 :1587.
36. Avarvari N, Maigrot N, Ricard L, Mathey F, Le Floch P (1999) *Chem Eur J* 5:2109.
37. Cataldo L, Choua S, Berclaz T, Geoffroy M, Mézailles N, Ricard L, Mathey F, Le Floch P (2001) *J Am Chem Soc* 123:6654.
38. Choua S, Dutan C, Cataldo L, Berclaz T, Geoffroy M, Mézailles N, Moores A, Ricard L, Le Floch P (2004) *Chem Eur J* 10:4080.
39. Moores A, Ricard L, Le Floch P (2003) *Angew Chem Int Ed* 42:4940.
40. Zhang Y, Tham FS, Nixon JF, Taylor C, Green JC, Reed CA (2008) *Angew Chem Int Ed* 47:1.
41. Moores A, Cantat T, Ricard L, Mézailles N, Le Floch P (2007) *New J Chem* 31:1493.
42. Blug M, Piechaczyk, Fustire M, Mézailles N, Le Floch P (2008) *J Org Chem* 73:3258.
43. Tran Huy NH, Donnadieu B, Mathey F (2007) *Organometallics* 26:6497.

44. Elschenbroich C, Bär F, Bilger E, Mahrwald D, Nowotny M, Metz B (1993) *Organometallics*, 12:3373.
45. Arnold L, Cloke FGN, Khan K, Scott P (1997) *J Organomet Chem* 77:528.
46. Knoch F, Kremer F, Schmidt U, Zenneck U, Le Floch P, Mathey F (1996) *Organometallics* 15:2713.
47. Böhm D, Geiger H, Knoch F, Kummer S, Le Floch P, Mathey F, Schmidt U, Zenneck U (1996) *Phosphorus Sulfur and Silicon* 109:173.
48. Le Floch P, Knoch F, Kremer F, Mathey F, Scholz J, Thiele KH, Zenneck U (1998) *Eur J Inorg Chem* 119.
49. Mézailles N, Ricard L, Mathey F, Le Floch P (2001) *Organometallics* 20:3304.
50. Doux M, Ricard L, Mathey F, Le Floch P, Mézailles N (2003) *Eur J Inorg Chem* 687.
51. Breit B (1996) *Chem Commun* 2071.
52. Breit B, Winde R, Harms K (1997) *J Chem Soc Perkin Trans* 2681.
53. Mézailles N, Avarvari N, Ricard L, Mathey F, Le Floch P (1998) *Inorg Chem* 37 :5313.
54. Doux M, Ricard L, Mathey F, Le Floch P, Mézailles N (2003) Eur J Inorg Chem 687.
55. Reetz M, Bohres E, Goddard R, Holthausen MC, Thiel W (1999) *Chem Eur J* 7:2101.
56. Waschbüsch K, Le Floch P, Ricard L, Mathey F (1997) *Chem Ber/Recueil* 130 :843.
57. Mézailles N, Le Floch P, Waschbüsch K, Ricard L, Mathey F, Kubiak CP (1997) *J Organomet Chem* 541:277.
58. Mézailles N, Avarvari N, Maigrot N, Ricard L, Mathey F, Le Floch P, Cataldo L, Berclaz T, Geoffroy M (1999) *Angew Chem Int Ed Engl* 38:3194.
59. Cataldo L, Choua S, Berclaz T, Geoffroy M, Mézailles N, Avarvari N, Mathey F, Le Floch P (2002) *J Phys Chem A* 106 :3017.
60. Le Floch P, Carmichael D, Ricard L, Mathey F, Jutand A, Amatore C (1992) *Organometallics*, 11:2475.
61. Rosa P, Mézailles N, Ricard L, Mathey F, Le Floch P (2001) *Angew Chem Int Ed* 40:4476.
62. Rosa, P, Ricard, L, Le Floch P (unpublished results).
63. Carmichael D, Le Floch P, Mathey F (1993) *Phosphorus Sulfur and Silicon* 77:255
64. Le Floch P, Mansuy S, Ricard L, Mathey F, Jutand A, Amatore A (1996) *Organometallics* 15 :3267.
65. Rosa P, Ricard L, Mathey F, Le Floch P (2000) *Organometallics*, 19:5247
66. Bakker MJ, Vergeer FW, Hartl F, Goubitz K, Fraanje J, Rosa P, Le Floch P (2000) *Eur J Inorg Chem* 843.
67. Bakker MJ, Vergeer FW, Hartl F, Rosa P, Ricard L, Le Floch P, Calhorda MJ (2002) *Chem Eur J* 8:1741.
68. Hartl F, Mahabiersing T, Le Floch P, Mathey F, Ricard L, Rosa P, Zalis S (2003) *Inorg. Chem* 42:4442.
69. Le Floch P, Maigrot N, Ricard L, Charrier C, Mathey F (1995) *Inorg Chem* 34:5070.
70. Rosa P, Ricard L, Mézailles N, Mathey F, Le Floch P (2000) *Angew Chem Int Ed* 39:1823.
71. Rosa P, Ricard L, Le Floch P, Mathey F, Sini G, Eisenstein O (1998) *Inorg Chem* 37:3154.
72. Lesnard H, Cantat T, Le Floch P, Demachy I, Jean Y (2007) *Chem Eur J* 13:2753.
73. Rosa P, Mézailles N, Ricard L, Mathey F, Le Floch P, Jean Y (2001) *Angew Chem Int Ed* 40:1251.
74. Mézailles N, Rosa P, Ricard L, Mathey F, Le Floch P (2000) *Organometallics* 19:2941
75. Le Floch P, Ricard L, Mathey F, Jutand A, Amatore C (1985) *Inorg Chem* 34:11.
76. Choua S, Sidorenkova H, Berclaz T, Geoffroy M, Rosa P, Mézailles N, Ricard L, Mathey F, Le Floch P (2000) *J Am Chem Soc* 122:12227.
77. Moores A, Goettmann F, Sanchez C, Le Floch P (2004) *Chem Commun* 2842.
78. Goettmann F, Moores A, Boissière C, Le Floch P, Sanchez C (2005) *Small* 1:636.
79. Vilain C, Goettmann F, Moores A, Le Floch P, Sanchez C (2007) *J Mater Chem* 17:3509.
80. Märkl G, Lieb F, Merz A (1967) *Angew Chem Int Ed Engl* 6:87.
81. Ashe III AJ III, Smith TW (1976) *J Am Chem Soc* 98:7861.
82. Dimroth K (1982) *Acc Chem Res* 15:58.

83. Doux M, Thuery P, Blug M, Ricard L, Le Floch P, Arliguie T, Mézailles N (2007) *Organometallics* 26:5643.
84. Moores A, Mézailles N, Ricard L, Le Floch P (2005) *Organometallics* 24:508.
85. Moores A, Mézailles N, Ricard L, Jean Y, Le Floch P, (2004) *Organometallics* 23:2870.
86. Doux M, Moores A, Mézailles N, Ricard L, Le Floch P (2005) *J Organomet Chem* 690:2407.
87. Doux M, Mézailles N, Ricard L, Le Floch P (2003) *Eur J Inorg Chem* 3878.
88. Doux M, Mézailles N, Melaimi M, Ricard, L, Le Floch P (2002) *Chem Commun* 1566.
89. Dochnahl M, Doux M, Faillard E, Ricard L, Le Floch P (2005) *Eur J Inorg Chem* 125.
90. Doux M, Ricard L, Le Floch P, Mézailles N (2004) *Dalton Trans* 2593.
91. Doux M, Mézailles N, Ricard L, Le Floch P (2003) *Organometallics* 22:4624.
92. Doux M, Le Floch P, Jean Y (2005) *J Mol Struct : THEOCHEM* 724 :73.
93. Doux M, Ricard L, Le Floch P, Jean Y (2005) *Organometallics* 24:1608.
94. Doux M, Le Floch P, Jean Y (2006) *Eur J Inorg Chem* 2035.
95. Doux M, Ricard L, Le Floch P, Jean Y (2006) *Organometallics* 25:1101.
96. Doux M, Mézailles N, Ricard L, Adkine P, Berclaz T, Geoffroy M (2005) *Inorg Chem* 44:1147.
97. Arliguie T, Doux M, Mézailles N, Thuery P, Le Floch P, Ephritikhine M (2006) *Inorg Chem* 45:9907.
98. Böhm D, Geiger H, Knoch F, Kummer S, Le Floch P, Mathey M, Schmidt U, Zenneck U (1996) *Phosphorus Sulfur and Silicon* 109:173.
99. Breit B (1999) *J Mol Cat A Chem* 143:143.
100. Reetz M, Li X (2005) *Angew Chem Int Ed* 44 :2692.
101. Neumann E, PhD Thesis (2006) PhD Thesis, Universität Basel.
102. DiMauro EF, Kozlowski MC (2002) *J Chem Soc Perkin Trans* 1:439.
103. Blug M, Mézailles N, Le Floch (2008) (unpublished results)
104. Breit B, Fuchs E (2004) *Chem Commun*, 694.
105. Fuchs E, Keller M, Breit B (2006) *Chem Eur J* 12:6930.
106. Breit B, Fuchs E (2006) *Synthesis* 13:2121.
107. Piecahczyk O, Doux M, Ricard L, Le Floch P (2005) *Organometallics* 25:1204.
108. Piechaczyk O, Cantat T, Mézailles N, Le Floch P (2007) *J Org Chem* 72:4228.
109. Mackewitz T, Ahlers W, Zeller E, Röper M, Paciello R, Knoll K, Papp R, Voss H (2002) BASF patent: WO 02 00669 A3.
110. Baber RA, Haddow MF, Middleton AJ, Guy Orpen A, Pringle PG, Haynes A, Williams GL, Papp R (2007) *Organometallics* 26:713.

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Synthetic Approaches to 1,2-Heteraphosphacyclanes

Irina L. Odinets and Inga M. Aladzheva

Abstract 1,2-Heteraphosphacyclanes have drawn the attention of synthetic chemists due to their association with various biological activities and their unusual properties. The focus of this chapter is on the synthetic approaches to heterocyclic compounds of this type, which are principally different for the compounds with three-membered, four-membered and larger ring size and differ greatly depending on the nature of the heteroatom in the ring.

Keywords 1,2-Azaphosphacyclanes, 1,2-Oxaphosphacyclanes, 1,2-Thiaphosphacyclanes

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1 Introduction

In recent years, increased interest has been paid to the chemistry of heterocyclic compounds, development of synthetic routes and investigation of the properties of novel types of heterocycles, mostly due to their practical application (e.g. in agrochemistry and the pharmaceutical chemistry). In full measure, this applies to phosphorus-containing heterocyclic compounds as well. Noteworthy is the known peculiarity of phosphorus-containing heterocyclic compounds compared to their acyclic analogues, which is manifested in the unusual structures (conformational and stereochemical) of the reaction products. Cyclic phosphorus compounds are often invoked with the purpose of studying the mechanisms of chemical transformations of organophosphorus compounds. Moreover, they are effectively used as synthons in organic synthesis. Phosphorus-containing heterocyclic compounds, particularly phosphates, play an important role in biochemical processes. Monoheteraphophacyclanes are represented in the literature mainly by five- and six-membered 1,2-oxaphosphacyclanes, which have found industrial application, particularly as non-inflammable hydraulic fluids and plasticizers [1, 2], additives to lubricants and flame retardants [3], thermostabilisers of synthetic fibres [4–6] and surfactants [7], or are used as synthons for hard-to-reach compounds [8].

Despite basic publications from 1960–1990 concerning the synthetic routes to these compounds, 2-oxo-1,2-oxaphospholanes have recently attracted a new wave of attention as sugar surrogates, since analogues with phosphorus atoms replacing the anomeric carbon could potentially serve as carbohydrate mimics. Therefore, new modern catalytic and stereoselective syntheses of these compounds have been developed. 1,2-Monoheteraphosphacyclanes having other heteroatoms in the ring (e.g. sulfur or nitrogen) became available later and are still investigated, but to a far lesser extent. Nevertheless, a variety of 1,2-azaphosphacyclanes attract attention due to high biological activity (e.g. as inhibitors of different enzymes) while 1,2-thiaphosphacyclanes demonstrating different tautomeric transformations (such as the rather rare ring-chain halogenotropic tautomerism) are of fundamental interest. Taking into account the prospects of these compounds and the fact that synthetic strategies postulated recently as novel are often based on previous detailed investigations never systematized in the literature, it seems useful to summarize the information available in the literature on the synthetic approaches to these compounds.

The basis of this review is a description of those approaches that are different for compounds with different ring size, i.e. for three-membered 1,2-heteraphosphiranes, four-membered 1,2-heteraphosphetanes, and compounds with larger ring size, namely the corresponding five-membered phospholanes, six-membered phosphinanes and their rare seven- and eight-membered analogues.

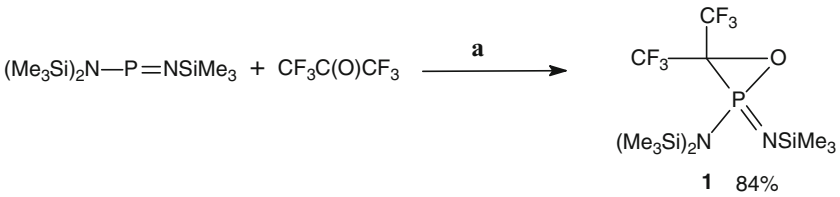
2 1,2-Heteraphosphiranes

Synthetic routes to three-membered saturated P,X-heterocycles (i.e. 1,2-heteraphosphiranes) are based mainly on the cycloaddition reactions of the stable two-coordinated phosphorus compounds. These heterocycles therefore became available only once

synthetic approaches to the stable $\sigma^2\lambda^3$-phosphanes and $\sigma^3\lambda^5$-phosphoranes had been developed.

2.1 1,2-Oxaphosphiranes

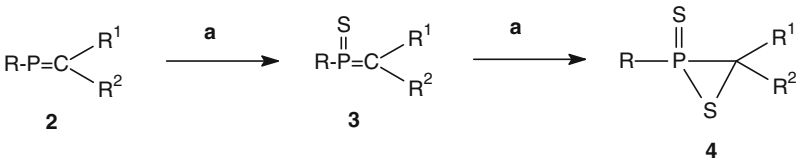
Cycloaddition of hexafluoroacetone to iminophosphine resulted in the only example of a three-membered P,O-heterocycle **1** known till now (Scheme 1) [9].



Scheme 1 **a** 2 days, 25 °C

2.2 1,2-Thiaphosphiranes

The general synthetic route to 2-thio-1,2λ^5-thiaphosphiranes is based on the addition of sulfur to methylidenephosphines **2**. This reaction proceeds in a step-by-step process: the addition of one equivalent of sulfur affords $\sigma^3\lambda^5$-methylidene(thioxo) phosphorane **3**, which reacts with the second equivalent of sulfur according to the [1 + 2]-cycloaddition scheme, affording the corresponding 2-thio-1,2λ^5-thiaphosphirane **4** (Scheme 2) [10–15].



R=$(Me_3Si)_2N$, t-Bu$(Me_3Si)N$, 2,6-$(Alk)_2C_6H_3$, 2,4,6-$(Alk)_3C_6H_2$ (Alk=Me,t-Bu)
R^1, R^2= H, Me, Ph, NMe_2, $SiMe_3$, CH=CH$(SiMe_3)$

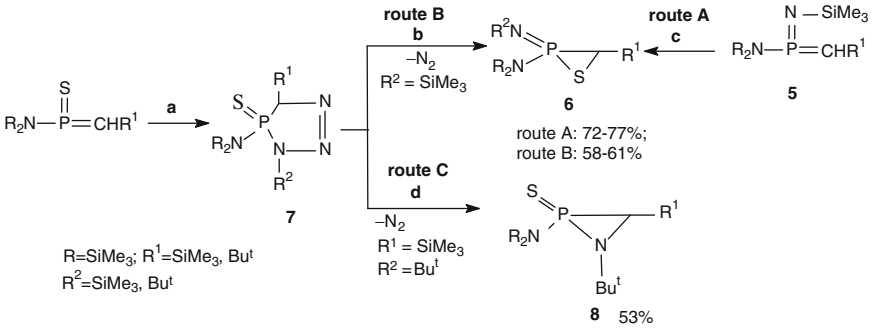
Scheme 2 **a** 1/8 S_8

The reaction is typically performed under elevated temperature to afford the final products in yields ranging from 17 to 77% depending on the particular substituents. However, using DBU (ca. 0.6 equiv.) allows the desired compounds to be obtained in yields close to the quantitative ones, even at room temperature (rt) [13, 14]. Despite the possibility of geometric isomerism for λ^5-thiaphosphiranes, the formation of two stereoisomers was mentioned in only one publication [14].

Evidently, cycloaddition of sulfur to the intermediate methylidene(thioxo)phosphorane is the step determining the type of λ^5-thiaphosphirane isomer formed. Most likely, this process is stereoselective and results in the least sterically hindered product.

The stability of any of the initial substrates, intermediate methylene(thioxo)phosphorane and 1,2λ^5-thiaphosphirane is defined by the nature of the substituents both at the phosphorus and carbon atoms. The choice of such substituents is sufficiently limited by such bulky groups as $[(Me_3Si)_2N$-; (^{t}Bu)(Me_3Si)N-; 2,4,6-$(Alk)_3C_6H_2$, where Alk = Me, ^{t}Bu; 2,6-$Me_2C_6H_3$, Ph, $SiMe_3$]. A trimethylsilyl moiety at the carbon atom and bis(trimethylsilyl)amino [10] and mesityl [11, 12] groups at the phosphorus atom manifest the most stabilizing effect. However, in the case of triarylmethylenphosphoranes, cleavage of the P–C bond resulting in the formation of metadithiophosphonates RPS_2 dominates during the sulfur addition [16–18].

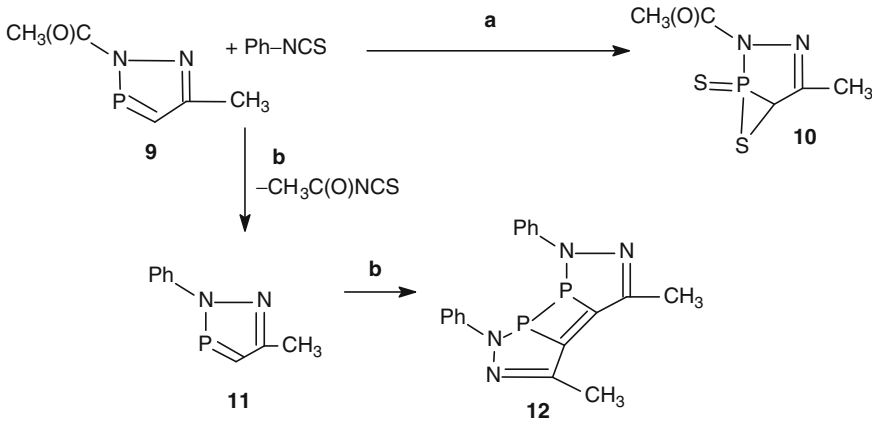
Similarly, [1 + 2]-cycloaddition of sulfur to methylene(imino)phosphoranes **5** leads to 2-imino-1,2λ^5-thiaphosphiranes **6** (route A in Scheme 3), obtained also by trimethylsilylazide or *tert*-butylazide addition to methylene(thioxo)phosphiranes followed by thermal decomposition of intermediate Δ^1-triazaphospholenes **7** (route B in Scheme 3) [19]. It should be noted that the photochemical decomposition of Δ^1-triazaphospholenes **7** results in an alternative structure with ring nitrogen atom, 2-thio-1,2-λ^5-azaphosphirane **8** (route C in Scheme 3) [19].



Scheme 3 **a** R^2N_3; **b** Δ; **c** S; **d** *h*ν

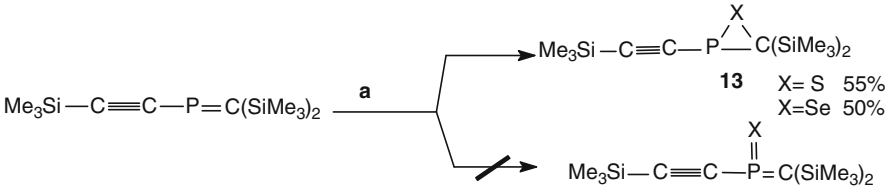
An unusual reaction of 2-acetyl-5-methyl-1,2,3-diazaphosphole **9** with phenyl isothiocyanate, either upon prolonged heating or in the presence of a catalytic amount of triethylamine, affords a fused 2-thioxo-1,2λ^5-thiaphosphirane **10** (Scheme 4) [20]. In this case also, changing of the reaction conditions for UV irradiation causes the change in its direction: the acetyl group at the N(2) atom of the starting phosphole is substituted for the phenyl group of phenyl isothiocyanate, giving the product **11**, which is partially dimerized during the reaction affording compound **12**.

As mentioned above, the addition of one equivalent of sulfur to methylidenephosphine usually gives rise to methylidene(thioxo)phosphorane rather than to thiaphosphirane or to their mixture with the former predominating. Nevertheless, exceptions to this rule are documented and comprise the formation of ethynyl-substituted 1,2λ^3-thia- and 1,2λ^3-selenaphosphiranes **13,** which are incapable of further sulfur

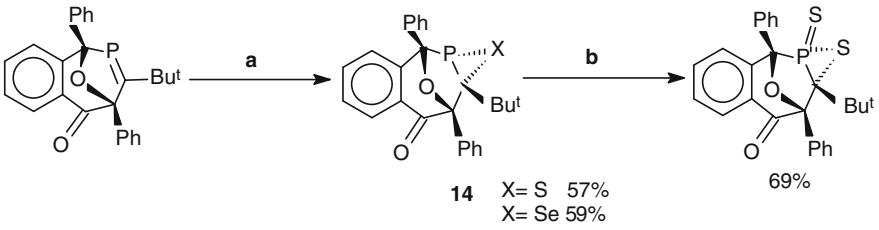


Scheme 4 **a** 90–130 °C, 53 h or cat.Et_3N, 1.5 months; **b** *hν*

addition (Scheme 5) [21]. Similarly, tricyclic compounds **14** with the *trans*-sulfur (selenium) atom relative to the bridged oxygen atom have been obtained (Scheme 6) [22].

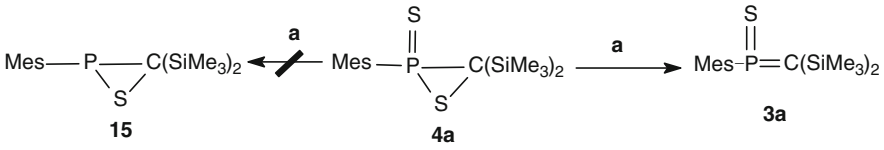


Scheme 5 **a** 1/8 S_8 or 1/*x* Se_x



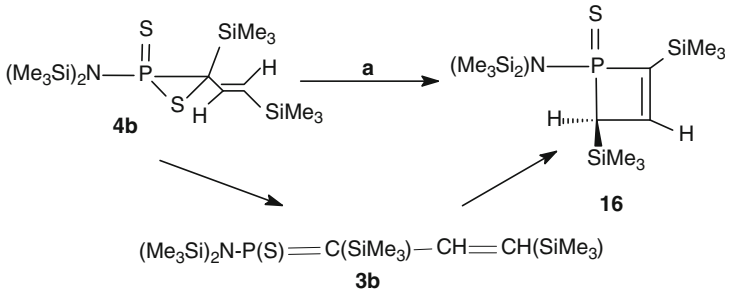
Scheme 6 **a** 1/8 S_8 or 1/*x* Se_x, 25 °C, $PhCH_3$, Et_3N; **b** X = S, 1/8 S_8, 25 °C, $PhCH_3$, Et_3N

With general considerations in mind, one could suggest a desulfurization of the corresponding 2-thio-1,2λ^5-thiaphosphiranes as a possible approach to 1,2λ^3-thiaphosphiranes. However, 2-mesityl-3,3-bis(trimethylsilyl)-2-thioxo-1,2λ^5-thiaphosphirane **4a** yields the corresponding methylidene(thioxo)phosphorane **3a** under the action of tributylphosphine rather than the expected λ^3-thiaphosphirane **15** (Scheme 7) [11, 12].



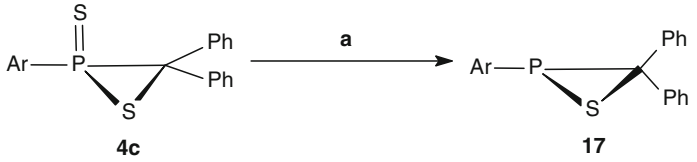
Scheme 7 **a** $^{n}Bu_3P$

Desulfurization of 2-thioxo-1,2λ^5-thiaphosphirane **4b** using triphenylphosphine affords phosphacyclobutene **16** as the product of intramolecular cyclization involving C=C and P=C bonds in the intermediate methylidene(thioxo)phosphorane **3b** (Scheme 8) [15]. The formation of the latter in the reaction was confirmed by ^{31}P NMR spectroscopy.



Scheme 8 **a** Ph_3P, C_6H_6, 20 °C

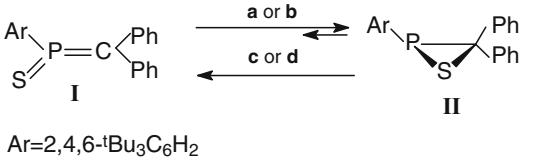
At the same time, 2-thioxo-2-(2,4,6-tri-*tert*-butylphenyl)-3,3-diphenyl-1,2λ^5-thiaphosphirane **4c** is desulfurized, readily giving the corresponding 1,2λ^3-thiaphosphirane **17** (Scheme 9) [13, 23]. Different phosphines were tested as desulfurization agents and tris(dimethylamino)phosphine proved to be the most efficient.



Scheme 9 **a** $(Me_2N)_3P$, C_6H_6, 20 °C, 3 h

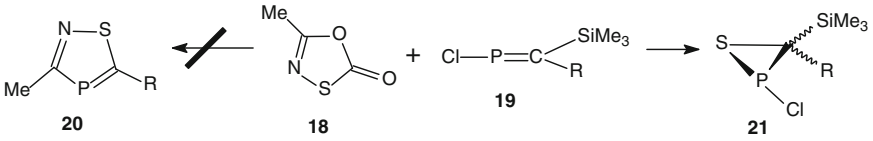
The distinction in the results of the reaction for different 2-thio-1,2λ^5-thiaphosphiranes suggests that the desulfurization affording 1,2λ^3-thiaphosphirane is governed by kinetic control, while the reaction giving more stable methylidene(thioxo) phosphorane is governed by thermodynamic control [23]. Investigation of the valence isomerism between σ^{3}λ^5-phosphoranes (**I**) and σ^{3}λ^3-phosphiranes (**II**) known for other phosphorus compounds [24–28], demonstrated that conversion of

a linear form to the cyclic one was possible only upon irradiation, while the reverse process could be both thermally and photochemically induced, though in the latter case to a considerably lesser extent (Scheme 10) [13, 23].



Scheme 10 **a** C_6D_6, Hg lamp, 100 W, 10 °C, 1.5 h; **b** C_6H_6, Xe lamp, 300 W, 2 h; **c** *m*-xylene, reflux in darkness, 16 h; **d** 100 °C, 7 days

The formation 1,2λ^3-thiaphosphiranes was also mentioned in the reaction of 5-methyl-1,3,4-oxathiazole-2-one **18** with *P*-chloromethylidenephosphines **19** affording, instead of the expected thiazaphospholenes **20,** a mixture of *E*- and *Z*-isomers of 2-chloro-1,2λ^3-thiaphosphiranes **21** (Scheme 11) (it may be mentioned that the reaction of 5-aryl-substituted oxathiazole with **19** yielded the corresponding thiazaphospholene) [28].

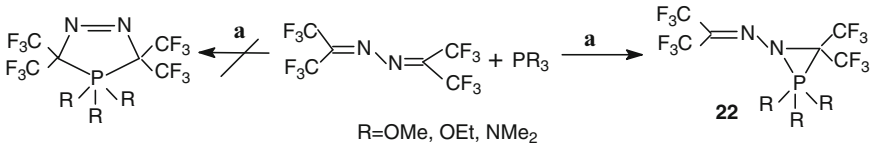


Scheme 11 R = Ph, 32%, *E*:*Z* = 75:25; R = $SiMe_3$, 22%

Thus, sulfur addition to methylidenephosphines is rather a convenient general route to 2-thio-1,2λ^5-thiaphosphiranes, although their analogues bearing three valent phosphorus atom are still difficult to obtain.

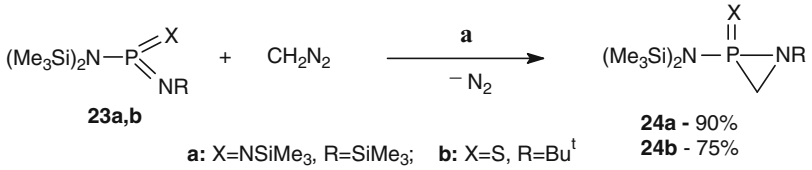
2.3 1,2-Azaphosphiranes

The first 1,2λ^5-azaphosphiranes **22** were prepared from addition of trialkylphosphites or tris(dimethylamino)phosphine to hexafluoroacetonazine in yields of 57–96% (Scheme 12) [29]. However, the main synthetic approaches to such compounds



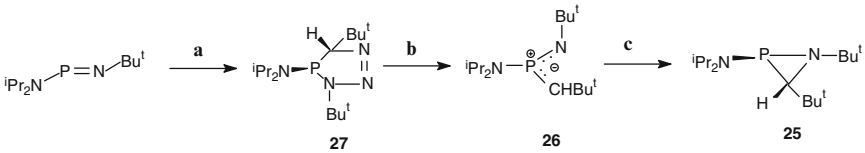
Scheme 12 **a** 0 °C, hexane

are also based on cycloaddition reactions to the stable $\sigma^2\lambda^3$-phosphanes and $\sigma^3\lambda^5$-phosphoranes. Thus, 1,2λ^5-azaphosphiranes **24** can be readily obtained via [1 + 2]-cycloaddition of diazomethane to diiminophosphorane **23a** and imino(thioxo) phosphorane **23b**, respectively (Scheme 13) [19, 30].



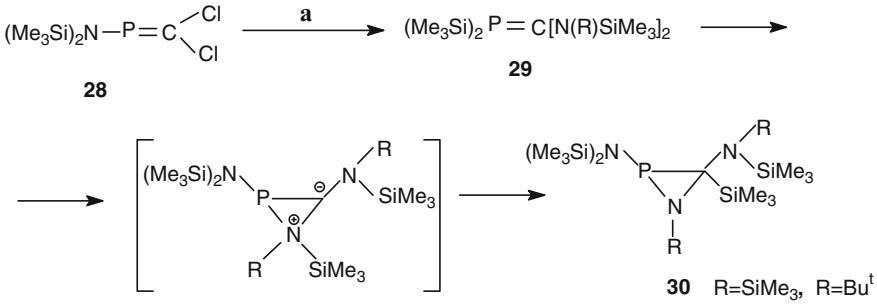
Scheme 13 **a** 0 °C, ether

As mentioned above, triazaphospholene **7** obtained from methylene(thioxo) phosphorane and *t*-butyl azide was changed to 2-thio-1,2λ^5-azaphosphirane **8** by photochemically induced elimination of N_2 (Scheme 3) [19]. Synthesis of 1,2λ^3-azaphosphiranes has been described only in two communications [24, 31]. Namely, λ^3-azaphosphirane **25** was obtained by valence isomerization of imino(methylene) phosphorane **26** formed by the N_2 elimination from [2 + 3]-cycloadduct **27** [24] (Scheme 14).



Scheme 14 **a** ^{t}BuCHN$_2$, –20 °C, THF; **b** rt, –N_2; **c** 140 °C, 5 min

The second approach to λ^3-azaphosphiranes comprises addition of lithium derivatives of silylated amides to the dihalogenated phosphaalkenes **28** resulting in unstable phosphaalkenes **29**, which slowly undergo a ring closure and 1,2-trimethylsilyl group migration to give λ^3-azaphosphiranes **30** as a mixture of two isomers (Scheme 15) [31].

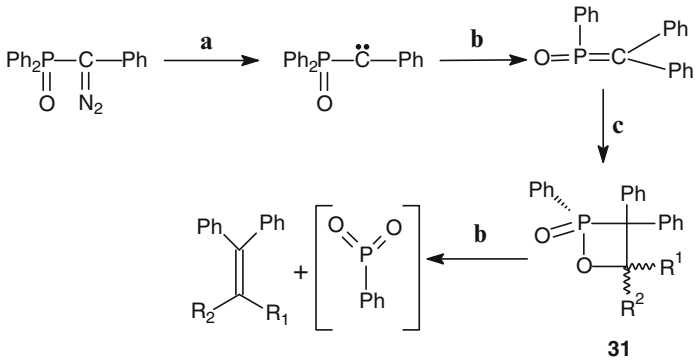


Scheme 15 **a** 2 $Me_3SiN(R)Li$, –70 °C, THF, –2LiCl

3 1,2-Heteraphosphetanes

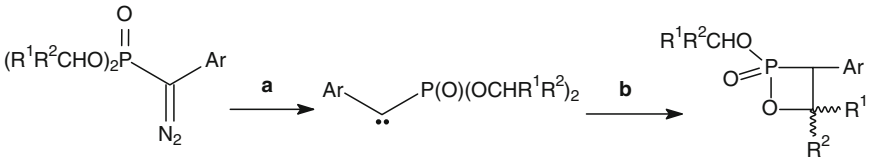
3.1 1,2-Oxaphosphetanes

Four-membered P,O-heterocycles **31** were obtained from [2 + 2]-cycloaddition of carbonyl compounds to phosphorylated carbenes generated from α-diazabenzylphosphine oxide under thermal- or photoinitiation (Scheme 16) [32–34]. 2-Oxo-1,2-



Scheme 16 **a** C_6H_6, reflux; **b** *hν*; **c** $R^1R^2C{=}O$

oxaphosphetanes based on aromatic aldehydes are photostable and were isolated in individual state, while those based on α,β-nonsaturated carbonyl compounds transform under reaction conditions to butadienes or hexatrienes and dioxophenylphosphorane. 1,2-Oxaphosphetanes **32** are formed also by flash-vacuum pyrolysis (FVP) of α-diazaphosphonates at rather low temparature (Scheme 17) [35].

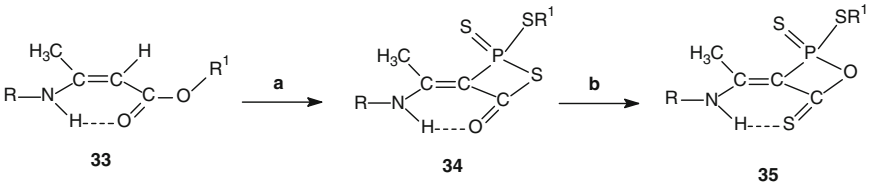


Ar=Ph, 4-Cl-XC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, 3-MeC_6H_4, 1(2)-$C_{10}H_7$;
R^1,R^2= H, Me, Et

Scheme 17 **a** FVP, $-N_2$; **b** <275 °C

3.2 1,2-Thiaphosphetanes

In the case of 1,2-thiaphosphetanes, all the known methods provide only 2-thioxo-1,2λ^5-derivatives. Thus, the reaction of alkylaminocrotonates **33** with P_4S_{10} gives 2-thioxo-1,2-thiaphosphetane-4-ones **34** [36]. However, being heated in benzene (for more than 30 min) or under chromatographic purification on silica gel, the latter rearrange spontaneously to the isomeric oxaphosphetanes **35** (Scheme 18). IR



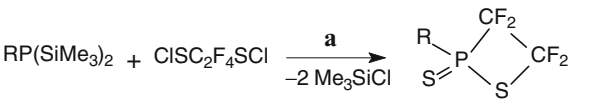
33 **34** **35**

R=R^1=Me, R=Et, R^1=Me, ^{i}Pr

Scheme 18 **a** P_4S_{10}, C_6H_6, rt; **b** C_6H_6, 60 °C, 20–60 min or column chromatography on silica gel

spectroscopy (using deuterium-exchange) indicates that the intramolecular hydrogen bond stabilizing the isomeric heterocycles formed is by far stronger in the thiocarbonyl product **35**. It was therefore proposed that the thiaphosphetane **34** represented a product of kinetic reaction control and the isomeric oxaphosphetane **35,** a product of thermodynamic control.

Perfluorinated 1,2-thiaphosphetanes **36** and **37** [37] have been obtained in two ways. The first method is based on the reaction of [bis(trimethylsilyl)]phosphines with 1,1,2,2-tetrafluoroethane-1,2-bissulfenyl chloride (Scheme 19), which has



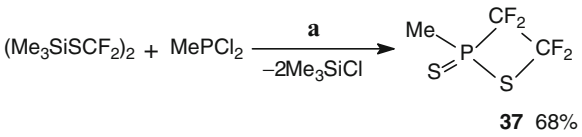
36 39-56%

R =Me, ^{t}Bu, Ph, 2,4,6-^{t}Bu$_3$C$_6$H$_2$

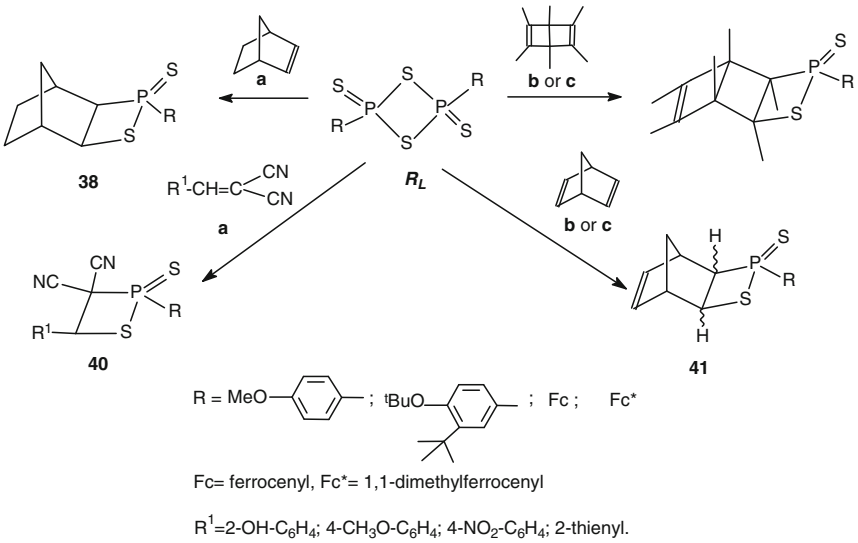
Scheme 19 **a** Et_2O, –78 °C

found application in the preparation of partially fluorinated heterocycles [38–40]. The second method comprises the reaction of dichloro(methyl)phosphine with 1,2-bis(trimethylsilylthio)-1,1,2,2-tetrafluoroethane and proceeds extremely readily at very low temperature (Scheme 20) [37].

Addition of the Lawesson reagents (R_L) to C=C double bonds may be considered the most general synthetic approach to 2-thio-1,2-thiaphosphetanes **38**–**41** (Scheme 21) [41, 42]. The putative reaction mechanism involves a nucleophilic attack on the *sp*^{2}-carbon atom by the monomeric R_L fragment, often referred to in the literature



Scheme 20 a Et_2O, –196 °C

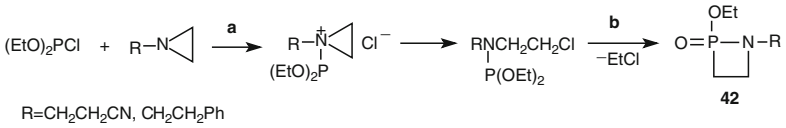


Scheme 21 **a** 80 °C, toluene,16 h; **b** 80 °C (R = Ar), toluene; **c** rt (R = Fc, Fc*)

as a dipolar dithiophosphonium ylide since its reactivity is similar to that of the Wittig reagents. The reaction rate depends mainly on the solubility of the starting dithiadiphosphetane, and the reaction can be performed both under ambient conditions (R = Fc*) and at elevated temperature over a prolonged reaction time (R = 4-$MeOC_6H_4$, just the Lawesson reagent).

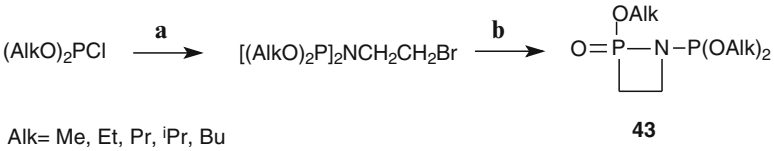
3.3 1.2-Azaphosphetanes

2-Oxo-1,2λ^5-azaphosphetanes **42** can be synthesized via an intramolecular Arbuzov reaction of *N*-2-chloroethyl amidoesters of P(III) acids proceeding under distillation in vacuo (Scheme 22) [43]. The starting substrates were obtained in turn from diethylchlorophospite addition to aziridines. Subsequently, the reaction of dialkylchlorophosphite and 2-bromoethylamine hydrobromide in 2:1 ratio in the presence of



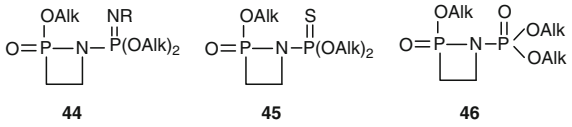
Scheme 22 **a** neat, 20 °C→60 °C (exothermic reaction), then 12 h at rt; **b** distillation in vacuo (0.02–0.04 Hg)

triethylamine was found to afford N,N-bis(phosphorylated) bromoethylamines **42** converted by thermolysis to N-phosphorylated 2-oxo-1,2λ^5-azaphosphetanes **43** in moderate yields (30–38%) (Scheme 23) [44].

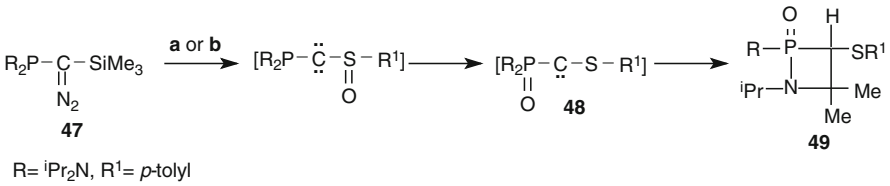


Scheme 23 **a** 0.5 $BrCH_2CH_2NH_2 \cdot HBr$, 1.5 Et_3N, 2–4 °C, C_6H_6:$CHCl_3$ = 2:1; **b** Δ

Phosphetanes **43** bearing the exocyclic P(III)-substituent react rapidly with organic azides or sulfur or undergo the Arbuzov reaction yielding 2-oxo-1,2λ^5-azaphosphetanes **44, 45** and **46**, respectively.



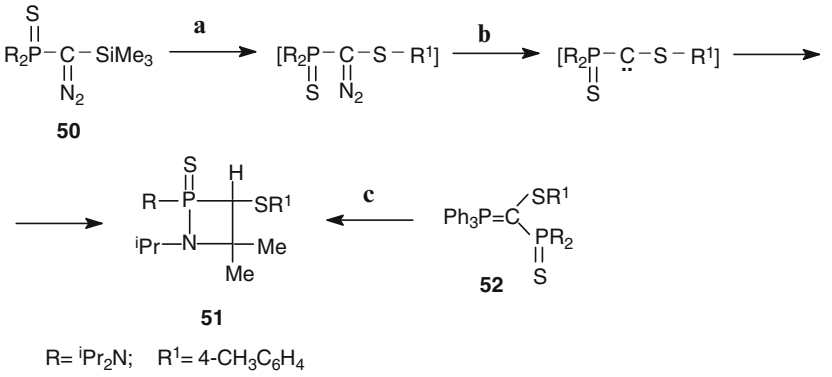
The second approach to 1,2-azaphosphetanes developed by Bertrand et al. [45–48] is based on the transformations of the phosphanyl- and thioxophosphoranyl-substituted diazomethanes. Thus, trimethylsilyl(phosphanyl)diazomethane **47** reacting with *p*-toluenesulfinylchloride or *p*-toluenesulfonylchloride affords the same 2-oxo-1,2λ^5-azaphosphetanes **49** (Scheme 24) [45]. Their formation is explained by insertion of intermediate carbene **48** into the methine C–H bond of one of the isopropyl groups at the phosphorus atom.



R= $^iPr_2N$, R^1= *p*-tolyl

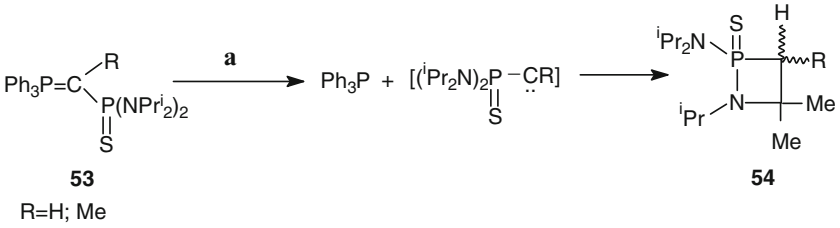
Scheme 24 **a** $R^1S(O)Cl$, C_6H_6, 20 °C, 10 min (–N_2, –Me_3SiCl) **b** R^1SO_2Cl, C_6H_6, 20 °C, 10 min (–N_2O, –Me_3SiCl)

Similarly, the reaction of (thioxophosphoranyl)(trimethylsilyl)diazomethane **50** with *p*-toluenesulphanyl chloride resulted in 2-thioxo-1,2λ^5-azaphosphetane **51** (Scheme 25). It should be mentioned that azaphosphetane **51** with *trans* arrangement of isopropylamino and *p*-toluenesulfanyl groups could also be obtained by photolysis of the phosphorus ylide **52** (Scheme 25) [46]. Moreover, photolytical cleavage of



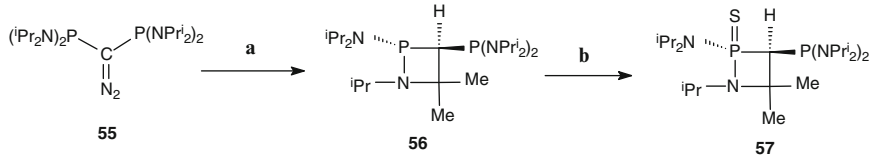
Scheme 25 **a** ClSR^1, benzene, 20 °C, 10 min; **b** –N$_2$, **c** *h*ν, benzene, 0 °C, 16 h

thiophosphoryl-substituted ylides to give triphenylphosphine and thioazaphosphetanes is the alternative route to such heterocycles (Scheme 26). For example, cleavage of **53** afforded **54,** the isomer with *trans* disposition of methyl and diisopropylamino groups being the major product (~4:1) in the case of R = Me [46].

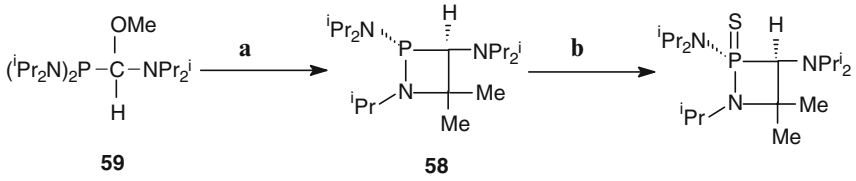


Scheme 26 **a** *h*ν, 0 °C, 3 days

Heating of bis[bis(diisopropylamino)phosphanyl]diazomethane **55** gave 1,2λ^3-azaphosphetane **56** quantitatively as a single diastereoisomer [47] (Scheme 27). Treatment of **56** with elemental sulfur afforded 2-thioxo-1,2λ^5-azaphosphetane **57**, whose X-ray crystal structure determination revealed *trans* disposition of the diisopropylamino group at the ring phosphorus atom and the second phosphorus moiety relative to the ring plane. Furthermore, 1,2λ^3-azaphosphetane **58**, characterized by the same disposition of the substituents, was obtained by thermolysis of hemiaminal **59.** The reaction proceeded through generation of (amino)(phosphanyl)carbene (Scheme 28) [48].

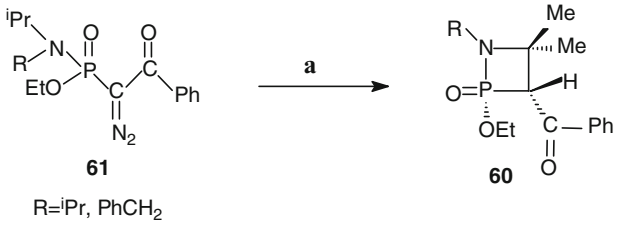


Scheme 27 **a** C_6H_6, reflux, 48 h; **b** 1/8 S_8



Scheme 28 **a** 160 °C, in vacuo; **b** 1/8 S_8, THF, 20 °C

Synthesis of 2-oxo-1,2λ^5-azaphosphetanes **60** was accomplished through rhodium-catalysed decomposition of α-diazo-β-ketophosphonamidates **61** that proceeded through intramolecular insertion of the carbene generated into the methine C–H bond of the isopropyl group (Scheme 29) [49]. Both insertion products were



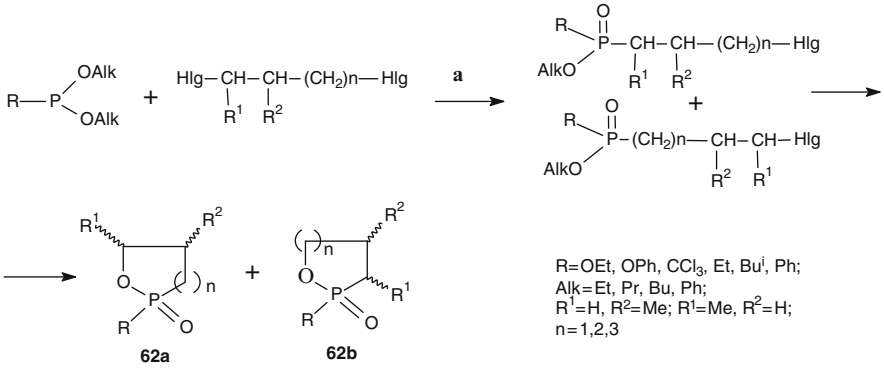
Scheme 29 **a** $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 4 h

formed diastereoselectively, in a ratio of ca. 10:1 in favour of the (S_P,R_C) relative configuration. The hydrolysis of **60** occurs rapidly in water with exclusive endocyclic P–N bond fission [50].

