Exciting Fields in P-Heterocyclic Chemistry

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Dedicated to Professor Károly Lempert on the occasion of his 80th birthday

In our laboratory, we have been dealing with the synthesis and utilization of P-heterocycles for almost two decades. In this paper, our recent results are summarised. In the first part, the synthesis and properties of phospholes with sterically demanding substituent on the phosphorus atom and the fragmentation-related properties of phosphole oxide-related 7-phosphanorbornenes are discussed. Then, new families of 6-membered P-heterocycles are introduced available by a ring enlargement method and subsequent modifications. In the next part, I show how bridged P-heterocycles were prepared and how they were utilised in fragmentation-related phosphorylations. Finally a novel reaction providing heterocyclic phosphoranes/ylides is discussed.

J. Heterocyclic Chem., **42**, 451 (2005).

1. Synthesis and reactivity of phospholes and phosphanorbornene derivatives.

The phospholes are considered to be close relatives of the family of pyrrol, furan and thiophen. A significant difference is, however, that the phospholes described in the literature are not aromatic at all, or they display only a slight extent of aromaticity [1]. This is well demonstrated by the comparison of the Bird-indexes of benzylphosphole (**1**), furan, pyrrol and thiophen (Figure 1).

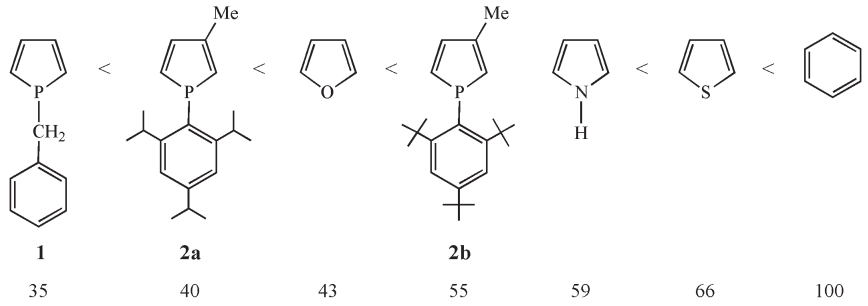


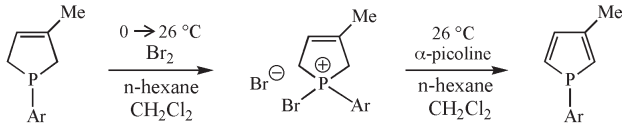
Figure 1

The lack of aromaticity is due to the pyramidal geometry around the phosphorus atom: the criterion of coplanarity is not fulfilled and hence the lone electron pair of the phosphorus cannot overlap with the p_z orbitals of the sp^2 carbon atoms. While in the case of pyrrol, the aromatic stabilization covers the energy requirement of the planarization, with phospholes there is a bigger barrier for the inversion.

We thought that the phosphole molecule might perhaps be planarized by the introduction of a bulky P-substituent, such as a 2,4,6-trialkylphenyl group and hence the aromaticity may be increased. Quantum chemical calculations suggested that with the increase in the size of the alkyl groups, the extent of the planarization was also increased [2-4]. This is well demonstrated by the Bird-indexes of 40 and 55, obtained for the triisopropylphenyl- and for the tri*tert*butylphenyl phospholes (**2a** and **2b**), respectively (Figure 1) [5,6]. The Bird-index of 55 obtained for the supermesitylphosphole sets a new record and suggests an aromaticity comparable with that of pyrrol and thiophen.

A more general synthesis of arylphospholes comprises the bromination of aryl-2,5-dihydro-1H-phosphole oxide **3**, in which case, the phosphorus atom of the substrate reacted with the bromine in a selective manner leaving the double-bond completely intact [6]. The phospholium salt (**4**) so obtained could be easily dehydrohalogenated to give the corresponding phosphole (**2**) (Scheme 1).

Scheme 1



Ar = 2,34,6-tri $^{i}PrC_6H_2$ (**a**), 2,4,6-tri $^{t}BuC_6H_2$ (**b**)

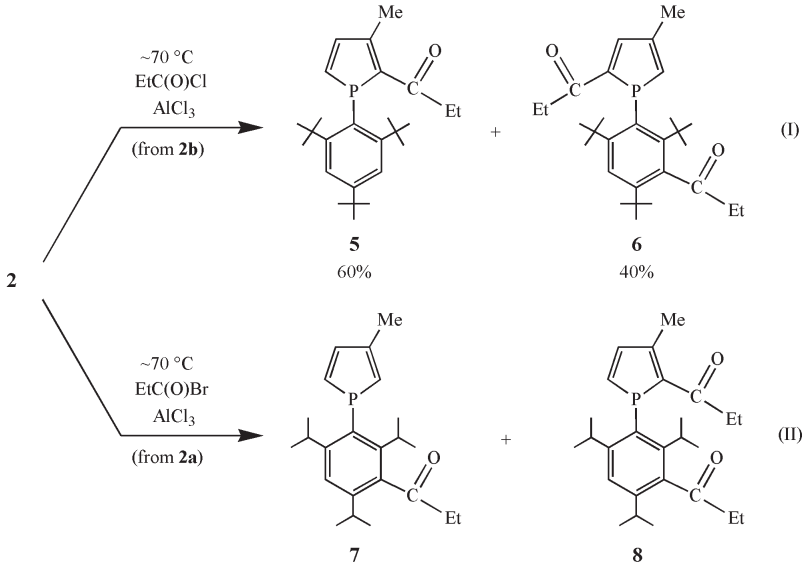
Aromaticity of the supermesitylphosphole (**2b**) was also manifested in chemical reactions: the phosphole under discussion underwent aromatic electrophilic substitution. In Friedel Crafts reaction with propionyl chloride, the mixture of 2-propionylphosphole (**5**), and a dipropionyl derivative (**6**) was formed [7]. It is interesting, that the most crowded 2-acyl derivative was formed; a similar situation was observed during the acylation of 3-methylpyrrol (Scheme2/I).

hetero ring took place only to a small extent [7]. Acylation of the trialkylphenyl ring was a concurrent reaction path. Eventually, products **7** and **8** could be isolated from the reaction mixture (Scheme 2/II).

