Isolable 1,2-Oxaphosphetanes: From Curiosities to Starting Materials for the Synthesis of Olefins

Fernando López-Ortiz*, Jesús García López, Ramón Álvarez Manzaneda and Isidro J. Pérez Álvarez

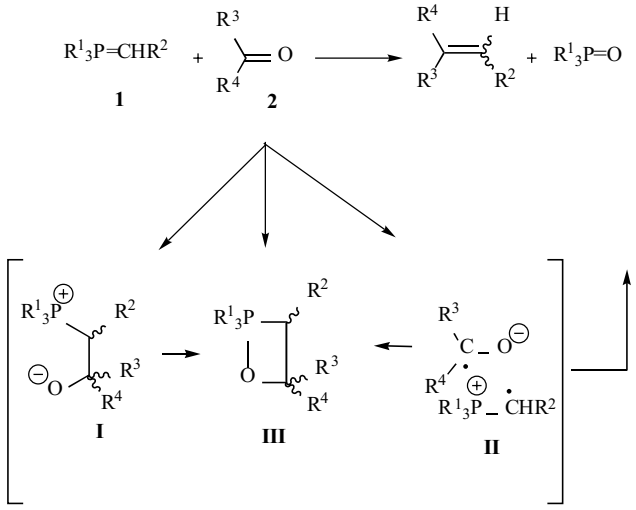
Área de Química Orgánica, Universidad de Almería, Carretera de Sacramento s/n, 04120 Almería, Spain

Abstract: 1,2-Oxaphosphetanes are well established intermediate species in the Wittig reaction. Initially, isolable 1,2-oxaphosphetanes represented a source of structural information aimed at supporting mechanistic studies. The evolution of the subject allows the envisaging of stable 1,2-oxaphosphetanes as precursors for the stereoselective formation of olefins.

Keywords: Oxaphosphetanes, olefination, Wittig, spiro-heterocycles, phosphorus ylides, phosphazenes.

I. INTRODUCTION

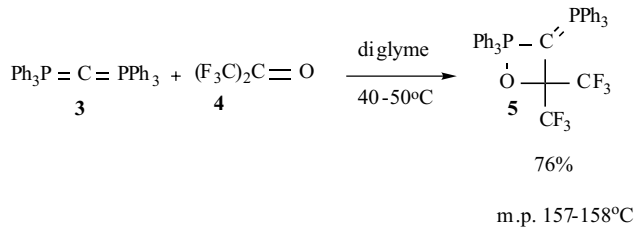
Carbon-carbon double bond forming reactions are among the most widely used processes in organic synthesis. The discovery that phosphorus ylides react with carbonyl compounds producing olefins represented a breakthrough in the way of achieving this apparently simple synthetic operation. Although this was first noted by Staudinger in 1919 [1], it was Wittig who more than three decades later recognized the real potential of this transformation [2]. Since then, it has become universally known as the Wittig reaction [3]. Soon after, phosphonates (Horner-Wadsworth-Emmons reaction) [4], phosphonamides (Corey reaction) [5], and phosphine oxides (Horner reaction) [6], demonstrated their utility as alternative reagents for olefination reactions.



Scheme 1.

Given the relevance of the Wittig and alike reactions, extensive experimental [7] and theoretical [8] work has been devoted to clarify the reaction mechanism. The greatest attention was paid to the first part of the reaction, the addition of a phosphorus-stabilized anion (**1**) to a carbon-oxygen double bond (**2**), because it was found to be the cause of the stereochemical outcome of the process. A variety of different species, betaines (**I**) [9], spin-pair diradicals (**II**) [10], and 1,2-oxaphosphetanes (**III**), have been proposed as possible reactive intermediates. However, only 1,2-oxaphosphetanes (**III**) have been fully identified [11] and occasionally isolated (Scheme 1).

Although a universal mechanism answering all questions raised by the large amount of experimental data available is still a matter of debate, there is a general agreement about the participation of 1,2-oxaphosphetanes in the synthesis of olefins mediated by phosphorus reagents. Concerning the Wittig reaction, it is well known that the standard *P*-triphenyl substituted stabilized ylides (Scheme 1, R^1= C_6H_5, R^2= CN, CO_2R) are characterized by a remarkable *E*-stereoselectivity in their reactions with aldehydes, whereas the unstabilized ones (Scheme 1, R^1= C_6H_5, R^2= alkyl) are highly *Z*-stereoselective. Theoretical calculations have shown that oxaphosphetane formation occurs quickly with unstabilized ylides, and that their decomposition determines the rate of the reaction. However, in the case of stabilized ylides the energy barriers for oxaphosphetane formation and decomposition are comparable [8, 12]. These reaction profiles explain why the detection and isolation of oxaphosphetanes have been possible only in reactions involving unstabilized ylides. In 1967, Birum and Matthews had already reported the structural characterization (NMR and X-ray study) of the first isolated 1,2-oxaphosphetane (**5**). Compound (**5**) was prepared in 76% yield by allowing hexaphenylcarbodiphosphorane (**3**) to react with hexafluoroacetone (**4**) (HFA) in dry diglyme [13] (Scheme 2).



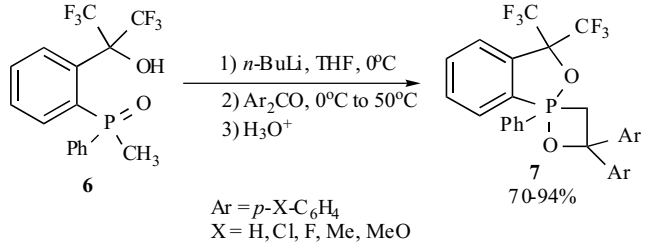
m.p. 157-158°C

Scheme 2.

*Address correspondence to this author at the Área de Química Orgánica, Universidad de Almería, Carretera de Sacramento s/n, 04120 Almería, Spain; Tel.: 34 950 015478; Fax: 34 950 015481; E-mail: flortiz@ual.es

1570-193X/04 $45.00+.00

The unexpected stability of (**5**) was assigned in part to the strong electron-withdrawing effect of the trifluoromethyl groups. As a matter of fact, apart from fluorine itself, trifluoromethyl substituents are the most extensively used structural fragments for the stabilization of oxaphosphetane rings. They are generally introduced either by direct reaction of the phosphorus derivative with a fluorinated ketone or *via* the Martin ligand [*ortho*-(hexafluoromethylhydroxy)phenyl] [14]. In the last case, additional stabilization is achieved through formation of a relatively rigid $4\lambda^5$-phospha-spiro (3.4) derivative. The five-membered ring arises from the bonding of the phosphorus atom of the oxaphosphetane to the oxygen of the ligand side-arm [15]. A representative example is shown in Scheme 3 for the synthesis of (**7**).

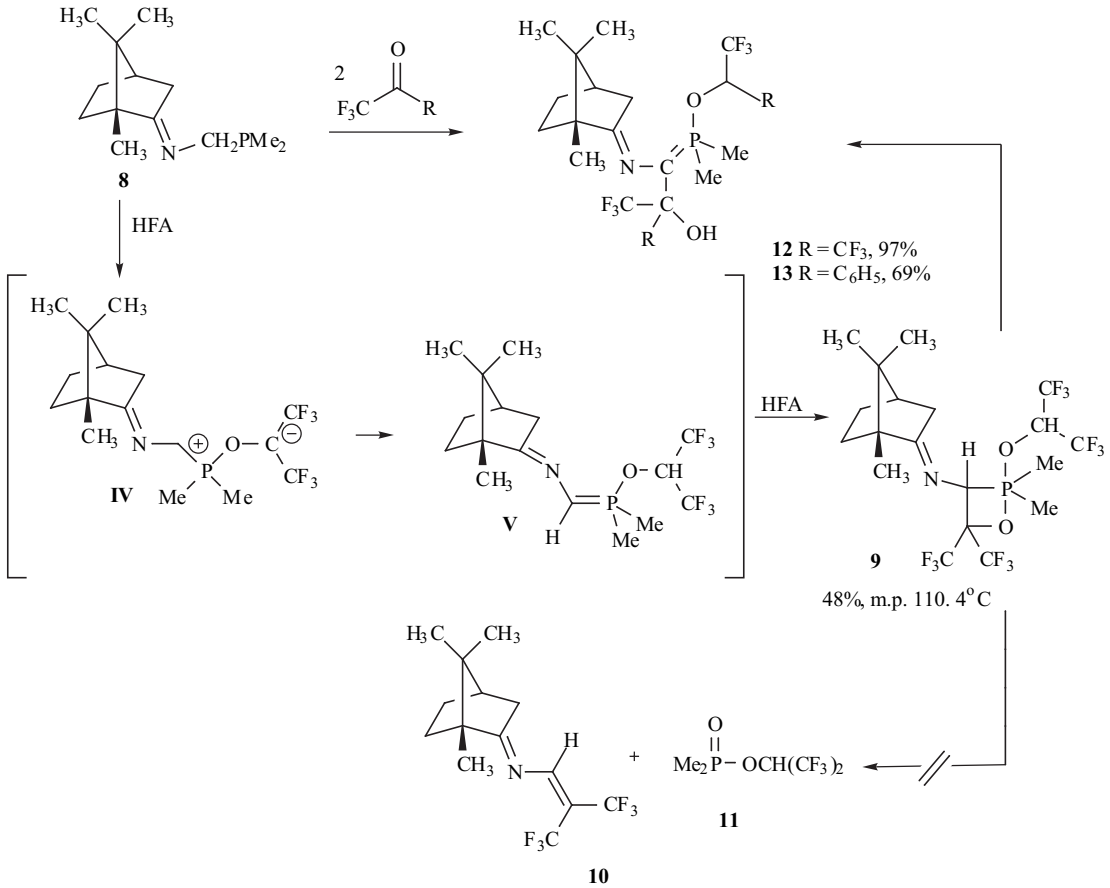


Scheme 3.