4 1,2-Heteraphospholanes and 1,2-Heteraphosphinanes

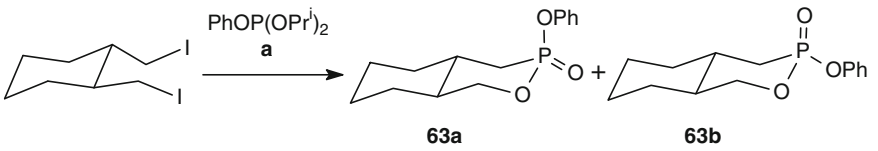
4.1 1,2-Oxaphospholanes and 1,2-Oxaphosphinanes

The reaction of phosphorus(III) acid esters with α,ω-dihaloalkanes at elevated temperature, proceeding via formation of ω-haloalkylphosphonate or ω-haloalkylphosphinate in the result of the Arbuzov–Michaelis reaction, is one of the first known synthetic approaches to 2-oxo-1,2-oxaphosphacyclanes **62** (Scheme 30) [1, 2, 51, 52].

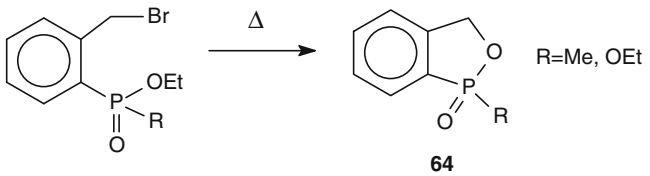


Scheme 30 **a** 150–190 °C, 2.5–12 h

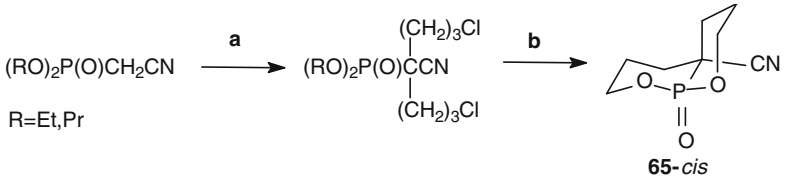
The convenient modification of this procedure comprises preliminary synthesis of ω-haloalkylphosphonates or phosphinates, including the functionalized ones, followed by intramolecular dealkylation [53, 54]. Both the rate of the cyclization and the yields of the heterocycles increase by catalytic action of lithium chloride (4 h, reflux) [55] or microwave irradiation (150 W, 10 min) [56]. The approach gives the possibility of obtaining both saturated fused bicyclic phostones **63** formed as a mixture of isomers [57] (Scheme 31), 3,4-benzo-1,2-oxaphospholanes **64** [58] (Scheme 32) and those bearing additional substituents in the ring [59], including bicyclic phosphabicyclodecan-1-oxide **65** (Scheme 33) [60].



Scheme 31 **a** Xylene, 180–190 °C, 3 h



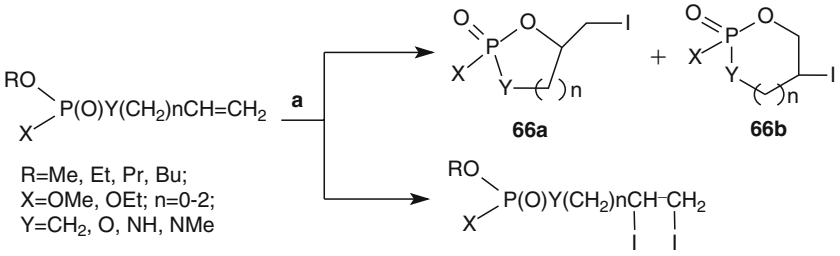
Scheme 32 **a** R = Me, distillation in vacuo; **b** R = OEt, 1,2-Cl_2-C_6H_4, reflux, 10 h followed by distillation in vacuo



Scheme 33 **a** $Br(CH_2)_3Cl$, 40%NaOH; **b** 200 °C, 0.1 Hg

Moreover, ω-haloalkyl-substituted phosphonic (phosphinic) acids as well as their thioanalogues also undergo intramolecular cyclization in the presence of a base, giving the corresponding (thio)phostones in rather good yields [61, 62]. Virtually no side products are formed during this cyclization (the isolated yield is 85–90%) and the reaction kinetic is approximately first order. In this case, too, the five-membered heterocyclic products were formed more rapidly than their six-membered analogues. The ratio of the rate constants for five- and six-membered heterocycle formation (k_5/k_6) is 4.3 (for the phosphinate anion) and 30 (for the thiophosphinate anion). So, this procedure has a general character and may be used both for the synthesis of 2-oxo-1,2λ^5-oxa- and 2-oxo-1,2λ^5-thiaphosphacyclanes.

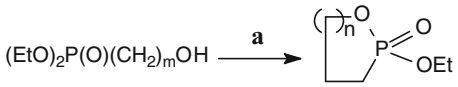
Cyclization of terminal unsaturated phosphonates under the action of iodine, proceeding via the formation of intermediate ω-haloalkyl-substituted compounds, presents a convenient alternative to the above procedures [63–65]. The reaction has a general character and besides 1,2-oxaphospholanes allows synthesis of the corresponding 1,3,2-dioxa- and 1,3,2-oxaza- derivatives (Scheme 34). The length of the linker



Scheme 34 **a** I_2, $CHCl_3$, 10 °C, 72 h

separating the phosphorus atom and vinyl moiety substantially influences the result of the reaction. The presence of three potential ring members (e.g. propylidene group; Y = CH_2, n = 2) resulted regioselectively in *cis*-isomers of iodomethyl-substituted derivatives **66a** under mild conditions (10 °C). When the amount of such groups is equal, two (Y = CH_2, n = 1) five- and six-membered cycles **66a** and **66b** are formed in ca 1:1 ratio, while further shortening of the linker leads to the linear iodine addition product only. It should be underlined that using bromine instead of iodine leads to the addition product of the electrophile to a double bond, independently of the other factors.

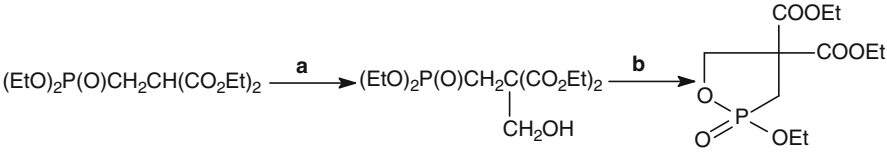
Besides the intramolecular cyclization of ω-haloalkyl-substituted compounds, a variety of five- and six-membered 2-oxo-1,2-oxaphosphacyclanes can be obtained via thermal cyclization of ω-hydroxyalkylphosphonates (preformed or obtained in situ) and related compounds [66–73]. As the reaction proceeds through intramolecular transesterification requiring a prolonged heating, use of bases such as lithium hydride, sodium hydride, sodium alcoholate, etc. accelerates the reaction and increases the yield of heterocycles **62** (Scheme 35) [54].



62

Scheme 35 **a** Δ, Base (Et_3N, LiH, NaH or NaOR), 12–48 h; for NaOEt as a catalyst $n = 1$ (93%), $n = 2$ (68%) [66]

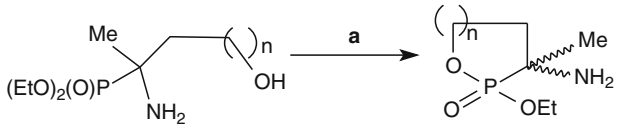
The intramolecular transesterification proceeds very rapidly in the case of five-membered 1,2-oxaphospholanes. This is the reason why linear ω-hydroxypropylphosphonates (phosphinates) could not be synthesized by base-catalyzed Michaellis–Bekker reaction of hydrophosphoryl compounds and ω-haloalcohols [70] during hydrogenolysis of γ-benzyloxy-phosphonates (phosphinates) [74, 75] or while performing an Arbusov reaction of γ-iodoalcohol [76, 77]. The design of functionalized w-hydroxyalkylphosphonates followed by intramolecular cyclization allowed the formation of a variety of biologically active substituted 2-oxo-1,2-oxaphosphacyclanes bearing a carbalkoxy group (compound **67**, Scheme 36) [78,



67 > 85 %

Scheme 36 **a** $(CH_2O)_n$, EtONa/EtOH; **b** 126 °C, 0.01 Hg

79] and amino group (compound **68**, phosphorylated analogues of α-methylhomoserine, Scheme 37) [80]. Moreover, cyclic α-aminophosphonates have shown promise in catalytic antibody synthesis [81].

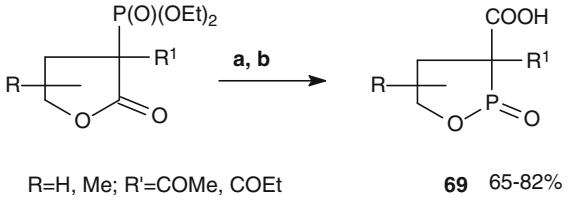


68 quant.

Scheme 37 **a** cat NaH/DME; for $n = 1$ rt, 7 h; for $n = 2$, 60 °C, 5 h

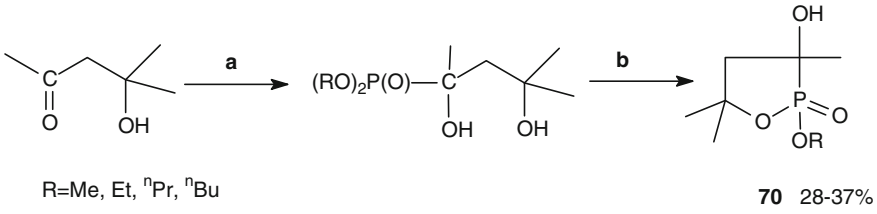
It should be noted that ω-acetoxyalkylphosphonates [82] and ω-acetoxyalkylphosphonic acids of different structures include carbohydrate-derived compounds [83] and that substituted phosphorylated benzenes [58] also afford the corresponding 2-oxo-1,2-phosphacyclanes under acid catalysis. Subsequent treatment of the cyclic

phoshonic acid esters, either by Me_3SiBr or under basic conditions, allowed preparation of free phostonic acids. Moreover, the synthesis of carboxy-substituted phostones **69** from α-phosphoryl-γ-butyrolactones is also based on the transesterification reaction (Scheme 38) [84].

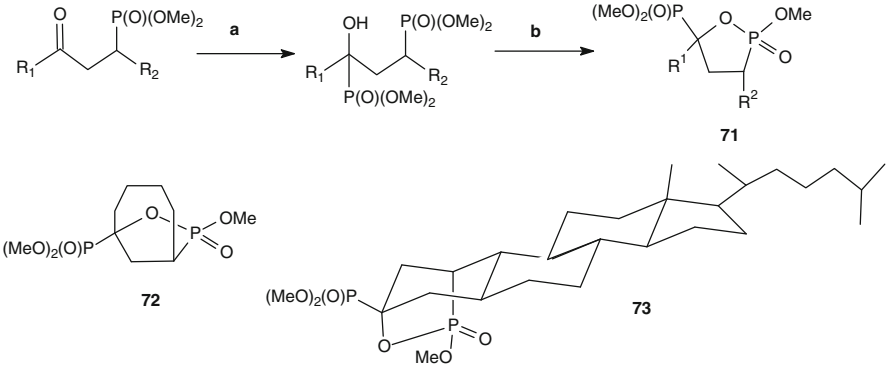


Scheme 38 **a** KOH; **b** HCl, $CHCl_3$

If the starting ω-hydroxyalkylphosphonate is obtained via the Abramov reaction, presenting a convenient route to α-hydroxyalkylphosphonates, the final heterocycles formed in the one-pot process may possess additional functionality such as a hydroxy (compound **70**, Scheme 39) [85] or phosphoryl group (compound **71**, Scheme 40) [86]. In the latter case, the starting carbonyl compounds of rather complex structure gave rise to directional synthesis of biologically active compounds **72** and **73**.

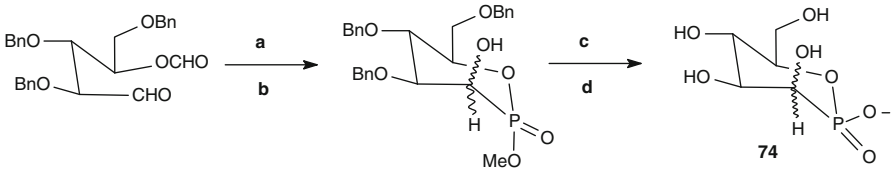


Scheme 39 **a** $(RO)_2P(O)H$, RONa; **b** RONa



Scheme 40 **a** $(MeO)_2P(O)H$, MeONa; **b** MeONa

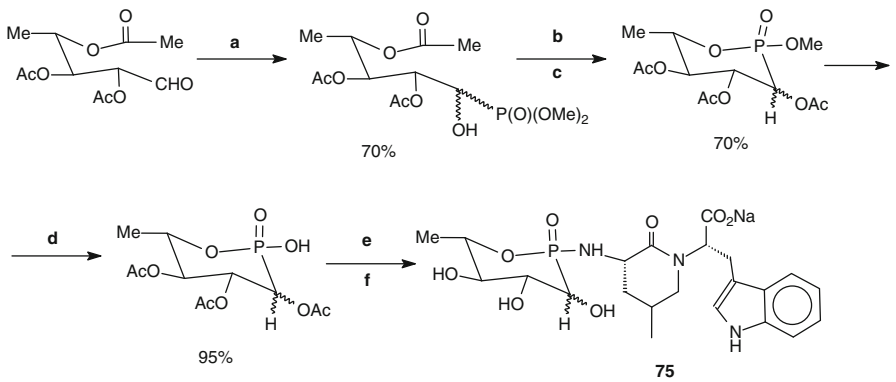
Moreover, transesterification of ω-hydroxyalkylphosphonates obtained via the Abramov reaction presents the main synthetic route to biologically active carbohydrates and sugar analogues having the 1,2-oxaphosphacyclane moiety [87–93]. These compounds, in which the anomeric carbon atom is replaced by phosphoryl group, may mimic the transition state involved in glycosidase-catalysed hydrolytic reactions and have been suggested as possible inhibitors of these enzymes. The synthesis is exemplified by preparation of phosphorylated analogues of d-glucopyranose and d-mannopyranose **74** (Scheme 41) [91]. The reaction does not proceed



Scheme 41 **a** $P(OMe)_3$, AcOH; **b** NaOMe/MeOH; **c** H_2, Pd/C, MeOH; **d** NaI, MeCN, reflux

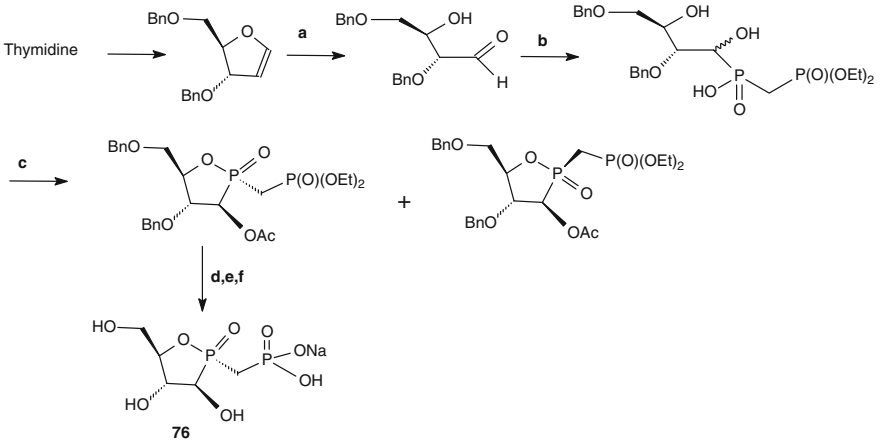
stereoselectively and results in four diastereomers in approximately equal amounts, which are successfully separated for gluco- and manno-isomers.

The same transesterification approach was used for the synthesis of synthetic phostone analogue **75** of phosphoamidone, which is a natural selective inhibitor of thermolisine and endoteline produced by *Actinomices*. (Scheme 42) [94].



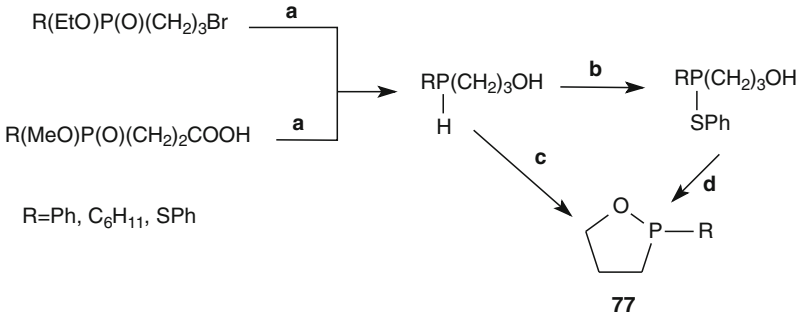
Scheme 42 **a** $P(OMe)_3$, AcOH; **b** NaOMe/MeOH; **c** Ac_2O, $BF_3.Et_2O$; **d** Me_3SiBr/THF; **e**l-Leu-Trp-OMe/Et_3N; **f** chromatography separation of epimers, deprotection

Following this strategy, a straightforward approach was developed to d-arabinose-derived methylenebisphosphonate **76** in which one phosphorus atom belongs to the 1,2-phospholane moiety (Scheme 43) [95]. This compound was designed as a possible transition state inhibitor of mycobacterial arabinosyltransferases, known to play a crucial role in the biosynthesis of arabinan part of the mycobacterial cell wall.



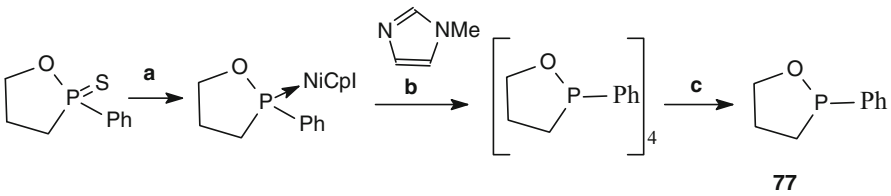
Scheme 43 **a** OsO_4, NMO, 12 h, rt, then NaIO4, 4 h, rt, 75%; **b** $(EtO)_2P(O)CH_2P(O)(OEt)_2$, K_2CO_3, 12 h, THF, rt, 55%; **c** Ac_2O, 1 h, rt, then pyridine, 12 h, 42%; **d** Me_3SiBr, CH_2Cl_2, rt, 24 h, then Et_3N, 65%; **e** BCl_3 (15 equiv), CH_2Cl_2, 12 h, –40 °C; **f** NaOH (0.1 N), 2 min, rt, then HCl (0.1 N) down to pH 6

Moreover, ω-hydroxyalkyl-substituted phosphorus(III) species also undergo cyclization to afford 1,2λ^3-oxaphospholanes **77**. To promote such cyclization, either phenyl disulfide [96] or *N*-chlorodiisopropylamine [97] was used (Scheme 44). It should be mentioned that 2-phenyl-1,2λ^3-oxaphospholane **77** (R = Ph) was also obtained via reduction of the corresponding 2-thioxo derivative proceeding through complexation with nickelecene (Scheme 45) [98, 99].



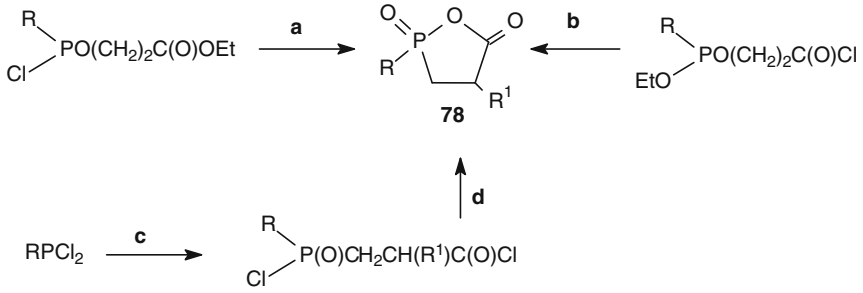
Scheme 44 **a** $LiAlH_4$, 28–30%; **b** PhSSPh, C_6H_6, rt, 15 h; **c** $ClNPr^i_2$, –78 °C, Et_2O, 20%; **d** –PhSH, 22–34%

Besides ω-halo- and ω-hydroxyalkyl-substituted phosphorus compounds, both C- and P-acid chlorides of mixed phosphonoalkyl-substituted carboxylic acids are inclined to intramolecular cyclization, yielding intracyclic anhydrides of these acids, namely 2,5-dioxo-1,2-oxaphospholanes **78** (Scheme 46) [100–103]. Reasonably, C-acid halides undergo cyclization more rapidly than their P-analogues. Moreover, as



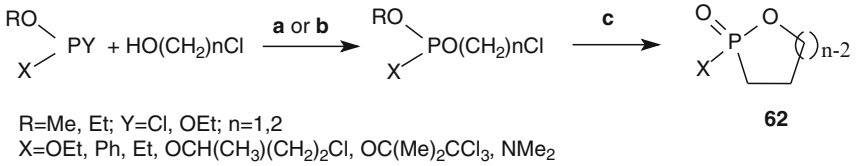
Scheme 45 **a** Cp_2Ni, CH_2=$CHCH_2I$, C_6H_6, 60 °C, 4 h; **b** 25 °C, 15 min; **c** 250 °C/1 Hg, 65%

addition of dichlorophosphines with acrylic or metacrylic acid just resulted in mixed P,C-acid halides, the cyclization of the latter under the action of water [104], excess of starting acid [105], acetic anhydride [105] or by countercurrent distillation [106] was used for the synthesis of 2,5-dioxo-1,2-oxaphospholanes **78** and their 4-methyl substituted derivatives in more than 94% yield (Scheme 46). These compounds found industrial application as ecologically friendly flame-retardants, giving thermostability to polymers and plastics [3].



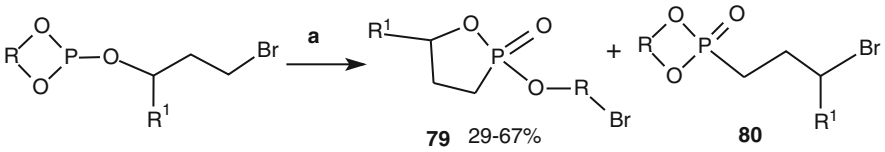
Scheme 46 **a** 230 °C, 5 h, 50%; **b** 100 °C, 2 h, 68% [103]; **c** CH_2=$C(R^1)COOH$, 0 °C, 100%; **d** H_2O or CH_2=$C(R^1)COOH$ or $(CH_3CO)_2O$, >94% [104–106]

The other approach to five- and six-membered 2-oxo-1,2-oxaphosphacyclanes **62** is based on the intramolecular Arbuzov reaction in a series of ω-haloalkyl esters of phosphorus(III) acids (Scheme 47) [55, 107, 108]. It should be mentioned that the phosphorus atom in the intermediate ω-haloalkyl ester may be a ring atom of the 1,3,2-diheteraphosphacyclane moiety, and that different 1,3,2-dioxa-, 1,3,2-oxaza- and 1,3,2-oxathia-λ^3-phosphacyclanes were used as starting substrates for



Scheme 47 **a** Y = Cl, Et_3N, 0 °C→20 °C; **b** Y = OEt, 120-150 °C; **c** 150-180 °C

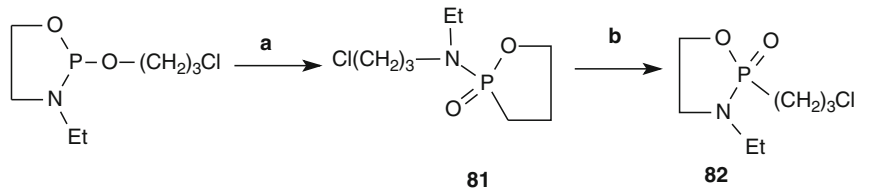
this reaction. In such cases, the nature of the substituents in the ω-haloalkyl ester moieties and heteroatoms in such 1,3,2-diheteraphosphacyclane rings define the ratio of intra- and intermolecular Arbuzov reaction products **79** and **80**, respectively (see, e.g., Scheme 48) [109, 110].



R = $MeCHCH_2$, $(CH_2)_3$; R^1=H;
R = $MeCHCH_2$, MeCHCHMe, $(CH_2)_3$; R^1=Me

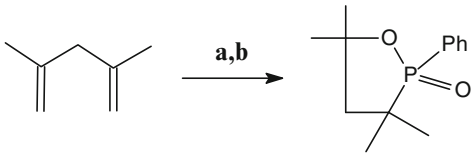
Scheme 48 **a** 110-120 °C, N_2

If the staring substrate presents cyclic amidophosphite, the reaction proceeds exclusively according to the intramolecular route at moderate temperature (note that amidophosphites undergo cyclization more rapidly than their phosphite analogues) while at elevated temperature, 2-oxo-1,2-oxaphospholane **81** easily undergoes isomerization to afford 2-oxo-1,3,2-oxazaphospholane **82** (Scheme 49) [111, 112].



Scheme 49 **a** ~130 °C; **b** ~160 °C

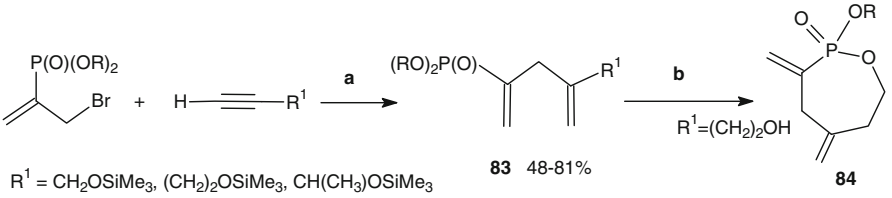
Alkyl-substituted 1,2-P,O heterocycles are obtained from cyclization of dienes in the presence of phosphino–aluminum complex followed by treatment with water (Scheme 50) [113].



Scheme 50 **a** $PhPBr_2.AlBr_3$, CH_2Cl_2; **b** 1 equiv. H_2O

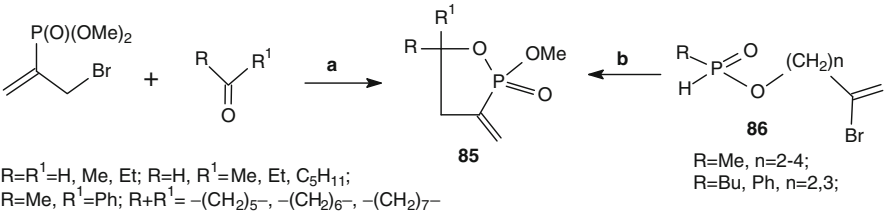
Unsaturated ketones were also used in such cyclizations, but if the ketone was prone to isomerization under acidic conditions, the final product possessed a 2-oxo-1,2-oxaphospholene structure [114]. However, both the above procedures lead to the desired compounds in yields of less than 20%. At the same time, phosphoryl-substituted

dienes **83** rapidly undergo cyclization in the presence of a base to give 3,5-dimethylene-1,2-oxaphosphepines **84** in high yield (~78%) (Scheme 51) [115].



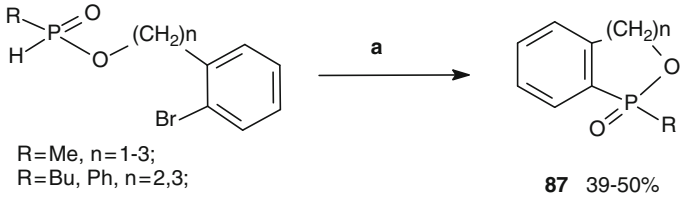
Scheme 51 **a** Zn, THF, 45–50 °C, ultrasound; **b** NaH, THF, 3 days

In terms of the yield and reaction rate, the Reformatskii reaction is a rather convenient route to biologically active 3-methylene-substituted 2-oxo-1,2-oxaphosphacyclanes **85**, including those having a spiro-structure (Scheme 52) [116, 117]. Metal-catalysed formation of the P–C bond was also successfully used for the synthesis of similar phostones [118]. Thus, 3-methylene-1,2-oxaphosphacyclanes **85** were formed in reasonable yields by palladium-catalysed intramolecular cyclization in a series of hydrophosphoryl compounds **86** (Scheme 52).

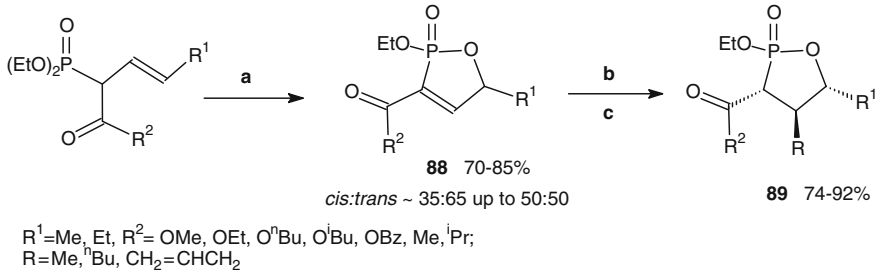


Scheme 52 **a** Zn, THF, reflux, 1 h; **b** cat. $Pd(PPh_3)_2Cl_2$, Et_3N, toluene, 110 °C, 17–69%

A similar palladium-catalysed approach was used to obtain fused benzophosphacyclanes **87** (Scheme 53) [119]. In both cases, the palladium-catalysed procedure allows creation of five- to seven-membered heterocycles in reasonable yields; however, the best results were achieved for the corresponding 1,2-oxaphospholanes. Furthermore, 2-oxo-1,2-oxaphospholenes **88** can be advantageously used as precursors for the synthesis of substituted phostones **89** (Scheme 54) [120].



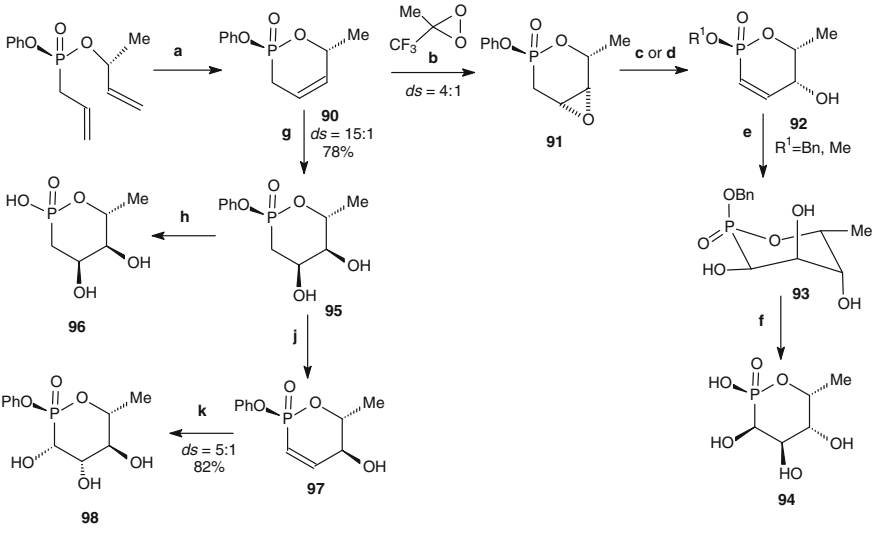
Scheme 53 **a** cat. $Pd(PPh_3)_2Cl_2$, Et_3N, toluene, 110 °C, 5–12 h



Scheme 54 **a** *m*-CPBA, $MgSO_4$, CH_2Cl_2; **b** performed using *cis-i*somers, RLi, RMgBr or R_2CuLi_2; **c** H_3O^+

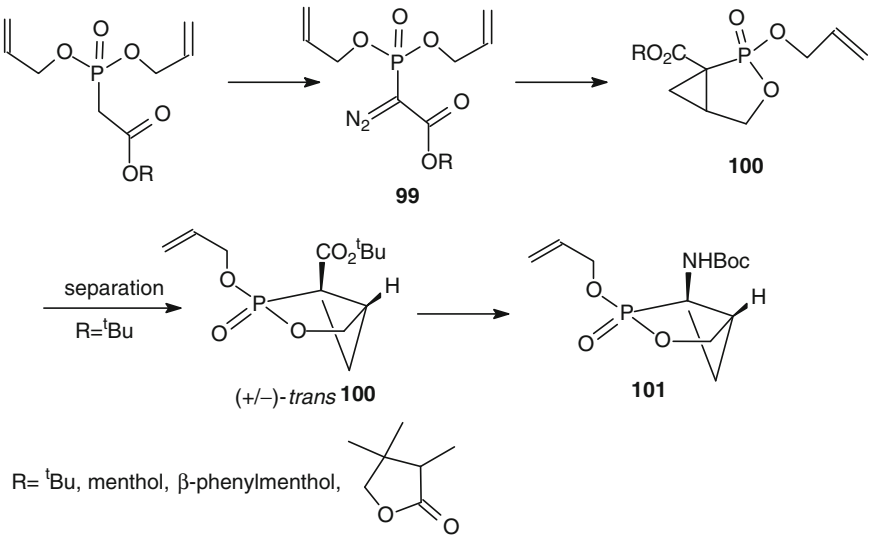
The alternative transition metal-catalysed synthesis of phostone analogues of carbohydrates is based on a ring-closure metathesis strategy [121–123] as a key step using an appropriate P-diene scaffold and Grubbs catalysts (I or II generation). This is followed by transformation of the unsaturated 1,2-oxaphosphacyclanes **90** formed to the saturated ones **91**, **93**, **94–96** and **98** bearing additional hydroxyl groups. Different strategies for stereoselective oxaphosphole–oxaphospholane transformation were reported [124], as illustrated in Scheme 55.

Furthermore, synthesis of fused phostones **100** via intramoleclar cyclopropanation mediated by $Rh_2(OAc)_4$ provides a powerful tool for the construction of constrained



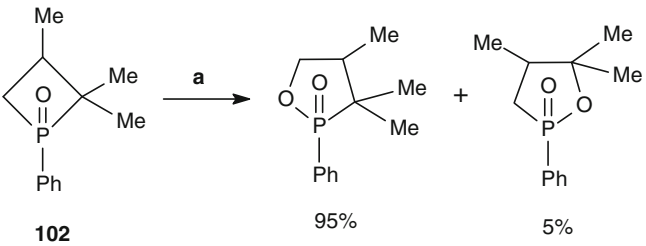
Scheme 55 **a** $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 68%; **b** CH_2Cl_2, –78 °C, 80%; **c** BnOLi, THF, 10 °C, 67%; **d** LiOMe, MeOH, 0 °C, 84%; **e** OsO_4, NMP, citric acid, acetone/MeCN/^{t}BuOH, 78%; **f** 10% Pd/C, EtOH, 100%; **g** OsO_4, NMM, *m*-CPBA, citric acid/acetone/^{t}BuOH; **h** PtO_2, H_2, MeOH, 93%; **j** (*1*) triphosgene, Et_3N, CH_2Cl_2, 96%; (*2*) KHMDS, THF, 87%; **k** OsO_4, NMP, citric acid, acetone/MeCN/^{t}BuOH 78%

systems from their diazo precursors **99** with high levels of diastereoselectivity and enantioselectivity (Scheme 56) [125, 126]. Further transformation of the compounds obtained gives rise to biologically active α-aminophosphonates **101**.



Scheme 56 **a** KO^{t}Bu, TsN_3; **b** $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 91%, *dr* from 5.5:1 up to 29.1:1 depending on R; **c** formic acid, neat; **d** $(COCl)_2$, CH_2Cl_2, DNF (cat.), 0 °C to rt; **e** NaN_3, CH_3CN, H_2O; **f** BuOH, reflux, 50% (five steps)

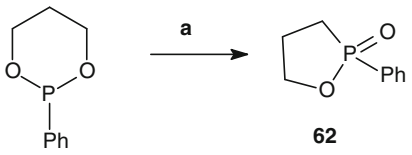
Concerning the other developed procedures to 1,2-oxaphosphacyclanes, an introduction of the oxygen atom into the P–C bond in the strained bridged P-heterocycles under the action of peracids such as *meta*-chloroperbenzoic acid (*m*-CPBA) should be mentioned [8, 127–132]. According to the accepted hypothesis of Quin [8], the decrease of steric strain of the C–P–C angle presents the driving force of the reaction, which proceeds both in the case of monocyclic phosphetan-1-oxides **102** (Scheme 57) and fused polycyclic compounds such as 7-phosphanorbornanes [129]. The compounds obtained were used as sources of metaphosphoric acid derivatives and effective phosphorylation agents for alcohols and nitrogen-containing heterocycles.



Scheme 57 **a** m-CPBA, $CHCl_3$, 25°C, 39 h

In contrast, different six-membered 2λ³–1,3,2-dioxaphosphinanes, including fused compounds, undergo thermal isomerization with narrowing of the cyclic size to give the corresponding 2-oxo-1,2-oxaphospholanes, as illustrated in Scheme 58 using 2-phenyl-1,3,2-dioxaphosphinane **103** as an example [98, 99, 133]. It should be noted that λ³–1,3,2-dithiaphosphinanes also undergo similar transformation to afford 2-thioxo-1,2-λ⁵-thiaphospholanes, however, in lower yield (36%) [102].

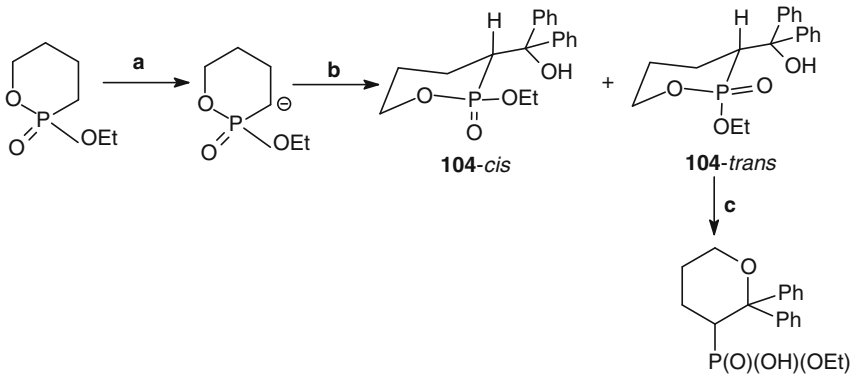
Scheme 58 **a** 250 °C, 24 h, 63%



103 **62**

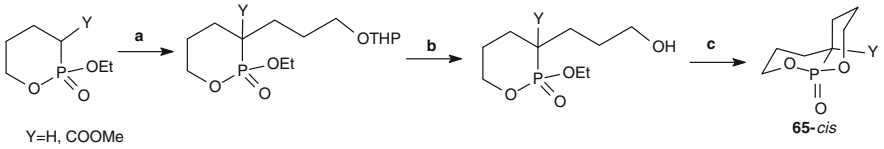
In some cases, further functionalization of the preformed phostones allows their more complex derivatives to be obtained. For example, α-alkylation of six-membered 2-oxo-1,2-oxaphosphinanes **62** opens the way to 3-hydroxymethyl-substituted heterocycle **104** as a mixture of *cis*- and *trans*-isomers. It is interesting to note that isomeric compounds possess different stability: the *cis*-isomer was isolated in an individual state while the *trans* isomer easily underwent intramolecular rearrangement to yield the compound **105** bearing the exocyclic phosphoryl moiety (Scheme 59) [134, 135]. Furthermore, synthesis of bicyclic compounds **65** (*cis*-isomers) is based on alkylation of monocyclic phostone by protected 3-bromopropane-1-ol followed by intramolecular transesterification (Scheme 60) [54].

In general, the main synthetic approaches to five- and six-membered 1,2-oxaphosphacyclanes are based on intramolecular cyclizations in a series of ω-halogenalkyl-, ω-hydroxyalkyl-, and ω-acetyloxyalkyl-substituted phosphorus compounds proceeding via different reaction mechanisms along with metal-catalysed transformations. As



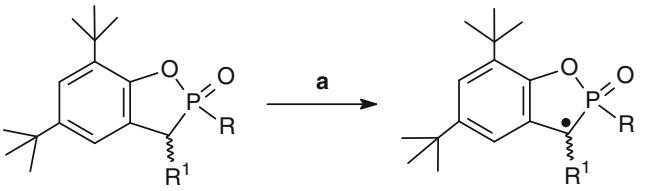
104-*cis* **104**-*trans* **105**

Scheme 59 **a** LDA, THF, –78 °C; **b** $Ph_2C(O)$; **c** CH_2Cl_2, 25 °C



Scheme 60 a LiTMP, THF, –78 °C, then $Br(CH_2)_3OTHP$; **b** MeOH/TsOH; **c** LiH/C_6H_6, Δ

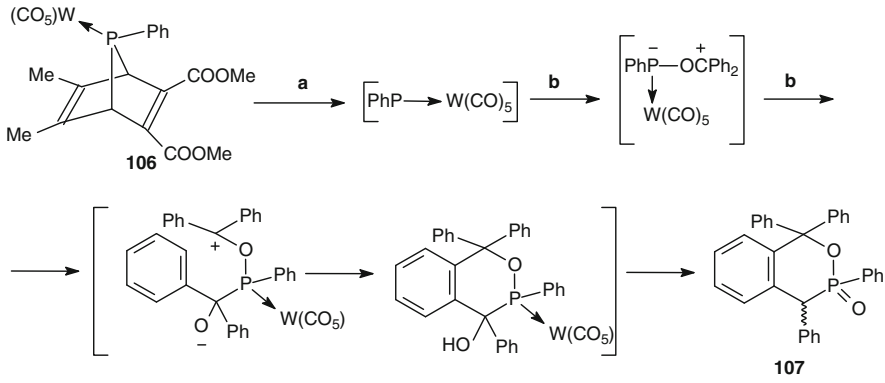
mentioned above, the same approaches can also be used for the synthesis of benzo[d]-2-oxo-1,2-oxaphosphacyclanes (e.g. compounds **64** and **87**) being the precursors of stabilized C-centred radicals [136, 137], a property associated with antioxidant potential. It should be mentioned that in the case of compounds with two possible diastereomeric forms, the C–H bond of the *cis*-isomer is more reactive towards hydrogen abstraction (Scheme 61).



R^1= 4-$CH_3OC_6H_4$, 3,5-$(CH_3)_2C_6H_3$, H, Me, Et, ^{i}Pr;
R=OH, OEt

Scheme 61 **a** ^{t}BuOO^{t}Bu, *h*ν

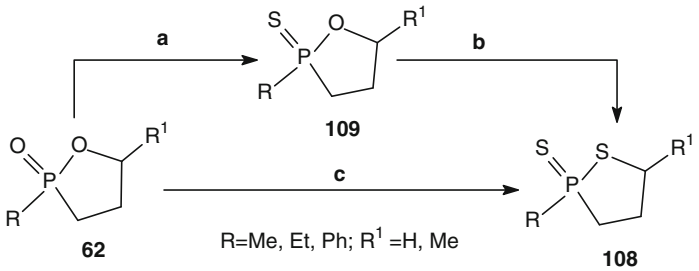
Finally, as mentioned above, intramolecular nucleophilic substitution reactions present the most developed approaches to 1,2-oxaphasphocyclanes. However, for this purpose electrophilic substitution can be used as well, which is illustrated by catalytic cleavage of tungsten complex **106** to afford substituted benzo[d]-2-oxo-1,2-oxaphosphinane **107** (Scheme 62) [138].



Scheme 62 **a** cat CuCl, 60 °C, toluene; **b** $Ph_2C(O)$

4.2 1,2-Thiaphospholanes and 1,2-Thiaphosphinanes

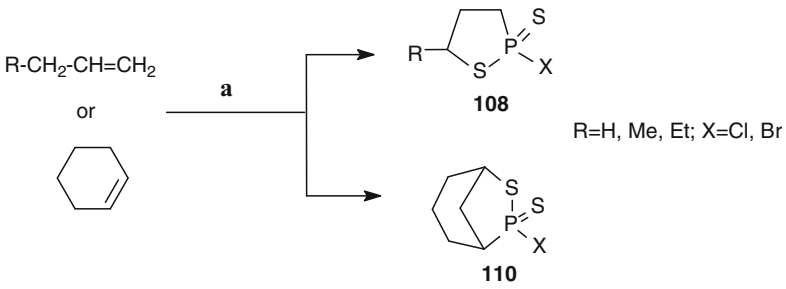
As convenient routes to five- and six-membered 2-oxo-1,2-oxaphosphacyclanes **62** had been developed, replacement of oxygen atoms by sulfur under the action of an excess of phosphorus pentasulfide was suggested as the first convenient route to 2-thioxo-1,2-thiaphosphacyclanes such as **108** [98, 139–141]. Such a replacement can be performed as a step-by-step process (at the first step compounds transform to 2-thio-1,2-oxaphasphocyclanes, e.g. **109**); however, drastic conditions are required for an exhaustive exchange (Scheme 63).



Scheme 63 **a** Δ, P_4S_{10}, $CH_3C_6H_5$, 3 h, 90 °C, 37% [140] or 1 h, 110 °C, 56% [98]; **b** Δ, P_4S_{10}, without solvent, 1 h; **c** Δ, P_4S_{10}, 160–250 °C, autoclave or Δ, P_4S_{10}, without solvent, 2 h, 36% [98] or Δ, P_4S_{10}, ClC_6H_5, 6 h, 38% [140]

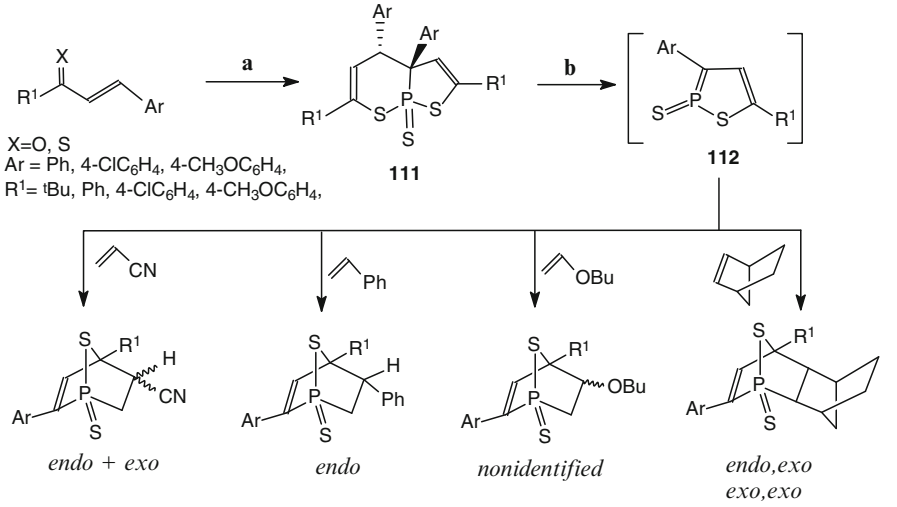
The other approach to 2-thioxo-1,2-thiaphospholanes **108** and **110** is based on the direct reaction of an unsaturated hydrocarbon, phosphorus pentasulfide and a thiophosphoric acid halide under drastic conditions (autoclave, 150–200 °C, 10–18 h) [142, 143]. When cyclic alkenes (e.g. cyclohexene) are used as the starting substrates, bicyclic compounds are formed with one of the rings representing 1,2-thiaphospholane (Scheme 64). These reaction products are used as antioxidant additives for motor oils, polymers and agrochemicals.

2,9-Dithia-1-thioxophosphabicyclo[4.3.0]nona-3,7-dienes **111** formed in the reaction of α,β-unsaturated ketones with P_4S_{10} in the presence of Et_3N should be

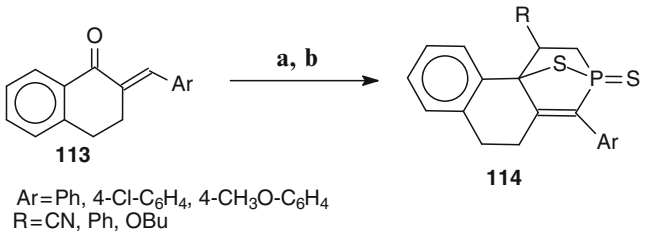


Scheme 64 **a** $P(S)X_3$, P_4S_{10}, Δ

mentioned as precursors of fused 2-thioxo-1,2-thiaphospholanes [144–146]. Thermolysis of such compounds in benzene occurs with the generation of 2-thioxo-1,2-thiaphospholes **112**, which act as cyclic heterodienes in [4 + 2]-cycloaddition reactions with acrylonitrile, styrene, butyl vinyl ether and norbornene (Scheme 65). Similarly, (*E*)-arylmethylidene-1,2,3,4-tetrahydronaphtalen-1-one **113** can be used as α,β-unsaturated ketone to give fused polycarbocycles **114**, wherein one of the rings is 2-thioxo-1,2-thiophospholene (Scheme 66) [145].



