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Heterophosphacyclanes in organic synthesis

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Abstract. The review gives a systematic account of the use of mono- and di-heterophosphacyclanes, containing σ^3-, σ^4-, and σ^5- phosphorus atoms, for the synthesis of phosphorus-free organic substances. Data concerning the reaction mechanisms, the reactivities of cyclic organophosphorus compounds, and the factors determining the synthetic result of their chemical reactions are presented. In certain cases, the effectiveness of the employment of cyclic and acyclic phosphorus-containing reagents is compared. The bibliography includes 178 references.

I. Introduction

At the present stage, the synthetic organic chemistry of phosphorus is developing mainly in two directions. The first involves the functionalisation of organophosphorus substrates of increasing complexity, based on the chemical transformations of the organic functional groups already present in the molecule. One achieves in this way the introduction into the organophosphorus compounds of definite atomic groups which are potentially responsible for certain useful properties of the compound being synthesised, say pesticidal, or others. Phosphorus-containing functional groups may not actually participate in the chemical steps, exerting a different kind of effect on the fragment being transformed, which is susceptible to estimation including quantitative estimation.[1]

The second direction concerns the synthesis of organic compounds with participation of phosphorus-containing substances, which, after being involved in particular synthetic operations, 'remove' the phosphorus-containing functional group from the reaction sphere and the target product does not contain a phosphorus atom. This type of employment of organophosphorus reagents in organic synthesis has come to be widely used and has a long tradition. The phosphorus-containing compounds of this kind include, for example, the Wittig reagents — phosphorus ylides used to convert oxo-compounds into alkenes. The search for new highly effective functionalising phosphorus-containing reagents is being prosecuted at the present time.

Since the publication of the first and only monograph[2] devoted to the application of organophosphorus reagents in organic synthesis, many new communications have appeared in which this problem has been developed further. Thus in the 1980s, new multipurpose highly effective phosphorus-containing reagents were described. Among them mention should first be made of Lawesson's reagent (LR) (see Cherkasov et al.[3] and Kava and Levinson[4] and the literature quoted therein) — 2,4-bis-(*p*-methoxyphenyl)-1,2,3,4-dithiadiphosphetane 2,4-disulfide — and Mitsunobu's reagent[5] (MR)† — a betaine obtained by the interaction of triphenylphosphine and dialkyl azodicarboxylate. They have found extensive application not only in experimental practice but also in industrial organic synthesis. A recent review has been devoted to the employment of unsaturated compounds of tetracoordinate phosphorus for the synthesis of complex organic compounds.[7]

New aspects of the synthesis of organic compounds involving the employment of reagents containing a phosphorus atom involved in different types of coordination have begun to develop recently. Thus chiral phosphines[8] and phosphonates[9] are used in the catalysis of organic reactions and methods are being developed for the functionalisation of organic compounds with the aid of metastable derivatives of tricoordinate pentavalent phosphorus[10] and also of compounds of dicoordinate phosphorus.[11,12]

This review is devoted to a vigorously developing branch of phosphorus chemistry — the chemistry of heterophosphacyclanes — in its new aspect, namely their application in organic synthesis. If one disregards fairly old review publications describing the use of individual types of compounds of this class,[2] then this is the first attempt to treat systematically and survey the data which have accumulated in this field since 1980. Individual earlier literature sources are quoted here only to the extent that they are needed for a complete description of the problem under discussion. This communication completes a series of reviews devoted to the chemistry of heterophosphacyclanes containing a phosphorus atom with coordination numbers of three,[14] four,[15] five,[16] and six.[17] Considered jointly, these communications provide a complete picture of this currently important field of organoelement chemistry.

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† After the publication of Mitsunobu's review,[5] an extensive literature describing the application of MR in organic synthesis appeared (more than 400 publications). As an example, we may point to one of the later studies on the use of MR in the total synthesis of 20-membered macrocyclic antibiotics — venturicidins A and B[6] (see also Section IV).

II. σ^3-Heterophosphacyclanes

The use of σ^3-1,3,2-diheterophospholanes and σ^3-1,3,2-diheterophosphorinanes, substances which are thermodynamically less stable than the σ^4-phosphorus- and σ^5-phosphorus-containing derivatives with a similar structure,[14] is frequently associated with their conversion into the latter, which subsequently effect particular synthetic operations.

In the context of the chemical transformations described here, the σ^3-diheterophosphacyclanes themselves are not of special preparative interest and in most cases their behaviour resembles that of structurally similar acyclic phosphorus(III) derivatives. For example, organic phosphorus(III) derivatives are capable of deoxidising (desulfurising) suitable substrates, being themselves oxidised to phosphoryl (thiophosphoryl) compounds. The inclusion of a phosphorus(III) atom in a heterocycle entails a decrease (in nucleophilic reactions) or an increase (in electrophilic reactions) of the reactivity of the organophosphorus reagent.

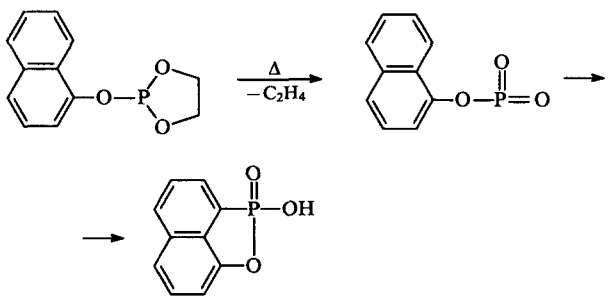
At the same time, thermal, photochemical, and chemical (for example as a result of substitution and disproportionation reactions) fragmentation processes involving or not involving the heterocyclic part of the molecule are extremely characteristic of σ^3-diheterophosphacyclanes, in contrast to the acyclic phosphorus(III) derivatives.

1. Thermal and photochemical fragmentation

The thermal reactions of cyclic esters of acids derived from phosphorus in the lowest oxidation state are usually associated with intramolecular rearrangements of the Arbuzov reaction type in those cases where the exocyclic fragment contains suitable functional groups, for example haloalkyl groups, and lead to organophosphorus products containing a phosphorus atom with a higher coordination number (CN).[14]

2-Aryloxy- and 2-alkoxy-1,3,2-dioxaphospholanes behave differently. On vacuum flash pyrolysis (700–800 °C, 0.001 Torr), they undergo fragmentation with liberation in the first stage of ethene and phosphorus-containing intermediates having the structure of metaphosphates‡ and undergoing further transformations.

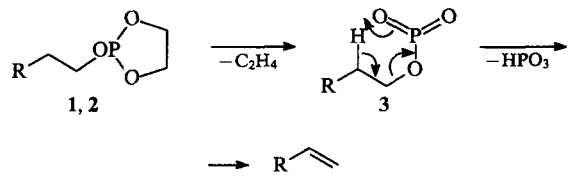
After liberating ethene, the aryl esters of ethylene phosphites are converted into the corresponding cyclic monoesters of arylphosphonic acids via the incorporation of the highly electrophilic pentavalent tricoordinate phosphorus atom in a sp^2-C–H bond of the aromatic fragment of the metaphosphates.[21–23]



According to Cadogan et al.,[21] the reaction described constitutes, in its intramolecular version, one of the most effective methods for the phosphorylation of aromatic nucleophilic substrates with the aid of highly electrophilic metastable phosphorus-containing reagents.

‡ We may note that in recent years there has been a marked growth of interest in these substances in connection with the appearance of the possibility of obtaining stable representatives of phosphorus compounds of this class and their use for the synthesis of natural organophosphorus products and in other phosphorylation reactions.[18–20]

However, if the exocyclic organyl fragment contains a β-hydrogen atom, alkenes are liberated—2-vinylpyridine in the thermolysis of the phospholane **1** or phenyl vinyl ether in the case of compound **2**, as well as polymeric metaphosphoric acid. Intramolecular phosphorylation does not occur and a process analogous to the Chugaev reaction and the β-elimination via a six-centre transition state **3** similar to it take place.[21]

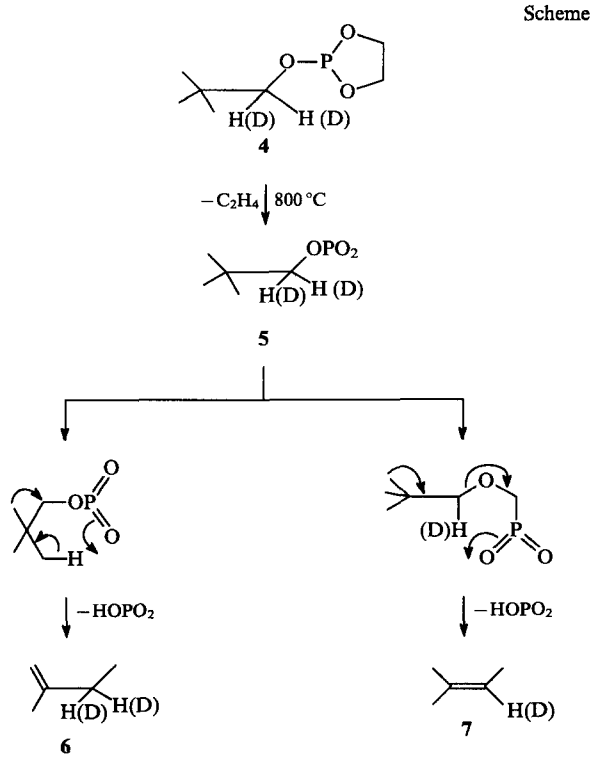


1, **2** **3**

1: R = Py
2: R = OPh

After the liberation of ethene, the pyrolysis of 2-neopentyloxy-1,3,2-dioxaphosphalane **4** under these conditions leads to the quantitative formation of a mixture of 2-methylbut-1-ene **6** and of its thermodynamically more stable isomer 2-methylbut-2-ene **7** in proportions of 2 : 1.[22,23] It is believed that the minor alkene **7** is formed as a result of the abstraction of an α-proton from the common intermediate **5**, whereas its isomer **6** arises through the elimination of a γ-proton and the unusual 1,2-methyl shift in the same intermediate metaphosphate (Scheme 1). The transformation of compound **5** into the alkenes **6** and **7** proceeds via a mechanism similar to the Wagner–Meerwein rearrangement but has the opposite polarity (there is a carbanionoid and not a carbonium ionoid transition state) and also in its concerted (and not sextet) variant.[24]

Scheme 1



This course of the reaction has been confirmed by the use of a deuteriated specimen of compound **4**, pyrolysis of which afforded the deuterium-containing alkenes **6**-d_2 and **7**-d_1 in proportions of 3.8 : 1. The observed deuterium isotope effect $k_H/k_D = 1.9$ agrees with the ratio of the deuteriated isomers obtained, indicating that the loss of hydrogen (deuterium) via the route leading to compound **7** is rate-determining.

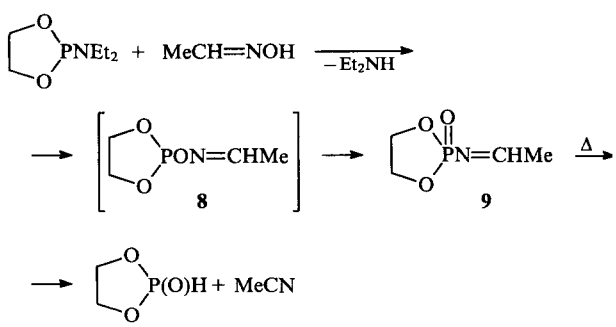
2. Reactions involving substitution at the σ^3-P atom

The thermally promoted fragmentation of diheterophosphacyclanes is frequently observed in the fractionation of the products of the interaction of cyclic phosphorous and phosphonous acid esters with electrophiles and nucleophiles. The elimination of phosphorus-free organic reaction products usually occurs in those cases where the exocyclic ester residue contains reactive functional groups. The cyclic skeleton of the phosphorus-containing substrate as a rule remains unchanged under these conditions. The above applies primarily to dioxaphospholanes.

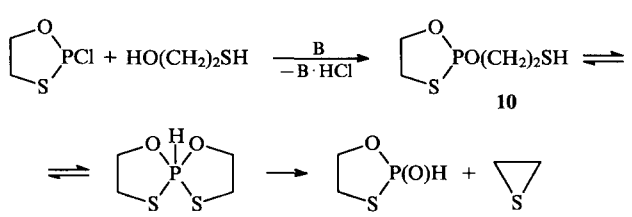
In the vast majority of cases, such reactions take place with participation of intermediates in which the CN of the phosphorus atom is four or five. The inclusion of the phosphorus atom in a ring, especially a five-membered ring, stabilises such intermediates and in many cases this makes it possible to identify them and to infer the reaction pathway.

The substitution of readily eliminated groups by functionalised alcohols, accompanied by the isomerisation of the intermediate cyclic phosphites to tetracoordinate and pentacoordinate phosphorus compounds, leads, as a result of thermolysis, to the formation of small organic molecules; the phospholane ring remains unchanged under these conditions.

The interaction of the diethylamide of ethylenephosphorous acid with an oxime probably proceeds via a stage involving the formation of the unstable phosphite **8**, which isomerises to the N-phosphorylated anil **9**; in the course of fractionation, the latter decomposes into ethylenephosphorous acid and acetonitrile.[25]

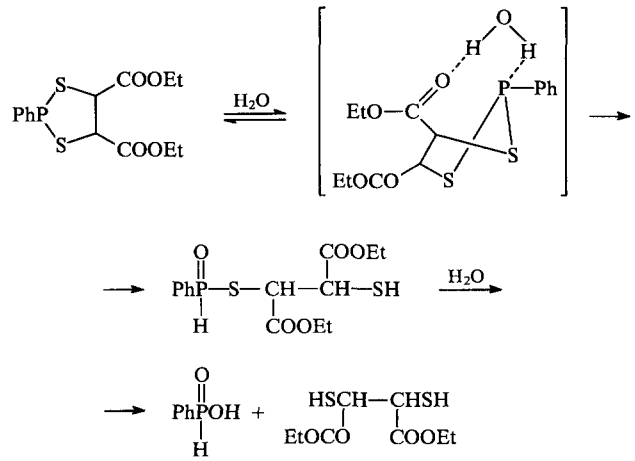


The esterification of 2-chloro-1,3,2-oxathiaphospholanes with mercaptoethanol in the presence of a base[26] does not stop at the 2-mercaptoethyl phosphite **10** stage, and is completed by the formation of a thiirane and a cyclic phosphorothious acid. It is difficult to say which of the intermediates—the phosphite intermediate **10** or the isomeric phosphorane intermediate **10a**—is responsible for the observed fragmentation.



We may note in this connection that a similar fragmentation of 1,2-dihydroxyalkylene derivatives of σ^5-P is an extremely characteristic property and is of preparative importance[16] (see also Subsection 3).

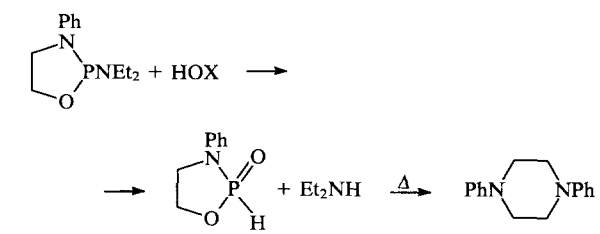
The endocyclic hydrolytic dissociation of the thioester linkages in 4,5-di(ethoxycarbonyl)-2-phenyl-1,3,2-dithiaphospholane takes place stepwise and leads to phenylphosphonous acid and diethyl dimercaptosuccinate.[27]



Kinetic study of the hydrolytic reaction led the authors to the conclusion that a hydrogen-bonded complex is formed prior to the establishment of equilibrium.

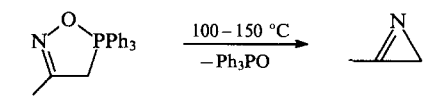
In contrast to the cyclic esters and thioesters of trivalent phosphorus acids, amidoesters containing an endocyclic tertiary nitrogen atom undergo a more profound transformation during the substitution reaction involving under these conditions a thermal fragmentation with cleavage of the oxazaphospholane ring.

On interaction with proton-containing nucleophiles (water,[30] acetic acid,[29,30] and ethanol[29]), 2-ethoxy-,[28] 2-phenyl-,[29] and 2-diethylamino-3-phenyl-1,3,2-oxazaphospholanes[29,30] afford *N,N*-diphenylpiperidine after fractionation. It has been suggested that, in the presence of a readily eliminated exocyclic group, the reaction takes place via a mechanism involving the nucleophilic substitution[30] of the exocyclic fragment.



X = H, COMe, Et.

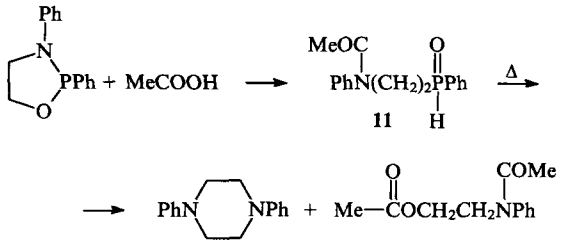
The formation of the final product is probably due to the decomposition of the *N*-phenyloxazaphospholane fragment of the unstable hydrophosphoryl intermediate at elevated temperatures (100–120 °C) during the substitution reaction or during fractionation. One cannot rule out the possibility that the decomposition is accompanied by the initial formation of three-membered nitrogen-containing heterocycles, similarly to the formation of azirenes on pyrolysis of σ^5-1,5,2-oxazaphospholenes.[31]



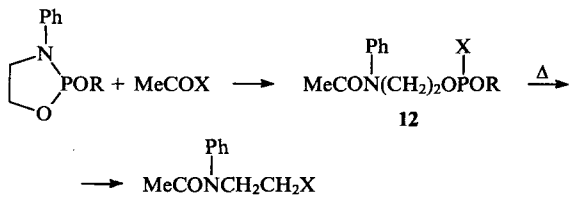
N-Phenylaziridine is evidently formed in the case under discussion, dimerising under the experimental conditions (see also Subsection 3). Naturally one cannot rule out also another mechanism of the formation of the piperidine ring from the phosphacyclane skeleton of the cyclic phosphoramidites.

The same synthetic result is attained also in the course of endocyclic substitution,[29] for example in the acetolysis of 2-diethylamino- or 2,3-diphenyl-1,3,2-oxazaphospholane.

The thermolysis of the phosphonite **11** makes it possible to obtain, together with *N*,*N*-diphenylpiperidine, also *N*-2-acetoxyethyl-*N*-phenylacetamide.



The oxazaphospholane ring may be cleaved not only by proton-containing nucleophiles but also by electrophiles — acetyl chloride [32] or acetic anhydride. [33]



X = Cl, OCOMe.

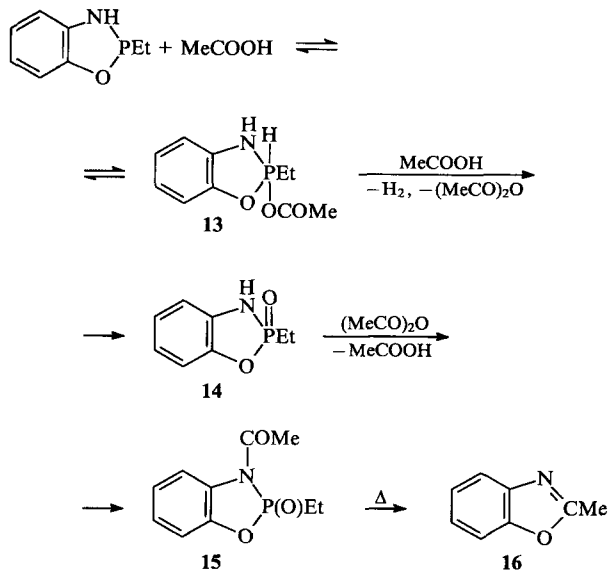
In both these cases, the interaction is evidently associated with the nucleophilic attack by the nitrogen atom on the carbonyl carbon atom of the acylating agent; the ring is then cleaved at the P–N bond. Further decomposition takes place with the elimination of the *O*-ester organyl fragment. It is difficult to reach definite conclusions about the mechanism of this unusual fragmentation of the functionalised phosphonites **11** or the phosphites **12**, again because the subsequent transformation of the 'phosphorus' part of the molecules remains unelucidated. One may only note that the elimination of the phosphorus-containing reaction products is associated with the dissociation of the sp^3-C–O bond in the *O*-ester group.

3. Reactions involving an increase in the coordination number of the σ^3-P atom

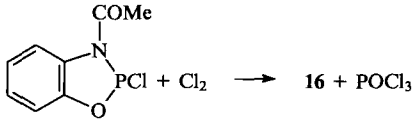
Decomposition accompanied by the opening of the ring at an endocyclic sp^2-C–O bond has been noted in the acylation of 2-ethyl-4,5-benzo-1,3,2-oxazaphospholane, [34] which is achieved under mild conditions (2 h, 20 °C) and represents a rare case of the oxidation of phosphorus(III) derivatives by carboxylic acids in the two-component version§.