Afarinkia examined the early literature on this topic [16]. A later review by Kawashima and Okazaki covered the work carried out up to 1996 [17]. Oxaphosphetanes containing fluorine atoms bonded to phosphorus are a particular class of these pentacoordinated phosphorus heterocycles. Their synthesis and reactivity has been very recently reviewed by Kolodiazhnyi and Schmutzler [18]. In this survey, we will report on the new developments made in the field of isolable 1,2-oxaphosphetanes up to July 2003 without restricting the coordination number of the phosphorus atom. The presentation will be based on the functional group of the phosphorus reagent used for the construction of the heterocycle.

II. PHOSPHINES

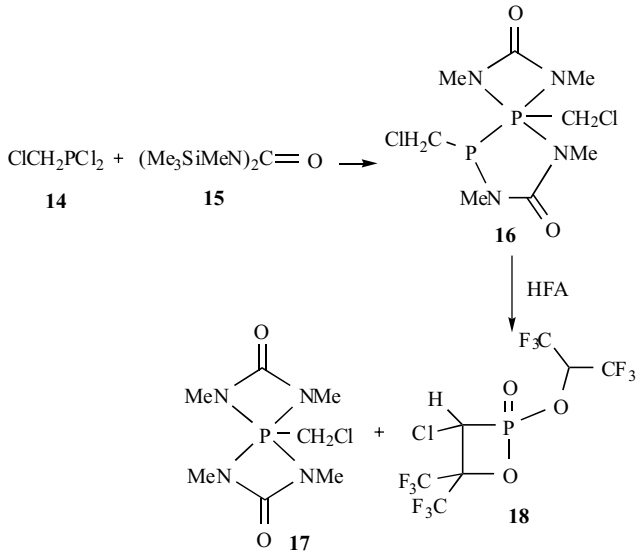
The most general strategy for building up the oxaphosphetane ring is based on the use of phosphines, either directly or as precursors of the corresponding phosphorus ylides. Oxidation of P(III) compounds with HFA was one of the first methods described for the synthesis of isolable oxaphosphetanes [16,17]. This chemistry involves the formation of the four-membered ring either in a one-step reaction or through thermolysis of a precursor 1,3-dioxaphospholane [19]. Phosphine (**8**) provided a new example of this methodology. HFA reacted with (**8**) to give the racemic 1,2-$\sigma^5\lambda^5$-oxaphosphetane (**9**) in moderate yield [20]. The participation of intermediates, such as (**IV**) and (**V**) in the reaction mechanism was previously proposed [21]. Compound (**9**) proved to be unstable at room temperature and evolved through ring opening. However, instead of the expected imine alkene (**10**) and phosphinic ester (**11**), the product isolated was the ylide (**12**) derived from the cleavage of the P-O bond and subsequent



Scheme 4.

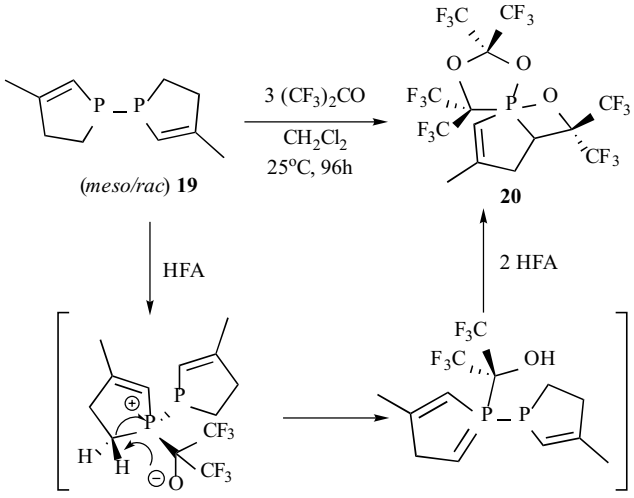
neutralization of the resulting alkoholate by deprotonating the most acidic CH adjacent to the phosphorus atom (Scheme 4). The analogous reaction of (**8**) with trifluoroacetophenone proceeded directly to the racemic ylide (**13**).

Phosphine (**16**), having a σ^3P–σ^5P bond, behaves in an unusual manner. This is rather the rule than the exception in compounds, where a phosphorus atom is influenced by another one directly bound to it. The reaction of (**16**) with HFA led to the phosphorus spirocycle (**17**) and oxaphosphetane (**18**) [22]. Compound (**18**) arises from the formal trapping of the Cl_2CHP moiety by two equivalents of the fluoroketone. This implies that a strong bond reorganization of the starting material occurred during the process, including the cleavage of the P-P bond (Scheme 5).



Scheme 5.

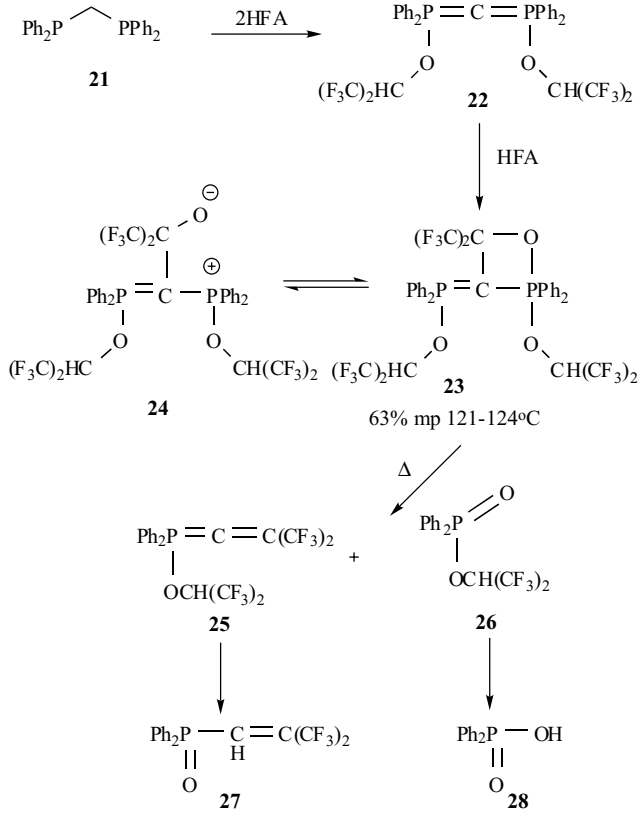
Phosphorus-phosphorus bond cleavage was also observed in the reaction of HFA with diphosphane (**19**), where both phosphorus atoms are in the same state of oxidation. Stirring the reagents for four days at room temperature in dichloromethane, resulted in a crude reaction mixture containing at least eight products. Recrystallization from diethyl ether afforded the phosphorane (**20**) in 15% yield



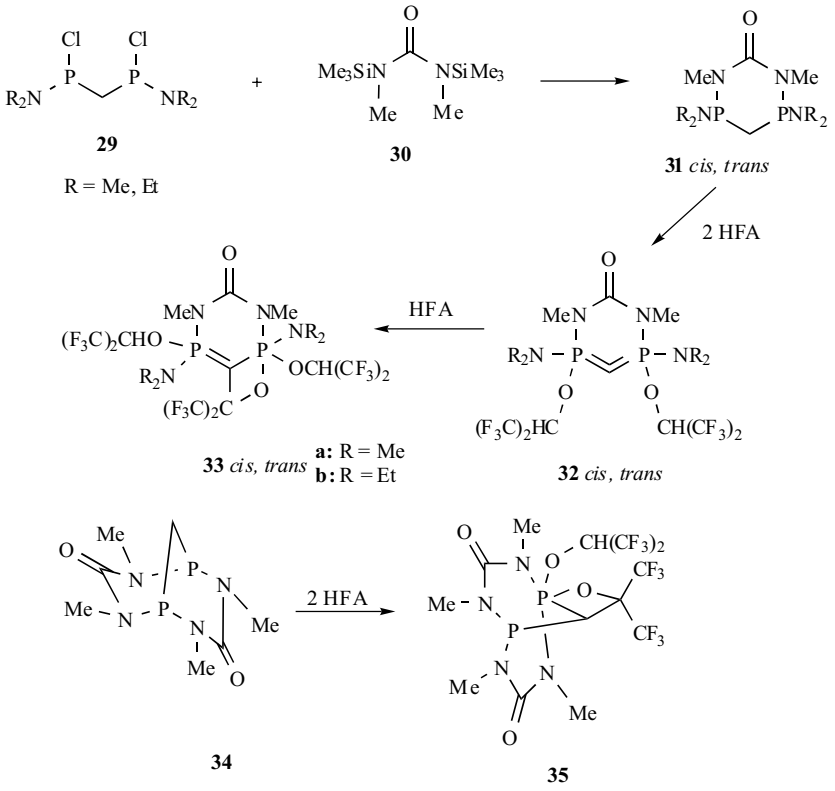
Scheme 6.

[23]. The X-ray structure of (**20**) indicated that the phosphorus atom adopts a distorted trigonal bipyramide. The tricyclic compound (**20**) was found to be unique for two reasons. Firstly, it was the first time that the oxidation of a phosphorus derivative with HFA provided a product containing an oxaphosphetane and a 1,3-dioxaphospholane fragment in the same molecule, and secondly, it was also the first time that in a pentacoordinated phosphorus a carbon atom displaced an oxygen atom from the preferred apical position. A possible mechanism for the formation of (**20**) is shown in Scheme 6.

