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Phosphorus Heterocycles II

21

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The overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which will suit to a larger heterocyclic community.
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Topics in Heterocyclic Chemistry ISSN 1861-9282
ISBN 978-3-642-12253-8 e-ISBN 978-3-642-12254-5
DOI 10.1007/978-3-642-12254-5
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2010924277

Cover design: WMX Design GmbH, Heidelberg, Germany

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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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 is also included which provides information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic ring are also dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.

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The individual volumes of *Topics in Heterocyclic Chemistry* are thematic. Review articles are generally invited by the volume editors.

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Preface

The success of the ongoing series "Topics in Heterocyclic Chemistry" being published by Springer Verlag motivated the publisher and the then Chief Editor to bring out two special volumes on "Phosphorus Heterocycles," and I was invited to shoulder this responsibility in the capacity of the Guest Editor.

The special volume "Phosphorus Heterocycles I" was published last year which included the following critical review articles:

Anellated Azaphospholes
Biological Activity of Aminophosphonic Acids and Their Short Peptides
Phosphinine Derivatives and their Use as Versatile Intermediates in P-Heterocyclic Chemistry
Spiro- and Tricyclic Phosphoranes with Six- and Higher-Membered Rings
The Chemistry of Phosphinines
Synthetic Approaches to 1,2-Heteraphosphacyclanes,
Phosphorus-Containing Calixarenes
From Phosphorus-Containing Macrocycles to Phosphorus-Containing Dendrimers.

After receiving an enthusiastic and active response and support from the academic community, particularly the organophosphorus chemists, we intensified our efforts to bring out the special volume, "Phosphorus Heterocycles II" at the earliest and now it is in your hands.

This volume includes six chapters.

The first chapter "Heterophenes Carrying Phosphorus Functional Groups as Key Structures" presents a detailed description of the recent advances made in this field. The recent studies of all-phosphorus-substituted aromatic compounds have revealed some unique properties of these heterocycles.

The second chapter "Synthesis and Biological Activity of 2,5-Dihydro-1,2-Oxaphosphole-2-Oxide Derivatives" deals with the recent synthetic methods, particularly those using phosphorylated allenes as the starting materials, of these compounds which show interesting biological properties.

The third chapter "Recent Developments in the Chemistry of N-Heterocyclic Phosphines" presents a survey on five- and six-membered phosphorus–nitrogen heterocyclic compounds whose rings combine a phosphazene or phosphazane unit

with an unsaturated C_2 or C_3 building block. It highlights the accomplishments in the exploration of the chemical properties at the border of classical organic heterocyclic chemistry and molecular organic chemistry.

The fourth chapter "Selected Five-Membered Phosphorus Heterocycles Containing a Stereogenic Phosphorus" presents the description of the synthesis and use of these compounds in a few asymmetric syntheses.

The fifth chapter "1-(2,4,6-Trialkylphenyl)-1H-Phospholes with a Flattened P-Pyramid: Synthesis and Reactivity" presents the interesting chemistry of these compounds including electrophilic substitution and Diels–Alder reactions and sigmatropic rearrangements, making a variety of organophosphorus compounds accessible.

The last chapter "Recent Advances in the Chemistry of Diazaphospholes" describes the chemistry of these compounds including their varied and versatile reactivities and different coordination modes in metal complexes.

I take this opportunity to express my sincere thanks to the people at Springer, particularly Ms. Ingrid Samide and Ms. Anette Lindqvist for their dedicated support in completing the project.

Jaipur, Spring 2010

Raj K. Bansal
Guest Editor

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Top Heterocycl Chem (2010) 21: 1–22
DOI: 10.1007/7081_2009_3

Published online: 19 June 2009

Heterophenes Carrying Phosphorus Functional Groups as Key Structures

Shigeru Sasaki

Abstract Heterophenes have contributed a great deal to the progress of π-conjugated systems such as benzenoid and quinoid compounds. Introduction of heterophenes in place of benzenoid or benzoquinoid structures in π-conjugated systems often leads to improvement of properties and stability as well as facile synthesis. In recent studies on phosphorus compounds, heterophenes such as thiophene and selenophene played a key role in the construction of unique π-conjugated systems. The focus of this chapter is on heterophenes carrying phosphorus functional groups as key structures. A series of phosphaquinoid compounds, which have low coordinated phosphorus as well as quinoid structure, have been synthesized during this decade, and those carrying thienoquinoid structure greatly contributed to diversity as well as understanding of properties. Cyclic π-conjugated systems completely substituted by heteroatoms have attracted considerable attention for a long time from structural as well as physical viewpoints. Although benzene carrying phosphorus substituents on all carbons has not yet been synthesized, recent studies on all-phosphorus-substituted aromatic compounds reached five-membered ring systems, and thiophene and selenophene fully substituted by phosphoryl groups were synthesized by unconventional manner and shown to have unique structure.

Keywords Heterophene • Phosphorus • Phosphoryl compounds • Quinoid compounds • Thiophene

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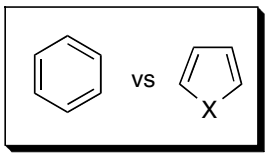
Content

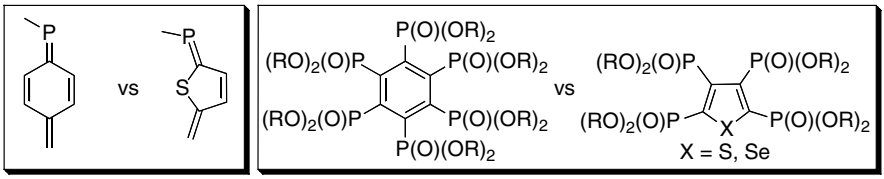
1 Introduction

Heterophenes represented by thiophene have greatly contributed to progress in π-conjugated systems. Because they have aromaticity to a certain degree and stability comparable to benzenes, every π-conjugated system possessing benzene rings have heterophene counterparts, which enables construction of various π-conjugated systems (Scheme 1). These heterophene analogs are expected to display not only properties similar to benzenes, but also unique properties coming from reduced aromaticity or introduction of heteroatoms. From synthetic viewpoints, heterophenes can be synthesized or introduced to π-conjugated systems by similar as well as very different ways to benzenes. In addition, they undergo several reactions less common in benzenes, such as oxidation or coordination of heteroatoms and cycloaddition as dienes.



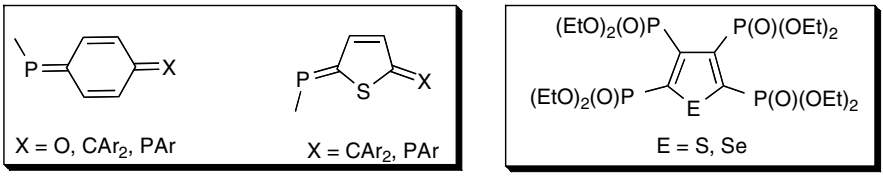
Scheme 1 Benzene vs heterophene

In the course of exploratory study on phosphorus compounds of unique structure and properties, we have been involved in the quite general subject of π-conjugated systems, that is, quinoid compounds and cyclic π-conjugated systems fully substituted by heteroatoms. Both subjects have attracted great interest for a long time and a large number of derivatives have been reported. In contrast, very little had been known for phosphorus derivatives. During synthetic as well as analytical studies on phosphaquinoid compounds, thienoquinoid compounds contributed to systematic studies of phosphaquinoid compounds in a complementary manner (Scheme 2). Benzenes carrying phosphorus substituents on all carbons have not been reported even now, but the introduction of thiophene or selenophene ring in place of benzene enabled us to construct aromatic ring carrying phosphoryl groups on all carbons anyway, and helped to reveal structure and properties.



Scheme 2 Heterophenes carrying phosphorus functional groups as key structures

In this review, synthesis, structure, and redox properties of phosphaquinoid compounds are described, keeping the contribution of thienoquinoid structures in mind in the first part. In the second part, synthesis and structure of phosphorus substituted thiophene and related compounds, especially tetraphosphoryl derivatives, are outlined (Scheme 3).

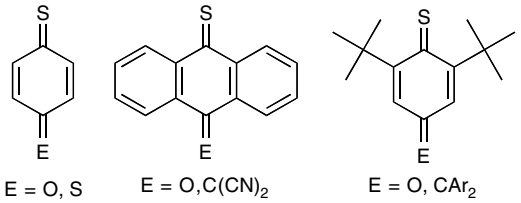


Scheme 3 Phosphaquinoid, phosphathienoquinoid compounds, and tetraphosphorylheterophenes

2 Phosphaquinoid and Phosphathienoquinoid Compounds

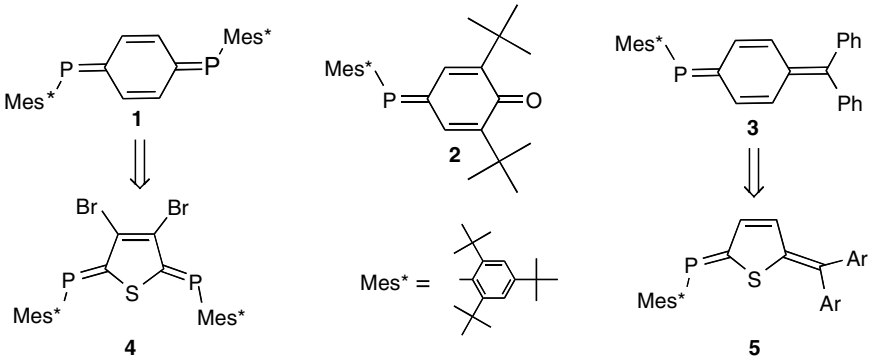
Quinoid compounds have played an important role in the broad area of science [1, 2]. Owing to their unique structure, they undergo various reactions and possess unique redox properties. Among various quinoid structures, *p*-xylylene and related compounds such as 1,4-benzoquinone and 1,4-quinodimethane are taken as representative quinoid molecules and have played a key role in material and biological sciences. In order to modify properties of 1,4-quinoid compounds, various π-conjugated systems carrying 1,4-quinoid structure have been synthesized. Since quinoid structure is reactive because of destabilization originated from benzenoid to quinoid structural change, substitution of *p*-xylylene structure to heterophenoquinoid structure, especially to thienoquinoid structure, has been employed to achieve practical stability without losing the unique properties of the quinoid molecules. In contrast to such modification, substitution of skeletal element of conventional quinoid molecules to heavier main group elements is regarded as a synthetic challenge to unusual structures, because such molecules have inherently unstable quinoid structure as well as double bonds composed of heavier main group elements. Several quinoid compounds possessing thiocarbonyl groups have been reported (Scheme 4). Matrix isolated thio- and dithiobenzoquinones were spectroscopically studied [3]. Thiobenzoquinone [4] and thiobenzoquinomethane [5] were stabilized

Scheme 4 Thioquinoid compounds [3–7]



thermodynamically with the aid of the anthracene skeleton. Thiobenzoquinone [6] and thiobenzoquinomethane sterically protected by *tert*-butyl groups were isolated as stable compounds [7].

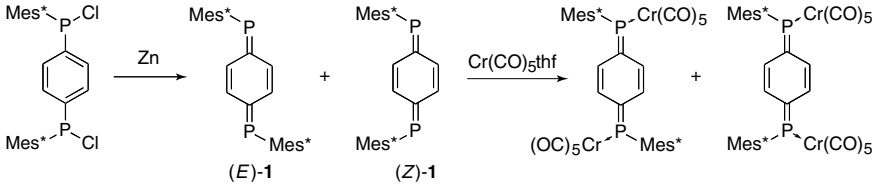
Quinoid molecules carrying low coordinated phosphorus atom were reported by Märkl et al. for the first time. They synthesized and characterized diphosphaquinone **1** and their chromium complexes [8] (Scheme 5). We synthesized phosphaquinone **2** and determined its structure and redox properties [9]. Subsequently, we moved to a systematic study of phosphaquinoid compounds. In the course of synthetic and analytical study of phosphaquinoid compounds, introduction of thienoquinoid structure in place of benzoquinoid structure greatly helped us. They not only contributed generalization of structure and properties of phosphaquinoid compounds, but also enabled isolation and investigation of redox properties of the compounds, which was unsuccessful for benzoquinoid derivatives. In this section, synthesis, structure, and properties of phosphaquinoid compounds are reviewed, especially focusing on those having thienoquinoid structure.



Scheme 5 Phosphaquinoid compounds

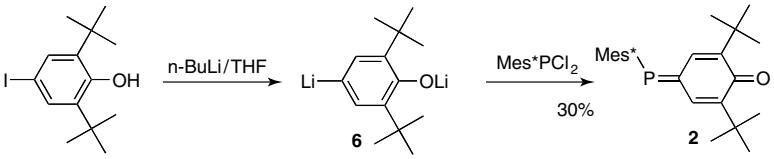
2.1 Synthesis

First stable phosphaquinoid compounds, diphosphaquinones **1** were synthesized by dechlorination of 1,4-bis(chlorophosphino)benzene and isolated as chromium complexes (Scheme 6) [8].



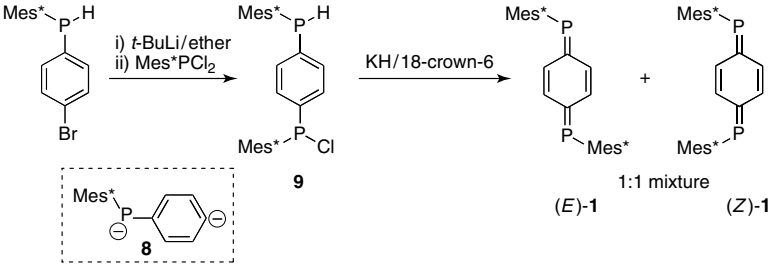
Scheme 6 Synthesis of diphosphaquinones [8]

In contrast, we employed 3,5-di-*tert*-butyl-4-oxidebenzenide dianion **6**, which is known as a strong nucleophile, for introducing the well-known sterically protected quinoid structure [10], as a key synthetic intermediate for the synthesis of phosphaquinone **2** (Scheme 7) [9]. Reaction of 2,4,6-tri-*tert*-butylphenyldichlorophosphine with in situ generated dianion **6** directly afforded phosphaquinone **2** along with bis(2,4,6-tri-*tert*-butylphenyl)diphosphene **7**, which was produced by reduction of the aryldichlorophosphine with the dianion, as a by product.



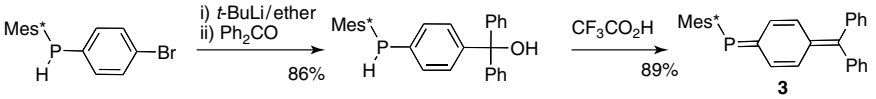
Scheme 7 Synthesis of phosphaquinone [9]

However, the analogous protocol for diphosphaquinones **1** was unsuccessful because of difficulty of generation of dianion **8**, and they were synthesized in a stepwise manner (Scheme 8). Diphosphaquinones **1** were synthesized by dehydrochlorination of 1-(chlorophosphino)-4-phosphinobenzene **9**, and obtained as an inseparable mixture of (*E*) and (*Z*) isomers [11].



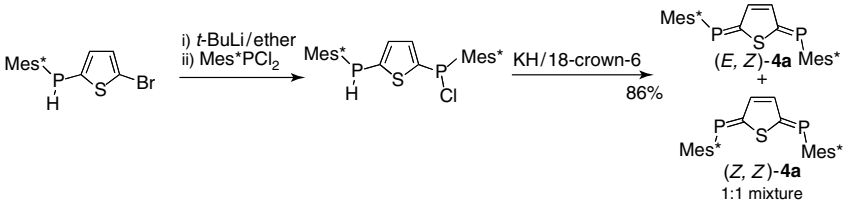
Scheme 8 Synthesis of diphosphaquinones [11]

Phosphaquinomethane **3** was synthesized by dehydration of diphenyl(4-phosphinophenyl)methanol (Scheme 9) [12]. Final dehydration can be accomplished by CF_3CO_2H/benzene, Ph_3CBF_4/benzene, or TsOH/benzene.



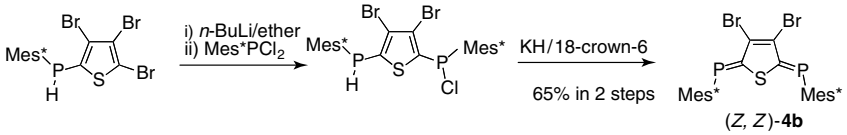
Scheme 9 Synthesis of phosphaquinomethane [12]

In order to synthesize phosphathienoquinoid compounds, we applied the above-mentioned procedure to analogous intermediates having thiophene. Diphosphathienoquinone **4a** was also obtained as a mixture of isomers (Scheme 10) [11].



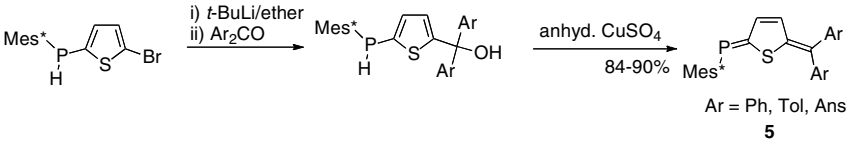
Scheme 10 Synthesis of dibromodiphosphathienoquinones [11]

In order to isolate a single isomer of diphosphathienoquinone, two bromo groups were attached to 3,4-positions to avoid formation of the (*E*)-form by steric repulsion between Br and Mes* groups. Analogous dehydrochlorination of the precursor afforded (*Z*,*Z*)-diphosphathienoquinone **4b** as a single isomer (Scheme 11) [11]. Diphosphathienoquinone **4b** did not undergo *EZ*-isomerization either under thermal or under photolytical condition.



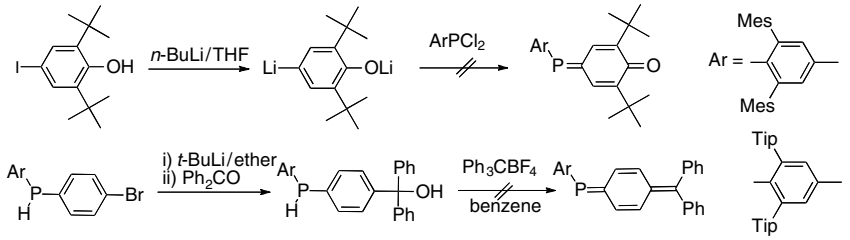
Scheme 11 Synthesis of dibromodiphosphathienoquinone [11]

Phosphathienoquinomethanes **5** were synthesized by dehydration of diaryl(phosphinothienyl)methanols similar to the corresponding benzoquinoid compound and obtained as (*Z*)-isomers (Scheme 12). Final dehydration was accomplished by anhydrous $CuSO_4$ [12], which was inert to the benzenoid precursor.



Scheme 12 Synthesis of phosphathienoquinomethanes [12]

Stability of the phosphaquinoid compounds depends unambiguously on the steric protection of 2,4,6-tri-*tert*-butylphenyl (=Mes*) groups. Because of inherently acute bond angle around low coordinated phosphorus, the Mes* group suffers from steric repulsion with nearest substituent. Attempted synthesis of phosphaquinoid compounds carrying *m*-terphenyl ligand was unsuccessful, probably because of severe steric repulsion arising from rigid and bulky ligand (Scheme 13) [13].



Scheme 13 Attempted synthesis of phosphaquinoid compounds carrying *m*-terphenyl ligand [13]

2.2 Structure

Structure of phosphaquinoid compounds **2**, **3**, **4**, and **5** was studied by ^{1}H, ^{13}C, and ^{31}P NMR [9, 11, 12]. Reflecting unsymmetrical structure of phosphabenzoquinoid compounds, ^{1}H NMR signals of benzoquinoid protons of **2** and **3** were nonequivalently observed accompanied by coupling with ^{1}H and ^{31}P nuclei. ^{13}C NMR chemical shifts of quinoid as well as thienoquinoid skeleton were similar to the conventional quinoid and thienoquinoid compounds of similar structures except for coupling with ^{31}P nucleus. ^{31}P NMR signals were observed in low field region typical of low coordinated phosphorus atoms (Table 1). Phosphaquinoid as well as phosphathienoquinoid compounds exhibited absorption in the visible region corresponding to their orange color.

Structures of some of the phosphaquinoid and phosphathienoquinoid compounds were further studied by X-ray crystallography (Table 2, Fig. 1) [9, 11, 12].

Table 1 Selected NMR and UV–Vis absorption data of phosphaquinoid compounds

	2	**3**	**5a**	**5b**	**5c**	**4b**
^{31}P NMR /δ	327.4[a]	244.4[b]	201.4[b]	189.9[b]	196.3[b]	211.2[b]
UV–Vis λ_{max}/nm (log ε)[c]	372 (4.34)	440 (4.49)	446 (4.49)	449 (4.60)	456 (4.60)	466 (4.39)

[a]In $CDCl_3$
[b]In CD_2Cl_2
[c]In hexanes

Table 2 Selected bond lengths (Å) and angles (°) of phosphaquinone **2**, diphosphathienoquinone **4b** and phosphathienoquinomethane **5b**

	2	**4b**	**5b**
P1–C1	1.705(2)	1.712(2)	1.704(2)
P2–C4		1.714(2)	
C2–C3	1.350(3)	1.359(3)	1.349(2)
C5–C6	1.347(3)		
C1–C2	1.443(3)	1.416(3)	1.450(2)
C3–C4	1.491(3)	1.415(3)	1.441(2)
C4–C5	1.484(3)		
C1–C6	1.445(2)		
S–C1		1.751(2)	1.747(2)
S–C4		1.743(2)	1.771(1)
Mes*-P1–C1	101.5(8)	98.1(1)	98.48(6)
Mes*-P2–C4		100.6(1)	
P1–C1–C2	126.5(1)	126.0(2)	125.0(1)
P2–C4–C3		124.7(2)	

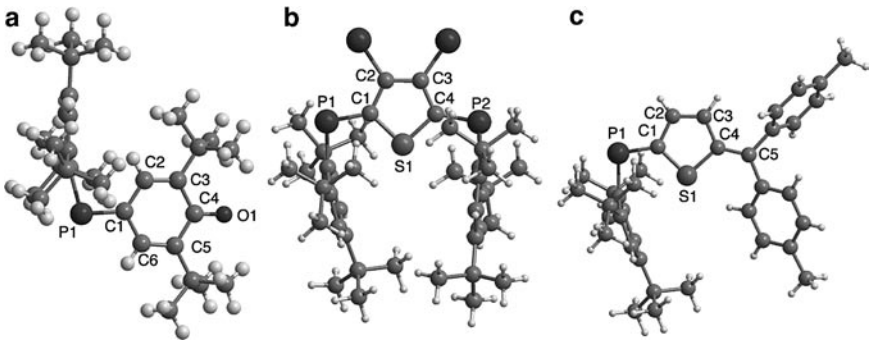
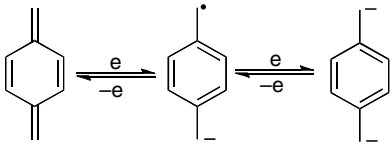


Fig. 1 Molecular structures of (**a**) phosphaquinone **2**, (**b**) diphosphathienoquinone **4b**, and (**c**) phosphathienoquinomethane **5b** obtained by X-ray crystallography

P–C bond lengths of **2**, **4b**, and **5b** lie in the longer range of known P=C double bond (1.61–1.71 Å [14]), suggesting conjugation to quinoid skeleton. On the other hand, the residual part was similar to the conventional quinoid compounds of similar structure. Owing to bulky Mes* group and acute C–P=C bond angle, C=P double bond of **2** points in the direction of a lone pair to release steric repulsion. Diphosphathienoquinone **4b**, which has two P=C double bonds in (*Z*)-form, has repulsion between two *p-tert*-butyl groups at the cost of planarity of π-conjugated system. Torsion angle (Mes*(*ipso*)-P1-P2-Mes*(*ipso*)) is 29.7°.

2.3 Redox Properties

One of the most important properties of quinoid compounds is the two step redox reaction. Quinoid compounds undergo one electron reduction to so-called semiquinone anion radicals, and further one electron reduction of semiquinone anion radicals gives dianions (Scheme 14).



Scheme 14 Redox process of quinoid compounds

In order to clarify redox properties of phosphaquinoid and phosphathienoquinoid compounds, electrochemical measurement and direct observation of the anion radical were carried out (Tables 3 and 4). Phosphaquinone **2** undergoes the first quasi-reversible reduction followed by the second irreversible reduction (Scheme 15) [9].

Table 3 Reduction potentials of phosphaquinoid compounds and hyperfine coupling constants of their anion radicals

Compound	$^{1}E_{red}$/V[a]	$^{2}E_{red}$/V[a]	E/V[b]	$a_{iso}(^{31}P)$/mT[c]	
2	−1.55	−2.45	0.90	9.3	Low reduction potential/ large ΔE/localized anion radical
4b	−1.60	−2.49	0.89	9.3 2.1	
3	−1.83	−2.24	0.41	5.7	High reduction potential/ small ΔE/delocalized anion radical
5a	−2.05	−2.35	0.30	5.2	
5b	−2.15	−2.47	0.32	4.9	
5c	−2.12	−2.48	0.36	4.6	
(*E*)-Mes*P=CHPh (**11**)	−2.23			5.4	Delocalized anion radical
(*E*)-Mes*P=PMes* (**7**)	−2.17			5.6	
Mes*MesP• (**10**)				10.3	Localized radical

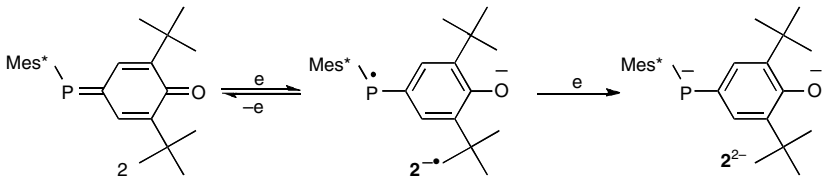
[a]Measured in THF with 0.1 mol L^{-1}*n*-Bu_4NClO_4. V vs Ag/Ag^+ (ferrocene/ferricinium = 0.18 V)
[b]$\Delta E = {}^{1}E_{red} - {}^{2}E_{red}$
[c]Obtained from sodium reduction in THF

Table 4 Hyperfine coupling constants obtained from EPR spectra of frozen solution and unpaired electron distribution of phosphaquinoid compounds[a]

Compound	^{31}P				^{13}C			
	$a_{//}$/mT	$a_{\perp}$/mT	A_f/mT /$\rho(P_{3s})$/%	A_p/mT /$\rho(P_{3p})$/%	$a_{//}$/mT	$a_{\perp}$/mT	A_f/mT /$\rho(C_{2s})$/%	A_p/mT /$\rho(C_{2p})$/%
2$^{-\bullet}$	0.25/1.7[b]	26.1	9.4/2	8.4/64				
4b$^{-\bullet}$	0.8	27.7	9.8/2	9.0/69				
	2.2	1.2						
3$^{-\bullet}$	0.8	15.3	5.6/1	4.8/37	0.7	1.9	1.1/2	0.4/10
5a$^{-\bullet}$	0.8	14.0	5.2/1	4.4/34	0.6	1.9	1.0/2	0.4/11
5b$^{-\bullet}$	0.4	13.1	4.7/1	4.2/32				
5c$^{-\bullet}$	0.37	12.6	4.4/1	4.1/31				

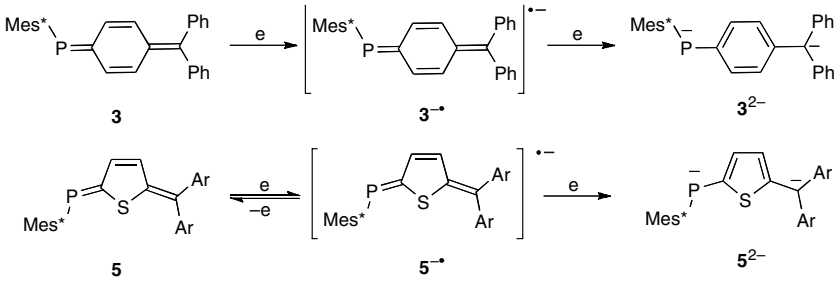
[a]Measured in THF. $A_f = (a_{//} + 2a_{\perp})/3$. $A_p = (a_{//} - a_{\perp})/3$. $\rho(P_{3s})$: unpaired electron density of phosphorus 3s orbital

[b]a_{xx}/a_{yy}



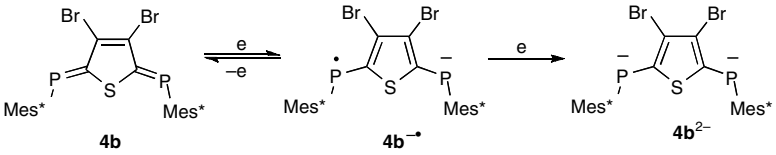
Scheme 15 Redox process of phosphaquinone **2**

Phosphaquinomethane **3** undergoes irreversible two step reduction (Scheme 16) [12]. Introduction of the thiophene skeleton improves the redox profile of quinomethane [12]. Thienoquinomethane **5** displays quasi-reversible two step reduction although thiophene skeleton raises reduction potential.



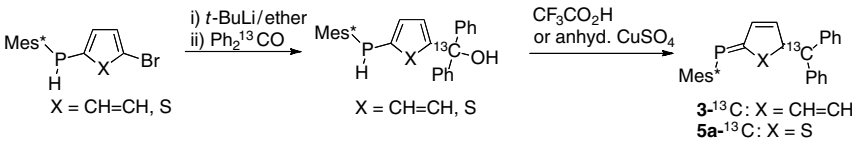
Scheme 16 Redox process of phosphaquinomethane **3** and phosphathienoquinomethane **5**

Diphosphathienoquinone **4b** shows most stable redox waves among the phosphaquinoid compounds synthesized by us (Scheme 17) [11]. The first reversible reduction and the second irreversible reduction were observed. In order to observe



Scheme 17 Reduction of diphosphathienoquinone **4b**

phosphasemiquinone anion radicals, an EPR study of chemical reduction of phosphaquinoid compounds was carried out. Unpaired electron distribution of phosphasemiquinones can be estimated from the ratio of anisotropic hyperfine coupling constants obtained from powder pattern of frozen solution to atomic hyperfine coupling constants [15]; anisotropic hyperfine coupling constants and unpaired electron distribution of phosphasemiquinones are summarized in Table 4. Upon reduction with a sodium mirror, phosphaquinone **2** [9], phosphaquinomethane **3** [12], and phosphathienoquinomethane **5** [12] gave two-line spectra due to hyperfine coupling with a ^{31}P nucleus, and anisotropic spectra obtained from the frozen solution afforded anisotropic hyperfine coupling constants. Unpaired electron distribution of phosphaquinomethane **3** and phosphathienoquinomethane **5a** was further clarified by introduction of a ^{13}C nucleus at the end of phosphaquinoid skeleton (Scheme 18).



Scheme 18 Synthesis of ^{13}C labeled phosphaquinomethane **3**–^{13}C and phosphathienoquinomethane **5a**-^{13}C [12]

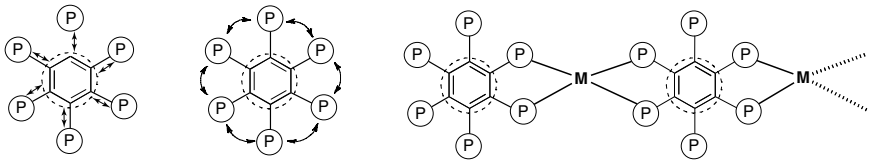
Solution of the ^{13}C labeled compounds gave four-line spectra due to coupling with ^{31}P as well as ^{13}C nuclei, which guarantees delocalization of an unpaired electron to the exocyclic C=C double bond [12]. Sodium mirror reduction of solution of diphosphathienoquinone **4b** gave four-line spectra resulting from coupling with two ^{31}P nuclei and the corresponding frozen solution gave anisotropic hyperfine coupling constants [11]. As shown in Table 4, most unpaired electrons reside in p orbitals for all the phosphaquinoid compounds discussed here, and phosphasemiquinones can be categorized to be π-radicals. More than 60% of unpaired electrons of anion radicals of phosphaquinone **2** and diphosphathienoquinone **4b** are localized in the phosphorus 3p orbital. On the other hand, anion radicals of phosphaquinomethane **3** and phosphathienoquinomethanes **5** have more delocalized character. Although unpaired electron is unevenly distributed to phosphorus, both ends of the

phosphaquinoid and phosphathienoquinoid skeleton have considerable spin density. Taking hyperfine coupling constants of anion radicals and reduction potentials of phosphaquinoid and phosphathienoquinoid compounds into consideration, these compounds are categorized into two groups (Table 3). Phosphaquinone **3** and diphosphathienoquinone **4b** are reduced at low reduction potential with large ΔE ($\Delta E = {}^{1}E_{red} - {}^{2}E_{red}$), and the corresponding phosphasemiquinone anion radicals have large hyperfine coupling with ^{31}P nuclei, suggesting localized anion radicals. On the other hand, phosphaquinomethane **3** and phosphathienoquinomethanes **5** have high reduction potentials with small ΔE and the corresponding anion radicals have smaller hyperfine coupling constant with ^{31}P nucleus, suggesting delocalized semiquinones. Isotropic as well as anisotropic hyperfine coupling constants of the former are very close to those of phosphinyl radicals such as **10** (Table 3) [16, 17]. On the other hand, those of phosphaquinomethane **3** and phosphathienoquinomethanes **5** are similar to anion radicals of low coordinated phosphorus compounds such as phosphaalkene **11** [18] and diphosphene **7** [19–22]. Therefore, phosphasemiquinone anion radicals of **2** and **4b** are considered to have a structure similar to phosphinyl radicals (Schemes 15 and 17). On the other hand, phosphaquinomethane **3** and phosphathienoquinomethanes **5** give delocalized phosphasemiquinones, which are close to conventional semiquinones (Scheme 16). Concerning redox potentials, the low potential of **2** and **4b** suggests a large contribution of quinoid structure to the neutral molecules. On the other hand, reduction potentials of **3** and **5** close to phosphaalkenes imply less contribution of quinoid skeleton as compared with **2** and **4b**.

To summarize, sterically protected phosphaquinoid compounds have been systematically studied with the aid of thienoquinoid structure. As shown by phosphaquinomethane and phosphathienoquinomethane, introduction of the thiophene ring in place of the benzene ring does not change fundamental properties of phosphaquinoid molecules and we can predict properties of phosphabenzoquinoid molecules from more stable or more easily accessible phosphathienoquinoid molecules. Phosphaquinoid molecules synthesized so far are still limited and there have been a large number of unsolved problems. Further progress such as construction of unexplored quinoid systems, extension of π-conjugated systems, construction of metal complexes, charge transfer complexes, and isolation of phosphasemiquinone anion radicals are expected.

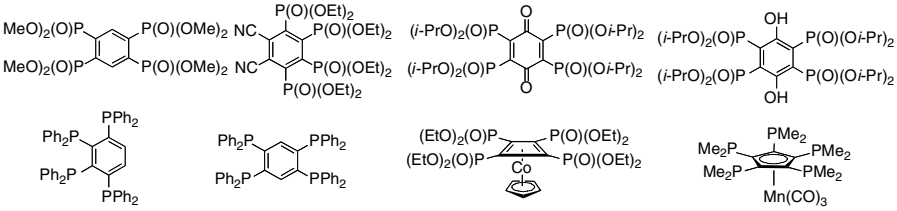
3 Phosphorus Substituted Thiophene and Related Compounds

Cyclic π-conjugated systems fully substituted by heteroatoms have attracted considerable attention for a long time. They have a beautiful structure of high symmetry and such compounds are expected to show intramolecular interactions between π-conjugated systems and heteroatoms, those among adjacent heteroatoms, and to construct molecular assembly based on coordination or hydrogen bonding of heteroatoms (Scheme 19). Benzenes carrying heteroatoms on all carbons are the most popular examples.



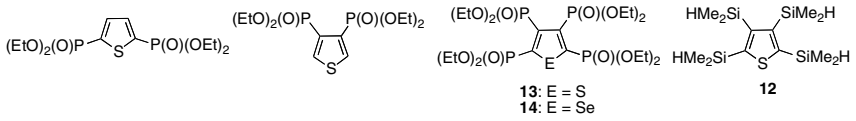
Scheme 19 Cyclic π-conjugated systems fully substituted by heteroatoms

Although benzenes substituted by six carbon, nitrogen, oxygen, silicon, and sulfur are well known [23–29], such compounds are exceptionally limited in the field of phosphorus chemistry. Benzenes carrying six phosphorus substituents have not been synthesized and only limited compounds such as tetraphosphoryl- [30, 31] or tetraphosphinobenzenes [32], tetraphosphorylquinone [33, 34], tetraphosphoryl-cyclobutadiene complexes [35, 36], and pentaphosphinocyclopentadienyl complexes [37] have been reported (Scheme 20).



Scheme 20 Cyclic π-conjugated systems carrying phosphorus substituents [30, 32, 33, 35, 37]

Thiophenes carrying heteroatoms on all carbons are also of interest. However, such studies on thiophenes are limited as compared with benzenes. Tetrasilylthiophene **12** has been reported recently [38]. We synthesized tetraphosphorylthiophene **13** and selenophene**14** recently [39] and would like to focus on studies on thiophenes carrying two to four phosphorus substituents in this section (Scheme 21).

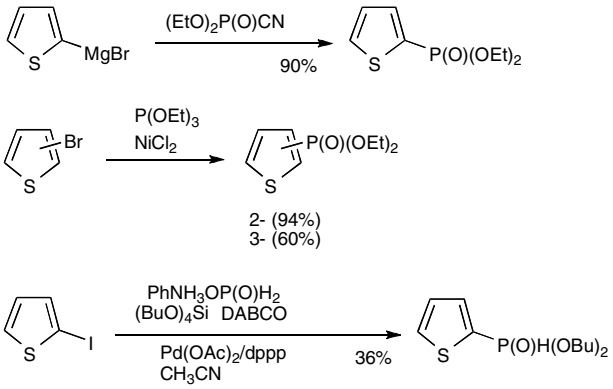


Scheme 21 Phosphorylthiophenes and related compounds [38, 39]

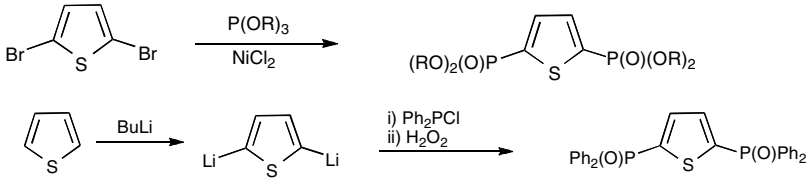
3.1 Synthesis

Phosphorylthiophenes such as thiophenephosphonic acid diesters can be synthesized by reaction of thienyllithium or Grignard reagents with phosphoryl electrophiles [40],

Arbusov reaction of thienyl halides with phosphites in the presence of nickel catalyst [41, 42], or palladium catalyzed phosphorylation of thienyl halides [43], and some of them are commercially available (Scheme 22). 2,5-Diphosphorylthiophenes were synthesized by Arbusov reaction of thienyl halides with phosphites in the presence of nickel catalyst [44] or reaction of 2,5-dilithiothiophene with phosphorus halides followed by oxidation [45] (Scheme 23).

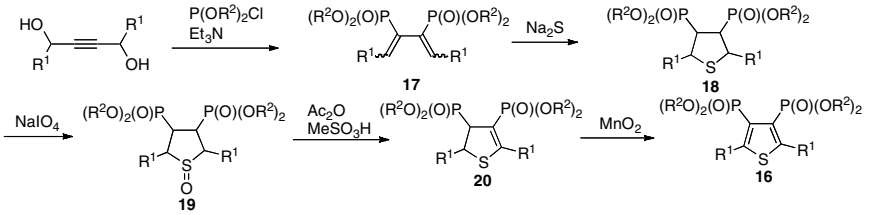


Scheme 22 Synthesis of phosphorylthiophenes [40, 41, 43]

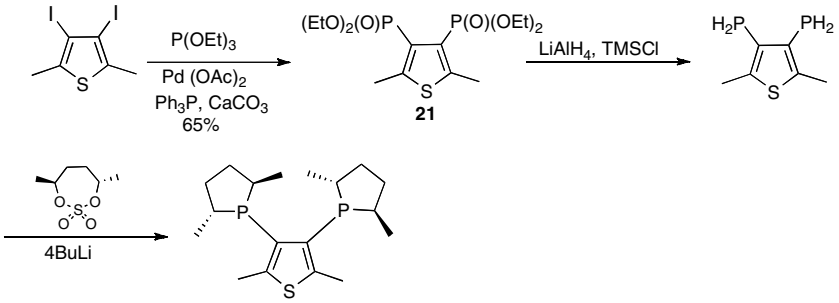


Scheme 23 Synthesis of 2,5-diphosphorylthiophenes [44, 45]

In contrast, synthesis of 3,4-diphosphorylthiophenes requires more elaboration because of low reactivity of 3,4-positions of thiophene and unavailability of 3,4-dihalo or dimetallated thiophenes. Minami et al. synthesized 3,4-diphosphoryl thiophenes **16** as shown in Scheme 24 [46]. Bis(phosphoryl)butadiene **17** was synthesized from 2-butyne-1,4-diol. Double addition of sodium sulfide to **17** gave tetrahydrothiophene **18**. Oxidation of **18** to the corresponding sulfoxide **19** followed by dehydration gave dihydrothiophene **20**. Final oxidation of **20** afforded 3,4-diphosphorylthiophene **16**. 3,4-Diphosphorylthiophene derivative **21** was also synthesized by Pd catalyzed phosphorylation of 2,5-disubstituted-3,4-dihalothiophene and converted to diphosphine ligand for Rh catalysts for asymmetric hydrogenation (Scheme 25) [47].

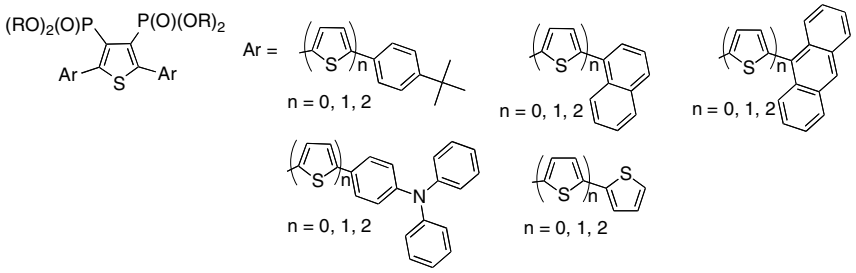


Scheme 24 Synthesis of 3,4-diphosphorylthiophenes by Minami et al. [46]



Scheme 25 Synthesis of 3,4-diphosphorylthiophene and conversion to diphosphine ligand [47]

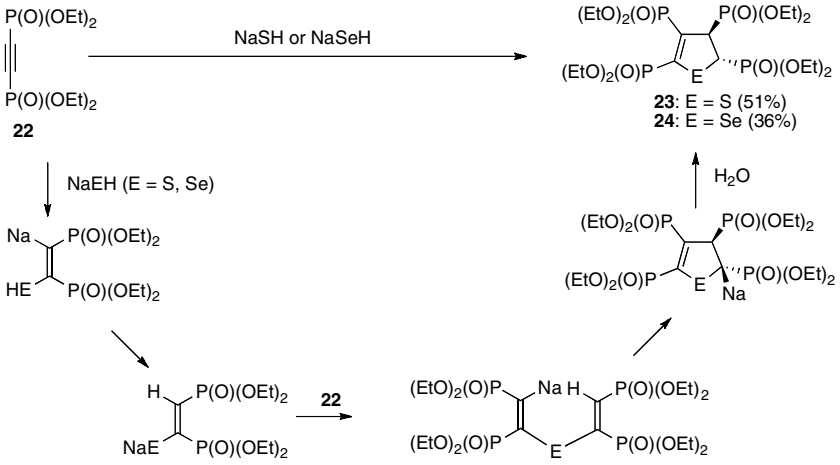
Since thiophenes are regarded as being good substructures for organic electronic materials, phosphorylthiophenes are taken as reference compounds for thiophene based materials [45] and phosphorylthiophenes such as **16** are employed as synthetic intermediates for phosphoryl substituted organic electronic materials such as oligothiophenes or thienylene bridged donors (Scheme 26) [46].



Scheme 26 Functional molecules derived from phosphorylthiophene **16** [46]

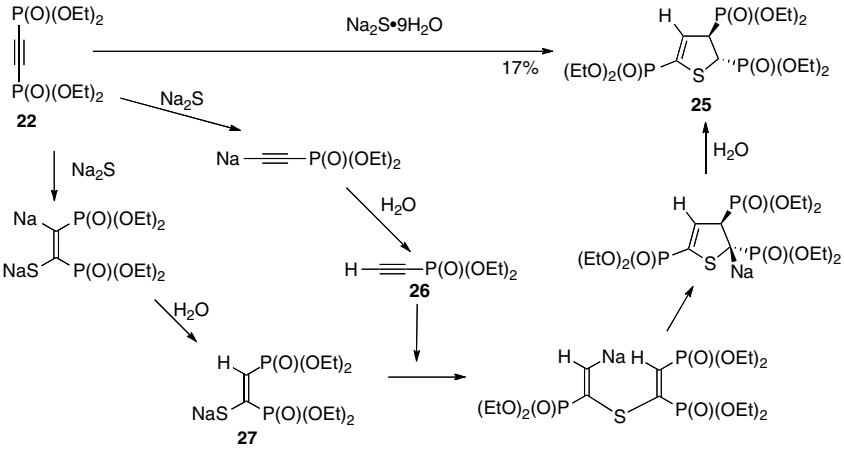
There has been no report focused on triphosphorylthiophenes to the best of my knowledge. Tetraphosphorylthiophene **13** was synthesized as outlined in Schemes 27 and 29 [39]. Reaction of diphosphorylacetylene **22** with sodium hydrosulfide

afforded tetraphosphoryldihydrothiophene **23** (Scheme 27). Sodium hydrosulfide adds to two molecules of diphosphorylacetylene **22**, and following intramolecular addition gives dihydrothiophene **23**. Initial addition of sulfur nucleophile to diphosphorylacetylene is reported to be *cis* addition [48]. Exclusive formation of 2,3-*trans* derivative is rationalized by *cis* addition in each step.



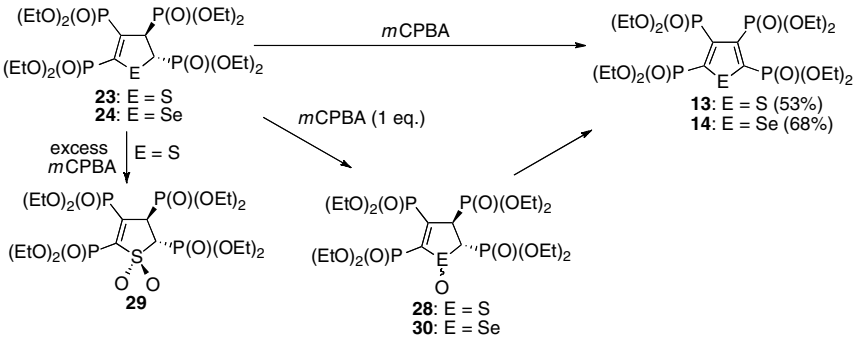
Scheme 27 Synthesis of tetraphosphoryldihydrothiophene and selenophene [39]

Similar reactions employing sodium sulfide in place of sodium hydrosulfide gave triphosphoryldihydrothiophene **25**. The higher nucleophilicity of sodium sulfide leads to formation of phosphorylacetylene **26**, which is attacked by sulfide intermediate **27** (Scheme 28).



Scheme 28 Synthesis of triphosphoryldihydrothiophene [39]

Oxidation of tetraphosphoryldihydrothiophene **23** with one equivalent of *m*CPBA gave corresponding sulfoxide **28** as an initial product, which was dehydrated during chromatographic separation to give tetraphosphorylthiophene **13** (Scheme 29). On the other hand, oxidation with excess *m*CPBA gave sulfone **29** as a stable product.



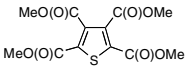
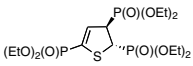
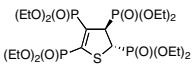
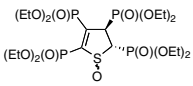
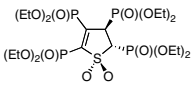
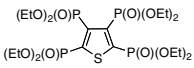
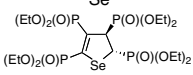
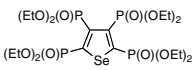
Scheme 29 Synthesis of tetraphosphorylthiophene and selenophene [39]

Tetraphosphorylselenophene **14** was synthesized in a similar manner (Schemes 27 and 29). Sodium hydroselenide added to diphosphorylacetylene **22** to give tetraphosphoryldihydroselenophene **24**. Oxidation of **24** with *m*CPBA gave tetraphosphorylselenophene **14**. As a result of the introduction of selenium in place of sulfur, **24** undergoes rapid conversion to tetraphosphorylselenophene **14** upon oxidation with *m*CPBA without showing intermediate, probably selenoxide **30**. Tetraphosphorylthiophene **13** and selenophene **14** resist further oxidation to the corresponding oxides because of the strong electron-withdrawing effect of four phosphoryl groups.

3.2 Structure

Structure of tetraphosphorylthiophene **13** and selenophene **14** was studied by conventional spectroscopy such as multinuclear NMR and UV-Vis spectroscopy. ^{13}C and ^{31}P NMR chemical shifts and UV-Vis absorption of tetraphosphorylthiophene and related compounds are summarized in Table 5. ^{31}P NMR signals of **13** and **14** are observed as AA′XX′ pattern around δ 8 and 10 in narrow range reflecting similar environment of phosphorus nuclei (Fig. 2). On the other hand, tetraphosphoryldihydrothiophene **23** and tetraphosphoryldihydroselenophene **24**, triphosphoryldihydrothiophene **25**, sulfoxide **28**, and sulfone **29** show phosphorus nuclei attached to sp^3 carbons in lower field with large coupling resulting from *trans*

Table 5 ^{13}C (101 MHz, $CDCl_3$, 293 K) and ^{31}P NMR (162 MHz, $CDCl_3$, 293 K) chemical shifts and UV–Vis absorption of tetraphosphorylthiophene in methanol and related compounds

Compound	^{13}C chemical shift/δ				^{31}P chemical shift/δ				UV–Vis
	C2	C3	C4	C5	P2	P3	P4	P5	λ_{max} (ε)/nm
									205 (1,870)[a,b]
	125.6[c]	127.3[c]	127.3[c]	125.6[c]					227 (5,900)[a]
	135.94[d]	136.86[d]	136.86[d]	135.94[d]					218 (16,218) 277 (11,200)
 **25**	45.3	48.2	146.4	121.7	22.5	23.9		12.0	253 (3,500) 279 (5,600)
 **23**	42.9	53.9	148.5	130.4	22.2	23.5	8.7	6.7	265 (4,000) 304 (4,300)
 **28**	53.9	60.7	152.9	149.8	20.1	18.8	7.1	5.9	
 **29**	43.6	59.0	147.5	145.1	14.2	19.3	1.3	7.2	229 (6,800) 305 (200)
 **13**	146.1	140.4	140.4	146.1	8.5	7.7	7.7	8.5	248 (5,700)
	131.0[c]	128.8[c]	128.8[c]	131.0[c]					250 (7,413)
 **24**	35.4	56.3	147.0	134.7	23.9	23.3	8.7	9.3	275 (4,100) 321 (3,600)
 **14**	155.4	142.5	142.5	155.4	10.6	10.0	10.0	10.6	268 (4,300)

[a][49]
[b]In water
[c][50]
[d][51]

configuration of phosphoryl groups and those attached to sp^2 carbons in higher field. ^{13}C NMR signals of **13** and **14** are observed in much lower field as compared with parent compounds, suggesting significant substituent effect of phosphoryl groups (Fig. 3). Tetraphosphorylthiophene **13** and selenophene **14** show considerable difference of ^{13}C chemical shifts. Parent thiophene [50], selenophene [50], and methoxycarbonyl derivatives [51] exhibit only a little difference of ^{13}C chemical

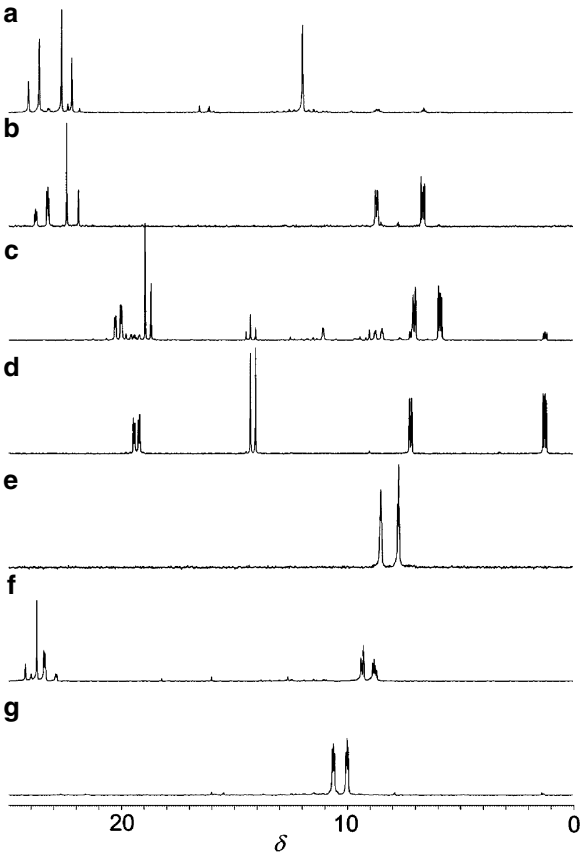


Fig. 2 ^{31}P NMR (162 MHz, $CDCl_3$, 293 K) of (**a**) **25**, (**b**) **23**, (**c**) **28**, (**d**) **29**, (**e**) **13**, (**f**) **24**, and (**g**) **14**

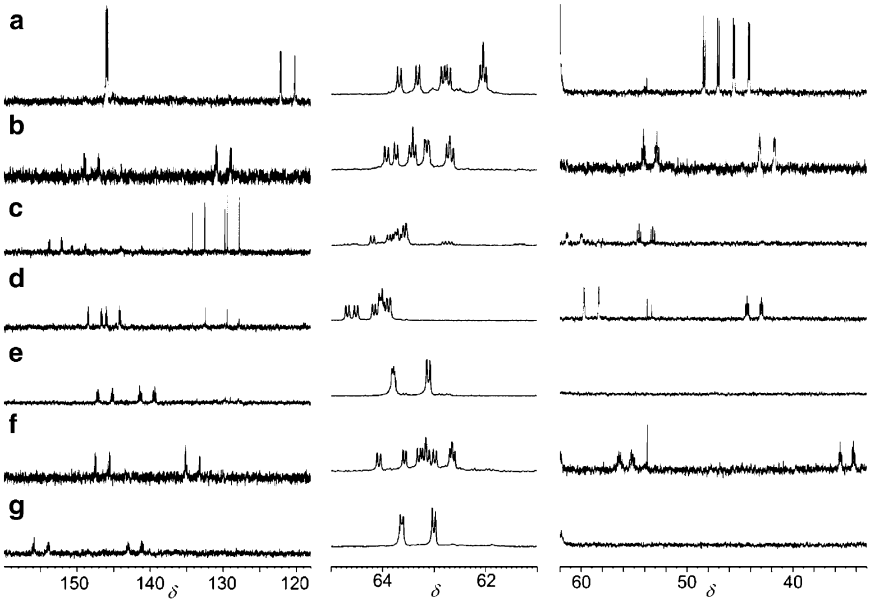
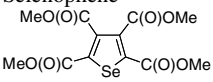
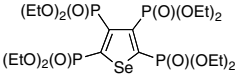
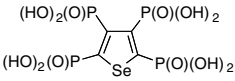


Fig. 3 ^{13}C NMR (101 MHz, $CDCl_3$, 293 K) of (**a**) **25**, (**b**) **23**, (**c**) **28**, (**d**) **29**, (**e**) **13**, (**f**) **24**, and (**g**) **14**

shifts. Tetraphosphoryldihydrothiophene **23** and tetraphosphoryldihydroselenophene **24**, triphosphoryldihydrothiophene **25**, sulfoxide **28**, and sulfone **29** exhibit sp^3 carbons accompanied by coupling with ^{31}P nuclei from δ 30 to 60. Structural difference between heterophene and dihydroheterophene is also reflected to methylene groups ($POCH_2CH_3$) observed in δ 60–65, where **13** and **14** show simple patterns. ^{77}Se NMR chemical shift of **14** lies in the lowest category as selenophenes [52] and close to those of selenophene oxides (δ 900–1,000) [53] and dioxides (δ 1,000–1,100) [54, 55], again suggesting significant substituent effect of phosphoryl groups (δ 929.5 (t, J= 49.9 Hz)) (Table 6). Substitution of electron-withdrawing groups such as methoxycarbonyl groups are reported to cause low field shift of ^{77}Se signal of selenophene [56]. Extremely low field shift of ^{77}Se NMR chemical shift

Table 6 ^{77}Se NMR chemical shift of tetraphosphorylselenophene and related compounds

Compound	Experimental	Theoretical HF/6–311G(2d, p)//B3LYP/6–311G (2d, p)[d]
CH_3SeCH_3	0[a]	0
Selenophene	605[b]	506
	699[c]	613
 **14**	929.5 (t, J= 49.9)[a]	
		842

[a]76.3 MHz, $CDCl_3$, 293 K
[b][52]
[c][56]
[d]Calculated by Gaussian 03

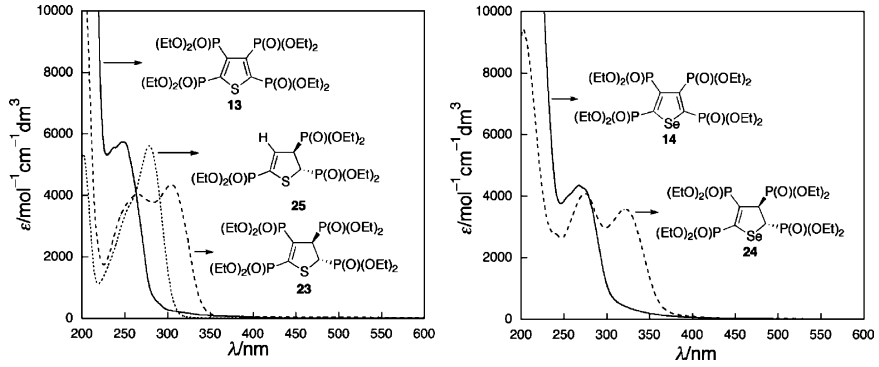


Fig. 4 UV–Vis spectra of tetraphosphorylthiophene **13**, tetraphosphoryldihydrothiophene **23**, triphosphoryldihydrothiophene **25** (*left*), tetraphosphorylselenophene **14**, and tetraphosphoryldihydroselenophene **24** (*right*) in methanol

of **14** is consistent with calculated chemical shift of simplified models, where a similar trend was observed, suggesting electronic effect of phosphoryl groups rather than steric effect of bulky dialkoxyphosphoryl groups [57]. Parent thiophene [49] and selenophene [52] are reported to exhibit UV absorption at λ_{max} (ε) 227 (5,900) and 250 (7,413) nm, respectively. Tetraphosphoryl derivatives **13** and **14** exhibit red shifted absorption at λ_{max}(ε) 248 (5,700) and 268 (4,300) nm, respectively (Figure 4). The substituent effect of phosphoryl groups on UV–Vis absorption is smaller than that of methoxycarbonyl group (λ_{max}(ε) 277 (11,220) nm) [58]. As compared to aromatic tetraphosphorylthiophene and selenophene, the corresponding dihydro derivatives exhibit UV absorption in longer wavelengths, probably because of push-pull alkene structure.

4 Conclusion

In this review, two typical structural motives in structural organic chemistry were reviewed in terms of phosphorus chemistry. As a result of the introduction of thiophene or selenophene in place of benzene, or thienoquinoid in place of benzoquinoid structure, we could get more stable compounds more easily without losing the expected characteristics. Such a strategy has a long history in π-conjugated systems and has contributed greatly in the development of unique materials; however, application to the chemistry of heavier main group elements is still limited and considerable room remains for further exploration. Since heterophenes showed the way to unique systems such as phosphaquinoid compounds and polyphosphorylated aromatic compounds, much progress in phosphorus substituted benzoquinoid or benzenoid compounds can be expected in the near future.

Acknowledgments The author gratefully thanks Dr. F. Murakami and Mr. K. Adachi of Tohoku University for their exhaustive research work on phosphaquinoid compounds and phosphorus substituted heterophenes, respectively. He expresses thanks also to Professors. M. Yoshifuji and N. Morita of Tohoku University for encouragement.

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Top Heterocycl Chem (2010) 21: 23–62
DOI 10.1007/7081_2009_4

Published online: 18 September 2009

Synthesis and Biological Activity of 2,5-Dihydro-1,2-Oxaphosphole-2-Oxide Derivatives

Dobromir D. Enchev

Abstract This chapter deals with the methods for the syntheses of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives, and some recent results of their biological activity testing. The electrophilic addition to 1,2-alkadiene- and alkatrienephosphonate derivatives is one of the easiest and fruitful synthetic strategies for obtaining these compounds in preparative amounts.

Keywords 1,2-Alkadienephosphonates • 1,2-Alkatrienephosphonates • 1,2-Oxaphosphole • Oxaphospholic cyclization

Contents

1 Introduction

Organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical [1–6], agricultural [7], and chemical agents [8–14]. Recently phosphorus heterocycles [15, 16] have received considerable interest

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because of their unique biological activities as hydrolytic enzyme inhibitors [17] and their anticancer effects [18–20], as well as because of their wide-ranging utilities as synthetic intermediates in organic syntheses. Consequently, much attention has been directed to the synthesis of these compounds [21–28]. Among them, particular interest was paid to the oxaphosphole derivatives. Numerous methods and synthetic protocols for synthesis of these compounds have been described. The literature overview shows that, among the other promising substrates for the preparation of oxaphosphole derivatives, the most fruitful ones are the phosphorylated allenes.

The unique combination of double bonds in the molecules of those compounds, each with different reactivity along with the easy preparation, makes phosphorylated allenes useful substrates for the synthesis of different cyclic and noncyclic organophosphorus compounds. Recent investigations increase the scope of application of phosphorylated allenes as precursors in organic syntheses. Most of them are accompanied by the formation of five- or six-membered phosphorus heterocycles, which in many cases demonstrate certain biological activity.

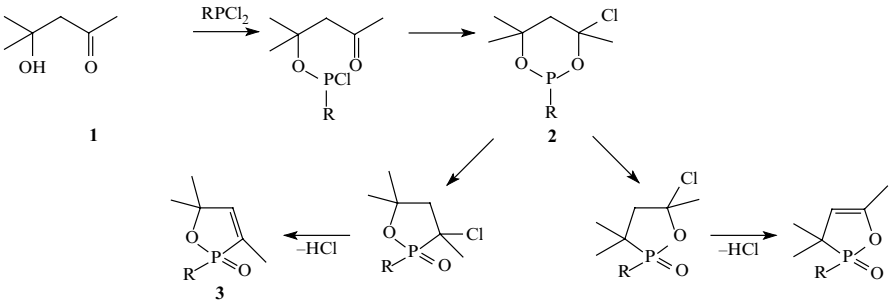
The subject matter of the present work is summarizing most useful methods for the preparative synthesis of the titled compounds, as well as submitting some recent data about their biological activity.

There are a number of other compounds with similar structure however; they are outside the scope of this review.

2 Methods for Synthesis of 2,5-Dihydro-1,2-Oxaphosphole-2-Oxide Derivatives

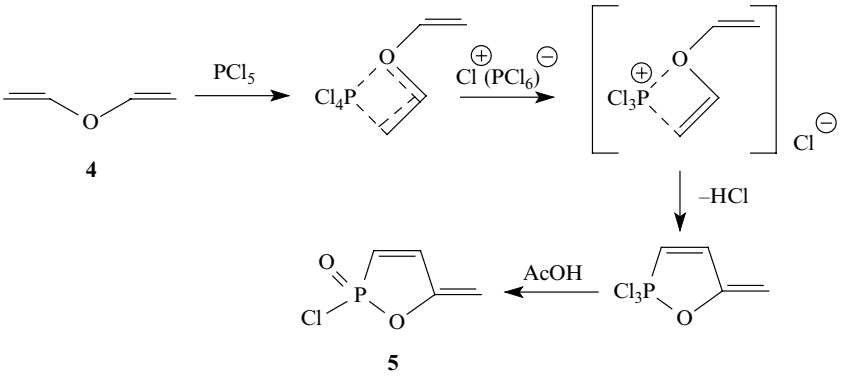
2.1 Historical Overview

The reaction of diacetone alcohol **1** with alkyldichlorophosphines afforded 3-chloro-1,2-oxaphospholane-2-oxide **2**. The latter undergo isomerization followed by dehydrochlorination to the corresponding 1,2-oxaphosphole derivatives **3** (Scheme 1) [29].