The process probably begins [34] with the 1,1-addition of acetic acid to the phosphorus(III) atom of the benzophosphacyclane. The unstable hydrophosphorane **13** formed is deacylated by a second acetic acid molecule and is oxidised to the phosphonate **14** with liberation of hydrogen. The subsequent endocyclic *N*-acylation leads to the final *N*-acylphosphonate **15**. During fractionation, the latter affords 2-methylbenzoxazole **16** in 20% yield.

It has been demonstrated by means of a special experiment that, on heating to 150–200 °C in vacuo (20 Torr), the phosphonate **15** gives rise to the benzoxazole **16** in 68% yield.

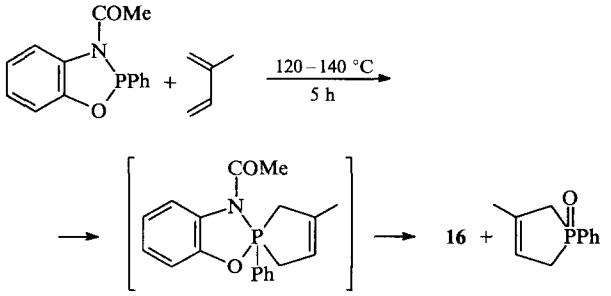


The formation of compound **16** as a result of the chlorination of 3-acetyl-2-chloro-4,5-benzo-1,3,2-oxazaphospholane has been established recently. [36]



Evidently in this case too the reaction leads to the formation of the addition product of chlorine to the σ^3-phosphacyclane — the corresponding trichlorophosphorane. The ultimate formation of phosphoryl chloride (and also apparently of ethyl metaphosphonate in the previous example) is clearly evidence in favour of the probable formation of a metastable aromatic intermediate of the acylamino-substituted dehydrobenzene type, or a similarly substituted phenyl radical, as a consequence of the heterolysis or homolysis of the sp^2-C–O bond.

Such fragmentation also takes place in the thermolysis of the unidentified product of the [1 + 4]-cycloaddition of 3-acetyl-2-phenyl-4,5-benzo-1,3,2-oxazaphospholane to 2-methylbutadiene. [37] Fractionation of the resulting mixture afforded the benzoxazole **16** and a cyclic phosphine oxide.



The fragmentation with cleavage of the diheterophospholane ring described above leads to a kind of transcyclisation of the phosphorus(III) substrate.

The endocyclic dissociation of the sp^2-C–O bond discussed here gives rise to interesting synthetic possibilities for the employment of the reactions of cyclic salicyl phosphites with carbonyl compounds activated by electron-accepting substituents.

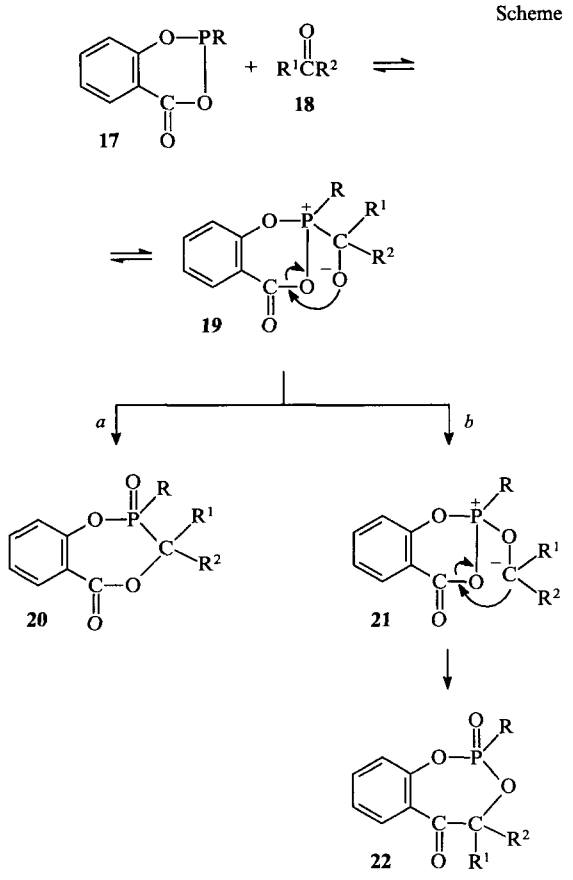
2-R-4-Oxo-5,6-benzo-1,3,2-dioxaphosphorinanes **17** — six-membered cyclic anhydrides containing the P(III)–O–C(O) fragment in the ring — readily interact with chloral, [38]

§ According to the data of Mukajama et al., [35] trialkyl phosphites are oxidised by carboxylic acids in the presence of hydrogen acceptors — diphenylmercury and dibenzoylethene.

hexafluoroacetone,[39] mesoxalic acid esters,[40] ethyl benzoylformate,[41] methyl trifluoropyruvate,[42] and hexafluoroacetylacetone[43] with insertion of the carbonyl reagent in the six-membered ring and the formation of dioxaphosphepanes — a class of phosphorus-containing heterocycles which are relatively difficult to obtain.

It has been suggested[41] that the process begins with the attack by the nucleophilic P(III) atom on the carbonyl carbon atom of the other reactant (compound **18**) (Scheme 2).

Scheme 2

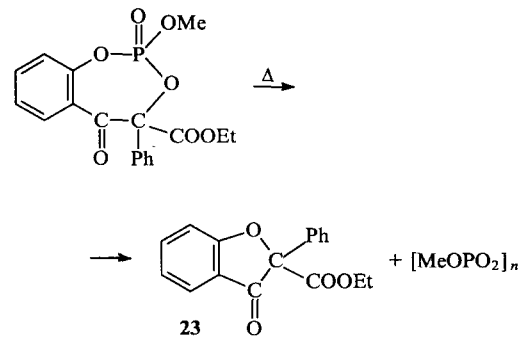


The dipolar ion **19** arising under these conditions may be stabilised via the intramolecular substitution at the carbonyl carbon atom by an oxy-anion (route *a*) with formation of the 1,4,2-dioxaphosphepane **20** (R^1 = H, R^2 = CCl_3); this reaction path occurs in the reactions of salicyl phosphites **17** with chloral.

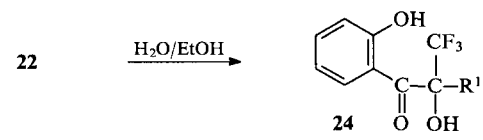
The remaining carbonyl reagents employed gives rise to 1,3,2-dioxaphosphepanes **22**, the formation of which is preceded by the rearrangement of the ion **19** to the ion **21** (P–O–C→P–C–O) and intramolecular substitution, with participation of the carbanion, at the carbonyl carbon ion in the zwitterionic intermediate **21** (route *b*). This case is of greatest interest from the standpoint of the problems discussed in the review because it entails the formation of a new C–C bond.

It has been shown[41] that the vacuum fractionation of the phosphepane **22** (R = OMe, R^1 = Ph, R^2 = COOEt) is accompanied by its complete decomposition, which resulted in the formation of ethyl 2,3-dihydro-3-oxo-2-phenylbenzofuran-2-carboxylate **23** in 80% yield.

It has been noted[41] that derivatives of 2,3-dihydro-3-oxo-2-phenylbenzofuran-2-carboxylic acid had not been described before the study by the above workers[41] and only data concerning the isomeric acid with the carboxy-group in the 3-position in the benzofuran ring had been available.[44,45]

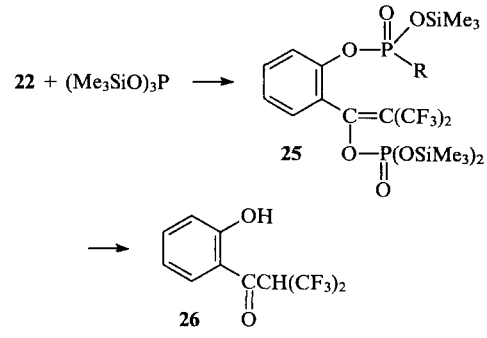


The protolytic reactions of the 1,3,2-dioxaphosphepanes **22**, obtained by the reaction of salicyl phosphites **17** (R = OMe) with hexafluoroacetone and hexafluoroacetylacetone provide the greatest possibilities for the synthesis of functionalised fluorine-containing ketones; the hydrolysis of the 1,3,2-dioxaphosphepanes in aqueous ethanol[43] leads to the hydroxyketones **24** (R^1 = CF_3 and CH_2COCF_3) respectively in a high yield.



R = OMe; R^1 = CF_3, CH_2COCF_3; R^2 = CF_3.

This method may be modified by phosphorylating the 1,3,2-dioxaphosphepanes **22** (R^1, R^2 = CF_3) with the aid of tris(trimethylsilyl) phosphite; hydrolysis of the diphosphate **25** makes it possible to obtain the ketone **26**, which does not contain α-hydroxy-substituents in the fluoroalkyl group.[46,47]

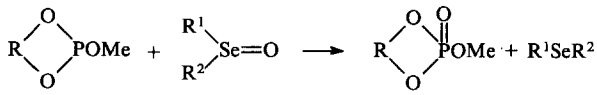


R^1 = R^2 = CF_3.

The driving force of the reactions described here is the well known tendency of phosphorus(III) derivatives to be converted into compounds with a thermodynamically stable phosphoryl group characterised by a high energy of the phosphorus–oxygen multiple bond.[14]

This property of the phosphorus(III) atom has been used in the reduction of oxides, sulfides,[48,49] and selenides[50,51] by σ^3-1,3,2-dioxaphospholanes and phosphorinanes.

Under mild conditions, selenoxides are reduced almost wholly in solution in benzene or chloroform by 2-methoxy-4-methyl-1,3,2-dioxaphospholane or 2-methoxy-4-methyl-1,3,2-dioxaphosphorinane in 5 min with an appreciable exothermic effect.

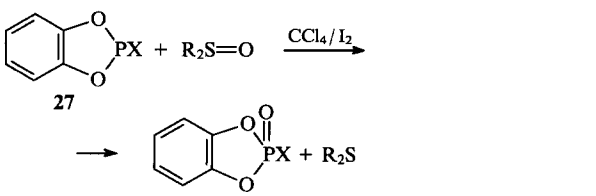


R = CH_2CHMe, $(CH_2)_2CHMe$;

R^1 = Ph, Bz; R^2 = Et Ph, Bz.

The retention of the configuration of the phosphorus atom in the cyclic phosphates obtained as a result of the oxidation reactions has been noted.

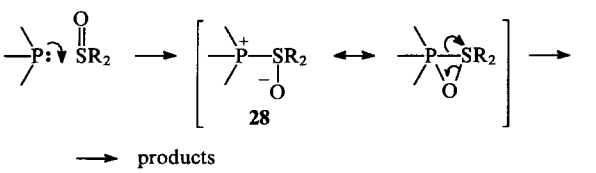
The deoxygenation of sulfoxides by 2-phenoxy-[50] and 2-chloro-1,3,2-benzodioxaphospholanes takes place readily in solution in CCl_4 at low temperatures, high temperature being required when acyclic phosphorus(III) derivatives are used.[51] Compounds **27** satisfy the principal requirements which must be met by reagents reducing sulfoxides to sulfides: they are readily available, are powerful electrophiles (electron-accepting agents), and can be easily removed after oxidation (by extraction with aqueous alkali).



X = Cl, OPh.

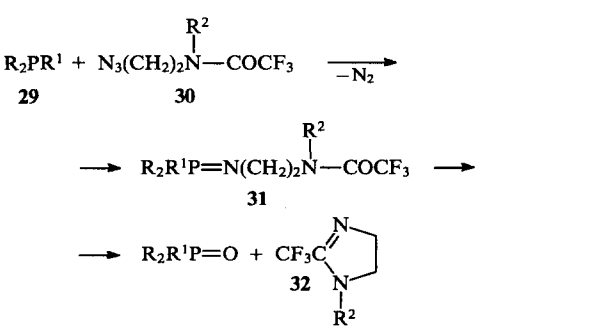
Traces of iodine catalyse the process, reducing the conversion time from 3 h to several minutes; the chloro-derivative **27** is very effective under these conditions. It deoxidises sulfoxides at room temperature over a short period.

It has been suggested [51] that the process involves the formation of the dipolar ion **28** as a result of the nucleophilic attack by phosphorus(III) on the sulfoxide sulfur atom.

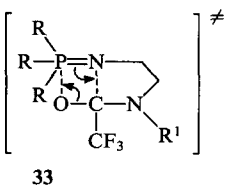


However, the increase in the rate of deoxidation when the phospholanes **27** containing highly electron-accepting substituents at the phosphorus atom are employed is more likely to be evidence in support of the nucleophilic interaction of the sulfoxide oxygen with the electrophilic phosphorus(III) atom. The ability of the latter to both give up and receive electrons (biphilicity) is manifested particularly strikingly when it is incorporated in the diheterophosphacyclane ring.[14]

The electron-accepting effect of the alkylenedioxy-substituent at the phosphorus(III) atom is manifested in the reaction of the phosphorus(III) derivatives **29** with the azidoamides **30**.[52]

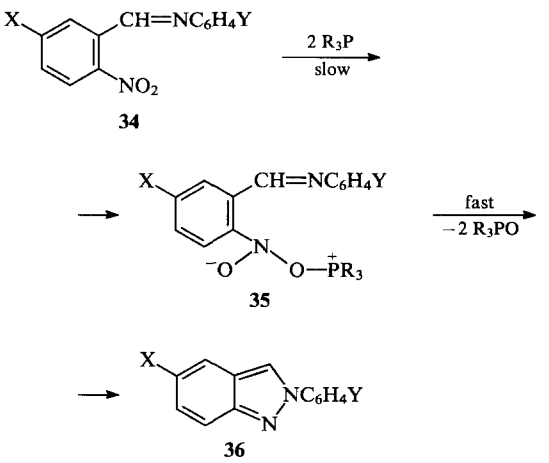


The incorporation of a phosphorus(III) atom in the five-membered ring of 2-diisopropylamino-1,3,2-benzodioxaphospholane **29** (R_2 = o-$C_6H_4O_2$, R^1 = Pr^i_2N) makes it possible to obtain 2-trifluoromethyl-2-imidazoline **32** (R^2 = H, Bu^t) in a high yield; triphenylphosphine affords only 20%–30% of the imidazoline **32** (R^2 = H) under these conditions; the yield increases to 80% (120 °C and 0.05 Torr). Tris-(dimethylamino)phosphine **29** (R = R^1 = Me_2N) does not yield even traces of the final product **32** over a period of 2 h at 120 °C. These experimental data can be best accounted for by the formation of a transition state **33** analogous to that in the Wittig reaction:



The nucleophilic attack by the carbonyl oxygen atom on the phosphimine phosphorus atom of the product **31** of the Staudinger reaction is facilitated in the presence of a powerful electron acceptor at this atom — the phenylenedioxy-substituent; by increasing the electron density at the imine phosphorus, the strongly electron-donating dialkylamino-group inhibits the Wittig reaction. Moderately strong electron acceptors (phenyl substituents) give rise to an intermediate result.

The opposite, deactivating effect of the incorporation of a phosphorus(III) atom in the five-membered dioxaphospholane ring has been established in a study of the kinetics of the reductive cyclisation of o-nitrobenzylideneanilines **34** to 2-substituted indazoles **36**.[53]



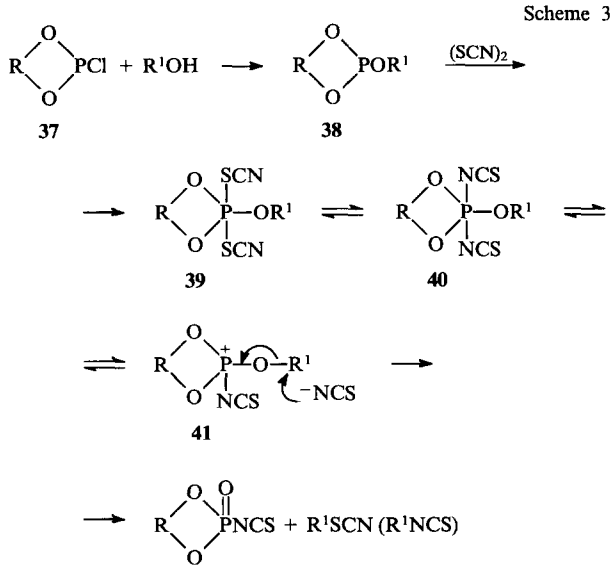
The introduction of electron-accepting substituents into aromatic rings and of electron-donating substituents at the phosphorus(III) atom promotes the occurrence of the process, the ratio of the rates of reaction of trialkyl phosphites and 2-alkoxy-1,3,2-dioxaphosphalanes being 7:1 under these conditions. Approximately the same ratio of the rates of quaternisation of cyclic and acyclic phosphites in the Arbuzov reaction led Armour et al.[53] to the conclusion that the rate-determining stage is nucleophilic attack by the phosphorus(III) atom of the deoxidising reagent on the oxygen of the nitro-group with formation of the intermediate **35**.

The very sharp increase (almost by two orders of magnitude) in the rate in the reaction of 2-ethoxy-1,3,2-diazaphospholane may be associated with the intermediate formation of a hydrogen-bonded complex favouring the reductive cyclisation. It is made up of the negatively charged oxygen atom in the zwitterion and the endocyclic NH fragment.

The ability to undergo readily a change in coordination number, observed in the reactions of phosphorus(III) derivatives and manifested particularly strikingly in σ^3-1,3,2-dioxaphospholanes, permits the use of these substances as condensing agents in the reactions of hydroxy-compounds with proton-containing nucleophiles.

It has been found [54-56] that alcohols are readily converted into thiocyanates and isothiocyanates in the reactions of 2-chloro-1,3,2-dioxaphospholanes **37** (Scheme 3).

Scheme 3

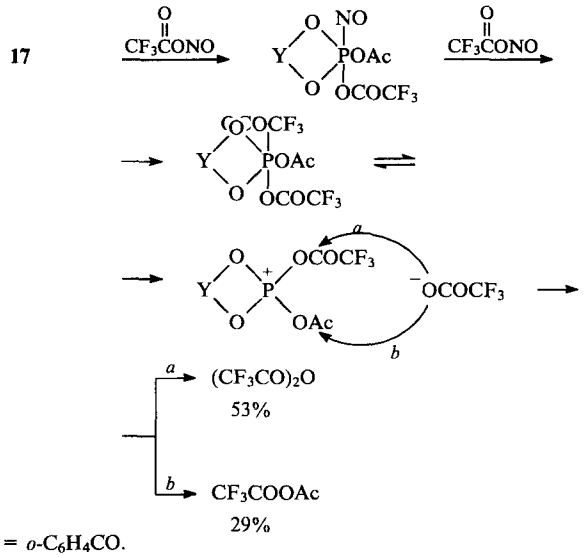


R = —CMe=CMe—; R^1 = Alkyl, R^2CO, $R^2_2P(O)$, $R^2_2P(S)$.

The products **38**, obtained by reacting phosphorochloridites with alcohols or carboxylic, dialkylphosphoric, and dialkylphosphorothioic acids, are made to react with thiocyanogen, which leads to alkyl and acyl isothiocyanates via a series of intermediates having the phosphorane (compounds **39** and **40**) and quasi-phosphonium (compound **41**) structures respectively. The use of secondary alcohols makes it possible to obtain isothiocyanates as well as thiocyanates. The dealkylation of the salt **41**, which proceeds via a mechanism involving nucleophilic substitution at the α-carbon atom of the alkoxy-group by the ambident anion SCN^-, is effected by the more bulky and nucleophilic sulfur atom for the n-alkyl group in primary alcohols. The increase in the degree of substitution at the α-sp^3-C atom (secondary alcohols) is accompanied by the competing S- and N-substitution.