Insertion of a methylene group between the two phosphorus atoms, as in bisphosphane (**21**), restored the expected reactivity of the phosphine moiety towards HFA. Thus, carbodiphosphorane (**22**) was the product obtained by treatment of (**21**) with two equivalents of HFA. Formation of (**22**) may be explained by a mechanism analogous to that shown in Scheme 4 for the synthesis of (**9**). In this case, the process leading to an ylide intermediate of type (**V**) is sequentially repeated for each phosphorus atom. The addition of a third equivalent of HFA to the bisylide (**22**) yielded oxaphosphetane (**23**) (Scheme 7), whose structure was established by an X-ray diffraction study [24]. This synthetic strategy has been previously used for the preparation of stable oxaphosphetanes [13, 25]. Interestingly, in solution the ^{19}F NMR spectrum showed a single signal for the CF_3 substituents linked to the four-membered ring. The chemical equivalence of these groups was interpreted by assuming that in solution the heterocycle opened to give the zwitterionic structure (**24**) by breaking the P-O bond. This situation would be one example of the reversible formation/breaking of the P-O bond that has been suggested in mechanistic studies of the Wittig reaction.



Scheme 7.



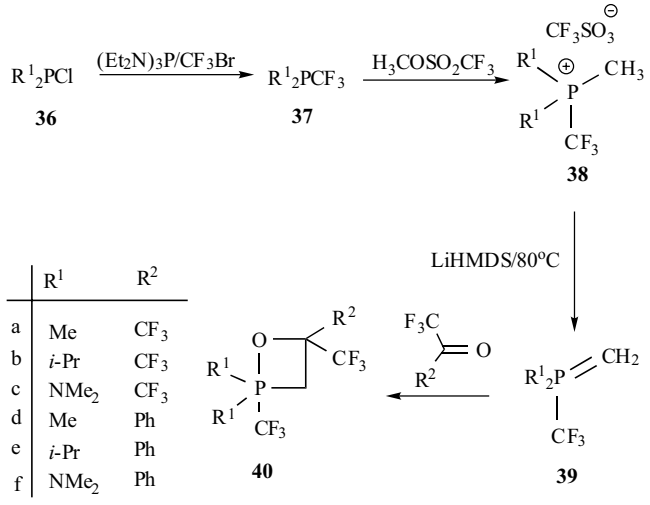
Scheme 8.

Compound (**23**) decomposed to the expected Wittig products (**25**) and (**26**) by heating a chloroform or toluene solution at 60-100 ºC. These products were unstable and evolved to the phosphine oxide (**27**) and diphenylphosphinic acid (**28**), respectively.

When the P–CH_2–P fragment is part of a cyclic structure, the reaction with HFA proceeds in much the same manner as for open chain derivatives. Diazadiphosphinanones (**31**), prepared in high yield by reaction of silylated urea (**30**) with bisphosphanes (**29**), smoothly added three equivalents of HFA yielding heterocycles (**33**) [26] (Scheme 8). Contrary to (**22**), the intermediate carbodiphosphoranes (**32**) could be only detected in the reaction mixture by NMR. Compounds (**33**) are stable and were isolated as a mixture of *cis*/*trans* isomers. The structure of (**33b-*trans***) was determined by single-crystal X-ray diffraction. The phosphorus atom of the oxaphosphetane ring showed a trigonal bipyramidal coordination, with one oxygen and one nitrogen atom occupying the apical positions. Geometrical limitations of the spirocyclic system constructed from the six-membered heterocycle determined that an oxygen-containing ligand coordinated with the phosphorus in an equatorial position.

The inclusion of the fragment P–CH_2–P into a bicyclic system limited the reaction with HFA to only one of the phosphorus atoms. Thus, in the reaction of compound (**34**) with an excess of HFA a mixture of polymeric material (82%) and oxaphosphetane (**35**) (18%) was obtained (Scheme 8). The process was slower than for (**31**), requiring 48 h for completion. The isolated product (**35**) was identified by NMR spectroscopic and analytical data.

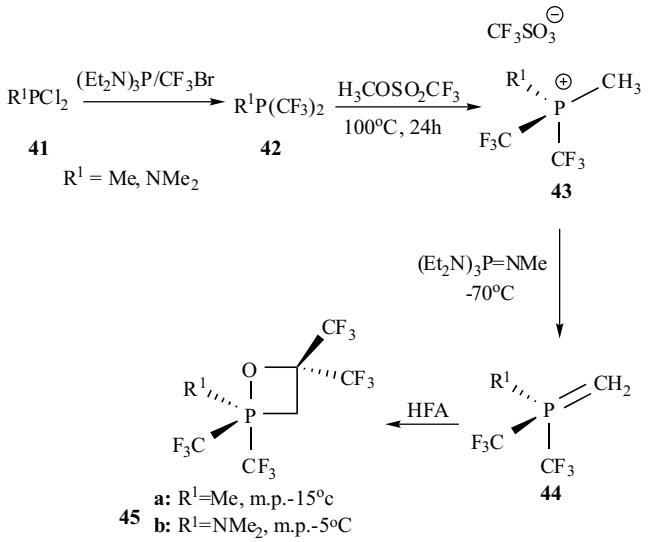
The strategy of stabilizing oxaphosphetanes through the incorporation of CF_3, substituents to the carbon atoms of the ring system was extended to the synthesis of heterocycles, where the CF_3 group is directly bound to phosphorus. The first *P*-trifluoromethylated 1,2-oxaphosphetanes synthesized (**40a-c**) proceeded from the trapping reaction of the unstable ylide (**39**) with HFA (**4**), *i.e.* it also contained CF_3 substituents bonded to carbon [27] (Scheme 9). Röschenthaler *et al.* prepared ylide (**39**) through the usual sequence of reactions. Trifluoromethylphosphines (**37**) were obtained by treating the chlorine derivatives (**36**) with $(Et_2N)_3P/CF_3Br$ (Ruppert reagent). Methylation of (**37**) with $CH_3OSO_2CF_3$ to give the phosphonium salt (**38**), followed by metalation with LiHMDS at –80 ºC, yielded the ylides (**39**). Subsequent addition of HFA afforded (**40a-c**) in low to moderate yields.



Scheme 9.

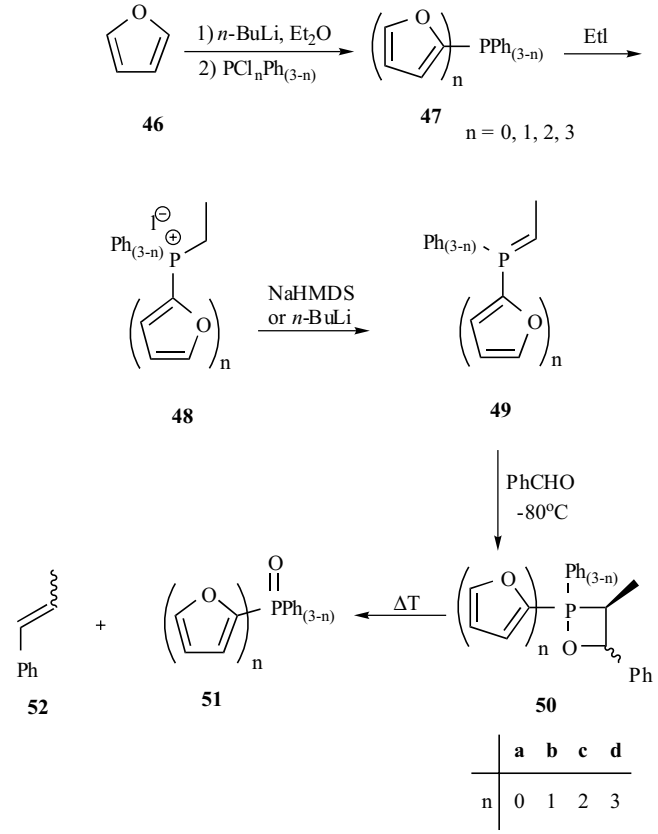
Oxaphosphetane (**40b**) was a solid that could be characterized by single-crystal X-ray diffraction. It showed a distorted trigonal bipyramid at phosphorus with the *P*-CF_3 group in an apical position, as expected from the apicophilicity rules [28]. Ylides (**39**) were also trapped with α,α,α-trifluoromethylacetophenone, although no experimental details were given about the isolation and structure identification of the corresponding oxaphosphetanes (**40d-f**) obtained [29].

The bis(trifluoromethylated) derivatives (**45**) were prepared in a similar way. In this case, the deprotonation of the required phosphonium salts (**43**) were carried out with the phosphazene base $(Et_2N)_3P{=}NMe$ at –70 ºC. The resulting ylides (**44**) were trapped with HFA (**4**), leading to the moisture-sensitive oxaphosphetanes (**45**) (Scheme 10), which were characterized by their NMR and MS spectra [30]. At room temperature Berry-pseudorrotation was fast on the NMR time scale, impeding to distinguish apical and equatorial *P*-CF_3 groups. Decreasing the temperature to 213 K in toluene-d_8 allowed resolving the signals for all CF_3 groups of the molecule. The chemical behavior of heterocycles (**40**) and (**45**) was not explored.



Scheme 10.