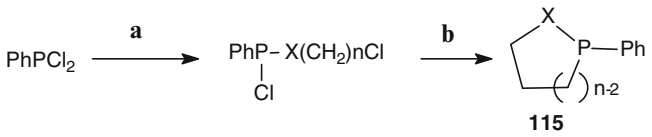
Scheme 65 **a** P_4S_{10}, Et_3N, CS_2; **b** Δ



Scheme 66 **a** P_4S_{10}, Et_3N, CS_2; **b** CH_2=CH-R, Δ

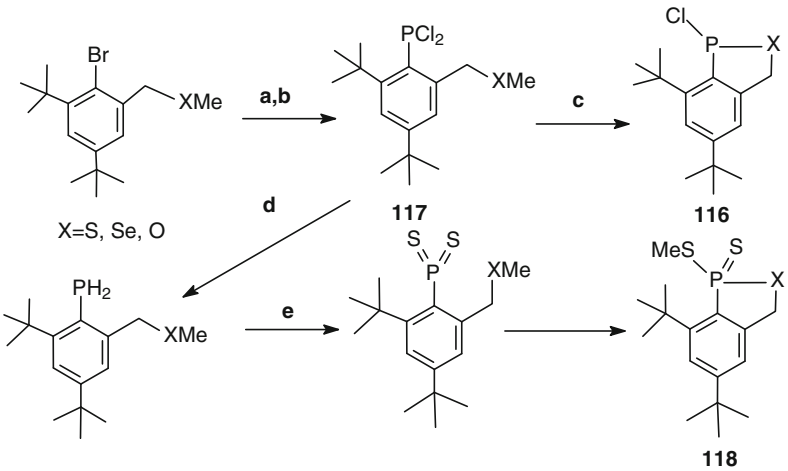
Some approaches to 1,2-thiaphosphacyclanes are similar to those suggested for their above-mentioned analogues bearing the oxygen atom. Thus, intramolecular cyclization of the organometallic derivatives of *O*- or *S*-(ω-chloroalkyl)phenylphosphonic acid chlorides affords five- and six-membered 1,2λ^3-heteraphosphacyclanes **115** (Scheme 67) [147, 148]. The corresponding products were obtained in higher yields in the case of five-membered phospholanes and for the oxygen-containing derivatives. 1,2λ^3-Heteraphosphacyclanes **115** were used as monomers in the ring-

opening polymerization under the action of alkyl halides to afford poly(phosphine oxides) and poly(phosphine sulfides) possessing good chelate-forming properties, including high extraction capacity towards the ions of some heavy metals.



Scheme 67 **a** $HX(CH_2)_nCl$, Py; **b** Li; X = O, *n* = 3 (37%), *n* = 4 (18%); X = S, *n* = 3 (10%), *n* = 4 (5%)

Fused 2-chloro-1,2λ^3-heteraphospholanes **116** (X = O, S, Se) are formed as a result of the intramolecular cyclization of 2,4-di-*tert*-butyl-6-(methylheteromethyl) phenyldichloro phosphines **117** (Scheme 68) [149]. It should be noted that the ease

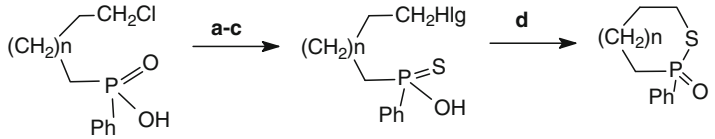


Scheme 68 **a** ^{n}BuLi, **b** PCl_3; **c** 0 °C (X = Se), rt, 10 h (X = O), 66 °C, 3 h or rt, 6 days (X = S); **d** $LiAlH_4$; **e** 1/8 S_8, DBU

of the formation of such heterocyclic compounds decreases in the order Se > O > > S. 2-Thio-1,2λ^5-analogues **118** (X = S) of such fused heterocycles were obtained from intramolecular rearrangement of σ^{3}λ^5-metadithiophosphonates, obtained in turn from sulfur addition to the corresponding primary phosphines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

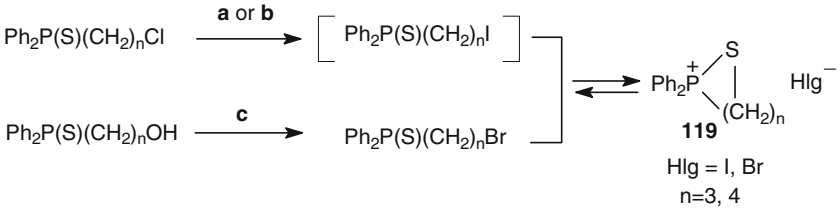
As mentioned above, 2-oxo-1,2λ^5-thiaphosphacyclanes similar to their analogues with the 1,2λ^5-oxaphosphacyclane ring, may be obtained via an intramolecular alklyation of ω-chloroalkylthiophosphinous acids in the presence of triethylamine (Scheme 69) [62].

A convenient route to 1,2-thiaphosphacyclanes is based on the intramolecular S-alkylation in a series of ω-haloalkylthiophosphoryl compounds [150–153]. Thus,



Scheme 69 **a** $(COCl)_2$; **b** P_2S_5, cat. $HC(O)NMe_2$, dioxane, reflux; **c** H_2O/acetone; **d** Et_3N

for ω-haloalkylphosphine sulfides the reaction gave five- and six-membered 1,2-thiaphosphacyclonium salts **119** under mild conditions (Scheme 70). The ease of formation of the cyclic salts is determined first of all by the nature of the halogen atom: the iodides undergo cyclization more rapidly than bromides, whereas chlorides do not undergo intramolecular S-alkylation upon either refluxing in acetone or under heating in the absence of a solvent(140 °C, 1.5 h). The second factor influencing



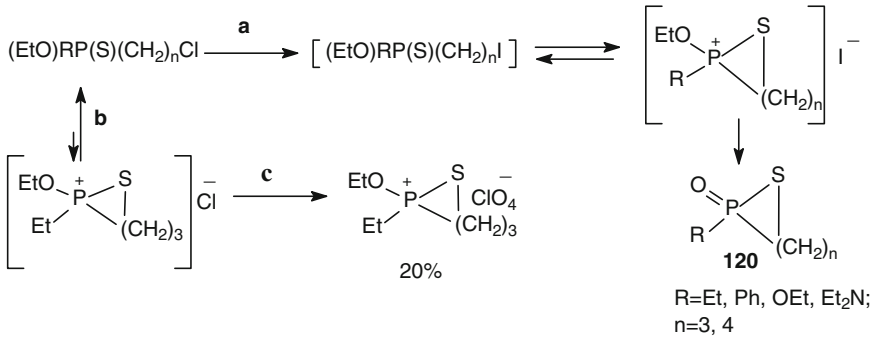
Scheme 70 **a** NaI, acetone, Δ; **b** NaI, CH_3CN, Δ; **c** PBr_3, C_6H_6

the reaction rate is the length of alkyl chain in the starting linear compound: 1,2-thiaphospholanium rings are formed more rapidly than six-membered 1,2-thiaphosphinanium ones. It should be noted that a tautomeric equilibrium between the cyclic form and the starting linear compound is established in solutions of 1,2-thiaphosphacyclanium salts, which is a rare case of ring–chain halogenotropic tautomerism. It is noteworthy that both cyclic and linear tautomers were isolated in the case of the corresponding bromides.

In intramolecular S-alkylation in the series of ω-iodoalkyl-substituted thiophosphoryl compounds bearing the alkoxy group at the phosphorus atom obtained in situ from the corresponding chloro derivatives[1], dealkylation of a phosphonium salt formed takes place according to the second step of the Arbuzov reaction, resulting in 2-oxo-1,2-thiaphosphacyclanes **120** (Scheme 71) [151, 154, 155]. In this case too, five-membered heterocyclic compounds (n = 3) are formed more rapidly than the six-membered ones (n = 4) (k_5/k_6 ~2). In addition to the alkyl chain length, the

[1]Chloroalkyl-substituted thiophosphinates and thiophosphonates are thermally stable and represent easily distilled liquids (b.p. = 105–165 °C/2–3 Hg). 3-Chloropropyl(phenyl)thiophosphinate (R = Ph, n = 3), which undergoes the intramolecular thione–thiol rearrangement into 2-oxo-2-phenyl-1,2-thiaphospholane under distillation in vacuo, is the only exception.

solvent used influences the cyclization rate: the reaction is faster in acetonitrile than in acetone. This may be connected with both the higher polarity and higher boiling temperature of MeCN. The nature of the substituent R at the phosphorus atom influences the cyclization rate to a lesser extent (it decreases in the order Et > Ph > OEt). The mechanism of the reaction was established quite reliably as the authors succeeded in isolation of the intermediate phosphonium salt bearing the ethoxy group when the nucleophilic chloride anion was replaced by perchlorate (Scheme 71). It should be noted that this was the first case where the intermediate product of thione–thiol rearrangement of the phosphorus thioacid esters was isolated as an individual compound.

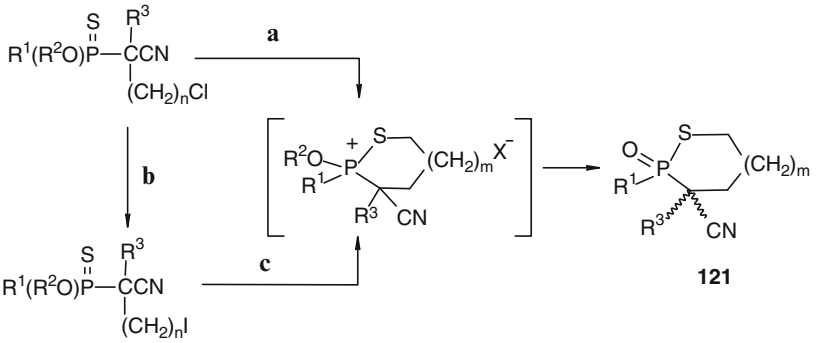


Scheme 71 **a** NaI, CH_3CN; Δ; **b** CH_3CN, Δ; **c** $NaClO_4$

Cyano-substituted thiophosphoryl compounds bearing a ω-haloalkyl moiety in the molecule undergoes the above-mentioned intramolecular transformation [156–160]. Thus, the corresponding ω-chloroalkyl derivatives undergo cyclization to 3-cyano-2-oxo-1,2-thiaphosphacyclanes **121** upon distillation in vacuo, while the cyclization of the ω-iodoalkyl-substituted compounds formed in situ from chloro derivatives proceed under milder conditions (Scheme 72). Cyano-substituted thiaphosphacyclanes **121** were formed as mixtures of stereoisomers differing in mutual disposition of the cyano group and the phosphoryl oxygen atom relative to the ring plane (*cis*-$R_{P*}R_{C*}$ and *trans*-$R_{P*}S_{C*}$). The isomer ratio varies from 7:3 to 3:7 depending on the cyclization procedure. In most cases, the mixtures were separated into individual isomers, the structures of which were investigated by X-ray diffraction analysis. Intramolecular S-alkylation also opens an efficient route to 6-cyano-2-oxa-10-thia(oxa)phosphabicyclodecane-1-oxide formed as a mixture of *cis*- and *trans*-isomers in a 2.3:1 ratio by thermal cyclisation of bis(3-chloropropyl)(dialkoxythiophosphoryl)acetonitriles [161].

3-Cyano-2-oxo-1,2λ^5-thiaphosphacyclanes can be reduced readily using trichlorosilane with retention of the ring structure, cyano group and stereochemistry, resulting in the corresponding 1,2λ^3-thiaphosphacyclanes possessing a tricoordinate phosphorus atom [162], which were used as bidentate ligands for Co(II), Ni(II) and Rh(I) complexes.

Therefore, the intramolecular S-alkylation is apparently inherent in various types of thiophosphoryl compounds with an ω-halogenoalkyl fragment. Thus there is a good reason to believe that the method for the preparation of 2-oxo-1,2-

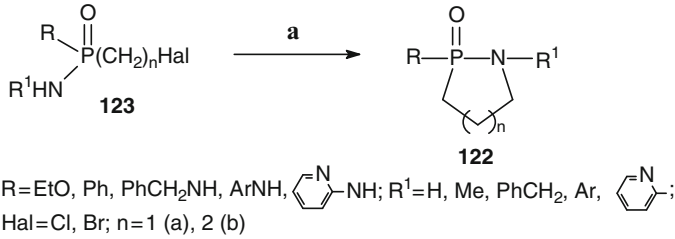


Scheme 72 **a** 200 °C/1 Hg; **b** NaI, CH_3CN, Δ; **c** Δ, 12–24 h;

thiaphosphacyclanes through intramolecular thione–thiol rearrangement is the most common and is of practical importance.

4.3 1,2-Azaphospholanes and 1,2-Azaphosphinanes

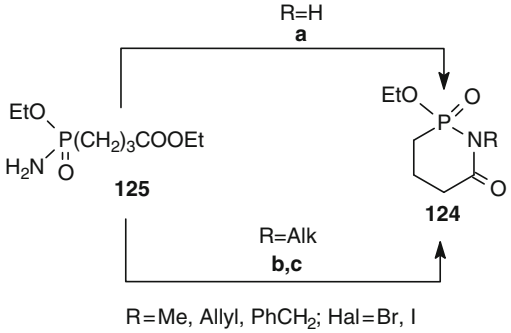
As mentioned above, ω-halogenoalkyl-substituted phosphorus compounds of different types tend to undergo intramolecular ring formation, opening a convenient approach to 1,2-oxa- and 1,2-thiaphosphacyclanes having five- to seven-membered rings. Therefore, intramolecular cyclization of ω-halogenoalkyl-substituted phosphoryl compounds having the P–N amide bond in the molecule also presents a convenient route to 2-oxo-1,2λ^5-azaphospholanes and 1,2λ^5-azaphosphinanes **122**. Such a synthesis was performed by Helferich as early as in 1962 [163, 164] starting from 3-halopropane- and 4-halobutanephosphonic acid arylamides **123** in the presence of aqueous NaOH (Scheme 73). Furthermore, a similar approach allowed an increase in the number of compounds differing in the substituents at the phosphorus and nitrogen atoms [165, 166].



Scheme 73 **a** NaOH/MeOH or NaH/xylene

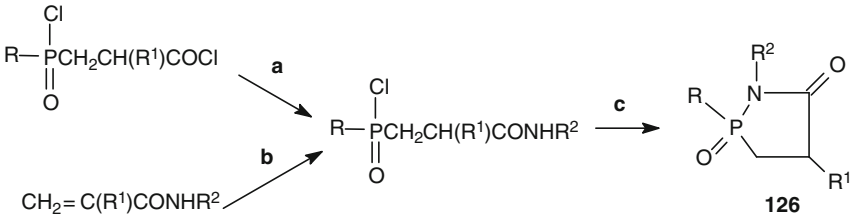
If a ω-carbalkoxy group is present in the starting linear compound instead of the halogen atom, a similar procedure allows synthesis of 2,6-dioxo-1,2-azaphosphinanes **124** by intramolecular cyclocondensation of amidophosphonic ester **125** [167].

The N-alkylated derivatives **124** can be readily obtained by similar cyclocondensation of **125** performed in the presence of haloalkanes (Scheme 74).



Scheme 74 **a** ^{t}BuOK, ^{t}BuOH, reflux; **b** ^{t}BuOK, ^{t}BuOH; **c** RHal, reflux

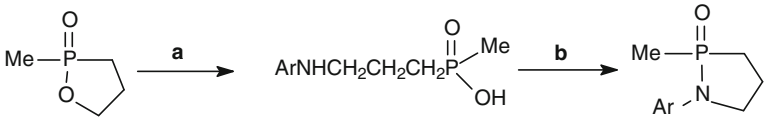
The synthesis of 2,5-dioxo-1,2-azaphospholanes **126** comprises a reaction of mixed P,C-acid chlorides with primary amines in the presence of a base [168, 169] or acrylic and metacrylic acid amides with alkyl- and phenyldichlorophosphines in the presence of acetic acid [170]. Both reactions resulted in the same intermediate product that subsequently cyclized to afford **126** (Scheme 75).



Scheme 75 **a** R^2NH_2, Et_3N, Δ; **b** $RPCl_2$, AcOH; **c** Δ

2-Oxo-1,2-azaphospholanes **122** were also obtained from the reaction of 1,2-oxaphospholanes **62** and anilines proceeding via the formation of linear (3-anilinopropyl)methylphosphinic acids (Scheme 76) [140] followed by cyclization with elimination of water.

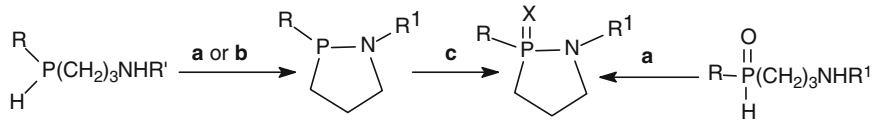
The synthesis of 1,2λ^3-azaphosphospholanes **127** is based on the reaction of the substituted 3-aminopropylphosphines with diaryl disulfides or with elemental bromine in the presence of triethylamine [171, 172] (Scheme 77). Furthermore, the cyclic P(III) compounds may be converted to the corresponding oxides **122** or sulfides **128,** useful as lubricating oil antioxidants and flame retardants in plastics and textiles.



62 **122**

Ar = Ph, p-MeC_6H_4, p-$MeOC_6H_4$, p-ClC_6H_4

Scheme 76 **a** $ArNH_2$, 180–200 °C, 10 h, 65–85%; **b** 230–260 °C/1 Hg

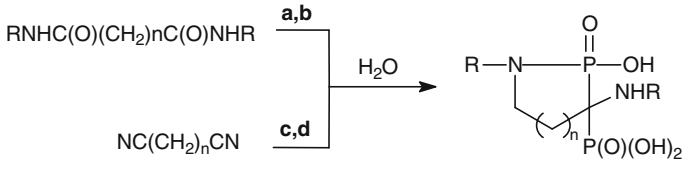


127 **122,128**

R = ^{i}Bu, $C_{16}H_{33}$, Ph; R^1 = H, Me, Et, Bu, Ph; X = O,S

Scheme 77 **a** PhSSPh; **b** Br_2, Et_3N; **c** 1/8 S_8

Functionalized five- to eight-membered dioxo-1,2-azaphosphacyclanes **129** were prepared by cyclization of dicarbocylic acid diamides and dinitriles with phosphorous acid and phosphorus halogenides followed by hydrolysis (Scheme 78) [173]. Such cyclic aminophosphonic acids were suggested as efficient complexing agents for Ca^{2+} for reduction of aorta calcification (on the rat model) and as hardening retardants for gypsum, etc.



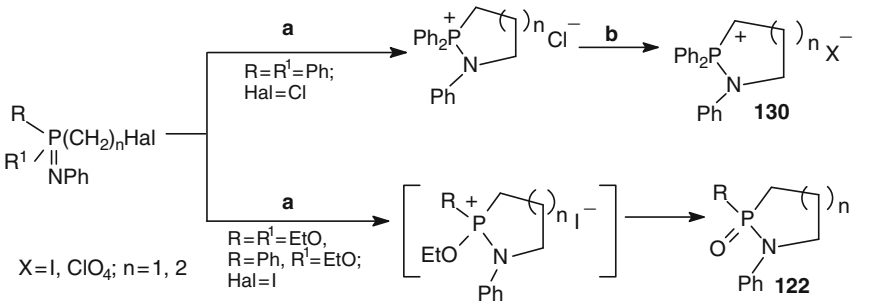
129

R = H, Me, Et, Bu; n = 1-4

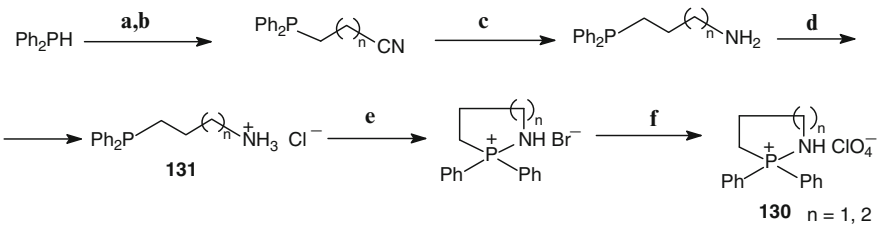
Scheme 78 **a** H_3PO_3, melting; **b** PCl_3, 70 °C; **c** PBr_3, 20 °C; **d** H_3PO_3, 70–80 °C

It should be mentioned that the starting linear P–N bond-containing compound undergoing intramolecular cyclization may possess a P=N imine moiety. This approach based on intramolecular P=N alkylation was used for the synthesis of both 1,2-azaphospholanium and 1,2-azaphosphinanium salts **130** [155] and 2-oxo-1,2-azaphosphacyclanes **122** (Scheme 79) [174].

In this context, the first synthesis of 1,2-azaphospholanium and 1,2-azaphosphinanium salts **130** performed by Yamamoto [175] should be mentioned. The compounds were obtained as a result of a multistep procedure comprising as the last step the treatment of ω-aminoalkyldiphenylphosphine hydrochlorides **131** with bromine and 2 equiv. of triethylamine (Scheme 80).

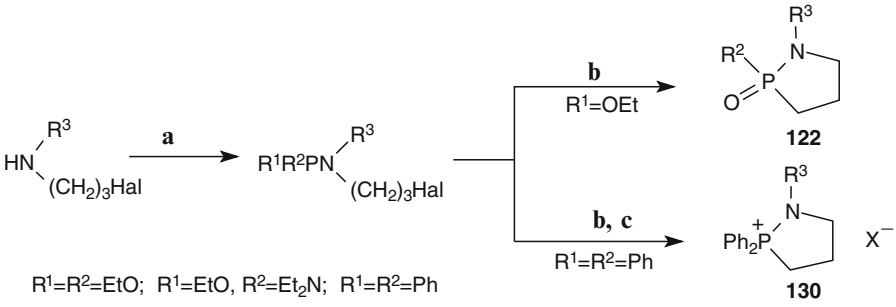


Scheme 79 **a** Δ; **b** NaX, CH_3CN, reflux



Scheme 80 **a** NaH; **b** $Br(CH_2)_2(CH_2)_nCN$; **c** $LiAlH_4$, Et_2O; **d** HCl aq., CH_2Cl_2; **e** Br_2, $2Et_3N$; **f** $LiClO_4$, H_2O

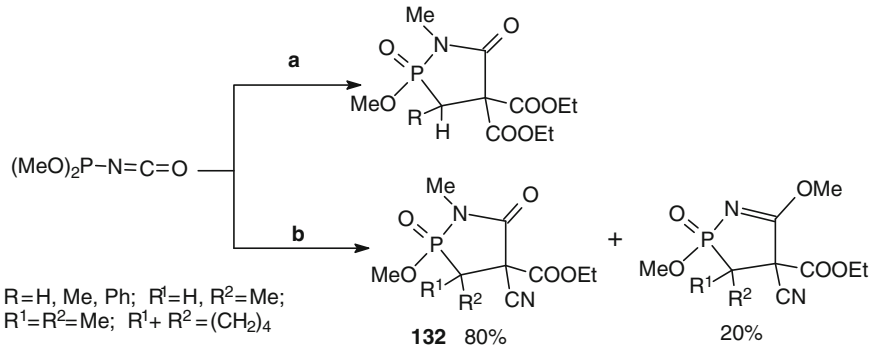
Intramolecular P-alkylation in a series of *N*-3-halopropyl amides of P(III) species presents a convenient alternative for the synthesis of different 1,2-azaphospholanes (Scheme 81) [176, 177]. This procedure allowed synthesis of 1,2-azaphospholanes **122** and **130** containing amino acid residues as potential drug-candidates.



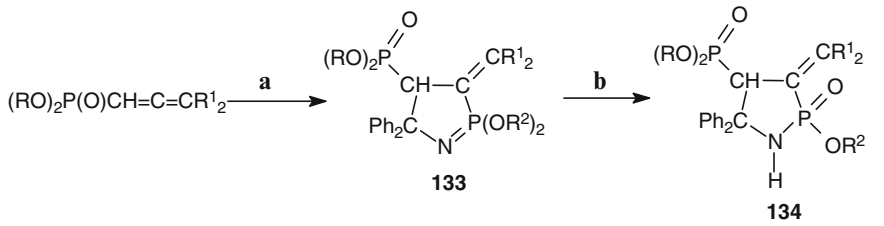
Scheme 81 **a** R^1R^2PCl, Et_3N, 0 °C; **b** Δ, 1–4 h; **c** NaX, CH_3CN, reflux

Some cycloaddition reactions present an alternative route to functionally substituted 1,2-azaphosphacyclanes. Thus, a series of functionalized 2,5-dioxo-1,2-azaphospholanes **132** has been prepared from cycloaddition of dimethylphosphorous acid isocyanate to alkylidenemalonic and alkylidenecyanoacetic acid esters

(Scheme 82) [178, 179]. The cycloaddition of diphenylmethyleneamidophosphites to γ,γ-disubstituted allenylphosphonates gave 1,2-azaphospholenes **133** that readily hydrolysed with 1,2-azaphospholanes **134** formation (Scheme 83) [180].

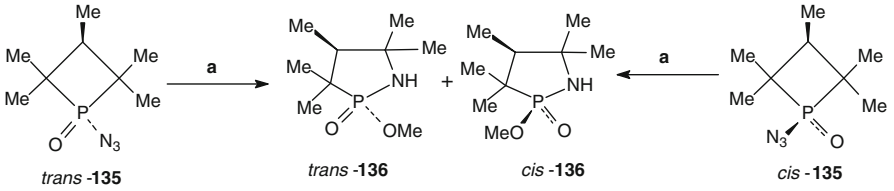


Scheme 82 **a** H(R)C=C(COOEt)$_2$; **b** R^{1}R^{2}C=C(CN)COOEt



Scheme 83 **a** Ph$_2$C=NP(OR^2)$_2$, 20 °C; **b** H$_2$O, rt

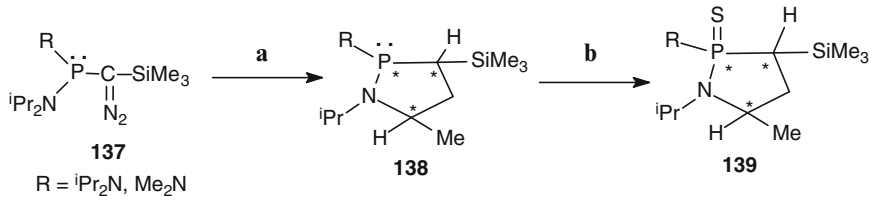
Photolysis of 1-azidophosphetane oxides **135** having methyl groups in various positions in methanol yielded 2-oxo-1,2-azaphospholanes as a result of the ring expansion [181]. Note that photolysis of either *cis* or *trans* phosphetanes **135** leads to the same ratio of *cis* and *trans* isomers of 2-oxo-1,2-azaphospholanes **136** (30:70) (Scheme 84) [182].



Scheme 84 **a** *hν*, MeOH

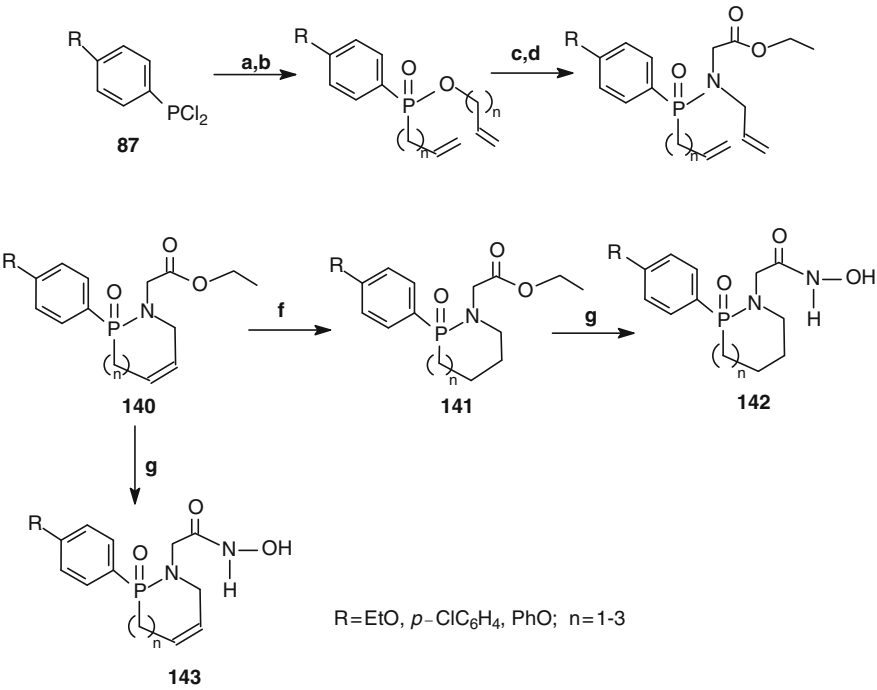
Carbenes derived from diazomethanes **137** are found to be surprisingly stable and yield four diastereoisomeres of 1,2λ^3-azaphospholanes **138** by pyrolysis at 300 °C probably through carbene insertion into the C–H bond of the methyl group of the isopropyl substituent (Scheme 85) [183, 184; *cf.* ref. 45–48]. After treatment of

138, bearing the isopropyl group with elemental sulfur, two major isomers of 2-thioxo-1,2-azaphospholane **139** were isolated in pure form.



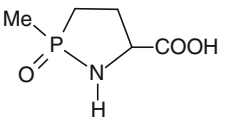
Scheme 85 **a** 300 °C/1 Hg; **b** 1/8 S_8

Similar to the synthesis of phostones through ring-closing metathesis strategy, six- to eight-membered 1,2-azaphosphacyclenes **140** obtained in the multistage synthesis from aryldichlorphosphines can be converted to saturated 1,2-azaphosphacyclanes **141** by hydrogenation (Scheme 86) [185]. Both unsaturated and saturated esters of these series were transformed by hydroxylaminolysis to compounds **142** and **143**, being potent MMP inhibitors and demonstrating high antitumour activity towards human fibrosarcoma.

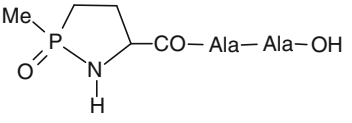


Scheme 86 **a** CH_2=CH$(CH_2)_n$OH, Et_2O, Py; **b** CH_2=CH$(CH_2)_n$Br, 130 °C, 16 h; **c** PCl_5, DCM; **d** *N*-allylglycine, Et_3N; **e** Grubbs catalyst, 5 mol%, DCM, rt; **f** H_2, 5% Pd/C, EtOH; **g** NH_2OTMS, KOH, MeOH, 0 °C

Finally, we should mention a series of synthetic approaches to L-pyrophosphinotricine **144**, a cyclic analogue of L-phosphinotricine, and its Ala–Ala peptide **145**, a cyclic analogue of "bialaphos" (tripeptide of L-phosphinotricine produced in nature by *Streptomyces hydroscopicus*) [186]. As the final step, the procedures comprised enzyme-catalysed hydrolysis and resolution of the racemic mixtures formed into optical antipodes by α-chymotripsin. Both 1,2-azaphospholane **144** and its tripeptide **145** exhibit antitumour activity. Moreover, tripeptide **145** displayed a greater bactericidal activity than the antibiotic bialaphos.



***L*-144**



145

5 Conclusion

The synthesis of 1,2-heteraphosphacyclanes having in the molecule both a three- and four-coordinated phosphorus atom and oxygen, sulfur or nitrogen as additional heteroatom has been discussed. The synthetic routes differ depending on the ring size and the nature of the heteroatom, and the merits and demerits of each approach have been discussed. For three-membered saturated P,E-heterocycles (i.e. 1,2--heteraphosphiranes), the synthesis is based mainly on the stable two-coordinated phosphorus compounds. The design of more rare four-membered compounds is based mostly on the corresponding carbene transformations, while for compounds having five-, six- and larger ring size, a variety of intramolecular cyclizations (alkylation, transesterification, cyclocondendensation, etc.) are the most common synthetic routes of practical importance.

References

1. Garner AY (1960) US patent 2916510. Chem Abstr 54:5571
2. Garner AY (1961) US patent 2953591. Chem Abstr 55:5346
3. Weissermel K, Kleiner HJ, Finke M, Felcht UH (1981) Angew Chem Int Ed Engl 20:223
4. Matsumoto T, Kanatsuki O, Hamada S (1989) Jpn Kokai Tokkyo Koho Yp 63280728. Chem Abstr 111:40152
5. Ueda A, Matsumoto T (1989) Jpn Kokai Tokkyo Koho Yp 63130595. Chem Abstr 110:39511
6. Ueda A, Matsumoto T (1988) Jpn Kokai Tokkyo Koho Yp 62185710. Chem Abstr 108:96114
7. Germanaud L, Brunel S, Chevalier Y, Perchec PLe (1988) Bull Soc Chim Fr 699.
8. Quin LD, Wu XP, Sadanaki ND, Lukes I, Ionkin AS, Day RO (1994) J Org Chem 59:120
9 Roeschenthaler GV, Sauerbrey K, Schmutzler R (1978) Chem Ber 111:3105

10. Niecke E, Wildbredt D-A (1981) J Chem Soc Chem Commun, p 72
11. Caira M, Neilson RH, Watson WH, Wisian-Neilson P, Xie Z-M (1984) J Chem Soc Chem Commum, p 698
12. Neilson RH (1983) Phosphorus Sulfur 18:43
13. Toyota K, Shimura K, Takahashi H, Yoshifuji M (1994) Chem Lett, p 1927
14. Yoshifuji M, Toyota K, Inamoto N (1985) Tetrahedron Lett 26:1727
15. Boyd BA, Toma RJ, Neilson RH (1987) Tetrahedron Lett 28:6121
16. Navech J, Majoral J, Kraemer R (1983) Tetrahedron Lett 24:5885
17. Van Der Knaap TA, Bickelhaupt F (1984) J Organomet Chem 277:351
18. Van Der Knaap TA, Klebach ThC, Lourens R, Vos M, Bickelhaupt F (1983) J Am Chem Soc 105:4026
19. Niecke E, Böske J, Krebs B, Dartmann M (1985) Chem Ber 118:3227
20. Arbuzov BA, Dianova EN, Zabotina EYa (1986) Chem Bull USSR Engl 35:154 (Izv Acad Nauk SSSR Ser Khim 169)
21. Appel R, Casser C (1985) Chem Ber 118:3419
22. Ruf SG, Dietz J, Regitz M (2000) Tetrahedron 56:6259
23. Toyota K, Takahashi H, Shimura K, Yoshifuji M (1996) Bull Chem Soc Jpn 69:141
24. Niecke E, Seyer A, Wildbredt DA (1981) Angew Chem Int Ed Eng 20:675
25. Niecke E, Leuer M, Wildbredt DA, Schoeller WW (1983) J Chem Soc Chem Commun 1171.
26. Niecke E, Schwichtenhövel K, Schöfer HG, Krebs B (1981) Angew Chem Int Ed Engl 20:963
27. Yoshifuji M, Ando K, Shibayama K, Inamoto N, Hirotsu K, Higuchi T (1983) Angew Chem Int Ed Engl 22:418
28. Märkl G, Hölzl W (1989) Tetrahedron Lett 30:4501
29. Burger K, Fehn J, Thenn W (1973) Angew Chem Int Ed Eng 12:155
30. Niecke E, Flick W (1975) Angew Chem Int Ed Engl 14:363
31. Dufour N, Caminade AM, Majoral JP (1989) Tetrahedron Lett 30:4813
32. Eskes H, Regitz M (1975) Tetrahedron Lett 16:447
33. Regitz M (1975) Angew Chem Int Ed 14:222
34. Regitz M, Eskes H (1980) Chem Ber 113:3303
35. Tomioka H, Watanabe M, Kobayashi N, Hirai K (1990) Tetrahedron Lett 31:5061
36. Dabrowska U, Dabrowski J (1976) Chem Ber 109:1779
37. Roesky HW, Otten U (1990) J Fluorine Chem 46:433
38. Roesky HW, Benmohamed N (1986) Chem Ztg 11:417
39. Roesky HW, Benmohamed N, Keller K, Kewelch N, Nolteneyer N, Scheldrick GM (1987) Z Naturforsch 42B:1249
40. Roesky HW, Thiel A, Noltemeyer M, Sheldrick GM (1985) Chem Ber 118:2111
41. Foreman MRStJ, Slawin AMZ, Woolins JD (1999) J Chem Soc Dalton Trans 1175.
42. Khidre MD, Yakost El-SMA, Mahran MRH (1998) Phosphorus Sulfur Silicon 133:119
43. Gubnitskaya ES, Semashko ZT, Parkhomenko VS, Kirsanov AB (1980) J Gen Chem USSR 50:1746 (Zh Obshch Khim 50:2171)
44. Gubnitskaya ES, Peresypkina LP, Parkhomenko VS (1986) J Gen Chem USSR 56:1779 (Zh Obshch Khim 56:2017)
45. Sicard G, Grützmacher H, Baceiredo A, Fischer J, Bertrand G (1989) J Org Chem 54:4426
46. Grützmacher H (1990) Z Naturforsch 45B:170
47. Menu MJ, Dartiguenave Y, Dartiguenave M, Baceiredo A, Bertrand G (1990) Phosphorus Sulfur Silicon 47:327
48. Goumri S, Leriche Y, Gornitzka H, Baceiredo A, Bertrand G (1998) Eur J Jnorg Chem 1539.
49. Afarinkia K, Cadogan JIG, Rees ChW (1992) J Chem Soc Chem Commun 285.
50. Laws AP, Stone JR, Page MI (1994) J Chem Soc Chem Commun 1223.
51. Bergesen K (1967) Acta Chem Scand 21:578
52. Bergesen K, Berge A (1972) Acta Chem Scand 26:2975
53. Pudovik AN, Muratova AA, Savel'eva VA (1964) Zh Obshch Khim 34:2582. Chem Abstr 61:14706

54. Cremer SE, Sommese AG, Rodriguez SA (1993) Phosphorus Sulfur Silicon 75:107
55. Stutz H, Henning H-G (1975) Z Chem 15:52
56. Villemin D, Simeon F, Decreus H, Jaffrers P-A (1998) Phosphorus Sulfur Silicon 133:209
57. Chang J-WA, Gorenstein DG (1987) Tetrahedron 43:5187
58. Miles JA, Grabiak RC, Cummins C (1982) J Org Chem 47:1677
59. Ismailov VM, Kantaeva MM, Akhmedov ShT, Moskva VV (1985) Zh Obshch Khim 55:1873; Chem Abstr 86:42937
60. Vinogradova NM, Lyssenko KA, Odinets IL, Petrovskii PV, Mastryukova TA, Kabachnik MI (1998) Phosphorus Sulfur Silicon 132:265
61. Chaudhry A, Harger MJP, Shuff P, Tompson A (1995) J Chem Soc Chem Comm 83.
62. Chaudhry A, Harger MJP, Shuff P, Tompson A (1999) J Chem Soc Perkin Trans I, p 1347
63. Zhao YF, Yan SJ (1985) J Org Chem 50:2136
64. Ye MC, Chai WG, Li LP, Zhao YF (1987) Tetrahedron Lett 28:2115
65. Ye MC, Li LP, Zhao YF (1988) Phosphorus Sulfur 39:79
66. Ivanov BE, Ageeva AB (1967) Chem Bull USSR Engl 16:228 (Izv Acad Nauk SSSR Ser Khim 226)
67. Ivanov BE, Ageeva AB (1967) Chem Bull USSR Engl 16: 1443 (Izv Acad Nauk SSSR Ser Khim 1494).
68. Ivanov BE, Ageeva AB (1967) Chem Bull USSR Engl 16: 1047 (Izv Acad Nauk SSSR Ser Khim 1090).
69. Ivanov BE, Ageeva AB (1967) Chem Bull USSR Engl 16: 1539 (Izv Acad Nauk SSSR Ser Khim 1600).
70. Chasar DW (1983) J Org Chem 48:4768
71. Belskii VE, Kudryavzeva LA, Destruganova KA, Valitova LA, Bukova TG, Ivanov BE (1983) Chem Bull USSR Engl 32:1279 (Izv Acad Nauk SSSR Ser Khim 1410)
72. Taylor SD, Kluger R (1991) J Am Chem Soc 113:5714
73. Songstad J (1967) Acta Chem Scand 21:1681
74. Yamamoto H, Yamamoto K, Inokawa S, Yamashita M, Armour MA, Nakashima TT (1983) J Org Chem 48:435
75. Racha S, Vargeese C, Vemishetti P, El-Subbagh HI, Abushanab E, Panzica RP (1996) J Med Chem 39:1130
76. Casero F, Cipolla L, Lay L, Nicotra F, Panza L, Russo G (1996) J Org Chem 61:1130
77. Morr M, Kakoschke C, Ernst L (2001) Tetrahedron Lett 42:8841
78. Ivanov BE, Kudryavzeva LA, Zyablikova TA (1970) Chem Bull USSR Engl 19:88 (Izv Acad Nauk SSSR Ser Khim 96)
79. Bentley RL, Dingwall JG (1985) Synthesis, p 552
80. Finet JP, Frejaville C, Lauricalla R, Moigne F, Stipa P, Tordo P (1993) Phosphorus Sulfur Silicon 81:17
81. Ryglowski A, Lazaro R, Roumestant ML, Viallephont PH (1996) Synth Commun 26:1739
82. Arbuzov BA, Yarmukhametova DKh (1960) Chem Bull USSR Engl 9:1645 (Izv Acad Nauk SSSR Ser Khim 1767)
83. Bosco M, Bisseret P, Eustache J (2003) Tetrahedron Lett 44:2347
84. Buechel KH, Roechling H, Korte F (1965) Liebigs Ann Chem 685:10
85. Rizpolozhenskii NI, Mukhametov FS (1967) Chem Bull USSR Engl 16:208 (Izv Acad Nauk SSSR Ser Khim 210)
86. Kalchhauser H, Ohler E (1991) Helv Chim Acta 74:417
87. Thiem J, Gunter M (1984) Phosphorus Sulfur 20:67
88. Thiem J, Gunter M, Paullsen H, Kopf J (1997) Chem Ber 110:3190
89. Wroblewski AE (1984) Carbohydr Res 125:C1
90. Wroblewski AE (1986) Tetrahedron 42:3595
91. Darrow JW, Drueckhammer AG (1994) J Org Chem 59:2976
92. Harvey TC, Simiand C, Weiler L, Whiters SJ (1997) J Org Chem 62:6722
93. Hanessian S, Rogel O (2000) J Org Chem 65:2667
94. Hanessian S, Rogel O (1999) Bioorg Med Chem Lett 9:1629
95. Bisseret P, Boiteau JG, Eustache J (2003) Tetrahedron Lett 44:2351

96. Grayson M, Farley CE (1967) J Chem Soc Chem Commun, p 830
97. Antczak S, Trippet S (1978) J Chem Soc Perkin Trans 1, p 1326
98. Mathey F, Thavard D (1976) J Organomet Chem 117:377
99. Mathey F, Mercier F (1980) J Chem Soc Chem Commun, p 191
100. Petrov KA, Neymusheva AA, Smirnov EV (1959) Zh Obshch Khim 29:1491. Chem Abstr 54:8600
101. Pudovik AN, Khairullin VK, Vasyanina MA (1967) Zh Obshch Khim 37:411. Chem Abstr 67: 64487
102. Pudovik AN, Khairullin VK, Vasyanina MA (1967) Zh Obshch Khim 37:455. Chem Abstr 67:32544
103. Khairullin VK, Vasyanina MA, Pudovik AN (1969) Zh Obshch Khim 39:341. Chem Abstr 71:30547
104. Finke M, Kleiner H, Lohmat E (1976) DE 2526689; (1977) Chem Abstr 86:140245.
105. Rupp W, Finke M (1977) German patent DE 2611694. Chem Abstr 88:23140
106. Gehrman K, Ohorodnik A, Lohmar E, Riechmann A (1976) German patent DE 2531290. Chem Abstr 86:121154
107. Pudovik AN, Faizullin EM, Yakovleva SV (1967) Zh Obshch Khim 37:460. Chem Abstr 67:43884
108. Arbuzov BA, Nuretdinova ON, Nikonova LZ, Goldfarb EI (1973) Chem Bull USSR Engl 22:600 (Izv Acad Nauk SSSR Ser Khim 627)
109. Arbuzov BA, Nikonova LZ, Nuretdinova ON, Anoshin NP (1975) Chem Bull USSR Engl 24:405 (Izv Acad Nauk SSSR Ser Khim 473)
110. Nuretdinova ON, Arbuzov BA, Guseva FF, Nikonova LZ, Anoshin NP (1978) Chem Bull USSR Engl 27:1892 (Izv Acad Nauk SSSR Ser Khim 1898)
111. Nuretdinova ON, Arbuzov BA, Guseva FF, Nikonova LZ, Anoshin NP (1974) Chem Bull USSR Engl 23:833 (Izv Acad Nauk SSSR Ser Khim 869)
112. Nuretdinova ON, Guseva FF (1988) Chem Bull USSR Engl 37:2178 (Izv Acad Nauk SSSR Ser Khim 2416)
113. Rudi A, Kashman Y (1981) Tetrahedron 37:4269
114. Rudi A, Goldberg I, Kashman Y (1985) Tetrahedron 41:5267
115. Knockel P, Normant JF (1984) Tetrahedron Lett 23:3725
116. Hoffmann HMR, Rabe J (1985) Angew Chem Int Ed Engl 24:94
117. Collard JN, Benezra A (1982) Tetrahedron Lett 23:3725
118. Xu Y, Li Z (1986) Tetrahedron Lett 27:3017
119. Xu Y, Zhang J (1985) Tetrahedron Lett 26:4771
120. Hah JH, Lee BS, Lee SY, Lee HY (2003) Tetrahedron Lett 44:5811
121. Bujard M, Gouverneur V, Mioskowski C (1999) J Org Chem 64:2119
122. Timmer MSM, Ovaa H, Filippov DV, van der Marel GA, van Boom JH (2001) Tetrahedron Lett 42:8231
123. Hetherington L, Greedy B, Gouverneur V (2000) Tetrahedron 56:2053
124. Stoinova DS, Hanson PR (2001) Org Lett 3:3285
125. Moore JD, Sprott KT, Wrobleski AD, Hanson PR (2002) Org Lett 4:2357
126. Moore JD, Hanson PR (2003) Tetrahedron Asym 14:873
127. Kashman Y, Averbouch O (1975) Tetrahedron 31:45
128. Kashman Y, Averbouch O (1975) Tetrahedron 31:53
129. Quin LD, Kisalus JC, Mesch KA (1983) J Org Chem 48:4466
130. Quin LD, Marsi BG (1985) J Am Chem Soc 107:3389
131. Quin LD, Szewczyk J, Szewczyk KM, McPhail AT (1986) J Org Chem 51:3341
132. Quin LD, Pete B, Szewczyk J, Hughes AN (1988) Tetrahedron Lett 29:2627
133. Singh G (1983) Phosphorus Sulfur 18:217
134. Lane TM, Rodriguez OP, Cremer SE (1995) Phosphorus Sulfur Silicon 103:63
135. Rodriguez OP, Lane TM, Cremer SE (1996) Phosphorus Sulfur Silicon 111:137
136. Perez-Prieto J, Galian RE, Miranda MA, Catalina F, Martin-Vargas N, Lopez-Ortiz F (2004) Org Lett 6:561

137. Perez-Prieto J, Galian RE, Burgos PO, Minana MCM, Miranda MA, Lopez-Ortiz F (2005) Org Lett 7:3869
138. Inubushi Y, Huy NHT, Ricard L, Mathey F (1997) J Organomet Chem 533:83
139. Arbuzov BA, Nikonova LZ, Nuretdinova ON (1973) Chem Bull USSR Engl 22:621 (Izv Acad Nauk SSSR Ser Khim 648)
140. Kleiner H-J (1980) Liebigs Ann Chem 324.
141. Polozov AM, Cremer SE (1999) Phosphorus Sulfur Silicon 147:335
142. Uhing EH (1978) US patent 4231970. Chem Abstr 94: 84303
143. Uhing EH (1985) US patent 4540526. Chem Abstr 104: 34193
144. Yamaguchi H, Kametani S, Karalasa T, Saito T, Motoki S (1982) Tetrahedron Lett 23:1263
145. Tanaka H, Kametani S, Saito T, Motoki S (1985) Bull Chem Soc Jpn 58:667
146. Uchida T, Kozawa K, Saito T, Motoki S (1984) Bull Chem Soc Jpn 57:1990
147. Kobayashi S, Suzuki M, Saegusa T (1985) Bull Chem Soc Jpn 58:2153
148. Kobayashi S, Tokunoh M, Saegusa T (1986) Macromolecules 19:466
149. Kamijo K, Toyota K, Yoshifuji M (1999) Chem Lett 567.
150. Aladzheva IM, Bykhovskaya OV, Lobanov DI, Lyssenko KA, Antipin MYu, Mastryukova TA, Kabachnik MI (1996) Mendeleev Commun 48.
151. Aladzheva IM, Bykhovskaya OV, Lobanov DI, Petrovskii PV, Lyssenko KA, Mastryukova TA, Kabachnik MI (1998) Russ J Gen Chem 68:1356 (Zh Obshch Khim 68:1421)
152. Lobanov DI, Aladzheva IM, Bykhovskaya OV, Petrovskii PV, Lyssenko KA, Antipin MYu, Mastryukova TA, Kabachnik MI (1997) Phosphorus Sulfur Silicon 128:165
153. Aladzheva IM, Leont'eva IV, Lobanov DI, Petrovskii PV, Lyssenko KA, Mastryukova TA, Kabachnik MI (1998) Zh Obshch Khim 68:1417
154. Bykhovskaya OV, Aladzheva IM, Lobanov DI, Petrovskii PV, Lyssenko KA, Mastryukova TA (2001) Russ J Gen Chem 71:369
155. Aladzheva IM, Bykhovskaya OV, Lobanov DI, Petrovskii PV, Lyssenko KA, Mastryukova TA (2002) Chem Heterocycl Comp Engl 95 (Khim Geterotsikl Soedin 105)
156. Odinets IL, Vinogradova NM, Artyushin OI, Petrovskii PV, Lyssenko KA, Antipin MYu, Mastryukova TA (1999) Mendeleev Commun, p 158
157. Odinets IL, Vinogradova NM, Lyssenko KA, Antipin MYu, Mastryukova TA (2000) Mendeleev Commun, p 216
158. Mastryukova TA, Odinets IL, Vinogradova NM, Lyssenko KA, Petrovskii PV (2001) Polish J Chem 75:1103
159. Odinets IL, Vinogradova NM, Lyssenko KA, Antipin MYu, Petrovskii PV, Mastryukova TA (2002) Heteroatom Chem 13:1
160. Odinets IL, Vinogradova NM, Lyssenko KA, Petrovskii PV, Mastryukova TA (2002) Phosphorus Sulfur Silicon 177:1787
161. Odinets IL, Vinogradova NM, Petrovskii PV, Mastryukova TA (2000) Heteroatom Chem 11:163
162. Odinets IL, Vinogradova NM, Matveeva EV, Golovanov DD, Lyssenko KA, Keglevich G, Kollár L, Roeschenthaler GV, Mastryukova TA (2005) J Organomet Chem 690:2559
163. Helferich B, Curtius U (1962) Liebigs Ann Chem 655:59
164. Helferich B, Schröder L (1963) Liebigs Ann Chem 670:48
165. Collins DJ, Hetherington JW, Swan JM (1974) Aust J Chem 27:1759
166. Hewitt DG, Newland GL (1977) Aust J Chem 30:579
167. Hewitt DG, Teese MW (1984) Aust J Chem 37:1631
168. Khairullin VK, Kondrat'eva RM, Pudovik AN (1968) Chem Bull USSR Engl 17:1298 (Izv Acad Nauk SSSR Ser Khim 1375)
169. Pudovik AN, Kondrat'eva RM, Khairullin VK (1969) Chem Bull USSR Engl 18:1937 (Izv Acad Nauk SSSR Ser Khim 2076)
170. Pudovik AN, Khairullin VK, Dmitrieva GV (1970) Zh Obshch Khim 40:1034.Chem Abstr 73:77331
171. Oehme H, Thamm R (1973) J Prakt Chem 315:526
172. Farley ChE, Grayson M, US Patent 3846374, 1974

173. Ploeger W, Schmidt-Dunker M, Gloxhuber CH (1975) German patent DE 2343195. Chem Abstr 83:28372
174. Mastryukova TA, Aladzheva IM, Bykhovskaya OV, Lobanov DI, Nemeryuk AM, Lyssenko KA, Petrovskii PV, Odinets IL (2002) Phosphorus Sulfur Silicon 177:1701
175. Sakai T, Kodama T, Fujimoto T, Ohta K, Yamamoto I (1994) J Org Chem 59:7144
176. Aladzheva IM, Lobanov DI, Bykhovskaya OV, Petrovskii PV, Lyssenko KA, Mastryukova TA (2003) Heteroatom Chem 14:506
177. Bykhovskaya OV, Aladzheva IM, Lobanov DI, Petrovskii PV, Lyssenko KA, Fedyanin IV, Mastryukova TA (2005) Russ Chem Bull 54:2642 (Izv Acad Nauk SSSR Ser Khim 2557)
178. Konovalova IV, Michailova NV, Gareev RD, Burnaeva LA, Anufrieva TV, Pudovik AN (1981) Zh Obshch Khim 51:989. Chem Abstr 85:62321
179. Konovalova IV, Michailova NV, Burnaeva LA, Pudovik AN (1982) Zh Obshch Khim 52:1290. Chem Abstr 97:144937
180. Khusainova NG, Bredichina ZA, Pudovik AN (1982) Zh Obshch Khim 52:1296. Chem Abstr 97:163101
181. Harger MJP (1974) J Chem Soc Perkin Trans I 2604.
182. Wiseman J, Westheiner FH (1974) J Am Chem Soc 96:4262
183. Igan A, Grutzmerker H, Baceiredo A, Bertrand G (1988) J Am Chem Soc 110:6463.
184. Gilette GR, Baceiredo A, Bertrand G (1990) Angew Chem Int Ed 29:1429.
185. Sørensen MD, Blæhr KA, Christensen MK, Høyer SL, Hjarnaa PJV, Björkling F (2003) Bioorg Med Chem 11:5461
186. Natchev IA (1989) J Chem Soc Perkin Trans I 125

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Phosphorus-Containing Calixarenes

Sergey Cherenok and Vitaly Kalchenko

Abstract Calixarenes are macro(hetero)cyclic compounds having three-dimensional molecular cavities and are ubiquitous as synthetic receptors in supramolecular chemistry. This paper provides an overview of studies on the phosphorus-containing calixarenes and thiacalixarenes, within the context of synthesis, metal cation binding, catalysis, molecular recognition and bioactivity.