We may note that a similar result is achieved in the conversion into the thiocyanate with the aid of a triphenylphosphine–thiocyanogen mixture (the so called Tamura's reagent [3]). The use of cyclic phosphorus(III) reagents makes it possible to carry out the process under very mild conditions. When the reaction was performed at the temperatures $-80 \rightarrow -30 \rightarrow +20$ °C, all the intermediates **39–41** generated in the reaction were detected by ^{31}P NMR spectroscopy. [53,54]

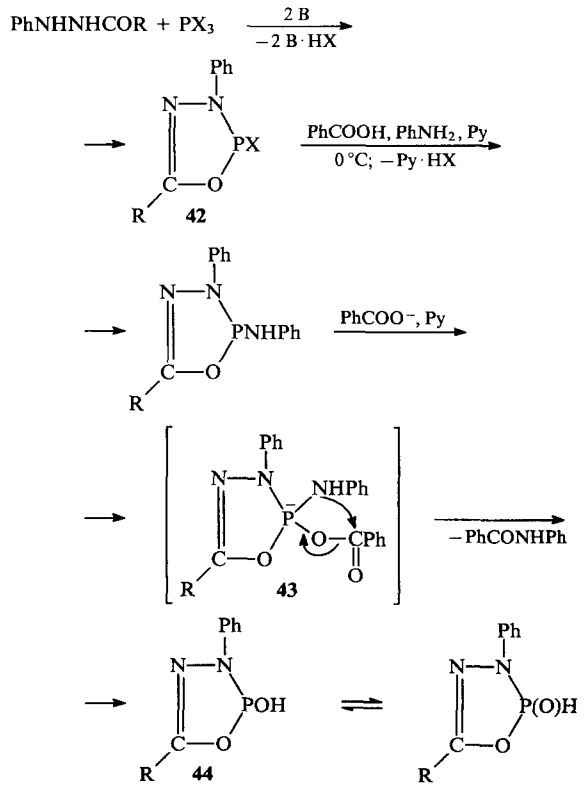
The condensing effect of cyclic phosphites is manifested in the reactions of the mixed anhydride **17** (R = OAc) with trifluoroacetyl nitrite.[57]



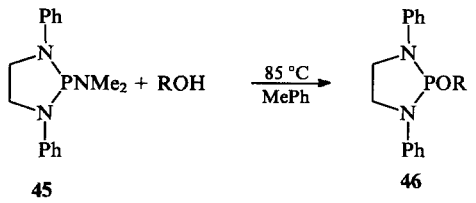
Y = *o*-C_6H_4CO.

It is assumed that in this case the process proceeds with participation of intermediates of the phosphorane and quasi-phosphonium types; the competing substitution by the trifluoroacetate anion of the trifluoromethylacetyl and acyl groups in the quasi-phosphonium salts affords the observed mixture of anhydrides as the products (routes *a* — main product, route *b* — a minor pathway).

This approach has been used recently to convert carboxylic acids into amides using the 2-X-5-R-3-phenyl-2,3-dihydro-1,3,4,2-oxadiazaphospholes **42**, obtained from phosphorus trihalides and 2-acylphenylhydrazine, as the condensing agents. [58] The process was carried out by adding compound **42** to a mixture of benzoic acid, aniline, and pyridine at 0 °C; the yield of the phenylamide of benzoic acid is nearly quantitative. It has been suggested that the key stage of the process is the formation of a type of pentacoordinate intermediate **43** and its subsequent decomposition into the final acylamide and the unstable cyclic acid **44**.

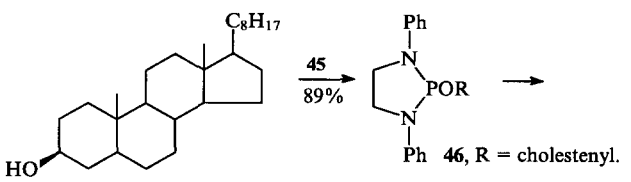


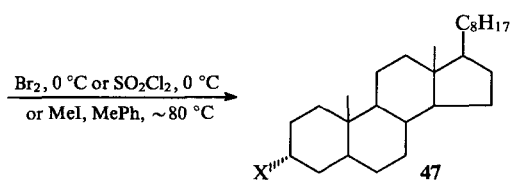
Finally, we may indicate also a method involving a kind of 'conservation' of alcohols, which is employed for their identification as part of the molecules of the readily crystallising 2-alkoxy-1,3,2-diazaphospholanes **46**, and their stereospecific conversion into organyl halides.[59] The cyclic phosphorous triamide **45** is converted on treatment with alcohols into alkoxy-derivatives, which are transformed into alkyl halides in accordance with the mechanism of the Arbuzov reaction.



45 **46**

For example, β-cholestanol has been converted in this way by the phosphoramide **45** into the corresponding ester **46**, from which the halides **47** were obtained in high yields.





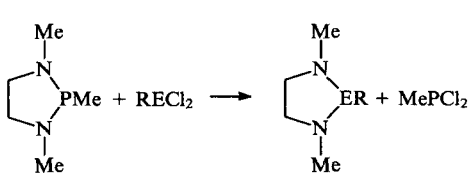
47

X = Cl (80%), Br (85%), I (75%).

As sometimes happens in the second stage of the Arbuzov reaction, the dealkylation of compound **46** is highly stereospecific with full inversion of configuration of the carbinol carbon atom.

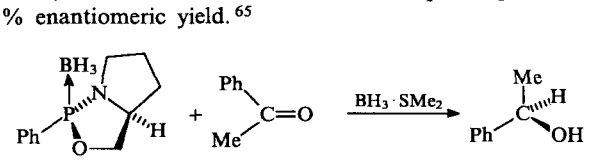
4. Other reactions

We may note that the studies carried out a fairly long time ago on the exchange of the phosphorus(III) atom for other elements via the reaction described by Eisenhut and Schmutzler[60] and Das and Zuckerman[61] were not developed further.



E = B, As; R = Ph, Cl.

Mention should be made of the cases where σ^3-oxazaphosphorinanes were used as chiral ligands in the metal [sic] complexes employed in asymmetric synthesis.[62-64] For example (2*R*, 4*S*)-2-phenyl-1,3,2-oxazaphosphorinane, coordinated to a boron hydride, reduces various ketones to the corresponding alcohols in 99% enantiomeric yield.[65]



However, a detailed consideration of this problem is outside the scope of this review.

III. σ^4-Diheterophosphacyclanes

Derivatives of tetracoordinate phosphorus have played an outstanding role in the development of methods for the conversion of carbonyl compounds into alkenes with the aid of phosphorus ylides (the Wittig reaction) and α-phosphorylated carbanions (the Horner–Wadsworth–Emmons reaction).[2,66-68] The introduction of a σ^4-P atom into the diheterophosphacyclane fragment is responsible for the specific behaviour of these phosphorus-containing reagents.

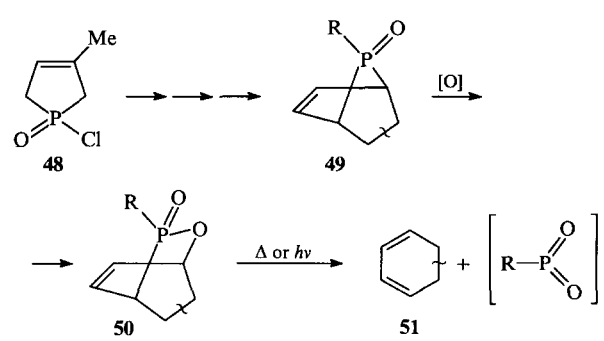
Other reactions of σ^4-diheterophosphacyclanes — thermal and photochemical fragmentation as well as solvolysis — have been less important in fine organic synthesis. We may note that the involvement of cyclic organophosphorus compounds in these processes has been exceptionally important for the development of methods of phosphorylation with the aid of metastable phosphorus-containing reagents[69] and nucleophilic substitution reactions at a tetrahedral phosphorus atom.[15]

1. Fragmentation of cyclic derivatives of tetracoordinate phosphorus

Like the analogous chemical processes with participation of cyclic phosphorus(III) derivatives, reactions of this type are used mainly for the generation of metastable derivatives of tricoordinate pentavalent phosphorus — metaphosphates and their amino- and thio-derivatives.

The formation of metaphosphates, which proceeds via the mechanism of the retrodiene synthesis, is accompanied by the liberation of phosphorus-free products obtained from the hydrocarbon skeleton of the initial, usually bicyclic, molecule.

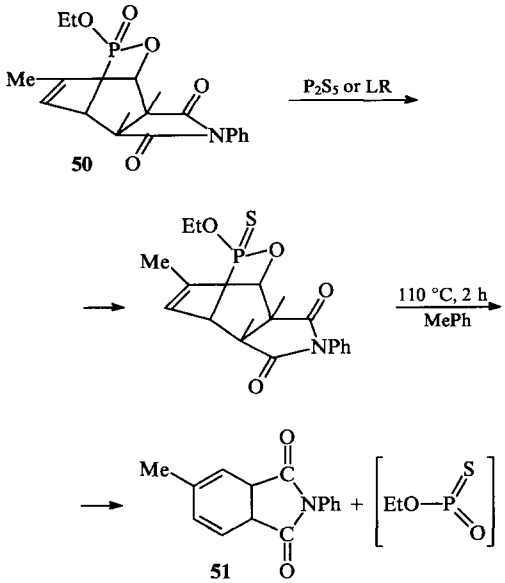
In a series of studies by Quin and coworkers,[69-74] it was found that derivatives of 2,3-oxaphosphabicyclo[2.2.2]octene **50**, obtained from compound **48**, constitute an excellent starting material for the generation of metaphosphates, which may be 'trapped' with the aid of suitable nucleophiles (alcohols, oxiranes, etc.).[69]



R = EtO, Me_2N, Bu^{t}O etc.

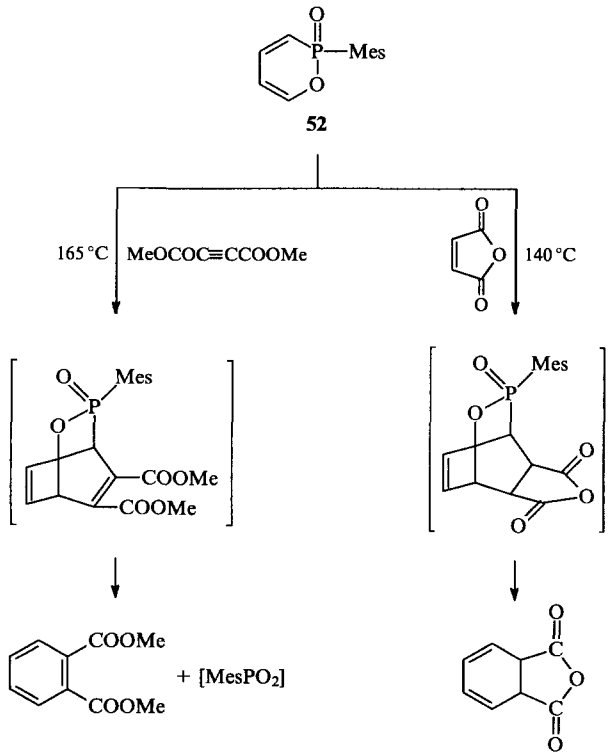
The initial cyclic phosphinochloridate **48** is converted into the strained 7-phosphanorbornene **49** via successive chemical transformations (for further details, see Quin et al.[69]). On treatment with peracids, compound **49** is converted into the phosphorylated derivative **50**.

The ease of the fragmentation of the phosphabicyclooctene depends on the conditions in this process: the thermal generation of the final products is achieved by heating in toluene at 100–110 °C; the photochemical fragmentation takes place very readily — at −75 °C under the influence of ultraviolet radiation. We may note that this constitutes a sharp difference between the bicyclic derivatives of σ^4-P and cyclic phosphites (see Subsection 1 of this Section), the decomposition of which requires heating to several hundreds of degrees. At a low temperature, it is possible to detect by ^{31}P NMR spectroscopy the metaphosphates obtained.[74] The high reactivity of the phosphacyclanes **50** is reflected in the ease of sulfurisation with the aid of P_2S_5 or Lawesson's reagent.[73]

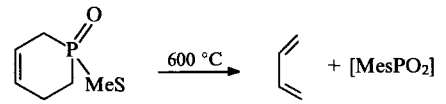


The reactions described here make it possible to obtain also the dihydrophthalimide **51** and other cyclic dienes together with the derivatives of metaphosphates and metaphosphorothioates which are difficult to obtain.

In the reaction of the phosphorus analogue of α-pyrone, namely mesityl(butadienyl) phosphinate **52**, with dienophiles, the formation of Diels–Alder adducts is only postulated: at the elevated temperature required for the cycloaddition, they decompose via the pathway described above with formation of Diels–Alder aromatic adducts or aromatic dihydro-adducts. The initial phosphacyclane thus plays the role of the supplier of butadiene.[75]

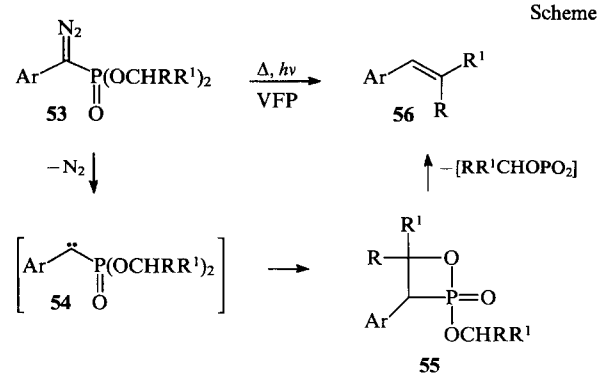


It is striking that the monocyclic alkene, which also serves as a source of the metaphosphonate and the diene, is pyrolysed under much more severe conditions.[75]



The intramolecular cyclisation of the carbenes **54**, obtained by vacuum flash photolysis (VFP) (350 °C, 10^{-5} Torr) of dialkyl α-diazobenzylphosphonates **53**, leads to the oxaphosphetanes **55**, which fragment under the reaction conditions to metaphosphates and substituted styrenes **56** (Scheme 4).[76]

Scheme 4



The cyclisation **54** → **55** takes place as a result of the intramolecular insertion of the carbene in a C–H bond of the ester alkyl group. The phosphacyclanes **55** can be isolated by vacuum flash photolysis at a lower temperature (275 °C) and this makes it possible to model the alkene elimination stage **55**→**56**. The high stability of the σ^4-oxaphosphetanes **55** (compared with the four-membered heterocyclic intermediates containing pentacoordinate phosphorus) in alkene formation reactions with the aid of phosphorus ylides and α-phosphorylated carbanions (see below) is striking.

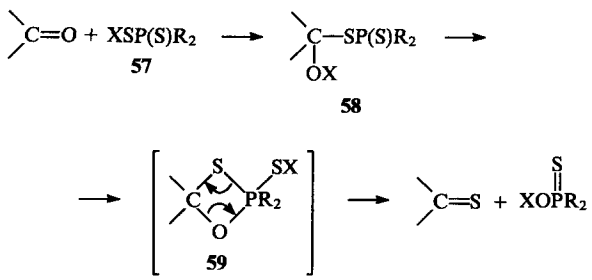
2. Nucleophilic substitution reactions

The highly electrophilic σ^4-P atom in σ^4-1,3,2-diheterophosphacyclanes is extremely sensitive to attack by charged or neutral nucleophiles: the rate of solvolysis of five-membered cyclic phosphates is several orders of magnitude higher than that of the tiralkyl phosphates with a similar composition.[15] The reason for this is believed to be the decrease in activation energy as a result of the involvement in the process of the thermodynamically stable pentacoordinate intermediate containing a diheterophospholane ring.[15] The equally high rates of cleavage of both endocyclic and exocyclic phosphorus–heteroatom bonds is striking. Acyclic and six-membered cyclic esters of σ^4-P acids react much more slowly. It is noteworthy that the diheterophosphorinane ring is relatively stable.

The endocyclic solvolytic reactions usually lead to phosphorus-containing acyclic products. This problem is outside the scope of this review, although it is important in the synthesis of biologically active phosphorus compounds. Among recent publications, we may mention a review[77] in which data are presented on the endocyclic hydrolysis of phosphazacyclanes used for the synthesis of phospholipids. The results of studies on the asymmetric synthesis of phosphorus-containing aminoacids using dioxa-, oxaza-, and diaza-phosphacyclanes have been surveyed in a review publication.[78] Finally, the photochemical decomposition of phosphate esters can also serve as a method of synthesis of unsaturated organics, which has been demonstrated in a recent review.[79].

There are few nucleophilic substitution reactions at the tetrahedral phosphorus atom forming part of the heterocycle which are used for the synthesis of phosphorus-free organic compounds. We may mention in the first place the so called

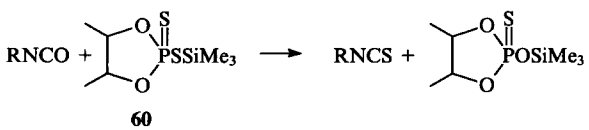
a sulfur atom on treatment with phosphorus dithio-acids or *S*-trimethylsilyl phosphorodithioates **57**.[3]



X = H, $SiMe_3$.

The reaction is completed by the addition of the dithio-derivatives **57** to the carbonyl group of the substrate; under mild conditions, the adducts **58** (X = $SiMe_3$) may be isolated. At an elevated temperature, the process develops further during fractionation and is completed by the formation of thiocarbonyl compounds and phosphorus-containing monothio-derivatives. The conversion of the hydroxy(siloxy)alkyl phosphorodithioates **58** into the final products takes place via a mechanism involving intramolecular nucleophilic substitution at the tetrahedral phosphorus atom.

The above method is especially effective for the conversion of aryl and acyl isocyanates into the corresponding isothiocyanates.[80-83] The silyl phosphorodithioate **60** is almost wholly converted into isocyanates and isothiocyanates at room temperature; the acyclic phosphorodithioates **57** (R = alkoxy-group) require heating in order to complete the reaction.



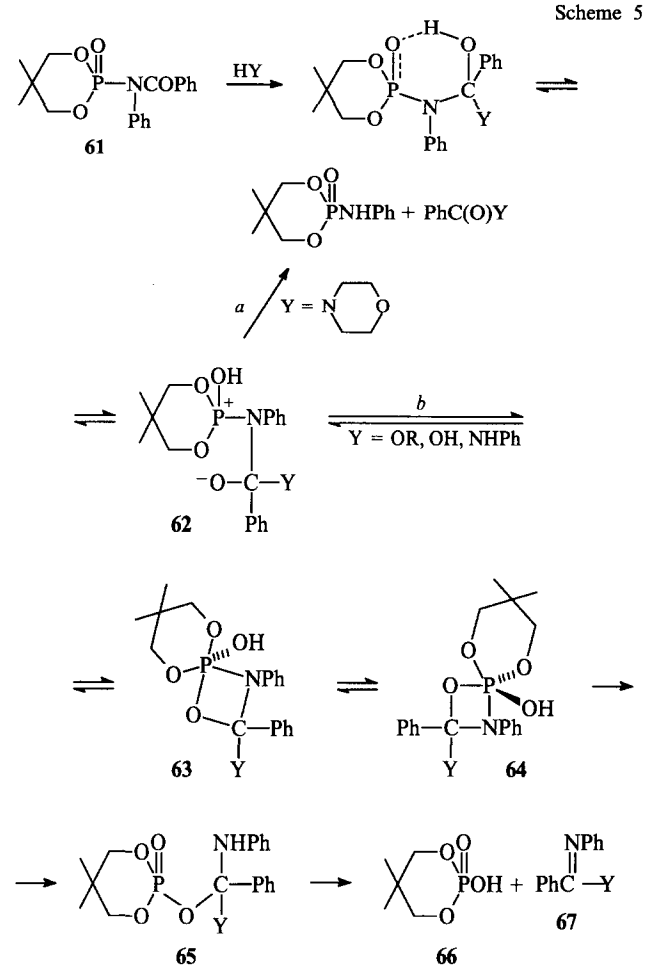
R = Ph, CCl_3CO, PhCO, $(EtO)_2PO$

The sharp increase in the sulfurising activity of phosphorodithioates following the introduction of a σ^4-P atom into a five-membered ring is most probably associated with the decrease in the energy of the type **59** intermediate.[82] The increase in the stability of phosphoranes as a result of spirocyclisation is well known.[16]

The comparatively low electrophilicity of the σ^4-P atom incorporated in a six-membered diheterophosphacyclane fragment may promote attack by an external nucleophile on an alternative electrophilic centre of the phosphorus-containing reagent if such is present. Thus the solvolysis of 2-(*N*-benzoyl-*N*-phenylamino)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane **61**[84] takes place exclusively with attack by nucleophiles on the carbonyl centre and is accompanied by the O,N-migration of the phosphoryl group (Scheme 5).

Depending on the nature of the nucleophile (HY), the process proceeds with dissociation of the C–N bond (route *a*) in the key intermediate **62** or via its cyclisation to compound **63** and pseudorotation to give compound **64** (route *b*) and is continued by the dissociation of the C–O bond in the phosphate **65**. The reaction with morpholine proceeds via route *a* to give *N*-benzoylmorpholine and the anilide of a cyclic phosphoric acid, while the reactions with water, alcohol and aniline take place via route *b*, which is associated with the phosphorylotropic transformations noted above. The phenylimide **67** (Y = OMe), obtained in the reaction with methanol,[80] methylates the cyclic acid **66** (2 h, room temperature). The conversion of the *N*-acylphosphoramidate **61** into the acid **66** and the phenylimide **67** is completed after 7 h on treatment with phenol and after 10 h

Scheme 5



R = Me, Ph, CMe_3.

on treatment with *tert*-butyl alcohol. Aniline affords the anilinium salt of the cyclic phosphoric acid **66** and a high yield of *N*-phenyliminobenzanilide **67** (Y = NHPh) as the reaction products.