It was observed that phospholes **2a** and **2b** entered into reaction with phosphorus tribromide [8,9]. The interaction of supermesitylphosphole with phosphorus tribromide afforded the 3-dibromophosphonio phosphole (**9**), after reaction with morpholine the phosphonous diamide, and finally after oxidation the phosphonic diamide (**10**). The reaction of **9** with methanol followed by hydrolysis led to H-phosphinate **11** (Scheme 3/I). A similar series of reactions with the triisopropylphenylphosphole furnished the corresponding 2-substituted products (**12**, **13** and **14**, respectively) (Scheme 3/II).

The phosphorylation is obviously controlled by the steric hindrance. The substitution reaction has less to do with the heteroaromaticity, and hence the mechanism

Scheme 2



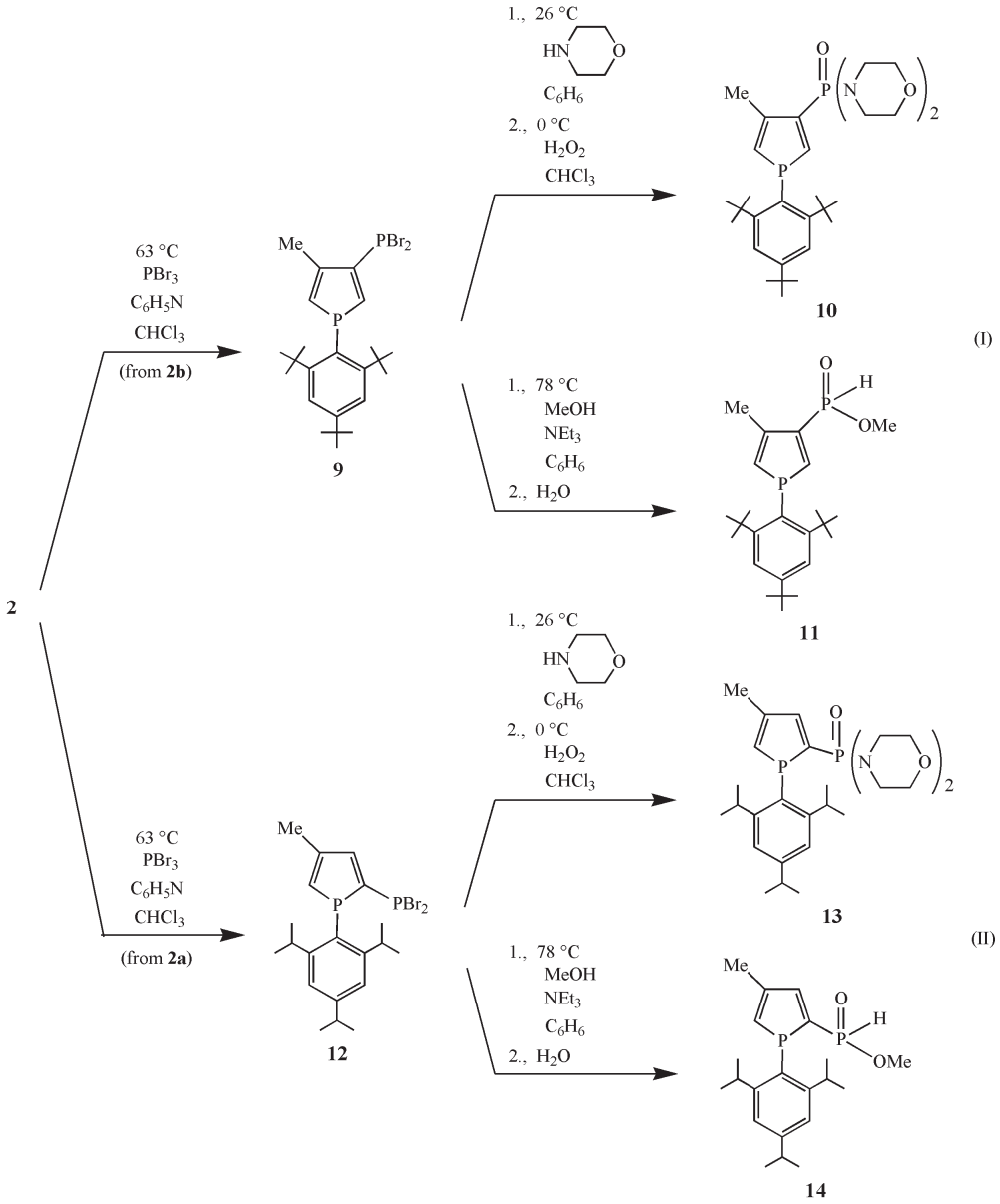
The use of other carboxylic acid chlorides, such as acetyl chloride [6] and butyril chloride [7] led to similar results: the corresponding monoacyl- and diacyl phospholes were found to form.

We wished to check the reactivity of triisopropylphenylphosphole, exhibiting a somewhat smaller Bird-index, than the tritertbutyl derivative, in aromatic electrophilic substitutions. We learned that the acylation of the

involves simple addition of the phosphorus tribromide on the double-bond followed by the loss of proton, pseudorotation and the departure of a bromide anion. It is interesting that the phosphorus atom of the phosphole practically resisted undergoing oxidation.