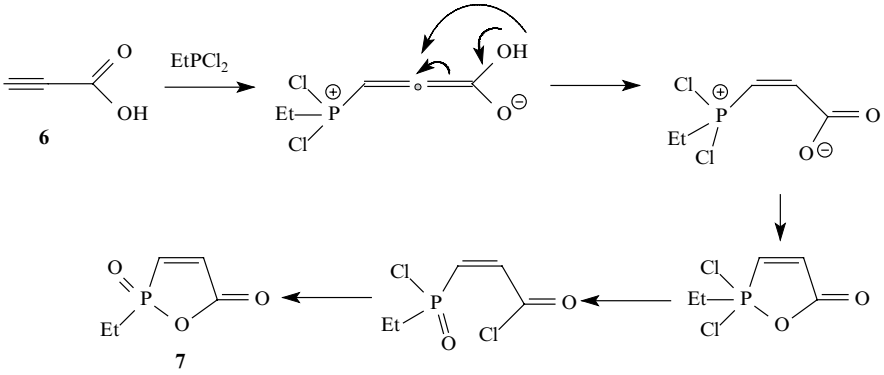
Scheme 1 Synthesis of 2-alkyl-3,5,5-trimethyl-5*H*-[1,2]-oxaphosphole-2-oxide **3**

Civunin et al. [30–32] described synthesis of similar compounds, from the reaction of phosphorus pentachloride with divinyl ether (Scheme 2).



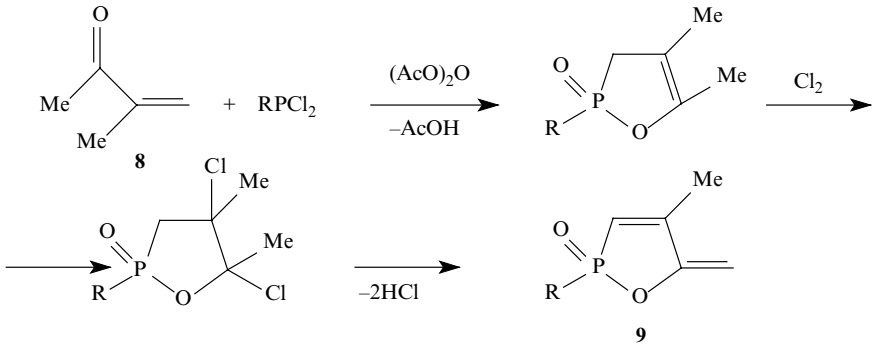
Scheme 2 Synthesis of 2-chloro-5-methylene-5*H*-[1,2]-oxaphosphole-2-oxide **5**

Later Pudovik et al. synthesized 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives from the reaction of propynoic acid with ethyldichlorophosphine (Scheme 3) [33].



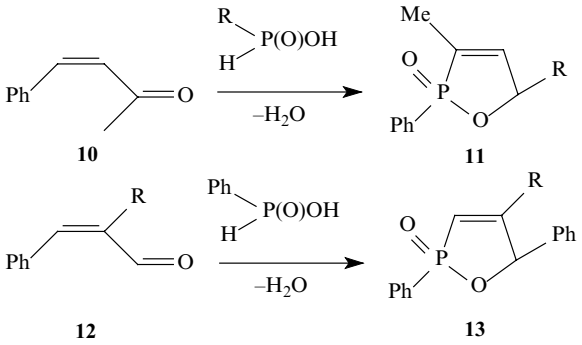
Scheme 3 Synthesis of 2-ethyl-2-oxo-2*H*-2λ^5-[1,2]-oxaphosphol-5-one **7**

The same authors also reported the preparation of 1,2-oxaphosphole derivatives from the reaction of alkyl(phenyl)dichlorophosphines with unsaturated ketones (Scheme 4) [33].



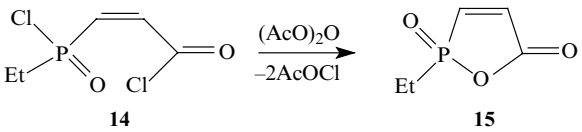
Scheme 4 Synthesis of 2-alkyl-4-methyl-5-methylene-5*H*-[1,2]-oxaphosphole-2-oxides **9**

The1,2-oxaphosphole derivatives were also obtained from the reaction of alkyl(aryl) phosphonic acids with α,β-unsaturated ketones or aldehydes (Scheme 5) [34, 35].



Scheme 5 Synthesis of 5-alkyl-3-methyl-2-phenyl-5*H*-[1,2]-oxaphosphole-2-oxides **11** and of 4-alkyl-2,5-diphenyl-5*H*-[1,2]-oxaphosphole-2-oxides **13**

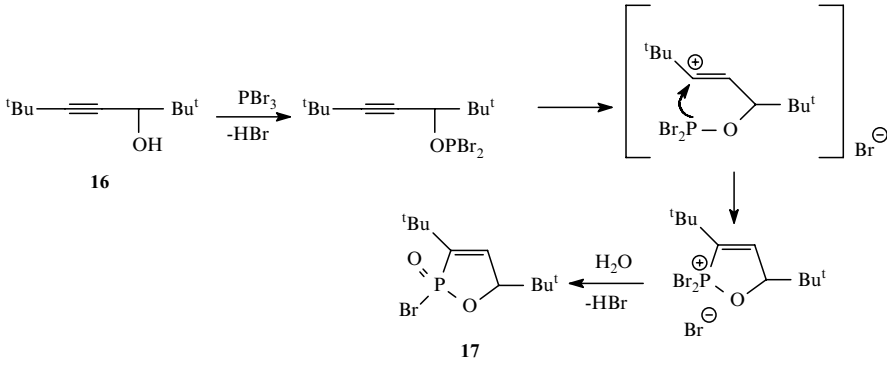
The same authors described obtaining similar compounds from the reaction of the chloride of methyl-$\beta-$chloroformylvinylphosphonic acid with acetic anhydride (Scheme 6) [36, 37].



$CHCl_3/CCl_4$, -8° - -10°C to room

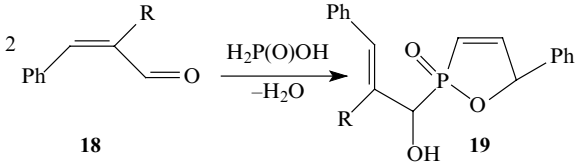
Scheme 6

Macomber and coworkers [38, 39] found that the reaction of 2,2,6,6-tetramethyl-4-heptyn-3-ol with phosphorus tribromide led to 3,5-disubstituted-2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives (Scheme 7).



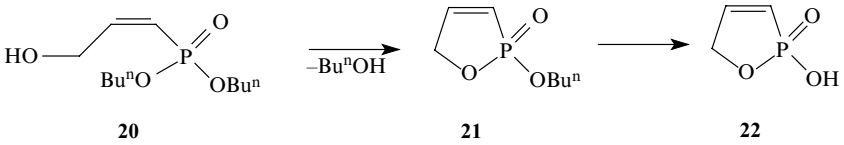
Scheme 7

These authors also reported the synthesis of 1,2-oxaphosphole derivatives from the reaction of hypophosphoric acid with α,β-unsaturated aldehydes (Scheme 8) [34].



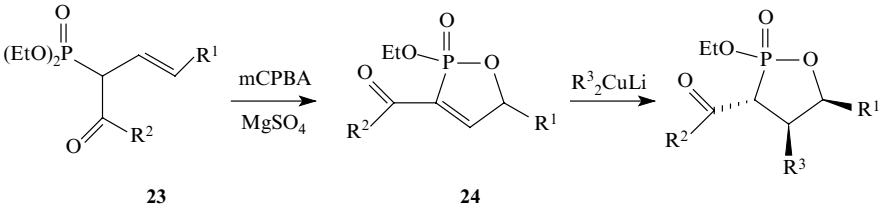
Scheme 8 Synthesis of 2-alkyl-1(2-oxo-5-phenyl-2,5-dihydro-2λ^5-[1,2]-oxaphosphol-2-yl)-3-phenylprop-2-en-1-oles **19**

Mashida and Sato [40] developed a method for the synthesis of the target compounds, based on the intramolecular rearrangement of the butyl esters of 3-hydroxipropene-1-phosphonic acid (Scheme 9).



Scheme 9 Synthesis of 2-butoxy-5*H*-[1,2]-oxaphosphole-2-oxide 21 and 2-oxo-2,5-dihydro-2λ^5-[1,2]-oxaphosphol-2-ol **22**

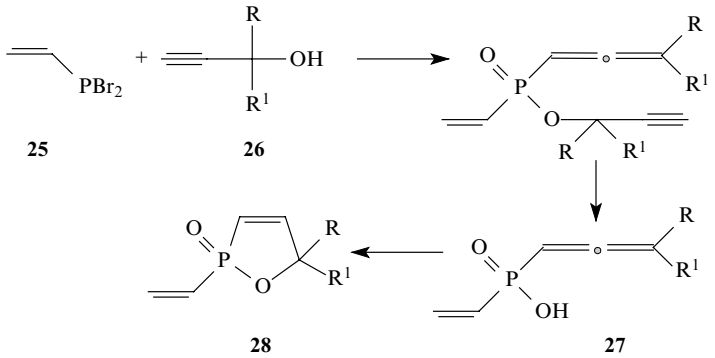
α-Acylallylphosphonates **23**, on reacting with *m*-chloroperbenzoic acid (*m*-CPBA) in presence of magnesium sulfate, afforded 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **24**. The subsequent reaction of the latter with lithiocuprate produced 1,2-oxaphospholanes stereoselectively (Scheme 10) [24].



23 **24**

Scheme 10 Synthesis of 1-(5-alkyl-2-ethoxy-2-oxo-2,5-dihydro-2λ⁵-[1,2]-oxaphosphol-3-yl)-alkanones **24**

Petrov and coworkers [41] showed that the reaction of dibromides of alkenephosphonic acids with acetylenic alcohols involved an acetylene–allene rearrangement. The products so formed hydrolyzed easily to the corresponding phosphinic acids. The latter on heterocyclization afforded 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives (Scheme 11).



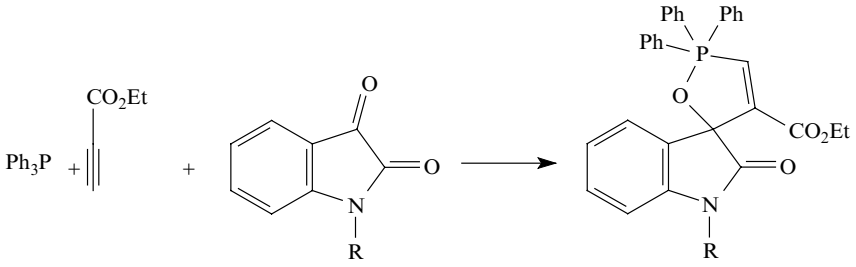
25 **26** **28** **27**

Et_2O, -5° - -8°C to room, isomerization, hydrolysis, cyclization

Scheme 11

All the synthetic protocols described above have limitations to some extent and the yields of the products were modest. In some cases the formation of 1,2-alkadienephosphonate derivatives is essential for obtaining the final cyclic products. This is the reason why many authors have used the higher reactivity of 1,2-alkadienephosphonates, discovered by Mark [42] in 1962 for the preparation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives. Since then, the oxaphospholic cyclization of 1,2-alkadienephosphonate system of double bonds has become the easiest method for the synthesis of these compounds. The special structure of phosphorylated allenes is responsible for their special properties, which has attracted the attention of chemists for a long time [43–46].

The synthesis of 2,5-dihydro-1,2-oxaphospholes via multicomponent or catalytic reactions has been published recently. For example, it was shown that the reaction of ethyl propiolate with triphenylphosphine in the presence of *N*-alkylisatins leads to spiroindole-derivatives of 1,2-oxaphosphpole-2-oxide (Scheme 12) [47].

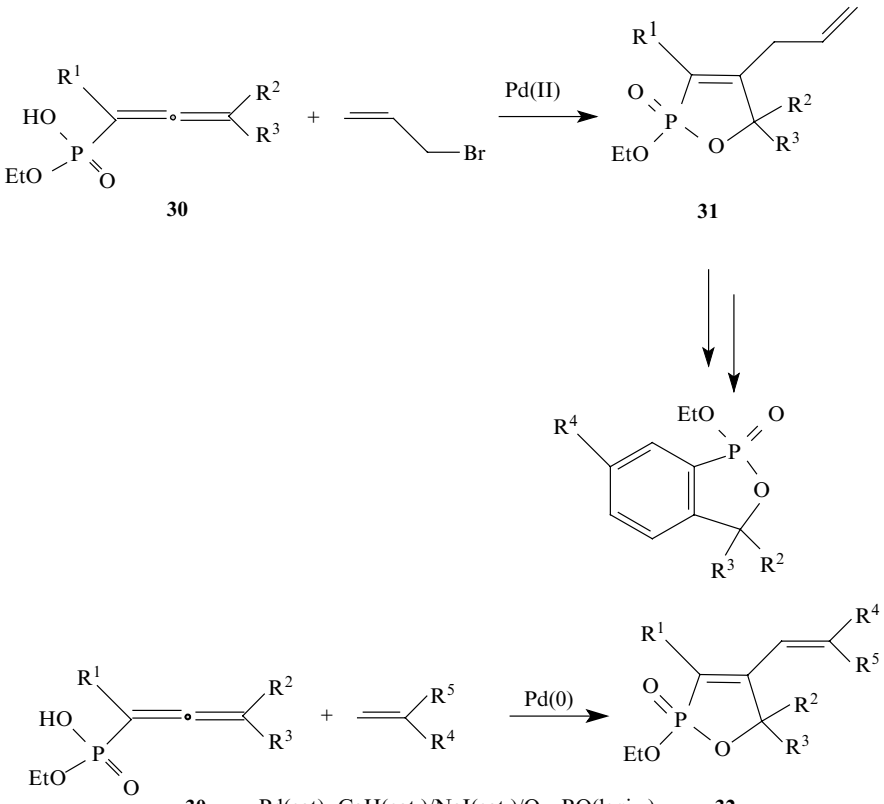


29

CH_2Cl_2, room t°C, 24h column chromatography

Scheme 12

A very interesting method for the preparation of 1,2-oxaphosphole-2-oxide derivatives, bearing 4-alkenyl- or 4-allyl-substituents in one pot tandem Pd(II) and Pd(0) catalytic reactions, was reported by Ma and coworkers (Scheme 13) [27, 28].



30 Pd(cat), CaH(cat.)/NaI(cat.)/O_2, BQ(leqiv.) **32**

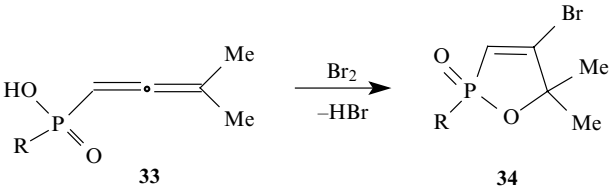
Scheme 13

2.2 *Electrophilic Addition to 1,2-Alkadienephosphonates*

Phosphorylated allenes have been widely used as building blocks for the synthesis of five- and six-membered phosphorus heterocycles [48–52].

2.2.1 Electrophilic Addition to 1,2-Alkadienephosphonic Acids

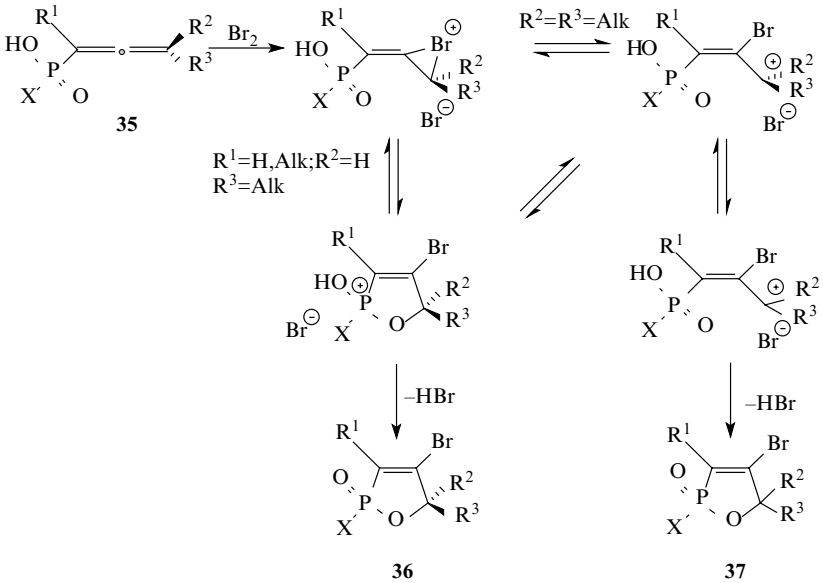
In 1977 Braverman and Reisman [53] reported the preparation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives from the reaction of allenylphosphinic and allenylphosphonic acids with bromine (Scheme 14).



R=Ph,OH $CHCl_3/CCl_4$, -10°C to room, 24h

Scheme 14

Macomber, using monosubstituted at C3 atom of the alkadienephosphonate system substrates [54], employed the same reaction (Scheme 15).

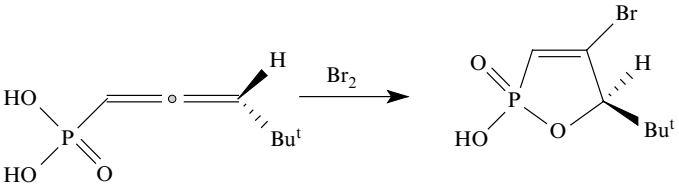


$CHCl_3/CCl_4$, -10°C to room, 24h

Scheme 15

In this context, it was suggested [53] that the reaction involved a tertiary carbocation intermediate that was in equilibrium with quasiphosphonium salt. The elimination of HCl from the latter, leads to the formation of 2,5-dihydro-1,2-oxaphosphole derivatives. Macomber [54], however, has shown that bromination of optically pure 1,2-alkadienephos-phonic acids occurred with 41% stereoselectivity. This fact has been taken in consideration as evidence that, by the bromination of 3-monosubstituted-1,2-alkadienephosphonic acids, the intermediates of the reaction were presumably bromonium ion or nonplanar secondary carbocation.

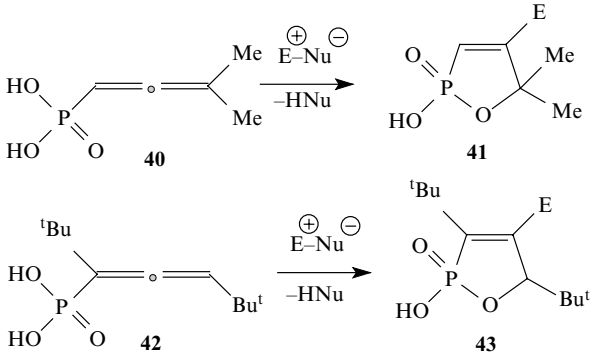
The bromination of the optically pure alkadienephosphonic acids proceeds with similar stereoselectivity [55], while in the case of allenic alcohols complete racemization of the product occurred (Scheme 16) [56].



38 $CHCl_3/CCl_4$, -10°C to room, 24h **39**

Scheme 16

In 1989 Macomber and coworkers showed that the reaction of 1,2-alkadienephosphonic acids with different kinds of electrophilic reagents gave 1,2-oxaphosphole derivatives (Scheme 17) [57].

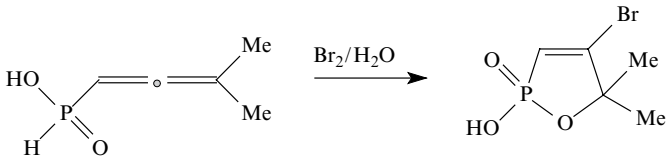


40 **41** **42** **43**

$CHCl_3/CCl_4$, -10°C to room, 24h, E-Nu=Cl_2, Br_2

Scheme 17

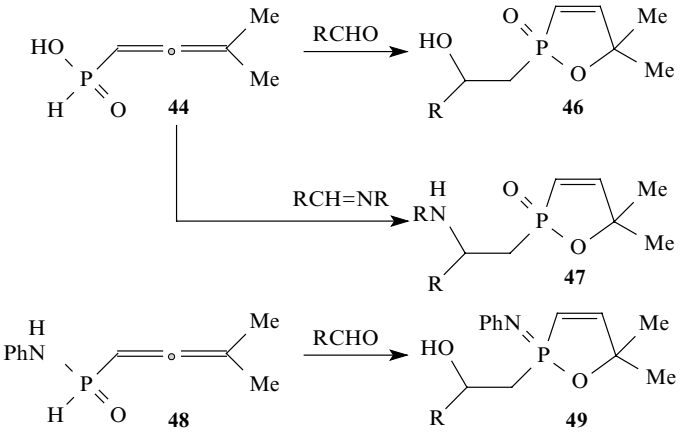
It was suggested that the reaction of 3-methyl-1,2-butadienephosphinic acid with bromine in water involved oxaphospholic cyclization and oxidation of the substrate (Scheme 18) [58].



44 $CHCl_3/CCl_4$, -10°C to room, 24h **45**

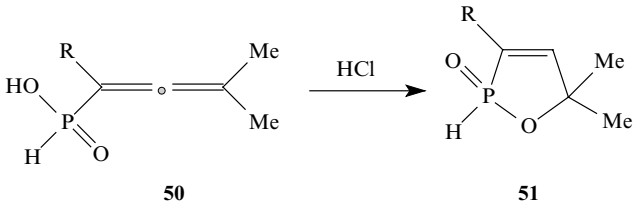
Scheme 18

The same substrate reacted with carbonyl compounds [59, 60] and with azomethines [60, 61] to afford 2,5-dihydro-1,2-oxaphosphole derivatives. Compounds **49** could also be produced by the use of the corresponding amides **48** (Scheme 19) [62].



Scheme 19 Synthesis of 2-substituted-2,5-dihydro-1,2-oxaphosphole-2-oxides **46**, **47** and **49**

The reaction of 3,3-disubstituted-1,2-alkadienephosphinic acids with HCl was also used to prepare the corresponding 1,2-oxaphosphole derivatives (Scheme 20) [63, 64].

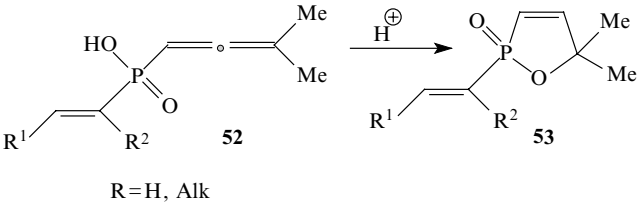


50 **51**

R = H, Alk $CHCl_3/CCl_4$, -10°C to room, 24h

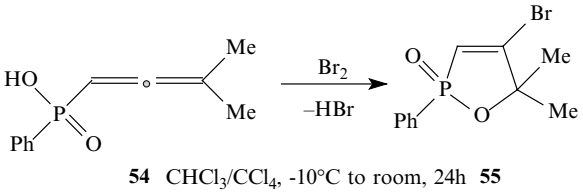
Scheme 20

Compounds **53** could be obtained from an acid-promoted oxaphospholic cyclization of phosphinic acid **52** in the presence of mineral acid and heating up to 100 °C (Scheme 21) [41]



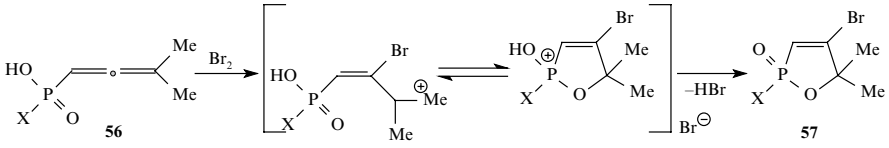
Scheme 21 Synthesis of 5,5-dimethyl-2-(1,2-dialkyletenyl)- 5*H*-[1,2]-oxaphosphole-2-oxides **53**

The synthesis of **55** has been accomplished as shown in Scheme 22 [65].



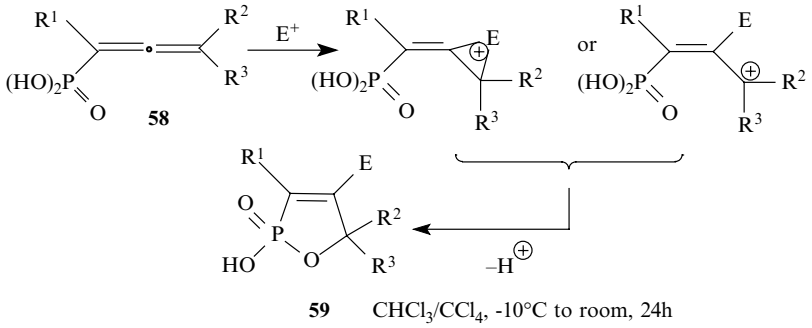
Scheme 22

On the other hand, the bromination of 3-methyl-1,2-butadienephosphonic acid **56** leads to the cyclic acid **57** (Scheme 23) [65].



Scheme 23

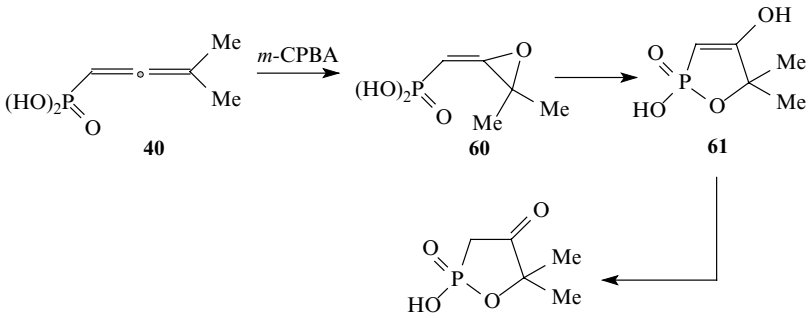
The reaction of 1,2-alkadienephosphonic acids with an electrophile E^+ [H^+, Br^+/$CHCl_3$, $Hg(OAc)_2$/AcOH] leads to 2,5-dihydro-1,2-oxaphosphole-2-oxides (Scheme 24) [66–69].



Scheme 24

The reaction occurs with high regio- and stereoselectivity.

Macomber has described the oxidation of 3-methyl-1,2-butadienephosphonic acid with 3-chloroperbenzoic acid to the corresponding cyclic allenic oxide, which undergoes rearrangement to produce the corresponding unstable 2,5-dihydro-1,2-oxaphosphole-2-oxide derivative (Scheme 25) [66].



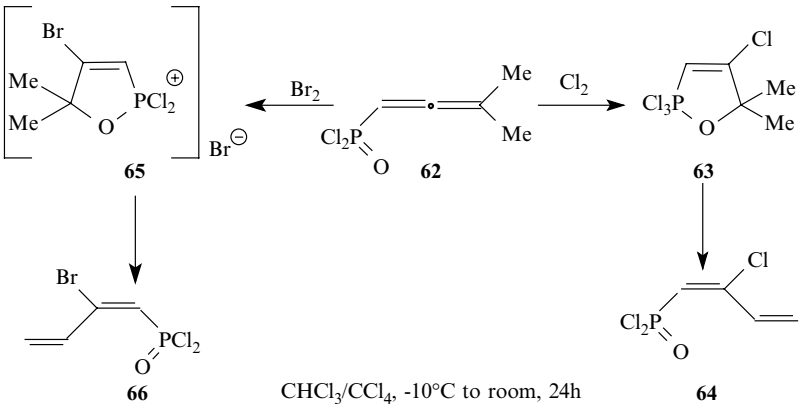
Scheme 25 Synthesis of 5,5-dimethyl-2-oxo-2,5-dihydro-2λ⁵-[1,2]-oxaphosphol-2,4-diol **59**

2.2.2 Electrophilic Addition to 1,2-Alkadienephosphonic Dichlorides

The halogenation of 1,2-alkadienephosphonic dichlorides leads to tetrahalogeno-2,5-dihydro-1,2-oxaphosphole derivatives or to the corresponding quasiphosphonium salts [70–79]. These compounds are stable in nonpolar solvents for several days, but decompose to 1,3-alkadienephosphonates on keeping for a longer time [71, 73–80].

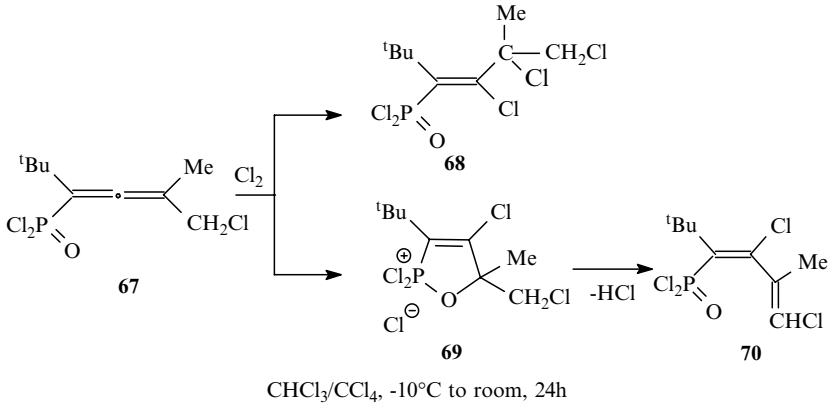
A detailed investigation of the reaction shows that, in the case of chlorine as reagent, the compounds with phosphorane structure were isolated, whereas in

the case of bromine, only compounds with phosphonium structure were obtained. Both products (with phosphorane or phosphonium structures) are unstable and decompose to the corresponding phosphorylated 1,3-dienes (Scheme 26) [70, 73, 74].



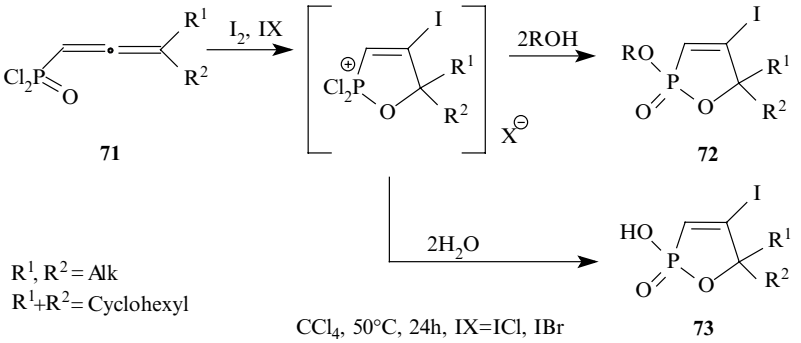
Scheme 26

1,2-Alkadienephosphonates with bulky substituents at the allene moiety react with chlorine with formation of 1,2-oxaphosphole-2-oxide intermediate **69** (Scheme 27) [78, 79].



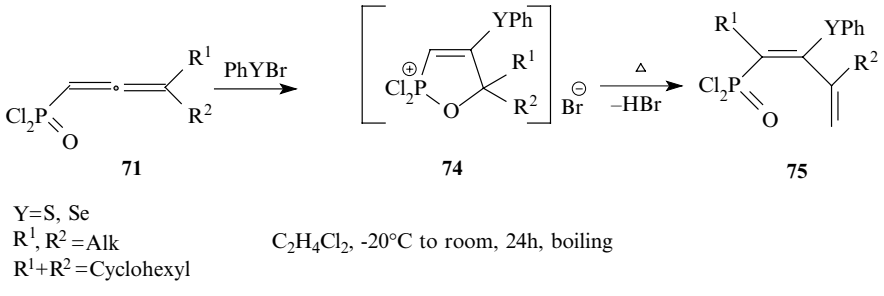
Scheme 27

The reaction of 1,2-alkadienephosphonic dichlorides with iodine and interhalogenides gave 4-iodo-2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives (Scheme 28) [81].



Scheme 28

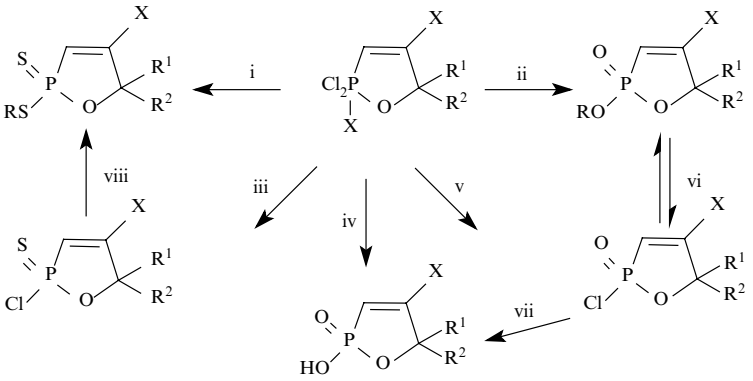
On reacting the same substrates with phenylsulphenyl- and with phenylselenenyl bromides, relatively stable cyclic phosphonium salts **74** were obtained (Scheme 29) [82].



Scheme 29

The possibility of obtaining the desired compounds is due to the higher stabilization of the phosphonium intermediate. Heating of the compounds **74** leads to the corresponding 1,3-dienephosphonates **75** [82].

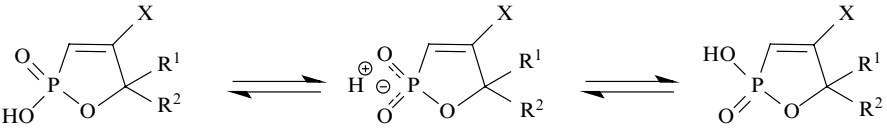
The cyclic phosphoranes so obtained demonstrate properties typical for the compounds with pentacoordinated phosphorus atom (Scheme 30) [78, 83].



i=2RSH, ii=2ROH, iii=RSH, iv=2H_2O, v=H_2O/ROH/SO_2, vi=ROH/$SOCl_2$, vii=H_2O, viii=RSH/B^-
R,R^1,R^2=Alk
R^1+R^2=Cyclohexyl

Scheme 30 Transformation of the cyclic phosphoranes

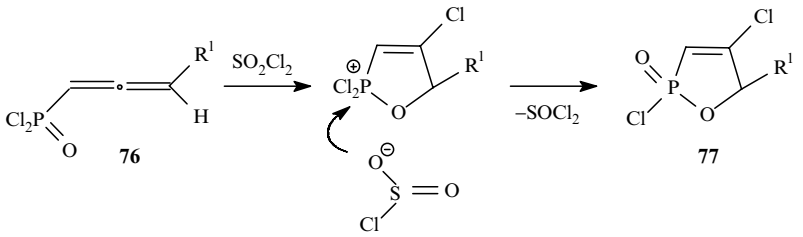
The phosphorus atom in the cyclic acids obtained from reaction IV, is achiral because of rapid proton exchange between two oxygen atoms (Scheme 31) [84].



Scheme 31 Cyclic acids equilibrium

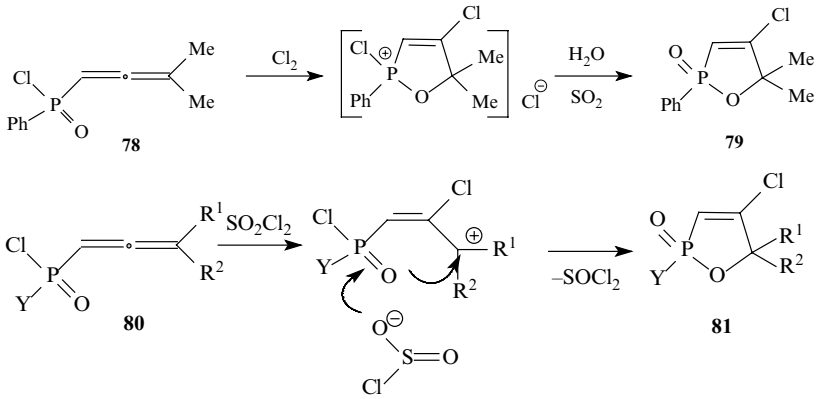
On the basis of X-ray analysis of 1,2-oxaphosphole derivatives authors suggested [68] that these compounds have planar symmetry or that there is a process of rapid conformational equilibrium.

Similar compounds were prepared by the same method, from the reaction of sulfuryl chloride and dichlorides of 1,2-alkadienephosphonic acids. It is noteworthy to emphasize that, in this case, 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives were isolated, even when 3-monosubstituted allenephosphonate were used as substrates (Scheme 32) [39, 85].



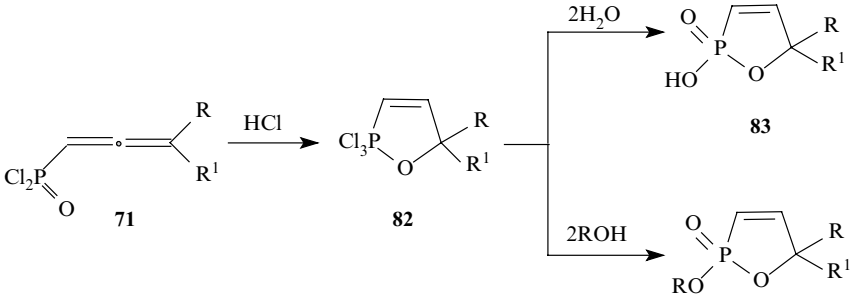
Scheme 32

A synthetic strategy as described above was employed [39, 79] for the preparation of **79** and **81** (Scheme 33).



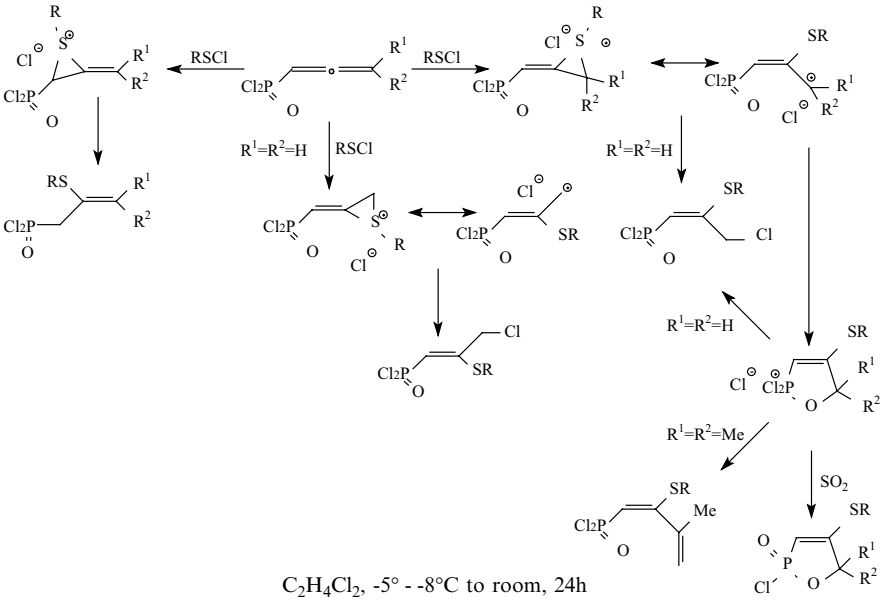
Scheme 33

`Macomber et al. achieved formation of cyclic phosphoranes **82** [86]. The latter on treatment with water or with alcohols gave the corresponding oxaphosphole derivatives (Scheme 34).



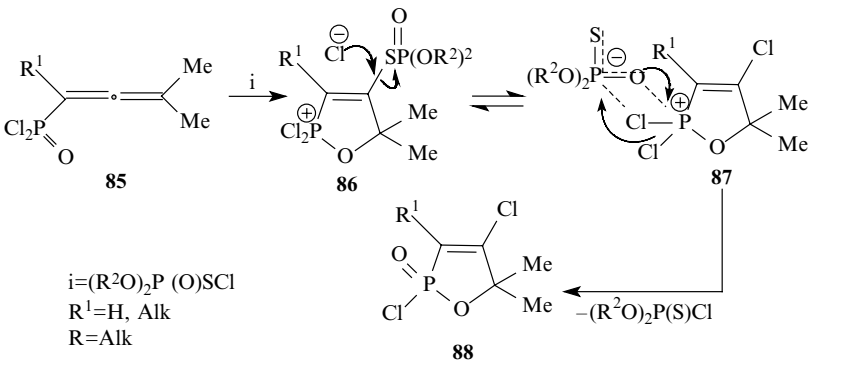
Scheme 34

The reaction of the 3,3-disubstituted-1,2-alkadienephosphonic dichlorides with alkylsulphenyl chlorides afforded, along with 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives, 1,2-adducts also. The use of sulfur dioxide in this reaction promoted the formation of the oxaphosphole product (Scheme 35) [22, 44, 71–73, 87–92].



Scheme 35

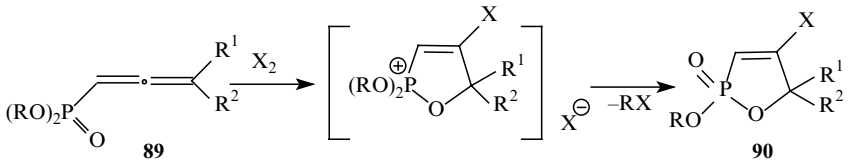
2,4-Dichloro-2-oxo-1,2-oxaphosphol-2-oxide derivatives could be produced from the reaction of dialkylphosphorylsulphenyl chloride with 1,2-alkadienephosphonic dichlorides (Scheme 36) [87, 89].



Scheme 36

2.2.3 Electrophilic Addition to 1,2-Alkadienephosphonic Dialkyl Esters

2,5-Dihydro-1,2-oxaphosphole-2-oxide derivatives were the main products obtained from halogenation of dialkyl esters of 1,2-alkadienephosphonic acids (Scheme 37) [53, 69, 79, 81, 93–100].



R, R^1,R^2=Alk, R^1+R^2= Cyclohexyl X=Cl, Br

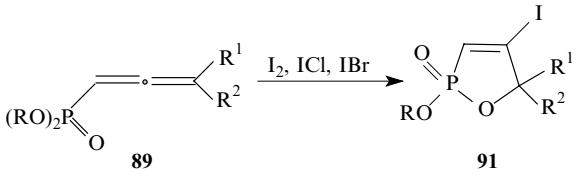
$C_2H_4Cl_2$, -5° - -8°C to room, 24h

Scheme 37

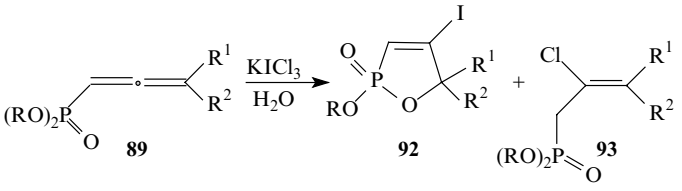
It is important to emphasize that in this reaction a spontaneous elimination of alkylhalide takes place. Detection of the eliminated alkylhalide is an additional evidence for the mechanism of the formation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives.

As underlined above, formation of these compounds by halogenation of dialkyl esters of 1,2-alkadienephosphonic acids is the major direction of the reaction. Even in the case of dialkyl esters of propadienephosphonic acid, some 1,2-oxaphosphole derivatives could be detected [86]. On using sulfuryl chloride as electrophilic reagent, only 3,3-disubstituted- and 3-monosubstituted substrates could be transformed in oxaphosphole derivatives [39]. Thus, the main role of the substituent at the C3 atom of the allenephosphonate system, for the formation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives, was demonstrated.

A similar procedure was employed [81, 101] for the synthesis of iodine-substituted 1,2-oxaphospholes (Scheme 38).



R, R^1, R^2=Alk, R^1+R^2= Cyclohexyl

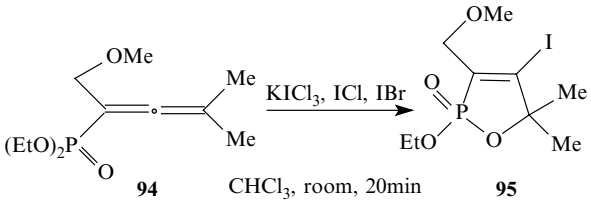


CCl_4, 50°C, 24h or $CHCl_3$, room, 20min

Scheme 38

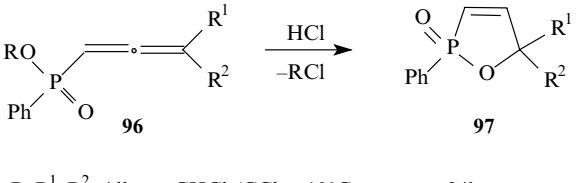
Early studies carried out by Angelov et al. [102] established the herbicidal activity of 4-iodo-2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **91**. Some of the tested compounds showed promising properties for further application as herbicides in farming.

Compounds **95** could be produced from the reaction of **94** with potassium dichloroiodate as well as with interhalides (Scheme 39) [101].



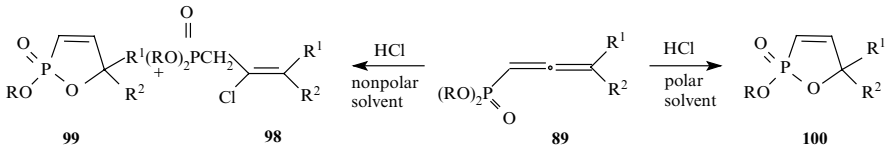
Scheme 39

The hydrohalogenation of phenyl(3-methyl-1,2-butadienyl) phosphinic esters involved protophilic attack of the reagent, followed by heterocyclization of the allenephosphonate system (Scheme 40) [103, 104].



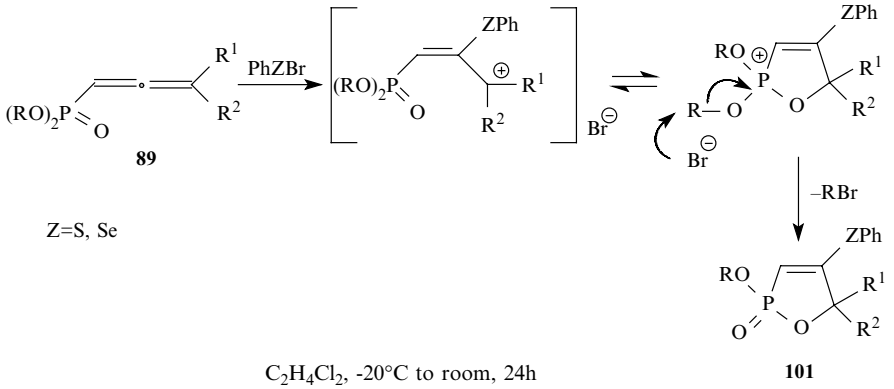
Scheme 40

On using 3,3-disubstituted-1,2-alkadienephosphonic dialkyl esters as the substrates in the above discussed reaction, a mixture of dialkyl esters of the 1,2-oxaphospholic acid and 1,2-adducts was obtained. The products ratio depends on nature of the substituents at the substrate, and on the polarity of the solvent (Scheme 41) [103, 104].



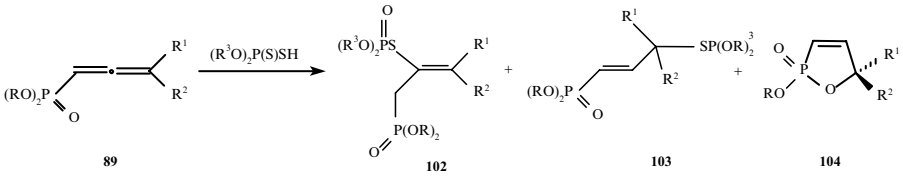
Scheme 41 Influence of the solvent polarity

Similar compounds were prepared via the same method, from the reaction of the same substrates with phenylsulphenyl- and phenylselenenyl bromides (Scheme 42) [105].



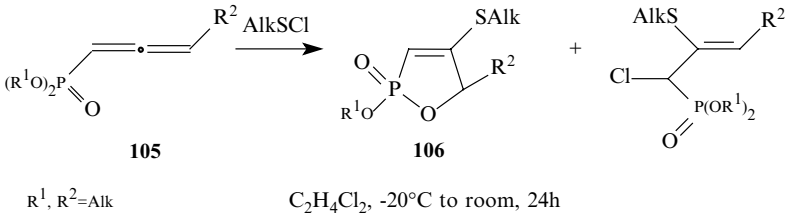
Scheme 42

It was established that the reaction of dialkyl esters of 1,2-alkadienephosphonic acids with phosphorus dithio acids gave small amount (5–6%) of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives (Scheme 43) [106].



Scheme 43 Synthesis of 2-alkoxy-5,5-dialkyl-5*H*-[1,2]-oxaphosphole-2-oxides **104**

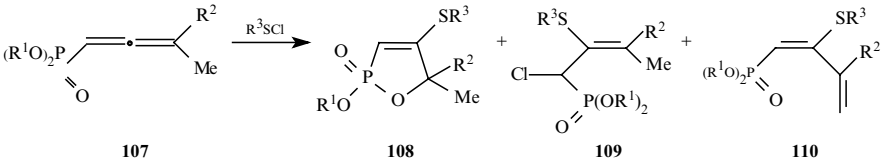
1,2-Oxaphospholic derivatives were also prepared from the reaction of 3-monosubstituted alkadienephosphonates with alkylsulphenyl chlorides (Scheme 44) [107].



Scheme 44

It has been reported that same reaction gave a complex mixture of products, i.e.,1,2-oxaphosphole derivatives, 1,2- and 2,3-adducts in 1:1:4 ratio [107].

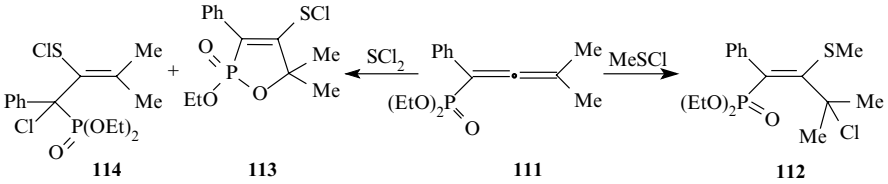
On reacting 3,3-disubstituted-1,2-alkadienephonic dialkyl esters with methylsulphenyl chloride, 1,2-oxaphosphole derivatives and 1,2-adducts were isolated [108]. In the case of dialkyl esters of 3-methyl-1,2-butadienephosphonic acid, the formation of dialkyl esters of 1,3-butadienylphosphonic acid was also detected (Scheme 45).



$C_2H_4Cl_2$, -20°C to room, 24h

Scheme 45

The analogous reaction with SCl_2 leads to1,2-oxaphosphole-2-oxide derivatives in high yields [109]. The cyclic compounds prepared in this manner react with nucleophilic reagents easily, allowing incorporation of oxaphosphole ring in many organic substrates (Scheme 46) [109, 110].

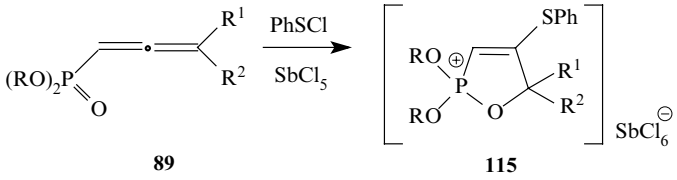


CH_2Cl_2, -20°C to room, 24h

Scheme 46

It has been established that alkadienephosphonates bearing bridge-substituent at C3 atom of the alenephosphonate system on reaction with alkyl(aryl)sulphenyl chlorides lead to the formation of spyrocompounds [111].

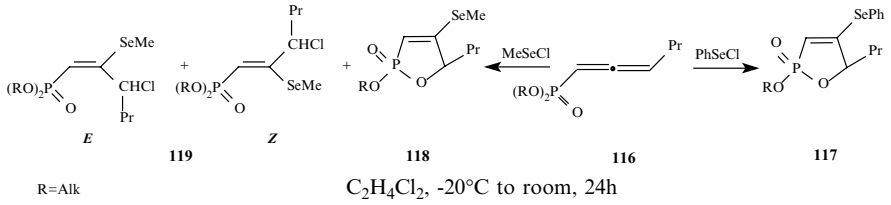
The reaction of diethyl ester of 3-methyl-1,2-butadienephosphonic acid with PhSCl/$SbCl_5$, leads to oxaphosphonium salt **115** (Scheme 47) [112].



$CHCl_3/CCl_4$, -10°C to room, 24h

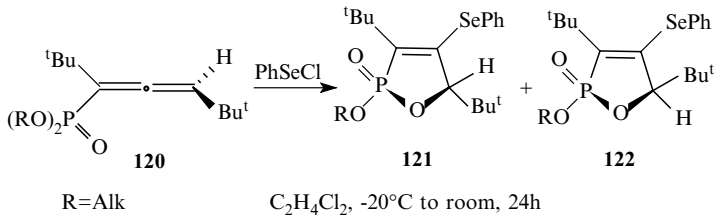
Scheme 47

Compounds **118** could be produced from the reaction of dialkyl esters of 3-monosubstituted-1,2-alkadienephosphonic acids with methylselenenyl chloride. It was established that, along with **118**, 2,3-adducts were also formed [113]. Use of phenylsulphenyl chloride in this reaction leads exclusively to the formation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **117** (Scheme 48) [113, 114].



Scheme 48

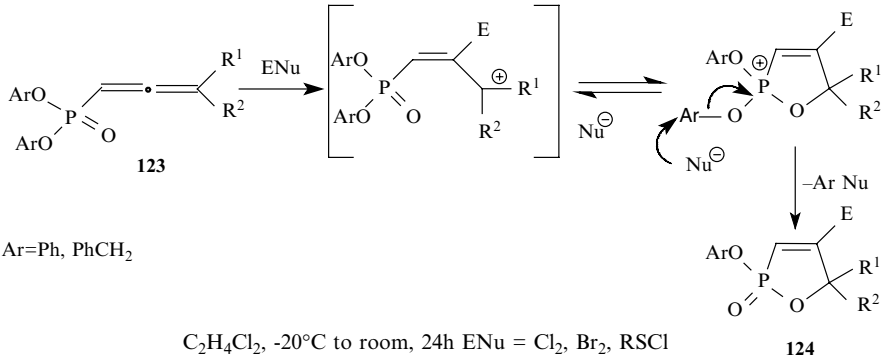
Compounds **120** were used as the starting material for establishing the stereoselectivity of the reaction of allenephosphonates with phenylselenenyl chloride (Scheme 49) [114].



Scheme 49

The reaction of dialkyl esters of 1,2-alkadienylphosphonic and phosphinic acids with methyl and phenylsulphenyl chloride, leads exclusively to 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives [113–115].

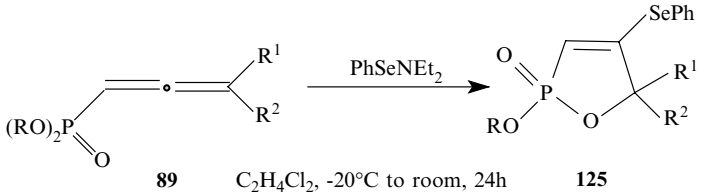
Regardless of the nature of the ester groups at phosphorus in the molecules of the 1,2-alkadienephosphonic substrate, the electrophilic addition leads to the formation of 1,2-oxaphosphole derivatives (Scheme 50) [116].



123 124

Scheme 50

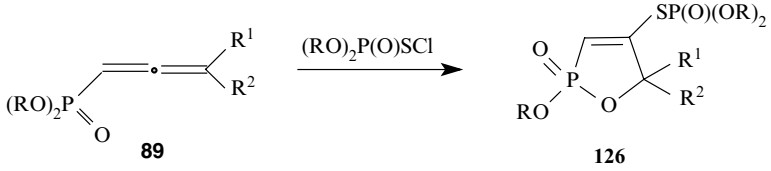
The synthesis of 4-phenylseleno-2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **125** is shown below (Scheme 51) [87].



89 125

Scheme 51

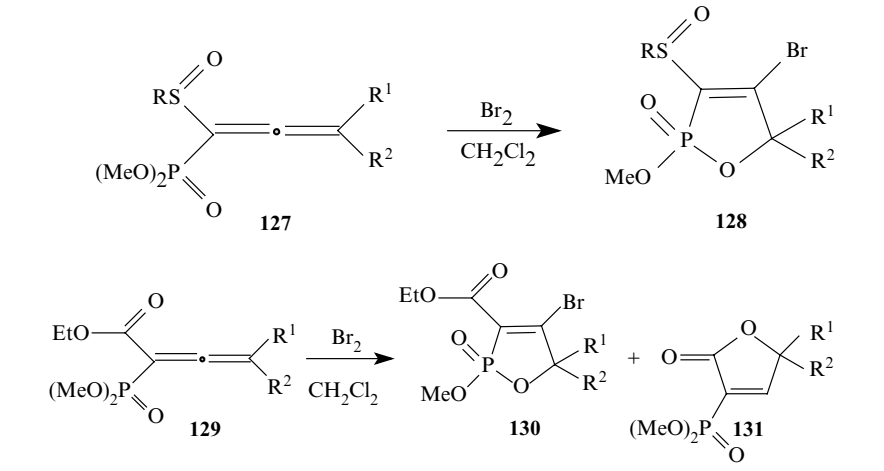
The 1,2-alkadienephosphonic dialkyl esters react smoothly with dialkoxyphosphonylsulphenyl chlorides, affording 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **126** (Scheme 52) [117].



89 126

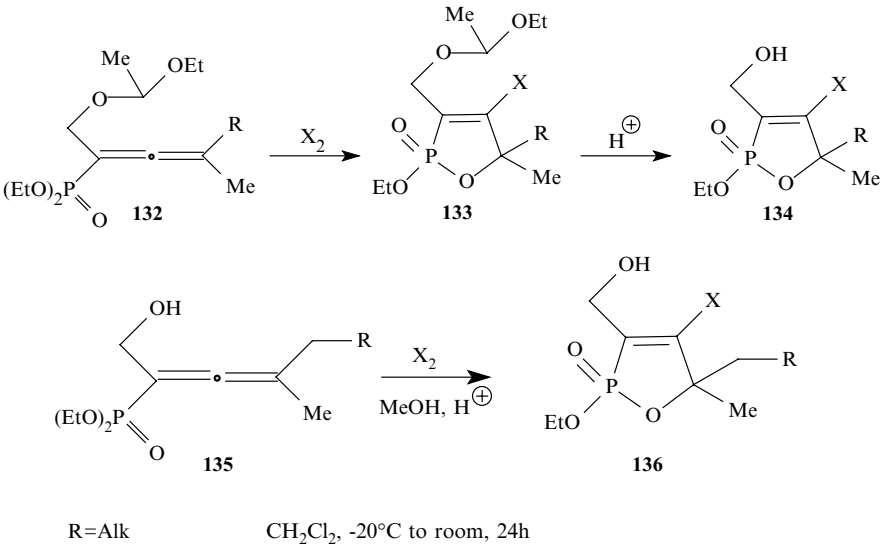
Scheme 52

Christov et al. [118–120] have described the synthesis of oxaphosphole derivatives **128** and **130** from bromination of bifunctionalized allenes (Scheme 53).



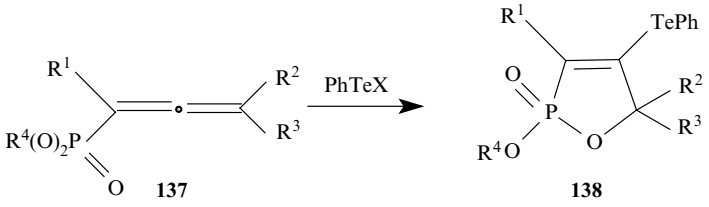
Scheme 53

A similar procedure was followed for the preparation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **134** possessing CH_2OH group at C3 atom of the oxaphosphole ring. The oxaphosphole products were obtained as E/Z mixture from the reaction of 1-substituted-1,2-alkadienephosphonic diethyl esters **135** with halogens (Scheme 54) [121, 122].



Scheme 54

The synthesis of oxaphosphole derivatives **138** has been reported from the reaction of allenephosphonic dialkyl esters with phenylteluryl halides (Scheme 55) [123].



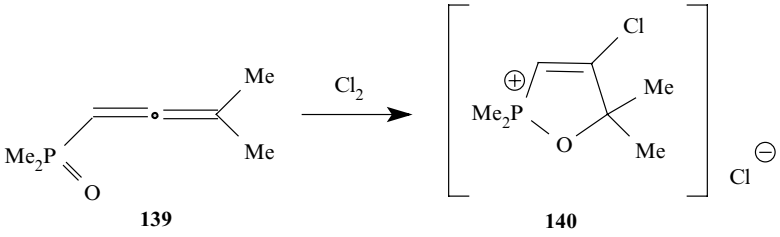
Scheme 55

A mechanism similar to that proposed for the reaction of allenephosphonic dialkyl esters with halogens has been suggested.

It is noteworthy that compounds **138** are good precursors in further synthesis, because of their good leaving phenylteluro group [123].

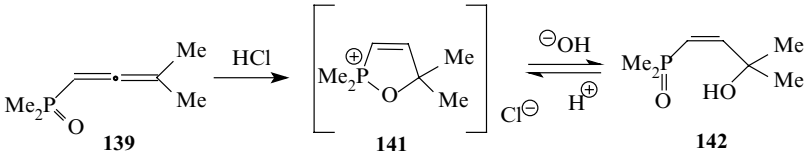
2.2.4 Electrophilic Addition to 1,2-Alkadienephosphonic Oxides

The chlorination of dimethyl(3-methyl-1,2-butadienyl)phosphine oxide has been reported to produce 2,5-dihydro-1,2-oxaphosphonium salts **140** (Scheme 56) [113].



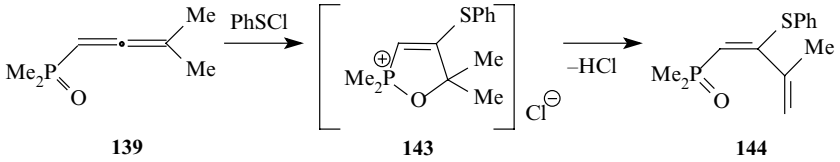
Scheme 56

Hydrochlorination of the same substrate leads to the cyclic unstable phosphonium salt **141** (Scheme 57) [103].



Scheme 57

The substrate **139** reacts with phenylsulphenyl chloride, affording cyclic phosphonium salt **143** which decomposes on heating to the corresponding 1,3-diene (Scheme 58) [107].

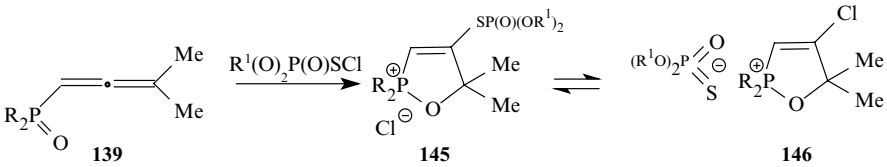


139 **143** **144**

$C_2H_4Cl_2$, -10° - -15°C to room, 24h

Scheme 58

The 1,2-alkadienephosphine oxides react smoothly with dialkoxyphosphonyl-sulphenyl-chlorides affording 2,5-dihydro-1,2-oxaphosphonium salts **145** and **146** (Scheme 59) [117].

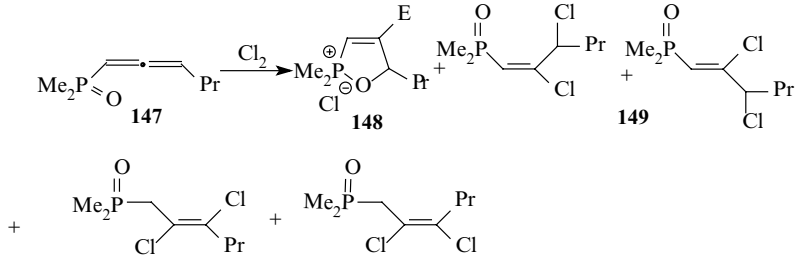


139 **145** **146**

R=Me, R1=Alk $C_2H_4Cl_2$, -10° - -15°C to room, 24h

Scheme 59

The cyclic phosphonium salts **140**, **141**, **143**, **145**, and **146** so obtained are evidence for the mechanism of the oxaphospholic cyclization and especially for the main role of the tertiary carbocation formation during the process. The additional data which support this assumption, come from the investigation of the same reaction, but with different substrate, i.e., dimethyl(1,2-hexadienyl)phosphine oxide **147**. In this case, the reaction mechanism involved formation of secondary carbocation that gives oxaphosphole product **148** only in 10% yield (Scheme 60) [124].

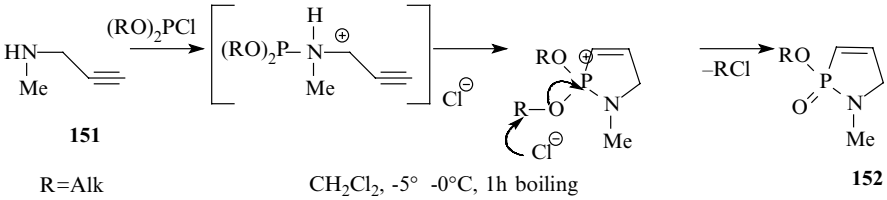


147 **148** **149** **150**

$C_2H_4Cl_2$, -10° - -15°C to room, 24h

Scheme 60

The mechanism of oxaphospholic cyclization was confirmed by isolating **152** in the reaction of *N*-methyl-*N*-propargylamine with dialkylchlorophosphite (Scheme 61) [125].