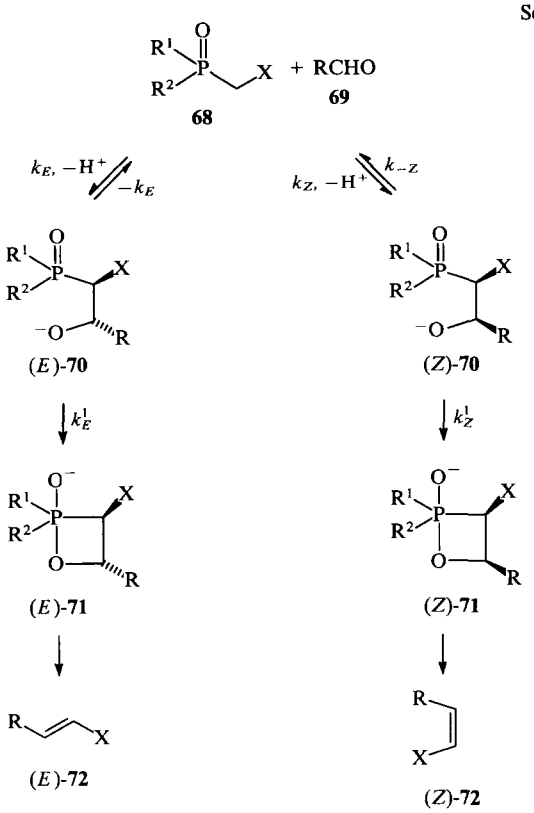
3. α-Phosphorylated carbanions

The reactions of α-phosphorylated stabilised carbanions with carbonyl compounds, for which the name 'Horner–Wadsworth–Emmons' (HWE) reaction has been established in recent years,[68] constitutes a classical method of synthesis of α,β-unsaturated carboxylic acid esters and other functionalised alkenes.

The HWE reaction as well as the Wittig reaction similar to it result in the preferential formation of the thermodynamically more stable (*E*)-alkenes. However, by varying the reaction conditions and the structure of the reactants, by introducing special additives, and by taking into account other factors, it is possible to vary the ratio of the (*E*)- and (*Z*)-products of the alkene formation process within wide limits.[66]

In the general case, the tendency towards formation of (*E*)- and (*Z*)-alkenes is considered from the standpoint of the reversibility of the formation of the intermediates, i.e. the ratios of the rates of the reaction stages k_{-E}/k_E^1 and k_Z/k_{-Z}^1 (Scheme 6).[67] Other conditions being equal, the increase in the stability of the (*E*)- and (*Z*)-alkoxides **70** and also of the pentacoordinate intermediates (*E*)- and (*Z*)-**71** determines the ease of their decomposition to alkenes. The process is kinetically controlled, (*Z*)-isomers are formed, whereas in the case where it is thermodynamically controlled there is a possibility of the reversibility of the process, leading to an increase in (*E*)-stereoselectivity.

Scheme 6



The tendency towards an increase in the 'reversibility factor' and hence in the ratio *E*/*Z* with increase in temperature and in the ease of the coordination of the metal-counterion in compound **70** (Li^+ is more effectively coordinated than Na^+ and K^+) has been established on numerous examples.[85,86] At the same time, an increase in the basicity of the medium and especially in the steric hindrance of the α-carbon atom in the carbonyl reactant **69** increases the content of the (*Z*)-isomer.[86] However, in the general case it is fairly difficult to predict the influence of the medium and structural factors on the stereochemical result of the HWE reaction because the conformational structure of the phosphonates **68**, the association of the carbanions obtained from them, and the relative contributions of all other factors may have a significant effect on the relative rates of the reactions leading to the (*E*)- and (*Z*)-isomers (see Scheme 6).

The influence of the environment of the σ^4-P atom and the synthetic consequences of its incorporation in the heterocycle are of special interest.

For the acyclic phosphonates **68**, it has been found that the replacement of the methoxy-groups in compound **68** ($R^1 = R^2 =$ MeO, X = COOEt) by the trifluoroethoxy-groups to give compound **68** ($R^1 = R^2 = CF_3CH_2O$, X = COOEt) in reactions with aldehydes leads to a sharp increase in the fraction of the (*Z*)-product up to the complete selectivity of the reaction with benzaldehyde. The methoxy-analogue of the phosphonate **68** gives rise exclusively to the *trans*-cinnamate **72** (R = Ph, X = COOEt) in this reaction, whereas the bis(fluoroethyl)phosphonate **68** wholly converts benzaldehyde into the *cis*-cinnamate ester **72** (R = Ph, X = COOEt). Evidently, this result is associated with the increase in the stability of the type **71** phosphoranes on enhancement of the electron-accepting properties of the substituents at σ^5-P, which is well known for phosphoranes.[16] This lowers the 'reversibility factor' and favours the (*Z*)-stereoselectivity.

This difference has been used recently for the (*Z*)- or (*E*)-selective conversion into alkenes in individual stages of the complex synthesis of a macrocyclic antibiotic—(+)-ikarugamicin.[87]

The phosphonates **68** of the σ^4-1,3,2-diheterophosphacyclane series have been recently investigated by various methods.[16,88–91] It was found that the stability and properties of the cyclophosphonate carbanions depend on the fine details of the steric structure, ring size, the structure of the acyclic functional groups, and the type of metal ion.

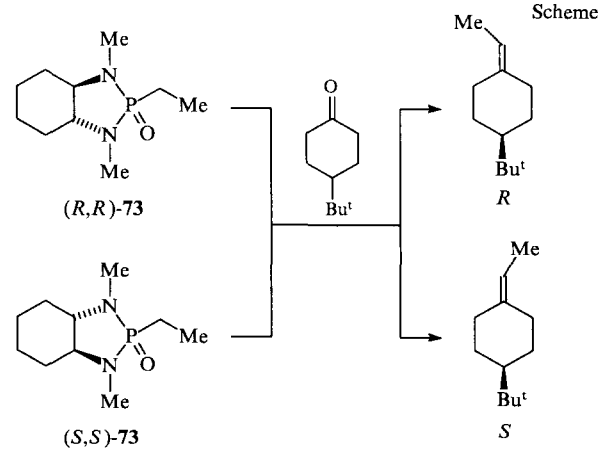
A distinctive feature of the conversion into an alkene with the aid of phosphacyclic carbanions is a high rate of reaction associated with the appreciable electrophilicity of the endocyclic σ^4-P atom (the tendency towards association and self-condensation is explained by the same feature[91]) and the distinct (*Z*)-specificity of the HWE reactions with participation of five- and six-membered cyclic phosphonates **68** ($R^1 + R^2$ = alkylene-1,2-dioxy- and -1,3-dioxy-, alkylene-1,2-diamino- and -1,3-diamino-, and alkylene-1-oxy-2-amino- and -1-oxy-3-amino).[16] The latter factor is associated with the stability of the pentacoordinate intermediates in which a σ^5-P atom is incorporated in the ring; it has been established that five-membered cyclic phosphonates exhibit an appreciably higher (*Z*)-selectivity [65% – 70% of the (*Z*)-isomer] than the six-membered and acyclic phosphonates.[15,68] This is a consequence of the well known stabilisation of phosphoranes by five-membered cyclic fragments (the five-membered ring effect).[16,17]

The rate of the HWE reaction increases markedly (almost by a factor of 20) when a phosphorus atom is incorporated in the dioxaphospholane ring in compound **68** [$R^1 + R^2$ = $OCH(CH_3)CH(CH_3)O$, X = COOEt] compared with the acyclic compounds **68** ($R^1 + R^2$ = OEt, X = COOEt). We may note, incidentally, that the latter is 35 times more reactive than the phosphine oxide **68** ($R^1 = R^2$ = Ph, X = COOEt).[68,92] These results are satisfactorily consistent with the hypothesis of the increased stability of the intermediate **70**: it increases for the following series of substituents at σ^5-P: phenyl < ethoxy- < alkylene-1,2-dioxy.

As already mentioned, the five-membered cyclic phosphonates **68** ($R^1 + R^2$ = alkylene-1,2-dioxy-, X = COOEt) were found to exhibit (*Z*)-selectivity, which increased sharply when the reaction was carried out with *tert*-butyl phosphonoacetate **68** [$R^1 + R^2$ = COH(Me)CH(Me)O, X = $COOBu^t$] at a low temperature (−20 °C) with lithium as the cation.[93] This feature has been used in the synthesis of pyrethroid insecticides (see Maryanoff and Reitz,[68] Tessier,[93] and the references quoted therein).

Unique diastereofacial selectivity has been demonstrated for the chiral diaminophosphonates (*R*,*R*)- and (*S*,*S*)-**73** synthesised from the two enantiomeric (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexanes.[94] An appreciable stereodifferentiating reactivity has been noted in the reactions of the potassium salts of the diazaphospholanes **73** with 4-*tert*-butylcyclohexanone: compound (*R*,*R*)-**73** forms a mixture of the isomeric (*R*)- and (*S*)-4-*tert*-butylcyclohexylideneethanes in proportions of 95 : 5; the use of the stereoisomer (*S*,*S*)-**73** inverts this ratio in favour of the (*S*)-alkene (Scheme 7).

Scheme 7



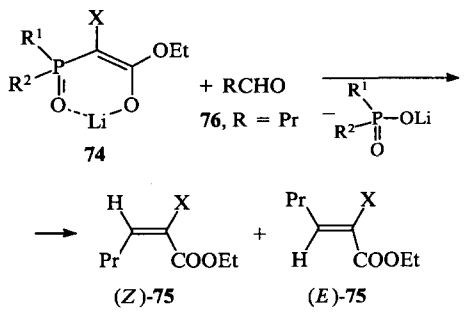
This stereochemical result of the HWE reaction with participation of compound **73** is difficult to explain from the standpoint of the 'reversibility factor'.[68,94] The cause of the above effect is more likely to be the initial topology of these cyclic phosphonates — their symmetry elements which predetermine in each case the nucleophilic attack on the carbonyl carbon atom in the sterically more accessible plane of the phosphorylated carbanion. It has been pointed out[94] that such asymmetric induction in the alkene formation reaction is useful for the synthesis of vitamins and pheromones or in the formation of chiral catalysts.

The stereospecific effect of the diazaphospholane fragment in the HWE reactions of lithium derivatives of the phosphonoacylates **74** with aliphatic aldehydes has been found in studies by Savignac and coworkers.[91,95–98] Table 1 presents the stereochemical results of the conversion of butyraldehyde into an alkene by treatment with α-n-propyl and α-chlorophosphonoacylates, which leads to the formation of a mixture of (*Z*)- and (*E*)-isomers. Oxygen-containing substituents, fluoroethyl substituents, as well as phosphorinane and dioxaphospholane reagents do not exhibit a stereospecific effect. We may only note that, in contrast to the α-alkylcyclophosphonates **74** (X = alkyl), their halo-substituted analogues **74** (X = Cl[96] and F[97]) were found to exhibit a considerable (*E*)-selectivity (cf. the data of Stiell and Gennari[85]).

The results of the formation of alkenes with the aid of derivatives of 1,3-dimethyl-2-oxo-1,3,2-diazaphospholanes constitute an isolated case. The reactions of compound **74** (X = Pr^n) lead to the preferential formation of the (*Z*)-isomers; the halo-substituted carbanions are distinguished by full (*E*)-stereoselectivity for chloro- and fluoro-substituents and for all the aldehydes **76** used in the alkene formation reaction.[96,97]

It is difficult to assign these results to only one cause. It has been shown,[97] for example, that the stereochemical effect depends on many external factors: the concentration of the phosphonate [the fraction of the (*Z*)-isomer falls with dilution], the temperature regime, the method of preparation of the lithium derivative **74**, and the nature of the alkene employed for this purpose as well as other additives (for example, lithium bromide and crown-ethers).

Table 1. The influence of substituents at the σ^4-P atom in the HWE reactions of the lithium salts of substituted α-phosphonoacetates with aldehydes.[91,96]

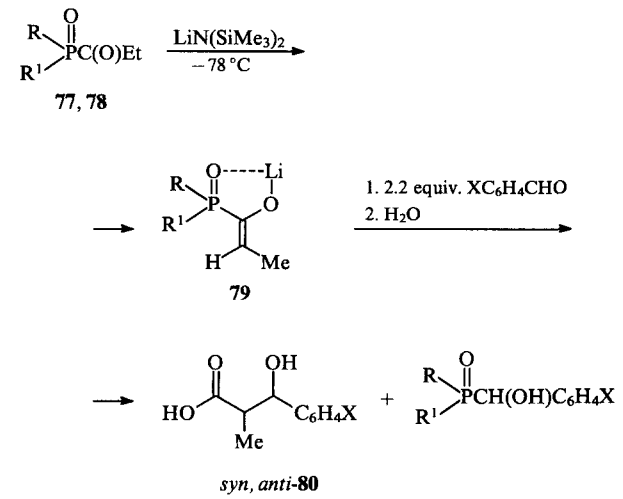


$R^1 + R^2$	Ratio of yields of (*Z*)- and (*E*)-isomers (%)	
	X = Pr^n (T = 20 °C)	X = Cl (T/°C)
$(EtO)_2$	37:63	55:45 (−20)
$(CF_3CH_2O)_2$	–	35:65 (−70)
$OCH_2C(Me_2)CH_2O$	61:39	25:75 (−40)
OCH(Me)CH(Me)O	62:38	–
$N(Et)(CH_2)_2N(Et)$	–	15:85 (−70)
$N(Me)CH_2)_2NMe$	76:24	2:98 (−70)
$N(Me)(CH_2)_3NMe$	Does not react	–
$(Me_2N)_2$	Does not react	–

The difficulty of assessing the factors which determine the stereochemical result of the reaction of compound **74** with the aldehyde **76** is caused, as noted above, by the tendency of the carbanions towards association and aggregation and by their equilibrium state associated with this behaviour, which is in its turn determined by the high electrophilicity of the endocyclic σ^4-P atom.

It is essential to emphasise that the use of cyclic α-phosphorylated carbanions in HWE reactions have a series of specific features associated with the greater reactivity of these substances due to their more pronounced sensitivity to the nucleophilic reactions of the endocyclic σ^4-P atom. Although the stereospecific effect of phosphacyclanes is not always easy to predict, it amounts as a rule to complete stereoselectivity. The latter is associated both with the characteristic features of the processes arising in the course of the HWE reactions of the cyclic intermediates and with the specific topology characteristic of cyclic reagents effecting the conversion into alkenes.

The base-promoted aldol condensation of diethyl propionylphosphonate **77**[99] and of its oxazaphosphorinane analogue **78**[100] with aromatic and aliphatic aldehydes is characterised by a high *syn*-diastereoselectivity (the ratio *syn* : *anti* = 98 : 2 and 94 : 6 for compound **80** obtained from compounds **77** and **78** respectively). The reaction makes it possible to produce the β-hydroxycarbonyl fragment of compound **80** under very mild conditions.

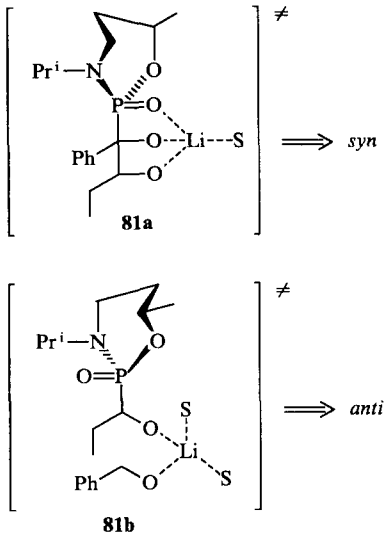


77: R = Pr^nCO, R^1 = OEt; **78**: R + R^1 = $OCH(CH_2)_2NPr^i$ (Me).

The authors[100] established that, when the N-substituent is fairly bulky, the chair conformation of the oxazaphosphorinane reagent **78** creates good possibilities for preferential enantiofacial selection (cf. the reagents **73**). The high degree of stereospecificity is in this case attributed to the formation of the highly organised transition state **81a** (Scheme 8).

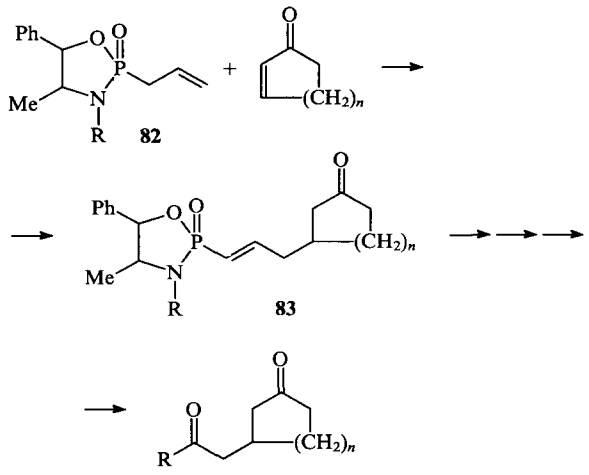
The tendency of lithium alkoxides of type **79** to associate, which was noted above, plays a significant role also in the reaction under discussion. The introduction of additives of the type of tetramethylethylenediamine (S), which coordinate the lithium ion, disturbs the stereocontrol: the increase in the fraction of the *anti*-conformer of **80** is attributed to the contribution by the activated complex **81b** formed with the phosphoryl group of the phosphacyclane liberated from the coordination sphere of lithium.

Scheme 8



S = solvent or additive.

Chiral allyl phosphonates having the oxazaphospholane structure, obtained from ephedrine **82** (R = Me) and its isopropyl analogue **82** (R = Pr^i), undergo 1,4-addition with cyclic enones, which leads to the formation of the 1,4-adducts **83** with a high enantioselectivity.[101] The latter have been converted into the corresponding aldehydes or acids with an oxocyclane structure.



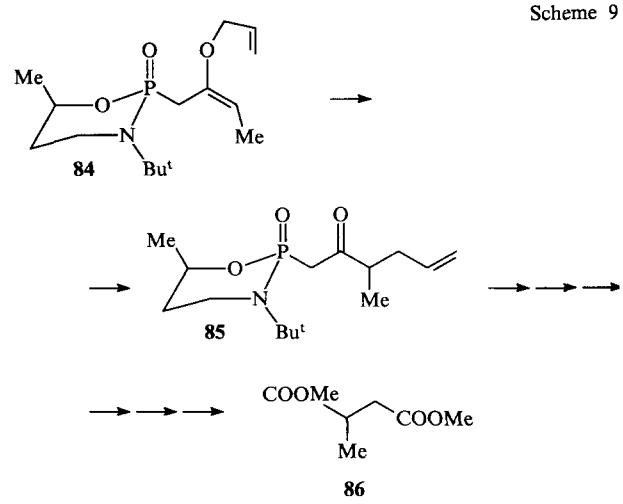
n = 1 - 4; R = H, OH.

The optical yield of the products increases greatly on passing from the methyl homologue (70% - 74%) to the isopropyl homologue **82** (88% - 98%). The authors[101] emphasise the likely usefulness of this reaction for the synthesis of natural products.

The stereochemical control achieved by chiral carbanions containing the oxazaphosphorinane ring gives rise to asymmetric induction of the phosphonamidates **85** in the Claisen rearrangement (Scheme 9).[102-104]

It has been established that the oxidative decomposition of the product of the Claisen rearrangement **85**, obtained from *cis*-**84**, leads to the (*S*)-dimethyl methylsuccinate **86**, while the *trans*-isomer affords the (*R*)-enantiomer.[102] As in the previous cases, the result of the rearrangement is associated with the topological characteristics of the lithium carbanions derived from compound **84**, which determine the course of the isomerisation of the carbanion-stabilised allyl vinyl ether on one of the 'opposite' surfaces (made up of the multiple bonds, the carbanionic centre, and the P = O fragment) relative to the structural elements of the phosphoramide ring.[103]

Scheme 9



The arenesulfonyl group also exerts a similar accelerating and stereoregulating influence on the Claisen rearrangement, but a number of advantages of the phosphorylated allylvinyl substrates have been noted:[104] the great ease of synthesis, the possibility of an extensive structural variation of the phosphorus-containing fragments, and the thorough knowledge of the chemistry of the phosphorus-stabilised carbanions.

The data presented in this section reveal the exceptionally wide prospects for the employment of phosphacyclanes in stereospecific organic and organoelement synthesis. The relatively high availability of the cyclic organophosphorus compounds functionalised in the endocyclic fragment, the possibility of varying the composition and steric structure of the phosphorus-containing heterocycle, and the very high reactivity of the compounds discussed here — all these properties leave no doubt that this field of the chemistry of cyclic organophosphorus compounds has a great future.

IV. σ^5-Mono- and diheterophosphacyclanes

Derivatives of pentacoordinate phosphorus have played an important role in the development of the chemistry of organophosphorus compounds. The problem of the synthesis of substances of this type with a hypervalent central atom, questions concerning the electronic and steric structures, the chemical transformation of phosphoranes, and the role of pentacoordinated intermediates in the reactions of organophosphorus compounds — these and other questions of the theoretical and synthetic chemistry of phosphorus continue to remain in the centre of attention of investigators. Among the recent review publications devoted to problems of the synthesis and properties of σ^5-phosphacyclanes, mention may be made of those of Kumaras et al.[105] and Gloede.[106] Attention should also be drawn to the experimental studies which have revealed the role of σ^5-1,3,2-dioxaphospholane intermediates in biological processes associated with phosphate transport (see, for example, Kluger and Taylor[107] and Breslow et al.[108]).