Despite their heteroaromaticity, the P-aryl phospholes (**2**) could also be involved in Diels Alder reaction [10]. In cycloaddition with N-phenylmaleimide, the corre-

Scheme 2

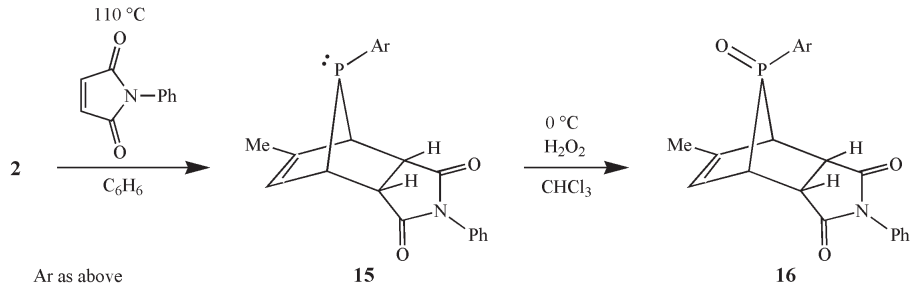


sponding 7-phosphanorbornene was formed as the mixture of two isomers, from among the major one (**15**) is shown in Scheme 4. To obtain stable products, the phosphine (**15**) was oxidized to the phosphine oxide (**16**). It was observed that the Diels Alder cycloaddition became reluctant with the increase of the aromaticity and steric hindrance.

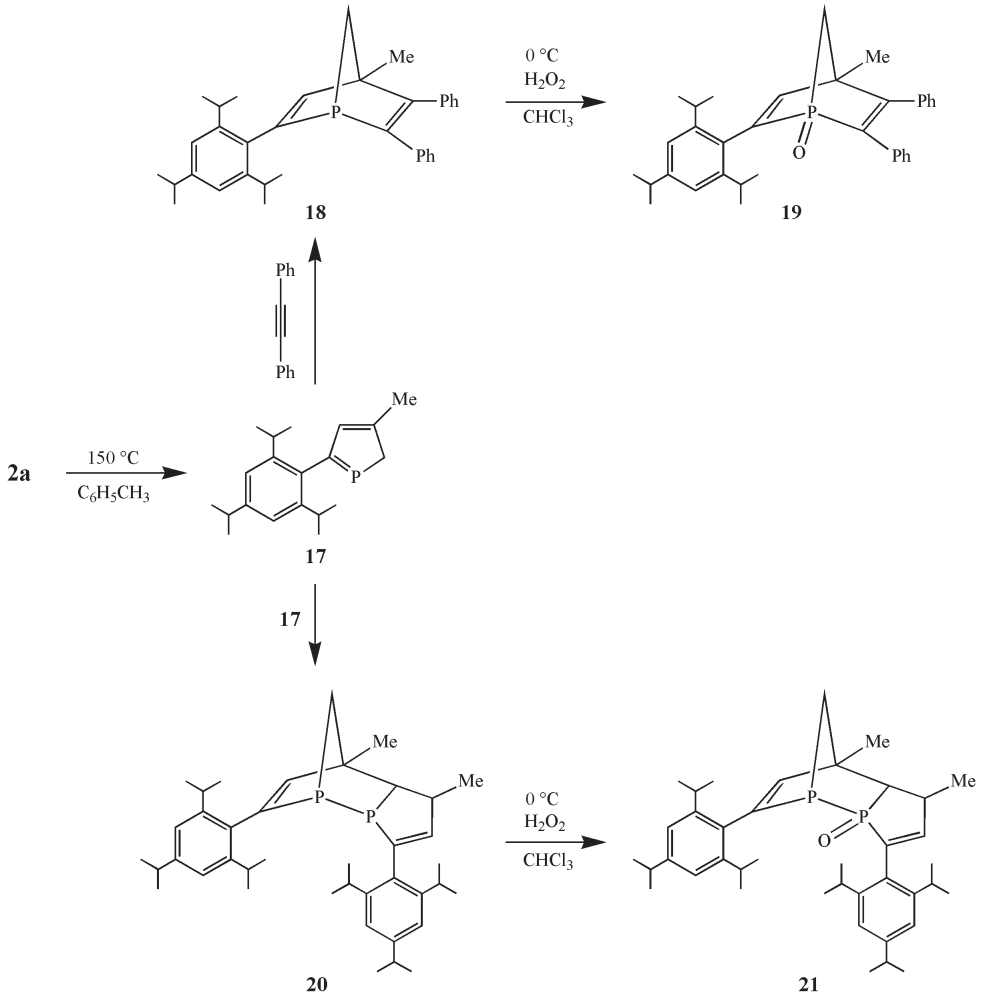
At 150 °C, the triisopropylphenylphosphole (**2a**) was converted to the corresponding 2H-phosphole (**17**) by a sigmatropic Ar*[1,5]* rearrangement. In the presence of diphenylacetylene as the trapping agent, the Diels Alder reaction led to 1-phosphanorbornene **18**, while in the absence of any dienophile added to the reaction mixture prior to the heating, dimer **20** was the product [11]. The cycloadducts (**18** and **20**) were stabilised by oxidation to afford phosphanorbornene 1-oxide **19** and hemioxide **21**, respectively (Scheme 5).

An uncontrolled oxidation of diphosphine **20** resulted in its decomposition.