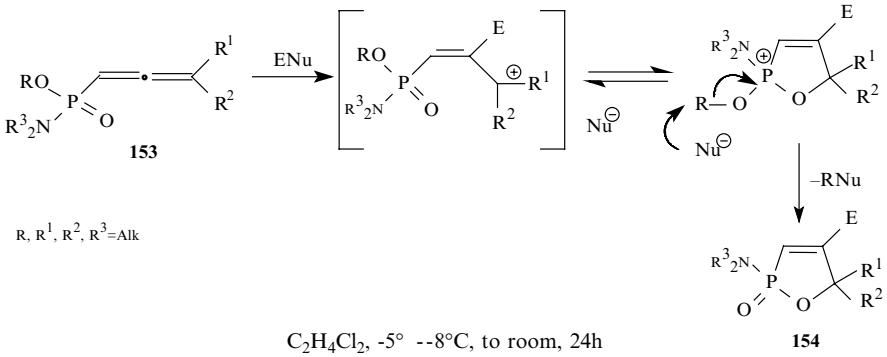


Scheme 61

Other authors followed similar synthetic sequence [126, 127].

2.2.5 Electrophilic Addition to 1,2-Alkadienephosphonic Amidoesters

Enchev et al. [128, 129] has reported the synthesis of 1,2-oxaphosphole derivatives, bearing *N*,*N*-dialkylamido-group at phosphorus **154** (Scheme 62).

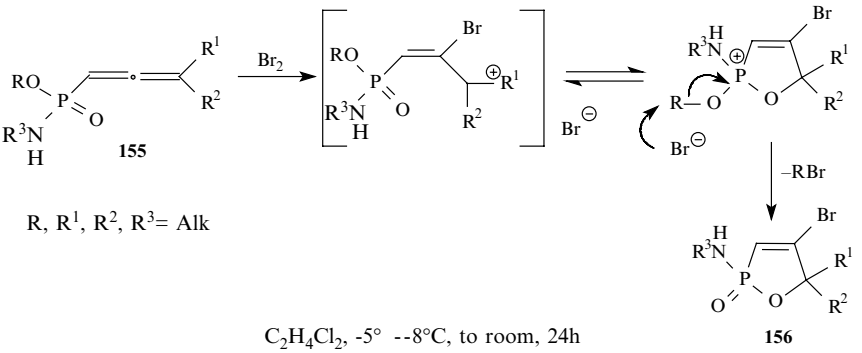


Scheme 62

This synthetic strategy makes the synthesis of amino derivatives of 2,5-dihydro-1,2-oxaphospholes possible.

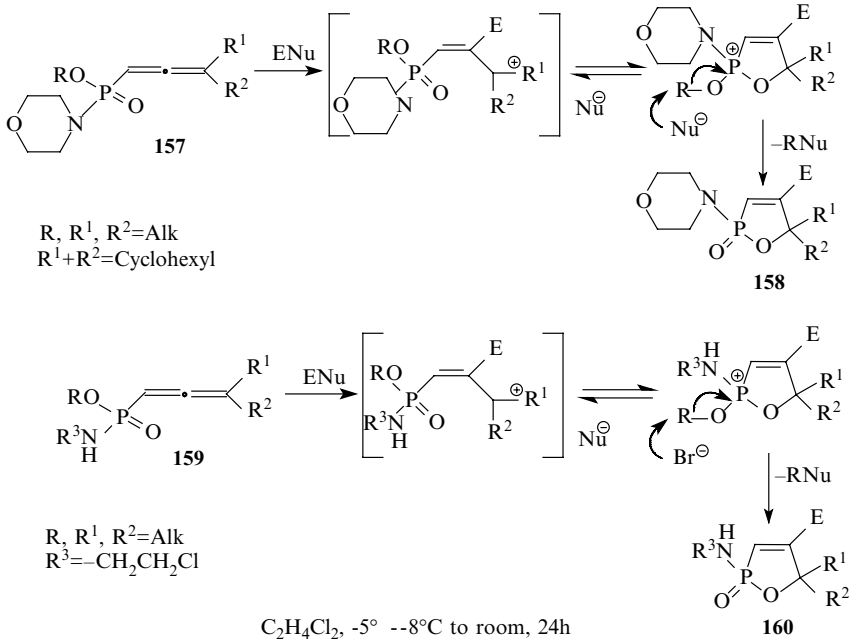
Furthermore, these compounds were found to possess growth-regulating activity [130, 131]. The same compounds were tested for their cytotoxic and cytomutagenic effects. As a result, only weak mutagenic and mytostatic properties of the compounds have been detected [132].

Authors employed similar method to prepare compounds **156** (Scheme 63) [133].



Scheme 63

The synthetic strategy described allowed the synthesis of *N*-morpholino-1,2-oxaphosphole derivatives [134], as well as 1,2-oxaphosphole derivatives, bearing *N*-2-chloroethyl group at phosphorus (Scheme 64) [135].



Scheme 64

Compounds **160** are still under investigation for their biological activity, as they are expected to exhibit such activity, because of their structure similarity to phosphorus amides bearing 2-chloroethyl substituent at nitrogen. It is well known that

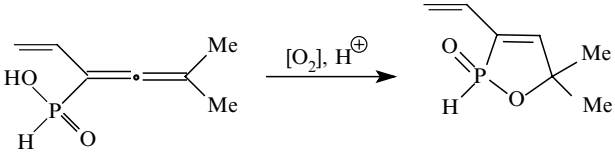
the latter have wide application as chemosterilizing insecticides or cytostatic agents [136–144].

The evaluation of antimicrobial activity of 1,2-oxaphosphole-2-oxides was reported by Haranath et al. [145].

2.3 *Electrophilic Addition to 1,2-Alkatrienephosphonates*

2.3.1 Electrophilic Addition to 1,2-Alkatrienephosphonic Acids

It was shown that 1,3,4-hexatrienephosphonic acid **161** reacted with hypophosphoric acid and air to give the corresponding 3-vinyl-2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **162** (Scheme 65) [64].

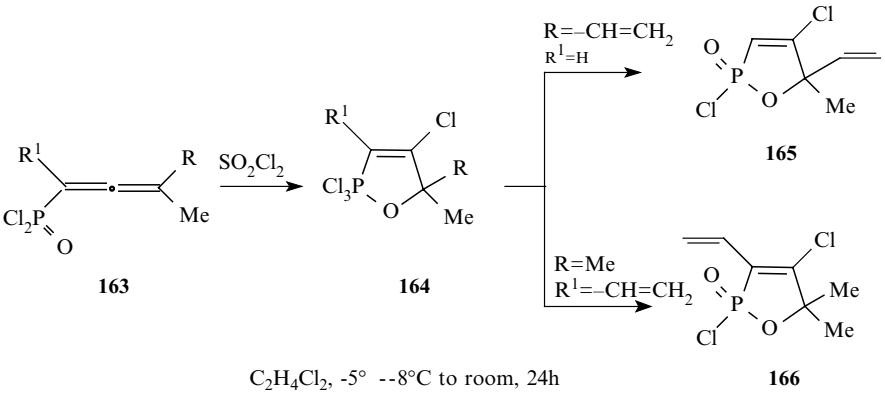


161 **162**

Scheme 65 Synthesis of 5,5-dimethyl-3-vinyl-5*H*-[1,2]-oxaphosphole-2-oxide **162**

2.3.2 Electrophilic Addition to 1,2-Alkatrienephosphonic Dichlorides

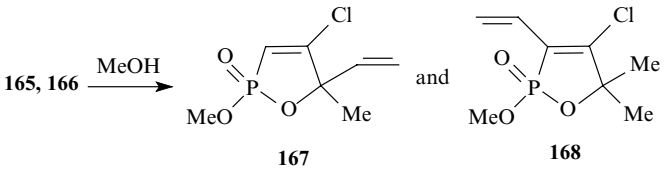
Compounds **168** and **169** were synthesized from the reaction of dichlorides of 1,2,4-pentatriene- and 1,3,4-hexatrienephosphonic acids with sulfurilchloride (Scheme 66) [146].



163 **164** **165** **166**

Scheme 66

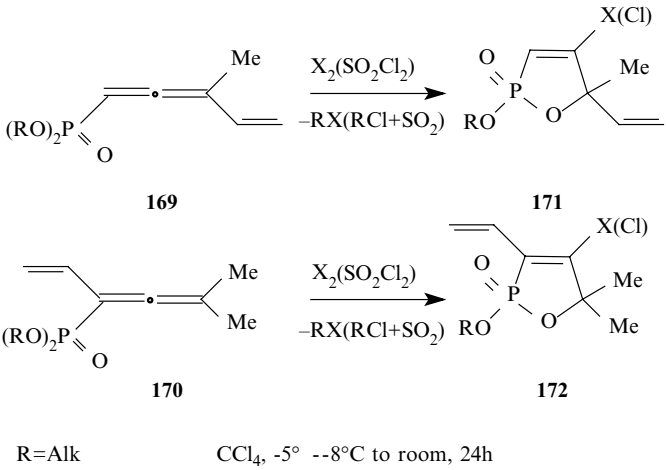
The reactivity of the chlorine atom at phosphorus was demonstrated in the reaction of these compounds with methanol (Scheme 67) [146].



Scheme 67

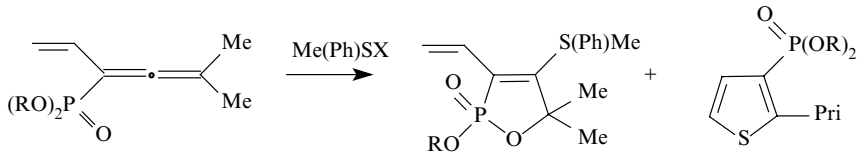
2.3.3 Electrophilic Addition to 1,2-Alkatrienephosphonic Dialkyl Esters

The above results encouraged authors [95, 99] to examine the reactivity of dialkyl esters of 1,2,4- and 1,3,4-alkatrienephosphonic acids **169** and **170**. These substrates on halogenation gave 3- or 5-vinylsubstituted-2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **171** and **172** (Scheme 68). Spectral investigations of this reaction show that, formation of oxaphosphole ring starts immediately after adding of the reagent.



Scheme 68

Dialkyl esters of 1,3,4-hexatrienephosphonic acid react with alkyl(phenyl)sulphenyl halides, to form mixture of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives and thiophene derivatives (Scheme 69) [147–149].

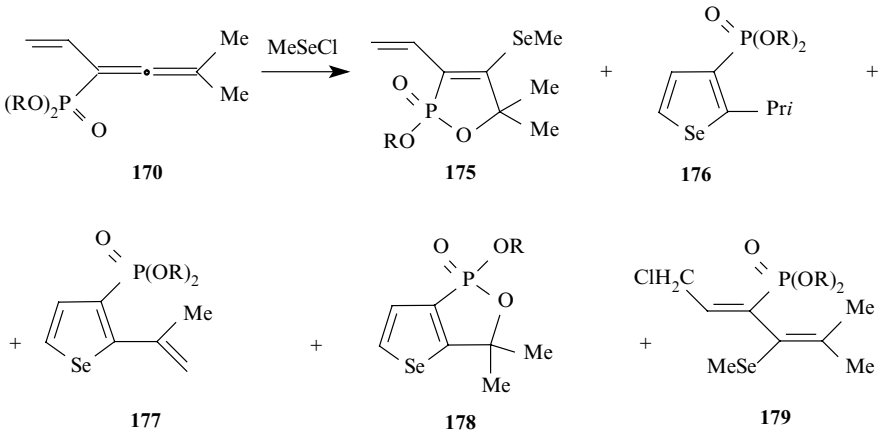


173 **176** **177**

CCl_4, -5° --8°C to room, 24h

Scheme 69

The same substrate **170** reacts with alkyl(phenyl)selenenyl chlorides to give predominantly 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **175** (Scheme 70) [150].



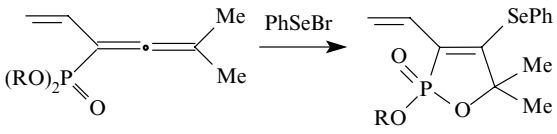
170 **175** **176**

177 **178** **179**

CCl_4, -5° --8°C to room, 24h

Scheme 70

The same substrates react with phenylselenenyl bromide to give only 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives (Scheme 71) [149].



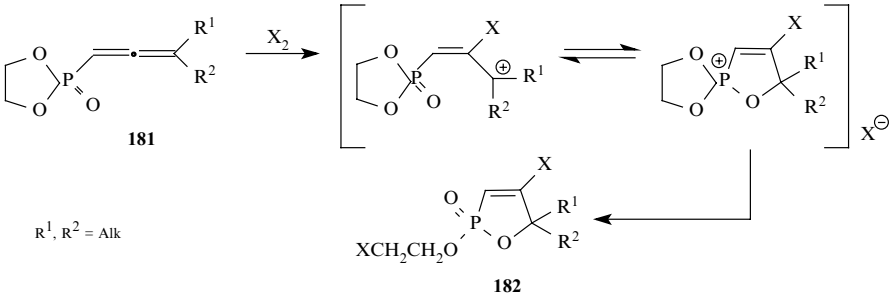
170 **180**

R=Alk $C_2H_4Cl_2$, -10° --15°C to room, 24h

Scheme 71

3 Electrophilic Addition to Allenesubstituted-1,3, 2-Dioxaphospholanes

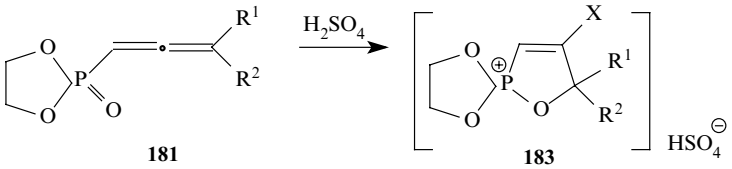
The halogenation of the allenesubstituted 2-oxo-1,3,2-dioxaphospholanes also leads to 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **182** (Scheme 72) [99].



Scheme 72

The mechanism of the reaction involves oxaphosphole ring closure followed by 1,3,2-dioxaphospholane rind opening.

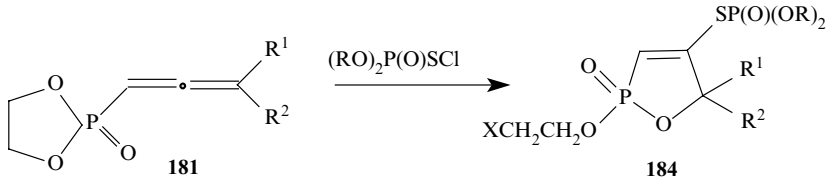
The reaction of **181** with sulfuric acid was then employed for establishing the postulated reaction intermediate (Scheme 73) [151].



Scheme 73

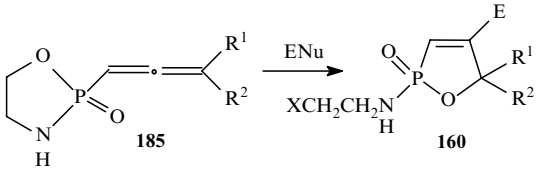
Compounds **181** react with alkylsulphenyl chlorides to form a mixture of 1,2-oxaphosphole derivatives and 1,2-adducts in 4:1 ratio. Decreasing the reaction temperature favored formation of oxaphosphole product. The same substrates reacted with phenylsulphenyl- and phenylselenenyl bromides to give only 1,2-oxaphosphole derivatives [133].

Similar to the reaction pathway discussed above, **181** reacts with dialkoxyphosphonyl-sulphenyl chlorides affording **184** (Scheme 74) [117].



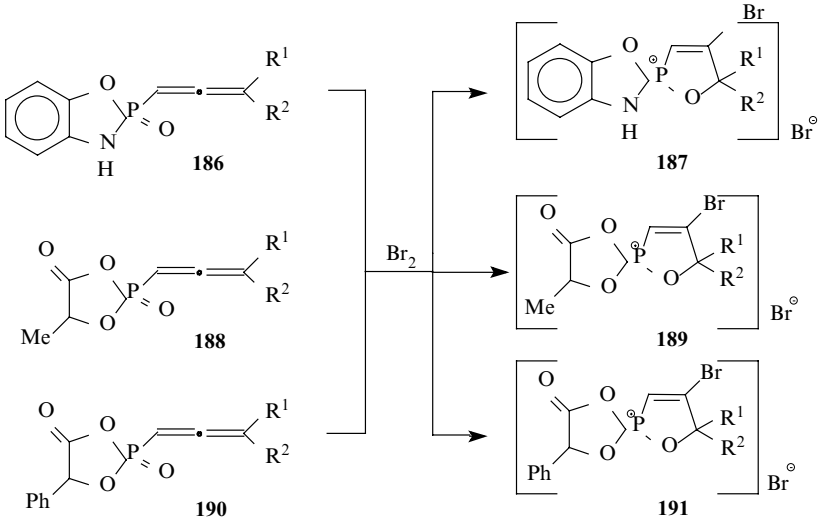
Scheme 74

In another synthetic strategy allenesubstituted-1,3,2-oxazaphospholanes **185** on reacting with electrophilic reagents afforded **160** (Scheme 75) [135].



Scheme 75

An attempt to obtain other evidence for the mechanism of the oxaphospholic cyclization has been made and is shown in Scheme 76 [152].

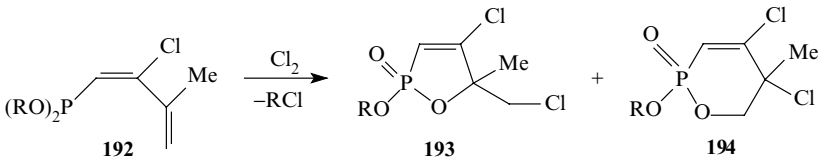


Scheme 76

4 Electrophilic Addition to 1,3-Alkadienephosphonates

4.1 Electrophilic Addition to 1,3-Alkadienephosphonic Dichlorides

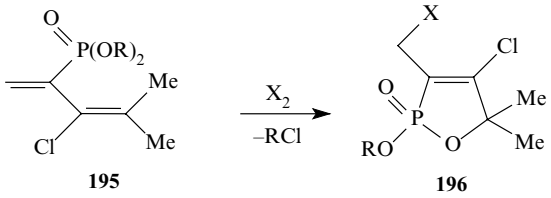
On chlorination of dialkyl esters of 2-chloro-3-methyl-1,3-butadienephosphonic acid in non-polar media, a mixture of five- and six-membered heterocyclic compounds was obtained (Scheme 77) [153, 154].



R=Alk $C_2H_4Cl_2$, -5° --0°C to room, 24h

Scheme 77

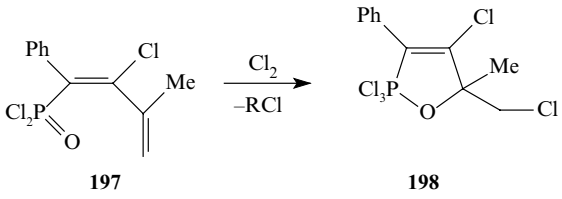
The 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives **196** were also obtained from the reaction of esters of 3-chloro-4-methyl-1,3-pentadiene-2-phosphonic acid with halogens (Scheme 78) [155, 156].



R=Alk $C_2H_4Cl_2$, -5° --0°C to room, 24h

Scheme 78

A similar procedure was followed for the synthesis of **198** (Scheme 79) [156].

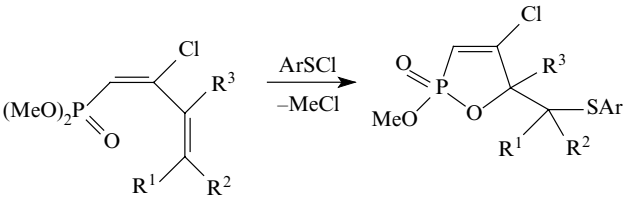


$C_2H_4Cl_2$, -5° - -0°C to room, 24h

Scheme 79

4.2 *Electrophilic Addition to 1,3-Alkadienephosphonic Dialkyl Esters*

The reaction of 2-chloro-1,3-alkadienephosphonates with arenesulphenylchlorides gave 2,5-dihydro-1,2-oxaphosphole derivatives in good to excellent yields (Scheme 80) [157].

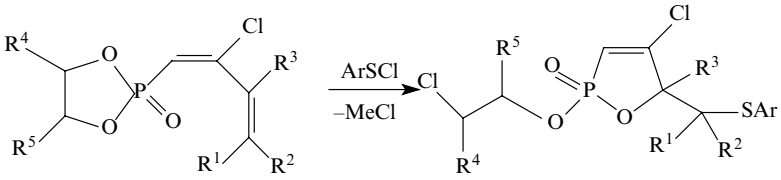


199 **200**

R^1, R^2, R^3=H, Alk $C_2H_4Cl_2$, -5° --0°C to room, 24h

Scheme 80

The reaction of 1,3-dienephosphonic-1,3,2-dioxaphospholanes with arenesulphenyl chlorides followed the mechanism discussed earlier to give **202** (Scheme 81) [158].

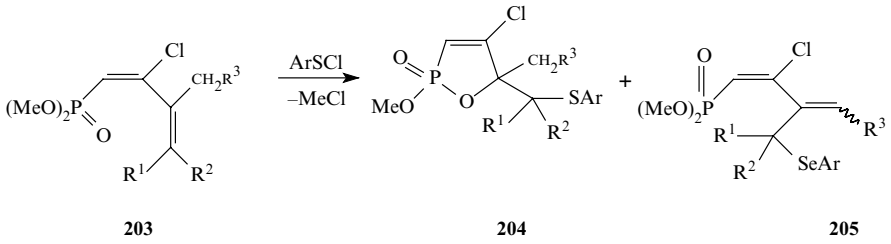


201 **202**

R^1, R^2, R^3, R^4, R^5=H, Alk $C_2H_4Cl_2$, -5° --0°C to room, 24h

Scheme 81

The target compounds were also obtained from the reaction of 2-chloro-1,3-alkadienephosphonic dialkyl esters with areneselenenyl chlorides (Scheme 82) [159].



203 **204** **205**

R^1, R^2, R^3=H, Alk $C_2H_4Cl_2$, -5° --0°C to room, 24h

Scheme 82

5 Conclusion

The submitted methods for preparation of target compounds based on the electrophilic addition reactions of 1,2-alkadiene- and alkatrienephosphonates show that they are very promising from synthetic point of view.

1,2-Alkadiene- and alkatrienephosphonates are available from acetylene–allene rearrangement of acetylene phosphites which could easily be prepared from the reaction of carbonyl compounds and 1-alkynes.

In this context the described methods for preparation of 2,5-dihydro-1,2-oxaphosphole-2-oxide derivatives have to be considered as synthetic protocols for transformation of carbonyl compounds in to P-containing heterocycles.

All the reactions are environmental friendly and proceed with almost total atom economy.

It is important to emphasize that all of the tested compounds are biologically active substances.

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Top Heterocycl Chem (2010) 21: 63–102
DOI 10.1007/7081_2009_5

Published online: 13 October 2009

Recent Developments in the Chemistry of *N*-Heterocyclic Phosphines

Dietrich Gudat

Abstract This chapter gives a survey on five- and six-membered phosphorus–nitrogen heterocyclic compounds whose rings combine a phosphazene (>N–P=N–) or phosphazane (>N–P(X)–N<) unit with an unsaturated C_2 or C_3 building block. Representatives contain structurally diverse species like aromatic 1,3,2-diazaphosphinines and (benzo)-1,3,2-diazaphospholes, cationic counterparts of subvalent main-group carbene analogues like 1,3,2-diazaphospholenium ions and phosphenium-diketiminates, and neutral heterocycles like 1,3,2-diazaphospholenes featuring unusual structures and reactivities. The exploration of these species developed rapidly in the last two decades in the wake of cutting edge research on multiple bonding and low coordination in the chemistry of heavier main-group elements, and the discovery of stable carbenes. This review summarizes the elaboration of synthetic approaches for different types of *N*-heterocyclic phosphine derivatives, discusses their characterization by physical and computational methods which furnished a thorough understanding of structure and bonding, and finally highlights accomplishments in the exploration of the chemical properties at the border of classical organic heterocyclic chemistry and molecular inorganic chemistry.

Keywords 1,3,2-diazaphospholes • 1,3,2-diazaphospholenes • 1,3,2-diazaphosphinines • 2,3-dihydro-1,3,2-diazaphosplinines diketiminto-phosphenium ions • N-heterocyclic phosphines • N-heterocyclc phosphenium ions • 1,2,3-diazaphospholenium ions

Abbreviations

Bu	Butyl
Cy	Cyclohexyl

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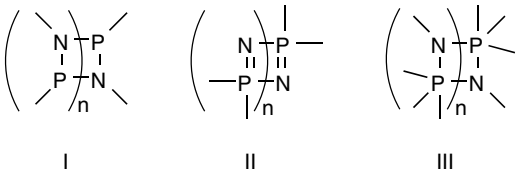
Contents

Dipp	2,6-Diisopropylphenyl
Et	Ethyl
Me	Methyl
NHP	*N*-heterocyclic phosphine ≅ 1,3,2-diazaphospholene
t-Bu	*tert*-Butyl

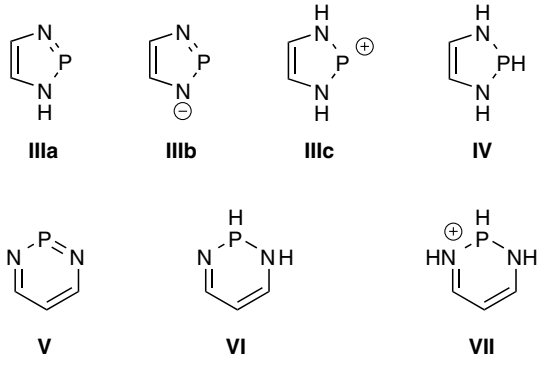
1 Introduction

Heterocyclic compounds featuring rings containing both phosphorus and nitrogen atoms range back to the work of Liebig and Wöhler [1] and belong presumably to the oldest inorganic ring systems known. Starting from these first beginnings, the chemistry of these species has seen a tremendous development which was driven both by the discovery of an enormous structural diversity of phosphorus–nitrogen heterocyclic frameworks and the fact that several of these species have found profound applications in inorganic synthesis. Some well known examples are the use of cyclic chlorophosphazenes as precursors to polyphosphazenes which represent one of the classical structural types of inorganic polymers [2], the use of proazaphosphatranes as powerful bases, nucleophiles, or catalysts in organic reactions [3], or the application of cyclic phosphoramidates in nucleotide synthesis. Although attempts to give a systematic overview on the diverse types of phosphorus–nitrogen containing ring structures may seem hopeless, it appears a good practical starting point to distinguish between heterocyclic rings featuring three-valent phosphorus atoms that carry still a lone-pair of electrons and display typical coordination numbers of two or three, and pentavalent phosphorus atoms featuring usually coordination numbers between four and six. Typical representatives of binary heterocycles of either type are cyclophosphazanes (**I**), and cyclophosphazenes (**II**) or cyclic phosphoranes (**III**), respectively (Structure 1).



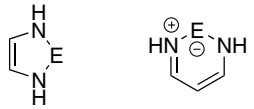
Structure 1 Generic representation of the structures of basic types of binary phosphorus–nitrogen heterocycles: cyclophosphazanes (**I**), cyclophosphazenes (**II**), cyclic phosphoranes (**III**)

Beside these binary heterocycles, a wealth of compounds is known whose cyclic structures contain other atoms in addition to phosphorus and nitrogen. A particular interesting and useful subclass is the one that comprises ternary heterocyclic systems containing additional carbon atoms, which may be considered to form a link between purely inorganic ring systems and classical organic heterocyclic compounds. This review focuses mainly on two families of such ternary heterocycles whose rings are formed by fusion of "phosphazane" or "phosphazene" type N–P–N moieties with unsaturated C_2 or C_3-fragments, respectively (Structure 2). The five-membered ring compounds represent derivatives of the parent 1,3,2-diazaphosphole **IIIa** or the corresponding 2,3-dihydro-derivative **IV**, respectively. Neutral 1,3,2-diazaphospholes **IIIa** are still rare and exist mainly as transient rather than isolable species but stable anionic (**IIIb**) and, in particular, a large number of cationic derivatives (**IIIc**) have been prepared. As the cation **IIIc** can formally be generated by either N-protonation of **IIIa** or, alternatively, P-hydride abstraction from **IV** (both approaches have in fact been established as viable synthetic routes), it may be considered as link between heterocycles of type **IIIa** and **IV**. Several stable six-membered heterocycles that are derivatives of neutral 1,3,2-diazaphosphinines **V** and 2,3-dihydro-1,3,2-diazaphosphinines **VI** have been reported but the most exciting development in this area is, without doubt, the recent discovery of cationic heterocycles **VII** which are best regarded as diketiminato-substituted phosphenium ions stabilized by an intramolecular donor–acceptor bond.



Structure 2 Parent representatives of phosphorus–nitrogen heterocycles covered in this chapter

Whereas a strong motivation for the exploration of the listed types of heterocycles came initially from the desire to characterize the potentially aromatic nature of the delocalized π-electron systems in 1,3,2-diazaphosphole (**III**) and 1,3,2-diazaphosphinine (**V**) derivatives, the recent development of the chemistry of cationic systems **IIIc**, **VII** was most strongly influenced by a generally rising interest in inorganic heterocycles that provide stabilization of an electron deficient main-group element E with a formal count of six valence electrons by interaction with neighboring π-donor substituents (cf. generic structures **VIII**, **IX** in Structure 3).



VIII **IX**

E = E =
B^-, Ga^- Ga, In
C, Si, Ge, Sn SiH, GeH
N^+, P^+, As^+, Sb^+ PH^+, AsH^+
S^{2+}, Se^{2+}

Structure 3 Generic representation of the structures of *N*-heterocyclic carbene analogues

The upsurge in the chemistry of the five-membered ring compounds **VIII** was triggered by the discovery of stable carbenes (**VIII**, E = C:) at the beginning of the 1990s, and the finding that these carbenes are powerful nucleophiles and valuable tools for many applications in coordination chemistry or catalysis [4–6]. This boom stimulated a quest for inorganic carbene analogues which are derived from the prototype by formal isoelectronic replacement of the divalent carbon atom by other elements of groups 13–16, and also increased the interest in cyclic phosphenium ions **IIIc** which had been discovered even before the carbenes [7] but received at first only moderate attention. Neutral *N*-heterocyclic phosphines (NHPs) **IV** entered the scene as synthetic precursors of cations **IIIc** and moved into focus as primary targets of further research when it was found that they exhibit likewise a quite unique bonding situation and appealing reactivity [8]. The exploration of the chemistry of six-membered ring cations **VII** started only very recently [9], reflecting attempts to extend recent achievements in the use of diketiminato-ligands for the stabilization of subvalent main-group element species to phosphorus compounds, and must still be considered to be at the beginning of its development.

In the remainder of this chapter, we will concentrate, after a few short remarks on some aspects of nomenclature, on the description of syntheses, physical properties, bonding situation, and chemical reactivity of NHP derivatives of the types **III–VII.**

2 Nomenclature

The naming of organophosphorus compounds is frequently a source of confusion owing to the (co)existence of several, more or less systematic, schemes for compound nomenclature. The designation of the parent neutral heterocycles **IIIa** as

1,3,2-diazaphospholes seems to be without alternative, and anions **IIIb** are then referred to as 1,3,2-diazaphospholides. The 1,2-dihydro-derivatives **IV** have been named both as 2,3-dihydro-1,3,2-diazaphospholes and 1,3,2-diazaphospholenes (NHP). Either the latter name or the acronym NHP (in analogy to the denomination of imidazoylidenes as NHC) will be used throughout this chapter, and fully saturated heterocycles are then called 1,3,2-diazaphospholidines. Cations of type **IIIc** can be formally classified as derivatives of either **IIIa** or **IV**, and may thus be designated as either 1,3,2-diazaphospholium or 1,3,2-diazaphospholenium ions, respectively. Both names have been used, and although the former would seem more appropriate to highlight the aromatic nature of the π-electron system, the term 1,3,2-diazaphospholenium ion seems to have been more widely applied and claims historical priority, and will thus be applied here as well, together with the designation as "cationic NHP." The neutral six-membered ring systems are designated as 1,3,2-diazaphosphinine (**V**) and dihydro-1,3,2-diazaphosphinine (**VI**), thus dispensing with the older designations of 1,3,2-diazaphosphorin and dihydro-1,3,2-diazaphosphorin, respectively. Cationic systems of type **VII** are referred to as cyclic β-diketiminato-phosphenium ions.

In principle, all compounds mentioned can contain either tervalent (λ^3) or pentavalent (λ^5) phosphorus atoms. We will in the following assume implicitly the presence of tervalent (λ^3) phosphorus atoms unless a different valence state is explicitly mentioned.

3 Five-Membered *N*-Heterocyclic Phosphines

3.1 Syntheses

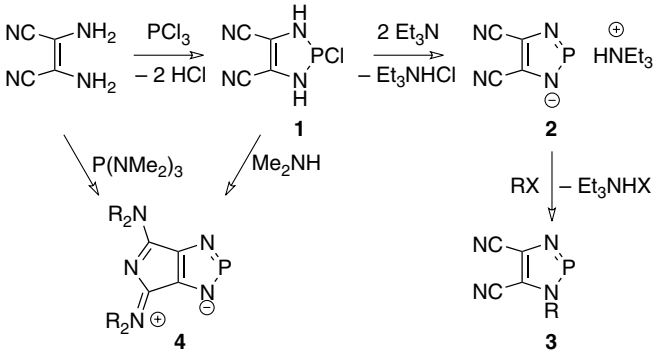
Construction of isolated or benzannulated five-membered rings of NHPs can be accomplished by means of various condensation or cycloaddition reactions all of which involve interaction of an electrophilic P_1 and a nucleophilic C_2N_2 building block. Salts containing 1,3,2-diazaphospholide anions or 1,3,2-diazaphospholenium cations can be directly accessed by some of these reactions but the products are in most cases neutral 1,3,2-diazaphospholes or NHP. A particularly concerted effort has been directed toward the synthesis of P-halogen-substituted NHP which are capable of undergoing further reactions via halide displacement or halide abstraction and serve thus as entry points for the preparation of a wide variety of neutral and cationic NHP derivatives. 1,3,2-Diazaphospholide anions are normally accessed by deprotonation of suitable *N*-H-substituted precursors.

3.1.1 Synthesis Via Heterocyclic Ring Assembly

1,3,2-Diazaphospholes and 1,3,2-Diazaphospholides

1,3,2-Diazaphospholes with an isolated ring have been prepared from diaminomaleonitrile and PCl_3 [10, 11]. Reacting both components in refluxing acetonitrile

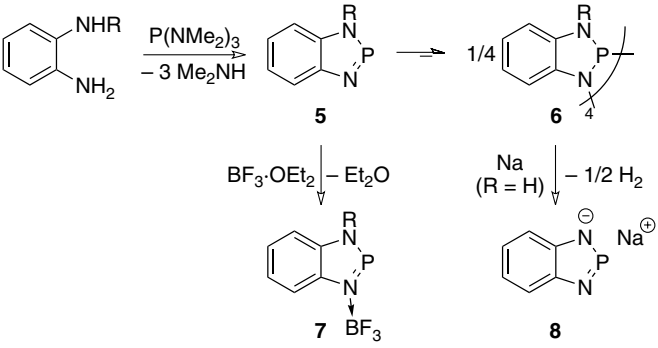
gave the isolable 2-chloro-1,3,2-diazaphospholene **1**; deprotonation with triethylamine yielded directly a diazaphospholide salt **2** which reacted further with alkyl or trimethylsilyl halides to produce neutral 1,3,2-diazaphospholes **3** (Scheme 1).



Scheme 1 Synthesis of 1,3,2-diazaphospholes with isolated rings (R = Alkyl, Me_3Si)

Treatment of **1** or **2** with secondary amines, or of diaminomaleonitrile with $P(NMe_2)_3$, gave the bicyclic phosphatriazapentalene **4** [12]. The reaction leading to **2** represents condensation of PCl_3 with an enediamine with subsequent base-induced dehydrohalogenation, and should be more generally applicable.[1] The fact that seemingly no other substrates apart from diaminomaleonitrile have been employed presumably reflects a lack of easily accessible starting materials.

Benzannulated 1,3,2-diazaphospholes **5** form readily upon condensation of monosubstituted *o*-phenylenediamines (R = H, alkyl, Ph) with $P(NMe_2)_3$ [13, 14] (Scheme 2). *N*-Alkylated products can be detected by NMR but evade isolation by



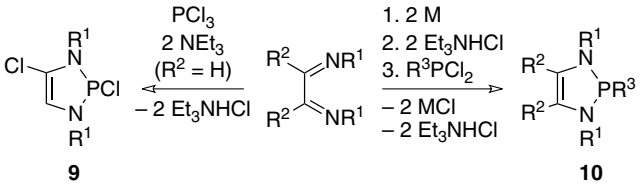
Scheme 2 Synthesis of benzannulated 1,3,2-diazaphospholes (R = H, Alkyl)

[1] This is indeed corroborated by the use of similar condensation reactions for the synthesis of triazaphosphole derivatives; cf. [15].

oligomerizing to the tetramers **6**. The aggregation is reversible, and the monomers may be recovered upon heating **6** in a suitable solvent. Formation of monomeric Lewis-acid adducts **7** is also observed upon treatment of **6** with $BF_3{\cdot}OEt_2$. Reaction of tetrameric **6** (R = H) with sodium is likewise accompanied by cleavage of the oligomer producing sodium benzo-1,3,2-diazaphospholide **8** [16]. The disassembly of the tetrameric unit upon metalation is in clear contrast to the behavior of the Sb-analogue of **6** (R = H) which reacted with lithium via conservation of the oligomeric structure and formation of a tetrameric lithium salt [17].

1,3,2-Diazaphospholenes

The most widely applied precursors for the synthesis of monocyclic NHPs are α-diimines which can be converted to the target heterocycles either in a two-step reaction sequence involving two-electron reduction of the diimine to an enediamide, enediamine, or α-aminoamine and subsequent condensation with PCl_3 [18–20] or a dichlorophosphine $RPCl_2$ [21], or via direct base-promoted reaction with PCl_3 [20, 22]. The latter reaction involves addition of a P–Cl bond to each imine moiety followed by base-promoted elimination of hydrogen chloride leading to 2,4-dichloro-1,3,2-diazaphospholenes **9** (Scheme 3) which were isolated in moderate to good



Scheme 3 Synthesis of 1,3,2-diazaphospholenes (R^1 = Alkyl, Aryl; R^2 = H, Alkyl; R^3 = Alkyl, Cl)

yields after crystallization. The reaction is applicable to both *N*-alkyl and *N*-aryl substituted diimines derived from glyoxal. Diimines derived from 1,2-diketones react via [4 + 1] cycloaddition to yield heterocyclic chlorophosphonium salts [22] which may be converted into NHPs after subsequent reduction [21].

The two-electron reduction of α-diimines to prepare the required starting materials for a subsequent condensation is usually achieved by reaction with lithium but other alkaline (Na) or alkaline earth (Mg) metals should be useful as well. The synthesis of the heterocycles **10** is either accomplished by direct metathesis of the formed metal enediamide with PCl_3[2] [19] or, alternatively, by quenching the diamide with a suitable acid to produce an enediamine or α-aminoimine, respectively, and subsequent base-induced condensation with PCl_3 or $RPCl_2$ [18, 20] (Scheme 3). 1,3-Di-*tert*-butyl-2-chloro-1,3,2-diazaphospholene was also prepared from the reaction

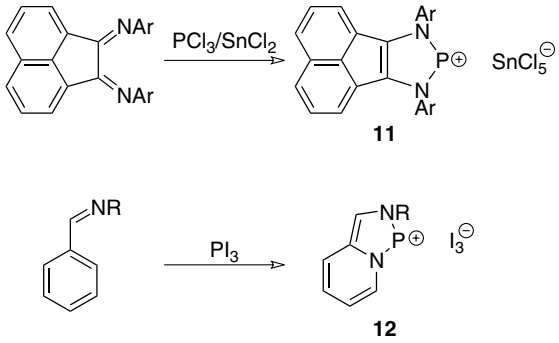
[2] The analogous reaction with $AsCl_3$ gives likewise access to As heterocycles, cf. [19].

of the enediamide with $SiCl_4$ to give first a 1,3,2-diazasilole which was then subjected to ring metathesis reaction with PCl_3 [23]. Although direct metathesis of the enediamide with PCl_3 would seem at first glance to be advantageous as it involves fewer and less time consuming steps, it was found that better yields of 2-chloro-NHPs could be obtained by following a protocol which involved initial protonation of the enediamides with Et_3NHCl and subsequent base-induced ring closure with PCl_3 [18]. As isolation of the intermediates is not required and the *tertiary* amine liberated in the first step is reused as acid scavenger in the second step, the whole synthesis can be carried out as a one-pot reaction. Using this protocol allows one to prepare multigram quantities of *N*-alkyl- and *N*-aryl-2-chloro-1,3,2-diazaphospholenes **10** with or without additional substituents in 3,4-position in one step from diazadienes with *overall* yields of 70–80%, and homologous As- and Sb-heterocycles were also prepared [24].

Benzannulated NHPs are straightforwardly accessible from *N*,*N*′-disubstituted *o*-phenylenediamines either via base-induced condensation with substituted dichlorophosphines [25] or PCl_3 [26], or via transamination with tris(dialkylamino) phosphines [13, 14, 27], respectively. An analogous NH-substituted derivative was obtained in low yield via transamination of *o*-phenylenediamine with ethoxy-bis(diethylamino)phosphine [28], and condensation of *o*-phenylenediamine with excess tris(diethylamino)phosphine furnished a 1,3-bis(phosphino)-substituted heterocycle [29]. Intermediates with one or two NH functions were detectable by spectroscopy but could not be isolated in pure form under these conditions. However, 2-chloro-benzo-1,3,2-diazaphospholene and the corresponding 1-phenyl derivative were prepared in acceptable yield via condensation of PCl_3 with *o*-phenylenediamine under microwave irradiation [30], or with *N*-phenyl-*o*-phenylenediamine under reflux [27], respectively, in the absence of additional base. The formation of tetrameric benzo-NHPs during transamination of *N*-alkyl-*o*-phenylenediamines with $P(NMe_2)_3$ has already been mentioned (cf. the section entitled "1,3,2-Diazaphospholes and 1,3,2-Diazaphospholides").

1,3,2-Diazaphospholenium Cations

Although 1,3,2-diazaphospholenium cations are usually prepared from neutral NHPs or 1,3,2-diazaphospholes via Lewis-acid induced substituent abstraction or *N*-alkylation, respectively (cf. Sect. 3.1.2), the group of Cowley was the first to describe a direct conversion of α-diimines into cationic heterocycles by means of a reaction that can be described as capture of a P(I) cation by diazabutadiene via [4 + 1] cycloaddition [31] (Scheme 4). The P(I) moiety is either generated by reduction of phosphorus trihalides with tin dichloride in the presence of the diimine [31] or, even more simply, by spontaneous disproportionation of phosphorus triiodide in the presence of the diimine [32]. The reaction is of particular value as it provides a straightforward access to annulated heterocyclic ring systems. Thus, the tricyclic structure of **11** is readily assembled by addition of a P(I) moiety to an acenaphthene-diimine [31], and the pyrido-annulated cationic NHP **12** is generated by action of appropriate



Scheme 4 Direct synthesis of 1,3,2-diazaphospholenium ions via redox reactions (Ar = Dipp; R = *t*-Bu, Dipp)

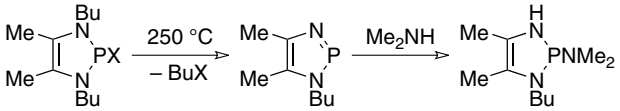
pyridine-carbaldimines upon PI_3 [33]. In addition to cyclic phosphenium cations, homologous arsenium ions were also obtained [31].

3.1.2 Syntheses Via Transformation of Other Heterocycles

The synthesis of new heterocyclic derivatives under conservation of a preformed cyclic structure is not only of particular importance for the synthesis of ionic 1,3,2-diazaphosphole or NHP derivatives but has also been widely applied to prepare neutral species with reactive functional substituents. The reactions in question can be formally classified as 1,2-addition or elimination reactions involving mutual interconversion between 1,3,2-diazaphospholes and NHP, and substitution processes. We will look at the latter in a rather general way and include, beside genuine group replacement processes, transformations that involve merely abstraction of a substituent and allow one to access cationic or anionic heterocycle derivatives from neutral precursors.

Addition Reactions

Transformations through 1,2-addition to a formal PN double bond within the delocalized π-electron system have been reported for the benzo-1,3,2-diazaphospholes **5** which are readily produced by thermally induced depolymerization of tetramers **6** [13] (Scheme 2). The monomers react further with mono- or difunctional acyl chlorides to give 2-chloro-1,3,2-diazaphospholenes with exocyclic amide functionalities at one nitrogen atom [34]. Similar reactions of **6** with methyl triflate were found to proceed even at room temperature to give 1-methyl-3-alkyl-benzo-1,3,2-diazaphospholenium triflates [35, 36]. The reported butyl halide elimination from NHP precursor **13** to generate 1,3,2-diazaphosphole **14** upon heating to 250 °C and the subsequent amine addition to furnish **15** (Scheme 5) illustrates another example of the reversibility of addition–elimination reactions [37].



13 **14** **15**

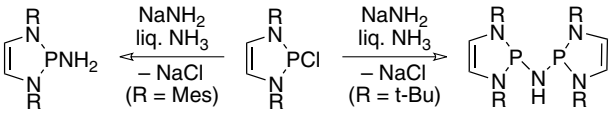
Scheme 5 Transformations of 1,3,2-diazaphospholenes by elimination/addition reactions (X=Cl, Br)

Substituent Displacement Reactions

Substitution reactions allow derivatization of NHPs under specific replacement of substituents at the carbon, nitrogen, or phosphorus atoms. C-Substitution reactions were studied in the case of the difunctional 1,3-dicyclohexyl-2,4-dichloro-1,3,2-diazaphospholene **9** (Scheme 3, R^1=Cy) which was found to display a diverse reactivity [38]. Thus, soft nucleophiles (triethyl phosphite, tributylphosphine) seem to react preferably under replacement of the C-chloro-substituent to give 4-phosphoryl- or phosphonio-derivatives whereas hard nucleophiles (EtOH) attack first the P–Cl and then the C–Cl functionality, and reactions with electrophiles ($SbCl_5$, MeI) proceed specifically via abstraction of P–Cl substituent to give 1,3,2-diazaphospholenium salts. 2-Hydrogen-4-chloro-1,3,2-diazaphospholenes were reported to isomerise under formal Cl/H-exchange to give the corresponding 2-chloro-derivatives, but the products could not be isolated [39]. Functionalization of N-substituents was observed in reactions of various NH-substituted NHPs with phosphorus electrophiles which allowed either introduction of additional phosphino substituents in 1,3-position, or resulted in condensation of two diazaphospholene rings through coupling of the NH-moiety with reactive P–N or P–Cl bonds of a second molecule [29].

Reactions leading to the modification of the functional groups at the phosphorus atom of NHPs have to date received the largest attention among all substitution processes and must certainly be considered to have the greatest synthetic significance. P-Chloro-derivatives were in most cases used as starting materials, and reactions under replacement of a chloride by another halogen, hydrogen, phosphino, amino, alkoxy, or alkyl substituents have been reported. The observed reactivity matches the typical behavior of all halogen-substituted phosphines. Halogen exchange reactions were carried out by treating P-chloro-NHPs with alkyl [38, 40] or trimethylsilyl halides [20, 41] which allowed replacement of a halogen atom by a heavier congener (i.e., substitution of Cl by Br, I, and of Br by I); fluoro-substituents may be introduced by reaction with silver fluoride [20]. A pyrido-annulated P-iodo-NHP was also obtained by reduction of a ionic diazaphospholenium triiodide with potassium [33]. P-Hydrogen-NHPs are accessible by reaction of P-halogen derivatives with complex hydrides such as $LiAlH_4$ or $LiBEt_3H$ [8, 18] whereas the corresponding reaction with $NaBH_4$ produces directly the corresponding borane adducts [8]. In all cases, care has to be taken to avoid overreduction causing P–N bond cleavage. Introduction of P-alkoxy and P-amino substituents is feasible by reaction of the P-chloro-derivatives with either an

alcohol or NH-functional amine in the presence of triethylamine as acid scavenger, or by metathesis with a suitable alkoxide or amide, respectively [38, 42]. Thus, reactions of P-chloro-NHPs with sodium amide in liquid ammonia were reported to yield either a P-amino-1,3,2-diazaphospholene **16** with an unsupported NH_2-group, or an imino-bis(diazaphospholene) **17** (Scheme 6) [42]. The formation of **17** results presumably from condensation of two molecules of a transient NH_2–NHP under liberation of ammonia, and the reaction seems to be controlled by the nature (aliphatic or aromatic) of the N-substituents. Introduction of P-phosphino substituents occurs readily upon metathesis of P-chloro-NHPs with suitable metal phosphides and allows one to access derivative featuring both acyclic (e.g. PPh_2) and cyclic (e.g. phospholyl) substituents [39, 43, 44]. In several cases, coupling of the P-chloro-heterocycle with trimethylsilyl phosphines was feasible, although longer reaction times may affect the yields and the reaction is presumably not generally applicable [43]. Coupling of a P-chloro-1,3,2-diazaphospholene with a P-stannyl-phosphine via dehydrostannylation has been reported in one case [45] but this reaction is likewise not generally applicable and its reversion (i.e., cleavage of the P–P bond in a phosphinyl-NHP upon reaction with trimethylstannyl chloride) has likewise been observed [39]. Symmetrical bis-1,3,2-diazaphospholenyls were obtained from magnesium reduction of P-chloro-substituted derivatives [46]. Alkylation of P-chloro-NHPs was mainly studied in reactions with metal cyclopentadienides to give P-cyclopentadienyl-1,3,2-diazaphospholenes [47] but coupling with reactive Grignard reagents like allyl or alkinyl magnesium halides was likewise successful [48].



Scheme 6 Synthesis of P-amino-NHPs from P-chloro-precursors and sodium amide

Substitution of P-substituents other than halogens has been reported for P-ethoxy-1,3,2-diazaphospholene and 1,3,2-diazaphospholene-2-oxide which react with trichlorosilane to yield the corresponding P-chloro-substituted heterocycles [49, 50]. This reaction reflects a typical behavior of phosphine derivatives undergoing halogen replacement similar to the previously discussed transformations.

Substituent Abstraction Reactions

Reactions of P-halogen-NHPs with Lewis acids leading to halide abstraction, or metathetic replacement of the halide by a nucleofugic, noncoordinating anion form by far the most important routes to access phosphenium ions in general [51, 52] and also 1,3,2-diazaphospholenium cations in particular. As Lewis acid assisted P–X

(X = halogen, mostly Cl) heterolysis must be considered an equilibrium process, strong electrophiles such as $SbCl_5$, $AlCl_3$, or $GaCl_3$ are normally employed in order to push the equilibrium completely to the side of the desired ionic product [51, 52]. Even if the first syntheses of 1,3,2-diazaphospholenium salts adhere to this scheme [7, 53], it was later found that, due to the unique high stability of the cation (see Sect. 3.2.3), weaker Lewis acids such as $GeCl_2$, $SnCl_2$ [18], or even I_2 (for P–I derivatives) [41], also ensure quantitative bond heterolysis.

Anion metathesis reactions frequently involve treatment of the neutral precursors with silver salts such as $AgBF_4$ or $AgPF_6$ which allow easy separation of AgX formed as by-product [20, 53] but $NaBPh_4$ has likewise been applied [32]. A salt containing an organometallic anion was prepared by treatment of a P-chloro-NHP with $Tl[Co(CO)_4]$ [54]. Condensation of P-halogen-NHPs with trimethylsilyl triflate accompanied by the formation of volatile trimethylsilyl halides turned out to provide a convenient route to highly pure 1,3,2-diazaphospholenium triflates [20, 55].

3.2 *Physical Properties, Structure, and Bonding*

1,3,2-Diazaphospholes, NHP, and their derivatives are thermally stable solids or liquids that are (with the exception of P-hydrogen and P-alkyl-derivatives) rather stable in dry air but hydrolyze more or less rapidly in moist air or upon dissolution in solvents that have not been rigorously dried. Neutral NHPs with P-hydrogen, P-phosphinyl, or P-alkyl substituents are readily soluble in hydrocarbon and ether solvents but may react with chlorinated solvents like CH_2Cl_2 (see Sect. 3.3). P-Halogen-NHPs display relatively low volatility and poor (if any) solubility in aliphatic hydrocarbons but are moderately soluble in toluene and dissolve readily in polar aprotic solvents (including CH_2Cl_2, CH_3CN), suggesting that these compounds are rather polar species. All ionic compounds are insoluble in aliphatic hydrocarbons and at best slightly soluble in aromatic hydrocarbons but dissolve readily in CH_2Cl_2 or CH_3CN.

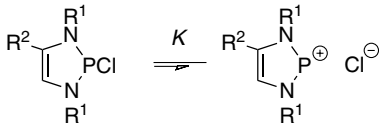
3.2.1 Spectroscopic Studies

NMR Spectroscopy

Routine identification and analytical characterization of all types of NHPs was preferably carried out by multinuclear NMR spectroscopy. Of particularly high diagnostic value are ^{31}P NMR spectra where rather specific chemical shift ranges for heterocycles with different types of P-substituents can be observed. The largest chemical shifts occur for anionic and neutral 1,3,2-diazaphospholes (220–300 ppm) and 1,3,2-diazaphospholenium cations (210–200 ppm). Chemical shifts of P-halogen-1,3,2-diazaphospholenes vary over an overall range of 200–110 ppm and decrease in the order I (205–190 ppm) > Br (194–185 ppm; two compounds

known) > Cl (160 – 140 ppm) > F (110 ppm; one compound known), thus displaying an inverse halogen dependence. Signals of P-phosphino-derivatives (170–135 ppm) appear generally more deshielded than those of P-amino-1,3,2-diazaphospholenes (95–75 ppm) but bis-1,3,2-diazaphospholenyls seem to be an exception and exhibit chemical shifts around 80 ppm [46]. P-Hydrogen substituted derivatives are characterized by the lowest shifts (75–55 ppm) and the occurrence of rather low values for $^{1}J_{PH}$ (140–220 Hz).

The ^{31}P NMR chemical shifts of P-chloro-NHPs (not of bromo or iodo derivatives [20, 41]) have from the very beginning been considered as peculiar owing to the observation of an exceptionally large solvatochromic behavior [23, 50, 53]. The strong deshielding ($\Delta\delta \approx 30$ ppm) in polar solvents was originally attributed to reflect a solvent driven shift in the dissociation equilibrium shown in Scheme 7. Although such spontaneous P–Cl dissociation is known for certain ylide-substituted chlorophosphines [56], this explanation was in the case of NHPs ruled out on the grounds of conductivity measurements which revealed that the degree of ionization even in the most polar solvents was negligible. The same conclusion was also obtained from NMR titration experiments which showed that the equilibrium constant of the dissociation process was in the order of 10^{-2}–10^{-3} l mol^{-1} (see Scheme 7). It suggests that the relative concentration of ionic species does not exceed a few percent [20]. In line with structural and computational studies (see Sects. 3.2.2 and 3.2.3), an alternative explanation of the solvatochromism was offered by relating the observed effects with polarization of P–Cl bonds by polar solvent molecules which results in a solvent dependent variation of bond distances.



R^1	R^2	K [mol l^{-1}]
t-Bu	Cl	$0.43(17) \cdot 10^{-3}$
t-Bu	H	$0.2(4) \cdot 10^{-3}$
Mes	H	$4.9(13) \cdot 10^{-3}$

Scheme 7 P–Cl Dissociation equilibrium for P-chloro-NHPs. (Data from [20])

Further insight into the bonding pattern of 1,3,2-diazaphospholenium cations, P-halogen- and P-phosphinyl-1,3,2-diazaphospholenes was derived from solid-state ^{31}P NMR studies [45, 57]. Analysis of anisotropic chemical shielding tensors of cationic and neutral P-halogen-NHPs [57] showed that the lower isotropic chemical shifts of the cations relative to open-chain phosphenium ions are, as in the case of carbenes and silylenes, mainly related to the variation of the most deshielded principal value (δ_{11}) of the chemical shift tensor and may be explained as resulting from improved π-conjugation in the heterocycle and a concomitantly increased n–π^* transition energy. P-Halogen-NHPs show a further decrease in δ_{11} with increasing P–X bond order, which is similarly attributable to an increasingly antibonding nature of the σ^*(P–X) orbital and a consequent increase in the n–π^* transition energies.

This effect allows one to monitor the perturbation of the π-electron system by interaction of the electrophilic phosphorus atom with a Lewis base. Following the same rationale, the still larger chemical shifts of neutral 1,3,2-diazaphospholes and 1,3,2-diazaphospholide anions are considered to reflect predominantly a reduction in n–π* transition energy due to destabilization of the n(P) orbital with an increasing number of lone-pairs on the NPN-moiety rather than differences in the charge densities or π-electron distribution in the heterocyclic ring [16].

Evaluation of trends in $^{1}J_{PP}$ coupling constants in solid-state ^{31}P NMR spectra of P-phospholyl-NHPs allowed one to establish an inverse relation between the magnitude of $^{1}J_{PP,solid}$ and P–P bond distances [45]. The distance dependence of $^{1}J_{PP}$ is in line with the dominance of the Fermi contact contribution, and is presumably also of importance for other diphosphine derivatives. At the same time, large deviations between $^{1}J_{PP}$ in solid-state and solution spectra of individual compounds and a temperature dependence of $^{1}J_{PP}$ in solution were also detected (Fig. 1); both effects

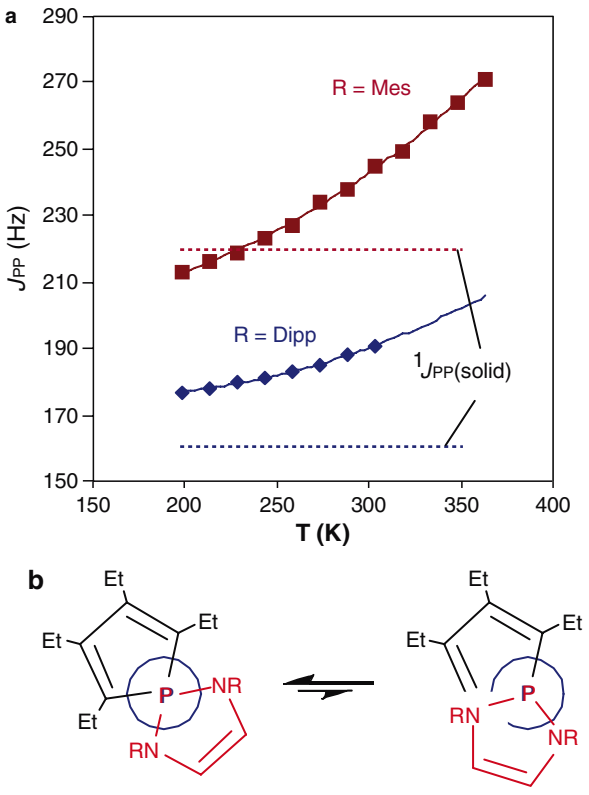


Fig. 1 (**a**) Comparison of measured values of $^{1}J_{PP}$ for two P-phospholyl-NHPs at different temperatures in solution (data denoted as *squares* or *diamonds*, respectively; *solid lines* represent fits of the temperature dependent variation) with values measured in the solid state (*dashed horizontal lines*). (**b**) Explanation of the observed variation in solution as a consequence of a dynamic equilibrium between *trans*- and *gauche*-rotamers. (Data from [45])

were attributed to result from an equilibrium between *trans*- and *gauche*-rotamers in solution in combination with similar solvent induced changes in bond lengths as had been suggested for P-chloro-NHPs.

Noteworthy NMR studies involving nuclei other than phosphorus have been carried out for some P-chloro-NHPs where the possible occurrence of spontaneous P–Cl bond dissociation was probed by ^{1}H NMR titrations and ^{35}Cl NMR [20], and for P-cyclopentadienyl derivatives where measurement of solid-state ^{13}C CP-MAS NMR spectra allowed one to substantiate the preservation of the circumambulatory ring migration of cyclopentadienyl groups in the solid state [47]. Several neutral and cationic derivatives have also been studied by ^{15}N NMR [20, 53].

Vibrational Spectroscopy

Studies of the vibrational spectra of a series of 1,3-di-*tert*-butyl-2-halogeno-1,3,2-diazaphospholenes revealed a diagnostically relevant variation of the characteristic ν(C=C) frequency [20]. The effect was, in accord with the computational studies, explained as reflecting increasing covalent P–X bond orders in the series X = (BF_4), Br, Cl, F which should lead in turn to stringent π-electron localization and concomitant strengthening of the C=C bond. A red shift of the ν(P–F) frequency by some 150 cm^{-1} with respect to the typical range for trivalent phosphorus compounds and the absence of characteristic bands attributable to ν(PCl) or ν(PBr) in the appropriate NHPs was interpreted as evidence for a pronounced bond-weakening effect arising from significant n(N)-σ*(P–X) hyperconjugation. A similar red shift by some 100 cm^{-1} was also observed for the ν(P–H) frequency of P-hydrogen-substituted NHPs and gave rise to the same interpretation [8, 18].

Photoelectron Spectroscopy

Study of the UV-photoelectron spectra of a series of 1,3-dibutyl-4,5-dimethyl-1,3,2-diazaphospholenes having different P-substituents revealed rather low energies of 6.1–7.2 eV for the first vertical ionization potential (IP) and a relatively large separation (1.7 eV) between first and second IP [58]. The band at lowest energy was attributed to ionization out of a delocalized π-orbital representing a slightly antibonding combination of π(C=C) and n_+(N) orbitals where the latter stands for the symmetric combination of the two nitrogen lone-pairs. The trends in IPs were found to correlate with Hammett σ-constants of P-substituents [58] as well as with one-electron oxidation potentials [59, 60], and the results were interpreted as supporting the presence of a single conjugated π-electron system in the heterocycle, as in an enediamine. The assignment of individual bands in the He(I)-photoelectron spectrum of P-diisopropylamino-1,3-dimethyl-benzo-1,3,2-diazaphospholene was less clear but the first IP (6.8 eV) was likewise assigned to represent ionization from an orbital with appreciable n(P) character [26].

3.2.2 Crystal Structure Studies

1,3,2-Diazaphospholide Anions and 1,3,2-Diazaphospholenium Cations

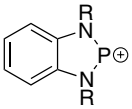
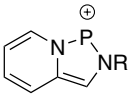
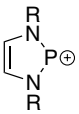
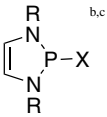
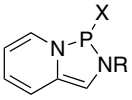
Structural studies on neutral 1,3,2-diazaphosphole derivatives do not seem to have been carried out. The 1,3,5-triaza-2-phosphapentalene **4** (Scheme 1) has a planar, essentially mirror symmetric, ring system and is formally uncharged but analysis of the bond lengths indicates that the π-electron distribution is best described by a zwitterionic structure consisting of anionic 1,3,2-diazaphospholide and cationic iminium-imidate fragments separated by C–C single bonds [12]. The bond distances in the phosphorus heterocycle are intermediate between standard distances for single and double bonds (cf. Table 1) and thus support the idea of a delocalized 6π-electron system with some aromatic character. The benzannulated anion **8** (Scheme 2) [16] and appropriate *N*,*N*'-diprotonated or dialkylated cations [16, 61] likewise display planar rings that contain, in contrast to **4**, a single delocalized 10π-electron system which is considered analogous to that of naphthalene. Individual bond lengths in both cations and the anion deviate only insignificantly from each other and are intermediate between standard single and double bond lengths (cf. Table 1), thus suggesting that presence or absence of N-substituents on the 1,3,2-diazaphosphole core has no visible effect on the π-electron delocalization [16]. The anions **8** bind via the nitrogen lone-pairs to the metal ions of two $[Na(THF)_2]^+$ moieties to form one-dimensional coordination polymers with a similar arrangement as in the As-analogue, $[C_6H_4N_2As][Li(THF)_2]$ [62]. Structural studies of the pyrido-annulated bicyclic cations **12** revealed that the five-membered rings display more pronounced bond length equalization than the six-membered rings [33].