The introduction of a σ^5-phosphorus atom into a monocyclic and especially a spirocyclic system favours the stabilisation of phosphoranes. The recognition of this fact promoted the concentration of the efforts of chemists in the search for new reagents containing a pentacoordinate phosphorus atom as well as various complex functionalised compositions, which in the course of reactions give rise to σ^5-P compounds participating in a particular chemical operation.

The synthesis of σ^5-phosphacyclanes, modelling the intermediates in the most important reactions of organophosphorus compounds, for example hydroxyphosphoranes (intermediates in nucleophilic substitution at a tetrahedral phosphorus atom)[16] or 1,2-oxaphosphetanes (substances postulated as intermediates

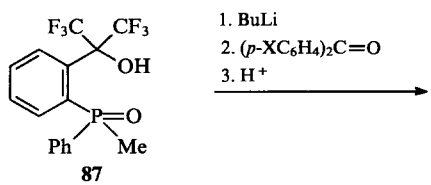
in the HWE and Wittig reactions)[109] assumed a particular importance. The synthesis and study of the transformations of the above substances have not only thrown light on their reaction mechanisms, but also made possible a specific approach to the selection of the optimum reagents and conditions for reactions with their participation in order to obtain complex organic substances, including natural products.

1. σ^5-1,2-Oxaphosphetanes and σ^5-1,2-oxaphospholanes

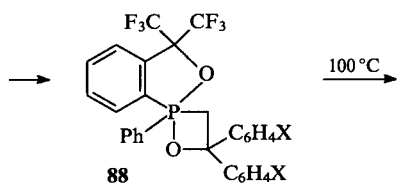
As already stated, the four-membered 1,2-oxaphosphacyclanes have been postulated as intermediates in reactions giving alkenes with the aid of Wittig reagents or α-phosphorylated carbanions. However, attempts to isolate and identify these substances, produced in the course of reactions involving conversion into alkenes, were unsuccessful for a long time: in the best case, it was possible to detect them by various spectroscopic methods.[110-113]

However, stable 1,2-oxaphosphetanes have been isolated recently and their thermal decomposition reactions, modelling the second stage of the HWE and Wittig reactions, have been investigated.[114,115,117-120]

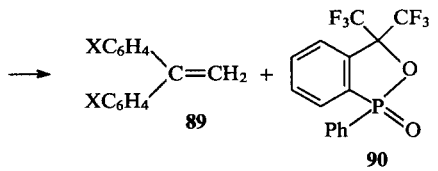
Successive treatment with butyllithium, diaryl ketones, and acids of the phosphine oxide **87**, containing the so called Martin's ligand[114,116] (acyclised aromatic ligand stabilised as a result of spirocyclisation as well as other unstable σ^5-P compounds, for example hydroxyphosphoranes[16]) together with the phenyl and methyl ligands makes it possible to obtain the stable spirocyclic 1,2-oxaphosphetanes **88**.



87



88



89 **90**

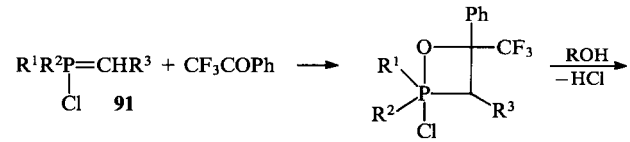
The phosphacyclanes **88**, which are entirely stable under the usual conditions (which has made it possible to establish their structure by X-ray diffraction[114]) are converted quantitatively on heating to 100 °C into 1,1-diarylethenes and the phosphinates **90** in accordance with the mechanism of the second stage of the Wittig and HWE reactions.

According to the Hammett equation, the rate of the decomposition reaction is

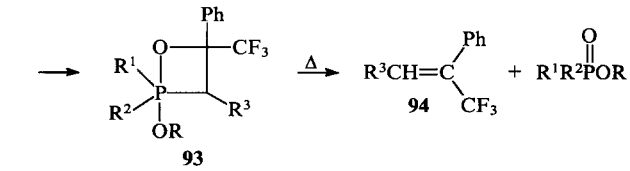
$$\lg(k/k_0) = -0.709\,(2\sigma_p^+) \qquad (r = 0.999),$$

with a negative reaction constant ($\rho = -0.709$), indicating the accelerating effect of the electron-donating substituent X. The relatively low sensitivity of the rate of decomposition to the polarity of the medium, the low negative activation entropy ($\Delta S^{\neq} = -5.7 \pm 0.75$ e.u.) and the small (in absolute magnitude) value of ρ indicate a concerted mechanism of the decomposition of compound **88** with a weakly polar transition state (slight asynchronicity in the dissociation of the P–C and C–O bonds in the oxaphosphetane fragment).

Stable 1,2-oxaphosphetanes **92** have been obtained by Kolodyazhnyi and coworkers[115,117] by the reaction of phenyl trifluoromethyl ketone with the halides **91** under very mild conditions (ether, 0 °C).

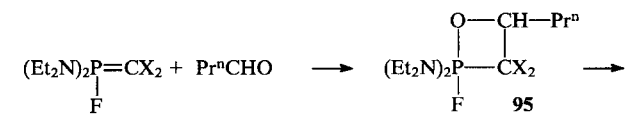


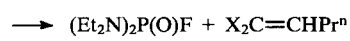
92



93 **94**

The chlorine atom in the chlorophosphinomethylene **91** is readily replaced by an ether group on treatment with methanol or phenol, while the 1,2-oxaphosphetanes **93** decompose on heating to the alkenes **94** and the corresponding phosphinates in accordance with the mechanism of the Wittig reaction. It is of interest that their precursors—2-halo-1,2-oxaphosphetanes **92**—do not exhibit a tendency to eliminate alkenes and on thermolysis as a rule undergo fragmentation with formation of the corresponding phosphorus-containing acyclic alkenes. The *P*-fluorophosphetanes **95**, decomposing to the *gem*-dihalide **96** and phosphorofluoridic diamides, constitute an exception.[118-120]



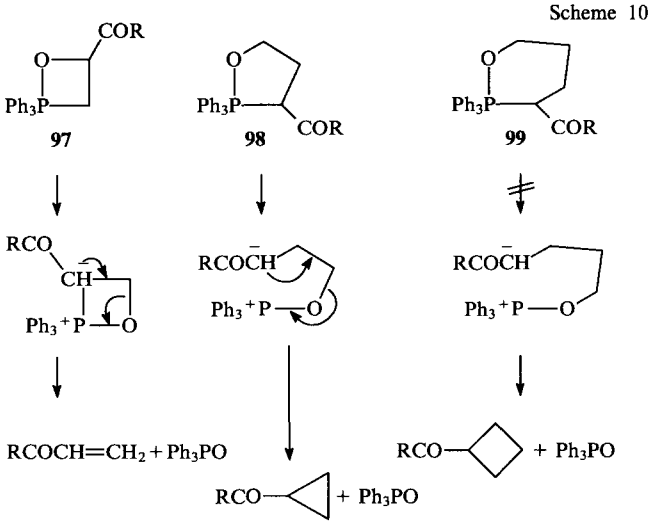


96

It has been postulated[119,120] that the electronegative atoms X favour the migration of the dihalomethylene group (and not of the oxygen atom) to the axial position in the phosphorane **95**, which results in the dissociation of the P–C (and not P–O) bond.

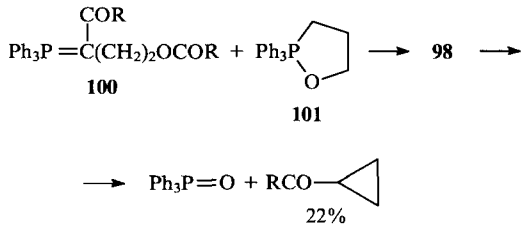
The conditions and nature of the decomposition of 1,2-oxaphosphacyclanes as well as the synthetic result of the fragmentation of the heterocycles depends significantly, other conditions being equal, on the size of the phosphorus–oxygen heterocycle.[121] The triphenyloxaphosphetanes **97** readily decompose in accordance with the general mechanism corresponding to the second stage of the Wittig reaction. The alkene is then produced more readily the more pronounced are the electron-accepting properties of the ring substituents (in this case, these are acyl or alkoxycarbonyl groups) (Scheme 10). It has been suggested[121,122] that the decomposition proceeds via a stage involving the open-chain phosphonium-carbanionic form of the intermediate, which results in the formation of a α,β-unsaturated ketones (for a phosphorane with an acyl substituent) and a phosphine oxide.

Scheme 10



The thermal decomposition of the 1,2-oxaphospholanes **98** to cyclopropyl ketones is achieved only in the presence of electron-accepting ring substituents, the unsubstituted ring being stable. The 1,2-oxaphosphorinanes **99**, even those containing electron-accepting substituents, are stable under the reaction conditions and do not decompose to cyclobutanes. It is believed [121] that these experimental results are influenced mainly by ring strain. These data are satisfactorily consistent with a repeatedly established fact — an increase in the chemical and thermal stability in the following series of phosphacyclanes: four-membered < five-membered < six-membered. [16]

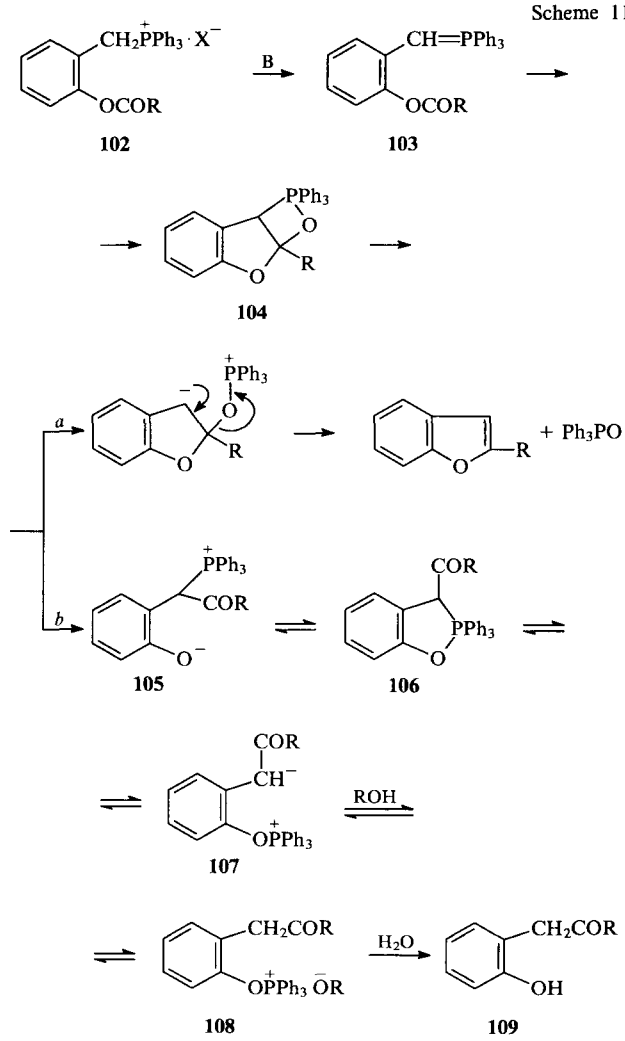
It is of interest that the cyclopropyl ketone can be obtained also as a result of the intermolecular transfer of the acyl group from the ylide **100** to the unsubstituted oxaphospholane **101**; the intermediate acyl-1,2-oxaphospholane **98** gives rise to the cyclopropyl ketone in 22% yield.



It has been established that the proton-donating properties of the medium can also determine the synthetic result of the decomposition of 1,2-oxaphosphetane. [123] Thus the intermediate four-membered tricyclic phosphorane **104**, obtained from 2-acyloxybenzylidenetriphenylphosphonium ylide **103** (which was in its turn obtained from the phosphonium salt **102**) decomposes in inert solvents to benzofurans via path *a* in accordance with an intramolecular acylation mechanism (**103** → **104**) (Scheme 11).

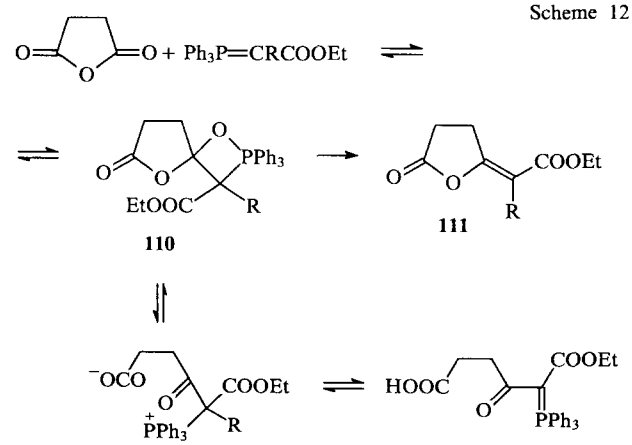
In proton-donating solvents (alcohols), the process proceeds with the successive cleavage and closure of rings via the phosphonium (compound **105**), benzophosphorane (compound **106**), and zwitterionic (compound **107**) intermediates. On treatment with alcohols, the last intermediate gives rise to the quasi-phosphonium salt **108**, the hydrolysis of which led to the isolation of the ketone **109** (Scheme 11, path *b*).

Scheme 11



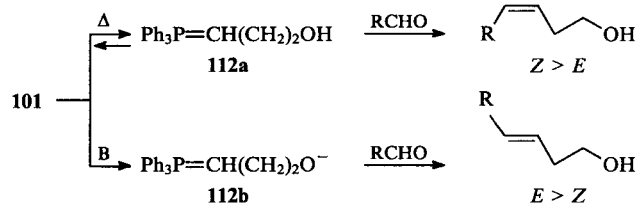
Increase in ring strain in systems incorporating the 1,2-phosphetane fragment naturally facilitates the decomposition of the intermediates in the Wittig or HWE reactions to the corresponding alkenes. The very unstable phosphacyclane **110**, obtained in the course of the conversion of succinic anhydride into an alkene by treatment with an ylide, may be stabilised not only via elimination of the alkene **111** but also as a result of rearrangement to the open-chain phosphonium (for R = H, Me) or ylide (for R = H) organophosphorus intermediates in the alkene formation reaction (Scheme 12). [124]

Scheme 12



R = H, Me.

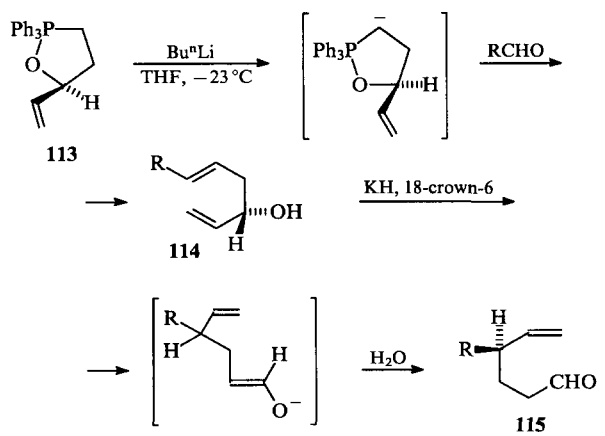
The data presented in this subsection and also in Subsection 2 indicate the relatively easy heterolysis of the phosphorus–oxygen and phosphorus–carbon bonds not only in the strained σ^5-1,2-oxaphosphetane ring but also in the σ^5-1,2-oxaphospholane ring. It has been established that the latter can be regarded as a latent ylide, which suggests that compounds of this series have the capacity to effect conversions into alkenes with the postulated involvement of the open-chain γ-oxido(hydroxy)ylide tautomeric form **112**. Furthermore, it has been shown in a series of studies [125–127] that the method of generation of the ylide **112** from the 1,2-oxaphospholane **101** determines to a significant extent the stereochemical result of the conversion of aldehydes into alkenes: the process whereby homoallyl alcohols are obtained as a result of the thermolysis of a phosphacyclane exhibits (*Z*)-selectivity and, in the presence of bases, (*E*)-selectivity.



The hydroxy-ylide **112a**, generated thermally from compound **101**, affords the (*Z*)- and (*E*)-alkenols (the ratio *Z* : *E* = 73 : 27 for R = Ph and 88 : 12 for R = C_6H_{11}) in the presence of benzaldehyde. The γ-oxidoylide **112b**, obtained by treating compound **101** with lithium bases, for example with $LiN(SiMe_3)_2$, gives rise to the (*E*)-stereoisomer in a mixture in which its content is high: *Z* : *E* = 4 : 96 (R = Ph) and 45 : 55 (R = C_6H_{11}).

As in the HWE reactions, in the cases described the stereochemical result of the alkene formation process is determined by the combined influence of a large number of factors, which determine the conditions governing the formation and interconversion of the zwitterionic and 1,2-oxaphosphetane intermediates. The nonstabilised ylides in the Wittig reactions are usually characterised by a high (*Z*)-stereoselective activity; [2] the anomalous (*E*)-stereoselectivity, noted above, of the ylides generated from phosphacyclanes can be explained, apart from all other factors, by the effect of the ω-nucleophilic groups in the ylide **112**. [127]

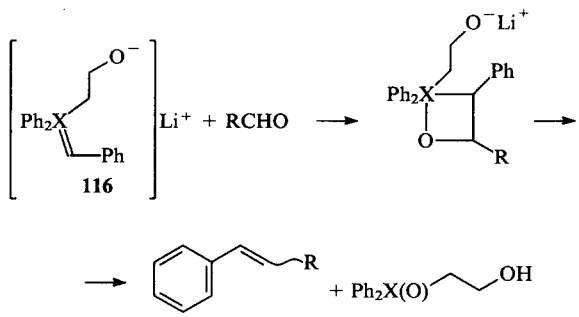
The approach thus developed to the *trans*-selective synthesis of alkenes has been extended to 5-vinyl-1,2-oxaphospholanes **113**, which were found [128] to react with benzaldehyde to form the phenyldienol **114** (R = Ph) with the isomer ratio *trans* : *cis* = 9 : 1.



The ratio of the stereoisomeric *cis*- and *trans*-dienes **114**, obtained from aliphatic aldehydes (R = alkyl), is close to the equilibrium value. It has been noted [124] that 3-hydroxy-1,5-dienes of type **114** are extremely valuable synthons in the synthesis of natural products such as leukotriene B and prostaglandins.

In a highly basic medium (potassium hydride in the presence of a crown-ether), the hydroxydiene undergoes the Cope rearrangement to the unsaturated aldehyde **115**. Thus the above method makes it possible, as it were, to introduce a further two carbon atoms at the carbonyl carbon atom of the initial aldehyde and suggests an approach to the synthesis of the hexenal substrates **115** via the 3-hydroxy-1,5-diene stage.

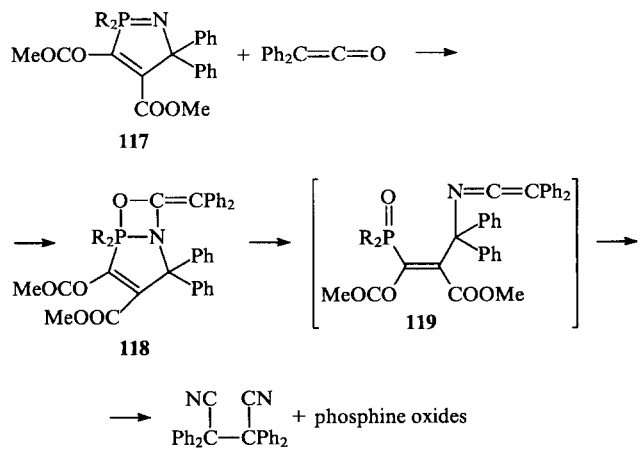
The ω-hydroxy-ylide *trans*-selectivity, described above, of the Wittig reaction proceeding via a stage involving the formation of a 1,2-phosphetane has found an interesting conformation when arsenic ylides were employed. [129] The β-oxidoylides **116** convert hexanal and piperonal into alkenes with different degrees of stereoselectivity depending on the nature of the central atom X: the ratio of the isomers of the substituted styrenes is *E* : *Z* = 70 : 30 for the phosphorus ylides **116** (X = P). The corresponding arsenic ylide **116** (X = As) ensures a highly selective synthesis of the (*E*)-alkene (100%).



X = P, As.

These results enabled Boudia et al. [129] to recommend arsenic ylides as alkene-forming reagents for the stereoselective synthesis of (*E*)-alkenes.