Scheme 4



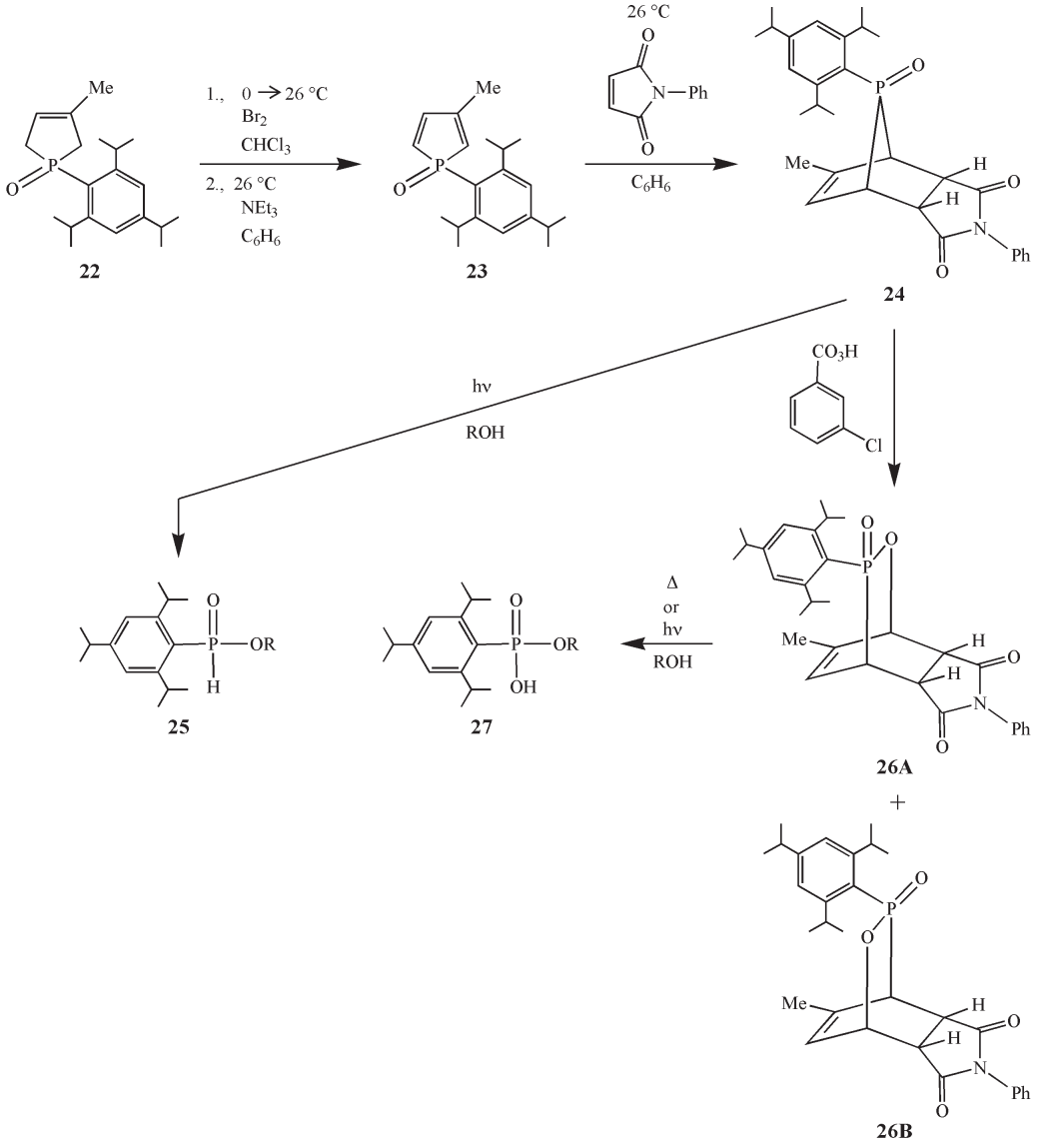
Scheme 5



It was pointed out that the formation of dimer **20** is reversible.

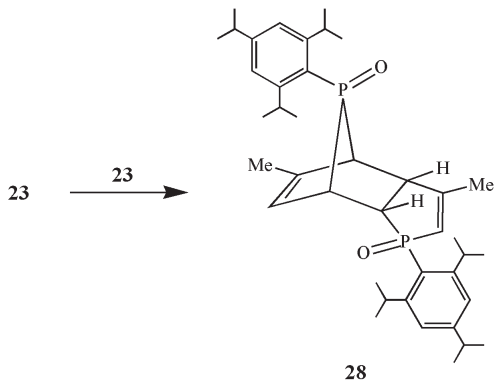
The phosphole oxide (**23**) prepared form the corresponding 2,5-dihydro-1H-phosphole oxide (**22**) via bromination and by double dehidrobromination of the intermediate so obtained entered into Diels Alder reaction with N-phenyl maleimide to yield 7-phosphanorbornene **24** (Scheme 6) [5]. In the absence of a dienophile added, the phosphole oxide (**23**) underwent dimerisation to afford product **28** (Scheme 7) [5].

Scheme 6



Under photochemical conditions, the 7-phosphanorbornene derivatives (**24** or **28**) were useful in fragmentation-related phosphorylations of alcohols [12,13]. Photolysis of cycloadduct **24** in an alcohol led to the corresponding H-phosphinate (**25**). In Baeyer-Villiger oxidation (on treatment by meta-chloroperbenzoic acid), phosphanorbornene **24** was converted to oxaphosphabicyclo[2.2.2]octene **26A**. In fact, the other regioisomer **26B** was also formed as the result of kinetic control, but it was not stable [14]. On thermolysis or on photolysis, the stable regioisomer (**26A**) underwent fragmentation to generate the corresponding methaphosphonate ($ArPO_2$) that, being a low-coordinate P-fragment, entered into a fast reaction with alcohols yielding phosphonic derivatives **27** (Scheme 6).