Keywords Calixarenes, Catalysis, Chirality, Biological activity, Molecular recognition, Organophosphorus compounds, Supramolecular chemistry

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1 Introduction

Calixarenes [1,2] and their thia-analogues (thiacalixarenes) [3] are synthetically available macro(hetero)cyclic compounds possessing cap-shaped molecular cavities formed by phenol rings linked through methylene groups or sulfur atoms. They are employed as the platform for introduction of a variety of functional groups at the phenol oxygen atoms (lower rim) and/or at the *para*-positions (upper rim). The compounds formed through multisite hydrogen bonding, specific stacking, electrostatic interactions etc. are widely used as molecular platforms for the construction of specific receptors capable of highly selective recognition between fairly similar species.

Calixarenes demonstrate a unique ability to recognize and to bind in the host–guest supramolecular complexes and thereafter to separate cations [4,5], anions [6,7], neutral molecules [1,8] and biomolecules [2] of appropriate sizes and architectures. Application of the calixarenes in different branches of chemistry, physics and biology [2,9,10] is well documented. During the last decade, calixarene derivatives, especially water-soluble and amphiphilic ones, have been the subject of growing interest in the biological domain [11,12].

The phosphorus-containing calixarenes functionalized with P(III) or P(V) functional groups are of particular interest [13–16]. Strong cation and hydrogen bond acceptor properties of the phosphorus functionalities make them excellent binding sites for molecular recognition [17].

In this review, we report the synthesis and functional properties of the phosphorus-containing calixarenes and thiacalixarenes, within the context of cationic and molecular recognition, extraction properties, catalytic properties and bioactivity.

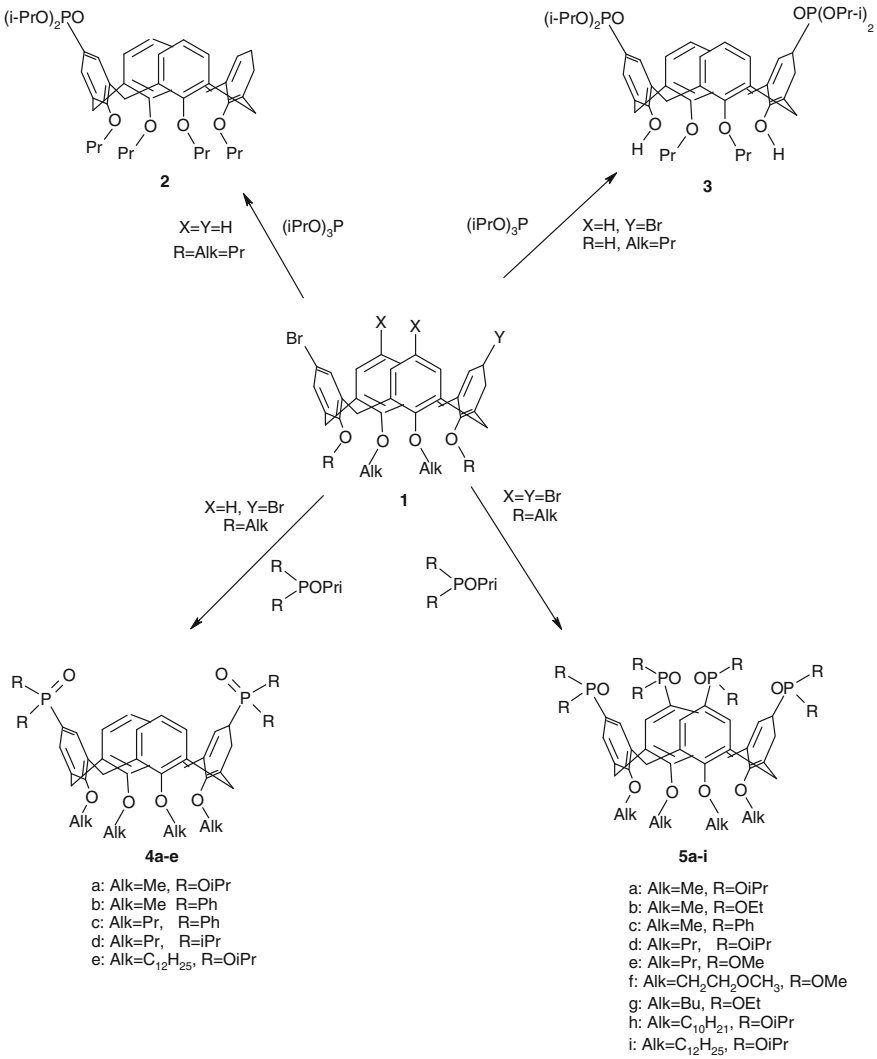
2 Calixarenes Bearing P(V) Phosphorus Groups at the Upper Rim

2.1 Calixarene Phosphonates and Phosphine Oxides

2.1.1 Phosphorylation of Bromocalixarenes

One of the preparative methods for the formation of the C_{Ar}–P bond is the metal-catalysed Arbuzov reaction [18]. For the first time, Markovsky applied the reaction

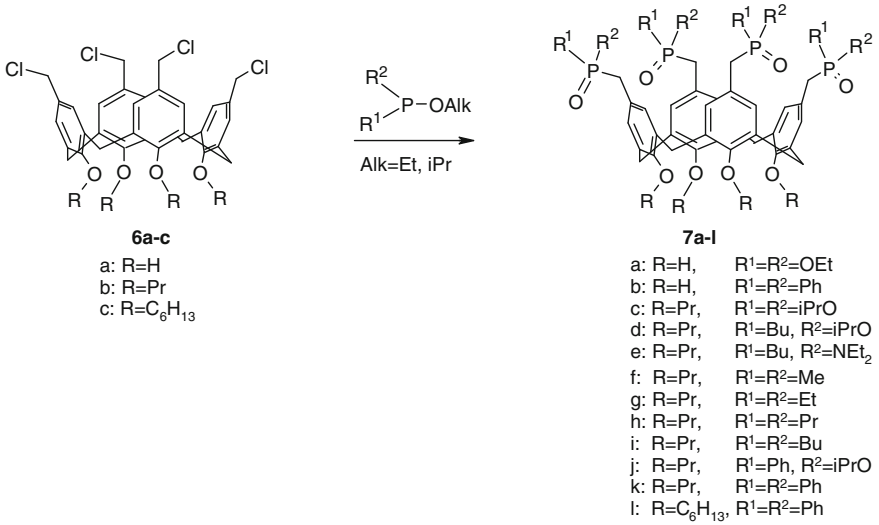
to the phosphorylation of tetrabromocalix[4]arene tetramethyl ether [19]. Later, calix[4]arenes **2**, **3**, **4** and **5** containing one, two or four phosphorus fragments at the upper rim of the macrocycle were synthesized by the reaction of the appropriate mono-, di- and tetrabromocalixarenes **1** with alkyl esters of P(III) acids (Scheme 1) [20–24]. High temperature (110–180 °C), excess of P(III) esters and catalytic quantitives of anhydrous nickel bromide are needed to obtain satisfactory yields of the calixarenes **2–5**.



Scheme 1 Phosphorylation of bromocalixarenes

2.1.2 Phosphorylation of Chloromethylcalixarenes

The first synthesis of calixarenes phosphorylated at the upper rim was carried out by Ungaro [25] and Shinkai [26] using the Arbuzov reaction of chloromethylcalix[4,6,8]arenes with a triethylphosphite. Using this approach, a series of tetraalkoxycalixarenes **7** bearing four phosphonomethyl groups was synthesized with yields of 65–98% by the Arbuzov reaction of tetrakis(chloromethyl)calix[4]arenes **6** with alkyl esters of P(III) phosphorus acids (Scheme 2) [27,28]. Calix[4]arene **7a** reacted with 6-bromomethyl-6-methyl-2,2-bipyridine and K_2CO_3 in refluxing MeCN to give calixarene-based podand **8** with a yield of 71% (Scheme 3) [29].



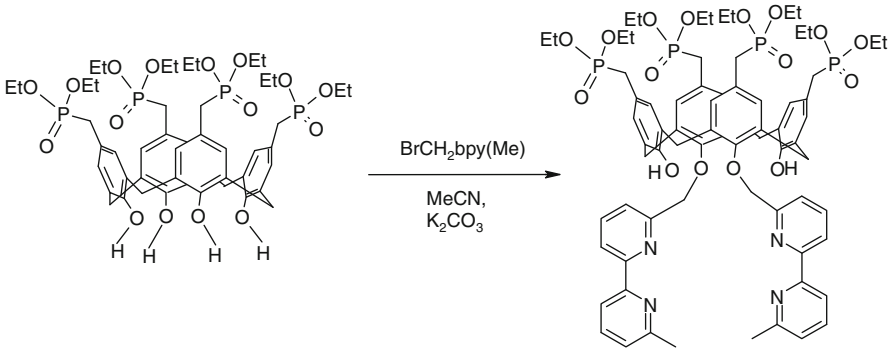
6a-c

a: R=H
b: R=Pr
c: R=C_6H_{13}

7a-l

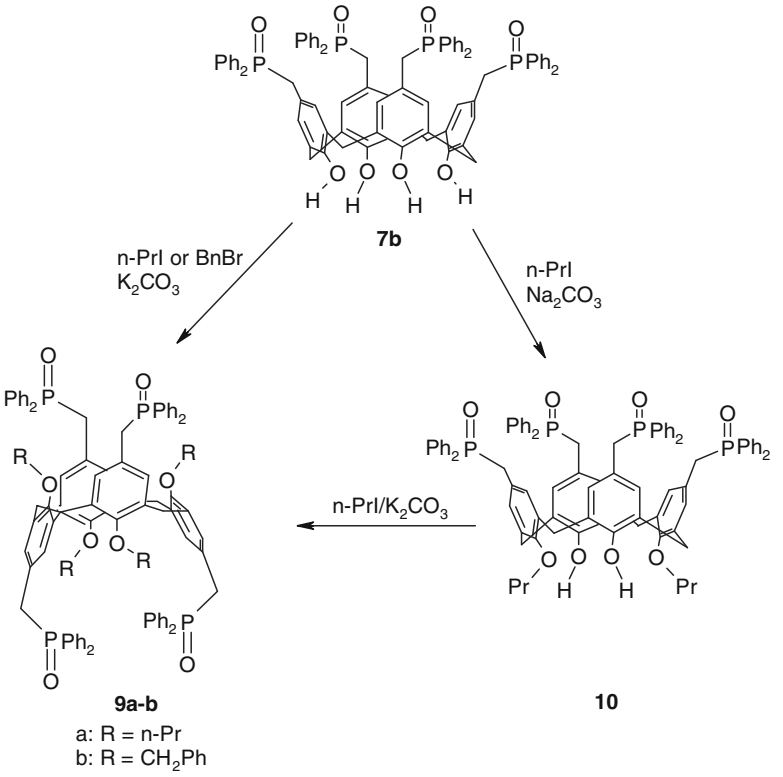
a: R=H, R^1=R^2=OEt
b: R=H, R^1=R^2=Ph
c: R=Pr, R^1=R^2=iPrO
d: R=Pr, R^1=Bu, R^2=iPrO
e: R=Pr, R^1=Bu, R^2=NEt_2
f: R=Pr, R^1=R^2=Me
g: R=Pr, R^1=R^2=Et
h: R=Pr, R^1=R^2=Pr
i: R=Pr, R^1=R^2=Bu
j: R=Pr, R^1=Ph, R^2=iPrO
k: R=Pr, R^1=R^2=Ph
l: R=C_6H_{13}, R^1=R^2=Ph

Scheme 2 Phosphorylation of chloromethylcalixarenes



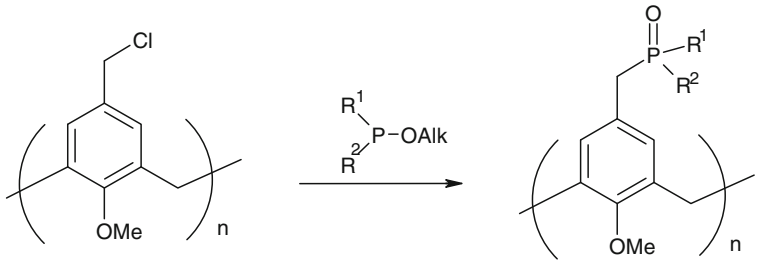
7a **8**

Scheme 3 Alkylation of the calixarene **7a**



Scheme 4 Alkylation of the calix[4]arene tetraphosphine oxide **7b**

Tetraphosphinoylcalix[4]arenes **9** adopting *1,3-alternate* conformation have been synthesized by the alkylation of calix[4]arene tetraphosphine oxide **7b** with propyl iodide or benzyl bromide in the presence of K_2CO_3. In contrast, when Na_2CO_3 was used instead of K_2CO_3 as a base in the reaction of **7b** with *n*-propyl iodide, di-O-propylation took place exclusively to give calix[4]arene **10** in the *cone* conformation. The *cone* di-O-propylated phosphine oxide **10** was converted to tetra-O-propylated phosphine oxide **9***1,3-alternate* in 91% yield by the reaction with PrI and K_2CO_3 (Scheme 4) [30]. Calix[6]arenes and calix[8]arenes **12** substituted with phosphonylmethyl groups were also prepared by the Arbuzov reaction of chloromethylcalix[6,8]arenes **11** with alkyl esters of P(III) phosphorus acids (Scheme 5) [25,26,31].



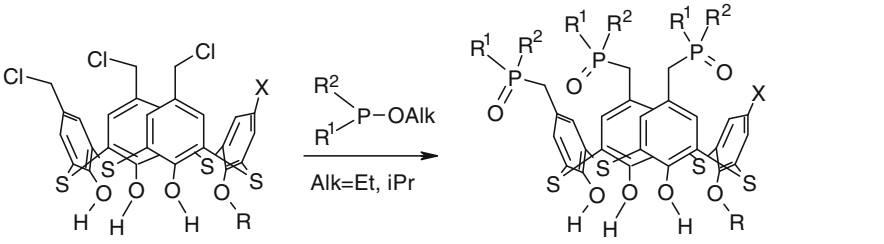
11a-b

a: n=6
b: n=8

12a-g

a: $R^1=R^2=OEt$, n=6
b: $R^1=R^2=OEt$, n=8
c: $R^1=R^2=OiPr$, n=6
d: $R^1=R^2=Ph$, n=6
e: $R^1=R^2=Bu$, n=6
f: $R^1=Ph$, $R^2=OiPr$, n=6
g: $R^1=Bu$, $R^2=OiPr$, n=6

Scheme 5 Phosphorylation of chloromethylcalix[6,8]arenes



13a-b

a: $X=CH_2Cl$, R=H
b: X=H, $R=C_{10}H_{21}$

14a-f

a: $R^1=R^2=OEt$, R=H, $X=CH_2P(O)(OEt)_2$
b: $R^1=R^2=iPrO$, R=H, $X=CH_2P(O)(OPr\text{-}i)_2$
c: $R^1=R^2=OBu$, R=H, $X=CH_2P(O)(OBu)_2$
d: $R^1=R^2=Ph$, R=H, $X=CH_2P(O)Ph_2$
e: $R^1=OiPr$, $R^2=Ph$, $X=CH_2P(O)(OPr\text{-}i)Ph$
f: $R^1=R^2=OEt$, $R=C_{10}H_{21}$, X=H

Scheme 6 Phosphorylation of chloromethylthiacalixarenes

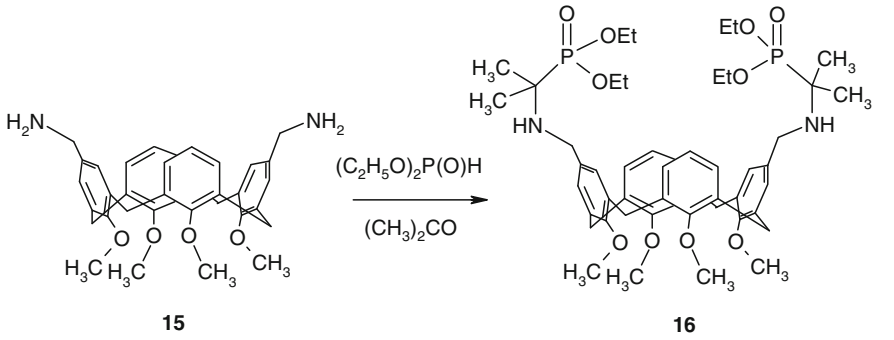
2.1.3 Phosphorylation of Chloromethylthiacalixarenes

Phosphorylated thiacalix[4]arenes **14** were prepared by the Arbuzov reaction of chloromethylthiacalixarenes **13** with esters of P(III) acids ($CHCl_3$, 4 h, r.t., twofold excess of the phosphorylating agent) (Scheme 6) [32,33]. The difference in the reactivities of thiacalixarene **13** and tetrakis-(chloromethyl)calix[4]arene **6**, which reacts with trialkylphosphites only under harsh conditions (long heating in solution of trialkylphosphite at 160–180 °C), may be noted.

2.2 Calixarene α-Aminophosphonates

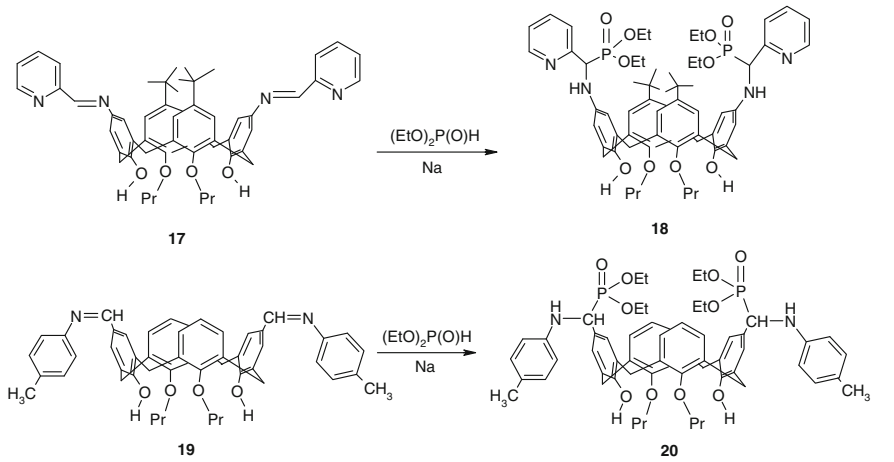
Calixarene **16**, which has two aminophosphonate groups at the upper rim of the macrocycle, has been synthesized by Konovalov and coworkers from aminomethylcalix[4]arene **15** using the Kabachnic–Fields reaction [34,35] (Scheme 7) [36].

An alternative synthesis of aminophosphonates is through the Pudovik reaction of imines with dialkylphosphites in the presence of metallic sodium. Calix[4]arene



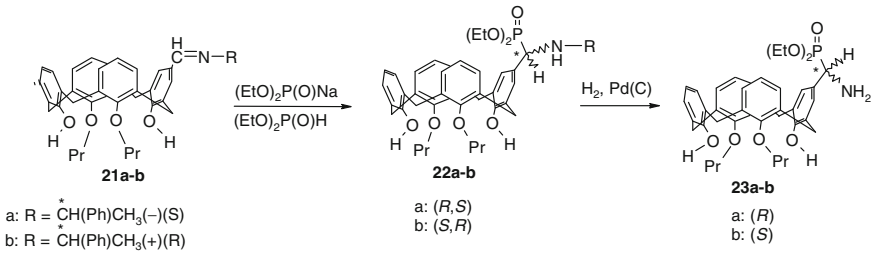
Scheme 7 Synthesis of the calixarene α-aminophosphonates by the Kabachnic–Fields reaction

bis-aminophosphonates **18** and **20**, existing as a diastereomeric mixture, were obtained from the addition of sodium diethylphosphite to the calixarene bisimines **17** and **19** (Scheme 8) [37–39].



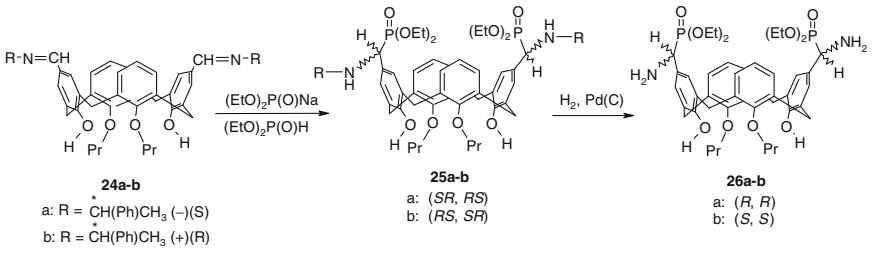
Scheme 8 Synthesis of the calixarene α-aminophosphonates by the Pudovik reaction

The addition of diethylphosphite sodium salt to the C=N bond of chiral iminocalixarenes **21**, obtained by condensation of monoformylcalixarene with (*R*) or (*S*) phenylethylamine, proceeds stereoselectively. The formation of (*RS*) or (*SR*) calixarene a-aminophosphonates **22** (Scheme 9) [39,40] results in high chemical yields (95%) and considerable diastereomeric excess (d.e. 85%). Chiral phenylethyl auxiliary groups of (*RS*) and (*SR*) diastereomers **22** were removed by hydration on Pd/C catalyst, giving (*R*) or (*S*) enantiomers of the calixarene aminophosphonates **23**.



Scheme 9 Synthesis of the optically pure calixarene α-aminophosphonates

The corresponding (*SR,RS*) and (*RS,SR*) calixarene bis-aminophosphonates **25** (Scheme 10) were obtained by the similar stereoselective addition of diethylphosphite sodium salt to the (*SS*) or (*RR*) diiminocalixarenes **24**. The compounds **25** have been transformed into optically pure (*RR*) and (*SS*) aminophosphonates **26** in a similar manner.

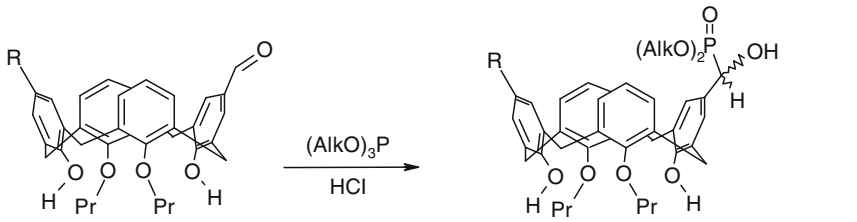


Scheme 10 Synthesis of the optically pure calixarene bis-α-aminophosphonates

2.3 Calixarene α-Hydroxyphosphonates

Dialkyl esters of calixarene α-hydroxyphosphonic acids **28a-c** were obtained as a racemic mixture from the reaction of 5-formylcalix[4]arene **27a** with trialkylphosphites in the presence of gaseous hydrogen chloride (Scheme 11) [39]. Similar

phosphorylation of 5,17-diformylcalix[4]arene **27b** results in the formation of calixarene bis-α-hydroxyphosphonate **28d–f** as a mixture of racemic (*RR* + *SS*) and meso (*RS*) stereoisomeres, possessing two chiral carbon atoms at the macrocycle wide rim (Scheme 11) [39].



27a-b
a: R=H
b: R=CHO

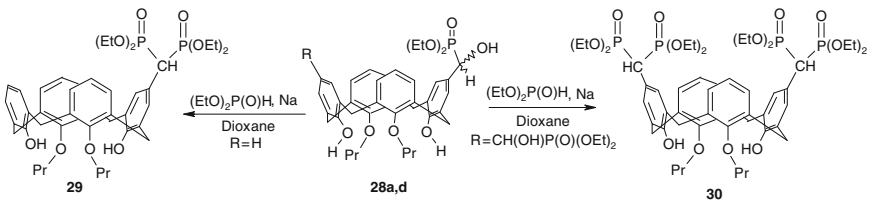
28a-f
a: R=H, Alk=Et
b: R=H, Alk=Pr
c: R=H, Alk=Bu
d: R=CH(OH)P(O)$(OEt)_2$, Alk=Et
e: R=CH(OH)P(O)$(OPr)_2$, Alk=Pr
f: R=CH(OH)P(O)$(OBu)_2$, Alk=Bu

Scheme 11 Phosphorylation of the formyl calixarenes by trialkylphosphites

The ratio of the stereoisomeric forms of calixarenes **28d–f** ranges from 65:35 to 90:10, depending on alkyl length in the phosphorylating agent, temperature of the reaction and concentration of hydrogen chloride in the reaction mixture. Racemic and meso-forms of α-hydroxyphosphonate **28d–f** were separated by crystallization or column chromatography on silica-gel [39,41].

2.4 Calixarene Methylenebisphosphonates

Hydroxyphosphonate **28a** was converted quantitatively to methylenebisphosphonate **29** by reaction with a large excess of $(EtO)_2P(O)Na$ in diethylphosphite/dioxane solution (Scheme 12) [42]. A possible mechanism of this reaction involves the base-mediated elimination of hydroxide ion from the hydroxyphosphonate **28a**, yielding the highly reactive phosphorylated quinonemethide. The addition of diethylphosphite to the quinonemethide leads to methylenebisphosphonate **29**. Under identical conditions, calixarene bis-α-hydroxyphosphonate **28d** provided calixarene bis-methylenebisphosphonate **30**.

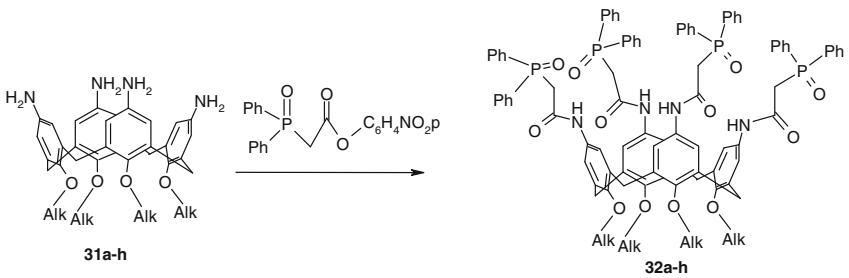


Scheme 12 Synthesis of the calixarene methylenebisphosphonates

The methylenebisphosphonates **29** and **30** were also prepared by one-pot reaction of aldehydes **27a**,**b** with a large excess of sodium diethylphosphite without isolation of α-hydroxyphosphonates **28** [42].

2.5 Calixarene Carbamoylphosphine Oxides and Diphosphine Dioxides

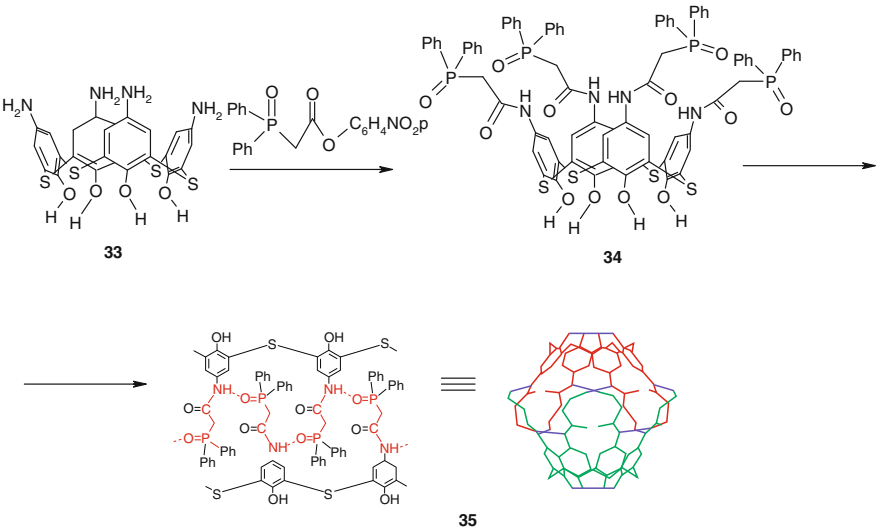
Calixarenes **32a**–**h** bearing four CMPO (carbamoylphosphine oxide) groups at the upper rim were prepared by Böhmer and coworkers with yields of 60–70% by treatment of calix[4]arene tetraamines **31a**–**h** with *p*-nitrophenol ester of (diphenylphosphinoyl)acetic acids (Scheme 13) [43,44]. A similar approach was used for the synthesis of calixarene bearing CMPO groups at the lower rim [45]. Thiacalix[4]arenes, in which the four methylene bridges of "usual" calix[4]arenes are replaced by sulfur atoms [46], have a slightly different size and shape [3,47].



Alk= C_3H_7(a), C_5H_{11} (b), $CH_2CH(C_4H_9)(C_2H_5)$ (c), $C_{10}H_{21}$ (d), $C_{12}H_{25}$ (e), $C_{14}H_{29}$ (f), $C_{16}H_{33}$ (g), $C_{18}H_{37}$ (h)

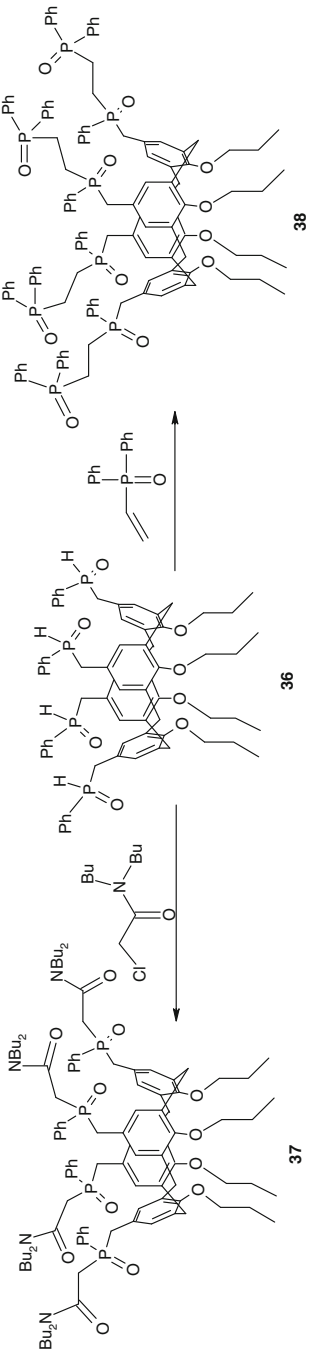
Scheme 13 Synthesis of the calixarene carbamoylphosphine oxides

CMPO-thiacalix[4]arene **34** with a yield of 70% was prepared by treatment of thiacalix[4]arene tetraamine **33** with *p*-nitrophenol ester of (diphenylphosphinoyl) acetic acids (Scheme 14) [48]. The CMPO-thiacalix[4]arene **34**, in contrast to similar CMPO-calix[4]arenes **32a**–**h**, forms dimeric capsule **35** (inner volume 370 Å) with S_8 symmetry in the crystalline state and in apolar solvents. The capsule is stabilized by eight intramolecular hydrogen bonds between the NH and O=P groups of adjacent CMPO functions.



Scheme 14 Synthesis and capsule formation of the thiacalixarene carbamoylphosphine oxides

The calix[4]arene **37**, functionalized with four CMPO dibutylaminocarbonylmethylphenylphosphinoyl groups, has been synthesized by the Michaelis–Becker reaction of hydrophosphinoyl calixarene **36** (obtained by reduction of isopropylphenylphosphonate **7j)** with the dibutylamide of monochloro acetic asid (Scheme 15) [49]. Molecule **37** is different from CMPO-calix[4]arene **32a** and CMPO-thiacalix[4]arene **34** by linkage of CMPO groups to the aromatic platform via carbon atoms.



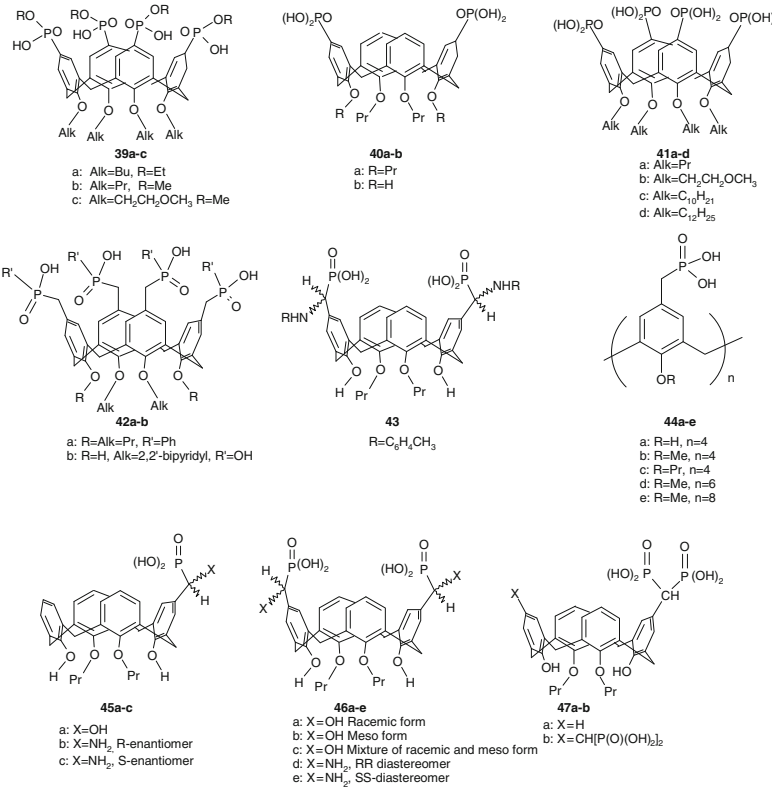
Scheme 15 Reaction of calixarene **36** with dibutylamide of monochloro acetic acid or vinyldiphenylphosphine oxide

Calixarene **38** containing diphosphine dioxide chelating groups at the wide rim was synthesized by the Michael addition of the P(O)–H function of **36** to the carbon–carbon double bond of vinyldiphenylphosphine oxide (Scheme 15) [49].

2.6 Calixarene Phosphonous and Phosphinous Acids

One of the most important routes to the synthesis of new bioactive compounds consists in functionalization of the calixarene skeleton with fragments of natural or artificial biologically active compounds [50,51]. Phosphonic acid derivatives, being metabolites of natural carbonic acids [52], are known to be bioactive compounds that inhibit specifically some fermentation reactions [53,54] and possess high cancerostatic, bacteriostatic, and cytotoxic activities [53,55].

Treatment of alkyl esters of calixarene phosphonic and phosphinic acids **3**, **4d**, **5c–f**, **7a**, **7c**, **8**, **12a–b**, **18**, **20**, **23**, **26**, **28**, **29** and **30** with bromotrimethylsilane and methanol give in quantitative yields calix[4]arenes **40–47** bearing fragments of the phosphonous, phosphinous, a-aminophosphonic, a-hydroxyphosphonic and methylenebisphosphonic acids (Scheme 16) [20,29,37–42,56,57].



Scheme 16 Calixarene phosphonous and phosphinous acids

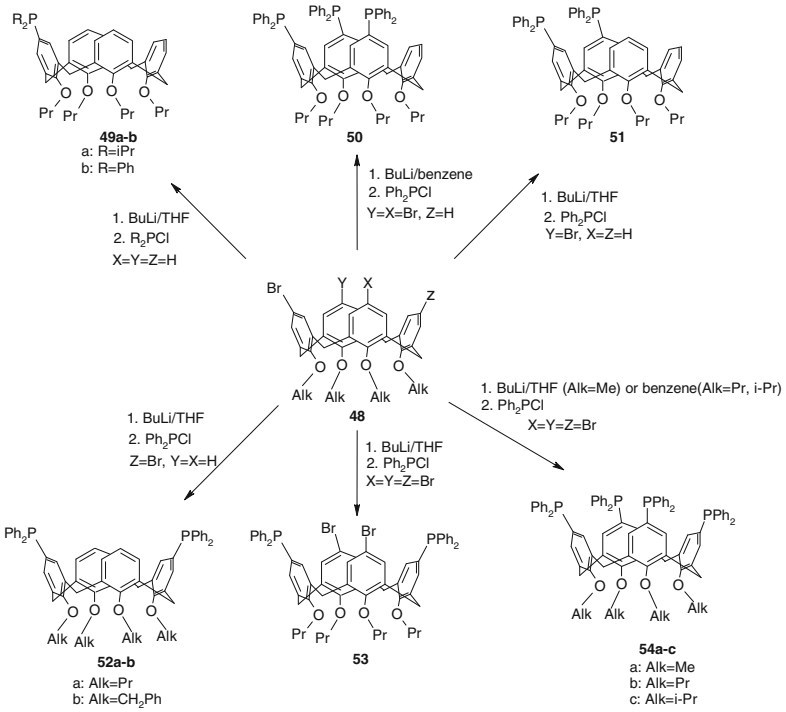
The reaction of calixarene dialkyl phosphonates **5d–f** with excess of LiBr in refluxed acetonitrile removes only one alkyl group from the phosphoryl group and affords calixarene monoalkylphosphonic acids **39** (Scheme 16) [20]. Complexing and biological properties of the acids are described in Sect. 6.

3 Calixarenes Bearing P(III) Phosphorus Groups at the Upper Rim

3.1 Phosphorylation of Bromocalixarenes

The first attempt at introduction of phosphine fragments into the upper rim of calix[4] arene was described in 1991 [58]. So, by interaction of tetrabromocalix[4]arene tetramethyl ether with *n*-BuLi and chlorodiphenylphosphine in THF solution, tetraphosphine **54a** was obtained with the aim of designing metal cation extractants (Scheme 17). The spectroscopic data reveal that tetramethoxycalixarene **54a** exists in multiple conformations (*cone*, *partial cone*, *1,2-alternate*, *1,3-alternate*), which are in equilibrium with each other. The use of propyl or benzyl residues at the lower rim is known to prevent such behaviour, and only the desired *cone* conformation is obtained.

Calixarenes **49** containing one phosphine group were obtained by the lithiation of monobromotetrapropoxycalix[4]arene with butyllithium, followed by the phosphination



Scheme 17 Synthesis of the calixarene phosphines following lithium/bromine exchange

reaction either with chlorodiphenylphosphine or chlorodiisopropylphosphine (Scheme 17) [59,60]. The regioselective upper-rim functionalization of calix[4]arene has been performed to prepare multisubstituted diphenylphosphine derivatives [61,62], which are potential multidentate ligands capable of coordination to soft transition metals.

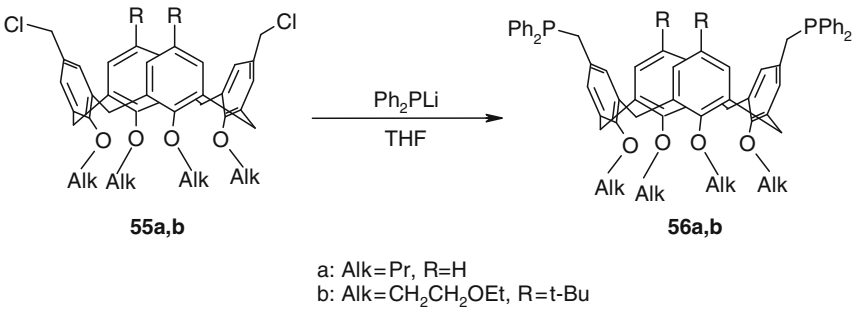
Using the Atwood procedure [58] (*n*-BuLi in THF at −78 °C), the lithiation reaction was attempted on tetrabromotetrapropoxycalixarene to synthesize tetraphosphine **54b** [61]. However, the 5,17-dibromo-11,23-bis(diphenylphosphino)-tetrapropoxycalix[4] arene **53** is selectively and reproducibly obtained, even with an excess of *n*-BuLi. Performing subsequent lithiation and phosphination of compound **53** does not lead to the desired tetraphosphine **54b**. However, the tetralithiated intermediate is predictably generated either with *n*-BuLi in benzene or with *t*-BuLi in benzene or THF. Subsequently, reactions with chlorodiphenylphosphine leads to **54b**,**c**. The calixarene **50** containing three diphenylphosphino groups at the upper rim has been similarly obtained. However, this procedure leads to modest yields of the product (Scheme 17).

Calixarenes **51**, **52** containing two diphenylphosphino groups in 5,17 positions or 5,11 positions of the upper rim were prepared via lithiation and phosphination reactions of the appropriate dibromocalixarenes with *n*-BuLi and $ClPPh_2$ in THF (Scheme 17) [62,63].

3.2 Phosphorylation of Chloroalkylcalixarenes

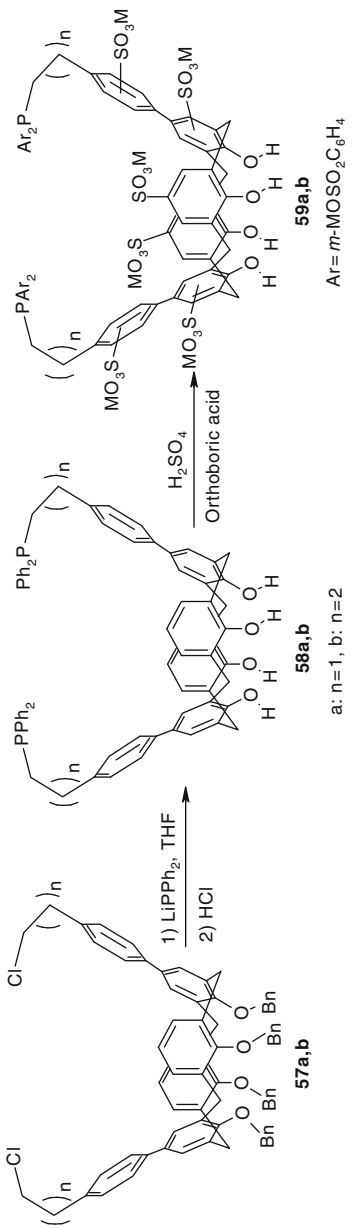
Ligands **56** possessing two distal phosphino groups attached at the upper rim of the calix[4]arene through a methylene bridge were prepared by subsequent treatment of **55** with 2 equiv. of Ph_2PLi (prepared in situ from Ph_2PH and BuLi) (Scheme 18) [64,65]. When a solution of **56** is exposed to air, it is readily oxidized to the phosphine oxide derivative.

Water-soluble diphosphinocalix[4]arenes **59** were synthesized starting from the bis-chloroalkyltetrabenzyloxycalix[4]arene **57** in two steps [66]. At the first stage,



Scheme 18 Synthesis of the calixarene phosphines from chloromethylcalixarenes

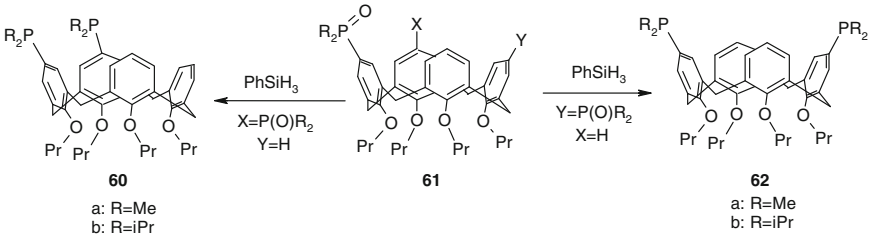
diphosphine **58** was prepared by treatment of **57** with 2 equiv. of Ph_2PLi. At the second stage, controlled sulfonations of the precursors **58** were conducted under mild conditions to avoid phosphine oxidation. As a result, desirable calixarene diphosphines **59** were obtained as precisely decasulfonated derivatives (Scheme 19).



Scheme 19 Synthesis of water-soluble diphosphinocalix[4]arenes **59**

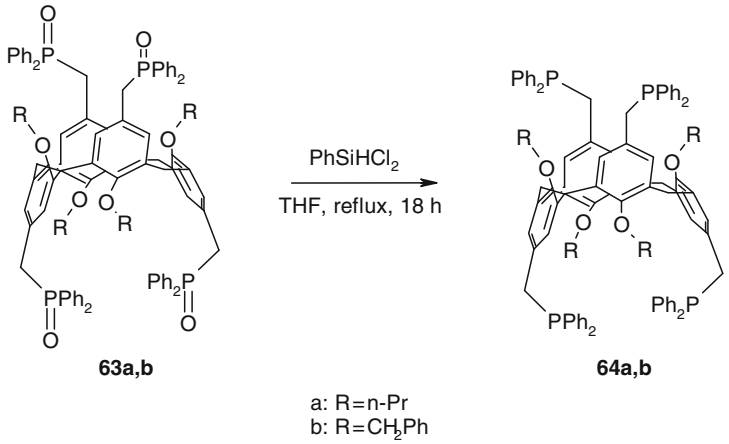
3.3 Reduction of Calixarene Phosphine Oxides

Calixarenes **60** and **62**, containing highly oxygen-sensitive dimethyl- or diisopropylphosphino groups, were prepared by reduction of the corresponding calixarene phosphine oxides **61** with phenylsilane (Scheme 20) [22,63].



Scheme 20 Reduction of the calixarene phosphine oxides

Reduction of **63** with $PhSiHCl_2$ in THF was carried out to afford tetrakis (diphosphinomethyl)-tetraalkoxycalix[4]arenes **64** in the *1,3-alternate* conformation (Scheme 21). In this reaction, the use of $PhSiH_3$ or Ph_2SiH_2 as reducing agent resulted in the formation of the undesired Ph_2PH as a side product via cleavage of the P–C bond [30].