In conclusion of this Subsection, we shall draw attention to the unusual decomposition of the bicyclic adduct **118** obtained in a study of the 'phosphoroimine' version of the Wittig reaction between the azaphosphole **117** and diphenylketene. [130]



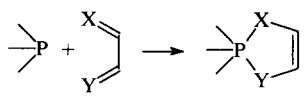
The spirocyclic 1,3,2-oxazaphosphetanes **118** (R = Me, Ph) isolated, which are stable in the crystalline state, decompose in chloroform at 48 °C in several minutes. However, contrary to expectations, the product of the intramolecular imination cannot be isolated. Instead of the latter, tetraphenylsuccinonitrile is obtained in 73% yield together with unidentified phosphorus-containing substances, tentatively assumed to be of the phosphine oxide type. It is believed that this reaction course is associated with the homolytic decomposition of compound **119**, characteristic also of other ketene imines, [130] and with the recombination of diphenylcyanomethyl radicals.

2. Thermolysis and solvolysis of 1,2-hetero- and 1,3,2-dihetero-phosphacyclanes and 1,2-hetero- and 1,3,2-dihetero-phosphacyclenes

Reactions of the above type play an important role in the strategy for the employment of cyclic reagents containing σ^5-P in organic synthesis. The relative thermodynamic lability of σ^5-1,3,2-diheterophosphacyclanes, the pronounced Lewis acidity of the σ^5-P atom and the associated high reactivity of phosphoranes in nucleophilic substitution reactions are factors which have determined the choice of the substances described here for the synthesis of a wide variety of complex organic compounds. Without claiming to cover fully all the examples of the use of thermal and solvolytic processes with participation of 1,3,2-diheterophosphacyclanes for the synthesis of phosphorus-free substances, we shall draw attention to the thoroughly investigated processes involving the fragmentation of σ^5-dioxaphospholane functional groups in compounds of hypervalent phosphorus[2,16,17] and also to the 'enediol-phosphorane' strategy for the synthesis of hydroxycarbonyl substances developed by Ramirez and coworkers.[131,132] A detailed consideration of these interesting chemical reactions is outside the scope of the problems covered by the present review, but has been thoroughly described in the literature sources mentioned above.

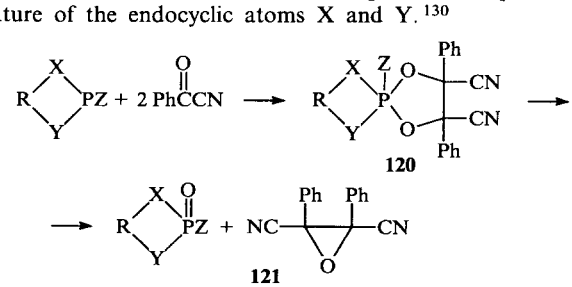
At the same time, new data have appeared during the last decade concerning the use of the thermal and solvolytic reactions of σ^5-1,3,2-diheterophosphacyclanes, mainly phospholanes and phospholenes, which are either specially synthesised for particular synthetic purposes or are formed as key intermediates in the multistage syntheses of polyfunctional organic compounds. Information about the role of pentacoordinated intermediates has been presented in a review;[16] only two examples of this kind, characterising the features of the application of the phosphorus-containing functionalising substances under discussion, are presented here.

One of the common synthetic procedures involving the use of the functionalising activity of phosphacyclanes is the thermal or solvolytic fragmentation of σ^5-1,3,2-dihetero- or σ^5-1,2-heterophoshacyclenes obtained from phosphorus(III) derivatives and α,β-unsaturated, α-dicarbonyl, diene, and similar synthons, which undergo [1 + 4]-cycloaddition with one another.



When subjected subsequently to thermal influences or entering into nucleophilic substitution reactions, as a rule with proton-containing nucleophiles, the σ^5-P adducts 'liberate' the carbon component of the ring and are converted into phosphoryl or similar reaction products.

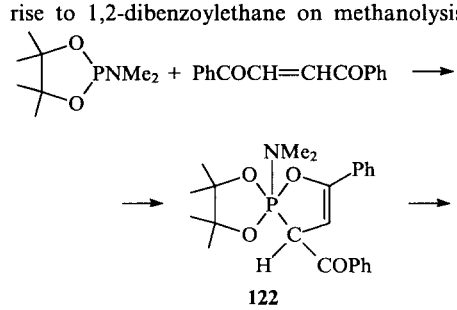
The phosphoranes **120**, which are obtained by the reaction of phosphorus(III) precursors with benzoyl cyanide, are fairly readily converted into the epoxides **121** on heating. The alkylenedioxy-analogue **120** (R = CH_2CH_2, X = Y = O) is fairly stable and decomposes on heating above 100 °C.[133,134] The diazaphospholane **120** (R = CH_2CH_2, X = Y = NMe) gives rise to an epoxide after being heated for 2 h at 80 °C and after being kept at room temperature for a long time. It has been noted that the *cis* : *trans* ratio of the isomers of compound **121** depends on the nature of the endocyclic atoms X and Y.[130]



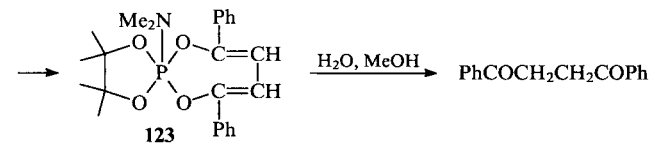
120

121

On treatment with proton nucleophiles, σ^5-1,3,2-diheterophosphacyclenes can decompose with formation of saturated organic products. Thus the spirocyclic aminophosphorane **122**, obtained from a phosphoramidite and 1,2-dibenzoylethene, gives rise to 1,2-dibenzoylethane on methanolysis.[135]



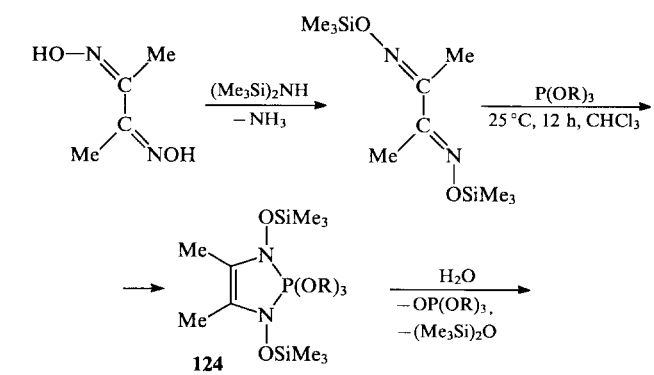
122



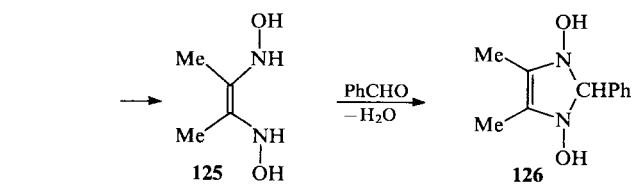
123

It has been established that under mild conditions the spirophosphorane **122** is converted into the σ^5-P-amide **123** containing a seven-membered ring. The amide actually fragments with cleavage of the phosphadiene ring. This unusual hydrogenation of an unsaturated diketone with the aid of water or methanol is based on the rarely encountered isomerisation of a five-membered ring to a seven-membered ring (**122** → **123**).

The hydrogenation on solvolysis of phosphacyclanes has been used to synthesise *cis*-2,3-bis(hydroxyamino)butene **125**.[136] Diacetyl dioxime is silylated, after which it is converted by reaction with phosphite into the phosphoranes **124** and these are hydrolysed, affording the butene **125**.



124

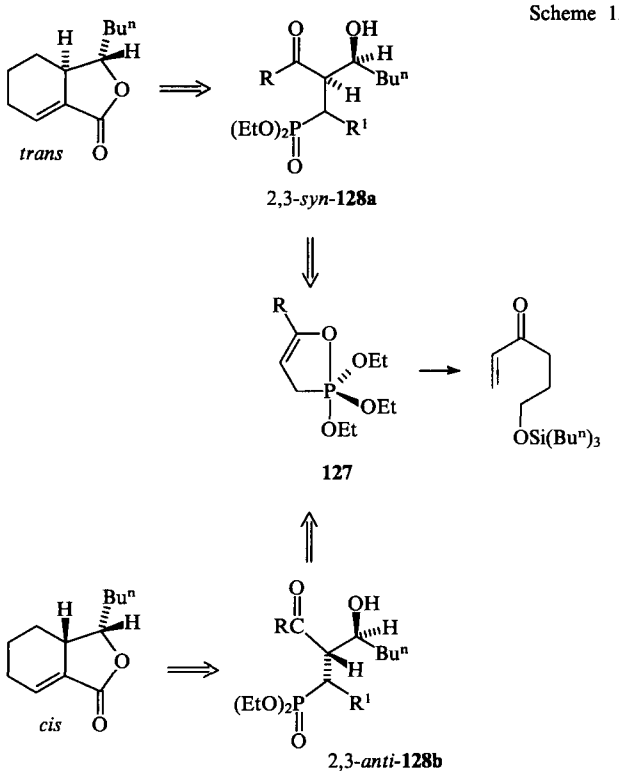


125 **126**

It has been shown that compound **125** can serve as a chelating ligand or as a precursor or nitrogen heterocycles; it readily gives rise to the imidazoline **126** on reaction with benzaldehyde.

The product of the [1 + 4]-cycloaddition of a α,β-unsaturated silylated ketone has been chosen as the key synthon in the synthesis of (+)-*trans*- and (+)-*cis*-neoknidylides.[133,134] Retrosynthetic analysis (Scheme 13) made it possible to develop a strategy for the synthesis of these natural products, including the formation of the highly substituted phosphonates **128a**, **b** and their conversion into the target products using the intramolecular HWE reaction.

Scheme 13

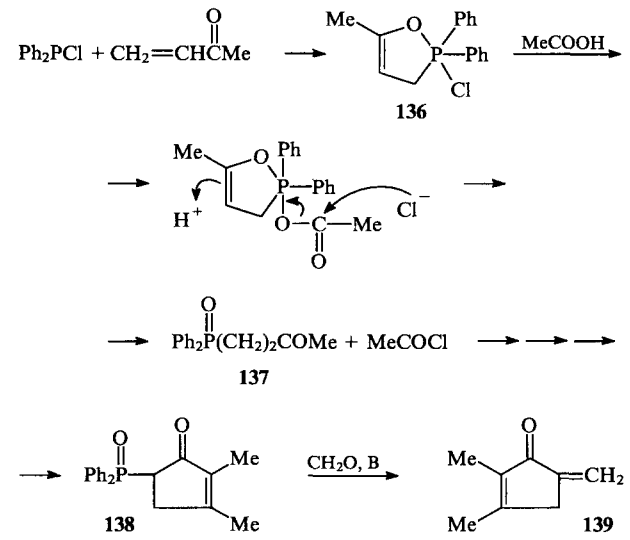


R = $(CH_2)_3OSi(Bu^n)_3$.

The above investigators used successfully the transformation of the 1,2-oxaphospholene **127** in order to synthesise biologically active natural products with the phosphonate structure.[138-140]

The ease of the closure and cleavage of the dioxaphospholane ring has been used for an unusual functionalisation in one of the stages of the total synthesis of natural benzoazepine derivatives of dihydroquinolines—chilenine and digallanezine (Scheme 14).[141] The closure of the benzoazepine ring **129**→**135** is attained by employing two organophosphorus reagents. The diketo-derivative of the γ-lactam **129** is converted into the γ-thiolactam **130** on treatment with Lavesson's reagent and the thiolactam is then converted into the 1,3,2-dioxaphospholene with the aid of trimethyl phosphite. The phosphorane **131**, identified on the basis of ^{31}P NMR spectroscopic data, undergoes a complex transformation under fairly severe conditions (refluxing of the phosphite) involving the closure to a seven-membered ring **131**→**132**, the substitution of trimethyl phosphate by a thiolate anion, the cleavage of the episulfide ring **132**→**133**, and finally the C→S propionyl shift with formation of the required polycyclic system **135**.

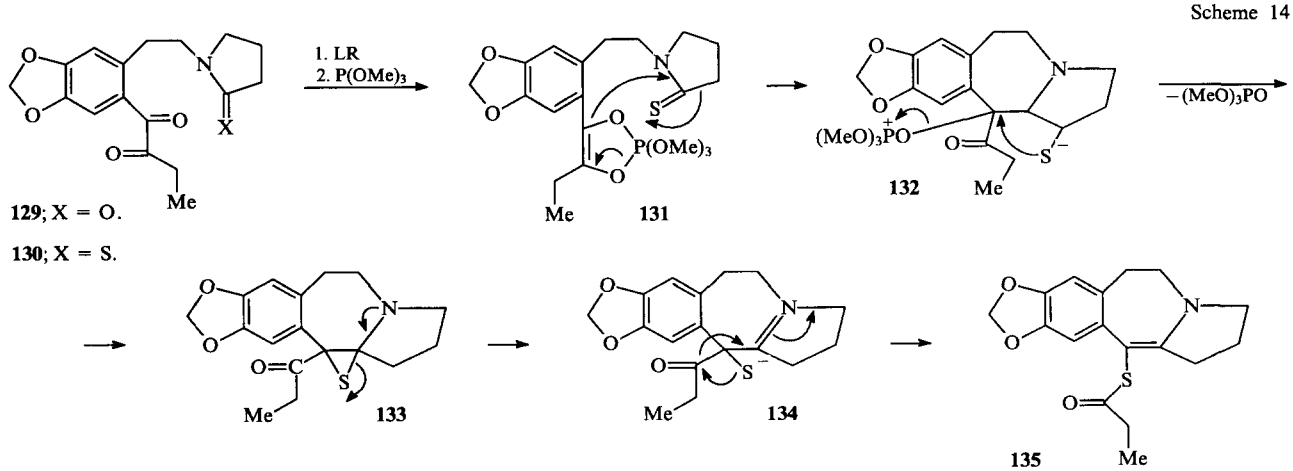
Cyclic phosphoranes—adducts formed in cycloaddition reactions—have been used also as precursors for the preparation of acyclic HWE reagents for subsequent use in the synthesis of natural products. Thus it has been shown[142] that the oxaphospholenes **136** can be conveniently employed for the synthesis of the β-ketophosphonates **137** by a reaction involving the cyclisation of compound **136** and subsequent deacylation.



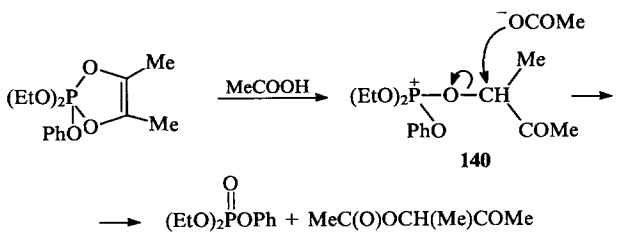
By means of a series of transformations in the aliphatic fragment, the phosphorylated ketone **137** has been converted into the phosphorylated cyclic enone **138**—the precursor of methylenomycin B **139**—a substance belonging to the family of the cyclopentanoid antibiotics. It is emphasised[138] that the 'phosphonate' strategy for the synthesis of compound **139** is convenient in view of the possibility of monitoring with the aid of ^{31}P NMR spectroscopy all the phosphorus-containing intermediates formed during the process.

The addition of α,β-unsaturated carbonyl and α-dicarbonyl compounds to phosphorus(III) substrates with the intermediate formation of 1,2-oxa- and 1,3,2-dioxa-phospholenes followed by the solvolytic cleavage of the five-membered phosphorus heterocycle constitutes in essence a synthetic route to products of the addition of proton nucleophiles to the unsaturated fragments of the initial 1,4-heterodiene. The functionalisation with the aid of acetic acid of the latent diacetyl to give α-acetoxyethyl methyl ketone (Scheme 15), which is similar to the 'hydrogenation' of unsaturated ketones or the dioxime examined above, has been described.[143]

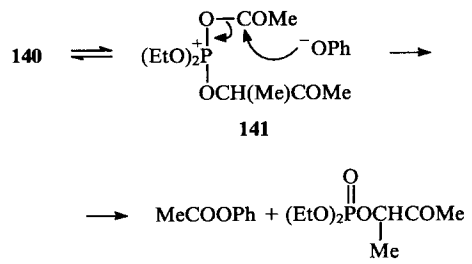
Scheme 14



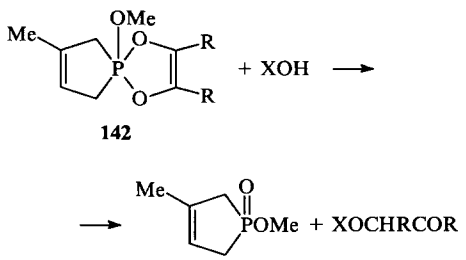
Scheme 15



The reaction is complicated by the dealkylation of the quasi-phosphonium salt **140** not only as a result of nucleophilic attack on the methylidyne carbon but also a result of the abstraction of the ethyl group. Furthermore, the ligand exchange **140**→**141** and deacylation by the phenoxide anion constitute an alternative route, which complicates the possible preparative use of the reaction described.



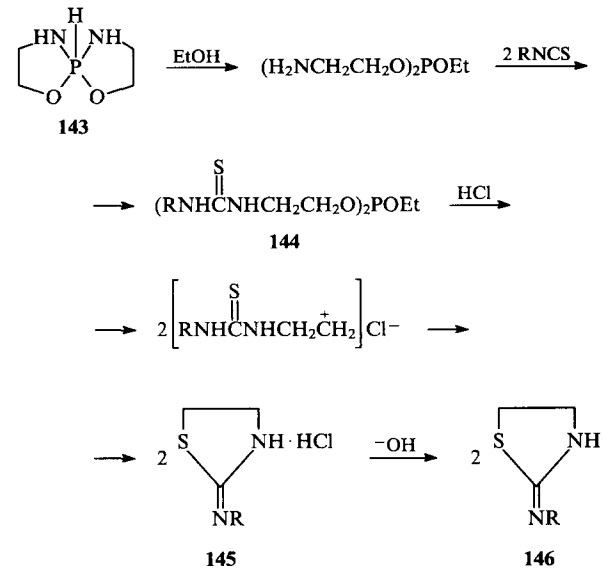
The enediol-phosphorane **142** (R = Me or Ph) is smoothly converted into the ketoalcohol (X = H) or α-acylated ether (X = Me) on decomposition of the dioxaphospholene ring as a result of hydrolysis or methanolysis.[144]



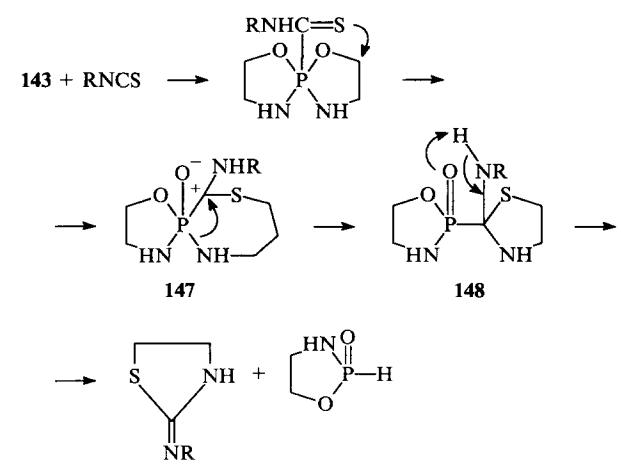
R = Me, Ph; X = H, Me.

As already stated, solvolysis accompanied by the dissociation of the phosphorus–heteroatom bond in saturated phosphacyclanes usually leads to phosphorus-containing acyclic substances. This renders even more unusual the reaction of spirocyclic oxazaphospholanes **143**, occurring when alkyl or aryl isothiocyanates are acted upon by σ^4-PH acids.[145,146] In alcohols, the process proceeds with dissociation of endocyclic phosphoramide bonds. The functionalisation of β-aminoethyl groups and acidolysis of the adduct **144** lead to phosphorus-free salts **145**, while 2-(phenylimino)thiazolidines **146** are formed when the system is rendered alkaline. The reaction proceeds under very mild conditions (25–30 °C) and involves the unusual dissociation of the C–O (and not P–O) bond in the intermediate phosphite **144**.[141]

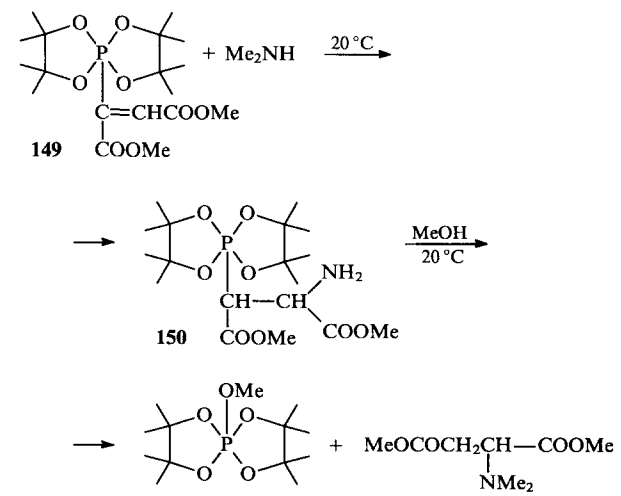
The same process, but this time requiring a higher temperature (80–100 °C), can be carried out also in aprotic solvents. The authors suggest[146] that in this case the process involves the addition of P–H to the isothiocyanate fragment and the rearrangement of the adduct with expansion of the ring to compound **147** caused by intramolecular *S*-alkylation. The endocyclic dissociation of the P–N bond and proton transfer in the intermediate **148** entail fragmentation to thiazolidines and unidentified cyclic hydrophosphoryl products. Two and one



alkylene-1-oxy-2-amino-fragments are involved in this reaction when the latter is carried out in alcohols and in an aprotic medium respectively.