Scheme 7



2. Synthesis of phosphine derivatives.

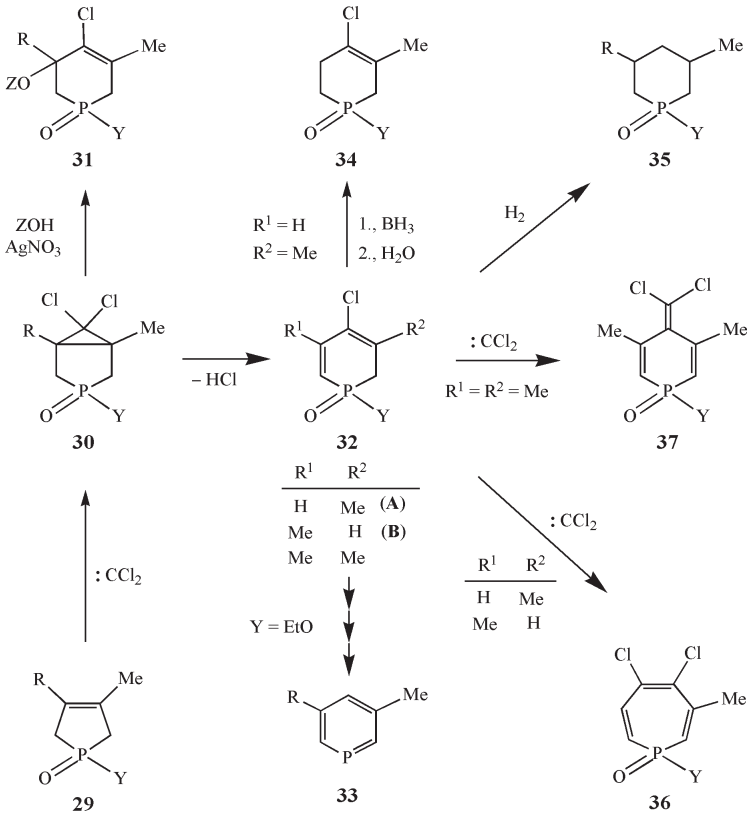
The dichlorocyclopropanation of 2,5-dihydro-1H-phosphole 1-oxides (**29**) gave phosphabicyclo[3.1.0]hexanes **30** that are useful intermediates for 3-substituted 1,2,3,6-tetrahydrophosphinine oxides (**31**) and for 1,2-dihydrophosphinine oxides **32** [15,16]. In case of monomethyl substitution, both products were formed as the mixture of double-bond isomers. For clarity, only the major isomer (**31**) is shown for the tetrahydrophosphinine oxide (Scheme 8). The dihydrophosphinine oxides (**32**) were versatile intermediates in the preparation of aromatic phosphinines (**33**) and in that of more saturated derivatives, such as tetrahydrophosphinine oxide **34** [17] (practically, only the major dihydrophosphinine isomer **32A** underwent hydroboration) and hexahydrophosphinine oxide **35** [18,19] (Scheme 8).

It was possible to expand the ring of dihydrophosphinine oxides **32** by the "dichlorocarbene" method to make phosphepine oxides (**36**) available [20]. At the same time, the similar reaction of the dimethyl derivatives (**32**, R^1=R^2=Me) furnished 4-dichloromethylene-1,4-dihydrophosphinine oxides (**37**) [21] (Scheme 8).

Quite recently, 1,2,3,6-tetrahydrophosphinine oxides with exocyclic P-function (**38**) were prepared by the Michael addition of diphenylphosphine oxide or dialkyl phosphites to dihydrophosphinine oxides (**32A**) (Scheme 9) [22,23]. The reaction took place in all cases in a diastereoselective manner.

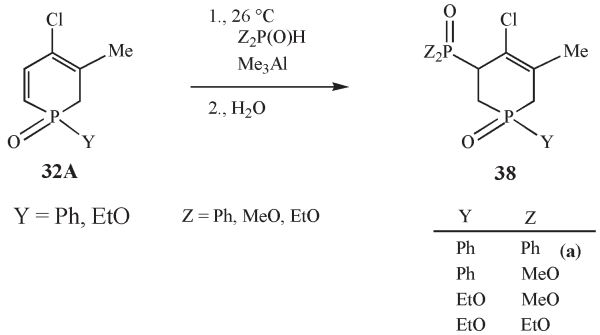
The relative energies obtained by *ab initio* calculations suggested that the *twist-boat* conformers are more favourable than the *half-chairs*. In the most stable forms shown in Figure 2, the exocyclic P-function is axial. It was

Scheme 8



R = H or Me; Y = alkyl, alkoxy, aryl

Scheme 9



Y = Ph, EtO Z = Ph, MeO, EtO

Y	Z	
Ph	Ph	(a)
Ph	MeO	
EtO	MeO	
EtO	EtO	

found that the stable conformers are stabilised by intramolecular interactions of novel type in which the exocyclic P-moiety plays an important role. Perhaps the most important interactions are those between the oxygen atom of the C_3–P=O group and the suitable hydrogen atom of the PCH_2 unit. The oxygen of the ring P=O moiety or that of the alkoxy group in the 3-P(O)$(OR)_2$ function may also participate in H-bonding (Figure 2).

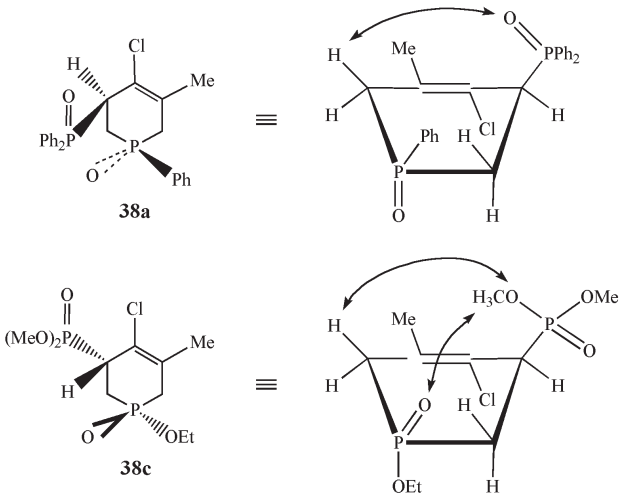
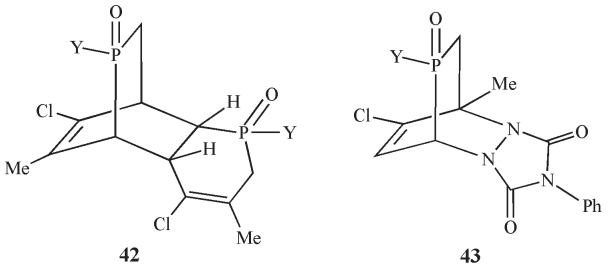