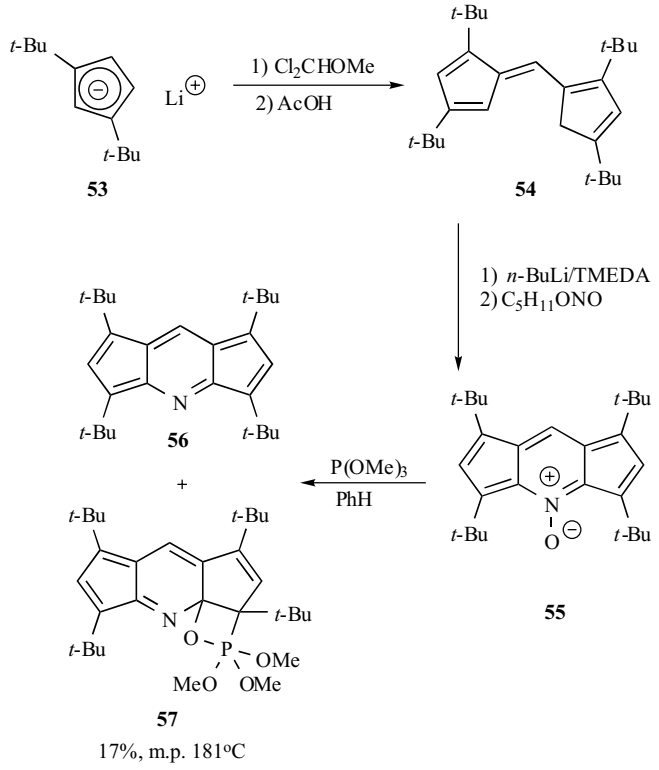
As mentioned above, coordination of phosphorus to fluorine-containing ligands or construction of polycyclic systems centered at phosphorus are the common features shown by all oxaphosphetanes isolated so far. However, the use of these structural constrains to stabilize the four-membered ring is not compulsory. A large number of oxaphosphetanes with structures much closer to the ones applied in organic synthesis have been characterized by NMR [7, 11] and occasionally by mass spectrometry [31]. Berger *et al.* found that by replacing the phenyl substituent of the standard triphenylphosphine used as starting material for Wittig reactions by 2-furyl groups, the *Z*-alkene (**52**) selectivity improved significantly [32]. The required phosphines (**47**) were readily accessible through known procedures, and quaternization to give the phosphonium salts (**48**) was achieved by the addition of ethyl iodide (Scheme 11). In order to obtain good yields of alkene the conventional Wittig procedure -ylide (**49**) formation by treatment of (**48**) with *n*-butillithium or NaHMDS, then addition of benzaldehyde at -80 ºC and stirring the reaction overnight at room temperature- had to be slightly modified. It was necessary to reflux the reaction for three hours in THF prior to the aqueous workup. This fact pointed out an increased stability of the oxaphosphetane intermediates. NMR monitoring of the reactions confirmed this hypothesis and revealed a half life close to two hours for the oxaphosphetane bearing three 2-furyl substituents (**50d**). This observation led to its isolation and X-ray characterization after recrystallization from chloroform. Oxaphosphetane (**50d**) is devoid of the stabilizing elements encountered in all previously published oxaphosphetane structures. In comparison with fluorinated oxaphosphetanes, the increased stability with respect to triphenyl derivatives was assigned to the electron-withdrawing capability of the 2-furyl groups.



Scheme 11.

III. PHOSPHITES

The synthesis of oxaphosphetanes using phosphites as starting materials are very scarce [16, 17, 33]. One recent example, albeit unexpected, has been reported by Hafner and co-workers in connection with the search for methods of preparing hetero-*s*-indacenes. They envisaged the synthesis of (**56**) by deoxygenation of the *N*-oxide (**55**) resulting from the sequence of reactions shown in Scheme 12. Treatment of (**55**) with trimethylphosphite in refluxing benzene produced the expected tricycle (**56**) in 75 % yields, together with 17% of a red solid, which was characterized by X-ray diffraction as the oxaphosphetane (**57**) [34]. Compound (**57**) was obtained as a sub-product and no further transformations were pursued.

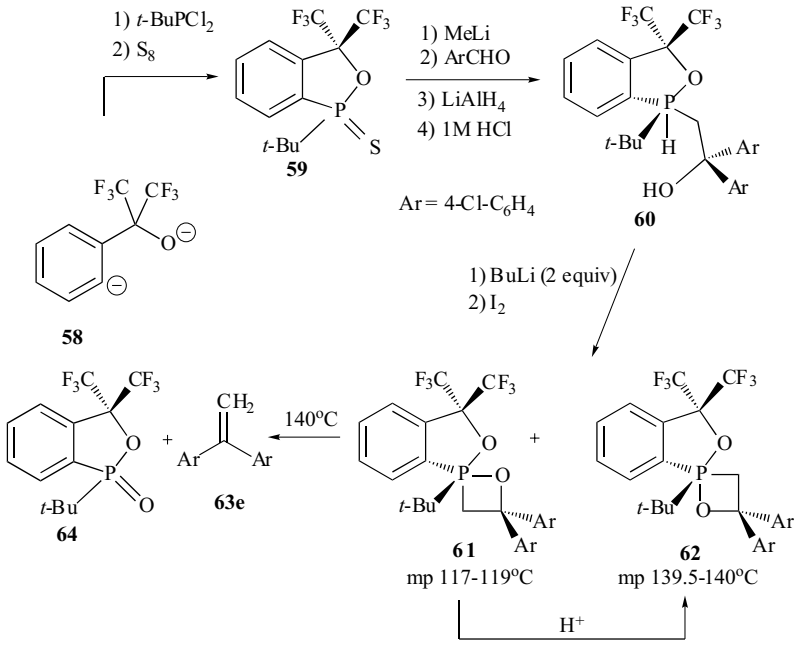


Scheme 12.

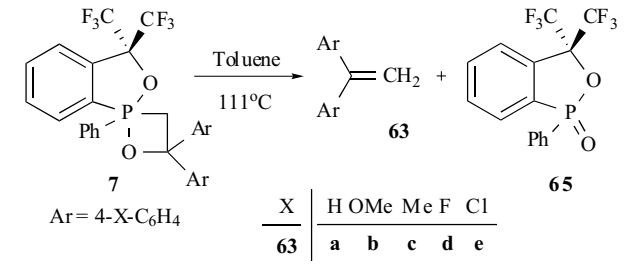
IV. PHOSPHINIC ESTERS

Akiba *et al.* made a recent contribution to the insight of the Wittig olefination mechanism through the synthesis of oxaphosphetane (**61**) having a *P*-coordination pattern contrary to the apicophilicity rules, *i.e.* an apical carbon and an equatorial oxygen atom. A number of experimental evidences suggest that the decomposition to the usual Wittig products of oxaphosphetanes having an apical oxygen, involves a previous pseudorotation step leading to a new oxaphosphetane, where a carbon atom occupies an apical position [7]. Theoretical calculations also support this model [12a]. Except for the tricyclic derivative (**20**), no other example of this particular type of oxaphosphetane has been reported. Moreover, the structure of (**20**) differs notably from the typical olefin-forming intermediates in the Wittig reaction. The synthesis of (**61**) is outlined in Scheme 13 [35]. The phosphorane precursor (**60**) was obtained in a one-pot reaction starting with the thiophosphinic ester (**59**) containing the Martin ligand. Curiously, this transformation failed when the *P*-oxide analog of (**59**) was used as starting material.

Cyclization of (**60**) by sequential addition of *n*-BuLi and iodine in diethyl ether at 0 ºC, provided a 1:1 mixture of the isomeric oxaphosphetanes (**61**) and (**62**). Crystallization from hexane gave the pure anti-apicophilic derivative (**61**) [c.f. the phosphorus-carbon coupling constants for the apical *vs*. equatorial carbon: $^1J_{PC}$= 29.4 and 106.7 Hz for (**61**) and (**62**), respectively], whose structure was confirmed by X-ray diffraction. Stereomutation of compound (**61**) to (**62**) was accelerated in the presence of acids and slowed down when DBU was present, suggesting that the isomerization is rather the result of a P–O bond breaking-recombination process. Quantitative olefin (**63e**) formation required prolonged heating of (**61**) at the melting point of 140 ºC. At lower temperatures only the isomer (**62**) was obtained. Thus, (**61**) represents an example of a thermodynamically stable oxaphosphetanes, in which pseudorotation is faster than alkene formation [7c]. This characteristic left the question about the structure of the direct precursor of the Wittig products unanswered. No data about the decomposition of (**62**) were given. The harsh conditions needed for completing the Wittig reaction for (**61**) contrast with the smooth decomposition of the closely related oxaphosphetanes (**7**) to the olefin (**63**) and the cyclic phosphinic ester (**65**) [15] (Scheme 14).

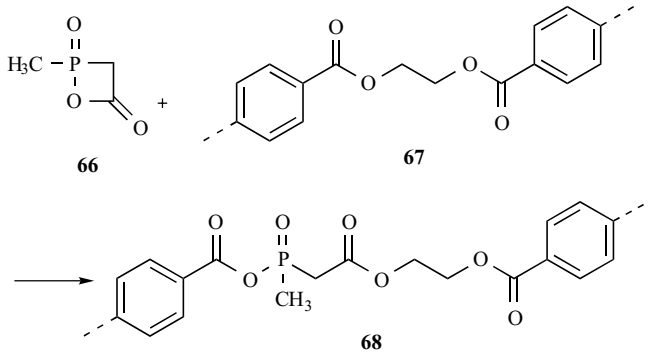


Scheme 13.



Scheme 14.