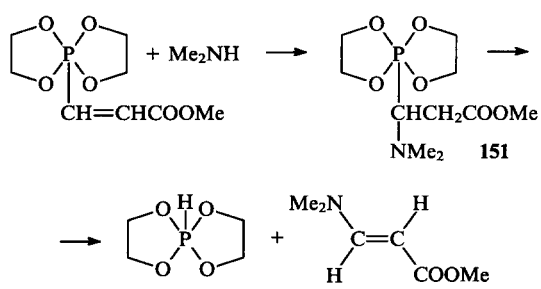


Only a few instances of the solvolysis of spirocyclic phosphoranes with retention of the cyclic skeleton of the phosphorus-containing reagent are known. Thus amination of the unsaturated spirophosphorane **149** and the subsequent methanolysis of the adduct **150** proceed with cleavage of the strong exocyclic P–C bond to give an aminosuccinic acid ester.[147]



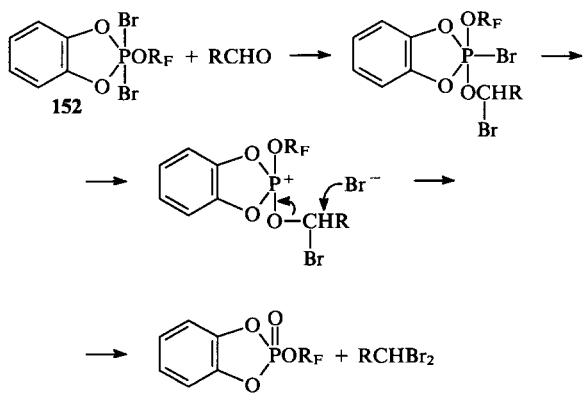
This rare example of the stability of the more labile ester linkages may be due to a tendency to retain the spirocyclic system, which, together with the tendency of oxyphosphoranes to be converted into a product with a phosphoryl group, can also become the driving force of chemical reactions with participation of phosphorus compounds.[15,16]

The exocyclic decomposition of substances of this kind is known also for thermal processes. Distillation of the adducts formed in the amination of compound **151** is accompanied by the formation of β-aminoacrylate. The synthetic result of such a process is a kind of substituton of the phosphaspirocyclane group at the vinyl β-carbon atom in the initial σ^4-P-acrylate.[148]

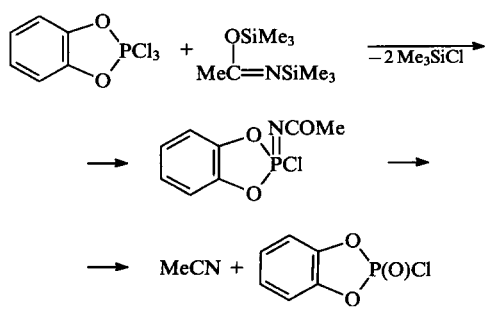


It is of interest to note that the reactions described in this subsection, involving the participation of unsaturated σ^5-phosphacyclane fragments, namely hydrogenation, the addition of proton nucleophiles, and substitution at unsaturated centres, resemble the unusual chemical behaviour of coordinated alkenes in transition metal π-complexes.[149]

We shall quote several new examples of the synthetic use of trihalo(phenylenedioxy)phosphoranes. The halogenating capacity of such phosphorus-containing reagents is well known.[106,150] However, it is characterised by a low selectivity in reactions with polyfunctional substrates. A new reaction of the phosphoranes **152** (R = $CH_2CF_2CHF_2$) with aliphatic and aromatic aldehydes, which proceeds via the insertion of the carbonyl group in the σ^5-P–Br bond and is completed by the *gem*-deoxyhalogenation of the initial substrate, has been described.[151]

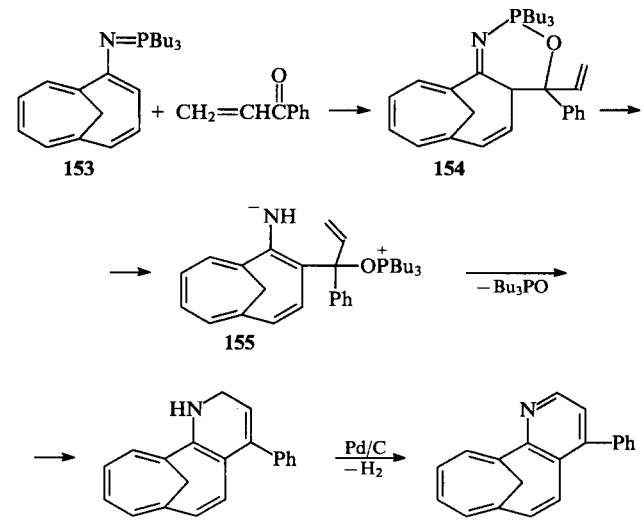


Several advantages of the use of compound **152** over phosphorus pentachloride or phenylenedioxyphosphorus trichloride have been noted.[151]



The oxidation-reduction reaction of a halophosphorane with disilylacetamide converts the latter into a nitrile.[152]

A rare case of the use of a latent ketone, bound in the six-membered phosphorus heterocycle, has been described.[153] The [4+2]-cycloaddition of the phosphimine **153** and phenyl vinyl ketone via a stage involving the formation of the adduct **154** and the betaine **155** in the presence of the Pd/C catalytic system leads to the formation of 4-phenyl-7,12-methanocyclodeca[*b*]pyridine.



The unusual regiochemistry of the phosphimine version of the Wittig reaction (cf. compound **118**) is striking in this example: the carbonyl carbon atom is oriented towards and adds to the ring C(2) atom and not to the imine nitrogen atom in compound **153**. The subsequent stepwise decomposition of the adduct **154** is responsible for the unusual design of the target tricyclopyridine.

3. The 'dioxaphospholane' methodology in organic synthesis

The type of reactions of σ^5-diheterophosphacyclanes described in this subsection is associated with the thermal decomposition of these compounds, which are specially synthesised for the functionalisation of organic substrates. The latter are, as it were, 'introduced' into the composition of the cyclic phosphorus-containing reagent, so that they can be made to undergo particular chemical transformations after phosphorylation. Evans called this approach the 'dioxaphospholane' methodology. It is characterised, as a rule, by high chemo-, regio-, and stereospecificities.

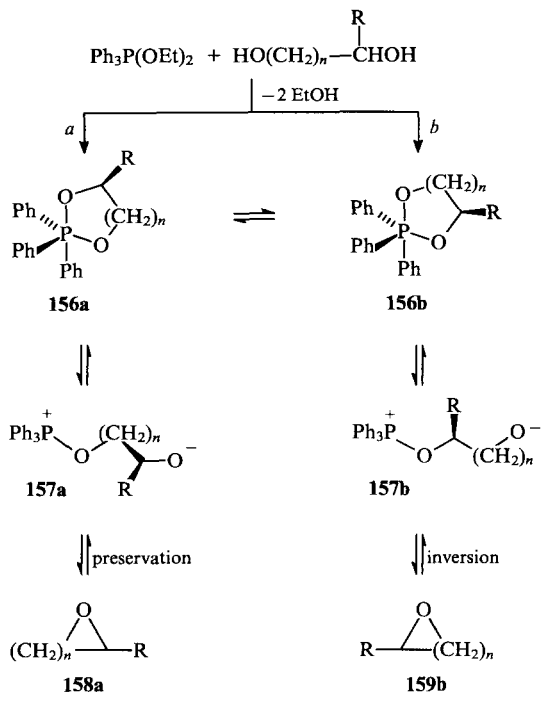
The thermal reactions of phosphoranes have been widely investigated, such studies including those undertaken in order to employ them in fine organic synthesis. Data on the thermal fragmentation of σ^5-phosphacyclanes, published mainly in the 1960s–1970s, are presented in two reviews.[16,154] During the last ten years, the dioxaphospholane methodology has expanded greatly, mainly in Evans' studies, and has served as an effective instrument for the functionalisation of organic compounds, mainly bifunctional substances with mobile hydrogen atoms.

Acyclic phosphoranes — pentaethoxyphosphorane,[155] bis-(neopentyloxy)triphenylphosphorane,[156] diethoxydiphenyl-polystyrylphosphorane,[157] and the especially widely used diethoxytriphenylphosphorane[158,159] — are extremely effective dehydrating agents which convert α,ω-diols and amino- and mercaptoalcohols into the corresponding oxacyclanes, azacyclanes, or thiacyclanes.

Optically active diols are cyclodehydrated to the corresponding cyclic ethers under relatively mild conditions — monosubstituted diols in 48 h at 40 °C and the sterically more hindered tri- and tetra-substituted diols over the same period but at 80–100 °C.[159,160] The phosphoranes obtained from *cis*-cyclohexane-diols are cyclodehydrated only at

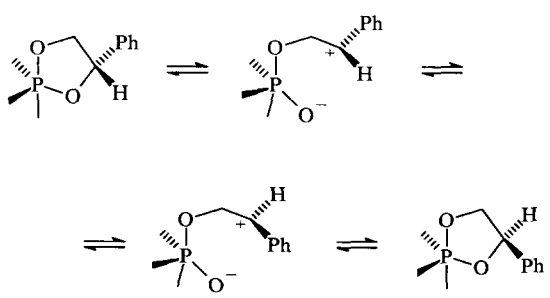
280–300 °C.[159,161] The synthetic result of these reactions has been explained from the standpoint of the transformation of the intermediates having the structure of σ^5-1,3,2-heterophosphacyclanes and of the betaines formed from them (Scheme 16).

Scheme 16



The regioselective distribution of the stereoisomeric ethers formed as a result of the cyclodehydration is associated with the decomposition in the sequence: cyclophosphorane **156**, betaine **157**, and ether **158** and also with the direction of the intramolecular nucleophilic attack by the oxyanion on the α-carbon atom. The preservation of the stereochemistry of the initial diol in the final cyclic product reflects the preferred direction of attack on the unsubstituted carbon atom (path *a*); the reaction via path *b* is more difficult the more bulky the substituents in the initial diol. Under these conditions, the configuration is inverted — the stereochemistry of the initial diol is altered. Attack via path *a* on the unsubstituted carbon atom is effected more readily and this is the reason for the higher content of the stereoisomer **158a** in the products of the cyclodehydration of diols.

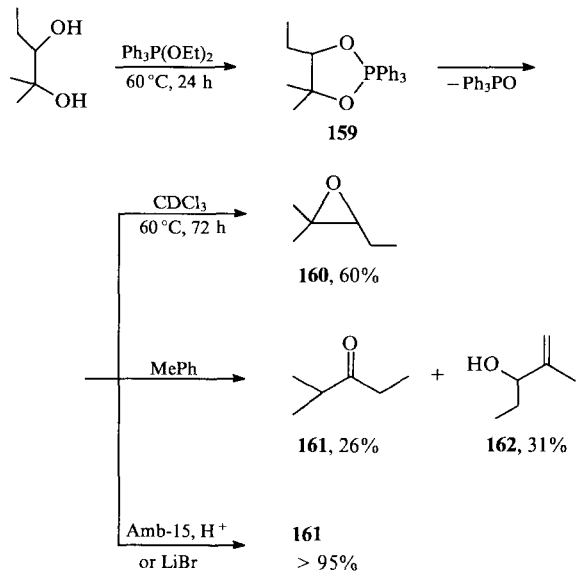
This postulate is in general valid: the regioselectivity of the cyclisation reaction increases with increasing bulk of the substituent R in the diol.[158] However, racemic styrene oxide was obtained in the reaction of (*S*)-(+)-phenylethane-1,2-diol. One of the possible causes of this is the irregular permutational isomerisation of the intermediate phosphacyclanes, which proceeds with dissociation of the C–O bond and not the P–O bond.



This type of isomerisation is due to the presence of favourable factors: the stabilising $(p-d)_\pi$ interaction of the equatorial phosphoryl oxygen atom with the phosphorus atom and of the carbonium ion centre with the phenyl substituent. Such racemisation of phosphoranes is a consequence also of the racemisation of the corresponding betaines and cyclic ethers. This example is quoted in order to demonstrate the stereochemical factors accompanying the synthetic use of the dioxaphospholane methodology.

Another extremely important condition governing the usefulness of this methodology in the cyclodehydration reaction is the size of the future oxacyclane. 1,2-Diols give rise in this reaction to alkene oxides in 85%–99% yields, 1,4- and 1,5-diols afford the corresponding five- and six-membered rings in 70%–80% yields, while butane-1,3-diol produces an oxetane with only 3% conversion, i.e. the diol mainly undergoes monoethylation. Similarly, hexane-1,6-diol is converted into oxepane (6%) and ethyl hydroxyhexyl ether (50%).[160]

In certain cases,[160] the conditions governing the decomposition of the key σ^5-1,3,2-dioxaphosphacyclanes are decisive in the reactions of diols, particularly tri- and tetra-substituted diols.

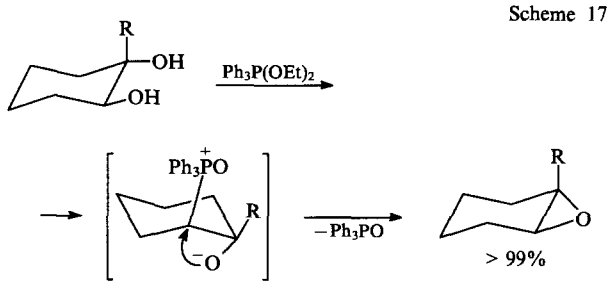


The dioxaphospholane **159**, obtained from 2-methylpentane-2,3-diol, reacts with LiBr (60 °C, 3 days, C_6D_6) to form only 2-methylpentan-3-one **161**; the same reaction in $CDCl_3$ gives 2,3-epoxy-2-methylpentane **160** (60%) as the only product; in toluene (100 °C), the ketone **161** is formed together with 3-hydroxy-2-methylpent-1-ene **162** (31%). The granulated polystyrenesulfonic acid (Amb-15) promotes the formation of the ketone **161**, possibly via the isomerisation of the epoxide **160**. The allyl alcohol **162** is obtained as a result of the intramolecular abstraction of a proton, which leads to the corresponding betaine.

The most unexpected result is the formation of a ketone (in this and other cases), which is associated with the migration of a hydride ion in a type **159** phosphorane or the corresponding betaine.

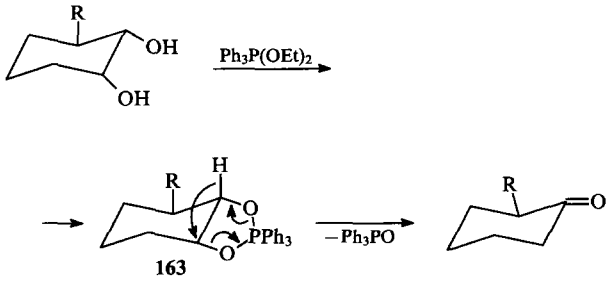
This phenomenon has been studied in detail in relation to cyclohexane- and methylcyclohexane-1,2-diols (Scheme 17).[159,160] The *trans*-diols are converted quantitatively into the corresponding epoxides via the general intramolecular nucleophilic substitution mechanism (the 3-*exo*-*tet*-mechanism[160]).

Scheme 17



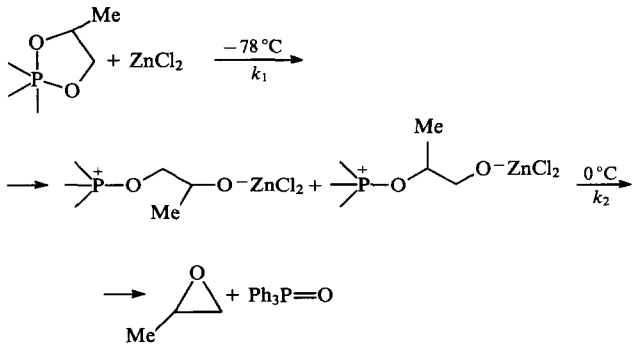
R = H, Me.

The reaction of *cis*-hexane-1,2-diol (boiling dichloromethane, 48 h) with an acyclic phosphorane affords the readily vacuum-distilled 1,3,2-dioxaphospholane **163**.



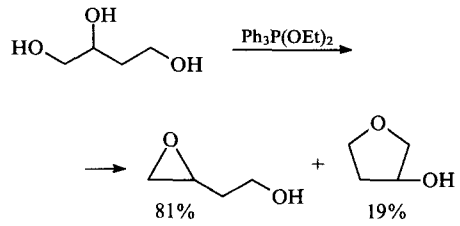
The vacuum thermolysis of compound **163** (220 °C, 15–23 Torr) gives rise to a quantitative yield of a cyclohexanone. The synchronous 1,2-hydride shift in the phosphorane **163** or in the corresponding betaine has been suggested [159,160] to account for the formation of the cyclic ketone.

An increase in the number of substituents in the initial diol promotes the stabilisation of the resulting cyclophosphoranes and a higher temperature is required for their decomposition (> 200 °C), the yield of the target oxacyclanes diminishing. In order to suppress this unfavourable factor, it has been suggested that Lewis acids be employed. [162,163] Thus the cyclodehydration of 1,2-diols in the presence of lithium bromide takes place at room temperature without side reactions, affording oxiranes in a high yield. The stronger Lewis acid $ZnCl_2$ induces the decomposition of the phosphorane to the betaine at −78 °C and cyclisation to the epoxide at 0 °C. This acceleration is caused by the facilitation of the dissociation of the ether bond in the phospholane as a result of coordination of the endocyclic oxygen atom to the Lewis acid; the stabilisation of the oxide (alkoxide?) anion by the acid also favours the overall course of the process.



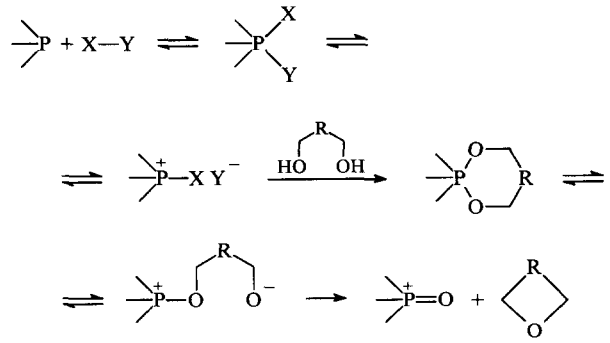
A kinetic study [162] of this process established the irreversibility of the formation of the betaine in the reaction promoted by $ZnCl_2$ ($k_2 \gg k_1$); apart from anything else, [162,163] this determines the stereospecificity of the cyclodehydration in the zinc chloride-induced reaction. The lithium ion, which exhibits a much lower tendency towards coordination, permits the existence of equilibrium between the betaines and the stereochemical result of the reaction is regulated by the relative rates of the intramolecular S_N2 attack by the oxyanion on the α-carbon atom.

The cyclodehydration of triols by means of the 'dioxaphospholane' methodology is a much more complex process because the phosphorylation is then coupled with the chemoselectivity of the hydroxyl involvement of the substrates. [164] In the general case, the formation of five-membered dioxaphosphacyclanes is preferred to the formation of rings of any other size. Thus butane-1,2,4-triol reacts with an equivalent of $Ph_3P(OEt)_2$ to form 3,4-epoxy-1-butanol (81%) and tetrahydro-3-furanol (19%).