Figure 2

3. Synthesis and utilisation of phosphabicyclo[2.2.2]-octene derivatives.

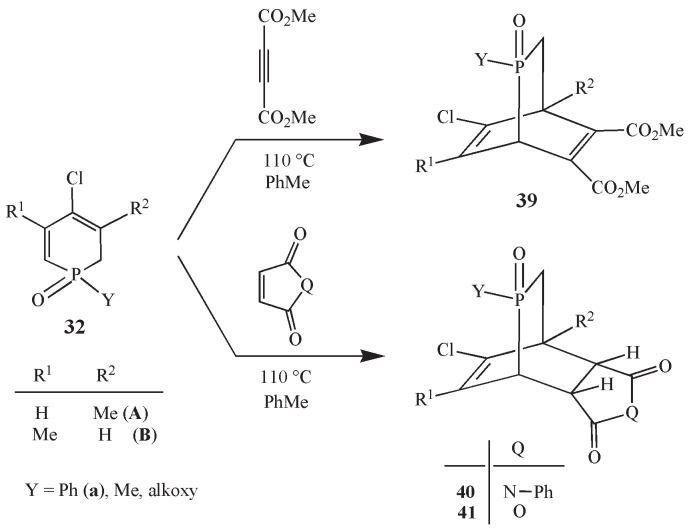
The next topic includes a study on the synthesis and properties of phosphabicyclooctene derivatives and on their utilization in phosphorylations [24,25]. The Diels Alder reaction of dihydrophosphinine oxides (**32**) and dienophiles, such as dimethyl acetylenedicarboxylate and maleic acid derivatives led to phosphabicyclooctadiene (**39**) [26] or to phosphabicyclooctene oxides [27] (**40**, **41**), respectively. Starting from the double-bond isomers of the dihydrophosphinines (**32**), the cycloadducts (**39-41**) were also obtained as the mixture of isomers. According to the P-function, the new precursors (**39-41**) were tertiary phosphine oxides or phosphinic esters (Scheme 10).

Precursors of new type (**42**) were introduced by the dimerisation of 1,2-dihydrophosphinine oxides (**32**) [28,29]. The application of triazolindione as the dienophile led to diazaphosphabicyclooctene **43** [30,31].



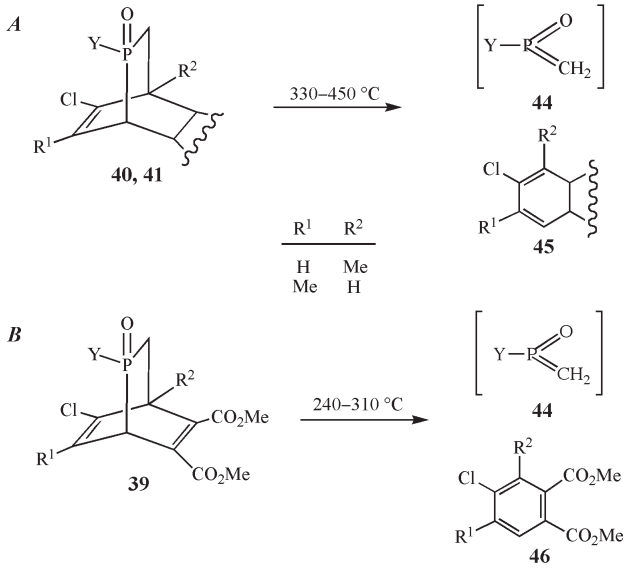
Thermal examination of the phosphabicyclooctenes revealed that the bridging moiety was ejected in the range of 330–450 °C (, in an exothermic process). The same range for the phosphabicyclooctadienes is lower (240–310 °C) (Scheme 11) [32]. This means that the bicyclooctenes (**40**, **41**) are thermally more stable, than the bicyclooctadienes (**39**). Assuming product-like transition states, the value of activation energy is less for the fragmentation of bicyclooctadienes, as this goes with the formation of an

Scheme 10



aromatic phthalate (**46**), while in the other case a dihydro derivative (**45**) is the by-product. This situation was evaluated also by semiempirical calculations.

Scheme 11



X-ray analysis also confirmed the above conclusions.

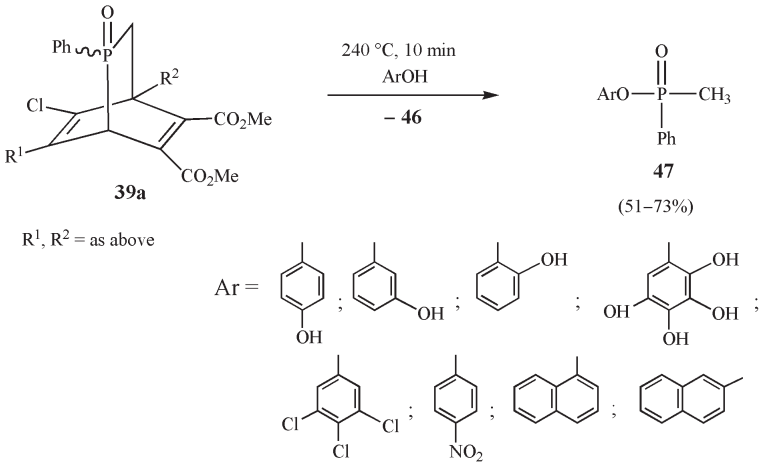
The thermoinduced fragmentations of phosphabicyclooctadienes (**39a**) were utilised in phosphorylations [33]. As a consequence of the relatively high temperature (240 °C) required, non-volatile hydroxy compounds, such as phenole or naphtole derivatives had to be used. The fragmentation took place fast, and the yields of the phosphinic esters (**47**) were acceptable (Scheme 12). The inevitable polymerization of the low-coordinated fragment decreased the efficiency of the phosphorylations. The phosphabicyclooctenes (**40**) were not found to be efficient in the phosphorylation of hydroquinone.

Due to the increased thermostabiliby of the phosphabicyclooctenes (**40**, **41**), the UV light-mediated fragmentation seemed to be more attractive [34,35]. Irradiation of the acetonitrile solution of the isomeric mixture of the precursor (**40a**) in the presence of simple alcohols led to the corresponding phosphinates (**49**, Nu=RO) (Scheme 13). Small-scale preparative experiments afforded the phosphorylated products (**49**, Nu=RO) in good yields after flash column chromatography. The method shown is a good choice for the phosphorylation of primary and secondary alcohols.