Quite a few structural studies have been performed on monocyclic 1,3,2-diazaphospholenium salts that contain cations with isolated rings, and it has been pointed out that not only do the individual endocyclic bonds in all compounds fall in very narrow ranges but also the strict planarity of the rings and the observed bond length equalization (all distances are intermediate between single and double bonds, Table 1) provide strong evidence for efficient π-electron delocalization in the ring [55]. Analysis of the interaction of the cations with adjacent anions in the crystal revealed that the shortest inter-ion contacts come close to the sum of van-der-Waals radii and are larger than in the structure of salts with saturated cyclic or acyclic phosphenium cations. Distinct interion interactions leading to a supramolecular assembly of anions and cations were, however, observed for a 1,3,2-diazaphospholenium triiodide whose anion can be considered to display a particularly large degree of polarizability [41]). Both the efficient bond length equalization and the lack of strong interactions between oppositely charged ions have been interpreted in terms of a particularly high cation stability [52, 55].

1,3,2-Diazaphospholenes

Comprehensive studies of molecular structures of neutral NHPs have been in particular performed for P-halogen, P-amino, and P-phosphino derivatives; in

Table 1 Typical ranges of bond distances (in Å) in the rings of 1,3,2-diazaphosphole and 1,3,2-diazaphospholene derivatives

Ring structure	No. of structures	P–N	N–C	C–C	Refs.
 [a]	2	1.64–1.67	1.34–1.38	1.37–1.43	[12, 16]
	2	1.63–1.65	1.38–1.40	1.38–1.41	[16, 61]
	2	1.69–1.71	1.35–1.40	1.39	[33]
	18	1.66–1.69	1.36–1.39	1.34–1.38	[7, 18, 20, 32, 53, 55]
 [b,c]	14 (X = F, Cl, N_3)	1.65–1.68	1.37–1.43	1.33–1.35	[19, 20, 22, 41, 53, 55, 83]
	2 (X = Br, I)	1.66–1.67	1.38–1.39	1.35	[41]
	2 (X = H)	1.69–1.72	1.41–1.42	1.32–1.33	[8, 18]
	12 (X = PR_2)	1.70–1.74	1.40–1.42	1.32–1.34	[39, 43, 44, 45]
	5 (X = NR_2)	1.70–1.73	1.40–1.41	1.32–1.33	[42]
	2 (X = C_5R_5)	1.71–1.74	1.40–1.42	1.32–1.33	[47]
	1	1.72–1.74	1.41–1.43	1.34	[33]

[a] Anions **8**, **9**

[b] Structures containing both isolated and benzannulated rings

[c] For report of an exceptionally short P–N bond outside the usual range cf. [72]

addition, some P-hydrogen and P-cyclcopentadienyl substituted compounds were also studied. The heterocyclic rings of all compounds display more or less folded envelope conformations and can be grouped into two sets each of which is distinguished by a rather narrow distribution of endocyclic bond lengths (cf. Table 1). The first group contains P-halogen and P-azido derivatives and is set apart by a shortening of C–C and a lengthening of C–N bonds as compared to 1,3,2-diazaphospholenium cations; the second group includes all remaining compounds and is distinguished by a further decrease in C–C and a slight increase in P–N bond lengths. Even though interpretation of the data using quantitative structure correlation was not possible [55], it has been suggested that increasing bond length

alternation is associated with a general deterioration of cyclic π-electron delocalization [8, 18, 39].

The structures of P-chloro-NHPs invited attention due to the very early discovery of species with exceptionally long P–Cl bonds [19, 22, 53] which stimulated discussions about a possible ionic nature of these compounds. This perception was later contradicted by a survey of a series of crystal structure analyses which revealed that the observed P–Cl bond lengths (2.24–2.70 Å), even though being much longer than a normal single bond (<2.18 Å), remain still in a range suggesting significant covalent interaction [55]. Further structure correlation analysis revealed that changes in P–Cl and P–N distances are uncorrelated with variations in N–C and C–C bond lengths, and the bond lengthening was attributed to strong n(N)-σ*(P–Cl) hyperconjugation. Although the connection between P–Cl bond lengthening and shortening of P–N bonds that was established for P-chloro-NHPs is also observable for other diaminochlorophosphines $(R_2N)_2PCl$, the variance and absolute values of P–Cl bond lengths in NHP are much larger than in the reference compounds (Fig. 2), thus underlining that the P–Cl bond is "softer" (i.e. more easily polarizable) than usual [55]. This hypothesis is also supported by the deviation in P–Cl bond lengths found for 1,3-di-*tert*-butyl-2-chloro-1,3,2-diazaphospholene and its toluene solvate [20] and provided the motivation to view P-chloro-NHPs as neither genuine ionic nor covalent compounds but rather as contact ion-pairs between a chloride anion and a phosphenium cation [20, 55].

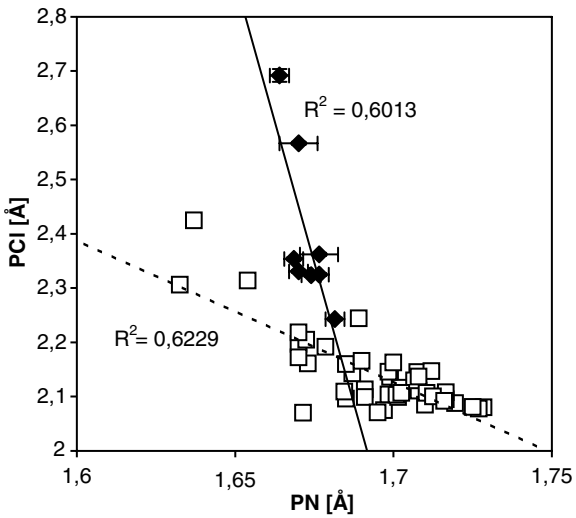


Fig. 2 Plot of P–Cl distances (in Å) vs average P–N distances (in Å) for P-chloro-NHPs (*diamonds*) and for all compounds $(R_2N)_2PCl$ (except P-chloro-NHPs) listed in the CSD data base (*open squares*). The *solid and dashed lines* represent the result of linear regression analyses. R^2 is the square of the correlation coefficient in the regression analysis. (Reproduction with permission from [55])

Crystal structure studies of NHPs with other halogen substituents revealed that a P–F bond was less affected by hyperconjugation [20] but P–Br and P–I derivatives showed increased bond lengthening [41]; the solid-state structure of the latter consists of ion-pairs which assemble via secondary P···I interactions to a one-dimensional coordination polymer and may, in contrast to the case of P–Cl derivatives, in fact be regarded as picturing partial bond dissociation. Even if the distortion is without doubt facilitated by a lower dissociation energy of P–I as compared to P–Cl bonds, its origin is, according to computational studies, not purely intramolecular but results in part from intermolecular charge polarization in the crystal.

The P–P bonds in P-diphenylphosphino and, in particular, P-phospholyl-NHPs (2.35–2.70 Å) are much longer than normal single bonds (2.21 Å) [39, 43, 45] and can even exceed the distances in compounds with "one-electron bonds" (2.43–2.63 Å) where two phosphorus atoms are formally connected by a single bonding electron [63, 64]. Although phospholyl rings in these compounds resemble, as in other known phospholes, more closely the structure of a conjugated diene than an aromatic heterocycle, the P–P–C bond angles at the phosphole P-atom are unusually small (79–89°), and their decrease correlates with lengthening of P–P distances and widening of the angle between the two ring planes [45]. As a consequence, an increase in P–P distance is accompanied by a shift of the NHP-moiety from a peripheral position toward a point above the centroid of the phosphole ring (Fig. 3). A consistent explanation for these distortions, which were found to originate primarily from crystal packing forces rather than intramolecular influences, was derived from computational studies (see Sect. 3.2.3). The P–P bonds are thus, like the P–X bonds in P-halogen-NHPs, pictured as highly polarized dative (donor–acceptor) interactions, and an increase in P–P distances is rationalized as reflecting increasing bond ionicity which favors a closer approach of the phosphenium cation fragment to the center of the negative charge in the phosphole π-system [45].

The crystal structures of P-hydrogen and P-cyclopentadienyl NHPs are likewise distinguished by the presence of elongated P–H and P–C bonds. Based on support

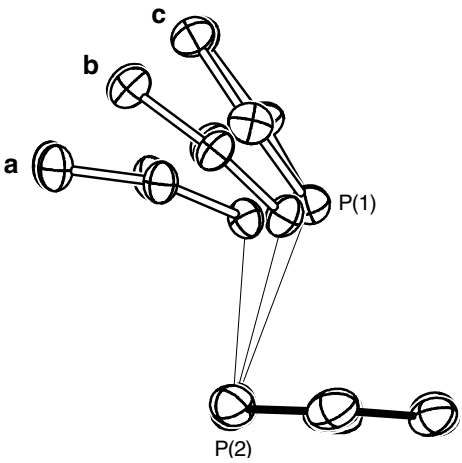


Fig. 3 Overlay of the cyclic cores of three different P-phospholyl-NHPs: (**a**) (3,4-dimethylphospholyl)-1,3-di-mesityl-1,3,2-diazaphospholene; (**b**) (2,3,4,5-tetraethylphospholyl)-1,3-di-mesityl-1,3,2-diazaphospholene; (**c**) (2,3,4,5-tetraethylphospholyl)-1,3-di-mesityl-4,5-dimethyl-1,3,2-diazaphospholene. The molecular structures are arranged in a way that the phosphole rings containing the P(2)-atoms are superimposed on each other

from computational and chemical investigations, the structural distortions were once again interpreted as indicating increased ionic bond polarization which introduced a pronounced hydridic character for P-hydrogen NHPs [8, 18].

In contrast to the previously discussed compounds where all bonds to exocyclic P-substituents tended to become long and concomitantly weak, crystal structure studies of a series of monocyclic P-amino-NHPs [42] and a pyrido-annulated derivative [33] revealed that in some cases exocyclic P–N bonds may be even shorter than endocyclic ones. Although computational studies suggested this effect arising from a competition of bond-weakening effects induced by n(N)-σ*(P–N) hyperconjugation interactions involving the lone-pairs of both endocyclic and exocyclic nitrogen atoms, it remains to date unclear how the balance of the different interactions is related to the nature of the substituents present.

3.2.3 Computational Studies

During the last few years, both neutral and cationic 1,3,2-diazaphospholes and NHP have been studied extensively by computational methods. The best part of these studies focused on a discussion of π-electron delocalization and their implication on chemical reactivities and stabilities, the explanation of the unique ionic polarization of exocyclic P–X bonds noted for some species, and the evaluation of structural and spectroscopic properties with the aim of helping in the interpretation of experimental data.

π-Delocalization and Aromaticity of 1,3,2-Diazaphosphole Derivatives

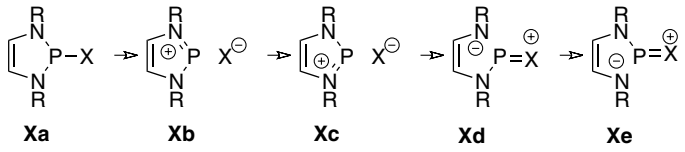
Whereas π-electron delocalization and aromatic character in several other types of heterophospholes has been broadly studied and reviewed [65], analyses of the bonding situation in the neutral 1,3,2-diazaphosphole ring system are confined to a recent study dealing with the benzannulated derivative **5** (Scheme 2, R = H) and its conjugate acid and base, respectively [16]. The analysis includes the evaluation of aromatic stabilization energies from isodesmic ring separation and isomerisation reactions as well as geometric (Bird index, bond shortening index) and magnetic [NICS(0), NICS(1)] criteria and leads one to conclude that both rings in all three species are aromatic. Analysis of trends in NICS(1) values and stabilization energies show that the aromaticity of the five-membered rings decreases slightly when the number of attached protons increases whereas the aromaticity of the six-membered rings displays a small change in the opposite direction.

The observed planarity and bond length equalization in 1,3,2-diazaphospholenium cations likewise suggest that these compounds have substantial π-electron delocalization and possess possibly aromatic character. Several studies were undertaken to quantify the degree of π-delocalization by computational calculations using the interpretation of population analyses, ELF calculations, evaluation of magnetic criteria [nucleus independent chemical shift (NICS) values], and the

analysis of thermochemical cycles based on isodesmic or homodesmic reaction energies [20, 53, 66, 67]. The current state of the discussion is marked by a recent paper by Tuononen et al. [67] who performed a comprehensive analysis of the bonding situation in a series of isoelectronic heterocycles of type **VIII** (Structure 3) with various main-group elements and concluded that the electronic structure of the phosphenium cation (**VIII**, E=P$^+$) is closely similar to that of the isoelectronic carbene (**VIII**, E=C), and that both species feature delocalized 6π-electron systems with a high degree of aromatic character. It has been pointed out, however, that assessment of the thermodynamic stability of 1,3,2-diazaphospholenium ions should not be based alone on evaluation of aromaticity as the actual stabilization by π-delocalization effects is much smaller than in other types of aromatic phosphorus heterocycles [66], and the donation of the nitrogen lone-pairs together with σ-bond polarization resulting from the large electronegativity difference between N and P$^+$ also contribute significantly – and presumably more importantly than aromaticity – to the total stabilization.

P–X Bond Polarization in 1,3,2-Diazaphospholenes

Computational studies of the electronic structure of various NHPs with different types of P-substituents (X = Halogen, H, PR_2, NR_2) were carried out by using DFT or MP2 methods and revealed that the P–X bonding is influenced by competition between n(N)-σ*(P–X) and n(X)-σ*(P–N) hyperconjugation interactions that can be described by bond/no-bond resonance involving the canonical structures **Xa**–**Xe** (Structure 4; **Xd,e** are not applicable for X = H) [8, 18, 20, 39, 42, 45, 68]. The characteristics of exocyclic and endocyclic P–N bonds in P-amino-NHPs seem to be determined by a balance between both effects whereas bonding in P-halogen, P-hydrogen, and P-phosphino derivatives is dominated by the n(X)-σ*(P–N) interaction (higher contribution of ionic canonical structures **Xb,c**) and a concomitant bond polarization that is reflected in reduced covalent bond orders and an increased charge separation P(δ$^+$)–X(δ$^-$). The finding that the degree of n(N)-σ*(P–X) hyperconjugation is particularly large for P-halogen derivatives led to a description of these compounds as Lewis acid–base complexes with a "dative" (or highly polarized covalent) bond [20]. A similar depiction (albeit with higher covalent bonding contribution) was also proposed for P-phospholyl substituted NHPs [45].



Structure 4 Canonical structures describing the bonding situation in 1,3,2-diazaphospholenes

Chemical Reactivity Aspects and Frontier Orbital Considerations

Phosphenium ions are often referred to as carbene analogues because they are isoelectronic with carbenes and show many parallels in their chemical reactivity. 1,3,2-Diazaphospholenium ions, like all diaminophosphenium ions, may still not be considered as isolobal to carbenes as their frontier orbitals do not represent a combination of lone-pair and empty p-orbital as in a singlet carbene; the HOMO is rather a delocalized π-orbital with large coefficients on the phosphorus and carbon atoms that resembles the HOMO of a phospholide anion, and the LUMO is an antibonding combination of p-orbitals at phosphorus and nitrogen looking similar to the antibonding π_3*-orbital of an allyl anion [66] (Fig. 4). Although in the frame of frontier orbital theory, such significant variations in the nature of frontier orbitals are anticipated to imply changes in reactivity patterns, this is actually not observed. It has been pointed out that this apparent contradiction may be rationalized if one considers that phosphenium ions usually react as electrophiles, and the dominant frontier orbital interaction thus involves the LUMO of the cation and the HOMO of the reaction partner [66]. As the largest lobe in the LUMO and the largest positive partial charge are still centered at the phosphorus atom, the topology of frontier orbital or charge interactions remains the same as in reactions of (electrophilic) carbenes, and no changes in reactivity patterns are thus expected.

Quantitative assessment of the electrophilic character of various types of phosphenium ions has been attempted using computational studies on hydride and halide exchange reactions, and the results attribute to 1,3,2-diazaphospholenium ions a lower electrophilicity (and thus higher stability) than other types of phosphenium ions [20, 66]. The gain in stability due to aromatic π-delocalization is predicted to be somewhat larger than inductive stabilization resulting from exhaustive *N*-alkylation of the parent diaminophosphenium ion, $[P(NH_2)_2]^+$.

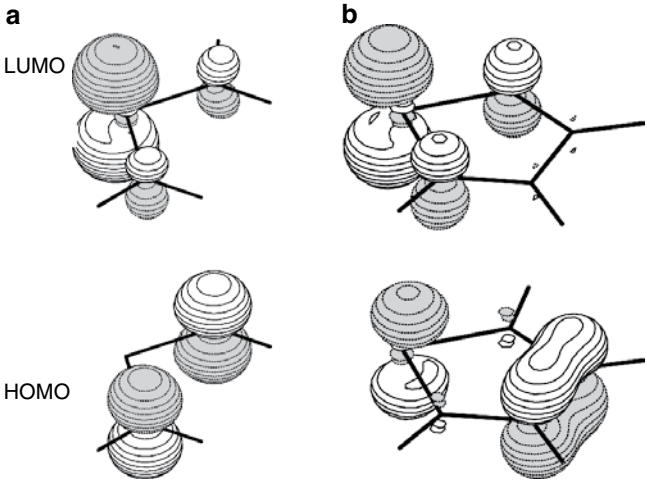
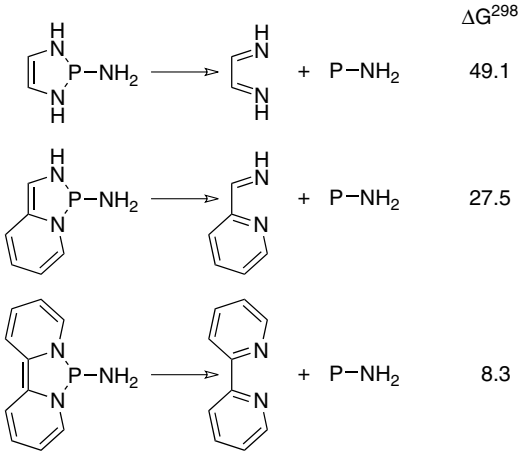


Fig. 4 Representations of HOMO and LUMO of: (**a**) $[(H_2N)_2P]^+$; (**b**) $[(CH)_2(NH)_2P]^+$. The surfaces shown represent electron densities of 0.10 and 0.09. (Reproduction with permission from [66])

Analysis of frontier orbital and charge interactions has also been used to analyse Lewis acid–base reactions of a 1,3,2-diazaphospholenium cation with P-halogen or P-hydrogen substituted NHPs. It has been found that both reactions proceed via formation of P…X rather than P…P donor–acceptor bonds which have been observed in other known reactions between phosphenium ions and phosphine derivatives, and yield complexes that are distinguished by a symmetrical P…X…P bridged structure [18, 68]. Analysis of the electron distribution in the case of X=H suggested a description of this interaction as three-center, two-electron bond, which led to perceive the phosphenium-phosphine adduct as isolobal to a hydride-bridged species like $[B_2H_7]^-$ and emphasized the pronounced hydride character of P-hydrogen substituted NHPs. A reasonable explanation for the preferred formation of P…X…P over P…P bonded adducts was given by considering the low electrophilicity of 1,3,2-diazaphospholenium cations which disfavors orbital-controlled reactions (formation of a dative P–P bond) over charge-controlled reactions (formation of X-bridged adducts with a higher degree of ionic bonding), and thus makes these species harder Lewis acids than other phosphenium ions.

The presumed balance between n(N)-σ*(P–X) and n(X)-σ*(P–N) hyperconjugation in P-amino-NHPs suggested that a high degree of n(X)-σ*(P–N) charge transfer should induce a weakening of endocyclic P–N bonds and thus facilitate ring fragmentation reactions like the electrocyclic [4+1]-cycloreversion shown in Scheme 8. Computational studies indicated that this reaction, although being highly endothermic for molecules with isolated rings, becomes energetically more favorable for annulated heterocycles whose fragmentation products may gain additional stabilization energy from rearomatization of the remaining ring fragment, and is under these conditions predicted to provide a viable approach for the generation of free phosphinidenes [69].



Scheme 8 Computed free reaction energies (in kcal mol^{-1} at the B3LYP/6-311+G(d,p) level) for [1+4]-cycloreversion reactions of 1,3,2-NHPs with isolated and annulated rings. (Data from [69])

Finally, a preliminary computational study on the dimerization of 1,3,2-diazaphospholenyl radicals suggested that the easy formation of these species might be facilitated by a very low dissociation energy of the corresponding dimer [46].

Computational Studies of Structural and Spectroscopic Properties

Comprehensive comparisons of computed molecular structures of isolated molecules in the gas phase with experimental data available from X-ray diffraction studies allowed a concise description of the bond length equalization and electron delocalization effects in the rings of both cationic and neutral NHP derivatives but failed to give a quantitative prediction of the exceptional bond lengthening in P-halogen and P-phospholyl substituted NHPs [20, 45]. Although it has been suggested that part of the discrepancies arise from inadequate treatment of electron correlation and may be reduced by using more elaborate theoretical models, explicit computational studies on molecules in solution [68] or in the solid state [41] (using periodic boundary conditions) revealed that the bond lengthening owes not exclusively to intramolecular effects (hyperconjugation) but depends to a significant extent on intermolecular interactions. Calculations simulating the influence of solvent effects on the P–Cl bond of P-chloro-NHPs reveal that the bond lengthening also increases with the dielectric constant of the solvent [68]. In total, these findings explain the "intermolecular" influence in terms of fine-tuning of the electrostatic interaction in phosphenium cation–halide anion pairs by a dielectric medium or intermolecular dipolar polarization by surrounding molecules, and further strengthen the perception of P-halogen NHPs as ion paired Lewis acid–base complexes rather than covalent molecules. It has been pointed out that solvent induced bond polarization should also allow to explain the unique solvent dependence of NMR chemical shifts of P-chloro NHPs [20].

Explicit computational studies have also been used to predict and analyze various magnetic parameters. Computed anisotropic magnetic shielding tensors of 1,3,2-diazaphospholenium ions and neutral NHPs served to establish the orientation of the principal axis system of the shielding tensor in the molecular frame and confirmed that the fairly small isotropic ^{31}P NMR chemical shifts of the cations owe to very low values for the most deshielded principal value σ_{11} and are attributable to improved π-conjugation in the heterocycle and concomitantly increased n–π* transition energy [57]. Calculations of $^{1}J_{PP}$ in P-phosphanyl substituted NHPs disclosed that the dominant contribution to the one-bond coupling arises from the Fermi contact term and gave a theoretical foundation for the observed correlation between $^{1}J_{PP}$ and bond distances [45]; furthermore, the calculations allowed one to analyze the anisotropy and conformational dependence of the *J*-coupling. The DFT calculations of the spin density in diazaphospholenyl radicals have also been used to confirm the π-delocalization of the unpaired electron and thus to help the interpretation of the observed EPR parameters [46].

3.3 Chemical Reactivity

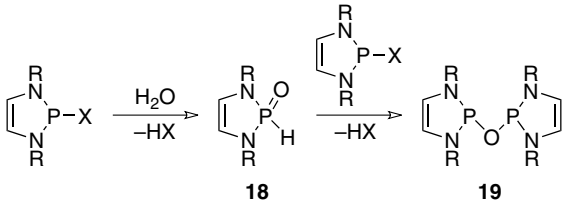
A large part of the chemical reactions of 1,3,2-diazaphosphole and NHP derivatives reported to date include transformations under substitution of functional substituents at the C, N, or P ring atoms. The interest in several of these displacement processes was mainly directed by the desire to develop synthetic pathways for specifically

substituted compounds, and these reactions have already been dealt with in the Section entitled "Substituent Displacement Reactions." In addition, a more general exploration of the activation of polarized exocyclic P–X bonds between elements of similar electronegativity (X = H, P, C) has been attempted. In the following, the results of these studies will be described together with some reports dealing with the coordination chemistry of cationic or neutral NHP derivatives.

Apart from substitution, addition reactions of 1,3,2-diazaphospholes or their benzannulated analogues and ring metatheses leading to formal displacement of the phosphorus atom by another main-group element have been reported. Most of these examples have also been dealt with in the context of Sect. 3.1.2 or are serendipitous results that have only briefly been mentioned in the context of a more extensive investigation [18], and will not be explicitly repeated here. The [4 + 1]-retro-addition reactions of annulated NHP derivatives generating α-diimines and transient phosphinidenes (Scheme 8) have been theoretically predicted [69] but are still awaiting experimental verification. An interesting case of a [4 + 2]-cycloaddition-cycloreversion sequence leading to ring transformation was reported for the reaction of 1,3,2-diazaphospholes with alkynes to give 1,2-azaphospholes and nitriles [70].

Preceding the treatment of individual reactions, some general comments on the chemical reactivity of NHP derivatives seem appropriate. All neutral NHPs are readily soluble in polar aprotic organic solvents like ethers or acetonitrile. P-Hydrogen and P-phosphino derivatives are also soluble in aliphatic and aromatic hydrocarbons but may undergo bond activation in chlorinated solvents (see below). P-Halogenated NHPs and diazaphospholenium salts are generally insoluble in aliphatic and at best moderately soluble in aromatic hydrocarbons but form stable solutions in CH_2Cl_2 or $CHCl_3$.

Reports on the sensitivity of many neutral and cationic NHP derivatives towards air and moisture reveal in most cases pronounced reactivity even with traces of H_2O causing P–X bond hydrolysis whereas genuine oxidation processes appear to play a role only for P–H and P-alkyl NHPs [71]. Controlled hydrolysis proceeds at low temperature as depicted in Scheme 9 to give secondary phosphine oxides **17** as initial product which may react further with excess NHP to phosphinous acid anhydrides **18**.[3] Both products may be obtained as isolable products starting from P-chloro NHPs [48]. Hydrolysis at ambient temperature may be unselective and



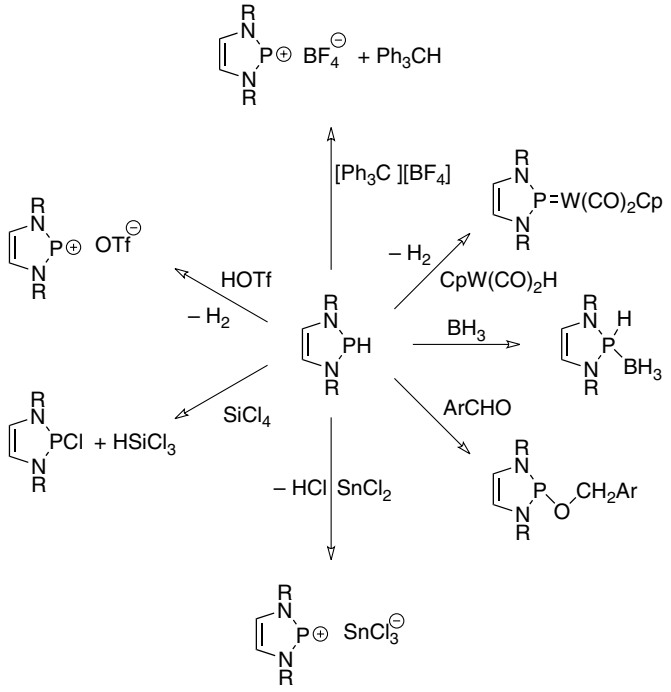
Scheme 9 Products formed by controlled hydrolysis of P-substituted NHPs (X = H, PR_2, Halogen)

[3] Condensation to yield the secondary product is often favored when solutions of NHPs are exposed to moist air or solvents and may result in formation of a mixture of **17** and **18**.

proceed often via ring cleavage [38]. Owing to the ionic polarization of P–H or P–P bonds (see Sect. 3.2.3) hydrolysis occurs even if secondary phosphines and diphosphines are usually not considered particularly moisture sensitive. P-Chloro-1.3-di-*tert*-butyl-1,3,2-diazaphospholene, on the other hand, was reported to be inert in the presence of a stoichiometric amount of hydrogen chloride [18] whereas a P-alkyl derivative was found to react with acids under ring cleavage [72].

3.3.1 P-Hydrogen NHPs as Hydride Transfer Reagents

The most noteworthy chemical property of P-hydrogen NHPs is their ability to act as molecular hydrides in contrast to other secondary phosphines which act as weak acids (Scheme 10). Reactions with inorganic or organometallic acids thus produce dihydrogen and a 1,3,2-diazaphospholenium salt or complex, respectively, and reaction with a triphenylcarbenium salt proceeds with formation of triphenylmethane [8]. Aldehydes and ketones do not react to give α-phosphino-carbinols but are reduced to diazaphospholene derivatives of the corresponding alcohols [8, 18]; this reduction displays a certain chemoselectivity as aldehydes or diaryl ketones are converted at much higher rates than alkyl ketones [18]. Tetrachlorides of group 14 elements react via hydride/

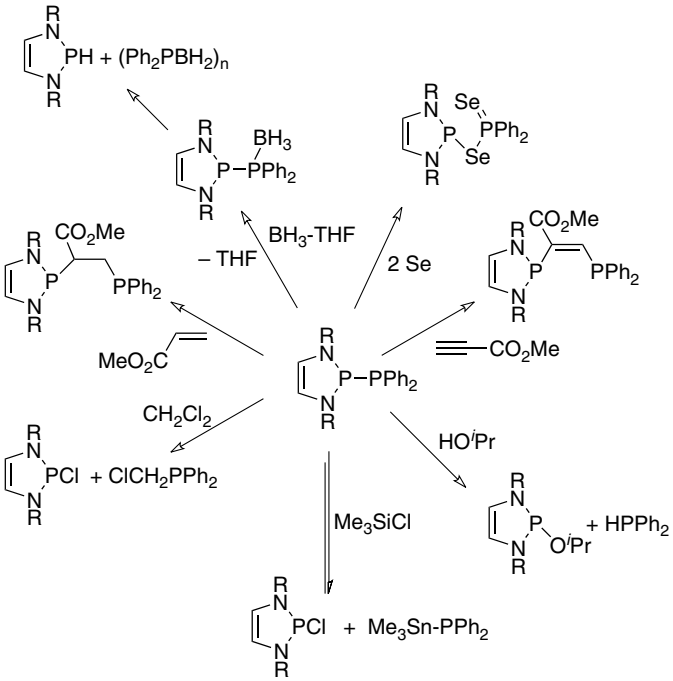


Scheme 10 Reaction patterns of P-hydrogen substituted NHPs

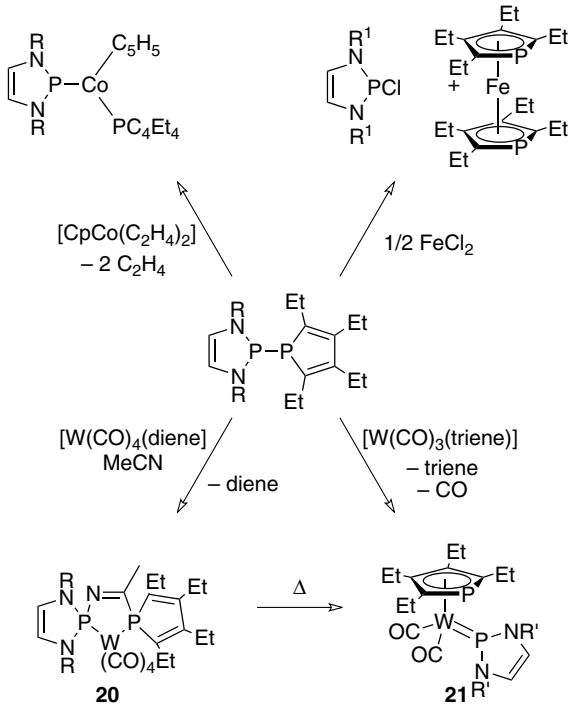
chloride metathesis to give either a mixture of chlorohydrocarbons EH_nCl_{4-n} (n=0–3, E=C) or pure $EHCl_3$ which is stable (E=Si) or decays via reductive elimination of hydrogen chloride and chloride transfer to give phosphenium trichlorogermanates or -stannates, respectively (E=Ge, Sn) [18]. Further reduction of $EHCl_3$ (E=C, Si) with excess of P-hydrogen NHPs is unselective and yields a mixture, EH_nCl_{4-n} (n=0–3), but $SnCl_2$ or $SnCl_3^-$ are cleanly reduced to the element. Reactions of P-hydrogen-NHPs with P-chloro-NHPs or 1,3,2-diazaphospholenium triflates allowed the first experimental detection of intermolecular exchange of a hydride, rather than a proton, between phosphine derivatives [18].

3.3.2 P–P Bond Activation and Cleavage

The ionic P–P bond polarization renders P-phosphino-NHPs highly active reactants for various metathesis and addition reactions at exceedingly mild conditions. Metathesis is observed in reactions with alcohols, chloroalkanes, and complex transition metal halides (Schemes 11 and 12) [39, 73]. Of particular interest are the reactions with chlorotrimethylstannane which yield equilibria that are driven by a subtle balance of P–X bond strengths to yield either diphosphines or P-chloro-NHPs as preferred product (Scheme 11). Chlorotrimethylsilane does not react with

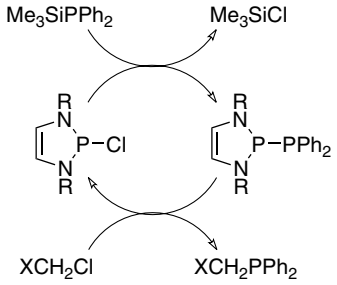


Scheme 11 Reaction patterns of P-diphenylphosphino substituted NHPs



Scheme 12 Reaction patterns of P-phospholyl substituted NHPs

P-phosphino-NHPs but the reverse reaction of a P-chloro NHP with diphenyltrimethylsilylphosphine and subsequent reaction with a chloroalkane can be combined to produce high yields of P-alkyl-diphenylphosphines [74]. Since the chloro-NHP is recovered in the second step, the overall reaction can be performed by employing this species merely as catalyst (Scheme 13). NMR investigations confirm that the appropriate P-phosphino-NHPs are in fact key intermediates in the resulting catalytic cycle, and it has been pointed out that P–X bond polarization represents a crucial factor for the overall acceleration of the catalyzed P–C



Scheme 13 NHP-catalyzed P–C cross coupling between silyl phosphines and chloroalkanes

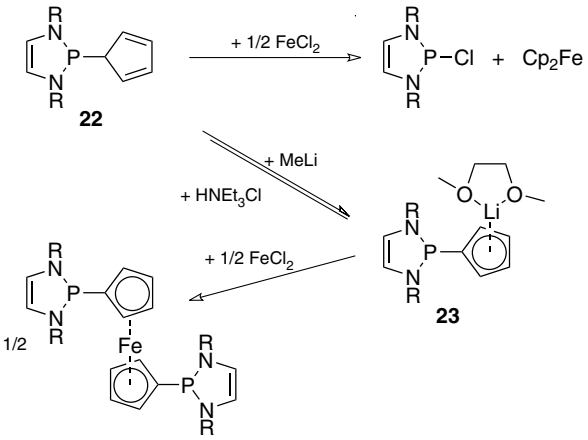
cross coupling reaction. As this effect is intimately connected with the high stability of *N*-heterocyclic phosphenium cations, the reaction was considered as the first organocatalytic transformation that relies decisively on the electrophilic rather than the nucleophilic character of an organophosphorus catalyst.

Alkenes and alkynes that are activated by one or more electron withdrawing substituents react with P-phosphino-NHPs with addition ("phosphinyl-phosphination") to the double or triple bond (Scheme 11), thus allowing access to unsymmetrical bis-phosphine ligands of potential metal chelating ability in one step from simple organic precursors [39, 43, 44, 73, 75]. Additions of alkynes occur more easily and have also been observed for other types of diphosphines whereas addition to alkenes seems to be restricted to substrates with highly reactive P–P bonds and is thus more or less specific for phosphino-NHPs. The addition chemoselectivity depends on the type of activating functional group; vinyl ketones undergo 1,4-addition to give a P-(β-phosphino-enolato)-NHP whereas α,β-unsaturated esters or nitriles react exclusively via 1,2-addition to the alkene or alkyne moiety [44]. Additions to unsymmetrically substituted multiple bonds produce a single regioisomer in which the exocyclic phosphino-substituent of the starting material ends up at the more electrophilic carbon atom. All additions to alkynes are also stereospecific and produce exclusively *Z*-ethylene-bis-phosphines whereas the stereochemistry of the addition to alkenes depends on the substrate [44]; cyclic maleic imide was reported to give a single product with *cis*-configuration of the phosphino-groups whereas acyclic fumaric or maleic esters gave a mixture of *cis*- and *trans*-configurated products which may, however, isomerize after coordination to a transition metal to give a single chelate complex having the stereochemically more favorable *trans*-configuration. The different stereochemical preferences have been explained by assuming that the addition to alkenes proceeds via transient carbanions which may be configurationally unstable and undergo epimerization unless the configuration is fixed by incorporating the reactive center into a stable ring structure [44]. A similar mechanism involving configurationally more stable vinylidene-carbanions was also proposed for phosphinyl-phosphination of alkynes [76]. An appealing facet of additions to triple bonds is further represented by the reaction between P-phosphino-NHPs, acetonitrile, and $[W(CO)_4(\text{cyclooctadiene})]$ which proceeds via phosphino-phosphination of the nitrile triple bond and formation of chelate complex **20** (Scheme 12) [75]. It has been shown that both the activation of the nitrile by metal coordination and the ionic polarization and concomitant activation of the P–P bond are crucial for the formation of **20** [73], and that the addition may be reversed during thermolysis which resulted in clean conversion of **20** into the phosphenium-phospholide complex **21** [75].

The cause for the high P–P bond reactivity in metathesis and addition reactions of P-phosphino-NHPs was further rationalized when it was established that attack of electrophiles at the PR_2-substituent facilitates bond cleavage reactions by further boosting the polarization and weakening of the P–P bond and may thus be considered to induce an "autocatalytic" activating effect [77].

3.3.3 Reactions of P-Cyclopentadienyl NHPs

P-Cyclopentadienyl-NHPs undergo, in the same manner as the isoelectronic P-phospholyl-derivatives, metathesis reactions with transition metal chlorides to produce appropriate metal cyclopentadienyls and P-chloro-NHPs [47]. The C_5H_5-substituted derivative **22** on reacting with butyl lithium undergoes deprotonation to give a lithium cyclopentadienyl complex **23** whose further reaction with iron dichloride produced directly a 1,1′-bis-NHP-ferrocene (Scheme 14). The different reactivity patterns of **22** and **23** are lucidly illustrated by comparing the structural parameters available from single-crystal X-ray diffraction studies: the phosphorus and the allylic carbon atom in **22** are connected by a substantially lengthened P–C bond (1.95 Å) which is well in accord with the presence of some ionic bond polarization, whereas the corresponding bond in **23** (1.79 Å) can be considered a normal single bond distance which does not imply any particularly high reactivity.



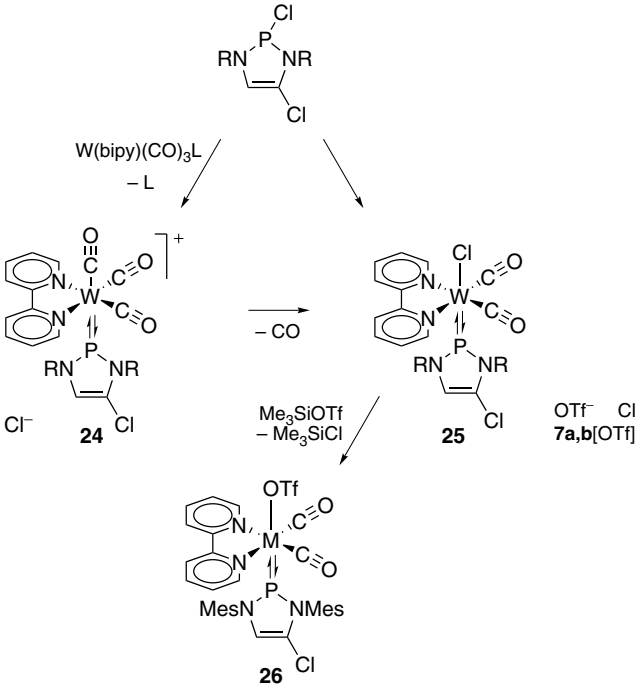
Scheme 14 Reaction patterns of a P-cyclopentadienyl substituted NHP (R = Mes)

3.3.4 Coordination Chemistry of NHPs

Although both neutral phosphines and phosphenium cations are widely used as P-donor ligands in transition metal complexes, reports on the preparation of simple coordination compounds with NHP-ligands are still rare. Neutral species do not seem to have been the target of systematic investigations, apart from a study describing the spectroscopic detection of highly unstable and rather poorly characterized NHP-silver complexes [78], and the reaction of [W(bipy)$(CO)_3$(MeCN)] with a P-chloro-NHP to give a likewise unstable yet spectroscopically characterized complex **24** (Scheme 15) which decarbonylates at room temperature to produce the isolable neutral phosphenium complex **25** [79]. This reaction was considered remarkable as the occurrence of spontaneous P–Cl heterolysis without assistance of

a Lewis acid contradicts a common reaction pattern of chlorophosphines which are normally reluctant to undergo chloride abstraction reactions when coordinated to a metal atom; the observed formation of **24** owes presumably to a pronounced π-basicity of the metal fragment.

The direct synthesis of neutral phosphenium complexes was reported from ionic 1,3,2-diazaphospholenium triflates or neutral P-chloro-1,3,2-diazaphospholenes with complexes [W(bipy)$(CO)_3$(L)] (L = CO, MeCN, see Scheme 15) [79]. Triflato-complexes like **26** undergo ligand displacement reactions with triphenylphosphine to yield cationic phosphenium complexes. Formation of a neutral complex of a 1,3,2-diazaphospholenium ligand was also reported via thermally induced decarbonylation of an ionic phosphenium tetracarbonylcobaltate [54]. Quite interestingly, spectroscopic and structural data indicate that 1,3,2-diazaphospholenium ligands receive a larger amount of MLCT than the corresponding 1,3,2-diazaphospholidinium ligands with CC-saturated heterocyclic rings, which contrasts with the lower electrophilicity of the cationic NHP-moiety as compared to non-conjugated diaminophosphenium species [79]. Explanation for this – at first glance illogical – finding is feasible if one considers that aromatic 1,3,2-diazaphospholenium cations, although being intrinsically weaker electrophiles, still have a larger charge capacity than non-aromatic diaminophosphenium ions and are thus able to accept higher overall charge transfer from a π-basic metal fragment; furthermore, subtle inductive substituent effects may also play a role.



Scheme 15 Complexation reactions of NHPs

Neutral benzo-1,3,2-diazaphospholes or their tetrameric cycloaddition products react with hard Lewis acids to give N-coordinated Lewis acid–base complexes [13, 80, 81]; this reaction can be used to disassemble the otherwise stable oligomers into monomeric units at ambient temperature.

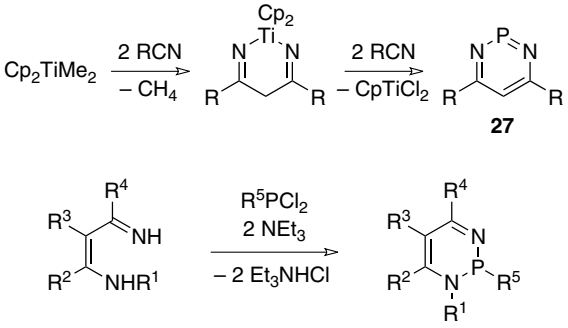
3.3.5 Oxidation Reactions

All phosphines are in principle capable of undergoing reactions via formal oxidation of the lone-pair. Following this general scheme, several NHPs were reported to react with dioxygen, sulfur, organic azides, or chlorine to give corresponding cyclic phosphine oxides, phosphine sulfides, phosphine imines, or chlorophosphonium chlorides, respectively [71, 72, 82]. 1,3,2-Diazaphospholes, NHP, and 1,3,2-diazaphospholenium cations were also reported to react with α-diimines or α-diketones via [1 + 4] cycloaddition to give appropriate spirocyclic phosphorane derivatives [27, 37, 38, 72, 80]. Thermolysis of P-azido-NHPs was reported to proceed via cleavage of dinitrogen to produce rather stable cyclodiphosphazenes which were further found to be capable of undergoing mono- or diprotonation at the imino-nitrogen atoms [83]. ESI-FT-ICR mass spectrometry reveals that the cations upon collision induced activation undergo interesting fragmentation processes leading to cleavage of either four- or five-membered rings that are presumably best described as [2 + 2] or [1 + 4] retro-cycloadditions.

4 Six-Membered *N*-Heterocyclic Phosphines

4.1 Syntheses

Fully unsaturated 1,3,2-diazaphosphinines are readily prepared in fair yields of 40–45% in a one-pot reaction from Cp_2TiMe_2 (Scheme 16) [84, 85]. The starting material is first reacted with pivalonitrile or benzonitrile to give 1,3,2-diazatitanacyclohexadienes

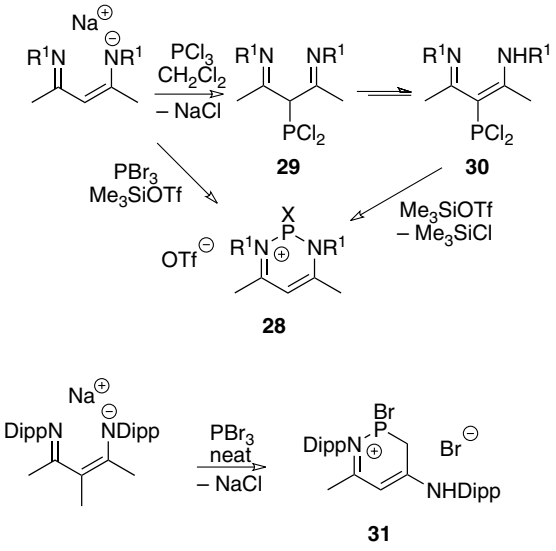


Scheme 16 Synthesis of 1,3,2-diazaphosphinines (R = *t*-Bu, Ph) and 1,2-dihydro-1,3,2-diazaphosphinines (R^1, R^4 = Aryl, Cy; R^2, R^3 = H, Me; R^5 = Me_2N, Ph)

which are then quenched by subsequent addition of phosphorus trichloride followed by triethylamine. The heterocycles **27** are highly air and moisture sensitive and are usually directly employed for subsequent reactions; however, the 4,6-di-*tert*-butyl-derivative has also been isolated as crude product in 40% yield after a simple work-up procedure involving filtration of insoluble products and evaporation of volatiles, and has been characterized by multinuclear NMR data. It has been pointed out that this compound seems to be preferable as starting material for further synthetic transformations as it is more readily separated from unreacted nitrile and is slightly more stable than the phenylated derivative as the bulkier substituents offer superior steric protection [85].

Neutral 2,3-dihydro-1,3,2-diazaphosphinines are straightforwardly accessible from condensation of 4-amino-1-azabutadienes with appropriately substituted dichlorophosphines or PCl_3 (Scheme 16). The reactions are generally carried out in benzene in the presence of triethylamine as acid scavenger, and the products are isolated in excellent yields of 86–96% [86, 87].

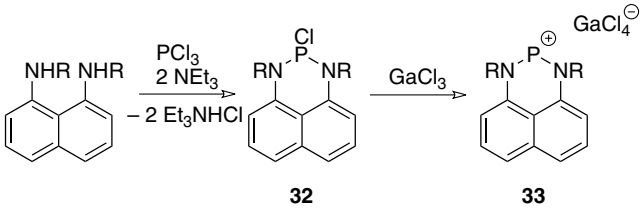
Salts of 2,3-dihydro-1,3,2-diazaphosphininium cations **28** (Scheme 17) that can be regarded as β-diketiminato-substituted phosphenium ions stabilized by an intramolecular donor–acceptor interaction are accessible from reaction of Na- or Li-β-diketiminates with phosphorus trihalides followed by treatment with a Lewis acid [9, 88, 89]. Detailed studies of the reaction of diketiminate salts with PCl_3 show that the attack of the electrophile occurs at the γ-carbon atom to yield bis-imines **29** as initial products which exist in solution in a slow dynamic equilibrium with the corresponding aminoimine tautomers **30** [9]. Reaction of the mixture of tautomers with trimethylsilyl triflate in CH_2Cl_2 solution was reported to proceed via abstraction of one chloride and rearrangement to give the salt **28**. Even though the products were



Scheme 17 Synthesis of β-diketiminate stabilized phosphenium salts (R^1 = Dipp, C_6F_5; X = Br, Cl)

isolated in reasonable yields, it must be noted that the outcome of the reaction seems to depend sensitively on subtle variations in the structure of the reactants and reaction conditions, and that other products may result when these parameters are varied. Thus, whereas reaction of an α-methyl-diketiminate with phosphorus tribromide under similar conditions as were applied for the synthesis of **28** gave a P-bromo-substituted heterocycle with similar structure [89], treatment of an Na-diketiminate with neat PBr_3 in the absence of any solvent produced an isomeric heterocycle **31** [88, 90]. Reaction of the corresponding Li-diketiminate took a still more complicated course and provided a coupling product with a complex multicyclic molecular structure [88]. Coupling of two diketiminato units was also observed in the reaction of a K-diketiminate with PI_3 which gave a moderate yield of a 4-substituted P-iodo-2,3-dihydro-1,3,2-diazaphosphinine [91]. Although the observation of short N···P contacts between the imino-nitrogen and the phosphorus atom of **29** was interpreted in terms of interactions between these atoms that might facilitate rearrangement into the cyclic phosphenium ions **28** [9], further work is certainly required to obtain a detailed understanding and full control of these reactions.

Heterocyclic phosphines **32** were prepared from base-induced condensation of a secondary 1,8-diamino-naphthalene with phosphorus trichloride (the corresponding As- and Sb-analogues were obtained analogously) and converted into cyclic phosphenium cations **33** by Lewis acid promoted halide abstraction using $GaCl_3$ or trimethylsilyl triflate as reagents (Scheme 18) [15, 92].



Scheme 18 Synthesis of naphtho-annulated six-membered phosphenium heterocycles

In addition to the previously noted heterocycle syntheses under ring assembly, reaction of a cationic P-bromo-1-aryl-2,3-dihydro-1,3,2-diazaphosphininium salt **28** (X = Br) with sodium hydroxide in toluene gave the corresponding P-hydroxy derivative (see Sect. 4.3) [89].

4.2 Physical Properties, Structure, and Bonding

Apart from characterization of the individual types of six-membered heterocycles by routine spectroscopic methods, several cationic cyclic diketiminato-phosphenium ions and 1,8-diamidonaphthalene-derived P-chlorophosphines and phosphenium ions, respectively, were characterized by single-crystal X-ray diffraction studies. The P-halogen- and P-hydroxy-substituted cyclic diketiminato-phosphenium ions **28**

[9, 88, 89] contain six-membered rings that are characterized by a practically coplanar arrangement of the endocyclic carbon and nitrogen atoms whereas the phosphorus atoms deviate from this plane by 0.35–0.55 Å. The P-substituent is nearly orthogonal to the NPN plane and exocyclic phosphorus–halogen or phosphorus–oxygen bonds are rather short (P–Cl in **28** 2.07–2.09 Å, P–O 1.58 Å). The endocyclic bond distances (P–N 1.69–1.74 Å, N–C 1.34–1.38 Å, C–C 1.37–1.41 Å) lie generally between standard single and double bond distances; however, the rings are not symmetrical but display a perceptible bond alternation which reveals a somewhat localized electron distribution [9, 89]. Although DFT calculations on a cation **28** have been reported to yield energy optimized molecular structures whose metrical parameters lie within 2% of the experimentally observed values [9], it has not been reported whether the calculations also reproduce the observed bond length alternation or provide a rational explanation for its occurrence. Analysis of the structure of the frontier orbitals revealed that the HOMO and LUMO are aryl ring bonding and β-diketiminate-π* in character [9]. These findings are in fact compatible with the description of the cations **28** as intramolecular phosphenium ion-Lewis base complexes which differ from genuine phosphenium ions in lacking a particular electrophilic character at the phosphorus atom, and explain that these compounds display, in spite of their likewise positive charge, distinctly different chemical properties than genuine phosphenium ions.

Single-crystal X-ray structural studies on the 1,8-diamidonaphthalene-derived cyclic chlorophosphines **32** (Scheme 18) [92, 93] revealed the presence of six-membered heterocyclic rings with superficially similar conformations as observed for P-halogen-diketiminato-phosphenium ions and likewise rather short (2.15–2.17 Å) P–Cl bonds. The pyramidal coordination geometry of the phosphorus atoms and the P–N bond lengths (1.67–1.68 Å) match the appropriate parameters for five-membered ring NHPs. In contrast, the cations of the salts **33** (Scheme 18) obtained after chloride abstraction are distinguished by nearly planar six-membered rings with distinctly shorter P–N bonds (1.61–1.63 Å) [92, 93]. Interestingly, the C–N bond distances in the six-membered rings remain similar in both cations and neutral chlorophosphines. Quantum chemical studies confirmed the dative stabilization of the phosphenium center by the adjacent π-donating amino-groups which is characteristic of all aminophosphenium ions, but did not make any mention about the possible extension of the π-delocalization over the naphthalene ring system.

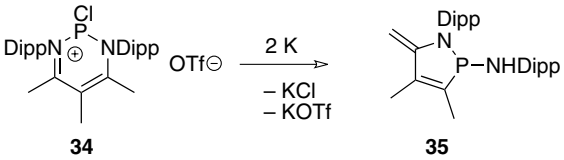
A DFT study on 1,3,2-diazaphosphinines and related six-membered heterocycles [94] revealed that formal isoelectronic replacement of CH-groups in α- or β-position of the phosphorus by nitrogens induces a general destabilization of the heterocyclic ring compared to phosphinine which is for the 1,3,2-diaza-isomer approximately 6 kcal mol^{-1} (at B3LYP/6-31G* level) lower than for the 1,3,5-diaza-isomer. Estimation of the aromaticity by calculation of NICS values showed that the introduction of nitrogens directly adjacent to the phosphorus significantly reduces the aromatic π-delocalization and at the same time induces a 1,4 dipolar character through an increase of the positive charge on the P-atom. This phenomenon was considered to provide an explanation for the high reactivity of 1,3,2-diazaphosphinines towards alkynes (see Sect. 4.3) and does not occur in 1,3,5-diazaphosphinines which

exhibit poor dipolar character. The apparent contradiction between higher overall stability but lower aromaticity of 1,3,2- diazaphosphinines as compared to that of 1,3,5-diazaphosphinines was resolved by pointing out that the superior stability of the 1,3,2-isomers can be ascribed to the presence of a more stable σ-skeleton.

4.3 Chemical Reactivity

Systematic studies of chemical reactivities have been carried out for both 1,3,2-diazaphosphinines and the corresponding 1,2-dihydro-derivatives. 1,2-Dihydro-l,3,2-diazaphosphinines react via a unique [5+2] cycloaddition to dimethyl acetylen-edicarboxylate to furnish bicyclic iminophosphoranes which may subsequently undergo further rearrangement to yield isomeric ylides [87, 95]. The significance of 1,3,2-diazaphosphinines lies in their use to react with alkynes under formation of phosphinines [84, 85]. The transformation is like the 1,3,2-diazaphosphole/1,2-azaphosphole transformation [70] accomplished in two steps; the first one proceeds via initial [4+2]-cycloaddition of the starting materials to give a bicyclic intermediate which then undergoes subsequent [4+2]-cycloreversion under extrusion of a nitrile and rearomatization of the heterocyclic ring to give a 1,2-diazaphosphinine. This intermediate can be characterized by ^{31}P NMR but is usually directly subjected to a second [4+2]-cycloaddition/cycloreversion sequence with the same or a different alkyne which furnishes finally the desired phosphinine. Reaction of both 1,3,2-diazaphosphinines and 1,2-azaphosphinines with unsymmetrical alkynes were reported to proceed in general regiospecifically [85], with the more electronegative carbon atom of the alkyne always reacting at the highly electropositive phosphorus. The reaction sequence described is particularly useful because it tolerates a large variety of functional groups and has been successfully applied to the synthesis of phosphinines bearing a variety of functional substituents as well as to linear or macrocyclic oligo-phosphinines with two to four phosphinine rings [85].

Detailed investigations of the chemical reactivity of the diketiminato-stabilized phosphenium cations like **28** (Scheme 17) are to date rare and include only two reports dealing with the substitution and reduction of P-halogen-derivatives. Thus, reaction of **28** (X=Br) with sodium hydroxide in toluene was reported to proceed with displacement of the halide substituent at phosphorus and conservation of the heterocyclic ring to give a mixture of bromide and triflate salts containing a P-hydroxy-substituted cation, both of which were isolated in small yields [89]. The products are remarkable as they represent one of very few examples of a stable phosphinous acid which does not rearrange to the tautomeric secondary phosphine oxide. Potassium reduction of the P-chloro-substituted derivative **34** produced the 1,2-azaphospholine **35** (Scheme 19) [96]. A plausible, yet speculative, reaction mechanism based on the results of DFT calculations was formulated which suggests that the reaction involves a two step reduction of the starting material to give first a mono- and then a biradical intermediate. The latter reacts further via a sequence involving extrusion of a chloride, ring closure to a bicyclic intermediate and, finally, valence isomerization to furnish the observed product.



34 **35**

Scheme 19 Reduction of a β-diketiminate stabilized phosphenium salt

5 Concluding Remarks

The current review attests that NHPs featuring an NPN motif as a part of fully or partially unsaturated five- and six-membered rings have been and are still attracting great interest. The status of the chemistry of five-membered 1,3,2-diazaphosphole and NHP and six-membered 1,3,2-diazaphosphinine ring systems has reached some maturity whereas β-diketiminato-stabilized phosphenium ions are only freshly emerging. The achievements accomplished in the field to date illustrate that even though the compounds studied behave of course in many aspects as typical phosphines and show predictable chemical behavior, they also display some unexpected properties that led to the discovery of new and unique reactions like the elaboration of new access to highly functionalized phosphinine derivatives, the unprecedented discovery of hydride behavior of secondary phosphine derivatives, or the stabilization of phosphinous acid tautomers. The experimental exploration of these aspects in connection with spectroscopic, structural, and computational studies directed at gaining a detailed understanding of their molecular origin have given stimulating impetus in the context of a renaissance of main-group chemistry [97] during the last few years, and it is hoped that the future continuation of this development will lead to further exciting discoveries in this field.

Acknowledgments I am very much indebted to numerous coworkers and undergraduate students as well as many collaboration partners for their very engaged work and significant contributions to the chemistry outlined in this review. All their names appear in the list of references. I would also like to thank the Universität Stuttgart, Universität Bonn, and Deutsche Forschungsgemeinschaft for the financial support that was required to perform these studies.

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Top Heterocycl Chem (2010) 21: 103–147
DOI 10.1007/7081_2009_6

Published online: 8 January 2010

Selected Five-Membered Phosphorus Heterocycles Containing a Stereogenic Phosphorus

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Abstract This review presents the synthesis of selected five-membered phosphorus heterocycles containing a stereogenic phosphorus in an optically active form. Their utility in a few asymmetric reactions is also briefly mentioned.

Keywords 1,3,2-bis-heterophospholes • 1,3,2-bis-heterophosphrinanes • Asymmetric inductions • Optical activity

Contents

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1 Introduction

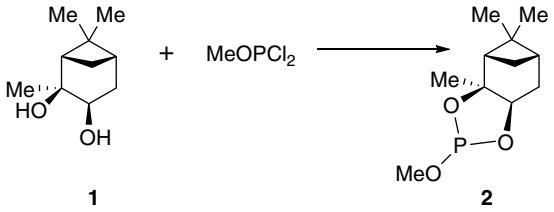
The first phosphorus-containing heterocycles were prepared as early as the late nineteenth century. But, the importance of phosphorus-containing substances in biological processes was only realized in the middle of the last century and this gave a strong impetus for developing studies related to a variety of functionalized phosphorus-containing heterocycles, especially structures having phosphorus-heteroatom bonds such as 1,3,2-bis-heterophospholes and 1,3,2-bis-heterophosphinanes [1]. The six-membered ring system is found in cyclophosphamide and iphosphamide, commonly used as anticancer drugs [2]. Many of their derivatives have been synthesized to determine their structure–activity relationships [3]. Moreover, as a consequence of their valuable synthetic utility, these derivatives, especially compounds with five and six-membered rings, have attracted considerable interest as synthetic tools. Recently, a few phosphorus-stabilized carbanions derived from 3-alkyl-1,3,2-oxazaphosphorinane 2-oxides have been applied with great success to the highly diastereoselective formation of a carbon–carbon bond [4, 5]. A number of 1,3,2-bis-heterophospholenes and phosphiranes have been reported to behave effectively as chiral ligands which induce stereoselective carbon–carbon or carbon–hydrogen bond formation in asymmetric aldol reactions [6, 7], allylations of aldehydes [8], α-alkylations of *P*-alkyl derivatives [9], reductions of ketones [10], and other reactions, which can be considered as examples of asymmetric metal complex catalysis [11–13], including the catalytic allylic substitution processes [14]. It is also interesting to note the use of a few structures as chiral derivatizing agents for the resolution of chiral alcohols [15].

It should be expected that the absolute configuration at a stereogenic phosphorus atom of these chiral molecules will have a remarkable influence on their bioactivities. The configurational stability of a stereogenic phosphorus atom in these structures also allows their use as key substrates in the asymmetric synthesis of other optically active derivatives. In such syntheses, the absolute configuration at a newly created stereogenic center is obviously correlated with the absolute configuration at the stereogenic phosphorus atom of the starting phosphorus-containing heterocyclic ring. Therefore, the enantio- and diastereoselective synthesis of optically active phosphorus heterocylces containing a stereogenic phosphorus still constitutes the prime challenge for phosphorus chemists. This review, which deals with the syntheses of such optically active heterocycles having phosphorus, due to space limitation, is devoted to the procedures applied only for the five-membered rings.

2 1,3,2-Dioxaphospholanes

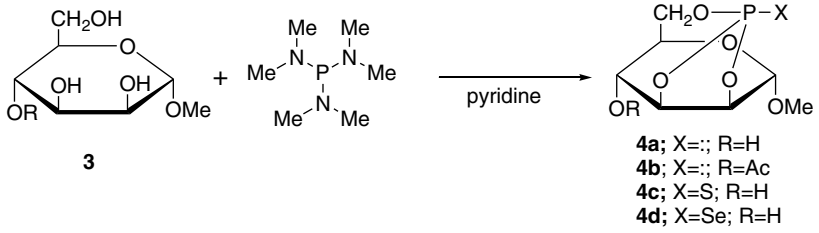
2.1 With a Tricoordinated Phosphorus Atom

The vicinal diol of the monoterpene series, (1*S*,2*S*,3*R*,5*S*)-(+)-2,6,6-trimethylbicyclo [3.1.1]heptane-2,3-diol (**1**), was converted upon reaction with methyl dichlorophosphite into a tricyclic phosphite **2** showing a 95:5 ratio of epimers differing at the phosphorus stereocentre (Scheme 1). Its complexes with Rh(I) and Pd(II) were found to have the structures: $(\mu\text{-Cl})_2[Rh(CO)L]_2$ and *cis*-Cl_2PdL_2 respectively [16].



Scheme 1 Synthesis of a tricyclic phosphite **2**

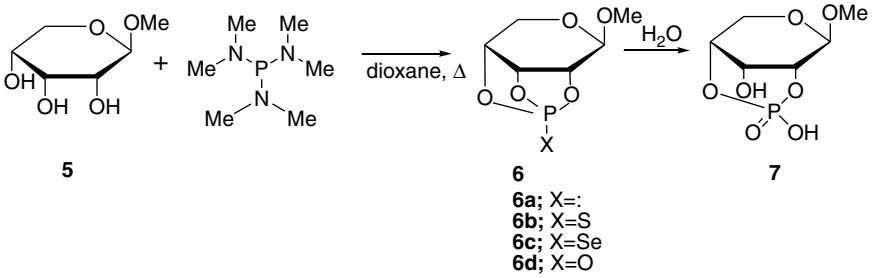
Thermal phosphitylation of methyl α-D-mannopyranoside (**3**) with $P(NMe_2)_3$ in pyridine or tetramethylurea gave 40% of α-methyl-D-mannopyranoside – 2,3,6-bicyclophosphite (**4a**). It underwent acetylation giving the corresponding acetate **4b;** sulfuration, and selenation afforded the corresponding pentavalent thio (**4c)** and seleno (**4d)** derivatives, respectively (Scheme 2). The trivalent acetate **4b** was found to react with CuBr, $Rh(CO)_2(acac)$ and Cl_2 [17].



Scheme 2 Phosphitylation of methyl α-d-mannopyranoside (**3**) with $P(NMe_2)_3$

A similar reaction of methyl β-D-ribopyranoside (**5**) with $P(NMe_2)_3$ in dioxane gave 2,3,4-bicyclophosphite of β-methyl-D-ribopyranoside, **6a** in 90% yield. It was sulfurated and selenated to give the corresponding thiophosphate **6b** and selenophosphate **6c** in 89 and 81% yields, respectively. Oxidation of **6a** with hydrogen peroxide gave cyclic phosphate **6d** (92%), whereas its hydrolysis in aqueous

dioxane gave diastereomeric phosphonates **7** (2 isomers) whose crystal structure was determined by X-ray analysis (Scheme 3) [18].