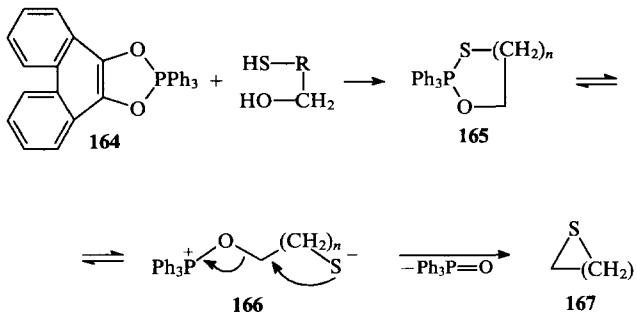
We may note that, as in the case where cyclodehydration is carried out by means of 'combined' phosphorus-containing reagents (PPh_3 + CCl_4; Mitsunobu's reagent), when this methodology is used there is a decrease in the tendency towards the formation of oxacyclanes on passing from three- and five-membered rings to six-membered rings and further to four- and seven-membered rings, which reflects the change in ring strain and cyclisation entropy on intramolecular nucleophilic substitution. [161]

The course of the cyclodehydration of bifunctional organic substrates discussed here may be induced, as already mentioned, not only by oxyphosphoranes but also by two-component condensed systems including phosphorus(III) compounds and organic molecules capable of biphilic interaction with the phosphorus(III) atom — dialkyl peroxides, carbon tetrachloride, and azodicarboxylate. [161,165,166] In all cases, the key intermediates in the cyclodehydration process are cyclophosphoranes obtained by the esterification of the acyclic phosphoranes (phosphonium salts) arising in the two-component system. In this case, the overall mechanism is described by the following sequence of reactions:

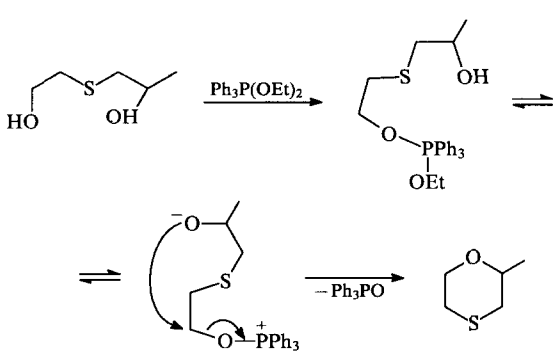


X = Y = OEt; X = Cl, Y = CCl_3; X–Y = ROCON=NCOOR.

Among the effective cyclodehydrating agents, 2,2,2-triphenyl-4,5-(2′,2″-biphenylene)-1,3,2-dioxaphospholane (**164**), which is more stable and convenient to handle than acyclic phosphoranes, merits special attention. The adduct **164** obtained from triphenylphosphine and phenanthrenequinone is stable in inert solvents and is especially effective for the cyclodehydration of mercaptoalcohols to cyclic sulfides.

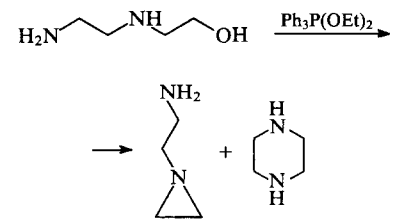


The reaction proceeds in accordance with the general mechanism: the transesterification to σ^5-oxathiaphosphacyclane **165** is followed by intramolecular substitution by the thiolate anion in the betaine **166**, which leads to the thiacyclanes **167** with three-membered (n = 1), five-membered (n = 3), and six-membered (n = 4) rings (yield > 80%). Special mention must be made of the high yield of thietanes (n = 3, 80%) compared with the yield of oxetane (3%), which enabled the authors[166] to emphasise the universality of the dioxaphosphorane methodology involving the use of compound **164**. The compound is also convenient because of the absence of reactions involving the alkylation of diols (mercapto- and aminoalcohols) of the kind occurring in the reactions with $Ph_3P(OEt)_2$. We may also mention the successful employment of this process for the synthesis of 1,4-oxathianes.[167]



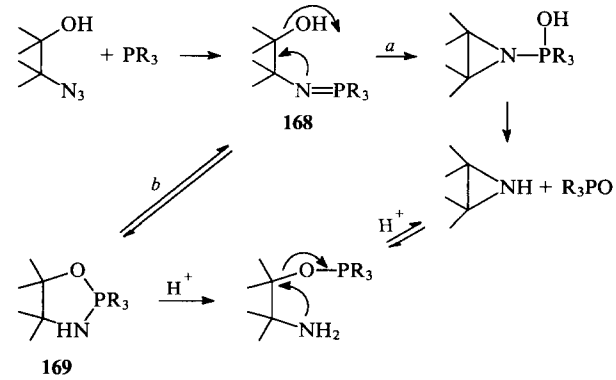
The effectiveness of the 'dioxaphospholane' methodology in cyclodehydration has also been demonstrated by the synthesis from 2-amino-2-benzylethanol and *trans*-2-aminocyclohexanol, with the aid of the phosphacyclene **164**, of the corresponding aziridines in 60% and 71% yields respectively. In this case too, the phosphacyclene was found to have an advantage over $Ph_3P(OEt)_2$, which exhibited only an *N*-ethylating capacity when an attempt was made to cyclodehydrate *trans*-2-aminocyclohexanol — *trans*-2-(*N*-ethylamino)cyclohexanol was obtained instead of the aziridine.[168]

Nevertheless, the use of this methodology in general makes it possible to convert *N*-alkyl- and *N*-aryl-β-aminoalcohols into the corresponding *N*-organylaziridines under relatively mild conditions (60 °C, 24–48 h).[168] This reaction has been noted for its high stereoselectivity — the retention of the configuration of the 'amino'-carbon atom. For example, the enantiomerically homogeneous (*S*)-(+)-2-amino-1-propanol and (*S*)-(−)-2-amino-3-phenyl-1-ethanol are cyclodehydrated with the aid of $Ph_3P(OEt)_2$ to the enantiomerically pure (*S*)-(+)-2-methylaziridine and (*S*)-(−)-2-benzylaziridine respectively (yield 85%).[168] At the same time, the chemoselectivity of the reaction is low: 2-[(2-aminoethyl)amino] ethanol affords a 1 : 1 mixture of aziridine and piperazine as a result of cyclodehydration.



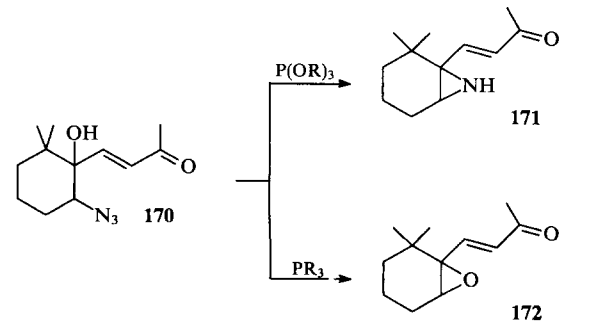
An unexpected feature has been noted for this reaction[168] — the identity of the free energy of cyclodehydration in the formation of three-membered and six-membered nitrogen heterocycles.

The concept of the appearance–decomposition of σ^5-1,3,2-oxazaphospholanes, which is close to the 'dioxaphospholane' methodology, proved fruitful also in explaining the routes leading to the conversion of azidoalcohols into aziridines on treatment with phosphorus(III) derivatives — triethyl and trimethyl phosphites or triphenylphosphine.[169,170] The process takes place in the presence of water or methanol and leads to aziridines under relatively mild conditions.

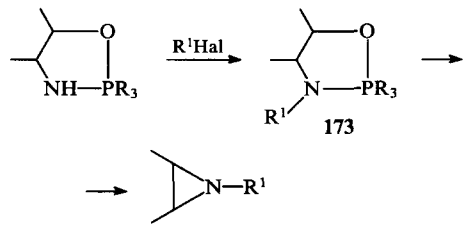


According to NMR spectroscopic data, path *b* is preferred because the decomposition of the product of the Staudinger reaction (the imine **168**), bypassing the phosphorane **169**, presupposes the unlikely intramolecular substitution of the hydroxy-group in the phosphimine **168**.[170] When the substituents are chosen appropriately in the initial azidoethanol, it is possible to isolate and identify both the phosphimines **168** and the oxazaphospholanes **169**. Furthermore, the interconversion **168**⇄**169** can be readily detected from ^{31}P NMR spectra.

We may draw attention to a very interesting fact which has not received a sufficiently convincing explanation: the synthesis of the bicyclic aziridine **171** from the corresponding azidohydrin is readily achieved on treatment with trimethyl or triethyl phosphite, whereas tertiary phosphines afford a complex mixture of substances, from which the epoxide **172** has been isolated.[171]



It was shown subsequently[172] that the range of aziridines obtained on fragmentation of σ^5-oxazaphospholanes can be extended by alkylating the endocyclic nitrogen atom with alkyl halides in the presence of strong bases (BuLi, NaH, or KH).

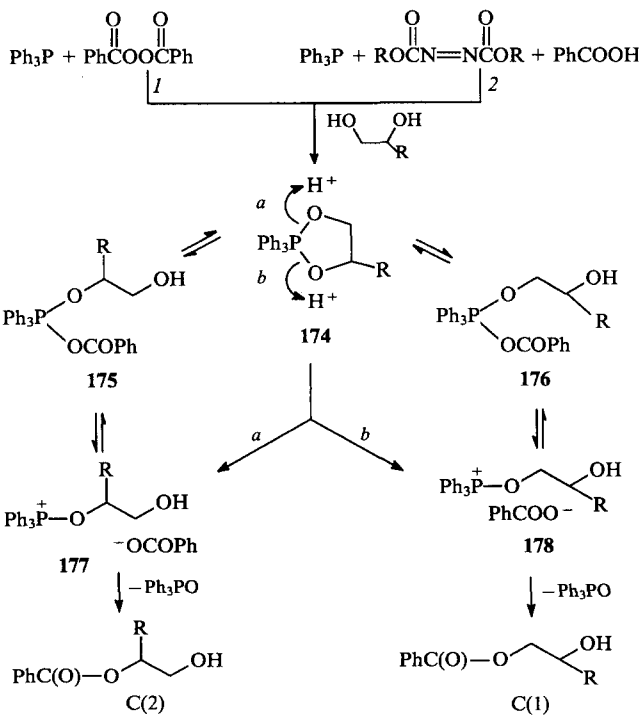


The conversion of compound **173** into *N*-substituted aziridines is facilitated by the addition of acid catalysts.

The key stage in cyclodehydration processes when the methodology under discussion is employed is undoubtedly the intramolecular S_N2 substitution at the α-carbon atom in the quasi-phosphonium intermediate by a thio-, amino-, or oxy-anion. It determines the synthetic (stereochemical result). The synthetic diversity of the reactions carried out using the 'dioxaphospholane' methodology has been achieved by involving 'external' nucleophiles in the reaction. In this case, the substitution of the nucleophilic phosphoryl fragment constitutes in essence the second stage (dealkylation) of the Arbuzov reaction, which, like all S_N2 reactions, takes place with inversion of configuration of the carbon atom. This determines the stereospecificity of the reactions under discussion, but in a number of instances an unusual chemoselectivity of the functionalisation of the organic substrates is observed.

The monobenzoylation of asymmetric 1,2-diols (propane-1,2-diol and 1-phenylethane-1,2-diol) in which two dehydrating systems are employed — triphenylphosphine–benzoyl peroxide (1:1) and triphenylphosphine–dialkyl azodicarboxylate (Mitsunobu's reagent) — leads to kinetically and thermodynamically less stable isomers: C(2)-benzoates [C(2):C(1) = 8:1 for methyl-substituted diols and 96:1 for phenyl-substituted diols] (Scheme 18).[173–175]

Scheme 18

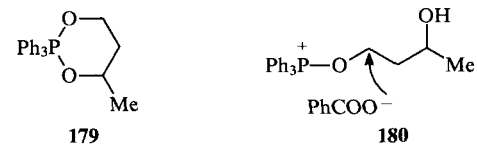


R = Me, Ph.

The chemoselectivity of the benzoylation of diols can be best explained on the hypothesis of the formation and acid-catalysed decomposition of the same key σ^5-1,3,2-dioxaphospholane intermediate **174** [obtained when acyclic intermediates (not shown in Scheme 18) are esterified by diols] in the oxidative addition of benzoyl peroxide (reaction *1*) or the Mitsunobu reaction (reaction *2*) (Scheme 18).

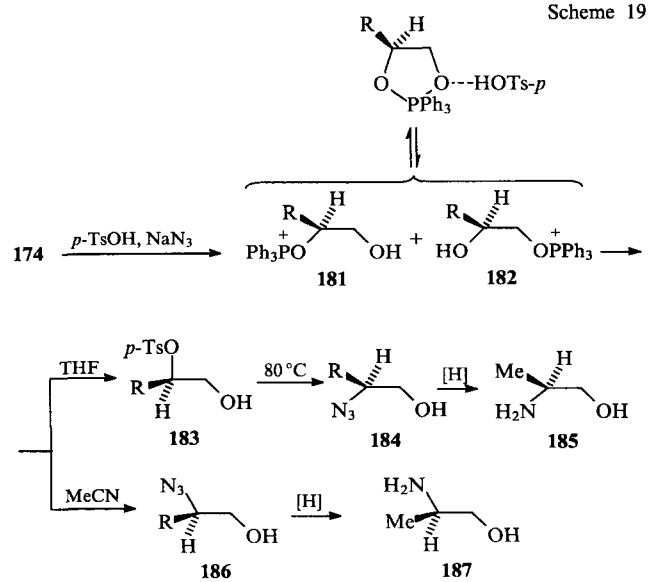
If it is postulated that the rate-determining stage is nucleophilic substitution by the benzoate ion, a reaction typical of the second stage of the Arbuzov reaction, then preference should be given to path *b* via which the less substituted C(1) centre in compound **178** is attacked. However, the overwhelming advantage of pathway *a* [attack by the benzoate on the C(2) atom] led the authors to the conclusion[173] that the rate-determining reaction path involves the formation of a hydrogen bond between compound **174** and HOC(O)Ph, which takes place more readily for the oxygen atom attached to the unsubstituted C(1) atom. The process therefore takes place via path *a* with S_N2 substitution at the C(2) atom in the ion **177**. The inclusion of the acyloxyphosphoranes **175** and **176** in the scheme has been confirmed experimentally[173] and reflects the sequence of the diol phosphorylation steps with the preferential P-attack on the primary hydroxyl in compound **176**.

A detailed study of the mechanism of the Mitsunobu reaction[174] (reaction 2 in Scheme 18) also made it possible to determine the key role of the cyclic intermediate **174**. An indirect confirmation has been obtained in the benzoylation of butane-1,3-diol. In this case, the attack by the benzoyl group is to a large extent directed to the primary and not the secondary carbon atom, which may indicate that the cyclic six-membered intermediate **179** is not involved in the process. The latter takes place via the acyclic quasi-phosphonium salt **180** in accordance with the mechanism of the Arbuzov reaction.[173]



The hypothesis of the selective decomposition of σ^5-1,3,2-dioxaphospholanes by nucleophiles has become the basis of the stereospecific functionalisation, developed by Evans and coworkers,[176–178] of diols, in which the strategy of the regioselective dioxaphospholane methodology is employed. the reaction of σ^5-1,3,2-dioxaphospholane **174** (R = Me)

Scheme 19



with toluene-*p*-sulfonic acid in the presence of sodium azide affords initially the regioisomeric oxyphosphonium ions **181** and **182** in almost equal amounts, the ions being in dynamic equilibrium with the initial phosphorane, detected by ^{31}P NMR spectroscopy at low temperatures (−78 °C) (Scheme 19).[172]

At the usual temperature (25 °C), the sulfonate anion rapidly substitutes the phosphine oxide, affording (*R*)-2-(4-methylbenzoylsulfonyloxy)1-propanol **183** in >95% yield with a high degree of stereospecificity at the C(2) centre. The regioisomer with the tosylate group attached to the C(1) atom was not detected. Heating of the reaction mixture containing NaN_3 (80 °C, 8 h, THF) converts the tosylate **183** into (*S*)-2-azidopropanol **184** with an almost complete inversion of the configuration.

The same reaction in acetonitrile does not produce the sulfonate ester. The azide (*R*)-**186** was obtained instead in 93% yield. In highly polar media, the strongly nucleophilic N_3^- ion wins the competition with the tosylate ion; the substitution **181**→**186** takes place with complete inversion of the configuration at the C(2) centre. The configurational identity of the latter has been confirmed by the hydrogenation of the azides **184** and **186** to the known aminoalcohols (*S*)-**185** and (*R*)-**187** respectively (Scheme 19).

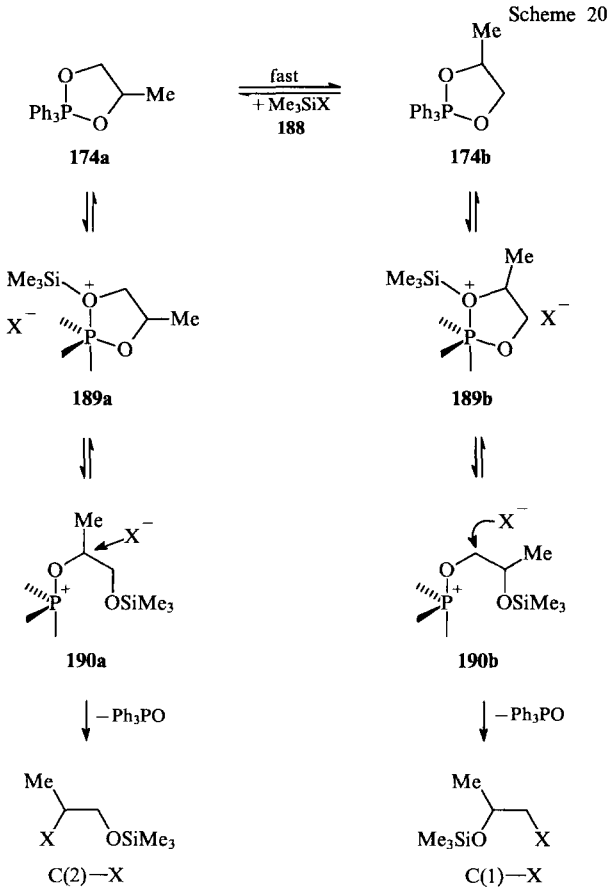
In this case, the experimental results can also be explained satisfactorily on the hypothesis of the initial coordination of compound **174** to toluene-*p*-sulfonic acid with participation of the sterically more accessible oxygen atom at the C(1) centre. This more apicophilic 'complex' oxygen atom is preferentially abstracted from the σ^5-P atom. The oxyphosphonium ion **181** activates the C(2) centre for nucleophilic attack. Thus the stereochemical outcome of reactions involving nucleophilic substitution in chiral 1,2-diols, 'protected' in the form of σ^5-1,3,2-dioxaphospholanes, consists in the inversion of the configuration at the C(2) centre in polar media and double inversion (overall retention of configuration) at this centre in nonpolar media.[172]

The idea of regulated protonation in the reactions of latent diols has been developed in relation to silicon-containing nucleophiles.[177,178] The interaction of the cyclane **174**, obtained from propane-1,2-diol, with the silylated nucleophiles **188** under very mild conditions leads to the regioisomeric siloxanes C(2)−X and C(1)−X with the former predominating, up to the almost complete regioselectivity for X = SPh or N_3 (Scheme 20).

By analogy with the selective protonation mechanism in reactions with benzoic or toluene-*p*-sulfonic acids, the nucleophilic selection in favour of C(2) is explained by the difficulty of the oxygenophilic attack by silicon on the apical oxygen atom in the rotational isomer **174b**, since in the structure of compound **189b** the silicon atom is subjected to a strong 'sandwich' type steric influence by the equatorial phenyl group and the close 2-methyl group. The preferential silylation of the oxygen atom at the C(1) centre in the structure **189a** is responsible for the ease of the nucleophilic attack on the C(2) centre in the quasi-phosphonium salt **190a**. The possibility of detecting the ions **190** by ^{31}P NMR spectroscopy makes it possible to determine the ratio of the regioisomeric ionic intermediates, which corresponds to the regioisomeric composition of the products obtained [C(2)−X: C(1)−X], the first regioisomer being favoured in all cases.

We believe that the experimental data presented in this review constitute convincing evidence for the importance and likely usefulness of heterophosphacyclanes in fine organic synthesis. The availability of phosphorus compounds of the type described, the wide variety of the valence and coordination states, the ease of the transition from one coordination state to another and hence the diversity of the structural and electronic types of organophosphorus compounds, the relative lability which at the same time permits the identification of different metastable states, the strength of the phosphorus−heteroatom bond, and the, as a rule, satisfactory solubility in media of different polarity are factors, which, together with other features, frequently lead investigators to make a choice in favour of phosphorus-containing reagents

Scheme 20



in the development of a strategy for the synthesis of polyfunctional organic substances. A characteristic of diheterophosphacyclanes, such as the stabilisation of cyclic hypervalent structures, is frequently also an attractive feature of these reagents: they permit well-founded inferences concerning the reaction paths of the substances.

An important positive property of cyclic organophosphorus reagents is the possibility of an extensive variation of the structures of both the cyclic and acyclic fragments of the molecule; this makes it possible, for example, to protect bifunctional and polyfunctional organic substances by organophosphorus functional groups (especially those containing a σ^5-phosphorus atom).

Finally one should include among the fairly important advantages of the use of cyclic organophosphorus reagents in multistage chemical processes the possibility of monitoring them by spectroscopic methods, especially ^{31}P NMR spectroscopy, because the characteristic regions in which the NMR signals of the phosphorus atom are manifested are sharply differentiated as a function of its valence and coordination states and its immediate environment.

Thus it is easy to foresee the growth of interest in these chemical compounds, which provide investigators concerned with synthesis a unique instrument for the functionalisation of organic substrates.

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