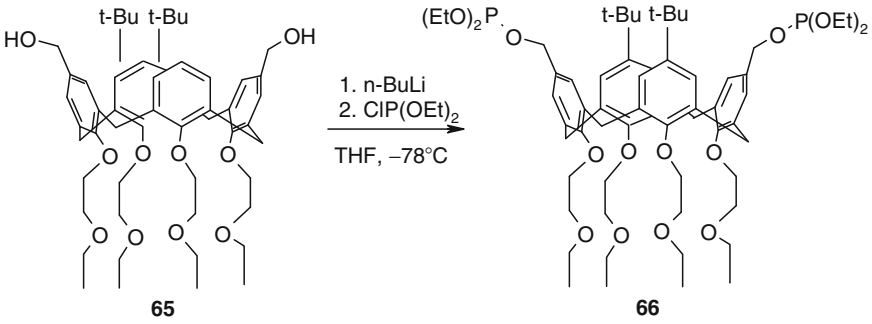


Scheme 21 Reduction of the calixarene phosphine oxides in the *1,3-alternate* conformation

3.4 Phosphorylation of Methylolcalixarene

Calixarene diphosphite **66** was obtained in 93% yield by the reaction of bis-methylol calixarene **65** with 2 equiv. of *n*-BuLi in THF at −78 °C and subsequent treatment

with diethylchlorophosphite (Scheme 22) [65]. Compound **66** can be handled in air. No hydrolysis was observed when the compound was dissolved in wet $CDCl_3$.



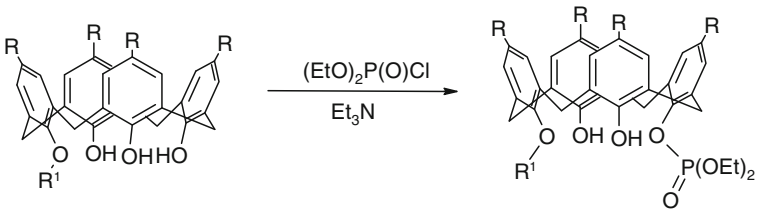
65 **66**

Scheme 22 Phosphorylation of the methylolcalixarene

4 Calixarenes Bearing P(V) Phosphorus Groups at the Lower Rim

4.1 Calixarene Phosphates

Calix[4]arenes **68** having one or two diethoxyphosphoryl groups at the lower rim have been synthesized via phosphorylation of the calix[4]arenes **67** by diethylchlorophosphate in the presence of triethylamine (Scheme 23) [67,68]. Insertion of the second substituent occurs regioselectivity, exclusively into the distal position.



67a-e

a: R=R¹=H
b: R=t-Bu, R¹=H
c: R=C(O)$C_{11}H_{23}$, R¹=H
d: R=H, R¹=Et
e: R=t-Bu, R¹=Et

68a-e

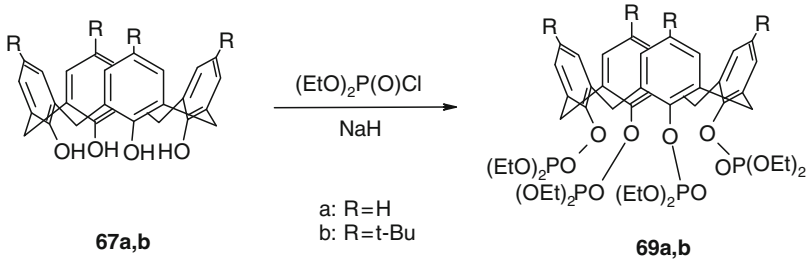
a: R=H, R¹=P(O)(OEt)$_2$
b: R=t-Bu, R¹=P(O)(OEt)$_2$
c: R=C(O)$C_{11}H_{23}$, R¹=P(O)(OEt)$_2$
d: R=H, R¹=Et
e: R=t-Bu, R¹=Et

Scheme 23 Selective phosphorylation of calix[4]arenes by diethylchlorophosphate

Detailed study of phosphorylation of *p-tert*-butylcalix[4]arene **67b** with diethylchlorophosphate in the presence of triethylamine in chloroform showed that along with the *cone* conformation, the *1,2- alternate* conformer is also formed where the phosphorylated benzene rings are directed to different sides of the principal plane of the macrocycle [67]. However, the phosphorylation of *tert*-butyl-depleted calix[4]arene **67a** proceeds under similar conditions stereospecifically, yielding the *cone* conformer of calixarene **68a** exclusively.

Calix[4]arenes **69** containing four dialkoxyphosphoryl groups at the lower rim have been synthesized by treatment of the starting tetrahydroxycalix[4]arenes **67a**,**b** with diethylchlorophosphate in the presence of excess of sodium hydride (Scheme 24) [69,70].

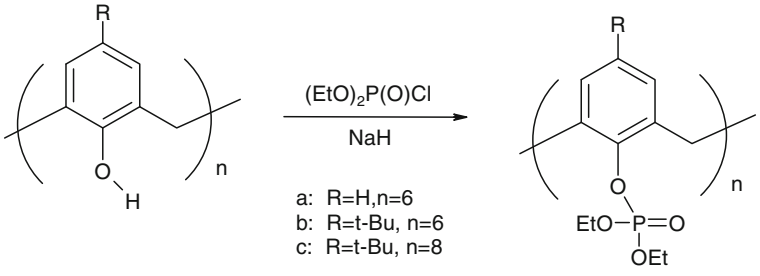
Calix[6]arenes **71a**,**b** and calix[8]arene **71c**, which contain six or eight phosphoryl groups, were synthesized from the reaction of the corresponding hydroxycalix[6,8]



67a,b **69a,b**

Scheme 24 Phosphorylation of calix[4]arenes by diethylchlorophosphate

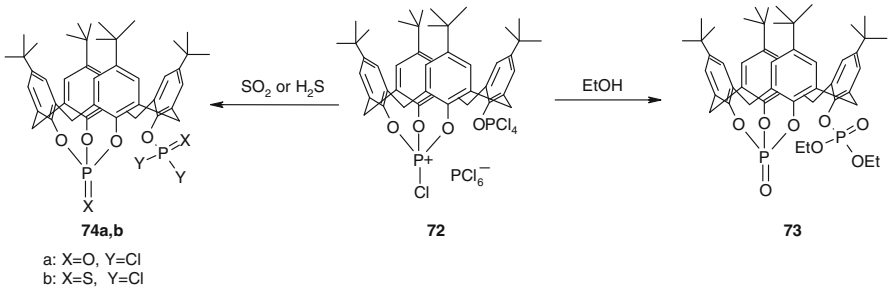
arenes **70a–c** with diethylchlorophosphate and sodium hydride (Scheme 25) [71–73].



70a-c **71a-c**

Scheme 25 Phosphorylation of calix[6]arenes and calix[8]arenes by diethylchlorophosphate

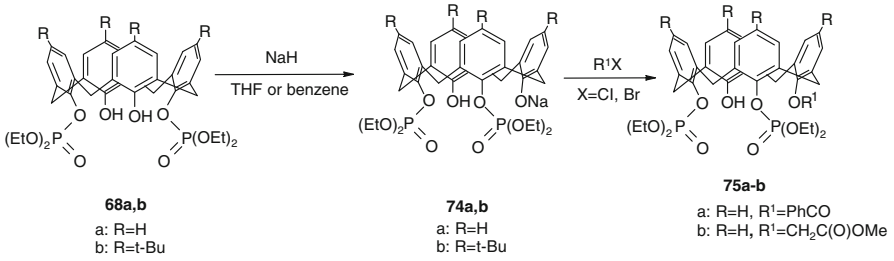
Calixarene phosphonium salt **72**, formed from *tetr*-butylcalix[4]arene **67b** and phosphorus pentachloride, reacts with ethanol, sulfur dioxide and hydrogen sulfide to give the corresponding calixarene diphosphates **73** and **74a** or calixarene thiophosphate **74b** (Scheme 26) [74–76].



Scheme 26 Transformations of calixarene phosphonium salt **72**

4.1.1 Inherently Chiral Calixarene Phosphates

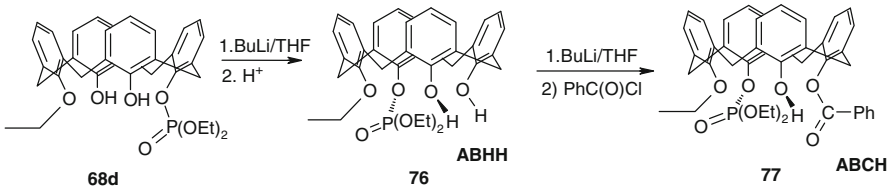
Phosphoryl groups of the calixarenes **68** demonstrate remarkable mobility. Phosphorotropic isomerization of the distally substituted diphosphorylcalixarenes **68** proceeds smoothly under the influence of 1 mol of sodium hydride in THF or benzene solution and leads to the proximally substituted diphosphorylcalixarenes **74** (Scheme 27) [77,78]. Inherently chiral calixarenes **75a**,**b** with an **AABH** substitution type possessing no symmetry plane were obtained by following alkylation or acylation of salt **74**.



Scheme 27 Phosphorotropic isomerization of the distally substituted diphosphorylcalixarenes

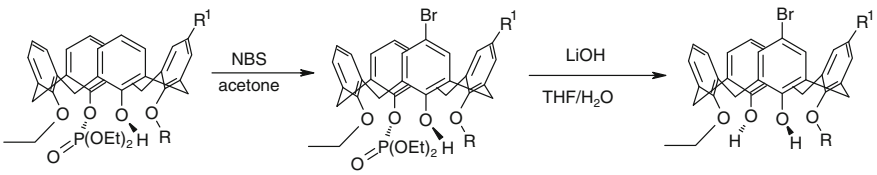
The interaction of 25-ethyl-27-diethoxyphosphorylcalix[4]arene **68d** with 1 mol of *n*-BuLi also leads to migration of the diethoxyphosphoryl fragment to the proximal position from the distal one (Scheme 28) [79,80]. Hydrolysis of the lithium salt using a dilute hydrochloric acid leads to the formation of chiral calixarene **76** with an **ABHH** substitution type at the macrocycle lower rim. Inherently chiral

calixarene **77** of **ABCH** type was obtained by the acylation of calixarene **76** with benzoyl chloride (Scheme 28). The acylation proceeds regioselectively and results in the formation of isomer **77** with proximal positioning of benzoyl and phosphoryl groups.



Scheme 28 Synthesis of inherently chiral calixarene phosphate **77**

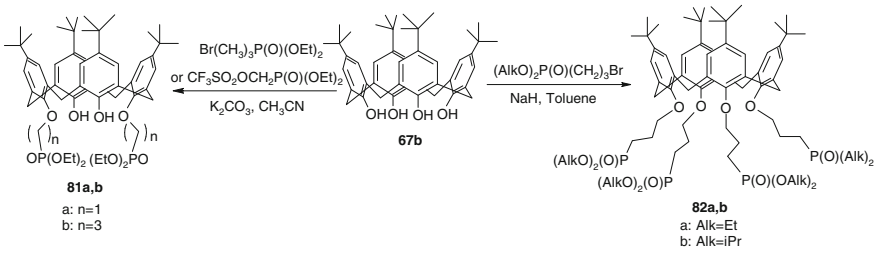
Chiral calixarenes are typically obtained by means of asymmetric arrangement of substituents at the upper or lower macrocycle rim. Phosphorotropic isomerization opens convenient methods for the synthesis of such calixarenes, the chirality of which is induced by the asymmetric superposition of the substituents at the lower and upper rims. For example, inherently chiral calixarenes **80a** with a $_{\mathbf{AHHH}}^{\mathbf{HHBH}}$ substitution pattern and calixarene **80b** with a $_{\mathbf{AHHH}}^{\mathbf{HBHH}}$ substitution pattern, were obtained by bromination of the calixarenes **78** at the wide rim, followed by hydrolytic cleavage of the phosphoryl or acyl groups from bromides **79** [81] (Scheme 29).



Scheme 29 Synthesis of inherently chiral calixarenes **80**

4.2 Calixarene Phosphonates

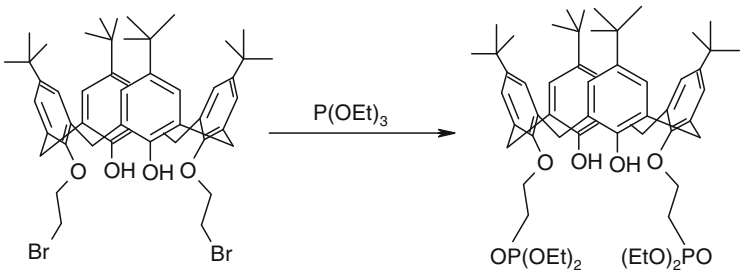
Calix[4]arenes **82** bearing four phosphonate groups at the lower rim were prepared by the Williamson alkylation of *p-tert*-butylcalix[4]arene **67b** with dialkyl (3-bromopropyl)phosphonate in the presence of large excess of sodium hydride (Scheme 30) [82–84].



Scheme 30 Synthesis of the calixarene phosphonates by the Williamson alkylation

Calixarene diphosphonate **81a** was prepared by alkylation of *p-tert*-butylcalix[4] arene **67b** with a triflate derivative of methylolphosphonate. Attempts to use less reactive alkylating agents did not afford the disubstituted product under the conditions employed [85]. Compound **81b** was prepared by alkylation of *p-tert*-butylcalix[4]arene **67b** with diethyl 3-bromopropylphosphonate under mild conditions in refluxing acetonitrile.

Calixarene bisphosphonate **84** was prepared by the Arbuzov reaction of bis-bromoethylcalixarene **83** with triethylphosphite (Scheme 31). Attempts to alkylate *p-tert*-butylcalix[4]arene with diethyl 2-bromoethylphosphonate in acetonitrile–K_2CO_3 failed and resulted in complete decomposition of the reagent and formation of diethylvinylphosphonate.

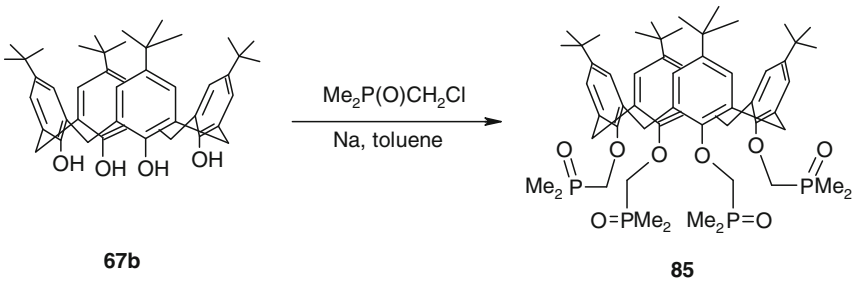


Scheme 31 Synthesis of calixarene phosphonate **84** by the Arbuzov reaction

4.3 Calixarene Phosphine Oxides

The lower-rim substituted calix[4]arene tetraphosphine oxide **85** has been synthesized with 46% yield via the Williamson reaction by refluxing the tetrasodium derivative

of *p-tert*-butylcalix[4]arene **67b** and chloro(dimethylphosphinoyl)methane in toluene or xylene (Scheme 32) [86].

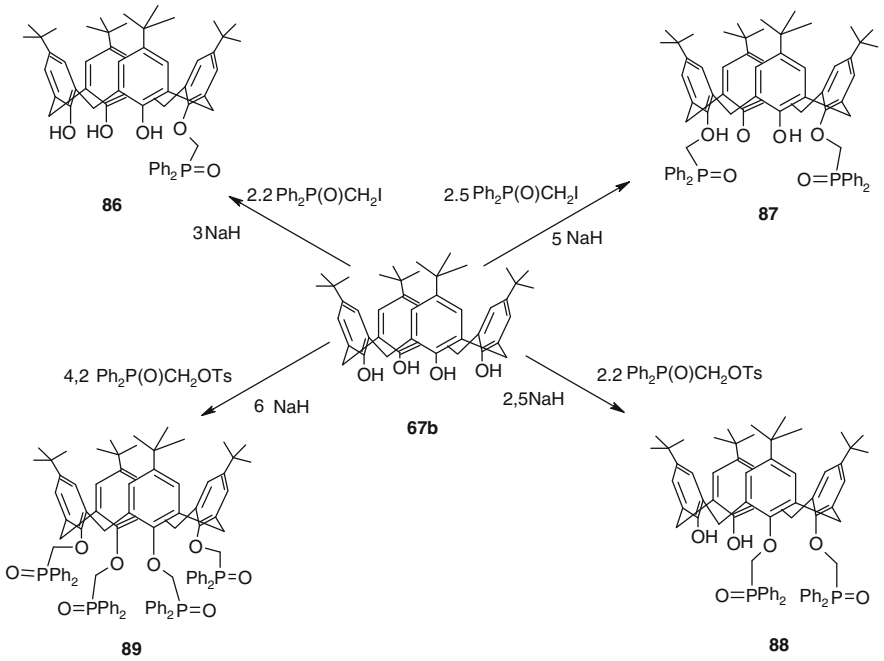


67b **85**

Scheme 32 Synthesis of calix[4]arene tetraphosphine oxide **85** by the Williamson reaction

Calix[4]arenes **86–89** containing one, two (in proximal or distal position) and four $CH_2P(O)Ph_2$ groups at the lower rim have been prepared from *p-tert*-butylcalix[4]arene **67b** (Scheme 33) [87,88].

It was found that the rate of phosphorylation is dependent upon the nature of the leaving group in the alkylation reagent. In particular, there were marked differences in the rates of the alkylation with $Ph_2P(O)CH_2I$ and $Ph_2P(O)CH_2OTs$, which could

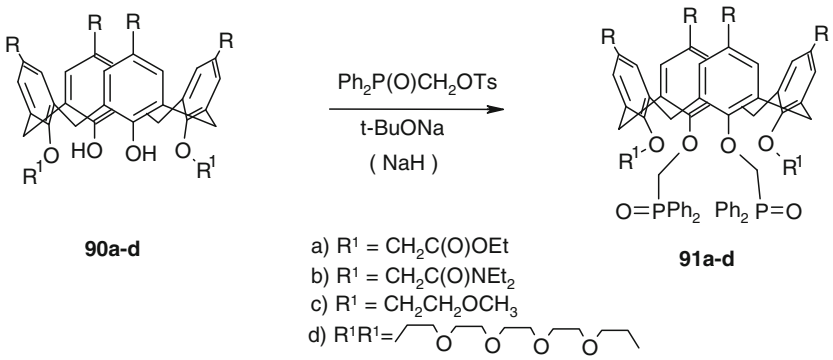


Scheme 33 Synthesis of calix[4]arene tetraphosphine oxides **86–89** by the Williamson reaction

be exploited to prepare calixarenes with the required number of phosphine oxide substituents. Using this approach, together with careful selection of the concentration and type of deprotonating agent, it is possible to selectively prepare a range of the lower rim-modified calixarenes.

Reaction of disubstituted calixarenes **90** with 2 equiv. of *t*-BuONa or NaH and subsequent treatment with 2 equiv. of $Ph_2P(O)CH_2OTs$ yielded the corresponding calixarene diphosphine oxides **91**, containing distally positioned ester, carbamoyl, ether or crown ether functions (Scheme 34) [88–91].

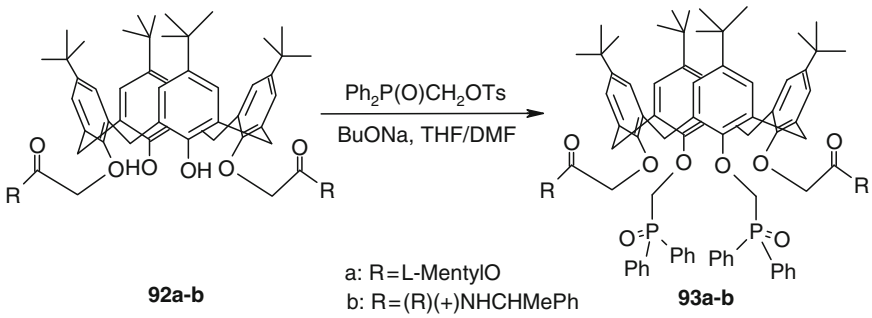
It has been found [89] that the use of *t*-BuONa as a base is a crucial point for the selective formation of a mixed tetra-alkylated *cone* conformer starting from a distally dialkylated *cone* precursor. On using *t*-BuOK instead of *t*-BuONa, the *partial cone* isomer of the calixarene **91a**, in which one phosphoryl group is positioned *anti* with respect to the three other pendant groups, was formed selectively.



Scheme 34 Synthesis of disubstituted calix[4]arene tetraphosphine oxides **90**

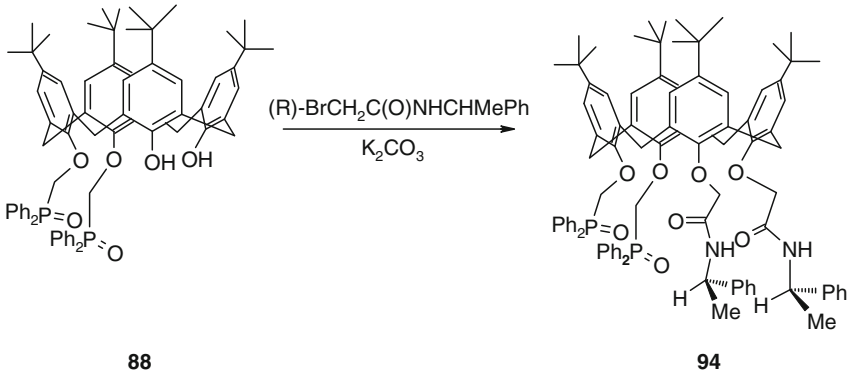
4.4 Chiral Calixarene Phosphine Oxides

Calixarene diphosphine oxides **93** functionalized distally by either l-menthyloxycarbonylmethyl or (R)-(+)-*N*-(2-phenylethyl)carbamoylmethyl fragments were synthesized by treatment of the chiral precursors **92** with 2 equiv. of $Ph_2P(O)CH_2OTs$ (Scheme 35) [90,92].



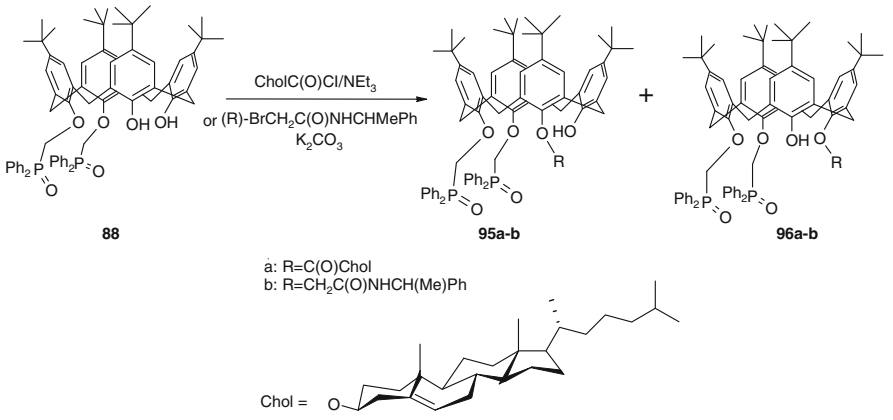
Scheme 35 Synthesis of the distally substituted chiral calixarene phosphine oxides

Calixarene **94**, containing two proximal phosphine oxide groups and two chiral 2-phenylethylcarbamoylmethyl groups, was obtained by dialkylation of the calixarene disphosphine oxide **88** with chiral (R)-(+)-*N*-(2-phenylethyl)carbamoylmethylbromide (Scheme 36) [93].



Scheme 36 Synthesis of the proximally substituted chiral calixarene phosphine oxides

An equimolar diastereomeric mixture of inherently chiral calixarene diphosphine oxides **95a** and **96a** was synthesized by acylation of calixarene **88** bearing proximal diphosphine oxide groups with cholesteryl chloroformiate (Scheme 37). The attempt of the authors to separate the obtained diastereomeric mixture by column chromatography on silica gel failed, because of the close R_f values of the diastereoisomers [93].

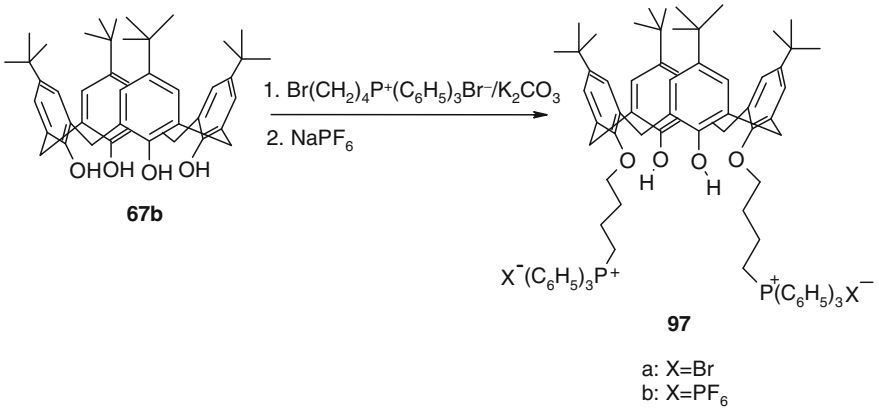


Scheme 37 Alkylation of the proximally substituted calixarene phosphine oxide

Attempts to separate by column chromatography an equimolar mixture of diastereoisomers **95b** and **96b** obtained by alkylation of calixarene disphosphine oxide **88** with chiral R-(+)-*N*-2-phenylethylcarbamoylmethylbromide were, however, successful [93].

4.5 Calixarene Phosphonium Salts

Calix[4]arenes **97a** bearing two alkytriphenylphosphonium groups have been prepared by reaction of *p-tert*-butylcalix[4]arene **67b** with 2 equiv. of commercial 4-bromobutyltriphenylphosphonium bromide in the presence of 1 equiv. of K_2CO_3 in refluxing acetonitrile for 9 h (Scheme 38) [94]. For the efficient anion complexation, salt **97a** was treated with $NaPF_6$ in chloroform with the formation of **97b**.



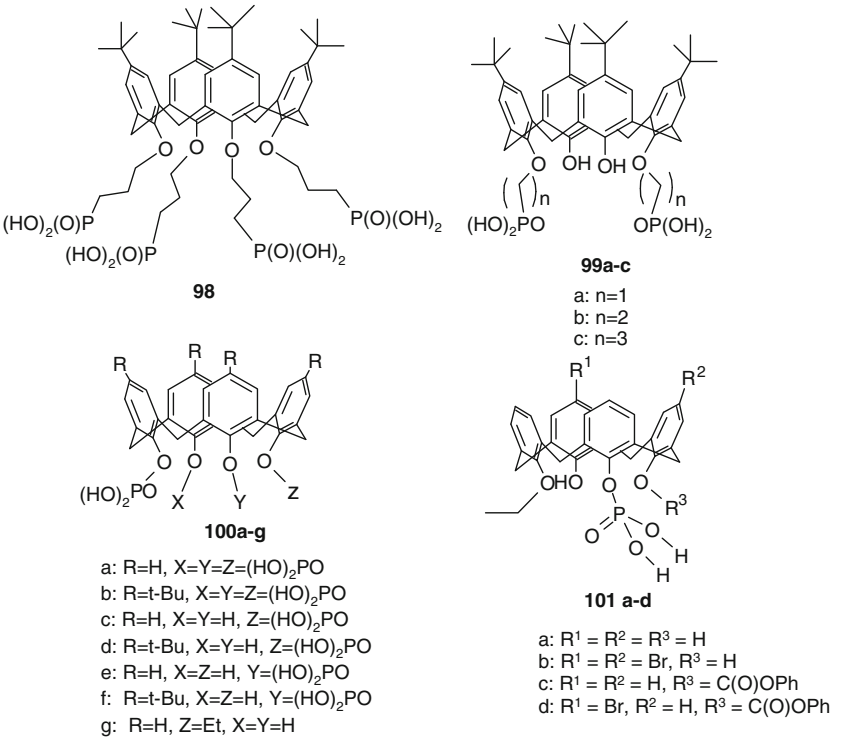
Scheme 38 Synthesis of the calixarene phosphonium salts

4.6 Calixarene Phosphoric and Phosphonous Acids

Calixarenes **98** and **99** (Scheme 39), in which the phosphonic acid groups are connected to the calixarene platform by a methylene, ethylene or propylene bridges, were synthesized by subsequent treatment of the corresponding calixarene phosphonates **81**, **82** and **84** with Me_3SiBr and methanolysis of the silyl esters formed [82–85].

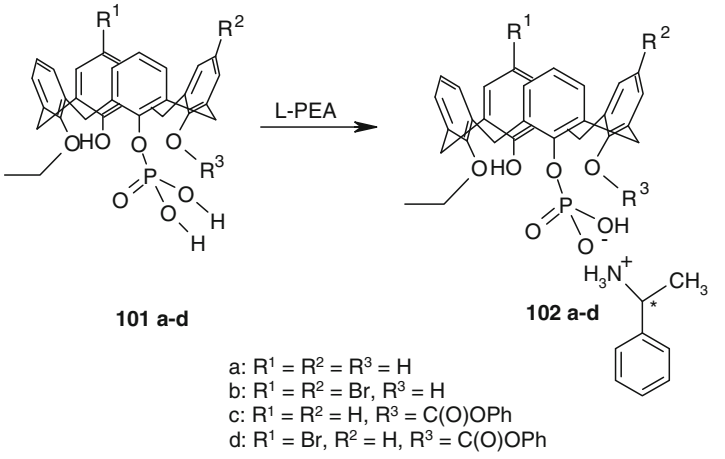
Calixarene phosphates **68**, **69**, **75**, **76**, **77** and **79** were transformed into the corresponding calixarene phosphoric acids **100** and **101** (Scheme 39) after processing with trimethylbromosilane and methanol [79].

Because design of chiral receptors requires optically pure compounds, the development of methods of enantioseparation of inherently chiral calixarene has garnered



Scheme 39 Calixarene phosphoric and phosphonous acids

much attention [95]. For the separation, calixarene phosphorus acids **101** were transformated into diastereomeric salts **102** by the reaction with l-phenylethylamine (Scheme 40) [79,96]. Salts **102** dissociate weakly in polar solvents. This enables



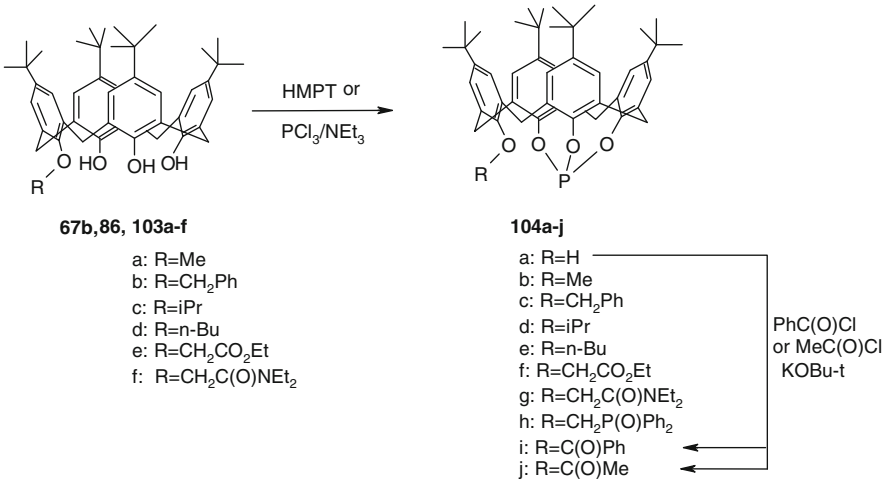
Scheme 40 Synthesis of the diastereomeric salts of calixarene phosphoric acids

separation of the diastereomers by normal HPLC techniques, without resorting to chiral columns [79,96].

5 Calixarenes Bearing P(III) Phosphorus Groups at the Lower Rim

5.1 Calixarene Phosphites

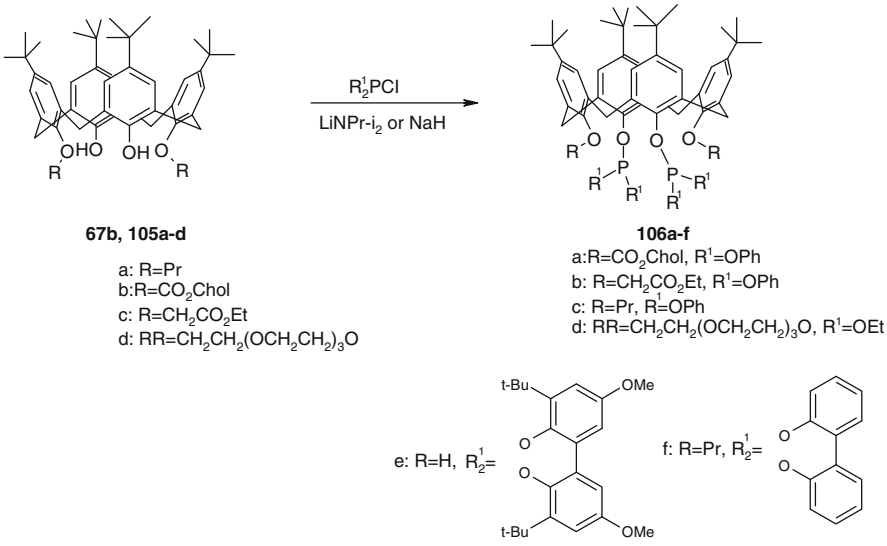
Calix[4]arene phosphite **104a** was synthesized by Lattman [97,98] using the reaction of *p-tert*-butylcalix[4]arene **67b** with hexamethylphosphorus triamide (HMTP). In the presence of amine bases, **104a** was allowed to react with acyl chlorides with formation of acylated calixarene phosphites **104h**,**i** (Scheme 41) [99].



Scheme 41 Synthesis of calixarene phosphites **104**

Calixarene phosphites **104b–e** were synthesized by the reaction of monoalkylated calix[4]arenes **103a–d** with HMPT in the presence of a mild acid like tetrazole (Scheme 41) [99]. The calixarene phosphites **104f–h** were also obtained in high yields through the reaction of monofunctionalized *p-tert*-butylcalix[4]arenes **86** and **103e–f** with PCl_3/NEt_3 (Scheme 41) [100]. Calixarene phosphinoxide-phosphite **104h** is remarkably stable towards aqueous NaOH, but the presence of slightly acidic water (NH_4Cl/H_2O) results in cleavage of a P–O bond and selective formation of hydrophosphoryl function. Slow oxidation occurred when a solution of **104h** was allowed to stand in air for several days, affording the mixed phosphineoxide-phosphate.

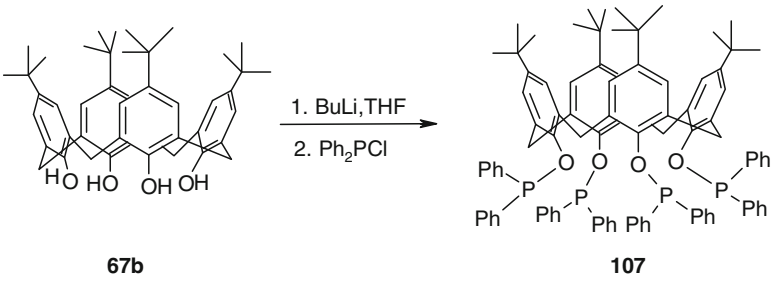
Calixarenes **106** containing two phosphite groups were synthesized by the interaction of corresponding tetrahydroxycalixarene **68b** or dihydroxy calixarenes **105a–d** with dialkylchlorophosphites in presence of a strong base (Scheme 42) [101–103].



Scheme 42 Synthesis of calixarene phosphites **106**

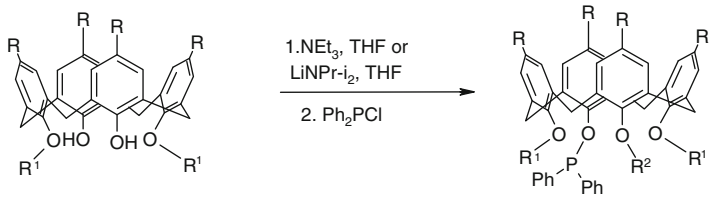
5.2 Calixarene Phosphinites

Calixarene tetraphosphinites **107** were prepared by the interaction of calixarene **67b** tetralithium salt with Ph_2PCl (Scheme 43) [104]. This reaction can be carried out either in two steps, with isolation of the lithium salt or as a one-pot procedure.



Scheme 43 Synthesis of calixarene tetraphosphinite **107**

Calixarenes **109** containing one or two diphenylphosphinite groups were synthesized by the interaction of hydroxycalixarenes **67a** and **108** with diphenylchlorophosphine in the presence of the corresponding bases (Scheme 44) [105–108]. In each case, the key step is the deprotonation of one or two phenol moieties followed by the reaction with diphenylchlorophosphine. The reaction of diesters **108c–d** with a large excess of NEt_3 in THF and subsequent addition of Ph_2PCl (1 equiv.) gave selectively the monophosphinites **109a-b**. All attempts to insert a second Ph_2P group using NEt_3 were unsuccessful. The formation of the bis-phosphinites **109c–k** requires the use of a strong base such as $LiN(Pr\text{-}i)_2$ or BuLi.



67a, 108a-g

a: R=t-Bu, R^1=Et
b: R=t-Bu, R^1=Pr
c: R=H, R^1=CH_2CO_2Et
d: R=t-Bu, R^1=CH_2CO_2Et
e: R-t-Bu, R^1=R^2=CH_2CO_2Me
f: R=t-Bu, R^1=CH_2CO_2(-)menthyl
g: R=t-Bu, R^1=CO_2Chol

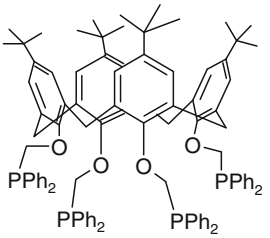
109a-k

a: R =H, R^1=CH_2CO_2Et, R^2=H
b: R=t-Bu, R^1=CH_2CO_2Et, R^2=H
c: R=H, R^1=H, R^2=PPh_2
d: R=t-Bu, R^1=Et, R^2=PPh_2
e: R=t-Bu, R^1=Pr, R^2=PPh_2
f: R-t-Bu, R^1=CH_2CO_2Me, R^2=PPh_2
g: R=t-Bu, R^1=CH_2CO_2Et, R^2=PPh_2
h: R=H, R^1=CH_2CO_2Et, R^2=PPh_2
j: R=t-Bu, R^1=CH_2CO_2(-)menthyl, R^2=PPh_2
k: R=t-Bu, R^1=CO_2Chol, R^2=PPh_2

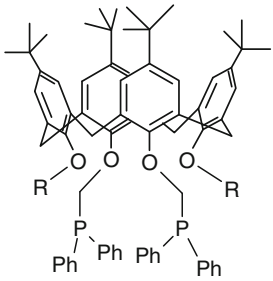
Scheme 44 Synthesis of calixarene phosphinites **109**

5.3 Calixarene Phosphines

Calix[4]arenes **110–113** bearing phosphino groups at the lower rim of the macrocycle were synthesized by reduction of the corresponding calixarene phosphine oxides **89**, **91a–c**, **93** and **94**, with $PhSiH_3$ at 100 °C (Scheme 45) [89,90,92,109]. Calix[4]arenes phosphines **115**, in which the phosphino groups are two carbon atoms away from the phenolic oxygens, have been obtained through exposure of the calixarene di- or tetratosylates **114** to sodium diphenylphosphide or lithium diphenylphosphide in dioxane-THF (Scheme 46) [92,110–112]. Under similar conditions, calix[6,8]arenes containing six or eight phosphino groups connected to the macrocyclic platform by ethylene spacers were obtained [110].

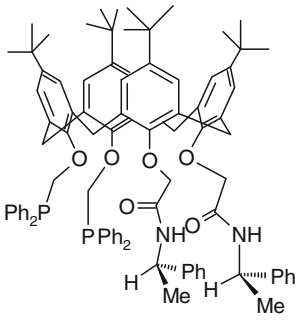


110



111a-e

a: R=CH_2CO_2Menthyl
b: R=CH_2CO(R)(+)NHCHMePh
c: R=CH_2CO_2Et
d: R=CH_2CONEt_2
e: R=CH_2CH_2OEt



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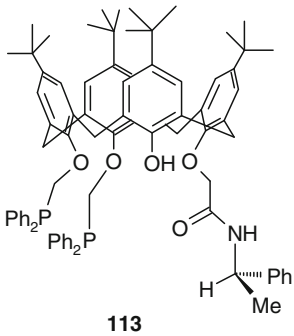
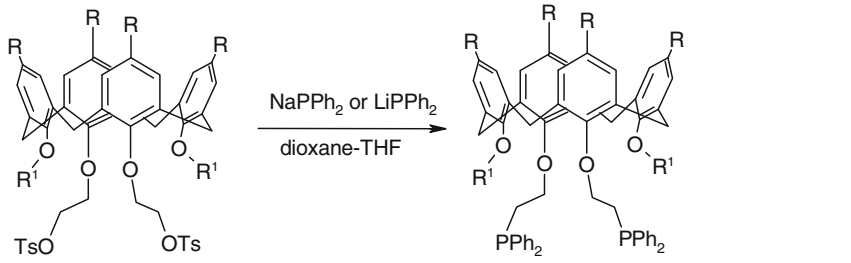


113

Scheme 45 Calixarene phosphines



114a-e

a: R^1=CH_2CH_2OTs, R=H
b: R^1=CH_2CH_2OTs, R=t-Bu
c: R^1=CH_2CH_2OMe, R=t-Bu
d: R^1=Pr, R=H (1,3-alternate)
e: R^1=CH_2CH_2OTs, R=H (1,3-alternate)

115a-e

a: R^1=$CH_2CH_2PPh_2$, R=H
b: $R^{1'}$=$CH_2CH_2PPh_2$, R=t-Bu
c: R^1=CH_2CH_2OMe, R=t-Bu
d: R^1=Pr, R=H (1,3-alternate)
e: R^1=$CH_2CH_2PPh_2$, R=H (1,3-alternate)

Scheme 46 Synthesis of calix[4]arene phosphines **115**

6 Properties of the Phosphorus-Containing Calixarenes

6.1 Complexation of Alkali and Alkali Earth Metals

Calix[4]arene tetraphosphates **69a**,**b** have a high affinity for lithium ions [113,114]. The stability constants in THF solutions for **69a** are 4.2×10^6 for Li^+, 4.4×10^5 for Na^+, 8.7×10^4 for K^+ and 6.1×10^4 for Cs^+. A cavity formed simultaneously by four oxygen atoms of the P=O groups and four phenolic oxygen atoms is quite suitable for incapsulation of the lithium cation, but it is small for the Na, K and Cs cations.

The diphosphine oxide/diamide and tetraphosphine oxide substituted *p-tert*-butylcalix[4]arenes **91b** and **89** in the *cone* conformation were tested for their complexing affinity and transport ability of alkali metal ions [115,116]. Both compounds form 1:1 complexes with alkali ions. The strong complexing ability of the amide functionality was confirmed by the higher affinity of **91b** for Li^+, Na^+, and K^+ relative to **89**. NMR studies of the complexation of **91b** suggested that Na^+ and K^+ were incapsulated in the cavity to form a C_2 symmetrical complex. Both have transport efficiencies similar to their respective complexing abilities: Na^+=Li^+>K^+>Rb^+>Cs^+ for **91b** and K^+>Rb^+>Li^+>Cs^+>Na^+ for **89**.

In recent years, there has been considerable interest in the development and application of solid lipid nanoparticles (SLNs) as alternative transport systems to liposomes [117], polymeric nanospheres [118] or nanocapsules [119]. They have seen application in cosmetics, drug delivery and drug targeting.

Amphiphilic calix[4]arene phosphonic acids **41c**,**d** form stable monolayers at the air–water interface and show clear interactions with Na^+, Mg^{2+} and Ca^{2+} ions with formation of SLNs (d = 150–12,00 nm) in aqueous solutions and on the air–water interface. Noncontact mode AFM images of the SLNs show that some aggregation may occur and that the size of the aggregates is much greater than that observed for the liposomes based on amphiphilic calixresorcinarenes [120] or amphiphilic cyclodextrins [121].

The ionophoric properties of the calixarene phosphonates **82a**,**b** were studied by using them as the active material in electrochemical sensors and ion-selective membrane electrodes [83,122]. Complexation behaviour towards alkali, alkali earth and some transition metal ions (Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}) were studied. Both compounds are highly calcium-selective, irrespective of the plasticizer used.

6.2 Complexation of Transition Metals

The complexing ability of the tetrasodium salt of calixarene acid **42b** towards Cu(I) salts was observed in water by UV–vis spectroscopy [29]. The addition of $Cu(MeCN)_4PF_6$ to an aqueous solution of the ligand resulted in the formation of a 1:1 complex, characterized by the specific metal-to-ligand charge transfer band at ca. 455 nm encountered in tetrahedral copper(I)/heterocycle complexes.

Monomeric and polymeric 1:2 complexes of calix[4]arene tetraphosphine oxide **7h** with Co(II) or Ni(II) nitrates were synthesized with almost quantitative yields

by the reaction of salts $M(NO_3)_2 \cdot 6H_2O$ (M=Co, Ni) with **7h** [28]. In the monomeric complexes each metal cation is coordinated by two bidentate NO_3 ligands, as well as by two proximal P=O groups at the calixarene skeleton. In the nickel metallopolymer, one sort of cation is bound by the two proximal P=O groups but other cations link neighbouring calixarene molecules through P=O–Ni–O=P chains.

Calixarene phosphine **107**, on reacting with the iron(0) cyclooctene carbonyl complex $[Fe(CO)_3(h^2\text{-}C_8H_{14})_2]$ in a hexane solution at low temperature, afforded structure **107** $[Fe(CO)_3]_2$ [104]. The phosphinocalix[4]arene acted as a bidentate ligand with each pair of PPh_2 groups complexing an $Fe(CO)_3$ fragment in a *cis* configuration. It was also determined that each Fe atom was complexed in a pseudo-trigonal bipyramidal geometry.

6.3 Complexation of Lanthanides and Actinides

The ability of calixarenes **32**, which have four CMPO $[NHC(O)CH_2P(O)Ph_2]$ groups at the upper rim, to extract Eu(III), Th(IV), Np(V), Pu(IV) and Am(III) from a 1 M HNO_3 solution into dichloromethane or *o*-nitrophenyl hexyl ether was studied [43,44]. The calixarene-based complexants are superior to the classical CMPO (i-$Bu_2NC(O)CH_2P(O)(Oct)Ph$) in their complexing ability because of cooperativity among the ligating groups within one molecule. In a representative example, a 10^{-4} M solution of **32f** in dichloromethane complexed 54% of the Th(IV) from an initial concentration of 10^{-4} M in 1 M HNO_3. The CMPO complexed only 12% Th(IV), even though its initial concentrations were set at 10^{-2} M to obtain a measurable level of complexation. Studies in supported liquid membranes show the calixarenes to be more efficient transport agents than CMPO.

Binding properties of the tetraalkoxycalix[4]arenes **32a**, **37** and **38** substituted at the upper rim with four CMPO [$–NHC(O)CH_2P(O)Ph_2$ or $–CH_2P(O)(Ph)CH_2C(O)NBu_2$] and diphosphine dioxide functions towards trivalent lanthanide and actinide cations were investigated by complexation studies in methanol and liquid–liquid extraction studies in the context of the radiowaste partition [49].

Calixarenes **37** and **38** extract Yb^{3+} (39 and 48% correspondingly) and Gd^{3+} (66 and 9% correspondingly) more efficiently than calixarene CMPO **32a** (6.6 and 0% correspondingly), but extract La^{3+} and Eu^{3+} less well (98 and 64% for compound **32a**, 81 and 13% for compound **37**) [49].

The extraction of americium and europium by calix[4]arenes **7e–k** with an $–CH_2P(O)Alk_2$ group at the upper rim and by calixarene phosphonic acids **42a** was investigated [27,123]. The calix[4]arene phosphine oxides and phosphonic acid show a considerable cooperative effect and extract Am and Eu approximately 200 times better than the corresponding modelling acyclic compounds. Distribution coefficients markedly depend on the electronic features of the phosphorus atom substituents, length of the alkyl substituents and vary in the order $Bu_2P(O) > PhAlkP(O) > Ph_2P(O) > Ph(i\text{-}PrO)P(O) > (i\text{-}PrO)_2P(O)$.

Calixarene phosphonous acids **98** and **99** and calixarene phosphonate **82a** were used as extractants for certain lanthanide ions (La^{3+}, Eu^{3+}, Yb^{3+}) [82,85]. The extraction studies show that calixarene phosphonous acids **98** and **99** are efficient extraction

agents for the larger lanthanides, and much more efficient than CMPO. Because of the presence of groups that can be deprotonated, the extraction behaviour of the ligands **98** and **99** decreases with increasing acidity. The extraction efficiencies decrease with increasing length of the CH_2 spacer; the dependence is not monotonic, and an extraordinary selectivity was observed for the extractions of the heavy lanthanides by **99c**. The separation factor for Yb^{3+} over La^{3+} differs by nearly three orders of magnitude. The extraction efficiency of Ln^{3+} for all of the ligands studied increased significantly with decreasing ionic radius. Compound **82a** did not extract Ln^{3+} ions into chloroform solutions from the aqueous phases (pH 2–5.5).

Calixarene tetraphosphine oxide **85** interacts with trivalent lanthanium ions (La, Eu and Tb) in acetonitrile to yield both 1:1 ($\log \beta_1 = 11.4 \pm 1.5$) and 1:2 ($\log \beta_2 = 19.6 \pm 1.8$) complexes [86]. Calix[6]arene **44d** possessing six methylenephosphonic acid groups bonded to the aromatic rim were shown to have a high affinity for the uranyl ions [124]. A 1:1 complex was formed with a stability constant of $10^{17.5}$ M^{-1}.

6.4 Complexes of Silver, Gold and Platinum Group Metals and Their Catalytic Properties

Calixarenes **89** and **91a,b**, with phosphine oxide ligands [125] have been tested for their ability to complex Ag(I) and their performances compared to that of dicyclohexano-18-crown-6. The affinity for Ag(I) was found to be in the order **91b** > crown = **89** > **91a**. The good performance of **91b** was attributed to the strong coordinating ability of the amide groups, the large number of oxygens available for complexation, and a better matching of the cavity size generated by the four pendant arms for Ag(I). The NMR and IR data substantiated an encapsulated Ag(I) ion in the ionophoric cavity of **91b**. It was also possible to complex trace amounts of Ag(I) from a large excess of Cu(II). Transport studies with **91b** gave results comparable to those of the complexation studies.