For the sake of completeness we must mention that a cyclic phosphinic ester, (**66**), was used in the synthesis of co-polyesters (**68**) [36] (Scheme 15). Compounds analogs to (**66**) have been previously described by Kawashima and co-workers [37].

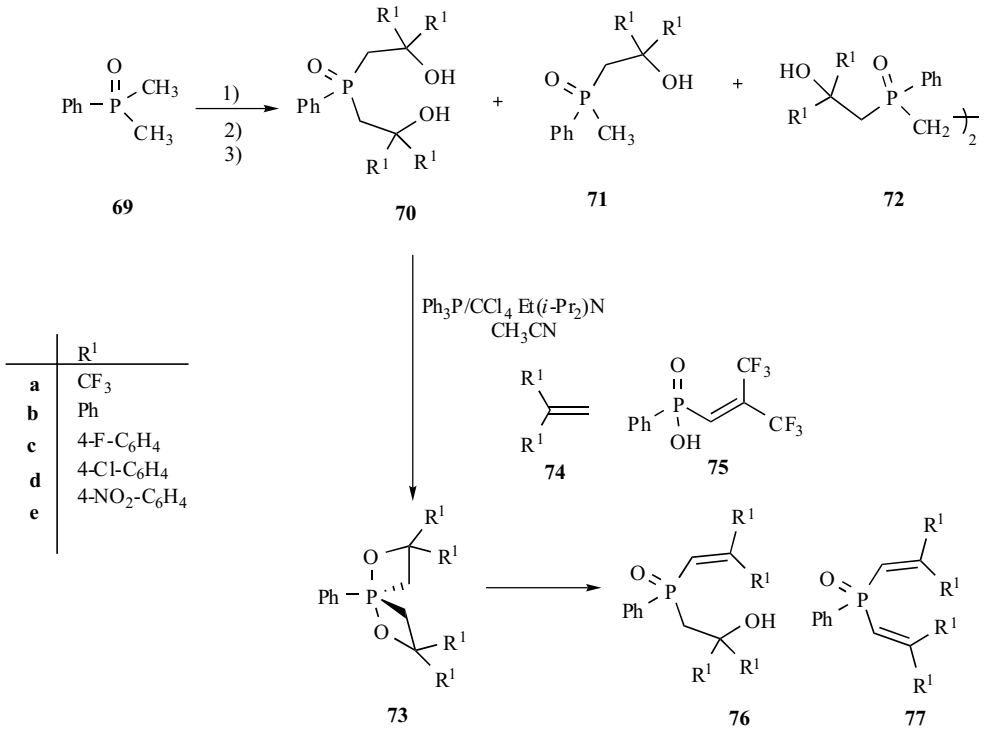


Scheme 15.

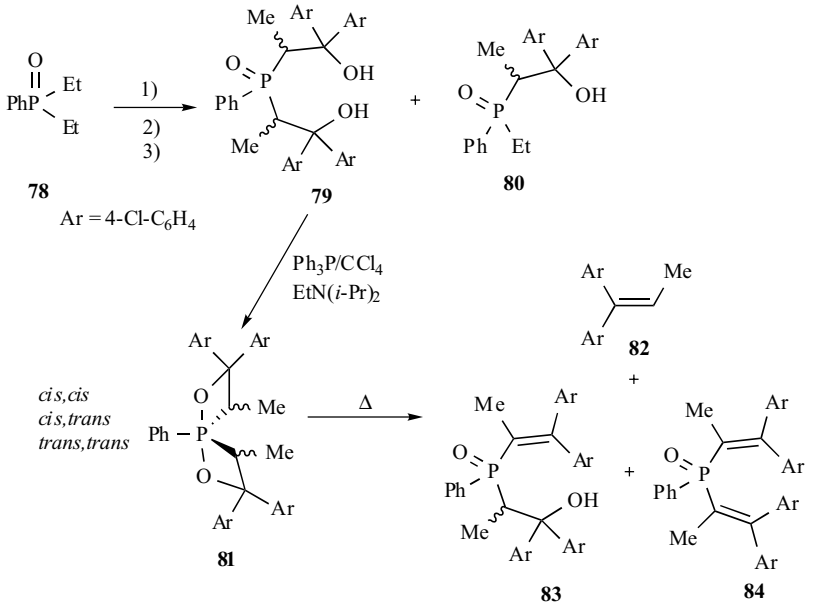
V. PHOSPHINE OXIDES

Dimethylphenylphosphine oxide (**69**) was the starting material used by the group of Kawashima and Okazaki to synthesize the first bis-oxaphosphetane (**73a**) in 1994. The heterocyclic subunits of the new pentacoordinated phosphorus compound shared the phosphorus atom, giving rise to a spirocycle. It is conceivable, that thermolysis of (**73a**) could produce double olefin extrusion. However, only one equivalent of olefin (**74a**) was formed, together with the vinylphosphinic acid (**75**) [38] (Scheme 16). The failure to achieve double olefination was considered as being due to the electron-withdrawing effect of the CF_3 groups. This hypothesis was later demonstrated by preparing new spirocyclic bis-oxaphosphetanes without trifluoromethyl substituents. The synthetic procedure was the same applied for (**73a**). Double metalation of (**69**) with *n*-BuLi followed by addition of the corresponding ketone and then aqueous NH_4Cl allowed the obtaining of the dihydroxiphosphine oxides (**70b-d**) in good yields. Minor quantities of the monoadducts (**71**) were also formed. The reaction with 4,4-dinitrobenzophenone was much less efficient. In this case, other competing processes were taking part (most probably single electron transfer) as revealed by the isolation of the dimer (**72**). Double cyclization of (**70**) by treatment with Ph_3P/CCl_4 (Appel reagent) provided the expected bis-oxaphosphetanes (**73b-e**) [39] (Scheme 16). They were generated in-situ in acetonitrile and subsequently heated, giving a mixture of the expected olefin, the open chain isomer (**76**) and its dehydration product (**77**). From the conversion yield of olefin (>150%) the conclusion was reached that double olefination had indeed occurred.

The analogous process of diethylphenylphosphine oxide (**78**) proceeded in the same manner (Scheme 17). Even though, the reaction contained a complex mixture of stereoisomers due to the prochirality of the ethyl groups attached to the phosphorus. Cyclization of the isomeric diols (**79**) led to all possible *cis*/*trans* derivatives (**81**), which were



Scheme 16. 1) *n*-BuLi (2-5 equiv), THF, –72ºC, 5h, –30ºC to –20ºC, 4h; 2) $R^1{}_2CO$, –72ºC, –30ºC to –20ºC, 1h, 25ºC, 2h; 3) aq. NH_4Cl.

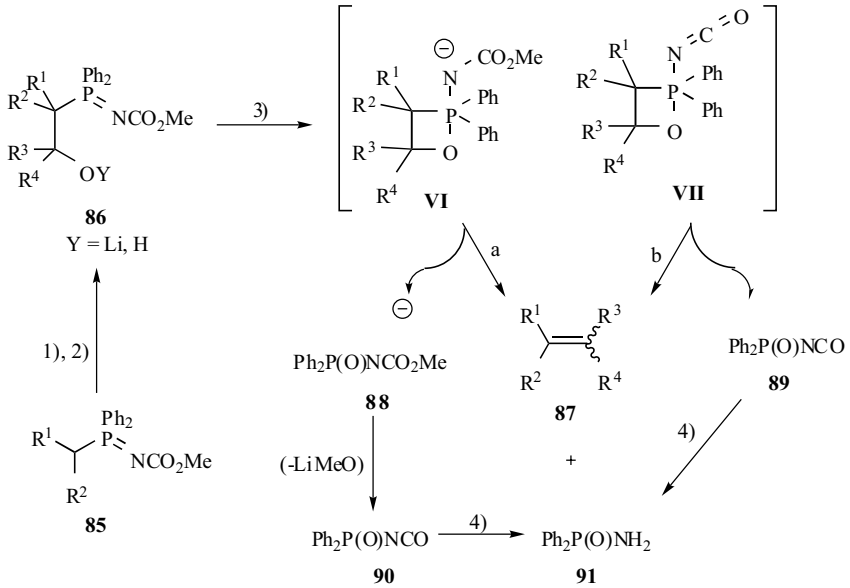


Scheme 17. 1) *n*-BuLi (2.3 equiv), -78ºC to 25ºC, 10 min; 2) Ar_2CO (2.19 equiv); 3) aq. NH_4Cl.

recrystallized and identified through X-ray diffraction analysis [40]. In the solid state, the isomers *cis*,*cis* and *cis*,*trans* showed a distorted trigonal bipyramidal structure with two apical oxygen atoms. In contrast, the structure of the *trans*,*trans* derivative corresponded to a distorted square pyramide with the phenyl group occupying the apical position. Significantly, in solution the ^{31}P chemical shift of all three diastereomers occurred in the range -31.2 to -33.6 ppm, indicating that all of these have a trigonal bipyramide (TBP) structure. Thermolysis of (**81**) resulted in a mixture similar to that found for (**73**). Although moderated, the yields of olefin (**82**) (127 to 158%) showed again that double olefination had taken place.