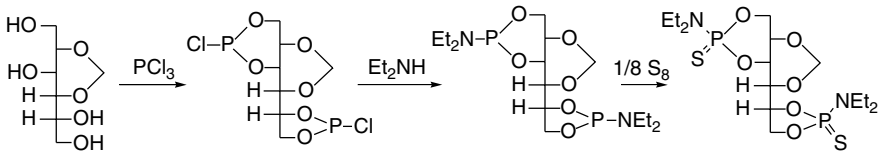


5 **6** **7**

6a; X=:
6b; X=S
6c; X=Se
6d; X=O

Scheme 3 Synthesis of 2,3,4-bicyclophosphite of β-methyl-d-ribopyranoside, **6a** and its selected reactions

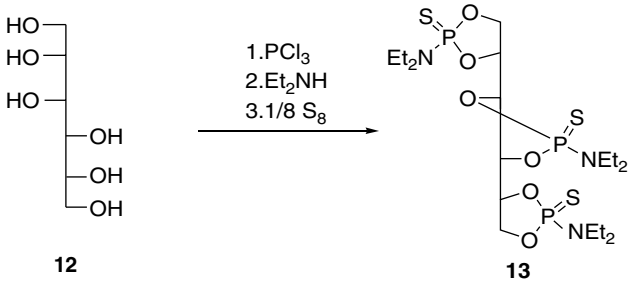
Diphosphitylation of 2,4-*O*-methylene-D-glucitol (**8**) with phosphorus trichloride in dioxane gave 1,3:5,6-bis-*O*-(chlorophosphite) **9** (99.5%). Its amination with diethylamine in benzene-diethyl ether afforded the corresponding bis-amidophosphites **10.** Their reaction with sulfur afforded three P-diastereomers of cyclic thiophosphate **11** in 24.8, 4.8, and 19.5% yields (Scheme 4) [19].



8 **9** **10** **11**

Scheme 4 Synthesis of 1,3:5,6-bis-*O*-(chlorophosphite) **9**, bis-amidophosphites **10**, and P-diastereomers of cyclic thiophosphate **11**

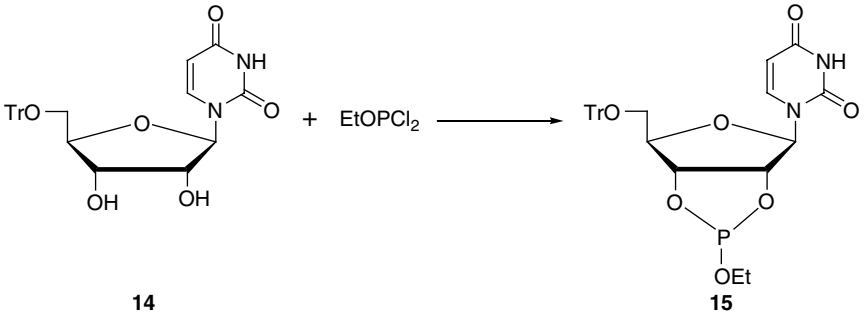
A similar reaction sequence, which begins with the trisphosphitylation of mannitol (**12**) afforded three P-diastereomers of cyclic trithiophosphate **13** via the corresponding tricoordinated tris-chlorophosphite and amidophosphite (Scheme 5) [20].



12 **13**

Scheme 5 Synthesis of P-diastereomers of cyclic tris-thiophosphate **13**

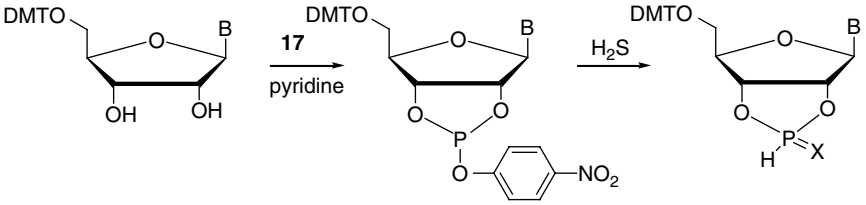
A convenient synthesis of uridine 2′,3′-cyclic phosphite **15** (as a 3:4 mixture of diasteroisomers because of the chirality at phosphorus) was based on the reaction of the suitably protected uridine derivative **14** with ethyl dichlorophosphite carried out in the presence of triethylamine and anhydrous ethanol (Scheme 6) [21]. After adding ethanol into the reaction medium, an efficient chromatographic separation of the crude reaction product was achieved on silica gel with diethyl ether giving analytically pure phosphite **15** in 75% yield**.** It is interesting to note that without adding ethanol, **15** is very unstable.



14 **15**

Scheme 6 Synthesis of uridine 2', 3'-cyclic phosphite **15**

4-Nitrophenyl 2′,3′-*O,O*-cyclic phosphites **18a–d** were formed rapidly and cleanly as two diasteroisomers in the reaction of 5′-*O*-protected ribonucleosides **16a–d** with tris(4-nitrophenyl) phosphite (**17**) in the presence of pyridine [reaction time: less than 3 min at room temperature in DMF/pyridine (9:1 v/v) solution (monitored by ^{31}P-NMR)]. Their sulfhydrolysis, which is also very rapid using an excess of hydrogen sulfide at room temperature, gave cyclic *H*-phosphonothioates **19a–d** (Scheme 7) [22]. In this reaction, the corresponding 2′,3′-*O,O*-cyclic



16 a-d
a; B = uracil-1-yl
b' B = adenin-9-yl
c; B = cytosin-1-yl
d; B = guanin-9-yl
DMT= 4,4'-dimethoxytrityl

18 a-d

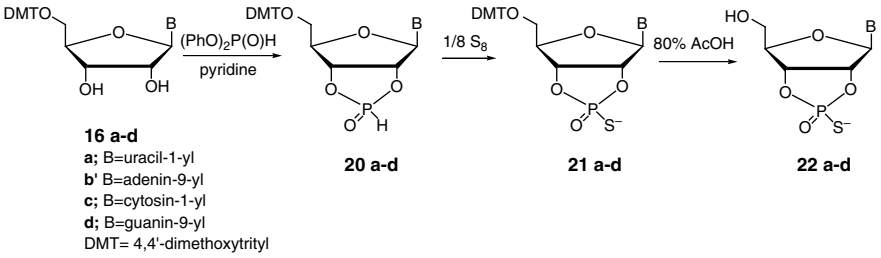
19 or **20 a-d**
19; X=S
20; X=O

Scheme 7 Synthesis of cyclic *H*-phosphonothioates **19a–d**

H-phosphonates **20a–d** were detected as the only side products (10–15%). They were produced by the competitive hydrolysis of the intermediate **18a–d** which could be checked completely by carrying out sulfhydrolysis in the presence of trimethylsilyl chloride.

2.2 With a Tetracoordinated Phosphorus Atom

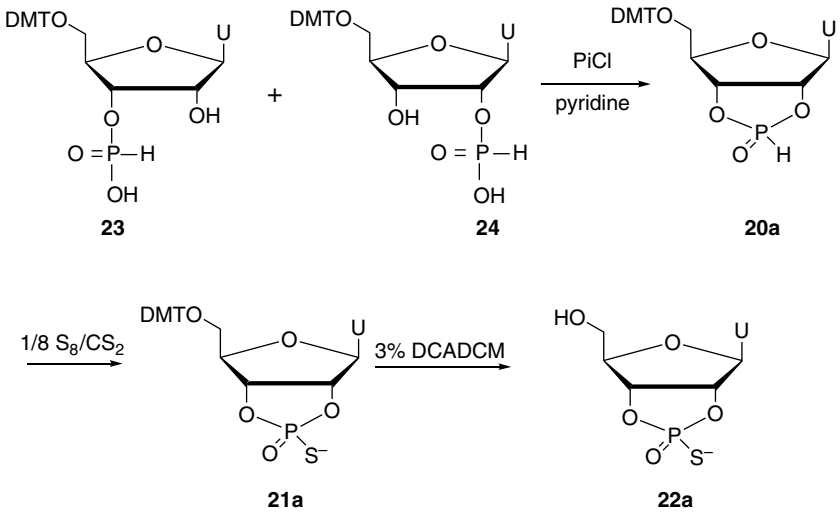
The 2′,3′- *O,O*-cyclic *H*-phosphonates **20a–d** were formed, as ca 1:1 mixture of diastereomers (as monitored by ^{31}P-NMR), in the reaction of 5′-protected ribonucleosides **16a–d** with diphenyl *H*-phosphonate in pyridine. Their sulfurization readily afforded the expected cyclic phosphorothioates **21a–d** which upon subsequent removal of the 5′-protecting group afforded the respective nucleoside 2′,3′-*O,O*-cyclophosphorothioates **22a–d** in excellent yields (70–90%) (Scheme 8) [23].



Scheme 8 Synthesis of nucleoside 2', 3'-*O,O*-cyclophosphorothioates **22a–d** via the 2',3'- *O,O*-cyclic *H*-phosphonates **20a–d**

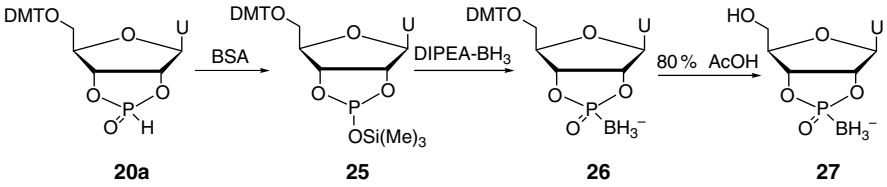
An alternative approach for the synthesis of 2′,3′-*O,O*-cyclic *H*-phosphonate **20a** was based on the condensation of a mixture of uridine 3′- and 2′-*H*-phosphonates (**23** and **24** respectively) induced by pivaloyl chloride (Scheme 9) [24]. Its reaction with elemental sulfur in carbon disulfide gave 5′-*O*-DMT-uridine 2′,3′-cyclic phosphorothioate (**21a**) which after final deprotection afforded the desired 2′,3′-cyclic phosphorothioate **22a** (Scheme 9). Its S_P and R_P diastereomers were separated by HPLC [24].

In this context, it is interesting to note that the first synthesis of 2′,3′-*O,O*-cyclic phosphorothioate **22a** was reported by Eckstein in 1968 [25]. He also isolated pure R_P diastereomer by fractional crystallization of the triethylammonium salts [26] and used it as reference to determine the absolute configurations of the other phosphorothioate analogues [27]. 2′,3′-*O,O*-Cyclic *H*-phosphonate **20a** was used as a key substrate for the synthesis of uridine 2′,3′-*O,O*-cyclic boranophosphate **27**. Silylation of *H*-phosphate **20a** gave the phosphite triester **25** (two diastereomers). Its boronation, with simultaneous removal of the trimethylsilyl group, was achieved by its reaction with borane-*N,N*-diisopropylethylamine complex (DIPEA-BH_3).



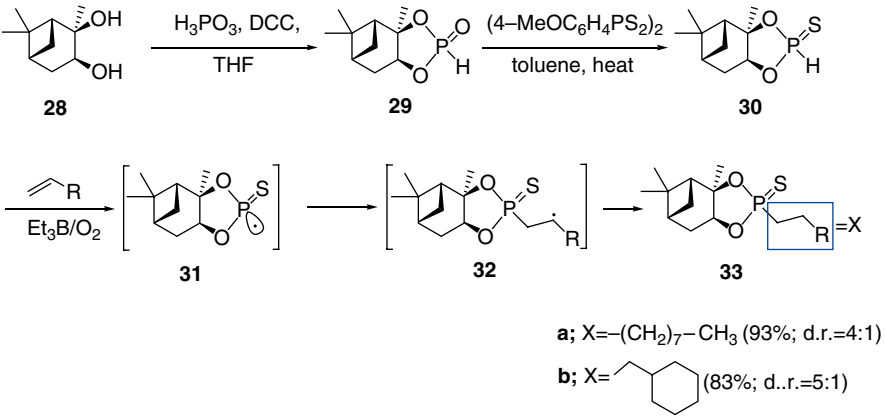
Scheme 9 Synthesis of 2',3'-*O,O*-cyclic phosphorothioate **22a** via 2',3'-*O,O*-cyclic *H*-phosphonate **20a**

The formed 5′-protected 2′,3′-*O,O*-cyclic boranophosphate **26** was finally deprotected by acid treatment and isolated in 70% overall yield by ion-exchange chromatography (Scheme 10) [24]. The two pure P-diasteromers of **27** were separated by HPLC.



Scheme 10 Synthesis of 5'-protected 2',3'-*O,O*-cyclic boranophosphate **26** and its deprotection

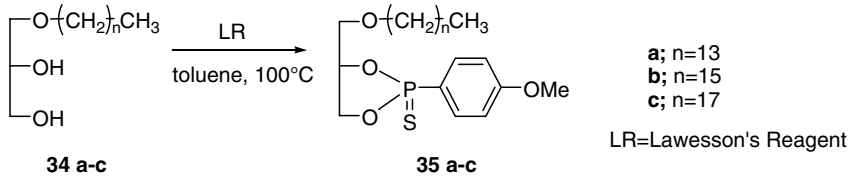
P-Chiral *O,O*-cyclic *H*-phosphonate **29** (formed as a 1:1 mixture of diastereomers) was isolated as a product of the coupling of phosphonic acid with (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol **28** in the presence of dicyclohexylcarbodiimide (Scheme 11). Its treatment with Lawesson's reagent afforded the *H*-thiophosphonate **30** as a 9:1 mixture of inseparable diastereomers (as indicated by the ^{1}H NMR spectrum) in an overall yield of 45%. It is interesting to note that on repeating this procedure several times, the ratio of diastereomers of **30** was found to vary, although it was generally in the range of 4–9:1 and that the reaction temperature was an important factor. Heating an 8:1 mixture of isomers of **30** in toluene for 3 days led



Scheme 11 Synthesis of thiophosphonates **33** via the intermediate radicals **31** and **32**

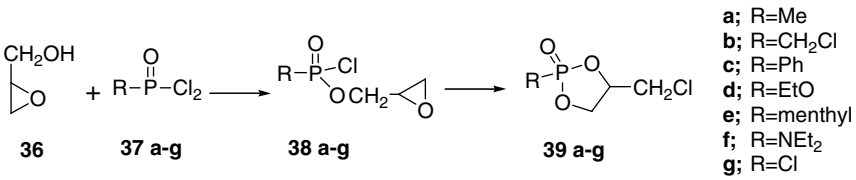
to epimerisation and the formation of a 2:1 mixture. The *H*-thiophosphonate **30** reacted with a series of alkenes (alkynes) (at room temperature in THF in the presence of triethylborane) to give the corresponding saturated (unsaturated) thiophosphonates **33** via the intermediate radicals **31** and **32** as shown in Scheme 11. It was shown that the addition of the intermediate phosphonothioyl radical **31** to electron-rich alkenes or alkynes occurred with retention of configuration at phosphorus atom [28].

A few cyclic phospholipid analogues **35a–c** ($n = 13$, 15, 17) were prepared in 78, 38, and 85% yields respectively, by reacting the corresponding 1-glyceryl ethers **34a–c**, with Lawesson's reagent (Scheme 12) [29].



Scheme 12 Synthesis of cyclic phospholipid analogues **35a–c**

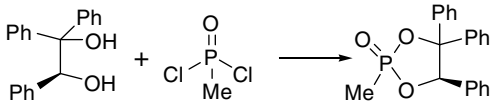
A series of 2(*R*)-4-chloromethyl-1,3,2-dioxaphospholane-2-oxides **39a–g** were formed in the reaction of glycidol **36** with an equimolar amount of dichloro phosphonates (phosphoranes) **37a–g** in the presence of a base. Their formation results from the involvement of the hydroxy and epoxy groups in a tandem process yielding first monoglycidyl esters of the corresponding P acids **38a–g**, which then change into dioxaphospholanes **39a–g** (regiospecifically and without racemization of the chiral center present in the glycidyl moiety) (Scheme 13) [30].



36 37 a-g 38 a-g 39 a-g

Scheme 13 Synthesis of 2(*R*)-4-chloromethyl-1,3,2-dioxaphospholane-2-oxides **39a–g**

The cyclic phosphonate **41** was formed in the reaction of (*R*)-1,1,2-triphenyl-1,2-ethanediol (**40**) with methanephosphonyl dichloride in a highly diastereoselective manner (dr = 9:1) (Scheme 14) [31].



40 **41**

Scheme 14 Reaction of (*R*)-1,1,2-triphenyl-1,2-ethanediol (**40**) with methanephosphonyl dichloride

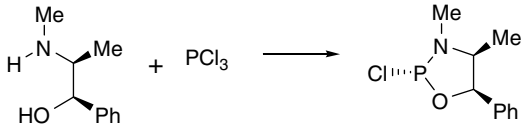
3 1,3,2-Oxazaphospholanes (1,3,2-Oxazaphospholidines)

3.1 Derived from Ephedrine Alkaloids

3.1.1 With a Tricoordinated Phosphorus Atom

2-Chloro-1,3,2-oxazaphospholane (chlorophosphoramidite) **43** derived from (1*R*,2*S*)-(-)-ephedrine **42** was prepared for the first time as early as 1977 by its reaction with phosphorus trichloride (Scheme 15) [32, 33]. Later, similar procedures were reported for its isolation as a single epimer which, on the basis of spectroscopic and derivatisation studies, has been assigned $\boldsymbol{R}_P$ configuration [34–36].

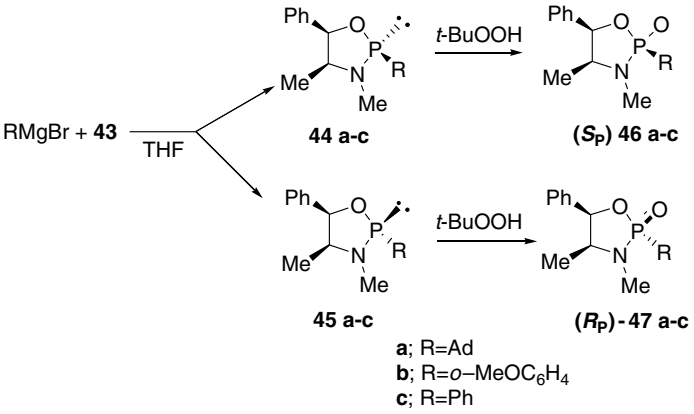
The chlorine atom of **43** may be displaced readily by carbon-based nucleophiles with predominant overall retention of configuration at the phosphorus atom, similar to that observed in pentacoordinated analogues [37, 38]. In some reactions, unselective substitution was observed [39]. This approach was successfully applied for the



(1*R*,2*S*)–**42** (R_P)–**43**

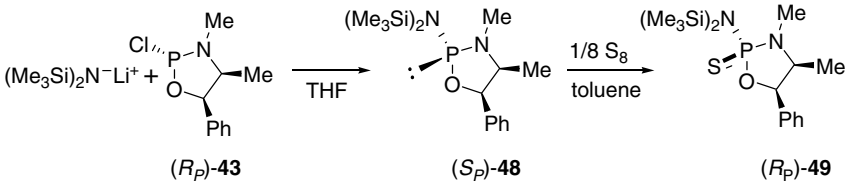
Scheme 15 Synthesis of 2-Chloro-1,3,2-oxazaphospholane (chlorophosphoramidite) **43**

preparation of P-chiral monophosphines carrying a bulky adamantyl residue. Reaction of 2-adamantylmagnesium bromide with **43** leading to both R_P and S_P diastereomers of 2-adamantyl-1,3,2-oxazaphopspholidine-2-oxide, **46a** and **47a,** after oxidation of the initially produced tricoordinated amidophosphites **44a** and **45a** respectively, constitutes a key step (Scheme 16) [40]. This protocol was also used for the preparation of analogous 2-aryl-1,3,2-oxazaphospholidine-2-oxides, **46b,c** and **47b,c.** In the reaction with *o*-methoxyphenylmagnesium bromide, a single diastereomer was isolated, and with phenylmagnesium bromide, the diastereomer formed with the retention of configuration predominated (Scheme 16) [36].



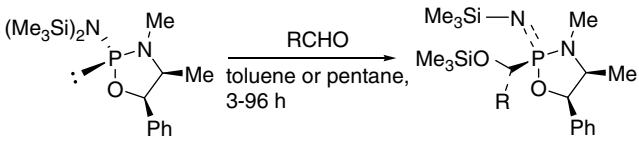
Scheme 16 Synthesis of 2-aryl-1,3,2-oxazaphospholidine-2-oxides, **46b,c** and **47b,c**

In an analogous manner, **43** reacts smoothly with $LiN(SiMe_3)_2$, in THF at reduced temperature to afford the product of halide-atom metathesis **48**, which upon oxidation with sulfur changed into the very stable pentavalent thionobisamide **49** with complete stereoselectivity (Scheme 17) [41–43].



Scheme 17 Synthesis of pentavalent thionobisamide **49**

On the basis of NMR and derivatisation studies, the configuration at phosphorus in **48** was shown to be *S*. It phosphonylates aldehydes readily via the Abramov reaction to afford α-siloxyimidophosphonate esters **50** (Scheme 18) [41–43] with diastereomeric excess (de) up to 96% (for R = *t*-Bu). The reactions proceed smoothly



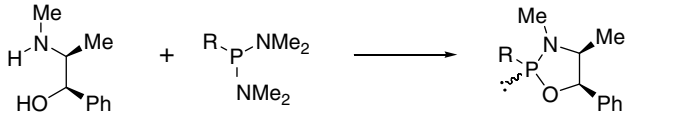
(S_P)-**48 a-e** (S_P)-**50 a-e**

R	de (%)	Yield (%)
Ph	92	83
t-Bu	96	84
2-$C_{10}H_7$	91	86
p-NC-C_6H_4	91	93
p-O_2N-C_6H_4	90	97

Scheme 18 Synthesis of α-siloxyimidophosphonate esters **50**

in either pentane or toluene solvent at ambient temperature over the course of minutes (for aryl aldehydes) to several days (alkyl aldehydes and *p*-$MeOC_6H_4CHO$). In each case, NMR spectroscopy reveals that both major and minor product esters have the *S* configuration. This observation supports the suggestion that the Abramov reaction proceeds with *retention* of configuration at phosphorus.

The asymmetric synthesis of 2-aryl(alkyl)-1,3,2-oxazaphospholidines **52** was based on the reaction of achiral organophosphonous diamides **51** with L-ephedrine (**42**) (Scheme 19) [44]. The diastereomeric excess ranges from 0% (R = Ph) to 95%

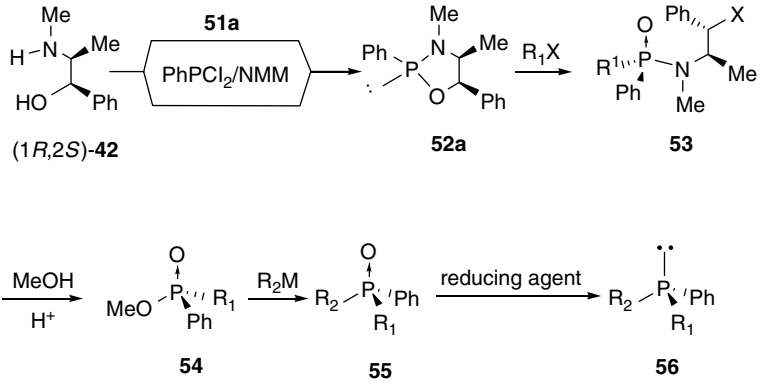


(1*R*,2*S*)-**42** **51 a-c** **52 a-c**
a; R=Ph
b; R=Me
c; R=*t*-Bu

Scheme 19 Synthesis of 2-aryl(alkyl)-1,3,2-oxazaphospholidines **52**

(R = *t*-butyl). Analysis of the ^{13}C-^{31}P` and `^{1}H-^{31}P` coupling constants allowed the structural assignment of **52a–c** as (2*S*,4*S*,5*R*).

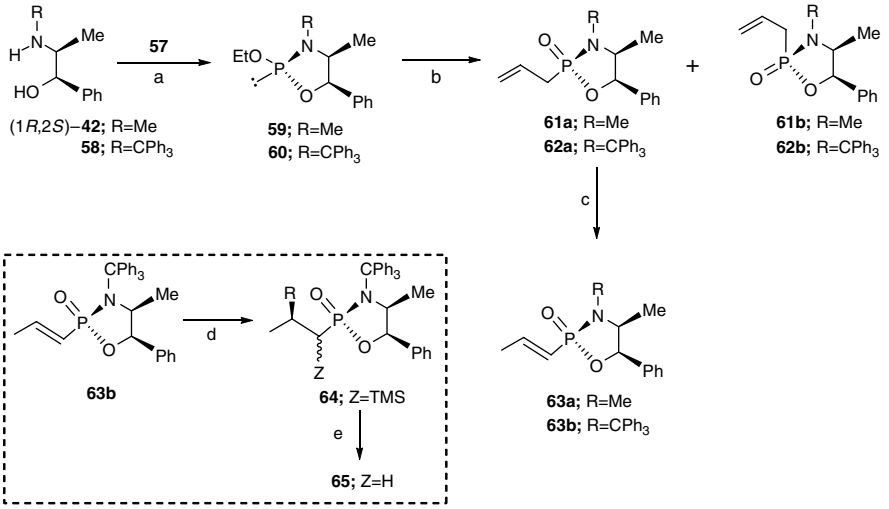
A modification of this procedure allowed the isolation of 1,3,2-oxazaphospholidine **52a** as a single diastereomer [41] and its application to asymmetric synthesis of enantiomerically and diastereomerically pure phosphinic acid derivatives **53** and **54** and tertiary phosphine oxides **55** (Scheme 20) [45]. A few years later, a similar approach for the synthesis of enantiomerically pure tertiary phosphine oxides **55**



Scheme 20 Synthesis of diastereomerically pure phosphinic acid derivatives **53**

was based on the isolation of 1,3,2-oxazaphospholidine **52a** as a single diastereomer in the reaction of dichlorophenylphosphine with (-)-ephedrine (**42**) in the presence of *N*-methylmorpholine (NMM) (Scheme 20) [46]. It should be noted, however, that decreasing the reaction time led to a diastereomeric mixture of 1,3,2-oxazaphospholidine **52a** [47]. Prepared phosphine oxides **55** could be converted to the corresponding phosphines **56** [45–47].

2-Ethoxy-1,3,2-oxazaphospholidine **59** was prepared as a single diastereomer from (-)ephedrine (**42**) and ethyl dichlorophosphite **57.** Its Arbusov reaction with allyl bromide gave the corresponding allyl phosphonates **61a,b** as a diastereomeric mixture which could be separated by flash column chromatography and crystallization (Scheme 21) [48]. On applying a similar protocol, starting from

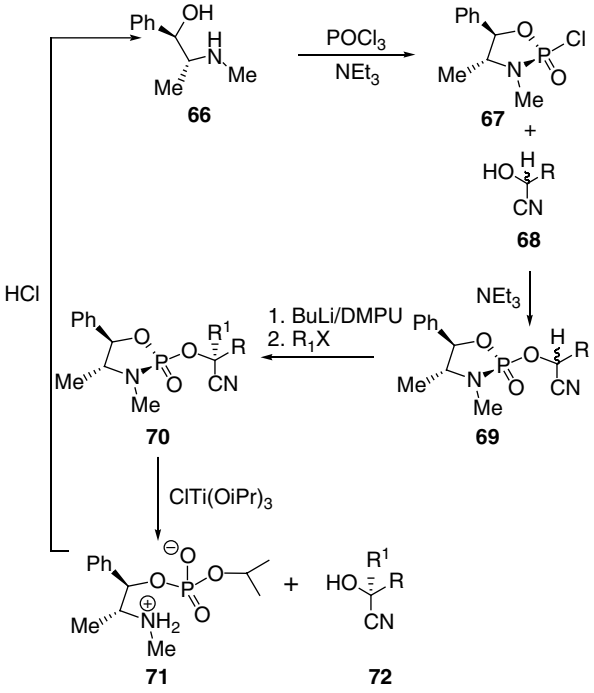


Scheme 21 Synthesis of vinylphosphonates **63a,b** and their conversion to diastereomeric phosphonates **64** or **65**

N-trityl-(1*R*,2*S*)-norephedrine (**58**), the corresponding allyl phosphonates **62a,b** were obtained via the Arbusov rearrangement of 2-ethoxy-1,3,2-oxazaphospholidine **60**. The absolute configuration of the major diastereomer, **62a** was determined by X-ray as (2*S*,4*S*,5*R*).The reaction of the major diastereomer of allyl phosphonates **61a** and **62a** with DBU afforded the corresponding vinylphosphonates **63a,b** (Scheme 21) [48]. Nucleophilic addition to these resulted in induction of chirality at the β-position of the stereogenic phosphorus atom in the initially produced diastereomeric phosphonates **64** or **65** (Scheme 21) [48].

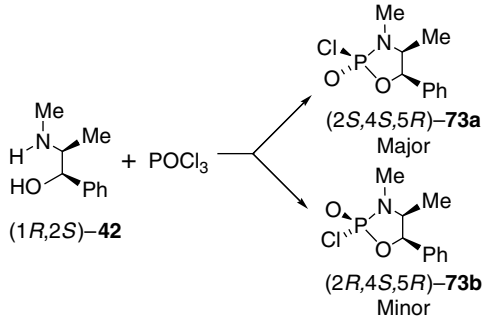
3.1.2 With a Tetracoordinated Phosphorus Atom

The first report on the reaction of D-pseudoephedrine **66** with phosphoryl chloride appeared as early as 1962 [49]. More recently it was found that this condensation gave 2-chloro-1,3,2-oxazaphospholidine 2-oxides **67** as a single diastereomer which was subsequently esterified with racemic aldehyde cyanohydrins **68** without racemization at the phosphorus atom. The prepared diastereomeric esters **69** were used as substrates for the asymmetric synthesis of optically active cyanohydrins **72**, which involves the intermediate formation of the tertiary esters **70**, as shown in Scheme 22 [50].



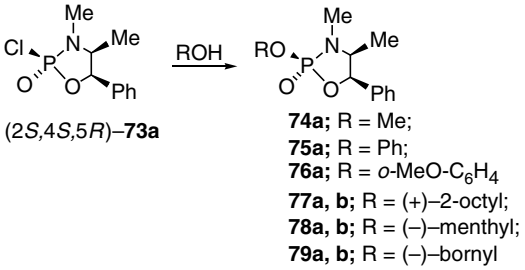
Scheme 22 Asymmetric synthesis of optically active cyanohydrins **72**

A similar reaction of (-)-ephedrine (**42**) was reported to give 2-chloro-1,3,2-oxazaphospholidine 2-oxide either as a single diastereomer (2*S*,4*S*,5*R*)-**73a** [51–53] or as the isomeric pair **73a**,**b**, which could be separated by chromatography over silica gel (Scheme 23) [32, 54].



Scheme 23 Synthesis of 2-chloro-1,3,2-oxazaphospholidine 2-oxides **73a,b**

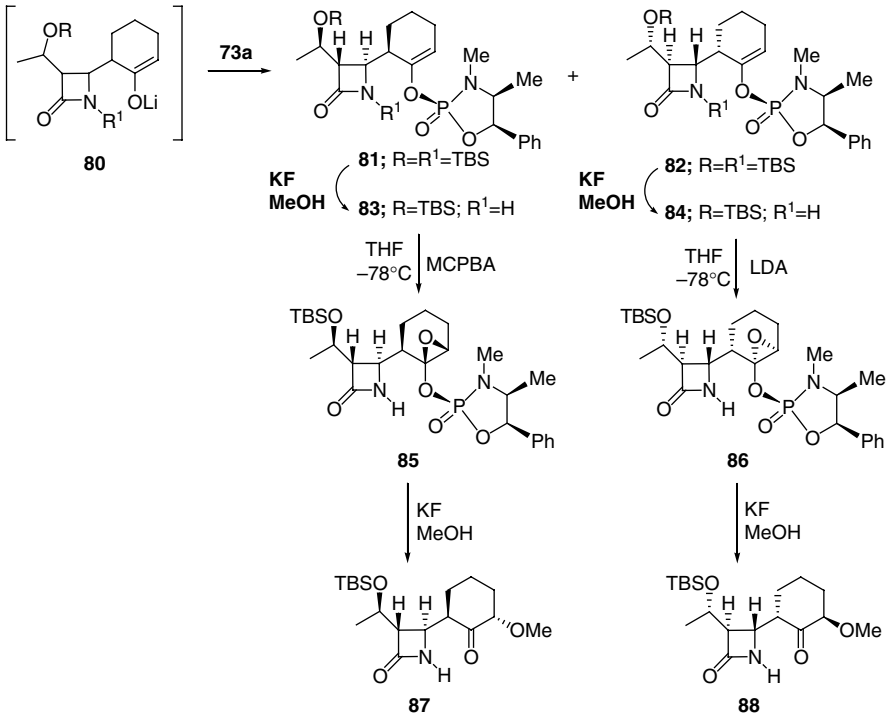
The diastereomerically pure chlorides **73a** and **73b** afforded the corresponding *P*-substitution products on reaction with nucleophiles. Thus **73a** and **73b** could be converted readily into the corresponding alkoxy-derivatives on treatment with an alcohol in the presence of triethylamine and into aryloxy-derivatives upon treatment with the sodium salt of the appropriate phenol at room temperature. Replacement of chlorine by an alkoxy- or aryloxy-group occurred with *retention* of configuration, e.g., **73a** gave **74a**, **75a**, and **76a**. Similarly, **74b** and **75b** could be obtained from **73b** (Scheme 24) [32, 38, 54].



Scheme 24 Reaction of the diastereomerically pure chlorides **73a** and **73b** with nucleophiles

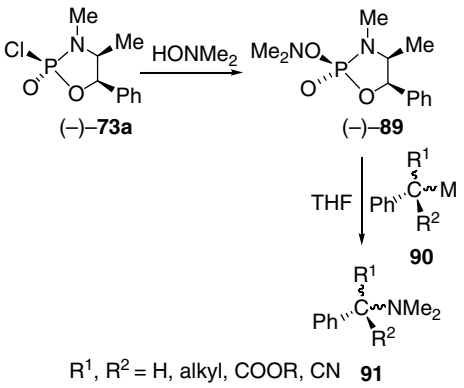
The configurations at phosphorus in compounds **73–76** were assigned on the basis of ^{1}H-NMR data assuming that in phosphorus-containing heterocycles, the protons in a 1,3-*cis*-relation to a P=O group are deshielded. Thus, since H4 and H5 resonate at lower field in compounds **73a–76a** than in compounds **73b–76b,** the P=O group must be *cis* to H4 and H5 in the 'a' series [32]. These assignments were fully supported by the crystal structure studies of **75a**, which showed that this

diastereomer has (2*R*,4*S*,5*R*)-configuration at the stereogenic centers and appears as a C(5) envelope in which this atom is below the O(1)-P(2)-N(3)-C(4) plane. The diastereoisomer **75b**, having (2*S*,4*S*,5*R*)- configuration, adopts half-chair conformation with C(4) above and C(5) below the O(1)-P(2)-N(3) plane [47]. The condensation of **73a** with optically active alcohols afforded the corresponding diastereomeric esters **77a,b–79a,b** which are suitable for the quantification of enantiomeric excesses of alcohols [55]. Diastereomeric enol amidophosphates **81** and **82** were prepared in 82% overall yield by reacting enantiomeric lithium enolates **80** (generated in situ) with **73a**. They were converted to the corresponding *N-H* derivatives **83** and **84** via selective *N*-deprotection with potassium fluoride in methanol. After chromatographic separation, the pure diastereomeric enolates **83** and **84** were oxidized to the epoxides **85** and **86** respectively with complete diastereoselectivity. The latter in turn afforded the enantiomeric 4-methoxy trinems **87** and **88** via epoxide ring-opening in the presence of methanol (Scheme 25) [56].



Scheme 25 Synthesis of the enantiomeric 4-methoxy trinems **87** and **88**

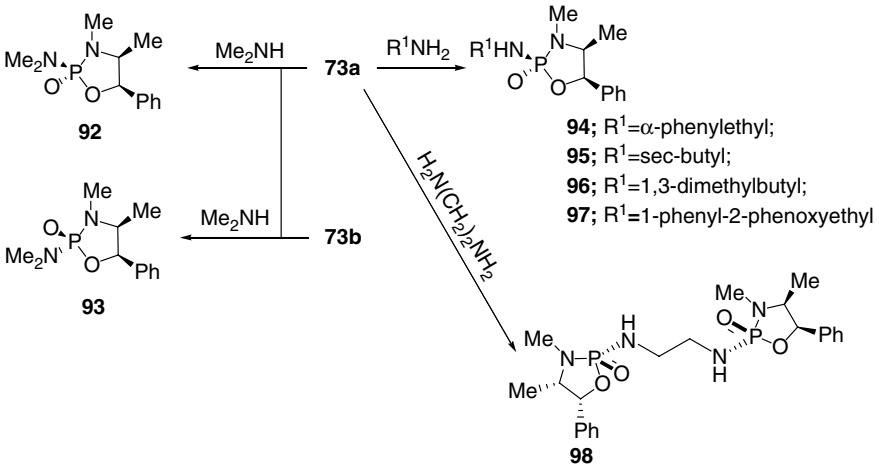
N,N-Dimethylhydroxylamine reacts with **73a** to give the chiral amination reagent **89** with *retention* of configuration at the phosphorus atom. On reacting (-)- **89** with



Scheme 26 Synthesis of optically active amines **91** using the chiral amination reagent **89**

organometallic compounds **90**, optically active amines **91** having enantiomeric excesses in the range of 26–62% were obtained (Scheme 26) [57].

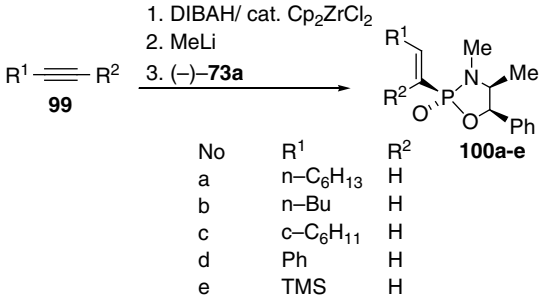
The chlorides **73a** and **73b** on reacting with dimethylamine in benzene afforded the amidates **92** and **93** respectively with complete diastereoselectivity. [58] The diastereomeric amides **94–96** were prepared in a similar manner by reacting **73a** with chiral primary amines (optically active or racemic) and the isolated amides were applied for quantification of enantiomeric excesses of the amines of interest (Scheme 27) [55]. A similar reaction with 1,2-diaminoethane gave bisphosphoramide **98** [59].



Scheme 27 Selected reactions of the chlorides **73a** and **73b**

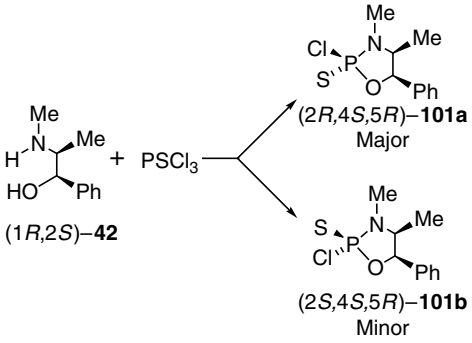
In sharp contrast to the above mentioned conversions of **73a**, its reaction with *O*-ethyl thiophosphate is nonstereoselective (90% inversion and 10% retention). Moreover, with a fluoride anion, complete loss of stereochemistry was observed [60]. An efficient synthesis of diastereomerically pure vinyl phosphonates **100a–e** was

based on the reaction of **73a** with the "ate" complexes of vinylalkanes prepared in situ from zirconocene dichloride catalyzed hydroalumination of 1-alkynes **99** with diisobutylaluminum hydride (DIBAH) (Scheme 28) [61].



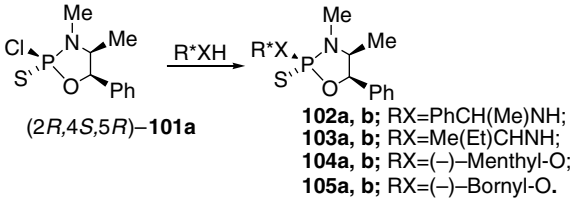
Scheme 28 Synthesis of diastereomerically pure vinyl phosphonates **100a–e**

The reaction of (-)-ephedrine (**42**) with thiophosphoryl chloride was reported to give 2-chloro-1,3,2-oxazaphospholidine 2-thione as the isomeric pair **101a**,**b**, which could be separated by chromatography over silica gel [32] or recrystallization (Scheme 29) [55].



Scheme 29 Synthesis of 2-chloro-1,3,2-oxazaphospholidine 2-thiones **101a,b**

The condensation of **101a** with chiral alcohols or amines afforded the corresponding diastereomeric derivatives **102a,b–105a,b** which are suitable for quantification of enantiomeric excesses of alcohols or amines of interest (Scheme 30) [55].

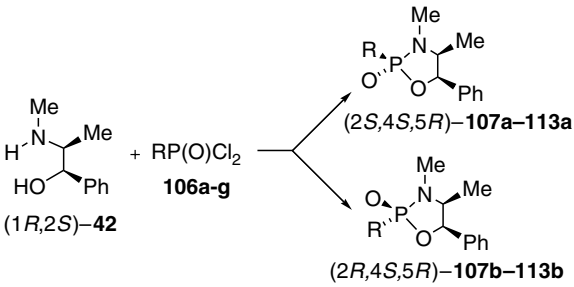


Scheme 30 Condensation of **101a** with chiral alcohols or amines

Table 1 Synthesis of 2-alkyl(aryl)-2-oxo-1,3,2-oxazaphospholidines (2*S*,4*S*,5*R*)–**107a–113a** and (2*R*,4*S*,5*R*)–**107b–113b**

R	No	Yield (%) a	Yield (%) b	Reference
Me	107	9	12	[32]
Ph	108	33	28	[32]
$PhCH_2$	109	40	31	[62]
$PhCH_2$	109	41	20	[63]
$NphCH_2$	110	54	24	[63]
m-C_6H_5–C_6H_4	111	43	25	[63]
$ClCH_2$	112	15	45	[64]
CH_2=CH–CH_2	113	45	45	[65]

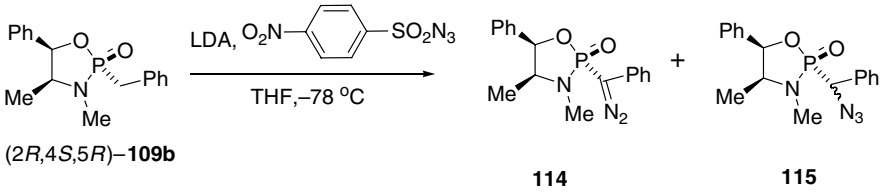
Treatment of (-)-ephedrine (**42**) with a variety of alkyl(aryl)phosphonic dichlorides **106a–d** afforded the isomeric pairs of the corresponding 2-alkyl(aryl)-2-oxo-1,3,2 oxazaphospholidines (Scheme 31 and Table 1) [32, 62–65].



Scheme 31 Synthesis of 2-alkyl(aryl)-2-oxo-1,3,2-oxazaphospholidines (2*S*,4*S*,5*R*)**–107a–113a** and (2*R*,4*S*,5*R*)–**107b–113b**

They were easily separated by standard chromatography [32] or HPLC [37] over silica. The yields of the isolated products (**107a and b**) were low because some decomposition occurred during chromatography over silica [32]. No details have been reported regarding the optimization of the yields or determining whether ratios of isomers are constant or vary with time or with the conditions of preparation.

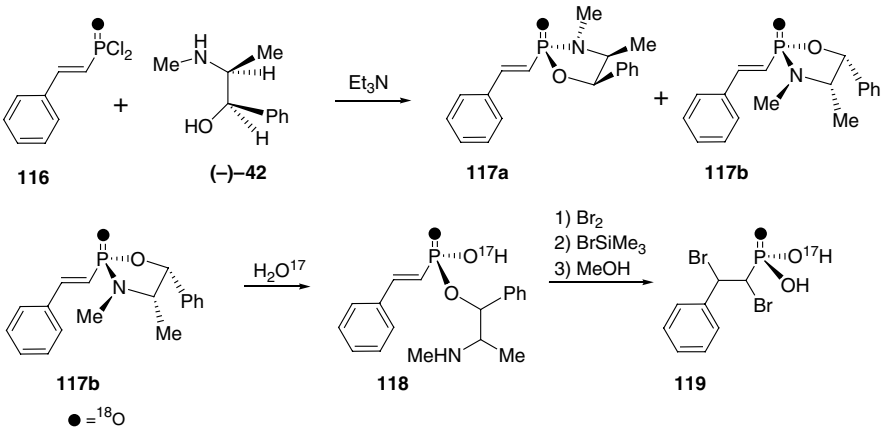
On reacting **109b** with LDA followed by 4-nitrobenzenesulfonyl azide, the diazo compound **114** was formed along with the corresponding azide **115** (Scheme 32).



Scheme 32 Reaction of the 2-oxo-1,3,2-oxazaphospholidine (2*R*,4*S*,5*R*)–**109b** with 4-nitrobenzenesulfonyl azide

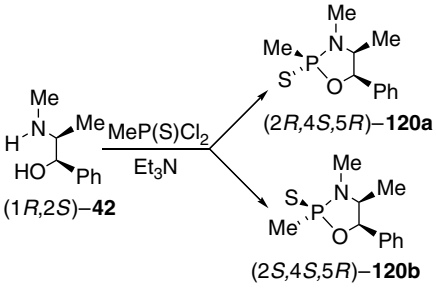
All attempts to separate **114** and **115** were unsuccessful and the diazo compound was obtained only in low yield, still contaminated with traces of azide [62].

It is interesting to note that [(E)-2-phenylethenyl]-[O^{18}]phosphonic dichloride (**116**) upon treatment with (-)-ephedrine (**42**) in the presence of triethylamine afforded an equimolar mixture of (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-2,3-dimethyl-5-phenyl-2-[(E)-2-phenylethenyl]-1,3,2-oxazaphospholidin-2-[^{18}O]one **117a** and **117b**. The two diastereomers were completely separated by flash chromatography and the diastereomer **117b** was hydrolyzed with water H_2O-^{17}O to the corresponding monoester **118** which was finally converted to dihydro-(1,2-dibromo-2-phenyl- 1-ethyl) (*R*)-**^{16}O,^{17}O,^{18}O** phosphonic acid **119** (Scheme 33) [66].



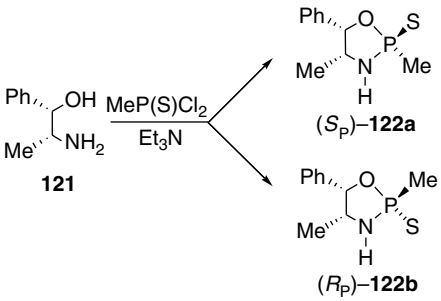
Scheme 33 Synthesis of dihydro-(1,2-dibromo-2-phenyl- 1-ethyl) (*R*)-^{16}**O**,^{17}**O**,^{18}**O** phosphonic acid **119**

Treatment of (-)-ephedrine (**42**) with methylthiophosphonic dichloride afforded a mixture of the isomeric 2-methyl-1,3,2 oxazaphospholidine-2-thiones **120a,b,** from which the pure isomers could be separated in approximately equal quantities by chromatography over silica (Scheme 34) [32].



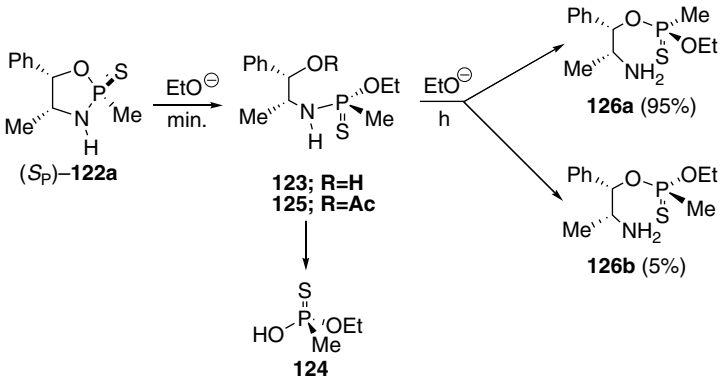
Scheme 34 Synthesis of 2-methyl-1,3,2 oxazaphospholidine-2-thiones **120a,b**

A similar condensation of (+)-norephedrine (**121**) gave the corresponding 2-methyl-1,3,2 oxazaphospholidine-2-thiones **122a,b** which were separated by rapid, medium pressure chromatography (Scheme 35) [67].



Scheme 35 Synthesis of 2-methyl-1,3,2 oxazaphospholidine-2-thiones **122a,b**

Both diastereomers of the thione **122** underwent stereospecific ring opening with alkoxides as shown below in Scheme 36. Thus, on reacting with sodium ethoxide, **122a** was rapidly converted due to endocyclic P–O cleavage into the thiophosphonoamidate **123** which afforded the thioacid **124** via acid catalyzed hydrolysis of the acetylated derivative **125**. Storage of the basic solution of **122a** for several hours led to endocyclic P–N cleavage generating diastereomeric thiophosphonates **126a,b** in quantitative yield [67].

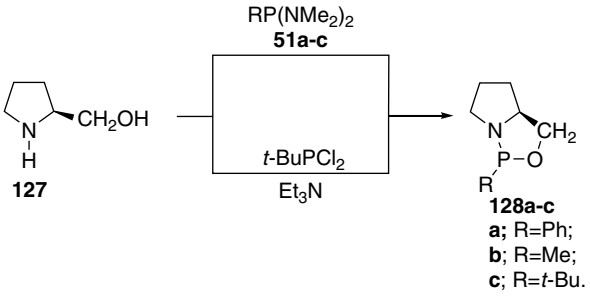


Scheme 36 Stereospecific ring opening reaction of thione **122a** with sodium ethoxide

3.2 *Derived from Other 1,2-Aminoalcohols*

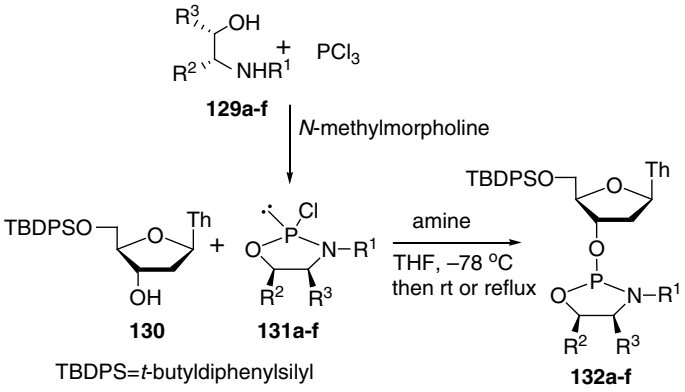
3.2.1 With a Tricoordinated Phosphorus Atom

Synthesis of 1,3,2 oxazaphospholidines **128a–c** derived from (*S*)-prolinol **127** was based either on the thermal aminoalcoholysis of the latter with prochiral alkyl(aryl) phosphonousdiamides **51a–c** or its condensation reaction with *t*-butylphosphonous dichloride carried out in the presence of triethylamine (Scheme 37) [68]. The diastereomeric excesses of the prepared derivatives ranged from 80 to 95%.



Scheme 37 Synthesis of 1,3,2 oxazaphospholidines **128a–c**

A series of 2-chloro-1,3,2-oxazaphospholidine derivatives **131a–f** were prepared by reaction of six enantio-pure alcohols **129a–f** with phosphorus trichloride carried out in the presence of an organic base as HCl scavenger (Scheme 38) [69]. The ^{31}P and ^{1}H-NMR spectra of crude **131a, d, e** containing a small amount of the HCl salt produced during the synthesis of **131**, as well as the distilled samples, indicated that the formed chloro derivatives were ca. 1:1 mixtures of the *cis* and *trans* isomers.



Scheme 38 Synthesis of the nucleoside 3'-*O*-oxazaphospholidine derivatives **132a–f**

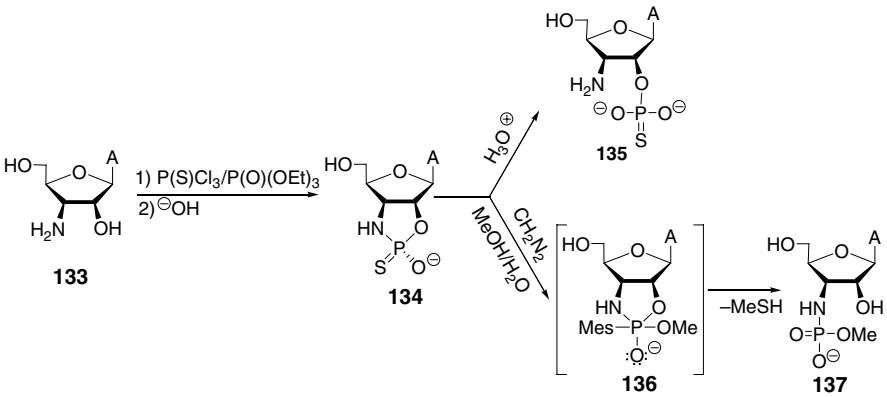
Table 2 Synthesis of the nucleoside 3'-*O*-oxazaphospholidine derivatives **132a–f**

132	R^1	R^2	R^3	Amine	Conditions	*Trans/cis*	Yield (%)
a	Me	H	Ph	Et_3N	rt/30 min	95:5	77
				Et_3N	reflux	59:41	
b	Me	Me	Ph	Et_3N	rt/30 min	88:12	
				iPr_2NEt	rt/30 min	88:12	64
c	Me	Ph	Ph	iPr_2NEt	rt/30 min	92:8	
	Me	Ph	Ph	iPr_2NEt	Reflux	97:3	96
d	*i*Pr	H	Ph	Et_3N	rt/30 min	93:7	64
e	Me	H	*i*Pr	Et_3N	rt/30 min	85:15	
f	Me	*i*Pr	H	iPr_2NEt	rt/30 min	44:56	

On the other hand, **131b, c, f** were found as a single diastereomer in each case. On allowing 2-chlorooxazaphospholidine derivatives **131a–f** to react with 5′-*O*-(*t*-butyldiphenylsilyl)thymidine [5′*O*(TBDPS)thymidine] **130** under different reaction conditions, the nucleoside 3′-*O*-oxazaphospholidine derivatives **132a–f** were formed with moderate to excellent diastereoselectivity. Among the resulting compounds, diastereo pure *trans*-**132a–d** were very easily isolated by simple silica gel column chromatography in modest to excellent yields, and used as the monomer units for a study on the condensation reactions with 3′-*O*-protected nucleosides (Scheme 38 and Table 2) [69].

3.2.2 With a Tetracoordinated Phosphorus Atom

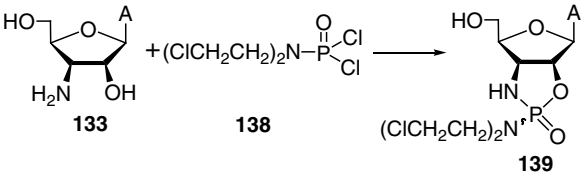
The reaction of 3′-amino-3′-desoxyadenosine **133** with thiophosphoryl chloride afforded 3′,5′-cyclothionophosphonate derivative **134** as a mixture of *P*-diastereomers, which were separated by chromatography (Scheme 39) [70]. The P–N bond cleavage,



Scheme 39 Synthesis of 2'–thionophosphonate bis-anion **135** and 3'-amido monoanion **137**

observed at pH = 5, changed them into the corresponding 2′-thionophosphonate bis-anion **135**, whereas their methylation with diazomethane in water-methanol solution gave, after removal of methyl mercaptan from the intermediate pentacoordinate derivative **136,** 3′-amido monoanion **137** (Scheme 39) [70].

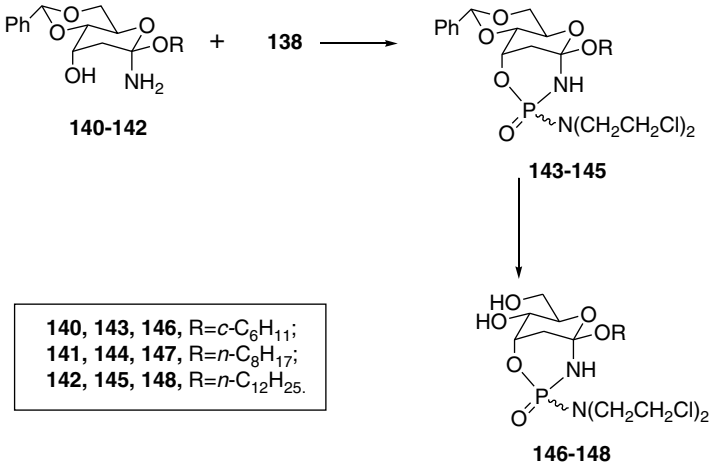
A cyclic nucleotide, 2′,3′-bis(2-chloroethyl)aminophosphoryl-3′-amino-3′-deoxyadenosine (**139**) showing antitumor activity, was prepared in 40% yield starting from 3′-amino-3′-deoxyadenosine **133** by its phosphorylation with *N,N*-bis-(2-chloroethyl) amidophosphoryl dichloride **138**. Both *P*-diastereomers separated by column chromatography exhibit activity against KB tumor cell cultures (Scheme 40) [71].



Scheme 40 Synthesis of 2',3'-bis(2-chloroethyl)aminophosphoryl-3'-amino-3'- deoxyadenosine **139**

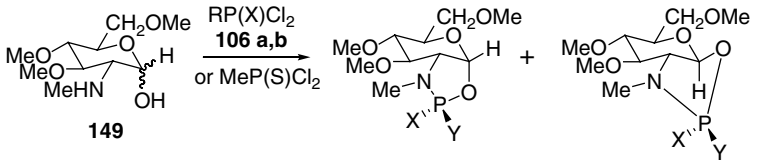
Similarly, a series of cyclophosphamides **143–145** were synthesized in good yields (78–87%) with very high diastereoselectivity by reacting alkyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-allopyranosides **140–142** with *N,N*-bis-(2-chloroethyl) amidophosphoryl dichloride **138**. Subsequent hydrogenolysis of cyclophosphamides **143–145** gave excellent yields (85–90%) of cyclophosphamides **146–148** which show higher hydrophilicity than their precursors (Scheme 41) [72].

The reaction of 2-deoxy-3,4,6-tri-*O*-methyl-2-methylamino-D-glucopyranose **149** with methyl(phenyl)phosphonic dichlorides (**106a–b**) or methylthiophosphonic dichloride in benzene in the presence of triethylamine afforded mixtures of four isomers of the corresponding 1,3,2 oxazaphospholidine-2-ones **150, 151** and



Scheme 41 Synthesis of cyclophosphamides **146–148**

2-thiones **152** as shown in Scheme 42. The α- and β-terms used in the compound numbers indicate the structure derived from α- or β -D-glucopyranose, respectively. The *cis* and *trans* notations indicate the relative disposition of the P=X group and



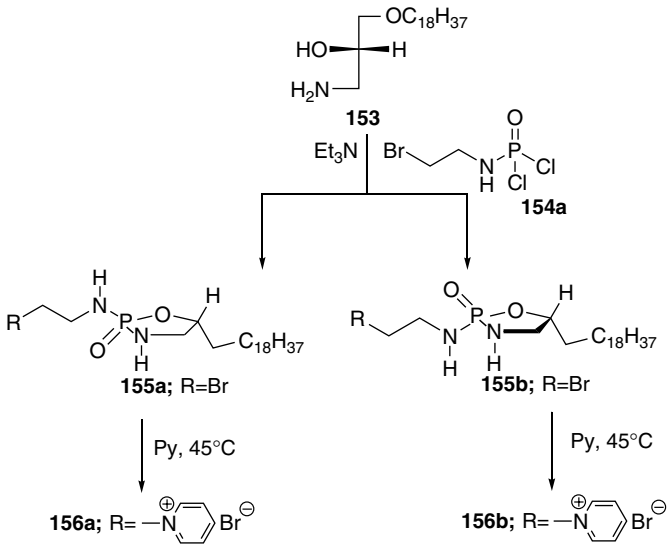
Compound	X	Y	[Yield (%)]
150 β-trans	Me	O	36
150 β-cis	O	Me	36
150 α-trans	Me	O	42
150 α-cis	O	Me	42
151 β-trans	Ph	O	36
151 β-cis	O	Ph	36
151 α-trans	Ph	O	12
151 α-cis	O	Ph	12
152 β-trans	Me	S	25
152 β-cis	S	Me	25
152 -α-trans	Me	S	25
152 α-cis	S	Me	25

α-series **150-152** β-series

Scheme 42 Synthesis of 1,3,2 oxazaphospholidine-2-ones **150**, **151** and 2-thiones **152**

the C-1 proton of the sugar residue (Scheme 42) [73]. Due to difficult isomer separation, each isomer could be obtained in pure state only in low yield.

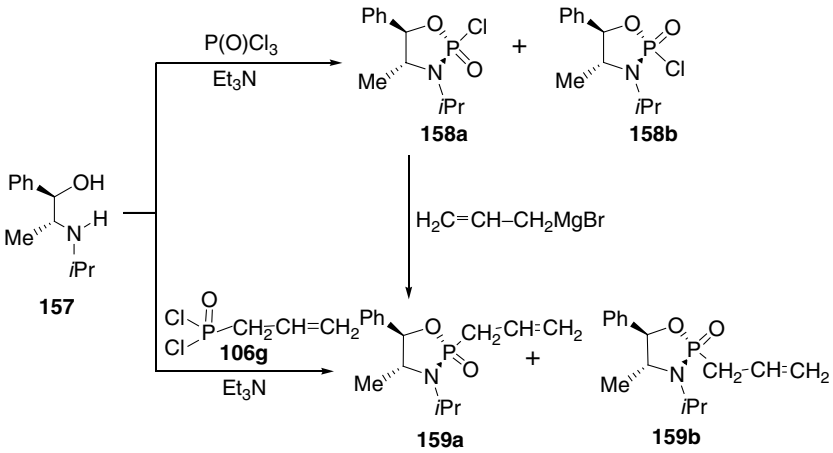
Reaction of the (*S*)-amino alcohol **153** with *N*-(2-bromoethyl)phosphoramidic dichloride (**154**) in the presence of triethylamine led to the formation of two diastereomers of 1,3,2 oxazaphospholidine-2-one **155** (**a** and **b**) (Scheme 43) [74].



Scheme 43 Synthesis of 1,3,2 oxazaphospholidine-2-one **155** a and b and their conversion to the pyridinium salts **156a** and **156b**

They were isolated in 27 and 26% yields respectively by chromatography. Assignment of the configuration at the P-atom was based on the observation that a P=O bond causes deshielding effect on the C-5 proton of the sugar residue. Introduction of a positively charged N-function was achieved by conversion of each diastereomer **155a** and **155b**, in low yield, to the hygroscopic pyridinium salts **156a** and **156b**, respectively (Scheme 43) [74].

2-Chloro-1,3,2 oxazaphospholidine-2-oxide **158a** was formed stereoselectively in the reaction of (1*R*,2*R*)-(-)-α-(1-isopropylaminoethyl)benzyl alcohol **157** and phosphoryl chloride in the presence of triethylamine (Scheme 44) [65, 75].