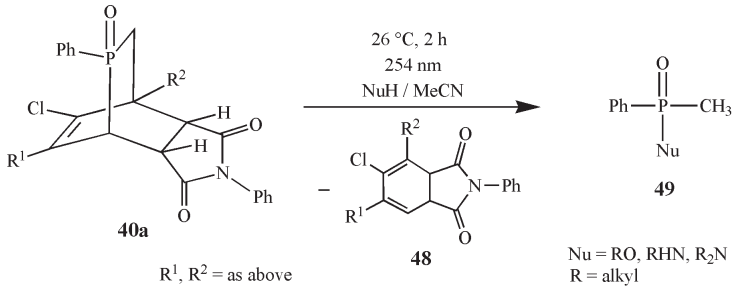
Similarly, our procedure was also suitable for the phosphorylation of primary amines to afford phosphinic amides (**49**, Nu=RHN) (Scheme 13). The secondary amines could, however, be phosphorylated in only low yields.

For the photolysis of phosphabicyclootadienes (*e.g.* **39a**), an elimination-addition reaction path involving the ejection of a methylenephosphine oxide (**50**) in the rate-determing step followed by its fast reaction with an alcohol was substantiated. A similar mechanism seemed to be valid also for the fragmentation of the phosphabicyclooctenes (*e.g.* **40a**). Existence of the elimination-addition mechanism involving methylene phosphine oxide (**50**) as the intermediate was confirmed by the fact that the fragmentation took also place in the absence of any alcohol [34] (Scheme 14). In this

Scheme 12

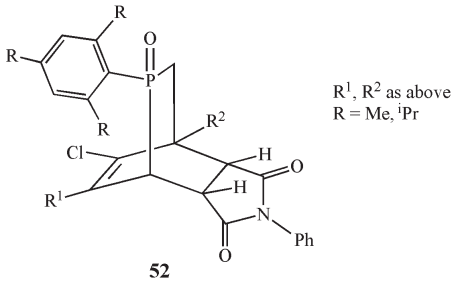


Scheme 13

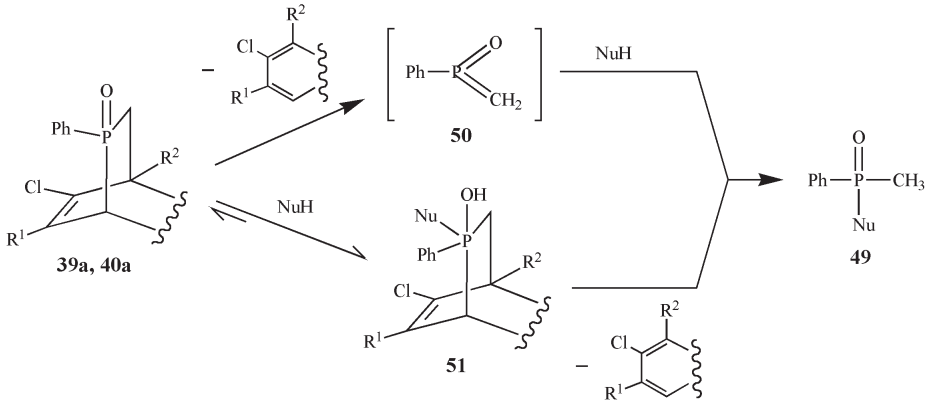


case, the result of these photolyses was a precipitate, presumably the polymer of the low-coordinate fragment. We observed, however, that the fragmentation was faster in the presence of an alcohol, moreover the rate was dependent on the molar excess of the protic species. Nature of the alcohol have also had an impact on the reaction time: the fragmentation was slower in the presence of isopropyl alcohol, than in methanol. These observations are consistent with the involvement of the alcohol in the rate-determining step [27]. According to this, the alcohol is added on the phosphoryl group of the starting material to give an intermediate with a pentacoordinated phosphorus atom (**51**). This adduct is then fragmented to afford the phosphorylated product (**49**) (Scheme 14).

mechanistic examinations [37]. We could prove that the first step of the AE mechanism, the addition of the nucleophile on the P=O group is reversible [36]. Interrupting the photolysis of a phosphabicyclooctene carried out in the



Scheme 14

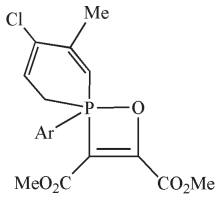


The results of concurrent reactions using equimolar mixtures of different alcohols seemed to support the above conclusions [36]. As was expected, there was a significant selection between the alcohols. This shows clearly the role of nucleophility in the fragmentation suggesting at least the partial involvement of the AE mechanism. Phosphabicyclooctenes with sterically demanding substituent on the phosphorus atom (**52**) were also useful in the presence of ^{18}O-water, we could point out the starting material labeled with ^{18}O isotope. This is possible only through a reversible addition.

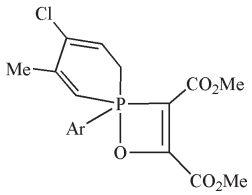
It can be concluded that the photochemical fragmentation of the phosphabicyclooctenes (**40**) takes place according to concurrent elimination–addition and addition–elimination mechanisms. Proportions of the two pathways seem to be comparable.

4. A novel reaction between cyclic phosphine oxides and dimethyl acetylenedicarboxylate.

The P-(2,4,6-triisopropylphenyl)-dihydrophosphinine oxide (**53B**), obtained as a single isomer, was reacted with dimethyl acetylenedicarboxylate at 150–160 °C. Spectroscopical analysis of the product isolated in a good yield suggested that it was not the expected Diels Alder cycloadduct (**54**) (Scheme 15) [38,39].