VI. PHOSPHAZENES

λ^5-Phosphazenes are isoelectronic with phosphorus ylides and phosphine oxides. Similar to phosphine oxides, alkyldiarylphosphazenes can be metalated by alkyllithiums or lithium amides [41]. However, the chemistry of these species has received much less attention [42]. Phosphazenyl-stabilized carbanions have been mainly used as synthons for the preparation of phosphorus-nitrogen heterocycles [43]. Their reactivity towards carbonyl compounds had been described as a method for preparing β-hydroxy derivatives with total *C*-regioselectivity and excellent diastereoselectivity [44]. Very recently, López-Ortiz *et al.* demonstrated that phosphazenes (**85**) are also suitable starting materials for the synthesis of olefins. α-Lithiated *N*-methoxycarbonylphosphazenes smoothly react with aldehydes and ketones to give di-, tri-, and tetra-substituted olefins (**87**) in high yield [45]. By analogy with the olefination reactions based on phosphorus ylides and phosphine oxides reagents, the carbon-carbon double bond formation step was considered to proceed through an oxaphophetane intermediate (**VI**-**VII**) (Scheme 18). This



Scheme 18. 1) *n*-BuLi, -35 ºC, THF; 2) R^3R^4CO, rt; 3) 4-20 h; 4) H_2O.

assumption was supported by the observation in the ^{31}P NMR spectra of the crude of the reactions of minor resonances (1-7 %) in the chemical shift range of –70 to –40 ppm.

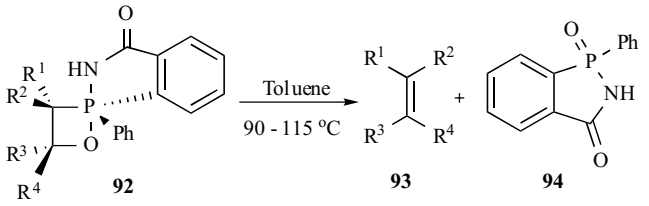
Attempts of isolating compounds related to the intermediate species (**VI-VII**) led to the discovery of a new class of bicyclic 1,2-oxaphosphetanes (**92**). The sequence of reactions begins with the metalation of phosphazenes (**85**). This step was accomplished by treating (**85**) with 2.2 equiv of *t*-BuLi in THF at –30 ºC for 30 min. Then, the appropriated carbonyl compound was added at –95 ºC and the reaction mixture was stirred for 150 min at this temperature. Finally, aqueous workup provided the oxaphosphetanes (**92**) in high yield and with moderate to excellent stereoselectivities [46] (Scheme 19, Table 1). In the construction of spirocycles (**92**) two new carbon-carbon bonds have been created. One at the position α with respect to the phosphorus, and a second one at the *ortho* position of one *P*-phenyl ring. These new bonds revealed the participation of a precursor dianionic species (**VIII**), which represented the first example of the formation of a dianion of a non-silylated phosphazene [47]. The reaction mechanism leading to (**92**) is completed by assuming a cyclocondenation of (**VIII**) to the monolithiated phosphazene (**IX**), and subsequent addition of this new anion to the corresponding aldehyde or ketone.

Compounds (**92**) proved to be exceptionally stable and could be purified by flash chromatography or recrystallization without decomposition. They are one of the few examples of isolable spirocyclic oxaphosphetanes, whose stability is not derived from the presence of fluorine-containing substituents [48]. The structural identification was based on the NMR spectroscopic study. Additionally, the structure of (***trans*-92a**) was confirmed by X-ray diffraction analysis. Oxaphosphetanes (**92**) were transformed quantitatively and stereospecifically into olefins (**93**) and benzazaphosphol (**94**) by heating a toluene solution at 90-115 ºC (Scheme 20). ^{31}P NMR monitoring of the process showed a first order kinetic with respect to the starting heterocycle. The olefins were extracted from the crude reaction mixture with hexane. Solvent evaporation afforded pure alkenes without contamination of the by-product (**94**). Compounds (**92**) represent the first evidence of the participation of oxaphosphetanes in the synthesis of olefins through phosphazenes. They can be readily accessed through a process compatible with a large variety of aliphatic and aromatic aldehydes and ketones. The simplicity and high efficiency of the olefination reaction mediated by oxaphosphetanes (**92**) convert phosphazenes into a promising alternative to the most popular organophosphorus reagents currently applied for carbon-carbon double bond forming reactions.

Table 1. Yields (%) and *dr* of the Oxaphosphetanes 92 Obtained[a]

Comp.	R^1	R^2	R^3	R^4	*Trans:cis*	Yield
92a	Me	Me	H	*i*-Pr	49:51	93
92b	Me	Me	H	*t*-Bu	27:73	87
92c	Me	Me	H	4-MeO-C_6H_4	40:60	93
92d	Me	H	($CH_2CH_2CH_2CH_2CH_2$)		95:5	82
92e	Me	*n*-Bu	Me	Ph	76:24[b]	62
92f	Me	Me	Me	Ph	10:90	89

[a]The diastereoisomers were separated by precipitation in diethyl ether or column chromatography. The descriptors *trans/cis* indicate the spatial relationship between the *P*-phenyl ligand and the highest rank substituent linked to the stereogenic carbons of the oxaphosphetane. [b]*Trans*/*cis* descriptors indicate the orientation of the methyl groups, in both stereoisomers the phenyl rings are *cis*.



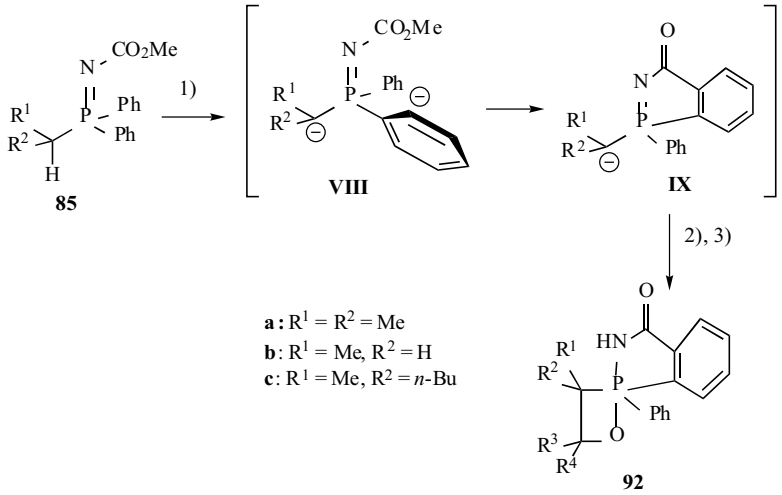
92

93

94

92	R^1	R^2	R^3	R^4
a	Me	Me	H	4-MeO-C_6H_4
b	Me	H	[$CH_2(CH_2)_3CH_2$]	
c	Me	*n*-Bu	Me	Ph
d	*n*-Bu	Me	Me	Ph

Scheme 20.



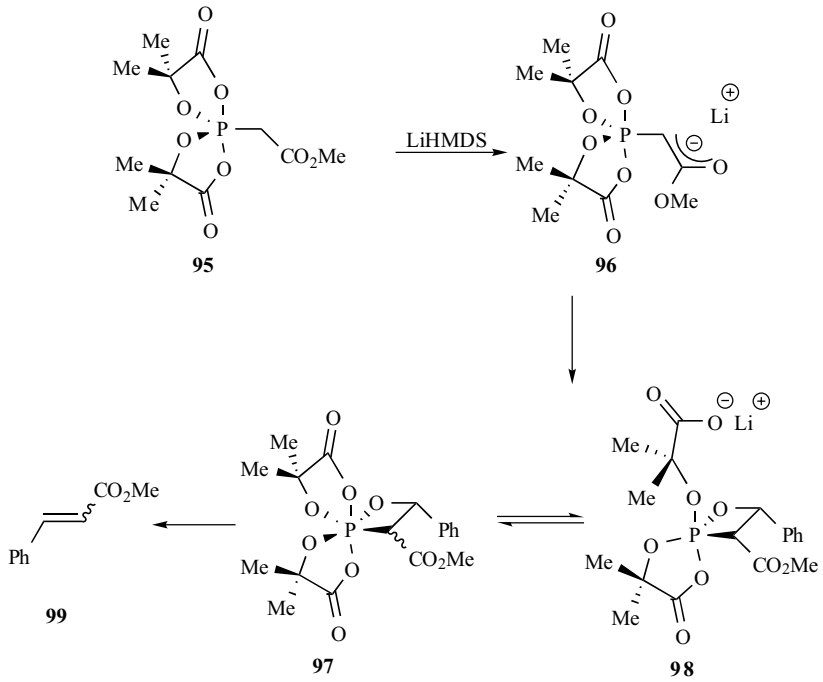
Scheme 19. 1) *t*-BuLi 2.2 equiv, THF, -35 ºC, 30 min; 2) R^3R^4CO, -95 ºC, 150 min; 3) H_2O.

VII. PHOSPHORANES (10-P-5)

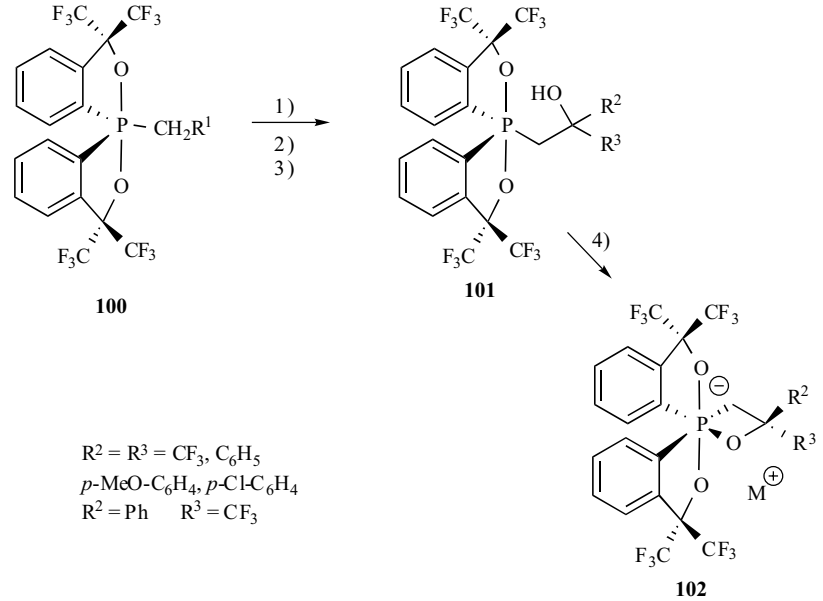
Pentacoordinated phosphoranes are compounds with unique properties, which have attracted a great attention since their discovery [49]. A reason for this interest stems from the important role they play in many biological processes. For example, pentaoxyphosphoranes may serve as model compounds for reaction intermediates occurring in enzymatic reactions [50].