Reaction of $AgBF_4$ with calix-crown **106d** resulted in quantitative formation of the complex [Ag**106d**]BF_4 in which the Ag(l) ion lies inside the cavity constituted by the crown ether fragment and the two phosphorus arms.

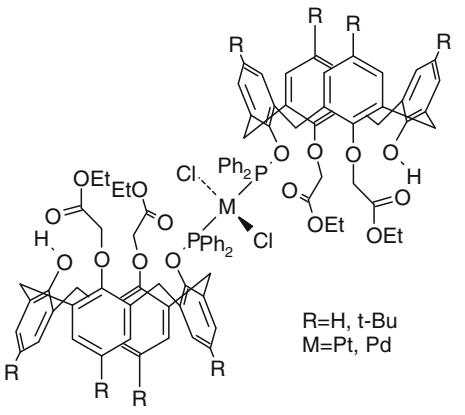
The binding properties of calix[4]arene phosphine **110** to gold have been investigated [126,127]. Reaction of **110** with [AuCl(THT)] (THT = tetrahydrothiophene) in a 1:4 ratio forms a tetranuclear complex where the Au(I) is bound to the phosphorus(III) atoms ($\log \beta_1 = 4.4$). Reaction of **110** with [AuCl(THT)] in a 1:1, 1:2 or 1:3 ratio yields a mixture with varying levels of auration. The coordinative properties of the disubstituted calixarenes diphosphines **111** with [Au(THF)(SC_4H_8)]BF_4, [PtH(Cl)(PPh_3)] and [Rh(CO)$_2$(THF)$_2$]BF_4 have been investigated [90,91,109,128].

The reaction of *1,3-alternate* calix[4]arenes phosphine ligands **115d**,**e** with [Rh(cot)$_2$]BF_4 (cot = cyclooctatetraene) produced the encapsulated rhodium complex, [Rh{(*P*,*P*)-diphen-calix[4]arene}]BF_4 [111,112]. As revealed by a single-crystal X-ray diffraction study, the rhodium centre has a bent coordination environment

with a P–Rh–P angle of 135.66(3)°. Palladation of **115d** employing $[Pd(MeCN)_4](BF_4)_2$, yielded the chelate palladium complex in which the palladium centre has a slightly bent configuration. Treatment of the **115d** with $Pd(cod)Cl_2$ (cod = cyclooctadiene) and $[Pd(h^3\text{-}C_4H_7)(THF)_2]BF_4$ leads to the isolation of the monometallic complexes. The reaction of **115e** with $AgBF_4$ produced the encapsulated two silver complexes $[Ag_2\{(P,P,P,P)\text{-tetraphen-calix[4]arene}\}](BF_4)_2$. The solid state structure shows that the encapsulated silver undergoes a substantial p-interaction with two opposite arene rings.

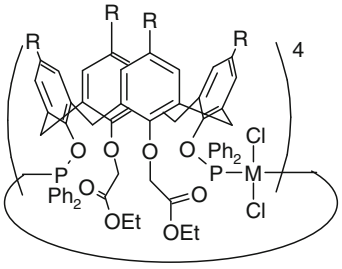
Calix[4]arene substituted with two ethoxycarbonylmethoxy and two diphenylphosphinomethoxy groups **111c** has been investigated for its ability to complex platinum, rhodium and ruthenium [89]. When reacted with $PtCl_2(PhCN)_2$ in THF, Pt(II) is chelated by the two P(III) donor atoms in a *cis* geometry. *Cis* chelation is also observed with rhodium. However, when $RuCl_3$ was reacted with CO followed by addition to the ligand **111c**, chelation of Ru(III) is achieved through a *trans* geometry.

The monophosphinito/diester calix[4]arenes **109a**,**b** form *trans*-$[MCl_2L_2]$ (L = ligand) complexes **116** (M = Pd(II) or Pt(II)), exclusively [106,107]. The *trans* arrangement of the chloride ligands was deduced from the presence of a single Pt–C1 absorption band in the far IR region. Selective formation of the *trans* complex may be due to the sterically demanding calixarene substituent.



R=H, t-Bu
M=Pt, Pd

116

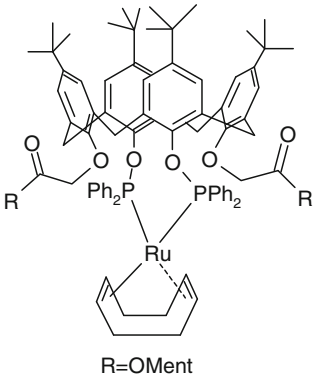


M=Pt, Pd

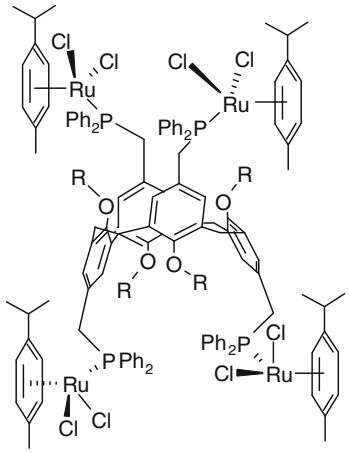
117

The reaction of 2 equiv. of the mixed diphosphinite-diesters **109g**,**h** with $[PtCl_2(PhCN),]$ in THF afforded tetrametallic complex **117**. The tetrameric nature of this compound was deduced from the molecular weight determination experiments (vapour-phase osmometry in CH_2Cl_2).

Chelating behaviour was observed when the chiral diphosphinite **109j** was treated with $[Rh(cod)(THF)]^+$. This reaction resulted in the formation of the monomeric complex **118**.



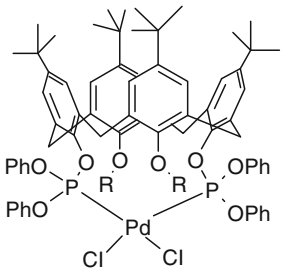
118



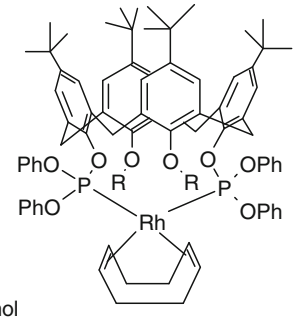
119

The reaction of *1,3-alternate* phosphinocalix[4]arene **64a** with 2 equiv. of $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2 solution afforded the tetranuclear ruthenium complex **119** in quantitative yield. The spectroscopic observations indicated that the compound **119** retained the original *1,3-alternate* conformation in solution state [30].

Palladium **120** and rhodium **121** complexes are formed from the reaction of calixarene diphosphite **106a** with 1 equiv. of $[PdCl_2(cod)]$ [101] and $[Rh(cod)_2]BF_4$, respectively.



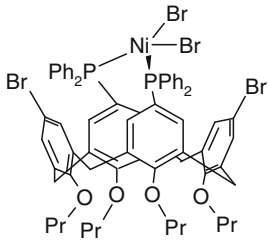
120



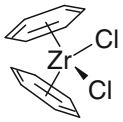
121

R = CO_2Chol

Diphosphinocalixarene **53b** form 1:1 chelate type complex **122** with $NiBr_2$ [129].



122



123

Authors have demonstrated that a mixture of **122** and zirconium complex **123** can, in combination with methylaluminoxane, be employed efficiently for producing linear low-density polyethylene either via orthogonal tandem catalysis or sequential two-step, one-pot catalysis. This provides a rare example of tandem copolymerization in which the copolymer produced contains only ethyl branches [129].

The hydroformylation of water-insoluble internal olefins has been realized in biphasic systems via the use of rhodium complexes of water-soluble calix[4]arenediphosphines **59** [66,130]. This catalytic system resulted in a good level of activity and reusability.

Reaction of **56b** with $[RuCl_2(p\text{-cymene})]_2$ resulted in the formation of the dinuclear complex **56b**$[RuCl_2(p\text{-cymene})]_2$ while the rhodium complex **56b**$[RhCl(norbornadiene)]_2$ was formed by reaction of **56b** with $[RhCl(norbornadiene)]_2$. Complex **56b**$[RhCl(norbornadiene)]_2$ catalyses hydroformylation of styrene (CO/H_2 = 1, P = 40 bar, 70 °C, styrene/Rh »585) in the presence of NEt_3, from which linear and branched aldehydes were obtained in a 9:91 ratio [65].

Treatment of calixarene diphosphines **52b** and **56a** with PdMeCl(cod), $PtCl_2$(cod) and $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$ gives polymeric phosphine-coordinated Pd(II) and Pt(II) species, respectively [62,64]. Calixarene **56a** reacts with $[RhCl(cod)]_2$ to give a di-rhodium complex that is an active catalyst for the hydroformylation of 1-octene and gives mostly nonanal and branched octanals with 90% yield [64].

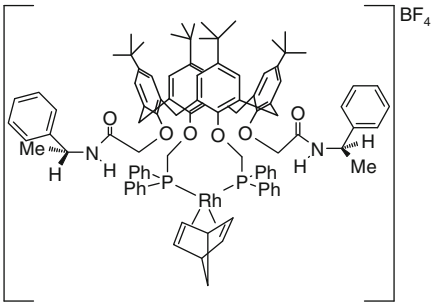
Proximal calixarene phosphines **51** and **60a**,**b** and their distal analogoue calixarenes **52a** and **62a**,**b** react with $[(cod)RhCl]_2$ to give a corresponding di-rhodium complex. The catalytic hydroformylation of terminal alkenes using Rh complexes has been investigated under various conditions. The TOFs are generally larger (up to 250 h^{-1}) for 1-hexene, but depend on the nature of the phosphine for styrene, vinyl acetate, vinyl benzoate and vinyl *p-tert*-butylbenzoate [63].

Chelating and catalytic properties of calixarene monophosphites **104a**,**b**,**d**,**f**,**g**,**h**,**j** were investigated [99,100,131]. The rhodium complexes of the calixarene monophosphites were tested as catalysts for 1-octene hydroformylation. The fastest catalysis occurred with phosphite **104d** (TOF ca. 8100). The activity decreases in the order **104d > 104j > 104h > 104f > 106b >106g** [99,100]. The rhodium complex

of **104a** catalyses hydroformylation of 1-hexene with high selectivities and high substrate conversion to aldehyde, but with poor regioselectivities [131].

The rhodium complexes of calixarene diphosphites **106a–d** and diphosphonites **109e**,**g**,**k** were synthesised in situ by reaction with $[Rh(acac)(CO)_2]$ as catalysts for the hydroformylation of 1-octene and styrene. It was shown that rhodium complexes of calixarene diphosphonites **109e**,**g**,**k** are more effective catalysts for hydroformylation of 1-octene (TOF = 1219) than the complexes of calixarene diphosphites **106a–d** (TOF = 1045). At the same time, rhodium complexes of calixarene diphosphite **106a–d** appeared to be more efficient at styrene hydroformylation catalysis than the complexes of calixarene diphosphonites **109e**,**g**,**k** (TOF = 789 and 210 correspondingly). It is remarkable that calixarenes **106a–d** and **109e**,**g**,**k** complexes significantly increase the content of linear aldehydes in comparison to non-calixarene phosphite complexes [101].

Rhodium **124** [90] and palladium **125** [92] complexes result from the reaction of calixarene diphosphine containing chiral amide substituents **111b** with $[Rh(norbornadiene)BF_4]_2$ or $Pd(\eta^3\text{-}C_3H_4Me)(THF)_2BF_4$. Rhodium complex **124** catalyses hydroformylation of styrene leading to a mixture of 2-phenylpropanal and 3-phenylpropanal in a 95:5 ratio. Such a high regioselectivity of hydroformylation is a first for rhodium phosphine catalysts [90].



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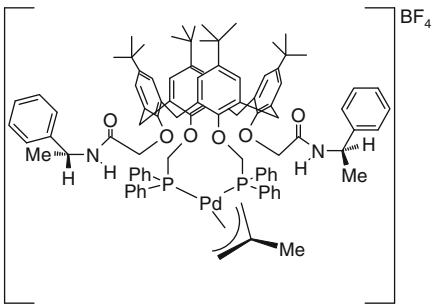
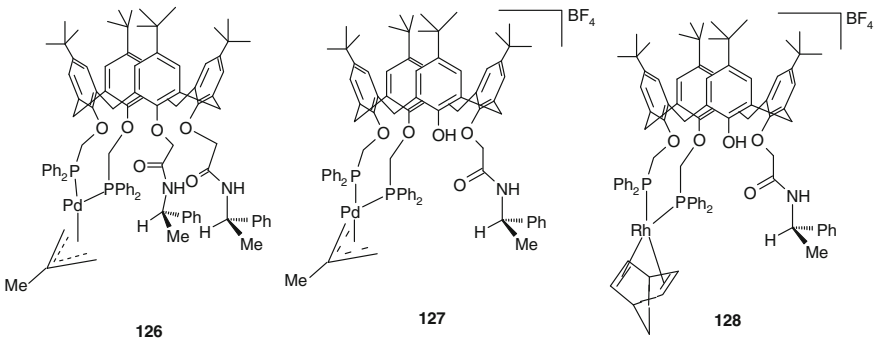


125

However, similar stereoselectivity is also observed in a case of rhodium complexes of calixarene diphosphines **111e** and **115c** [92].

The reaction of diphosphine **112** with $[Pd(Me\text{-}allyl)(THF)_2]BF_4$ results in the formation of stable palladium complex **126**, which was used as a catalyst for the alkylation of 1,3-diphenylprop-2-enyl acetate and dimethylmalonate in the presence of BSA (BSA = $Me_3SiOC(NSiMe_3)\text{-}CH_3$) [93].



126 127 128

The reaction of chiral calixarene diphosphine **113** with [Pd(Me-allyl)$(THF)_2BF_4$] or [Rh(bicycloheptadien)Cl]$_2$ and $AgBF_4$ resulted in palladium or rhodium chelate complexes **127** and **128** [93].

Palladium complex **127** was used as a catalyst for the stereoselective alkylation of 1,3-diphenylprop-2-enyl acetate by dimethylmalonate (e.e. 67%). At the same time, using palladium complexes of calixarene diphosphines **125** and **126**, having two similar distal or proximal (R)-(+)-*N*-(2-phenylethyl)carbamoylmethoxyl substituents, did not show significant asymmetric induction (e.e. is 0 and 16%, respectively). Rhodium complex **128** also efficiently catalyses the stereoselective hydrogenation of dimethylitaconate (TOF = 2000, e.e = 48%). At the same time, complex **126** is practically inactive for the same reaction (TOF = 10, e.e = 0%).

Thus, metal complexes of inherently chiral calixarenes with two proximal phosphine groups are more effective catalysts than their distal regioisomers. Also, an asymmetrically substituted macrocycle transmits chiral information to the catalytically active centre more efficiently than one consisting of only asymmetric carbon atoms as peripheral substituents.

6.5 Complexation of Organic Molecules

The formation of supramolecular complexes between calix[4]arene diphosphorus acid **100c** and a series of amino acids and metal salts has been investigated by electrospray mass spectrometry (ES/MS) combined with ^{1}H NMR [132]. From the NMR results, it was ascertained that the amino acids complex exterior to the cavity of the calixarenes. Multiple complexes between **100c**, amino acids and cations are observed by ES/MS. In particular, zinc forms strong tertiary complexes with cysteine, serine and histidine. Competition experiments involving mixtures of amino acids and **100c** in the presence of zinc show remarkable selectivity for the complex calix[4]arene-Zn^{2+}-histidine.

Complexation of calix[4]arene phosphonous acids **40b**, **41a** and **43** with herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) or atrazine (AT) in water has been

investigated by the reversed phase HPLC method [56]. The association constants of the 1:1 complexes in 820–5108 M^{-1} 2,4-D and 2624–6653 M^{-1} AT have been determined from the relationship between the capacity factor of the herbicides and concentration of the calixarene in the mobile phase. The association constants are dependent on the conformation and stereochemical mobility of the calixarene skeleton, the number of dihydroxyphosphoryl groups at the upper rim and the acid–base properties of the herbicides.

Calix[4]arenes **41a**,**b** and **39b**,**c**, bearing phosphonic acids or lithium methylphosphonate groups accordingly at the upper rim, form complexes with ephedrine, norephedrine and noradrenaline hydrochlorides in aqueous solution (K up to 145 M^{-1}) [20].

The pure racemic form and equimolar mixtures of racemic and meso-forms of the calixarene bis-a-hydroxymethylphosphonic acids **46a**,**c** were investigated as molecular receptors for l-amino acids and dipeptides using isothermal titration calorimetry [41,133]. The stability constants are in the range 3000–17,000 M^{-1} (25,000–45,000 M^{-1} for dipeptides). Racemic form **46a** leads to more stable complexes than the equimolar mixture **46c**. Analysis of the effect of pH on the stability constants confirms the presence of strong electrostatic interactions between the host and guest.

Calixarene tetraphosphonate **39a** forms highly stable molecular capsules with a complementary half-sphere of tetraaminocalix[4]arene in polar solvents [134]. Calixarene **39a** has high affinity in methanol for arginine and lysine derivatives (pK_a = 1.8) and is able to bind proteins in the stearic acid monolayer [135]. Due to these properties, calixarene **39a** was investigated as receptor for protein detection. "Naked eye" colour detection of proteins was achieved by embedding calixarene tetraphosphonate **39a** within vesicles and the chromatic polymer polydiacetylene [136]. Dramatic visible absorbance changes were induced through electrostatic interactions between the protein surface and the vesicle-incorporated hosts. The colorimetric assay constitutes a generic platform for high-sensitivity detection of soluble proteins and for evaluation of protein surface charge distribution.

The host–guest complexation of the upper rim diisopropoxyphosphoryl derivatives of dipropoxy- or tetrapropoxycalix[4]arenes **2**, **3**, **4d** and **5d** with uracil derivatives in methanol/acetonitrile/tetrahydrofuran/water (15:10:5:70 v/v) solution was investigated by reversed-phase HPLC [24]. The association constants of the 1:1 complexes in 1550–54,300 M^{-1} were determined. Molecular dynamic simulation of the complexes was performed.

6.6 Biological Activity

The use of calixarenes, either directly or as molecule scaffolds, for the construction of bioactive molecules, has seen considerable recent growth [11].

Calixarene methylenebisphosphonic acids **47** displayed strong inhibition of calf intestine alkaline phosphatase [42,137]. The inhibition constants (K_i = 0.38 mM for **47b**) were found to be considerably lower than those of the simple

methylenebisphosphonic acid (K_i = 67 mM). The action of phosphorylated calix[4]arene **47** is concordant with partial mixed-type inhibition.

Optically pure calixarene α-aminophosphonic acids **45b**,**c** and **46d**,**e** were investigated as inhibitors of porcine kidney alkaline phosphatase. The K_i value characterizing the dissociation constant of the enzyme–inhibitor complex is much smaller for calixarene aminophosphonic acids **45b** and **45c** (76 and 32 μM), as well as for **46d** and **46e** (86 and 1.6 μM) in comparison to K_i of the model (*S*)-4-hydroxybenzene α-aminophosphonic acid (590 μM). The inhibition constants significantly depend on the absolute configuration of the aminophosphonyl fragments carbon atoms. Inhibition stereoselectivity $K_i(RR)/K_i(SS) = 50$ ($\Delta\Delta G = 9.6$ kJ mol^{-1}) is observed for the calixarene bis-aminophosphonic acids **46d**,**e**.

It was found that calix[4]arenes **46c** and **47a**, bearing fragments of hydroxyphosphonic and methylenebisphosphonic acid at a concentration of 100 μM, inhibited enzymatic activity of oubaine-sensitive Na^+, K^+-ATPase by 86–98% and did not practically affect activity of Mg^{2+}-ATPase. These calixarenes were more efficient than ouabaine in suppressing enzymatic activity of the sodium pump. In the presence of the calixerenes **46c** and **47a**, the value of the appearance constant of inhibition $I_{0.5}$ was <0.1 μM. Calixarene methylenebisphosphonic acid **47a** ($I_{0.5}$ = 33 ± 4 nm) is the most efficient inhibitor of Na^+, K^+-ATPase activity among the studied calixarenes [37,138]. Calixarene **47a** also increases affinity of the Na^+, K^+-ATPase to the cardiac glycoside ouabaine [139].

Thus, preorganizing phosphonic acids fragment using a calixarene platform provides a promising approach for the design of alkaline phosphatase inhibitors and calcium pump effectors.

7 Conclusion

This review demonstrates that combination of the phosphorus-containing receptor groups and macrocyclic cavity helps to define supramolecular interactions a priori and supplies significant potential for application in various fields of chemistry, physics, biology and material science. One of the promising application fields may be chiral metallocomplexing catalysis. The design of artificial water-soluble receptors, able to mimic enzymes (or influence them), is also an interesting theme. Biorelevant phosphoryl groups may play an important role in these processes.

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References

1. Gutsche C (1998) Calixarenes revisited. The Royal Society of Chemistry, Cambridge
2. Asfari Z, Böhmer V, Harowfield J, Vicens J (eds) (2001) Calixarenes 2001. Kluwer, Dordrecht
3. Iki N, Miyano S (2001) J Inclusion Phenom Macrocyclic Chem 41:99

4. De Namor A, Pugliese A, Casal A, Llerena M, Aymonino P, Velarde F (2000) Phys Chem Chem Phys 4355
5. Talanova G, Hwang H, Talanov V, Bartsch R (1998) Chem Commun, p 419
6. Pelizzi N, Casnati A, Friggeri A, Ungaro R (1998) J Chem Soc Perkin Trans 2, p 1307
7. Budka J, Lhotak P, Michlova V, Stibor I (2001) Tetrahedron Lett 42:1583
8. Arena G, Contino A, Gulino F, Magri A, Sciotto D, Ungaro R (2000) Tetrahedron Lett 41:9327
9. Lumetta G, Rogers R, Gopalan A (eds) (2000) Calixarenes for separations. American Chemical Society, Washington
10. Mandolini L, Ungaro R (eds) (2000) Calixarenes in action. Imperial College Press, Singapore
11. Perret F, Lazar A, Coleman A (2004) J Drug Sci Tech 14:3
12. Da Silva E, Lazar A, Coleman A (2004) J Drug Sci Tech 14:3
13. Antipin I, Kazakova E, Habicher W, Konovalov A (1998) Russian Chem Rev 11:905
14. Alexandratos S, Natesan S (2000) Ind Eng Chem Res 39:3998
15. Finocchiaro P, Consiglio G (2000) Het Chem 11:493
16. Armspach D, Bagatin I, Engeldinger E, Jeunesse C, Harrowfield J, Lejeune M, Matt D (2004) J Iran Chem Soc 1:10 (Chem Abstr 143:338328)
17. Schrader T (1999) J Incl Phenom Macrocyclic Chem 34:117
18. Tavs P (1970) Chem Ber 103:2428
19. Kalchenko V, Atamas L, Pirozhenko V, Markovsky L (1992) Zh Obshch Khim 62:2623 (Chem Abstr 119:72704)
20. Witt D, Dziemidowicz J, Rachon J (2004) Het Chem 15:155
21. Houel E, Lazar A, Silva E, Coleman A, Solovyov A, Cherenok S, Kalchenko V (2002) Langmuir 18:1374
22. Wieser-Jeunesse C, Matt D, Cian A (1998) Angew Chem Int Ed 37:2861
23. Ozegowski S, Costisella B, Gloede J (1996) Phosphorus Sulfur Silicon 119:209
24. Kalchenko O, Marcinowicz A, Poznanski J, Cherenok S, Solovyov A, Zielenkiewicz W, Kalchenko V (2005) J Phys Org Chem 18:578
25. Almi M, Arduini A, Casnati A, Pochini A, Ungaro R (1989) Tetrahedron 45:2177
26. Arimura T, Nagasaki T, Shinkai S, Matsuda T (1989) J Org Chem 54:3766
27. Klimchuk O, Atamas L, Miroshnichenko S, Kalchenko V, Smirnov I, Babain V, Varnek A, Wipff G (2004) J Incl Phenom Macrocyclic Chem 49:47
28. Kostin G, Borodin A, Torgov V, Kuratieva N, Naumov D, Miroshnichenko S, Kalchenko V (2007) J Incl Phenom Macrocyclic Chem 59:45
29. Psychogios N, Regnouf-de-Vains J-B (2002) Tetrahedron Lett 43:7691
30. Takenaka K, Obora Y, Tsuji Y (2004) Inorg Chim Acta 357:3895
31. Rudzevich Y, Drapailo A, Rudzevich V, Miroshnichenko S, Kalchenko V, Smirnov I, Babain V, Varnek A, Wipff G (2002) Russ J Gen Chem 72:1736
32. Kasyan O, Swierczynski D, Drapailo A, Suwinska K, Lipkowski J, Kalchenko V (2003) Tetrahedron Lett 44:7167
33. Kasyan O, Healey E, Drapailo A, Zaworotko M, Cecillon S, Coleman A, Kalchenko V (2007) J Incl Phenom Macrocyclic Chem 58:127
34. Kabachnik M, Medved T (1952) Doclady Acad Nauk S.S.S.R 83:689 (Chem Abstr 1953, 47:2724h)
35. Fields E (1952) J Am Chem Soc 74:1528
36. Antipin I, Stoikov I, Pinkhassik E, Fitseva N, Stibor I, Konovalov A (1997) Tetrahedron Lett 38:5865
37. Veklich T, Kosterin S, Rodik R, Cherenok S, Boiko V, Kalchenko V (2006) Ukrainian Biochem J 78:70 (Chem Abstr 146:200695)
38. Markovsky L, Kalchenko V, Solovyov A, Finocchiaro P, Failla S, Atamas L, Consiglio G, Tsymbal I (1998) Anales Quim 94(3):164
39. Solovyov A, Cherenok S, Tsymbal I, Failla S, Consiglio G, Finocchiaro P Kalchenko V (2001) Het Chem 12:58

40. Cherenok S, Vovk A, Muravyova I, Shivanyuk A, Kukhar V, Lipkowski J, Kalchenko V (2006) Org Lett 8:549
41. Zielenkiewicz W, Marcinowicz A, Cherenok S, Kalchenko V, Poznaski (2006) Supramol Chem 18:167
42. Vovk A, Kalchenko V, Cherenok S, Kukhar V, Muzychka O, Lozynsky M (2004) Org Biomol Chem 2:3162
43. Arnaud-Neu F, Böhmer V, Dozol JF, Grüttner C, Jakobi RA, Kraft D, Mauprivez O, Rouquette H, Schwing-Weill M-J, Simon N, Vogt W (1996) J Chem Soc Perkin Trans 2, p 1175
44. Matthews S, Saadioui M, Böhmer V, Barboso S, Arnaud-Neu F, Schwing-Weill M, Carrera A, Dozol J F (1999) J Prakt Chem 341:264
45. Arduini A, Böhmer V, Delmau L, Desreux J, Dozol J F, Carrera M, Lambert B, Musigmann C, Pochini A, Shivanyuk A, Ugozzoli F (2000) Chem Eur J 6:2135
46. Kumagai H, Hasegawa M, Miyanari S (1997) Tetrahedron Lett 38:3971
47. Lhotak P (2004) Eur J Org Chem 1675
48. Kasyan O, Kalchenko V, Bolte M, Böhmer V (2006) Chem Commun, p 1932
49. Atamas L, Klimchuk O, Rudzevich V, Pirozhenko V, Kalchenko V, Smirnov I, Babain V, Efremova T, Varnek A, Wipff G, Arnaud-Neu F, Roch M, Saadioui M, Böhmer V (2002) J Supramol Chem 2:421
50. Marra A, Scherrmann M, Dondoni A, Casnati A, Minari P, Ungaro R (1994) Angew Chem Int Ed Engl 33:2479
51. Vreekamp R, Duynhoven J, Hubert M,Verboom W, Reinhoudt D (1996) Angew Chem Int Ed Engl 35:1215
52. Patel D, Rielly-Gauvin K, Ryono D (1990) Tetrahedron Lett 31:5587
53. Schwender C, Beers S, Malloy E, Cinicola J, Wustrow D, Demarest K, Jordan J (1996) J Bioorg Med Chem Lett 6:311
54. Beers S, Schwender C, Loughney D, Malloy E, Demarest K, Jordan J (1996) J Bioorg Med Chem 10:1693
55. Sikorski J, Miller M, Braccolino D, Cleary D, Corey S, Font J, Gruys K, Han C, Lin K, Pansergan P, Rean J, Schnur D, Sbah A, Walker M (1993) Phosphorus Sulfur Silicon 76:375
56. Kalchenko O, Solovyov A, Cherenok S, Starodub N, Kalchenko V (2003) J Incl Phenom Macrocyclic Chem 46:19
57. Nagasaki T, Arimura T, Shinkai S (1991) Bull Chem Soc Jpn 64:2575
58. Hamada F, Fukugami T, Murai K, Orr G, Atwood J (1991) J Incl Phenom Mol Recogn 10:57
59. Vèzina M, Gagnon J, Villeneuve K, Drouin M, Harvey P (2000) Chem Commun, p 1073
60. Vezina M, Cagnon J, Villeneuve K,Harvey P (2001) Organometallics 20:273
61. Gagnon J, Vezina M, Harvey P (2001) Can J Chem 1439
62. Takenaka K, Obora Y, Jiang L, Tsuji Y (2002) Organometallics 21:1158
63. Plourde F, Gilbert K, Gagnon J, Harvey P (2003) Organometallics 22:2862
64. Fang X, Scott B, Watkin J, Carter C, Kubas G (2001) Inorg Chim Acta 317:276
65. Bagatin I, Tholnnessen H, Matt D, Jones P (1999) Inorg Chem 38:1585
66. Shimizu S, Shirakawa S, Sasaki Y, Hirai C (2000) Angew Chem Int Ed 39:1256
67. Kalchenko V, Lipkowski J, Simonov Y, Vysotsky M, Suwinska K, Dvorkin A, Pirozhenko V, Tsimbal I, Markovsky L (1995) Zh Obshch Khim 65:1199 (Chem Abstr 1996, 124:202411z)
68. Shahgaldian P, Coleman A, Kalchenko V (2001) Tetrahedron Lett 42:577
69. Burne L, Harrowfield J, Hockless D, Peachey B, Skeleton B, White A (1993) Aust J Chem 46:1673
70. Goren Z, Biali S (1990) J Chem Soc Perkin Trans 1, p 1484
71. Markovsky L, Kalchenko V, Vysotsky M, Pirozhenko V, Simonov Y, Dvorkin A, Iatsenko A, Lipkowski J (1997) Supramol Chem 8:85
72. Regnouf J, Pellet-Rostaing S, Lamartine R (1994) Tetrahedron Lett 35:8147
73. Jamssen , Verboom W, Harkema S, Hummel G, Reinhoudt D, Pochini A, Ungaro R, Prados P, Mendoza J (1993) J Chem Soc Chem Commun, p 506

74. Glode J, Keitel I (1995) Phosphorus Sulfur Silicon 104:103
75. Costisella B, Gloede J (1994) J Phosphorus Sulfur Silicon 89:39
76. Gloede J, Costisella B, Ramm M (1993) Phosphorus Sulfur Silicon 84:217
77. Markovsy L, Visotsky M, Tairov M, Lipkowski J, Slovikovska A, Simonov Yu (1999) Ukr Khim Zh (Russ. Ed) 65:117 (Chem Abstr 2000, 132:237144g)
78. Kalchenko V, Vysotsky M, Tairov M, Lipkowski J, Slovikovska A, Simonov Yu (1999) Ukr Khim Zh (Russ. Ed) 65:117 (Chem Abstr 2000, 132:237144g)
79. Tairov M, Vysotsky M, Kalchenko O, Pirozhenko V, Kalchenko V (2002) J Chem Soc Perkin Trans 1, p 1405
80. Markovsky L, Vysotsky M, Tairov M, Kalchenko V (1999) Phosphorus, Sulfur Silicon 144:89
81. Vysotsky M, Tairov M, Pirozhenko V, Kalchenko V (1998) Tetrahedron Lett 39:6057
82. Matulkova I, Rohovec J (2005) Polyhedron 24:311
83. Bocheska M, Hoffmann M, Lesiska U, Luks E, Radeska-Paryzek W (2005) Tetrahedron 61:12307
84. Bocheska M, Hoffmann M, Lesiska U (2004) J Incl Phenom Macrocyclic Chem 49:57
85. Jurecˇka P, Vojtísek P, Novotný K, Rohovec J, Lukes I (2002) J Chem Soc Perkin Trans 2, p 1370
86. Saulnier L, Varbanov S, Scopelini R, Elhabiri M, Bünzli G, (1999) J Chem Soc Dalton Trans, p 3919
87. Dieleman C, Loeber C, Matt , De Cian A, Fischer J (1995) J Chem Soc Dalton Trans, p 3097
88. Dieleman C, Matt D, Jones P (1997) J Organomet Chem 545–546:461
89. Loeber C, Matt D, De Cian A, Fischer J (1994) J Organomet Chem 475:297
90. Loeber C, Wieser C, Matt D, De Cian A, Fischer J, Toupet L (1995) Bull Soc Chim Fr 132:166
92. Jeunesse C, Dieleman C, Steyer S, Matt D (2001) J Chem Soc Dalton Trans, p 881
93. Dieleman C, Steyer S, Jeunesse C, Matt D (2001) J Chem Soc Dalton Trans, p 2508
94. Hamdi A, Chun Nam K, Ju Ryu B (2004) Tetrahedron Lett 45:4689
95. Vysotsky M, Schmidt C, Böhmer V (2000) Adv Supramol Chem 7:139
96. Kalchenko O, Tairov M, Vysotsky M, Lipkowski J, Kalchenko V (2000) Enantiomer 5:385
97. Khasnis D, Lattman M, Gutsche C (1990) J Am Chem Soc 112:9422
98. Khasnis D, Burton J, Lattman M, Zhang H (1991) J Chem Soc Chem Commun, p 562
99. Parlevliet F, Kiener C, Fraanje J, Goubitz K, Lutz M, Spek A, Kamer P, Leeuwen P (2000) J Chem Soc Dalton Trans, p 1113
100. Steyer S, Jeunesse C, Matt D, Welter R, Wesolek M (2002) J Chem Soc Dalton Trans, p 4264
101. Steyer S, Jeunesse C, Harrowfield J, Matt D (2005) J Chem Soc Dalton Trans, p 1301
102. Sarkar A, Nethaji M, Krishnamurthy S (2008) J Organomet Chem 693:2097
103. Kunze C, Selent D, Neda I, Schmutzler R, Spannenberg A, Borner A (2001) Het Chem 12:577
104. Jacoby D, Floriani C, Chiesi-Villa A, Rizzoli C (1993) J Chem Soc Dalton Trans, p 813
105. Matt D, Loeber C, Vicens J, Asfari Z (1993) J Chem Soc Chem Commun, p 604.
106. Faidherbe P, Wieser C, Matt D, Harriman A, De Cian A, Fischer J (1998) Eur J Inorg Chem, p 451
107. Loeber C, Matt D, Briard P, Grandjean D (1996) J Chem Soc Dalton Trans, p 513
108. Cameron B, Veggel F, Reinhoudt D (1995) J Org Chem 60:2802
109. Wieser C, Matt D, Toupet L. Bourgeois H, Kintzinger J (1996) J Chem Soc Dalton Trans, p 4041
110. Malone J, Marrs D, McKervey M, O'Hagan P, Thompson N, Walker A, Arnaud Neu F, Mauprivez O, Schwing-Weill M, Dozol JF, Rouquette H, Simon N (1995) J Chem Soc Chem Commun, p 2151
111. Kim S, Kim J, Shon O, Lee S, Park K, Kang S, Ko J (2004) Inorg Chem 43:2906
112. Kim S, Seung Kim J, Kuk Kim S, Suh H, Kang S, Ko J (2005) Inorg Chem 44:1846
113. Kalchenko V, Visotsky M, Shivanyuk A (1996) Phosphorus Sulfur Silicon 109:513
114. Lukin O, Vysotsky M, Kalchenko V (2001) J Phys Org Chem 14:468

115. Yaftian M, Burgard M, Matt D, Wieser C, Dieleman C (1997) J Incl Phenom Mol Recogn Chem 27:127
116. Baaden M, Wipff G, Yaftian M, Burgard M, Matt D (2000) J Chem Soc Perkin Trans 2, p 1315
117. Gregoriadis G (1988) Liposomes as drug carriers, recent trends and progress. Wiley, New York
118. Couvreur P, Dubernet C, Puissieux (1995) Eur J Pharm Biopharm 41:2
119. Damage C, Michel C, Aprahamian M, Couvreur P, Devissaguet J (1990) J Controlled Release 13:233
120. Tanaka Y, Miyachi M, Kobuke Y (1999) Angew Chem Int Ed 38:504
121. Ravoo B, Darcy R (2000) Angew Chem Int Ed 39:4324
122. Bochen´ska M, Hoffmann M, Lesin´ska U (2004) J Incl Phenom Macrocyclic Chem 49:57
123. Smirnov I, Karavan M, Babain V, Kvasnitskiy I, Stoyanov E, Miroshnichenko S (2007) Radiochim Acta 95:97
124. Nagasaki T, Arimura T, Shinkai S (1991) Bull Chem Soc Jpn 64:2575
125. Yaftian M, Burgard M, Bachiri A, Matt D, Wieser C, Dieleman C (1997) J Incl Phenom Mol Recogn Chem 29:137
126. Dieleman C, Matt D, Neda I, Schmutzler R, Thonnessen H, Jones P, Harriman A (1996) J Chem Soc Dalton Trans, p 2115
127. Dieleman C, Matt D, Harriman A (2000) Eur J Inorg Chem, p 831
128. Loeber C, Matt D, DeCian A, Fischer (1994) J Organomet Chem 475:297
129. Semeril D, Lejeune M, Matt D (2007) New J Chem 31:502
130. Shirakawa S, Shimizu S, Sasaki Y (2001) New J Chem 25:777
131. Cobley C, Ellis D, Orpen G, Pringle P (2000) J Chem Soc Dalton Trans, p 1109
132. Perret F, Morel-Desrosiers N, Coleman A (2002) J Supramol Chem 2:533
133. Zielenkiewicz W, Marcinowicz A, Poznaski J, Cherenok S, Kalchenko V (2005) J Mol Liquids 121:8
134. Zadmard R, Schrader T, Grawe T, Kraft A (2002) Org Lett 4:1687
135. Zadmard R, Schrader T (2005) J Am Chem Soc 127:904
136. Kolusheva S, Zadmard R, Schrader T, Jelinek R (2006) J Am Chem Soc 128:13592
137. Mishenko I, Cherenok S, Muzichka O, Vovk A, Kalchenko V, Kukhar V (2006) Ukrainian J Org Pharm Chem 4:31 (Chem Abstr 146:457423)
138. Labinzeva R, Slinchenko N Veklich T, Rodik R, Cherenok S, Boyko V, Kalchenko V, Kosterin S (2007) Ukrainian Biochem J 79:44 (Chem Abstr 148:229931)
139. Veklich T, Shkrabak O, Kosterin S, Rodik R, Cherenok S, Boyko V, Kalchenko V (2006) Ukrainian Biochem J 78(6):53 (Chem Abstr 2006, 147:89903)

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From Phosphorus-Containing Macrocycles to Phosphorus-Containing Dendrimers

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Abstract Various methods of synthesis of phosphorus-containing macrocycles are described. They are obtained in good to quantitative yields, thanks to the presence of phosphorhydrazone (P–N–N=) linkages in their structure. Multi-macrocyclic species and cryptands possessing the same linkage are also described. Various types of reactions, including complexation properties of the macrocycles are also reviewed. In the last part, the use of the same linkage for the elaboration of phosphorus-containing dendrimers is described, with emphasis on dendrimers incorporating macrocycles in some part of their structure (terminal groups, core or interior).

Keywords Cryptand, Dendrimer, Macrocycle, Phosphorhydrazone, Phosphorus

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1 Introduction

The history of phosphorus-containing macrocycles dates back more than one century, when H.N. Stokes prepared and isolated for the first time in 1897 higher members of the tri- and tetraphosphonitrilic chloride series $(PNCl_2)n$ where n is 5, 6 or 7 [1]. However, after this pioneering work, intensive studies in the field of phosphorus-containing macrocycles appeared only in the middle of the 1970s, presumably due to experimental difficulties such as multi-step procedures, high dilution, low yields, and instability (particularly in the case of phosphines). Nevertheless, besides the potential complex-forming properties often observed with heteroatom-containing macrocycles [2], phosphorus macrocycles may take advantage of the special properties of phosphorus species such as diverse degrees of coordination (potentially from 2 to 6), and a palette of chemical reactions larger than with carbon. We published in 1994 an extensive review emphasizing the various methods of synthesis of phosphorus-containing macrocycles [3]. Since that time, several papers have appeared in this field, expanding the scope of these compounds. Among the most recent and original examples in this field one can cite in particular macrocycles incorporating phosphorus and other heteroatoms such as selenium and oxygen [4] or selenium and nitrogen [5] in their structure, mixed ligands including in the same cycle phosphole, thiophene and pyrrole [6], and even chiral phosphorus-containing catenanes [7].

The present review emphasises a particularly large family of phosphorus-containing macrocycles that we discovered 20 years ago [8]. Contrary to all the other types of macrocycles, these are synthesized in nearly quantitative yields in a one-pot procedure, without high dilution or template techniques, thanks to the use of a particular linkage called phosphorhydrazone (P–N–N=) [9, 10]. This linkage was later also found to be particularly useful for the synthesis of phosphorus-containing dendrimers[1], which will be discussed at the end of this review. The most general strategy for the synthesis of macrocycles is illustrated in Fig. 1. The reaction is generally a [2 + 2] cyclocondensation[2] between two equivalents of a phosphodihydrazide and two equivalents of a

[1] Dendrimers are a very special type of polymers, hyperbranched and multifunctional, having a perfectly defined structure, due to their step by step synthesis (never by polymerization)

[2] This notation does not refer to the mechanism but to the number of partners that associate in the macrocycle

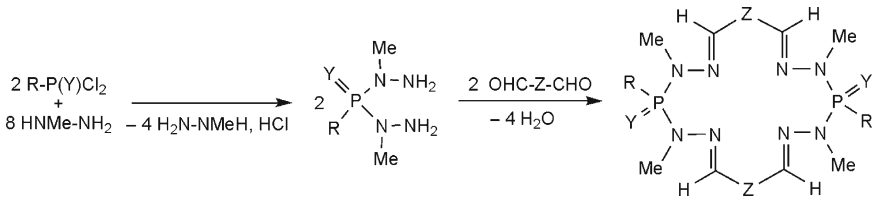

Fig. 1 Main method of synthesis of phosphorhydrazone macrocycles

dialdehyde, with only water as by-product. The phosphorhydrazides are synthesized by reaction of dichlorophosphine oxide or sulphide with four equivalents of methylhydrazine (two for the grafting, two for scavenging the HCl generated) [11].

2 Macrocycles Derived from Cyclocondensation

2.1 Macrocycles Derived from [2 + 2] Cyclocondensation

As indicated above, this is the most frequent type of cyclocondensation that is observed using phosphodihydrazides, and it occurs with very different types of dialdehydes.

2.1.1 Two Phosphorus Atoms in the Macrocycles

Starting from relatively simple dialdehydes, 20- or 22-membered macrocycles were isolated, depending on the size of the dialdehyde. The substituents on the phosphorus can be varied: Y is either O or S, and R can be Ph, PhO, or NMe_2 or even an azide [12] or chloride [13], and the linker between the aldehydes is either furan, pyridine, 1,3- [8] and 1,4- [14] disubstituted benzene, thiophene [15], or pyrrole and methylpyrrole [16] (see Fig. 2). 18-Membered macrocycles were obtained in the same way starting from OHC–C≡C–CHO or its cobalt complex [14, 17], or from a dithiolethione [18]. The use of a TTF derivative affords larger (26-membered) macrocycles [18]. Later, the same principle was applied to larger dialdehydes built from carbosilane derivatives, affording mixed (phosphorus/silicon) 28-membered macrocycles [19] (Fig. 2).

Very recently, our methodology was applied by Chandrasekhar et al. for the synthesis of 42- and 46-membered macrocycles [20], and a 36-membered macrocycle built from a dialdehyde of cyclotriphosphazene [21]. In the latter case, four phosphorus atoms are included in the macrocycle (Fig. 3).

2.1.2 Four Phosphorus Atoms in the Macrocycle

The use of phosphorylated dialdehydes allows the introduction of two additional phosphorus atoms in the macrocyclic structure, and affords larger macrocycles.

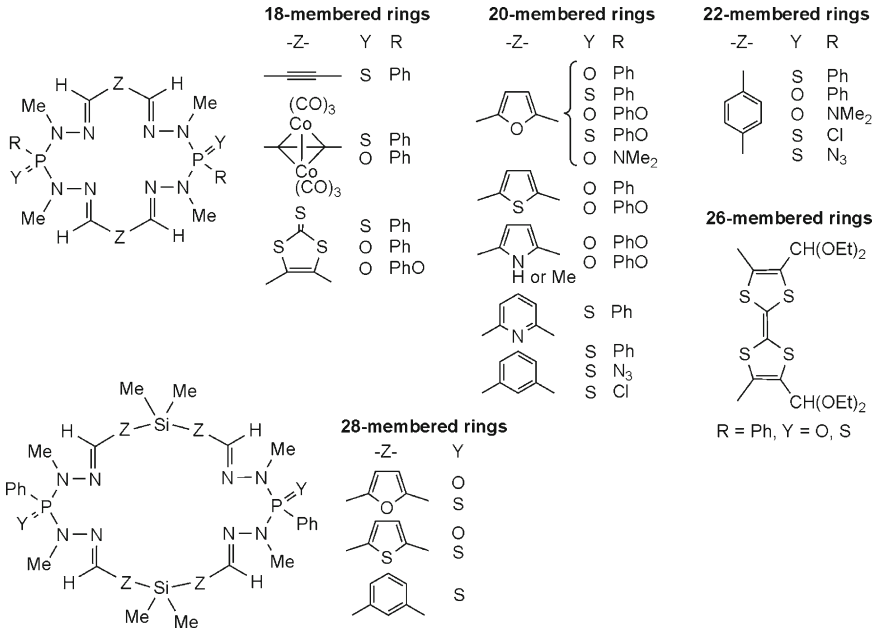

Fig. 2 Phosphorhydrazone macrocycles possessing two phosphorus atoms in their structure and derived from [2 + 2] cyclocondensations

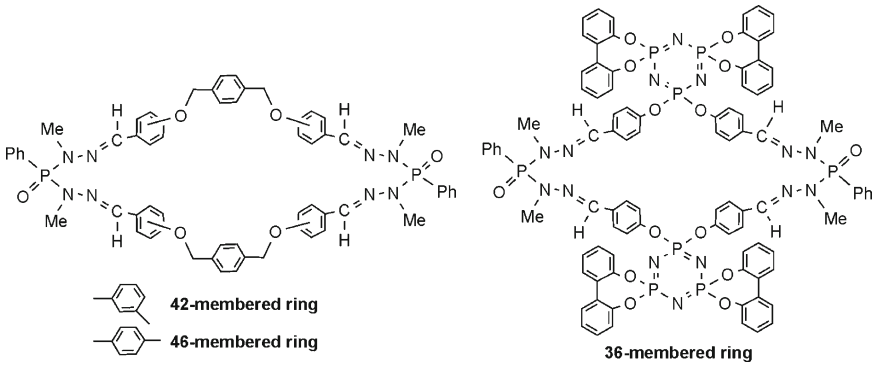

Fig. 3 Phosphorhydrazone macrocycles obtained by Chandrasekhar et al.

The example shown in Fig. 3 was obtained by Chandrasekhar, but we had previously obtained numerous tetraphosphorus macrocycles. The additional phosphorus atoms also allow increasing the diversity of structures. Indeed, they can be tri- or tetracoordinated, and they can be linked to the aldehydes through P–C [22] or P–O bonds. In the latter case, we have synthesized 28-, 32- and 36-membered macrocycles,

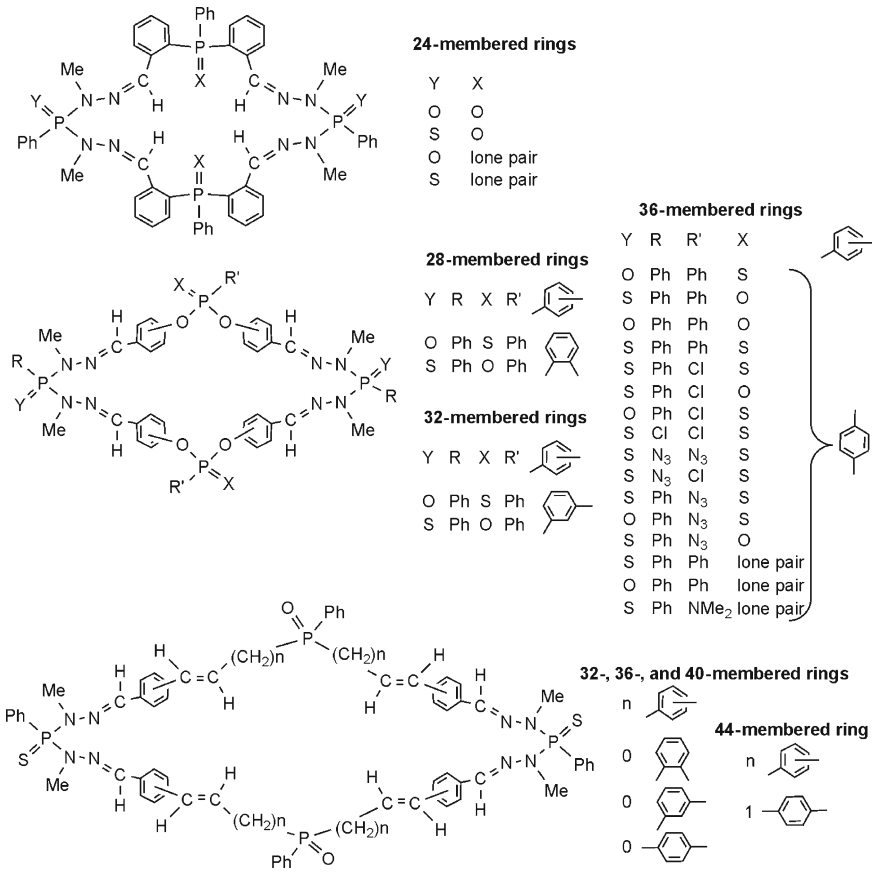

Fig. 4 Macrocycles incorporating four phosphorus atoms

depending on the type of aryl groups used [23]. The substituents of both types of phosphorus atoms can be diversified (oxygen or sulphur; phenyl or chloride). These substituents can also be azides [12, 13] and the phosphorus atoms can be tricoordinated [24]. Using vinyl or allyl phosphorus derivatives, very large macrocycles were obtained, up to 44-membered rings [25] (Fig. 4).