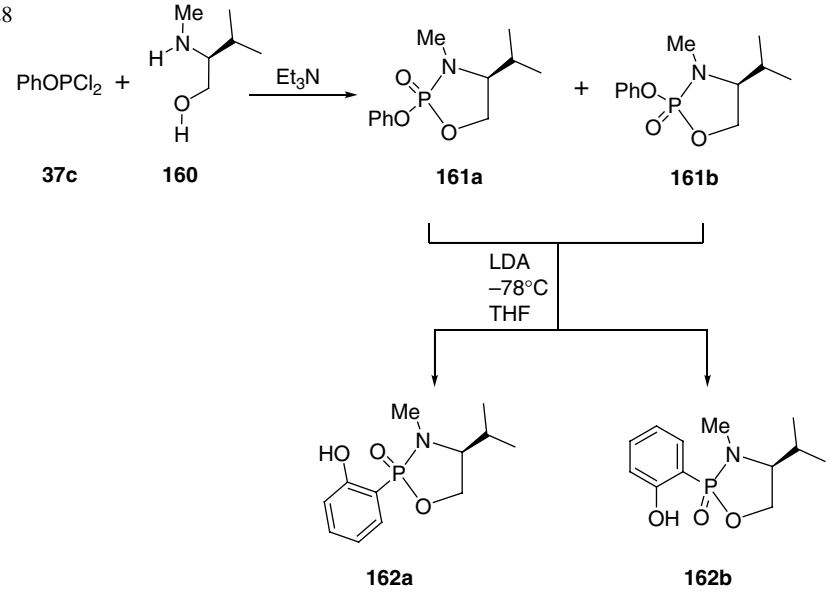


Scheme 44 Synthesis of (2*S*,4*R*,5*R*)-2-propenyl-1,3,2 oxazaphospholidine-2-oxides **159a,b**

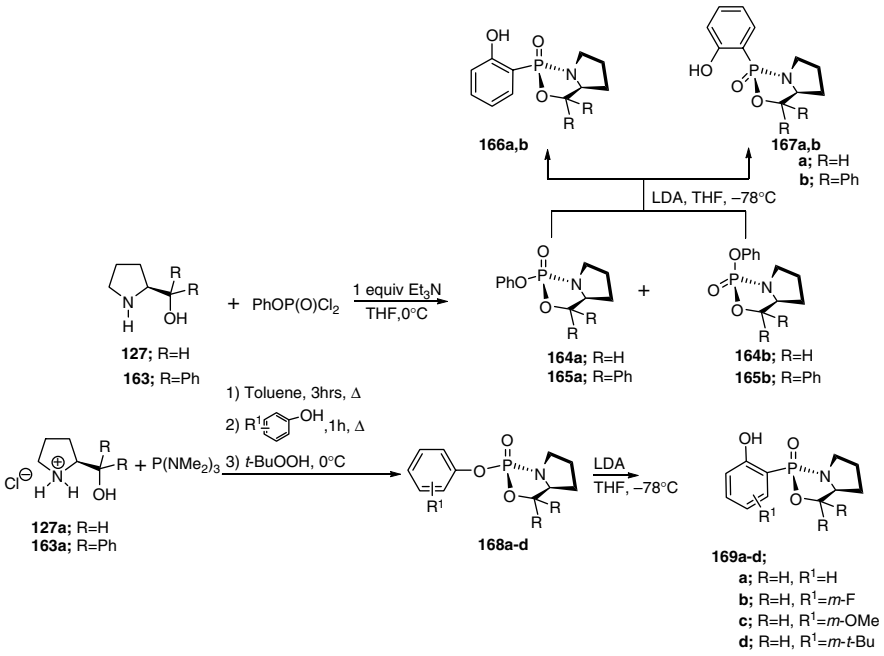
The pure diastereomer **158a** was isolated in 67% yield by recrystallization of the crude reaction mixture containing **158a** and **158b** in the ratio of 93:7. It was converted stereospecifically to (2*S*,4*R*,5*R*)-2-propenyl-1,3,2 oxazaphospholidine-2-oxide **159a** upon treatment with allylmagnesium bromide. This diastereomer was also generated by the coupling reaction of alcohol **157** with 2-propene-1-phosphonyl dichloride in the presence of triethylamine (Scheme 44) [75]. However, this condensation gave a 1:1 mixture of **159a** and its 2-*R* isomer **159b.**

2-Phenoxy-1,3,2 oxazaphospholidine-2-oxides **161a and 161b** were formed stereoselectively in the reaction of (*S*)-2,3-dimethyl-2-amino-1-butanol **160** with phenyl phosphonodichloride **37c** in the presence of triethylamine (Scheme 45) [76]. The crude reaction mixture containing **161a and 161b** in a ratio of 3:1, was separated chromatographically, and subjected to a P–O to P–C rearrangement by reacting with LDA in THF at −78°C giving stereospecifically diastereomerically pure *o*-hydroxyaryl phosphine oxides **162a** and **162b** respectively (Scheme 45) [76].

A similar synthesis of chiral (*o*-hydroxyaryl)oxazaphospholidine oxides **166a–b**, **167a–b,** and **169a–d** derived from (*S*)-prolinol **127** and its diphenyl derivative **163** was achieved from precursors **164a–b**, **165a–b,** and **168** which were easily available from two different procedures as outlined in Scheme 46 [77]. The first pathway gave the two expected diastereomers of **164** and **165** in a ratio



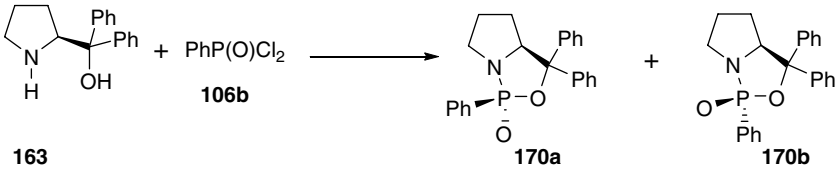
Scheme 45 Synthesis of diastereomerically pure *o*-hydroxyaryl phosphine oxides **162a** and **162b**



Scheme 46 Synthesis of (*o*-hydroxyaryl)oxazaphospholidine oxides **166a–b** and **167a–b** and (*o*-hydroxyaryl)oxazaphospholidine oxides **169a–d**

varying from 50:50 to 70:30, depending on the nature of the R groups. On the other hand, diastereomerically pure precursors **168** were easily available by exchange at 110°C in toluene between tris(dimethylamino)phosphane and (*S*)-prolinol hydrochloride (**127a**) or (*S*)-diphenylprolinol hydrochloride (**163a**) followed by addition of the desired phenol**.** Oxidation of crude phosphanes with *tert*-butylhydroperoxide afforded the expected compounds **168a–d** in yields ranging from 62 to 82%. They were converted to the diastereomerically pure *o*-hydroxyarylphosphine oxides **169a–d** by reacting with LDA in THF.

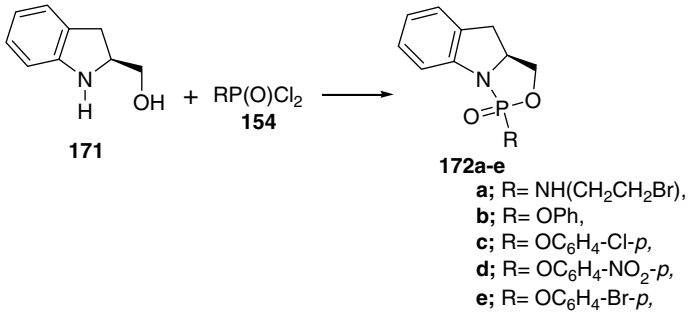
2-Phenyl-1,3,2 oxazaphospholidine-2-oxides **170a** and **170b** were formed as a 7:1 diastereomeric mixture in the reaction of (*S*)-diphenylprolinol (**163**) and phenylphosphonic dichloride in the presence of triethylamine (Scheme 47) [78].



Scheme 47 Synthesis of 2-phenyl-1,3,2 oxazaphospholidine-2-oxides **170a** and **170b**

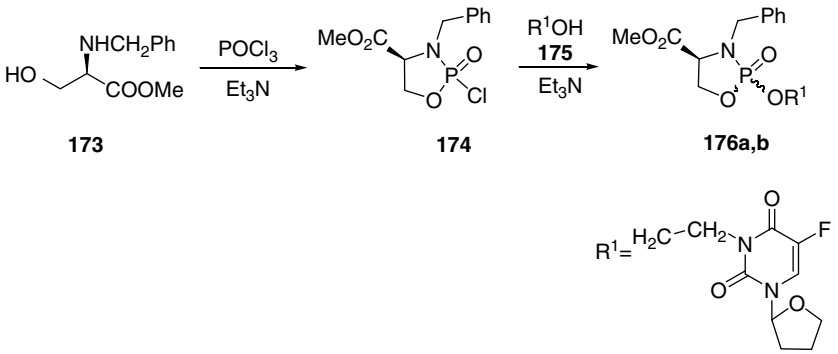
They were applied as effective reagents for the asymmetric reduction of ketones with borane.

Reaction of the (*S*)-amino alcohol **171** with *N*-(2-bromoethyl)phosphoramidic dichloride or aryl phosphonodichloridates **154** in the presence of triethylamine led to the formation of a single diastereomer in each case of 1,3,2 oxazaphospholidine-2-ones **172a–e** (taking into consideration that in the ^{31}P-NMR spectra only one singlet in the range 6.49–2.45 ppm was observed) (Scheme 48) [79].



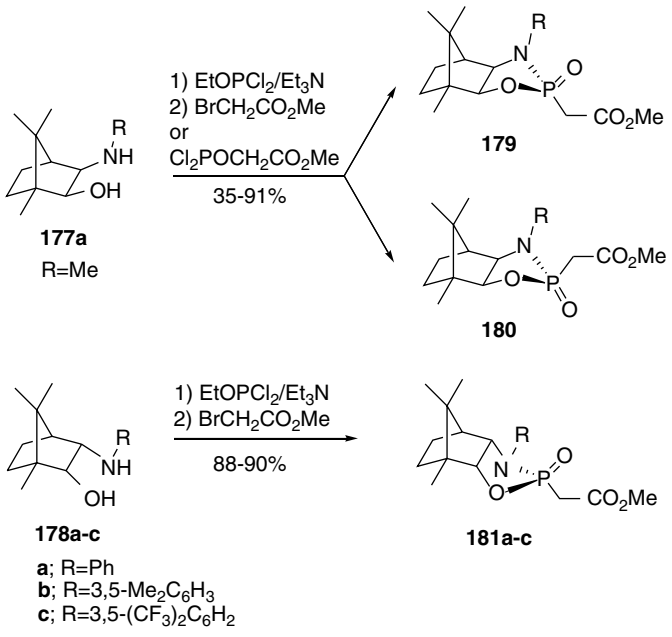
Scheme 48 Synthesis of 1,3,2 oxazaphospholidine-2-ones **172a–e**

N-Benzyl-*O*-methyl-L-serinoate (**173**) was condensed with phosphoryl trichloride giving cyclic chloridate **174** that reacted with the Tegafur derivative **175** with the formation of almost equal amounts of 2-alkoxy-1,3,2 oxazaphospholidine-2-oxides **176a** and **176b** (Scheme 49) [80].



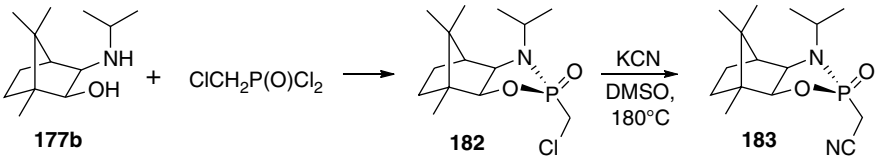
Scheme 49 Synthesis of 2-alkoxy-1,3,2 oxazaphospholidine-2-oxides **176a** and **176b**

A rich family of 2-alkoxycarbonyl-1,3,2-oxazaphospholidine-2-oxides **179–181** was prepared from the reaction of camphor derived aminoalcohols **177** and **178** with either methoxycarbonyl phosphonic dichloride or ethyl dichlorophosphite followed by the reaction with methyl bromoacetate. The reaction with aminoalcohol **177a** afforded the phosphorus epimers **179** and **180,** in ratios from 1/1 to 12/1 depending on the *N*-substituent which could be separated easily by column chromatography. The reaction with aminoalcohols **178a–c,** however, gave a single epimer **181a–c** in each case (Scheme 50) [81].



Scheme 50 Synthesis of 2-alkoxycarbonyl-1,3,2-oxazaphospholidine-2-oxides **179–181**

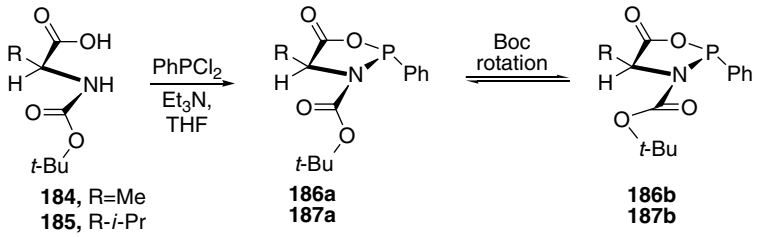
A similar condensation of **177b** with chloromethyl phosphonic dichloride gave 2-chloromethyl-1,3,2-oxazaphospholidine-2-oxide **182** which was converted into the cyano derivative **183** by reaction with potassium cyanide in anhydrous dimethyl-sulfoxide (Scheme 51) [82].



Scheme 51 Synthesis of 2-chloromethyl-1,3,2-oxazaphospholidine-2-oxide **182** and its conversion into the cyano derivative **183**

3.3 Other 1,3,2-Oxazaphospholanes

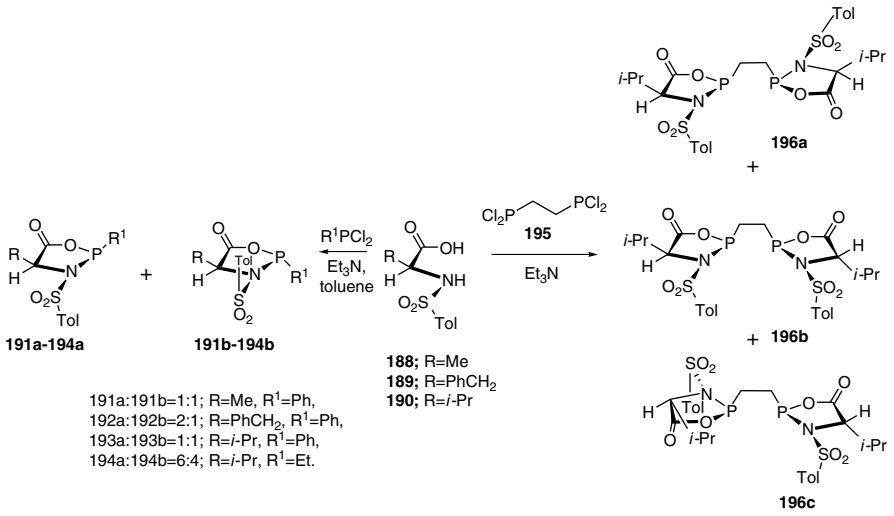
The reaction of *N*-Boc protected amino acids alanine (**184**) and valine (**185**) with phenyldichlorophosphine in the presence of NEt_3 was reported to lead to the clean formation of essentially one compound in each case, the P-chiral, tricoordinated, 1,3,2-oxazaphospholidinones **186** and **187** respectively (Scheme 52) [83].



Scheme 52 Synthesis of 1,3,2-oxazaphospholidinones **186** and **187**

The isolated compounds were found to be sensitive to a number of conditions that were not completely reproducible. Thus, upon standing at room temperature under nitrogen, the lifetimes vary from 1 day to many weeks, and standing at room temperature under vacuum gave the same variability. It is interesting to note that the ^{1}H-NMR spectra of both compounds were broadened by a dynamic process which was attributed to Boc rotation generating rotational isomers **186a–b** and **187a–b** (Scheme 52) [83].

A similar reaction of *N*-toluenesulfonyl derivatives of (*S*)-alanine, phenylalanine, and valine (**188–190**) with $PhPCl_2$ gave 4-methyl, benzyl, and isopropyl derivatives of 2-phenyl-1-*p*-toluenesulfonyl-1,3,2-oxazaphospholidin-5-one, **191–193** in high yields (Scheme 53) [84]. The ratios of the (2*S*,4*S*)/(2*R*,4*S*) diastereomers (which were designated as *cis/trans* isomers) were 1:1, 2:1, and 10:1 for **191a**,**b**, **192a**,**b**, and

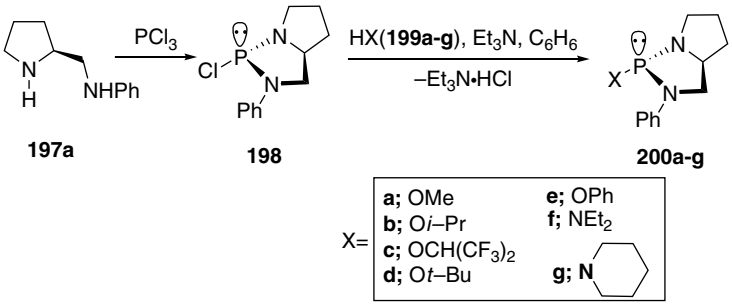


Scheme 53 Synthesis of 2-phenyl-1-*p*-toluenesulfonyl-1,3,2-oxazaphospholidin-5-one **191–193** and the *cis/cis*, *cis/trans*, and *trans/trans* diphosphorus heterocycles **196a–c**

193a,**b**, respectively. In the case of **191a**,**b**, both isomers were isolated by crystallization, but in other cases, only the major isomer could be separated. The X-ray crystal structure analysis of **193a** shows that the isopropyl and phenyl groups are mutually *cis* and that the tolyl moiety is oriented s-*trans* to both the isopropyl and phenyl groups. Reaction of **190** with **195** gave a 56:38:7 mixture of the *cis/cis*, *cis/trans*, and *trans/trans* diphosphorus heterocycles **196a–c**. The major isomer, **196a** was isolated free of the other diastereomers by crystallization. Reaction of **190** with $EtPCl_2$ gave a 6:1 mixture of *cis/trans* isomers of the ethyl-substituted heterocycles **194a**,**b** as an inseparable oil (Scheme 53) [84].

4 1,3,2-Diazaphospholanes

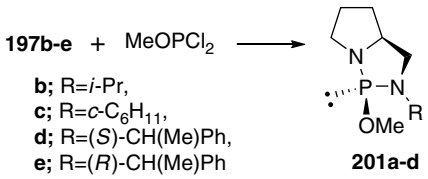
Diastereomerically pure (2*R*,5*S*)-1,3-diaza-2-chloro-3-phenyl-2-phosphabicyclo[3.3.0] octane (**198**), the first example of an optically active 2-chloro- 1,3,2-diazaphospholane, was very recently prepared by the reaction of (*S*)-2-anilinomethyl)-pyrrolidine (**197a**) with phosphorus trichloride in the presence of NEt_3 (Scheme 54) [14]. A one-step phosphorylation of the corresponding alcohols or amines **199a–g** with this reagent gave a series of monodentate diamidophosphites **200a–g** (Scheme 54) [14]. The ^{31}P NMR spectroscopic data for **200a–g** indicated that while compounds **200a–c** and **200f** were formed as single stereoisomer in each case, **200d–e** and **200g** each contained from 2 to 26% of the second stereoisomer. In all cases, the major stereoisomer has a pseudoequatorial orientation of the exocyclic substituent at the phosphorus atom (this induces *R* configuration at the *P* stereocenter). Very recently, this methodology has been extended to the preparation of (2*R*,5*S*)-1,3-diaza-2-alkoxy-3-phenyl-2-phosphabicyclo[3.3.0]octanes (**200**) derived from terpene alcohols.



Scheme 54 Synthesis of (2*R*,5*S*)-1,3-diaza-2-chloro-3-phenyl-2-phosphabicyclo[3.3.0]octane **198**

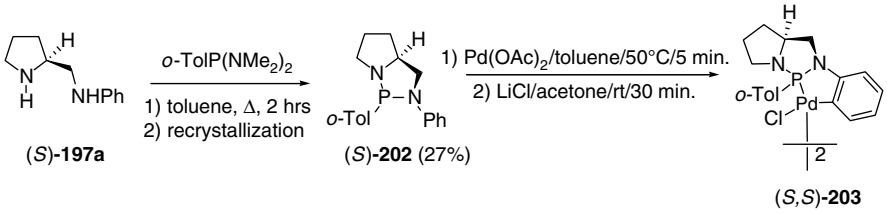
The isolated bicyclic derivatives induced very high stereoselectivity (ee's up to 99%) in the Pd catalyzed allylic substitution reaction [85].

Almost diastereomerically pure (2*R*,5*S*)-1,3-diaza-2-methoxy-3-alkyl-2-phosphabicyclo[3.3.0]octanes (**201a–d**) were formed in the reaction of (*S*)-2-anilinomethyl)-pyrrolidines (**197b–e**) with methyl dichlorophosphite in the presence of NEt_3 (Scheme 55) [86]. With these ligands, high stereoselectivity (ee's up to 91%) was observed in the Pd catalyzed allylic amination reaction [86].



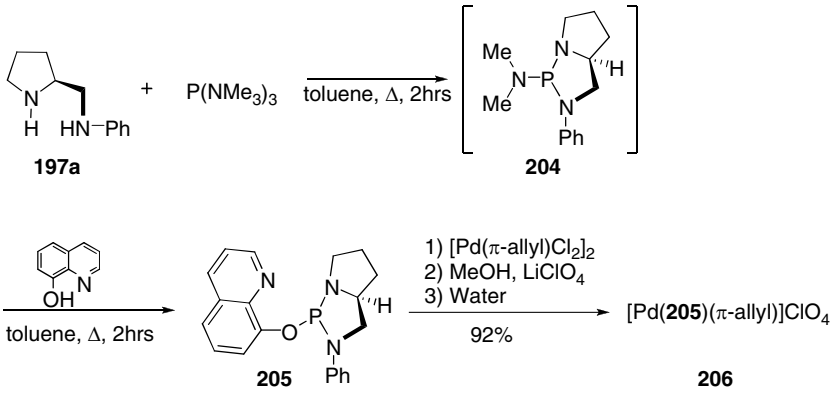
Scheme 55 Synthesis of (2*R*,5*S*)-1,3-diaza-2-methoxy-3-alkyl-2-phosphabicyclo[3.3.0]octanes **201a–d**

Diastereomerically pure (2*R*,5*S*)-1,3-diaza-2-(2-methylphenyl)-3-phenyl-2-phosphabicyclo[3.3.0]octane [(*S*)-**202**] was formed in the thermal reaction of (*S*)-2-(anilinomethyl)pyrrolidines (**197a**) with *o*-TolP$(NMe_2)_2$ and isolated in 27% yield after recrystallization (Scheme 56) [87]. Its cyclopalladation with palladium diacetate followed by anion metathesis gave dimer (*S,S*)-**203** (Scheme 56) [87].



Scheme 56 Synthesis of (2*R*,5*S*)-1,3-diaza-2-(2-methylphenyl)-3-phenyl-2-phosphabicyclo[3.3.0]octane **202** and its conversion to dimer **203**

A useful method for large-scale synthesis of diastereomerically pure (2*R*,5*S*)-3-phenyl-2-(8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane (**205**) was based on a similar reaction of tris(dimethylamino)phosphine with (*S*)-**197a** generating the intermediate **204** which, by addition of 8-hydoxyquinoline followed by additional refluxing gave the final product. Recrystallization of the crude reaction mixture afforded diastereomerically pure **205** as a solid, stable to air and moisture in 98% yield (Scheme 57) [88]. It was converted to complex **206** by mixing with



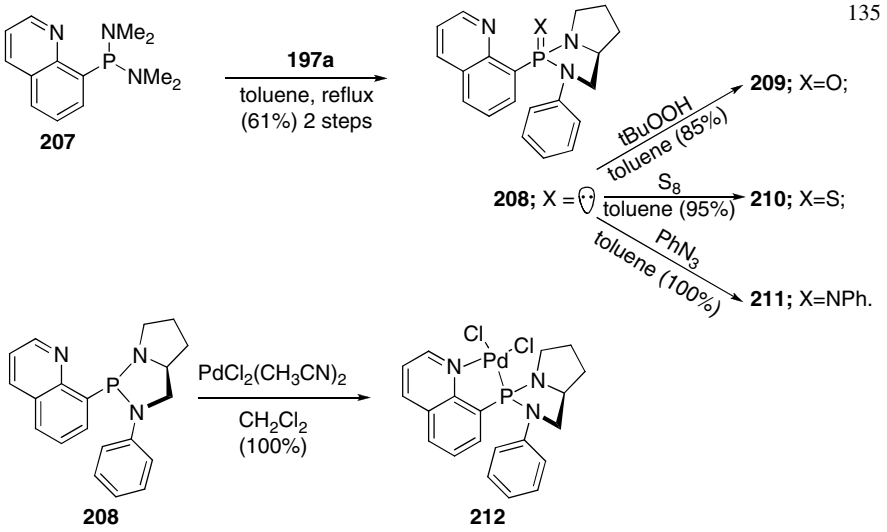
197a 204 205 206

Scheme 57 Synthesis of diastereomerically pure (2*R*,5*S*)-3-phenyl-2-(8-quinolinoxy)-1,3-diaza-2-phosphabicyclo[3.3.0]octane **205** and its conversion to complex **206**

an equimolar amount of bis(dichloro)bis(π−allyl)dipalladium in methanol, followed by addition of $LiClO_4$. Recrystallization afforded the expected palladium complex **206** in 92% yield as crystalline solid, stable to air and moisture (Scheme 57) [88]. Its X-ray analysis supported the proposed structure for **205** with *R* absolute configuration at the tricoordinated phosphorus and showed its bidentate chelating ability towards Pd through the phosphorus atom and the nitrogen atom of the quinoline ring (Scheme 57) [88].

A fully diastereoselective exchange reaction between 8-bis(dimethylaminophosphinyl)-quinoline (**207**) and (*S*)-2-(anilinomethyl)pyrrolidine (**197a**) afforded another ligand with a tricoordinated phosphorus atom characterized as the pure diasteromer **208**. It was converted into the diazaphospholidine P-oxide **209** and the corresponding P-sulfide **210** by reaction with *t*-butylhydroperoxide or sulfur respectively. Its reaction with phenyl azide gave the chiral iminodivazaphospholidine **211** having two different basic amine sites closely positioned to accept a proton between the nitrogens. Mixing an equimolar amount of $PdCl_2(CH_3CN)_2$ and ligand **208** in methylene chloride gave complex **212** in quantitative yield (Scheme 58) [89]. The X-ray analysis of the latter confirmed the chelating ability of ligand **208** towards palladium and the S_P absolute configuration of the phosphorus atom [89].

A highly diastereoselective exchange reaction between a variety of bis(dimethylamino)arylphosphines and (*S*)-2-(anilinomethyl)pyrrolidine (**197a**) and its *N*-aryl analogues constituted a key step in the synthesis of a series of substituted monodonor diazaphospholidine ligands, **213–220** [90, 91] (Figure 1).



Scheme 58 Synthesis of diazaphospholidine **208** and its conversion to complex **212**

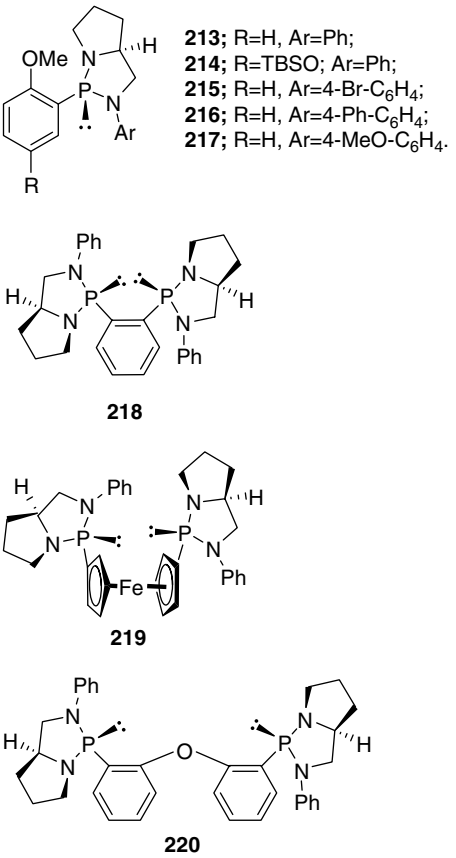
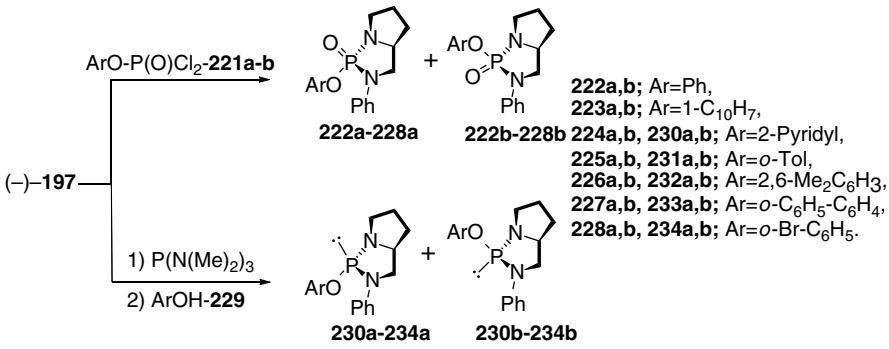


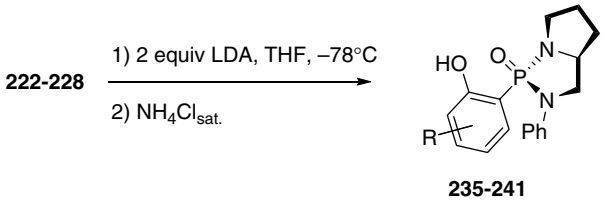
Figure 1

Exchange reactions between aryl phosphorodichloridates **221a–b** and (*S*)-2-(anilinomethyl)pyrrolidine (**197**) afforded the two expected diastereomers of diazaphospholidines **222–223** in a diastereomeric ratio ranging from 60:40 to 50:50 with yields from 76 to 95% (Scheme 59) [76]. On the other hand, only one diastereomer of each of the diazaphospholidines **224–228** was isolated by exchange reactions between tris(dimethylamino)phosphine and (*S*)-2-(anilinomethyl)pyrrolidine (**197**) followed by addition of the desired phenol **229** and oxidation of the crude diaminophosphites **230–234** with tert-butylhydroperoxide (Scheme 59) [76, 92].



Scheme 59 Synthesis of diazaphospholidine derivatives **222–234**

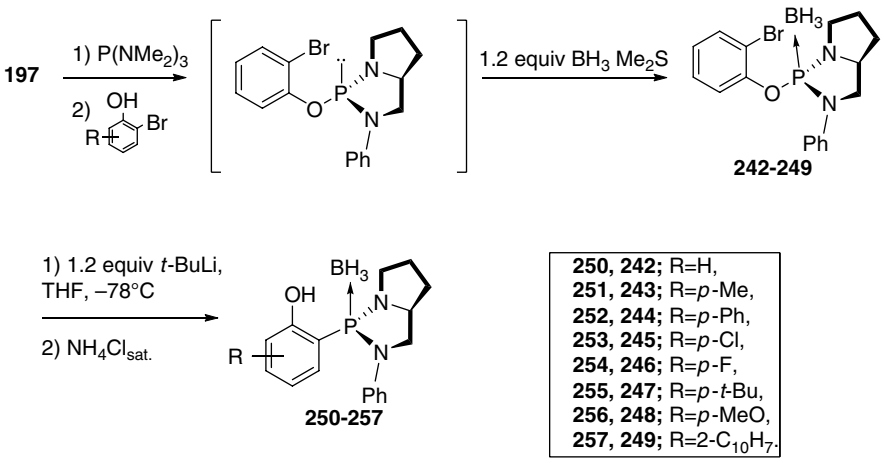
The prepared diazaphospholidines **222–228** were converted stereospecifically to the corresponding *o*-hydroxyarylphosphonamides **235–241** via [1, 3] P–O to P–C rearrangement (Scheme 60) [76, 92].



Scheme 60 Synthesis of *o*-hydroxyarylphosphonamides **235–241** via [1, 3] P–O to P–C rearrangement of diazaphospholidines **222–228**

This methodology was applied successfully also for the diastereoselective synthesis of a series of P-stereogenic (o-hydroxyaryl)diazaphospholidine – borane complexes **250–257** (yields ranging from 40 to 86%) via the reaction sequence shown in Scheme 61 with a one-pot formation of the appropriate (*o*-bromoaryloxy) diazaphospholidine-borane complexes **242–249** in yields ranging from 70 to 92% (Scheme 61) [93].

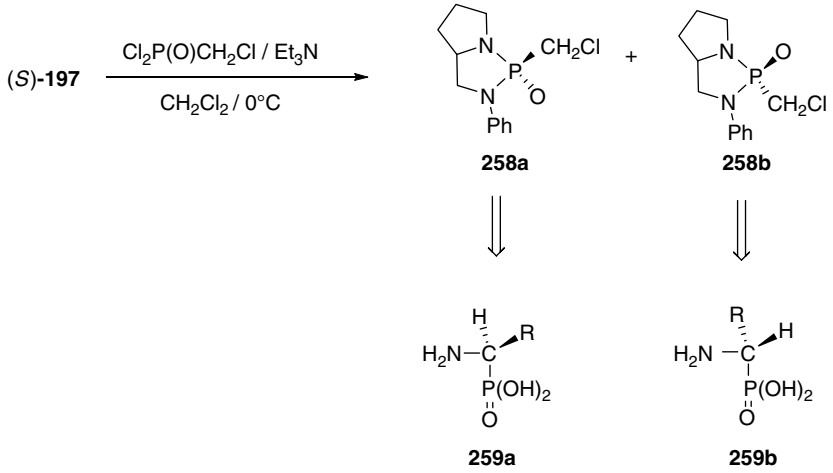
Reaction of **197** with chloromethylphosphonyl dichloride gave a mixture of **258a** and **258b**, which were conveniently separated by column chromatography.



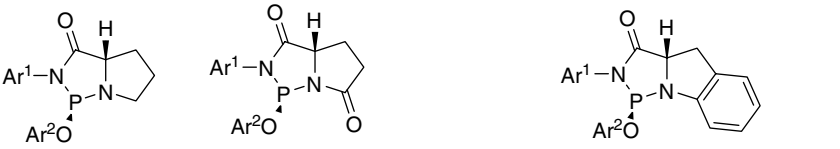
Scheme 61 Synthesis of P-stereogenic (o-hydroxyaryl)diazaphospholidine – borane complexes **250–257**

The isolated, pure diastereomers were used as key substrates for the preparation of enantiomerically pure α-aminoalkylphosphonic acids **259a** and **259b** (Scheme 62) [94].

A rich family of diazaphospholes **260–262** having hexahydro-1*H*-pyrrolo [1,2-*c*][1, 3, 2]diazaphosphole backbone was readily prepared by the reaction of phenylphosphorodichloridite or another P(III) precursor with anilides of (*S*)-proline, (*S*)-pyroglutamic acid , and (*S*)-indoline carboxylic acid in high yields diastereoselectively [95].



Scheme 62 Synthesis of enantiomerically pure α-aminoalkylphosphonic acids **259a** and **259b**



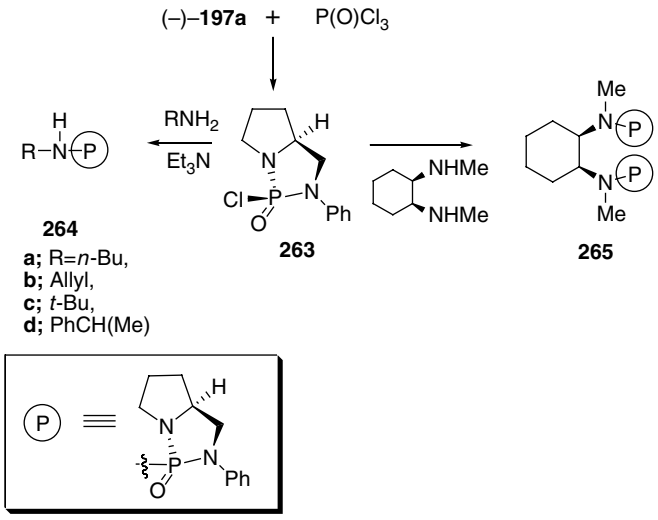
260
a; Ar^1=Ph; Ar^2=Ph

261
a; Ar^1=Ph; Ar^2=Ph
b; Ar^1=2,6-Me_2-C_6H_3; Ar^2=Ph
c; Ar^1=3,5-*i*-Pr_2-C_6H_3; Ar^2=Ph

262
a; Ar^1=Ph; Ar^2=2,6-Me_2-C_6H_3

Figure 2

A number of 1,3,2-diazaphospholidine derivatives **264–265** having (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo[3.3.0]octene moiety (labeled as P) were prepared using diastereomerically pure (5*S*)-1,3-diaza-2-chloro-2-phospha-2-oxo-3-phenylbicyclo[3.3.0]octane (**263**) as a key substrate. Its preparation was in turn based on the reaction of phosphoryl chloride with (-)-**197** (Scheme 63) [96–100].



264
a; R=*n*-Bu,
b; Allyl,
c; *t*-Bu,
d; PhCH(Me)

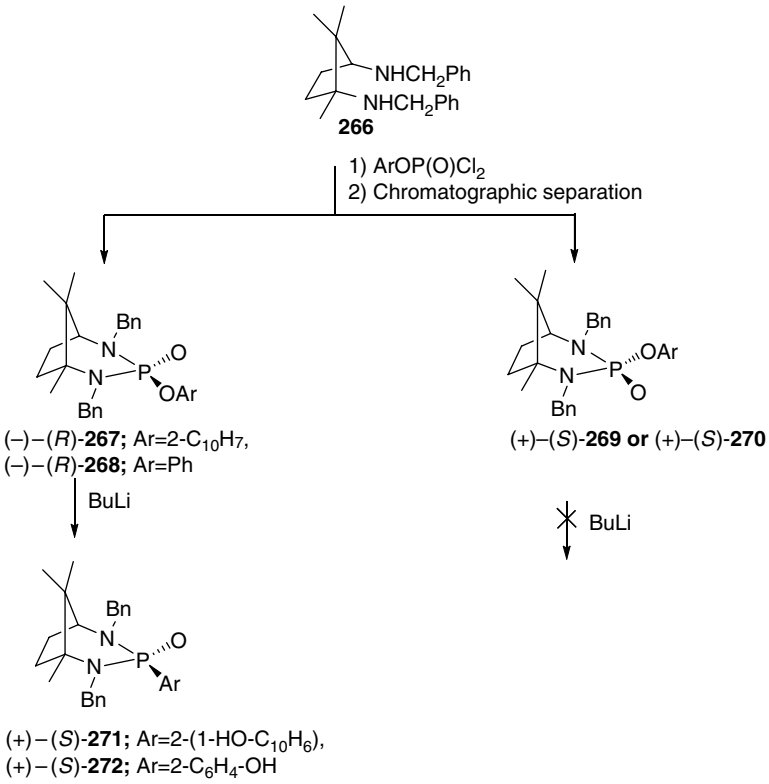
263

265

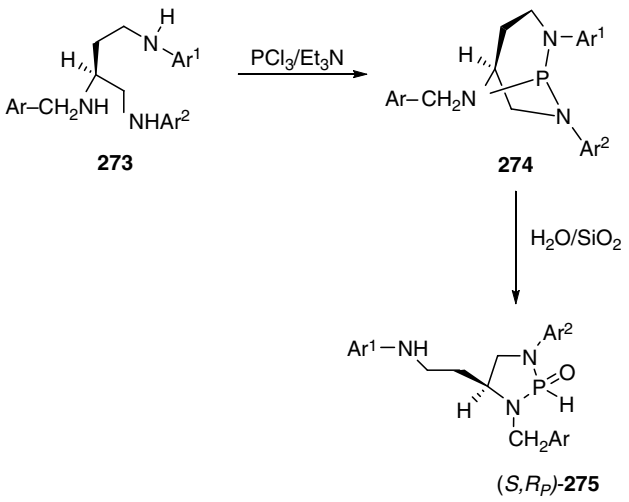
Scheme 63 Synthesis of 1,3,2-diazaphospholidine derivatives **264–265**

Two bifunctional *o*-hydroxyarylphosphorodiamidates **271, 272** were prepared starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-di-(*N*-benzyl)amine (**266**) via P–O to P–C rearrangement of the corresponding diastereomeric phosphorodiamidates **267–268** separated on column chromatography. It may be mentioned that in the rearrangement of diastereomeric phosphorodiamidates **269–270**, no desired product was obtained (Scheme 64) [101].

A number of P-chirogenic diaminophosphine oxides (DIAPHOXs) **275** derived from aspartic acid were prepared via hydrolysis of triaminophosphine intermediate **274**, generated in a fully diastereoselective reaction of triamines **273** with phosphorus trichloride (Scheme 65) [102, 103].

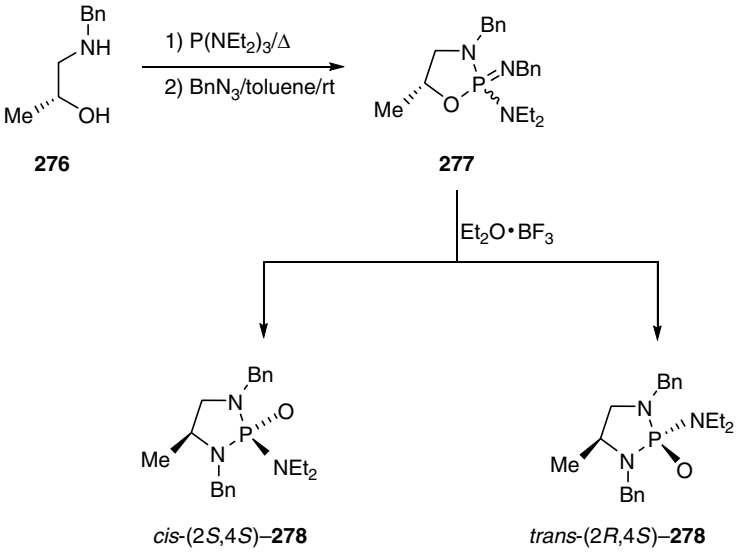


Scheme 64 Synthesis of bifunctional *o*-hydroxyarylphosphorodiamidates **271** and **272**



Scheme 65 Synthesis of diaminophosphine oxides (DIAPHOXs) **275**

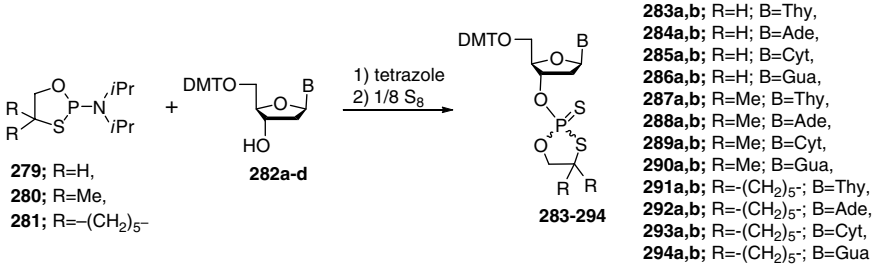
Chiral diazaphosphoramides **278** were obtained from imide–amide rearrangement of the corresponding oxazaphosphorimidate precursors **277** derived from optically active (*R*)-*N*-1-benzylaminopropan-2-ol (**276**) (Scheme 66) [104].



Scheme 66 Synthesis of diazaphosphoramides **278**

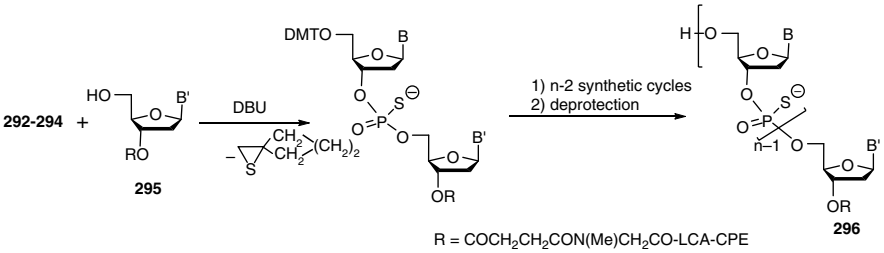
5 1,3,2-Oxathiaphospholanes

A series of diastereomerically pure 5′-*O*-DMT-nucleoside 3′-*O*-(2-thio-1,3,2-oxathiaphospholanes) and their oxathiaphospholane ring-substituted analogues **283–294** were isolated in 80–83% yield by column chromatography on silica gel of the appropriate diastereomeric mixtures [the ratio ca 55:45 (^{31}P NMR assay)] obtained from the reaction of 2-*N,N*-diisopropylamino- 1,3,2-oxathiaphospholane **279–281** with 5′-*O*-DMT-nucleosides **282a–d** in the presence of tetrazole (phosphitylation), followed by addition of sulfur (Scheme 67) [105–107].



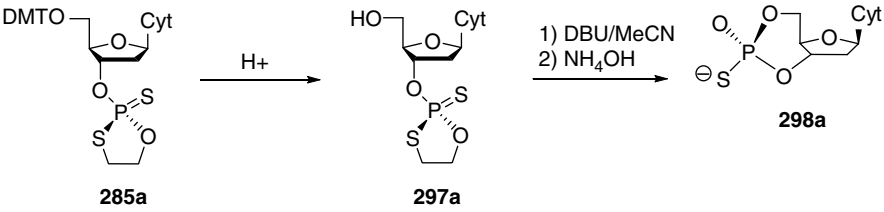
Scheme 67 Synthesis of diastereomerically pure 5'-*O*-DMT-nucleoside 3'-*O*-(2-thio-1,3,2-oxathiaphospholanes) and its oxathiaphospholane ring-substituted analogues **283–294**

The selected pure diastereomers were used for the synthesis of stereoregular oligonucleoside phosphorothioates (S-Oligos) having the general structure **296** with the use of 5′-*O*-DMT-nucleosides **295** immobilized on controlled pore glass via a DBU-resistant saracosinyl-succinoyl linker (Scheme 68) [105].



Scheme 68 Synthesis of stereoregular oligonuc1eosidephosphorothioates **296**

It is of interest to note that diastereomerically pure S_P- and R_PN^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholanes **297a** and **297b**, ,which were prepared from chromatographically separated S_P- and R_P-5′-*O*-DMT-precursors **285a** and **285b**, after 5 min treatment at room temperature with equimolar amount of DBU in anhydrous acetonitrile gave quantitatively S_P- and R_P-deoxycytidine cyclic 3′5′-*O,O*-phosphorothioates **298a** and **298b**. (in scheme 69 only the "**a**" diastereoisomers are shown) The adjacent mechanism of this intramolecular

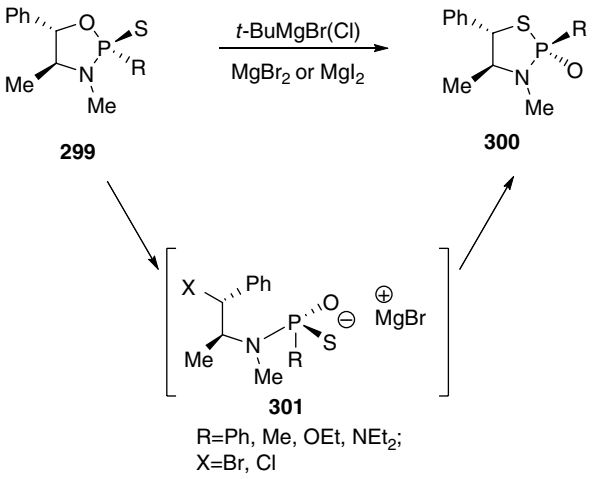


Scheme 69 Synthesis of deoxycytidine cyclic 3',5'-*O,O*-phosphorothioates **298a** and **298b**

cyclization was suggested to be responsible for the retention of configuration at phosphorus (Scheme 69) [107].

6 1,3,2-Azathiaphospholanes

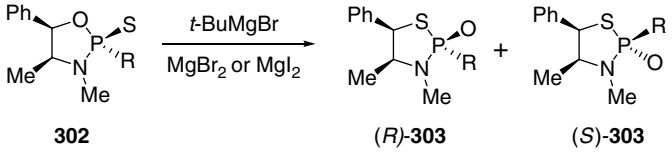
The initial C–O bond cleavage (by attack of a/the bromide ion at the benzylic carbon, followed by recyclization of the intermediate **301** by selective alkylation at sulfur) was suggested to be responsible for a stereospecific rearrangement of 2-substituted-1,3,2 -oxazaphospholidine-2-thiones **299** derived from (-) pseudoephedrine into



Scheme 70 Stereospecific rearrangement of 2-substituted- 1,3,2-oxazaphospholidine-2-thiones **299**

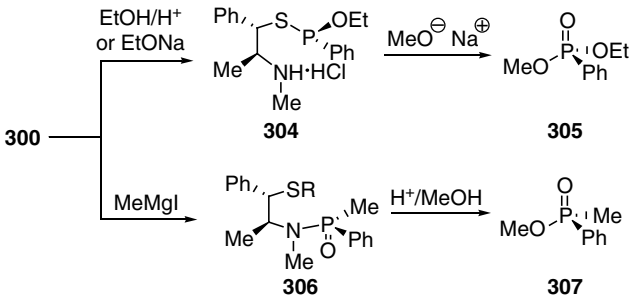
the corresponding 1,3,2-thiazaphospholidine-2-ones **300** occurring during heating of **299** and *t*-butylmagnesium chloride (or magnesium bromide) (Scheme 70) [108, 109].

It is of interest to note that in the case of oxaazaphosphospholidines **302** derived from (-)-ephedrine (**42**), some inversion at the benzylic carbon occurred giving a mixture of the *P*-epimeric derivatives **303** (Scheme 71) [108]. Halide exchange with inversion of configuration in the intermediate was suggested as the most likely explanation for the loss of stereospecificity.



Scheme 71 Stereospecific rearrangement of oxaazaphosphospholidines **302**

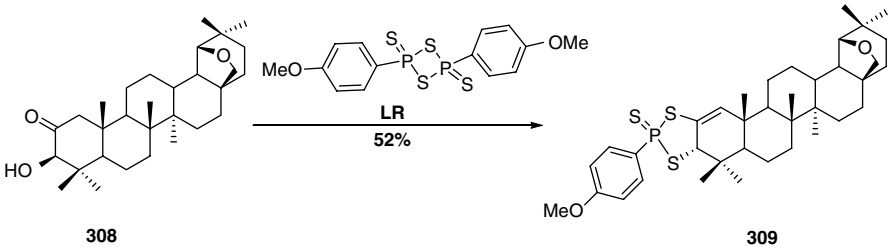
The phosphonyl adduct **300** reacted with a dilute solution of anhydrous hydrogen chloride in ethanol or with sodium ethoxide to afford an essentially quantitative yield of the P–N cleaved product **304** with inversion of configuration. Addition of sodium ethoxide to a solution of **304** in methanol resulted in the formation of enantiomerically pure (+)-(*S*)-ethyl methyl phenylphosphonate (**305**). It also reacted quantitatively with methylmagnesium iodide at room temperature to give the product of P–S bond cleavage **306**, which upon acid catalyzed methanolysis afforded enantiomerically pure (+)-(*R*)- methyl methylphenylphosphinate (**307**) (Scheme 72) [108].



Scheme 72 Interconversions of phosphonyl adduct **300**

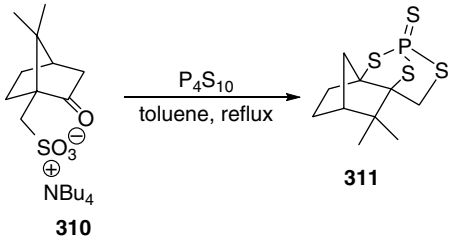
7 1,3,2-Dithiaphospholanes

Reaction of hydroxyketone **308** with Lawesson's reagent afforded dithiaphospholane **309** as a single P-diastereomer in 52% yield after HPLC purification (Scheme 73) [110].



Scheme 73 Reaction of hydroxyketone **308** with Lawesson's reagent leading to dithiaphospholane **309**

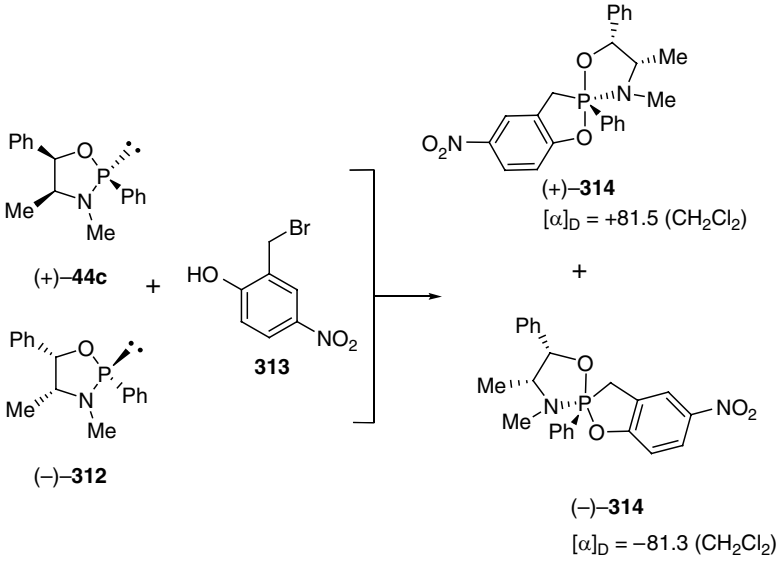
Earlier, the first chiral tetrathiophosphate derivative **311**, in which one can recognize 1,3,2-dithiaphospholane subunits, was synthesized in good yield by reacting tetrabutylammonium camphoryl-D-sulfonate (**310**) with phosphorus pentasulfide (Scheme 74) [111].



Scheme 74 Synthesis of chiral tetrathiophosphate derivative **311**

8 Hypervalent Structures with a Pentacoordinated Phosphorus and Two Five-Membered Rings

On reacting each enantiomer of the chiral 1,3,2-oxazaphospholidine (+)-**44c** and (−)-**312** with one equivalent of **313,** a mixture of spirophosphoranes **314** was formed. They were stable enough to be isolated by flash chromatography giving:(+)-**314** and (−)-**314** from (+)-**44c** and (−)-**312** respectively. The assignment of absolute configurations to the two enantiomers of **314** was based on the absolute configuration of the starting tricoordinate derivatives (+)-**44c,** (−)-**312** and the rule setting the oxygen atoms in apical positions (Scheme 75) [112].



Scheme 75 Synthesis of optically active spirophosphoranes **314**

Acknowledgments This account was in part financially supported (as grant PDZ-KBN-126-TO9/2004 for J.D.) in the frame of a scientific project by the government fund created to support science in the 2006–2009 period.

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Top Heterocycl Chem (2010) 21: 149–173
DOI 10.1007/7081_2009_19

Published online: 4 February 2010

1-(2,4,6-Trialkylphenyl)-1*H*-Phospholes with a Flattened P-Pyramid: Synthesis and Reactivity

György Keglevich

Abstract The 1*H*-phospholes with a 2,4,6-trialkylphenyl substituent on the phosphorus atom synthesized in our laboratories are of aromatic character due to their flattened P-pyramid. Hence, they may undergo aromatic electrophilic substitution, such as Friedel–Crafts acylations. The arylphospholes were functionalized via the regioselective reaction with phosphorus tribromide to give substituted phospholes that may be ligands in rhodium complexes used in hydroformylations. Despite their aromaticity, the arylphospholes may be involved in Diels–Alder cycloaddition with dienophiles to provide 7-phosphanorbornene derivatives useful in fragmentation – related phosphorylations. At elevated temperature, the aryl-1*H*-phospholes were converted to the 2*H*-derivatives by a sigmatropic rearrangement to furnish, after trapping, 1-phosphanorbornadienes. The complexation and the oxidation reactions of the sterically hindered arylphospholes are also discussed.

Keywords 1-Aryl-1*H*-phospholes • Aromaticity • Reactions • Sterically demanding P-substituent • Synthesis

Contents

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1 Introduction: 1*H*-Phospholes

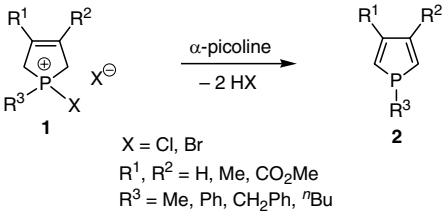
The phosphacyclopentadienes with phosphine function are called 1*H*-phospholes and they form an important part of contemporary P-heterocyclic chemistry. Phosphole chemistry has undergone an intensive development, which is well demonstrated by the fact that while in the first edition of *Comprehensive Heterocyclic Chemistry* (1984), only several pages were devoted to phospholes [1], the second edition (1996) discusses this topic in a lengthy chapter [2]. Besides these, exhaustive monographs have been published in P-heterocyclic chemistry also incorporating the new developments of phosphole chemistry [3, 4]. The first review in the subject was written by Mathey [5].

Recent reviews on 1*H*-phospholes were published by Mathey in *Science of Synthesis* [6] and by Quin in *Current Organic Chemistry* [7]. Reau and co-workers performed intensive research in the subject of p-conjugated systems incorporating phosphole and other heteroles, such as thiophene and silole and the results were summarized in review articles [8–12]. This line was explored further by Hiroshi et al. in respect of benzophospholes and dibenzophospholes [13], as well as phosphole-containing calixpyrroles, calixphyrins, and porphyrins [14]. Börner et al. reviewed, among others, heterocyclic P-ligands, including phospholes and their application in catalysis [15, 16]. Pyridylphospholes and phospholyl species, the important ligands in coordination chemistry [17], are utilized in phosphametallocenes [18]. In a related field to phospholes, Bansal et al. summarized the recent results on heterophospholes, including diazaphospholes, oxadiphospholes, and analogs, as well as triphospholes [19–22]. The chemistry of transient 2H-hospholes was reviewed by Mathey [23].

Beside aromaticity and syntheses there are a number of reactions, such as substitutions, (cyclo)additions, modification of the phosphorus atom, rearrangements, conversion to metallic derivatives and to coordination complexes, etc. that may be of interest due to the unique features.

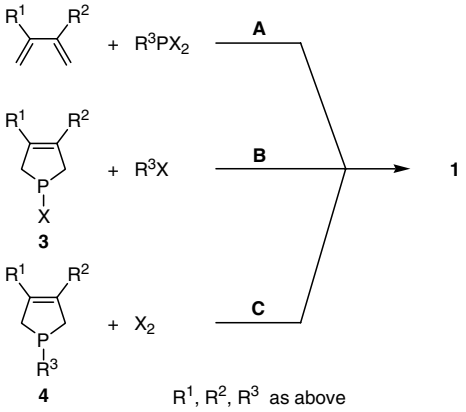
At the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, we have been dealing with the synthesis and utilization of P-heterocycles for more than two decades. In this chapter, the synthesis and properties of phospholes with bulky substituent on the phosphorus atom are described.

A practical synthesis of phospholes (**2**) was suggested by Mathey. The method involves the double dehydrohalogenation of phospholium salts (**1**) by a suitable base, such as α-picoline to give the phospholes in good yields (Scheme 1) [24, 25].



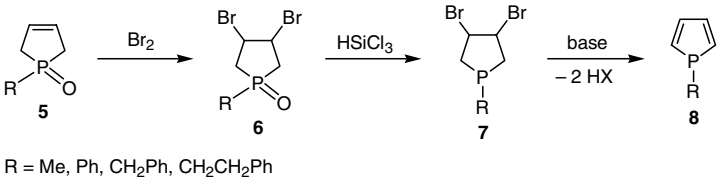
Scheme 1 A practical method for the synthesis of phospholes

The phospholium salts (**1**) are available from the McCormack cycloaddition of butadiene derivatives with phosphonous dihalogenides (Route A/Scheme 2) [26–28], from quaternization of chlorophospholenes (**3**) with alkylhalogenides (Route B/Scheme 2) [29] or from the reaction of alkylphospholenes (**4**) with bromine or chlorine (Route C/Scheme 2) [29]. In the latter case, the halogen reacts selectively with the phosphorus atom.



Scheme 2 Possibilities for the preparation of phospholium salts

A less efficient method for the preparation of phospholes involves the bromination of phospholene oxides (**5**), the deoxygenation of the dibromophospholane oxides (**6**) so obtained with trichlorosilane, and finally dehydrobromination of dibromophospholanes **7** (Scheme 3) [30, 31].



Scheme 3 A historical route to phospholes

One may consider phospholes to belong to the family of five-membered P-heterocycles pyrrole, furan, and thiophene. A significant difference, however, is that the phospholes described in the literature display only a slight extent of aromaticity. This is well demonstrated by the comparison of the Bird-indexes [32] of benzylphosphole [33], furan, pyrrole, and thiophene (Fig. 1). The Bird-index is an indicator of aromaticity based on the bond-equalizaton. It is the maximum (100) for benzene.

Beside the bigger size of the phosphorus atom, as compared to that of nitrogen, the lack of aromaticity is due to the P-pyramide: the criterion of coplanarity is not fulfilled and so the lone electron pair of the phosphorus cannot overlap with the p_z orbitals of the sp^2 carbon atoms (Fig. 2). While in the case of pyrrole, the aromatic stabilization covers the energy requirement of planarization, in the case of phospholes, there is a bigger barrier for the inversion.

The electron-delocalization in the hypothetical planar phospholes is shown in Fig. 3.

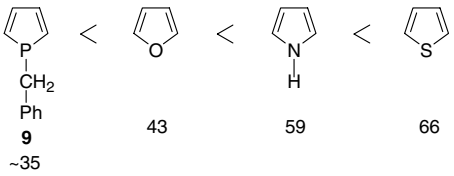


Fig. 1 The aromaticity of five-membered heterocycles characterized by the Bird-Index [32]

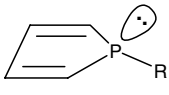


Fig. 2 Stereostructure of phospholes

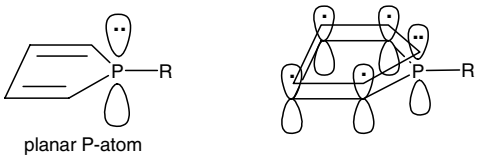
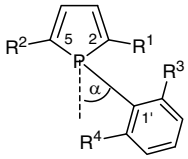


Fig. 3 Stereostructure and electron-delocalization in hypothetical aromatic phospholes

Table 1 The effect of *ortho* substituents on the flattening of the phosphorus atom (OOP angle) in substituted arylphospholes (**10**)



10

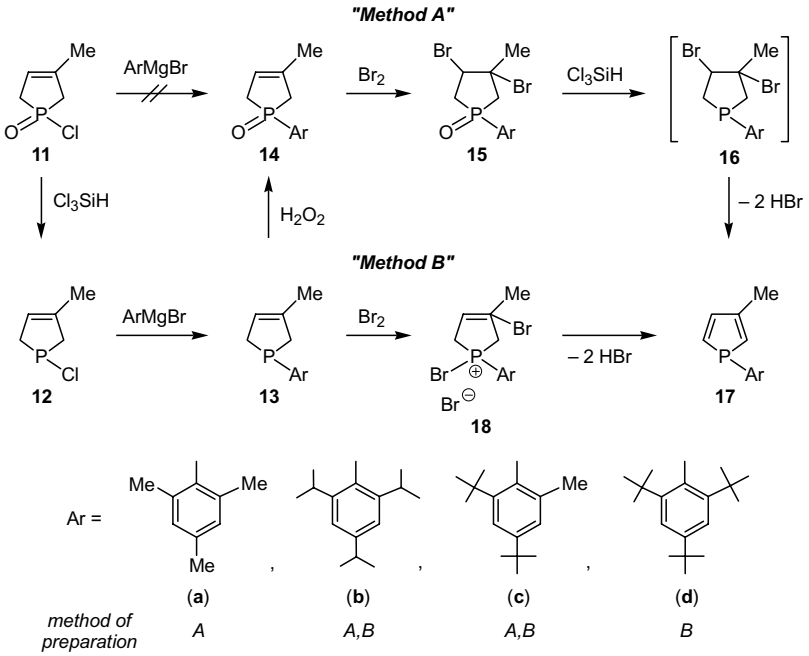
				α (deg)	
R^1	R^2	R^3	R^4	MNDO	HF/6-31G*
H	H	H	H	62.0	68.3
H	H	Me	Me	55.5	59.5
H	H	*i*Pr	*i*Pr	52.6	
H	H	Me	*t*Bu	53.7	
H	H	*t*Bu	*t*Bu	49.1	49.0
*t*Bu	*t*Bu	*t*Bu	*t*Bu	41.0	

Nyulászi summarized the theoretical background of the aromaticity of phospholes and the possibilities of establishing aromatic phospholes [34].

The author of this paper and Quin thought that the phosphole molecule (**10**) might perhaps be planarized by the introduction of a sterically demanding P-substituent and hence the aromaticity might be increased. Semiempirical and, in a few cases, ab initio calculations were carried out to evaluate the effect of the *ortho* substituent of the aryl ring on the geometry of the phosphole molecule. The calculations suggested that with the increase in the size of the alkyl groups, the extent of the planarization was also increased. The planarization was measured by the "Out of Plane" (OOP) angle – that means the angle connecting the P–$C_{1'}$ bond to the C_2–P–C_5 plane. Already two methyl groups have some effect, but the presence of two *tert*-butyl groups is much more efficient. The most planarized molecules contained *tert*-butyl substituents also in positions 2 and 5 of the phosphole ring (Table 1) [35].

2 Synthesis of 1-(2,4,6-Trialkylphenyl)phospholes

We have developed a method for the synthesis of phospholes (**17**) with 2,4,6-trialkylphenyl substituent on the phosphorus atom. The chlorine atom of the chlorophospholene oxide (**11**) could not be substituted due to the considerable steric hindrance. After deoxygenation of the phosphinic chloride **11** by trichlorosilane, the aryl group could be easily introduced by the reaction of phosphinous chloride **12** with arylmagnesium bromide. Following the oxidation of arylphospholene **13a–c**, bromine was added on the double-bond of phospholene oxide **14a–c** that was then deoxygenated. The elimination of two equivalents of hydrogen bromide from phosphine **16a–c** took place spontaneously to afford the expected phospholes (**17a–c**), (*Method A*, Scheme 4) [35–38]. In the case of the 2,4,6-tri-*tert*-butylphenyl substituent, the steric hindrance prevented deoxygenation of the dibromophospholane oxide (**15d**). In another route the phosphorus atom of the arylphospholene (**13d**) reacted with one equivalent of bromine in a selective manner leaving the double-bond completely intact. The phospholium salt (**18d**) so obtained could be easily dehydrohalogenated to give the corresponding phosphole (**17d**), (*Method B*, Scheme 4) [39]. *Method B* was also efficient in the preparation of arylphospholes **17b,c**.