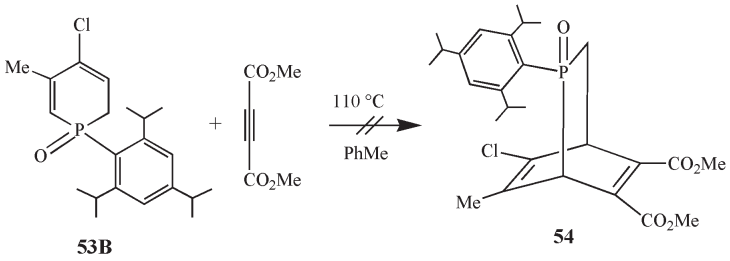


56$_1$



56$_2$

Scheme 15

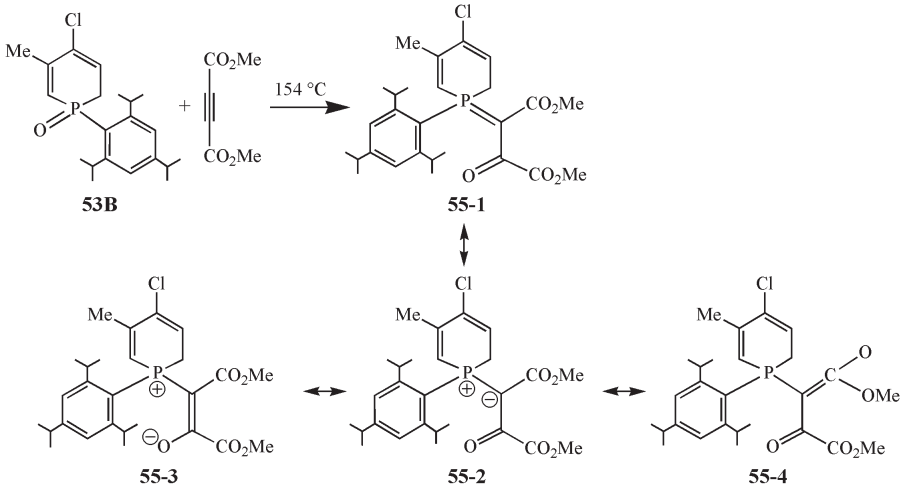


53B **54**

Interestingly, a β-oxophosphorane (**55**) was the product that is the isomer of the expected phosphabicyclooctadiene **54**. The unexpected product (**55**) exists under four resonance structures, such as phosphorane **55-1**, ylide **55-2**, enolate **55-3** and stabilised ylide **55-4** and can be called to be a stabilised phosphonium ylide (Scheme 16).

The reaction of the P=O group of cyclic phosphine oxides (**57**) with dimethyl acetylenedicarboxylate affording phosphoranes/ylides (**59**) proved to be general [41]. The extended protocol for the novel reaction is shown in Scheme 17. According to this, 5- and 6-membered cyclic phosphine oxides (**57**) can be

Scheme 16



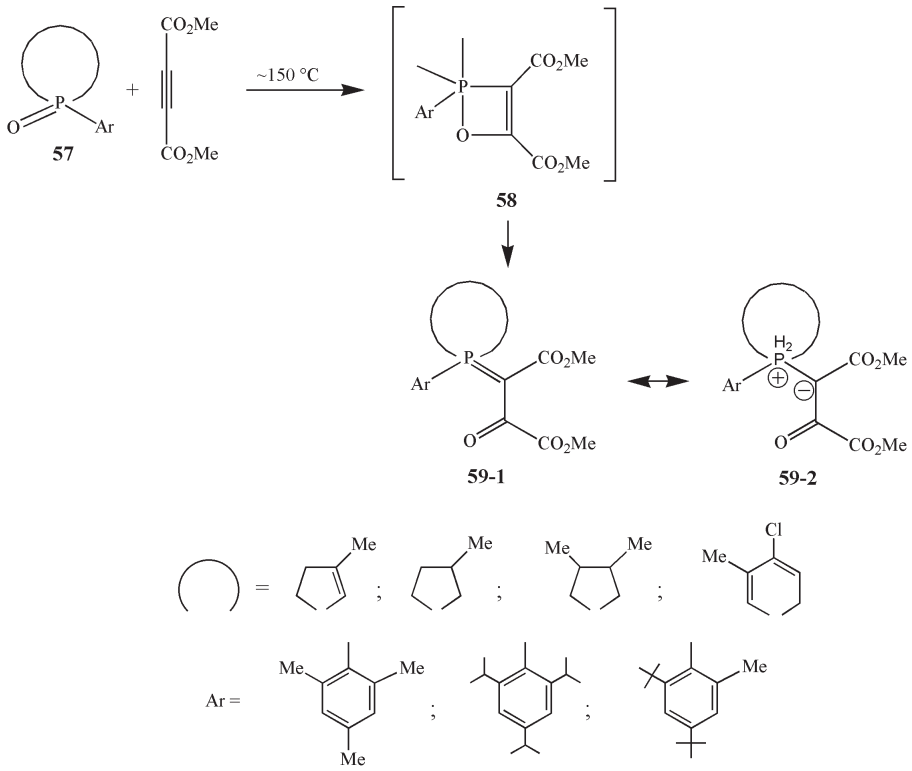
53B **55-1** **55-3** **55-2** **55-4**

The possible intermediate of the novel reaction is oxaphosphete **56** that may exist in two forms (**56$_1$** and **56$_2$**) [40]. Semiempirical quantum chemical calculations suggested that the species with equatorial oxygen atom (**56$_1$**) is more stable than the other one with axial oxygen atom (**56$_2$**). For this, **56$_1$** was assumed to be the real intermediate.

the starting materials bearing a 2,4,6-trialkylphenyl substituent on the phosphorus atom.

Reactions of the β-oxophosphoranes/ylides [42], as well as the mechanism of the novel reaction have been studied in details [43].

Scheme 17



Acknowledgements.

I wish to acknowledge the skilful and enthusiastic contributions of all co-workers, students and collaborators whose names appear in the list of references. The author thanks the Hungarian National Science Foundation (OTKA T 042479) for financial support.

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