2.1.3 Six Phosphorus Atoms in the Macrocycle

The use of diazadiphosphetidine rings linked to two benzaldehydes allowed the synthesis of very large macrocycles (36- and 40-membered rings, depending on the meta or para position of the aldehydes). The degree of coordination of the phosphorus atoms of the diazadiphosphetidine ring can be varied (tri- or tetracoordinated) [26] (Fig. 5).

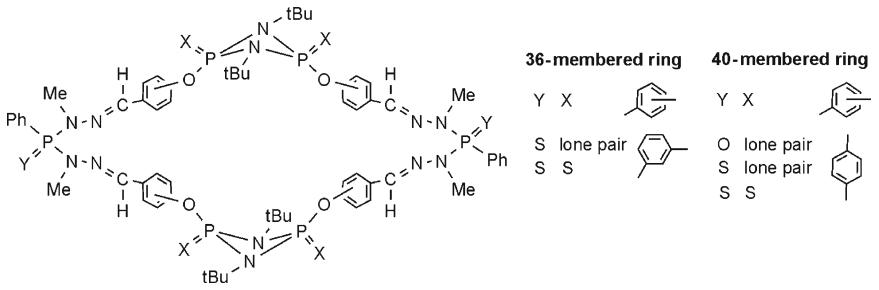

Fig. 5 Macrocycles incorporating six phosphorus atoms in their structure and derived from [2 + 2] cyclocondensations

2.2 Macrocycles Derived from [1 + 1] Cyclocondensation

Besides [2 + 2] cyclocondensations, [1 + 1] cyclocondensations were observed in some cases when using very large and flexible dialdehydes. When the final product resembles a product obtained from the [2 + 2] cyclocondensations shown in Figs. 2, Fig. 4 and Fig. 5, the yield is generally high; this is for example the case for the alkyne derivative shown in Fig. 6, equivalent to the ones shown in Fig. 2, but with the advantage of not being symmetrical (P=O on one side, P=S on the other side) [14]. The same tendency was observed with the vinyl and allyl phosphine oxide derivatives: the 16-membered ring was obtained in very low yield, whereas the 18- and 22-membered rings were predominant [25]. An analogous behaviour was observed with flexible semi-crown ether dibenzaldehydes, which afforded 20- and 23-membered rings as major products [27]. Even a 16-membered ring was obtained when using a di-meta dialdehyde [27]. On the other hand, the rigidity imparted by the diazadiphosphetidine ring afforded only a very small amount (5%) of the product derived from [1 + 1] cyclocondensation, even if it is a 18-membered ring [28] (Fig. 6). This method can also afford mono-functionalized macrocycles [27], useful for the elaboration of multi-macrocyclic species (see Sect. 2.1.1).

Another way to observe [1 + 1] cyclocondensation consists of using very long phosphodihydrazides. Such compounds can be isolated when reacting two equivalents of "classical" phosphodihydrazides with one equivalent of diazadiphosphetidine dialdehydes, to afford the tetraphosphorus dihydrazides shown in Fig. 7. [1 + 1] Cyclocondensations between these special dihydrazides and various dialdehydes afford 29-, 30- and 32-membered macrocycles [26].

2.3 Macrocycles Derived from [3 + 3] or [4 + 4] Cyclocondensation

We have seen above that in some cases besides [2 + 2] reactions, long reagents may afford [1 + 1] cyclization reactions provided the number of bonds in the cycle is at least 16.

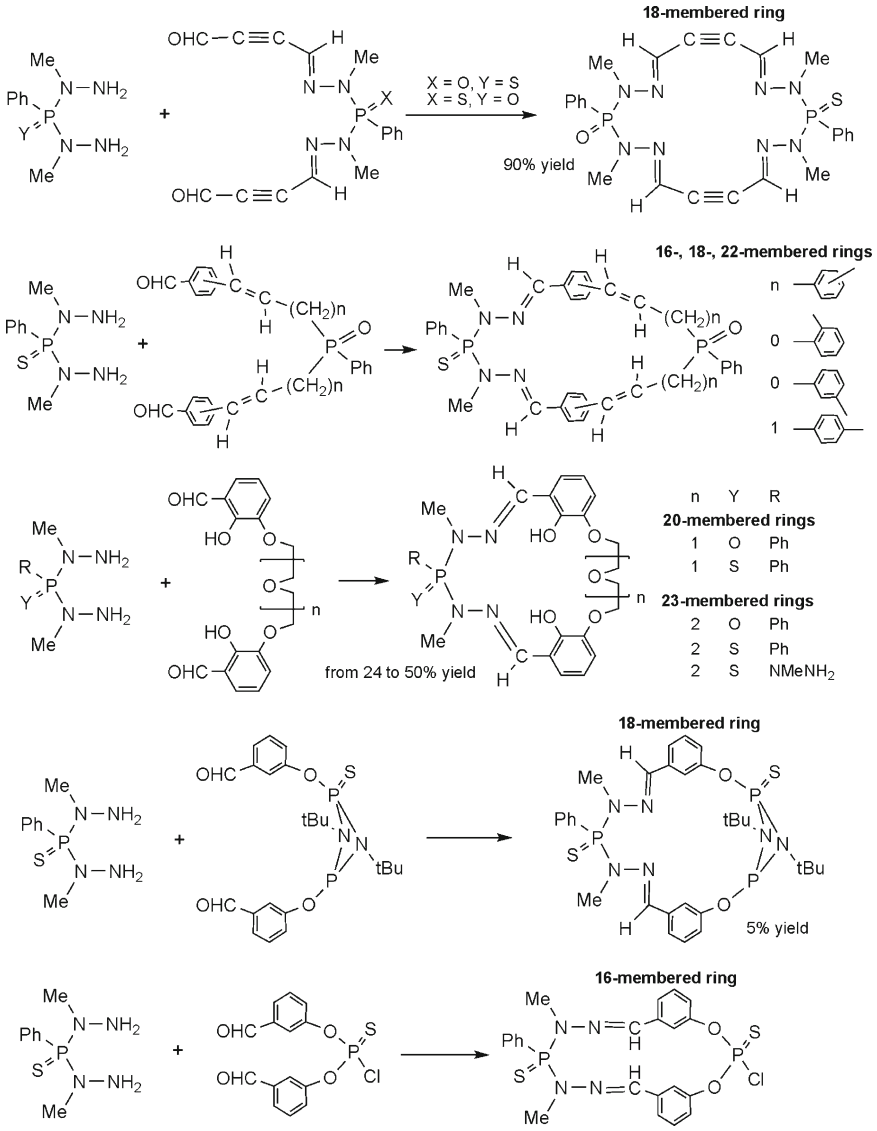

Fig. 6 Macrocycles derived from [1 + 1] cyclocondensations

On the contrary, it can be expected that the shortest dialdehydes may afford the [3 + 3] or eventually [4 + 4] cyclo products. We have indeed isolated such species in very low yield starting from furan [18] and as major product starting from pyrrole and methylpyrrole [16] dialdehydes for the [3 + 3] cyclocondensation. The product derived from the [4 + 4] cyclocondensation was observed only with pyrrole, and isolated in very low yield (Fig. 8).

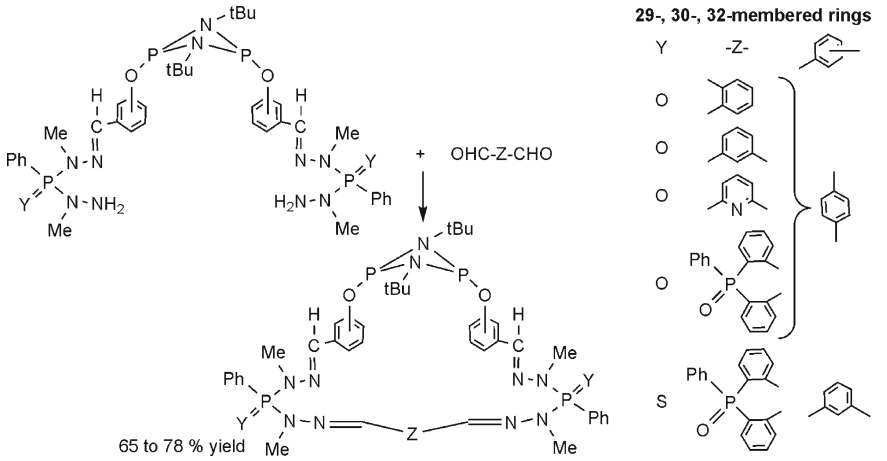

Fig. 7 Other types of macrocycles derived from [1 + 1] cyclocondensations

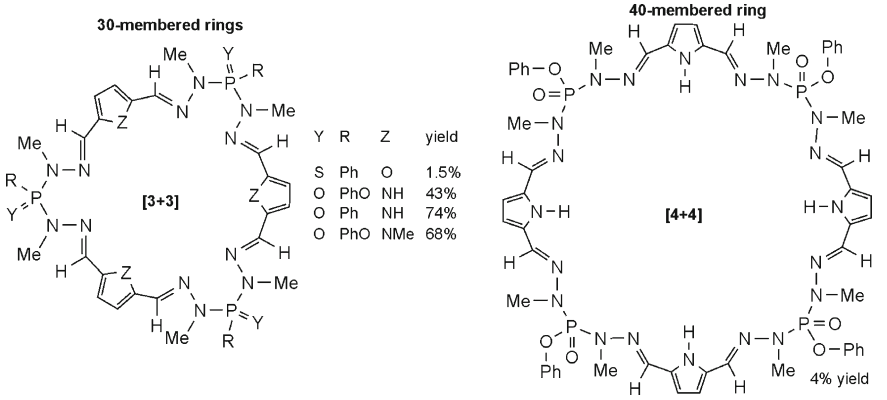

Fig. 8 Rare examples of macrocycles derived from [3 + 3] and [4 + 4] cyclocondensations

3 Cyclization by Substitution Reaction

Besides condensations, it is also possible to use substitution reactions to obtain macrocycles, often of the same type as the ones obtained by condensations, and possessing in all cases phosphorhydrazone linkages. In fact, we have created a real "game of building blocks" [29], playing with condensation and substitution reactions to synthesize phosphorus-containing macrocycles.

3.1 Substitution of Phenols

Hydroxybenzaldehydes are first condensed with the phosphodihydrazides in most cases of substitution reaction for obtaining macrocycles, and then a derivative having two labile entities (chloride or methyl) is used to react with the phenol groups. The difunctional derivatives can be $RP(X)Cl_2$ [23] or silicon compound (R'_2SiCl_2) used in basic conditions, or metallic derivatives (Cp_2ZrMe_2 or Cp_2TiMe_2) [30]. In all cases, [2 + 2] cyclizations by substitution were observed (Fig. 9). However, the position of the OH group was found to be particularly important in the case of the reaction with silicon derivatives: ortho subtituents did not afford any macrocycles, and the reaction was too slow with meta substituents to isolate a macrocycle [31].

Instead of hydroxybenzaldehydes, dihydroxybenzaldehyde can be condensed with a phosphodihydrazide, affording a compound with four OH groups. Its reaction with PCl_3 or $RB(OH)_2$ affords high coordination derivatives (P^V and B^{IV}, respectively). However, phosphorus and boron derivatives behave very differently: [2 + 2] cyclizations were observed with phosphorus and equilibrium between P^V and P^{III} species was noted [23]. On the other hand, only the products derived from [1 + 1] reactions were obtained with the boron derivatives [32] (Fig. 10).

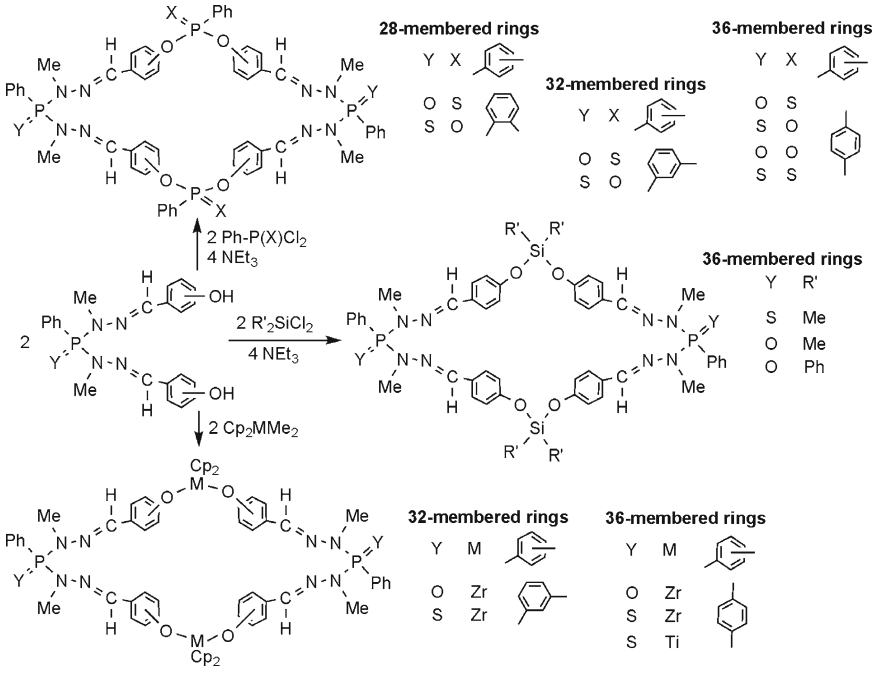

Fig. 9 Macrocycles derived from [2 + 2] cyclizations by substitution of phenols

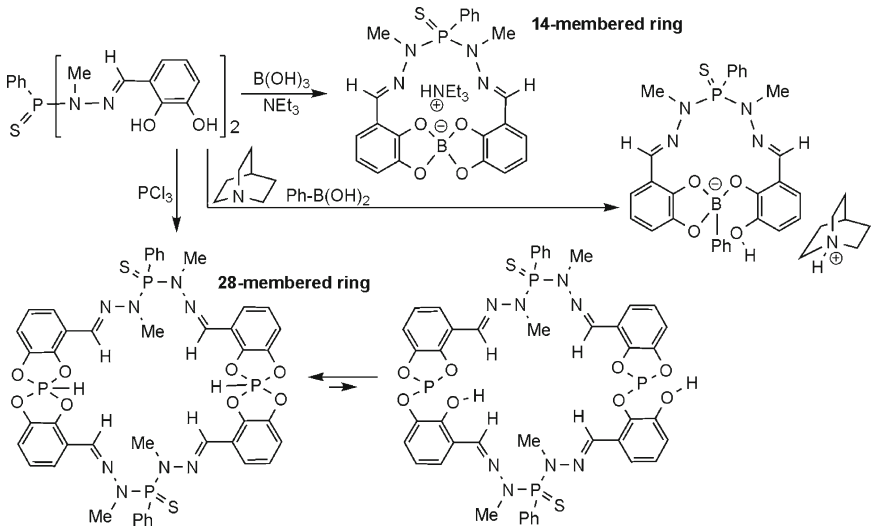

Fig. 10 High coordination macrocyclic derivatives of boron and phosphorus

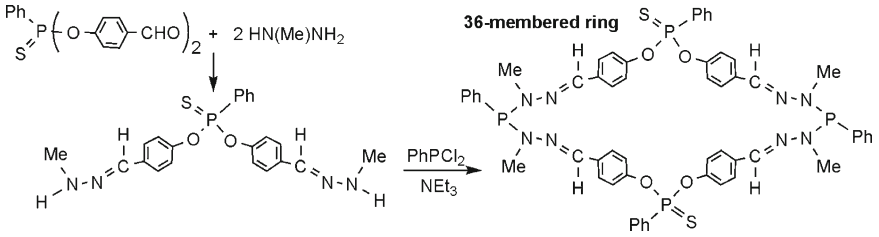

Fig. 11 Macrocycles derived from [2 + 2] cyclizations by substitution of amines

3.2 Substitution of Amines

Another way to perform substitution reactions to obtain phosphorhydrazone macrocycles consists first of the condensation of methylhydrazine with a dialdehyde, followed by the reaction with $PhPCl_2$ under basic conditions. Such a method allows introducing P^{III} derivatives into the macrocycle [24] (Fig. 11).

4 Characterization and Mechanistic Studies

4.1 Mechanism

Many methods of synthesis of macrocycles necessitate the use of a template (often a metal or a salt) that associates the diverse elements of the future macrocycle around it [33]. The methods shown in this review are different, and the four reactions generally needed for the cyclization should not proceed simultaneously but step-by-step.

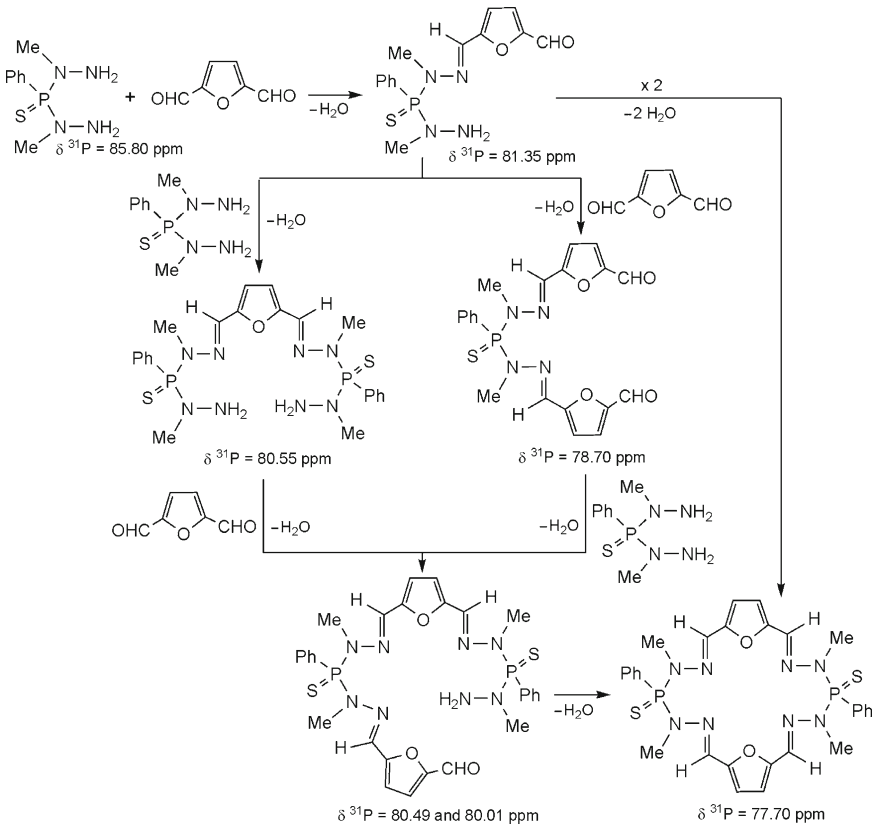

Fig. 12 Mechanism of cyclization deduced from variable temperature ^{31}P NMR experiments

In order to obtain a deeper insight into the synthetic pathway of the cyclocondensation, variable temperature ^{31}P NMR studies were carried out in several cases, and particularly in the case of furan dicarboxaldehyde [14]. The result is shown in Fig. 12; the first step is a hydrazido-aldehyde. Some of the intermediates, particularly the dialdehyde and the dihydrazide, were even isolated.

Molecular modelling of analogous hydrazido-aldehyde shows that the distance between the NH_2 and the CHO is large for all the lowest energy conformers, and that it is impossible to realize an intramolecular condensation [25]. Another insight into the mechanism was provided by TTF-dialdehyde derivatives: the *cis* isomer shown in Fig. 2 affords the expected macrocycles, but the *trans* isomer failed, illustrating the importance of the geometry of the dialdehyde [18].

4.2 Characterization by ^{31}P NMR and X-ray Diffraction

Condensation reactions are easily detected both by ^{1}H NMR and IR spectroscopy, which display the disappearance of the signals corresponding to the aldehydes.

However, the most informative technique is ^{31}P NMR. Indeed, the chemical shifts of phosphorus atoms are sensitive both to the chemical environment and to modification of the bond angles around phosphorus [34]. The condensation reactions induce a down-field shift of several ppm on going from the phosphodihydrazides to the phosphodihydrazones (typically from 86 to 78 ppm in the case of Ph–P(S)$(NMeN)_2$). When a single macrocyclic species exists in solution, a single signal is obtained; on the other hand, the presence of several species, for instance arising from [1 + 1] and [2 + 2] cyclocondensations, gives additional signals in ^{31}P NMR spectra.

Obviously, mass spectrometry gives information about the number of partners involved in the cyclization, but the best method to ascertain the three-dimensional structure of these macrocycles is X-ray diffraction. Very few compounds crystallized, thus only four macrocycles could be characterized by X-ray diffraction [35]: two derived from [1 + 1] cyclocondensations [27, 28], and two arising from [2 + 2] cyclocondensations [14, 16]. The latter cases are the most interesting ones, because they allow one to control how the external substituents of phosphorus are placed. As can be seen in Fig. 13, identical substituents lie on the same side of the mean plane of the macrocycle obtained from furan dialdehyde (see in particular the oxygen atoms) [14]. A similar behaviour was observed for the other structure determined by X-ray diffraction, obtained from pyrrole dialdehyde [16].

Such a finding raises a question concerning the stereochemistry around phosphorus and of the macrocycle when two (or more) phosphorus atoms are part of the ring. For instance, five diastereoisomers can be expected in the case of tetraphosphorus macrocycles, as illustrated in Fig. 14. Even if the presence of these diastereoisomers could not be detected by ^{31}P NMR when small substituents were linked to phosphorus, we recently discovered a way to detect them, as will be illustrated in Sect. 5.3.2.

Contrary to the previous case, with only two phosphorus atoms and an unsymmetrically substituted dialdehyde, ^{31}P NMR displays the presence of two products, characterized by three signals in a 1:1:2 ratio. Both phosphorus atoms are equivalent

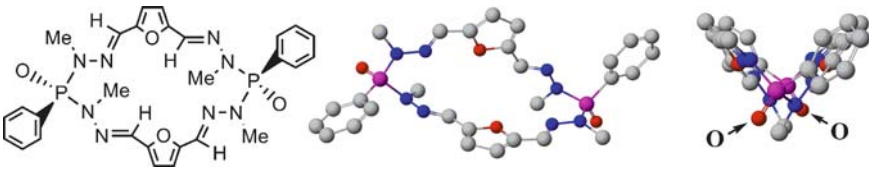

Fig. 13 Two views of the structure obtained by X-ray diffraction of the macrocycle

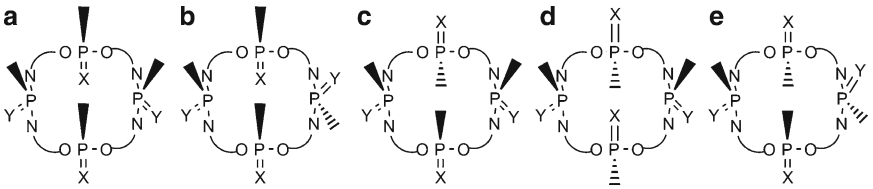

Fig. 14 The five possible diastereoisomers of tetraphosphorus macrocycles

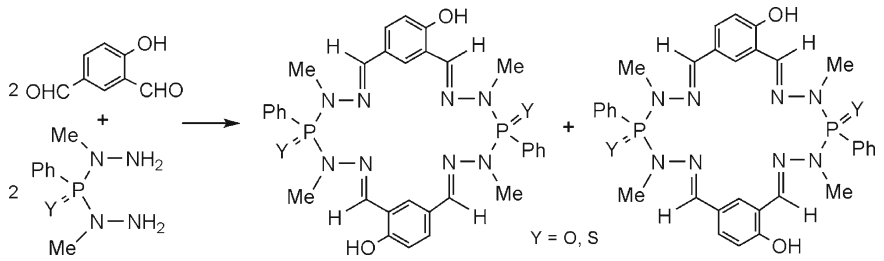

Fig. 15 Two regioisomers obtained by [2 + 2] cyclocondensation

for one product, but different for the other; both macrocycles are obtained in a 1:1 ratio, as indicated by the intensity of the signals [14, 36] (Fig. 15).

5 Reactivity of Functionalized Macrocycles

The presence of numerous heteroatoms in these macrocycles is potentially useful for studying their complexation properties; however, numerous other reactive sites exist in these macrocycles. Indeed, one may expect that the hydrazone linkages could be reduced, that the P=S or P=O groups might be alkylated, and that the R and R' substituents might be labile substituents or have another reactive site. These various possibilities are illustrated in Fig. 16, and will be emphasized in the following paragraphs.

5.1 Reactivity of the Hydrazone Linkages

The phosphorhydrazone linkages are particularly stable [37]; contrary to imines, they are not sensitive to water and are difficult to reduce. In fact, it was possible to reduce them only when using drastic conditions (excess of $LiAlH_4$ in refluxing THF), and only with very stable macrocycles. The four N–H groups obtained in this way are reactive, for instance with formaldehyde. Such a reaction decreases the size of the macrocycles as shown in Fig. 17 [38].

5.2 Reactivity of the P=O or P=S linkages

Reaction of strong alkylating agents such as triflates might occur on all the electron-rich sites such as nitrogen, oxygen or sulphur. In fact, methyl triflate reacts only with P=S linkages and trimethylsilyl triflate reacts only with P=O linkages. These alkylation reactions are very specific: even when using a large excess of triflate, the alkylation never occurred on nitrogen. Such reactions were performed with macrocycles derived from furan dicarboxaldehyde, 1,3- and 1,4-benzene dicarboxaldehyde [38],

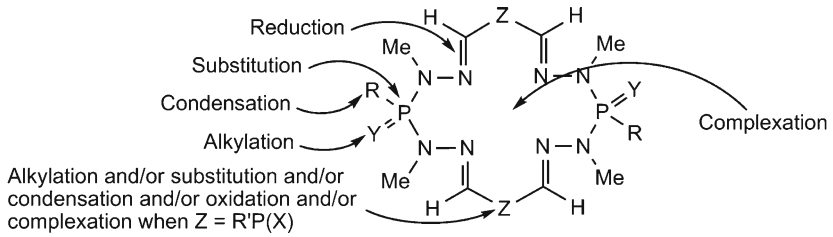

Fig. 16 The various types of reactions expected to occur with phosphorhydrazone macrocycles

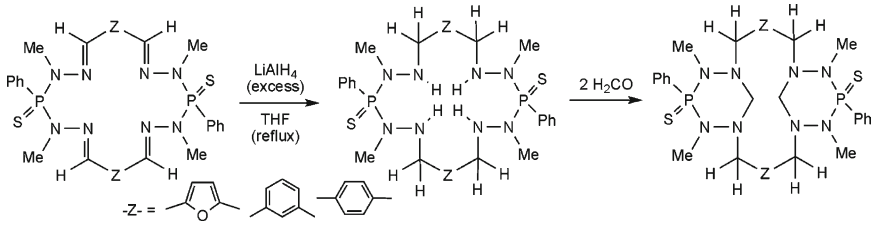

Fig. 17 Reactivity of hydrazone linkages

and zirconium derivatives [30]. The high specificity of these reactions is also illustrated with a macrocycle bearing both P=S and P=O groups. Two equivalents of methyl triflate and two equivalents of trimethylsilyl triflate lead to a tetra cationic macrocycle [22]. In general, the P–O–$SiMe_3$ groups have a tendency to destabilize the structure, whereas the P–S–Me groups are more stable. However, the alkylation induces a weakening of the P–S bond, which can be easily cleaved using $P(NMe_2)_3$ [39]. Two tricoordinated phosphorus atoms are generated in the macrocycle using this reaction, even in the case of the presence of P=O bonds [24] (Fig. 18). We later used this very interesting reaction to obtain highly sophisticated dendritic species [40] (see Sect. 8.3).

5.3 Reactivity of the P–R Linkages

Obviously, when the R substituents on phosphorus are aryl groups, no reaction can be expected. However, the R substituents can be a chloride, suitable to induce a substitution reaction, or an azide, useful in particular for Staudinger reactions.

5.3.1 Substitution Reactions

It is well known that P–Cl bonds easily undergo substitution reactions under basic conditions. We have tested the reactivity of methylhydrazine. As expected, the reaction occurs only on the NHMe side, affording a macrocycle with two pendant NH_2 groups.

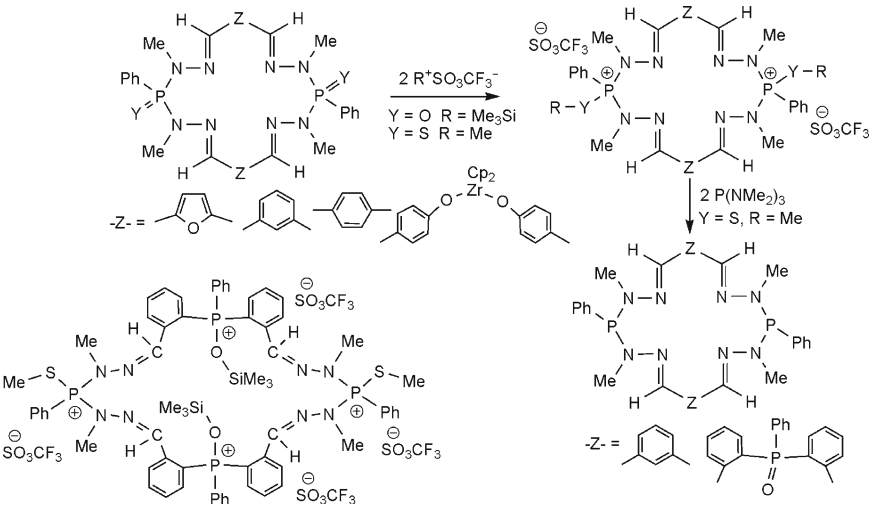

Fig. 18 Reactivity of P=O and P=S groups with alkyl triflates

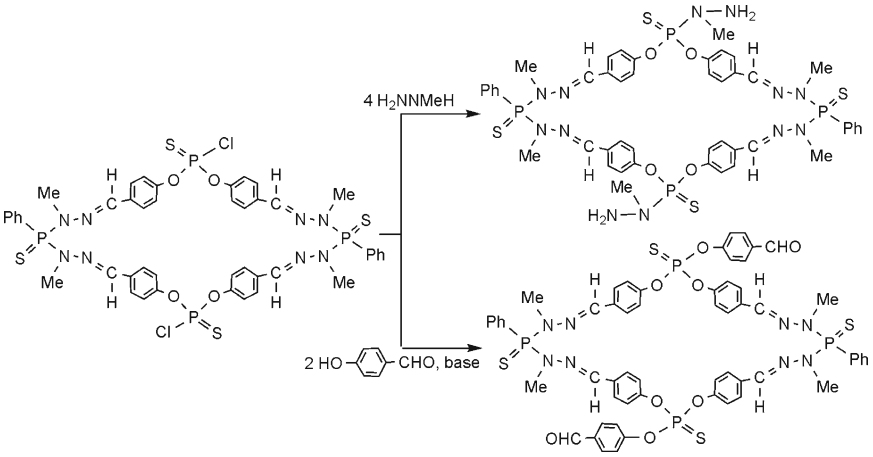

Fig. 19 Substitution reactions on P–Cl groups

Analogously, reaction of hydroxybenzaldehyde affords a macrocycle with two pendant aldehydes [23] (Fig. 19). These substitution reactions were found later to be suitable for obtaining cryptands (see Sect. 7).

More surprisingly, the P–N_3 linkages were found to be also suitable for substitution reactions. Indeed, they have demonstrated a pseudo-halogen behaviour when reacted with the sodium salt of phenols, but only when they are linked to a P(X)$(OAr)_2$ group and not to a P(Y)$(NMeN)_2$ group. This surprising reaction was experienced using the sodium salt of two phenols. It was even found that the substitution

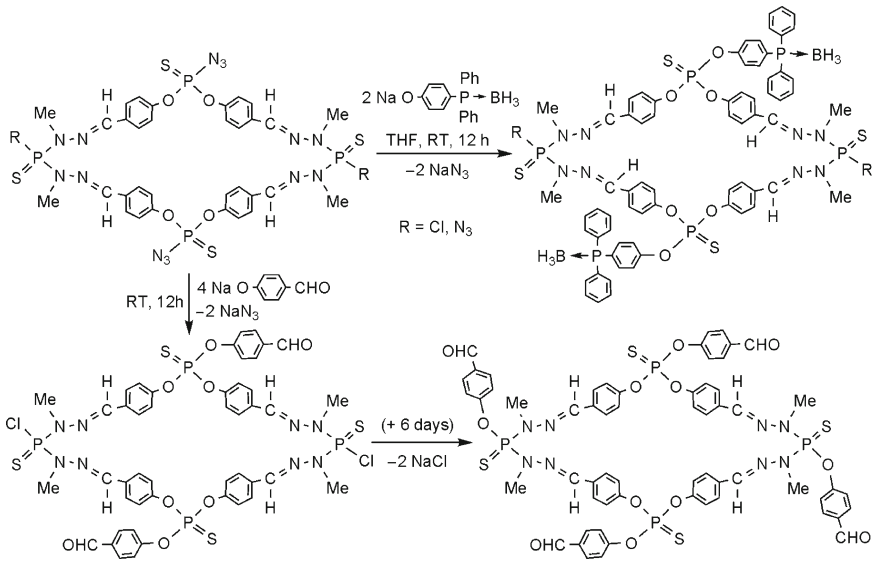

Fig. 20 Substitution reactions on P–N_3 groups

reaction occurs more rapidly with N_3–P(S)$(OAr)_2$ than with Cl–P(S)$(NMeN)_2$. Such reaction afforded multi-functionalized macrocycles having two or four pendant functions (Fig. 20) [41].

5.3.2 Staudinger Reactions

The Staudinger reaction [42] that we used is the reaction of azides with phosphines, to afford iminophosphorane bonds (P=N). A spectacular use of this reaction allowed us to amplify topological differences in the macrocycle (see Fig. 14), which become detectable by ^{31}P NMR. The first step consists of Staudinger reactions between the macrocycle and four equivalents of the monoaldehyde of triphenylphosphine. Such a reaction occurs with evolution of nitrogen, and creates four P=N–P=S linkages, much more stable than classical P=N linkages and we have proven their utility for synthesizing dendrimers [43]. A dendron also possessing such a linkage and a NH_2 group at the core reacts readily with the four aldehyde functions of the macrocycle in a second step, to afford an original example of a dendrimer having a macrocycle as the core [44] (Fig. 21) (see Sect. 8.2 for other examples).

^{31}P NMR spectroscopy appears to be a very useful tool to monitor all these reactions. The spectrum of the starting macrocycle displays two singlets (one for the O–P–O linkages, and the other for the N–P–N linkages). The Staudinger reaction induces the disappearance of both singlets accompanied by the appearance of two systems of two doublets, caused by two types of P=N–P=S linkages (P=S linked to two O, or to two N). Even at this step, it is impossible to detect the presence of any isomer of the macrocycle.

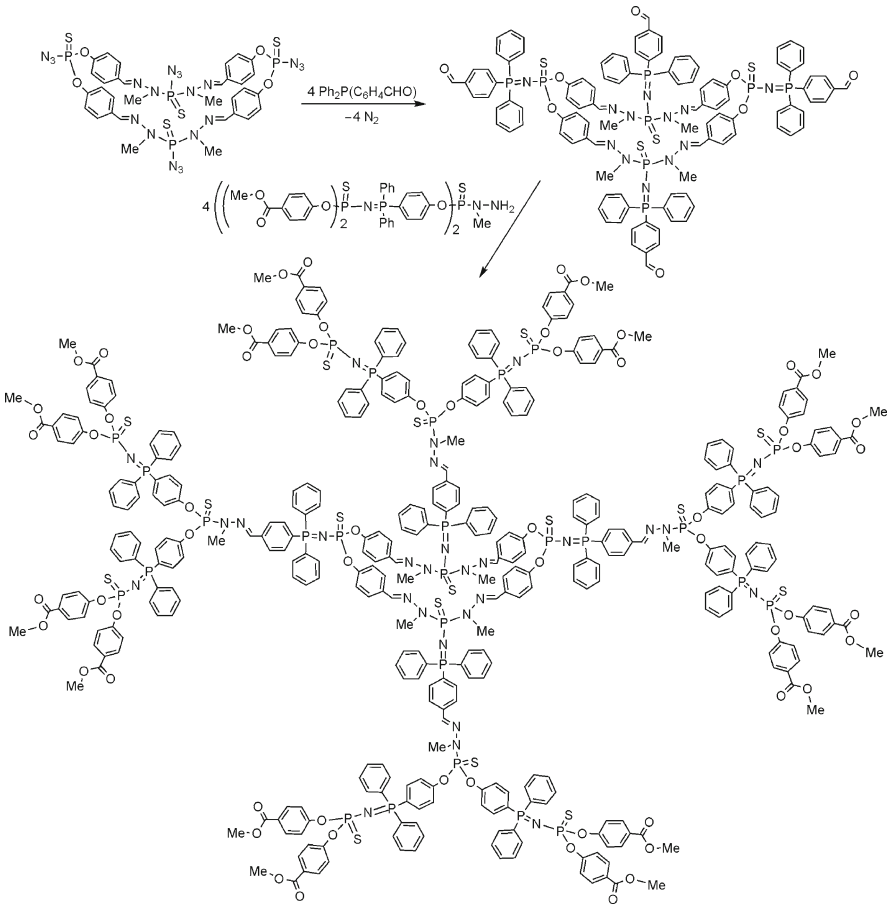

Fig. 21 Grafting of four dendrons to a tetraphosphorus macrocycle

In sharp contrast, the grafting of the four dendrons has a dramatic influence on the shape of the ^{31}P NMR signals corresponding to the same P=N–P=S linkages. Indeed, numerous signals are observed, typical of "frozen" structures. Thus, one may attribute the phenomenon observed to the existence of diastereoisomers of the macrocycle, which become detectable for the first time thanks to the dendrons [44] (Fig. 22).

5.4 Complexation Properties

The presence of specific functions in some macrocycles such as triple bonds or phosphines allows the direct complexation of metals on these sites. Such reactions were carried out with large excess of $Co_2(CO)_8$ in the former case [14] and with a stoichio-

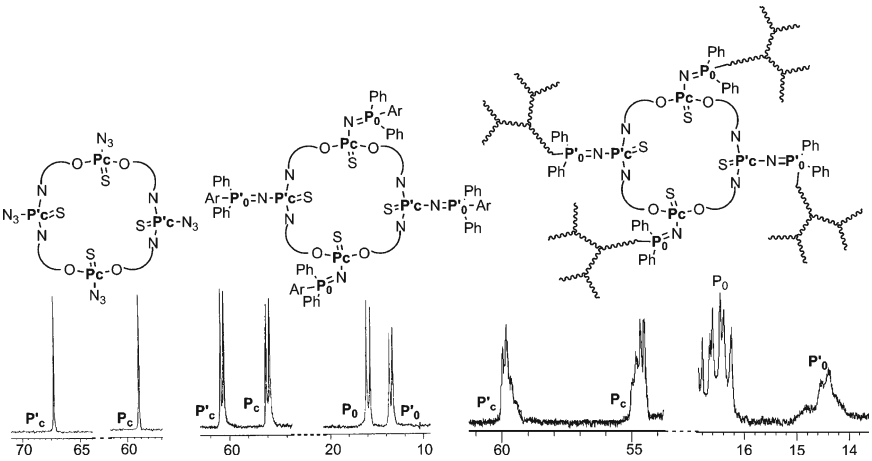

Fig. 22 Variation of the ^{31}P NMR spectra when connecting four dendrons to the macrocycle. Only the signals corresponding to the P=N–P=S linkages connected to the macrocycle are given

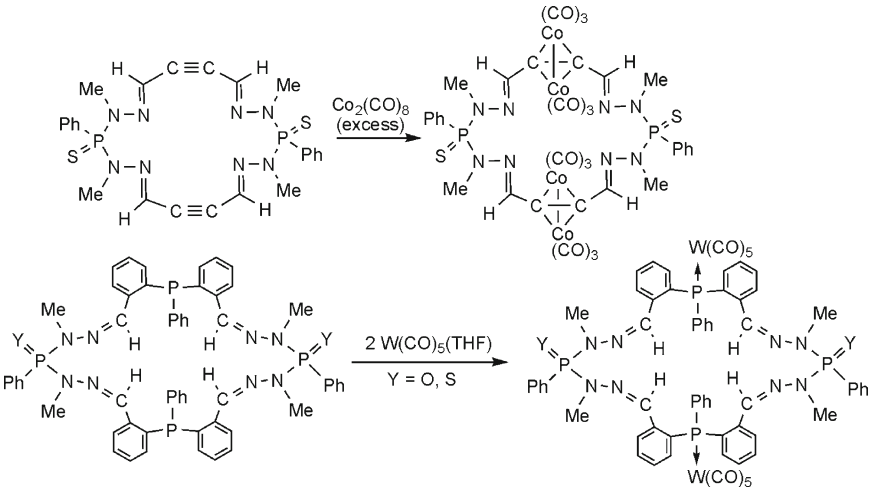

Fig. 23 Complexation properties of specific functions in the macrocycles

metric amount of $W(CO)_5$(THF) in the latter case (Fig. 23) [22]. These complexation reactions are quantitative, but they do not take profit of the macrocyclic structure.

On the contrary, various metallic salts were used to take profit of the entire cycle as the ligand. The interaction is generally strong and results in the precipitation of the complex, which is insoluble in organic solvents and water. This insolubility precludes full characterization of the complex, but IR studies indicated the implication of P=S, P=O and C=N groups. The interaction is driven by both the size of the macrocycle and of the cation. With all metallic cations, except with barium, 1:1 complexes are obtained (1 macrocycle/1 metal). With barium salts (the largest cation

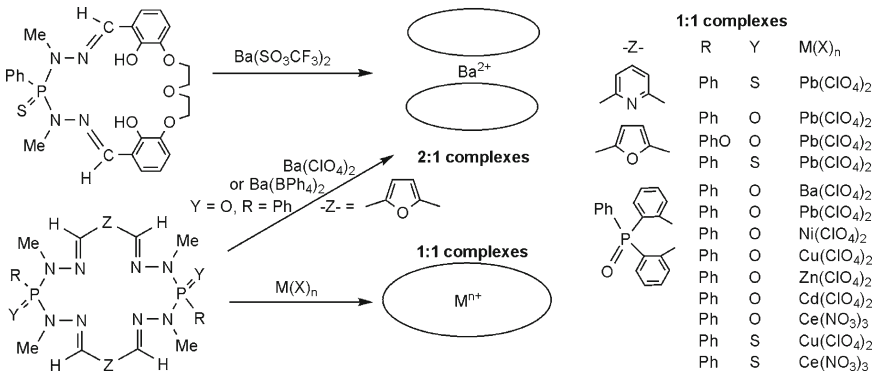

Fig. 24 Complexation properties of macrocycles towards various cations

tested), the complexes comprise two macrocycles per barium cation for the 20-membered rings, but one macrocycle per barium cation for the 24-membered rings, as shown in Fig. 24. The type of macrocycle used for the 1:1 complexation comprises pyridine and furan [45], and phosphine oxide [22, 45] derivatives. The 2:1 complexation was reported to occur from furan [8] and semi-crown ether derivatives. In the latter case, the structure was confirmed by X-ray diffraction [27].

6 Multi-Macrocyclic Species

Some multi-macrocyclic species were in fact obtained during attempts to synthesize cryptands (see Sect. 7), starting from a phosphotrihydrazide, and using either di- or trialdehydes. In the case of the semi-crown ether dialdehyde, the reaction yields cleanly a bimacrocyclic species, bridged by the semi-crown ether [27]. In all the other cases, using a tri- or diverse dialdehydes, the condensation reactions yield only polymers constituted of macrocycles [46] (Fig. 25).

The reaction of the semi-crown ether dialdehyde with the hexahydrazide built from a cyclotriphosphazene did not afford the expected trimacrocyclic species, but an intractable polymer. However, if the reaction is carried out in the presence of barium triflate, the expected trimacrocycle can be separated from polymers and isolated in 10% yield; it does not incorporate any Ba derivative, which served only as a template for the building [47] (Fig. 26).

However, the best way to obtain cleanly multi-macrocyclic species consists of associating functionalized macrocycles. This can be done in several ways. An “all phosphorus” derivative in which both macrocycles and the linker contain phosphorus atoms is obtained quantitatively by substitution reaction of a monofunctionalized macrocycle with a difunctional linker [27] (Fig. 27).

The reaction of tetraphosphorus macrocycles functionalized by two or four azides with two or four equivalents of a phosphine functionalized by a crown ether derivative affords sophisticated multi-macrocyclic structures in which either three

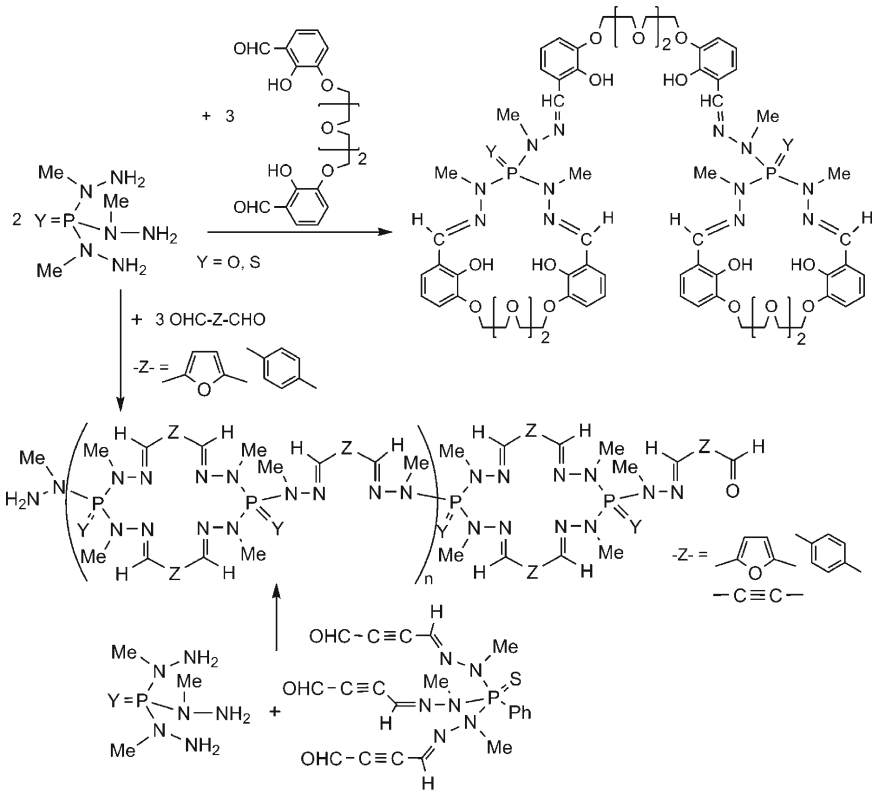

Fig. 25 Synthesis of two types of multi-macrocyclic compounds: bimacrocycle and polymers constituted of macrocycles

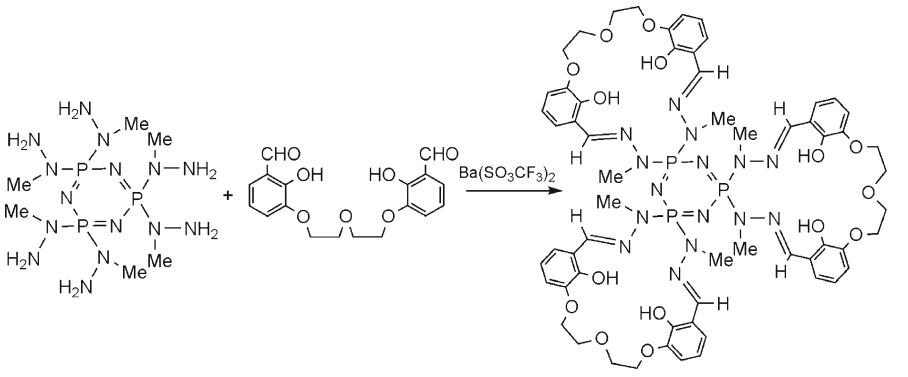

Fig. 26 Trimacrocyclic species built from a cyclotriphosphazene in the presence of barium salt

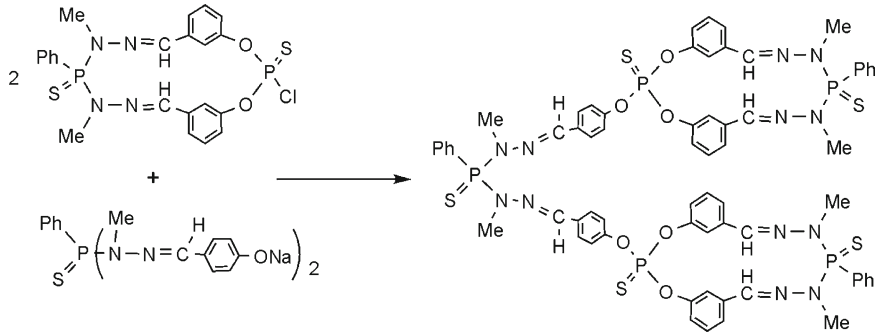

Fig. 27 Bimacrocyclic compound obtained in quantitative yield

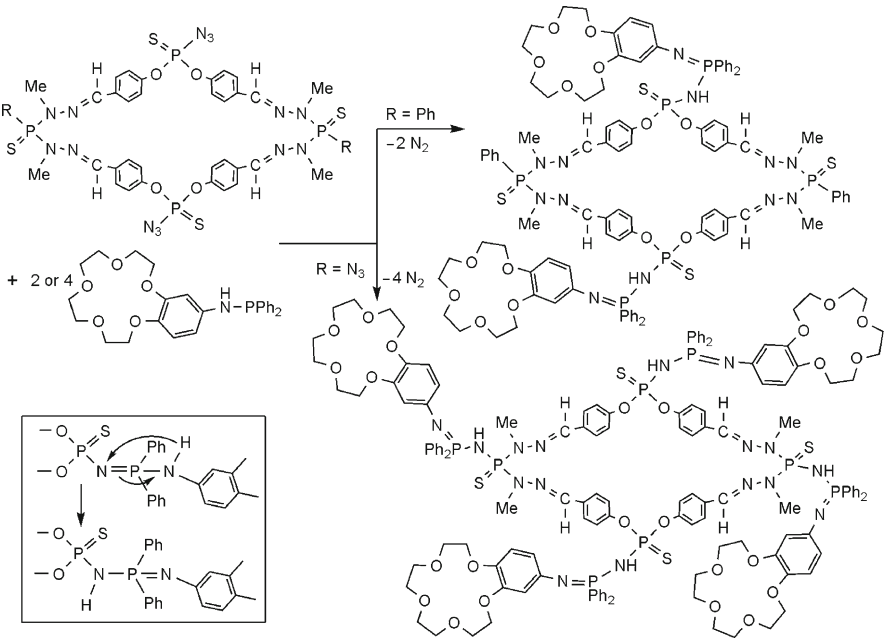

Fig. 28 Tri- and pentamacrocyclic species obtained by Staudinger reactions

macrocycles are associated in a linear fashion, or the central macrocycle bears four macrocycles in a way that is reminiscent of the principle of dendrimers (Fig. 28). Surprisingly, the Staudinger reaction does not afford the expected S=P–N=P–NH linkages, instead the S=P–NH–P=N linkages are formed by a spontaneous migration of the proton from one nitrogen to the other [27].