Scheme 4 Synthesis of 1-(2,4,6-trialkylphenyl)phospholes

3 Aromaticity of 1-(2,4,6-Trialkylphenyl)phospholes

The new arylphospholes were examined by means of photoelectron spectroscopy and, in three cases, by X-ray crystallography [36, 39, 40]. The ionization energy of 7.5 eV obtained for the 2,4,6-tri-*tert*-butylphenylphosphole (**17d**) is the smallest value that has ever been recorded for phospholes [41].

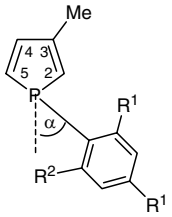
The OOP angles calculated from the ionization energies were in good agreement with the angles predicted by the semiempirical calculations [35]. With increasing planarization, the P–C and the C_3–C_4 bonds were significantly shortened, at the same time the double-bonds were somewhat elongated. This equalization in the bond lengths refers to a considerable aromatic stabilization (Table 2) [36, 39]. The Bird-index of 55 obtained for 2,4,6-tri-*tert*-butylphenylphosphole (**17d**) sets a new record and suggests an aromaticity that is comparable with that of pyrrole and thiophene placing phosphole **17d** into the family of heteroaromatic compounds with five-membered ring.

4 Reactivity of 1-(2,4,6-Trialkylphenyl)phospholes

4.1 Aromatic Electrophilic Substitutions

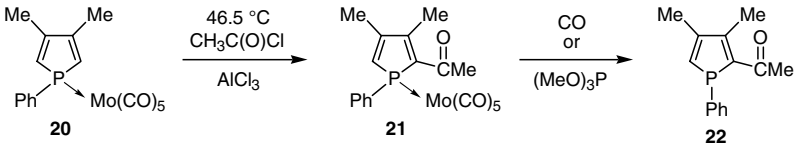
The 3,4-dimethyl-1-phenylphosphole (the so called "Mathey-phosphole") entered into Friedel–Crafts acylation only through its molybdenum complex (**20**). Elimination of the $Mo(CO)_5$ moiety from product **21** furnished 2-acylphosphole **22** (Scheme 5) [42].

Table 2 Experimental evidences on the flattening of the phosphorus atom in arylphospholes



					Bond distances (Å)					
R^1	R^2		IE (eV)	α (deg)	P–C_2	C_3–C_4	C_5–P	C_2–C_3	C_4–C_5	BI
H	H	(**19**)	8.5	68	~1.783[a]	1.438[a]	1.783[a]	1.343[a]	1.343[a]	35.5[a]
Me	Me	(**17a**)	8.1	60						
*i*Pr	*i*Pr	(**17b**)	7.9	56	1.782	1.436	1.778	1.340	1.366	40.4 [36]
*t*Bu	Me	(**17c**)	7.9	56	1.768	1.426	1.761	1.343	1.333	42.3 [40]
*t*Bu	*t*Bu	(**17d**)	7.5	45	1.750	1.390	1.763	1.347	1.352	54.9 [39]

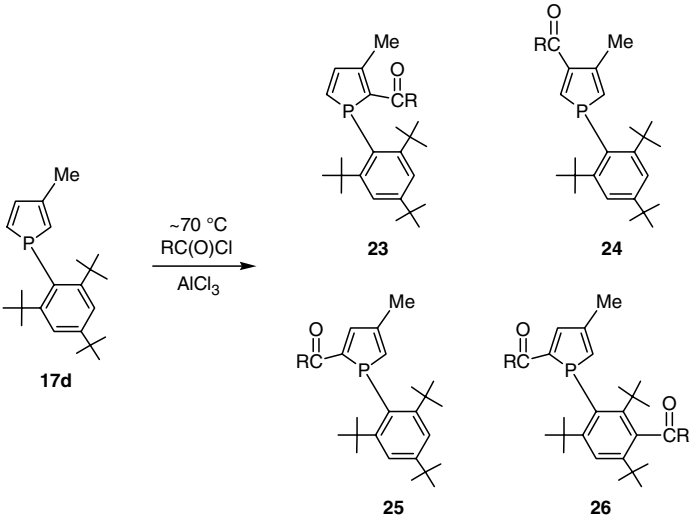
[a]For phosphole **9** [32, 33]



Scheme 5 Friedl-Crafts acylation of the "Mathey-phosphole" in the coordination sphere

Aromatic electrophilic acylations were described only in the coordination sphere of the phospholide anion involving phosphacymantrenes [43, 44] or phosphaferrocenes [45].

Aromaticity of 2,4,6-tri-*tert*-butylphenylphosphole (**17d**) was also revealed in chemical reactions: phosphole **17d** could undergo aromatic electrophilic substitution. In reaction with acetyl chloride, a mixture of 2-, 4-, and 5-acetyl phospholes (**23a**, **24a,** and **25a**, respectively), as well as a diacetyl derivative (**26a**) were formed (Scheme 6) [39]. Interestingly, the most crowded 2-acetyl derivative (**23a**) was the main product of the Friedel–Crafts reaction. A similar situation was observed for 3-methylpyrrol [46].



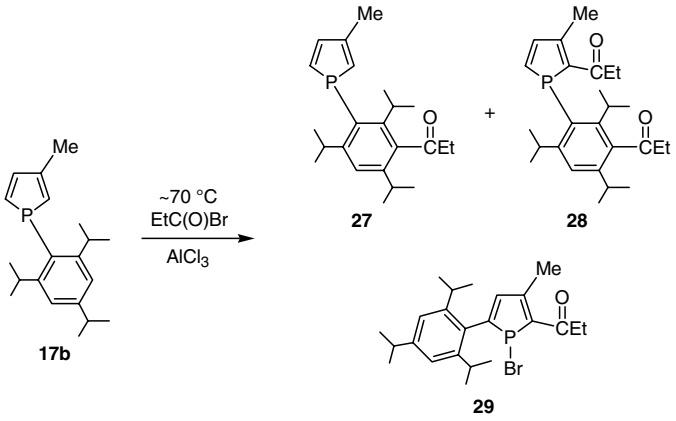
R	Product composition [%]			
	23	**24**	**25**	**26**
Me (**a**)	31	16	9	44
Et (**b**)	~60	*	*	~40
Pr (**c**)	~60	*	*	~40

*not relevant

Scheme 6 Friedl-Crafts acylation of 1-(2,4,6-tri-*tert*-butylphenyl)phosphole

The use of other simple carboxylic acid chlorides led to similar results: the corresponding monoacyl- and diacyl-phospholes (**23b,c** and **26b,c**) were formed. In these cases, the 2-acylphosphole (**23b,c**) was practically the only monoacylderivative that was formed (Scheme 6) [27]. The yields were all in the range of 21–50%.

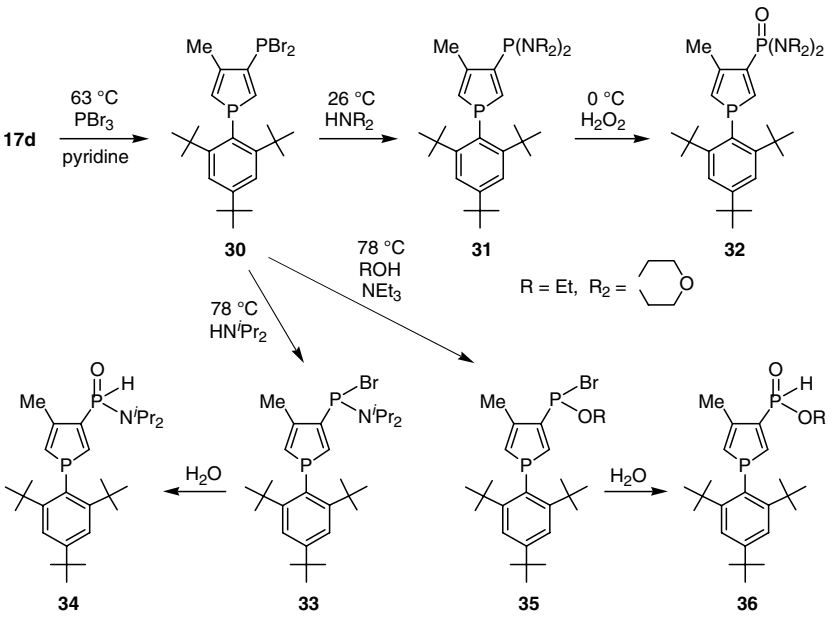
We wished to evaluate the reactivity of triisopropylphenylphosphole (**17b**), exhibiting a somewhat smaller Bird-index, than the tri-*tert*-butyl derivative (**17d**) (40.4 vs. 54.9). It was found that the acylation of the hetero ring took place only to a small extent. Acylation of the trialkylphenyl ring was a concurrent reaction path, but the major product was 2-acyl-5-aryl-bromophosphole (**29**) shown in Scheme 7 [47].



Scheme 7 Friedl-Crafts reaction of 1-(2,4,6-triisopropylphenyl)phosphole

4.2 Reactions with Phosphorus Tribromide

It was found that the 2,4,6-tri-*tert*-butylphenylphosphole (**17d**) entered into reaction with phosphorus tribromide to give the 3-dibromophosphoniophosphole (**30**). The latter was reacted with secondary amines to form phosphonous diamides (**31**), which on oxidation gave the phosphonamides (**32**) (Scheme 8) [48, 49]. It was surprising that the phosphorus atom of the phosphole ring resisted oxidation. Stereospecific J_{PP} and J_{PC} couplings confirmed the position of the P-function as 3. In the reaction of intermediate **30** with diisopropylamine, only one of the bromine atoms could be replaced, to give an *H*-phosphinic amide (**34**) after hydrolysis (Scheme 8) [49]. Also, monosubstitution was the result of the reaction of the dibromophosphine (**30**) with alcohol to furnish an *H*-phosphinate (**36**) after hydrolysis (Scheme 8) [49].

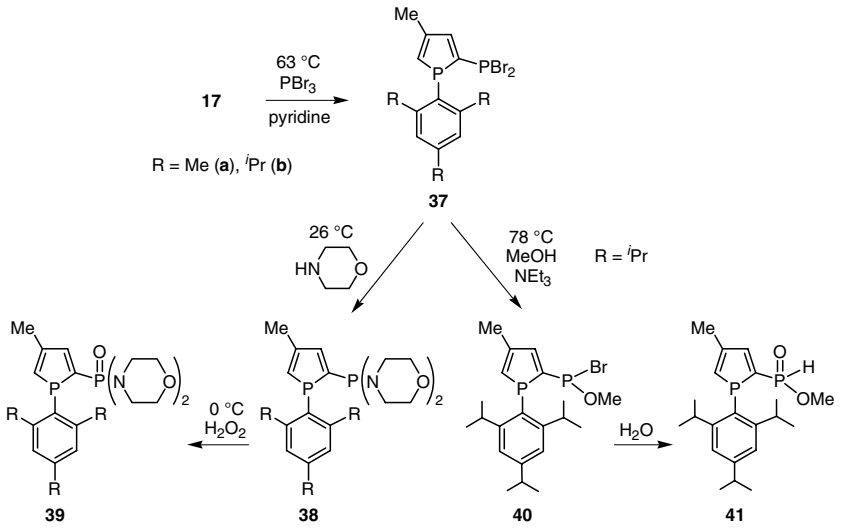


Scheme 8 Phosphonylation and phosphinylation of 1-(2,4,6-tri-*tert*-butylphenyl)phosphole

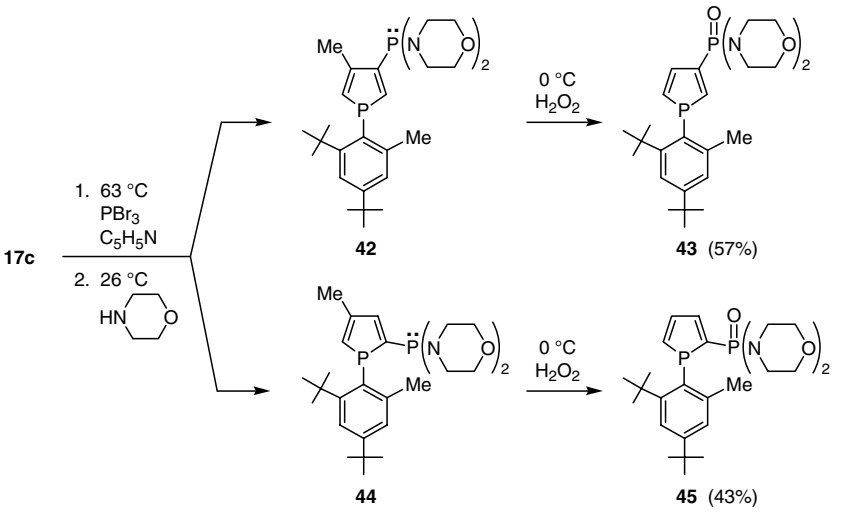
A similar reaction sequence of triisopropylphenylphosphole or mesitylphosphole (**17b** and **17a**, respectively) with phosphorus tribromide afforded the corresponding 2-substituted products. The reaction of dibromophosphine **37** with nucleophiles followed by oxidation or hydrolysis gave phosphonic or *H*-phosphinic derivatives (**39** or **41**, respectively) (Scheme 9) [48, 49]. The regioselectivity is obviously the consequence of the presence or the lack of the steric hindrance; with ortho *tert*-butyl groups, only position 3 is available, while with the smaller triisopropyl substituent, position 2 may be the appropriate reaction site.

The mechanism may involve a nucleophilic attack of the double-bond of the phosphole (**17**) on the phosphorus atom of phosphorus tribromide to provide intermediates that are stabilized by the loss of proton, pseudorotation, and finally the departure of a bromide anion [48, 49].

The reaction of arylphospholes with phosphorus tribromide was extended to di-*tert*-butyl-methylphenylphosphole (**17c**) leading after further steps, to a mixture of 3- and 2-substituted products (**43** and **45**, respectively) (Scheme 10) [40]. The di-*tert*-butyl-tolyl substituent clearly occupies an intermediate position between the triisopropylphenyl and tri-*tert*-butylphenyl ones regarding the steric hindrance caused by the *ortho* alkyl substituents.



Scheme 9 Phosphonylation and phosphinylation of 1-(2,4,6-trialkylphenyl)phospholes

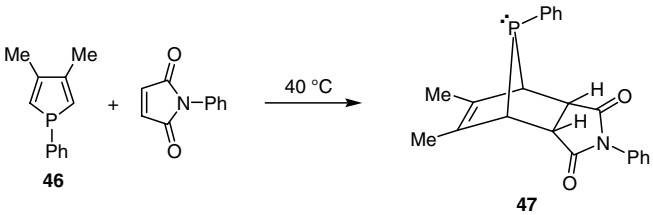


Scheme 10 Phosphonylation of 1-(2,4-di-*tert*-butyl-6-methylphenyl)phosphole

Preliminary studies showed that phospholes without any aromaticity could also be involved in reaction with phosphorus tribromide, although these reactions were not too efficient. This means that the above substitution protocol has not much to do with the heteroaromaticity.

4.3 Diels–Alder Reactions

The Diels–Alder reaction of phospholes was not studied extensively. It was known, however, that the cycloaddition of the Mathey phosphole (**46**) with *N*-phenylmaleimide afforded 7-phosphanorbornene **47** (Scheme 11) [50]. Similar reactions with fumaronitrile or with another unit of phosphole led to products with the same *anti* configuration of the bridging P-moiety [51, 52].



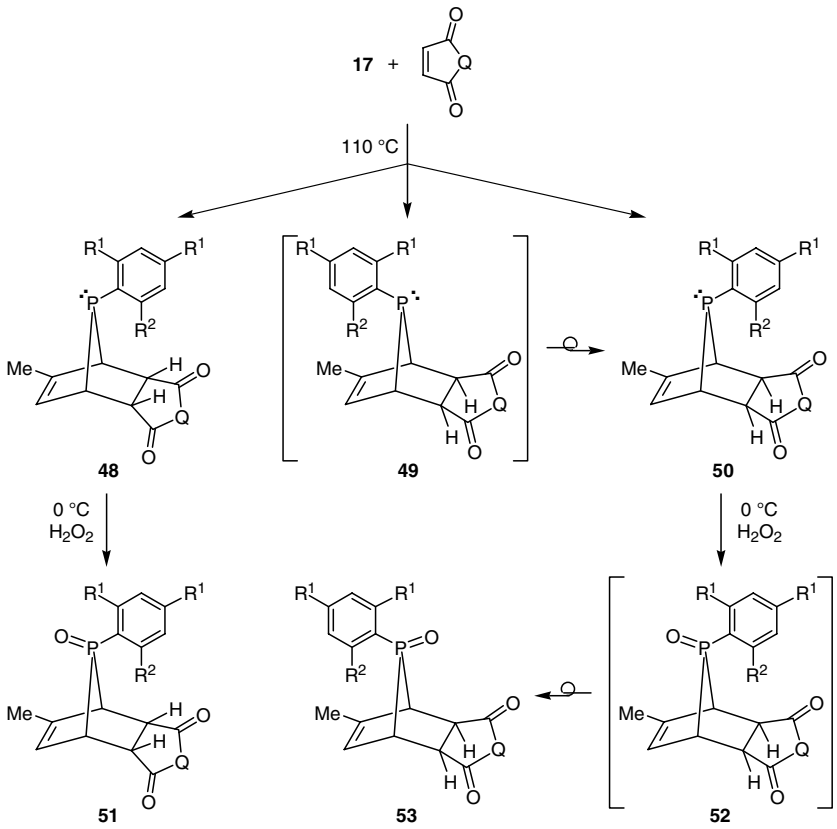
Scheme 11 Diels-Alder-reaction of the "Mathey-phosphole"

Despite their heteroaromaticity, the aryl phospholes (**17**) could also participate in Diels–Alder cycloaddition. In reaction with *N*-phenylmaleimide (NPMI), mostly the endo ring-fused phosphanorbornene containing the aryl group *anti* to the double-bond (**48**) was formed. In certain cases, the other isomer with similar P-configuration, but with exo ring fusion (**50**) was also formed. Stereostructure of the phosphanorbornenes (**48** and **50**) was confirmed by stereospecific $^{2}J_{PC}$ couplings obtained from the ^{13}C NMR spectra. It is believed that at first, the *syn* isomer (**49**) is formed under kinetic control, that is inverted at phosphorus to give the thermodynamically more stable *anti* product (**50**) (Scheme 12) [53–55]. It was found that the Diels–Alder reaction became sluggish with the increase of aromaticity and steric hindrance. In order to obtain stable products, the phosphines (**48** and **50**) were converted to phosphine oxides (**51** and **52**, respectively). In this case, another inversion at the phosphorus atom of species **52** was observed to furnish **53** (Scheme 12) [53–55]. The 7-phosphanorbornene 7-oxides (**51** and **53**) were obtained in 33–68% yield.

An analog (**56**) of isomer **53** was prepared by a structure proving synthesis (Scheme 13). It was proved that the *syn* isomer (**57**) obtained after deoxygenation is transformed spontaneously to the *anti* form (**58**). Phosphine (**58**) was stabilized as the phosphine oxide (**59**) (Scheme 14) [55].

4.4 Sigmatropic Rearrangements

It was found that the P-phenyl substituent of phospholes may undergo migration to carbon forming the corresponding 2*H*-phosphole intermediate [56, 57]. The reaction is shown for the double rearrangement of biphosphole **60** to generate intermediate

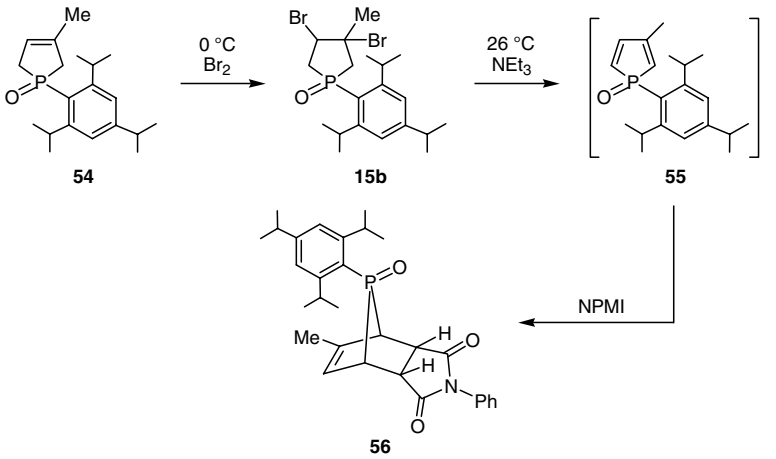


R[1]	R[2]	Q	**48** [%]	**50**	**51**	**53**
Me	Me	N–Ph	100	–	100	–
^{i}Pr	^{i}Pr	N–Ph	90	10	88	12
^{t}Bu	Me	N–Ph	42	58	46	54
^{t}Bu	^{t}Bu	N–Ph	100	–	100	–
^{i}Pr	^{i}Pr	N–Me	100	–	100	–
^{i}Pr	^{i}Pr	O	100	–	100	–

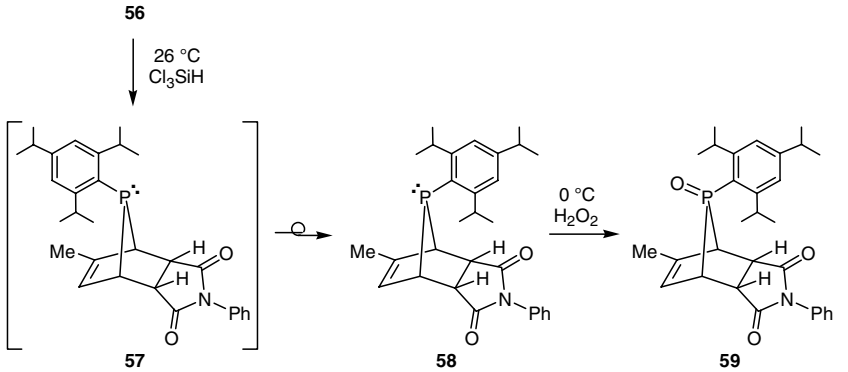
Scheme 12 Diels-Alder reaction of 1-(2,4,6-trialkylphenyl)phospholes

61 that was trapped by two equivalents of diphenylacetylene affording the racemate of BIPNOR (**62**) that is a useful bidentate P-ligand in the optically active form (Scheme 15) [58].

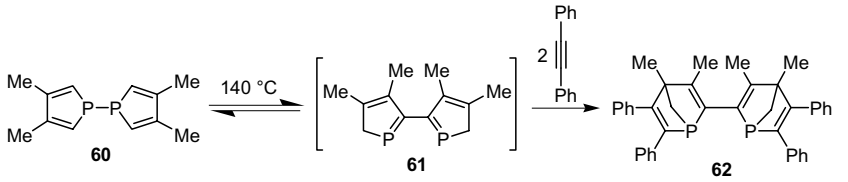
We observed that the slightly aromatic triisopropylphenyl-1*H*-phosphole (**17b**) underwent a sigmatropic rearrangement at 150°C to afford the corresponding



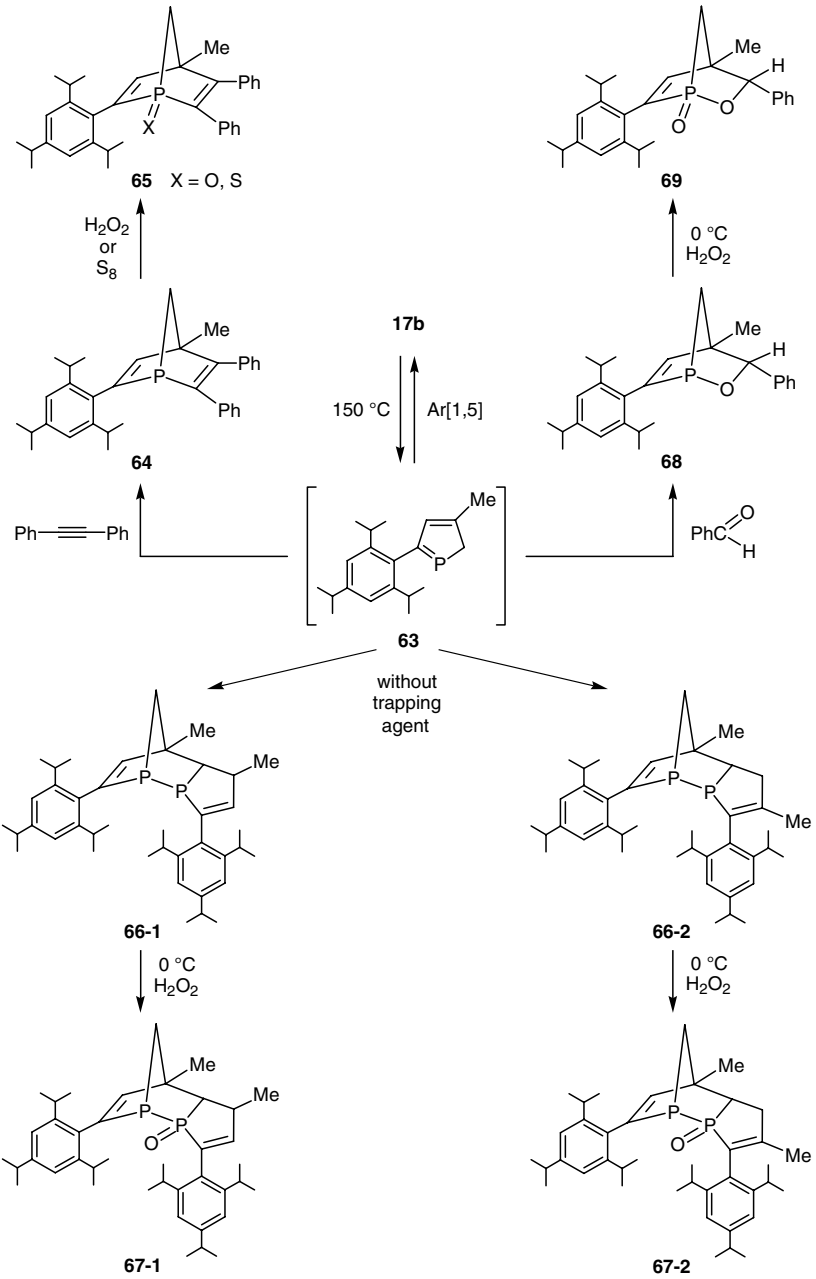
Scheme 13 Trapping reaction of an intermediate arylphosphole oxide



Scheme 14 A *syn* to *anti* isomerisation sequence within a 7-phosphanorbornene derivative



Scheme 15 Synthesis of recemic BIPNOR



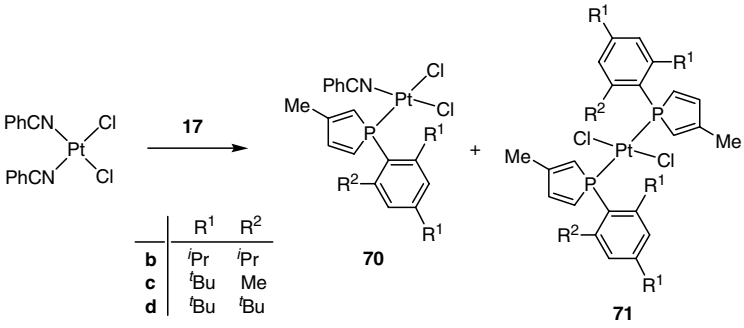
Scheme 16 Generation and utilization of an intermediate *2H*-phosphole

2*H*-phosphole (**63**) that was trapped by diphenylacetylene to yield an aryl-1-phosphanorbornadiene (**64**). Intermediate **63** could also be dimerized leading to the isomers of 1,2-diphosphanorbornene derivative **66** or trapped by benzaldehyde to afford the oxaphosphanorbornene (**68**) as one isomer (Scheme 16) [40, 59]. The

tervalent species (**64**, **66,** and **68**) were converted to the corresponding P-oxides (**65**, **67,** and **69**, respectively). A careful oxidation of the dimers (**66-1** and **66-2**) led to hemi-oxides (**67-1** and **67-2**, respectively). Further oxidation of the latter species (**67-1** and **67-2**) led to the decomposition of the dimeric structure. In the case of the phosphanorbornadiene, the P-sulfide was also prepared.

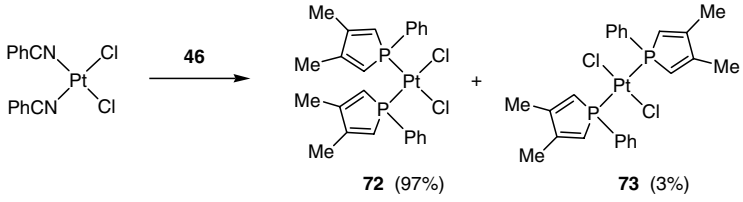
4.5 Complexation Reactions: Platinum and Rhodium Complexes

The phospholes are important ligands in transition metal complex catalysts. The complexing ability of trialkylphenylphospholes (**17**) differs significantly from that of "common or garden variety" phospholes. In reaction with dichlorodibenzonitrile platinum, the complexes **70** and **71** containing one or two phosphole ligands were found to have been formed with *cis* and *trans* geometry, respectively (Scheme 17) [60, 61]. Stereostructure of the complexes (**70** and **71**) was evaluated on the basis of stereospecific Pt–P NMR couplings.



Scheme 17 Conversion of 1-(2,4,6-trialkylphenyl)phospholes to Pt(II) complexes

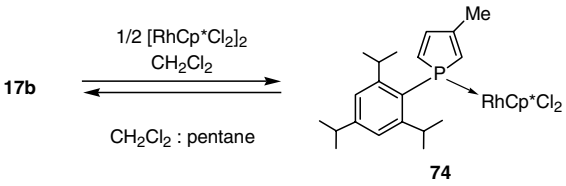
The result of the complex forming reaction of the Mathey phosphole (**46**) is quite different as in this case, the predominant product is the bis(phosphole) complex with *cis* geometry. (Scheme 18) [62].



Scheme 18 Conversion of the "Mathey-phosphole" to the corresponding Pt(II) complex

With increasing steric hindrance and aromaticity, the rate of the reaction of the trialkylphenylphospholes (**17a-c**) with dichlorodibenzonitrile platinum decreased, but due to the electron-releasing ability of the trialkylphenyl ring, the complexation took place in all cases on the P-center.

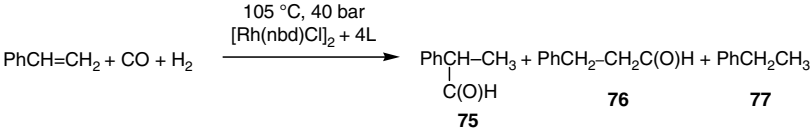
In the series of 1-(2,4,6-trialkylphenyl-)3-methyl-1*H*-phospholes (**17**), only the isopropyl substituted one (**17b**) entered into reaction with dimeric (pentamethylcyclopentadienyl)rhodium dichloride to afford Rh(III) complex **74** in a reversible manner. After a careful workup, **74** could be prepared and characterized (Scheme 19).



Scheme 19 Conversion of triisopropylphenylphosphole to the corresponding Rh(III) complex

Complex **74** as a preformed catalyst, as well as the $Rh(acac)(CO)_2$ + 2(**17b**) in an in situ catalytic system were useful in the hydroformylation of styrene and gave the branched aldehyde in regioselectivities of 65–96% [63].

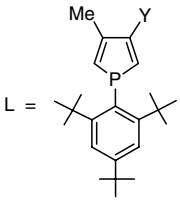
It was also evaluated how phosphorylation of the arylphosphole ligands (**17b,d**) affects the activity of the in situ rhodium complex in the hydroformylation of styrene (Scheme 20).

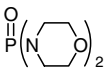


Scheme 20 Testing an in situ formed Rh-arylphosphole complex hydroformylation

The chemoselectivity (R_c = **[[75]** + **[76]]**/ **[[75]** + **[76]** + **[77]]** ×100) was found to be excellent (≥98%) in all cases, while the regioselectivity was improved in the case of certain substituents (Table 3) [49, 64].

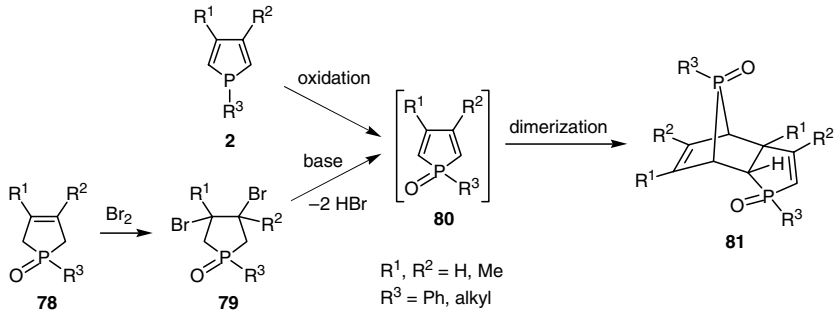
Table 3 Hydroformylation of styrene in the presence of $[Rh(nbd)Cl]_2$ +4L phosphole ligands at 100°C, 40 bar



Y	Reaction time (h)	Conversion (%)	Regioselectivity (%) $\frac{[75]}{[75]+[76]}\times 100$
H	6	99	66
	6	98	57
	6	99	62
	6	90	72
	2	98	75
	2	99	80

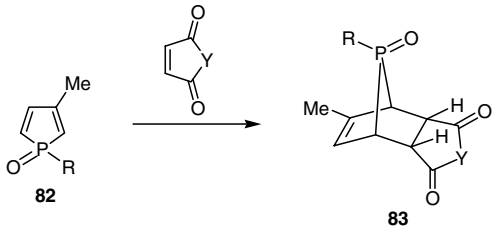
4.6 Oxidation Reactions

It is known that the phosphole oxides (**80**), obtained either by the oxidation of phospholes (**2**) or by the dehydrobromination of dibromophospholane oxides (**79**) undergo spontaneous dimerization to furnish cycloadducts **81** (Scheme 21) [4, 65].



Scheme 21 Regio- and stereospecific cyclodimerisation of phosphole oxides

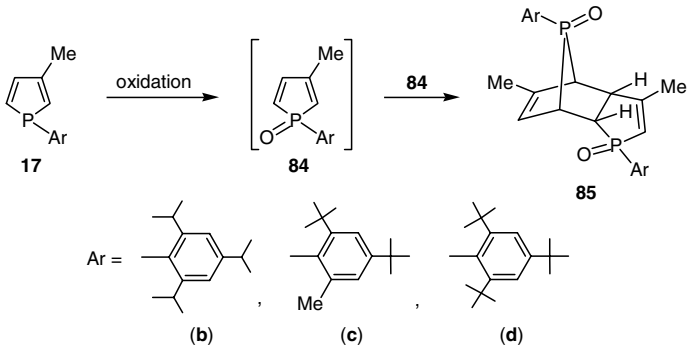
Generating the phosphole oxides (**82**) in the presence of trapping agents, such as maleic acid derivatives, phosphanorbornenes of type **83** were obtained (Scheme 22) [4, 65].



R = Ph, alkyl, alkoxy, dialkylamino
Y = NPh, NMe

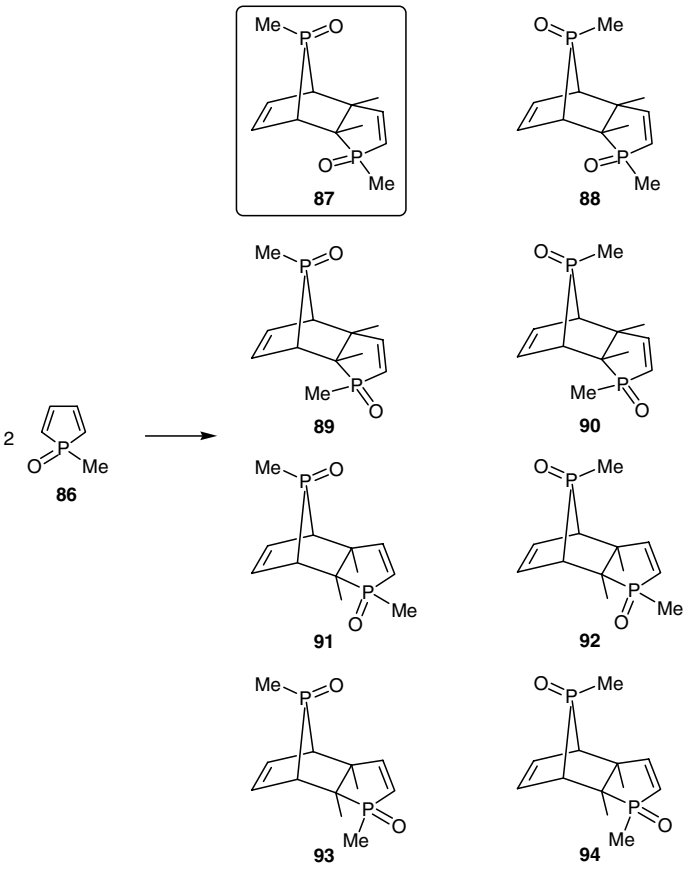
Scheme 22 Trapping of phosphole oxides

Oxidation of arylphospholes (**17**) by peroxides led to phosphole oxides (**84**) that dimerized to the corresponding phosphanorbornene derivatives (**85**) (Scheme 23) [36, 38, 66]. As in earlier cases, the cyclodimerization took place in a regio- and stereospecific manner. The interesting observation was that, due to the bulky P-substituent, oxidation was slower and the phosphole oxides (**84**) became relatively stable; hence, they could be characterized by NMR.



Scheme 23 Regio and stereospecific cyclodimerisation of trialkylphenylphosphole oxides

Regarding cyclodimerization of phosphole oxides, although a number of isomers could be envisaged, only a single isomer was formed in all cases. If there is a methyl group in position 3, in total 64 isomers can be imagined; but if there is no methyl group, the number of the possible isomers is only 8 (see Scheme 24). The favored isomer is where the phosphole rings are joined in the *endo* fusion and where the oxygen atoms of the phosphoryl groups are directed towards the center of the molecule (as in isomer **87**).

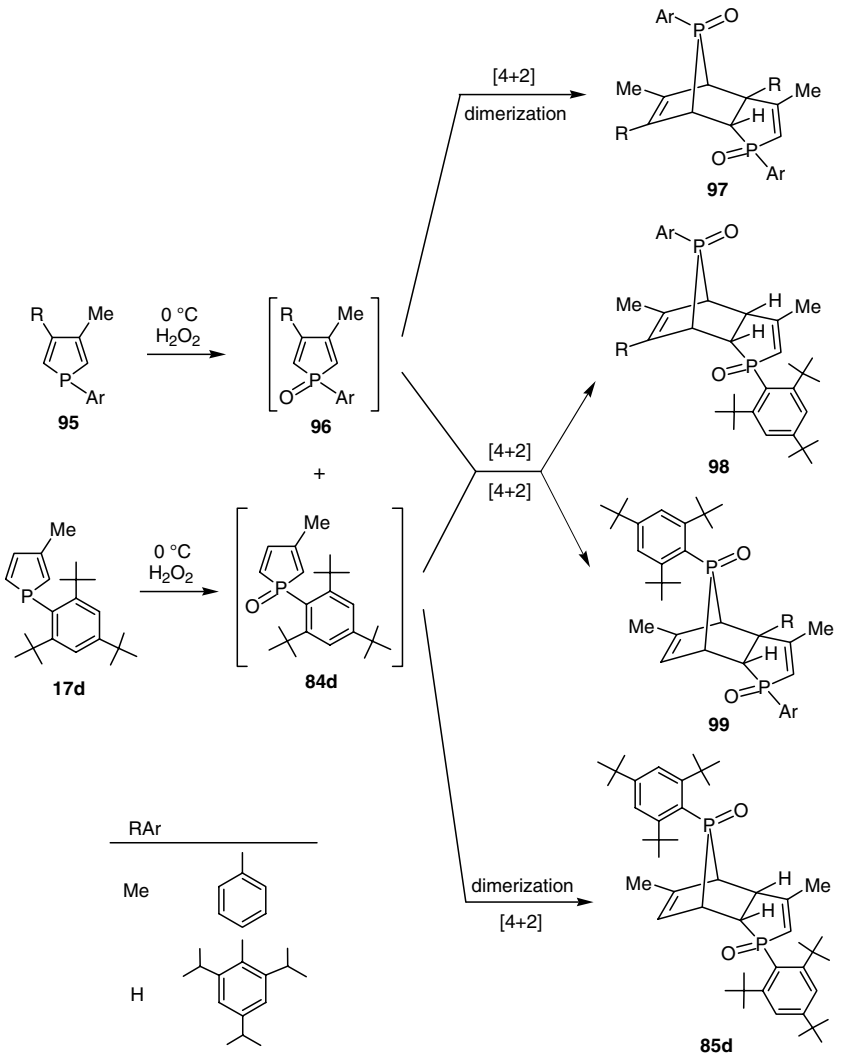


Scheme 24 Possible isomers in the cyclodimerisation of 1-methylphosphole oxide

Semiempirical and ab initio calculations were performed on the cyclodimerization of 1-methylphosphole oxide (**86**). The relative order of the values of the heat of formation for the transient states leading to the possible isomers (**87–94**) confirmed that the formation of the isomer prepared (**87**) is indeed favored to a high extent (Scheme 24) [67]. The selectivity can be explained by steric reasons and kinetic factors.

Mixed phosphole oxide dimers (**98** and **99**) were prepared by the possible combinations of two different phosphole oxides (**96** and **84d**), generated simultaneously in the same flask. In the reaction shown, homo dimers **97** and **85d** were also formed (Scheme 25) [68].

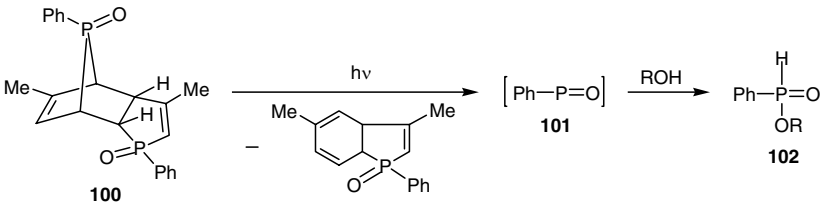
The instability of phosphole oxides is the consequence of their antiaromaticity [69].



Scheme 25 Dimerisation of two different phosphole oxides leading to homo and heterodimers

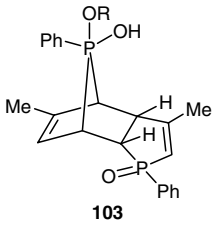
5 Fragmentation of Phosphole-Based 7-Phosphanorbornenes

The photolysis of 7-phosphanorbornenes (like **100**) was suggested to provide phosphinidenes (like **101**) that reacted with an alcohol to give the corresponding *H*-phosphinate (e.g. **102**) (Scheme 26) [70–72].

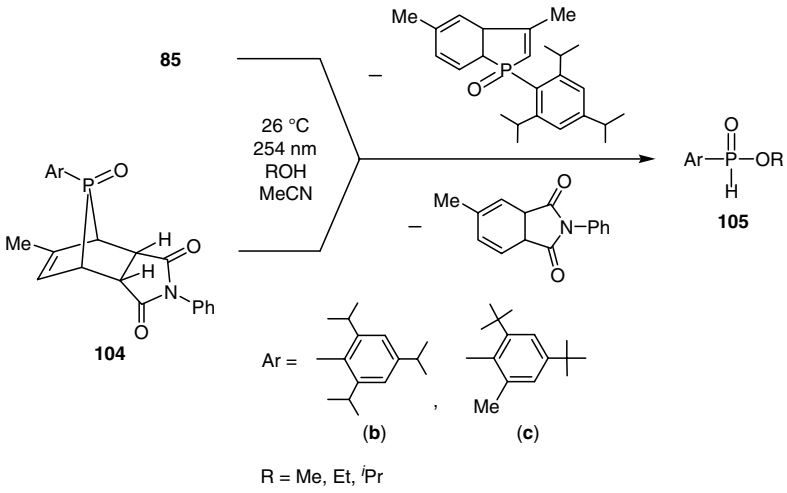


Scheme 26 A possible fragmentation-phosphorylation route

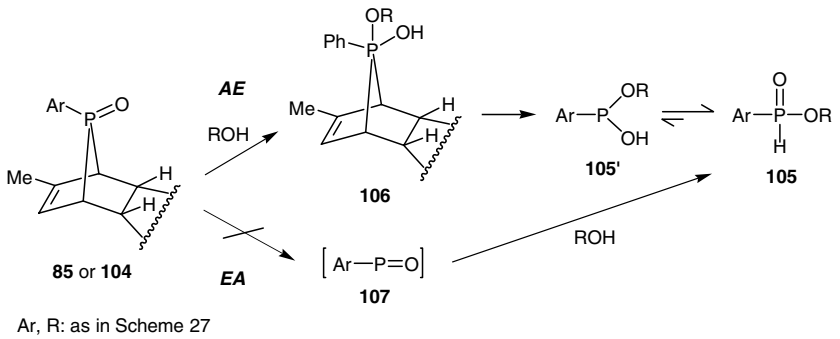
Later on, an intermediate with a pentavalent pentacoordinated phosphorus atom (**103**) was suggested on the basis of kinetic examinations [73].



The P-aryl phosphanorbornenes (**85** and **104**) prepared by us served as excellent model compounds in photoinduced fragmentation-related phosphorylations. On the one hand, new *H*-phosphinates (**105**) were synthesized (Scheme 27), while on the other hand, our experiments indicating a high sensitivity towards the steric effects substantiated the AE mechanism involving a pentacoordinated pentavalent intermediate (**106**) (Scheme 28) [74, 75].

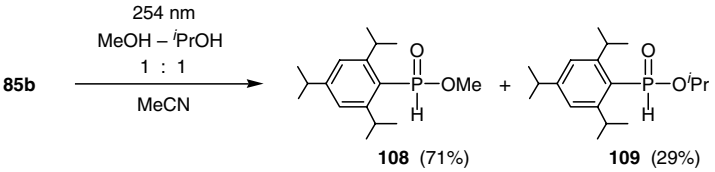


Scheme 27 The use of 7-phosphanorbornene derivatives in the phosphorylation of alcohols



Scheme 28 Mechanism for the fragmentation-related phosphorylations

Concurrent reactions using an equimolar mixture of methanol and isopropylalcohol (Scheme 29) again confirmed the importance of the steric factors.



Scheme 29 The role of steric factors in the fragmentation-related phosphorylation

6 Conclusion

The new family of phospholes with 2,4,6-trialkylphenyl substituent on the phosphorus atom show, in many respects, a special reactivity. Due to the flattening of the P-pyramid, the arylphospholes exhibit aromaticity and hence underwent Friedel–Crafts reactions. The regioselective functionalization through reaction with phosphorus tribromide gave a variety of phospholes with an exocyclic P-moiety. Novel phosphole platinum and rhodium complexes were prepared and a part of them was tested in hydroformylation reactions.

Despite the aromatic character, the arylphospholes could also participate in Diels–Alder reactions to give new type of 7-phosphanorbornenes. These products together with phosphanorbornenes obtained by the regio- and stereospecific dimerization of arylphosphole oxides were useful model compounds in the UV light mediated fragmentation-related phosphorylation of alcohols. A novel mechanism was substantiated.

The sigmatropic rearrangement of 1*H*-phospholes to the 2*H* derivatives gives a new entry to novel 1-phosphanorbornadienes after trapping with tolane.

Acknowledgement Thanks are due to the National Scientific and Research Found (OTKA, Grant No. K 067679) for their financial support.

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Top Heterocycl Chem (2010) 21: 175–206
DOI 10.1007/7081_2009_20

Published online: 4 February 2010

Recent Advances in the Chemistry of Diazaphospholes

Neelima Gupta

Abstract Diazaphospholes, incorporating two nitrogen atoms (one σ^3,λ^3 and the other σ^2,λ^3) in addition to a σ^2,λ^3-phosphorus in the five-membered ring, constitute a well-investigated category of heterophospholes. Possibility of different combinations of three heteroatoms has made available a number of representatives through different synthetic routes. In this chapter, an account of the reports on the chemistry of diazaphospholes made during the last 10–12 years is presented, which highlights new routes and the use of novel reagents for their synthesis, structural aspects and their reactivity towards cycloaddition and complexation reactions, in particular.

Keywords Coordination compounds • Cycloaddition reactions • Diazaphosphenium cation • Diazaphospholes • Phosphaaromatics

Contents

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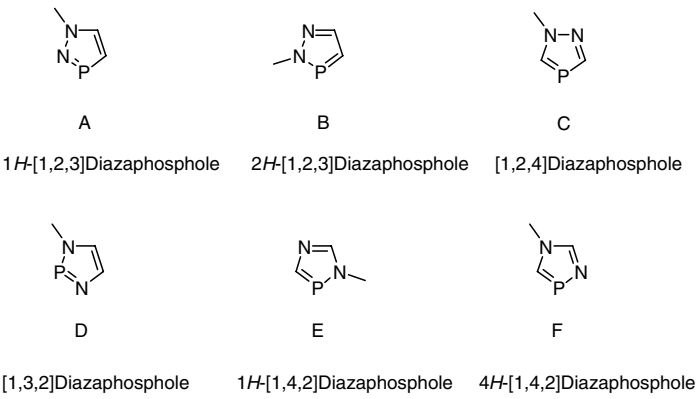
1 Introduction and Classification

Diazaphospholes constitute the most widely investigated class of heterophospholes, the 6π-aromatic phosphorus heterocycles [1, 2]. Diazaphospholes are unique in the manner that the five-membered ring incorporates one σ^2,λ^3- as well as one σ^3,λ^3-nitrogen in addition to the σ^2,λ^3-phosphorus atom. First diazaphosphole representative, i.e. 2*H*-[1,2,3]diazaphosphole was obtained as early as 1967 [3] and until 1980s the interest of organophosphorus chemists remained in the development of different synthetic routes and in investigating their varied reactivity due to the structural diversity within the class [4]. On the basis of the relative positions of the three heteroatoms in the five-membered ring, six monocyclic diazaphosphole systems (**A–F**) are possible and all of them have been reported (Structure 1).



Structure 1 Possible monocyclic diazaphosphole systems

During the last 10–15 years, more emphasis has been on the development of new synthetic routes for obtaining variously substituted less common representatives and new varieties of *CC*- or *CN*-anellated bicyclic diazaphosphole systems. *CC*-Anellation is possible in **A**, **B,** and **D**, out of which benzo anellated representative of only **D** has been reported. But, *CN*-fused derivative of **D** is not reported, though

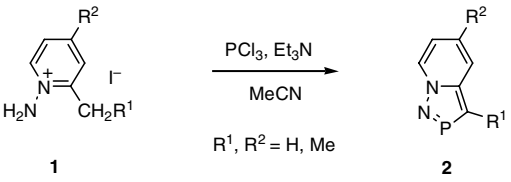
in principle, *CN*-anellation is possible in all cases except **B**. For the last two decades, our research group is engaged in the experimental and theoretical studies of heterophospholes, of which diazaphospholes comprise a significant segment. During the last few years, diverse reactivity of endocyclic as well as exocyclic functionalities of diazaphospholes has been investigated. They act as versatile dienophiles or dipolarophiles in cycloaddition reactions and provide varied coordination modes in metal complexes. With the advancement of theoretical methods, experimental results have been often supported by theoretical calculations. Recent developments in the chemistry of diazaphospholes by our group at Jaipur and other researchers is covered in this review so as to highlight less studied novel aspects, which have potential for further investigations. Although a significant number of reports regarding nonaromatic σ^3- and σ^4-diazaphospholes are also available in literature, the present review is limited to the synthesis, structure, and reactions of aromatic σ^2-diazaphospholes.

In the past, several general reviews on heterophospholes [2, 4–6] have covered the chemistry of diazaphospholes reported until early 1990s. Synthetic routes to different classes of diazaphospholes have been reviewed [7]. Analogy between the synthesis of anellated diazaphospholes and their nonphosphorus analogs has also been reviewed [8]. Some recent advances in the chemistry of anellated diazaphospholes made by our group have been included in a review on anellated azaphospholes [9]. The reviews on the synthetic applications of phosphalkynes also describe the synthesis of diazaphospholes from these synthons [10–12]. Present review aims to highlight and update important reports related to the chemistry of diazaphospholes which have mainly appeared during the last 15 years.

2 Synthesis

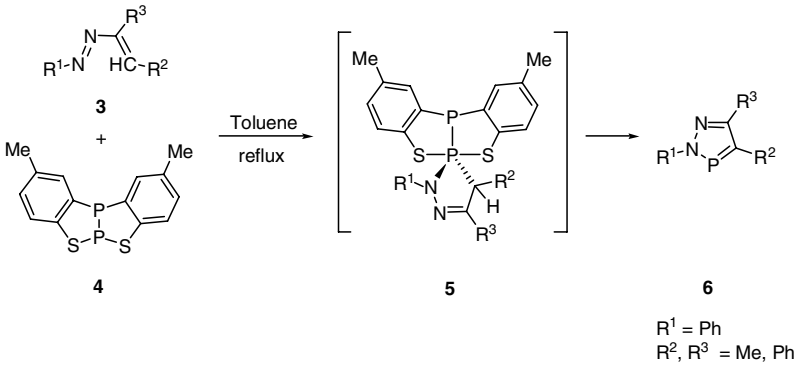
2.1 [1,2,3]Diazaphospholes

Monocyclic 2*H*-[1,2,3]diazaphospholes (**B**) are easily accessible from the condensation of the four-membered chain incorporated in hydrazones or azoalkanes with phosphorus trichloride making available a large number of representatives that have been intensively studied [2, 4, 7]. In contrast, their 1*H*-isomers (**A**) are less known and are obtained only as second minor product during the synthesis of 2*H*-[1,2,3]diazaphospholes in some cases. A facile synthesis for pyrido-anellated azaphospholes has been developed in our group by making use of 1,2-disubstituted pyridinium salts for condensation with phosphorus trichloride [8, 13–15]. Accordingly, cyclocondensation of 2-alkyl-1-aminopyridinium iodides (**1**) with phosphorus trichloride in the presence of triethylamine affords pyrido-anellated 1*H*-[1,2,3]diazaphospholes, i.e. [1,2,3]diazaphospholo[1,5-*a*] pyridines (**2**) (Scheme 1) [16].



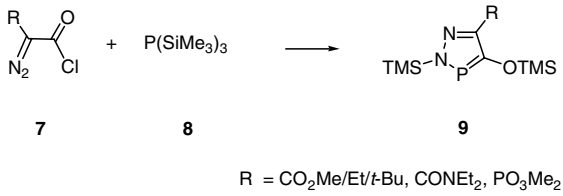
Scheme 1 Synthesis of 1*H*-[1,2,3] diazaphospholes from 1-amin-opyridinium iodides

Baccolini et al. developed a novel method for the synthesis of 2-phenyl derivatives of 2*H*-[1,2,3]diazaphospholes [17], which are otherwise difficult to obtain from the condensation of hydrazones and PCl_3. Fused benzothiadiphosphole **4** was used as a phosphorus furnishing reagent in its reaction with conjugated phenylazoalkenes **3** to obtain 2-phenyl-[1,2,3]diazaphospholes (**6**, R^1 = Ph) via intermediacy of a spiro-cyclic adduct **5** (Scheme 2).



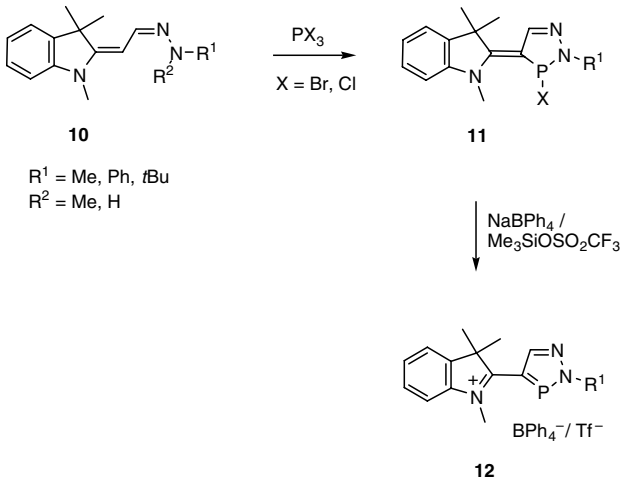
Scheme 2 Synthesis of 2-phenyl-[1,2,3]diazaphospholes using fused benzothiadiphosphole

Use of tris(trimethylsilyl)phosphine as the phosphorus furnishing reagent in condensation reaction with α-diazocarboxylic chlorides (**7**) gave 2-trimethylsilyl-[1,2,3]diazaphospholes (**9**) in good yields (Scheme 3) [18].



Scheme 3 Synthesis of 2-trimethylsilyl-[1,2,3]diazaphospholes

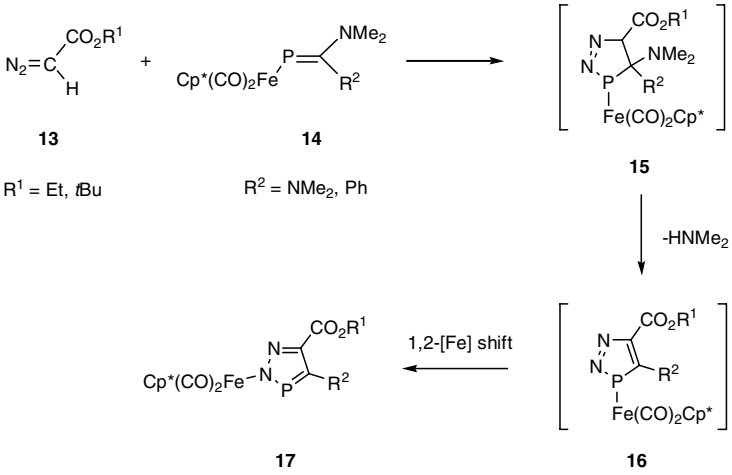
As mentioned earlier, condensation of hydrazones with phosphorus trichloride has been widely used for the synthesis of a variety of 2*H*-[1,2,3]diazaphospholes [2, 4, 7]. A number of diversely substituted 2*H*-[1,2,3]diazaphospholes have been obtained in good yields by employing an improved procedure involving the treatment of ketone acylhydrazones with PCl_3 [19]. In an analogous reaction sequence, while attempting phosphorylation of hydrazones (**10**) of formyl-1,3,3-trimethyl-2-methyleneindolines, ionic [1,2,3]diazaphospholes have been obtained. Reaction of **10** with P(III) halides generated initially the covalent methylene-3-halo-[1,2,3]diazaphospholines (**11**), which could be easily converted into ionic diazaphospholes **12** on treatment with sodium tetraphenylborate or trimethylsilyl triflate (Scheme 4) [20].



Scheme 4 Ionization of *P*-halo-[1,2,3]diazaphospholines

1,3-Dipolar cycloaddition reactions of diazoalkanes with functionalized phosphaalkenes or phosphaalkynes usually result in regioselective formation of [1,2,4]diazaphospholes [1, 2, 4, 7]. Grobe et al. observed in some cases, the formation of [1,2,3]diazaphosphole as the minor product [21]. They later used perfluoro-2-phosphapropene in reaction with a variety of diazo compounds $R(H)C{=}N_2$ (R = H, Ph, CO_2Et, Me_3Si) at low temperatures, when the reaction followed reversed regioselectivity to yield [1,2,3]diazaphospholes via 1,3-*H* shift [22]. From a similar reaction with diphenyldiazomethane, the cycloaddition is spontaneously followed by N_2 elimination to give a phosphirane derivative. DFT and RHF level calculations establish that the [3+2] cycloaddition of both, the perhydro- and the perfluoro-2-phosphapropene is kinetically controlled explaining the observed regioselectivity in each case [22].

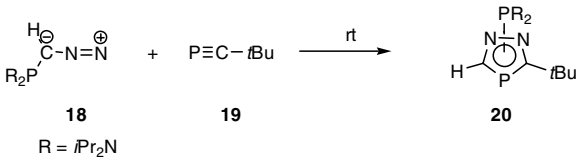
Weber et al. reported the use of metallophosphaalkene **14** for [3+2] cycloaddition with diazoacetates when the reversed regioselectivity was observed again and subsequent α-elimination followed by sigmatropic 1,2-shift of metal fragment from phosphorus to nitrogen gave 2-metallo-[1,2,3]diazaphospholes (**17**) (Scheme 5) [23, 24]. Structure of **17** (R = *t*Bu) has been established by X-ray analysis. Interestingly, the ^{31}P NMR chemical shift of **17** at δ ~229 is very close to that of metal free 2*H*-[1,2,3]diazaphospholes [25].



Scheme 5 Synthesis of 2-metallo-[1,2,3]diazaphospholes by [3+2] cycloaddition

2.2 [1,2,4]Diazaphospholes

[1,2,4]Diazaphospholes constitute the widely studied category of diazaphospholes [1, 2, 4]. In analogy with the well-known 1,3-dipolarophilic reactivity of alkynes, participation of phosphaalkynes in [3+2] cycloaddition reactions has been thoroughly investigated and utilized for the synthesis of heterophospholes [2, 4, 7]. Accordingly, bulky *tert*-butylphosphaethyne, on account of its stability and required reactivity, is reported to undergo regiospecific cycloaddition with diazoalkanes to give [1,2,4]diazaphospholes in quantitative yields [26–28]. Following the same methodology, *N*-phosphino-[1,2,4]diazaphosphole (**20**) was obtained quantitatively from the reaction of bis(diisopropylamino)phosphinodiazomethane (**18**) with *tert*-butylphosphaethyne (**19**) at room temperature (Scheme 6) [29]. On the contrary, the corresponding silylated phosphinodiazomethane did not react with *tert*-butylphosphaethyne even on heating at 50°C [29].



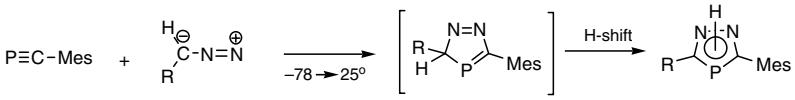
18 **19** **20**

R = *i*Pr$_2$N

Scheme 6 Regiospecific [3+2] cycloaddition of phosphinodiazomethane with phosphaethyne

In order to explain highly regioselective formation of [1,2,4]diazaphospholes over [1,2,3]diazaphospholes in these cycloadditions, preliminary ab initio calculations were carried out at different levels for unsubstituted model compounds, HCP and CH_2N_2. However, the difference between the calculated barriers for the initial [2+3] cycloaddition step in the two cases was not found enough to explain the observed regioselectivity [30]. Recently, regioselective formation of [1,2,4]diazaphosphole has been reinvestigated theoretically at the DFT level by considering the effect of the size of the substituent (H, Me, *t*Bu) on phosphaalkyne, when it is found that with the increasing size of the substituent, calculated barrier for the formation of [1,2,3]diazaphosphole becomes higher, making the reaction kinetically controlled in favor of [1,2,4]diazaphosphole [31].

In an attempt to investigate the synthetic utility of aryl-substituted phosphaalkynes using similar methodology, Regitz and coworkers found that the reactivity of the stabilized tri-*tert*-butylphenylphosphaethyne was remarkably reduced due to extreme shielding by 2,4,6-tri-*tert*-butylphenyl (super mesityl, Mes*) group making it unsuitable for [3+2] cycloadditions [32]. Although, comparatively less bulkier mesitylphosphaethyne **21**, which possesses reasonable stability as well as reactivity, underwent cycloaddition with α-azoalkanes (**13**) at low temperature resulting in the regiospecific formation of 3*H*-[1,2,4]diazaphosphole (**22**), that on aromatization by a sigmatropic 1,5-proton shift furnished [1,2,4]diazaphosphole (**23**) in good yields (Scheme 7).