Recently, the application of these compounds in olefination reactions has been explored. Evans Jr. and co-workers showed that spirooxyphosphorane (**95**) can be deprotonated at the carbon linked to the phosphorus by treatment with LiHMDS, and that the resulting carbanion (**96**) undergoes the Wittig reaction to yield olefins (**99**) when they were allowed to react with benzaldehyde [51] (Scheme 21). Temperature variations strongly influenced the *E/Z* ratio of the olefins obtained. A ^{31}P NMR study of the process led to the first observation of a hexavalent oxyphosphorane (**97**) bearing an oxaphosphetane ring. They were identified as a mixture of diastereomers (δ_P –106.1 to –116.8 ppm) in rapid equilibrium with the pentacoordinated oxaphosphetane (**98**). The decomposition of both intermediates afforded the cynnamates (**99**), with the *trans* (thermodynamic control) and *cis* (kinetic control) adducts giving rise to the *E* and *Z* alkene, respectively.

Soon after, the groups of Akiba [52 a-b] and of Kawashima and Okazaki [51c] independently reported the



Scheme 21.



Scheme 22. 1) R^1 = H, *n*-BuLi; R^1 = SPh, LiNaph (2 equiv); 2) R^2R^3CO; 3) NH_4Cl; 4) KH, 18-crown-6 or KOBu^t, DMSO.

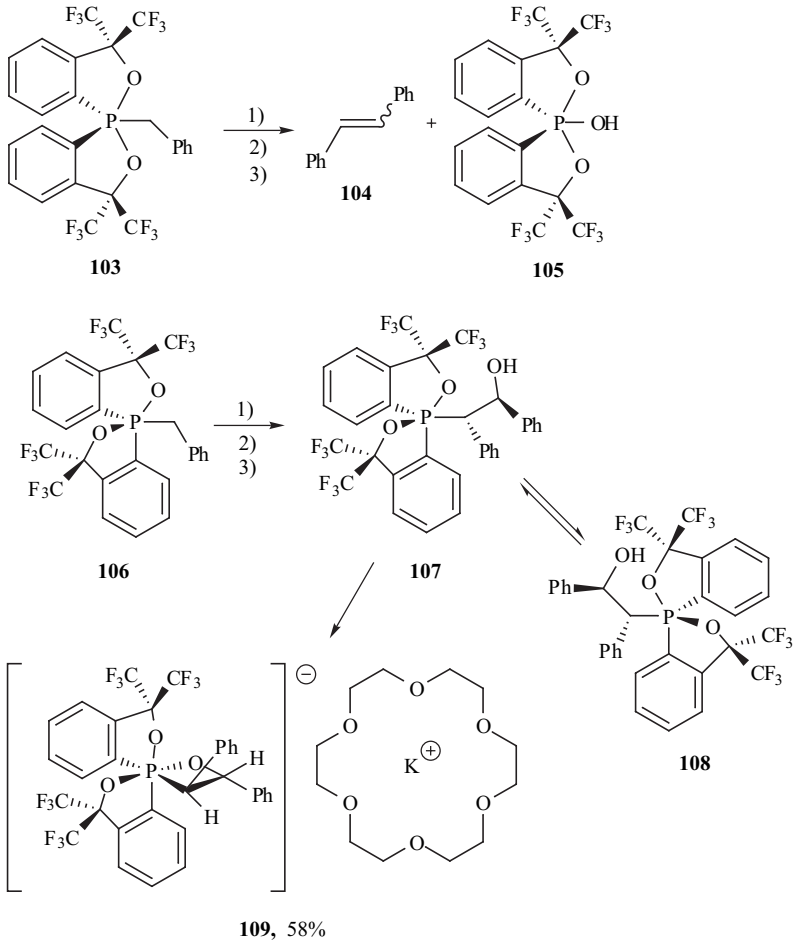
extension of this chemistry to pentacoordinated phosphoranes incorporating the bidentate Martin ligand (**100**) (Scheme 22). Again, the structures of the 12-P-6 phosphates (**102**) were determined *in situ* by NMR spectroscopy. Thermolytic (80-100 ºC, THF:C_6D_6 5:1) fragmentation to an olefin was only observed for the derivative doubly substituted at the four-membered ring with two CF_3 groups, albeit in moderate yield (40%).

Very recently, Akiba and co-workers succeeded in isolating and characterizing through X-ray diffraction analysis the first hexacoordinated phosphorane (**109**) containing an oxaphosphetane heterocycle [53] (Scheme 23). Lithiation of phosphorane (**103**) with *n*-BuLi in THF, followed by reaction with benzaldehyde afforded *Z/E*-stilbenes (**104**) (*Z:E* ratio of 59:41) in high yield (91%). In contrast, the analogous reaction of isomer (**106**), having an apical carbon and an equatorial oxygen, do not progress beyond the formation of the diastereomeric adduct (**107**) and (**108**). Interestingly, increasing the reaction time more than 24 h resulted in the isomerization of (**108**) to the product of thermodynamic control (**107**). Even though, the low temperature ^{31}P NMR spectrum showed two signals indicating a low energy barrier of inversion at the phosphorus center through a one-step pseudorotation process. Metalation of (**107**) with KH in THF produced three species (detected by ^{31}P NMR), which equilibrate to the most stable one (**109**). This could be isolated and recrystallized from hexane. These crystals proved to be stable for months at room temperature in the air and allowed the first X-ray characterization of a 12-P-6 phosphate containing an oxaphosphetane substructure.

Thermal decomposition of (**109**) to *trans* stilbene was quantitatively achieved upon heating a THF solution at 60 ºC for 4 days [54], and the activation parameters determined by NMR monitoring of the transformation ($\Delta H^{\ddagger}$ = 27.1 ±0.8 kcal/mol, $\Delta S^{\ddagger}$ = 0.4 ±2.5 e.u., and $\Delta G^{\ddagger}_{298}$ =27.0 kcal/mol). The low magnitude of the activation entropy was interpreted as an indication that structural changes are not essential for the decomposition due to the fact that the P-C being broken in the process is already elongated.

VIII. CONCLUSIONS

Carbon-carbon double bond forming reactions mediated by organophosphorus reagents have been a topic of interest for a long time. The availability of methods for the synthesis of isolable oxaphosphetanes represent a fundamental contribution to the understanding of the reaction mechanism of these processes. On the other hand, oxaphosphetanes stable in air at room temperature can be used as starting materials for the stereospecific synthesis of alkenes. The incorporation of phosphazenes and phosphoranes to the armory of Wittig-type olefination reagents may be envisaged as a source of future innovations that would contribute to widen the range of applications of these compounds.



Scheme 23. 1) *n*-BuLi, THF; 2) PhCHO; 3) H^+.

IX. ACKNOWLEDGEMENTS

We wish to thank the European Community (FEDER project 1FD97-1651) and Ministerio de Ciencia y Tecnología (project PPQ2001-3266) for financial support. M. J. Iglesias is gratefully acknowledged for art graphics.