7 Cryptands

Cryptands are bimacrocyclic species constituted of three chains linked together at two nodes; they are generally more difficult to synthesize than classical "mono"-macrocycles [48]. Only a few examples of such compounds incorporating phosphorus in their structure, generally at one or both nodes, are known [49]. Theoretically, there exists only four ways to synthesize cryptands; they differ mainly by the number of reactions needed. Of course, the lowest number of reactions affords the highest chance to obtain the cryptand in reasonable yield. Consequently, we have only tried the methods **F** and **G** shown in Fig. 29, necessitating two and three reactions, respectively.

In most cases, we have applied the type **F** reactivity to synthesize cryptands, for instance, the reaction of a diphenol sodium salt with a difunctional macrocycle possessing two P–Cl functions. Such a reaction affords a symmetrical cryptand, having three identical chains end-capped by two thiophosphates (Fig. 30) [50].

Other types of difunctional macrocycles possessing two azide groups were used to undergo Staudinger reactions with diphosphines bridged by a long chain. Various types of less symmetrical cryptands, in which one chain is different from the other two, were isolated in this way. Such reactions are compatible with the presence of other functional groups, for instance P–Cl functions (Fig. 31) [12].

The same type of assembling principle was then applied to a macrocyclic diphosphine, affording the most original type of phosphorus cryptands ever synthesized, isolated in 75% yield despite the complexity of the structure. This compound is composed

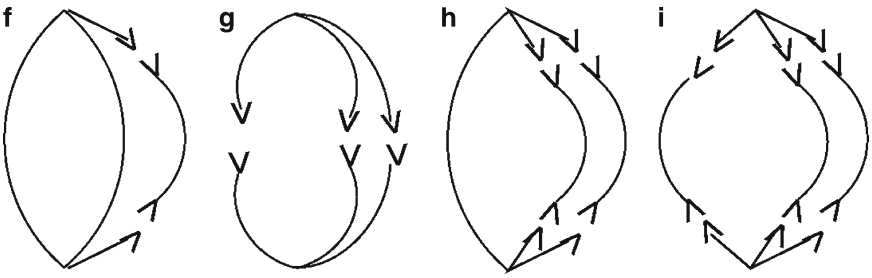

Fig. 29 Four theoretical methods of synthesis of cryptands

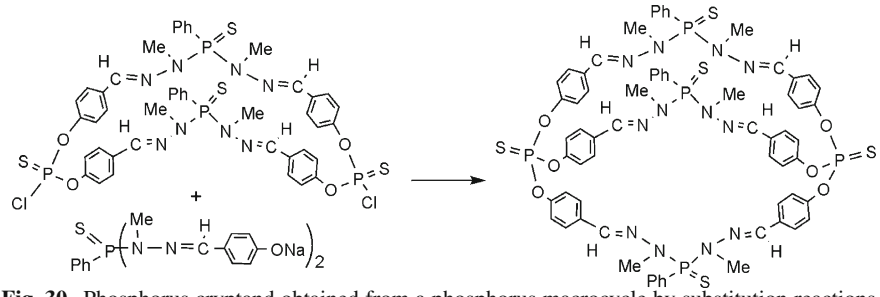

Fig. 30 Phosphorus cryptand obtained from a phosphorus macrocycle by substitution reactions

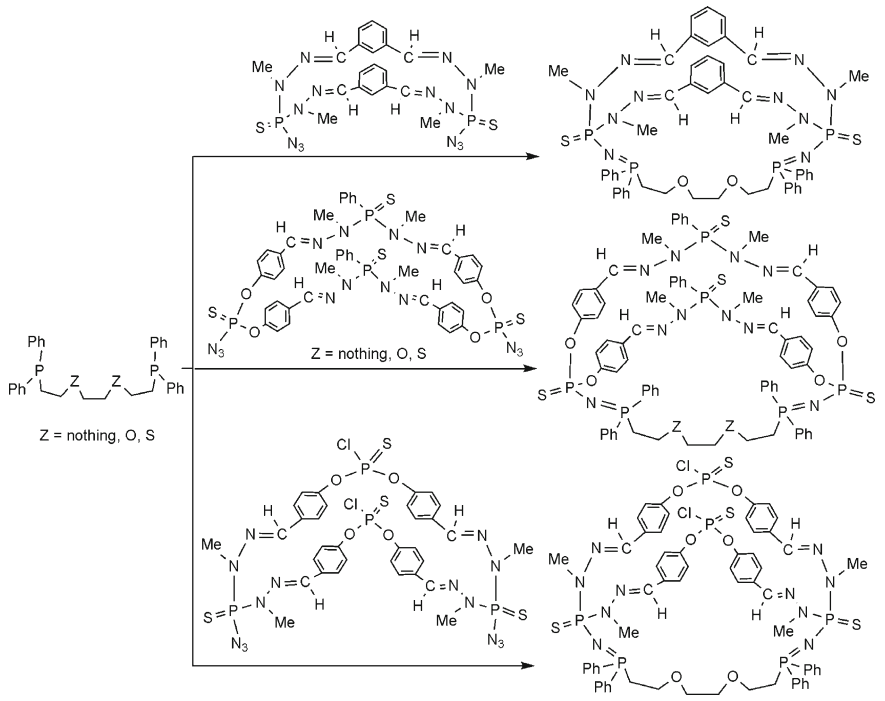

Fig. 31 Phosphorus cryptands obtained from phosphorus macrocycles by Staudinger reactions

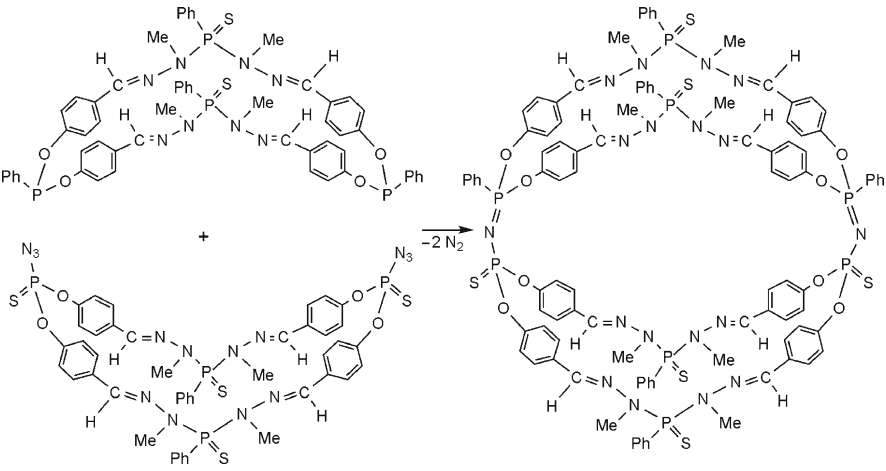

Fig. 32 Spherand structure obtained by Staudinger reactions between two macrocycles

of four identical chains end-capped by two Ph–P=N–P(S) linkages and can be called a "spherand" (Fig. 32) [12].

The type **G** reactivity often leads to polymers, as illustrated in Fig. 25. However, in one case, a cryptand could be isolated in the reaction of phosphotrihydrazides

with phosphorus dialdehydes. These compounds are symmetrical by nature, with three identical chains capped by two P(Y) (Y=O, S) groups (Fig. 33) [50].

8 Towards Dendrimers

We have a great deal of experience in the synthesis and study of properties of dendrimers incorporating in their structure phosphorhydrazone linkages [51], with almost 200 papers published in this field to date. Some of these dendrimers incorporate macrocycles in their structure. In these cases, the phosphorus atoms are generally not included in the macrocyclic chain, but in the substituents of the macrocycles. Numerous types of compounds can be envisaged, but in the case of phosphorus-containing dendrimers, four types of compound incorporating macrocycles in their structures are already known: the simplest compounds have macrocycles as terminal groups (type **J**); in some cases one macrocycle is located at the core of the dendrimers (type **K**) or dendrons (type **L**); and finally several macrocycles are incorporated as pendant arms inside a very sophisticated structure (type **M**) (Fig. 34).

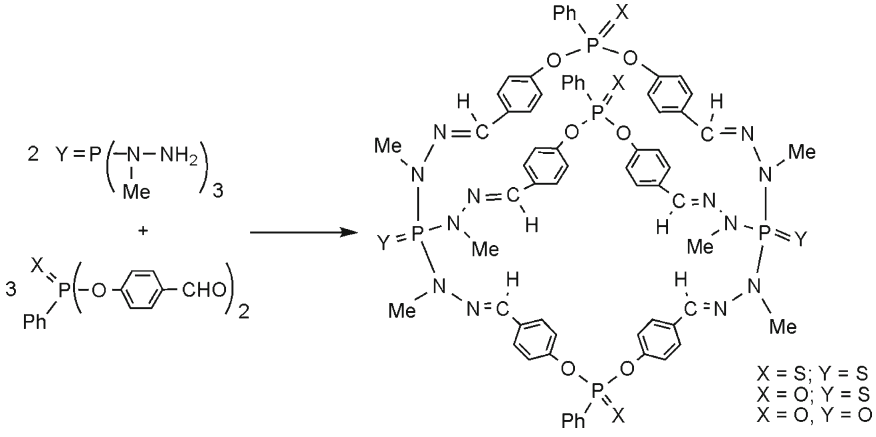

Fig. 33 Cryptands obtained from phosphotrihydrazides

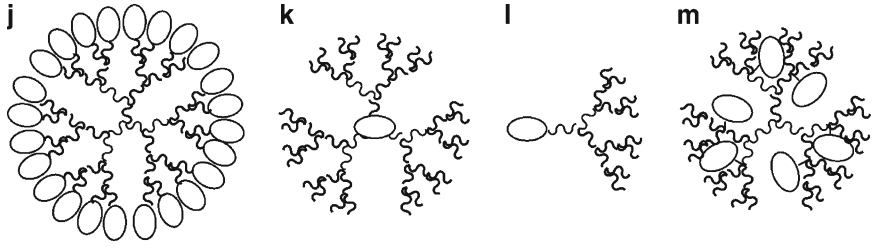

Fig. 34 Various types of phosphorus dendrimers incorporating macrocycles in their structure

8.1 Macrocycles as Terminal Groups of Dendrimers

The phosphorus-containing dendrimers possessing in their structure phosphorhydrazone linkages are built in two steps: a substitution reaction of Cl by hydroxybenzaldehyde under basic conditions, followed by a condensation reaction between aldehydes and the phosphorhydrazide, $H_2NNMe–P(S)Cl_2$. We have seen in all the previous paragraphs that both reactions are particularly useful for synthesizing macrocycles. Their use for growing dendrimers is shown in Fig. 35; it is important to note that both reactions are totally quantitative, with sodium chloride and water as sole by-products. Each time the number of terminal groups is multiplied (generally by 2), a new generation is created. These reactions were carried out up to the 12th generation [52] starting from the trifunctional core $P(S)Cl_3$ (highest generation obtainable), and up to the 8th generation starting from the hexafunctional core, $N_3P_3Cl_6$ [53] (Fig. 35). The structure of these dendrimers is chemically robust, but sensitive to UV laser irradiation [54].

These dendrimers have either $P(S)Cl_2$ or aldehyde as terminal groups, and both were found to be useful for the grafting of macrocycles as terminal groups (type **J** in Fig. 34). Starting from an aldehyde terminal function, a very simple method for grafting macrocycles consists of condensation reactions with a macrocycle bearing one NH_2 group. The first example concerns an amino crown ether (4-aminobenzo-15-crown-5), which was treated with generations 1, 2, 3 and 4 of the dendrimer. Such bulky substituents necessitate a prolonged time of reaction, up to 3 weeks with the 4th generation dendrimer (48 crown ethers as terminal groups) (Fig. 36) [55]. The complexing ability of the second generation was tested: 12 equivalents of sodium tetraphenyl borate were complexed by the second generation which possesses 12 crown ethers as terminal groups [56].

Three types of tetra-aza-macrocycles were treated with the $P(S)Cl_2$ terminal groups, in the presence of K_2CO_3. Each Cl is expected to react with one NH. In the

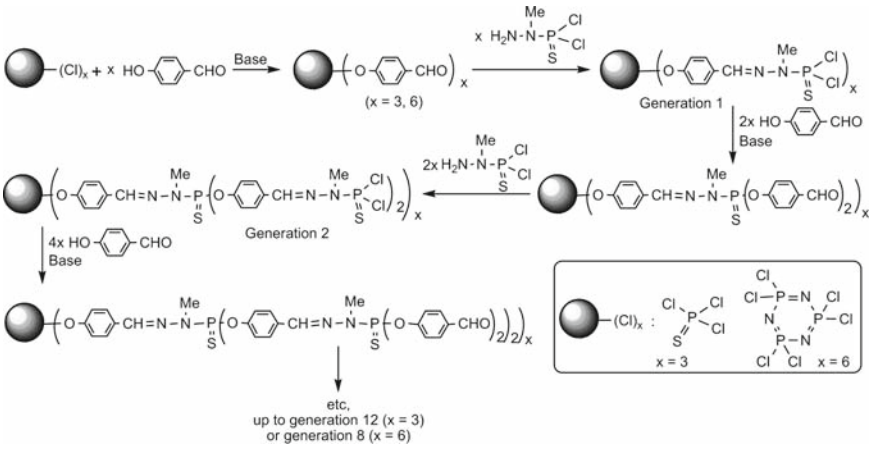

Fig. 35 Main method of synthesis of phosphorhydrazone-containing dendrimers

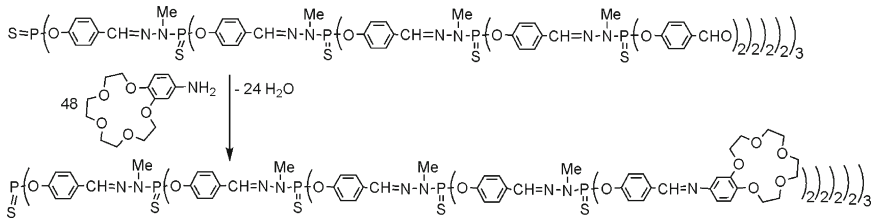

Fig. 36 Grafting of crown ethers to the terminal groups of dendrimers

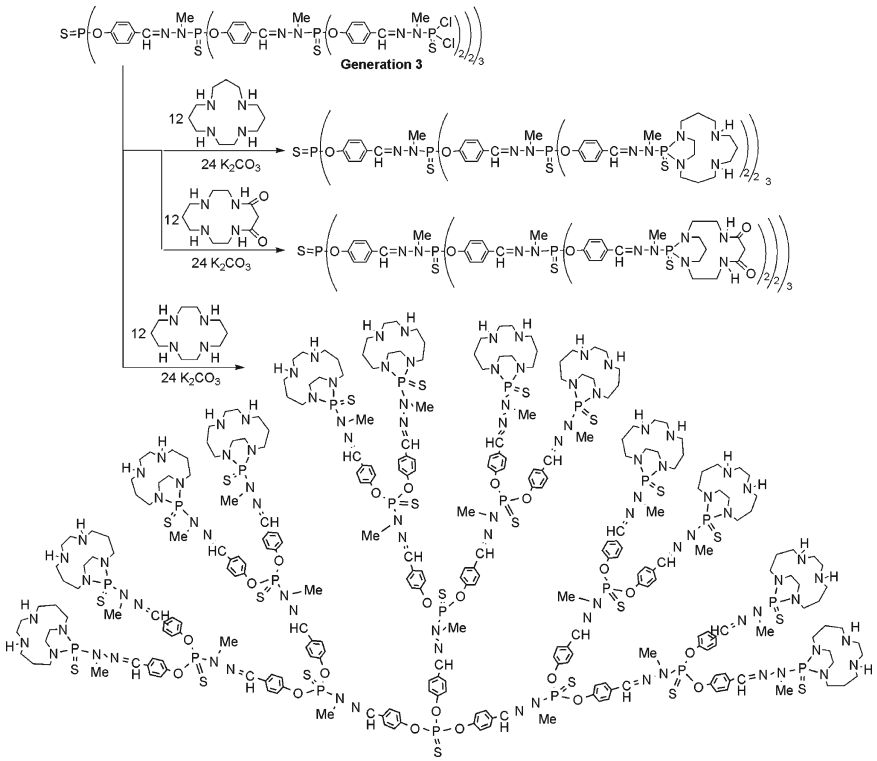

Fig. 37 Grafting of tetraazamacrocycles to the terminal groups of dendrimers

case of 1,4,8,11-tetrazacyclotetradecane (cyclam) and 1,4,8,12-tetrazacyclopentadecane, the grafting can lead either to the 5-membered rings of type diazaphospholane, or 6-membered rings of type diazaphosphorinane. Surprisingly, these reactions were highly specific, and only 5-membered heterocycles were created in both cases. In the case of 1,4,8,11-tetrazacyclotetradecane-5,7-dione, only 6-membered rings were expected due to the well-known low reactivity of amides, and they were indeed obtained. These reactions afforded 12-, 13- or 14-membered monophosphatetraazamacrocycles linked to the surface of dendrimers [57] (Fig. 37). Such reactions were carried out from generation 1 (three macrocycles) to generation 3 (12 macrocycles).

We have recently used condensation reactions to graft other aminomacrocycles through alkyl-imine linkages, which should be less stable than the diaryl linkage obtained in Fig. 36. To overcome this problem, the reaction was carried out in the presence of $NaBH_4$ to reduce the imine linkages (and not the hydrazone linkages). Such reactions were used with generations 0, 1 and 4 of the dendrimers built from the hexafunctional core, and allowed the grafting of 6, 12 and 96 triazatriolefinic 15-membered macrocycles, respectively (Fig. 38). Reaction of these compounds with $Pd(PPh_3)_4$ and $Pd_2(dba)_4$ afforded either discrete palladium complexes (1 Pd per macrocycle), or Pd-nanoparticles; their diameters were from 2.4 to 5.7 nm with a narrow

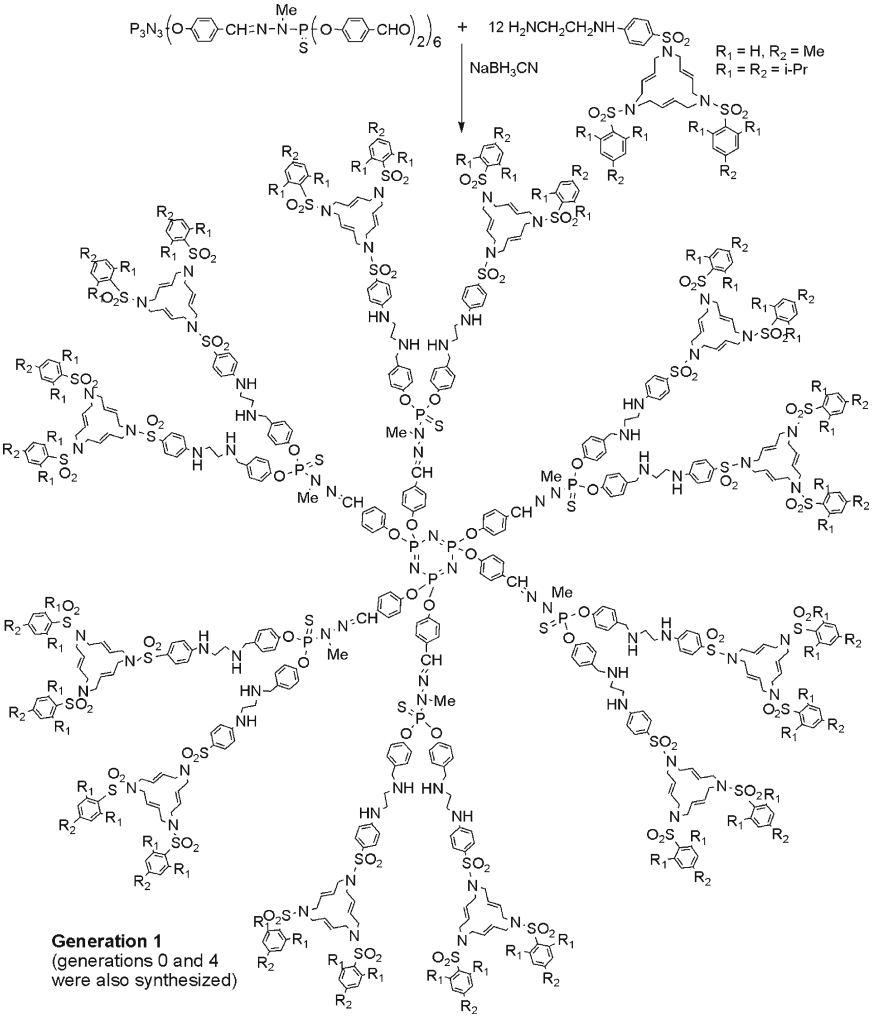

Fig. 38 Grafting of triazatriolefinic macrocycles to the terminal groups of dendrimers

size distribution (±1.0 nm), depending on the Pd^0 source, the dendrimers generation, and the ratio Pd/macrocycle. The catalytic properties of these compounds were assayed for the Heck reaction; they were found to be efficient and reusable [58].

Besides condensations, the other type of well-known reaction of aldehydes is the Wittig reaction. It was applied to a crown-ether TTF derivative bearing a phosphonium substituent and the 4th generation dendrimer. This particular macrocyclic dendritic system (Fig. 39) is able to respond electrochemically. It is potentially usable as a chemo-sensor, since its electrochemical response is modified when interacting with a guest ion, such as barium, and the modification of the response depends on the amount of Ba^{2+} added [59].

8.2 Macrocycles at the Core of Dendrimers or Dendrons

We have already shown in Fig. 21 an example of a phosphorus macrocycle used as the core of a second generation dendrimer (type **K** compound in Fig. 34). In this case, dendrons were grafted in the last step to the core by a divergent process [44]. There exists another method for synthesizing dendrimers having a macrocycle as the core which is a divergent process: the dendritic branches are built step-by-step starting from the core. For this purpose we used an octaaldehyde phthalocyanine. This 16-membered octaazamacrocycle is reacted with the phosphorhydrazide, then with hydroxybenzaldehyde, in the way already shown in Fig. 35. These reactions were carried out up to generation 5 [60], then to generation 7 (Fig. 40). Remarkably, the green colour due to the phthalocyanine core remains very bright even for the seventh generation. Furthermore, the phthalocyanine core is usable as a sensor and a probe for determining the properties of the internal structure, and its influence on the core. Indeed, the variation of the intensity and wavelength of the Q-band of the phthalocyanine with increasing generations, demonstrates an increased isolation (disappearance of aggregation) and that the branches mimic the influence of a highly polar solvent such as DMF. The increased isolation of the core is also demonstrated by fluorescence:

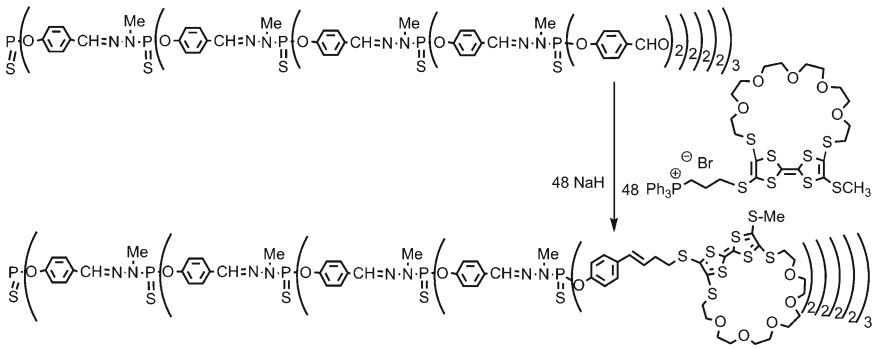

Fig. 39 Grafting of crown-ether TTF derivatives to the terminal groups of dendrimers

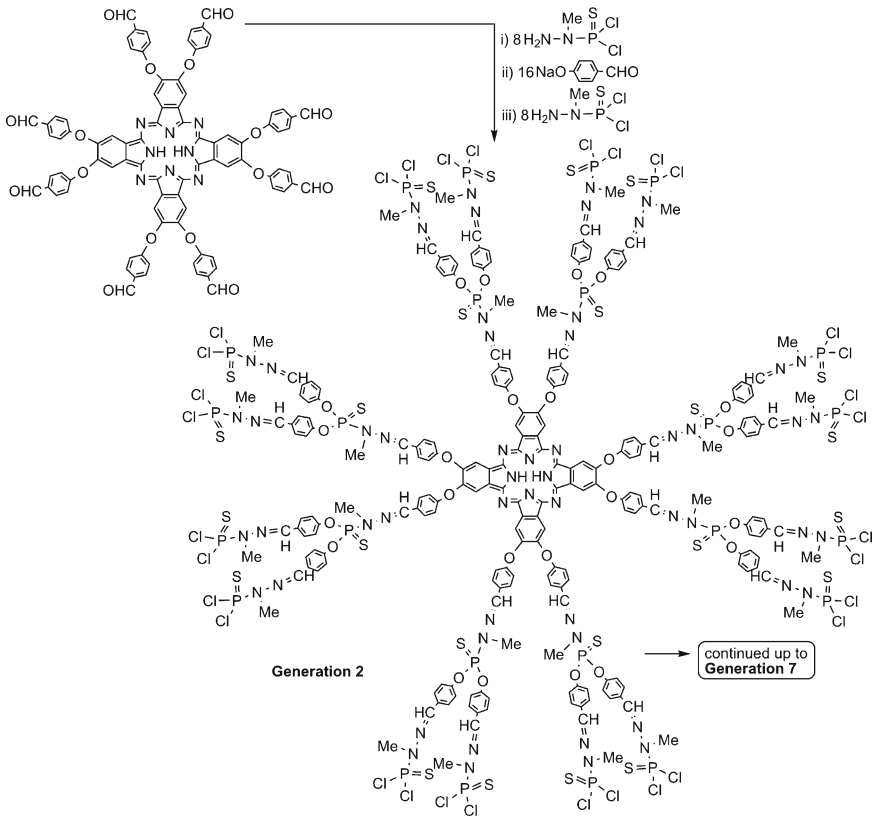

Fig. 40 Synthesis of dendrimers from a phthalocyanine core

the fluorescence quantum yield is higher for generations 3 and 4 than for generation 1. However, the core remains accessible to small molecules, as shown by the addition of NaOH, which induces a dramatic diminishing of the fluorescence intensity [61]. The phthalocyanine core can be used also to trap metal ions, especially copper and cobalt cations, inducing a total loss of fluorescence (Fig. 41) [62]. Grafting ammonium terminal groups induces solubility in water, interesting for biological experiments as a fluorescent transfection agent [63].

We have also synthesized dendrons possessing one vinyl group at the core, suitable to undergo Michael-type additions with primary and secondary amines. Water-soluble vinyl dendrons having ammonium terminal groups were grafted to the surface of latex nanoparticles coated by cyclam. Such a reaction produces dendrons having one macrocycle as the core (type **L** compound in Fig. 34) and linked to the nanolatex (Fig. 42). The number of dendrons linked to one nanoparticle depends on the generation, but the number of ammonium groups is almost constant (600–800 ammonium groups

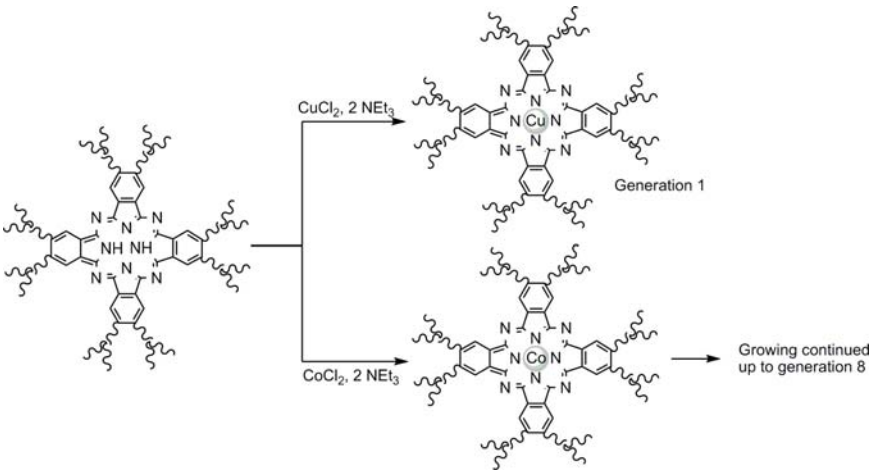

Fig. 41 Complexation properties of the phthalocyanine core of dendrimers

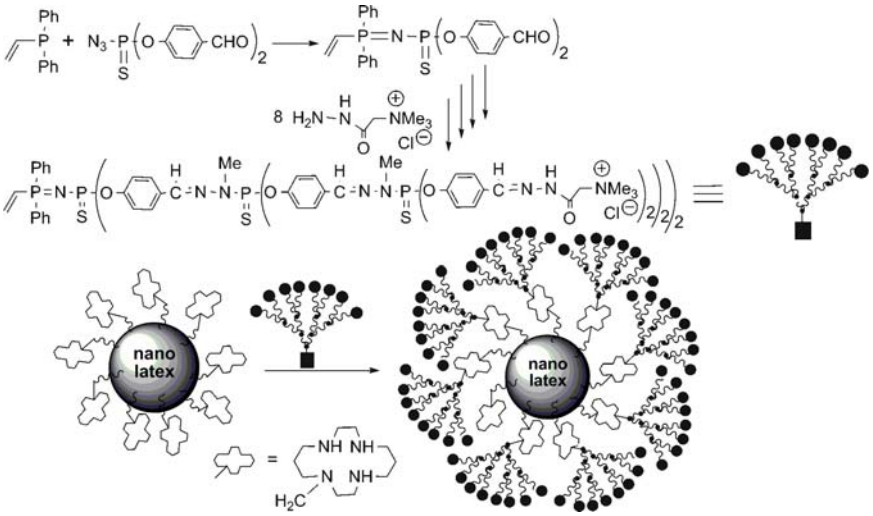

Fig. 42 Dendrons linked to a nanoparticle through a tetraazamacrocycle

per particle, whatever the generation of the dendron used). Interestingly, the presence of these dendrons improves the stability of aqueous suspensions of the nanolatex, as well as the thermal stability. Despite the presence of the dendron layer, the macrocycle at the core retains its metal-complexing ability. Indeed, a Cu(II)-binding capacity of 0.2-mmol per g of nanoparticles was measured, demonstrating the permeability of the dendritic shell [64].

8.3 Macrocycles inside the Structure of Dendrimers

The P=N–P=S linkages obtained by Staudinger reactions as indicated in Sect. 5.3.2 were found to be suitable for the functionalization of macrocycles, and for the synthesis of functionalized dendrimers [65]. Furthermore, these P=N–P=S linkages are specifically alkylated on sulphur with methyl triflate. The other P=S groups are not alkylated [66], contrary to what was previously observed in the case of macrocycles (see Sect. 5.2). The difference is presumably due to the different environment around the P=S groups (one carbon, two nitrogen atoms in the case of macrocycles; one nitrogen, two oxygen atoms in the case of dendrimers), which induce a different electronic repartition [67]. Desulphurization of the P=N–P=S linkages is obtained with $P(NMe_2)_3$, affording a P^{III} atom inside the structure of the dendrimer [40], suitable to undergo another Staudinger reaction. If the azide bears two aldehyde functions, it can be used for various types of reactions [68, 69], and in particular for the condensation with the amino crown ether, already used as terminal groups in Fig. 37. In the present case, the macrocycles are linked as pendant groups inside the structure of the dendrimer, resulting in the highly sophisticated dendritic structure shown in Fig. 43 (type **M** compound in Fig. 34) [70].

9 Conclusions

We have seen that phosphorhydrazone-containing macrocycles can be synthesized in three different ways: the most preferred is the condensation of hydrazides with aldehydes; substitution reactions on phenols also have great potential, whereas substitution reactions on NH have been rarely used. In all cases, the predominant type of cyclization necessitates two molecules of each partner; macrocycles having from 18 to 44 bonds in the ring were synthesized by these [2 + 2] reactions. The [1 + 1] reactions were also observed in some cases, leading to macrocycles having from 14 to 32 bonds in the ring. Macrocycles arising from [3 + 3] and [4 + 4] cyclizations were observed rarely (Fig. 44).

These macrocycles are isolated in good to quantitative yields without using any high dilution or template techniques, in sharp contrast to all other types of macrocycles. This is because of the use of phosphodihydrazides, which provide the geometry suitable for the cyclization and a good stability of the ring. Moreover, these compounds offer a large palette or reactivity (including the complexation of cations), and some of them are useful precursors of original cryptands, also isolated in very good yields.

The phosphorhydrazone linkages are also extremely useful for synthesizing very stable dendrimers in quantitative yields; indeed they provide one of the four most widely used types of dendrimers in the world (the three others are polyamidoamine (PAMAM) dendrimers [71], polypropyleneimine (PPI) dendrimers [72] and polyarylether dendrimers [73]). These phosphorus-containing dendrimers possess a versatile reactivity at all levels (terminal groups, internal branches, core), which

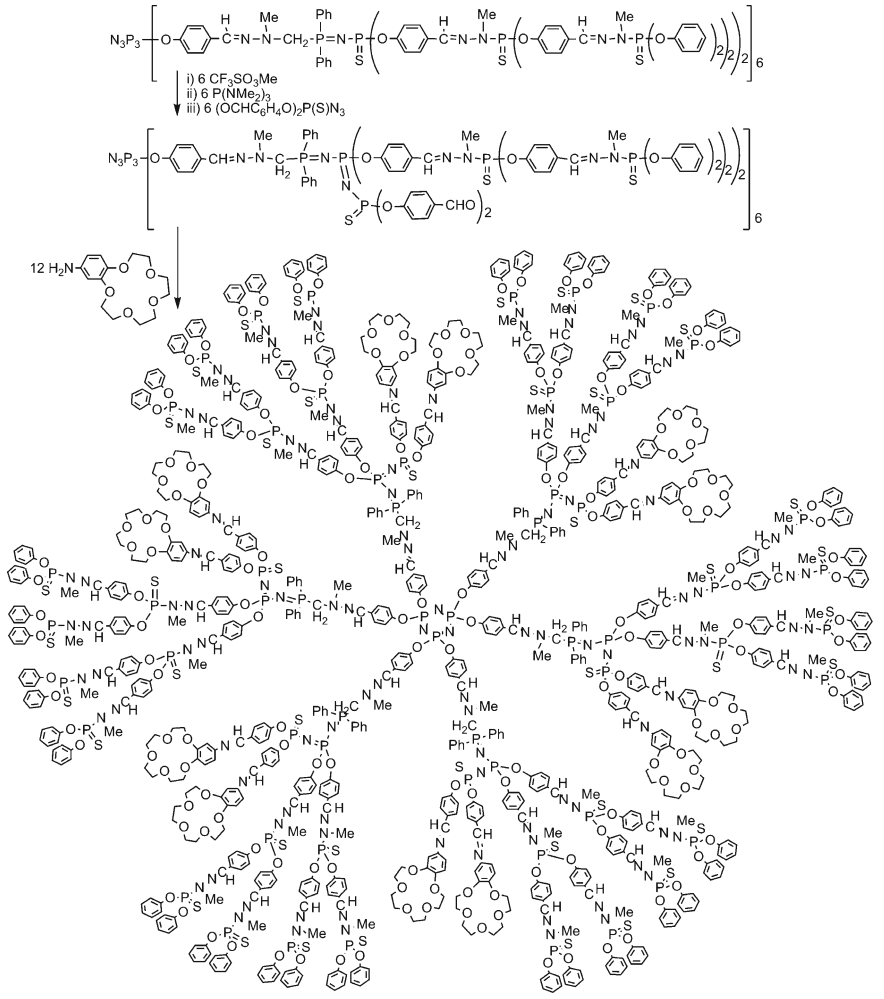

Fig. 43 Grafting of 12 crown ethers in the internal structure of dendrimers

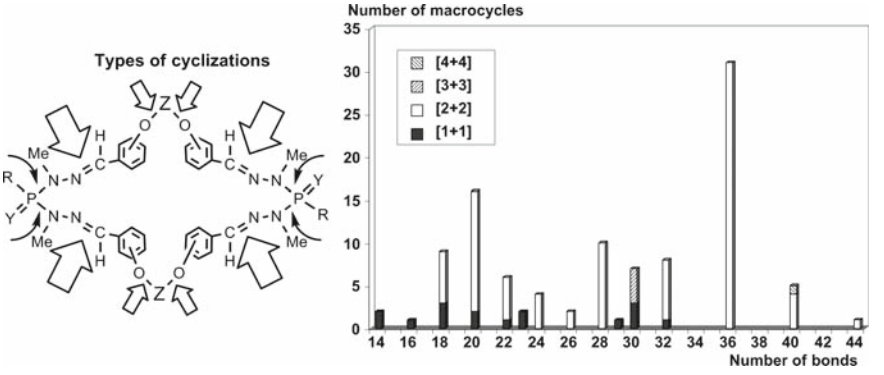

Fig. 44 Types of cyclizations and number of macrocycles of each size obtained from phosphodihydrazides

allowed finding applications in very diverse fields, such as catalysis [74], nanomaterials [75] (e.g. organic nanotubes [76] and nanocontainers [60]), chemical sensors [61], biosensors [77], medical imaging [78], or as activators of the human immune system [79], to name but a few. The dendrimers which include macrocycles in their structure were reviewed at the end of this paper, to illustrate again the high synthetic potential of phosphorhydrazones.

References

1. Stokes HN (1897) Am Chem J 19:782
2. Pedersen CJ (1967) J Am Chem Soc 89:7017
3. Caminade AM, Majoral JP (1994) Chem Rev 94:1183
4. Hua G, Li Y, Slawin AMZ, Woollins JD (2008) Angew Chem Int Ed 47:2857
5. Gonzales-Calera S, Eisler DJ, Morey JV, McPartlin M, Wright DS (2008) Angew Chem Int Ed 47:1111
6. Matano Y, Miyajima T, Nakabuchi T, Imahori H, Ochi N, Sakaki S (2006) J Am Chem Soc 128:11760
7. Theil A, Mauve C, Adeline MT, Marinetti A, Sauvage JP (2006) Angew Chem Int Ed 45:2104
8. Majoral JP, Badri M, Caminade AM, Delmas M, Gaset A (1988) Inorg Chem 27:3873
9. Galliot C, Caminade AM, Dahan F, Majoral JP (1993) Angew Chem Int Ed Engl 32:1477
10. Colombo-Khater D, He Z, Caminade AM, Dahan F, Kraemer R, Majoral JP (1993) Synthesis 1145
11. Majoral JP, Kraemer R, Navech J, Mathis F (1976) Tetrahedron 32:2633
12. Mitjaville J, Caminade AM, Mathieu R, Majoral JP (1994) J Am Chem Soc 116:5007
13. Mitjaville J, Caminade AM, Majoral JP (1995) Synthesis 952
14. Badri M, Majoral JP, Caminade AM, Delmas M, Gaset A, Gorgues A, Jaud J (1990) J Am Chem Soc 112:5618
15. Oussaid B, Garrigues B, Caminade AM, Majoral JP (1992) Phosphorus Sulfur Silicon 73:41
16. Oussaid B, Garrigues B, Jaud J, Caminade AM, Majoral JP (1993) J Org Chem 58:4500
17. Majoral JP, Badri M, Caminade AM, Gorgues A, Delmas M, Gaset A (1990) Phosphorus Sulfur Silicon 49–50:413
18. Badri M, Majoral JP, Gonce F, Caminade AM, Sallé M, Gorgues A (1990) Tetrahedron Lett 31:6343
19. Launay N, Denat F, Caminade AM, Majoral JP, Dubac J (1994) Bull Soc Chim Fr 131:758
20. Chandrasekhar V, Andavan GTS, Azhakar R, Pandian BM (2007) Synth React Inorg Met Org Nano-Met Chem 37:725
21. Chandrasekhar V, Andavan GTS, Azhakar R, Pandian BM (2004) Tetrahedron Lett 47:8365
22. Gonce F, Caminade AM, Majoral JP (1991) Tetrahedron Lett 32:203
23. Colombo D, Caminade AM, Majoral JP (1991) Inorg Chem 30:3365
24. Prévoté D, Galliot C, Caminade AM, Majoral JP (1995) Heteroatom Chem 6:313
25. Galliot C, Caminade AM, Majoral JP, Kuznikowski M, Zablocka M, Pietrusiewicz KM (1995) Chem Ber 128: 443
26. Gonce F, Caminade AM, Boutonnet F, Majoral JP (1992) J Org Chem 57:970
27. Mitjaville J, Caminade AM, Daran JC, Donnadieu B, Majoral JP (1995) J Am Chem Soc 117:1712
28. Gonce F, Caminade AM, Jaud J, Vignaux P, Majoral JP (1992) Bull Soc Chim Fr 129:237
29. Majoral JP, Caminade AM (1992) The chemistry of inorganic ring systems. In: Steudel R (ed) Studies in Inorganic Chemistry, vol. 14, chap. 12. Elsevier Science, Amsterdam, p 209
30. Colombo-Khater D, Caminade AM, Delavaux-Nicot B, Majoral JP (1993) Organometallics 12:2861
31. Caminade AM, Colombo-Khater D, Mitjaville J, Galliot C, Mas P, Majoral JP (1993) Phosphorus Sulfur Silicon 75:67

32. Richelme S, Claparols C, Leroy E, Caminade AM, Munoz A (2000) Phosphorus Sulfur Silicon 161:143
33. Curtis NF (1968) Coord Chem Rev 3:3
34. Majoral JP, Caminade AM, Igau A (1994) In: Quin LD, Verkade JG (eds) Phosphorus-31 NMR spectral properties in compound characterization and structural analysis, chap. 5. VCH, Deerfield Beach, FL, USA, p 57
35. Caminade AM, Majoral JP (1996) Synlett 1019
36. Majoral JP, Badri M, Caminade AM (1991) Heteroatom Chem 2:45
37. Galliot C, Caminade AM, Dahan F, Majoral JP (1993) Angew Chem Int Ed Engl 32:1477
38. Majoral JP, Badri M, Caminade AM, Delmas M, Gaset A (1991) Inorg Chem 30:344
39. Omelanczuk J (1992) J Chem Soc Chem Commun 1718
40. Galliot C, Larré C, Caminade AM, Majoral JP (1997) Science 277:1981
41. Magro G, Caminade AM, Majoral JP (2003) Tetrahedron Lett 44:7007
42. Staudinger H, Hauser E (1921) Helv Chim Acta 4:861
43. Merino S, Brauge L, Caminade AM, Majoral JP, Taton D, Gnanou Y (2001) Chem Eur J 7:3095
44. Turrin CO, Maraval A, Magro G, Maraval V, Caminade AM, Majoral JP (2006) Eur J Inorg Chem 2556
45. Caminade AM, Kraemer R, Majoral JP (1996) Inorg Chim Acta 246:47
46. Badri M, Caminade AM, Majoral JP, Gorgues A (1991) Phosphorus Sulfur Silicon 56:123
47. Kraemer R, Galliot C, Mitjaville J, Caminade AM, Majoral JP (1996) Heteroatom Chem 7:149
48. Lehn JM (1978) Acc Chem Res 11:49
49. Caminade AM, Kraemer R, Majoral JP (1997) New J Chem 21:627
50. Mitjaville J, Caminade AM, Majoral JP (1994) J Chem Soc Chem Commun 2161
51. Launay N, Caminade AM, Lahana R, Majoral JP (1994) Angew Chem Int Ed Engl 33:1589
52. Lartigue ML, Donnadieu B, Galliot C, Caminade AM, Majoral JP, Fayet JP (1997) Macromolecules 30:7335
53. Launay N, Caminade AM, Majoral JP (1997) J Organomet Chem 529:51
54. Blais JC, Turrin CO, Caminade AM, Majoral JP (2000) Anal Chem 72:5097
55. Launay N, Caminade AM, Majoral JP (1995) J Am Chem Soc 117:3282
56. Launay N, Slany M, Caminade AM, Majoral JP (1996) J Org Chem 61:3799
57. Prévôté D, Donnadieu B, Moreno-Manas M, Caminade AM, Majoral JP (1999) Eur J Org Chem 1701
58. Badetti E, Caminade AM, Majoral JP, Moreno-Manas M, Sebastian RM (2008) Langmuir 24:2090
59. Le Derf F, Levillain E, Gorgues A, Sallé M, Sebastian RM, Caminade AM, Majoral JP (2001) Angew Chem Int Ed 40:224
60. Leclaire J, Coppel Y, Caminade AM, Majoral JP (2004) J Am Chem Soc 126:2304
61. Leclaire J, Dagiral R, Fery-Forgues S, Coppel Y, Donnadieu B, Caminade AM, Majoral JP (2005) J Am Chem Soc 127:15762
62. Leclaire J, Dagiral R, Pla-Quintana A, Caminade AM, Majoral JP (2007) Eur J Inorg Chem 2890
63. Maszewska M, Leclaire J, Cieslak M, Nawrot B, Okruszek A, Caminade AM, Majoral JP (2003) Oligonucleotides 13:193
64. Larpent C, Geniès C, De Sousa Delgado AP, Caminade AM, Majoral JP, Sassi JF, Leising F (2004) Chem Commun 1816
65. Merino S, Brauge L, Caminade AM, Majoral JP, Taton D, Gnanou Y (2001) Chem Eur J 7:3095
66. Brauge L, Caminade AM, Majoral JP, Slomkowski S, Wolszczak M (2001) Macromolecules 34:5599
67. Larré C, Caminade AM, Majoral JP (1997) Angew Chem Int Ed Engl 36:596
68. Larré C, Donnadieu B, Caminade AM, Majoral JP (1998) J Am Chem Soc 120:4029
69. Cadierno V, Igau A, Donnadieu B, Caminade AM, Majoral JP (1999) Organometallics 18:1580

70. Larré C, Bressolles D, Turrin C, Donnadieu B, Caminade AM, Majoral JP (1998) J Am Chem Soc 120:13070
71. Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P (1985) Polymer J 17:117
72. Buhleier E, Wehner W, Vögtle F (1978) Synthesis 155
73. Hawker CJ, Fréchet JMJ (1990) J Am Chem Soc 112:7638
74. Ouali A, Laurent R, Caminade AM, Majoral JP, Taillefer M (2006) J Am Chem Soc 128:15990
75. Caminade AM, Majoral JP (2004) Accounts Chem Res 37:341
76. Feng CL, Zhong XH, Steinhart M, Caminade AM, Majoral JP, Knoll W (2007) Adv Mater 19:1933
77. Le Berre V, Trevisiol E, Dagkessamanskaia A, Sokol S, Caminade AM, Majoral JP, Meunier B, François J (2003) Nucl Acids Res 31:e88
78. Krishna TR, Parent M, Werts MHV, Moreaux L, Gmouh S, Charpak S, Caminade AM, Majoral JP, Blanchard-Desce M (2006) Angew Chem Int Ed 45:4645
79. Griffe L, Poupot M, Marchand P, Maraval A, Turrin CO, Rolland O, Métivier P, Bacquet G, Fournié JJ, Caminade AM, Poupot R, Majoral JP (2007) Angew Chem Int Ed 46:2523

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