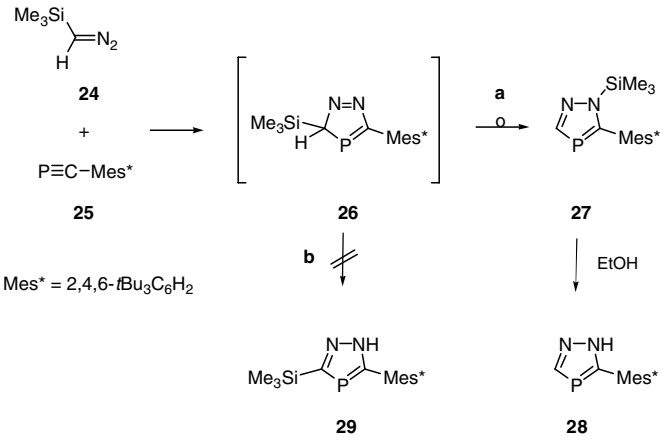
21 **13** **22** **23**

R = CO_2Me, CO_2Et

Scheme 7 Regiospecific [2+3] cycloaddition of mesitylphosphaethyne

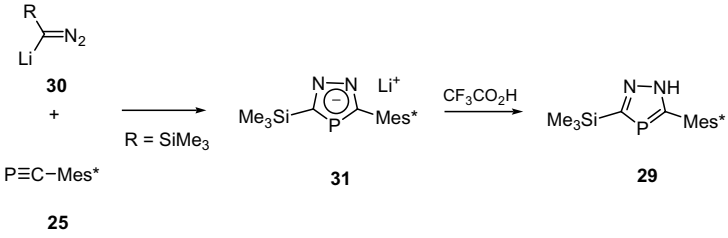
More recently, [2+3] cycloaddition reaction of the tri-*tert*-butylphenylphosphaethyne (**25**) has been reinvestigated, when in spite of the steric encumbrance of extremely bulky Mes* group, the use of trimethylsilylated diazomethane (**24**) makes its cycloaddition successful, which is followed by $SiMe_3$/H migration yielding bulky [1,2,4]diazaphospholes [33]. Phosphaalkyne **25** reacts with **24** in a regioselective manner to form intermediate cycloadduct **26**, which undergoes facile aromatization

by preferential migration of silyl group to furnish 1,5-disubstituted [1,2,4]diazaphosphole **27** (Scheme 8). Greater migratory aptitude of the silyl group as compared to *H*-shift has been explained by B3LYP/6-31+G level calculations. Further treatment of **27** with ethanol resulted in desilylation to afford Mes* substituted [1,2,4]diazaphosphole **28**.



Scheme 8 [2+3] Cycloaddition of tri-*tert*-butylphenylphosphaethyne with silyldiazomethane (**a**) 1,3-silyl shift; (**b**) 1,3-*H* shift

On the other hand, 3,5-disubstituted [1,2,4]diazaphosphole **29** could be obtained from the reaction of tri-*tert*-butylphenylphosphaethyne (**25**) with freshly prepared lithiated trimethylsilyldiazomethane (**30**) and subsequent treatment of the initially formed diazaphospholide ion (**31**) with trifluoroacetic acid (Scheme 9) [33].

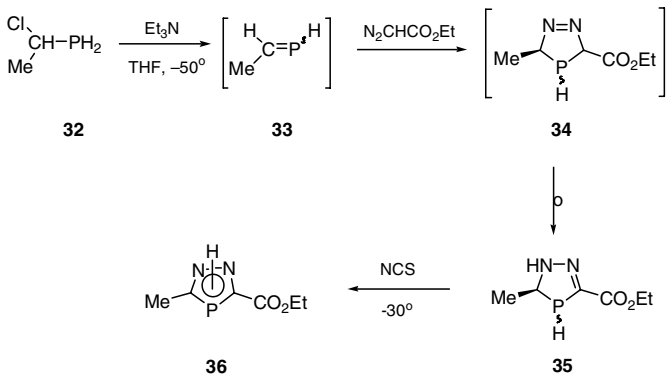


Scheme 9 Reaction of tri-*tert*-butylphenylphosphaethyne with lithiated diazomethane

Reaction of lithiated silyl- and diaminophosphino-diazomethanes (**30**, R = Me_3Si, $(R'_2N)_2P$) with triphosphenium salt, $[((Me_2N)_3P)_2P]^+BPh_4^-$ to give the respectively substituted [1,2,4]diazaphospholes has also been described to take place via the corresponding phosphaalkynes. Triphosphino substituted [1,2,4]diazaphosphole has been obtained by thermolysis of the phosphino-phosphiranyl-diazomethane via the

transient formation of the phosphino-phosphaalkyne [34]. Similar to phophaalkynes, functionalized phosphaalkenes have also been reported to react regiospecifically with diazoalkanes or sydnones. The initially formed [3+2] cycloadduct undergoes facile α-elimination and 1,5-*H* shift on heating or at room temperature to give [1,2,4] diazaphospholes [2, 4, 7]. The methodology was extended to the diazoketones, when the cycloaddition of trialkylsilyl diazoketones and phosphaalkenes gave 3-acyl-[1,2,4]diazaphospholes [35, 36].

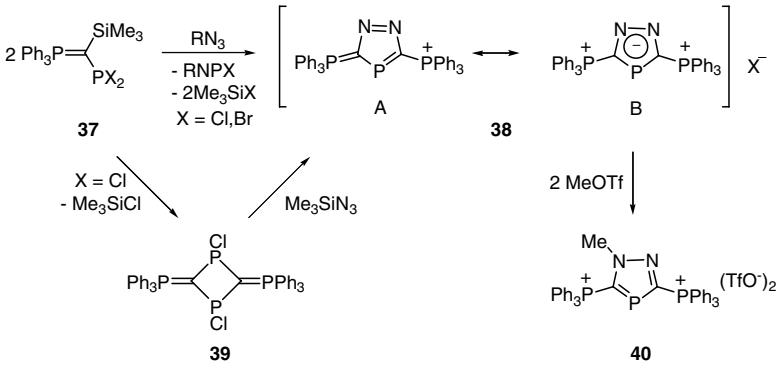
Denis and coworkers [37] could trap transient simple phosphaalkene **33,** generated by HCl elimination from chlorophosphine **32** at low temperatures [38], by ethyl diazoacetate at −50°C. Aromatization of the initially formed isomeric *E*-/*Z*-cycloadducts **35** to [1,2,4]diazaphospholes **36** could be achieved via *P*-chlorination/dehydrochlorination sequence at −30°C using *N*-chlorosuccinimide (Scheme 10).



Scheme 10 Synthesis of [1,2,4]diazaphosphole from transient phosphaalkene

The only method reported so far, for the preparation of 3,5-unsubstituted [1,2,4] diazaphopholes, is the condensation of 2-phosphaallyl cation with hydrazines. This route also provides a good method for obtaining 3,5-homo substituted [1,2,4]diazaphopholes [39, 40]. New [1,2,4]diazaphosphole representatives have been prepared by this route for extensive X-ray structure investigations [41].

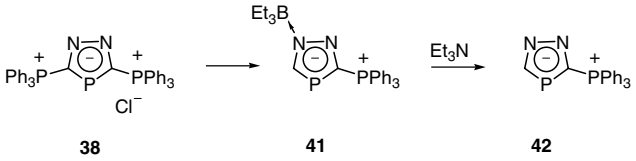
A synthetic approach towards remarkably stable ionic triphenylphosphonio substituted [1,2,4]diazaphosphole from ylidyl dihalophosphines has been reported [42]. Reaction of an excess amount of ylidyl halophosphine **37** with a variety of azides, such as trimethylsilylazide, triphenylsilylazide, tosylazide, or sodium azide led to 3,5-bis(triphenylphosphonio)-[1,2,4]diazaphospholide halide (**38**) (Scheme 11). Alternatively, dichloro-1,3-diphosphetane **39** obtainable from **37**, reacted with trimethylsilyl azide at low temperature to yield **38**. Ionic nature of **38** has been confirmed by ion exchange reactions ($X = BPh_4^-$, BF_4^-, $SbCl_6^-$). By the appearance of an AB_2 spin system in the ^{31}P NMR spectrum, cation of **38** may be considered as a diphosphonio-substituted [1,2,4]diazaphospholide, as represented by resonance structure **B**. As a consequence, reaction of **38** with methyl trifluoromethanesulfonate leads to



Scheme 11 Synthesis of ionic 3,5-bis(triphenylphosphonio)-[1,2,4]diazaphospholide halide from ylidyl dihalophosphines

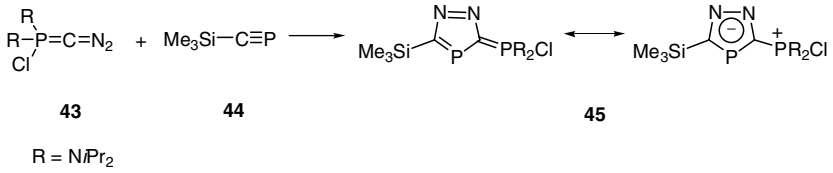
N-methylation affording dicationic 1-methyl-diphosphonio-[1,2,4]diazaphosphole (**40**), which gives three different ^{31}P NMR signals.

Later, a zwitterionic monophosphino-[1,2,4]diazaphospholide **42** was obtained from the reaction of 3,5-bis(triphenylphosphonio)-[1,2,4]diazaphospholide chloride (**38**) with complex boron hydrides [43]. In the initial step, selective extrusion of one PPh_3 group takes place to yield the boron adduct of type **41**, which on further reaction with triethylamine liberates zwitterionic diazaphospholide **42** (Scheme 12).



Scheme 12 Synthesis of zwitterionic phosphonio-[1,2,4]diazaphospholide

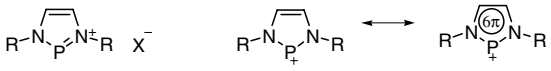
Using an alternative route involving [3+2] cycloaddition of phosphoranediyldiazomethane (**43**) with trimethylsilylphosphaethyne (**44**), 5-trimethylsilyl derivative (**45**) of the zwitterionic 3-phosphino-[1,2,4]diazaphospholide (**42**) was obtained (Scheme 13) [44].



Scheme 13 Synthesis of zwitterionic phosphonio-[1,2,4]diazaphospholide from phosphaacetylene

2.3 *[1,3,2]Diazaphospholes*

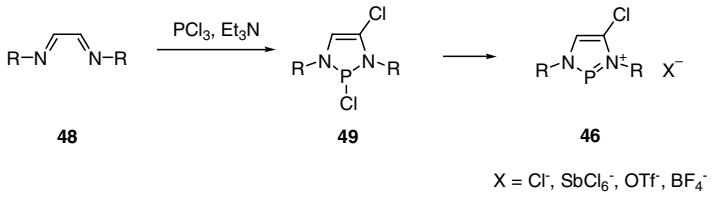
Only limited number of neutral monocyclic [1,3,2]diazaphosphole representatives have been reported, which have mostly been prepared by [4+1] cyclocondensation of diaminomaleodinitrile (DAMN) with P(III) reagent and the alkylation of the initially formed 1,3,2-diazaphospholide [2, 4, 7]. During recent times, 6π-aromatic [1,3,2]diazaphospholium ions of type **46** [45], more often represented as cyclic phosphenium cation **47** [46, 47], have attracted more attention due to their isoelectronic nature with "Arduengo carbenes". Nature of bonding and aromaticity of these cations have been the subject of several experimental and theoretical studies (Structure 2) [48–52].



46 **47**

Structure 2 [1,3,2]Diazaphosphenium cation

[1,3,2]Diazaphospholium salt **46** was first isolated [45] as hexachloroantimonate ($X = SbCl_6$) by chloride abstraction from dichloro-dihydro-[1,3,2]diazaphosphole (**49**), which in turn is accessible from the reaction of 1,2-diiminoethane or 1,4-diazabutadiene (**48**) with phosphorus trichloride and triethylamine [53]. Since then, a number of differently substituted [1,3,2]diazaphospholium salts have been obtained from cyclic chlorophosphines by chloride abstraction using a Lewis acid or ion exchange reactions (Scheme 14) [49, 50]. In an alternative approach, chlorophosphine **49** is first reduced to the corresponding phosphine, which on reaction with trityl tetraflouroborate or triflic acid is converted to **46** [54].

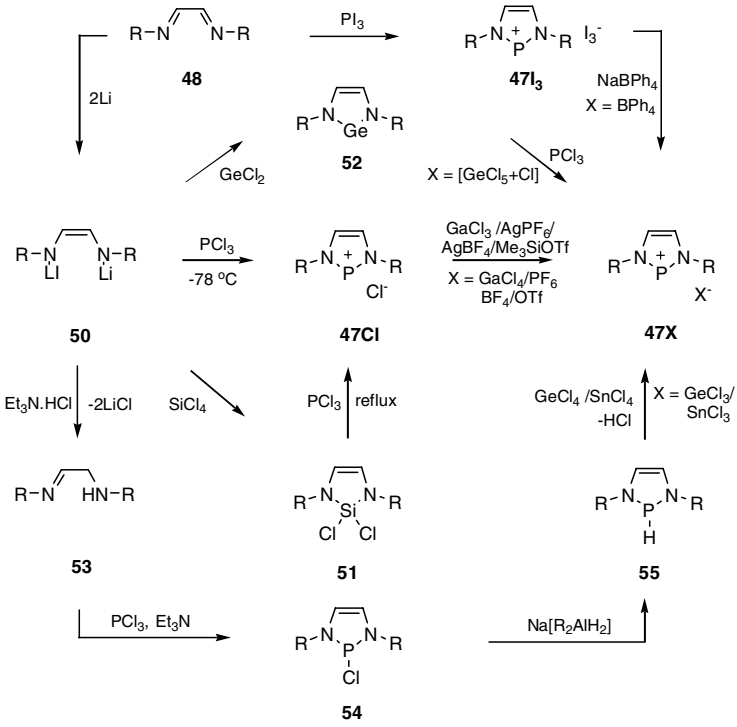


48 **49** **46**

X = Cl^-, $SbCl_6^-$, OTf^-, BF_4^-

Scheme 14 Synthesis of [1,3,2]diazaphospholium salts from diazadienes

Denk et al. reported the first synthesis of 4,5-unsubstituted [1,3,2]diazaphosphenium chloride, **47Cl** from the dilithio reduction product **50** of 1,2-diiminoethane, via cyclic dichloro-diazasilane **51** by means of metathetical reaction of the latter with PCl_3 (Scheme 15) [46]. 1,3-Di-*tert*-butyl-[1,3,2]diazaphosphenium tetrachlorogallate [46], hexafluorophosphate [52], tetrafloruborate [49], and 1,3-dimesityl-[1,3,2]diazaphosphenium triflate [49] were obtained as stable crystalline solids from the

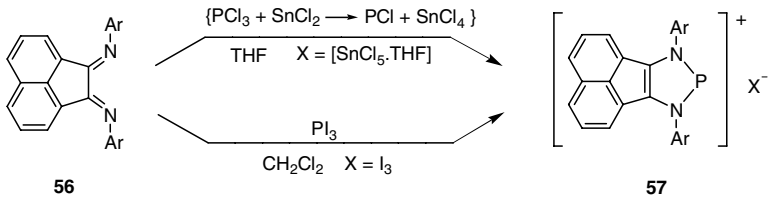


Scheme 15 Different routes to [1,3,2]diazaphosphenium salts

reaction of **47Cl** with $GaCl_3$, $AgPF_6$, $AgBF_4$, or Me_3SiOTf, respectively. Although the attempt to obtain ionic **47** directly from the reaction of **50** with PCl_3 at room temperature failed, during the same time, Cowley and coworkers could isolate crystalline **47Cl** from similar reaction at low temperature (−78°C) [47] (Scheme 15). As an alternative synthetic route, redox reaction of diazagermylene **52** with PCl_3 afforded phosphenium ion **47**, which crystallized with equimolar quantities of $GeCl_5^-$ and Cl^- anions in the form of $[\mathbf{47}]_2[GeCl_5^-][Cl^-]$ [47].

More recently, reaction of *P*-hydrogen-substituted [1,3,2]diazaphospholene **55** with tetrachlorides of group 14 elements has been reported to proceed via hydride/chloride metathesis to give the phosphenium salts **47X** (X = $GeCl_3$/$SnCl_3$) (Scheme 15) [55]. This reactivity presents a case of "Umpolung" as compared to known reaction of phosphines. Hydridic nature of the P–H bond has been attributed to the bond weakening because of the presence of *N*-lone pair associated hyperconjugative interactions [54, 56]. The diazaphospholene **55** is obtainable from chlorodiazaphopholene **54** by hydride transfer using sodium bis(methoxyethoxy) aluminiumdihydride. Besides, **54** has been prepared by an improved one pot method involving protonation of dianion **50** with triethylammonium hydrochloride and reaction of the resulting α-aminoaldimine **53** with PCl_3 in the presence of triethylamine [55].

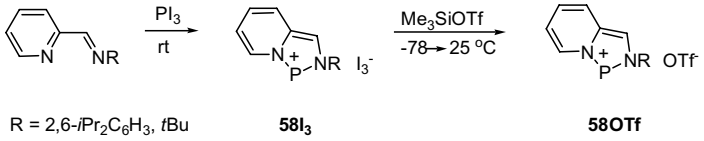
In analogy with synthesis of triphosphenium ion involving redox reaction of PCl_3 with $SnCl_2$ in presence of bis(phosphines) reported by Schmidpeter et al. [57], Cowley and coworkers recently treated 1,2-bis(diisopropylphenylimino)acenaphthene (**56,** dpp-BIAN) with equimolar mixture of PCl_3 and $SnCl_2$ in THF solution at ambient temperature to obtain a phosphenium compound anellated with acenaphthene ring, i.e. [(dpp-BIAN)P][$SnCl_5$.THF] (**57**) (Scheme 16) [58]. In a parallel one step approach, redox reaction of phosphorus triiodide with equimolar quantity of dpp-BIAN (**56**) in CH_2Cl_2 yields related phosphenium triiodide **57** ($X^- = I_3^-$) (Scheme 16). It has been proposed that initial interaction of dpp-BIAN with PI_3, results in the formation of [(dpp-BIAN)PI] and molecular I_2, which is followed by abstraction of I^- by I_2 [58]. Likewise, by making use of the reaction of diazadienes **48** with phosphorus triiodide, several monocyclic *N*-alkyl/aryl [1,3,2]diazaphosphenium triiodides (**47I$_3$**) have been obtained in >80% yields [59, 60]; further reaction of **47I$_3$** with $NaBPh_4$ afforded the respective tetraphenylborates (Scheme 15).



Scheme 16 Synthesis of [(dpp-BIAN)P][$SnCl_5$.THF]/[I_3] from the reaction of (dpp-BIAN) with (PCl_3 + $SnCl_2$) or PI_3

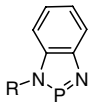
Shortly after this, Gudat and coworkers followed Cowley's approach involving redox reaction of phosphorus triiodide to synthesize the pyrido anellated phosphenium triiodides (**58I$_3$**) by treating 2-carbimino pyridines with PI_3 in THF at room temperature. The triiodide salts thus obtained have been converted into the triflates (**58OTf**) by addition of excess trimethylsilyl triflate (Scheme 17). **58OTf** have been characterized by single crystal X-ray diffraction studies and a similar degree of aromaticity as in the monocyclic cations has been assigned on the basis of computational calculations [51].

Previous attempts to synthesize benzo[1,3,2]diazaphosphole (**59**) in an analogous manner from benzene-1,2-diimines by Malavaud et al. led to tetrameric cyclo-phosphazanes, which existed in equilibrium with monomer only at



Scheme 17 Synthesis of pyrido anelleted [1,3,2]diazaphosphenium salts

Structure 3 Benzo[1,3,2] diazaphosphole



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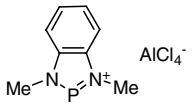
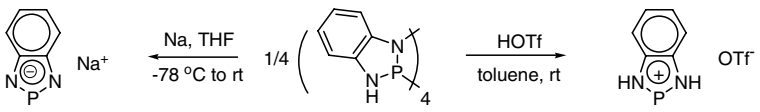


60

elevated temperature [61, 62]. Later, a monomeric *N*-alkylated representative, 1,3-dimethyl-[1,3,2]benzodiazaphospholium tetrachloroaluminate **60** was obtained by chloride abstraction from *P*-chloro-1,3-dimethylbenzazaphosphole (Structure 3) [63].

Very recently, Gudat and coworkers have reported preparation of isoelectronic benzo[1,3,2]diazaphospholide anion **62** and benzo[1,3,2]diazaphospholium cation **63** from same cyclo-tetraphosphazane precursor **61** [64]. Anion **62** (δ ^{31}P 271), was obtained in quantitative yield from the reaction of **61** with equivalent amount of sodium metal at −78°C, while the cation **63** (δ ^{31}P 212) could be obtained by treating **61** with Brønsted acid, TfOH at room temperature (Scheme 18). Structures of sodium benzo[1,3,2]diazaphospholide and benzo[1,3,2]diazaphospholium triflate have been determined by X-ray analysis and their theoretically calculated aromaticities have been found to be comparable to the neutral benzo[1,3,2]diazaphosphole **59** (R = H). The latter was not accessible by thermal cleavage of the tetramer **61** due to its limited thermal stability [62]. An attempt to generate the same via proton transfer reaction between **62** and **63** at low temperature also failed and again led to the tetrameric **61** [64]. Relatively higher stability of both the anion **62** and the cation **63** as compared to the unusually high tendency of neutral benzodiazaphosphole for oligomer formation has been attributed to the presence of like charge on the molecules in former cases, which prevents their oligomerization. Calculations of magnetic and geometrical aromaticity indexes confirm aromatic character of the five-membered ring in the cation of type **63** that is lost upon introduction of a substituent at the phosphorus atom, which thereby facilitates reaction of *P*-amino substituted anellated diazaphospholenes under cleavage of the fused ring system [51].

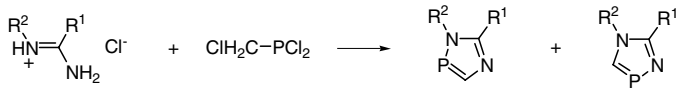


62 **61** **63**

Scheme 18 Synthesis of benzo[1,3,2]diazaphospholide anion and benzo[1,3,2]diazaphospholium cation

2.4 [1,4,2]Diazaphospholes

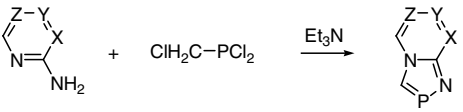
[1,4,2]Diazaphospholes could be synthesized quite late [65, 66] and in some of the earlier literature reports, have been inaccurately numbered as [1,3,4]diazaphospholes. Monocyclic [1,4,2]diazaphospholes are mostly obtained [66] as a mixture of 1*H*- (**66**) and 4*H*- (**67**) isomers from [3+2] cyclocondensation of alkylamidinium chlorides (**64**) with (chloromethyl)dichlorophosphine (**65**) [67] (Scheme 19).



64 **65** **66** **67**

Scheme 19 Synthesis of monocyclic [1,4,2]diazaphospholes from [3+2] cyclocondensation

A variety of anellated 1*H*- and 4*H*-[1,4,2]diazaphospholes could be obtained by our research group via [3+2] cyclocondensation and [4+1] cyclocondensation routes [7–9]. Condensation of 2-aminoazines (**68**) with chloromethyldichlorophosphine (**65**) proceeds with complete regioselectivity to afford 3-unsubstituted [4,5]-anellated [1,4,2]diazaphospholoazines (**69**) (Scheme 20). In this manner, [1,4,2]diazaphospholo [4,5-*a*]pyridine, -[4,5-*a*]pyrimidine, -[4,5-*c*]pyrimidine, -[4,5-*a*]pyrazine, and -[4,5-*a*]quinoline have been prepared [68, 69].

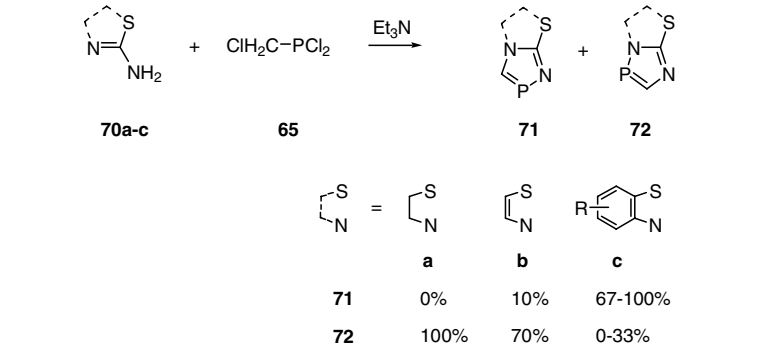


68 **65** **69**

X / Y / Z = CH / N

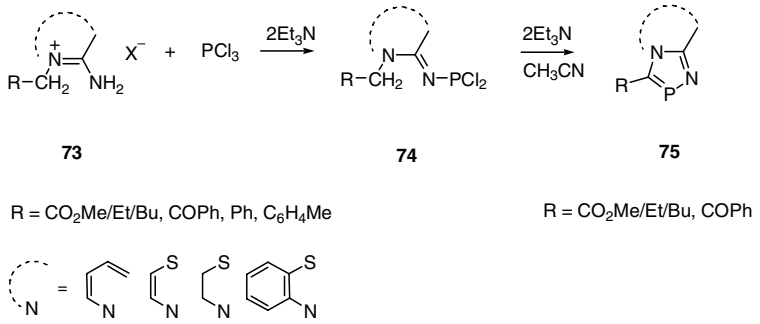
Scheme 20 Synthesis of 3-unsubstituted [4,5]-anellated [1,4,2]diazaphospholoazines from regioselective [3+2] cyclocondensation

On the other hand, condensation of 4,5-dihydrothiazole-2-amine (**70a**) with **65** follows reversed regioselectivity to give 1*H*-isomer, i.e. 5,6-dihydrothiazolo[2,3-*e*][1,4,2]diazaphosphole (**72a**). However, from similar reaction of thiazole-2-amine (**70b**) and benzothiazole-2-amine (**70c**), a mixture of 1*H*- and 4*H*- regioisomers is obtained (Scheme 21) [69].



Scheme 21 Synthesis of thiazolo[3,2-*d*]- and -[2,3-*e*][1,4,2]diazaphospholes

Extending our facile methodology of anellated azaphospholes, involving [4+1] cyclocondensation of 1,2-disubstituted cycloiminium salts with PCl_3 in the presence of Et_3N [13, 70–72] to 1-alkyl-2-aminocycloiminium salts (**73**), we obtained 3-substituted [1,4,2]diazaphospholes (**75**) anelleted to pyridine, thiazole, dihydrothiazole, and benzothiazole systems [73–75]. The reaction proceeds via intermediacy of aminodichlorophosphine **74**, which can be isolated by carrying out the reaction with limited amount of base in a non-polar solvent such as toluene (Scheme 22). The intermediate **74** undergoes intramolecular cyclization to afford anelleted 3-substituted [1,4,2]diazaphosphole **75**, only if the *N*-methylene group is sufficiently activated (R = CO_2Me, CO_2Et, CO_2Bu, COPh, etc.) [73, 76, 77].



Scheme 22 Synthesis of 3-substituted [1,4,2]diazaphospholes

3 X-ray Structure Analysis and Theoretical Calculations

NMR spectroscopy (^{31}P, ^{1}H, ^{13}C) and mass spectrometery have been extensively employed for establishing structures of the diazaphospholes. The solid state ^{13}C and ^{15}N CPMAS NMR spectra of 3,5-di-substituted [1,2,4]diazaphospholes have been recorded [78]. Several X-ray crystal structures have been reported for a number of

differently substituted [1,2,4]diazaphopsholes [33, 41, 42, 78–80]. Diazaphosphole ring in all cases is almost planar, the endocyclic CPC angle being 85–87° [2]. In solid state, while the 1*H*-[1,2,4]diazaphosphole crystallizes in a helix of the order 3 [41], 1*H*-5-(2,4,6-tri-*tert*-butylphenyl)-[1,2,4]diazaphosphole forms a trimer [33]. On the other hand, bulky 1*H*-3,5-di-*tert*-butyl-[1,2,4]diazaphosphole [41] and 1*H*-3-trimethylsilyl-5-(2,4,6-tri-*tert*-butylphenyl)-[1,2,4]diazaphosphole [33] exist as dimers, revealing association due to the presence of intermolecular N–H…N hydrogen bonds. In the case of 1*H*-3,5-diphenyl-[1,2,4]diazaphosphole, two different cyclic dimers with disordered N-H…N hydrogen bonds are observed showing *Intermolecular Solid State Proton Transfer*, due to which a dynamic equilibrium within the two isomers is present [79]. Intermolecular N–H…N hydrogen bonding has been rationalized by carrying out DFT calculations [78, 79].

Molecular structures of a good number of [1,2,3]diazaphosphole representatives have already been investigated and previously reviewed [2]. Recent investigations pertain to the geometries of their metal complexes [18, 81–83]. In the X-ray determined geometry of 2-metallo-[1,2,3]diazaphospholes (**17**, Scheme 5), the Fe atom lies in the plane of the diazaphosphole ring [22, 23], while the ring bond distances are comparable to those reported previously for 2-acetyl-5-methyl-[1,2,3]diazaphosphole [2, 4], and the endocyclic angle at phosphorus was found somewhat greater (91°).

We have recently investigated X-ray structure of 3-methoxycarbonyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine as first example of molecular structure determination for [1,4,2]diazaphosphole ring [84]. The ester substituent lies strictly in the molecular plane with carbonyl group in the *trans* orientation with the formal C=P bond. Endocyclic P–N and P–C bonds are averaged between respective single and double bond lengths.

During the last decade, a number of reports regarding X-ray structure determination of [1,3,2]diazaphosphenium ions have appeared [50–52, 55, 58, 59, 63, 64]. It is found interesting to note that while in *P*-hydro diazaphospholenes, there is considerable deviation from planarity [54, 55], the diazaphosphenium ring (P-N, 1.66–1.69 Å; C-N, 1.37–1.39 Å; C-C, 1.34–1.39 Å) is strictly planar indicating aromatic stabilization.

X-ray structures of isoelectronic and planar benzo[1,3,2]diazaphospholide (**62**) and benzo[1,3,2]diazaphospholium ions (**63**) reveal some interesting features [64]. Benzodiazaphospholide unit binds to metal ions of two $[Na(THF)_2]^+$ moieties *via* nitrogen lone pairs forming a zig-zag chain. Benzodiazaphospholium triflate presents a remarkable example of stabilization of phosphenium cation exclusively by π-delocalization without any steric or inductive influences. In this case, two crystallographically independent pairs of cations and anions were observed; phosphorus atom of one is surrounded by six oxygen atoms from three triflates, whereas the second has short contacts with two oxygen neighbors and π-electron systems of two adjacent cations. Pyrido anellated phosphenium triflates (**58OTf**) also exhibit similar structural features including bond length equalization and hence similar aromatic character as of benzodiazaphospholium ion [51].

Due to their isoelectronic relationship with "Arduengo carbenes", stabilization of cyclic phosphenium ions by π-electron delocalization has been a matter of debate.

The calculated enthalpies of isodesmic reactions suggest a weak aromatic character of these ions [85]. Aromatic stabilization energy (ASE) of monocyclic [1,3,2]diazaphospholenium ions has been found to be comparable to that of pyrrole. Cyclic delocalization was supported by the calculation of magnetic susceptibility, charge distribution, and natural bond orbital (NBO) analysis [48]. Computational calculations of anellated *N*-heterocyclic phosphenium ions [51, 64], which include the evaluation of NICS, isomer stabilization energies (ISE), Bird index (BI), and bond shortening index (BDSHRT), indicate similar degree of aromaticity as in related monocyclic cations.

Comparison of the conjugative abilities of P=C and C=C bonds in five membered rings including the four categories of diazaphospholes has been made on the basis of π ionization energies and heat of ring fragmentation reactions [86]. It has been inferred that in conjugative interactions, C=C bond is similar to P=C rather than to N=C bond. Our theoretical studies about the effect of CH/P exchange in the pyrido anellated mono-, di-, and triazoles at DFT level are in conformity with this conclusion [87].

4 Reactions

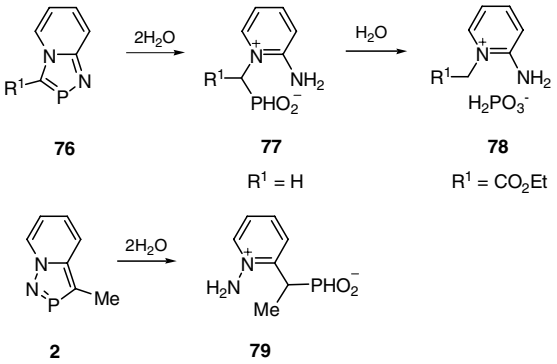
Diazaphospholes, on account of the presence of several functionalities, undergo a variety of reactions. Due to easy accessibility, reactivity of [1,2,3]diazaphospholes (**B**) has been most widely investigated. Reactions of diazaphospholes reported until mid 1990s have been reviewed several times [1, 2, 4, 6, 7]. The reactions reported during more recent times have been highlighted herein and have been categorized according to endocyclic functionalities present within the diazaphosphole ring which include C=P double bond and the lone pairs of ring phosphorus as well as nitrogen and exocyclic functionalities.

4.1 1,2-Addition of Polar Reagents

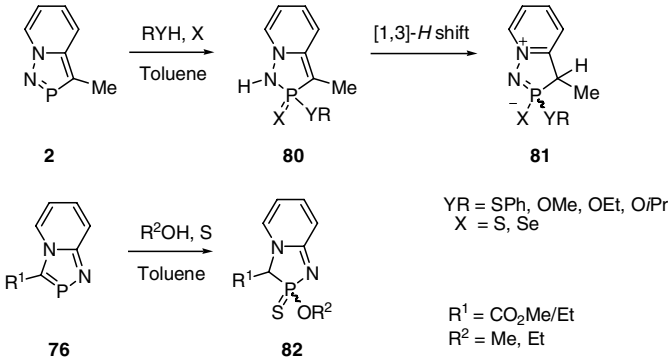
A variety of polar reagents add to P=C or P=N bond when more electronegative part is bonded to phosphorus. Addition of two water molecules on P=C bond in [1,4,2]diazaphospholo[4,5-*a*]pyridine (**76**) and P=N bond in [1,2,3]diazaphospholo[1,5-*a*]pyridine (**2**) causes ring opening (Scheme 23) [16, 68]. In the case of **76** (R = CO_2Et), further hydrolysis to pyridinium salt **78** was observed [73].

Addition of alcohol occurs on P=N bond of [1,2,3]diazaphospholo[1,5-*a*] pyridine (**2**) and P=C bond of [1,4,2]diazaphospholo[4,5-*a*]pyridine (**76**) in the presence of sulfur or selenium. In the case of **2**, addition is followed by 1,3-*H* shift and a catalytic amount of the respective alkoxide is required for completion of reaction at room temperature. The reaction of **2** with thiophenol is completed at reflux temperature in the presence of sulfur (Scheme 24) [88].

In continuation to previously reported 1,2-addition of protic reagents such as alcohols, glycols, amines, etc. on C=P moiety of 2*H*-[1,2,3]diazaphospholes [1, 2, 4, 7],



Scheme 23 Hydrolysis of diazaphospholopyridines

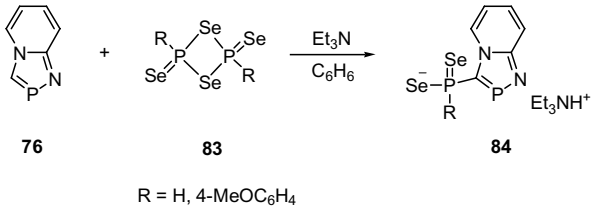


Scheme 24 Addition of polar reagents on N=P or C=P bond of diazaphospholopyridines

more reports involving similar reactions have appeared [89–93]. Formation of spirophosphorane derivative as a result of initial 1,2-addition of bifunctional reagent followed by 1,1-addition of the second functionality on phosphorus atom has also been described [94, 95].

4.2 N-Alkylation and C-Substitution

σ^2-Nitrogen of the diazaphosphole ring in [1,4,2]diazaphospholo[4,5-*a*]pyridines [73], [1,2,3]diazaphospholo[1,5-*a*]-pyridines [16] and thiazolo[3,2-*d*][1,4,2]diazaphospholes [74] is methylated in preference to phosphorus on reaction with Me_2SO_4 to furnish *N*-methylated salts; however, no reaction was observed with methyl iodide in each case. In another interesting reaction, [1,4,2]diazaphospholo[4,5-*a*] pyridine (**76,** R^1 = H) on treatment with 1,3,2,4-diselenadiphosphetane-2,4-diselenides **83** and Et_3N afforded the respective diselenophosphinates **84** (Scheme 25) [96].

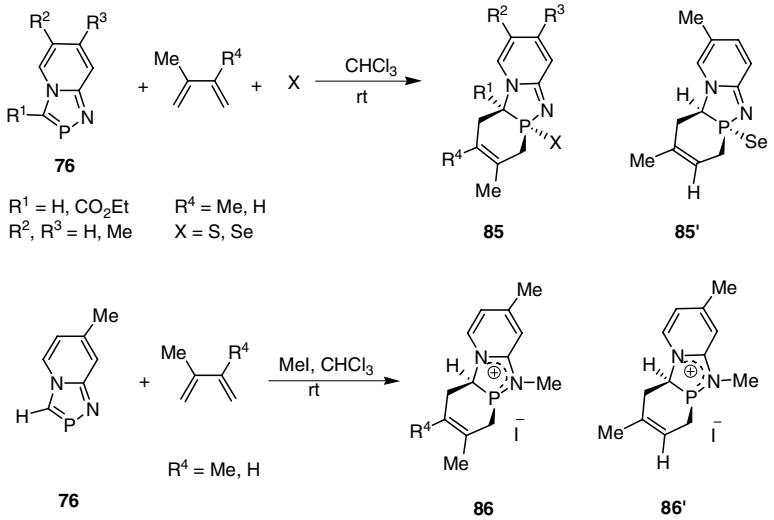


Scheme 25 Diselenophosphinylation of [1,4,2]diazaphospholo[4,5-*a*]pyridine

4.3 [2+4] Cycloaddition

P=C moiety in heterophospholes undergoes cycloaddition reactions with a variety of dienes and dipoles to afford a range of new heterocycles having bridgehead phosphorus atom [2, 4, 97, 98]. Previously, the reactivity of diazaphospholes towards cycloaddition reactions has been investigated to a limited extent [98].

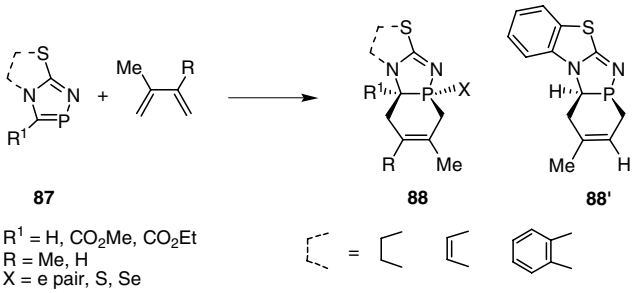
As a variety of anellated diazaphospholes have been synthesized in our group, we have investigated their Diels-Alder (DA) reactions experimentally as well as theoretically. [1,4,2]Diazaphospholo[4,5-*a*]pyridines **76** underwent DA reaction with butadienes with high diastereo- and regioselectivity that could be completed at room temperature in the presence of sulfur or selenium [99]. The reaction with unsymmetrical diene, isoprene yielded a 4:1 mixture of two regiomers **85** and **85′** (Scheme 26). When a similar reaction of **76** (R^1 = H) with 1,3-butadiene or isoprene was carried out in the presence of methyl iodide, methylation occurred at the σ^2,λ^3-nitrogen to afford **86**. In the case of isoprene, two regioisomers **86** (R^4 = H) and **86′** were formed regioselectively, the former being the major one (70%) (Scheme 26).



Scheme 26 Diels–Alder reaction of [1,4,2]diazaphospholo[4,5-*a*]pyridines

Since the diazaphosphole **76** does not react with methyl iodide, it was concluded that methylation occurs after the [2+4] cycloadduct is formed. The observed regioselectivity has been explained on the basis of DFT calculations [99].

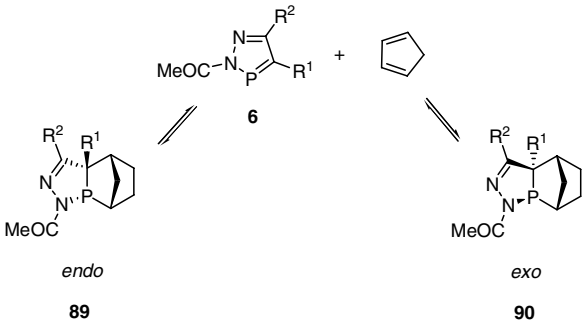
Likewise, thiazolo[3,2-*d*][1,4,2]diazaphospholes and their 5,6-dihydro and benzo derivatives (**87**) reacted with 2,3-dimethylbutadiene and with isoprene with or without sulfur/selenium to give [2+4] cycloadducts **88** and **88′** diastereo- and regioselectively (Scheme 27) [100].



Scheme 27 Diels–Alder reaction of thiazolo[3,2-*d*][1,4,2]diazaphospholes

We have carried out DFT level investigations to explain the observed stereo and regioselectivities. Concerted nature of the mechanism has been confirmed by the involvement of aromatic but asynchronous transition structures as confirmed by their NICS values in each case [101, 102].

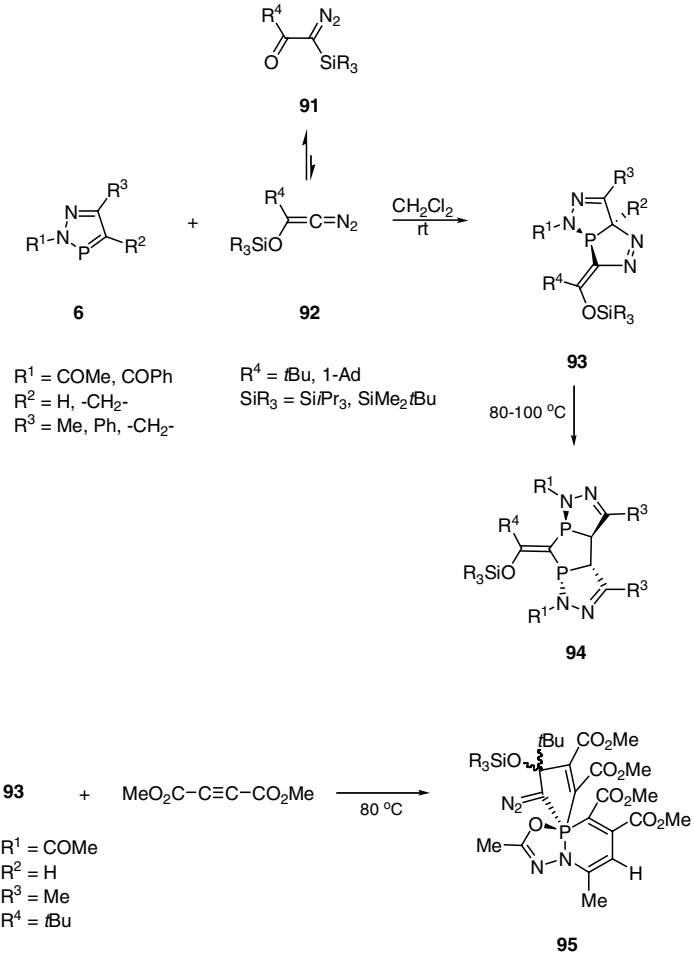
Guo et al. have reported Diels–Alder reaction of differently substituted 2-acetyl-[1,2,3] diazaphospholes, **6** with cyclopentadiene and obtained both endo and exo cycloadducts in moderate yields depending on the reaction conditions (Scheme 28). By quenching the room temperature reaction after only 5 min, endo product **89** was obtained exclusively in 65–75% yields, while prolongation of reaction time to 3 days led to the isolation of only exo product **90** in 50–75% yields [19].



Scheme 28 Diels–Alder reaction of 2-acetyl-1,2,3-diazaphospholes

4.4 [2+3] Cycloaddition

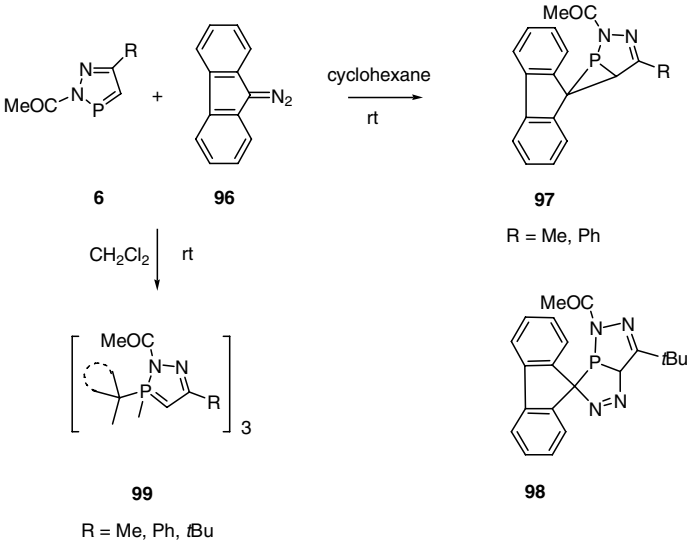
Diazaphospholes are known to undergo facile 1,3-dipolar cycloaddditions with a variety of dipoles [2, 4, 7, 98]. During recent years, some interesting [2+3] cycloaddition reactions have been reported. 2-Acyl-[1,2,3]diazaphospholes **6** were reported to undergo [2+3] cycloaddition with diazocumulene **92**, the minor equilibrium isomer of α-diazo-α-silyl ketones **91**, to form a bicyclic cycloadduct **93** (Scheme 29). Thermolysis of the cycloadduct results in the formation of tricyclic phosphorus heterocycle **94**, which can be explained due to the possibility of two parallel reactions of cycloadduct. On the one hand, extrusion of molecular nitrogen from **93**



Scheme 29 1,3-Dipolar cycloaddition of 1-diazo-2-silyloxy-1-alkene and thermolysis of the cycloadduct

generates novel 3-alkylidene-[1,2,3](λ^5)-diazaphosphole, which is trapped by the parent diazaphosphole molecule generated by parallel cycloreversion reaction occurring at high temperature. Heating of the cycloadduct **93** in the presence of excess amount of DMAD resulted in the formation of a mixture of diastreomeric 1:2 adducts, spiro-λ^5-phosphorane **95** that could be characterized by X-ray crystallography [103, 104].

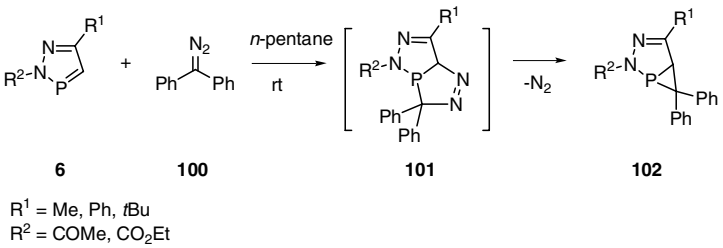
Recently, [2+3] cycloaddition reaction of 2-acetyl-[1,2,3]diazaphosphole (**6**) with 9-diazofluorenes (**96**) has been reported [105, 106]. From the reaction in cyclohexane at rt, bicyclic phosphirane **97** was obtained as a result of the loss of nitrogen from the initial cycloadduct (Scheme 30). The cycloadduct, 3-spiro substituted 3*H*-[1,2,4]diazaphospholo-fused [1,2,3]diazaphosphole (**98**) could be isolated in good yield at room temperature in one case; (R = *t*Bu) its stability was assigned to the presence of bulky *tert*-butyl group at 7-position. Use of polar solvent like dichloromethane led to the cyclic trimeric compound **99** (Scheme 30).



Scheme 30 [3+2] Cycloaddition of 2-acetyl-[1,2,3]diazaphosphole with 9-diazofluorene

A similar reaction with diphenyldiazomethane gives phosphabicyclohexene **102** exclusively by elimination of nitrogen atom from initial cycloadduct **101** (Scheme 31) [105].

Reactivity of diazo compounds towards 1,3-dipolar cycloaddition reactions with 1*H*-[1,2,3]-, 2*H*-[1,2,3]-, [1,3,2]-, and [1,2,4]diazaphospholes has been rationalized by FMO approach using DFT calculations [107]. In most of the cases, $HOMO_{Dipole}$-$LUMO_{Dipolarophile}$ interaction has been found to control the reactivity and among different categories of investigated heterophospholes, 2-acyl-substituted [1,2,3] diazaphospholes exhibit highest dipolarophilic reactivity.



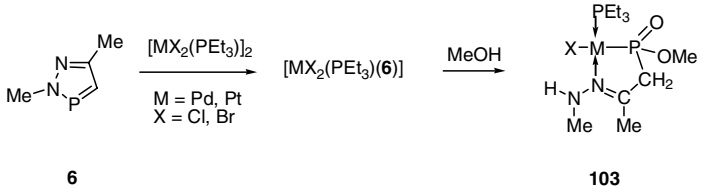
Scheme 31 [3+2] Cycloaddition of 2-acetyl [1,2,3]diazaphosphole with diphenyldiazomethane

4.5 Coordination Reactions

The coordination chemistry of diazaphospholes has attracted much attention during the last decade. Among various categories of diazaphospholes, coordination behavior of [1,2,3]- and [1,2,4]diazaphospholes has been investigated. They provide a variety of ligating sites, in addition to the phosphorus and =N– lone pairs; π coordination of the type η^2 and η^5 is also possible. In 4-phosphino-[1,2,3] diazaphospholes, coordination takes place via exocyclic phosphino phosphorus. Accordingly, complexation reactions can be subdivided into two categories-

4.5.1 Coordination via Endocyclic Moieties

Low valent transition metal centers preferentially coordinate to the phosphorus in diazaphospholes. Accordingly, *P*-coordinated complexes of [1,2,3]diazaphospholes with Cr, W, Fe, and Mn carbonyls were obtained as early as 1980 [1, 2, 4]. Later, Kraaijkamp et al. observed [108] both *P*- or *N*-coordination modes in complexes of [1,2,3]diazaphospholes with $MX_2(PEt_3)$ (M = Pt, Pd; X = Cl, Br). Methanolysis of these complexes led to the diazaphosphole ring opening and formation of five membered metallacyclic *P,N*-chelates (**103**), incorporating *P*-bonded phosphonite and *N*-coordinated hydrazone functionalities (Scheme 32) [109].



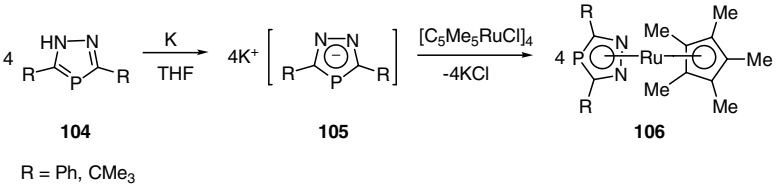
Scheme 32 Synthesis and methanolysis of palladium/platinum complexes of [1,2,3]diazaphospholes

Deprotonated 1*H*-[1,2,4]diazaphospholes, exhibit aromatic delocalization by virtue of 6π electrons like cyclopentadienyl ligand in the anionic ring, which, in addition to the donor lone pairs on *N* or/and *P* heteroatoms, makes them promising ligands with varied coordination modes. However, till the last decade, they had

received little attention in this respect and most of their coordination reactions have been reported during the last few years.

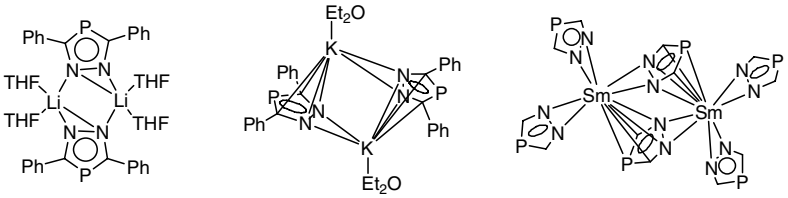
Lithium complex bearing a η^1:η^1-[1,2,4]diazaphospholide ligand, [(η^1:η^1-dp)-(μ-Li)(DME)]$_2$ (DME = 1,2-dimethoxyethane) was first reported by Gudat and coworkers [43]. Lithium [1,2,4]diazaphospholide further binds to two $M(CO)_5$ fragments by coordination via the lone pair of the P and one N atom. Formation of mononuclear *P*-coordinated complexes as intermediates is supported by indication of more efficient M→L back donation for *P*- than for *N*-bound fragment by X-ray and spectroscopic studies.

Zheng et al. treated potassium [1,2,4]diazaphospholides, obtained from the reaction of 3,5-disubstituted-[1,2,4]diazaphospholes with metallic potassium in THF, with $[Cp^*RuCl]_4$ to afford [(η^5-dp)RuCp*] type pseudoruthenocene complex (**106**) (Scheme 33). Sandwich structure with almost eclipsed orientation of two π-bonded ligands has been confirmed by X-ray crystal structure determination [110]. Catalytic application of [(η^5-dp)RuCp*] complexes in the Heck reaction has also been investigated [111].



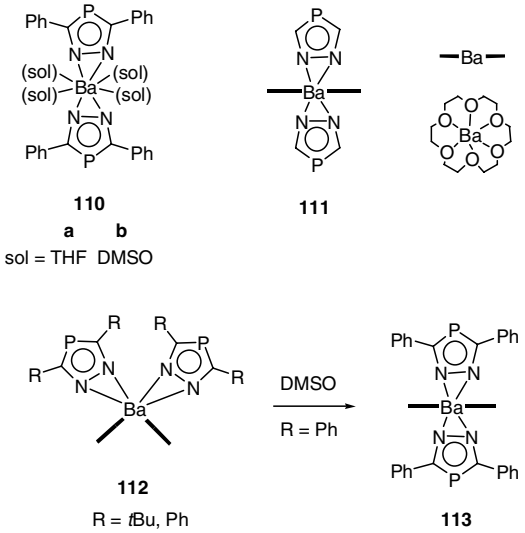
Scheme 33 Synthesis of pseudoruthenocene complex of [1,2,4]diazaphospholides

Quite recently, structural conformations of several alkali metal complexes of [1,2,4]diazaphospholides with different coordination modes have been investigated. From the reaction of 3,5-diphenyl-[1,2,4]diazaphosphole with *n*BuLi in THF, a dimeric [(η^2:η^1-3,5-Ph_2dp)Li(THF)]$_2$ complex (Structure **107**) with mixed endo–exo-multidentate bridging coordination sites has been obtained. Alternatively, the reaction with KH in Et_2O affords a polymeric [(η^2:η^4-3,5-Ph_2dp)K(Et_2O)$_2$]$_n$ complex **108**, the structure of which has been established by X-ray crystallography [112]. Similarly, several 3,5-disubstituted [1,2,4]diazaphospholide samarium complexes have also been reported. Different coordination modes, η^1, η^2, η^4, and η^5 of diazaphospholide ring e.g. in **109**, have been evinced by X-ray crystal structure analysis (Structure 4) [113].



Structure 4 Different coordination modes of [1,2,4]diazaphospholide

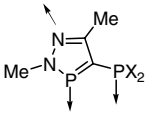
Subsequently, several barium [1,2,4]diazaphospholide complexes have been prepared by transamination of $Ba[N(SiMe_3)_2]_2(THF)_2$ and [1,2,4]diazaphospholes and have been characterized by X-ray crystallography [114]. The reaction of 3,5-diphenyl-[1,2,4]diazaphosphole in THF or DMSO results in $[(\eta^2(N,N)\text{-}3,5\text{-}Ph_2dp)_2Ba(THF)_4]$ **110a** and $[(\eta^2(N,N)\text{-}3,5\text{-}Ph_2dp)_2Ba(DMSO)_4]$ **110b** having trans orientation of the two diazaphosphole rings. When the reaction is carried out in the presence of 18-crown-6, unsubstituted [1,2,4]diazaphosphole in THF or DMSO a *trans*-bis([1,2,4]diazaphospholide)-(18-crown-6)-barium complex **111** is obtained, while under similar conditions in a mixture of THF and hexane, bulky 3,5-di-substituted diazaphospholes, *cis*-bis([1,2,4]diazaphospholide)-(18-crown-6)-barium complex **112** is obtained, which presents the first barium complex with two organic ligands on the same side of 18-crown-6. In the case of diphenyl substituted diazaphosphole, initially formed *cis* complex **112** on leaving the DMSO solution changes into *trans* isomer **113** (Scheme 34).



Scheme 34 Formation of *cis* and *trans* barium [1,2,4] diazaphospholide complexes

4.5.2 Coordination via Exocyclic Moieties

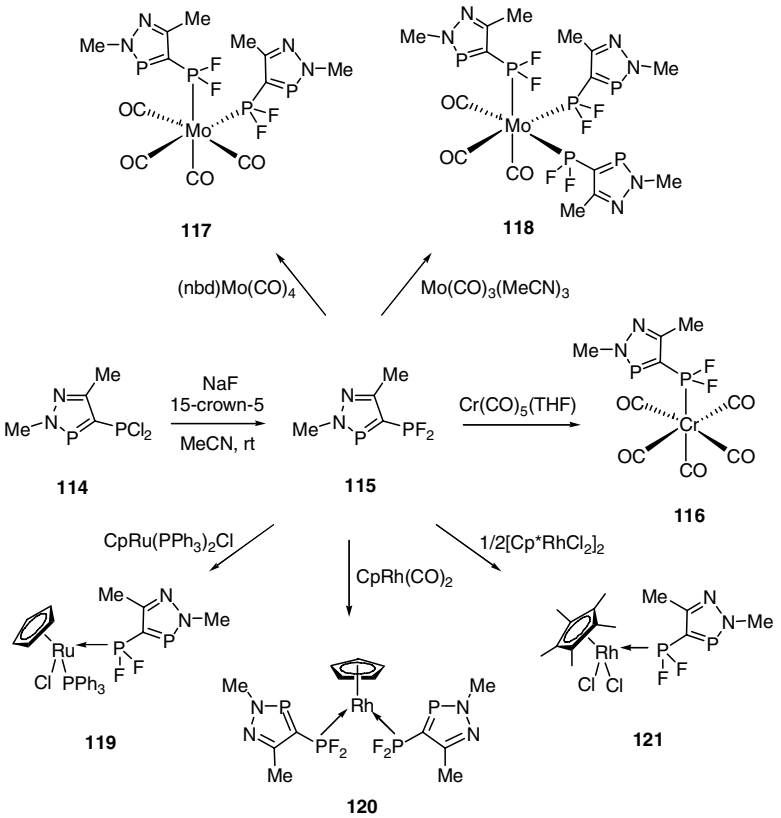
Coordination behavior of 2,5-dimethyl-4-phosphino-[1,2,3]diazaphosphole as potential multifunctional ligand has been investigated for complexation with a variety of metal centers. Despite the presence of three possible coordination sites, coordination takes place via exocyclic phosphino phosphorus (Structure 5) [81–83, 115].



Structure 5 Potential coordination sites in 4-phosphino-[1,2,3]diazaphosphole

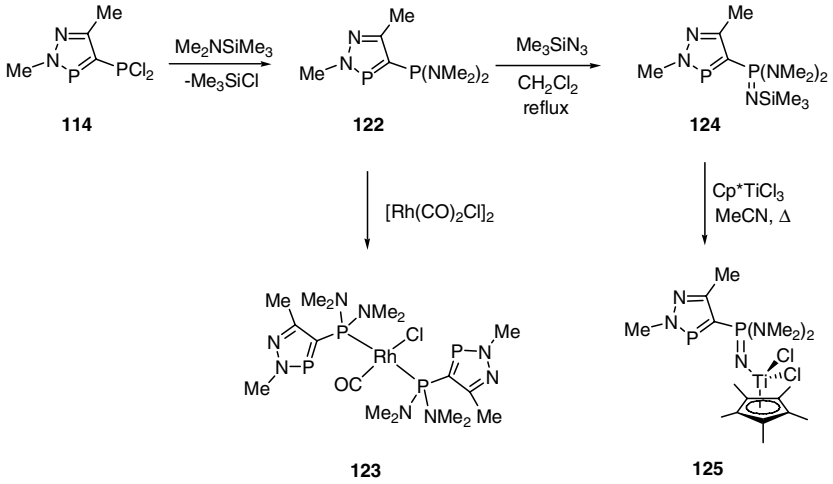
Investigation of the coordination chemistry of 4-difluorophosphino-2,5-dimethyl-2*H*-[1,2,3]diazaphosphole (**115**) by Cavell and coworkers displayed in all cases, the coordination of metal center with exocyclic phosphorus only, which has been verified by X-ray structure determination in many cases [81–83, 115]. The difluorophosphino ligand **115** was obtained by fluorination of the corresponding dichloro derivative **114** using sodium fluoride in the presence of a small amount of 15-crown-5 [115] (Scheme 35). Coordination behavior of difluorophosphine ligand has been found to be similar to that of phosphorus trifluoride due to better π acceptor properties. While the treatment of **115** with $Cr(CO)_5(THF)$ afforded pentacarbonylchromium complex **116** in good yields, attempts to synthesize the corresponding Mo and W complexes were not successful [115]. However, *cis*-$Mo(CO)_4$(**115**)$_2$ and *fac*-$Mo(CO)_3$(**115**)$_3$ could be obtained from the reaction of 2 and 3 equivalents of **115** with (nbd)$Mo(CO)_4$ and $Mo(CO)_3(MeCN)_3$, respectively [115] (Scheme 35).

The reaction of 4-difluorophosphino-[1,2,3]diazaphosphole **115,** even in an excess amount, with $CpRu(PPh_3)_2Cl$ resulted in the formation of monosubstituted complex $CpRu(PPh_3)$(**115**)Cl only (Scheme 35). In contrast to the monosubstitution



Scheme 35 Transition metal complexes from 2,5-dimethyl-4-phosphino-[1,2,3]diazaphosphole

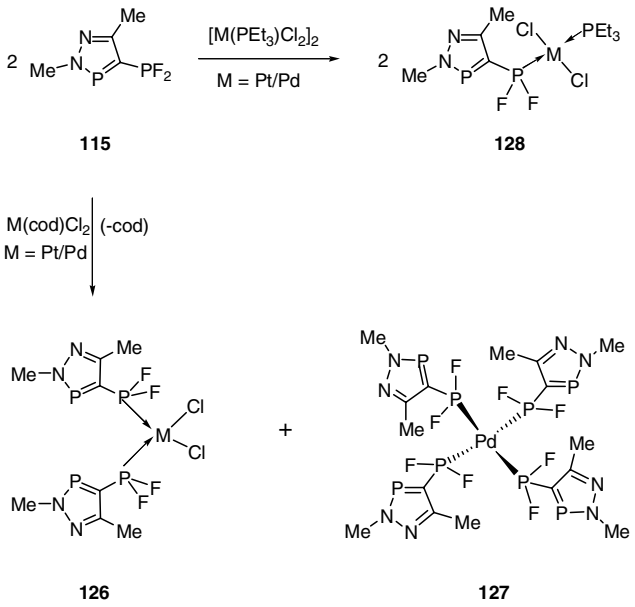
by general phosphines on reaction with $CpRh(CO)_2$, **115** replaces both carbonyls to give disubstituted rhodium(I) complex **120** [82]. On the other hand, the monosubstituted Rh(III) complex **121** was obtained from the reaction with rhodium(III) dimer, $[Cp^*RhCl_2]_2$ (Scheme 35). Although the reaction of $[Rh(CO)_2Cl]_2$ with **115** was unsuccessful and led to the decomposition of reactants, its reaction with 4-bis(dimethylamino)phosphino-[1,2,3]diazaphosphole (**122**) yielded exclusively *trans*-Rh(CO)Cl(**122**)$_2$ complex (**123**) incorporating a square planar rhodium metal center (Scheme 36) [82].



Scheme 36 Metal complexes of 4-bis(dimethylamino)phosphino-[1,2,3]diazaphosphole

Exocyclic phosphorus of aminophosphinodiazaphosphole **122** on oxidation with trimethylsilyl azide gave (((trimethylsilyl)imino)phosphorano)diazaphosphole (**124**); the latter by transmetalation reaction with Cp^*TiCl_3 at elevated temperatures yielded titanium iminophosphorane **125** (Scheme 36) [83].

4-Difluorophosphino-[1,2,3]diazaphosphole **115** on treatment with cyclooctadienylplatinum or palladium dichloride replaced cyclooctadienyl ligand and yielded the disubstituted *cis* complex **126**; however, in the case of palladium, reduced palladium(0) complex **127** was also formed (Scheme 37), though the attempts to separate the two were unsuccessful [81]. Corresponding platinum(0) complex, Pt(**115**)$_4$ was obtained from an unexpected reductive-elimination reaction of **115** with Pt(cod)ClMe. The reaction of **115** with bridged dimers $[M(PEt_3)Cl_2]_2$ (M = Pd or Pt) afforded *trans* phosphine complexes **127** having metal center bonded with two different phosphine ligands.



115 128

126 127

Scheme 37 Pd and Pt complexes of 4-difluorophosphino-[1,2,3]diazaphosphole

5 Concluding Remarks

In this chapter, synthesis, structure, and reactions of various classes of diazaphospholes have been reviewed. Recently used synthetic methods and variations for obtaining diversely substituted diazaphospholes have been discussed. On account of the cycloadditions on P=C bond of [1,4,2]- and [1,2,3]diazaphospholes, a number of organophosphorus compounds incorporating a bridgehead phosphorus atom have become accessible. Recently reported complexation reactions of diazaphospholes, illustrate their capability to form transition metal complexes via different coordination modes.

Acknowledgment The author acknowledges financial support from the Department of Science and Technology (DST), New Delhi.

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