X. REFERENCES

[1] Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
[2] Wittig, G.; Geissler, G. *Liebig Ann. Chem.* **1953**, *580*, 44.
[3] Kolodiazhnyi, O. I. *Phosphorus Ylides. Chemistry and Applications in Organic Synthesis*, Wiley-VCH: Weinheim, **1999**.
[4] Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
[5] Corey, E. J.; Kwiatkowsky, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5652.
[6] Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61.
[7] a) Marianoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1. (c) Vedejs, E.; Peterson, M. J. *Adv. Carbanion Chem.* **1996**, *2*, 1.
[8] For some leading references see: (a) Mari, F.; Lahti, P. M.; McEwen, W. E. *J. Am. Chem. Soc.* **1992**, *114*, 813. (b) Yamataka, H.; Nagase, S. *J. Am. Chem. Soc.* **1998**, *120*, 7530. (c) Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280. (d) Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.-I-; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001**, *57*, 1715.
[9] For a review see: a) Borisova, I. V.; Nechaev, M. S.; Khrustalev, V. N.; Zemlyanskii, N. N.; Ustynyuk, Y. A. *Russ. Chem. Bull, Int. Ed.* **2002**, *51*, 721. (b) Reynolds, K. A.; Finn, M. G. *J. Org. Chem.* **1997**, *62*, 2574. (c) Neumann, R. A.; Berger, S. *Eur. J. Org. Chem.* **1998**, 1095. (d) Schröder, U.; Berger, S. *Eur. J. Org. Chem.* **2000**, 2601.
[10] Yamataka, H.; Nagareda, K.; Takatsuka, T.; Ando, K.; Hanfusa, T.; Nagase, S. *J. Am. Chem. Soc.* **1993**, *115*, 8570. (b) Yamataka, H.; Takatsuka, T.; Hanafusa, T. *J. Org. Chem.* **1996**, *61*, 722.
[11] Vedejs, E.; Marth, C. F. In *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Quin, L. D.; Verkade, J. G., Ed.; VCH: Weinheim, **1994**; Chap. 23, pp.297-313.
[12] Restrepo-Cossio, A. A.; Cano, H.; Mari, F.; Gonzalez, C. A.; *Heteroatom Chem.* **1997**, *6*, 557. (b) Restrepo-Cossio, A. A.; Gonzalez, C. A.; Mari, F. *J. Phys. Chem. A.* **1998**, *102*, 6993.
[13] Birum, G. H.; Matthews, C. N. *J. Org. Chem.* **1967**, *32*, 3554.
[14] Perozzi, E. F.; Michalak, R. S.; Figuly, G. D.; Stevenson III, W. H.; Dess, D. B.; Ross, M. R.; Martin, J. C. *J. Org. Chem.* **1981**, *46*, 1049.
[15] Kawashima, T.; Kato, K.; Okazaki, R. *J. Am. Chem. Soc.* **1992**, *114*, 4008. Correction, *J. Am. Chem. Soc.* **1998**, *120*, 6848.
[16] Afarinkia, K. *Heterocycles* **1992**, *34*, 369.
[17] Kawashima, T.; Okazaki, R. *Synlett* **1996**, 600.
[18] Kolodiazhnyi, O. I.; Schmutzler, R. *Synlett* **2001**, 1065.
[19] Oram, R. K.; Trippett, S. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1300. (b) Röschenthaler, G.-V. *Z. Naturforsch.* **1978**, *33b*, 131. (c) Hacklin, H.; Röschenthaler, G.-V. *Zeit. Anorg. Allg. Chem.* **1988**, *561*, 49.
[20] Borkenhagen, F.; Neda, I.; Thönnessen, H.; Jones, P. G.; Schmutzler, R. *Zeit. Anorg. Allg. Chem.* **1998**, *650-624*, 650.
[21] Ramirez, F.; Smith, C. P.; Pilot, J. F. *J. Am. Chem. Soc.* **1968**, *90*, 6726. (b) Ul-Haque, M.-; Caughlan, C. N.; Ramirez, F.; Pilot, J. F.; Smith, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 5229.
[22] Neda, I.; Pinchuk, V. A.; Thönnessen, H.; Ernst, L.; Jones, P. G.; Schmutzler, R. *Zeit. Anorg. Allg. Chem.* **1997**, *623*, 1325.
[23] Vollbrecht, S.; Vollbrecht, A.; Jeske, J.; Jones, P. G.; Schmutzler, R.; du Mont, W.-W. *Chem. Ber.* **1997**, *130*, 819.
[24] Schevchenko, I. V.; Mikolenko, R. N.; Lork, E.; Röschenthaler, G.-V. *Eur. J. Inorg. Chem.* **2001**, 2377.
[25] Verma, S.; Athale, M.; Bokadia, M. M. *Indian J. Chem. Sect. B.* **1981**, *20*, 1096.
[26] Schevchenko, I. V.; Mikolenko, R. N.; Chernega, A.; Rusanov, E. B.; Grützmacher, H. *Eur. J. Inorg. Chem.* **2001**, 195.
[27] Dieckbreder, U.; Lork, E.; Röschenthaler, G.-V.; Kolomeitsev, A. A. *Heteroatom Chem.* **1996**, *7*, 281.
[28] In trigonal bipyramidal structures the most electronegative groups occupy preferentialy the apical positions. (a) Trippett, S. *Phosphorus, Sulfur* **1976**, *1*, 89. (b) Matsukawa, S.; Kajiyama, K.; Kojima, S.; Furuta, S.-Y.; Yamamoto, Y.; Akiba, K.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4718.
[29] Kolomeitsev, A. A.; Görg, M.; Dieckbreder, U.; Lork, E.; Röschenthaler, G.-V. *Phosphorus, Sulfur, and Silicon* **1996**, *109-110*, 597.
[30] Dieckbreder, U.; Röschenthaler, G.-V.; Kolomeitsev, A. A. *Heteroatom Chem.* **2002**, *13*, 650.
[31] Wang, C.-H.; Huang, M.-W.; Lee, C.-Y.; Chei, H.-L.; Huang, J.-P.; Shiea, J. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1168.
[32] Appel, M.; Blaurock, S.; Berger, S. *Eur. J. Org. Chem.* **2002**, 1143.
[33] Huang, Y.; Arif, A. M.; Bentrude, W. G. *Phosphorus, Sulfur, and Silicon* **1995**, *103*, 225, and references therein.
[34] Balaban, T. S.; Schardt, S.; Sturm, V.; Hafner, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 330.
[35] Kojima, S.; Supino, M.; Matsukawa, S.; Nakamoto, M.; Akiba, K.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 7674.
[36] Kaki, Werner, Stibal, W.; Deibert, S. Patent to Ems-Inventa A.-G. WO 9735903. *Chem. Abstr.* **1997**, *127*, 307821.
[37] Kawashima, T.; Takami, H.; Okazaki, R. *Chem. Lett.* **1994**, 1487.
[38] Kawashima, T.; Takami, H.; Okazaki, R. *J. Am. Chem. Soc.* **1994**, *116*, 4509.
[39] Kawashima, T.; Okazaki, R.; Okazaki, R. *Phosphorus, Sulfur, and Silicon* **1997**, *124-125*, 379.
[40] Kawashima, T.; Okazaki, R.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2500.
[41] a) Schmidbaur, H.; Jonas, G. *Chem. Ber.,* **1967**, *100*, 1120. (b) Barluenga, J.; López, F.; Palacios, F. *J. Chem. Research* (*S*) **1985**, 211. (c) López-Ortiz, F.; Peláez-Arango, E.; Tejerina, B.; Pérez-Carreño E.; García-Granda, S. *J. Am. Chem. Soc.* **1995**, *117*, 9972. (d) Fernández, I.; Álvarez-Gutiérrez, J.; Kocher, N.; Leusser, D.; Stalke, D.; González, J.; López-Ortiz, F. *J. Am. Chem. Soc.* **2002** , *124*, 15184.
[42] a) Johnson, A. W. *Ylides and Imines of Phosphorus*, John Wiley, New York, **1993**. (b) Cristau, H. J.; *Chem. Rev.* **1994**, *94*, 1299.
[43] a) Álvarez-Gutiérrez, J. M.; López-Ortiz, F. *Tetrahedron Lett.* **1996**, *37*, 2841. (b) Andújar, C. M.; Pérez-Álvarez, I.; López-Ortiz, F. *Tetrahedron* **2002**, *58*, 2569. (c) López-Ortiz, F. *Curr. Org. Synthesis*, submitted.
[44] a) Barluenga, J.; López, F.; Palacios, F. *Synthesis* **1988**, 562. (b) Álvarez-Gutiérrez, J. M.; Peralta-Pérez, E.; Pérez-Álvarez, I.; López-Ortiz, F. *Tetrahedron* **2001**, *57*, 3075.
[45] Peralta-Pérez, E.; López-Ortiz, F. *Chem. Commun.* **2000**, 2029.
[46] García-López, J.; Peralta-Pérez, E.; Forcén-Acebal, A.; García-Granda, S.; López-Ortiz, F. *Chem. Commun.* **2003**, 856.
[47] Hitchcock, P. B.; Lappert, M. F.; Wang, Z-X. *Chem. Commun.* **1997**, 1113.
[48] There are only two additional examples of spirocycles containing one oxaphosphetane ring. The singularity of their structures limited their synthetic applications. (a) Bestamnn, H. J.; Roth, K.; Wilhelm, E.; Böhme, R.; Burzlaff, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 876. (b) Trishim, J. G.; J. G.; Konovalova, I. V.; Burangulova, R. N.; Burnaeva, L. A.; Chistokletov, V. N.; Pudovik, A. N. *Tetrahedron Lett.* **1989**, *30*, 577.
[49] Burgada, R.; Setton, R. in *The Chemistry of Organophosphorus Compounds: Phosphonium Salts, Ylides and Phosphoranes*; Hartley, F. R., Ed.; Wiley-Interscience: Chichester, **1994**; Vol. *3*, pp 185-272.
[50] Holmes, R. R.; Day, R. O.; Deiters, J. A.; Swamy, K. C. K.; Holmes, J. M.; Hans, J.; Burton, S. D.; Prakasha, T. K. in *Phosphorus Chemistry. Developments in American Science*; Walsh, E. W.; Griffith, E. J.; Parry, R. W.; Quin, L. D., Eds.; ACS Symposium Series 486: Washington, **1992**; Chapter 2, pp. 18-40. Holmes, R. R.; *Chem. Rev.* **1996**, *96*, 927.
[51] Bojin, M. L.; Barkallah, S.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 1549.
[52] Kojima, S.; Akiba, K-Y. *Tetrahedron Lett.* **1997**, *38*, 547. (b) Kojima, S.; Takagi, R.; Akiba, K-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5970. (c) Kawashima, T.; Watanabe, K.; Okazaki, R. *Tetrahedron Lett.* **1997**, *38*, 551.
[53] Akiba, K.-Y.; Matsukawa, S.; Kajiyama, K.; Nakamoto, M.; Kojima, S.; Yamamoto, Y. *Heteroatom Chem.* **2002**, *13*, 390.
[54] Matsukawa, S.; Kojima, S. Kajiyama, K.; Yamamoto, Y.; Akiba, K-Y.; Re, S.; Nagase, S. *J. Am. Chem. Soc.* **2002**, *124*, 13154.